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Qadhi, Rawabi Sohiel (2026) *Proton pump inhibitor co-prescription and hospitalisation risk in patients receiving cardiovascular medications: a real-world observational study.* PhD thesis.

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Proton Pump Inhibitor Co-prescription and Hospitalisation Risk in Patients Receiving Cardiovascular Medications: A Real-World Observational Study

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Thesis submitted in fulfilment for the degree of Doctor of Philosophy (PhD)

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June 2026

Abstract

Background: Cardiovascular disease remains the leading cause of global mortality and commonly requires long-term pharmacotherapy with anticoagulants, antiplatelet agents and cardiac glycosides. Proton pump inhibitors (PPIs) are among the most frequently co-prescribed medications in these populations, both for gastroprotection during antithrombotic therapy and for concurrent acid-related disease. PPIs have well-characterised pharmacokinetic interactions with cardiovascular drugs through cytochrome P450 inhibition, alterations in gastric pH, and modulation of P-glycoprotein. However, the extent to which these mechanistic interactions translate into clinically meaningful harm in routine care remains uncertain, and existing observational evidence is heterogeneous and susceptible to confounding by indication.

Aim: This thesis investigated whether co-prescription of PPIs with three classes of cardiovascular medications -digoxin, oral anticoagulants (warfarin, dabigatran, and factor Xa inhibitors) and clopidogrel - is associated with measurable changes in hospitalisation risk in a large, real-world population, and whether such risks differ by drug class.

Methods: Three retrospective cohort studies were conducted using linked electronic health records from NHS Greater Glasgow and Clyde, accessed through the West of Scotland Safe Haven (1 January 2014 – 31 December 2020). Adults aged ≥51 years with relevant index conditions were followed for up to two years. Drug exposure was modelled as a time-varying covariate across four mutually exclusive categories (no exposure, index drug only, PPI only, concurrent exposure), with a 7-day carry-over applied after each prescription. Hazard ratios (HRs) for arrhythmia-related hospitalisation (digoxin cohort), bleeding and treatment failure (oral anticoagulant cohorts), and bleeding-related hospitalisation (clopidogrel cohort) were estimated using time-dependent Cox proportional hazards models within an inverse probability of treatment weighting

(IPTW) framework. Simon–Makuch survival curves were used for complementary visualisation, and reporting followed STROBE guidelines.

Results: In the digoxin cohort (n=23,351), concurrent digoxin–PPI exposure was associated with a modest but significant increase in arrhythmia-related hospitalisation (HR 1.20, 95% CI 1.03–1.39; p=0.023), whereas digoxin and PPI monotherapies were close to the null. The oral anticoagulant findings varied markedly by class. Concurrent warfarin–PPI exposure was associated with elevated bleeding risk (HR 2.13, 95% CI 1.25–3.63; p=0.005; n=29,765). For dabigatran (n=30,985), concurrent exposure was associated with increased treatment failure (HR 1.71, 95% CI 1.10–2.66; p=0.018), while the bleeding analysis could not be reliably estimated owing to sparse concurrent exposure. Factor Xa inhibitor cohorts (n=27,713) showed lower bleeding risk with concurrent PPI use (HR 0.55, 95% CI 0.43–0.69; p<0.001) and a neutral effect on treatment failure (HR 0.99, 95% CI 0.90–1.08; p=0.785). In post-stroke patients receiving clopidogrel (n=8,109), concurrent PPI use was not associated with bleeding-related hospitalisation (HR 0.83, 95% CI 0.53–1.30; p=0.415). Across all three studies, PPI monotherapy showed no association with adverse outcomes.

Conclusions: The effect of PPI co-prescription on clinical outcomes differs by cardiovascular drug rather than acting uniformly. Concurrent use was associated with a modest increase in arrhythmia risk with digoxin and a higher bleeding risk with warfarin, but no increased risk with clopidogrel or factor Xa inhibitors. PPI use on its own was not associated with harm in any cohort. These findings support tailoring monitoring and drug choice to the specific cardiovascular agent, rather than avoiding PPI co-prescription altogether in patients who need gastroprotection.

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Acknowledgement

I would like to express my deepest gratitude to all those who have supported me throughout my PhD journey.

First and foremost, I am incredibly grateful to my husband, Rani Al-Sairafi, for his constant support, patience, and encouragement. To my two wonderful daughters, Raghad and Retal, thank you for being my source of joy and motivation every day.

I would also like to thank my parents, Suhail and Azzah, for their endless love, prayers, and unwavering belief in me. My deepest appreciation goes to my sisters, Roah and Noha, for their unwavering support and understanding. I am especially grateful to them for taking care of my daughters during my absence; their dedication made it possible for me to continue and complete this journey, and I am profoundly thankful for everything they have done. My sincere appreciation also goes to my brother, Ghaith, for his support and understanding. I am also thankful to my mother-in-law, Jehan, and my brothers-in-law for their kindness and encouragement.

My heartfelt thanks go to my supervisor, Professor Sandosh Padmanabhan, for his guidance, understanding, and continuous support throughout this journey. I am truly grateful for the opportunity to work with him. He has been approachable, kind, and very understanding, and I have learned a great deal from him — not only academically, but also from his qualities as a person and an educator. His professionalism, politeness, and support have made him an exceptional supervisor.

A special thanks to Tran Quoc for his hard work and dedication to my project, and to his wife, Ngoc Le, for her kindness and support. I am also grateful to all members of the lab team for their cooperation and assistance.

I would also like to extend my heartfelt thanks to all those who kept me in their prayers and supported me quietly — your kindness meant more than words can express.

On a personal note, I would like to thank myself for staying strong during a very difficult time when my brother was going through serious challenges that affected our whole family. Although I was away from them, I kept going with my PhD and stayed committed to finishing it.

Finally, I am deeply grateful to the friends I met in Glasgow, who became like a family away from home. Their companionship, kindness, and shared experiences have enriched this journey in countless ways.

Author's Declaration

I declare that this thesis is my own work and that it has been written by me in its entirety. This thesis has not been submitted for any other degree at the University of Glasgow or any other institution.

Rawabi Qadhi

June 2026

List of Abbreviations

ABCB1	ATP-Binding Cassette Sub-Family B Member 1
ACE	Angiotensin-Converting Enzyme
ACEi	Angiotensin-Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
ADME	Absorption, Distribution, Metabolism and Excretion
ADP	Adenosine Diphosphate
AF	Atrial Fibrillation
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
ASA	Acetylsalicylic Acid
AT-III	Antithrombin III
ATC	Anatomical Therapeutic Chemical (classification)
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BNF	British National Formulary
CCB	Calcium Channel Blocker
CES1	Carboxylesterase 1
CI	Confidence Interval
CNS	Central Nervous System
COX-1	Cyclooxygenase-1
CPH	Cox Proportional Hazards
CPRD	Clinical Practice Research Datalink
CR	Clopidogrel Resistance
CrCl	Creatinine Clearance
CT	Computed Tomography
CVD	Cardiovascular Disease
CYP / CYP450	Cytochrome P450
DAG	Directed Acyclic Graph
DAPT	Dual Antiplatelet Therapy
DDD	Defined Daily Dose
DDI	Drug–Drug Interaction
DES	Drug-Eluting Stent
DOAC	Direct Oral Anticoagulant
DTI	Direct Thrombin Inhibitor
DVT	Deep Vein Thrombosis
ECL	Enterochromaffin-like (cell)
ECG	Electrocardiogram
ECT	Ecarin Clotting Time
EHR	Electronic Health Record
EMA	European Medicines Agency
EPR	Electronic Patient Record
eDRIS	Electronic Data Research and Innovation Service
ESC	European Society of Cardiology
FDA	United States Food and Drug Administration

GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GIB	Gastrointestinal Bleeding
GORD	Gastro-Oesophageal Reflux Disease
HF	Heart Failure
HIT	Heparin-Induced Thrombocytopenia
HR	Hazard Ratio
ICD-10	International Classification of Diseases, Tenth Revision
INR	International Normalised Ratio
IPTW	Inverse Probability of Treatment Weighting
IQR	Interquartile Range
IV	Intravenous
KUB	Kidney, Urinary and Bladder (disease)
LML	Log-Minus-Log (plot)
LTA	Light Transmission Aggregometry
MAR	Missing At Random
MCAR	Missing Completely At Random
MDR1	Multidrug Resistance Protein 1
MI	Myocardial Infarction
MNAR	Missing Not At Random
MRA	Mineralocorticoid Receptor Antagonist
NHS	National Health Service
NHSGG&C	NHS Greater Glasgow and Clyde
NICE	National Institute for Health and Care Excellence
NOAC	Non-Vitamin K Antagonist Oral Anticoagulant
NRS	National Records of Scotland
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTE-ACS	Non-ST-Segment Elevation Acute Coronary Syndrome
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
NTI	Narrow Therapeutic Index
OAC	Oral Anticoagulant
OR	Odds Ratio
OTC	Over-The-Counter
P2Y12	Platelet ADP receptor subtype P2Y12
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic(s)
PE	Pulmonary Embolism
P-gp	P-Glycoprotein
PIS	Prescribing Information System
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitor
PT	Prothrombin Time
RCT	Randomised Controlled Trial
SCCS	Self-Controlled Case Series
SCI-Store	Scottish Care Information Store
SERCA2a	Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase 2a
SGLT2	Sodium-Glucose Co-Transporter 2

SIMD	Scottish Index of Multiple Deprivation
SMD	Standardised Mean Difference
STEMI	ST-Segment Elevation Myocardial Infarction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCT	Thrombin Clotting Time
TIA	Transient Ischaemic Attack
TN-C	Troponin C
TRE	Trusted Research Environment
TTP	Thrombotic Thrombocytopenic Purpura
UA	Unstable Angina
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WHO	World Health Organization
WPW	Wolff–Parkinson–White (syndrome)
ZES	Zollinger–Ellison Syndrome

Chapter 1 Introduction

This chapter provides the rationale for the research undertaken in this thesis and reviews the literature on which it is based. It is organised in nine sections. Section 1.1 introduces the cardiovascular diseases whose pharmacological management motivates the thesis. Section 1.2 outlines acid-related gastrointestinal diseases and the role of proton pump inhibitors. Section 1.3 reviews drug–drug interaction mechanisms, with particular attention to pharmacokinetic interactions and P-glycoprotein-mediated transport. Sections 1.4 through 1.7 provide detailed reviews of the four medication classes central to this thesis: proton pump inhibitors (Section 1.4), digoxin (Section 1.5), anticoagulants, including oral anticoagulants (Section 1.6), and antiplatelet agents, with a focus on clopidogrel (Section 1.7). Section 1.8 synthesises the interaction evidence across all three cardiovascular drug classes to identify shared and drug-specific vulnerabilities. Finally, Section 1.9 summarises the current state of knowledge, articulates the knowledge gaps this thesis addresses, and states the research aims and objectives.

1.1 Cardiovascular Diseases

Cardiovascular diseases (CVDs) include disorders of the heart and blood vessels, such as coronary artery disease, cerebrovascular disease, peripheral artery disease, and aortic atherosclerosis, which collectively result in events such as myocardial infarction, stroke/Transient Ischaemic Attack (TIA), limb ischaemia, and aortic aneurysm rupture. These acute events frequently lead to chronic consequences, including heart failure, arrhythmias, and lasting functional impairment, which diminish quality of life and require ongoing medical care [1, 2].

Significant advancements in hygiene, vaccination, socioeconomic development, education, and healthcare over the 20th century resulted in a decline in deaths from infectious diseases, accompanied by an increase in noncommunicable diseases. During this epidemiological transition, CVD became the predominant cause of mortality and morbidity globally, a burden anticipated to grow as

populations age faster than in prior generations; current estimates indicate approximately 19.8 million deaths in 2022 due to CVD, predominantly in low- and middle-income nations [3, 4]. In the United Kingdom, cardiovascular disease accounts for approximately one quarter of all deaths, with an estimated 7.6 million people living with CVD; Scotland bears a disproportionate burden relative to the rest of the UK, with higher age-standardised CVD mortality rates, particularly in areas of socioeconomic deprivation such as those served by NHS Greater Glasgow and Clyde [5]. This epidemiological context is directly relevant to the present thesis, which uses data from this health board area and therefore reflects a population with high cardiovascular morbidity, significant polypharmacy, and frequent co-prescribing of proton pump inhibitors alongside cardiovascular medications.

Despite major advances in prevention, diagnosis, and treatment, cardiovascular disease remains the leading cause of mortality worldwide. A substantial proportion of this burden arises not from lack of effective therapies, but from the complexity of managing patients with multimorbidity and long-term pharmacotherapy. These challenges underscore the importance of understanding how commonly co-prescribed medications interact in real-world clinical practice.

1.1.1 Acute coronary syndrome

Acute coronary syndrome (ACS) results from sudden coronary blood-flow obstruction, most often due to plaque rupture with thrombus formation. It includes unstable angina (UA) and myocardial infarction (MI), the latter subdivided into Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) and ST-Segment Elevation Myocardial Infarction (STEMI). Myocardial infarction reflects actual myocardial necrosis triggered by this abrupt ischemia [1, 2].

Patients typically present with chest pain or pressure, dyspnoea, diaphoresis, and nausea; atypical symptoms are frequent in women, the elderly, and those with diabetes. Diagnosis relies on Electrocardiogram (ECG) alterations (distinguishing STEMI from NSTEMI) together with elevated cardiac troponins, supported by additional imaging or biomarkers when needed [1].

Management emphasises rapid reperfusion—primary Percutaneous Coronary Intervention (PCI) as first-line for STEMI or thrombolysis if PCI is not immediately available. NSTEMI and UA are managed with a risk-stratified approach, often involving early invasive strategies in high-risk patients. Core pharmacotherapy includes dual antiplatelet therapy (DAPT), anticoagulation, beta-blockers, Angiotensin-Converting Enzyme (ACE) inhibitors/Angiotensin Receptor Blockers (ARBs), and statins. In the long-term, secondary prevention and lifestyle modification are central to reducing recurrence and improving outcomes [1, 2].

1.1.2 Heart Failure

Heart failure is a clinical syndrome of impaired cardiac filling or ejection causing exertional dyspnoea, fatigue, and fluid retention. Aetiologies include ischaemic heart disease, hypertension, valvular disease, and cardiomyopathies; diagnosis integrates clinical assessment, natriuretic peptides, and echocardiography. Guideline-directed therapy (ACEi/ARB/ARNI, beta-blockers, Mineralocorticoid Receptor Antagonists (MRAs), Sodium-Glucose Co-transporter-2 Inhibitors (SGLT2 inhibitors), and devices when indicated, improves symptoms and survival [1, 2].

1.1.3 Arrhythmias

Cardiac arrhythmias arise from abnormalities in impulse formation or conduction and range from benign ectopy to life-threatening ventricular tachyarrhythmias. Management is individualised: medications for rate/rhythm control, catheter ablation for suitable substrates, and devices (pacemakers, implantable cardioverter-defibrillators) for bradyarrhythmias or malignant ventricular rhythms [1, 2].

1.1.4 Atrial fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by disorganised atrial activation and an “irregularly irregular” ventricular response. It is associated with palpitations, dyspnoea, fatigue, and heightened risks of thromboembolism (notably ischaemic stroke) and heart failure; management

combines rate or rhythm control with anticoagulation according to stroke risk [1, 2].

1.1.5 Pulmonary embolism

Pulmonary embolism (PE) is an obstruction of pulmonary arteries—usually by thrombi from deep veins, presenting with acute dyspnoea, pleuritic pain, tachycardia, and hypoxaemia. Computed Tomography (CT) pulmonary angiography is the diagnostic standard; anticoagulation is first-line, with systemic thrombolysis or embolectomy reserved for haemodynamically unstable or high-risk patients [1].

1.1.6 Transient Ischaemic Attack (TIA) / Ischaemic stroke

Transient ischaemic attack (TIA) causes brief focal neurological symptoms without infarction, whereas ischaemic stroke reflects persistent arterial occlusion with tissue injury. Rapid reperfusion with intravenous (IV) thrombolysis and/or mechanical thrombectomy in eligible patients improves outcomes; secondary prevention targets the cause (e.g., anticoagulation for AF, antiplatelets for atherosclerotic disease) [1, 2].

1.1.7 Venous Thromboembolism (VTE)

VTE comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE). DVT often presents with unilateral leg swelling, pain, warmth, and erythema; embolisation to the lungs produces PE. Mainstays are prompt anticoagulation and risk-tailored duration; complications include post-thrombotic syndrome and, after PE, chronic thromboembolic pulmonary hypertension [1].

The long-term care of significant cardiovascular disorders, including coronary artery disease, heart failure, arrhythmias, and hypertension, generally involves the chronic administration of many drugs, such as antiplatelets, anticoagulants, ß-blockers, statins, and antiarrhythmic agents. Polypharmacy in these individuals elevates the likelihood of significant drug–drug interactions, many of which may affect treatment efficacy or safety profiles [6, 7]. In standard clinical practice, PPIs are among the most commonly prescribed additional drugs, especially for

gastro-oesophageal reflux disease (GORD), ulcer prophylaxis, and the prevention of gastrointestinal bleeding during antithrombotic treatment [8, 9]. Due to the shared metabolic pathways of PPIs with certain cardiovascular medications, particularly through cytochrome P450 isoenzymes, their pharmacological characteristics may alter the efficacy or safety of cardiovascular treatments [10]. Consequently, it is essential to examine PPIs, their clinical indications, and the potential for drug–drug interactions in patients receiving cardiovascular therapies [11].

1.2 Acid-Related Gastrointestinal Diseases

Gastric acid secretion is driven by neurocrine, paracrine, and endocrine signals acting on parietal cells. Acetylcholine, histamine, and gastrin bind to receptors on the basolateral surface of these cells. Gastrin can directly stimulate acid release but mainly acts by triggering enterochromaffin-like (ECL) cells to release histamine, which in turn activates histamine receptors on the parietal cell. Receptor activation initiates intracellular signalling that ultimately stimulates the H^+/K^+-ATPase proton pump, the final common pathway for acid secretion. This pump exchanges intracellular hydrogen ions for luminal potassium, releasing acid into the stomach. While H2 receptor antagonists block histamine stimulation upstream, PPIs act directly at the final step by inhibiting the proton pump [12]. An imbalance in gastric acid secretion—either excessive, as observed in Zollinger–Ellison syndrome, or diminished, as seen in atrophic gastritis, can interfere with normal physiology and result in clinical symptoms requiring acid suppression therapy with PPI [13].

1.2.1 Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is a chronic illness resulting from the backward flow of gastric contents into the oesophagus, due to the dysfunction of the lower oesophageal sphincter. It is among the most prevalent gastrointestinal disorders globally. Typical symptoms include heartburn and acid regurgitation; nevertheless, individuals may additionally exhibit chest pain, chronic cough, and episodes of asthma. Risk factors include obesity, hiatal hernia, tobacco use,

alcohol consumption, and specific food triggers. Chronic reflux diminishes quality of life and, if left untreated, may lead to complications. PPIs are the primary therapeutic option, offering enhanced acid suppression relative to H2 antagonists, resulting in rapid symptom relief and mucosal restoration. Lifestyle adjustments, such as weight reduction, elevating the head of the bed, and avoiding late meals, are significant adjuncts [14, 15].

Complications of GORD involve erosive oesophagitis, characterised by recurrent acid exposure leading to mucosal inflammation and erosions; oesophageal strictures, arising from chronic wounds and inflammation that constrict the lumen and interfere with swallowing; and Barrett's oesophagus, wherein the normal squamous epithelium is substituted by columnar epithelium, a premalignant alteration that heightens the risk of adenocarcinoma. These disorders exhibit the same underlying reflux mechanism and benefit from acid suppression, with PPIs playing a pivotal role in diminishing recurrence and limiting progression [14, 15].

1.2.2 Zollinger–Ellison Syndrome (ZES)

Gastrin-secreting neuroendocrine tumours, also known as gastrinomas, are the root cause of ZES. These tumours typically originate in the pancreas or the duodenum. An excessive amount of gastrin causes a significant increase in the amount of gastric acid that is secreted, which can lead to severe or recurrent peptic ulcers, gastro-oesophageal reflux disease, and persistent diarrhoea. Management requires high-dose PPI therapy to control acid output. The definitive treatment focuses on the gastrinoma (tumour producing gastrin) by either surgical or oncologic therapy [13].

1.2.3 Peptic ulcer

Peptic ulcer disease is characterised by a disruption in the mucosal layer of the stomach or proximal duodenum that reaches the muscularis propria, resulting from an imbalance between protective mechanisms and gastric acid/pepsin activity. The two major causes are *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs) use, with less common factors including Zollinger–Ellison syndrome, cancer, and extreme stress. Patients typically exhibit

epigastric pain, frequently associated with meals, in addition to bloating, nausea, or haemorrhage in more severe cases. Diagnosis is confirmed with endoscopy or non-invasive *H. pylori* tests. Management includes the eradication of *H. pylori* when detected and acid suppression using PPIs, which offer enhanced ulcer healing and symptom relief compared to H2 blockers [16].

1.2.4 Functional dyspepsia

Functional dyspepsia is a prevalent problem that is characterised by uncomfortable upper abdominal symptoms such as epigastric pain, burning, early satiety, and postprandial fullness. This condition occurs when there is no structural pathology present in the upper abdomen. GORD and peptic ulcer disease frequently overlap with functional dyspepsia, which is considered a disorder of gut–brain interaction. Treatment consists of testing for *Helicobacter pylori* and eradication if positive. For patients with predominant epigastric pain or burning, empirical PPI therapy may provide symptomatic relief when *H. pylori* has been excluded [17].

1.2.5 Gastrointestinal infections

Although PPIs do not serve as treatments for gastrointestinal infections, prolonged acid suppression has been linked to a higher risk of enteric infections, such as *Clostridioides difficile* and bacterial gastroenteritis. The process relates to diminished stomach acidity, which typically functions as a defence against ingested microorganisms. Clinicians are therefore urged to prescribe PPIs carefully, considering the benefits in relation to the risk of infection, especially in at-risk or hospitalised patients [8, 18].

1.2.6 Stress ulcer prophylaxis

Critically ill patients, particularly those requiring mechanical ventilation or exhibiting coagulopathy, face a significant risk of stress-induced mucosal injury and haemorrhage. Stress ulcers are believed to result from mucosal ischaemia and excessive acid release during critical disease. PPIs are often used preventively in intensive care units to diminish stomach acid output and minimise clinically severe

haemorrhage. Nonetheless, research indicates that they should be allocated exclusively to individuals with significant risk factors, as excessive usage may subject patients to the infection risks linked to prolonged acid suppression [19].

The acid-related conditions described in this section represent the clinical indications for which PPIs are prescribed. Many of these indications overlap with cardiovascular disease — for example, the need for gastroprotection during antiplatelet or anticoagulant therapy. This overlap means that PPIs are frequently co-prescribed with cardiovascular medications, creating the potential for pharmacokinetic and pharmacodynamic drug–drug interactions that form the central concern of this thesis.

1.3 Drug-Drug Interactions

The clinical relevance of the disease entities and drug classes described above converges on a common problem: the increasing burden of drug–drug interactions in patients with cardiovascular polypharmacy [6, 7].

Drug-drug interactions (DDIs) occur when the pharmacological effect of one medicine alters the pharmacological action, systemic exposure, or clinical response of another. These interactions can be advantageous when used for therapeutic benefit, as observed in specific antibiotic or cardiovascular combinations, or they may be harmful, resulting in treatment failure, toxicity, or life-threatening adverse drug responses [6] – dependent on drug properties, patient characteristics, and prescribing context [6, 7]. The probability of DDIs increases with the number of concurrently prescribed medications and is particularly elevated in patients with chronic conditions requiring long-term polypharmacy, such as cardiovascular disease, diabetes, and neurodegenerative disorders.[7, 20].

The burden of clinically relevant drug-drug interactions is considerable. Adverse drug interactions contribute significantly to hospital admissions, extended lengths of stay, elevated healthcare expenses, and higher mortality. It is estimated that 0.6% to 5% of all hospital admissions are directly due to DDIs, with elevated rates

observed in older persons [6]. In older people with numerous comorbidities, the probability of experiencing a drug-drug interaction (DDI) is near-universal, particularly with the administration of narrow therapeutic index medications [7, 20]. A narrow therapeutic index drug is defined as one for which small changes in systemic concentration lead to marked changes in pharmacodynamic response, such that the margin between the minimum effective concentration and the minimum toxic concentration is small. The U.S. Food and Drug Administration operationally defines NTI drugs as those where a less than two-fold difference in median lethal dose and median effective dose, or minimum toxic and minimum effective concentrations in the blood, exists [21, 22]. Digoxin and warfarin are prototypical examples of NTI drugs relevant to this thesis, and their susceptibility to clinically significant drug–drug interactions is a direct consequence of this property. The distribution of the most common drug–drug interactions by type and frequency is summarised in Table 1.1.

While the mechanisms underlying drug–drug interactions are increasingly well characterised, their translation into clinically meaningful outcomes remains uncertain. In particular, most evidence is derived from pharmacokinetic studies or controlled trial populations that do not reflect the complexity of patients with cardiovascular disease, who are frequently older, multimorbid, and exposed to long-term polypharmacy. This gap between mechanistic understanding and real-world clinical impact forms a central motivation for the present thesis.

Table 1.1 Distribution of most common DDIs by type and frequency
Distribution of most common drug-drug interactions by type and frequency. Pharmacokinetic interactions account for the largest proportion (30%), followed by neurological (22%) and cardiologic (18%) effects. Adapted from [23]

Type interactions	Main characteristics of localized interactions	Distribution
Pharmacokinetics	Changes in serum levels of the drug, increase or decrease in metabolism and/or excretion	30%
Neurological	Toxicity, prolonged sedation	22%
Cardiologic	Cardiotoxicity, prolonged QT wave interval, cardiac arrest	18%
Hematological	Increased risk of bleeding	7%
Renal	Nephrotoxicity, renal failure	5%
Endocrine/Metabolic	Change in glycemia	4%
Respiratory	Risk of respiratory depression	4%
Others	Risk of skin rash	3%
Muscular	Rhabdomyolysis, muscle weakness	3%
Gastrointestinal	Diarrhea, nausea, ulceration	2%
Hepatic	Hepatotoxicity	1%

1.3.1 Types of interactions

Drug-drug interactions are often categorised as pharmacodynamic (PD) or pharmacokinetic (PK). Pharmacodynamic interactions occur when multiple medications affect identical receptor systems or physiological processes, resulting in synergism, additivity, or antagonism.[6, 7]. Pharmacokinetic interactions happen when one drug alters the absorption, distribution, metabolism, or excretion (ADME) of another, thus modifying its concentration–time profile at the site of action [7]. Clinical impact ranges from small and self-limiting to significant and possibly life-threatening (e.g., severe haemorrhage, malignant arrhythmias, renal failure), frequently requiring the avoidance of specific combinations or intensive monitoring [6].

1.3.2 Mechanism of interaction

1.3.2.1 Pharmacodynamic interactions

Pharmacodynamic interactions arise from the cumulative effects of drugs at target receptors or through converging physiological pathways. Synergistic and additive effects can be therapeutically beneficial when intentionally coupled; nevertheless, they also contribute to numerous undesirable outcomes when overlapping pharmacology is unacknowledged. Antagonism occurs when one medicine reduces the efficacy of another (e.g., competitive antagonists or functional opposition of physiological systems), and intentional antagonism directs reversal techniques for specific toxicities [6, 7]. Clinically, unintended pharmacodynamic interactions frequently manifest as pronounced central nervous system depression, impaired haemostasis due to synergistic antithrombotic effects, or haemodynamic instability when rate-limiting or vasodilatory agents are co-administered; these patterns are expected based on the pharmacological properties of the involved agents and constitute a significant portion of severe drug-drug interaction harm [6, 7].

1.3.2.2 Pharmacokinetic interactions

Pharmacokinetic interactions occur when a perpetrator drug alters the ADME of a victim drug, thereby changing systemic exposure and, consequently, therapeutic effect or toxicity [7].

Absorption: Interactions within the gastrointestinal tract may influence the rate (time to maximum concentration; tmax) and extent (area under the curve; AUC) of absorption. Key mechanisms encompass alterations in gastric pH (impacting dissolution/ionisation), modified gastrointestinal motility (affecting residence duration and peak concentrations), and chemical or physical interactions (e.g., adsorption/chelation) that diminish the percentage of medication available for absorption. Formulation variables, such as enteric coating and controlled release, can render these effects clinically significant when dissolution is dependent upon particular pH levels or transit conditions [7].

Distribution: Competition for plasma protein binding sites (albumin, α1-acid glycoprotein) can temporarily elevate the unbound (active) proportion of strongly bound drugs. Although redistribution and enhanced clearance frequently balance alterations in total exposure, displacement is clinically significant for narrow therapeutic index medications, as small increases in free concentration may trigger toxicity [7].

Metabolism: The liver cytochrome P450 (CYP) system and conjugative pathways are common sites of pharmacokinetic interactions. Enzyme inhibition reduces metabolic clearance and elevates exposure; its level and timing are contingent upon the potency and half-life of the inhibitor. Enzyme induction enhances enzyme expression or activity, reduces exposure, and often exhibits a gradual onset and offset governed by protein turnover. Interindividual variability—stemming from genetics, age, disease, and environmental influences—affects susceptibility and adds to unpredictability across patients [6, 7].

Excretion and transport: Renal elimination may be modified through alterations in glomerular filtration (renal haemodynamics), tubular secretion/reabsorption

(transporter competition, urine pH), or biliary excretion. Drug transporters, such as P-glycoprotein/ABCB1 and others, play a crucial function in the intestine, liver, kidney, and blood-tissue barriers. Inhibition of transporters elevates systemic exposure by diminishing efflux or enhancing absorption; induction of transporters reduces exposure by enhancing efflux or clearance. Age-associated declines in renal function enhance the clinical significance of these alterations, especially for medications with narrow therapeutic indices [6, 7, 20].

PK interactions are often clinically silent; concentration changes may go undetected until loss of efficacy or frank toxicity occurs. Anticipation requires knowledge of ADME pathways (enzymes, transporters, clearance routes) and recognition that multiple PK mechanisms can act simultaneously in the same patient [7].

1.3.3 Outcomes of drug interactions

Outcomes range from therapeutic failure, when exposure is reduced below the effective threshold, to toxicity, when exposure exceeds the safe range. High-impact outcomes include bleeding, arrhythmias (including QT-prolonging arrhythmia risk with susceptible combinations), central nervous system depression, electrolyte disturbances that precipitate cardiac events, and acute renal failure [6]. Many such events are preventable with anticipatory prescribing, routine renal/hepatic function assessment, and avoidance or close monitoring of high-risk combinations [6, 7]. Table 1.2 provides examples of clinically significant drug–drug interactions, illustrating the mechanisms and clinical consequences that clinicians must anticipate.

Table 1.2 Examples of clinically significant DDIs
Mechanisms and clinical consequences. Common high-risk combinations involve anticoagulants, cardiac glycosides, and narrow therapeutic index medications

Interaction	Mechanism	Clinical consequence	Reference
Warfarin + macrolides/azoles/amiodarone	CYP inhibition (↓ metabolism), PK	↑ INR/bleeding	Day 2017; Delafuente 2003
Warfarin + rifampicin/carbamazepine/phenytoin/St John's wort	CYP induction (↑ metabolism), PK	↓ Anticoagulant effect	Day 2017
Warfarin + aspirin/NSAIDs	Additive haemostatic impairment, PD	Major bleeding	Delafuente 2003
DOACs + strong P-gp/CYP3A4 inhibitors	Transporter/enzyme inhibition, PK	↑ Exposure → bleeding	Day 2017
DOACs + strong P-gp/CYP3A4 inducers	Induction (↓ exposure), PK	↓ Anticoagulant effect	Day 2017
Digoxin + clarithromycin (± P-gp inhibitors)	P-gp inhibition, PK	↑ Digoxin → toxicity	Delafuente 2003
Digoxin + rifampicin (± P-gp inducers)	P-gp induction, PK	↓ Digoxin effect	Lavan 2021
ACEI/ARB + K^+-sparing diuretics	Additive hyperkalaemia, PD	Hyperkalaemia	Mangoni 2003
ACEI/ARB + diuretic + NSAID	Haemodynamic/renal effect, PD/PK	Acute kidney injury	Mangoni 2003
H_2 blockers/PPIs + acid-dependent drugs	↑ Gastric pH, PK	↓ or ↑ Absorption	Delafuente 2003
Antacids/iron/calcium + tetracyclines	Chelation, PK	↓ Absorption → failure	Delafuente 2003
Grapefruit juice + CYP3A4 substrates	Enteric CYP3A4 inhibition, PK	↑ AUC/Cmax → toxicity	Delafuente 2003
β-blocker + non-DHP CCB	Additive AV block, PD	Bradycardia/hypotension	Mangoni 2003
SSRIs/SNRIs + serotonergic drugs	Excess serotonin, PD	Serotonin syndrome	Day 2017
Two QT-prolonging agents	Additive QT or ↑ levels, PD/PK	Torsades de pointes	Day 2017

1.3.4 Factors that increase risk

Polypharmacy is the primary catalyst for DDIs; the likelihood of experiencing at least one potential interaction surpasses 50% with five concurrent medications and nears 100% with seven or more drugs — a consequence of the exponential growth in potential pairwise combinations [7]. Ageing elevates risk due to diminished renal function, modified hepatic metabolism, variations in body composition and protein binding, and increased pharmacodynamic sensitivity [7, 20]. Multimorbidity and fragmented care among various prescribers increase the risk of unrecognised interactions, particularly with medications that have a narrow therapeutic index, where small variations in dosage can lead to significant clinical consequences [6, 7]. Lifestyle and self-medication factors (alcohol, smoking, over-

the-counter medications, herbal supplements) introduce variability by modifying enzymes and transporters, thus confounding prediction and prevention [6].

1.3.5 Role of P-Glycoprotein in DDIs

P-glycoprotein (P-gp; Multidrug Resistance Protein 1 (MDR1)/ ATP-binding cassette sub-family B member 1 (ABCB1)) is a membrane efflux transporter that shapes drug–drug interactions by modulating absorption, distribution, metabolism, and excretion alongside classical pharmacodynamic (synergism/antagonism) and pharmacokinetic pathways (ADME) [24, 25]. Expressed on the apical surface of enterocytes, hepatocytes, renal proximal tubules, and brain capillary endothelium, P-gp limits oral uptake, facilitates biliary and renal clearance, and restricts tissue penetration of many xenobiotics and drugs [25, 26] (Figure 1.1).

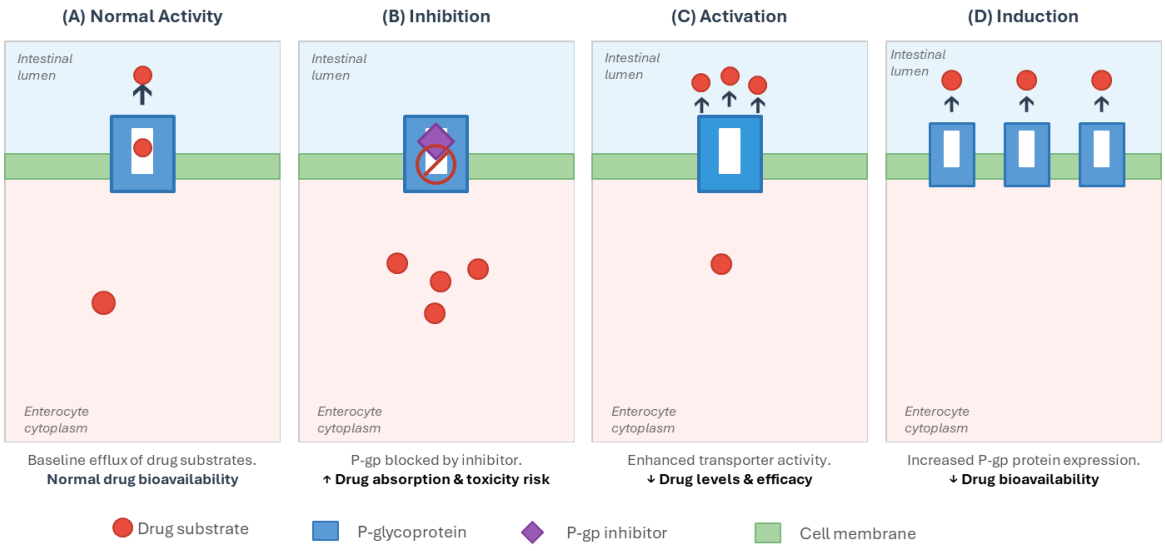


Figure 1.1 Schematic representation of P-glycoprotein (P-gp) function
P-gp is an ATP-dependent efflux transporter on the apical surface of enterocytes that pumps drug substrates from the cytoplasm back into the intestinal lumen, limiting their systemic absorption. (A) Normal activity: constitutive efflux produces the expected oral bioavailability of P-gp substrates such as digoxin and clopidogrel. (B) Inhibition: a P-gp inhibitor blocks efflux, allowing substrate to accumulate in the enterocyte and increasing systemic exposure — the principal mechanism of clinically significant P-gp-mediated drug-drug interactions. (C) Activation: intrinsic activity of existing transporters is enhanced without a change in protein abundance, increasing efflux and reducing plasma substrate concentrations. (D) Induction: chronic exposure to inducers upregulates ABCB1 transcription and increases transporter numbers, lowering oral bioavailability and risking sub-therapeutic exposure. Inhibition therefore predisposes to toxicity through increased exposure, whereas activation and induction risk therapeutic failure through reduced exposure

Like CYP-mediated DDIs, well known for inhibitor/inducer effects, especially via CYP3A4, P-gp–mediated DDIs arise predictably when substrates are co-administered with P-gp inhibitors (increase exposure) or inducers (decrease exposure), producing parallel pharmacokinetic consequences in animals and humans [25, 27]. However, the extent to which P-glycoprotein–mediated interactions translate into adverse clinical outcomes in heterogeneous real-world populations remains uncertain [6].

Mechanistically, inhibition reflects competition at multiple drug-binding sites or interference with ATP hydrolysis, whereas induction increases efflux capacity; both alter systemic and tissue concentrations and can be clinically critical for narrow-therapeutic-index medicines [27]. Because P-gp is abundant in the liver and the kidney, its inhibition can cause xenobiotic accumulation and organ-specific toxicity; cardiac transporter expression likewise influences myocardial drug levels (e.g., ß-blockers, cardiac glycosides) [28].

Genetic MDR1/ABCB1 polymorphisms further modify exposure (e.g., reduced renal clearance of certain substrates), and intestinal P-gp can limit, but does not invariably prevent, oral absorption; several good substrates remain adequately bioavailable, underscoring that “P-gp substrate” does not equate to “poor bioavailability” [25, 27, 29]. Food and co-medications may also modulate transporter function (e.g., grapefruit juice effects observed in P-gp–expressing systems), adding variability at the gut wall [28]. Given these liabilities, regulators European Medicines Agency (EMA)/ U.S. Food and Drug Administration (FDA) recommend prospective evaluation of P-gp interactions for new drugs, with attention to substrate/perpetrator selectivity, sites of action, sequestration, and elimination pathways—especially in polypharmacy, acid-related therapies, and the elderly, where clinically significant DDIs are more likely [25, 26, 30].

In summary, drug–drug interactions arise through predictable pharmacodynamic, pharmacokinetic, and transporter-mediated mechanisms, and are particularly prevalent in patients with polypharmacy and chronic disease. While many interactions lead to treatment failure or toxicity, most are anticipatable through

knowledge of the mechanistic pathways involved — including CYP enzyme inhibition, P-gp modulation, and pH-dependent absorption changes — and are mitigable through careful prescribing and monitoring. These mechanisms are directly relevant to the interactions between proton pump inhibitors and cardiovascular medications examined in this thesis.

1.4 Proton Pump Inhibitors (PPIs)

Proton pump inhibitors (PPI) are among the most commonly prescribed co-medications worldwide, particularly in older adults with cardiovascular multimorbidity [8, 9]. PPIs are potent acid-suppressive agents that irreversibly block the gastric H^+/K^+-ATPase enzyme, the final pathway of acid secretion in parietal cells. Since their introduction in the late 1980s, PPIs have transformed the management of acid-related gastrointestinal disorders by providing superior and sustained acid suppression compared to histamine-2 receptor antagonists. They are now considered first-line therapy for GORD, peptic ulcer disease, and as part of *Helicobacter pylori* eradication regimens, as well as for prophylaxis in patients at high risk of gastrointestinal bleeding. Their widespread use, effectiveness, and tolerability have established PPIs as one of the most frequently prescribed drug classes worldwide [8].

The five widely used PPIs are omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. While they share the same mechanism of action and are often considered clinically interchangeable, they differ in pharmacokinetics, metabolism, potency, and duration of acid suppression [31].

PPIs are among the most frequently co-prescribed medications in patients with cardiovascular disease, largely for gastroprotection during antiplatelet or anticoagulant therapy. Although generally considered safe, their widespread use, shared metabolic pathways, and potential to influence drug absorption and transport raise concerns about clinically relevant interactions. Understanding whether these interactions translate into adverse outcomes in routine care is therefore of particular importance [31].

1.4.1 Epidemiology

The use of PPIs has significantly increased over the last thirty years, and they currently rank among the most often prescribed medications worldwide. Historical utilisation data demonstrate this expansion: in the United States, approximately 119 million PPI prescriptions were dispensed in 2009, generating around USD 13.6 billion in sales and establishing PPIs as one of the most heavily prescribed drug classes nationally [9]. In Europe, prescribing quantities have increased linearly; for instance, Germany utilised 3.475 billion defined daily doses in 2014, despite no significant expansion in allowed indications—prompting enquiries over the rationale for such extensive use [8].

Recent population-based cohorts provide insight into the demographics of PPI users. In the PERSIAN Guilan Cohort (Iran; n = 10,520; baseline 2014–2017), the prevalence of PPI use was 4.8%, with a higher prevalence in females (6.1%) than males (3.3%). Low physical activity (OR ≈ 1.72), reflux, multimorbidity, and NSAID use were independently associated with increased likelihood of PPI consumption [32]. Concurrently, hospital-based research underscores substantial levels of inappropriate prescribing. In a Scottish geriatric population (mean age 84 ± 7 years), 41% of inpatients were administered PPI; 85.8% of these prescriptions lacked a definitive rationale (i.e., overprescribed), and possible drug–drug interactions were prevalent, especially among those who were overprescribed [33]. This analysis indicates that polypharmacy and elevated comorbidity scores independently predict inappropriate PPI consumption, highlighting the need for prescribing review in vulnerable older patients [33].

In various contexts, numerous studies convey a dual message: PPIs are essential for specific indications, although their excessive use is widespread. A recent narrative review synthesising international datasets and recommendations indicates that up to 60% of prescriptions may lack an appropriate indication and advocates systematic appraisal and deprescribing measures [8]. Recent safety literature, including a systematic review and meta-analysis, indicates a correlation between PPI exposure and gastric cancer in observational studies

(pooled relative risk ≈ 1.80), while also highlighting concerns regarding heterogeneity and residual confounding; these results advocate for regular risk-benefit assessments instead of immediate withdrawal when indications are effective [34]. Earlier clinical studies contend that, due to costs and potential adverse effects, PPIs should be restricted to evidence-based indications [8].

In the United Kingdom, PPIs remain among the most frequently dispensed medications. NHS Digital data indicate that over 55 million prescription items for PPIs were dispensed in primary care in England during 2022–2023, with omeprazole and lansoprazole accounting for the majority of prescriptions [35]. In Scotland, the prescribing landscape is broadly comparable; data from the Public Health Scotland Prescribing and Medicines team indicate sustained high-volume PPI prescribing, particularly among older adults with cardiovascular comorbidities [36]. The NHSGGC health board, from which the data for this thesis are drawn, serves a population of approximately 1.2 million and is characterised by significant socioeconomic deprivation and high rates of polypharmacy — conditions that predispose to both extensive PPI use and elevated risk of drug–drug interactions. This prescribing context underscores the public health relevance of examining PPI co-prescribing patterns in the study population.

1.4.2 Indications

PPIs are indicated for a broad spectrum of acid-related gastrointestinal disorders. Their primary approved uses include (GORD), both erosive and non-erosive forms, where PPIs are more effective than histamine-2 receptor antagonists in achieving symptom control and mucosal healing. They are also established as first-line therapy in peptic ulcer disease, whether idiopathic, NSAID-induced, or associated with *Helicobacter pylori* infection, and are a core component of eradication regimens for *H. pylori*. In addition, PPIs are indicated for the prevention of gastroduodenal ulcers in high-risk patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin. Other well-recognised clinical indications include Zollinger–Ellison syndrome and the prevention of recurrent upper gastrointestinal bleeding after endoscopic haemostasis [8, 37].

PPIs are also used in a number of off-label or situational indications. These include prophylaxis in patients at risk of stress-related mucosal bleeding, functional dyspepsia, eosinophilic oesophagitis, and as an adjunct in patients on dual antiplatelet therapy to lower gastrointestinal bleeding risk [37]. The principal clinical indications for PPI therapy are summarised in Table 1.3.

Table 1.3 Clinical indications for PPI therapy across different GI conditions

Summary of the principal clinical indications for proton pump inhibitor therapy across acid-related and other gastrointestinal conditions, including their therapeutic role and clinical application.

Condition	Cause	Presentation	PPI Role	Reference
GERD	LES dysfunction ± hiatal hernia; gastric reflux	Heartburn, regurgitation; extra-esophageal symptoms possible	First-line for acid suppression & mucosal healing	Clarret, 2018 (GERD)
Zollinger–Ellison Syndrome (ZES)	Gastrinoma → hypergastrinemia → massive acid hypersecretion	Refractory/Multiple ulcers, diarrhea, severe GERD	High-dose PPIs essential for acid control; tumor therapy per staging	Jensen, 2023 (ZES)
Peptic Ulcer Disease (PUD)	H. pylori, NSAIDs; less common: ZES, malignancy, severe stress	Epigastric pain (meal-related), nausea, bleeding	Cornerstone of healing; part of H. pylori eradication regimens	Malik, 2023 (PUD)
Functional Dyspepsia	Disorder of gut–brain interaction; no structural disease	Epigastric pain/burning, early satiety, post-prandial fullness	Trial of PPI for acid-related symptom control (after H. pylori test-and-treat)	Francis, 2024 (StatPearls)
Gastrointestinal Infections (context)	Infectious esophagitis (Candida/HSV/CMV) vs reflux injury	Odynophagia, dysphagia, chest pain (pathogen-dependent)	PPIs not curative for infection; role is reflux control; judicious use	Antunes, 2023 (Esophagitis)
Stress Ulcer Prophylaxis (ICU)	Critical illness ± mechanical ventilation, coagulopathy	Stress-related mucosal damage → upper GI bleeding risk	Prophylaxis for high-risk patients; avoid routine overuse	Malik, 2023 (PUD)

1.4.3 Mechanism of action

Gastric acid secretion is induced by acetylcholine, gastrin, and histamine, which operate on parietal cells; all three substances converge on the apical H^+/K^+-ATPase ("proton pump"), the ultimate step in acid secretion. PPIs are weak bases designed with enteric coatings that can survive gastric conditions, be absorbed in the small intestine, and subsequently accumulate in the acidic canaliculi of activated parietal cells, where acid-mediated transformation converts them into sulphenamide intermediates that irreversibly bind to cysteine residues on the H^+/K^+-ATPase enzyme. The outcome is significant inhibition of both basal and meal-induced acid secretion until new pumps are produced—an essential factor explaining why steady-state efficacy requires several days despite brief plasma half-lives. PPIs can diminish pepsin activity and can inhibit *H. pylori* urease in vitro, while enhancing the efficacy of specific antibiotics; nevertheless, they do not eliminate *H. pylori* when used alone [38]. The mechanism of PPI-mediated acid suppression is illustrated in Figure 1.1.

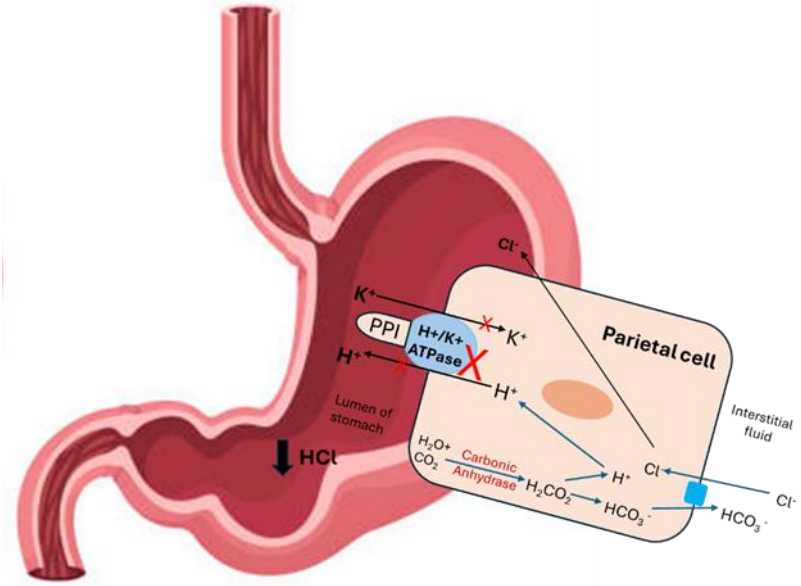


Figure 1.2 Mechanism of proton pump inhibitor (PPI) action
PPIs irreversibly inhibit the gastric H^+/K^+-ATPase (proton pump) on the apical membrane of parietal cells, blocking the final step of acid secretion and reducing gastric HCl output.

1.4.4 Pharmacokinetics and pharmacodynamics

All marketed PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) are acid-labile prodrugs given as enteric-coated formulations (or IV for selected agents). Peak plasma concentrations occur ~0.5–3 h after dosing; food delays absorption, so administration 30–60 minutes before a meal enhances effect by synchronising drug exposure with pump activation. Despite elimination half-lives of only a few hours, the covalent, irreversible pump inhibition produces a pharmacodynamic effect lasting 24 hours or more, with full effect after 2–4 days of daily dosing as additional active pumps are exposed and inactivated. Recovery of acid secretion after a dose reflects synthesis and membrane insertion of new pumps (typically 72–96 h after a single dose) [38].

Hepatic metabolism occurs primarily via CYP2C19 (and CYP3A4). Genetic polymorphisms in CYP2C19 alter exposure and response: poor metabolisers achieve higher intragastric pH and greater *H. pylori* eradication rates, whereas rapid/extensive metabolisers may have lower exposure and reduced response at standard doses. The prevalence of CYP2C19 phenotypes varies by ancestry (e.g., higher rates of poor metabolisers in East Asian populations). PPIs are generally well tolerated; the short plasma half-life contributes to a low incidence of dose-related toxicity, with dose adjustments mainly considered in marked hepatic impairment [8, 38].

From a PD standpoint, a practical integrative metric is percent time with intragastric pH > 4 over 24 h. Indications like severe erosive oesophagitis or post-haemostasis ulcer bleeding benefit from maintaining pH > 4 for ≥16 h/day. This target is influenced by dose, dosing time, genotype (CYP2C19), *H. pylori* status (which can augment acid suppression), and adherence [31, 38].

1.4.4.1 Comparative Pharmacology of the Different PPIs

Although PPIs share the same mechanism of action, their pharmacokinetic and pharmacodynamic characteristics vary, resulting in modest yet clinically relevant differences. Omeprazole was the first compound introduced and remains the reference molecule for this drug class. Its S-isomer, esomeprazole, undergoes

slower hepatic clearance and achieves higher systemic exposure, leading to more sustained acid suppression. Lansoprazole demonstrates rapid absorption and a short plasma half-life, whereas pantoprazole exhibits a slower onset and lower peak plasma concentration but fewer drug–drug interactions because of its reduced dependence on CYP2C19 metabolism. Rabeprazole, partially metabolised by non-enzymatic pathways, provides a rapid onset of action with minimal interindividual variability [8, 31, 38].

Head-to-head comparisons reveal that while the overall clinical efficacy among PPIs is similar, subtle pharmacodynamic differences exist. Esomeprazole and rabeprazole generally maintain intragastric pH above 4 for a longer proportion of the dosing interval—approximately 14 and 12.1 hours, respectively—compared with omeprazole (11.8 h), lansoprazole (11.5 h), and pantoprazole (10.1 h). These differences, though small, may become clinically important in patients requiring maximal and sustained acid suppression, such as those with severe gastro-oesophageal reflux disease or peptic ulcer bleeding [8, 38].

Genetic variation in CYP2C19 activity further modifies systemic exposure and pharmacodynamic response. Poor metabolisers achieve higher plasma concentrations and greater acid inhibition, while rapid metabolisers may experience reduced efficacy at standard doses, sometimes necessitating higher or twice-daily dosing. Consequently, in rapid metabolisers or patients on multiple CYP2C19 substrates—such as those receiving clopidogrel—PPIs with lower CYP2C19 dependence, notably rabeprazole and pantoprazole, are often preferred. These pharmacokinetic and pharmacodynamic distinctions, though modest, enable clinicians to select specific PPIs according to patient characteristics, co-medications, and therapeutic goals [9, 31, 38]. A comparative summary of the pharmacodynamic properties and clinical features of individual PPIs is presented in Table 1.4.

Table 1.4 Comparative pharmacodynamic properties and clinical features of PPIs

Summary of the key pharmacodynamic differences among individual proton pump inhibitors, including their relative acid-suppressive effects and clinically relevant characteristics.

Drug	CYP2C19 Dependence	Mean Hours pH > 4	Relative Acid Suppression	Major Features / Clinical Notes	References
Esomeprazole	Moderate	~14 h	Highest	S-isomer of omeprazole; higher systemic exposure; prolonged suppression	Aguilera-Castro et al., 2016; Mössner, 2016
Rabeprazole	Low / partly non-enzymatic	~12 h	High	Rapid onset; minimal variability and low interaction potential	Aguilera-Castro et al., 2016; Andrawes et al., 2025
Omeprazole	High	~11.8 h	Moderate	Reference compound; strong CYP2C19 dependence; variable response	Mössner, 2016; Syafhan et al., 2018
Lansoprazole	High	~11.5 h	Moderate	Rapid absorption; short half-life; higher interaction risk	Aguilera-Castro et al., 2016; Andrawes et al., 2025
Pantoprazole	Low	~10 h	Slightly lower	Slower onset; minimal CYP2C19 inhibition; preferred with polypharmacy	Mössner, 2016; Syafhan et al., 2018; Andrawes et al., 2025

1.4.5 Administration

PPIs are acid-labile and formulated to prevent degradation in the stomach. They are usually provided as enteric-coated tablets or capsules, granules for suspension, or, less commonly, combined with bicarbonate to transiently neutralise gastric acid. Intravenous formulations of omeprazole, pantoprazole, and esomeprazole are available for cases requiring rapid acid suppression, such as upper gastrointestinal bleeding or perioperative management [8, 37].

Once-daily doses are typically administered before breakfast, though twice-daily regimens add a dose before dinner. Patients with predominantly nocturnal symptoms may take the single daily dose 30 minutes before the evening meal [37].

Clinical guidelines support high-dose or twice-daily regimens when stronger acid suppression is required—for example, in severe gastro-oesophageal reflux disease, Zollinger–Ellison syndrome, or *Helicobacter pylori* eradication therapy. The Maastricht V and Italian 2015 guidelines recommend doses equivalent to omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg twice daily, noting that low doses are ineffective. Studies also show that higher doses or increased dosing frequency can improve *H. pylori* eradication rates without added adverse effects [39].

1.4.6 Safety: adverse effects and monitoring

PPIs are generally regarded as safe and well-tolerated, especially in short-term use; however, the growing prevalence of long-term therapy has drawn attention to several potential adverse effects. Most short-term reactions are mild and self-limiting, including headache, nausea, abdominal discomfort, constipation, diarrhoea, and flatulence. Rare hypersensitivity reactions such as rash or urticaria have also been reported [8, 37].

Long-term use has been associated with electrolyte disturbances, particularly hypomagnesaemia, which may lead to muscle weakness, arrhythmias, or seizures. This effect is thought to result from reduced intestinal magnesium absorption and typically resolves upon discontinuation [37]. Chronic PPI therapy may also contribute to vitamin B_{12} deficiency, iron malabsorption, and hypocalcaemia, as gastric acidity facilitates absorption of these nutrients. Over time, these deficiencies can lead to anaemia, osteoporosis, or increased fracture risk, especially in elderly or malnourished patients [8, 37].

The reduction of gastric acidity can disrupt the gut's natural defence against ingested pathogens, increasing the risk of *Clostridium difficile* and other enteric infections. Observational studies have also linked PPIs to community-acquired pneumonia and small intestinal bacterial overgrowth, though causality remains debated.[37]. Similarly, concerns have been raised regarding potential associations with chronic kidney disease, dementia, and cardiovascular events,

but these remain inconclusive and largely derived from retrospective analyses rather than controlled trials [37].

Monitoring suggestions emphasise the identification and management of preventable risks. For patients undergoing extended or high-dose treatment, regular evaluation of blood magnesium, vitamin B_{12}, and renal function is advisable, especially in individuals with additional comorbidities or concurrent diuretic therapy. Routine bone density testing is not widely advised but may be considered for elderly individuals or those with additional osteoporosis risk factors [37].

Overall, PPIs remain a cornerstone of acid-related disease management, with an excellent safety profile when prescribed at the lowest effective dose and regularly re-evaluated for ongoing necessity. Most long-term complications are rare, and their risks are outweighed by the clear therapeutic benefits when used appropriately [8, 34].

1.4.7 Contraindications

PPIs are among the safest pharmacological agents, and absolute contraindications are rare. The main contraindication is a known hypersensitivity to a PPI or any component of its formulation, which can manifest as rash, urticaria, or, rarely, anaphylaxis. Because of structural similarities within the class, cross-reactivity between different PPIs may occur, so substitution should be approached cautiously [37].

Relative contraindications include severe hepatic impairment, as PPIs are extensively metabolised by hepatic cytochrome P450 enzymes—mainly CYP2C19 and CYP3A4. Although clinical studies suggest standard doses are generally well tolerated, careful monitoring and potential dose adjustment may be necessary in patients with marked liver dysfunction [8].

Caution is advised in patients at higher risk of osteoporotic fractures or hypomagnesaemia, as prolonged PPI therapy may slightly diminish calcium and

magnesium absorption. Patients with recurrent *Clostridium difficile* infection or chronic kidney disease should be monitored regularly due to the documented, yet minimal, risk of aggravation associated with extended acid suppression [37].

1.4.8 Food and herbal interactions

The absorption and metabolism of PPIs can be influenced by food, herbal supplements, and physiological factors, though most effects are clinically minor. Meals delay absorption by slowing gastric emptying and altering intragastric pH; therefore, PPIs should be taken 30–60 minutes before meals to align drug exposure with proton pump activation for optimal efficacy [40]. Routine dietary components such as fat, protein, caffeine, or alcohol have little impact on PPI pharmacokinetics or therapeutic action [41].

In contrast, certain herbal products can meaningfully affect PPI metabolism. St John's Wort (*Hypericum perforatum*) induces CYP3A4, accelerating omeprazole clearance and reducing plasma concentrations, while *Ginkgo biloba* enhances CYP2C19 activity, also leading to decreased omeprazole exposure. Both may reduce acid suppression and therapeutic efficacy [40, 41].

Experimental data suggest that flavonoid- and polyphenol-rich foods may modulate CYP enzymes *in vitro*, but no consistent evidence supports a significant clinical effect [40]. Overall, food and herbal interactions with PPIs are mild, with enzyme-inducing herbal supplements being the main concern for reduced treatment response [40, 41].

1.4.9 Drug interactions

PPIs are involved in several pharmacokinetic drug–drug interactions, primarily via gastric pH elevation, CYP enzyme inhibition, and P-gp modulation. Among the PPIs, omeprazole and esomeprazole have the highest potential to inhibit CYP2C19 and CYP3A4, while pantoprazole and rabeprazole show a much lower risk due to weaker enzyme affinity and partial non-enzymatic metabolism [24, 40, 41].

The most clinically relevant drug interaction involves clopidogrel, a prodrug activated by CYP2C19. Omeprazole and esomeprazole inhibit this enzyme, decreasing the formation of clopidogrel's active metabolite and attenuating its antiplatelet activity. This effect is not shared by pantoprazole or rabeprazole, which are therefore preferred in patients requiring dual antiplatelet therapy [41].

By increasing gastric pH, PPIs can reduce absorption of weakly acidic drugs such as ketoconazole, itraconazole, and atazanavir, leading to subtherapeutic levels. This interaction also affects mycophenolate mofetil, reducing systemic exposure to mycophenolic acid, whereas enteric-coated mycophenolate sodium remains unaffected. In contrast, the absorption of acid-labile drugs like penicillins may be enhanced under the same conditions [40].

Inhibition of hepatic metabolism contributes to interactions with warfarin, phenytoin, diazepam, and citalopram, as omeprazole competes for CYP2C19 and CYP3A4 pathways. These interactions can raise plasma concentrations and increase toxicity risk, necessitating close monitoring or dose adjustment. Conversely, pantoprazole's lower enzyme inhibition results in minimal interaction with these drugs [41].

PPIs can also alter the pharmacokinetics of certain antiviral agents. Co-administration of omeprazole or lansoprazole with HIV protease inhibitors such as atazanavir, indinavir, or nelfinavir significantly reduces their absorption—sometimes by more than 90%—due to decreased solubility at higher pH. These combinations are generally contraindicated. In contrast, raltegravir exposure can increase when taken with omeprazole because of improved solubility and inhibition of P-gp [41].

An additional clinically important interaction is reported with methotrexate, where PPIs, especially omeprazole, can delay renal clearance and elevate serum methotrexate levels, increasing the risk of toxicity. The mechanism is not fully understood but may involve inhibition of renal drug transporters. Overall, although most PPI interactions are modest, they may become clinically relevant in patients

on multiple medications or narrow-therapeutic-index drugs. Selection of pantoprazole or rabeprazole is advisable in complex regimens due to their minimal CYP2C19 inhibition and limited interaction profiles [40, 41].

PPIs also interact with digoxin, a narrow therapeutic index cardiac glycoside that is a substrate of P-glycoprotein. By inhibiting intestinal P-glycoprotein, PPIs — particularly omeprazole and lansoprazole — may increase digoxin absorption by 10–30%, potentially elevating serum concentrations towards or beyond the toxic threshold [41-43]. Additionally, PPI-induced elevation of gastric pH reduces acid-catalysed hydrolysis of digoxin in the stomach, further increasing the fraction of intact drug available for absorption [41]. Pantoprazole appears to have a more neutral interaction profile with digoxin, with one study reporting no significant pharmacokinetic interaction at therapeutic doses [44]. The clinical significance of this interaction in routine care is uncertain and is examined in Chapter 3 of this thesis.

1.5 Cardiac Glycoside (Digoxin)

Having established the pharmacology and interaction profile of proton pump inhibitors, the following sections review the three cardiovascular drug classes whose interactions with PPIs are examined in this thesis. The first of these is digoxin.

Cardiac glycosides (CGs), also known as cardiotonic steroids, form a class of compounds that include ouabain, digitoxin, digoxin, and digitalis leaf preparations. “Prepared digitalis,” a powdered mixture derived from foxglove plants, must be biologically standardised due to variability among preparations. *Digitalis lanata*, or white foxglove, serves as the primary source of digoxin, while *Strophanthus gratus* is a typical source of ouabain (strophanthin-G), a pure glycoside also obtainable from other botanical sources [45]. Despite extensive mechanistic and trial data, uncertainty persists regarding digoxin safety in contemporary polypharmacy settings, particularly when co-prescribed with commonly used agents such as PPIs. The pharmacology of digoxin and the clinical evidence for toxicity and DDI are described below.

Chemically, cardiac glycosides are composed of two main components: a glycone (sugar) moiety and an aglycone (steroid) core. The aglycone portion determines pharmacological activity, while the glycone affects pharmacokinetics and potency. Structural diversity arises from variations in the lactone ring—cardenolides contain a five-membered butyrolactone ring, while bufadienolides possess a six-membered pyrone ring. These differences, along with the type of attached sugars (e.g., glucose, rhamnose, or mannose), influence the compound's biological effects and potency [46, 47].

Digoxin ($C_{41}H_{64}O_{14}$), first isolated from *Digitalis lanata* by Sydney Smith in 1930, shares structural similarities with other digitalis glycosides such as digitoxin and gitoxin, differing mainly in the presence or absence of hydroxyl groups on the steroid nucleus. For instance, digitoxin lacks a hydroxyl group at the C-12 position, while gitoxin has one at C-16. The addition of sugars like digitalose enhances digoxin's pharmacological potency and bioavailability [48].

1.5.1 Indications

In systolic heart failure with sinus rhythm, digoxin enhances left ventricular ejection fraction and reduces pulmonary capillary wedge pressure; it also elevates cardiac output both at rest and during exertion. Neurohormonal effects include diminished plasma renin activity and decreased serum noradrenaline, in addition to raised heart-rate variability as an indicator of improved baroreflex activation [49].

For rate control in atrial fibrillation—including AF occurring with diastolic HF—digoxin is appropriate to manage the ventricular response, particularly when symptom onset is tied to AF. In patients in sinus rhythm, it is best positioned as second-line therapy after ACE inhibitors, beta-blockers, and diuretics; conversely, in AF it may be a first-choice agent for resting rate control. In chronic AF, adequate resting ventricular rate can be achieved with digoxin alone or combined with diltiazem, verapamil, or beta-blockers [50].

Outside cardiology, historical epidemiology from the mid-1960s noted lower mortality among oncology patients receiving cardiac glycosides, and digoxin-treated breast cancer patients showed reduced tumour cell proliferation compared with non-digitalis users [51]. Subsequent retrospective studies across tumour types (e.g., breast, prostate) frequently observed reduced incidence with digoxin exposure; however, breast cancer incidence was increased, consistent with a putative oestrogen-mimetic effect of digoxin [52]. These oncologic observations remain exploratory and do not constitute established indications.

1.5.2 Mechanism of action

Digoxin exerts its primary cellular effect by binding the α-subunit of the sarcolemmal Na^+/K^+-ATPase, inhibiting Na^+ extrusion and diminishing the transmembrane Na^+ gradient. The reduced Na^+ gradient limits Ca^{2+} efflux via the Na^+/Ca^{2+} exchanger, increasing intracellular Ca^{2+}. Enhanced Ca^{2+} uptake into the sarcoplasmic reticulum by SERCA2a augments SR Ca^{2+} content; subsequent release during systole strengthens excitation–contraction coupling at the myofilament level, producing a positive inotropic effect [53].

In addition to its inotropic effects, digoxin regulates autonomic equilibrium. Numerous investigations indicate enhanced vagal (vagotonic) responses accompanied by diminished sympathetic activity; at lower daily dosages (<0.25 mg/day), these neurohormonal effects occur, while larger doses (>0.25 mg/day) more distinctly exhibit positive inotropy [50]. Parasympathomimetic activities induce negative chronotropy and dromotropy, resulting in a decreased sinus rate and atrioventricular junction conduction, thereby enhancing ventricular rate regulation, especially pertinent in AF [54, 55].

The antiadrenergic actions further diminish sympathetic stimulation in heart failure, without the tachyphylaxis observed with certain other inotropes. The modulation of afferent baroreceptor signalling aids in sympathetic restraint, in conjunction with Na^+/K^+-ATPase inhibition-induced elevations in intracellular Ca^{2+} [54]. Although digoxin exhibits positive inotropic effects, the absolute enhancement in contractility is modest compared to agents utilised in acute left-

ventricular failure; its therapeutic significance comes from the synergistic effects of enhanced contractile performance and parasympathetic modulation of heart rate and conduction, beneficial in heart failure, particularly in the presence of atrial fibrillation [53, 54].

Safety is closely tied to electrolytes: hypokalaemia heightens Na^+/K^+-ATPase binding and toxicity risk, whereas potassium repletion mitigates this vulnerability [53, 54]. Finally, digoxin is a P-gp substrate; intestinal absorption, renal elimination, and CNS penetration are all P-gp–dependent, and many well-described drug interactions stem from P-gp inhibition or induction [56]. The mechanism of digoxin's positive inotropic effect is illustrated in Figure 1.3.

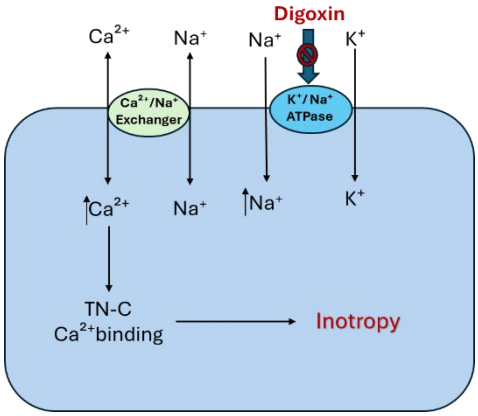


Figure 1.3 Mechanism of action of digoxin
Digoxin inhibits the Na^+/K^+-ATPase pump, reducing potassium influx and sodium efflux. The resulting increase in intracellular sodium concentration diminishes the electrochemical gradient driving the Na^+/Ca^{2+} exchanger, leading to reduced calcium efflux and increased intracellular calcium levels. Enhanced calcium binding to troponin C (TN-C) produces a positive inotropic effect.

1.5.3 Pharmacokinetics and pharmacodynamics

Absorption: oral bioavailability depends on formulation: ~85% for the liquid preparation and ~60–75% for tablets [57, 58]. Roughly 80% of an oral dose is absorbed—predominantly in the proximal small intestine. Onset of action occurs

~30 minutes to 2 hours after oral dosing and ~15–30 minutes after intravenous administration. Intramuscular dosing is generally unsuitable due to variability and risk of elevated creatine phosphokinase levels [55]. Age-related alterations, diminished saliva production, elevated gastric pH, protracted gastric emptying, and reduced intestinal surface area, may slow the absorption rate (extended time to peak) without necessarily affecting the overall extent of absorption. For the majority of orally taken medications, such as digoxin, routine dose modifications alone due to gastrointestinal ageing are unnecessary; variations in absorption are more frequently influenced by illness conditions [59].

Distribution: Protein binding ranges from ~10–40%; only the unbound fraction is pharmacologically active. For polar compounds like digoxin, protein binding does not play a dominant role in PK behaviour [60].

Metabolism: Digoxin metabolism undergoes limited hepatic metabolism and does not meaningfully affect cytochrome P450 activity. With ageing, phase I clearance tends to decline even without major changes in phase II pathways; reduced hepatic metabolic capacity (on the order of ~60% for some drugs) can increase plasma concentrations and prolong half-lives [59].

Therapeutic effects include improved contractility and renal perfusion, with downstream diuresis, reduced oedema, and symptom relief. Given the narrow therapeutic window, PK factors (renal function, body weight), PD sensitivity, and drug–drug interactions must be integrated into dosing and monitoring to minimise toxicity, especially during long-term therapy or after overdose [48].

1.5.4 Administration

Dosing requires individualisation based on age, lean body mass, and renal function. Nominal “initial dose” guidance is only a starting point and should be adjusted—particularly if a cardiac glycoside has been given within the preceding two weeks. Because IV bioavailability exceeds oral, reduce the dose by ~33% when converting from oral to intravenous administration. In adults and adolescents >10 years, rapid oral loading may be achieved with 750–1500 micrograms as a single dose (or

divided if urgency is lower or toxicity risk is higher, e.g., in older adults). Typical maintenance doses are 125–250 micrograms daily, with lower or higher doses as needed according to sensitivity and renal function. Older patients and those with renal impairment often require down-titration to avoid accumulation and toxicity [61].

Route of administration influences both speed and predictability of effect. Intravenous dosing is preferred for rapid digitalisation given superior bioavailability; intramuscular injection is discouraged due to ~80% absorption and risks of local irritation or myonecrosis. Oral administration yields ~75% bioavailability but can be reduced by high-fibre meals or by intestinal flora capable of metabolising the drug. Clinical monitoring should include baseline electrolytes (especially potassium) and measurement of plasma digoxin 6–12 hours after the final loading dose to confirm therapeutic levels. A commonly cited therapeutic serum concentration is 0.5–2 ng/mL [57]. The therapeutic window was historically defined as 1–2 µg/L (equivalent to 1–2 ng/mL), but post-hoc analyses of the DIG trial refined the optimal target for heart failure to 0.5–0.9 µg/L, with levels ≥1.2 µg/L associated with increased mortality. The elimination half-life is ~1.5–2 days (36–44 hours) and is prolonged in renal impairment. Volume of distribution is ~7.3 L/kg and is reduced in kidney disease and hypothyroidism (increased in hyperthyroidism) [59].

For dose calculation in obesity, use lean body mass because digoxin does not distribute substantially into adipose tissue; this avoids overdosing. In individuals with normal renal function, the half-life is ~36 hours but extends with renal insufficiency [55]. Neonates—particularly preterm infants—have reduced renal clearance and therefore require dose reductions beyond standard guidance. After the neonatal period, children require proportionally higher doses than adults on a mg/kg or body-surface-area basis; by >10 years of age, dosing aligns with adult ranges adjusted for body weight and renal function [59].

1.5.5 Safety: adverse effects and monitoring

For monitoring, digoxin has a narrow therapeutic index and requires meticulous, continuous monitoring. Optimal serum concentrations are typically between 0.8 to 2.0 ng/mL, with the risk of toxicity increasing as values near 2.0 ng/mL. Because over 70% of digoxin is excreted renally, renal function, particularly the glomerular filtration rate (GFR), must be monitored consistently to prevent accumulation. Regular electrolyte monitoring is crucial; changes in potassium levels, specifically, may cause toxicity. ECG monitoring must observe specific alterations associated with continuous treatment: downsloping ST-segment depression (the “reverse tick” sign), reduced QT interval, longer PR interval, and T-wave flatness or inversion [57, 61]. Clinically, digoxin has not been linked to elevations in aminotransferases or alkaline phosphatase, and significant liver impairment is not an acknowledged concern despite decades of usage.

Serum digoxin and routine labs should be checked one week after initiation and periodically thereafter, especially after dose or interacting-drug changes. Radioimmunoassays are commonly used; draw blood ≥6 hours after a dose to avoid distribution-phase artefacts. Interpret levels in clinical context (electrolytes, thyroid status), since toxicity can occur at lower concentrations in susceptible states [57, 61].

Adverse effects vary with clinical status, co-medications, and dose. Up to 20% of patients experience side effects: ~50% cardiac, 25% gastrointestinal, and ~20% CNS/miscellaneous. Misuse is a concern due to availability; intentional ingestion may occur. Intoxication is common yet rarely fatal and is most often unintentional (e.g., product confusion) [58].

Debate around digitalis safety sharpened in the late 1990s. In the DIG trial, there was a trend toward lower CHF mortality (RR 0.88; 95% CI 0.77–1.01) and a significant reduction in CHF hospitalisation (RR 0.72; 95% CI 0.66–0.79), with larger relative risk reductions in patients with LVEF ≤25%, more severe symptoms, and cardiomegaly. A 2015 editorial underscored that clinicians prescribing narrow-

therapeutic-index agents such as digoxin must understand PK, benefits, risks, and patient education in depth [45].

1.5.6 Digoxin toxicity

Early reports noted high toxicity rates: in 1971, 25% of treated patients had "definite" toxicity and 6% "possible," with >40% mortality among toxic cases. By the 1980s–1990s, estimated toxicity fell to 4–5%; in the DIG trial, toxicity was reported in 11.9% of patients on digoxin. A 1996 multicentre U.S. analysis found digoxin poisoning accounted for <0.1% of hospital admissions. The long-term decline parallels routine serum monitoring, PK-guided dosing, and improved awareness of DDIs [56]. While cardiac glycosides share a core mechanism (largely defined by digoxin/ouabain), glycoside-specific differences may alter clinical effects and toxicity profiles [47]. Serum concentration relates to risk: in AF, levels ≥1.2 ng/mL correlate with higher mortality, whereas 0.5–0.9 ng/mL reduced mortality and hospitalisations in HF (including preserved systolic function); higher levels reduced HF hospitalisation but did not lower all-cause mortality [58].

Clinical presentation ranges from gastrointestinal (anorexia, nausea, vomiting, diarrhoea, abdominal pain) to neurological/visual (fatigue, drowsiness, colour disturbances) and cardiac (bradycardia, AV block, dysrhythmias; hyperkalaemia in acute cases). GI symptoms dominate many cases: ~19.6% of toxic presentations are GI-predominant; in classic series with high-dose digitoxin, nausea/anorexia appeared in ~80%, vomiting in ~40%, abdominal discomfort in ~65% [47, 56, 62]. Acute poisoning typically presents with prominent GI symptoms within hours; chronic poisoning often adds electrolyte disturbances and bradyarrhythmias. Severe intentional overdoses carry ~20% mortality; digoxin-specific Fab is a major therapeutic advance with favourable safety [58].

Predisposing factors include reduced absorption (food, charcoal, antacids), hypokalaemia from corticosteroids/diuretics, renal dysfunction, and age. Ageing alone has limited impact on total bioavailability (typically 70–80% remains), though absorption rate may slow; toxicity incidence rises from ~1% at >40 years to ~3% by age 85. In severe toxicity, mortality can approach ~20% [58, 62].

1.5.7 Narrow Therapeutic Index (NTI)

Drugs with a narrow therapeutic index (NTI) have a small margin between effective and toxic concentrations; minor dose or exposure changes (including DDIs) can cause harm [63]. Digoxin is widely used yet challenging to quantify at low concentrations [64]. Historically, the therapeutic window was 1.0–2.5 nmol/L (0.8–2.0 µg/L), with toxicity more likely >2.5 nmol/L. Contemporary HF targets are 0.6–1.2 nmol/L (0.5–1.0 µg/L)—roughly half the older range. Post hoc DIG analyses linked 0.6–1.0 nmol/L (0.5–0.8 µg/L) with better outcomes, whereas ≥1.5 nmol/L (1.2 µg/L) associated with higher mortality and toxicity [56].

Clinically, a tight window means consistent bioavailability, assay-aware monitoring, and attention to patient factors (renal function, weight, thyroid status, electrolytes) are critical. Ageing brings physiological/pathological changes that influence absorption, response, sensitivity, and DDIs, reinforcing the need for careful administration and follow-up [59]. Cardiovascular polypharmacy magnifies risk: DDIs account for ~50% of ADRs in cardiac patients; P-gp notably contributes because many cardiovascular agents act as both substrates and functional inhibitors, amplifying exposure in NTI drugs such as antiarrhythmics, oral anticoagulants, and digoxin [6, 7].

1.5.8 Contraindications

Because of its distinct physiological effects, digoxin is contraindicated in several clinical situations. The drug should not be administered to patients with acute myocardial infarction, known digoxin hypersensitivity, ventricular fibrillation, or myocarditis, as it may exacerbate conduction disturbances or myocardial injury. In myocarditis, the inotropic stimulation induced by digoxin can worsen inflammation and increase the risk of arrhythmias [57, 65].

Specific circumstances require heightened attention. Renal insufficiency diminishes digoxin clearance, increasing the risk of buildup and toxicity. Electrolyte imbalances, specifically hypercalcaemia or hypocalcaemia, can unpredictably modify the cardiac effects of digoxin. Individuals with bradycardia, sinoatrial node dysfunction, or atrioventricular block are susceptible to worsened

conduction problems or additional decreases in heart rate. Endocrine conditions affect toxicity risk: hypothyroidism diminishes digoxin metabolism and extends its half-life, whereas hyperthyroidism enhances clearance and diminishes therapeutic efficacy [57].

In atrial fibrillation, certain subgroups are at elevated risk. In hypertrophic cardiomyopathy, digoxin's positive inotropy can exacerbate left ventricular outflow tract obstruction, raise intraventricular pressure gradients, and provoke cavitary obliteration. In Wolff–Parkinson–White (WPW) syndrome, particularly in the presence of AF with rapid ventricular response, digoxin shortens the refractory period of accessory pathways, predisposing to dangerous ventricular arrhythmias or fibrillation. Thus, while digoxin remains a valuable therapeutic agent, its use under contraindicated or high-risk conditions can produce serious or fatal consequences, necessitating careful assessment and close monitoring [65].

Digoxin is not contraindicated during pregnancy, although dosage requirements may vary due to altered pharmacokinetics. Some pregnant patients require higher doses to maintain therapeutic levels. Despite measurable foetal exposure, no consistent evidence indicates adverse foetal or neonatal effects when maternal serum concentrations remain within the normal range. However, maternal digitalis toxicity can be harmful to the foetus. Although digoxin is excreted in breast milk, concentrations are minimal, and breastfeeding is not contraindicated [61].

In summary, digoxin should be avoided in patients with structural or conduction abnormalities, acute myocardial injury, or electrolyte and endocrine disorders that alter its clearance or electrophysiologic response. Safe use depends on precise dose adjustment, vigilant monitoring, and a full assessment of comorbid conditions before initiation.

1.5.9 Interactions

Several substances and drugs can modify digoxin absorption and toxicity. Dietary fibre, antacids, activated charcoal, and antidiarrhoeal agents reduce

gastrointestinal absorption of digoxin, thereby lowering its bioavailability. Conversely, corticosteroids and potassium-depleting diuretics enhance the risk of digoxin toxicity by promoting hypokalaemia. Although food may delay the rate of absorption, overall bioavailability is not significantly affected [58].

A well-documented interaction occurs with potassium-lowering agents such as furosemide and thiazide diuretics; resulting hypokalaemia sensitises the myocardium to digoxin and increases toxicity risk. Concurrent intravenous calcium administration can precipitate arrhythmias, and combining digoxin with ß-blockers may cause excessive bradycardia [58].

Diuretic therapy frequently leads to hypokalaemia and hypomagnesaemia, both of which lower the threshold for digoxin toxicity. The use of potassium-sparing diuretics (e.g., spironolactone) can mitigate this risk, but co-administration requires close monitoring of renal function and serum electrolytes [50].

1.5.10 Transporter-mediated interactions (P-gp)

Digoxin is a P-gp substrate; inhibitors raise exposure by enhancing absorption and/or reducing renal clearance, while inducers lower exposure [61]. P-gp is expressed apically in enterocytes, hepatocytes, renal tubules, and the BBB [25, 26]. Multiple binding sites enable competitive inhibition or ATP-hydrolysis blockade. Cardiac, hepatic, and renal P-gp localisation means inhibition can increase tissue exposure and organ-specific toxicity [28].

MDR1/ABCB1 polymorphisms can reduce renal clearance of digoxin. Intestinal P-gp can limit oral absorption—digoxin remains a canonical substrate with 50–85% bioavailability, illustrating that P-gp substrate status does not automatically imply poor bioavailability. Interpret levels clinically; avoid assuming malabsorption solely from P-gp status [27, 29].

Because of its narrow therapeutic range and strong DDI potential, digoxin is a high-alert medication; concentration changes track with physiology, disease, and co-medications. In older adults, digoxin toxicity ranks fourth among adverse drug

events; utilisation has declined substantially (historically reported at 31.4%), reflecting heightened caution [62, 63]. The key pharmacological properties of digoxin are summarised in Table 1.5.

Table 1.5 Digoxin Pharmacology Summary

AF, atrial fibrillation; HF, heart failure; NTI, narrow therapeutic index; P-gp, P-glycoprotein; GFR, glomerular filtration rate; ECG, electrocardiogram; IV, intravenous; h, hours; Na^+/K^+-ATPase, sodium-potassium adenosine triphosphatase.

Aspect	Details	References
Drug class	Cardiac glycoside (positive inotropic, negative chronotropic).	(Campbell & MacDonald, 2003); (Eichhorn & Gheorghiade, 2002)
Mechanism of action	Inhibits Na+/K+-ATPase → ↑ intracellular Ca2+ → stronger contraction; increases vagal tone → slows AV conduction.	(Pagel & Warltier, 2011); (Patocka et al., 2020)
Indications	Heart failure with reduced EF, atrial fibrillation/flutter for rate control.	(Albert et al., 2016); (Ferrari et al., 2019)
Pharmacokinetics	Oral bioavailability ~60–80%; half-life ~36 h; mainly renal excretion; P-gp substrate.	(Currie et al., 2011); (Grogan & Preuss, 2024); (Doherty et al.,)
Onset of action	Oral: 30–120 min; IV: 5–30 min.	(Currie et al., 2011)
Duration of effect	2–6 days (depending on renal function).	(Medicines.org.uk SmPC, 2024); Doherty et al., 1978)
Metabolism	Limited hepatic metabolism; primarily excreted unchanged in urine.	(Patocka et al., 2020); (Grogan & Preuss, 2024)
Excretion	Renal (~60–80%).	(Currie et al., 2011);(Medicines.org.uk SmPC, 2024)
Therapeutic monitoring	Narrow index: monitor serum levels (target 0.5–2.0 ng/mL).	(Campbell & MacDonald, 2003); (Agency SmPC, 2024); (David & Shetty, 2024)
Adverse effects	GI upset, visual changes (yellow/green vision), arrhythmias, CNS effects.	(Bauman et al., 2006);(Patocka et al., 2020)
Drug interactions	P-gp inhibitors, AV-nodal blockers, diuretics (electrolyte disturbances).	(Albert et al., 2016);(Medicines.org.uk SmPC, 2024)

In contrast to digoxin, oral anticoagulants (commonly prescribed medications in cardiovascular practice) present a different risk profile, where drug-drug interactions may influence bleeding risk, treatment persistence, or thromboembolic protection rather than direct cardiotoxicity - necessitating separate evaluation [10, 11, 66].

1.6 Anticoagulants

Haemostasis is a complex biological system where the proper interaction of procoagulation and anticoagulation mechanisms keeps blood flowing freely through healthy blood vessels and produces thrombi when necessary to stop bleeding from damaged blood vessels. The development of a blood clot (partial or entire blockage), whether in venous or arterial blood vessels, limits the blood's normal flow and has clinical consequences [67]. Thrombosis is so serious that it is considered as the leading cause of death worldwide. Myocardial infarction (MI), stroke, or venous thromboembolism are the main clinical manifestations of the condition, which is brought on by vascular blockage [68]. The most prevalent cardiac arrhythmia is AF, which is more prevalent in older people and those with comorbidities such as diabetes mellitus, heart failure, coronary heart disease, valvular heart disease, hypertension, and chronic kidney disease [69]. Anticoagulation is the main treatment for preventing and treating thrombosis. It is frequently used, although its use is often linked to adverse drug events and higher readmission rates [68, 69].

Anticoagulants act at multiple points within the coagulation cascade, either directly inhibiting key enzymes such as thrombin and factor Xa, or indirectly through vitamin K antagonism or antithrombin potentiation [70, 71]. Clinically, they are administered either parenterally (heparins) or orally, the latter comprising vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) [72]. The coagulation cascade, its regulatory mechanisms, and the specific sites targeted by anticoagulant agents are described in Section 1.6.1.

1.6.1 Coagulation cascade

The coagulation cascade is a sequential series of enzymatic processes that produces a stable blood clot following vascular damage. Zymogens, inactive clotting proteins, circulate in plasma. Upon system activation, each protein is transformed into its active enzymatic form, subsequently initiating the next step. This "chain reaction" rapidly escalates and generates fibrin, the network that fortifies the platelet plug [73].

There are two main ways to start the cascade. The extrinsic pathway begins when tissue factor, a membrane protein exposed by damaged tissue, binds factor VII in the presence of calcium. The tissue factor–VIIa complex rapidly activates factor X (and to a lesser extent factor IX). The intrinsic, or contact, pathway can start when blood meets a negatively charged surface, such as collagen or artificial tubing. In this arm, factor XII activates factor XI, which activates factor IX. Activated factor IX (IXa) then works with its cofactor factor VIIIa on a phospholipid surface—usually activated platelets—to form the "tenase" complex that also activates factor X [73].

Both pathways converge at the same pathway involving factor Xa. Factor Xa, in conjunction with its cofactor factor Va, calcium, and a phospholipid surface, constitutes the prothrombinase complex, which catalyses the conversion of prothrombin (factor II) into thrombin (factor IIa). Thrombin serves as the principal effector: it cleaves fibrinogen into fibrin, activates factor XIII to cross-link fibrin strands, and enhances its own production by activating factors V, VIII, and XI, in addition to robustly activating platelets. The final outcome is a robust, cross-linked fibrin clot that halts haemorrhaging while the vessel undergoes repair [74].

The body restricts and eliminates the clot. Antithrombin, tissue factor pathway inhibitor, and protein C/protein S systems are natural anticoagulants. Endothelial tissue plasminogen activator (tPA) transforms plasminogen to plasmin, which digests fibrin into soluble fragments and reopens the vessel during healing [73].

These biological pathways are reflected in laboratory assays. Prothrombin time, international Normalised Ratio (INR) reflects the extrinsic and common pathways and is sensitive to factors II, VII, and X — three of the four vitamin K–dependent clotting factors. Warfarin additionally depletes factor IX, which is reflected in the aPTT (intrinsic pathway). The intrinsic and common pathway are shown by the activated partial thromboplastin time (aPTT) These interactions explain why vitamin K antagonists like warfarin, which inhibit vitamin K–dependent factors, prolong the INR. Clinically, imbalance towards clotting causes thrombosis (e.g.,

deep-vein thrombosis, myocardial infarction, ischaemic stroke), while imbalance towards inhibition or breakdown causes bleeding [68].

1.6.2 Oral Anticoagulants

Oral anticoagulation medication can significantly reduce the occurrence of ischaemic strokes in patients with atrial fibrillation, resulting in a decrease in absolute risk from 6.0% to 2.2%. Oral anticoagulation is more effective than not receiving any anticoagulant therapy or being treated with aspirin. The net benefit is applicable to nearly all patients, with the exception of those who have an extremely low risk of stroke [69].

Vitamin K antagonists (VKAs) were the earliest class of anticoagulants that can be taken orally, which is a notable benefit compared to heparins that need to be given through injection. Previously, VKAs were the established method for administering oral anticoagulant therapy [68]. VKAs have been the only type of oral anticoagulant medicines used in clinical practice for several decades for the prevention of venous and arterial thromboembolic events, both for primary and secondary prevention [75].

In order to address the limitations of VKAs, direct oral anticoagulants (DOACs) have been created. These DOACs have a broader range of effectiveness and do not require frequent monitoring. DOACs have a lower likelihood of drug-drug interactions compared with VKAs, which is an additional advantage. DOACs consist of dabigatran, which inhibits factor IIa (thrombin), and rivaroxaban, edoxaban, and apixaban, which inhibit factor Xa. Dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban, a direct factor Xa inhibitor, have been approved for clinical usage in numerous countries [68, 71, 75]. The sites of action of these agents within the coagulation cascade are illustrated in Figure 1.4.

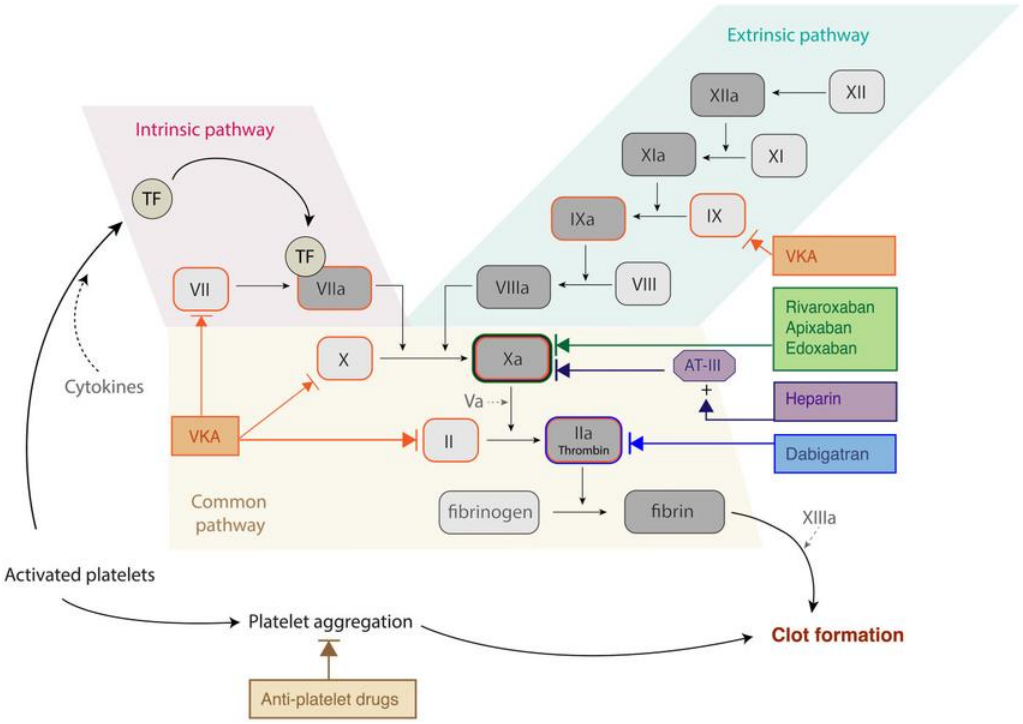


Figure 1.4 Coagulation cascade
Coagulation cascade showing the sites of action of various anticoagulant and antiplatelet agents. The intrinsic pathway (right, teal) is initiated by contact activation, while the extrinsic pathway (left, pink) is triggered by tissue factor (TF) exposure. Both pathways converge at factor Xa in the common pathway (centre, beige), leading to thrombin (IIa) generation, fibrin formation, and clot stabilisation by factor XIIIa. Vitamin K antagonists (VKAs) inhibit synthesis of factors II, VII, IX, and X. Direct oral anticoagulants target specific factors: rivaroxaban, apixaban, and edoxaban inhibit factor Xa, while dabigatran directly inhibits thrombin. Heparin enhances antithrombin III (AT-III) activity, indirectly inhibiting both Xa and thrombin. Antiplatelet drugs prevent platelet aggregation, a parallel contributor to clot formation. Adapted from [76].

1.6.2.1 Vitamin K Antagonists (VKAs)

Warfarin has been the established treatment for a diverse range of medical conditions for many decades. It is classified as a vitamin K antagonist (VKA) and belongs to a group of compounds known as hydroxycoumarins. It was derived from dicoumarol, a naturally occurring anticoagulant found in fermented clover. The term warfarin was introduced by Karl Paul Link, who attributed it to the organisation that supported his research, Wisconsin Alumni Research Foundation. Originally utilised as a rodenticide, its clinical application emerged following a specific event with a military trainee. Warfarin is the preferred Vitamin K antagonist in numerous nations. Phenprocoumon and acenocoumarol are also implemented in various European regions [70].

Warfarin is frequently used for long-term prevention of thromboembolic complications and oral anticoagulant treatment of VTE in patients with AF associated with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis for stroke prevention [72]. In comparison to heparins, VKAs are preferred due to oral administration. However, some disadvantages of using VKAs include slow mode of action, and low therapeutic window that required intense monitoring [68].

1.6.2.1.1 Mechanism of action

Vitamin K promotes the synthesis of gamma-carboxyglutamic acid residues in vitamin K-dependent coagulation factors (FII, FVII, FIX, and FX), which is essential for their biological activity. Vitamin K antagonists (VKAs) work by blocking the enzyme vitamin K epoxide reductase, which is necessary for converting vitamin K into its active form, vitamin KH2. The activity of VKA can be reversed by administering exogenous vitamin K by injection. Single-nucleotide polymorphisms in the VKORC1 gene may reduce the effectiveness of vitamin K recycling, requiring increased administration of warfarin [70].

1.6.2.1.2 Pharmacokinetics and pharmacodynamics

Warfarin is a compound that consists of two different forms, known as enantiomers, which are called the R and S enantiomers. It is highly water-soluble, rapidly absorbed from the gastrointestinal tract with approximately 100% oral bioavailability, and reaches its highest levels in the blood approximately 90 minutes after being taken orally. Warfarin is carried in the bloodstream by plasma proteins, primarily albumin. Therefore, it is important to be cautious while using warfarin together with other medications that also bind strongly to proteins [75, 77].

The half-life of racemic warfarin is between 36 and 42 hours, with the R-warfarin isomer having a half-life of 45 hours and the S-warfarin isomer having a half-life of 29 hours. It undergoes hepatic metabolism by enzymatic mechanisms. The S enantiomer is roughly 2.7-3.8 times more effective than the R enantiomer. It is largely metabolised through oxidative metabolism, with over 90% of the process

being carried out by the CYP2C9 enzyme of the cytochrome P450 system. CYP3A4 also contributes to the metabolism, but in a smaller amount. The less potent R enantiomer is metabolised through oxidative processes, with roughly 60% of it being metabolised. The primary enzymes responsible for this metabolism are CYP1A2 and CYP3A4, with a smaller contribution from CYP2C19. Cytochrome P450 inducers and inhibitors have the ability to modify its impact. Warfarin metabolites are predominantly excreted renally, with a smaller proportion in the faeces [70, 75, 77].

1.6.2.1.3 Clinical indications

Patients with VTE who are treated with parenterally delivered medications, such as heparin derivatives may experience significant discomfort from necessary intravenous or subcutaneous injections [78]. Oral anticoagulants are more convenient to administer, making them a possible alternative for treating thrombotic conditions, depending on the patient's specific demands and their medical indication [78]. Warfarin is a highly effective treatment for preventing VTE in both primary and secondary prevention. It is also effective in preventing systemic embolism in patients with prosthetic heart valves or AF. Additionally, warfarin is used for primary prevention of acute myocardial infarction in high-risk men and for preventing stroke, recurrent infarction, or death in patients with acute myocardial infarction [75, 79].

1.6.2.1.4 Administration

Warfarin tablets come in 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg strengths and are used once a day, preferably in the afternoon or evening to adjust the dose based on the latest lab results. Metabolism, vitamin K intake, genetics, vitamin K-dependent clotting factor amount, concomitant disease, plasma protein binding, pharmacological interactions, laboratory results; INR, and adherence affect dose-response. Dosing for adults should follow evidence-based standards [79].

In particular populations, no labelled dose adjustment is needed for hepatic or renal impairment, however sensitivity may be increased in obstructive jaundice, hepatitis, or cirrhosis, and reduced renal function increases bleeding risk. Close

INR monitoring is recommended in these cases. Haemodialysis doesn't eliminate warfarin. Warfarin crosses the placenta and can cause foetal bleeding and adverse effects. It has been Category D for women with mechanical valves and Category X for others, and many specialists advise against its use in the first trimester and around birth. Warfarin is not excreted into milk and is compatible with nursing, however infants should be monitored for bruising and bleeding. More cautious dose and tighter follow-up are needed for older persons due to falls, interactions, cognitive difficulties, and environmental factors that increase bleeding risk [79].

Dietary counselling should emphasise consistency rather than avoidance: high-vitamin K foods like kale, Brussels sprouts, spinach, and green tea leaves reduce anticoagulant effect, while cranberry juice, grapefruit juice, and alcohol increase warfarin's effect and bleeding risk; patients should be advised to maintain consistent rather than restricted intake of vitamin K-rich foods [75, 78].

1.6.2.1.5 Reversal of warfarin

Oral or subcutaneous administration of Vitamin K is the primary method for achieving warfarin reversal. Intravenous (IV) injection is efficacious but is linked to side effects, including allergy and hypersensitivity reactions, such as face flushing, diaphoresis, and chest discomfort, hypotensive episodes, and respiratory distress. The intravenous route should be employed only when alternative routes are difficult, and the associated risk is warranted. Quick haemostatic restoration in cases of haemorrhage can be accomplished by administering vitamin K in conjunction with fresh frozen plasma or prothrombin complex concentrates and recombinant factor VIIa [75, 77].

1.6.2.1.6 Adverse reactions

The primary adverse effect of warfarin is bleeding, with the risk increasing significantly as the severity of anticoagulation rises, particularly when the INR reaches approximately 5.0. Regardless of intensity, significant haemorrhage is more probable in individuals with a previous history of bleeding (notably gastrointestinal), advanced age, severe comorbidities (such as cancer, renal or hepatic disease, hypertension, and prior stroke), alcohol misuse, and those

receiving concurrent antiplatelet medications; the combination of warfarin and aspirin increases bleeding risk by almost 50 percent compared to warfarin alone [75]. In overall findings, warfarin elevates the incidence of major bleeding by approximately 0.3–0.5% annually and intracranial haemorrhage by roughly 0.2% per year in comparison to controls; elevated target INRs (>3) correlate with increased haemorrhage rates, highlighting the importance of lower targets in high-risk patients and optimising time within the therapeutic range [75]. Clinically, significant haemorrhage can happen in several locations (e.g., cerebral, gastrointestinal, intraocular, joints), requiring practical instruction for patients on identifying and addressing simple bruising, nosebleeds, and minor cuts, accompanied by personalised risk evaluation and periodic plan modifications [79].

Uncommon nonhaemorrhagic consequences include skin necrosis and limb gangrene, generally occurring between days 3 and 8 of treatment, resulting from significant thrombosis in dermal venules/capillaries (skin necrosis) or substantial venous outflow blockage (limb gangrene) [75]. Such events are associated with acquired or hereditary protein C deficiency (and, less frequently, protein S deficiency) and may be triggered by substantial initial doses that temporarily inhibit natural anticoagulants; limb gangrene has also been noted in patients with heparin-induced thrombocytopenia treated with warfarin without suitable initial bridging using a direct thrombin inhibitor [78, 79]. Purple toe syndrome is an uncommon condition that occurs 3–8 weeks after the initiation of therapy, characterised by sudden, painful, bilateral purple discolouration of the toes and lateral aspects of the foot; it is believed to be symptomatic of cholesterol microembolisation [75, 79].

1.6.2.1.7 Contraindications

Warfarin's narrow therapeutic index and long list of contraindications or dosage instability increase bleeding risk and require extra careful monitoring. Two serious limitations are pregnancy, where transplacental exposure can cause foetal bone malformations and haemorrhagic disorders, making warfarin contraindicated, and a history of heparin-induced thrombocytopenia (HIT), which can cause

catastrophic thrombotic complications when protein C is suppressed early in therapy [70, 78].

Beyond those facts, certain clinical conditions significantly enhance haemorrhagic risk and are severe cautions. Pre-existing bleeding diseases, gastrointestinal ulcers, GI or small-bowel/stomach tube drainage, hepatic disease with poor haemostasis, and recent trauma or severe surgery increase bleeding risk. Cancer, collagen vascular disease, and haemorrhage, necrosis, and gangrene are further high-risk disorders. Advanced age or illness requires lower initial dose; malnutrition and poor nutritional state destabilise response; and hepatic, renal, and congestive heart disease hinder safe anticoagulation. Cardiometabolic comorbidities—such as cerebrovascular or coronary disease and severe diabetes—are concerns, as are thyroid dysfunctions (both hyperthyroidism and hypothyroidism) and infections or disturbances of intestinal flora (e.g., sprue or recent antibiotic therapy) that affect vitamin K metabolism and warfarin efficacy [78].

Interactions are a major risk with warfarin. Many medicines can raise or lower its effect (via enzyme changes or protein-binding)—classic examples include metronidazole, cephalosporins, and fluconazole. Liver disease further destabilises control by impairing vitamin-K–dependent clotting-factor synthesis. Dietary vitamin K also influences anticoagulant control; large or inconsistent intake of vitamin K-rich foods can reduce anticoagulant efficacy, and patients should be counselled to maintain consistent dietary patterns [70]. Special caution is required when initiating warfarin in patients with protein C or protein S deficiency, given the risk of skin necrosis described in Section 1.6.2.1.6, and in those with indwelling epidural catheters due to the risk of spinal haematoma [78].

1.6.2.1.8 Monitoring and safety

Warfarin therapy needs regular lab monitoring to be safe and effective. The INR standardises prothrombin time across labs and is the preferred test. In most cases, the therapeutic INR is 2.0–3.0, although mechanical mitral targets 2.5–3.5. In hospitalised patients, INR should be tested daily during initiation; once stable,

testing is usually done every 4 weeks, with early rechecks when the INR is out of range or when interacting drugs are introduced, stopped, or dosed [79, 80].

Safety monitoring goes beyond INR. Pre-therapy haemoglobin/haematocrit and bleeding indicators such as black, tarry stools, nosebleeds, and fresh bruises should be checked, then reassessed every six months. Liver, kidney, and stool occult blood tests may be indicated depending on clinical context and INR values [79].

A higher than normal INR and/or haemorrhage indicate toxicity. Hold warfarin and give vitamin K immediately. Oral vitamin K should lower the INR within 24 hours for patients without substantial bleeding. Intravenous vitamin K can be used for a faster or bigger impact, but subcutaneous vitamin K is inconsistent and should be avoided. Prothrombin complex concentrate, fresh frozen plasma, or activated factor VII may reverse significant bleeding. Stop warfarin, give vitamin K and plasma, and use unfractionated or low-molecular-weight heparin to treat warfarin-related skin necrosis in the first week [79, 80].

1.6.2.1.9 Interactions

Warfarin's PK is affected by competition for plasma protein-binding sites and inhibition/induction of CYP enzymes implicated in its metabolism. Thus, CYP2C9, CYP1A2, and CYP3A4 inhibitors may enhance warfarin exposure, enhancing its anticoagulant impact and bleeding risk. In contrast, CYP2C9, CYP1A2, and CYP3A4 inducers may increase warfarin metabolism and clearance, reducing its pharmacological effects.[75, 77].

Drug interactions occur due to reduced absorption, modified clearance (either inhibition or induction, occasionally stereoselective), or pharmacodynamic effects on vitamin K–dependent pathways. Cholestyramine may diminish the efficacy of warfarin by limiting its absorption. Inhibitors of S-warfarin clearance, including metronidazole and trimethoprim-sulfamethoxazole, as well as dual-enantiomer inhibitors like amiodarone, enhance anticoagulation, while R-isomer inhibitors such as cimetidine or omeprazole have more moderate effects. Enzyme inducers,

such as rifampicin and barbiturates, together with likely influences from carbamazepine, griseofulvin, aminoglutethimide, nafcillin, and dicloxacillin, diminish anticoagulation by enhancing hepatic metabolism. Antibiotics included in practice comprise metronidazole, cephalosporins, and fluconazole [70, 75]. Due to discrepancies across sources on specific combinations, mechanism-based assessments and evidence-rated summaries are preferred, and dosage adjustments should correspond to the measured INR when therapy is initiated or discontinued [75].

Various medications enhance effects by non-metabolic mechanisms: second- and third-generation cephalosporins obstruct vitamin K recycling, thyroxine elevates clotting-factor turnover, and recurrent paracetamol administration may elevate the INR, probably via VKOR inhibition by a metabolite. Concurrent antiplatelet medications and NSAIDs, especially COX-2 inhibitors, elevate the risk of haemorrhage [75].

1.6.2.1.10 Interactions with PPIs

PPIs may interact with vitamin K antagonists (VKAs) via hepatic CYP pathways, yet the degree of interaction depends on each PPI. Omeprazole competitively inhibits CYP2C19 and has long been recognised for its ability to modify warfarin metabolism; while clinically significant effects are inconsistent, they remain probable, therefore requiring additional INR monitoring when medication modifications include omeprazole. Esomeprazole exhibits study indications for interaction with R-warfarin; however, these often did not reach clinical significance. In contrast, new results indicate that dexlansoprazole does not affect the pharmacokinetics of prevalent CYP probes, such as warfarin [24, 41].

Among particular PPIs, pantoprazole has the most consistently "neutral" interaction profile with VKAs, since many trials involving volunteers and patients indicate no major metabolic interaction with warfarin or phenprocoumon. Rabeprazole was also not identified as participating in metabolic interactions with warfarin in previous research. Considering the generally comparable antisecretory efficacy within the class, these variations in interaction potential can inform the

selection when co-prescribing with narrow therapeutic index medications such as warfarin [41, 66].

From a practical perspective, gastroenterology and cardiology guidelines highlight the necessity of INR monitoring upon the initiation or stop of a PPI in patients using VKAs, highlighting both pharmacokinetic and individual patient variability [81]. Observational syntheses in a cardiology position paper indicate that PPI co-therapy correlates with reduced hospitalisations for upper gastrointestinal bleeding in anticoagulated patients, while effect sizes are variable and confounding factors may be present.[81] A recent two-regional study (England & Hong Kong) examining confounding factors revealed no indication that PPIs alter the gastrointestinal bleeding (GIB) risk associated with oral anticoagulants (OACs); the increased bleeding observed with OAC+PPI in cohort analyses was mostly due to residual confounding rather than a causal relationship [11].

1.6.2.2 Direct Oral Anticoagulants (DOACs)

The main benefit of VKAs over heparins is oral administration, however the anticoagulant action may take days to appear, requiring close monitoring. Up until recently, hospitalised patients with anticoagulants were given heparins for 5-7 days before VKAs began to work. When two anticoagulant medicines are present in the patient's circulation during the bridging period, the bleeding risk increases significantly [68, 69]. Accordingly, clinicians globally emphasise the need for non-vitamin K antagonists oral anticoagulants (NOACs) with quick antithrombotic effects, predictable PK and PD profiles, and minimal medication, food, and herbal medicine interactions. Research has focused on developing medications with a wider therapeutic window, enabling fixed-dose regimens without routine laboratory monitoring, save in emergencies. The initial oral thrombin inhibitor, ximelagatran, was discontinued due to liver toxicity.

The NOACs are approved as alternatives to warfarin but are not approved for individuals with mechanical heart valves. These novel medications include dabigatran etexilate (the thrombin inhibitor), rivaroxaban, apixaban, and

edoxaban, which are direct factor Xa inhibitors. These medications collectively are also known as direct-acting oral anticoagulants (DOACs) [69, 70].

1.6.2.2.1 Dabigatran

Dabigatran etexilate is the first direct oral anticoagulant (DOAC) that functions as a reversible, competitive inhibitor of thrombin (factor IIa). By binding to the active site of thrombin, it inhibits the conversion of fibrinogen to fibrin, the activation of clotting factors V, VIII, XI, and XIII, and diminishes thrombin-mediated platelet activation, so blocking both fibrin production and thrombin amplification [77]. Dabigatran is delivered as dabigatran etexilate, a dual prodrug, due to its high polarity and slow absorption, which allows conversion to the active structure post-absorption [70, 75].

Dabigatran and its acyl-glucuronide metabolites are powerful, reversible direct thrombin inhibitors exhibiting significant antithrombotic properties. The medication has been approved in the United States, European Union, Canada, and Japan for the prophylaxis of stroke and systemic embolism in individuals with non-valvular atrial fibrillation, and furthermore in the EU and Canada for the primary prevention of VTE post-elective hip or knee replacement surgery [77].

Pharmacodynamic and pharmacokinetics: Dabigatran pharmacodynamically extends thrombin clotting time (TCT), activated partial thromboplastin time (aPTT), and ecarin clotting time (ECT), with TCT and ECT exhibiting a linear correlation to plasma concentrations, while aPTT reaches a plateau at elevated levels. Dabigatran's characteristics make it effective in inhibiting thrombin-mediated clot formation, although regular monitoring is typically unnecessary. Specialised tests, such as dilute thrombin time or ECT, may be utilised in specific therapeutic scenarios [70, 75].

Dabigatran etexilate exhibits low oral bioavailability (about 6–7%), which is improved by its formulation with a tartaric acid core to facilitate absorption. Maximum plasma concentrations are reached approximately two hours post-administration, and steady-state levels are achieved within two to three days.

Dabigatran exhibits approximately 35% protein binding, with around 15% existing as glucuronide conjugates. The terminal elimination half-life ranges from 12 to 17 hours following several doses, with prolongation observed in cases of renal impairment or among elderly individuals. Approximately 80–85% of the medication is eliminated intact via urine, rendering renal function a crucial factor in determining exposure and safety. Significant renal dysfunction can more than double drug accumulation, although hepatic impairment has no impact [75, 77].

Adverse effects: The primary adverse effect of dabigatran is haemorrhage, with overall incidence rates comparable to or slightly lower than those of warfarin, depending upon dosage. It diminishes the likelihood of intracranial haemorrhage relative to warfarin but presents an elevated risk of gastrointestinal bleeding, particularly at increased dosages [75].

The often observed non-haemorrhagic adverse effects of dabigatran include dyspepsia, abdominal discomfort, gastritis-like symptoms, dizziness, headache, fatigue, and breathing difficulties. Gastrointestinal issues arise more commonly than with warfarin and may result in treatment discontinuation; however, using the capsules with meals helps reduce these effects. In contrast to the previous thrombin inhibitor ximelagatran, dabigatran has not been associated with hepatotoxicity; however, clinical trials observed a slight rise in the risk of myocardial infarction [70, 78].

Idarucizumab (Praxbind), a humanised monoclonal antibody fragment, is the approved specific reversal agent for dabigatran; it binds dabigatran with high affinity and provides complete reversal of anticoagulant activity within minutes of intravenous administration. When idarucizumab is unavailable, supportive measures including drug withdrawal, hydration, and haemodialysis (which can remove approximately 60% of circulating dabigatran) may be employed. Prothrombin complex concentrates or recombinant factor VIIa may also be considered [70, 75].

Interactions: Unlike warfarin, dabigatran is not metabolised by cytochrome P450 enzymes, thereby avoiding CYP-mediated drug interactions [72, 75].

Dabigatran etexilate is a substrate of the P-gp efflux transporter, which significantly influences its absorption and excretion. Pharmaceuticals that obstruct P-glycoprotein, including ketoconazole, quinidine, amiodarone, and verapamil, can markedly elevate dabigatran plasma concentrations, accordingly elevating the risk of haemorrhage. P-gp inducers, such as rifampicin or St. John's wort, lower medication exposure and can affect its anticoagulant efficacy [75].

The impact of interactions between different medicines varies. Atorvastatin, though a CYP3A4 substrate, decreases dabigatran exposure (AUC) by approximately 18%, however this alteration is not clinically significant. Conversely, coadministration with antiplatelet medicines (aspirin, clopidogrel, ticlopidine, glycoprotein IIb/IIIa inhibitors) or NSAIDs significantly elevates the risk of bleeding due to synergistic effects on platelet inhibition or gastric mucosal damage [70, 75].

Food interactions with dabigatran are minimal. A meal rich in fat and calories prolongs the duration to achieve maximum peak concentration (Cmax) from 2 to 4 hours, while the total absorption (AUC) stays constant [70] This indicates that meals may delay the onset of dabigatran's activity without diminishing its overall anticoagulant efficacy. However, drugs that elevate gastric pH, such as PPIs, may diminish dabigatran bioavailability. Pantoprazole pretreatment lowered Cmax by 40% and AUC by 32% in healthy volunteers; however, the therapeutic significance of this reduction is still unclear [75].

1.6.2.2.2 Factor Xa inhibitors

1.6.2.2.2.1 Rivaroxaban

Rivaroxaban is a specific, reversible inhibitor of factor Xa at the active site. It targets both free Xa and Xa associated with the prothrombinase complex (including clot-associated Xa), inhibiting thrombin synthesis without directly

influencing platelet aggregation; however, by reducing thrombin, it indirectly reduces thrombin-induced platelet activation [75].

Pharmacokinetics and Pharmacodynamics**:** Oral bioavailability is high (about 80–100%), onset is fast with peak action occurring in approximately 1–4 hours, and food enhances exposure (increased AUC, increased Cmax) while slightly postponing tmax; higher dosages are administered with food [75, 77]. Metabolism occurs through CYP3A4/5 and CYP2J2, with elimination primarily renal (~66%, approximately one-third unaltered) and the remaining via faecal/biliary pathways. The half-life is around 5–9 hours (around 11–13 hours in older persons) [82]. Routine monitoring is unnecessary; PT/aPTT may be prolonged but are inconsistent, and when a level is clinically required, an anti-factor Xa assay calibrated to rivaroxaban is recommended [75, 82].

Indications**:** Approved uses include VTE prophylaxis after hip/knee replacement, treatment and secondary prevention of DVT/PE, stroke prevention in non-valvular atrial fibrillation, extended VTE risk reduction after an index event, thromboprophylaxis in acutely ill medical patients, and vascular protection in CAD/PAD with aspirin; ACS use with antiplatelets is specified in some settings [77, 82].

Safety, monitoring/reversal: bleeding is the primary side effect; indicators of hepatic toxicity were limited in trials, and common non-haemorrhagic symptoms are often minor (e.g., gastrointestinal disturbances); caution is advised in cases of renal or hepatic impairment and among older persons according to Beers Criteria [75, 82]. Baseline laboratory assessments and regular renal/CBC evaluations are recommended; drug-level testing is designated for specific circumstances (urgent haemorrhage/surgery, significant weight/age variations, unexplained incidents) using anti-Xa calibrated to rivaroxaban [82]. In cases of severe haemorrhage: withhold the medication, consider administering activated charcoal if intake was recent, use andexanet alfa when accessible, or try a 4-factor prothrombin complex concentrate when andexanet is not available; fresh

frozen plasma FFP and rFVIIa are ineffective, and dialysis is not beneficial due to significant protein binding [75, 82].

Interactions: Strong combined CYP3A4 and P-gp inhibitors (for example, azole antifungals, HIV protease inhibitors) can raise exposure and are best avoided; strong inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St John's wort) can lower exposure and reduce effect [75]. Earlier data suggest no clinically meaningful interaction with atorvastatin, digoxin, or midazolam, whereas transporter effects (for example, BCRP) and the additive bleeding risk with multi-agent antiplatelet therapy have also been highlighted [75, 82].

1.6.2.2.2.2 Apixaban

Mechanism: Apixaban is a highly selective, reversible, direct factor Xa inhibitor that targets both free and prothrombinase-complex–bound Xa, interrupting thrombin generation without requiring antithrombin and with no direct effect on platelet aggregation [83]. Unlike warfarin, apixaban does not require antithrombin as a cofactor and acts independently of hepatic synthesis of coagulation factors, enabling a rapid and predictable anticoagulant effect [83].

Pharmacokinetics and Pharmacodynamics: Oral bioavailability is around 50%, with peak concentrations occurring at approximately 3 to 4 hours. Protein binding is around 87%, and the volume of distribution is approximately 21 litres. Elimination occurs via dual pathways (renal and faecal), with renal clearance accounting for approximately 27% and an apparent half-life of about 12 hours. Exposure is dose-linear up to 10 mg. Anti-Xa-mediated assays demonstrate concentration-dependent effects, but typical PT/aPTT changes are inconsistent and ineffective for monitoring [70, 83].

Safety, monitoring, and bleeding management/reversal: The primary risk is haemorrhage (severe bleeding $\lesssim$3% in trials); routine INR monitoring is unnecessary, however patients require clinical observation for bleeding. For elective procedures, stop for 24 hours (low-bleed-risk) to 48 hours (moderate–high-risk) prior to intervention, then restart once haemostasis has been

determined. Andexanet alfa is the authorised reversal medication for life-threatening bleeding associated with factor Xa inhibitors; 4-factor prothrombin complex concentrates (PCCs) are used when andexanet is unavailable, whereas it is still under investigation. Apixaban is contraindicated for valve replacement surgery and should be avoided during pregnancy and nursing due to insufficient safety data [83].

Interactions: As a CYP3A4 and P-gp substrate, apixaban exposure rises with strong combined inhibitors (e.g., ketoconazole, ritonavir)—dose reduction or avoidance is advised—and falls with strong inducers (e.g., rifampicin, carbamazepine, phenytoin), which should be avoided [83]. Concomitant antiplatelets, NSAIDs, and even SSRIs/SNRIs can increase bleeding risk; food and gastric-pH–altering drugs don't meaningfully affect absorption [83].

Indications: Apixaban is approved for stroke/systemic embolism prevention in non-valvular atrial fibrillation, treatment of DVT/PE, reduction of recurrent DVT/PE after initial therapy, and postoperative VTE prophylaxis after hip or knee replacement [70, 83].

1.6.2.2.2.3 Edoxaban

Mechanism: Edoxaban is a selective, reversible, competitive inhibitor of factor Xa; it inhibits free Xa and prothrombinase-complex activity, lowering thrombin generation and fibrin formation without requiring antithrombin, with only indirect effects on platelets. Early pharmacology work also notes high selectivity for Xa and activity against prothrombinase-bound Xa, consistent with its class behaviour [70, 84].

Pharmacokinetics (PK) and Pharmacodynamics (PD): The onset is rapid (t_max approximately 1–2 hours), the terminal half-life is approximately 10–14 hours, and elimination occurs via dual pathways: approximately 50% is excreted unaltered in urine, with the remaining eliminated through biliary and intestinal routes; edoxaban is a slight substrate of CYP3A4 [84]. Previous studies indicate comparable parameters (t_max ~1–1.5 h, half-life ~8.6–10.7 h) and highlight

mostly renal excretion [70]. Routine coagulation monitoring is not necessary; PT/aPTT variations are minor and variable, and when a level is clinically needed an anti-Xa assay may be used, recognising decreasing efficacy at excess therapy values [78, 84].

Indications: Approved uses include the prevention of stroke/systemic embolism in non-valvular atrial fibrillation and the treatment of DVT/PE following 5–10 days of first parenteral anticoagulation; avoid usage in NVAF when CrCl exceeds 95 mL/min due to reduced efficacy compared to warfarin at the investigated dosage. A dose reduction of 30 mg once daily is indicated for those with a creatinine clearance of 15–50 mL/min or a body weight of less than 60 kg. In contrast to rivaroxaban or apixaban, edoxaban is not approved for postoperative venous thromboembolism prevention [84].

Safety, surveillance, and haemorrhage management/reversal: bleeding is the primary side effect; further precautions are neuraxial anaesthesia or spinal puncture due to the risk of epidural/spinal haematoma, as well as the boxed warning regarding thrombosis associated with premature withdrawal. Conducting baseline and periodic assessments of renal function and liver tests is recommended, along with increased renal monitoring when creatinine clearance is below 50 mL/min; prothrombin time and activated partial thromboplastin time are not beneficial for dosage modification, and anti-Xa testing is designated for specific circumstances [84]. In cases of severe haemorrhage: discontinue the medication, apply local and supportive interventions, contemplate activated charcoal for recent consumption, acknowledge that dialysis has not been shown useful; there is no approved edoxaban-specific antidote, and 4-factor prothrombin complex concentrates are frequently used off-label. Andexanet alfa is the designated reversal agent for apixaban and rivaroxaban, with ambiguous, off-label application for edoxaban [82-84].

Interactions: As a P-gp substrate, exposure can change with P-gp modulators; Strong P-gp inhibitors increase edoxaban exposure; strong P-gp inducers reduce it; both should be managed carefully. Additive bleeding risk occurs with agents

affecting Haemostasis (anticoagulants, antiplatelets/NSAIDs, thrombolytics, SSRIs/SNRIs). Specific cautions include defibrotide (additive bleeding) and mifepristone (increase edoxaban levels) [84]. The pharmacokinetic and pharmacodynamic properties of DOACs are summarised in Table 1.6, with clinical use, reversal, and interactions detailed in Table 1.7. A comparative summary of OAC–PPI interactions across all oral anticoagulants is presented in Table 1.8.

Table 1.6 Summary of DOACs Pharmacology

Summary of the pharmacological characteristics of direct oral anticoagulants, including their mechanisms of action, pharmacokinetic and pharmacodynamic properties, elimination pathways, and principal clinical indications.

Drug	Target	Oral Bioavailability (%)	Tmax (h)	Half-life (h)	Protein Binding (%)	Renal Elimination (%)	Key Metabolism	Transporters
Dabigatran	Thrombin (FIIa), direct reversible inhibitor (prodrug)	≈6–6.5	1–2 (food delays Tmax)	12–17	≈35	≈80 (unchanged)	Prodrug hydrolyzed by esterases; minimal CYP involvement	P-gp substrate
Rivaroxaban	Factor Xa, direct reversible inhibitor	≈80–100	2–4 (food may delay Tmax; ≥15–20 mg with food)	5–9 (elderly up to ~13)	>90	≈66 (36% unchanged); ≈28% fecal	CYP3A4/5 & CYP2J2 (≈30%); rest hydrolysis	P-gp substrate
Apixaban	Factor Xa, direct, reversible	≈50	3–4	≈12 (8–15)	≈87	≈27	Predominantly CYP3A4; renal + fecal elimination	P-gp substrate
Edoxaban	Factor Xa, direct, reversible	≈60–62	1–2	10–14	≈40–60	≈50 (unchanged)	Minor CYP3A4; biliary/intestinal + renal routes	P-gp substrate

Table 1.7 Summary of DOACs Use, Reversal, Monitoring, Interactions

Summary of the clinical use of direct oral anticoagulants, including their principal indications, reversal strategies, monitoring requirements, and clinically relevant drug interactions.

Drug	Food Effect	Reversal	Monitoring Notes	Key Interactions	Core Indications (selected)
Dabigatran	Delays Tmax; AUC ≈ unchanged	Idarucizumab; supportive care	No routine test; aPTT↑ (nonlinear), dTT/ECT useful if needed	P-gp inhibitors ↑ levels; P-gp inducers ↓ levels	NVAF stroke prevention; VTE prophylaxis post hip/knee; VTE treatment (per label)
Rivaroxaban	Take 15–20 mg doses with food	Andexanet alfa; PCC if unavailable	No routine test; PT may prolong (assay-dependent); anti-Xa (calibrated) if needed	Strong CYP3A4 + P-gp inhibitors ↑ levels; strong inducers ↓ levels	NVAF stroke prevention; VTE treatment; post-op VTE prophylaxis; CAD/PAD with aspirin
Apixaban	No meaningful effect	Andexanet alfa; PCC if unavailable	No routine test; mild PT/aPTT changes; anti-Xa (drug-calibrated) if needed	Strong CYP3A4/P-gp inhibitors ↑ levels; inducers ↓ levels	NVAF stroke prevention; VTE treatment; post-op VTE prophylaxis
Edoxaban	No clinically relevant effect (summary)	PCC; andexanet effect uncertain/variable	No routine test; anti-Xa (drug-calibrated) if needed	P-gp inhibitors/inducers alter levels; minimal CYP3A4 involvement	NVAF stroke prevention (CrCl ≤95 mL/min); VTE treatment after 5–10 days parenteral

Table 1.8 Comparative Summary of OAC–PPI Interactions

Comparative summary of the potential pharmacokinetic and pharmacodynamic interactions between proton pump inhibitors and oral anticoagulants, including their proposed mechanisms and clinical implications.

Anticoagulant Class	Effect on Bleeding Risk with PPI	Effect on Treatment Failure / Thromboembolism with PPI	Mechanistic Considerations	Overall Interpretation
Warfarin	Substantial increase in bleeding risk; hazard approximately doubled compared with warfarin alone	Protective effect of warfarin attenuated; increased hazard for treatment failure	CYP2C19 inhibition by PPIs may alter warfarin metabolism; unstable anticoagulation	Clinically important interaction; avoid unnecessary PPI use in warfarin patients
Dabigatran	No significant increase in bleeding observed; estimates neutral	No loss of efficacy; treatment failure risk unchanged	PPIs reduce absorption via increased gastric pH but may raise levels via P-gp inhibition; net effect appears balanced	No evidence of harmful interaction; PPI co-use appears safe
Factor Xa Inhibitors (apixaban, rivaroxaban, edoxaban)	Point estimates suggest modest bleeding increases, but confidence intervals wide and mostly nonsignificant	No clear evidence of reduced efficacy	Absorbed mainly via passive diffusion; limited CYP metabolism; less susceptible to PPI influence	Interaction unlikely to be clinically meaningful; further research needed due to small numbers

1.7 Antiplatelet

Platelets are essential elements of proper haemostasis. Subsequent to endothelial damage, platelets become activated and initiate many processes that result in thrombus formation. Disruption of this mechanism may result in atherosclerosis and thrombotic disorders [77, 85]. Arterial thrombosis is a prevalent cause of ischaemic stroke, myocardial infarction, and limb gangrene. This medical condition is the main cause of morbidity and mortality in developed nations. Atherothrombosis is essentially a process driven by platelets. Pharmaceutical research has been focused on the formulation of antiplatelet agents aimed at critical routes of platelet activation [86]. Several receptors and proteins present potential therapeutic targets. Anticoagulants have poor efficacy in the prevention of arterial thrombotic illness; therefore, antiplatelet agents have emerged as the primary pharmacological intervention for the prevention of coronary and cerebrovascular diseases [77].

Numerous antiplatelet medications have been produced over time for different indications. Three categories of antiplatelet medicines are presently approved for clinical application: (i) cyclooxygenase-1 (COX-1) inhibitors (aspirin); (ii) adenosine diphosphate (ADP) P2Y12 receptor antagonists, including the thienopyridines (clopidogrel, prasugrel) and the non-thienopyridine agents (ticagrelor, cangrelor); and (iii) glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban). In addition to aspirin, the primary antiplatelet medication, thienopyridines (ticlopidine, clopidogrel, prasugrel), particularly in combination with aspirin, have become routine antiplatelet treatments [86].

Antiplatelet drugs are categorised into oral and parenteral treatments, with oral agents further classified according to their mechanism of action. Aspirin is the first antiplatelet agent and functions as a cyclooxygenase inhibitor. Additional oral antiplatelet agents comprise clopidogrel, ticagrelor, prasugrel, cilostazol, and dipyridamole. Glycoprotein IIb/IIIa inhibitors, like tirofiban and eptifibatide, are exclusively available as parenteral medicines and are used during the acute phases of acute coronary syndrome [87].

1.7.1 ADP receptor antagonists P2Y12 inhibitors

Adenosine diphosphate (ADP) is an essential platelet agonist located at the site of endothelial damage. It is crucial for platelet activation, adhesion, and aggregation by interacting with particular receptors on the platelet membrane. The receptors are classified within the P2 family, which is subdivided into P2X ligand-gated ion channel receptors and P2Y G-protein-coupled receptors. The P2Y1 and P2Y12 receptors enhance the platelet response to ADP. P2Y1 is crucial for beginning platelet aggregation by causing a conformational shift and mobilising calcium, whereas P2Y12 enhances and stabilises the aggregation response. The P2X1 receptor promotes transmembrane calcium influx in response to ADP, however it does not substantially influence platelet aggregation and remains unchanged by thienopyridines [77, 88].

A variety of medications have been formulated to obstruct the P2Y12 receptor and prevent platelet activation, which is essential in the management of

cardiovascular illnesses linked to thrombus formation. Thienopyridines, like clopidogrel and prasugrel, irreversibly block the P2Y12 receptor, although newer medicines such as ticagrelor, cangrelor, and elinogrel offer reversible inhibition. These medications inhibit ADP-mediated platelet activation, thereby reducing the risk of arterial thrombosis and related disorders. Ticlopidine, a first-generation thienopyridine, is not approved in specific regions such as the UK; yet, the advancement of these medicines emphasises the therapeutic significance of targeting ADP pathways in platelet-mediated mechanisms [77, 88].

1.7.1.1 Clopidogrel

Clopidogrel (Plavix), a second-generation oral thienopyridine, necessitates the metabolic conversion of a prodrug by CYP2C19. The active metabolite, a highly unstable molecule, irreversibly binds to and inhibits the P2Y12 receptor via a disulphide bridge [89]. Ticlopidine, a first-generation thienopyridine with comparable efficacy, was replaced by clopidogrel due to enhanced tolerability, diminished occurrence of haematological adverse effects, expedited onset of action, and a convenient once-daily dosing schedule. Since the long-term clinical outcome has significantly improved, dual antiplatelet therapy with aspirin and the P2Y12 receptor antagonists ticagrelor, prasugrel, or clopidogrel has emerged as the clinical gold standard for patients with ACS and/or undergoing PCI [90]. Prasugrel is a prodrug and third-generation thienopyridine. However, ultrarapid hydrolysis by human carboxylesterase-2 creates an intermediate metabolite that requires only a single-step hepatic CYP oxidation to generate its active metabolite, making prasugrel more efficient than clopidogrel. Prasugrel's active metabolite permanently inhibits the P2Y12 receptor's ADP-binding site [91].

Annually, over 1.2 million people with Acute Coronary Syndrome (ACS) are hospitalised in the United States due to cardiovascular events. In 2010, clopidogrel (Plavix), with $8.8 billion in sales, was the second-best-selling branded medication in the United States [90]. Patients with ACS and those having coronary stenting are treated with dual antiplatelet therapy, which involves aspirin and a P2Y12 receptor antagonist. Ticlopidine, a P2Y12 receptor antagonist, lowers stent thrombosis risk compared to usual therapy. To minimise atherothrombotic

occurrences, ticlopidine was replaced with clopidogrel due to haematological side effects. After its market authorisation, clopidogrel's pharmacokinetics, pharmacodynamics, and interindividual variability were extensively studied, unlike the newer P2Y12 receptor antagonists prasugrel and ticagrelor, which were studied in advance [92].

1.7.1.1.1 Chemical composition

Clopidogrel is a thienopyridine derivative, chemically designated as (αS)-α-(2-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester. The chemical formula is $C_{16}H_{16}ClNO_2S$, and the molecular weight is 321.82 g/mol. The chemical comprises a chlorophenyl moiety linked to a thienopyridine ring system, with a methyl ester functional group integral to its structure. It is additionally referred to as methyl (+)-(S)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate and is designated as SR-25990 by manufacturers. The percent composition of clopidogrel comprises carbon (59.71%), hydrogen (5.01%), chlorine (11.02%), nitrogen (4.35%), oxygen (9.94%), and sulphur (9.96%). This structural arrangement is essential for its pharmacological efficacy as an antiplatelet drug [93]

Both ticlopidine and clopidogrel are thienopyridine medications with minor structural variations. The addition of a methoxy carbonyl group on the benzylic position of clopidogrel increases its pharmacological activity and improves its safety profile. Clopidogrel is the S(+)-enantiomer of the racemate; the R(−)-enantiomer is essentially inactive in antithrombotic models, underscoring the stereospecificity of P2Y12 receptor inhibition and supporting the development of clopidogrel as a single-enantiomer drug [93].

1.7.1.1.2 Mechanism of action

Clopidogrel is a prodrug that requires in vivo biotransformation via a two-step process mediated by cytochrome P450 enzymes, specifically CYP2C19 and CYP3A4, to generate its active metabolite. This active metabolite specifically and irreversibly inhibits the P2Y12 adenosine diphosphate (ADP) receptor located on the platelet surface. Inhibiting this receptor blocks the subsequent activation of

the glycoprotein IIb/IIIa receptor complex, hence lowering platelet aggregation and thrombus development. This mechanism supports the antithrombotic properties of clopidogrel, which last for the duration of a platelet's lifespan (7–10 days) due to its irreversible binding. Platelet function begins recovering with the production of new platelets, achieving complete restoration often within five days, which is essential for surgical planning [94, 95].

The mechanism of action of clopidogrel exceeds basic blockage of the P2Y12 receptor. It displays substantial antithrombotic activity in both arterial and venous thrombosis models, significantly higher than aspirin and ticlopidine in its efficacy. In arterial thrombosis models, clopidogrel has roughly 100-fold greater potency than aspirin and is 50 times stronger than ticlopidine. The suppression of ADP-induced platelet aggregation is crucial in the formation of venous thrombosis under low thrombogenic circumstances. Clopidogrel has been demonstrated to diminish thrombin formation and reduce platelet-induced procoagulant activity in endothelial cells, emphasising its extensive influence on coagulation pathways. Moreover, clopidogrel can impede platelet-leukocyte interactions, thrombin receptor agonist peptide-induced platelet activation, and the production of inflammatory markers, hence enhancing its therapeutic efficacy in thrombosis prevention [93, 95].

1.7.1.1.3 Pharmacokinetics and pharmacodynamics

Following oral administration, approximately 50% of the clopidogrel dose is absorbed from the gastrointestinal tract. Absorption is limited by P-gp, a transmembrane efflux transporter encoded by the ABCB1 gene, which actively pumps clopidogrel back into the intestinal lumen, reducing the quantity available for systemic distribution. Variability in P-gp activity, influenced by genetic variants in the ABCB1 gene, contributes to inter-individual differences in clopidogrel efficacy [90, 96].

Following absorption, clopidogrel experiences significant first-pass metabolism in the liver. Approximately 85-90% of absorbed clopidogrel is hydrolysed by carboxylesterase 1 (CES1) into the inactive carboxylic acid metabolite (SR26334),

which is eliminated in urine and faeces. Approximately 10-15% undergoes a crucial two-step oxidative bioactivation process facilitated by the cytochrome P450 (CYP450) enzyme system. Initially, CYP2C19, in conjunction with CYP1A2 and CYP2B6, transforms clopidogrel into an intermediate, pharmacologically inactive metabolite, 2-oxo-clopidogrel. Thereafter, this intermediate is subjected to further oxidation by CYP2C19, CYP3A4, CYP2C9, and CYP2B6, resulting in the formation of the pharmacologically active thiol metabolite (R-130964 or clop-AM). Following this multi-step procedure, less than 2% of the ingested clopidogrel dosage reaches systemic circulation as the active metabolite. The limited bioavailability of clopidogrel is a significant constraint in its administration, resulting in diversity in therapeutic responses among individuals [90, 92, 96, 97].

It is important to acknowledge that platelet activation does not rely solely on the P2Y12 pathway; other agonists, including thromboxane A2, thrombin, collagen, and serotonin, also play a role. Consequently, factors affecting both P2Y12-dependent and independent signal transduction pathways might influence clopidogrel responsiveness and should be considered when evaluating patient-specific treatment outcomes and possible resistance [90, 92, 96].

Clopidogrel demonstrates a slower and less consistent beginning of action compared to prasugrel, another P2Y12 receptor inhibitor. Prasugrel experiences a more direct metabolic activation, avoiding the significant involvement of CYP2C19. This single-step activation enhances the bioavailability of its active metabolite, yielding a more immediate, consistent, and strong antiplatelet effect. Although both medications yield equipotent active metabolites, prasugrel's enhanced pharmacokinetic profile, characterised by improved absorption and less variability, makes it beneficial in specific therapeutic contexts. Nonetheless, prasugrel's enhanced efficacy correlates with an elevated risk of haemorrhage, requiring careful patient selection. Clopidogrel continues to be an essential component in clinical practice due to its shown efficacy, especially when adjusted to consider genetic variants and individual patient characteristics [92, 97].

1.7.1.1.4 Administration

Clopidogrel typically commences with a loading dose of 300–600 mg to facilitate rapid inhibition of ADP-induced platelet aggregation, visible within 2 hours and with maximum inhibition after around 6 hours. For patients not requiring a loading dose, a daily maintenance dose of 75 mg is administered to reach steady-state maximum platelet inhibition over many days. This regimen effectively manages diseases including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and post-percutaneous coronary intervention (PCI), frequently in conjunction with aspirin. For patients with ST-elevation myocardial infarction (STEMI) undergoing fibrinolytic therapy, a loading dosage of 300 mg is advised for individuals aged 75 years or younger, succeeded by a daily dose of 75 mg for a duration of up to one year. In patients above 75 years of age, the loading dose is excluded, and just the maintenance dose is administered [94, 98].

Clopidogrel can be taken independently of meals; however, its metabolism relies on the cytochrome P450 enzyme CYP2C19. Consequently, medications that inhibit CYP2C19, such as omeprazole or lansoprazole, must be avoided to prevent diminished activation of clopidogrel. Likewise, drugs that inhibit gastrointestinal motility, such as opioids, might block absorption in acute situations and should be administered with caution. Human pregnancy and lactation data for clopidogrel are limited; although animal studies have not shown teratogenicity, use during pregnancy is generally avoided unless clearly necessary. A daily dosage of 75 mg is standard for the long-term management of disorders including secondary prevention of thromboembolism in atrial fibrillation, symptomatic carotid stenosis, peripheral artery disease, and coronary artery bypass graft surgery. Notably, clopidogrel does not require dosage changes for renal or hepatic impairment, making it widely relevant across varied patient populations [94].

1.7.1.1.5 P-gp and clopidogrel

P-Glycoprotein (P-gp), commonly known as ABCB1 or MDR1, is a vital membrane-bound efflux transporter. Active transport of medicines, poisons, and xenobiotics across cellular membranes is powered by ATP hydrolysis [99]. Intestinal, liver, kidney, and blood-brain barrier epithelial cell apical membranes contain most P-

gp. P-gp protects vital organs like the brain and central nervous system by aggressively removing potentially hazardous chemicals from cells [100].

P-gp is well-known to affect drug absorption, distribution, metabolism, and excretion (ADME). P-gp reduces oral medication bioavailability by pumping them back into the intestinal lumen, limiting bloodstream absorption [101]. It increases biliary and urine drug excretion in the liver and kidneys, respectively. Drug access into the central nervous system is limited by P-gp in the blood-brain barrier, protecting the brain against neurotoxic substances [99]. Importantly, P-gp substrates typically overlap with CYP3A4 substrates, creating a coordinated oral drug barrier [101].

P-gp strongly impacts the pharmacokinetics of medications such as clopidogrel, an antiplatelet medicine. Clopidogrel is a prodrug involving metabolic activation in the liver, with its intestinal absorption limited by P-glycoprotein-mediated efflux. Research utilising Caco-2 cells, a model of intestinal epithelial cells, showed the inhibition of P-gp enhanced the absorptive flux of clopidogrel by 5 to 9 times, whereas its intracellular accumulation markedly increased upon P-gp activity suppression. This discovery indicates that P-gp acts as a barrier to clopidogrel absorption, with changes in the MDR1 (ABCB1) gene further influencing interindividual variability in clopidogrel bioavailability. Carriers with the MDR1 3435T/T genotype demonstrate reduced plasma concentrations of clopidogrel in comparison to those with the 3435C/T or 3435C/C genotypes [101].

The lack of P-gp has been demonstrated to modify the metabolic activation of clopidogrel. In Abcb1a/1b knockout (KO) mice, systemic exposure to the active metabolite of clopidogrel (H4) was markedly elevated relative to wild-type (WT) animals, suggesting that P-gp restricts clopidogrel activation by regulating its availability to metabolising enzymes. Moreover, the deletion of P-gp resulted in an upregulation of Cyp3a11 (the murine equivalent of human CYP3A4) and a downregulation of carboxylesterase 1 (CES1), which catalyses the hydrolysis of clopidogrel into inactive metabolites. This alteration in enzymatic equilibrium

fosters increased synthesis of the active metabolite, accordingly elevating clopidogrel's antiplatelet efficacy [100].

1.7.1.1.6 Clinical indications

Clopidogrel is a commonly prescribed antiplatelet agent suggested for many clinical disorders, especially associated with cardiovascular disease. It is FDA-approved for the management of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) in patients receiving fibrinolytic treatment. Furthermore, clopidogrel is essential in secondary prevention efforts for patients with a history of recent myocardial infarction, ischaemic stroke, or confirmed peripheral arterial disease. Its application involves percutaneous coronary interventions (PCI) in acute coronary syndromes and stable ischaemic heart disease, as well as in symptomatic carotid artery stenosis and to reduce the risk of thromboembolic events in atrial fibrillation [94, 102].

The drug's antiplatelet action is utilised to lower the danger of vascular events by irreversibly blocking the platelet P2Y12 ADP receptor, a mechanism essential for preventing thrombus formation. In clinical practice, clopidogrel is frequently used alongside aspirin as part of dual antiplatelet treatment (DAPT), especially after percutaneous coronary intervention (PCI) or coronary stent installation, in order to avoid stent thrombosis. Moreover, it has shown effectiveness in decreasing cardiovascular incidents in individuals with peripheral arterial disease and following peripheral artery bypass grafting. Clopidogrel's flexibility and proven safety record, in contrast to prior medicines such as ticlopidine, render it fundamental in the treatment of atherothrombotic conditions [88, 94].

1.7.1.1.7 Drug interactions

Drug interactions with clopidogrel, especially those affecting CYP2C19, significantly reduce its efficacy. CYP2C19 metabolism converts clopidogrel to clop-AM. Clop-AM plasma concentrations can be reduced by CYP2C19 inhibitors, reducing platelet inhibition and antiplatelet effects. DDIs can dramatically affect clopidogrel's pharmacokinetics and pharmacodynamics because patients typically

take other drugs. Interactions may affect platelet activation and aggregation, affecting therapeutic flexibility and clinical consequences. To ensure efficacy and safety, clopidogrel prescribing should include DDI evaluation [90, 103].

Clopidogrel is metabolised into an active form via the CYP enzyme-mediated metabolic pathway. This process involves multiple isoenzymes, including CYP2C19, CYP3A4, CYP1A2, CYP2C9, among others, with the most significant being CYP3A4 (~40%) and CYP2C19 (~45%) contribute to the production of clopidogrel's active metabolite; thus, the concurrent use of CYP3A4 and CYP2C19 inhibitors may influence clopidogrel metabolism. In addition to clopidogrel, the CYP3A4 pathway also metabolises statins and calcium channel blockers, while the CYP2C19 pathway metabolises PPIs [96].

The interaction between clopidogrel and proton pump inhibitors is discussed in detail in Section 1.7.1.1.15.

1.7.1.1.8 Clinical implications of P-gp interactions

The function of P-gp can be altered by inhibitors, inducers, or genetic polymorphisms, thus affecting the therapeutic efficacy and toxicity of its substrates. The co-administration of P-gp inhibitors, including cyclosporine, verapamil, and quinidine, can enhance drug bioavailability by diminishing P-glycoprotein-mediated efflux. P-gp inhibitors could boost the plasma concentrations and antiplatelet effects of clopidogrel. Conversely, P-gp inducers like rifampicin may lower clopidogrel bioavailability by increasing efflux from intestinal cells, resulting in decreased therapeutic efficacy [99]. Genetic polymorphisms in MDR1 (ABCB1), particularly the 3435T/T variation, are associated with enhanced efflux activity, reduced clopidogrel bioavailability, and inferior cardiovascular outcomes in certain patients [101].

Genetic polymorphisms in MDR1 (ABCB1), specifically the 3435T/T variant, impact P-glycoprotein's function, thus impacting clopidogrel's absorption and bioavailability. Individuals with the 3435T/T genotype demonstrate increased P-gp activity, resulting in enhanced efflux of clopidogrel into the intestinal lumen,

reduced plasma drug concentrations, and decreased therapeutic effectiveness. This polymorphism, along with the inhibitory effects of specific PPIs on both CYP2C19 and P-glycoprotein, could worsen clopidogrel resistance, especially in genetically predisposed individuals. These findings highlight the significance of personalised medicine in antiplatelet medication, where genetic testing and drug interaction analysis can customise treatment protocols to maximise efficacy and reduce adverse cardiovascular effects [101].

1.7.1.1.9 Contraindications

Clopidogrel is contraindicated in certain medical cases where its antiplatelet effects may present serious dangers. Active pathological haemorrhage, including gastrointestinal or cerebral bleeding, constitutes a principal contraindication. The irreversible inhibition of platelet aggregation by clopidogrel can worsen bleeding in certain circumstances, potentially resulting in life-threatening consequences. Furthermore, anyone with a documented hypersensitivity to clopidogrel or any of its components should avoid using the medication. Hypersensitivity reactions, such as rash, pruritus, angioedema, and, in rare instances, anaphylaxis, require the urgent discontinuation of the medicine and consideration of alternate treatments [94, 98].

Significant hepatic impairment is a crucial contraindication for clopidogrel use, as the medication depends on hepatic metabolism for its conversion into the active metabolite. Deficient liver function may result in inadequate medication activation, reducing therapeutic efficacy while concurrently elevating the risk of severe consequences such as haemorrhaging. Moreover, significant liver impairment is frequently linked to coagulopathy, worsening the haemorrhagic risks associated with clopidogrel use. This highlights the necessity of assessing liver function prior to beginning medication, especially in individuals with pre-existing hepatic disorders [94, 98].

The use of clopidogrel is typically contraindicated during the postoperative period for individuals having operations or invasive procedures associated with a significant risk of haemorrhage. To reduce this risk, the medication is often

discontinued at least 5–7 days before surgery in order to speed up recovery of platelet function. In specific high-risk cardiovascular scenarios, such as recent coronary stent insertion, the continuation of antiplatelet medication may be essential despite the risk of bleeding, necessitating careful multidisciplinary coordination. The combination of clopidogrel with other anticoagulant or antiplatelet medicines markedly increases bleeding risks, requiring attention to detail in patients with bleeding disorders or factors that expose them to haemorrhage. Use during pregnancy and breastfeeding is generally avoided due to limited human safety data, although it may be considered when the maternal benefit clearly outweighs the risk to the foetus or infant [94, 98].

1.7.1.1.10 Demographic factors of clopidogrel PK and PD

Clopidogrel's pharmacokinetics are affected by age, sex, race, and body weight, which affect drug response differences between individuals. Older patients had greater rates of insufficient platelet inhibition after clopidogrel. Although systemic clop-AM exposure may not differ, elderly people are at higher risk of cardiovascular events and bleeding problems. These data suggest dose changes or other therapy may be better for older groups to optimise efficacy and minimise side effects [90, 103].

Some studies suggest that women may respond less to clopidogrel than men due to increased residual platelet activity. Other studies show little pharmacodynamic differences between sexes, suggesting further research is needed. Racial and ethnic distinctions are important due to genetic variation, especially in the CYP2C19 enzyme, which bioactivates clopidogrel. Asians are more likely to have poor metaboliser genotypes, which may limit efficacy and increase cardiovascular events. Finally, obesity can lower plasma active metabolite concentrations and increase platelet reactivity, requiring modified dose [90, 103].

1.7.1.1.11 Clopidogrel resistance (CR)

There is no universal definition of CR, however the most common is the medicine losing the effect it was meant to have. CR is typically defined as a patient experiencing thrombotic events after clopidogrel medication, with no inhibition

of platelet activity in laboratory tests. Some researchers call it clinical resistance in individuals who have experienced thromboembolism and other side effects after long-term oral clopidogrel medication. The prevalence of CR varies by location and race. CR incidence ranges from 5-44% in Western countries to 20-65% in Asian populations, according to literature [96].

Multiple fundamental factors contribute to clopidogrel resistance. Individual factors such as age, gender, weight, long-term medicines, and stress may contribute to clopidogrel resistance. Primarily, genetic variables include mutations in the P2Y12 gene, P450 CYP3A gene, and COX1 gene, as well as polymorphisms in platelet glycoprotein receptors, influence resistance. Moreover, excessive platelet synthesis by the bone marrow, platelet transfusions, non-adherence to therapy, inadequate dosing, hepatic cell absorption, and specific medication interactions, including non-steroidal anti-inflammatory medicines (NSAIDs), contribute to clopidogrel resistance [104].

1.7.1.1.12 Adverse effects and monitoring

Clopidogrel is typically well-tolerated; yet, it is linked to various undesirable effects, as is the case with any medication. A notable and concerning adverse effect is an elevated risk of haemorrhage, including gastrointestinal bleeding and, less frequently, cerebral haemorrhage. The risk of gastrointestinal bleeding associated with clopidogrel is lower than that of aspirin, making it a preferred choice for individuals with a history of gastrointestinal complications. Patients must be observed for indications of excessive haemorrhage, especially when clopidogrel is administered alongside other antiplatelet or anticoagulant medications, as the risk of bleeding may be markedly increased [88, 94].

Additional common adverse effects of clopidogrel include gastrointestinal symptoms, including diarrhoea and abdominal discomfort, with dermatological reactions such as rash and itching. Infrequent but severe adverse events include thrombotic thrombocytopenic purpura (TTP), a potentially fatal illness marked by thrombocytopenia, haemolytic anaemia, renal impairment, and neurological manifestations. While instances of TTP have been documented, they are

infrequent and frequently considered as accidental. The comprehensive safety profile of clopidogrel, especially its reduced incidence of haematologic problems relative to its predecessor ticlopidine, has established it as a prevalent antiplatelet drug in clinical practice [94, 98].

Platelet function tests (PFTs) are used to assess the antiplatelet effect of clopidogrel on platelet aggregation. Light transmission aggregometry (LTA) remains the gold standard but has practical limitations. Ideal PFTs should be cost-effective, require minimal technical expertise, demonstrate high sensitivity and specificity, and provide rapid results. Standardised protocols with quality control and validated reference ranges are needed to reliably quantify antiplatelet effects and identify patients at risk of clopidogrel resistance [102, 104].

Patients on clopidogrel should be monitored for signs of bleeding, both visually and by laboratory tests (haemoglobin and haematocrit). Numerous patients may exhibit genetic variations in the CYP enzymes. The CYP2C19 enzyme is the most extensively researched in relation to medication metabolism and response. Genetic testing may be recommended for patients at elevated risk of unfavourable outcomes, such as those undergoing PCI with a greater chance of stent thrombosis, before initiating medication. Additionally, following drug administration, platelet function tests can be employed to assess patient response. There are multiple viewpoints regarding the established level for failure to respond and the appropriate management technique [94].

1.7.1.1.13 Relevant clinical trials

After the Canadian Cooperative Study Group (1978) showed that aspirin acetylsalicylic acid (ASA) reduced major strokes in mild stroke patients, other trials showed its benefits in unstable angina and acute myocardial infarction. A 1988 meta-analysis found that aspirin in secondary prevention reduced major cardiovascular events by 25% and mortality by 10% without worsening intracranial haemorrhage. Aspirin became the primary secondary cardiovascular preventive medication due to its safety and efficacy. A 1994 meta-analysis by the Antiplatelet Collaborative Trialists disputed the idea that platelets play a minor role in venous

thrombi development, showing that aspirin reduces postoperative VTE and pulmonary embolism [105].

The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) research (2005) examined the impact of including clopidogrel into routine aspirin treatment in 3,491 patients with ST-segment elevation myocardial infarction (STEMI) undergoing fibrinolytic therapy. The research indicated that the concomitant use of clopidogrel and aspirin markedly diminished the likelihood of cardiovascular mortality, recurrent myocardial infarction, or stroke in comparison to aspirin monotherapy. This advantage was noted without a significant rise in the risk of severe haemorrhage. The results underscored the significance of dual antiplatelet therapy in enhancing clinical outcomes for STEMI patients receiving fibrinolysis [106].

The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial was a major, randomised, double-blind, multinational study that compared the long-term efficacy and safety of clopidogrel (75 mg daily) versus aspirin (325 mg daily) in lowering ischaemic events in atherosclerotic vascular disease patients. Over 19,000 patients with recent ischaemic stroke, myocardial infarction, or symptomatic peripheral artery disease were followed an average of 1.91 years. Compared to aspirin, clopidogrel reduced the risk of ischaemic stroke, myocardial infarction, and vascular mortality by 8.7% ($p = 0.043$). Both groups had adverse effects, although clopidogrel was marginally safer, especially for gastrointestinal bleeding and discomfort. These studies showed that clopidogrel prevents thrombotic events better and safer than aspirin in high-risk patients [107].

The PCI-CURE substudy examined the efficacy of clopidogrel pretreatment and long-term therapy in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients receiving percutaneous coronary intervention. In 2,658 patients, adding clopidogrel to aspirin reduced the risk of the primary endpoint—cardiovascular mortality, myocardial infarction, or urgent target-vessel revascularisation—within 30 days of PCI (4.5% vs. 6.4%, relative risk 0.70, $p=0.03$).

Prolonged clopidogrel treatment reduced cardiovascular mortality or myocardial infarction by 31% (p=0.002) and glycoprotein IIb/IIIa inhibitor use by 0.001. This method did not increase severe bleeding (p=0.64), demonstrating the efficacy of clopidogrel pretreatment and continued administration in preventing major cardiovascular events in this high-risk population [108].

Long-term clopidogrel therapy and loading dosage timing in elective or likely PCI patients were examined in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Compared to aspirin alone, one-year clopidogrel medication reduced the risk of death, myocardial infarction (MI), and stroke by 26.9% in 2,116 patients (P=0.02). Although clopidogrel pretreatment did not reduce occurrences at 28 days overall, a prespecified subgroup analysis revealed that taking it at least 6 hours before PCI may reduce adverse events by 38.6% (P=0.051). The incidence of severe bleeding over one year was somewhat greater in the clopidogrel group (8.8% vs. 6.7%), but not statistically significant (P=0.07). The research group's findings emphasise the necessity of extended clopidogrel medication after PCI for avoiding ischaemic episodes and recommend loading dosage timing [109].

A prespecified substudy of CLARITY-TIMI 28 — PCI-CLARITY — examined outcomes specifically in the 1,863 patients who subsequently underwent percutaneous coronary intervention. Clopidogrel pretreatment reduced cardiovascular mortality, MI, and stroke (3.6% vs. 6.2%; OR 0.54; P = .008), with a 41% reduction from randomisation to 30 days (7.5% vs. 12.0%; OR 0.59; P = .001), without an increase in TIMI major or minor bleeding (2.0% vs. 1.9%; P > .99), strongly supporting early clopidogrel introduction in STEMI patients planned for PCI [110].

This large-scale experiment examined the benefits of adding clopidogrel to aspirin in 45,852 acute myocardial infarction patients. Clopidogrel (75 mg daily) or placebo, along with aspirin and other usual therapies, was randomly assigned to patients for up to 4 weeks. Clopidogrel reduced composite death, reinfarction, or stroke risk by 9% (p=0.002) and overall mortality by 7% (p=0.03). These advantages were consistent across patient groups and irrespective of other therapies. Even in

aged or fibrinolytic patients, clopidogrel did not raise the risk of major bleeding. Clopidogrel effectively reduces hospitalisation mortality and major vascular events when added to routine MI treatment, according to the study [111].

The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) trial compared clopidogrel and aspirin to aspirin alone in reducing cardiovascular events in a large cohort of high-risk individuals. Over 15,000 patients were studied for myocardial infarction, stroke, and cardiovascular death. The combo therapy reduced the primary endpoint slightly, but not significantly. Dual therapy may help individuals with established cardiovascular disease more than those without, according to subgroup analysis. The trial showed that patient selection may optimise dual antiplatelet therapy while balancing bleeding risk [112].

The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organisation to Assess Strategies in Ischaemic Syndromes (CURRENT-OASIS 7) trial assessed the effectiveness and safety of double-dose clopidogrel versus standard-dose in acute coronary syndrome patients receiving percutaneous coronary intervention. This large-scale randomised trial of nearly 25,000 participants showed that the double-dose regimen reduced stent thrombosis and reduced the risk of major cardiovascular events, particularly in PCI patients. However, the larger dose raised serious bleeding risk. The trial stressed the significance of individualised antiplatelet medication, balancing efficacy and bleeding risk [113]. The pharmacological properties of clopidogrel are summarised in Table 1.9.

Table 1.9 Summary of clopidogrel pharmacology

Summary of the pharmacological characteristics of clopidogrel, including its mechanism of action, pharmacokinetic and pharmacodynamic properties, metabolism, elimination, and principal clinical indications.

Aspect	Details	References
Drug class	Thienopyridine antiplatelet agent (P2Y12 receptor inhibitor).	(Barrowman, 2021; Thachil, 2016)
Mechanism of action	Prodrug, requires hepatic CYP450 (mainly CYP2C19) conversion to active metabolite. Irreversibly blocks platelet P2Y12 receptor → inhibits ADP-mediated platelet aggregation.	(Remko, 2016)
Indications	Secondary prevention of atherothrombotic events (MI, ischemic stroke, peripheral arterial disease); often used in dual antiplatelet therapy with aspirin after PCI/stenting.	(Barrowman, 2021)
Pharmacokinetics	Oral absorption; ~85% hydrolyzed by esterases to inactive metabolite; ~15% metabolized by CYP2C19 → active metabolite. Peak plasma: ~1 h (parent), 30–60 min (active). Half-life (parent): ~6 h.	(Thachil, 2016)
Onset of action	Requires biotransformation; antiplatelet effect begins within 2 hours of loading dose; maximal effect 3–7 days of daily dosing.	(Remko, 2016)
Duration of effect	Irreversible binding → effect lasts for platelet lifespan (~7–10 days).	(Remko, 2016)
Metabolism	Hepatic (CYP2C19 major; CYP3A4, CYP2B6 minor).	(Thachil, 2016)
Excretion	Urinary (~50%), fecal (~46%).	(Barrowman, 2021)
Adverse effects	Bleeding (GI, intracranial), bruising, rare thrombotic thrombocytopenic purpura (TTP).	(Barrowman, 2021; Thachil, 2016)
Drug interactions	PPIs (esp. omeprazole) may reduce activation via CYP2C19 inhibition; caution with other anticoagulants/antiplatelets.	(Remko, 2016)

1.7.1.1.14 Drug regulatory reviews (FDA review/MHRA or equivalent)

Clopidogrel, sold as Plavix, was FDA-approved on November 17, 1997, to minimise atherothrombotic events. Myocardial infarction, ischaemic stroke, and vascular mortality in patients with recent MI, stroke, or peripheral artery disease are examples. Clopidogrel was later licensed for use in combination with aspirin in patients with acute coronary syndrome (ACS), including unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), to lower the risk of cardiovascular mortality, MI, and stroke [103].

The FDA gradually increased clopidogrel uses. After the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) and CLARITY-TIMI 28 studies, it was authorised for ST-segment elevation myocardial infarction (STEMI). STEMI

patients' relative risk of death, recurrent MI, or stroke was considerably lowered by clopidogrel, aspirin, and conventional care in these studies. The extended indication providing clinicians with an evidence-based treatment option for the most severe presentation of acute coronary syndrome [103].

The European Medicines Agency (EMA) authorised clopidogrel for sale in Europe on July 14, 1998. It was licensed for use in patients with recent myocardial infarction, ischaemic stroke, established Peripheral Arterial Disease (PAD), and ACS, including PCI and thrombolytic or fibrinolytic treatment patients. Clopidogrel was later approved for AF patients who could not take vitamin K antagonists (VKAs) yet were at risk of vascular events. The EMA approved clopidogrel for its risk-benefit profile in lowering ischaemic events, leading to its widespread use in European clinical practice [114].

Several important clinical trials, including CURE, CAPRIE, COMMIT, CLARITY-TIMI 28, and DAPT, showed that clopidogrel reduced cardiovascular events in distinct patient categories, supporting its approval. The FDA and EMA monitor clopidogrel's safety, updating healthcare practitioners on bleeding risks and other side effects. One of the most prescribed antiplatelet medications worldwide is clopidogrel [114].

1.7.1.1.15 Clopidogrel-PPI interactions: Evidence and controversies

The interaction between PPIs and clopidogrel is one of the most extensively studied yet consistently controversial drug-drug interactions in cardiovascular pharmacology. Clopidogrel requires CYP2C19-mediated bioactivation to produce its active antiplatelet metabolite, and specific PPIs—especially omeprazole and esomeprazole—are strong CYP2C19 inhibitors [40, 41]. Clopidogrel and PPIs are both substrates and modulators of P-glycoprotein, potentially leading to interactions at various pharmacokinetic levels [100, 101].

Research suggests that taking omeprazole or esomeprazole with clopidogrel can lower plasma levels of its active metabolite and lessen platelet inhibition. The strongest impacts of CYP2C19 inhibition are shown with omeprazole and

esomeprazole, while pantoprazole and rabeprazole have less impact [40, 41]. P-gp inhibition by PPIs may increase clopidogrel intestinal bioavailability, while CYP2C19 suppression may lower conversion to active metabolites, potentially reducing therapeutic efficacy [100, 101].

The clinical importance of PPI-clopidogrel interaction is debated. Consistent observational studies link PPI usage to higher cardiovascular events in clopidogrel-treated patients [90, 96, 115]. Results may be influenced by indication, as PPI patients had increased comorbidities, bleeding risk, and complex prescription regimens, which are independently linked to unfavourable outcomes [90, 92].

Conflicting pharmacokinetic and clinical outcome data have led to inconsistent guideline recommendations. Some guidelines suggest using pantoprazole or rabeprazole instead of omeprazole or esomeprazole for gastroprotection in clopidogrel-treated patients, while others suggest the interaction should not impact acid suppression decisions [92]. Current guidelines encourage not withdrawing gastroprotection when clinically required, but admit uncertainty in optimal PPI selection [90, 96].

The regulatory response to the pharmacokinetic evidence was substantial. In November 2009, the United States Food and Drug Administration issued a boxed warning advising against the concomitant use of omeprazole with clopidogrel, on the basis that omeprazole reduces the antiplatelet activity of clopidogrel by inhibiting CYP2C19-mediated bioactivation [103]. The European Medicines Agency issued a similar but less restrictive advisory, recommending that the combination be discouraged but stopping short of contraindication [116]. These regulatory actions generated significant clinical uncertainty and prompted calls for a definitive randomised trial.

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) was designed to address this question. This double-blind, placebo-controlled randomised trial enrolled 3,873 patients requiring dual antiplatelet therapy and randomised them to omeprazole or placebo. The primary cardiovascular endpoint

— a composite of cardiovascular death, myocardial infarction, revascularisation, or ischaemic stroke — showed no significant difference between groups (hazard ratio 0.99; 95% CI 0.68–1.44), while the primary gastrointestinal endpoint — overt or occult gastrointestinal bleeding, symptomatic gastroduodenal ulcers, erosions, or obstruction — was significantly reduced with omeprazole (hazard ratio 0.34; 95% CI 0.18–0.63) [117]. Although the trial was terminated early due to loss of funding and was therefore underpowered for definitive conclusions on cardiovascular outcomes, COGENT provided the strongest available evidence against a clinically meaningful interaction and shifted the risk–benefit calculus towards gastroprotection where indicated. The trial's findings stand in notable contrast to the earlier observational literature, which had consistently suggested harm — a discrepancy widely attributed to confounding by indication in the observational studies [118].

Several subsequent systematic reviews and meta-analyses have attempted to reconcile the conflicting evidence. A systematic review [119] found that the association between PPI use and adverse cardiovascular events was present in observational studies but absent in randomised trials and propensity-matched analyses, supporting the hypothesis that confounding rather than a true pharmacological interaction accounts for the observed associations [119]. Similarly, Cardoso (2015)[120] conducted a systematic review of randomised trials and found no evidence that PPI co-therapy increased the risk of major adverse cardiovascular events in clopidogrel-treated patients.

Essential enquiries remain insufficiently answered. The conflict centres on whether the interaction leads to clinically significant increases in thrombotic events in real-world populations, as observational relationships may indicate confounding rather than causation. Secondly, data on the comparative effectiveness of individual PPIs in patients treated with clopidogrel is limited; the majority of research either combine all PPIs or compare only omeprazole with non-use. Third, there is a deficiency of large-scale real-world research analysing hospitalisation outcomes, as opposed to combination endpoints or indirect markers.

This study investigates the gaps by analysing real-world hospitalisation outcomes linked to PPI co-prescription in a substantial, heterogeneous cohort of clopidogrel users, employing stratified analyses to compare individual PPIs. This research emphasises hospitalisation—an objectively defined and clinically significant outcome—providing evidence to guide therapeutic decision-making concerning PPI selection for individuals requiring antiplatelet medication.

1.8 PPI Interactions Across Cardiovascular Drug Classes

This introduction has provided an extensive overview of three principal cardiovascular medication classes, digoxin, oral anticoagulants, and clopidogrel, commonly co-prescribed with PPIs in clinical settings. Analysing the interaction patterns of these various pharmacological drugs uncovers shared mechanistic elements and emphasises drug-specific susceptibility that justify comparative analysis.

1.8.1 Shared characteristics in interaction mechanisms

PPIs interact with cardiovascular medications through three shared pharmacokinetic mechanisms. The first is cytochrome P450 enzyme inhibition, principally at CYP2C19 and to a lesser extent CYP3A4. Within the PPI class, omeprazole and esomeprazole are the strongest CYP2C19 inhibitors, lansoprazole exerts an intermediate effect, and pantoprazole and rabeprazole show minimal inhibition — the latter because rabeprazole undergoes substantial non-enzymatic metabolism. This hierarchy is clinically relevant for cardiovascular drugs that depend on CYP2C19 for bioactivation (clopidogrel) or on CYP-mediated clearance (warfarin) [24, 40, 41]

The second shared mechanism is P-gp modulation. P-gp is expressed at the apical surface of enterocytes, hepatocytes, renal proximal tubules, and brain capillary endothelium, where it limits oral absorption and facilitates biliary and renal clearance of its substrates. PPIs act as both substrates and inhibitors of P-gp, creating scope for altered exposure to cardiovascular drugs that are themselves P-gp substrates — including digoxin, dabigatran, and, to a lesser extent, the factor

Xa inhibitors and clopidogrel. Genetic variation in the encoding gene (ABCB1/MDR1) further modifies the magnitude of these interactions between individuals [25, 29].

The third shared vulnerability is narrow therapeutic index status combined with cardiovascular polypharmacy. Digoxin and warfarin are classical narrow therapeutic index drugs in which small changes in systemic exposure can produce clinically significant toxicity or loss of effect. The likelihood of encountering at least one potential drug–drug interaction exceeds 50% with five concurrent medications and approaches 100% with seven or more — a threshold routinely exceeded in cardiovascular populations who are older, multimorbid, and exposed to long-term therapy. These patient-level factors amplify the clinical consequences of the pharmacokinetic mechanisms above, even when the underlying effect sizes are modest [6, 7].

Although these mechanisms are common to all three medication classes, the magnitude and clinical relevance of the resulting interactions differ substantially by drug. Drug-specific interaction profiles, including the evidence on PPI-induced changes in exposure and antithrombotic or inotropic effect, are detailed in Sections 1.4.9, 1.5.9, 1.6.2.1.10, 1.6.2.2.1, and 1.7.1.1.15.

1.8.2 Comparative implications

The varying interaction profiles among these drug classes highlight the need for drug-specific evaluations instead of class-wide studies of PPI-cardiovascular drug interactions. Digoxin's susceptibility arises from its reliance on P-gp and its narrow therapeutic index. Interactions with warfarin predominantly involve regulation of CYP enzymes, exhibiting unique variances in inhibitory potency specific to PPIs. Dabigatran demonstrates unusual susceptibility due to its pH-dependent absorption and P-gp transport mechanisms. Factor Xa inhibitors exhibit reduced interaction potential but remain inadequately characterised. Clopidogrel interactions encompass both CYP2C19 inhibition and P-gp modulation, supported by substantial molecular data, but lacking definitive clinical impact. Significantly, for all three medication classes, considerable gaps exist in real-world outcome

data assessing whether these pharmacokinetic and mechanistic interactions result in clinically significant increases in adverse events requiring hospitalisation. Furthermore, comparative information assessing outcomes with specific PPIs—especially pantoprazole and rabeprazole, which exhibit modest CYP2C19 inhibition—remains rare across all cardiovascular medication classes.

1.8.3 Research gap

Despite extensive mechanistic understanding and trial-based evidence for individual cardiovascular drugs, significant uncertainty remains regarding the real-world clinical consequences of drug–drug interactions in routine care. Randomised trials typically exclude older patients with multimorbidity, polypharmacy, — precisely the populations most vulnerable to adverse drug interactions [6, 7]. Furthermore, existing interaction warnings are often derived from pharmacokinetic studies rather than patient-centred outcomes such as hospitalisation [6]. A further challenge is that the observational studies which do examine clinical outcomes are highly susceptible to confounding by indication — the systematic bias whereby patients prescribed PPIs differ from those not prescribed PPIs in ways that independently predict adverse outcomes[119]. Because PPIs are selectively prescribed to patients with higher gastrointestinal bleeding risk, greater comorbidity, and more complex pharmacotherapy, unadjusted and inadequately adjusted observational estimates may overstate or misattribute interaction-related harm. Addressing this bias requires analytical approaches that can account for the dynamic, time-varying nature of both PPI prescribing and cardiovascular drug exposure — a methodological consideration that has shaped the design of the studies in this thesis. This study systematically examines hospitalisation outcomes linked to PPI co-prescription with digoxin, oral anticoagulants, and clopidogrel, including stratified analysis by specific PPI agents. This thorough, comparative methodology facilitates the identification of interaction concerns distinct to drug classes versus those that are shared, while supplying information to guide PPI selection for the millions of patients globally who require both cardiovascular drugs and gastroprotection.

1.9 Summary And Rationale For The Current Study

1.9.1 Current state of knowledge

Cardiovascular disease is the major cause of death worldwide, requiring long-term pharmacological therapy with anticoagulants, antiplatelet medicines, and cardiac glycosides [1, 2]. PPIs are among the most frequently co-prescribed medications in these populations, prescribed for gastroprotection during antithrombotic therapy or for concurrent acid-related conditions [33, 66]. However, PPIs undergo CYP450-mediated metabolism, alter gastrointestinal pH, and function as both substrates and modulators of P-gp - properties that create predictable pharmacokinetic interactions with cardiovascular medication [40, 41]. Omeprazole and esomeprazole exhibit the greatest CYP2C19 inhibitory potency, whereas pantoprazole and rabeprazole have minimal effects. Despite this pharmacological understanding, an estimated 40–60% of PPI prescriptions lack a clear indication, resulting in widespread and potentially unnecessary exposure to interaction risk in cardiovascular populations [8]

The evidence base for each drug combination differs in maturity and consistency. The PPI–clopidogrel interaction is the most extensively studied, with well-documented pharmacodynamic effects that have not consistently translated into clinical harm in randomised or adequately adjusted observational studies [117, 119]. The PPI–digoxin interaction is supported by mechanistic and pharmacokinetic data but has not been evaluated in large clinical outcome studies. The PPI–oral anticoagulant interactions are heterogeneous, with pH-dependent absorption effects on dabigatran, CYP-mediated effects on warfarin, and incompletely characterised P-glycoprotein-mediated effects on factor Xa inhibitors [41, 77]. Across all three drug classes, the translation from pharmacokinetic perturbation to clinical consequence in routine care remains uncertain.

Digoxin, a narrow therapeutic index drug and P-gp substrate, is highly susceptible to transporter-mediated interactions, influencing absorption and renal clearance [25, 27]. Warfarin interacts with CYP2C9, CYP1A2, and CYP3A4, with omeprazole

suppressing CYP2C19 and pantoprazole showing neutral effects [41, 75]. Pantoprazole pretreatment has been shown to reduce dabigatran exposure by 30–40%, attributed to pH-dependent effects on dissolution and P-glycoprotein-mediated transport [75]. Variable CYP3A4 and P-glycoprotein-mediated transport of factor Xa inhibitors has theoretical interaction potential [75, 83, 84]. Clopidogrel is bioactivated by CYP2C19, although only 15% converts to an active metabolite, making it susceptible to inhibitors and P-glycoprotein-mediated efflux [90, 101]. Clinical outcome evidence is still controversial, as observational relationships may be influenced by indication [90, 96].

1.9.2 Knowledge gaps

Despite significant research and clinical investigations, the therapeutic impact of PPI-cardiovascular medication interactions is still poorly understood.

First, there is insufficient evidence comparing PPI interaction patterns across various cardiovascular medication classes. Most literature on drug interactions focuses on individual drug combinations, particularly PPI-clopidogrel interactions. This fragmentation hinders knowledge of drug-specific or class-wide interaction concerns and limits evidence-based recommendations for PPI use in cardiovascular medicines [6].

Second, limited real-world data exists on hospitalisation outcomes, in contrast to surrogate endpoints or composite outcomes. This is a critical gap because hospitalisation represents an objectively defined, clinically significant event with substantial consequences for both patients and health systems. A systematic review and meta-analysis estimated that approximately 1.3% of hospital admissions are attributable to drug–drug interactions, rising to over 5% in elderly populations [121]; yet the contribution of specific PPI–cardiovascular drug combinations to these admissions has not been systematically quantified.

Third, direct oral anticoagulant evidence is limited compared to warfarin literature. Although dabigatran has been shown to reduce exposure by 30-40% with pantoprazole [75], it is unclear if these pharmacokinetic changes result in

clinically significant differences in bleeding or thrombotic outcomes. A thorough study of clinical outcomes with PPI co-prescription for factor Xa inhibitors is missing.

Fourth, there is no systematic study of longitudinal outcomes in anticoagulated individuals. Managing anticoagulant therapy requires balancing thrombotic risk (treatment failure) with bleeding risk. Although drug interactions may alter the balance, most studies only assess one outcome category in the same group using consistent methodologies. Examining both bleeding and treatment failure outcomes is necessary to fully understand the clinical risk profile.

Fifth, large-scale outcome studies lack individual PPI comparisons. Most clinical outcome studies approach PPIs as a homogeneous class or focus on a few individual drugs, despite known pharmacological variations, particularly in CYP2C19 inhibition potency. Evidence-based PPI selection for gastroprotection patients may reduce interaction risks while maintaining benefits.

Although limited, real-world data from large, diverse populations in routine clinical practice settings provides the most externally solid foundation for clinical guidelines and prescribing decisions. The research considers the complexity of real-world patients, including comorbidities, polypharmacy, and practice variation, which can impact medication interaction risks.

These knowledge gaps affect clinical practice. Insufficient data in current guidelines leads to inconsistent recommendations, leaving doctors without clear guidance for millions of patients worldwide who require concurrent cardiovascular and gastroprotective pharmacotherapy. Quantifying the burden of PPI-related drug interactions on hospital admissions is crucial for patient safety, health policy, and resource allocation choices [6].

1.9.3 Aim of this thesis

The overarching research question addressed by this thesis is does co-prescription of PPIs with cardiovascular medications translate into clinically detectable harm,

as measured by hospitalisation, in real-world patient populations? This thesis aims to answer this question by investigating the association between PPI co-prescription and hospitalisation risk in patients receiving three major classes of cardiovascular medications - digoxin, oral anticoagulants (warfarin, dabigatran, and factor Xa inhibitors), and clopidogrel - using linked electronic health records (HER) from NHS Greater Glasgow and Clyde, with time-varying exposure classification and methods designed to address confounding by indication.

The main objectives are:

1. To determine whether PPI co-prescription is associated with altered drug class-specific hospitalisation risk in patients receiving digoxin, oral anticoagulants, or clopidogrel in a large, real-world population.

2. To examine whether PPI-associated hospitalisation risks differ across oral anticoagulant classes (warfarin, dabigatran, factor Xa inhibitors), reflecting heterogeneity in pharmacological interaction profiles.

3. To assess bidirectional clinical outcomes in anticoagulated patients by examining both bleeding-related and treatment-failure-related hospitalisations, capturing the safety–effectiveness balance inherent to anticoagulant therapy.

4. To contextualise PPI-associated hospitalisation risks in clinically meaningful terms for each medication class, including relative and absolute risk considerations.

5. To explore whether hospitalisation risk varies by individual PPI agent within each cardiovascular drug class, thereby informing evidence-based PPI selection in patients requiring both cardiovascular pharmacotherapy and gastroprotection.

This study employs a retrospective observational cohort design using linked EHRs from NHS Greater Glasgow and Clyde (NHSGGC), spanning 1 January 2014 to 31 December 2020. Drug exposure is modelled as a time-varying covariate, and IPTW is used to address confounding by indication - an approach that reflects current best practice in pharmacoepidemiological research on drug–drug interactions. This research concentrates on hospitalisation as the principal outcome, an objectively defined, clinically significant event with considerable ramifications for patient morbidity and healthcare expenditures, while analysing current prescribing trends across varied patient demographics, thereby offering externally valid evidence pertinent to clinical decision-making. Given the observational design, findings are interpreted as associations rather than causal effects, with attention to confounding by indication and prescribing context.

The findings will inform evidence-based recommendations for PPI prescribing in patients requiring cardiovascular medications, support guideline development, and enhance medication safety initiatives by highlighting context-specific interaction risks.

Chapter 2 Methods

2.1 Introduction

The accuracy of drug exposure assessment is a critical determinant affecting the validity of pharmacoepidemiological research. Comprehensive research increasingly relies on health care data gathered from pharmacies, health insurers, and general practitioners, each presenting specific benefits and disadvantages. Pharmacy dispensing data offer the most accurate depiction of prescription-only drug utilisation, particularly for chronic drugs, as they can track refill patterns and evaluate patient compliance. Nonetheless, numerous sources often exclude over-the-counter (OTC) drugs, and documentation from general practitioners may lack full prescription details.

Moreover, the examination of drug-event associations requires meticulous evaluation of the dosage, duration, and timing of drug administration, along with the possible risk window within which a drug may influence the outcome. Misclassification could happen when exposure assessment challenges pharmacokinetic and pharmacodynamic principles, especially when carry-over effects remain beyond the active treatment duration. Initial pharmacoepidemiological studies frequently depended on patient interviews to obtain drug usage data, leading to considerable recall bias. Patients with serious illnesses were more inclined to accurately recall their medication usage, while hospital records were inadequate. These limitations, in addition to binary classifications of drug usage that led to non-differential misclassification, likely resulted in prior studies underestimating the true effects of medications [122].

Modern pharmacoepidemiology addresses these challenges through the use of comprehensive EHRs and sophisticated analytical methods. This thesis employs linked prescribing data, hospital records, and advanced survival analysis techniques to assess time-varying drug exposures and their association with clinical outcomes. Accordingly, the analytical approach centres on a marginal structural Cox proportional hazards modelling framework with time-varying drug

exposure, implemented using inverse probability of treatment weighting (IPTW) to address time-varying confounding and approximate clinically relevant causal contrasts in longitudinal observational data, with Simon–Makuch extensions of Kaplan–Meier methods used to visualise survival patterns under dynamic exposure states. The following sections describe the data sources, study design, exposure classification methods, and statistical approaches used to examine drug-drug interactions while minimising bias and misclassification.

2.2 Study Design

This thesis comprises three retrospective cohort studies conducted using linked electronic health records (EHRs) from NHS Greater Glasgow and Clyde (NHSGG&C). The study period spanned from 1 January 2014 to 31 December 2020. The final ten months of accrual and follow-up therefore overlapped with the first and second waves of the COVID-19 pandemic (from March 2020), a period during which both the incidence of the study outcomes and the ascertainment of those outcomes through hospital admission may have been altered. The implications of this overlap are considered in the discussion and limitations of the individual study chapters and in the overall discussion. Each study examines drug-drug interactions involving proton pump inhibitors (PPIs) and their effects on clinical outcomes in specific patient populations. All three studies share common methodological approaches while addressing distinct clinical questions:

Question 1: To investigate interactions associated with digoxin and PPIs in patients with atrial fibrillation (AF), with the primary outcome of hospitalisation due to arrhythmia.

Question 2: To examine interactions associated with oral anticoagulants (OACs: warfarin, dabigatran, and factor Xa inhibitors) and PPIs in patients with AF, pulmonary embolism (PE), venous thromboembolism (VTE), transient ischaemic attack (TIA), and/or ischaemic stroke. This study assesses two outcomes: general bleeding events and treatment failure.

Question 3: To evaluate interactions between clopidogrel and PPIs in patients prescribed clopidogrel following TIA and/or ischaemic stroke, with the primary outcome of general bleeding events.

A retrospective cohort design was selected for several methodological reasons. First, the primary research questions concern the comparative risk of clinical outcomes across dynamic, time-varying exposure states, which requires a longitudinal framework capable of accommodating changes in medication status throughout follow-up. Cohort designs are the natural choice for such questions because they allow direct estimation of incidence rates and hazard ratios across exposure groups while preserving the temporal sequence between exposure and outcome [123]. Second, the availability of linked EHRs with prescription-level data enabled reconstruction of individual medication histories with sufficient granularity to implement time-dependent exposure modelling.

A case-control design would not readily accommodate the time-varying nature of drug exposure without nested case-control sampling within the cohort, which offers no efficiency advantage when the full cohort is accessible in electronic records. A self-controlled case series (SCCS) design, which eliminates time-invariant confounding by using each patient as their own control, was considered but was not appropriate because it requires the assumption that the occurrence of the outcome event does not affect subsequent exposure — an assumption that is violated when hospitalisation for arrhythmia or bleeding leads to medication changes [124]. A case-crossover design was similarly unsuitable because it is optimised for acute, transient exposures rather than the chronic, sustained medication use patterns examined here [125]. A new-user (incident user) restriction design was considered; however, because many patients in this elderly population were already established on their index medications at the start of the study period, restricting to new users would have substantially reduced sample size and potentially introduced selection bias by excluding patients with longer treatment histories who may differ systematically from initiators. The implications of including prevalent users are discussed in the limitations section below (Section 2.13).

Patients aged 51 years and older were followed for two years from their index prescription. The age threshold of 51 years was selected to focus the analysis on middle-aged and older adults, who represent the population at highest risk of polypharmacy, drug-drug interactions, and the cardiovascular and gastrointestinal outcomes under study. This threshold reflects the clinical epidemiology of the index conditions: atrial fibrillation prevalence increases markedly after age 50 [126], and the co-prescription of PPIs with cardiovascular medications is concentrated in older populations with multiple comorbidities. Younger patients were excluded because the pathophysiology, prescribing patterns, and risk profiles for these conditions differ substantially in younger age groups, and their inclusion would have introduced clinical heterogeneity without meaningful gains in statistical power.

All studies utilised a consistent analytical framework. Drug exposure was modelled as a time-dependent covariate using Cox proportional hazards regression, following the methodological framework established by Stricker and Stijnen (2010) [122]. Patients were censored at the conclusion of follow-up, death, transfer out of the health board area, or loss to follow-up.

Table 2.1 Overview of Three Drug-Drug Interaction Studies

Summary of the three retrospective cohort studies examining proton PPI interactions with cardiovascular medications. All studies used linked electronic health records from NHS Greater Glasgow and Clyde, included patients aged ≥51 years, and employed a two-year follow-up period with time-varying exposure classification. AF, atrial fibrillation; PE, pulmonary embolism; VTE, venous thromboembolism; TIA, transient ischaemic attack; OAC, oral anticoagulant; PPI, proton pump inhibitor.

Study	Study Population	Index Drug(s)	Co-drug	Primary Outcome(s)
1	Patients with atrial fibrillation (AF)	Digoxin	PPIs	Hospitalization due to arrhythmia
2	Patients with AF, PE, VTE, TIA, and/or ischemic stroke	Oral anticoagulants (warfarin, dabigatran, factor Xa inhibitors)	PPIs	Bleeding events; Treatment failure
3	Patients prescribed clopidogrel following TIA and/or ischemic stroke	Clopidogrel	PPIs	Bleeding events

2.2.1 Reporting standards

This thesis follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cohort studies [127]. The STROBE statement comprises a checklist of 22 items considered essential for transparent reporting of observational research. These items address key aspects of study reporting including: clear specification of study design and setting; definition of participants, exposures, and outcomes; description of potential sources of bias and how they were addressed; explanation of statistical methods used to control for confounding; presentation of key results with effect estimates and precision measures; and discussion of limitations, generalisability, and interpretation of findings [127].

The intention of STROBE is to provide guidance on how to report observational research transparently, rather than to prescribe how studies should be designed or conducted. Adherence to these reporting standards facilitates critical appraisal by readers and supports the inclusion of study findings in systematic reviews [127].

2.2.2 Follow-up and censoring

Individuals entered the analytical cohort at the date of eligibility for inclusion, defined by the presence of a recorded diagnosis of the index condition. Follow-up commenced at cohort entry and continued for a maximum of two years, ending at the earliest occurrence of the study-specific outcome, death from any cause, transfer out of the health board area, loss to follow-up, or administrative censoring at the end of the study period, with follow-up time partitioned into discrete intervals to reflect changes in drug exposure and covariate status over time. A two-year follow-up period was selected to balance competing considerations: it is sufficiently long to capture a meaningful number of outcome events for the relatively low-incidence endpoints under study (arrhythmia-related hospitalisation, bleeding, and treatment failure), while being short enough to minimise the accumulation of time-varying confounding and secular changes in prescribing practice that become increasingly difficult to control over longer observation windows. Additionally, a two-year window reduces the proportion of

follow-up time during which patients may have discontinued or substantially changed their medication regimens, thereby maintaining the clinical relevance of the exposure classification. This duration is broadly consistent with the observation periods used in prior studies of PPI-cardiovascular drug interactions, which have ranged from one to approximately two years [128, 129].

In the primary analysis, death was treated as a censoring event, with individuals contributing person-time until death or the end of follow-up, whichever occurred first. Censored observations—those in which the outcome of interest had not occurred by the end of follow-up—were handled using standard survival analysis methods [130]. Right censoring, the most common form encountered in these studies, occurred when participants remained event-free at the administrative end of follow-up or when observation terminated for reasons other than the outcome of interest. This approach yields cause-specific hazard ratios, which estimate the instantaneous rate of the outcome of interest among individuals who have not yet experienced the outcome or died — that is, the hazard in those still "at risk" at each time point [131]. Survival analysis methods, including the Kaplan-Meier estimator and Cox proportional hazards models, are specifically designed to incorporate censored observations, providing unbiased estimates as long as censoring is non-informative [130]. However, in an elderly population with substantial comorbidity, death represents a competing risk that may preclude the occurrence of the study outcome. If drug exposure affects mortality differently across exposure groups, informative censoring at death could bias cause-specific hazard ratio estimates. The direction of this potential bias depends on the relationship between exposure and mortality and cannot be determined a priori. To assess the sensitivity of results to this assumption, competing risks analyses using Fine and Gray subdistribution hazard models were conducted [132]. The cause-specific hazard ratio remains the primary estimand because it has a direct causal interpretation (the effect of exposure on outcome rate among survivors), whereas the subdistribution hazard conflates the effect of exposure on the outcome with its effect on the competing event. Both estimands are reported to provide a complete picture.

Study-specific details regarding eligibility criteria, follow-up periods, and censoring events are provided in the respective results chapters (Chapters 3–5).

2.3 Data Sources

2.3.1 NHS Scotland Safe Havens

NHS Scotland enables the use of comprehensive, linked electronic patient records (EPR) for research through a network of Data Safe Havens, which offer secure access to patient data under established information governance and ethical approval frameworks. A Safe Haven is a secure research facility managed by qualified staff adhering to established information governance standards, where patient-level electronic records can be linked to other datasets and accessed in de-identified form to protect privacy while enabling population-level investigations [133].

This collaborative model includes the National Safe Haven, supplemented by four regional Safe Havens that operate in compliance with relevant laws and professional standards, and are responsible for data relating to individuals within their geographic authority [134]. This study used data from the West of Scotland Safe Haven, administered by NHS Greater Glasgow and Clyde in partnership with the University of Glasgow, which was established from the former Glasgow Safe Haven. The West of Scotland Safe Haven provides de-identified electronic patient records and related administrative health data for the NHSGG&C community, enabling secure linkage across treatment settings and timeframes to assist epidemiological and health services research [133, 134].

This study involves human participants, but consent for participation was not obtained because this study involved only de-identified, routinely collected NHS data accessed under delegated ethics approval through the West of Scotland Safe Haven. Delegated research ethics approval was granted for linkage to NHS patient data by the Local Privacy and Advisory Committee at NHS GG&C. Cohorts and de-identified linked data were prepared by the West of Scotland Safe Haven Research Database at NHS GG&C. A data access agreement was executed between the

University of Glasgow and NHS Greater Glasgow and Clyde specifying the permitted data use, retention period, and destruction requirements. Analyses were conducted using routinely collected patient data for which individual consent was not required, within a Trusted Research Environment, in line with REC-approved protocols and UK General Data Protection Regulation (GDPR) and no patient-level data were removed from the facility.

2.3.2 Prescribing and dispensing data

Drug exposure episodes were defined using dispensing records from the Prescribing Information System (PIS), available through the Safe Haven. PIS captures prescriptions dispensed at community pharmacies and provides the most accurate available representation of outpatient prescription-only medication use [135].

These data sources closely reflect actual exposure for prescription-only medications, as they represent medications that were dispensed rather than merely prescribed. Prescription records for each participant were transformed into analysable variables representing daily usage, cumulative dosage, and anticipated refill dates, facilitating the assessment of adherence patterns over time.

2.3.3 Clinical outcomes

Clinical outcomes and comorbidities were identified using the International Classification of Diseases, Tenth Revision (ICD-10) coding system. ICD-10 is a comprehensive classification system developed and maintained by the World Health Organization (WHO) for coding diagnoses, medical conditions (morbidity), and causes of death (mortality) [136]. The system translates descriptive clinical diagnoses into standardised alphanumeric codes, enabling systematic recording, analysis, and comparison of health data across different healthcare settings, countries, and time periods [137].

ICD-10 represents a critical tool in epidemiological research, as it provides a common language for documenting and monitoring diseases and health conditions worldwide. The standardised coding structure facilitates large-scale data linkage,

quality assessment, and international health comparisons [136, 137] . In this study, ICD-10 codes were extracted from hospital admission records, outpatient visits, and death certificates within the Safe Haven to identify:

- Index conditions defining study eligibility (e.g., atrial fibrillation, ischaemic stroke, transient ischaemic attack, pulmonary embolism, venous thromboembolism)
- Primary study outcomes (e.g., hospitalisation due to arrhythmia, bleeding events, treatment failure)
- Comorbidities used for risk adjustment and propensity score calculation

Specific ICD-10 codes used for outcome and comorbidity definitions are presented in Table 2.2.

Outcome identification was restricted to hospitalised events to maximise the specificity of ICD-10 coding for clinically significant endpoints. The implications of this restriction, including the potential for outcome misclassification and underestimation of event burden, are discussed in Section 2.13.6.

Table 2.2 ICD-10 Codes for Index Conditions and Primary Outcomes

Condition	ICD-10 Codes	Description / Notes
Atrial Fibrillation (AF)	I48	Primary AF diagnostic code
Arrhythmia / Tachycardia	I47, R00	Includes supraventricular or unspecified tachycardia
Transient Ischaemic Attack (TIA)	G459	Transient ischemic attack (unspecified)
Ischemic Stroke	I63	Cerebral infarction
Pulmonary Embolism (PE)	I26, I269	Pulmonary embolism and infarction
Venous Thromboembolism (VTE)	I26, I260, I269, I82, I824, I8240, I82401, I82402, I82403, I8290	Venous thrombosis and embolism (deep vein + pulmonary)
Bleeding (general + GI + systemic)	I60, I61, I62, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K920, K921, K922, R040, R041, R042, R048, R049, R58	Includes intracranial, GI, respiratory, and systemic hemorrhage

International Classification of Diseases, Tenth Revision (ICD-10) codes used to identify index conditions for study eligibility and primary study outcomes across the three cohort studies. Codes were extracted from hospital admission records, outpatient visits, and death certificates within the Safe Haven. AF, atrial fibrillation; GI, gastrointestinal; ICD-10, International Classification of Diseases, Tenth Revision; PE, pulmonary embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

2.3.4 Mortality Data

Mortality data. Date and cause of death were obtained from the National Records of Scotland (NRS) death registration dataset, linked at the individual patient level within the Safe Haven. Cause of death is coded to ICD-10 by NRS coders based on the medical certificate of cause of death. Death was used in two ways: (i) as a censoring event for the primary analysis, with follow-up terminating at the date of death, and (ii) as a source of outcome ascertainment, with a death counted as an outcome event when the certified cause of death matched the outcome ICD-10 codes used in the corresponding hospital admission outcome definition.

2.3.5 Limitations of available data

Although pharmacy and hospital dispensing records offer comprehensive data on prescriptions, these sources do not capture OTC medications [122]. This limitation has particular relevance for the present studies because low-dose omeprazole (10 mg) and pantoprazole (20 mg) are available without prescription in the United Kingdom, meaning that some patients classified as PPI-unexposed may have been using OTC PPIs. This non-differential exposure misclassification would bias PPI-associated hazard ratios toward the null, making any observed associations conservative estimates of the true effect. The magnitude of this bias is likely to be modest in this elderly population, as the majority of PPI prescribing in elderly patients with cardiovascular comorbidities occurs through general practice rather than OTC purchase [138], and is therefore captured in the Prescribing Information System. Furthermore, the data indicate prescriptions dispensed but cannot verify that patients consumed the medications as prescribed. For chronic drugs requiring regular refills, dispensing data are the accepted standard for exposure assessment in pharmacoepidemiological research [122].

Ethnicity was not included among the covariates in these analyses. Although an ethnicity field is held within the West of Scotland Safe Haven, it was recorded as missing or 'not known' for more than half of the individuals across the three cohorts, an incompleteness consistent with the recognised historical under-recording of ethnicity in Scottish routinely collected health data.[139] This degree of missingness precluded both reliable descriptive reporting of the cohorts' ethnic composition and any valid use of ethnicity for stratification or confounder adjustment: complete-case analysis would have discarded the majority of the sample, and imputation would have rested on untestable assumptions about data that were unlikely to be missing at random. Ethnicity is nonetheless of direct relevance to the pharmacological questions addressed in this thesis, because the frequency of reduced-function CYP2C19 alleles, which govern the metabolism of both clopidogrel and several PPIs, varies substantially by genetic ancestry [140]. The incompleteness of ethnicity recording, and the consequent inability to use it even as a coarse population-level proxy for this variation, is therefore an

acknowledged limitation, addressed in Section 5.4.7.2 and in Chapter 6 (Sections 6.8.1 and 6.9.6).

2.4 Exposure Definition and Classification

2.4.1 Time-varying drug exposure

Drug exposure was modelled as a time-dependent covariate to accurately capture the dynamic nature of medication use throughout the follow-up period. Individual medication histories present significant analytical challenges: patients may use a variety of medications at different dosages, switch between treatments, or discontinue therapy during follow-up. Creating an analysable dataset from the thousands of marketed medication items available in Western countries represents a substantial administrative and pharmacological challenge [122].

Prescription records were used to create ongoing exposure timelines for each participant to handle these complications. For each dispensing event, the duration of the exposure window was calculated as the total quantity dispensed divided by the prescribed daily dose, yielding the anticipated number of days of supply. For example, a prescription of 56 omeprazole 20 mg capsules with a prescribed dose of one capsule daily would generate a 56-day exposure window commencing on the dispensing date. Where the prescribed daily dose was not explicitly recorded, the defined daily dose (DDD) as specified by the World Health Organization Anatomical Therapeutic Chemical (ATC) classification was used as the default assumption [122]. Overlapping prescriptions of the same medication were handled by extending the exposure window from the end of the current supply rather than allowing overlap, on the assumption that the patient would complete one supply before commencing the next. Exposure status was updated dynamically throughout follow-up based on the timing of prescription episodes, rather than being fixed at cohort entry. A 7-day carry-over period was applied following the anticipated end date of each prescription supply to account for residual pharmacological effects and typical prescription refill behaviour. This duration was selected on pharmacokinetic and pragmatic grounds. For PPIs, which have elimination half-lives of 1–2 hours but exert pharmacodynamic effects on gastric

acid secretion lasting 2–3 days after discontinuation due to irreversible PPI [141], a 7-day window conservatively captures any residual drug effect. For digoxin, which has a half-life of 36–48 hours, five half-lives (the conventional threshold for near-complete elimination) would require approximately 7.5–10 days [142]. For oral anticoagulants, elimination half-lives range from approximately 5–15 hours for factor Xa inhibitors to approximately 40 hours for warfarin, for which a 7-day window approaches five half-lives. The 7-day period also accommodates minor delays in prescription refills, which are common in routine care.

2.4.2 Four-category exposure classification

For each study, drug exposure was classified into four mutually exclusive, time-varying categories to assess both individual drug effects and potential interactions:

- No exposure (reference group): Neither the index drug (digoxin, OAC, or clopidogrel) nor PPI
- Index drug only: Exposed to index drug without concurrent PPI
- PPI only: Exposed to PPI without concurrent index drug
- Concurrent exposure: Exposed to both index drug and PPI simultaneously

The unexposed group (neither index drug nor PPI) was selected as the statistical reference category to provide a common baseline against which all three active exposure states could be compared, facilitating estimation of individual drug effects as well as their combination. The four-category model with ‘no exposure’ as reference allowed assessment of the association of each medication relative to no exposure and the association of combined exposure when both medications were used concurrently. The four-category classification was retained for descriptive transparency and to display the full exposure structure.

However, because the clinically meaningful question in each study is whether adding a PPI to established index-drug therapy alters outcome risk, the clinically relevant contrast is concurrent (index drug plus PPI) exposure versus index-drug monotherapy. The primary models retained the ‘no exposure’ group as the

statistical reference category; index-drug monotherapy was not used as the reference category in a re-fitted interaction model.

Where a contrast between two non-reference exposure states is of interest, valid statistical inference requires estimation of a linear combination of model coefficients using the full variance-covariance matrix of the fitted Cox model. Although the point estimate for the concurrent-exposure versus index-drug-monotherapy contrast can be obtained from the difference between the corresponding model coefficients (log hazard ratios), a valid standard error and 95% confidence interval cannot be obtained by combining the individually reported hazard ratios and their confidence interval because this ignores the covariance between the coefficient estimates [143]. A contrast and its 95% confidence interval could be obtained either by re-fitting the model with the relevant monotherapy group as the reference category or, equivalently, by estimating the linear combination of coefficients using the model's estimated variance-covariance matrix [143].

In the present analyses, the models were not re-fitted with index-drug monotherapy as the reference category, and valid confidence intervals for these contrasts could not be estimated within the resources available for this analysis. Accordingly, derived point estimates for the clinically relevant concurrent-exposure versus index-drug-monotherapy contrasts, where reported, are presented descriptively without confidence intervals or formal statistical inference. Statistical inference is therefore confined to the primary model comparisons with the "neither drug" reference group.

Patients could move between exposure categories throughout follow-up based on prescription fills and discontinuations, with person-time allocated to each category according to the individual's current exposure status.

PPIs were modelled as a drug class rather than as individual agents to reflect real-world prescribing patterns and to preserve statistical power. This approach estimates the average effect of PPI exposure rather than agent-specific risks,

which is clinically relevant given that prescribers often select among PPIs based on formulary availability rather than pharmacological distinctions. Individual PPI agents included in this classification were omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. This classification strategy biases results toward the null if agent-specific effects vary substantially, making any observed associations conservative estimates of effect [144].

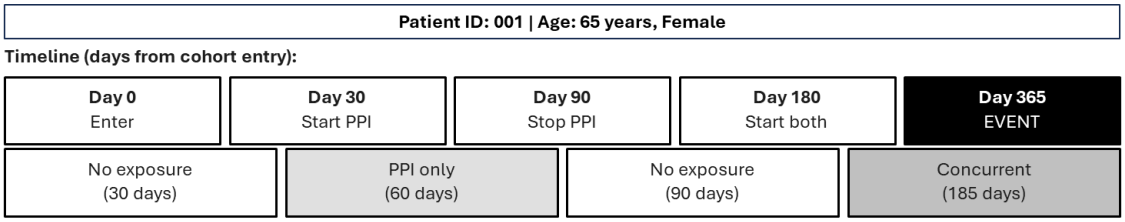
2.4.3 Start-stop structure

To implement time-dependent exposure in survival analysis, the patient-level data were restructured into a start-stop (interval) format. Each observation represented a discrete time interval during which the drug exposure status remained stable. For each patient, the follow-up period was segmented into multiple intervals based on:

- Dates of drug initiation
- Dates of drug discontinuation
- Dates of the study endpoint (event occurrence or censoring)

The indicator variable was assigned a value of 1 for the final interval if the event occurred during that interval, and 0 otherwise. This data format allowed the Cox model to revise exposure status at each time point when a patient's medication regimen altered, offering an accurate temporal representation of drug usage trends.

Figure 2.1 illustrates this start-stop data structure using a hypothetical patient timeline.



Corresponding Start-Stop Data Structure:

Patient ID	Age	Sex	Start (days)	Stop (days)	Exposure Category	Exposure Description	Event
001	65	F	0	30	0	No exposure	0
001	65	F	30	90	2	PPI only	0
001	65	F	90	180	0	No exposure	0
001	65	F	180	365	3	Concurrent exposure	1

Figure 2.1 Illustration of Start-Stop Data Structure

Example of the start-stop (interval) data structure used to implement time-varying drug exposure in Cox proportional hazards regression. The upper panel shows a hypothetical patient timeline with exposure changes over 365 days from cohort entry. The lower panel demonstrates the corresponding data structure, where each row represents a discrete time interval with stable exposure status. Exposure categories: 0 = no exposure (reference); 1 = index drug only; 2 = PPI only; 3 = concurrent exposure (both). The event indicator equals 1 for the final interval if the outcome occurred, and 0 otherwise. This structure allows the Cox model to update exposure status dynamically throughout follow-up.

2.5 Statistical Analysis

The statistical analysis was designed to evaluate whether concurrent exposure to index medications and PPIs is associated with altered risk of study-specific clinical outcomes, while explicitly accounting for the dynamic nature of prescribing and the substantial potential for confounding by indication. The analytical strategy was grounded in contemporary causal inference principles for longitudinal observational data and combined time-varying exposure modelling, IPTW, and survival analysis to approximate clinically relevant causal contrasts under clearly stated assumptions [130], within a marginal structural Cox proportional hazards modelling framework.

All analyses were conducted using routinely collected individual-level healthcare data from NHS Greater Glasgow and Clyde. Effect estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and statistical significance was assessed using two-sided tests with an α level of 0.05. Figure 2.2 provides a schematic overview of the analytical framework applied across all three studies.

The following sections describe the survival analysis framework underpinning these methods, beginning with fundamental concepts before detailing their specific application to the present research questions.

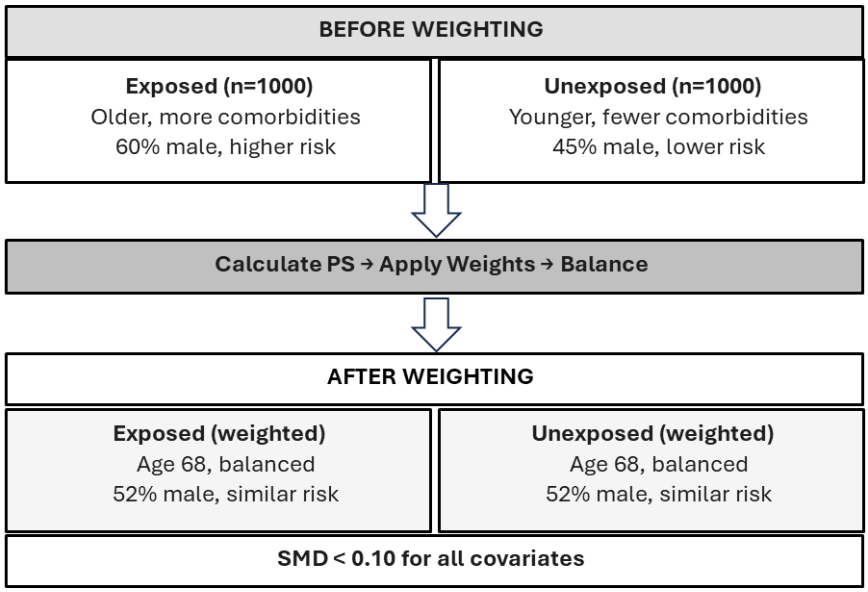


Figure 2.2 Overall Analytical Framework
Schematic representation of the analytical framework applied across the three retrospective cohort studies. Time-varying drug exposure was modelled using a start-stop data structure with a 7-day carry-over period. Time-dependent Cox proportional hazards regression with inverse probability of treatment weighting (IPTW) was used to estimate study-specific hazard ratios, and Simon-Makuch curves were used to visualise survival across dynamic exposure groups. AF, atrial fibrillation; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant; PPI, proton pump inhibitor.

2.5.1 Survival analysis

Survival analysis is a statistical technique widely utilised in evidence-based medicine to evaluate time-to-event data, where the "event" includes outcomes such as death, hospitalisation, recurrence, or recovery, not limited to mortality. Unlike traditional statistical approaches that assess outcomes only at the conclusion of a study, survival analysis takes into account the timing of events, making it particularly suitable when the duration until an outcome is clinically relevant. By integrating time as a variable, survival analysis enhances the understanding of outcome dynamics during follow-up periods, regardless of their duration [145].

These procedures provide comparisons between individuals or groups, such as treatment A vs treatment B, using techniques like Kaplan-Meier-based estimations and log-rank tests, which are nonparametric and optimal for estimating and comparing survival functions across groups. Cox proportional hazards models are commonly employed to evaluate the impact of covariates on the hazard or risk of an event. Originally designed for medical research, survival analysis has now been applied across other fields, including engineering and finance. Fundamental principles include the survival function (the likelihood of not experiencing the event within a designated interval) and the hazard rate (the immediate frequency at which the event happens over time). The appropriate handling of censoring and trimming is essential for minimising bias, particularly by avoiding the selection of persons based on known or anticipated event outcomes [146].

2.5.2 Censored data in survival analysis

Censored data is a crucial element of survival analysis, including observations in which the event of interest has not yet happened, or its exact date is indeterminate. In contrast to other statistical methods that may discard missing values, survival analysis considers censored data as essential information that enhances the study [145, 146].

Right censoring is the most common type, occurring when a patient is still event-free at the conclusion of the study period (end-of-study censoring) or when observation ends for reasons other than the event of interest, such as loss to follow-up, death from competing causes, or transfer out of the study area. Right-censored data can affect the estimated overall survival time but, when handled properly, does not introduce bias. Left censoring occurs when the exact time of initial exposure or event onset is unclear, for example, if a condition is confirmed before surgery but the time it started cannot be determined [145].

Survival analysis methods such as the Kaplan-Meier estimator and the Cox proportional hazards model are specifically designed to work with time-to-event data and can provide reliable risk estimates even when follow-up data is incomplete due to censoring. Well-designed studies anticipate participant dropout

and end-of-study censoring, recognising that censored observations provide important information and should never be ignored [145].

2.5.3 Causal and statistical estimands

The causal estimand motivating the analyses in this thesis is the contrast in the instantaneous risk of study-specific outcomes that would be observed if, at a given time point, an individual were concurrently exposed to an index drug and a PPI, compared with the risk that same individual would experience under an alternative exposure state (e.g., index drug alone, PPI alone, or neither drug), conditional on their observed clinical history [130].

Because this causal estimand cannot be directly identified from observational data, the analyses target a statistical estimand defined as the cause-specific hazard ratio comparing time-varying exposure states in a weighted Cox proportional hazards model. This estimand represents the ratio of hazards between exposure states at time t, conditional on survival to that time and on measured covariates, within a pseudo-population created through IPTW [130, 147, 148].

Under the standard identifying assumptions—consistency, positivity, conditional exchangeability given measured covariates, and correct model specification—these statistical estimates can be interpreted as approximations to the underlying causal contrast [147]. However, as with all observational studies, residual confounding by unmeasured factors remains possible. The findings are therefore interpreted as causally compatible associations rather than definitive causal effects, and study-specific limitations are discussed in each results chapter.

2.5.4 Descriptive statistics

Baseline characteristics were described by exposure group using frequencies and percentages for categorical variables and means with standard deviations (or medians with interquartile ranges where appropriate) for continuous variables. Standardised mean differences (SMDs) were computed to assess covariate

imbalance among exposure groups prior to weighting, with SMD values exceeding 0.10 indicating potentially meaningful imbalance by conventional criteria [149].

These descriptive analyses served to characterise the study populations, identify potential confounders associated with both exposure and outcome, and provide justification for the subsequent application of inverse probability of treatment weighting. Covariate balance was re-assessed after weighting to confirm that the pseudo-population achieved acceptable balance across exposure groups.

2.5.5 Statistical software

All statistical analyses were performed using R (version 4.3.0) [150] (R Core Team, 2024). Data manipulation and visualisation utilised the tidyverse collection of packages [151], including dplyr, tidyr, ggplot2, and lubridate [152]. Large datasets were managed using data.table [153].

Survival analyses employed the survival package [154] for model fitting and survminer [155] for visualisation. Propensity score methods were implemented using MatchIt [156] and twang [157], with inverse probability of treatment weighting derived using methods appropriate for multiple exposure groups. Model diagnostics and output presentation utilised finalfit [158], broom [159], and rstatix [160], with ggpubr [161] used for publication-ready plots. String manipulation was performed using stringr [162], and plot arrangement and axis formatting were handled by gridExtra [163] and scales [164], respectively. Additional modelling capabilities were provided by lme4 [165], msm [166], MASS [167], nnet [168], and pscl [169].

2.6 The Cox Proportional Hazards (CPH) Regression Model

The Cox proportional hazards (CPH) model is a widely used semiparametric technique in survival analysis that assesses the influence of explanatory variables on the probability of an event occurring over time [145, 170]. Unlike the Kaplan-Meier technique, which estimates survival curves without covariates, the Cox model determines hazard ratios using multiple variables (covariates) to identify

which factors affect event risk. It is particularly beneficial in clinical research because it accommodates censored data, does not require assumptions about the underlying survival time distribution, and facilitates the simultaneous analysis of many risk factors [145, 170].

The model compares risk levels between those who experience the event and those who do not, according to factors that may influence the outcome. Regression coefficients for each variable provide the hazard ratio (HR). A statistically significant hazard ratio greater than 1 signifies that the variable is associated with a higher likelihood of the event occurring, while an HR less than 1 indicates a protective effect [145].

2.6.1 The proportional hazards assumption

A basic principle of the Cox model is the proportional hazards (PH) assumption, which states that the hazard ratio, the relative risk of an event between groups, remains constant over the follow-up period. The influence of a covariate on the hazard is believed to be consistent over time. This assumption must be confirmed to validate the model's outcomes [145, 170].

Methods for testing the PH assumption include:

- Log-minus-log (LML) plot: A visual tool where parallel survival curves among groups indicate that the proportional hazards assumption holds.
- Schoenfeld residual test: A statistical method that evaluates the relationship between residuals and event time. Schoenfeld residuals are determined by the difference between the actual covariate values of patients who encountered an event and the values predicted by the Cox model. According to the proportional hazards assumption, these residuals should be randomly distributed and uncorrelated with time. However, if the residuals exhibit a time-dependent trend, apparent visually in a residual plot or statistically through a statistical test, this signifies an error of the assumption [170].

The Schoenfeld test provides a more objective assessment than visual approaches; nonetheless, its sensitivity to sample size and limitations in hypothesis testing indicate that it is most effective when used in conjunction with graphical evaluations [170].

When the proportional hazards assumption is violated, such as when a drug's effect changes over time, the outcomes derived from the traditional Cox model may be misleading. In such cases, researchers may use time-dependent Cox regression models or stratified Cox models to obtain more accurate hazard estimates. Verifying this assumption is therefore an essential step prior to interpreting Cox model outcomes, particularly in clinical and pharmaco-epidemiological research [145, 170].

2.7 Time-Dependent Cox Proportional Hazards Model

The time-dependent Cox proportional hazards model is a strong modification to standard survival analysis, intended to integrate factors that change over the research period. These time-dependent factors represent actual clinical and behavioural modifications, including the beginning or end of treatment, as well as physiological measurements (e.g., blood pressure) that alter over time. In contrast to fixed covariates that remain unchanged during follow-up, time-dependent variables allow the model to revise the projected hazard as new information becomes available, which enhances the accuracy of risk assessment [171]. This methodology is especially important in longitudinal research when patients' exposure status and clinical conditions change over time. The ability to predict these changes enables researchers to avoid the assumption that risk factors exert a uniform impact across time, an assumption frequently inconsistent with clinical reality [171].

2.7.1 Implementation with non-fixed time intervals

A fundamental feature of time-dependent Cox models is their functionality with non-fixed time intervals: the data is segmented into intervals of differing lengths based on the timing of covariate modifications. When a patient begins or ends a

medicine during follow-up, the model modifies their exposure status accordingly, and a new interval begins. The duration of these time segments varies for each individual and is dictated by real changes in exposure or health status, rather than fixed calendar intervals [172].

This flexibility allows the model to accurately reflect short-term effects of exposures and variations in variables, thereby improving both the validity and statistical power of the analysis. Nonetheless, it also presents issues in application and interpretation. For example, when covariates change due to illness severity or clinical worsening, it can be challenging to decide whether alterations in survival are due to the covariate's effect or the worsening of the underlying health condition [171].

2.7.2 Handling violations of the proportional hazard assumption

Time-dependent Cox regression is particularly beneficial when the proportional hazards assumption is violated, specifically, when the effect of a covariate on the hazard rate varies over time. In such cases, researchers may model time-dependent coefficients by:

- Interacting covariates with time functions (e.g., log(time)) to allow the effect to vary smoothly over follow-up
- Using step functions that assign distinct coefficients to different time intervals
- Employing stratified Cox models to address non-proportionality by permitting different baseline hazards across covariate categories while maintaining the effects of other covariates constant

Stratification is particularly useful for managing confounders—situations where the relationship between an exposure and an outcome is confounded by another variable—that violate the proportional hazards assumption. However, stratification requires categorisation of continuous variables and adequate sample size within each stratum [170].

Time-dependent Cox models, especially those with variable time intervals, provide a sophisticated and adaptable method for modelling dynamic relationships in survival data, provided researchers remain cognizant of the complexity in interpretation and the assumptions essential to the model [170-172].

2.8 Application to Current Study

Retrospective cohort studies were performed to assess the relationship between time-varying exposure to index drugs (digoxin, oral anticoagulants, or clopidogrel), PPIs, and their combination, and the risk of study-specific clinical outcomes. Recognising that patients might start or stop either treatment during follow-up, drug exposure was treated as a time-dependent covariate in a Cox proportional hazards model structured in a start-stop format as described above.

Model specification included:

Outcome: Study-specific clinical events (hospitalisation due to arrhythmia, bleeding events, or treatment failure)

Exposure categories: Four mutually exclusive time-varying groups (no exposure, index drug only, PPI only, concurrent exposure)

Reference group: Patients with no exposure to either medication

Adjustment covariates: Baseline characteristics including age, sex, comorbidities, and other clinically relevant variables (specified in each results chapter)

Hazard ratios (HRs) and 95% confidence intervals were calculated for each exposure category relative to the reference group. Standard errors were calculated using robust (sandwich) variance estimators to account for within-subject correlation resulting from repeated observations across intervals.

The proportional hazards assumption was evaluated using Schoenfeld residuals for each covariate. Where violations were detected, appropriate modifications were implemented (e.g., stratification or time-interaction terms).

2.8.1 Covariate selection and confounding framework

Covariates for inclusion in the propensity score models were selected based on a combination of clinical knowledge and the established epidemiological principle that variables associated with the outcome should be included in propensity score models regardless of their association with treatment assignment, as their inclusion improves precision without introducing bias [173]. Conversely, variables associated with treatment assignment but not the outcome (instrumental variables) were excluded, as their inclusion can amplify bias from unmeasured confounding and reduce precision [174].

The following categories of covariates were included across all three studies, with study-specific variations detailed in Chapters 3–5:

Demographic variables: Age (continuous), sex, and socioeconomic position measured by the Scottish Index of Multiple Deprivation (SIMD) 2016 decile, which reflects area-based deprivation encompassing income, employment, health, education, housing, geographic access, and crime domains.

Comorbidities: Conditions identified from ICD-10 diagnostic codes recorded prior to or at cohort entry, including cardiovascular disease (ischaemic heart disease, heart failure, hypertension, peripheral vascular disease), cerebrovascular disease, diabetes mellitus, chronic kidney disease, respiratory disease (chronic obstructive pulmonary disease, asthma), gastrointestinal disease (peptic ulcer disease, gastro-oesophageal reflux disease, gastrointestinal haemorrhage), liver disease, mental health conditions, neurological disease, and musculoskeletal disease. These comorbidities were selected because they are known to influence both prescribing decisions (particularly PPI use) and the risk of the study outcomes.

Concomitant medications: Baseline prescriptions for medications known to interact with or modify the risk associated with the index drugs, including antiplatelet agents, antihypertensives, statins, non-steroidal anti-inflammatory drugs, corticosteroids, and selective serotonin reuptake inhibitors.

Healthcare utilisation: Duration of index hospitalisation (where applicable), as a proxy for illness severity.

Several potentially important confounders were unavailable in the administrative dataset: body mass index, smoking status, alcohol consumption, dietary vitamin K intake (relevant to the warfarin cohort), OTC medication use, and serum drug levels. The absence of these variables represents a source of residual unmeasured confounding.

A formal directed acyclic graph (DAG) was not used to guide covariate selection, as the complexity of the multi-drug, multi-outcome framework would have required multiple DAGs and the clinical literature does not provide unambiguous evidence for all causal pathways. Instead, covariate selection was guided by the disjunctive cause criterion [175], which recommends including all measured pre-treatment covariates that are causes of the exposure, the outcome, or both, and excluding instrumental variables. This approach has been shown to provide consistent and efficient estimates under a wider range of conditions than DAG-based minimal adjustment sets.

2.8.2 Data and code availability

The individual patient-level data used in this thesis cannot be shared publicly due to information governance restrictions governing NHS Scotland Safe Haven data. Data access may be requested through the West of Scotland Safe Haven and is subject to ethical approval and a formal data access agreement. All statistical analyses were conducted using R (version 4.3.0), and the complete analytical code, including data processing, exposure classification, propensity score estimation, IPTW implementation, Cox model fitting, and Simon-Makuch curve generation, is available from the author upon reasonable request.

2.9 Propensity Score Methods and Inverse Probability of Treatment Weighting

Observational studies are increasingly used to assess the effects of treatments, exposures, and interventions. However, a consequence of the absence of random allocation is that treated participants frequently have systematic baseline differences from control subjects. This imbalance in baseline characteristics leads to confounding, making direct comparison of outcomes between groups problematic. To address this, statistical methods such as propensity score (PS) approaches are employed to control for the confounding effects of measured variables [132, 176].

The propensity score represents the likelihood that an individual would undergo therapy based on their observable baseline characteristics, usually determined by logistic regression. Propensity score techniques may reduce the restrictions associated with traditional multivariable regression modelling by combining all measurable factors into a singular probability score. This simplification allows researchers to mimic randomised experimental conditions in observational data and to generate less biased estimates of treatment effects when confounding is sufficiently addressed [176, 177].

2.10 Inverse Probability of Treatment Weighting (IPTW)

Inverse Probability of Treatment Weighting (IPTW) is a propensity score-based technique used in observational research to enhance comparability between treated and untreated groups, approximating what would be expected in randomised controlled trials. Because treatment decisions in real-world data are not randomised, considerable differences often exist between individuals who receive treatment and those who do not, potentially leading to biased outcomes [176].

In IPTW, researchers first generate a propensity score representing the probability that an individual receives the treatment based on observed baseline factors such as age, sex, and comorbidities [132].

Each individual is then assigned a weight:
Treated individuals: weighted by the inverse of their propensity score (1/PS)
Untreated individuals: weighted by the inverse of one minus their propensity score (1/(1-PS))

Applying these weights generates a pseudo-population—a synthetic representation of the sample in which baseline attributes are equilibrated across treatment groups, thus simulating the effects of randomisation [132, 176]. This re-weighting allows researchers to estimate treatment benefits with diminished bias, contingent upon the precise measurement and inclusion of all key confounders in the propensity score model [132].

In the resulting pseudo-population, treated and untreated individuals are balanced with respect to their measured baseline characteristics, such that observed differences in outcomes can be more confidently attributed to the treatment rather than to confounding [176]. Among the various propensity score approaches available, IPTW was selected for the present study due to its ability to preserve the full study sample while creating a pseudo-population suitable for estimating marginal treatment effects.

2.10.1 Application to current study

To mitigate confounding by indication and systematic baseline differences between exposure states, IPTW was applied to create a pseudo-population in which measured baseline covariates were balanced across time-varying exposure groups [144, 178].

Time-varying propensity scores were estimated using multinomial logistic regression models predicting membership in each of the four mutually exclusive exposure categories as a function of measured baseline covariates (described in Section 2.8.1). Multinomial logistic regression was selected because the exposure variable comprises four nominal categories, and this approach provides well-calibrated probability estimates suitable for the construction of inverse probability weights [144]. The `twang` and `WeightIt` R packages were used to

implement the weighting, with generalised boosted models examined as an alternative specification during model development. The multinomial logistic regression approach was preferred in the final analyses because it produced more stable weight distributions and comparable covariate balance to the boosted model specification. Stabilised weights were constructed as the ratio of the marginal probability of the observed exposure to the conditional probability given covariates, improving precision and reducing variance inflation compared with unstabilised weights [178].

Weight distributions were examined for each study, and extreme weights above the 99th percentile were trimmed to reduce the influence of potential positivity violations and improve estimate stability [144]. Covariate balance before and after weighting was assessed using absolute standardised mean differences, with values below 0.10 indicating acceptable balance. Study-specific weight distributions and balance diagnostics are reported in the respective results chapters. Following the application of IPTW, appropriate visualisation methods were required to display survival patterns across the dynamically changing exposure groups.

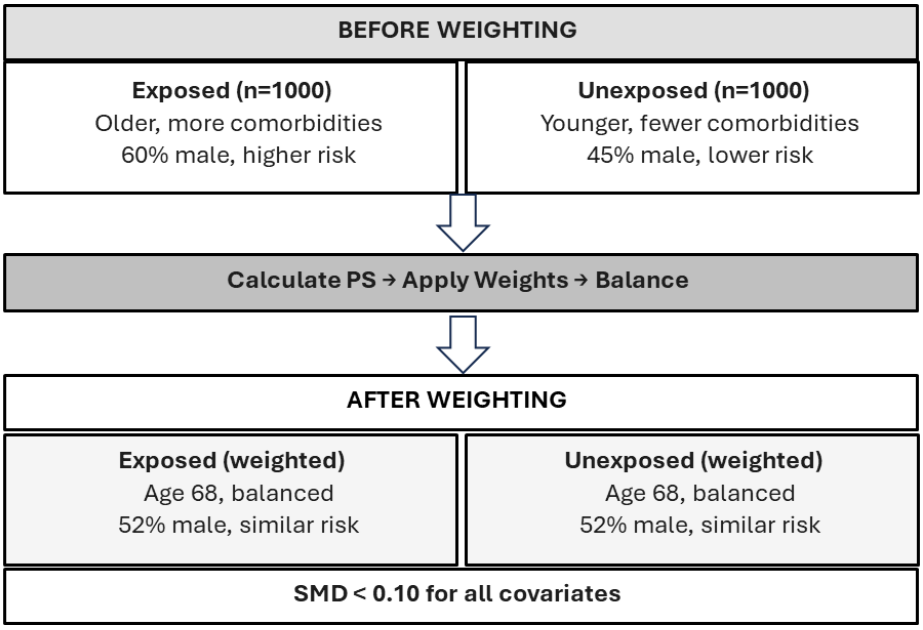


Figure 2.3 Inverse Probability of Treatment Weighting (IPTW) Conceptual Framework

Illustration of inverse probability of treatment weighting methodology. Propensity scores represent the probability of receiving each exposure category given measured baseline covariates. Individuals are weighted by the inverse of their probability of receiving their observed exposure, creating a pseudo-population in which baseline characteristics are balanced across exposure groups. This approach approximates the conditions of a randomised trial, allowing estimation of treatment effects with reduced confounding bias. PS, propensity score; IPTW, inverse probability of treatment weighting.

2.11 Visualisation: Simon and Makuch's Modified Kaplan-Meier Method

Traditional Kaplan-Meier curves assume static group membership from the study's beginning, which is inappropriate when exposure status changes over time. To address this limitation, Simon and Makuch (1984) developed a technique for graphically visualising survival curves with time-dependent covariates [179, 180].

The Simon and Makuch method is an extension of standard Kaplan-Meier survival analysis that accommodates time-dependent covariates—variables that can change throughout the follow-up period. This method allows individuals to switch between exposure groups over time based on their current medication status. For example, a patient who initiates PPI therapy during the study would be classified as part of the "no PPI" group prior to starting the medication and as part of the "PPI-exposed" group thereafter [179-181].

2.11.1 Methodology

The technique uses the same approach as Kaplan-Meier for calculating survival probability; however, its principal innovation lies in the definition of risk sets. For each event time, the method includes individuals who are at risk and currently belong to the relevant exposure group according to their most recent covariate status. This dynamic approach allows group sizes to change over time as patients move between exposure categories [179, 180].

The authors recommend initiating the survival plot at a time point when each group contains an adequate number of individuals for stable estimation, as one group may initially comprise very few members. Events occurring before this designated starting point are excluded from the visualisation but may still be included in the comprehensive Cox regression analysis [179, 180].

2.11.2 Advantages and application

This approach is especially valuable in observational research or clinical settings where exposures, treatments, or conditions change over time. It provides a more accurate representation of survival outcomes than categorising individuals into static groups based solely on baseline status, which can yield misleading results. The Simon and Makuch technique helps researchers understand not only the association between an exposure and a specific outcome but also the importance of the timing of that exposure [179, 181].

In the present study, Simon and Makuch plots were created to visually evaluate survival probability across the four exposure groups over time. Participants allocated risk time to the corresponding treatment group and moved between curves upon the beginning of a new drug or discontinuation of existing therapy. This technique enabled a dynamic representation of survival across time-varying exposure groups and avoided the exposure misclassification that would arise in standard Kaplan-Meier curves from fixing treatment group membership at baseline.

2.12 Missing Data

Complete-case analysis was employed for the primary analyses because missing data were minimal across all studies (less than 2% for key covariates). Individuals with missing values for variables included in the propensity score models were excluded from the weighted analyses.

The validity of complete-case analysis depends on the mechanism generating the missing data. Under the taxonomy of Rubin (1976), data may be missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR) [182]. Complete-case analysis yields unbiased estimates under MCAR and can provide unbiased estimates of regression coefficients under certain MAR conditions, specifically when missingness depends on the outcome variable rather than the covariates [183]. Given that the administrative healthcare data used in these studies achieve high completeness for core demographic and clinical variables — as these are recorded as part of routine clinical care rather than elicited through research instruments — the MCAR assumption was considered plausible. The variables most likely to have missing data in this setting are socioeconomic position (SIMD) and certain comorbidity indicators; missingness in these variables is most likely attributable to administrative recording practices rather than to the patient's exposure or outcome status, which is consistent with MCAR.

Multiple imputation was considered but not implemented because the proportion of missing data was insufficient to meaningfully alter effect estimates, and the computational burden of imputation within an IPTW framework with time-varying exposures was substantial. Sensitivity analyses excluding all individuals with any missing covariate data yielded hazard ratios and confidence intervals that were substantively identical to the primary complete-case results, supporting the robustness of the findings to the missing data handling strategy. Study-specific details regarding the proportion and pattern of missing data are reported in each results chapter.

2.13 Potential Sources of Bias and Mitigation Strategies

Observational pharmacoepidemiological studies are susceptible to multiple sources of bias that may distort the estimation of drug-outcome associations. This section systematically describes the biases relevant to the present studies, their expected direction of effect, and the strategies employed to mitigate them.

2.13.1 Confounding by indication

Confounding by indication is the most important threat to validity in these studies. It arises because the clinical factors that determine whether a patient receives a PPI (e.g., gastrointestinal risk, polypharmacy, frailty) may themselves be associated with the study outcomes [184]. For example, patients prescribed PPIs may be sicker, older, or more multimorbid than those who are not, creating a spurious association between PPI exposure and adverse outcomes. The expected direction of this bias is away from the null, as patients prescribed PPIs tend to have higher baseline risk.

This bias was addressed through IPTW, which created pseudo-populations in which measured baseline covariates were balanced across exposure groups (Section 2.10). Covariate balance was verified using standardised mean differences, with values below 0.10 indicating acceptable balance. However, IPTW can only address confounding by measured variables; residual confounding from unmeasured factors (e.g., frailty, OTC medication use, dietary habits, alcohol consumption, and smoking status) cannot be excluded and represents a fundamental limitation of the observational design.

2.13.2 Immortal time bias

Immortal time bias occurs when a period of follow-up during which the outcome cannot occur (because the exposure has not yet been initiated) is incorrectly attributed to the exposed group, artificially inflating the apparent survival benefit of treatment [185]. In drug interaction research, this bias is particularly relevant because patients may initiate one or both medications at different times during follow-up.

This bias was addressed by modelling drug exposure as a time-dependent covariate using a start-stop data structure (Section 2.4.3). Person-time was allocated to the exposure state actually experienced at each time point, ensuring that periods before drug initiation were correctly classified as unexposed. This approach eliminates immortal time bias by design, as no pre-treatment person-time is misattributed to the treated group [186].

2.13.3 Protopathic bias

Protopathic bias occurs when early symptoms of an undiagnosed outcome lead to initiation of the exposure under study, creating a false appearance that the exposure caused the outcome [187]. In the present studies, protopathic bias could arise if gastrointestinal symptoms heralding a bleeding event prompted PPI prescription shortly before the bleeding diagnosis was recorded, making it appear that PPI use was associated with bleeding. The expected direction is away from the null, inflating the apparent risk associated with PPI exposure.

This bias was partially mitigated by excluding patients with prevalent outcome events prior to cohort entry. However, no lag period was imposed between PPI initiation and the start of risk attribution, which means that PPI prescriptions initiated in response to prodromal symptoms could still be misclassified as causing the outcome. The time-varying exposure classification partially addresses this concern by ensuring that any PPI-outcome association is based on concurrent temporal alignment rather than baseline classification. Nevertheless, protopathic bias cannot be fully excluded and should be considered when interpreting associations between PPI exposure and bleeding outcomes. A sensitivity analysis imposing a 30-day lag period between PPI initiation and risk attribution was not conducted but would strengthen future investigations.

2.13.4 Prevalent user bias

The inclusion of prevalent (existing) users of index medications and PPIs introduces potential bias because prevalent users represent a selected population of individuals who have already tolerated the medication without experiencing the outcome — a form of depletion of susceptibles [188]. Additionally, baseline

covariates measured at cohort entry may be influenced by prior drug use, violating the requirement that confounders temporally precede both exposure and outcome.

In these studies, patients could be prevalent users of their index medication (digoxin, OAC, or clopidogrel) and/or PPIs at cohort entry. Restricting to new (incident) users of both drugs would have substantially reduced sample sizes and potentially introduced selection bias by excluding the majority of the clinically relevant population. The time-varying exposure classification partially mitigates this concern by capturing medication changes during follow-up, but the initial exposure state at cohort entry may still reflect prevalent use. This is acknowledged as a residual limitation, and the direction of bias is towards the null (conservative), as prevalent users who have tolerated the drug interaction are retained in the cohort.

2.13.5 Exposure misclassification

Prescription dispensing data indicate that a medication was supplied but do not confirm ingestion. Non-adherence (failure to take dispensed medications) leads to overestimation of true exposure duration, while over-the-counter PPI use (available without prescription in the United Kingdom) leads to underestimation of PPI exposure in patients classified as unexposed. Both forms of misclassification are likely non-differential with respect to the outcome (i.e., equally likely in those who do and do not experience the event), which biases hazard ratios toward the null [123]. The use of dispensing data rather than prescribing data provides a closer approximation to actual medication use, as it requires the patient to have physically collected the prescription from a pharmacy.

2.13.6 Outcome misclassification

Clinical outcomes were identified using ICD-10 codes from hospital admission records. The positive predictive value of ICD-10 coding for the outcomes under study varies: systematic reviews suggest that ICD-10 codes for atrial fibrillation have a positive predictive value of approximately 70–96%, while codes for gastrointestinal bleeding have positive predictive values of 80–95% depending on

the specific codes and healthcare setting [189]. Any outcome misclassification is likely non-differential with respect to exposure status, as coding practices are unlikely to differ between PPI-exposed and unexposed patients, biasing results toward the null.

Restricting outcome identification to hospitalised events enhances specificity for clinically significant outcomes but reduces sensitivity, as events managed in primary care or emergency departments without admission are not captured. This trade-off was considered acceptable given the study's focus on clinically meaningful drug-drug interaction effects.

2.13.7 Selection bias and informative censoring

Selection bias may arise if the patients included in the analytical cohort are not representative of the broader population of interest. The exclusion of patients with less than one day of follow-up and those with missing demographic data could introduce selection bias if these exclusions are related to both exposure and outcome. However, the proportions excluded were small and are reported in each study's flow diagram.

Informative censoring occurs when the probability of censoring is related to the outcome. In these studies, death (ascertained from the National Records of Scotland death registration dataset; Section 2.3.4) was treated as a censoring event in the primary analysis. If exposure to concurrent medications affects mortality risk, then censoring by death may be informative, potentially biasing hazard ratio estimates. The direction of this bias depends on the relationship between exposure and mortality: if concurrent exposure increases mortality, censoring at death removes high-risk individuals from the risk set, potentially underestimating the true hazard. This concern is addressed through competing risks sensitivity analyses described in Section 2.2.2.

2.13.8 Channelling bias

Channelling bias occurs when prescribers preferentially direct one treatment to patients with specific characteristics, creating systematic differences between

exposure groups [190]. In these studies, PPIs are preferentially prescribed to patients with gastrointestinal comorbidity, higher bleeding risk, or greater polypharmacy burden. Similarly, the choice among anticoagulants may reflect channelling based on renal function, age, or perceived bleeding risk. IPTW was applied to address measured channelling effects, and covariate balance was verified. However, channelling based on unmeasured clinical judgement — such as a clinician's subjective assessment of a patient's frailty — cannot be fully adjusted for.

2.13.9 Healthy user bias

Healthy user bias may operate if patients who adhere to preventive medications (such as PPIs for gastroprotection) are systematically healthier or more health-conscious than those who do not. This would bias the PPI-only group toward better outcomes relative to the unexposed group, potentially masking a true harmful effect of PPI exposure. The direction of this bias depends on the comparison being made and is difficult to predict with certainty. IPTW adjusts for measured differences in health status, but unmeasured health-seeking behaviours remain a potential source of residual confounding.

2.14 Summary

This chapter has described the methodological framework employed across the three retrospective cohort studies examining drug-drug interactions between proton pump inhibitors and cardiovascular medications. The analytical approach centred on time-dependent Cox proportional hazards regression within a marginal structural modelling framework, with drug exposure modelled as a dynamic covariate using a start-stop data structure that allowed patients' exposure status to change throughout the two-year follow-up period. A 7-day carry-over period was applied following each prescription to account for residual drug effects. To address confounding by indication, IPTW was applied using stabilised weights derived from multinomial logistic regression models, creating pseudo-populations in which measured baseline covariates were balanced across the four exposure categories. Covariate selection followed the disjunctive cause criterion, and

covariate balance was verified using standardised mean differences. The proportional hazards assumption was evaluated using Schoenfeld residuals, and Simon-Makuch modified Kaplan-Meier curves were generated to visualise survival patterns across dynamically changing exposure groups. Potential sources of bias — including confounding by indication, immortal time bias, protopathic bias, prevalent user bias, exposure and outcome misclassification, selection bias, channelling bias, and healthy user bias — were systematically identified and their mitigation strategies described. Sensitivity analyses including competing risks models, carry-over period variation, weight truncation assessments, and E-values for unmeasured confounding, together with formal inference on the concurrent-versus-monotherapy derived contrast, were planned but not formally conducted due to time and data-access constraints. This limitation is acknowledged, and these analyses are recommended for future work to strengthen causal inference. Study-specific details regarding patient populations, outcome definitions, and covariate specifications are presented in the respective results chapters (Chapters 3–5).

Chapter 3 PPI Use and Arrhythmia Risk in Digoxin-Treated Atrial Fibrillation Patients

3.1 Introduction

Digitalis glycosides have been used in cardiovascular medicine for more than two centuries. Although their usage has diminished, digoxin continues to be significant for the treatment of heart failure with reduced ejection fraction and atrial fibrillation with rapid ventricular response, especially in hypotensive patients for whom alternative agents are contraindicated [45, 191]. Digoxin is designated as a high-alert medication because of its narrow therapeutic window and likelihood of drug-drug interactions (DDIs), which contribute to almost 50% of adverse events in cardiovascular treatment [192, 193]. Serum digoxin levels change due to physiological factors, disease conditions, and concurrent medications, with toxicity in elderly individuals often resulting from improper dosing, renal impairment, polypharmacy, and electrolyte imbalances such as hypokalaemia and hypomagnesaemia, which decrease the threshold for digoxin-induced arrhythmias [44, 194].

PPIs are frequently recommended to older persons, resulting in significant potential for interactions in polypharmacy contexts [27, 195]. PPIs modify the pharmacokinetics of digoxin by increasing stomach pH, which diminishes acid hydrolysis and improves absorption [42], and by inhibiting intestinal P-glycoprotein (P-gp), an ATP-dependent efflux transporter responsible for digoxin excretion [41, 43]. P-gp, encoded by the ABCB1 gene, is expressed in the apical membranes of enterocytes, renal tubular cells, and hepatocytes, where it functions as a gatekeeper limiting oral bioavailability and facilitating elimination of substrate drugs [30]. In vitro investigations reveal that omeprazole, lansoprazole, and pantoprazole interfere with P-glycoprotein-mediated digoxin efflux [196, 197], while in vivo analyses indicate that omeprazole enhances digoxin absorption by 10–30%, whereas pantoprazole and rabeprazole cause minimal effects [33, 198, 199]. This chapter evaluates whether these

pharmacological mechanisms manifest as a clinically observable association with arrhythmia-related hospitalisation in patients with atrial fibrillation in routine care, rather than directly quantifying causal effects or drug concentrations.

3.1.1 Central research question and analytical approach

This study aimed to determine if the concurrent use of PPIs and digoxin in patients aged 51 and older with atrial fibrillation (AF) was associated with a greater incidence of arrhythmia-related hospital admissions. We hypothesised that concurrent exposure would be associated with higher arrhythmia risk, consistent with known pharmacological mechanisms.

Digoxin is a medication with a limited therapeutic index, functioning as a substrate for the P-gp transporter and experiencing low hepatic metabolism [29, 193]. PPIs, commonly used for gastrointestinal protection, can block intestinal P-gp and increase gastric pH [41, 43]. By elevating gastric pH, PPIs may diminish the acid hydrolysis of digoxin in the stomach, thereby enhancing the proportion of unchanged medication available for absorption. Furthermore, prolonged PPI medication has been associated with electrolyte imbalances, notably hypomagnesaemia, which can induce arrhythmias [200]. These mechanisms offer physiologic justification for an elevated risk of arrhythmic events when PPIs and digoxin are co-prescribed.

A dynamic cohort study design with a two-year follow-up was utilised to test this hypothesis. PPI exposure was recreated as time-dependent, allowing patients to alter their exposure status throughout the follow-up period. The statistical analysis utilised time-dependent Cox proportional hazards models, incorporating causal correction using IPTW [180, 201]. Simon–Makuch extensions of Kaplan–Meier procedures were employed to illustrate survival probabilities across varying exposure states [180].

3.2 Methods

3.2.1 Study design and setting

This study employed a retrospective cohort design using routinely collected electronic health record (HER) data from NHS Greater Glasgow and Clyde, which serves a population of approximately 1.2 million residents in the west of Scotland. The study followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies [127].

This study involves human participants, but consent for participation was not obtained because this study involved only de-identified, routinely collected NHS data accessed under delegated ethics approval through the West of Scotland Safe Haven. Delegated research ethics approval was granted for linkage to NHS patient data by the Local Privacy and Advisory Committee at NHS GG&C. Cohorts and de-identified linked data were prepared by the West of Scotland Safe Haven Research Database at NHS GG&C. Analyses were conducted within a Trusted Research Environment, in line with REC-approved protocols and UK General Data Protection Regulation (GDPR), and no patient-level data were removed from the facility. Full details of the study design, data sources, and Safe Haven infrastructure are provided in Chapter 2 (Sections 2.2 and 2.3).

3.2.2 Study population and eligibility criteria

The source population comprised all adults aged 51 years and older with a recorded diagnosis of atrial fibrillation between 1 January 2014 to 31 December 2020. Atrial fibrillation was identified using ICD-10 diagnostic codes (I48.0, I48.1, I48.2, I48.3, I48.4, I48.9) from primary and secondary care encounters. Patients were included if they had at least one recorded prescription for any cardiovascular medication during the study period, indicating active engagement with cardiovascular care. Exclusion criteria were: (1) prevalent arrhythmia-related hospitalisation prior to cohort entry; (2) missing demographic data; and (3) follow-up time of less than 7 days. The study flowchart is presented in Figure 3.1.

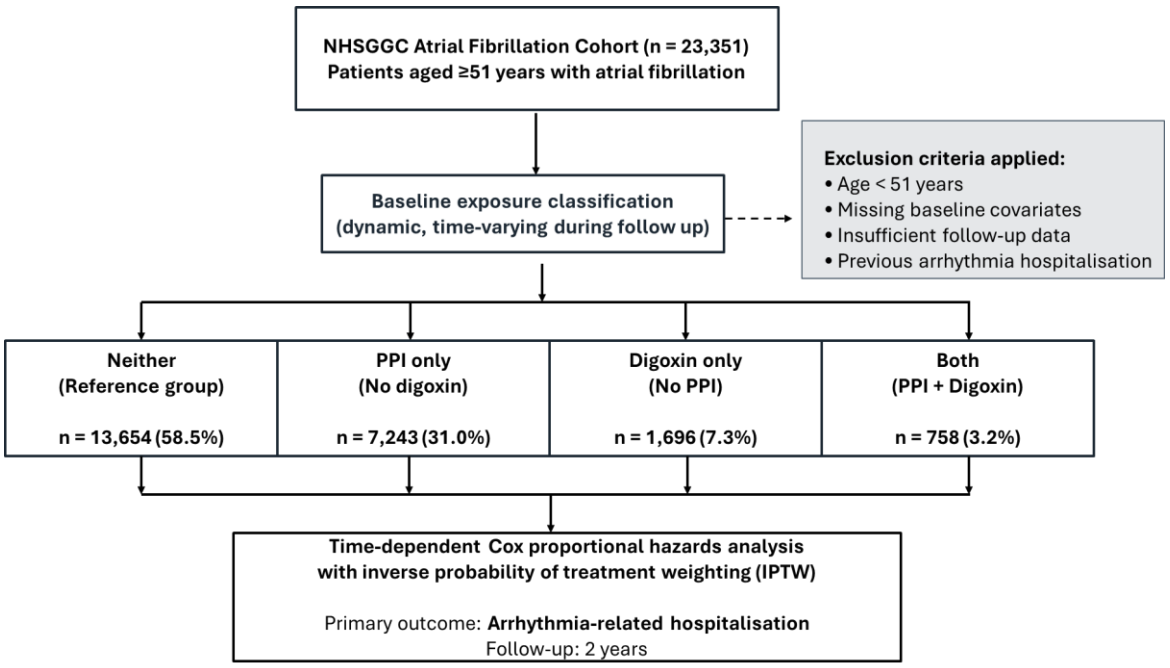


Figure 3.1 Flowchart illustrating the study design

NHSGGC, NHS Greater Glasgow and Clyde; PPI, proton pump inhibitor; IPTW, inverse probability of treatment weighting. The flowchart depicts cohort selection from the initial atrial fibrillation population, application of exclusion criteria, baseline exposure classification into four mutually exclusive groups, and analytical approach. Exposure states were dynamic and time-varying during the 2-year follow-up period, with the primary outcome being arrhythmia-related hospitalisation.

3.2.3 Follow up and censoring

Individuals entered the analytical cohort at the time of eligibility for inclusion with a recorded diagnosis of atrial fibrillation. Follow-up commenced at cohort entry and continued for a maximum of two years, ending at the earliest occurrence of arrhythmia-related hospitalisation, death, loss to follow-up, or administrative censoring [130]. Time since cohort entry was used as the underlying time scale in all survival analyses. Death was treated as a censoring event in the primary analysis; the implications of this approach, including potential competing risks from differential mortality across exposure groups, are discussed in Section 2.2.2.

3.2.4 Exposure definitions and time-varying structure

Exposure to digoxin and PPIs was modelled as time-varying, reflecting real-world prescribing patterns in which medications may be initiated, discontinued, or re-initiated during follow-up. At any given time point, individuals were classified into one of four mutually exclusive exposure states: Neither digoxin nor PPI; PPI only; Digoxin only; Concurrent digoxin and PPI (Both).

Individuals were permitted to transition between exposure states over time, and person-time was allocated accordingly. This approach ensures that each participant contributed risk time aligned with their current exposure status and avoids immortal time bias and exposure misclassification that would arise from static baseline exposure definitions [202]. A 7-day carry-over period was applied after the anticipated end of each prescription supply to account for residual pharmacological effects and typical refill behaviour, consistent with the pharmacokinetic properties of both digoxin and PPIs, as detailed in Section 2.4.1. The resulting exposure structure corresponds directly to the time-varying Simon-Makuch curves and Cox regression analyses presented in the Statistical analysis section.

PPIs were modelled as a class to reflect real-world prescribing patterns and to preserve statistical power. This approach estimates the average effect of PPI exposure rather than agent-specific risks, which is clinically relevant given that prescribers often select among PPIs based on formulary availability rather than pharmacological distinctions. Individual PPI agents included omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. This classification strategy biases results toward the null if agent-specific effects vary substantially, making the observed association conservative.

3.2.5 Outcome definition

The primary outcome was hospitalisation due to arrhythmia, ascertained from the principal discharge diagnosis of inpatient admission record using ICD-10 codes I47 and R00, as listed in Table 2.2 (Chapter 2, Section 2.3.3), encompassing paroxysmal tachycardia and abnormalities of heartbeat. This outcome definition

predominantly captures tachyarrhythmia or unspecified rhythm abnormalities and does not specifically identify clinically important manifestations of digoxin toxicity, such as bradyarrhythmia, atrioventricular block, or pacemaker implantation. This is particularly relevant because digoxin is prescribed for rate control in atrial fibrillation, meaning that some arrhythmia-related hospitalisations may reflect the underlying indication for treatment rather than digoxin toxicity, introducing potential confounding by indication. Restricting outcome ascertainment to hospitalised events also biases the outcome towards more severe cases and may under-represent arrhythmic events managed in ambulatory setting, although it increases specificity for clinically significant events requiring hospital-level care. These limitations are considered further in the Discussion.

3.2.6 Covariates and confounding structure

Measured covariates included age, sex, socioeconomic position (SIMD 2016 deciles), comorbidities (cardiovascular, respiratory, neurological, renal/kidney-urinary-bladder, musculoskeletal, endocrine, gastrointestinal, liver/gallbladder/pancreatic disease, cancer, infection, and mental health conditions), concomitant cardiovascular medications (ß-blockers, calcium channel blockers, antiarrhythmic agents, and oral anticoagulants), and measures of healthcare utilisation (including admission duration).

These variables were selected a priori based on clinical relevance and prior evidence linking them to both medications prescribing patterns and arrhythmia risk. The substantial baseline imbalance observed across several of these domains motivated the use of IPTW, as described below. Covariate selection followed the disjunctive cause criterion, including all measured pre-treatment variables that are causes of the exposure, the outcome, or both, as detailed in Section 2.8.1 [173, 175].

3.2.7 Statistical analysis

3.2.7.1 Analytical objective and overarching framework

The statistical analysis was designed to evaluate whether concurrent exposure to digoxin and PPIs is associated with an increased risk of arrhythmia-related hospitalisation in a real-world cohort of adults with atrial fibrillation, while explicitly accounting for the dynamic nature of prescribing and the substantial potential for confounding by indication. The analytical strategy was grounded in contemporary causal inference principles for longitudinal observational data and combined time-varying exposure modelling, IPTW, and survival analysis to approximate clinically relevant causal contrasts under clearly stated assumptions [130].

All analyses were conducted using routinely collected individual-level healthcare data. Effect estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and statistical significance was assessed using two-sided tests with an α level of 0.05.

The full statistical analysis framework, including the survival analysis approach, causal estimand specification, and analytical rationale, is described in detail in Chapter 2 (Sections 2.5–2.8).

3.2.7.2 Causal estimand, statistical estimand, and interpretation

The causal estimand motivating this analysis is the contrast in the instantaneous risk of arrhythmia-related hospitalisation that would be observed if, at a given time point, an individual with AF were concurrently exposed to digoxin and a PPI, compared with the risk that same individual would experience under an alternative exposure state (e.g. digoxin alone, PPI alone, or neither drug), conditional on their observed clinical history [130, 147].

Because this estimand cannot be directly identified from observational data, the analysis targets a statistical estimand defined as the cause-specific hazard ratio comparing time-varying exposure states in a weighted Cox proportional hazards model. This estimand represents the ratio of hazards between exposure states at

time t, conditional on survival to that time and on measured covariates, within a pseudo-population created through IPTW [130, 147, 148].

The hazard ratios reported in the Results are therefore statistical estimates of this weighted, time-dependent estimand. Under the standard identifying assumptions of consistency, positivity, conditional exchangeability given measured covariates, and correct model specification, these estimates can be interpreted as approximations to the underlying causal contrast [147]. As discussed later, residual confounding by unmeasured factors remains possible, and the findings are therefore interpreted as causally compatible associations rather than definitive causal effects. Further discussion of causal and statistical estimands in the context of this thesis is provided in Section 2.5.3.

3.2.7.3 Descriptive statistics

Baseline characteristics were described by exposure group by using frequencies and percentages for categorical variables, and medians with interquartile ranges for continuous variables. Standardised mean differences (SMDs) were computed to assess covariate imbalance among exposure groups, with SMD values beyond 0.10 suggesting potentially significant imbalance [149]. These descriptive analyses were employed to delineate the degree of baseline imbalance and to justify the later implementation of IPTW.

3.2.7.4 Inverse probability of treatment weighting (IPTW)

To mitigate confounding by indication and systematic baseline differences between exposure states, IPTW was applied to create a pseudo-population in which measured baseline covariates were balanced across time-varying exposure groups [144, 178]. Time-varying propensity scores were estimated using multinomial logistic regression models predicting exposure state as a function of measured covariates. Stabilised weights were constructed as the ratio of the marginal probability of the observed exposure to the conditional probability given covariates, improving precision and reducing variance inflation [144, 178]. Weight distributions were examined, and extreme weights above the 99th percentile were trimmed to reduce the influence of potential positivity violations [144, 203]. Full

details of the IPTW methodology, including the conceptual framework and weight construction procedure, are provided in Sections 2.9 and 2.10.

Covariate balance before and after weighting was assessed using absolute SMDs, with values below 0.10 indicating acceptable balance. Extreme weights were examined, and trimming analyses were conducted to assess robustness.

3.2.7.5 Survival modelling

The primary inferential analysis employed an IPTW-weighted, time-dependent Cox proportional hazards model to estimate hazard ratios for arrhythmia-related hospitalisation associated with each exposure state. Individuals unexposed to both digoxin and PPIs served as the reference category [201]. Robust sandwich variance estimators were used to account for weighting and within-individual correlation due to repeated exposure transitions.

The proportional hazards assumption was evaluated using Schoenfeld residuals and graphical diagnostics. No material violations were identified, supporting the reporting of constant hazard ratios over the two-year follow-up period. Continuous covariates were assessed for linearity, and alternative specifications were explored where appropriate.

The analytical approach was designed to ensure that the statistical estimates, graphical displays, and narrative interpretation address the same underlying estimand. This analytical approach aligns with established best practice for causal inference in real-world pharmacoepidemiology, particularly for evaluating time-varying drug-drug interactions and is supported by a substantial methodological literature [186, 201].

3.2.7.6 Simon-Makuch curves

Simon-Makuch survival curves were constructed to provide a descriptive, non-parametric representation of arrhythmia-free survival under time-varying exposure [180]. These curves extend Kaplan-Meier methods to accommodate

exposure changes over follow-up and were used to visualise the magnitude and temporal pattern of survival differences between exposure states.

Although the primary Cox model used ‘neither drug’ as the reference category for statistical stability and interpretability, the clinically relevant estimand is the contrast between concurrent digoxin + PPI use versus digoxin alone. This contrast was derived from the fitted model and is reported as a descriptive point estimate; however, a valid confidence interval and p-value for this comparison could not be estimated within the resources available for this analysis. The Simon-Makuch method and its methodological basis are described in Section 2.11.

3.2.7.7 Missing data

Complete-case analysis was employed because missing data were minimal (<2% across all covariates) [182, 183]. Sensitivity analyses excluding individuals with any missing data yielded substantively identical results, supporting the robustness of the primary findings.

3.2.7.8 Software

All analyses were conducted using R version 4.3.0 (R Foundation for Statistical Computing). IPTW was implemented using the *WeightIt* package, and Cox proportional hazards models were fitted using the *survival* package, and Simon-Makuch survival curves were generated using the survminer package [154, 155].

3.3 Results

3.3.1 Cohort and exposure distribution

The analytical cohort comprised 23,351 individuals aged 51 years and older with a recorded diagnosis of atrial fibrillation. At baseline, 13,654 participants (58.5%) were unexposed to both digoxin and PPIs and constituted the reference group. A further 7,243 individuals (31.0%) received PPIs alone, 1,696 (7.3%) received digoxin alone, and 758 (3.2%) were concurrently exposed to both digoxin and a PPI.

Exposure status was dynamic over follow-up, reflecting real-world prescribing practice. Individuals could initiate or discontinue PPIs during the study period and therefore contribute person-time to multiple exposure categories. All subsequent analyses were conducted using time-varying exposure classification to ensure appropriate alignment between exposure status and risk time.

3.3.2 Baseline characteristics

Baseline demographic characteristics, comorbidities, and concomitant cardiovascular medication use stratified by exposure group are presented in Table 3.1.

Age distributions were broadly similar across exposure groups, with consistently high median ages and overlapping interquartile ranges, indicating limited baseline age imbalance.

In contrast, sex distribution showed clear and systematic imbalance across exposure states. The proportion of women increased progressively from the None group (47.9%) to PPI only (52.7%), Digoxin only (58.4%), and Both (61.7%). These differences correspond to absolute contrasts of approximately 10-14 percentage points between reference and digoxin-containing groups, levels that would be expected to yield SMDs exceeding the conventional 0.10 threshold [149]. This pattern indicates that sex was meaningfully associated with exposure status and therefore represented a potentially important confounder requiring adjustment.

Socioeconomic position, measured using SIMD 2016 deciles, was broadly similar across groups but demonstrated modest imbalance at the extremes of deprivation. Patients receiving PPIs, particularly those in the concurrent digoxin and PPI group, were more frequently drawn from the most deprived decile (23.9% in Both vs 20.1% in None), while representation in the least deprived deciles was slightly lower among PPI users. Although differences across most intermediate deciles were small, the enrichment of deprivation at the lower end of the SIMD distribution suggests that deprivation-related confounding was plausible and likely to contribute to baseline imbalance, particularly for PPI-containing exposure states.

Taken together, baseline characteristics indicate that while age distributions were well aligned across exposure groups, sex and socioeconomic deprivation exhibited non-trivial imbalance prior to adjustment, alongside exposure-related differences in group size. These patterns underscore the necessity of robust confounding control and provide the rationale for the subsequent use of IPTW to improve covariate balance and approximate exchangeability across time-varying exposure states.

Table 3.1 Baseline characteristics of the study cohort by digoxin and PPI exposure

Data presented as n (%) for categorical variables and median (interquartile range) for continuous variables. Exposure groups: neither digoxin nor PPI (n=13,654; 58.5%), PPI only (n=7,243; 31.0%), digoxin only (n=1,696; 7.3%), and concurrent digoxin-PPI use (n=758; 3.2%). Panel (a) summarises demographic characteristics, comorbid conditions, and baseline medication use. Exposure groups were mutually exclusive at baseline but time-varying during follow-up, allowing patients to transition between states. SIMD, Scottish Index of Multiple Deprivation 2016 (decile 1 = most deprived).

label	levels	None	PPI only	Digoxin only	Both	Total
Total N (%)		13654 (58.5)	7243 (31.0)	1696 (7.3)	758 (3.2)	23351
Age	Median (IQR)	78.7 (70.9 to 84.9)	79.1 (72.1 to 85.0)	78.1 (70.4 to 84.7)	77.9 (71.8 to 84.3)	78.7 (71.3 to 84.9)
SEX	M	7119 (52.1)	3427 (47.3)	706 (41.6)	290 (38.3)	11542 (49.4)
	F	6535 (47.9)	3816 (52.7)	990 (58.4)	468 (61.7)	11809 (50.6)
SIMD_2016_DECILE	1	2740 (20.1)	1658 (22.9)	344 (20.3)	181 (23.9)	4923 (21.1)
	2	2088 (15.3)	1193 (16.5)	269 (15.9)	130 (17.2)	3680 (15.8)
	3	1289 (9.4)	724 (10.0)	165 (9.7)	93 (12.3)	2271 (9.7)
	4+	7537 (55.2)	3668 (50.6)	918 (54.1)	354 (46.7)	12477 (53.4)
Beta_blockers	0	9633 (70.6)	4193 (57.9)	1262 (74.4)	462 (60.9)	15550 (66.6)
	1	4021 (29.4)	3050 (42.1)	434 (25.6)	296 (39.1)	7801 (33.4)
Edoxaban	0	13407 (98.2)	7040 (97.2)	1670 (98.5)	740 (97.6)	22857 (97.9)
	1	247 (1.8)	203 (2.8)	26 (1.5)	18 (2.4)	494 (2.1)
CCBs	0	11462 (83.9)	5492 (75.8)	1458 (86.0)	600 (79.2)	19012 (81.4)
	1	2192 (16.1)	1751 (24.2)	238 (14.0)	158 (20.8)	4339 (18.6)
Rivaroxaban	0	13499 (98.9)	7141 (98.6)	1690 (>99)	750 (>99)*	23084 (>98)
	1	155 (1.1)	102 (1.4)	6 (0.4)	<5 (<1)	267 (1.1)
Amiodarone	0	13564 (>99)	7179 (>99)	1685 (>99)*	750 (>99)*	23191 (>99)
	1	90 (0.7)	64 (0.9)	<5 (<1)	<5 (<1)	160 (0.7)
Apixaban	0	12917 (94.6)	6657 (91.9)	1648 (97.2)	717 (94.6)	21939 (94.0)
	1	737 (5.4)	586 (8.1)	48 (2.8)	41 (5.4)	1412 (6.0)
Flecainide	0	13571 (>99)	7192 (>99)	1690 (>99)*	750 (>99)*	23217 (>99)
	1	83 (0.6)	51 (0.7)	<5 (<1)	<5 (<1)	134 (0.6)
Dabigatran	0	13621 (>99)	7225 (>99)	1685 (>99)*	750 (>99)*	23295 (>99)
	1	33 (0.2)	18 (0.2)	<5 (<1)	<5 (<1)	56 (0.2)
CV	0	4177 (30.6)	1467 (20.3)	548 (32.3)	160 (21.1)	6352 (27.2)
	1	9477 (69.4)	5776 (79.7)	1148 (67.7)	598 (78.9)	16999 (72.8)
MSK	0	9794 (71.7)	4175 (57.6)	1194 (70.4)	445 (58.7)	15608 (66.8)
	1	3860 (28.3)	3068 (42.4)	502 (29.6)	313 (41.3)	7743 (33.2)
MentalHealth	0	11710 (85.8)	5296 (73.1)	1447 (85.3)	534 (70.4)	18987 (81.3)
	1	1944 (14.2)	1947 (26.9)	249 (14.7)	224 (29.6)	4364 (18.7)
Neurology	0	9466 (69.3)	3612 (49.9)	1147 (67.6)	359 (47.4)	14584 (62.5)
	1	4188 (30.7)	3631 (50.1)	549 (32.4)	399 (52.6)	8767 (37.5)
Respiratory	0	11276 (82.6)	5305 (73.2)	1307 (77.1)	493 (65.0)	18381 (78.7)
	1	2378 (17.4)	1938 (26.8)	389 (22.9)	265 (35.0)	4970 (21.3)
Diabetes	0	12415 (90.9)	6382 (88.1)	1552 (91.5)	662 (87.3)	21011 (90.0)
	1	1239 (9.1)	861 (11.9)	144 (8.5)	96 (12.7)	2340 (10.0)
Endocrine	0	12621 (92.4)	6497 (89.7)	1559 (91.9)	676 (89.2)	21353 (91.4)
	1	1033 (7.6)	746 (10.3)	137 (8.1)	82 (10.8)	1998 (8.6)
KUB	0	7608 (55.7)	3230 (44.6)	976 (57.5)	357 (47.1)	12171 (52.1)
	1	6046 (44.3)	4013 (55.4)	720 (42.5)	401 (52.9)	11180 (47.9)
Liver_GB_Panc	0	13328 (97.6)	6919 (95.5)	1661 (97.9)	728 (96.0)	22636 (96.9)
	1	326 (2.4)	324 (4.5)	35 (2.1)	30 (4.0)	715 (3.1)
Cancer	0	12392 (90.8)	6496 (89.7)	1581 (93.2)	694 (91.6)	21163 (90.6)
	1	1262 (9.2)	747 (10.3)	115 (6.8)	64 (8.4)	2188 (9.4)
GI	0	13452 (98.5)	7041 (97.2)	1661 (97.9)	730 (96.3)	22884 (98.0)
	1	202 (1.5)	202 (2.8)	35 (2.1)	28 (3.7)	467 (2.0)
Infection	0	13619 (>99)	7223 (>99)	1690 (>99)*	750 (>99)*	23294 (>99)
	1	35 (0.3)	20 (0.3)	<5 (<1)	<5 (<1)	57 (0.2)
adm_duration	Median (IQR)	6.0 (2.0 to 16.0)	5.0 (2.0 to 13.0)	7.0 (3.0 to 14.0)	7.0 (3.0 to 14.0)	6.0 (2.0 to 15.0)

*Counts have been rounded to comply with Safe Haven Statistical Discluser Thershold. SIMD deciles 4-10 merged into 4+ to avoid suppression of individual small counts. Suppressed counts (<5) have both count AND percentage supressed '<5(<1)'.

Baseline comorbidity burden differed substantially across exposure groups, with systematic enrichment of multimorbidity in PPI-containing states, particularly among those concurrently exposed to digoxin and PPIs. Cardiovascular comorbidity was highly prevalent overall (72.8%) and was more common in PPI users (79.7% in PPI only; 78.9% in Both) than in the None group (69.4%), representing an absolute difference of approximately 9–10 percentage points and suggesting material baseline imbalance likely exceeding an SMD of 0.1. In contrast, cardiovascular comorbidity among digoxin-only users (67.7%) was similar to the reference group.

Marked differences were observed for musculoskeletal, mental health, neurological, respiratory, and renal (KUB) comorbidities, all of which were substantially more prevalent in PPI-containing exposure states. Musculoskeletal disease was present in 42.4% of the PPI-only group and 41.3% of the Both group compared with 28.3% in the None group, representing one of the largest absolute contrasts in the table. Similarly, mental health conditions affected 26.9% of PPI-only and 29.6% of Both patients, versus 14.2% in the None group. Neurological disease showed particularly pronounced imbalance, affecting over half of patients in the PPI-only (50.1%) and Both (52.6%) groups compared with 30.7% in the None group. These differences are sufficiently large that substantial pre-weighting SMDs would be expected, indicating strong confounding potential.

Respiratory and kidney/urinary/bladder (KUB) comorbidities followed a similar pattern. Respiratory disease was present in 26.8% of PPI-only and 35.0% of Both patients, compared with 17.4% in the None group, while KUB comorbidity affected 55.4% and 52.9% of these groups respectively, versus 44.3% in the reference group. These patterns are consistent with greater overall disease burden and healthcare complexity among PPI users and would be expected to contribute meaningfully to baseline imbalance prior to adjustment.

In contrast, diabetes, endocrine disorders, liver/gallbladder/pancreatic disease, cancer, gastrointestinal diagnoses, and infection were less strongly differentiated across exposure groups, with smaller absolute differences that would be less likely to generate large SMDs individually, although some enrichment of gastrointestinal

and endocrine conditions was still evident among PPI users. Median admission duration was longer in digoxin-containing groups (7.0 days in Digoxin only and Both) compared with None (6.0 days) and PPI only (5.0 days), suggesting higher healthcare utilisation and illness severity among digoxin users.

Overall, these baseline data demonstrate substantial and clinically coherent pre-weighting imbalance across multiple comorbidity domains, particularly for neurological, mental health, musculoskeletal, respiratory, cardiovascular, and renal disease, with imbalance concentrated in PPI-containing exposure states. These patterns provide strong justification for the subsequent application of IPTW to improve covariate balance and reduce confounding by multimorbidity and healthcare complexity in the time-dependent analyses.

Patterns of concomitant medication use differed meaningfully across exposure groups, particularly for rate-control agents and oral anticoagulants, indicating substantial baseline imbalance prior to adjustment. ß-blocker use was common overall (33.4%) but varied markedly by exposure state, affecting 29.4% of the None group compared with 42.1% of PPI-only and 39.1% of the concurrent digoxin and PPI group, while being less frequent among digoxin-only users (25.6%). These absolute differences of approximately 10-13 percentage points relative to the reference group suggest SMD likely exceeding 0.1, consistent with differential cardiovascular disease burden and treatment strategies across exposure states.

Calcium channel blocker (CCB) use exhibited a similar pattern, with higher prevalence in PPI-only (24.2%) and Both (20.8%) groups compared with the None group (16.1%), while remaining lower in the digoxin-only group (14.0%). This divergence in rate-control therapy indicates clinically meaningful variation in treatment profiles across exposure categories and represents another likely contributor to pre-weighting imbalance.

Use of antiarrhythmic agents was uncommon across all groups. Amiodarone exposure ranged from 0.2% to 0.9% and flecainide from 0% to 0.7%, with small absolute differences that are unlikely to generate large SMD individually, though

their inclusion remains important given known interactions with digoxin and arrhythmic risk.

Oral anticoagulant prescribing also varied by exposure state. Apixaban use was more frequent in PPI-only (8.1%) and Both (5.4%) groups than in the None group (5.4%), while being substantially lower in digoxin-only patients (2.8%). Edoxaban showed modest enrichment among PPI users (2.8% in PPI only and 2.4% in Both vs 1.8% in None), whereas dabigatran and rivaroxaban were infrequently prescribed and showed minimal variation across groups. These patterns suggest non-random allocation of anticoagulant therapy, potentially reflecting differences in renal function, bleeding risk, or clinical frailty across exposure states.

Collectively, the observed differences in ß-blocker use, CCB use, and selected oral anticoagulants indicate clinically coherent but non-trivial pre-weighting imbalance in cardiovascular co-therapy, particularly among PPI-containing exposure states. These imbalances reinforce the need for comprehensive confounding adjustment and provide a clear rationale for the subsequent application of IPTW to achieve improved covariate balance before estimation of time-dependent hazard ratios.

3.3.3 Covariate balance after inverse probability of treatment weighting (IPTW)

Given the substantial baseline imbalance observed across multiple demographic, comorbidity, and medication domains - particularly for sex, multimorbidity, cardiovascular co-therapy, and healthcare complexity - IPTW was applied to improve exchangeability across time-varying exposure states. Figure 3.2 presents absolute SMDs for all covariates included in the propensity score model, before and after weighting, using the maximum pairwise imbalance across exposure groups.

Prior to weighting, several covariates demonstrated pronounced imbalance, with absolute SMDs exceeding 0.20 and, in some cases, approaching or exceeding 0.40–0.50. These large pre-weighting SMDs were consistent with the descriptive

baseline findings, reflecting enrichment of multimorbidity, polypharmacy, and socioeconomic deprivation in PPI-containing exposure states. In particular, variables related to neurological disease, mental health conditions, musculoskeletal disease, respiratory disease, renal impairment, sex, and cardiovascular co-therapy contributed substantially to the observed imbalance.

After application of IPTW, covariate balance improved markedly across the full set of variables, with the majority of post-weighting SMDs reduced to below the conventional threshold of 0.10, indicating acceptable balance. The largest pre-weighting imbalances showed the greatest absolute reductions, demonstrating effective reweighting of the cohort toward a pseudo-population in which observed covariates were more evenly distributed across exposure states. A small number of covariates remained marginally above the 0.10 threshold after weighting, but none approached the levels of imbalance observed prior to adjustment.

Overall, these diagnostics indicate that IPTW substantially mitigated the systematic baseline differences identified in the unweighted cohort, particularly those related to multimorbidity and cardiovascular treatment patterns. The improvement in covariate balance supports the use of weighted, time-dependent Cox proportional hazards models for estimation of exposure effects and strengthens the internal validity of the subsequent hazard ratio estimates, while recognising that residual confounding from unmeasured factors cannot be fully excluded.

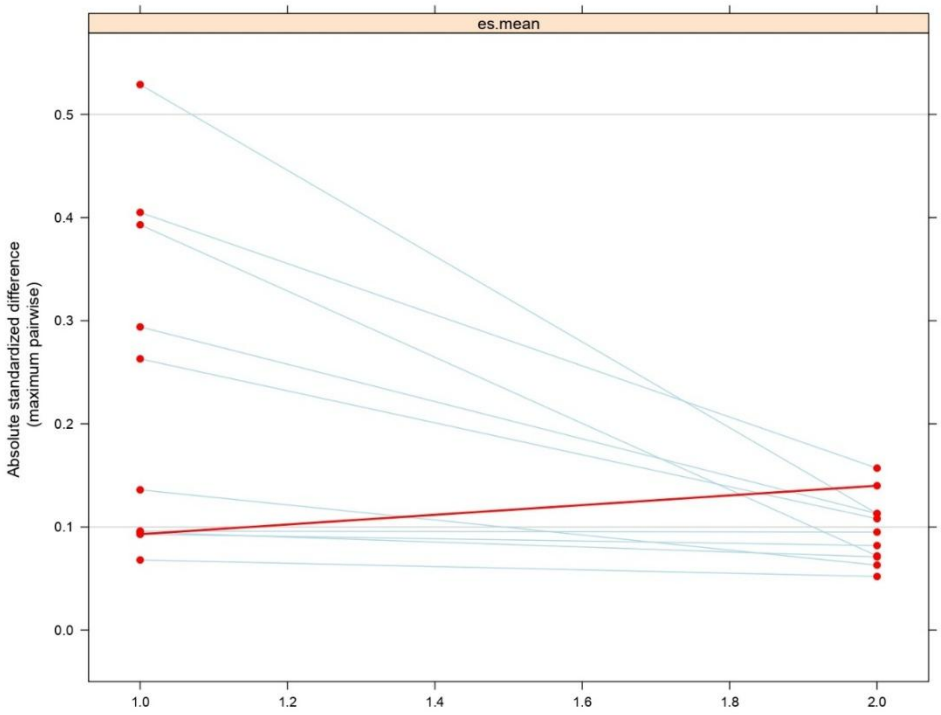


Figure 3.2 IPTW Covariate Balance Plot

Covariate balance before and after inverse probability of treatment weighting (IPTW). The plot displays absolute standardized mean differences (SMDs) for all covariates included in the propensity score model. Each line connects the pre-weighting (left) and post-weighting (right) SMD for a single covariate. Points in red indicate covariates with SMD >0.10 before weighting. After IPTW, most covariates achieved SMD <0.10 (indicated by the es.mean threshold line), demonstrating substantial improvement in covariate balance and supporting the assumption of exchangeability across exposure groups.

3.3.4 Event incidence and follow-up

During the two-year follow-up, arrhythmia-related hospitalisations accrued steadily across all exposure states. Incidence was highest among patients prescribed digoxin, with or without a PPI, and numbers at risk declined more steeply in these groups, reflecting both higher event incidence and elevated mortality in this older, comorbid cohort. Visual inspection of cumulative incidence suggested small absolute differences between groups over time, with similar numbers-at-risk trajectories overall.

3.3.5 Time-varying survival experience by exposure state (Simon-Makuch analysis)

Time-varying arrhythmia-free survival by exposure state was examined using Simon-Makuch curves, which account for dynamic changes in digoxin and PPI exposure over follow-up and avoid immortal time bias. Note that these time-zero risk set sizes differ from the baseline exposure counts in Table 3.1, as the Simon-Makuch method assigns individuals to exposure groups based on their current time-varying medication status at each time point rather than a fixed baseline classification. At cohort entry, numbers at risk were largest in the None group (n=15,251), followed by PPI only (n=8,098), Digoxin only (n=67), and Both (n=32), reflecting the relative prevalence of exposure states at baseline.

Survival probability declined steadily across all groups over time. In the early follow-up period, curves were closely aligned, with minimal separation observed during the first 100-200 days. As follow-up progressed, modest divergence emerged. By approximately 400 days, the number at risk had declined to around 8,634 in the None group, 2,693 in the PPI-only group, 845 in the Digoxin-only group, and 295 in the concurrent digoxin and PPI group. At this time point, arrhythmia-free survival probabilities remained tightly clustered, but the Both group consistently exhibited the lowest survival, while the PPI-only curve closely overlapped with the None group.

By the end of follow-up (730 days), numbers at risk were 7,586 for None, 2,005 for PPI only, 721 for Digoxin only, and 224 for Both. At this stage, arrhythmia-free survival probabilities remained above 0.50 for the None and PPI-only groups, while the Digoxin-only and concurrent exposure groups showed modestly lower survival, with the Both group consistently lowest throughout follow-up. The absolute separation between groups at two years was less than 5–7 percentage points across all exposure states, confirming that the relative ordering of curves was consistent — None and PPI only highest, Digoxin only intermediate, and Both lowest — but that absolute differences remained small.

No major curve crossings or abrupt changes in slope were observed, and the separation between groups appeared gradual rather than time-specific. Overall, the Simon-Makuch curves (Figure 3.3) demonstrate that concurrent digoxin and PPI exposure was associated with persistently lower arrhythmia-free survival over time, but that absolute differences were modest, providing visual context for the relative hazard estimates derived from the IPTW-weighted, time-dependent Cox regression.

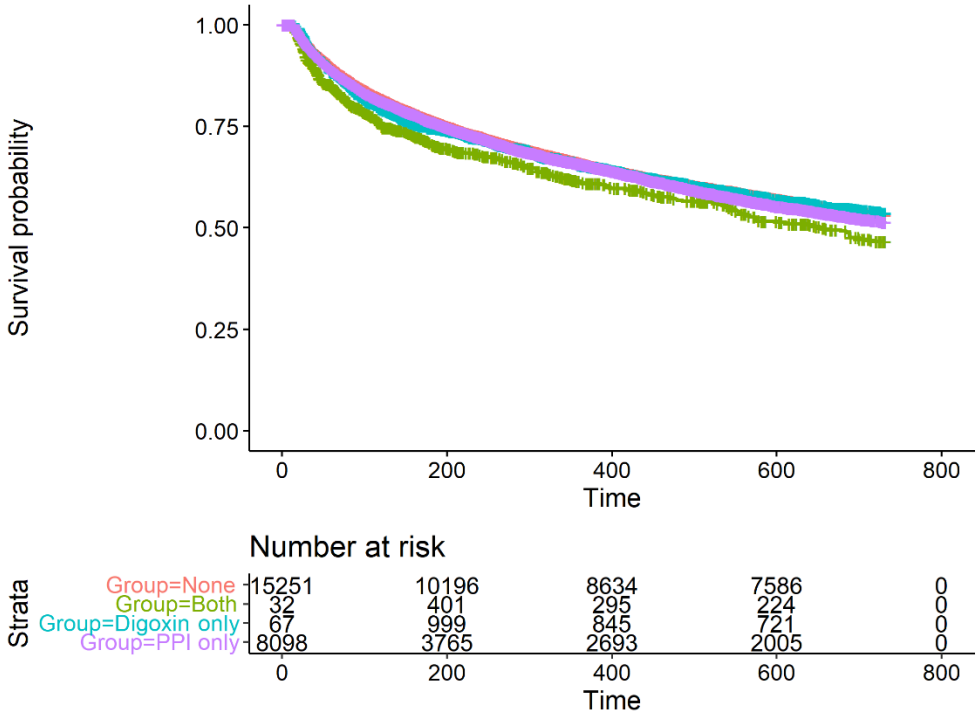


Figure 3.3 Simon-Makuch Survival Curves

Simon-Makuch survival curves showing arrhythmia-free survival probability by time-varying exposure status over 2-year follow-up (N=23,351). The curves account for dynamic changes in digoxin and PPI exposure throughout the follow-up period, avoiding immortal time bias. The curves demonstrate modest separation between groups, with the concurrent digoxin and PPI group (Both, green line) showing the lowest arrhythmia-free survival probability throughout follow-up. The PPI-only group (purple line) closely overlaps the reference group (None, red line), while the Digoxin-only group (turquoise line) tracks between these.

3.3.6 Multivariable time-dependent Cox regression results

Results from the IPTW-weighted, time-dependent Cox proportional hazards model for arrhythmia-related hospitalisation are shown in Table 3.2. After adjustment for demographic factors, socioeconomic position, comorbidities, concomitant medications, and admission duration, concurrent exposure to digoxin and PPIs was associated with a statistically significant increase in hazard compared with patients exposed to neither drug (HR 1.195, 95% CI 1.025-1.394; p = 0.023). In contrast, digoxin alone (HR 1.053, 95% CI 0.952-1.166; p = 0.315) and PPI alone (HR 0.984, 95% CI 0.932-1.038; p = 0.548) were not associated with a materially different hazard relative to the reference group. These estimates indicate that the observed elevation in risk was specific to concurrent exposure rather than to either drug in isolation, as illustrated in Figure 3.4.

The primary Cox model used the 'neither drug' group as the reference category. The hazard ratios reported in this chapter therefore quantify the association between each exposure state and the outcome relative to patients exposed to neither digoxin nor a PPI; they do not, on their own, estimate the effect of adding a PPI to digoxin monotherapy. The approximate point estimate for the clinically relevant contrast between concurrent exposure and digoxin monotherapy was 1.13 (obtained as 1.195 ÷ 1.053). However, a valid 95% confidence interval cannot be derived by combining the separately reported confidence interval, because this would ignore the covariance between the two coefficient estimates. A valid confidence interval and formal statistical inference for this contrast could not be obtained within the resources available for this analysis. Accordingly, the approximate hazard ratio of 1.13 is reported as a descriptive point estimate only, and statistical inference in this chapter is confined to comparisons against the unexposed reference group.

These model-based estimates are consistent with the time-varying Simon-Makuch survival curves, which showed persistently lower arrhythmia-free survival for the concurrent digoxin and PPI group over follow-up, but only modest absolute separation between exposure states, with survival probabilities at approximately

two years differing by less than 5-7 percentage points. The gradual and approximately parallel divergence of the Simon-Makuch curves over time also supports the proportional hazards assumption underlying the weighted Cox model.

Among covariates, increasing age was associated with a small but statistically significant increase in hazard (HR per year 1.007, 95% CI 1.001-1.013; p = 0.023), while sex was not independently associated with arrhythmia-related hospitalisation (female vs male HR 0.972, 95% CI 0.877-1.076; p = 0.581). Socioeconomic position, measured by SIMD 2016 deciles, showed no clear gradient after adjustment, with hazard ratios for all deprivation categories overlapping unity.

Several comorbidities were independently associated with increased hazard. Musculoskeletal disease was associated with a modest elevation in risk (HR 1.118, 95% CI 1.005-1.244; p = 0.040), while respiratory disease (HR 1.255, 95% CI 1.123-1.403; p < 0.001) and kidney/urinary/bladder (KUB) comorbidity (HR 1.220, 95% CI 1.097-1.357; p < 0.001) demonstrated stronger associations. Other comorbidity categories, including neurological disease, diabetes, endocrine disorders, gastrointestinal disease, liver/gallbladder/pancreatic disease, and cancer, were not significantly associated with the outcome after adjustment.

Patterns of association for concomitant medications were clinically coherent. Calcium channel blocker use was associated with a modest reduction in hazard (HR 0.862, 95% CI 0.747-0.996; p = 0.043), while ß-blockers showed no independent association (HR 1.006, p = 0.906). Among oral anticoagulants, apixaban (HR 0.850, 95% CI 0.765-0.944; p = 0.002) and edoxaban (HR 0.758, 95% CI 0.659-0.871; p < 0.001) were associated with lower hazard, whereas dabigatran and rivaroxaban were not. Antiarrhythmic agents (amiodarone and flecainide) showed no statistically significant associations, although estimates were imprecise due to low prevalence.

Admission duration was not independently associated with arrhythmia-related hospitalisation after adjustment (HR 0.999, 95% CI 0.997–1.001; p = 0.493). The

proportional hazards assumption was supported by Schoenfeld residual diagnostics confirming no material violations, and was further corroborated by the gradual, approximately parallel divergence of the Simon-Makuch curves over follow-up, consistent with a constant hazard ratio structure over the two-year period.

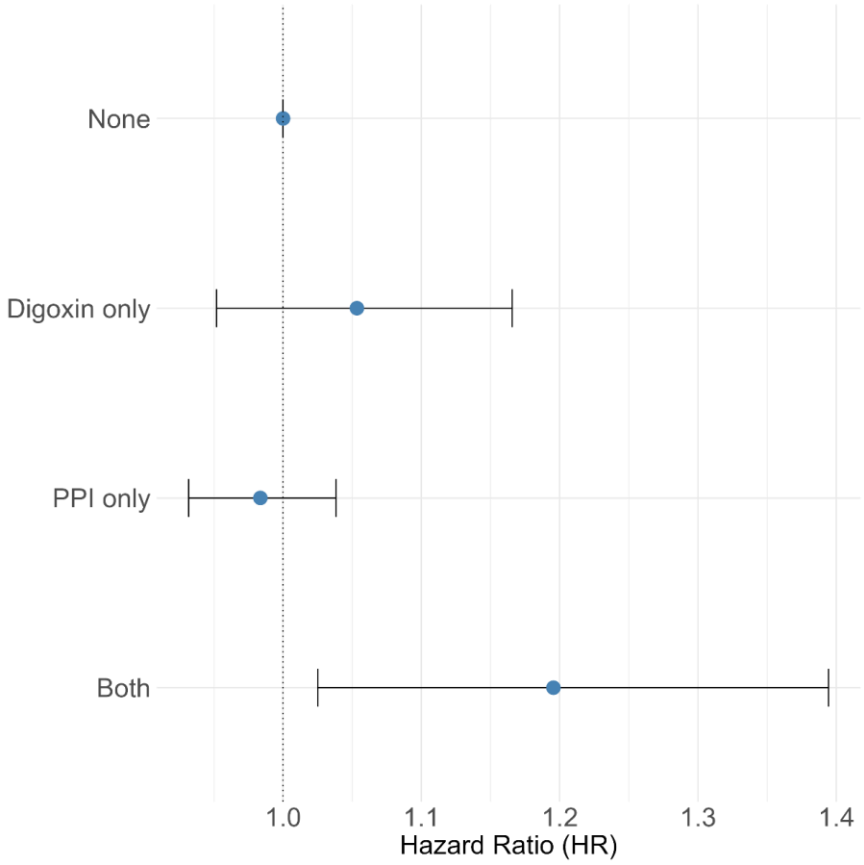


Figure 3.4 Forest Plot (Hazard Ratios)

Forest plot of adjusted hazard ratios (HR) with 95% confidence intervals for arrhythmia-related hospitalizations by exposure group from IPTW-weighted, time-dependent Cox model (N=23,351). The reference group (None=neither digoxin nor PPI) is represented by the vertical line at HR=1.0. Point estimates are shown as circles with horizontal lines indicating 95% confidence intervals. The concurrent exposure group (Both) demonstrates a statistically significant increase in hazard (HR=1.195, 95% CI 1.025-1.394, p=0.023), while PPI only (HR=0.984, 95% CI 0.932-1.038) and Digoxin only (HR=1.053, 95% CI 0.952-1.166) show effects approximating the null.

Table 3.2 Cox Proportional Hazards Model Results

Multivariable Cox proportional hazards model results for arrhythmia-related hospitalizations (N=23,351). Model includes time-dependent exposure classification with IPTW for confounding adjustment. Hazard ratios (HR) represent the relative hazard of arrhythmia-related hospitalization associated with each covariate. Reference categories: Group=None (neither digoxin nor PPI), Sex=Male, SIMD Decile=9, all medications and comorbidities=absent (0). Statistically significant associations (p<0.05) are observed for CCBs, Apixaban, Edoxaban, Age, MSK, Respiratory, KUB, and Group: Both.

Group	exp(coef)	lower .95	upper .95	P
Beta_blockers1	1.006	0.91	1.112	0.906
CCBs1	0.862	0.747	0.995	0.043
Amiodarone1	1.006	0.597	1.695	0.982
Flecainide1	0.911	0.658	1.262	0.576
Apixaban1	0.85	0.765	0.944	0.002
Dabigatran1	0.681	0.412	1.126	0.134
Edoxaban1	0.758	0.659	0.871	0
Rivaroxaban1	0.939	0.703	1.254	0.67
Age	1.007	1.001	1.013	0.023
SEXF	0.972	0.877	1.076	0.581
SIMD_2016_DECILE1	1.042	0.865	1.256	0.662
SIMD_2016_DECILE2	0.986	0.811	1.197	0.884
SIMD_2016_DECILE3	0.879	0.701	1.104	0.267
SIMD_2016_DECILE4	0.942	0.752	1.179	0.602
SIMD_2016_DECILE5	0.995	0.781	1.267	0.966
SIMD_2016_DECILE6	1.083	0.85	1.38	0.518
SIMD_2016_DECILE7	0.998	0.771	1.292	0.987
SIMD_2016_DECILE8	0.961	0.756	1.222	0.746
SIMD_2016_DECILE10	0.956	0.755	1.212	0.712
MSK1	1.118	1.005	1.244	0.04
Neurology1	1.039	0.934	1.156	0.478
Respiratory1	1.255	1.123	1.403	0
Diabetes1	1.091	0.937	1.27	0.264
Endocrine1	1.058	0.903	1.239	0.485
KUB1	1.22	1.097	1.357	0
Liver_GB_Panc1	1.124	0.907	1.394	0.285
Cancer1	1.031	0.876	1.213	0.715
GI1	1.038	0.783	1.377	0.794
adm_duration	0.999	0.997	1.001	0.493
GroupBoth	1.195	1.025	1.394	0.023
GroupDigoxin only	1.053	0.952	1.166	0.315
GroupPPI only	0.984	0.932	1.038	0.548

3.4 Discussion

This chapter examined whether concomitant prescribing of proton pump inhibitors and digoxin is associated with an increased risk of arrhythmia-related hospitalisation in a real-world cohort of adults aged 51 years and older with atrial fibrillation in NHS Greater Glasgow and Clyde. The principal finding was that concurrent exposure to digoxin and a PPI was associated with a modest but statistically significant elevation in hazard of arrhythmia-related hospitalisation compared with exposure to neither drug, whereas digoxin alone and PPI alone were both close to the null. Re-expressed against digoxin monotherapy, the clinically relevant comparator for patients already receiving digoxin, the derived point estimate corresponded to a hazard ratio of 1.13. However, because a valid confidence interval and p-value were unavailable for this contrast, it should be interpreted descriptively and does not establish a statistically supported difference between concurrent therapy and digoxin monotherapy. Statistical inference therefore remains based on the primary model comparison with the 'neither drug' reference group.

Importantly, the time-varying Simon-Makuch curves were directionally consistent with the regression findings but showed only modest absolute separation between exposure states over two years. This combination of a small-to-moderate relative effect with minimal absolute risk separation supports a justifiable interpretation of the findings that the observed measurable signal at the population level may be clinically relevant in vulnerable subgroups, rather than a large effect warranting universal avoidance of concomitant prescribing.

The motivation for this study arises from several intersecting gaps in the literature and in practice. From an evidence perspective, most of the available work on the PPI-digoxin interaction is mechanistic, pharmacokinetic, or based on isolated clinical reports [42, 45, 198, 199]. These sources establish biological plausibility but do not resolve whether the interaction translates into meaningful clinical harm in contemporary AF care, particularly within an older, multimorbid population in which both drugs may be prescribed for legitimate reasons. From a

knowledge standpoint, digoxin retains a role in AF management for selected patients, especially those in whom alternative rate-control strategies are less suitable, yet its narrow therapeutic index means that modest perturbations in exposure or physiological reserve can have disproportionate consequences [45, 191, 193]. From a practical standpoint, PPIs are commonly prescribed and are frequently continued long-term, sometimes without a continuing indication, making co-prescribing with narrow-therapeutic-index drugs an important candidate for medication review. Finally, from a methodological perspective, drug–drug interaction research is particularly susceptible to bias if exposures are treated as fixed at baseline; PPI use is often intermittent, and patients may start or stop therapy during follow-up. In this context, the present chapter's design, which treated exposure dynamically and aligned descriptive Simon-Makuch curves with a time-dependent Cox framework was a prerequisite for addressing a clinically meaningful question with reasonable validity.

To interpret the findings rigorously, it is essential to distinguish clearly between the causal estimand of interest, the statistical estimand used to approximate it, and the statistical estimates produced by the analysis. This distinction is central to modern causal inference in observational research and is particularly important in real-world studies of drug-drug interactions, where treatment status is dynamic and confounding by indication is pervasive [130, 147, 148].

The causal estimand motivating this analysis can be conceptualised as the contrast in the instantaneous risk of arrhythmia-related hospitalisation that would be observed if, at a given point in time, an individual with atrial fibrillation were concurrently exposed to digoxin and a PPI, compared with the risk that same individual would experience under an alternative exposure state (e.g. digoxin alone, PPI alone, or neither drug), conditional on their observed clinical history. This estimand is inherently time-varying, reflecting the fact that PPI exposure in routine care is not fixed at baseline but may be initiated, discontinued, or re-initiated during follow-up. Conceptually, it aligns with a per-time-unit causal contrast under hypothetical interventions on treatment history, rather than with a static "ever versus never" exposure contrast [147].

Because this causal estimand cannot be identified directly from observational data without assumptions, the study targets a statistical estimand that approximates it under explicit conditions. Specifically, the primary statistical estimand is the weighted cause-specific hazard ratio comparing exposure states in a time-dependent Cox proportional hazards model, where exposure status is updated over follow-up and individuals contribute person-time to different exposure categories as their prescribing status changes. This estimand represents the ratio of hazards of arrhythmia-related hospitalisation between exposure states at time t, conditional on survival up to that time and on measured covariates, in a pseudo-population created through IPTW [130, 148, 204].

This choice of estimand is critical for two reasons. First, by allowing exposure to vary over time, the analysis avoids immortal time bias and exposure misclassification that would arise from treating PPI use as fixed at baseline, a well-recognised source of bias in pharmacoepidemiology [185, 205]. Second, the use of IPTW explicitly targets exchangeability of exposure groups with respect to measured confounders, reweighting the observed cohort to approximate a hypothetical population in which treatment assignment at each time point is independent of prior measured covariates [130, 147, 148]. The balance diagnostics presented demonstrate substantial improvement in covariate balance after weighting, supporting the plausibility of this assumption for the variables observed.

The statistical estimates reported in this chapter - namely, the weighted hazard ratios and their confidence intervals - are therefore estimates of this statistical estimand. Under the standard identifying assumptions of consistency, positivity, correct model specification, and no unmeasured confounding, these estimates can be interpreted as approximations to the underlying causal estimand [130, 147, 148]. Importantly, the Simon–Makuch curves provide a complementary, non-parametric visualisation of the same time-varying estimand, illustrating how differences in arrhythmia-free survival accumulate over time across dynamically changing exposure states while remaining consistent with the proportional hazards structure of the Cox model [180].

At the same time, it is necessary to be explicit about the limits of causal interpretation. Although IPTW substantially reduced imbalance in measured covariates, it cannot account for confounding by factors that were unmeasured or imperfectly captured in routine data, such as frailty, functional status, illness severity, or clinician-specific prescribing preferences. These factors are plausibly associated with both PPI prescribing and arrhythmia risk in older patients with AF. Consequently, the most defensible interpretation is that this analysis provides robustly adjusted real-world evidence that is compatible with a causal effect of concurrent PPI-digoxin exposure, but does not constitute definitive proof of causality. This is consistent with best practice in observational pharmacoepidemiology and appropriately reflects both the strengths and the inherent constraints of real-world data analyses [130, 148, 201].

The direction and specificity of the association are nevertheless informative. The lack of a materially increased hazard for digoxin alone, coupled with a modest increase for concurrent exposure, argues against a simplistic interpretation that the results merely reflect the baseline risk profile of patients who receive digoxin. Equally, the near-null association for PPI alone suggests that the signal is not simply due to PPIs acting as a broad marker of ill-health. Instead, the pattern is compatible with a context-specific interaction risk representing the combination of digoxin's narrow therapeutic window with additional physiological or pharmacological perturbation associated with PPI exposure. At the same time, the modest absolute separation in the Simon-Makuch curves cautions against overstating clinical impact at the whole-cohort level. In a large older population with high baseline event rates and substantial competing risks, a relative increase in hazard can correspond to small absolute differences in risk over two years. This does not invalidate the finding; rather, it provides the correct scale for interpretation and suggests that the clinical relevance may be concentrated in susceptible individuals - those closest to the threshold at which small changes in exposure, electrolytes, or renal clearance translate into symptomatic arrhythmia and admission.

A further limitation specific to the timing of data collection concerns the overlap of the study period with the COVID-19 pandemic. Patient accrual and follow-up extended to 31 December 2020, and thus the final period of observation coincided with the first and second waves of SARS-CoV-2 infection in Scotland, beginning in March 2020. This has two distinct implications for the present analyses. First, SARS-CoV-2 infection is itself associated with several of the outcomes examined in this thesis: COVID-19 has been linked to both tachy- and brady-arrhythmias and to a coagulopathy that increases the risk of both thrombotic and haemorrhagic events. Because COVID-19 disproportionately affected older, multimorbid individuals [206], the same population under study here, infection status is a plausible unmeasured confounder that was not captured in the available data and could not be adjusted for. Second, the pandemic profoundly disrupted hospital activity, with substantial and non-random reductions in admissions for cardiovascular and other conditions during 2020 [207]. Because all outcomes in this thesis were ascertained through hospital admission, this disruption may have led to differential under-ascertainment of events in the final study year. The direction of the resulting bias is uncertain: under-ascertainment of admissions would tend to bias associations toward the null, whereas COVID-19-related arrhythmia and bleeding could inflate event counts in exposed and unexposed individuals alike. The proportion of person-time and events accruing during the pandemic period was limited relative to the full six-year window, so the overall impact is likely to be modest; nonetheless, this represents an uncontrolled source of both confounding and outcome misclassification, and the findings from the final study year should be interpreted with corresponding caution.

The time-varying analytical framework used in this thesis offers limited, partial reassurance in this respect, in that pandemic-era changes in prescribing are reflected in the updated exposure trajectory rather than fixed at baseline, and to the extent that pandemic-related infection risk and admission disruption were distributed similarly across the four exposure states, which were defined by medication use rather than by infection risk, any resulting bias would tend to act non-differentially and so to attenuate rather than inflate the between-group

hazard ratios. This reassurance is only partial as the framework is indexed on time since cohort entry rather than calendar date and therefore cannot isolate or adjust for the pandemic as a calendar-period confounder, cannot account for unmeasured infection status, and cannot recover events unascertained during periods of reduced hospital admission; nor can non-differential bias be assumed given the greater comorbidity burden of the combination-exposed group.

The biological plausibility of an interaction signal between PPIs and digoxin is well grounded, but it must be presented with appropriate caution given the absence of direct mediators in the present dataset. Digoxin is a substrate of the ATP-dependent efflux transporter P-gp and is predominantly eliminated renally, making transporter-related changes in absorption and distribution more plausible mechanisms than classic CYP-mediated metabolic interactions. Several PPIs have been shown in vitro to inhibit P-gp–mediated transport [196, 197], which offers a coherent pathway by which concurrent PPI therapy could increase systemic digoxin exposure. PPIs also raise intragastric pH, potentially altering the fraction of digoxin that remains unchanged and available for absorption [42]. In addition, chronic PPI use has been associated with hypomagnesaemia, and magnesium deficiency can lower the electrophysiological threshold for both atrial and ventricular arrhythmias and potentiate the arrhythmogenicity of digoxin [200]. These mechanisms are not mutually exclusive, and their convergence is what makes a modest clinical signal plausible. However, because the present analysis did not include digoxin serum concentrations, electrolyte measurements, or genotype information, the mechanistic discussion must be interpreted as contextual support rather than evidence of mediation. The findings cannot distinguish whether the increased hazard reflects modest increases in digoxin exposure, electrolyte-mediated vulnerability, residual confounding by frailty, or a combination of these pathways.

The existing literature is also consistent with a phenomenon of heterogeneous risk rather than large average effects. Pharmacokinetic studies have reported modest mean increases in digoxin exposure with omeprazole, with more pronounced increases in subsets of individuals [198, 199]. This pattern is clinically important

because digoxin toxicity has a threshold effect, as a modest increase in exposure may be inconsequential in many patients but clinically meaningful in those already near the upper end of the therapeutic range, in those with renal impairment, or in those with electrolyte vulnerability. Similarly, switch studies have observed that while mean digoxin concentrations may remain stable across changes in gastric acid suppression therapy, a meaningful minority experience increases of a magnitude that could be consequential in routine care [33]. This “tail risk” architecture fits the present chapter’s pattern: a modest relative hazard increase in the concurrent group, modest absolute survival separation, and plausible enrichment of vulnerability within the group of patients who receive both drugs.

At the same time, there are compelling counter-arguments that must be considered because they represent the most likely explanations for spurious association and therefore the most important threats to inference. Foremost is confounding by indication and by patient complexity. PPIs are frequently prescribed in older adults with a higher burden of comorbidity, polypharmacy, prior gastrointestinal pathology, bleeding risk, and healthcare utilisation [27, 195], and these same factors may correlate with arrhythmia risk and admission likelihood. Even with IPTW improving measured balance, it is possible that unmeasured frailty or severity of illness remains unevenly distributed across exposure states. In addition, patients receiving both digoxin and PPIs may be under closer clinical surveillance, more likely to be hospitalised for borderline symptoms, or more frequently coded with arrhythmia diagnoses, raising the possibility of differential outcome capture. Restriction of the endpoint to hospitalised arrhythmias mitigates some of the noise that would be present in outpatient diagnoses and increases specificity for clinically meaningful events, but it also introduces its own selection, capturing only the severest portion of the arrhythmia spectrum and potentially reflecting variation in admission thresholds. These competing explanations do not negate the biological plausibility of a true interaction; rather, they establish the appropriate caution with which the results should be generalised and the importance of presenting the findings as evidence that is compatible with causality but not uniquely explained by it.

A further interpretive issue concerns PPI heterogeneity. PPIs differ in their capacity to inhibit P-gp and in their metabolism via CYP2C19 [41, 43], and this heterogeneity has been highlighted in pharmacokinetic and pharmacology literature. Modelling PPIs as a class was a defensible choice to reflect routine practice and preserve statistical power, and it is consistent with the question most relevant to medication review: whether PPI exposure, as commonly used in the health system, carries incremental risk when co-prescribed with digoxin. However, class-level modelling will tend to average across agents and may dilute a stronger effect confined to higher-interaction PPIs. Therefore, the observed association should be interpreted as the average effect of PPI exposure in this setting rather than as an agent-specific risk estimate. This has two consequences. First, it suggests that the true risk for particular PPIs could be higher than the class estimate in some subgroups. Second, it means the results cannot yet support a prescriptive hierarchy of preferred PPIs in digoxin-treated patients, although they do justify that question as a rational direction for further work.

The broader implications of the findings are best understood through a medication-safety and health-systems lens. Preventable adverse drug reactions remain common in older adults and are frequently related to polypharmacy and drug interactions [208]. In such settings, a small increase in risk associated with a prevalent co-prescribing pattern may be important even if absolute differences appear small over a limited horizon. The practical message is therefore not one of prohibition but of proportionality - clinicians should maintain awareness of the possibility of incremental risk when prescribing PPIs in digoxin-treated AF patients, particularly where the indication for acid suppression is weak, where therapy has been continued beyond an appropriate duration, or where the patient has additional vulnerability such as renal impairment or high comorbidity burden. For hospital clinicians, this supports careful review at transitions of care and consideration of monitoring where clinically indicated. For general practitioners and pharmacists, it reinforces the value of periodic medication review and deprescribing initiatives that prioritise high-value therapy while reducing unnecessary long-term exposure.

In summarising the contribution of this chapter, it is most defensible to state that it advances the field by providing outcome-based evidence, in a large and representative AF population, that concurrent PPI–digoxin exposure is associated with a modest increase in the hazard of hospitalised arrhythmia, while contextualising this association appropriately within small absolute differences in survival and within the constraints of residual confounding and mechanistic unobservability. The result is persuasive because it is coherent - baseline imbalance necessitated robust adjustment; weighting substantially improved measured covariate balance; the Simon–Makuch curves and Cox model estimates showed consistency; and the direction of effect aligns with established pharmacological plausibility and with a broader understanding of digoxin as a drug for which small shifts can matter when patient reserve is limited.

A substantial limitation concerns the definition of the arrhythmia outcome. The outcome used in this study did not specifically evaluate clinically important manifestations of digoxin toxicity, including bradyarrhythmia, atrioventricular block, or pacemaker implantation [56, 58, 62]. This is particularly relevant because digoxin is prescribed for rate control in atrial fibrillation [50]; therefore, some arrhythmia-related hospitalisations may reflect the underlying indication for digoxin treatment rather than digoxin toxicity, introducing potential confounding by indication. A bradyarrhythmia outcome incorporating conduction disturbances and pacemaker implantation would provide a more specific assessment of potential digoxin toxicity and would be less directly related to the indication for digoxin therapy, but could not be analysed within the data-access and analytical resources available for this study. Consequently, the observed association between concurrent digoxin–PPI exposure and arrhythmia-related hospitalisation should not be interpreted as direct evidence of PPI-potentiated digoxin toxicity. Future studies should specifically evaluate bradyarrhythmia, atrioventricular block, and pacemaker implantation as more clinically specific outcomes.

Finally, the findings point clearly to the next steps required to strengthen causal inference and clinical translation. Linkage to therapeutic drug monitoring would allow direct assessment of whether concurrent PPI exposure increases digoxin

concentrations and whether such increases mediate arrhythmia risk. Incorporating electrolyte measurements, particularly magnesium and potassium, would permit evaluation of an important alternative pathway whereby PPIs could lower arrhythmic thresholds independently of digoxin exposure. Stratification by renal function and by individual PPIs would address the strongest biological and clinical hypotheses regarding heterogeneity of effect. Extending follow-up beyond two years would clarify whether the modest relative hazard persists, attenuates, or accumulates with longer exposure. These directions would not merely refine effect estimates but also convert an outcome-based signal into a more mechanistically anchored risk model capable of guiding more precise prescribing and monitoring strategies in routine AF care.

Chapter 4 Oral Anticoagulants, PPIs, and clinical outcomes in patients with thrombotic disease

4.1 Introduction

Oral anticoagulation therapy is essential for the prevention and management of thromboembolic events in individuals with atrial fibrillation, venous thromboembolism, and cerebrovascular diseases [68, 69]. Three different classes of oral anticoagulants are presently utilised in clinical practice: vitamin K antagonists (VKAs), predominantly represented by warfarin; direct thrombin inhibitors (DTIs), with dabigatran as the primary agent; and direct factor Xa inhibitors, which include rivaroxaban, apixaban, and edoxaban. Every class demonstrates distinct pharmacokinetic characteristics, therapeutic monitoring requirements, and drug–drug interaction patterns that affect their clinical efficacy and safety [72, 75]. Although oral anticoagulants are effective in diminishing the incidence of stroke and systemic embolism, they are associated with significant haemorrhagic risk, with serious bleeding events occurring in 2-4% of patients annually [69, 81]. Treatment failure, evidenced by recurrent thromboembolic events or mortality, constitutes another vital outcome dimension that influences clinical decision-making related to anticoagulant selection, dose, and concomitant drug management.

PPIs are among the most commonly given drugs for patients undergoing oral anticoagulation, with co-prescription rates exceeding 30% in certain groups [11, 81]. PPIs are frequently prescribed for gastroprotection in patients considered to be at heightened risk of gastrointestinal bleeding, especially those undergoing combined antithrombotic therapy or with a history of peptic ulcer disease [81]. The pharmacological interactions between PPIs and oral anticoagulants are complex and vary mechanistically among different kinds of anticoagulants. These interactions occur via several mechanisms, including the suppression of cytochrome P450 enzymes, changes in gastric pH that influence drug absorption, and the modification of drug transporter proteins, including P-gp [41, 72].

The primary interaction mechanism of warfarin is the suppression of CYP2C9, the main enzyme that metabolises the more pharmacologically active S-enantiomer of warfarin. Numerous PPIs, especially omeprazole and esomeprazole, demonstrate moderate inhibitory effect on CYP2C9, which may decrease warfarin clearance and elevate systemic exposure [41, 72]. Moreover, by increasing gastrointestinal pH, PPIs may potentially modify the breakdown and absorption properties of warfarin; however, this effect is regarded as clinically insignificant due to warfarin's nearly full bioavailability [75, 77]. The overall clinical consequences of these interactions on bleeding risk and anticoagulant effectiveness are not fully defined in real-world populations.

Dabigatran etexilate exhibits a significantly distinct interaction profile. Dabigatran, a prodrug requiring acid-mediated conversion to its active form, has pH-dependent absorption significantly diminished in the high stomach pH environment induced by PPI therapy [70, 209]. Clinical pharmacokinetic investigations have shown that simultaneous use of PPIs results in a 12-30% reduction in dabigatran exposure, generating theoretical concerns regarding decreased anticoagulant efficacy and the possibility of treatment failure [72, 209]. Moreover, dabigatran serves as a substrate for P-glycoprotein, an ATP-dependent efflux transporter found in intestinal enterocytes [70, 209]. P-glycoprotein, encoded by the ABCB1 gene, serves as a regulatory mechanism that restricts oral bioavailability and promotes drug excretion [41]. In vitro evidence indicates that some PPIs, notably omeprazole and lansoprazole, may impede intestinal P-glycoprotein, potentially mitigating the pH-related decrease in absorption [41, 72]. The therapeutic equilibrium between these conflicting mechanisms, reduced pH-dependent absorption and P-gp inhibition, has not been conclusively determined in standard care environments.

Direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) exhibit substrate affinity for P-glycoprotein, contrasting with dabigatran due to their pH-independent absorption characteristics. These drugs experience differing levels of hepatic metabolism through CYP3A4 and other cytochrome P450 enzymes, with PPIs demonstrating lower inhibitory effects on CYP3A4 relative to CYP2C9 [41,

210]. The main theoretical issue regarding PPI-factor Xa inhibitor interactions focusses on the modification of P-glycoprotein. In vitro studies have shown that omeprazole, lansoprazole, and pantoprazole can disrupt P-glycoprotein-mediated drug efflux [43]. The therapeutic significance of this interaction and its implications for modified bleeding or thrombotic risk have not been thoroughly assessed in various patient populations.

This chapter assesses whether the pharmacological interactions between oral anticoagulants and PPIs, which are mechanistically likely, result in clinically detectable relationships with bleeding episodes and treatment failure in patients with thromboembolic diseases undergoing regular therapy. This study investigates population-level correlations between changing medication exposure patterns and clinical outcomes, rather than directly quantifying causal effects or measuring drug concentrations, thereby offering evidence to guide prescribing decisions in practical contexts where both medications are often co-administered.

4.1.1 Central research questions and analytical approach

This study aimed to determine whether the concurrent use of oral anticoagulants and PPIs in patients aged 51 and older with thromboembolic indications was linked to altered risks of bleeding events and treatment failure in comparison to anticoagulant monotherapy or absence of either medication class. We hypothesised that concurrent exposure would show class-specific correlations consistent with established pharmacological interaction mechanisms.

We hypothesised that concurrent PPI exposure with warfarin would correlate with an elevated bleeding risk due to CYP2C9 inhibition and possible over-anticoagulation, while the impact on treatment failure would depend on the relationship between enhanced anticoagulation (which diminishes thrombotic events) and increased mortality from haemorrhagic complications. We hypothesised that co-administration of PPIs with dabigatran would diminish anticoagulant efficacy due to impaired pH-dependent absorption, potentially resulting in an elevated chance of treatment failure while concurrently reducing the risk of bleeding. We expected no clinically meaningful interactions for factor

Xa inhibitors due to the limited CYP enzyme inhibitory profile of PPIs and the pH-independent absorption of these drugs, but P-gp modulation was still a theoretical issue.

The analyses examined the subsequent specific research questions for each class of oral anticoagulants: One, does anticoagulant monotherapy influence the risks of bleeding and treatment failure in comparison to the absence of exposure to either anticoagulants or PPIs? Two, does PPI monotherapy independently affect the risk of bleeding or treatment failure in individuals with thromboembolic indications? Three, does simultaneous administration of oral anticoagulants and PPIs present an increased risk beyond that associated with anticoagulant monotherapy, indicating significant drug–drug interactions?

A dynamic cohort study design with a two-year follow-up period was employed to address these questions. Exposure to both oral anticoagulants and PPI were modelled as time-dependent, allowing patients to transition between exposure categories throughout the observation period as prescriptions were initiated, continued, or discontinued. This approach captures the temporal dynamics of real-world medication use patterns and avoids immortal time bias that would arise from fixed baseline exposure classification.

The statistical analyses used time-dependent Cox proportional hazards regression models, integrating IPTW to mitigate confounding by indication and account for measured baseline covariates [144, 148, 178]. Exposure status was categorised into four mutually exclusive, time-varying groups: no exposure to either medicine class (reference group), anticoagulant only, PPI only, and simultaneous exposure to both medications. This classification system allowed for the calculation of independent relationships for each exposure pattern while controlling for confounding factors arising from selective prescribing influenced by patient characteristics, comorbidity burden, and expected risks of bleeding or thrombosis.

IPTW was applied utilising propensity score models that included demographic features, socioeconomic factors, comorbidity profiles, and concurrent medication

usage. The efficacy of weighting was evaluated using standardised mean differences, with values under 0.1 signifying sufficient covariate balance among exposure groups. Time-to-event outcomes were illustrated using Simon-Makuch extensions of Kaplan-Meier survival curves, which account for time-varying exposures and offer clear representations of event-free survival probabilities across various exposure states [180].

This methodological framework enables strong observational inference concerning drug–drug interactions, while acknowledging the limitations of non-randomised study designs, such as potential residual confounding from unmeasured variables and the inability to conclusively establish causality without experimental manipulation.

4.2 Methods

4.2.1 Study design and setting

This chapter comprises three retrospective cohort studies, each evaluating a distinct class of oral anticoagulant: (1) warfarin (a vitamin K antagonist); (2) dabigatran (a direct thrombin inhibitor); and (3) direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban, evaluated as a single class). Each cohort was assessed independently for two primary outcomes: haemorrhagic events and treatment failure. The data source (linked NHS Greater Glasgow and Clyde electronic health records, 2014–2020), the Safe Haven analytical infrastructure, the ethical approvals governing access, and STROBE-compliant reporting are described in Chapter 2 (Sections 2.2 and 2.3) and applied as in Chapter 3 (Section 3.2.1).

4.2.2 Study population and eligibility criteria

4.2.2.1 Warfarin cohort

The source population for the warfarin cohort included all persons aged 51 and older who had a recorded prescription for warfarin and a documented diagnosis of at least one thromboembolic indication between 1 January 2014 and 31 December 2020. Qualifying indications included atrial fibrillation (ICD-10 code:

I48), pulmonary embolism (I26, I260, I269), venous thromboembolism (I26, I260, I269, I82, I824, I8240, I82401, I82402, I82403, I8290), transient ischaemic attack (G459), and ischaemic stroke (I63).

Patients were included if they had a minimum of one documented warfarin prescription during the study period, indicating active anticoagulant medication. The exclusion criteria included: (1) a prior bleeding event or treatment failure before cohort entry; (2) absence of demographic data; and (3) a follow-up duration of less than one day.

4.2.2.2 The dabigatran cohort

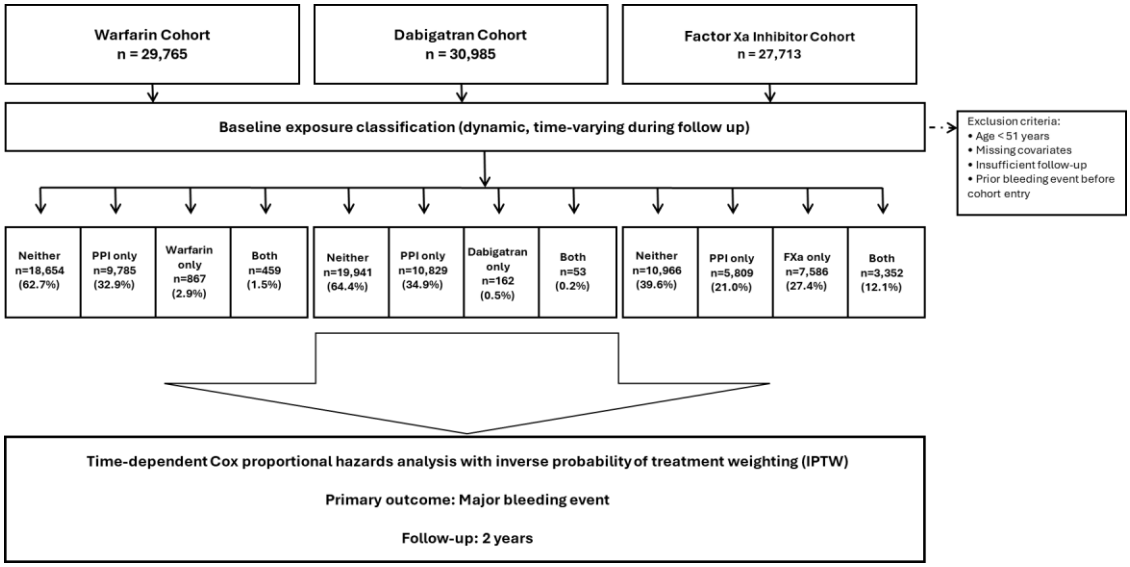
The dabigatran cohort comprised all adults aged 51 years and older with a recorded prescription for dabigatran etexilate and documented diagnosis as specified above for the warfarin cohort. Identical inclusion and exclusion criteria were applied.

4.2.2.3 Factor Xa inhibitor cohort

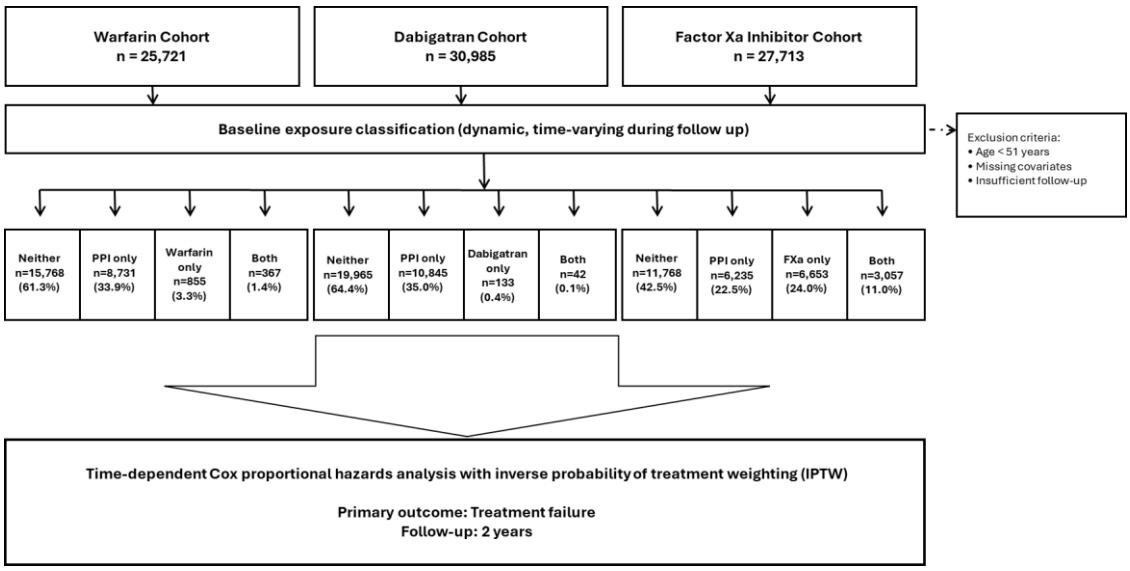
The cohort of factor Xa inhibitors comprised all persons aged 51 and older who had documented prescriptions for rivaroxaban, apixaban, or edoxaban, together with the indicated illnesses. The three drugs were examined as a collective class due to their common mode of action and similar pharmacokinetic characteristics [70, 72]. Identical inclusion and exclusion criteria were implemented.

For each of the three anticoagulant classes, Figure 4.1 (a–b) show the formation of study cohorts and the classification of baseline exposure. Figure 4.1(a) shows the bleeding outcome cohorts with outcome-specific exclusion criteria, and Figure 4.1(b) shows the treatment failure outcome cohorts.

The flowcharts illustrate the dynamic and time-varying characteristics of exposure classification, as well as the implementation of IPTW to address confounding by indication.



(a) The study design for warfarin, dabigatran, and factor Xa inhibitor cohort (bleeding outcome)



(b) The study design for warfarin, dabigatran, and factor Xa inhibitor cohort (Treatment failure outcome)

Figure 4.1 Cohort derivation and baseline exposure classification for oral anticoagulant analyses

4.1a Bleeding cohort. 4.1b Treatment failure cohort. Separate cohorts were constructed for warfarin, dabigatran, and factor Xa inhibitors after application of outcome-specific exclusion criteria. Baseline exposure groups represent concomitant proton pump inhibitor (PPI) and anticoagulant use at cohort entry and are shown for descriptive purposes. Exposure status was modelled as time-varying during follow-up in all analyses. Associations were estimated using time-dependent Cox proportional hazards models with IPTW over a maximum follow-up of 2 years.

4.2.3 Follow-up and censoring

Individuals entered the analytical cohort on the date of the initial prescription for the qualifying oral anticoagulant accompanied by a recorded thromboembolic indication and were followed for up to two years. The general framework for cohort entry, follow-up duration, time scale (time since cohort entry), and the treatment of death as a censoring event in the primary analysis is described in Chapter 2 (Section 2.2.2) and applied as in Chapter 3 (Section 3.2.3).

Because two outcomes were assessed (bleeding events and treatment failure), each was analysed in a separate model with mutual censoring: in bleeding analyses, individuals who experienced treatment failure were censored at that event, and in treatment failure analyses, individuals who experienced a bleeding event were censored at that event. This separation ensures that each model addresses a distinct clinical question while accounting for the competing event through censoring.

4.2.4 Exposure definitions and time-varying structure

Exposure to oral anticoagulants and PPIs was modelled as time-varying using the four-category framework described in Chapter 2 (Section 2.4) and applied as in Chapter 3 (Section 3.2.4). At any given time point, individuals were classified into one of four mutually exclusive exposure states: Neither (reference); PPI only; Anticoagulant only (warfarin, dabigatran, or a factor Xa inhibitor without concurrent PPI); or Both (concurrent anticoagulant and PPI). Individuals could transition between states throughout follow-up, with person-time allocated accordingly. The 7-day carry-over period applied after the anticipated end of each prescription supply, with pharmacokinetic justification specific to oral anticoagulants (warfarin half-life ≈40 h; factor Xa inhibitors 5–15 h), is detailed in Chapter 2 (Section 2.4.1). PPIs were modelled as a therapeutic class (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole), with the rationale and implications for effect estimation described in Chapter 2 (Section 2.4.2).

In the Factor Xa inhibitor cohort, rivaroxaban, apixaban, and edoxaban were evaluated as a single class on the basis of their shared mechanism of direct factor

Xa inhibition and broadly similar pharmacokinetic profiles [70, 72]. Despite differences in half-life, renal clearance, and extent of hepatic metabolism, their interactions with PPIs are fundamentally similar — predominantly involving P-gp modulation rather than the cytochrome P450 inhibition relevant to warfarin or the pH-dependent absorption changes affecting dabigatran [41, 43, 81]. This class-level approach prioritises clinical generalisability and statistical power over agent-specific resolution.

4.2.5 Outcome definitions

Bleeding events: the principal bleeding outcome was hospitalisation for bleeding, identified from inpatient admission records using ICD-10 codes for intracranial haemorrhage (I60–I62), gastrointestinal bleeding (K25–K28 sub-codes for haemorrhage and perforation; K920–K922), respiratory haemorrhage including haemoptysis (R040–R049), and other significant bleeding events (R58). The full code list is presented in Chapter 2 (Table 2.2). The rationale for restricting outcomes to hospitalised events, and the implications for event capture and outcome misclassification, are discussed in Chapter 2 (Sections 2.3.3 and 2.13.6) [11, 81].

Treatment failure: treatment failure was defined as a composite of recurrent thromboembolic events or all-cause mortality. Thromboembolic events were identified from hospital admission records and included ischaemic stroke (I63), transient ischaemic attack (G459), myocardial infarction (I21, I22), pulmonary embolism and venous thromboembolism (I26 and I82 series), and systemic embolism (I74); all-cause mortality was ascertained through linkage to the national death registry. The composite reflects the dual objectives of anticoagulant therapy — preventing recurrent thrombosis and limiting fatal consequences — and acknowledges that treatment failure may present as either recurrent thromboembolism or as mortality from bleeding, cardiovascular events, or other causes potentially affected by anticoagulation or drug–drug interactions [69, 75].

4.2.6 Covariates and confounding structure

Covariate selection followed the framework described in Chapter 2 (Section 2.8.1), which applied the disjunctive cause criterion [175] to identify pre-treatment causes of exposure or outcome and to exclude instrumental variables [173, 174]. Measured covariates included demographics (age, sex, SIMD 2016 decile); binary comorbidity indicators identified from ICD-10 codes recorded prior to or at cohort entry — covering cardiovascular disease (coronary artery disease, heart failure, peripheral vascular disease), hypertension, diabetes mellitus, respiratory disease, neurological, renal and urinary-bladder, musculoskeletal, endocrine, gastrointestinal, hepatobiliary and pancreatic disease, cancer, and mental health conditions; and hospitalisation duration as a proxy for illness severity.

Concomitant medications were modelled as binary indicators of baseline or follow-up exposure: statins (simvastatin, atorvastatin, pravastatin, fluvastatin, rosuvastatin), antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel, dipyridamole), and antiarrhythmic agents (amiodarone, sotalol, flecainide). In each cohort-specific analysis, exposure to anticoagulant classes other than the qualifying drug was included as an additional covariate to capture therapeutic transitions and bridging therapy (e.g., DOAC use in the warfarin cohort). Confounding by indication and residual unmeasured confounding (e.g., over-the-counter PPI use, dietary vitamin K intake) are discussed in Chapter 2 (Sections 2.8.1 and 2.13.1) and revisited in Section 4.4.7.

4.2.7 Statistical analyses

The analytical strategy combined time-varying exposure modelling, IPTW, and time-dependent Cox proportional hazards regression to estimate, under stated assumptions, the contrast in the instantaneous hazard of bleeding and of treatment failure between concurrent anticoagulant–PPI exposure and alternative exposure states (anticoagulant alone, PPI alone, or neither drug), conditional on observed clinical history. Effect estimates are reported as hazard ratios with 95% confidence intervals, with two-sided tests at an α level of 0.05. The full

development of the survival framework, the causal and statistical estimand specification, IPTW implementation, Simon-Makuch curve construction, and the handling of missing data is set out in Chapter 2 (Sections 2.5–2.12) and was applied as in Chapter 3 (Sections 3.2.7.1–3.2.7.8) [130, 148]. This subsection records only the analytical choices specific to the present cohorts.

Time-varying propensity scores were estimated using multinomial logistic regression on the covariates listed in Section 4.2.6, with stabilised weights truncated at the 99th percentile to limit the influence of extreme weights [203]. Covariate balance was assessed using absolute SMD before and after weighting, with values <0.10 considered acceptable [149]. Outcome models were IPTW-weighted, time-dependent Cox proportional hazards regressions with robust sandwich variance estimators to account for weighting and intra-individual correlation across exposure transitions [211].

Because the primary models parameterise exposure groups against the "neither drug" reference, the clinically relevant contrast for each cohort — concurrent anticoagulant–PPI therapy versus anticoagulant monotherapy — was derived from the fitted model coefficients (ß_Both − ß_Anticoagulant_only) and is reported alongside the primary estimates in Section 4.4.1. As noted in Chapter 2 (Section 2.4.2), a valid confidence interval for this contrast cannot be obtained by combining the separately reported estimates and could not be estimated within the resources available for this analysis; these derived contrasts are therefore reported as point estimates only, without confidence intervals or formal statistical inference. Statistical inference is therefore confined to the primary model comparisons against the unexposed reference group.

Missing data were minimal (<2% across covariates in all three cohorts); a complete-case analysis was used, and a sensitivity analysis excluding individuals with any missingness yielded substantively identical results. Several pre-specified sensitivity analyses were considered but not formally conducted: (i) restriction to atrial fibrillation as the sole thromboembolic indication; (ii) exclusion of the first 90 days of follow-up to mitigate prevalent-user bias; (iii) weight truncation at the

95th rather than 99th percentile; and (iv) E-value calculations for unmeasured confounding. The absence of these analyses is acknowledged as a methodological constraint and identified as priority post-thesis work.

All analyses were conducted in R (version 4.3.0) using the WeightIt package for IPTW, the survival package for Cox proportional hazards models, survminer for Simon-Makuch curves, and the tidyverse suite for data manipulation and visualisation.

4.3 Results

4.3.1 Cohort and exposure distribution

This chapter presents findings from three concurrent retrospective cohort studies investigating the correlation between oral anticoagulants, PPIs, and clinical outcomes in patients with thromboembolic indications Figure 4.1(a-b). The warfarin cohort included 29,765 individuals for bleeding analyses and 25,721 patients for treatment failure analyses. The dabigatran cohort comprised 30,985 individuals assessed for both bleeding and treatment failure outcomes. The cohort of Factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) included 27,713 individuals who were evaluated for both outcomes in a similar manner.

The baseline exposure distribution exhibited substantial variations among the three anticoagulant classes, reflecting different prescribing practices and patterns of clinical adoption (Table 4.1). In the warfarin group, the majority of patients commenced follow-up without exposure to either medication (62.7% for bleeding analyses; 61.3% for treatment failure analyses), with roughly one-third undergoing PPI monotherapy and minor proportions exposed to warfarin alone or in conjunction with other therapies. The dabigatran cohort had analogous trends, with 64.4% unexposed at baseline, 34.9-35.0% undergoing PPI monotherapy, and little exposure to dabigatran monotherapy (0.5% for bleeding; 0.4% for treatment failure) or concurrent medication (0.2% for bleeding; 0.1% for treatment failure). Conversely, the Factor Xa inhibitor cohort exhibited significantly elevated baseline anticoagulant usage, with only 39.6-42.5% unexposed, 21.0-22.5% on PPI

monotherapy, 24.0-27.4% getting Factor Xa inhibitor monotherapy, and much higher rates of concurrent exposure (11.0-12.1%).

Exposure status was classified as time-varying during follow-up, allowing patients to shift among the four mutually exclusive categories (no exposure, anticoagulation only, PPI only, or concurrent exposure) as prescriptions were initiated, continued, or discontinued. This methodology included the dynamic characteristics of actual medicine utilisation and guaranteed suitable temporal alignment between exposure status and risk duration for all subsequent analyses.

Table 4.1 Baseline exposure distribution across anticoagulant cohorts and outcomes

Data presented as n (%) for baseline exposure classification. Exposure groups are mutually exclusive at baseline but time-varying during follow-up, allowing patients to transition between states. "Neither" indicates no exposure to anticoagulant or PPI; "PPI Only" indicates PPI exposure without anticoagulant; "Anticoagulant Only" indicates anticoagulant exposure without PPI; "Both" indicates concurrent exposure to both anticoagulant and PPI. Different total N values between outcomes within the same anticoagulant class reflect outcome-specific exclusion criteria applied to avoid prevalent cases. All analyses used time-dependent Cox proportional hazards regression with IPTW and followed patients for up to 2 years

Exposure group	Warfarin		Dabigatran		Factor Xa Inhibitors	
	Bleeding (n = 29,765)	Treatment Failure (n = 25,721)	Bleeding (n = 30,985)	Treatment Failure (n = 30,985)	Bleeding (n = 27,713)	Treatment Failure (n = 27,713)
Total N	**29,765**	**25,721**	**30,985**	**30,985**	**27,713**	**27,713**
Neither (reference group)	18,654 (62.7%)	15,768 (61.3%)	19,941 (64.4%)	19,965 (64.4%)	10,966 (39.6%)	11,768 (42.5%)
PPI only (no anticoagulant)	9,785 (32.9%)	8,731 (33.9%)	10,829 (34.9%)	10,845 (35.0%)	5,809 (21.0%)	6,235 (22.5%)
Anticoagulant only (no PPI)	867 (2.9%)	855 (3.3%)	162 (0.5%)	133 (0.4%)	7,586 (27.4%)	6,653 (24.0%)
Both (anticoagulant + PPI)	459 (1.5%)	367 (1.4%)	53 (0.2%)	42 (0.1%)	3,352 (12.1%)	3,057 (11.0%)

4.3.2 Baseline characteristics

Baseline demographic, clinical, and pharmaceutical parameters exhibited significant variability among exposure groups and anticoagulant cohorts, indicating differences in prescribing patterns, patient profile, and clinical indication profiles (Table 4.2). The identified imbalances highlight the necessity of confounding adjustment using inverse probability of treatment weighting, as elaborated in Section 4.3.3.

Baseline characteristics of the study cohort at entry are presented in Table 4.2. Two parallel outcome analyses were carried out on this single cohort: one examining bleeding and one examining treatment failure (Table 4.3). Across all three anticoagulant cohorts, median age was high and broadly similar across exposure groups, with modestly higher ages observed among patients receiving PPIs, either alone or in combination with anticoagulants. These patterns indicate limited baseline age imbalance and suggest that age-related confounding, while present, was unlikely to be extreme prior to adjustment.

There were systematic differences in sex distribution across exposure groups in all three cohorts (Table 4.2). Female sex was more prevalent in PPI-only groups (54-55%) compared to unexposed patients (50%) and anticoagulant-only groups (48-53%). In patients concurrently receiving anticoagulants and PPIs, the prevalence of females differed across cohorts: warfarin (56%), dabigatran (49%), and factor Xa inhibitors (57%). The observed differences indicate a baseline sex imbalance that was addressed through inverse probability of treatment weighting.

The socioeconomic position, as assessed by the 2016 Scottish Index of Multiple Deprivation (SIMD) deciles, exhibited a broad distribution across exposure groups in all three cohorts (Table 4.2). Patients administered PPIs, especially those concurrently exposed to anticoagulants, exhibited a modest over-representation in lower socioeconomic deciles relative to unexposed individuals or those receiving only anticoagulants. The observed minor differences across intermediate deciles indicate a potential baseline imbalance associated with socioeconomic

disadvantage, highlighting the necessity for confounding adjustment, as addressed through IPTW in subsequent analyses.

Table 4.2 Baseline characteristics of the bleeding cohort by anticoagulant and PPI exposure

The table presents baseline characteristics of patients included in the bleeding analyses, stratified by baseline exposure to oral anticoagulants and proton pump inhibitors (PPIs). Characteristics are shown for four exposure groups: neither anticoagulant nor PPI, PPI only, anticoagulant only, and concurrent anticoagulant–PPI use. Panel (a) summarises demographic characteristics (b) comorbid conditions, while panel (c) summarises baseline medication use. All characteristics are reported prior to IPTW and correspond to covariates included in subsequent time-dependent Cox proportional hazards models.

(a) Summarises demographic characteristics

Variable	Level	WARFARIN COHORT					DABIGATRAN COHORT					FACTOR XA INHIBITOR COHORT				
		Neither	PPI Only	Warfarin Only	Both	Total	Neither	PPI Only	Dabigatran Only	Both	Total	Neither	PPI Only	Factor Xa Only	Both	Total
Total N (%)		18654 (62.7)	9785 (32.9)	867 (2.9)	459 (1.5)	29765	19941 (64.4)	10829 (34.9)	162 (0.5)	53 (0.2)	30985	10966 (39.6)	5809 (21.0)	7586 (27.4)	3352 (12.1)	27713
Age	Median (IQR)	76.3 (68.0 to 83.6)	77.7 (70.2 to 84.2)	73.9 (65.8 to 81.0)	75.2 (68.6 to 81.7)	76.7 (68.7 to 83.7)	77.6 (69.6 to 84.2)	78.3 (70.9 to 84.3)	78.1 (70.9 to 84.0)	80.0 (73.9 to 85.0)	77.8 (70.1 to 84.3)	78.1 (69.9 to 84.9)	78.3 (70.6 to 84.9)	76.8 (69.1 to 83.1)	77.7 (70.9 to 83.7)	77.7 (69.9 to 84.3)
Sex	Male	9320 (50.0)	4386 (44.8)	426 (49.1)	201 (43.8)	14333 (48.2)	9897 (49.6)	4862 (44.9)	85 (52.5)	27 (50.9)	14871 (48.0)	5444 (49.6)	2657 (45.7)	3626 (47.8)	1440 (43.0)	13167 (47.5)
	Female	9334 (50.0)	5399 (55.2)	441 (50.9)	258 (56.2)	15432 (51.8)	10044 (50.4)	5967 (55.1)	77 (47.5)	26 (49.1)	16114 (52.0)	5522 (50.4)	3152 (54.3)	3960 (52.2)	1912 (57.0)	14546 (52.5)
SIMD 2016	Decile 1 (most deprived)	3943 (21.1)	2282 (23.3)	162 (18.7)	118 (25.7)	6505 (21.9)	4050 (20.3)	2511 (23.2)	27 (16.7)	13 (24.5)	6601 (21.3)	2320 (21.2)	1370 (23.6)	1522 (20.1)	788 (23.5)	6000 (21.7)
	Decile 2	2891 (15.5)	1611 (16.5)	129 (14.9)	63 (13.7)	4694 (15.8)	3072 (15.4)	1786 (16.5)	20 (12.3)	8 (15.1)	4886 (15.8)	1762 (16.1)	958 (16.5)	1114 (14.7)	576 (17.2)	4410 (15.9)
	Decile 3	1764 (9.5)	987 (10.1)	85 (9.8)	59 (12.9)	2895 (9.7)	1875 (9.4)	1124 (10.4)	22 (13.6)	9 (17.0)	3030 (9.8)	1080 (9.8)	643 (11.1)	679 (9.0)	340 (10.1)	2742 (9.9)
	Decile 4+	10056 (53.9)	4905 (50.1)	491 (56.6)	219 (47.7)	15671 (52.6)	10944 (54.9)	5408 (49.9)	93 (57.4)	23 (43.4)	16468 (53.1)	5804 (52.9)	2838 (48.9)	4271 (56.3)	1648 (49.2)	14561 (52.5)

(b) Baseline comorbid conditions.

Variable	Level	WARFARIN COHORT					DABIGATRAN COHORT					FACTOR XA INHIBITOR COHORT				
		Neither	PPI Only	Warfarin Only	Both	Total	Neither	PPI Only	Dabigatran Only	Both	Total	Neither	PPI Only	Factor Xa Only	Both	Total
Cardiovascular disease	Yes	11779 (63.1)	7495 (76.6)	383 (44.2)	263 (57.3)	19920 (66.9)	13219 (66.3)	8330 (76.9)	133 (82.1)	44 (83.0)	21726 (70.1)	6638 (60.5)	4157 (71.6)	5173 (68.2)	2665 (79.5)	18633 (67.2)
Musculoskeletal disorders	Yes	5210 (27.9)	4156 (42.5)	149 (17.2)	142 (30.9)	9657 (32.4)	5520 (27.7)	4473 (41.3)	49 (30.2)	19 (35.8)	10061 (32.5)	2975 (27.1)	2283 (39.3)	2109 (27.8)	1429 (42.6)	8796 (31.7)
Mental health disorders	Yes	3066 (16.4)	2926 (29.9)	76 (8.8)	95 (20.7)	6163 (20.7)	3051 (15.3)	2993 (27.6)	23 (14.2)	14 (26.4)	6081 (19.6)	1591 (14.5)	1486 (25.6)	1229 (16.2)	1013 (30.2)	5319 (19.2)
Respiratory disease	Yes	3366 (18.0)	2834 (29.0)	106 (12.2)	102 (22.2)	6408 (21.5)	3663 (18.4)	3020 (27.9)	20 (12.3)	12 (22.6)	6715 (21.7)	1916 (17.5)	1510 (26.0)	1498 (19.7)	1018 (30.4)	5942 (21.4)
Neurological disorders	Yes	5757 (30.9)	5026 (51.4)	157 (18.1)	166 (36.2)	11106 (37.3)	6169 (30.9)	5366 (49.6)	50 (30.9)	25 (47.2)	11610 (37.5)	3124 (28.5)	2622 (45.1)	2521 (33.2)	1829 (54.6)	10096 (36.4)
Kidney/urinary/bladder disorders	Yes	7094 (38.0)	4952 (50.6)	342 (39.4)	239 (52.1)	12627 (42.4)	8457 (42.4)	5714 (52.8)	68 (42.0)	31 (58.5)	14270 (46.1)	4809 (43.9)	3070 (52.8)	2939 (38.7)	1683 (50.2)	12501 (45.1)
Cancer	Yes	1864 (10.0)	1192 (12.2)	51 (5.9)	38 (8.3)	3145 (10.6)	1954 (9.8)	1248 (11.5)	14 (8.6)	<5 (<1)	3220 (10.4)	1277 (11.6)	816 (14.0)	556 (7.3)	269 (8.0)	2918 (10.5)
Diabetes mellitus	Yes	1690 (9.1)	1200 (12.3)	69 (8.0)	49 (10.7)	3008 (10.1)	1842 (9.2)	1323 (12.2)	12 (7.4)	8 (15.1)	3185 (10.3)	1017 (9.3)	697 (12.0)	666 (8.8)	410 (12.2)	2790 (10.1)
Gastrointestinal disease	Yes	291 (1.6)	280 (2.9)	9 (1.0)	8 (1.7)	588 (2.0)	326 (1.6)	302 (2.8)	<5 (<1)	5 (9.4)	635 (2.0)	171 (1.6)	150 (2.6)	125 (1.6)	118 (3.5)	564 (2.0)
Endocrine disorders	Yes	1375 (7.4)	1009 (10.3)	47 (5.4)	38 (8.3)	2469 (8.3)	1508 (7.6)	1104 (10.2)	15 (9.3)	<5 (<1)	2630 (8.5)	759 (6.9)	569 (9.8)	629 (8.3)	345 (10.3)	2302 (8.3)
Liver/GB/pancreatic disease	Yes	457 (2.5)	480 (4.9)	8 (0.9)	16 (3.5)	961 (3.2)	472 (2.4)	496 (4.6)	<5 (<1)	<5 (<1)	973 (3.1)	318 (2.9)	309 (5.3)	140 (1.8)	121 (3.6)	888 (3.2)
Infection	Yes	38 (0.2)	26 (0.3)	5 (0.6)	<5 (<1)	70 (<5)	41 (0.2)	25 (0.2)	<5 (<1)	<5 (<1)	66 (0.2)	27 (0.2)	18 (0.3)	11 (0.1)	6 (0.2)	62 (0.2)
Hospital admission duration	Median (IQR)	6.0 (2.0 to 18.0)	6.0 (2.0 to 13.0)	8.0 (3.0 to 16.0)	7.0 (3.0 to 15.0)	6.0 (2.0 to 16.0)	6.0 (2.0 to 15.0)	5.0 (2.0 to 12.0)	8.0 (2.0 to 24.8)	6.0 (3.0 to 19.0)	6.0 (2.0 to 14.0)	7.0 (2.0 to 18.0)	6.0 (2.0 to 14.0)	5.0 (2.0 to 12.0)	5.0 (2.0 to 10.0)	6.0 (2.0 to 14.0)

(c) Summarises baseline medication use

Variable	Level	WARFARIN COHORT					DABIGATRAN COHORT					FACTOR XA INHIBITOR COHORT				
		None	PPI only	Warfarin only	Both	Total	None	PPI only	Dabigatran only	Both	Total	None	PPI only	FXa inhibitors only	Both	Total
Simvastatin	Yes	2562 (13.7)	2508 (25.6)	139 (16.0)	134 (29.2)	5343 (18.0)	3273 (16.4)	3003 (27.7)	27 (16.7)	15 (28.3)	6318 (20.4)	1754 (16.0)	1651 (28.4)	1282 (16.9)	880 (26.3)	5567 (20.1)
Aspirin	Yes	2102 (11.3)	2313 (23.6)	110 (12.7)	115 (25.1)	4640 (15.6)	2074 (10.4)	2270 (21.0)	12 (7.4)	12 (22.6)	4368 (14.1)	1413 (12.9)	1529 (26.3)	727 (9.6)	602 (18.0)	4271 (15.4)
Atorvastatin	Yes	2128 (11.4)	2249 (23.0)	100 (11.5)	100 (21.8)	4577 (15.4)	2519 (12.6)	2566 (23.7)	23 (14.2)	16 (30.2)	5124 (16.5)	1263 (11.5)	1279 (22.0)	1046 (13.8)	868 (25.9)	4456 (16.1)
clopidogrel	Yes	1063 (5.7)	1231 (12.6)	24 (2.8)	38 (8.3)	2356 (7.9)	1031 (5.2)	1180 (10.9)	<5 (<1)	5 (9.4)	2220 (7.2)	734 (6.7)	842 (14.5)	301 (4.0)	271 (8.1)	2148 (7.8)
Amiodarone	Yes	53 (0.3)	52 (0.5)	<5 (<1)	<5 (<1)	108 (0.4)	95 (0.5)	77 (0.7)	<5 (<1)	<5 (<1)	172 (0.6)	62 (0.6)	47 (0.8)	15 (0.2)	10 (0.3)	134 (0.5)
Pravastatin	Yes	78 (0.4)	83 (0.8)	6 (0.7)	6 (1.3)	168 (0.6)						110 (0.6)	97 (1.7)	42 (0.6)	33 (1.0)	282 (1.0)
Fluvastatin	Yes	<5 (<1)	6 (0.1)	<5 (<1)	<5 (<1)	10 (0.0)										
Dipyridamole	Yes	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)										
Ticagrelor	Yes	31 (0.2)	37 (0.4)	<5 (<1)	<5 (<1)	72 (0.2)						19 (0.2)	24 (0.4)	13 (0.2)	13 (0.4)	69 (0.2)
Prasugrel	Yes	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)										
Edoxaban	Yes	245 (1.3)	229 (2.3)	<5 (<1)	<5 (<1)	479 (1.6)	296 (1.5)	255 (2.4)	<5 (<1)	<5 (<1)	551 (1.8)					
Apixaban	Yes	716 (3.8)	553 (5.7)	9 (1.0)	<5 (<1)	1281 (4.3)	871 (4.4)	671 (6.2)	<5 (<1)	<5 (<1)	1548 (5.0)					
Rivaroxaban	Yes	122 (0.7)	73 (0.7)	<5 (<1)	<5 (<1)	197 (0.7)	186 (0.9)	122 (1.1)	<5 (<1)	<5 (<1)	308 (1.0)					
Dabigatran	Yes	22 (0.1)	15 (0.2)	<5 (<1)	<5 (<1)	37 (0.1)						26 (0.2)	12 (0.2)	15 (0.2)	<5 (<1)	57 (0.2)
Warfarin	Yes						1723 (8.6)	908 (8.4)	10 (6.2)	<5 (<1)	2642 (8.5)	1439 (13.1)	758 (13.0)	321 (4.2)	104 (3.1)	2622 (9.5)

*Data are expressed as n (%) for categorical variables and median (interquartile range, IQR) for continuous variables. Baseline characteristics were evaluated at cohort entry prior to the occurrence of outcomes and pertain to both bleeding and treatment failure analyses. Sample size: The bleeding analyses included 29,765 warfarin users, 30,985 dabigatran users, and 27,713 Factor Xa inhibitor users, following the exclusion of individuals with previous bleeding incidents. Treatment failure analyses included 25,721 warfarin users (a reduction of 4,044 patients, or 13.6%, due to the exclusion of existing treatment failure events at baseline), 30,985 dabigatran users (the same patient population as the bleeding cohort; minor differences in baseline exposure classification between outcomes reflect outcome-specific covariate assessment at cohort entry), and 27,713 Factor Xa inhibitor users (the same patient population as the bleeding cohort; minor differences in baseline exposure classification between outcomes reflect outcome-specific covariate assessment at cohort entry). The substantially higher rate of prevalent treatment failure exclusion in the warfarin cohort is consistent with the longer historical use and broader therapeutic indications of warfarin in patients with established thromboembolic disease.

**Counts have been rounded to comply with Safe Haven Statistical Discluser Thershold. Dominant binary counted rounded down by ?5 to nearest 5 to prevent back-calculation of suppressed values. SIMD deciles 4-10 merged into 4+ to avoid suppression of individual small counts. Supressed counts (<5) have both count AND percentage supressed '<5(<1)'.*

Table 4.3 Baseline characteristics of treatment failure cohort by OACs and PPIs exposure

The table presents baseline characteristics of patients included in the Treatment failure analyses, stratified by baseline exposure to OACs and PPIs. Characteristics are shown for four exposure groups: neither anticoagulant nor PPI, PPI only, anticoagulant only, and concurrent anticoagulant–PPI use. Panel (a) summarises demographic characteristics (b) comorbid conditions, while panel (c) summarises baseline medication use. All characteristics are reported prior to IPTW and correspond to covariates included in subsequent time-dependent Cox proportional hazards models.

(a) Summarises demographic characteristics

Variable	Level	WARFARIN COHORT					DABIGATRAN COHORT					FACTOR XA INHIBITOR COHORT				
		Neither	PPI Only	Warfarin Only	Both	Total	Neither	PPI Only	Dabigatran Only	Both	Total	Neither	PPI Only	Factor Xa Only	Both	Total
Total N (%)		15768 (61.3)	8731 (33.9)	855 (3.3)	367 (1.4)	25721	19965 (64.4)	10845 (35.0)	133 (0.4)	42 (0.1)	30985	11768 (42.5)	6235 (22.5)	6653 (24.0)	3057 (11.0)	27713
Age	Median (IQR)	77.0 (68.8 to 84.1)	78.1 (70.6 to 84.5)	74.8 (66.4 to 81.7)	75.0 (68.8 to 81.7)	77.3 (69.4 to 84.1)	77.6 (69.6 to 84.2)	78.3 (70.9 to 84.3)	78.0 (70.7 to 83.6)	79.7 (73.6 to 84.6)	77.8 (70.1 to 84.3)	78.2 (70.0 to 84.8)	78.4 (70.8 to 84.8)	76.5 (68.8 to 82.9)	77.4 (70.5 to 83.6)	77.7 (69.9 to 84.3)
Sex	Male	7743 (49.1)	3888 (44.5)	406 (47.5)	162 (44.1)	12199 (47.4)	9909 (49.6)	4868 (44.9)	71 (53.4)	23 (54.8)	14871 (48.0)	5817 (49.4)	2825 (45.3)	3201 (48.1)	1324 (43.3)	13167 (47.5)
	Female	8025 (50.9)	4843 (55.5)	449 (52.5)	205 (55.9)	13522 (52.6)	10056 (50.4)	5977 (55.1)	62 (46.6)	19 (45.2)	16114 (52.0)	5951 (50.6)	3410 (54.7)	3452 (51.9)	1733 (56.7)	14546 (52.5)
SIMD 2016	Decile 1 (most deprived)	3243 (20.6)	2046 (23.4)	163 (19.1)	89 (24.3)	5541 (21.5)	4055 (20.3)	2512 (23.2)	22 (16.5)	12 (28.6)	6601 (21.3)	2495 (21.2)	1464 (23.5)	1322 (19.9)	719 (23.5)	6000 (21.7)
	Decile 2	2435 (15.4)	1453 (16.6)	132 (15.4)	53 (14.4)	4073 (15.8)	3075 (15.4)	1788 (16.5)	16 (12.0)	7 (16.7)	4886 (15.8)	1885 (16.0)	1041 (16.7)	969 (14.6)	515 (16.8)	4410 (15.9)
	Decile 3	1484 (9.4)	868 (9.9)	82 (9.6)	46 (12.5)	2480 (9.6)	1879 (9.4)	1126 (10.4)	18 (13.5)	7 (16.7)	3030 (9.8)	1151 (9.8)	685 (11.0)	594 (8.9)	312 (10.2)	2742 (9.9)
	Decile 4+	8606 (54.6)	4364 (50.0)	478 (55.9)	179 (48.8)	13627 (53.0)	10956 (54.9)	5419 (50.0)	77 (57.9)	16 (38.1)	14468 (46.7)	6237 (53.0)	3045 (54.8)	3768 (56.6)	1511 (49.4)	14561 (52.5)

(b) Baseline comorbid conditions.

Variable	Level	WARFARIN COHORT					DABIGATRAN COHORT					FACTOR XA INHIBITOR COHORT				
		Neither	PPI Only	Warfarin Only	Both	Total	Neither	PPI Only	Dabigatran Only	Both	Total	Neither	PPI Only	Factor Xa Only	Both	Total
Cardiovascular disease	Yes	10354 (65.7)	6786 (77.7)	395 (46.2)	213 (58.0)	17748 (69.0)	13240 (66.3)	8345 (76.9)	107 (80.5)	34 (81.0)	21726 (70.1)	7188 (61.1)	4476 (71.8)	4529 (68.1)	2440 (79.8)	18633 (67.2)
Musculoskeletal disorders	Yes	4558 (28.9)	3775 (43.2)	164 (19.2)	116 (31.6)	8613 (33.5)	5527 (27.7)	4481 (41.3)	38 (28.6)	15 (35.7)	10061 (32.5)	3207 (27.3)	2458 (39.4)	1830 (27.5)	1301 (42.6)	8796 (31.7)
Mental health disorders	Yes	2572 (16.3)	2578 (29.5)	80 (9.4)	78 (21.3)	5308 (20.6)	3056 (15.3)	2998 (27.6)	16 (12.0)	11 (26.2)	6081 (19.6)	1703 (14.5)	1602 (25.7)	1084 (16.3)	930 (30.4)	5319 (19.2)
Respiratory disease	Yes	2994 (19.0)	2561 (29.3)	113 (13.2)	86 (23.4)	5754 (22.4)	3666 (18.4)	3023 (27.9)	18 (13.5)	8 (19.0)	6715 (21.7)	2086 (17.7)	1640 (26.3)	1298 (19.5)	918 (30.0)	5942 (21.4)
Neurological disorders	Yes	5007 (31.8)	4507 (51.6)	168 (19.6)	138 (37.6)	9820 (38.2)	6172 (30.9)	5374 (49.6)	45 (33.8)	19 (45.2)	11610 (37.5)	3390 (28.8)	2833 (45.4)	2196 (33.0)	1677 (54.9)	10096 (36.4)
Kidney/urinary/bladder disorders	Yes	6284 (39.9)	4488 (51.4)	346 (40.5)	203 (55.3)	11321 (44.0)	8469 (42.4)	5724 (52.8)	54 (40.6)	23 (54.8)	14270 (46.1)	5180 (44.0)	3323 (53.3)	2492 (37.5)	1506 (49.3)	12501 (45.1)
Cancer	Yes	1690 (10.7)	1084 (12.4)	50 (5.8)	28 (7.6)	2852 (11.1)	1956 (9.8)	1249 (11.5)	12 (9.0)	<5 (<1)	3220 (10.4)	1348 (11.5)	848 (13.6)	475 (7.1)	247 (8.1)	2918 (10.5)
Diabetes mellitus	Yes	1386 (8.8)	1038 (11.9)	72 (8.4)	41 (11.2)	2537 (9.9)	1846 (9.2)	1324 (12.2)	8 (6.0)	7 (16.7)	3185 (10.3)	1095 (9.3)	751 (12.0)	574 (8.6)	370 (12.1)	2790 (10.1)
Gastrointestinal disease	Yes	252 (1.6)	250 (2.9)	11 (1.3)	7 (1.9)	520 (2.0)	326 (1.6)	304 (2.8)	<5 (<1)	<5 (<1)	635 (<2.1)	183 (1.6)	170 (2.7)	111 (1.7)	100 (3.3)	564 (2.0)
Endocrine disorders	Yes	1197 (7.6)	911 (10.4)	48 (5.6)	29 (7.9)	2185 (8.5)	1512 (7.6)	1106 (10.2)	9 (6.8)	<5 (<1)	2630 (8.5)	825 (7.0)	620 (9.9)	548 (8.2)	309 (10.1)	2302 (8.3)
Liver/GB/pancreatic disease	Yes	400 (2.5)	431 (4.9)	13 (1.5)	9 (2.9)	853 (3.3)	472 (2.4)	497 (4.6)	<5 (<1)	<5 (<1)	973 (3.1)	338 (2.9)	329 (5.3)	112 (1.7)	109 (3.6)	888 (3.2)
Infection	Yes	34 (0.2)	22 (0.3)	5 (0.6)	<5 (<1)	62 (0.2)	41 (0.2)	25 (0.2)	<5 (<1)	<5 (<1)	66 (0.2)	28 (0.2)	18 (0.3)	10 (0.2)	6 (0.2)	62 (0.2)
Hospital admission duration	Median (IQR)	6.0 (2.0 to 15.0)	5.0 (2.0 to 12.0)	7.0 (3.0 to 15.0)	7.0 (3.0 to 15.0)	6.0 (2.0 to 14.0)	6.0 (2.0 to 15.0)	5.0 (2.0 to 12.0)	9.0 (3.0 to 25.0)	6.0 (3.2 to 17.8)	6.0 (2.0 to 14.0)	7.0 (2.0 to 18.0)	6.0 (2.0 to 14.0)	5.0 (2.0 to 12.0)	5.0 (2.0 to 10.0)	6.0 (2.0 to 14.0)

(c) Summarises baseline medication use

Variable	Level	WARFARIN COHORT					DABIGATRAN COHORT					FACTOR XA INHIBITOR COHORT				
		Neither	PPI only	Warfarin only	Both	Total	Neither	PPI only	Dabigatran only	Both	Total	Neither	PPI only	FXa inhibitors only	Both	Total
Simvastatin	Yes	2358 (15.0)	2343 (26.8)	152 (17.8)	108 (29.4)	4961 (19.3)	3274 (16.4)	3010 (27.8)	24 (18.0)	10 (23.8)	6318 (20.4)	1902 (16.2)	1772 (28.4)	1098 (16.5)	795 (26.0)	5567 (20.1)
Aspirin	Yes	1885 (12.0)	2065 (23.7)	119 (13.9)	90 (24.5)	4159 (16.2)	2074 (10.4)	2277 (21.0)	9 (6.8)	8 (19.0)	4368 (14.1)	1524 (13.0)	1658 (26.6)	579 (8.7)	510 (16.7)	4271 (15.4)
Atorvastatin	Yes	1901 (12.1)	2029 (23.2)	111 (13.0)	82 (22.3)	4123 (16.0)	2520 (12.6)	2570 (23.7)	21 (15.8)	13 (31.0)	5124 (16.5)	1369 (11.6)	1402 (22.5)	902 (13.6)	783 (25.6)	4456 (16.1)
clopidogrel	Yes	973 (6.2)	1098 (12.6)	30 (3.5)	35 (9.5)	2136 (8.3)	1031 (5.2)	1182 (10.9)	<5 (<1)	<5 (<1)	2220 (7.2)	782 (6.6)	892 (14.3)	242 (3.6)	232 (7.6)	2148 (7.8)
Amiodarone	Yes	52 (0.3)	48 (0.5)	<5 (<1)	<5 (<1)	103 (0.4)	95 (0.5)	77 (0.7)	<5 (<1)	<5 (<1)	172 (0.6)	62 (0.5)	50 (0.8)	14 (0.2)	8 (0.8)	134 (0.5)
Pravastatin	Yes	70 (0.4)	80 (0.9)	<5 (<1)	6 (1.6)	157 (0.6)	165 (0.8)	150 (1.4)	<5 (<1)	<5 (<1)	316 (1.0)	116 (1.0)	103 (1.7)	34 (0.5)	29 (0.9)	282 (1.0)
Fluvastatin	Yes						5 (<1)*	9 (0.1)	<5 (<1)	<5 (<1)	13 (0.0)	<5 (<1)	7 (0.1)	<5 (<1)	<5 (<1)	12 (0.0)
Dipyridamole	Yes						5 (<1)*	5 (<1)*	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)
Ticagrelor	Yes	28 (0.2)	38 (0.4)	<5 (<1)	<5 (<1)	69 (0.3)	30 (0.2)	40 (0.4)	<5 (<1)	<5 (<1)	70 (0.2)	24 (0.2)	28 (0.4)	7 (0.1)	10 (0.3)	69 (0.2)
Prasugrel	Yes						5 (<1)*	5 (<1)*	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)
Edoxaban	Yes	249 (1.6)	234 (2.7)	<5 (<1)	<5 (<1)	488 (1.9)	296 (1.5)	255 (2.4)	<5 (<1)	<5 (<1)	551 (1.8)					
Apixaban	Yes	743 (4.7)	582 (6.7)	11 (1.3)	<5 (<1)	1340 (5.2)	871 (4.4)	672 (6.2)	<5 (<1)	<5 (<1)	1548 (5.0)					
Rivaroxaban	Yes	120 (0.8)	77 (0.9)	<5 (<1)	<5 (<1)	199 (0.8)	186 (0.9)	122 (1.1)	<5 (<1)	<5 (<1)	308 (1.0)					
Dabigatran	Yes	24 (0.2)	17 (0.2)	<5 (<1)	<5 (<1)	41 (0.2)						32 (0.3)	14 (0.2)	8 (0.1)	<5 (<1)	57 (0.2)
Warfarin	Yes						1726 (8.6)	910 (8.4)	5 (3.8)	<5 (<1)	2642 (8.5)	1547 (13.1)	816 (13.1)	196 (2.9)	63 (2.1)	2622 (9.5)

* Data are expressed as n (%) for categorical variables and median (interquartile range, IQR) for continuous variables. Baseline characteristics were evaluated at cohort entry prior to the occurrence of outcomes and pertain to both treatment failure and bleeding analyses. Sample size: The treatment failure analyses included 25,721 warfarin users (a reduction of 4,044 patients, or 13.6%, relative to the bleeding cohort, due to the exclusion of individuals with existing treatment failure events at baseline), 30,985 dabigatran users (the same patient population as the bleeding cohort; minor differences in baseline exposure classification between outcomes reflect outcome-specific covariate assessment at cohort entry), and 27,713 Factor Xa inhibitor users (the same patient population as the bleeding cohort; minor differences in baseline exposure classification between outcomes reflect outcome-specific covariate assessment at cohort entry). For comparison, the bleeding analyses included 29,765 warfarin users, 30,985 dabigatran users, and 27,713 Factor Xa inhibitor users, following the exclusion of individuals with previous bleeding incidents. The substantially higher rate of prevalent treatment failure exclusion in the warfarin cohort is consistent with the longer historical use and broader therapeutic indications of warfarin in patients with established thromboembolic disease.

*Counts have been rounded to comply with Safe Haven Statistical Discluser Thershold. Dominant binary counted rounded down by ?5 to nearest 5 to prevent back-calculation of suppressed values. SIMD deciles 4-10 merged into 4+ to avoid suppression of individual small counts. Supressed counts (<5) have both count AND percentage supressed '<5(<1)'.

Baseline comorbidity burden differed substantially across exposure groups in all three anticoagulant cohorts, with systematic enrichment of multimorbidity in PPI-containing exposure states, particularly among patients concurrently exposed to anticoagulants and PPIs (Table 4.2). Cardiovascular disease exhibited a significant prevalence, impacting 44-82% of patients on anticoagulant monotherapy and 57-83% of those concurrently receiving anticoagulants and PPIs. The magnitude and direction of differences varied by anticoagulant type: warfarin exhibited significant enrichment in the Both group (57% vs 44% monotherapy), whereas dabigatran and factor Xa inhibitor cohorts displayed elevated cardiovascular comorbidity across all anticoagulant-containing exposure states. In unexposed patients, cardiovascular comorbidity ranged from 60% to 66%, intermediate between the range observed for anticoagulant monotherapy groups.

Marked differences were also observed for musculoskeletal, mental health, neurological, respiratory, and renal comorbidities, all of which were substantially more prevalent in PPI-containing exposure states across cohorts. Mental health conditions affected 9-16% of anticoagulant monotherapy patients compared with 21-30% of those receiving both drugs concurrently, representing substantial relative differences. Neurological and musculoskeletal conditions demonstrated particularly pronounced enrichment among PPI users, consistent with greater overall disease burden and healthcare complexity. Mental health conditions and respiratory disease followed similar patterns, with higher prevalence among patients receiving PPIs either alone or in combination with anticoagulants, suggesting clinically coherent confounding by indication.

Gastrointestinal diagnoses exhibited modest yet clinically significant differences among exposure groups. The prevalence of gastrointestinal disease among patients receiving both anticoagulants and PPIs varied from 2% to 9% in bleeding cohort analyses (2% for warfarin, 9% for dabigatran, and 4% for factor Xa inhibitors), in contrast to 1-2% observed in groups undergoing anticoagulant monotherapy. The observed absolute differences, though minimal, indicate effective clinical targeting of PPI therapy for patients with gastrointestinal risk factors.

Other comorbidities including, diabetes, endocrine disorders, liver and biliary disease, cancer, gastrointestinal diagnoses, and infection were less strongly differentiated across exposure groups, with smaller absolute differences that would be less likely to generate large SMD individually.

Taken together, these baseline patterns indicate substantial and clinically meaningful imbalance across multiple comorbidity domains, particularly in PPI-containing exposure states, and provide strong justification for the subsequent application of IPTW to improve covariate balance prior to outcome analyses.

Baseline healthcare utilisation, assessed using duration of hospital admission at cohort entry, differed across exposure groups in all three anticoagulant cohorts (Table 4.2). In the warfarin cohort, patients on anticoagulant monotherapy had the longest median admission duration of 8 days (IQR: 3-16), followed by those receiving both drugs concurrently at 7 days (IQR: 3-15). In contrast, the PPI-only and unexposed groups had shorter admissions, with median durations of 6 days (IQR: 2-13) and 6 days (IQR: 2-18), respectively. Comparable patterns were noted in the dabigatran cohort, wherein groups receiving anticoagulants exhibited longer hospital stays (8 days for monotherapy, 6 days for concurrent therapy) relative to patients receiving only PPIs or those unexposed. In the cohort of factor Xa inhibitors, admission durations exhibited greater similarity among exposure groups, with median values ranging from 5 to 7 days. This pattern suggests greater illness severity and healthcare complexity among patients prescribed anticoagulants and is consistent with the broader enrichment of comorbidity observed in these exposure states. Differences in admission duration further indicate plausible baseline imbalance in healthcare utilisation that could contribute to confounding if not adequately addressed.

Patterns of concomitant medication use differed across the three anticoagulant cohorts, reflecting variation in clinical context and treatment complexity (Table 4.2). Statin therapy was common across all cohorts, affecting approximately one-third to two-fifths of patients, consistent with the high prevalence of underlying cardiovascular disease. Antiplatelet agents were prescribed in a minority of patients, with aspirin and clopidogrel use generally observed in fewer than 10% of

individuals across cohorts, indicating that a subset of patients were managed with more complex antithrombotic regimens despite recognised bleeding risk.

Prescriptions for alternative oral anticoagulants were also observed within each cohort, affecting roughly 10–15% of patients in warfarin- and dabigatran-based cohorts and a smaller proportion of those initiated on factor Xa inhibitors. These findings suggest that modification of anticoagulant therapy occurred in routine care, although the present data do not permit attribution of such changes to specific clinical indications. Overall, the observed variation in concomitant medication use underscores the complexity of treatment pathways and reinforces the need for comprehensive confounding adjustment in subsequent weighted analyses.

The observed baseline imbalances indicate significant confounding by indication, since PPI prescriptions are consistently linked to advanced age, elevated comorbidity, heightened acute illness severity, and enhanced gastrointestinal risk factors. IPTW was utilised to rectify these imbalances and generate pseudo-populations with equitable covariate distributions, as detailed in the subsequent section.

4.3.3 Covariate balance after inverse probability of treatment weighting (IPTW)

IPTW was utilised to reduce confounding by indication and achieve covariate equilibrium among exposure groups in all three anticoagulant cohorts for analyses of both bleeding and treatment failure. Before weighting, significant imbalances were noted, with patients receiving PPIs consistently demonstrating advanced age, increased comorbidity burden, higher prevalence of gastrointestinal diseases, and extended hospitalisation duration compared to those undergoing anticoagulant monotherapy or no treatment. These imbalances indicated strong confounding by indication, as PPI prescriptions were assigned to patients with a higher expected risk of gastrointestinal bleeding and more clinical complexity.

Following application of IPTW, the majority of SMD for baseline covariates were reduced to below the 0.10 threshold across all three anticoagulant cohorts and both outcomes, indicating acceptable balance in the weighted pseudo-

populations. Stabilised weights were truncated at the 99th percentile to mitigate the influence of extreme values, and the resulting weight distributions did not indicate substantial positivity violations. The weighted pseudo-populations therefore provide a defensible basis for estimating exposure–outcome associations while accounting for measured confounding.

4.3.3.1 Bleeding outcome

Given the substantial baseline imbalance observed across multiple demographic, comorbidity, and concomitant medication domains — particularly for age, gastrointestinal disease, mental health conditions, cardiovascular co-therapy, and healthcare utilisation — IPTW was applied to improve exchangeability across time-varying exposure states. Figure 4.2 presents absolute SMDs for all covariates included in the propensity score model in the warfarin cohort, before and after weighting, using the maximum pairwise imbalance across exposure groups. Figure 4.3 presents the corresponding balance diagnostics for the Factor Xa inhibitor cohort.

Prior to weighting, several covariates in both cohorts (Figure 4.2 and Figure 4.3) demonstrated pronounced imbalance, with absolute SMDs exceeding 0.20 and, for a subset of variables, approaching or exceeding 0.40–0.50. These large pre-weighting SMDs were consistent with the descriptive baseline findings reported in Section 4.3.2, reflecting enrichment of multimorbidity, polypharmacy, and longer admission durations in PPI-containing exposure states. Variables related to age, gastrointestinal disease, mental health and respiratory conditions, cardiovascular disease, and concomitant antiplatelet and statin use contributed substantially to the observed imbalance.

Following application of stabilised inverse probability weights, covariate balance improved markedly across the full set of variables in both cohorts (Figure 4.2 and Figure 4.3), with the majority of post-weighting SMDs reduced to below the conventional threshold of 0.10, indicating acceptable balance in the weighted pseudo-populations. The largest pre-weighting imbalances showed the greatest absolute reductions, demonstrating effective reweighting toward pseudo-populations in which observed covariates were more evenly distributed across exposure states. A small number of covariates remained marginally above the 0.10

threshold after weighting, but none approached the levels of imbalance observed prior to adjustment. Comparable patterns of pre- and post-weighting balance were observed in the dabigatran cohort; given the consistency of these findings across all three anticoagulant cohorts, representative balance plots are shown for warfarin (Figure 4.2) and Factor Xa inhibitors (Figure 4.3) only.

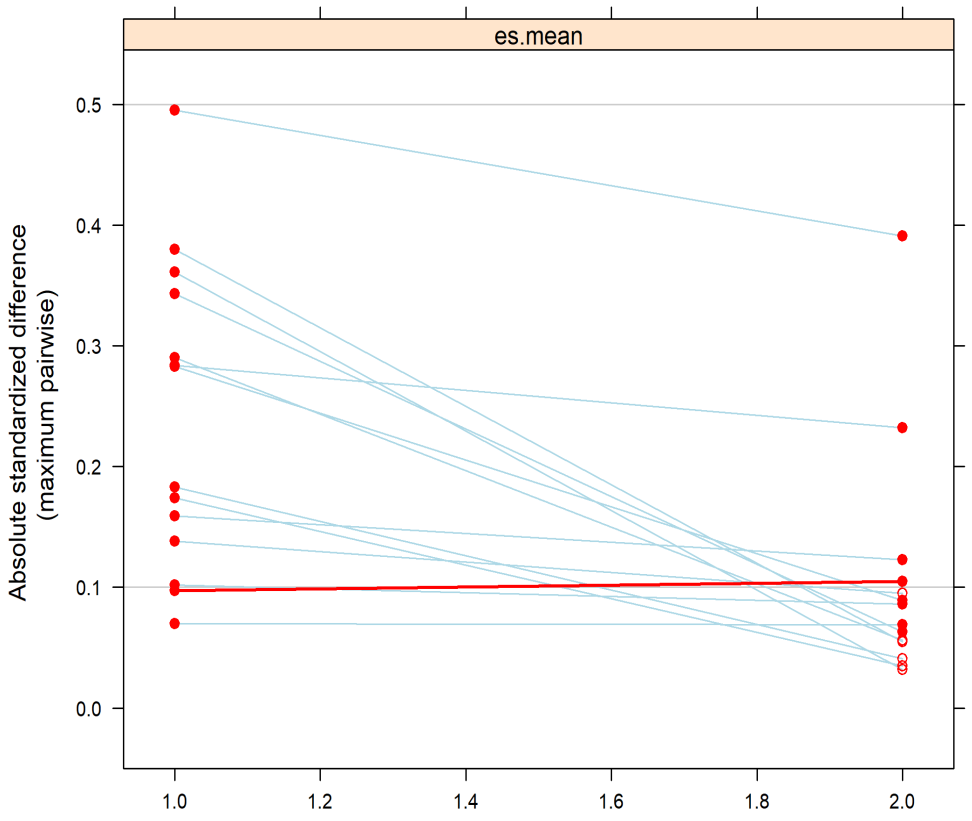


Figure 4.2 Standardised mean differences before and after IPTW - warfarin cohort (Bleeding Analyses)

The plot displays the maximum pairwise absolute standardised mean differences (SMDs) across exposure groups for all covariates included in the propensity score model. Each line connects the pre-weighting (left) and post-weighting (right) SMD for a single covariate, with the horizontal reference line denoting the 0.10 balance threshold. Following IPTW, most covariates achieved SMD below 0.10, demonstrating substantial improvement in covariate balance and supporting the assumption of exchangeability across exposure groups; a small number remained above the threshold.

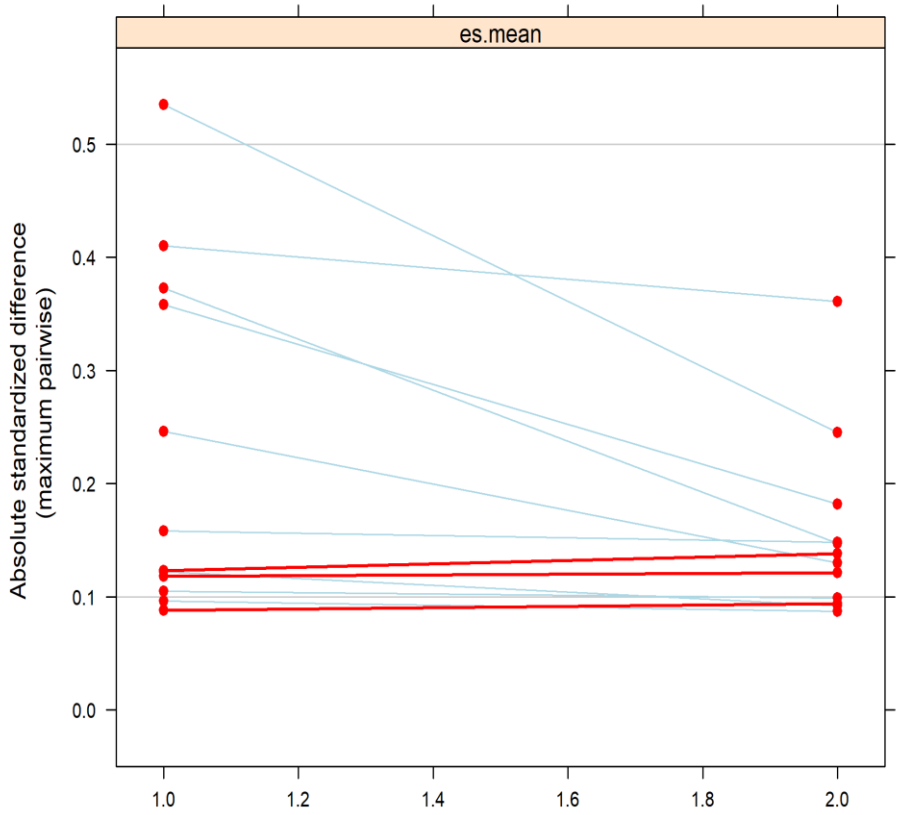


Figure 4.3 Standardised mean differences before and after IPTW - Factor Xa inhibitor cohort (Bleeding Analyses)

The plot displays the maximum pairwise absolute standardised mean differences (SMDs) across exposure groups for all covariates included in the propensity score model. Each line connects the pre-weighting (left) and post-weighting (right) SMD for a single covariate, with the horizontal reference line denoting the 0.10 balance threshold. Following IPTW, covariate balance improved overall, with the covariates exhibiting the greatest pre-weighting imbalance showing reduced SMDs; however, a number of covariates remained at or above the 0.10 threshold, including two to three with appreciable residual imbalance.

4.3.3.2 Treatment failure outcomes

Patterns of baseline imbalance for treatment failure analyses were broadly similar to those described for the bleeding analyses, with comparable enrichment of comorbidity, concomitant medication use, and healthcare utilisation in PPI-containing exposure states. Figure 4.4 presents absolute SMD before and after IPTW in the warfarin cohort, and Figure 4.5 presents the corresponding diagnostics for the Factor Xa inhibitor cohort.

Prior to weighting, several covariates in both cohorts (Figure 4.4 and Figure 4.5) demonstrated pronounced imbalance, with absolute SMDs exceeding 0.20 across domains including age, gastrointestinal disease, mental health conditions, cardiovascular disease, and length of admission, consistent with the descriptive findings presented in Section 4.3.2. Following application of stabilised inverse probability weights, covariate balance improved substantially, with the majority of post-weighting SMDs reduced below the conventional threshold of 0.10, indicating acceptable balance in the weighted pseudo-populations. The largest pre-weighting imbalances showed the greatest absolute reductions. A small number of covariates remained marginally above 0.10 following weighting, but none approached the levels of imbalance observed prior to adjustment. Comparable patterns were observed in the dabigatran cohort, and representative balance plots are shown for warfarin (Figure 4.4) and Factor Xa inhibitors (Figure 4.5) only.

The consistency of balance achievement across both bleeding and treatment failure analyses indicates that IPTW substantially mitigated systematic baseline differences identified in the unweighted cohorts, particularly those related to multimorbidity and concomitant cardiovascular therapy. The improvement in covariate balance supports the use of weighted, time-dependent Cox proportional hazards models for estimation of exposure effects and strengthens the internal validity of the subsequent hazard ratio estimates, while recognising that residual confounding from unmeasured factors cannot be fully excluded.

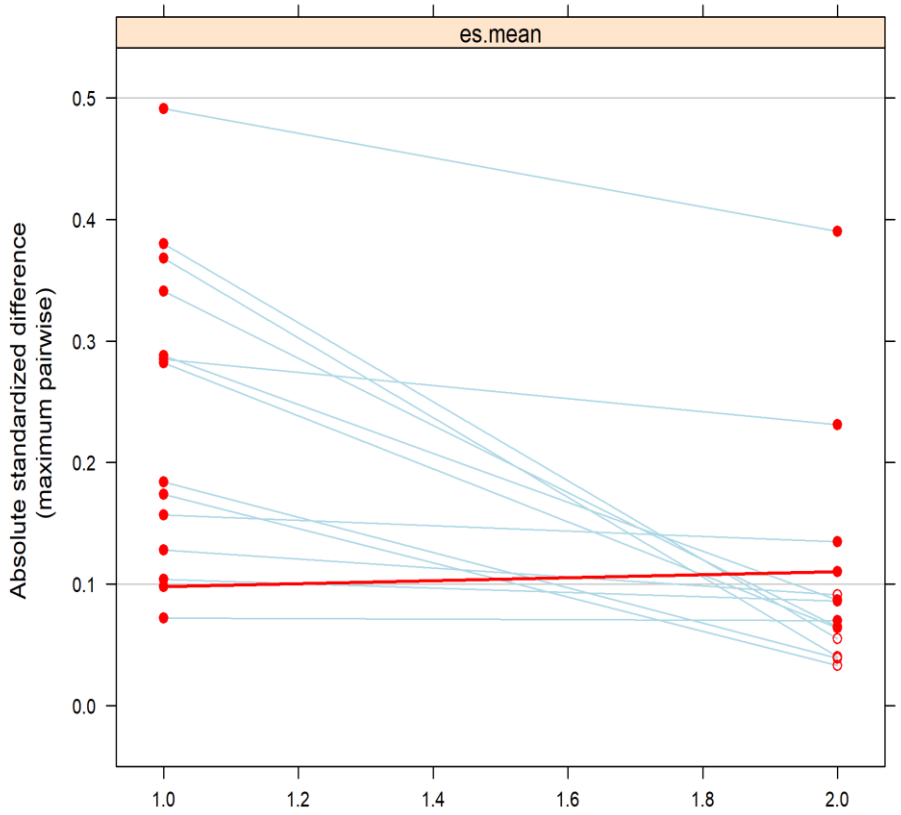


Figure 4.4 Standardised mean differences before and after IPTW - warfarin cohort (Treatment Failure Analyses)

The plot displays the maximum pairwise absolute standardised mean differences (SMDs) across exposure groups for all covariates included in the propensity score model. Each line connects the pre-weighting (left) and post-weighting (right) SMD for a single covariate, with the horizontal reference line denoting the 0.10 balance threshold. Following IPTW, most covariates achieved SMD below 0.10, demonstrating substantial improvement in covariate balance and supporting the assumption of exchangeability across exposure groups; a small number remained above the threshold.

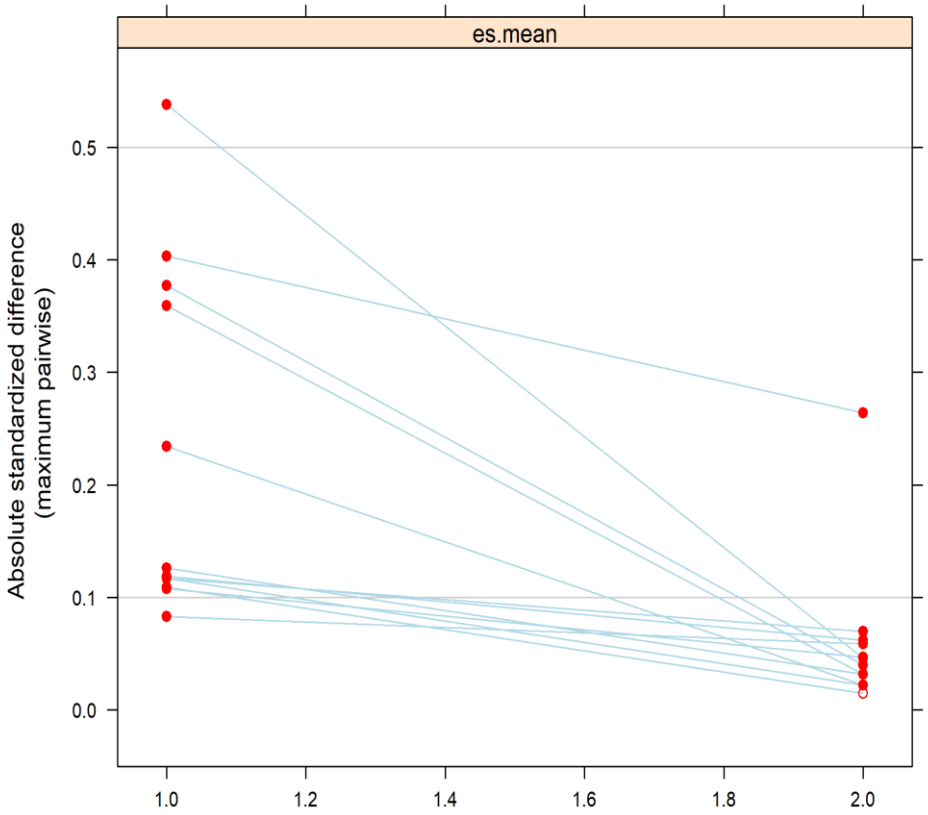


Figure 4.5 Standardised mean differences before and after IPTW - Factor Xa inhibitor cohort (Treatment Failure Analyses)

The plot displays the maximum pairwise absolute standardised mean differences (SMDs) across exposure groups for all covariates included in the propensity score model. Each line connects the pre-weighting (left) and post-weighting (right) SMD for a single covariate, with the horizontal reference line denoting the 0.10 balance threshold. Following IPTW, all but one covariate achieved SMD below 0.10, demonstrating substantial improvement in covariate balance and supporting the assumption of exchangeability across exposure groups; a single covariate remained above the threshold.

4.3.4 Time-varying survival experience by exposure state

The analyses of time-varying survival by exposure state utilised Simon-Makuch extensions of Kaplan-Meier survival curves, which accommodate time-varying exposure throughout the follow-up period and mitigate immortal time bias. These curves offer a descriptive, non-parametric illustration of event-free survival amid time-varying exposure patterns and illustrate the extent and temporal dynamics of survival differences between exposure states.

4.3.4.1 Bleeding outcomes

Simon-Makuch survival curves for bleeding-free survival are presented for each of the three anticoagulant cohorts in Figure 4.6 (warfarin), Figure 4.7 (dabigatran), and Figure 4.8(Factor Xa inhibitors). Exposure status was treated as time-varying, allowing individuals to transition between exposure states during follow-up; the curves therefore reflect bleeding-free survival under the time-updated exposure definitions described in Section 4.2.

In the warfarin cohort (Figure 4.6), bleeding-free survival remained high in all four exposure groups throughout the two-year follow-up period. Visible separation between the curves emerged early and was sustained for the remainder of follow-up. The concurrent warfarin–PPI exposure group ('Both') demonstrated the steepest decline in bleeding-free survival, followed by the warfarin monotherapy group. The 'Neither' and 'PPI only' curves remained closely aligned with one another and showed the highest bleeding-free survival throughout, indicating that PPI exposure in the absence of warfarin was not associated with materially altered bleeding-free survival. No curve crossings were observed, consistent with the proportional hazards assumption examined in the subsequent Cox regression analyses.

In the dabigatran cohort (Figure 4.7), bleeding events were uncommon across all exposure groups, and all curves remained at uniformly high survival probabilities throughout follow-up. The PPI monotherapy group demonstrated the steepest unadjusted decline in bleeding-free survival, consistent with the older age and greater comorbidity burden observed at baseline in this group; this crude difference was attenuated to the null after multivariable adjustment in the subsequent Cox model. The dabigatran monotherapy and concurrent dabigatran–PPI ('Both') groups remained essentially flat throughout follow-up. The corresponding hazard ratio estimate for the 'Both' group should be interpreted cautiously, as discussed in Section 4.4. No curve crossings were observed.

In the Factor Xa inhibitor cohort (Figure 4.8), bleeding-free survival remained high across all four exposure groups throughout follow-up, and the curves were tightly clustered for the majority of the observation period. The limited absolute separation between curves reflects the low overall absolute bleeding rate in this

cohort; the relative differences between exposure groups, which became apparent on the adjusted relative scale in the subsequent Cox model, are visually compressed when survival probabilities remain close to one. Modest visual divergence emerged in the latter half of follow-up, but no curve crossings were observed.

Collectively, the Simon-Makuch curves demonstrate that the magnitude and direction of visible separation between exposure groups varied across the three anticoagulant cohorts. The warfarin cohort showed the clearest pattern of reduced bleeding-free survival in the concurrent exposure group, consistent with the elevated hazard ratios subsequently identified in the Cox model. The dabigatran cohort showed an unadjusted reduction in bleeding-free survival in the PPI-only group that was attenuated on adjustment, while the small numbers of patients in the dabigatran monotherapy and concurrent exposure strata limit the precision of the corresponding hazard ratio estimates. The Factor Xa inhibitor cohort showed limited visual separation, reflecting low absolute event rates; the protective associations identified in the Cox model become apparent only on the relative scale.

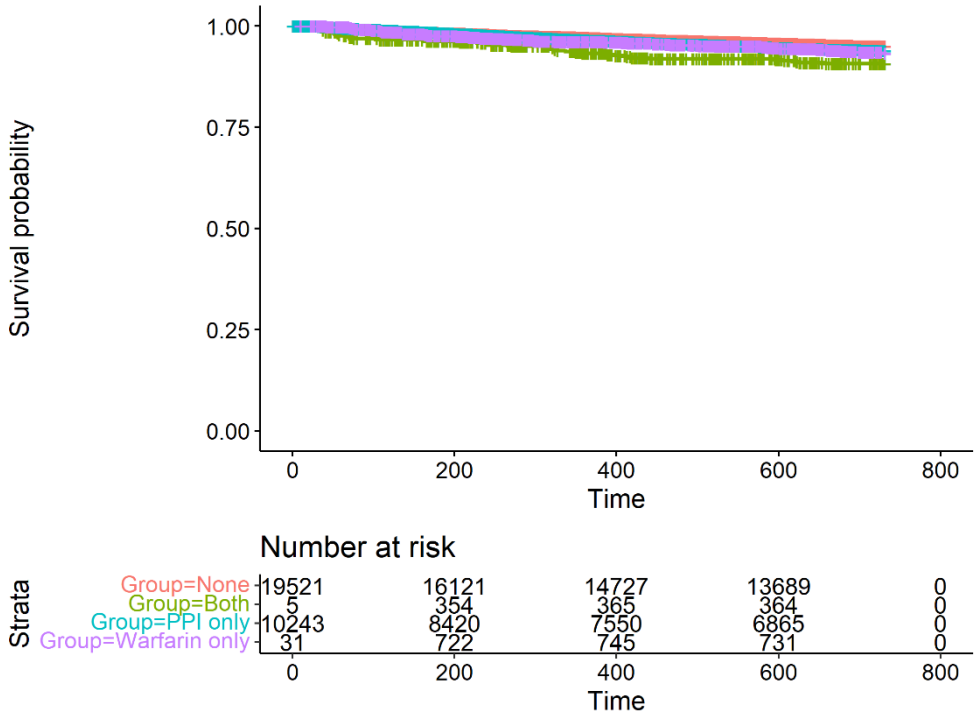


Figure 4.6 Time-varying bleeding-free survival by exposure state (warfarin)

Kaplan-Meier curves illustrating bleeding-free survival based on time-varying exposure status over a 2-year follow-up in the warfarin cohort (n=29,765). Exposure categories: Neither (red), PPI only (purple), Warfarin only (turquoise), Both (green). The Both group exhibits the lowest bleeding-free survival during the follow-up period, but the PPI-only curve closely parallels the Neither reference group.

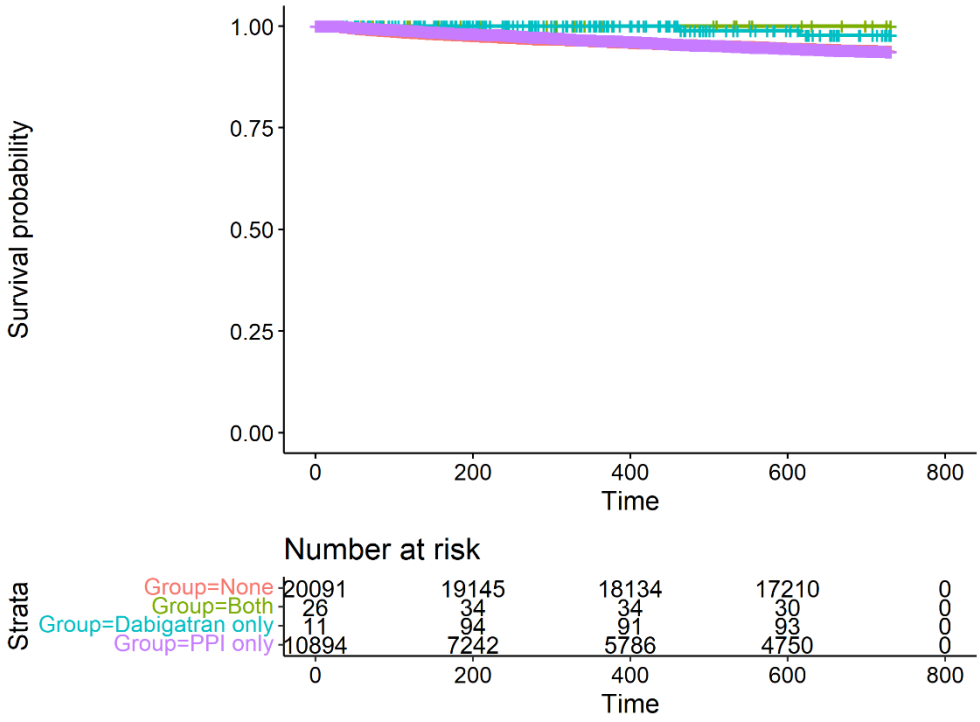


Figure 4.7 Time-varying bleeding-free survival by exposure state (dabigatran cohort)

Simon-Makuch curves illustrating bleeding-free survival based on time-varying exposure status in the dabigatran cohort (n=30,985). Exposure categories: Neither (red), PPI only (purple), Dabigatran only (turquoise), Both (green). Bleeding-free survival remained uniformly high across all exposure groups throughout the follow-up period. The combination of infrequent concurrent dabigatran-PPI exposure and low overall event rates constrained the statistical power available for the corresponding Cox regression analyses presented below.

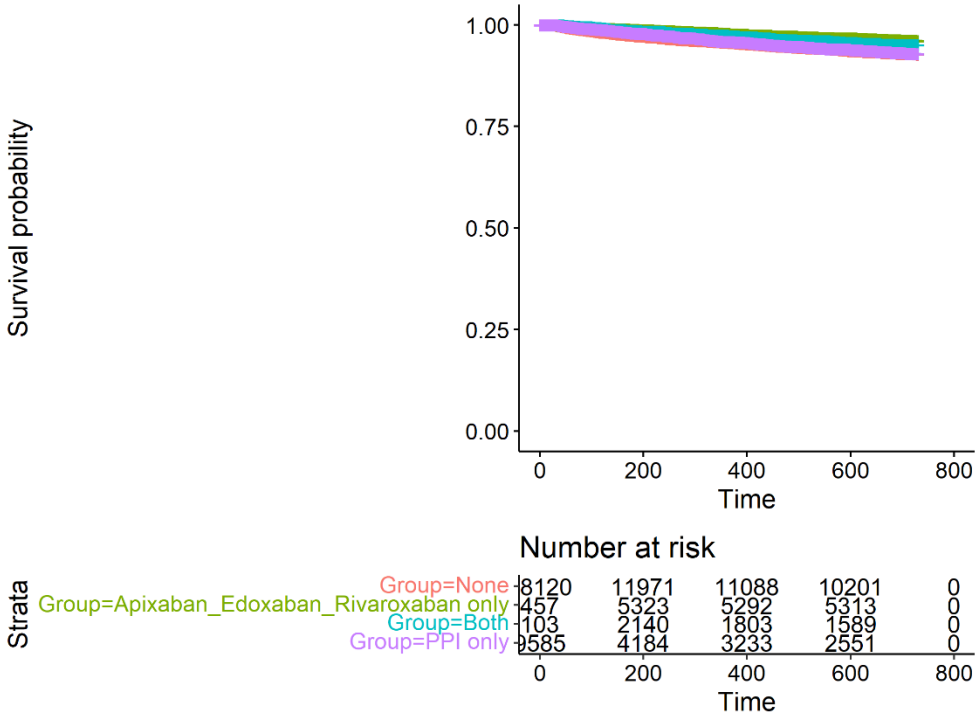


Figure 4.8 Time-varying bleeding-free survival by exposure state (Factor Xa inhibitor cohort)
Kaplan-Meier plots illustrating bleeding-free survival based on time-varying exposure status in the Factor Xa inhibitor cohort (n=27,713). Exposure categories: Neither (red), PPI only (purple), Factor Xa inhibitor only (turquoise), Both (green). All curves consistently exceed 0.95 during the follow-up period, indicating low rates of bleeding. Factor Xa-exposed groups have somewhat superior survival rates compared to the Neither/PPI-only groups.

4.3.4.2 Treatment failure outcomes

Simon-Makuch survival curves for treatment failure-free survival are presented for each of the three anticoagulant cohorts in Figure 4.9 (warfarin), Figure 4.10 (dabigatran), and Figure 4.11 (Factor Xa inhibitors). As for the bleeding analyses, exposure status was treated as time-varying, and the curves reflect treatment failure-free survival under the time-updated exposure definitions described in Section 4.2.

In the warfarin cohort (Figure 4.9), treatment failure events were uncommon across all exposure groups, and treatment failure-free survival remained uniformly high throughout the two-year follow-up period. The curves were tightly clustered, reflecting the low absolute event rate in this cohort. Modest visual separation was apparent, with the warfarin-containing exposure groups (warfarin monotherapy

and concurrent warfarin–PPI) showing higher survival than the 'None' and 'PPI only' groups, consistent with the absence of anticoagulant cover in the latter two groups. The limited absolute separation between curves is compatible with the relative differences subsequently identified on the adjusted hazard ratio scale, which are compressed visually when survival probabilities remain close to one. No curve crossings were observed, supporting the proportional hazards assumption examined in subsequent regression analyses.

In the dabigatran cohort (Figure 4.10), treatment failure events were substantially more frequent, and pronounced separation emerged between exposure groups over follow-up. The concurrent dabigatran–PPI exposure group ('Both') demonstrated the steepest decline in treatment failure-free survival, falling below all other groups by the end of follow-up. The dabigatran monotherapy group maintained the highest survival, while the 'None' and 'PPI only' groups occupied intermediate positions and tracked closely with one another. This visual pattern is consistent with concurrent PPI exposure attenuating the protective effect of dabigatran against thromboembolic events, anticipating the elevated hazard ratio identified for the 'Both' group in the subsequent Cox model. No curve crossings were observed.

In the Factor Xa inhibitor cohort (Figure 4.11), treatment failure events were frequent and survival declined steadily across all exposure groups throughout follow-up. The curves were tightly clustered for the majority of the observation period, with modest visual separation emerging in the latter half of follow-up. The Factor Xa monotherapy group demonstrated marginally higher treatment failure-free survival than the other groups, while the 'None', 'PPI only', and concurrent ('Both') groups tracked closely with one another. No curve crossings were observed, supporting the proportional hazards assumption examined in subsequent regression analyses.

Collectively, the Simon-Makuch curves for treatment failure demonstrate markedly different patterns across the three anticoagulant cohorts. The warfarin cohort displayed limited absolute separation between groups, reflecting a low overall event rate, with relative differences emerging on the adjusted scale in the subsequent Cox model. The dabigatran cohort showed the most pronounced visual

separation, with concurrent PPI use associated with lower treatment failure-free survival than dabigatran alone, anticipating the elevated hazard ratio reported in the subsequent Cox model and discussed further in Section Discussion. The Factor Xa inhibitor cohort showed modest visual separation, with monotherapy-exposed individuals demonstrating slightly higher survival than other groups. These visual patterns provide the descriptive context for the adjusted hazard ratio estimates presented in the subsequent Cox proportional hazards analyses.

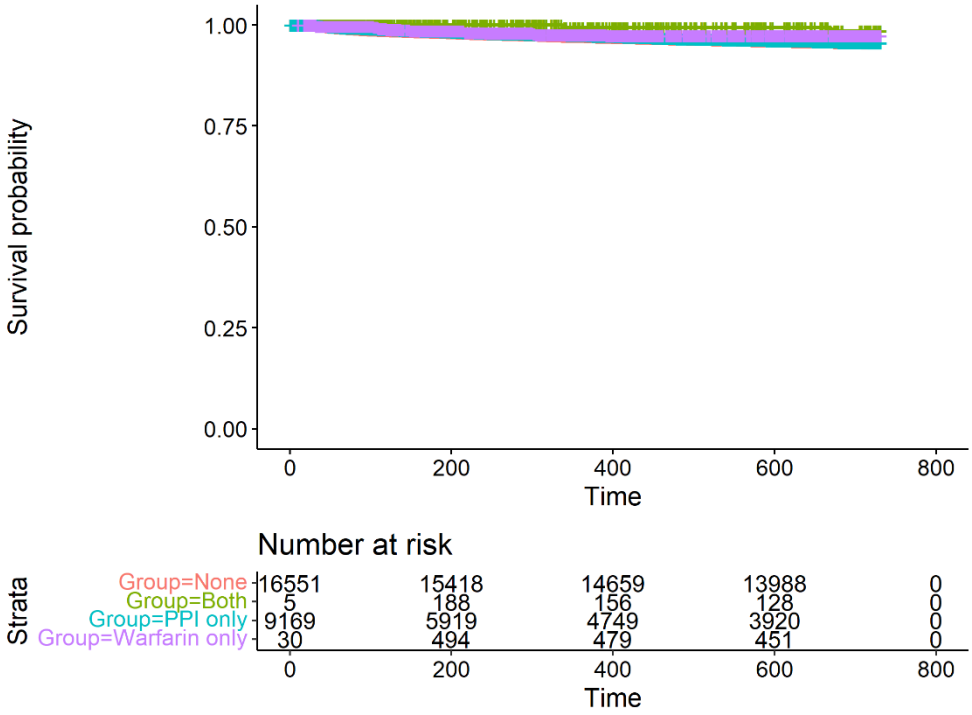


Figure 4.9 Time-varying treatment failure-free survival by exposure state (warfarin cohort)
Simon-Makuch curves illustrating treatment failure-free survival based on time-varying exposure status in the warfarin cohort (n=25,721). Exposure categories: Neither (red), PPI only (purple), Warfarin only (turquoise), Both (green). Treatment failure is defined as hospitalisation for ischaemic stroke, transient ischaemic attack, systemic embolism, myocardial infarction, or venous thromboembolism. Treatment failure-free survival remained high across all exposure groups throughout follow-up, with modest visual separation favouring the warfarin-containing exposure groups.

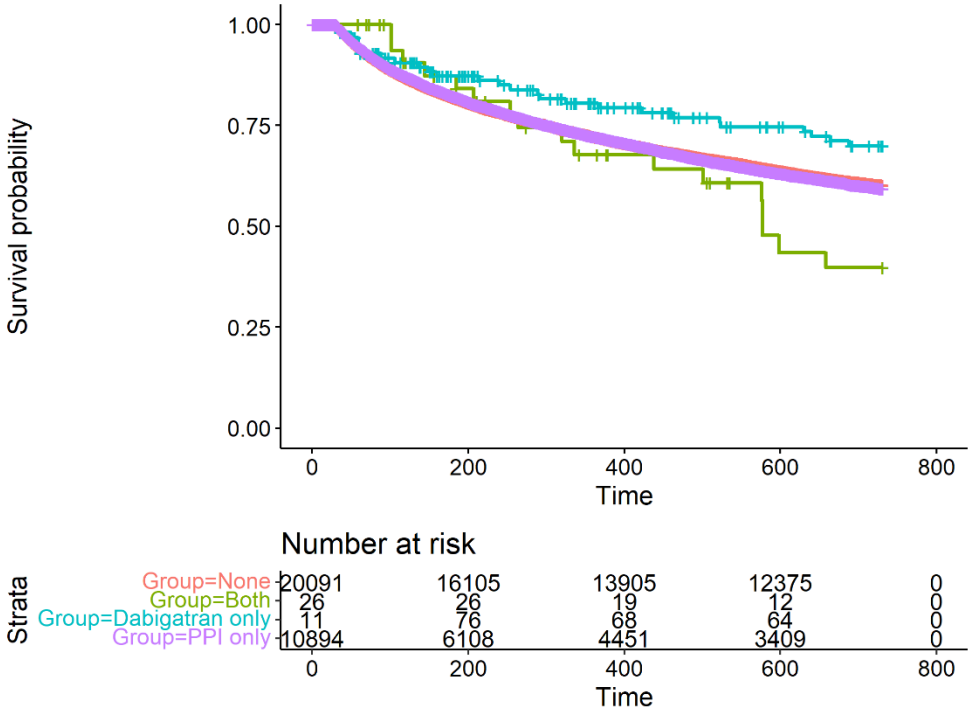


Figure 4.10 Time-varying treatment failure-free survival by exposure state – (dabigatran cohort)

Simon-Makuch curves illustrating treatment failure-free survival based on time-varying exposure status within the dabigatran cohort (n=30,985). Exposure categories: Neither (red), PPI only (purple), Dabigatran only (turquoise), Both (green). Treatment failure is defined as hospitalisation due to stroke, transient ischaemic attack (TIA), systemic embolism, myocardial infarction (MI), or venous thromboembolism (VTE). The dabigatran monotherapy group maintained the highest treatment failure-free survival throughout follow-up, while the concurrent dabigatran-PPI ('Both') group showed the steepest decline, falling below all other exposure groups by the end of follow-up.

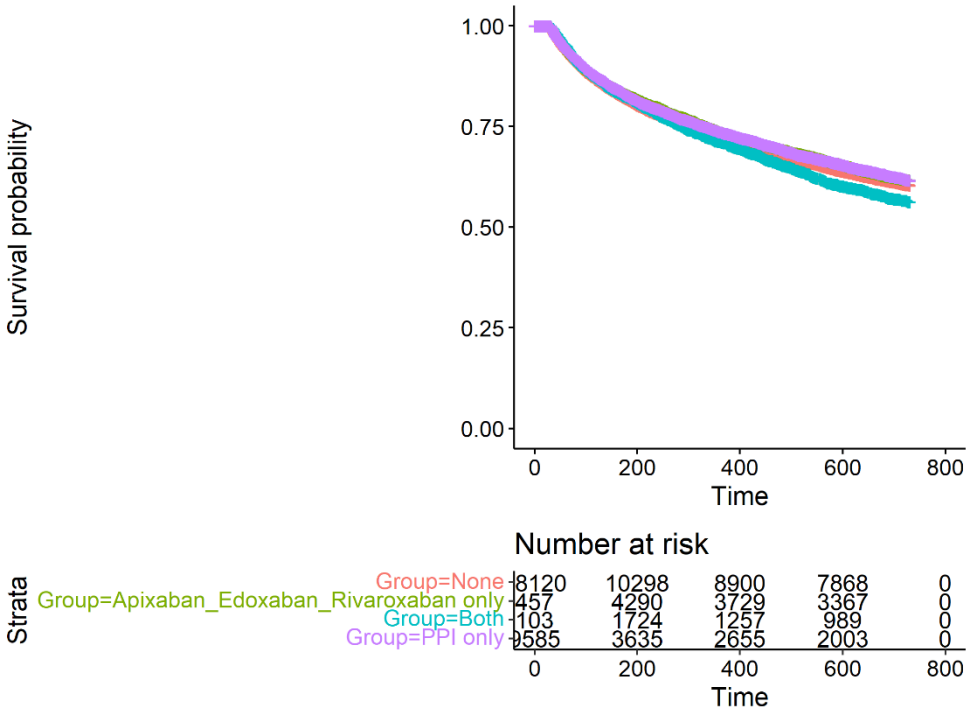


Figure 4.11 Time-varying treatment failure-free survival by exposure state – (factor Xa inhibitor cohort)

Simon-Makuch curves illustrating treatment failure-free survival based on time-varying exposure status within the Factor Xa inhibitor cohort (n=27,713). Exposure categories: Neither (red), PPI only (purple), Factor Xa inhibitor only (turquoise), Both (green). Treatment failure is defined as hospitalisation due to stroke, transient ischaemic attack (TIA), systemic embolism, myocardial infarction (MI), or venous thromboembolism (VTE). Treatment failure-free survival curves were tightly clustered across all four exposure groups throughout follow-up, with the Factor Xa monotherapy group showing marginally higher survival than the other groups.

4.3.5 Multivariable time-dependent Cox regression

Results from IPTW-weighted, time-dependent Cox proportional hazards models are presented for bleeding and treatment failure outcomes across the three anticoagulant cohorts (Table 4.4–Table 4.9; Figure 4.12–Figure 4.17). Following adjustments for demographic factors, socioeconomic status, comorbidities, concomitant medications, and length of admission, clear patterns were observed among different anticoagulant classes and outcome types.

4.3.5.1 Bleeding Outcomes

In the warfarin cohort (n=29,765), concurrent exposure to warfarin and PPIs was linked to a significantly elevated risk of bleeding (adjusted HR 2.13, 95% CI 1.25–3.63; p=0.005) (Table 4.4, Figure 4.12). Warfarin monotherapy exhibited a

significantly increased risk (adjusted HR 1.65, 95% CI 1.11–2.45; p=0.014), whereas PPI monotherapy revealed no significant association (adjusted HR 1.05, 95% CI 0.92–1.21; p=0.451). The estimates suggest an increased bleeding risk associated with concurrent warfarin and PPI therapy, aligning with the persistent divergence noted in the time-varying survival curves (Figure 4.6).

In the analyses of covariates, advancing age (adjusted HR 1.04 per year, 95% CI 1.01–1.06; p=0.002) and the highest level of deprivation (SIMD decile 1: adjusted HR 1.84, 95% CI 1.13–3.01; p=0.015) were linked to a heightened risk of bleeding. Cancer (adjusted HR 1.74, 95% CI 1.07–2.83; p=0.025) and liver, gallbladder and pancreatic disease (adjusted HR 2.40, 95% CI 1.37–4.21; p=0.002) exhibited significant associations. The proportional hazards assumptions were met.

Table 4.4 Warfarin cohort – multivariable Cox regression results for bleeding outcomes

Results of the IPTW-weighted, time-dependent Cox proportional hazards model for bleeding outcomes in the warfarin cohort (n=29,765). Reference categories: Neither (no warfarin or PPI exposure), male sex, SIMD decile 9 (least deprived), absence of each comorbidity or concomitant medication. Hazard ratios (HR) with 95% confidence intervals (CI) and p-values are presented.

Group	exp(coef)	lower .95	upper .95	P
Apixaban1	1.067	0.684	1.666	0.775
clopidogrel1	1.294	0.8	2.094	0.294
Dabigatran1	1.227	0.634	2.375	0.544
Edoxaban1	1.405	0.711	2.776	0.328
Rivaroxaban1	1.531	0.772	3.037	0.223
Aspirin1	1.244	0.844	1.833	0.27
Ticagrelor1	0.627	0.307	1.282	0.201
Atorvastatin1	0.928	0.638	1.349	0.694
Pravastatin1	0.905	0.43	1.903	0.792
Simvastatin1	1.006	0.678	1.492	0.976
Amiodarone1	0.647	0.393	1.067	0.088
Age	1.037	1.013	1.061	0.002
SEXF	1.007	0.747	1.358	0.961
SIMD_2016_DECILE1	1.84	1.126	3.005	0.015
SIMD_2016_DECILE2	1.388	0.825	2.334	0.217
SIMD_2016_DECILE3	1.641	0.92	2.928	0.094
SIMD_2016_DECILE4	1.671	0.755	3.699	0.205
SIMD_2016_DECILE5	1.016	0.558	1.849	0.959
SIMD_2016_DECILE6	1.193	0.645	2.205	0.574
SIMD_2016_DECILE7	2.465	1.172	5.184	0.017
SIMD_2016_DECILE8	1.111	0.612	2.019	0.729
SIMD_2016_DECILE10	2.036	1.014	4.089	0.045
Fluvastatin1	0	0	0	0
Prasugrel1	0	0	0	0
Dipyridamole1	20.606	5.688	74.649	0
CV1	0.787	0.487	1.273	0.329
MSK1	1.087	0.771	1.531	0.635
MentalHealth1	1.571	1.063	2.323	0.023
Respiratory1	1.18	0.832	1.675	0.353
Neurology1	0.795	0.564	1.118	0.187
KUB1	1.016	0.716	1.442	0.93
Cancer1	1.742	1.071	2.834	0.025
Diabetes1	0.903	0.574	1.421	0.659
GI1	0.822	0.395	1.713	0.601
Endocrine1	0.775	0.5	1.203	0.256
Liver_GB_Panc1	2.405	1.373	4.211	0.002
Infection1	0.529	0.161	1.744	0.296
adm_duration	0.997	0.992	1.002	0.248
Group Both	2.133	1.253	3.633	0.005
Group PPI only	1.055	0.918	1.211	0.451
Group Warfarin only	1.647	1.108	2.447	0.014

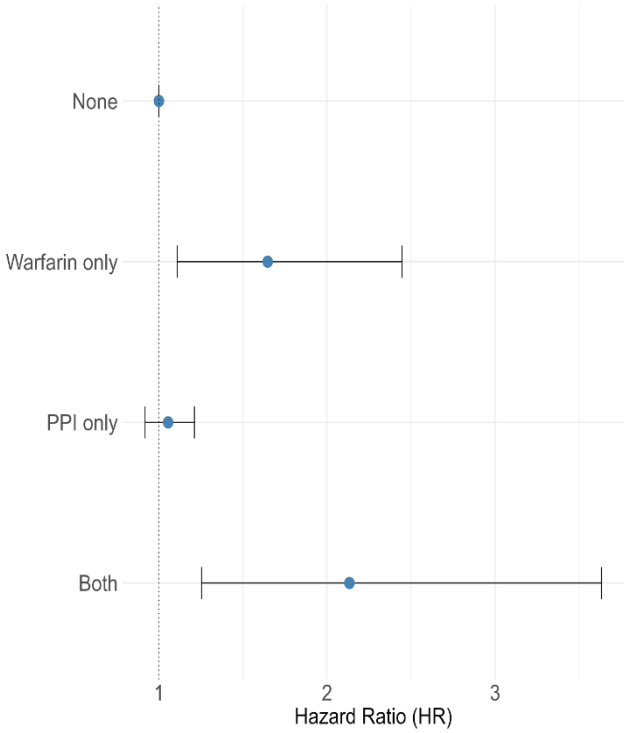


Figure 4.12 Warfarin cohort – forest plot of adjusted hazard ratios for bleeding outcomes.

A forest plot of adjusted hazard ratios and 95% confidence intervals for bleeding outcomes by exposure group in the warfarin cohort (n=29,765) using IPTW-weighted, time-dependent Cox model. Reference group (Neither) is shown as a vertical line at HR=1.0. Concurrent warfarin-PPI exposure significantly increases bleeding risk (HR 2.13), while PPI monotherapy has no effect.

In the dabigatran cohort (n=30,985), reliable estimates for concurrent dabigatran–PPI exposure were not achievable due to the small number of individuals in the concurrent exposure state combined with very low bleeding event counts (Table 4.5, Figure 4.13). Dabigatran monotherapy exhibited a non-significant trend towards decreased bleeding (adjusted HR 0.38, 95% CI 0.11–1.35; p=0.136), with the broad confidence interval indicating considerable uncertainty. PPI monotherapy demonstrated no significant association (adjusted HR 0.98, 95% CI 0.86–1.11; p=0.715).

The small concurrent exposure stratum and uniformly high bleeding-free survival across all dabigatran-exposed groups (Figure 4.7) resulted in an inadequate number of events for reliable hazard ratio estimation in the "Both" group. This limitation reflects actual prescribing trends, as dabigatran and PPIs are rarely co-prescribed simultaneously.

Age exhibited a modest correlation with heightened bleeding risk (adjusted HR 1.03 per year, 95% CI 1.01–1.05; p=0.005). The proportional hazards assumptions were met for groups with sufficient sample sizes.

Table 4.5 Dabigatran cohort – multivariable Cox regression results for bleeding outcomes

Result of time-dependent Cox proportional hazards model for bleeding outcomes in the dabigatran cohort (n=30,985) with IPTW. Reference categories: Neither (no dabigatran or PPI exposure), male sex, SIMD decile 9, absence of each comorbidity or concomitant medication. Concurrent dabigatran-PPI exposure results were not provided due to insufficient incidents and sparse exposure (n=53 at baseline).

Group	exp(coef)	lower .95	upper .95	P
clopidogrel1	0.614	0.444	0.849	0.003
Apixaban1	0.444	0.356	0.553	0
Edoxaban1	0.506	0.392	0.653	0
Rivaroxaban1	0.582	0.394	0.86	0.007
Warfarin1	0.731	0.564	0.947	0.018
Aspirin1	0.547	0.424	0.704	0
Atorvastatin1	0.836	0.651	1.075	0.163
Simvastatin1	1.902	1.01	3.58	0.046
Amiodarone1	1.12	0.714	1.757	0.621
Age	1.032	1.009	1.055	0.005
SEXF	1.28	0.797	2.056	0.307
SIMD_2016_DECILE1	2.167	1.129	4.158	0.02
SIMD_2016_DECILE2	2.305	0.962	5.518	0.061
SIMD_2016_DECILE3	1.222	0.869	1.717	0.249
SIMD_2016_DECILE4	1.351	0.85	2.148	0.204
SIMD_2016_DECILE5	1.129	0.778	1.638	0.524
SIMD_2016_DECILE6	1.441	0.931	2.232	0.101
SIMD_2016_DECILE7	1.496	0.963	2.323	0.073
SIMD_2016_DECILE8	1.109	0.671	1.834	0.687
SIMD_2016_DECILE10	1.186	0.796	1.766	0.402
CV1	1.011	0.785	1.303	0.931
MSK1	1.207	0.681	2.14	0.519
MentalHealth1	0.847	0.62	1.159	0.3
KUB1	0.995	0.599	1.651	0.983
Respiratory1	1.554	0.847	2.853	0.155
Neurology1	0.936	0.482	1.816	0.845
Diabetes1	1.981	0.746	5.259	0.17
Endocrine1	0.808	0.573	1.139	0.223
Cancer1	1.116	0.813	1.533	0.497
Liver_GB_Panc1	1.365	0.922	2.019	0.12
GI1	0.951	0.6	1.509	0.831
adm_duration	0.993	0.984	1.003	0.171
Group Both	0	0	0	0
Group Dabigatran only	0.381	0.108	1.353	0.136
Group PPI only	0.977	0.86	1.109	0.715

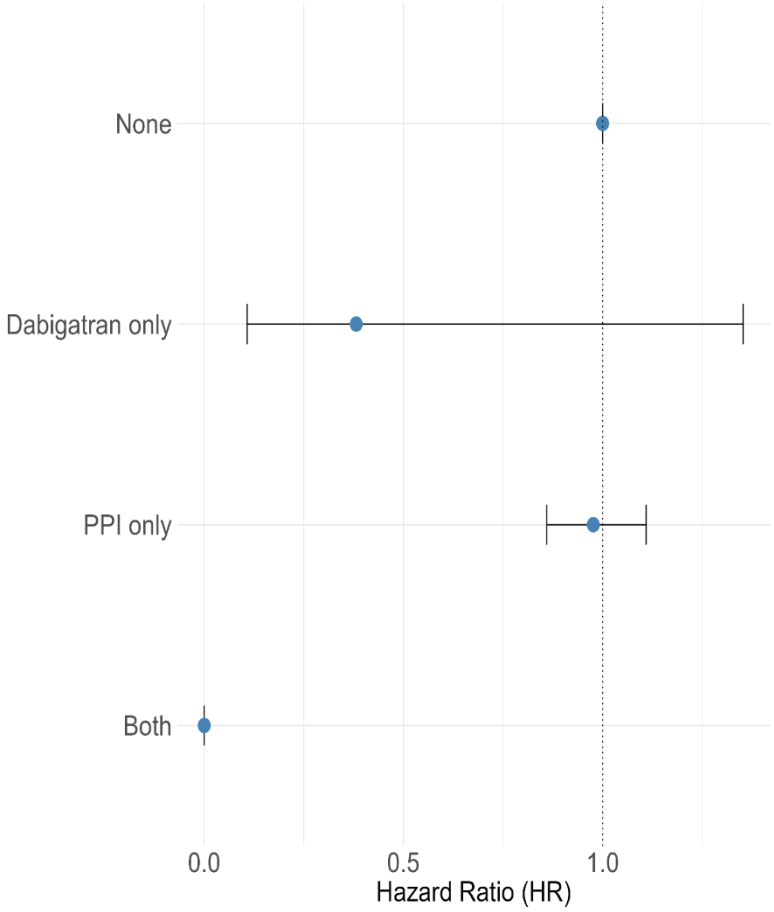


Figure 4.13 Dabigatran cohort – forest plot of adjusted hazard ratios for bleeding outcomes

Forest plot displaying adjusted hazard ratios and 95% confidence intervals for bleeding outcomes in the dabigatran cohort (n=30,985) by exposure group. Concurrent exposure findings are unavailable due to insufficient data and statistical instability. Dabigatran monotherapy has a large confidence interval due to limited occurrences. PPI monotherapy shows no significant association with bleeding.

In the cohort of Factor Xa inhibitors (n=27,713), both monotherapy and concurrent therapy exhibited a significantly lower bleeding hazard relative to the unexposed reference group (Table 4.6, Figure 4.14). Factor Xa monotherapy demonstrated a significant reduction in bleeding hazard (adjusted HR 0.49, 95% CI 0.41–0.58; p<0.001), and concurrent Factor Xa–PPI therapy showed a similarly reduced hazard (adjusted HR 0.55, 95% CI 0.43–0.69; p<0.001). PPI monotherapy demonstrated no significant association (adjusted HR 0.95, 95% CI 0.81–1.10; p=0.462).

These estimates indicate apparent protective associations of Factor Xa inhibitor exposure with bleeding relative to no anticoagulation. As discussed in Section 4.4, these associations are most plausibly attributable to confounding by indication

rather than a genuine pharmacological gastroprotective effect. The model-based estimates correspond with the modest absolute separation noted in the survival curves (Figure 4.8), where small visible differences reflect the low overall bleeding rate in this cohort.

In the analyses of covariates, age demonstrated an adjusted hazard ratio (HR) of 1.01 per year (95% CI 1.00–1.02; p=0.005), while female sex exhibited an adjusted HR of 0.80 (95% CI 0.68–0.93; p=0.004), both of which were linked to bleeding outcomes. The proportional hazards assumptions were met.

Table 4.6 Factor Xa inhibitor cohort – multivariable Cox regression results for bleeding outcomes

Result of time-dependent Cox proportional hazards model for bleeding outcomes in Factor Xa inhibitor cohort (n=27,713) with IPTW. Reference values: Neither, male, SIMD decile 9, no drugs or comorbidities. Factor Xa inhibitor exposure is associated with significantly reduced bleeding risk, both as monotherapy and in combination with PPI therapy.

Group	exp(coef)	lower .95	upper .95	P
clopidogrel1	0.691	0.55	0.869	0.002
Dabigatran1	0.171	0.054	0.542	0.003
Warfarin1	0.864	0.694	1.075	0.189
Aspirin1	0.753	0.566	1.003	0.052
Ticagrelor1	1.163	0.458	2.955	0.751
Atorvastatin1	0.995	0.818	1.21	0.959
Pravastatin1	1.317	0.675	2.568	0.42
Simvastatin1	1.024	0.841	1.247	0.813
Amiodarone1	1.017	0.535	1.932	0.959
Age	1.012	1.004	1.021	0.005
SEXF	0.795	0.68	0.93	0.004
SIMD_2016_DECILE1	1.158	0.878	1.527	0.3
SIMD_2016_DECILE2	1.353	1.009	1.813	0.043
SIMD_2016_DECILE3	1.243	0.894	1.728	0.196
SIMD_2016_DECILE4	1.119	0.786	1.592	0.532
SIMD_2016_DECILE5	1.157	0.813	1.646	0.419
SIMD_2016_DECILE6	1.386	0.959	2.002	0.082
SIMD_2016_DECILE7	1.241	0.863	1.785	0.244
SIMD_2016_DECILE8	1.068	0.737	1.547	0.729
SIMD_2016_DECILE10	1.077	0.753	1.541	0.685
CV1	0.998	0.762	1.307	0.988
MSK1	1.113	0.942	1.316	0.209
MentalHealth1	1.203	1.009	1.434	0.039
KUB1	1.125	0.957	1.323	0.155
Respiratory1	1.281	1.088	1.508	0.003
Neurology1	1.041	0.886	1.224	0.621
Diabetes1	0.85	0.674	1.072	0.171
Endocrine1	1.222	0.953	1.566	0.114
Cancer1	1.254	1.02	1.541	0.032
Liver_GB_Panc1	1.455	1.106	1.916	0.007
GI1	1.302	0.78	2.172	0.313
adm_duration	1	0.997	1.002	0.722
Group Factor Xa inhibitors only	0.486	0.406	0.582	0
Group Both	0.546	0.43	0.692	0
Group PPI only	0.946	0.815	1.098	0.462

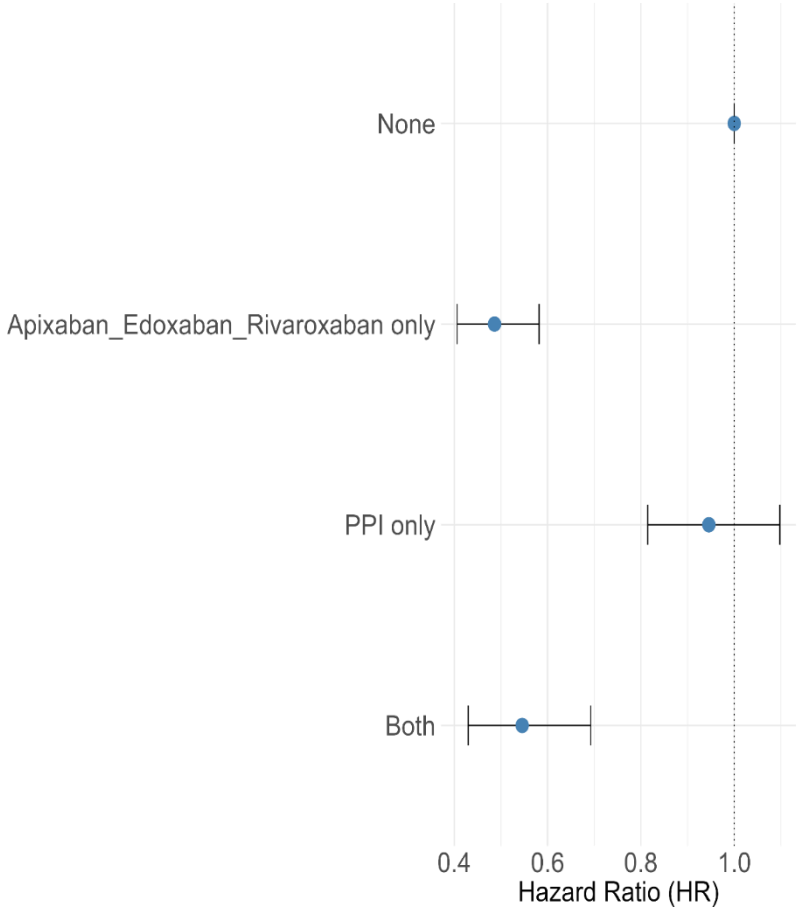


Figure 4.14 Factor Xa inhibitor cohort – forest plot of adjusted hazard ratios for bleeding outcomes

Forest plot of adjusted hazard ratios and 95% confidence intervals for bleeding outcomes in the Factor Xa inhibitor cohort (n=27,713). Both Factor Xa monotherapy and concomitant therapy show strong protective associations, with confidence intervals < HR=1.0. The PPI monotherapy confidence interval crosses the null value of 1.0, indicating no statistically significant association.

4.3.5.2 Treatment Failure Outcomes

In the warfarin cohort (n=25,721), concurrent exposure to warfarin and PPIs showed significant protection against treatment failure (adjusted HR 0.19, 95% CI 0.04–0.86; p=0.031) (Table 4.7, Figure 4.15). Warfarin monotherapy demonstrated significant protective effects (adjusted HR 0.48, 95% CI 0.26–0.88; p=0.018), whereas PPI monotherapy exhibited no significant association (adjusted HR 1.04, 95% CI 0.88–1.22; p=0.660).

These protective associations align with the benefits of therapeutic anticoagulation in the prevention of thromboembolic events. The pronounced point estimate for concurrent therapy (HR 0.19, 95% CI 0.04–0.86) must be interpreted with substantial caution. The wide confidence interval indicates severe statistical imprecision almost certainly driven by very few treatment failure events occurring during concurrent warfarin–PPI person-time. This estimate should be regarded as highly unstable, and the apparent protective association may be an artefact of sparse data rather than evidence of therapeutic benefit from combined warfarin–PPI therapy. The estimates correspond with the modest separation noted in the survival curves (Figure 4.9).

Table 4.7 Warfarin cohort – multivariable Cox regression results for treatment failure outcomes

Results of the IPTW-weighted, time-dependent Cox proportional hazards model for treatment failure outcomes in the warfarin cohort (n=25,721). Treatment failure is defined as hospitalisation for ischaemic stroke, TIA, systemic embolism, MI, or VTE. Reference categories: Neither (no warfarin or PPI exposure), male sex, SIMD decile 9, absence of each comorbidity or concomitant medication. Warfarin exposure is associated with strong protective associations, supporting therapeutic anticoagulation

Group	exp(coef)	lower .95	upper .95	P
Apixaban1	0.446	0.347	0.572	0
clopidogrel1	0.821	0.503	1.34	0.429
Dabigatran1	0.267	0.059	1.213	0.087
Edoxaban1	0.162	0.094	0.28	0
Rivaroxaban1	0.743	0.448	1.232	0.25
Aspirin1	0.409	0.304	0.551	0
Ticagrelor1	0.275	0.038	2.001	0.202
Atorvastatin1	0.959	0.66	1.394	0.826
Pravastatin1	0.63	0.217	1.83	0.396
Simvastatin1	0.914	0.641	1.302	0.618
Amiodarone1	0.41	0.145	1.161	0.093
Age	0.982	0.969	0.995	0.009
SEXF	1.143	0.783	1.67	0.488
SIMD_2016_DECILE1	1.335	0.936	1.905	0.111
SIMD_2016_DECILE2	1.703	0.951	3.047	0.073
SIMD_2016_DECILE3	1.658	0.991	2.773	0.054
SIMD_2016_DECILE4	1.267	0.822	1.951	0.283
SIMD_2016_DECILE5	0.934	0.623	1.401	0.742
SIMD_2016_DECILE6	0.774	0.51	1.176	0.231
SIMD_2016_DECILE7	1.748	1.076	2.841	0.024
SIMD_2016_DECILE8	0.604	0.382	0.956	0.031
SIMD_2016_DECILE10	1.039	0.619	1.747	0.884
CV1	0.743	0.522	1.059	0.1
MSK1	0.947	0.682	1.314	0.744
MentalHealth1	1.09	0.772	1.539	0.624
Respiratory1	1.239	0.912	1.684	0.17
Neurology1	1.127	0.763	1.665	0.548
KUB1	1.186	0.856	1.643	0.305
Cancer1	1.959	1.509	2.544	0
Liver_GB_Panc1	1.844	0.698	4.873	0.217
Diabetes1	1.118	0.719	1.739	0.62
GI1	0.97	0.556	1.693	0.914
Endocrine1	0.883	0.646	1.207	0.435
Infection1	0	0	0	0
GroupBoth	0.189	0.041	0.859	0.031
GroupPPI only	1.037	0.881	1.221	0.66
GroupWarfarin only	0.482	0.263	0.884	0.018

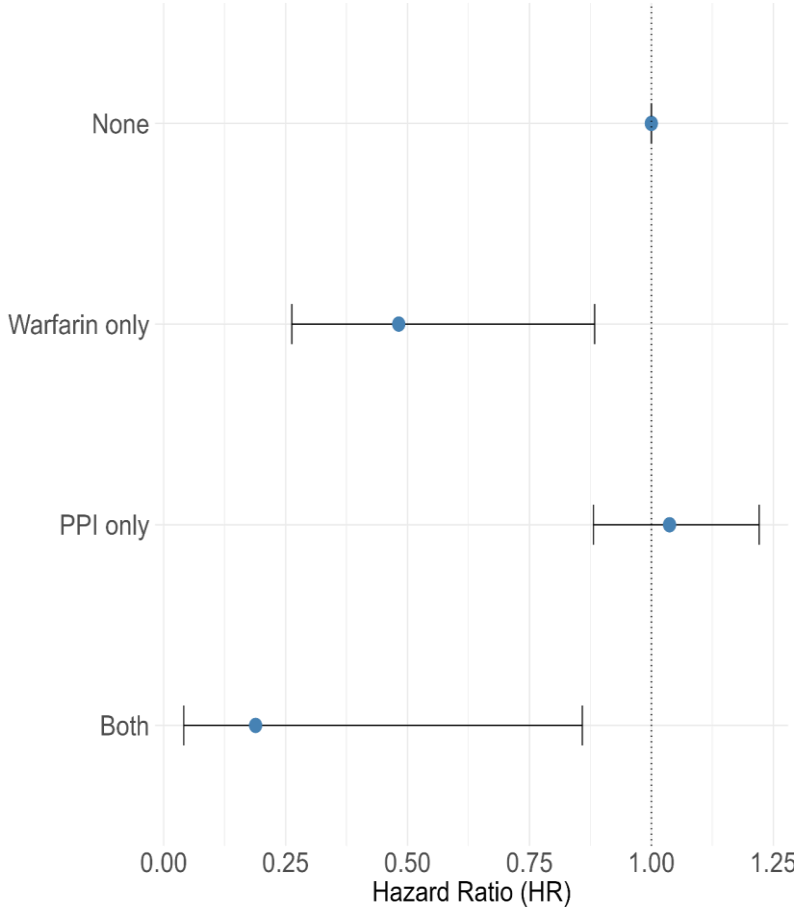


Figure 4.15 Warfarin cohort – forest plot of adjusted hazard ratios for treatment failure outcomes

Forest plot displaying adjusted hazard ratios and 95% confidence intervals for treatment failure outcomes in the warfarin cohort (n=25,721). Both warfarin-exposed groups show strong protective associations, with confidence intervals < HR=1.0, consistent with the expected therapeutic benefit of anticoagulation.

In the dabigatran cohort (n=30,985), concurrent dabigatran–PPI exposure was associated with a significantly elevated hazard of treatment failure (adjusted HR 1.71, 95% CI 1.10–2.66; p=0.018) (Table 4.8, Figure 4.16). Dabigatran monotherapy demonstrated a non-significant trend toward reduced treatment failure (adjusted HR 0.76, 95% CI 0.48–1.20; p=0.239), while PPI monotherapy showed no significant association (adjusted HR 1.04, 95% CI 0.96–1.12; p=0.391).

The increased risk associated with concurrent exposure aligns with the visual trend seen in the survival curves, where the "Both" group exhibited reduced treatment failure-free survival compared to dabigatran monotherapy (Figure 4.10). This pattern may reflect residual confounding by indication despite IPTW adjustment,

channelling bias with PPIs prescribed to patients at higher baseline thromboembolic risk, or pharmacokinetic interactions that reduce dabigatran bioavailability. The broad confidence interval (1.10–2.66) indicates the need for careful interpretation, with full discussion of competing explanations presented in Section 4.4.

Table 4.8 Dabigatran cohort – multivariable Cox regression results for treatment failure outcomes

Results of a time-dependent Cox proportional hazards model for treatment failure outcomes in the dabigatran cohort (n=30,985) with IPTW. A treatment failure is characterised as hospitalisation for stroke, TIA, systemic embolism, MI, or VTE. Neither (no dabigatran or PPI exposure), male sex, SIMD decile 9, absence of each comorbidity or concomitant medication. The unexpected finding of increased treatment failure risk associated with concurrent dabigatran-PPI exposure requires cautious interpretation.

Group	exp(coef)	lower .95	upper .95	P
Apixaban1	0.962	0.882	1.049	0.376
clopidogrel1	0.538	0.455	0.636	0
Warfarin1	1.017	0.91	1.136	0.772
Edoxaban1	0.9	0.811	1	0.049
Rivaroxaban1	0.9	0.768	1.055	0.194
Aspirin1	0.902	0.717	1.134	0.375
Ticagrelor1	0.858	0.54	1.363	0.516
Atorvastatin1	0.767	0.596	0.987	0.039
Pravastatin1	1.762	0.883	3.516	0.108
Simvastatin1	0.828	0.618	1.11	0.207
Amiodarone1	1.403	1.154	1.707	0.001
Age	0.999	0.985	1.013	0.919
SEXF	0.991	0.779	1.26	0.938
SIMD_2016_DECILE1	1.715	1.314	2.24	0
SIMD_2016_DECILE2	1.224	0.917	1.634	0.169
SIMD_2016_DECILE3	1.417	0.946	2.123	0.091
SIMD_2016_DECILE4	1.63	1.127	2.358	0.01
SIMD_2016_DECILE5	0.722	0.35	1.488	0.377
SIMD_2016_DECILE6	1.474	1.073	2.025	0.017
SIMD_2016_DECILE7	1.38	1.097	1.736	0.006
SIMD_2016_DECILE8	1.1	0.713	1.698	0.665
SIMD_2016_DECILE10	1.268	0.849	1.893	0.246
Fluvastatin1	1.623	0.59	4.468	0.348
Prasugrel1	8.185	1.248	53.702	0.028
Dipyridamole1	0.001	0	0.004	0
CV1	1.118	0.971	1.288	0.12
MSK1	0.85	0.676	1.068	0.163
MentalHealth1	0.961	0.759	1.217	0.743
KUB1	1.391	1.102	1.757	0.005
Respiratory1	1.321	1.044	1.671	0.02
Neurology1	1.279	1.013	1.616	0.038
Diabetes1	1.815	1.393	2.366	0
Endocrine1	0.903	0.632	1.289	0.573
Cancer1	1.384	0.992	1.93	0.056
Liver_GB_Panc1	0.916	0.693	1.21	0.536
GI1	1.114	0.361	3.434	0.851
Infection1	0.762	0.463	1.253	0.284
adm_duration	1.003	1.001	1.004	0.007
GroupBoth	1.708	1.096	2.663	0.018
GroupDabigatran only	0.758	0.478	1.202	0.239
GroupPPI only	1.035	0.957	1.12	0.391

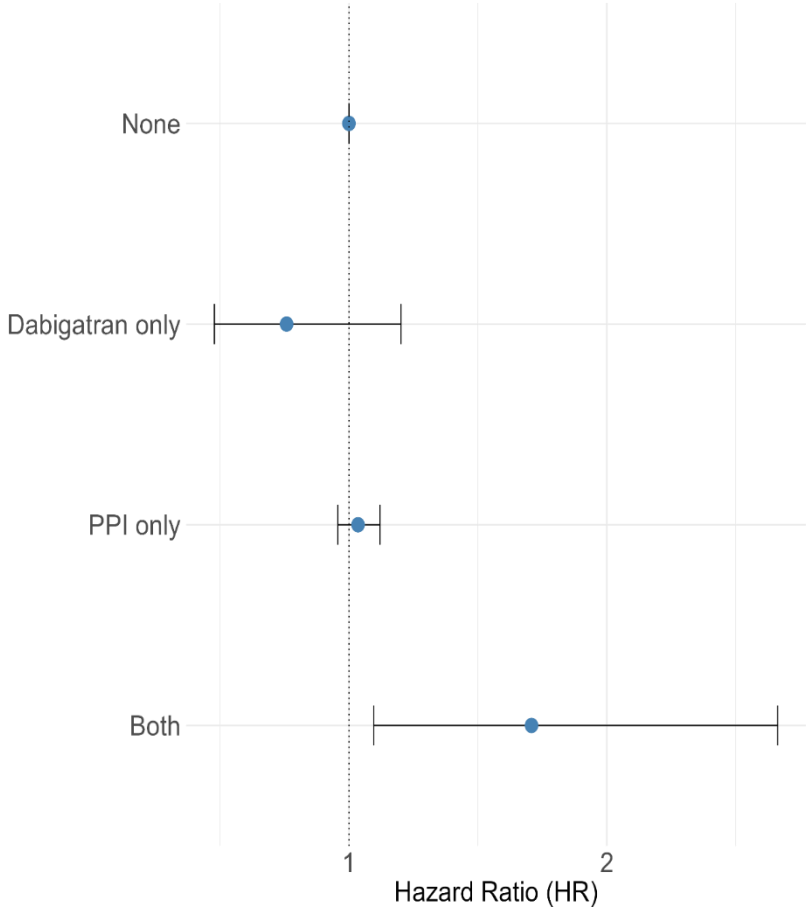


Figure 4.16 Dabigatran cohort – forest plot of adjusted hazard ratios for treatment failure outcomes

Forest plot displaying adjusted hazard ratios and 95% confidence intervals for treatment failure outcomes in the dabigatran cohort (n=30,985). Combining dabigatran with PPI increases the risk of adverse events (HR 1.71, confidence interval above HR=1.0), while monotherapy exhibits a protective tendency with a large confidence interval spanning null.

In the cohort receiving Factor Xa inhibitors (n=27,713), Factor Xa monotherapy exhibited a modest yet statistically significant reduction in treatment failure (adjusted HR 0.92, 95% CI 0.86–0.98; p=0.017) (Table 4.9, Figure 4.17). Concurrent Factor Xa–PPI therapy demonstrated no significant association (adjusted HR 0.99, 95% CI 0.90–1.08; p=0.785), while PPI monotherapy also exhibited no association (adjusted HR 0.95, 95% CI 0.89–1.01; p=0.083). Among covariates, renal and urinary tract disease (adjusted HR 1.31, 95% CI 1.22–1.40; p<0.001) and respiratory disease (adjusted HR 1.26, 95% CI 1.18–1.35; p<0.001) were the strongest independent predictors of treatment failure. Clopidogrel co-prescription was associated with reduced treatment failure risk (adjusted HR 0.77, 95% CI 0.68–0.88; p<0.001).

These estimates suggest that Factor Xa inhibitors offer limited protection against treatment failure, aligning with their therapeutic indication for thromboembolic prevention. The protective effect seen with monotherapy was not sustained during concurrent PPI therapy, although the confidence intervals exhibit considerable overlap. The estimates correspond with the slight divergence noted in the survival curves (Figure 4.11).

Table 4.9 Factor Xa inhibitor cohort: multivariable Cox regression results for treatment failure outcomes

Results of a time-dependent Cox proportional hazards model for treatment failure outcomes in the Factor Xa inhibitor cohort (n=27,713) with IPTW. A treatment failure is characterised as hospitalisation for stroke, TIA, systemic embolism, MI, or VTE. Neither (no Factor Xa inhibitor or PPI exposure), male sex, SIMD decile 9, absence of each comorbidity or concomitant medication. Factor Xa monotherapy offers limited protection, with no meaningful correlation with concurrent therapy.

Group	exp(coef)	lower .95	upper .95	P
clopidogrel1	0.770	0.676	0.877	0.000
Warfarin1	1.000	0.916	1.092	0.997
Dabigatran1	1.190	0.903	1.568	0.216
Aspirin1	0.878	0.767	1.005	0.059
Ticagrelor1	0.742	0.443	1.244	0.258
Atorvastatin1	0.928	0.859	1.003	0.059
Pravastatin1	0.732	0.535	1.001	0.051
Simvastatin1	0.997	0.923	1.076	0.931
Amiodarone1	1.169	0.952	1.437	0.137
Age	1.014	1.011	1.018	0.000
SEXF	0.894	0.839	0.952	0.001
SIMD_2016_DECILE1	1.139	1.010	1.284	0.034
SIMD_2016_DECILE2	1.084	0.955	1.230	0.213
SIMD_2016_DECILE3	1.073	0.936	1.232	0.312
SIMD_2016_DECILE4	1.167	1.008	1.351	0.039
SIMD_2016_DECILE5	1.042	0.901	1.205	0.580
SIMD_2016_DECILE6	1.192	1.020	1.394	0.028
SIMD_2016_DECILE7	1.120	0.963	1.303	0.142
SIMD_2016_DECILE8	1.014	0.870	1.181	0.860
SIMD_2016_DECILE10	0.896	0.767	1.046	0.165
Fluvastatin1	1.056	0.481	2.320	0.892
Prasugrel1	4.680	0.701	31.246	0.111
Dipyridamole1	0.001	0.000	0.004	0.000
CV1	1.146	1.046	1.255	0.003
MSK1	1.011	0.946	1.080	0.743
MentalHealth1	1.057	0.979	1.141	0.155
KUB1	1.307	1.224	1.396	0.000
Respiratory1	1.260	1.177	1.349	0.000
Neurology1	1.011	0.946	1.082	0.742
Diabetes1	1.110	1.009	1.221	0.032
Endocrine1	1.193	1.081	1.317	0.000
Cancer1	1.083	0.983	1.192	0.107
Liver_GB_Panc1	1.118	0.963	1.297	0.142
GI1	0.989	0.821	1.192	0.911
Infection1	1.023	0.606	1.728	0.932
adm_duration	0.999	0.998	1.000	0.070
Group Factor Xa inhibitors only	0.920	0.859	0.985	0.017
Group Both	0.988	0.902	1.081	0.785
Group PPI only	0.947	0.891	1.007	0.083

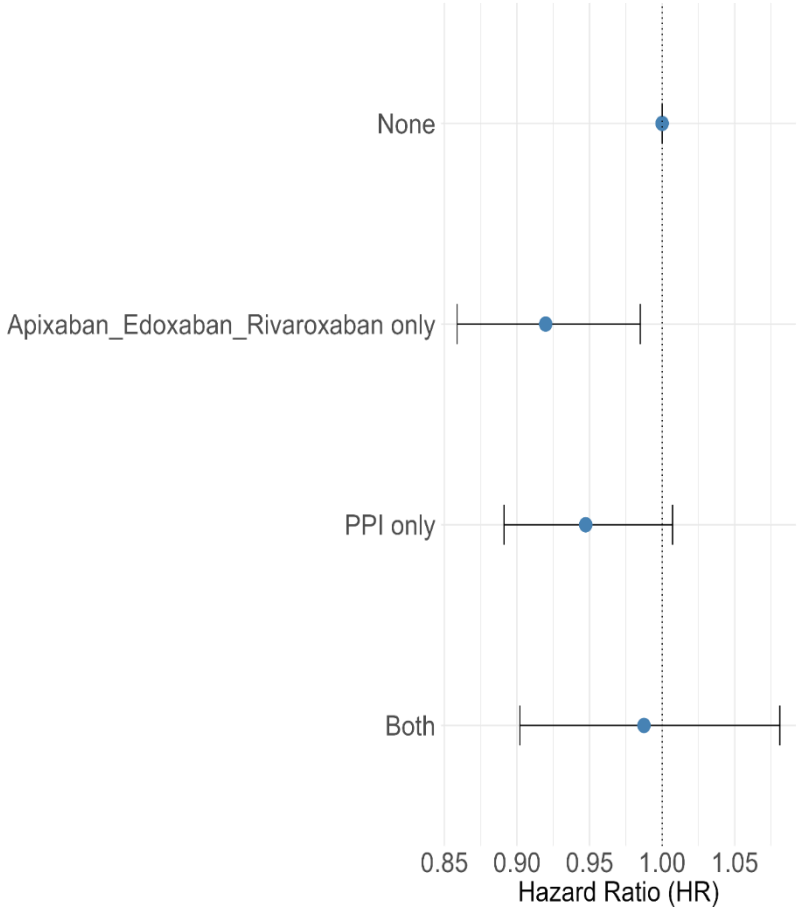


Figure 4.17 Factor Xa inhibitor cohort – forest plot of adjusted hazard ratios for treatment failure outcomes

Forest plot of adjusted hazard ratios and 95% confidence intervals for treatment failure outcomes in the Factor Xa inhibitor cohort (n=27,713). Factor Xa monotherapy shows a modest protective association (HR 0.92, 95% CI 0.86–0.98). Confidence intervals for concurrent therapy (HR 0.99) and PPI monotherapy (HR 0.95) cross the null value of 1.0, indicating non-significant associations.

4.3.6 Clinically relevant concurrent-exposure versus OAC monotherapy contrast

The primary Cox models used 'neither OAC nor PPI' as the reference category. The hazard ratio reported in this chapter therefore describe the association of each exposure state with the outcome relative to unexposed patients and do not, on their own, estimate the incremental effect of adding a PPI to anticoagulant monotherapy. That clinically relevant contrast requires estimation of a linear combination of model coefficients using the model's variance-covariance matrix and cannot be validly estimated by combining separately reported hazard ratio and their confidence intervals. A valid confidence intervals and formal statistical inference for this contrast could not be obtained within the resources available

for this analysis. Interpretation is therefore confined to comparisons against the unexposed reference group, and this constraint is acknowledged as a limitation in Section 4.4.7.

4.4 Discussion

4.4.1 Principal findings

This chapter investigates the association between concomitant prescribing of PPIs and oral anticoagulants and the altered risk of bleeding or treatment failure in adults aged 51 years and older with thromboembolic indications. Three classes of anticoagulants were analysed individually: warfarin, dabigatran, and Factor Xa inhibitors. The study populations included individuals with confirmed prescriptions for the qualifying anticoagulant and a documented diagnosis of at least one thromboembolic indication, such as atrial fibrillation, pulmonary embolism, venous thromboembolism, transient ischaemic attack, or ischaemic stroke.

The main finding indicated that the associations between PPI co-therapy and clinical outcomes varied substantially among different drug classes. In the case of warfarin, concurrent exposure to PPIs was associated with an elevated risk of bleeding (adjusted HR 2.13, 95% CI 1.25–3.63; p=0.005) and surprisingly indicated an inverse association with treatment failure (adjusted HR 0.19, 95% CI 0.04–0.86; p=0.031). However, the latter finding should be interpreted with caution due to the known bleeding risk and the possibility of residual confounding factors. In the case of dabigatran, concurrent exposure to PPIs was linked to an increased probability of treatment failure (adjusted HR 1.71, 95% CI 1.10–2.66; p=0.018). However, the associations with bleeding could not be accurately assessed due to limited concurrent exposure and minimal event occurrences. In the context of Factor Xa inhibitors, concurrent PPI co-therapy was associated with a lower risk of bleeding (adjusted HR 0.55, 95% CI 0.43–0.69; p<0.001) and showed no significant association with treatment failure (adjusted HR 0.99, 95% CI 0.90–1.08; p=0.785).

For the clinically relevant comparisons of concurrent anticoagulant-PPI therapy versus anticoagulant monotherapy, derived point estimates were: warfarin bleeding HR 1.30, warfarin treatment failure HR 0.39, dabigatran treatment

failure HR 2.25, factor Xa inhibitor bleeding HR 1.12, and factor Xa inhibitor treatment failure HR 1.07. These derived point estimates help frame the clinically relevant comparison of adding a PPI to established anticoagulant therapy, but they should be interpreted descriptively because valid confidence intervals and p-values could not be estimated within the resources available for this analysis.

The warfarin-PPI bleeding association supports targeted rather than routine gastroprotection and suggests closer monitoring when PPIs are co-prescribed. The dabigatran treatment failure finding, particularly when considered alongside pharmacokinetic evidence showing PPIs reduce dabigatran concentrations by 22–33% [212], raises questions about whether this association reflects true drug interaction or patient selection. The protective associations observed with Factor Xa inhibitors suggest this class may be safest for patients requiring concurrent PPI therapy. The class-stratified analytical approach was justified by these divergent patterns and by known mechanistic differences in how PPIs interact with different anticoagulants.

4.4.2 Context within existing literature

This study is motivated by multiple intersecting gaps in both the literature and practice. Most existing research on PPI-anticoagulant interactions is primarily mechanistic or pharmacokinetic. Competitive inhibition of cytochrome P450 2C19 by certain PPIs has been documented for warfarin, with some studies indicating modest effects on the INR and time in the therapeutic range [10, 213]. Clinical pharmacokinetic studies indicate that the concurrent use of PPIs reduces dabigatran exposure by 22–33%, attributed to alterations in gastric pH and potential inhibition of intestinal P-gp transport [212, 214, 215]. The theoretical basis for clinically significant interactions between Factor Xa inhibitors and PPIs is less effective due to pH-independent absorption; however, these agents continue to be substrates of P-gp [210, 216].

The translation of these pharmacokinetic observations to clinical outcomes is not fully resolved. Meta-analyses of observational studies indicate a 32–33% reduction in gastrointestinal bleeding with PPI co-therapy [217, 218]; however, the majority of the included studies are susceptible to confounding by indication. The single large randomised controlled trial (COMPASS) demonstrated no overall advantage

of routine PPI co-prescription in patients treated with rivaroxaban, indicating a number needed to treat of 982 to prevent a single gastroduodenal bleeding event [219]. Observational studies have indicated inconsistent associations: some demonstrate gastroprotection with dabigatran [220] and direct oral anticoagulants in general [221, 222], whereas others propose that these associations may be influenced by residual confounding [11, 223]. A randomised trial indicated no significant interaction between PPIs and the efficacy or safety of dabigatran in patients undergoing percutaneous coronary intervention [224]. Systematic reviews have identified concerns regarding the quality of evidence and discrepancies between randomised and observational data [225].

Co-prescription of PPIs with oral anticoagulants is frequently observed in routine clinical practice, with prevalence rates surpassing 30% in certain populations [221, 225]. A significant portion of this usage may not have a well-defined gastroprotective indication, indicating a potential for medication optimisation. From a knowledge perspective, the clinical stakes are considerable: treatment failure may lead to ischaemic stroke or systemic embolism, resulting in significant mortality and morbidity, while major bleeding events pose a considerable risk of permanent disability or death. If PPI co-therapy significantly modifies these risks via pharmacokinetic interactions or influences baseline bleeding risk, it directly impacts risk stratification and shared decision-making.

The present study addresses these gaps by examining population-level associations between time-varying PPI-anticoagulant exposure patterns and clinical outcomes across three anticoagulant classes in a contemporary, multimorbid population receiving routine care. The present findings can be situated within the context of specific prior studies. For warfarin, the observed adjusted HR of 2.13 (95% CI 1.25–3.63) for bleeding with concurrent PPI co-therapy is broadly consistent with, though larger in magnitude than, the findings of Lee et al. (2022) [226], who reported an adjusted odds ratio of 1.67 (95% CI 1.38–2.01) for gastrointestinal bleeding among warfarin users receiving concomitant PPIs in a Korean nationwide cohort. A more recent study by Wang et al. (2025) examined PPI-anticoagulant interactions using both case-crossover and cohort designs and found attenuated associations after applying rigorous confounding control methods, suggesting that much of the observed risk may reflect confounding by indication rather than a

true pharmacokinetic interaction [11]. For dabigatran, the present finding of increased treatment failure (adjusted HR 1.71) contrasts with randomised evidence from the RE-DUAL PCI trial subgroup analysis, which found no significant interaction between PPI use and dabigatran efficacy [224], and with the RE-LY trial post-hoc analyses, which reported no effect modification by PPI use on stroke or systemic embolism [227]. The divergence between these randomised findings and the present observational result strengthens the interpretation that confounding drives the observed association. For Factor Xa inhibitors, the observed protective bleeding association (adjusted HR 0.55) is consistent with findings from Ray et al. [228]. who reported reduced gastrointestinal bleeding among DOAC users receiving PPIs in a US Medicare cohort, and with a large Taiwanese cohort study by Chan et al. (2015) [220] that found a 34% reduction in gastrointestinal bleeding with PPI co-therapy among DOAC users. However, as discussed in Section 4.4.5, these protective associations are most plausibly explained by confounding by indication rather than genuine gastroprotection.

4.4.3 Methodological considerations and causal interpretation

The examination of PPI-anticoagulant relationships requires careful consideration of time-varying exposure and confounding by indication. PPIs are more frequently prescribed to patients exhibiting gastrointestinal symptoms, a history of bleeding, polypharmacy, or frailty-conditions that correlate with increased bleeding and thrombotic risk. Conventional cohort analyses that categorise exposure at baseline while disregarding subsequent changes are susceptible to immortal time bias, misclassification bias, and residual confounding [185, 186]. This analysis tackles the identified concerns by modelling PPI exposure as time-varying, employing IPTW to balance measured confounders at each time point, and utilising Simon-Makuch extensions of Kaplan-Meier curves to illustrate differences in event-free survival across dynamically changing exposure states [144, 180, 202].

The causal framework for this analysis can be articulated in three parts: the causal estimand, the statistical estimand, and the statistical estimates. The causal estimand represents the ideal quantity of interest-the effect of PPI co-therapy versus no PPI co-therapy on the hazard of bleeding or treatment failure in patients receiving oral anticoagulants. This corresponds to a hypothetical intervention in which PPI exposure is assigned, as in a randomised trial, with differences in

outcomes observed under identical conditions aside from PPI exposure. Because PPI exposure is time-varying, the estimand implicitly references a sequence of interventions over time, each conditional on prior exposure and covariate history, aligning with the marginal structural model framework [130, 148].

The statistical estimand is the weighted hazard ratio derived from a time-dependent Cox proportional hazards model utilising IPTW. The weights generate a pseudo-population that balances measured confounders across exposure groups at each time point, thereby simulating the exchangeability attained through randomisation [149, 178, 203]. In this pseudo-population, the hazard ratio quantifies the estimated local average causal effect of PPI exposure, depending upon the assumption that all confounders have been sufficiently measured and modelled. Simon-Makuch curves offer a non-parametric visualisation that demonstrates the accumulation of differences in event-free survival over time across varying exposure states [180].

The statistical estimates reported-the weighted hazard ratios and 95% confidence intervals-can be interpreted as approximations to causal effects under standard identifying assumptions: consistency (exposure levels are well-defined), positivity (all covariate patterns compatible with survival have non-zero probability of receiving each exposure), correct model specification (appropriate functional forms for propensity score and outcome models), and no unmeasured confounding (all common causes of exposure and outcome have been measured and controlled) [130, 229].

It is essential to clarify the limits of causal interpretation. While IPTW substantially reduced imbalance in observed covariates (SMD below 0.10), it remains unable to address confounding from unmeasured variables, including frailty, functional status, disease severity, symptom burden, clinician-specific prescribing preferences, adherence to prescribed medications, and OTC medication use-all of which are likely related to both PPI prescribing and bleeding or thrombotic risk. This analysis offers well-adjusted real-world evidence suggesting a causal effect of PPI co-therapy on clinical outcomes; however, it does not provide definitive proof of causality. This interpretation aligns with established practices in observational pharmacoepidemiology and accurately

represents both the advantages and limitations of analyses derived from routine care data [147, 201, 205]. The direction, magnitude, and specificity of the observed associations provide essential context for understanding the interactions between PPI co-therapy and various classes of oral anticoagulants in practice.

4.4.4 Biological plausibility and mechanisms of interaction

The observed associations between PPI co-therapy and clinical outcomes align with established pharmacological mechanisms for warfarin, diverge from pharmacokinetic predictions for dabigatran, and show minimal interaction potential for Factor Xa inhibitors. These patterns warrant detailed mechanistic examination to distinguish plausible drug–drug interactions from confounding by indication.

4.4.4.1 Warfarin-PPI interaction: CYP2C9 inhibition and bleeding risk

The relationship between concurrent warfarin and PPI exposure and increased bleeding risk aligns with the competitive inhibition of cytochrome P450 2C9 (CYP2C9), the main enzyme that metabolises the pharmacologically active S-enantiomer of warfarin [10, 213]. PPIs, especially omeprazole and esomeprazole, exhibit moderate inhibition of CYP2C9, which may reduce warfarin clearance and increase systemic exposure, potentially resulting in supratherapeutic anticoagulation and an increased risk of bleeding [213]. It should be noted that PPIs are themselves primarily metabolised by CYP2C19, and their differential inhibitory profiles across CYP isoenzymes contribute to agent-specific variation in interaction potential. The magnitude of CYP2C9 inhibition differs among PPI agents, with omeprazole and esomeprazole exhibiting greater inhibitory potency compared to pantoprazole or rabeprazole. However, this analysis modelled PPIs as a therapeutic class rather than estimating agent-specific effects, which may attenuate any differential interaction signal.

Clinical evidence substantiates this mechanistic rationale. Retrospective cohort studies indicate that patients on concurrent warfarin and PPI therapy have reduced time within the therapeutic INR range and increased bleeding rates compared to those on warfarin alone [10]. Classic pharmacokinetic interaction studies have shown modest increases in prothrombin time with concurrent administration of omeprazole; however, these effects are small and not

consistently clinically significant [213]. Recent observational analyses have yielded mixed results; some studies indicate an increased bleeding risk linked to PPI co-therapy, while others propose that the observed associations may be confounded by gastrointestinal risk factors rather than representing a genuine pharmacokinetic interaction [11, 226].

The current finding indicates a 2.13-fold increase in bleeding risk associated with concurrent warfarin and PPI exposure, surpassing predictions based on the modest CYP2C9-mediated pharmacokinetic effects documented in previous studies. This discrepancy indicates that minor pharmacokinetic variations may significantly impact clinical outcomes in routine-care populations with less intensive INR monitoring, or that residual confounding by indication plays a substantial role in the observed association.

4.4.4.2 Dabigatran-PPI interaction: The paradox of pharmacokinetics and clinical outcomes

The association between concurrent dabigatran and PPI exposure and the heightened risk of treatment failure represents a pharmacological paradox that requires careful analysis. Dabigatran etexilate is combined with tartaric acid to establish an acidic microenvironment that enhances dissolution and gastrointestinal absorption [214]. After absorption, the prodrug undergoes rapid hydrolysis by plasma and hepatic esterases to form dabigatran, the active direct thrombin inhibitor, via a pathway that does not involve cytochrome P450 enzymes [230]. Dabigatran etexilate is a substrate for P-glycoprotein, an ATP-dependent efflux transporter that restricts oral bioavailability by actively transporting drug molecules back into the intestinal lumen [231].

Clinical pharmacokinetic studies indicate that the concurrent use of PPIs decreases dabigatran plasma concentrations by roughly 22–33% [212]. The observed reduction is primarily due to an increase in gastric pH, which hinders the acid-dependent dissolution of dabigatran etexilate and decreases its absorption. In vitro studies indicate that PPIs may inhibit intestinal P-glycoprotein; however, in vivo research shows that the overall effect is a significant reduction in dabigatran exposure [231].

Clinical outcome data complicate this pharmacokinetic picture. Observational studies have reported reduced gastrointestinal bleeding among dabigatran users receiving gastroprotective therapy [232], while randomised trial subgroup analyses have not demonstrated a significant interaction between PPI use and dabigatran efficacy or safety in high-risk clinical settings [224].

The coexistence of diminished dabigatran exposure with neutral or protective bleeding outcomes, coupled with the absence of a consistent rise in thrombotic events, illustrates a pharmacologically counterintuitive pattern that cannot be easily explained by a simple causal pharmacokinetic mechanism. This pattern indicates confounding by indication, as PPIs are more frequently prescribed to patients with elevated baseline gastrointestinal risk and increased clinical complexity. The most restrictive interpretation is that the observed association between dabigatran–PPI co-therapy and treatment failure likely reflects patient selection rather than a causal pharmacokinetic effect. However, sparse concurrent exposure and low event counts introduce significant statistical uncertainty, preventing definitive conclusions.

An alternative interpretation is that a 22–33% reduction in dabigatran exposure is insufficient to meaningfully increase thrombotic risk in most patients, because fixed dosing produces anticoagulant effects well above the minimum required for stroke prevention. This pharmacodynamic reserve hypothesis remains uncertain and cannot be confirmed in the absence of direct drug-concentration or pharmacodynamic measurements.

4.4.4.3 Factor Xa inhibitors: Minimal interaction potential and protective associations

The associations observed for Factor Xa inhibitors, protective effects for bleeding and neutral effects for treatment failure, are consistent with minimal pharmacokinetic interaction potential combined with confounding by indication toward gastroprotection. Rivaroxaban, apixaban, and edoxaban exhibit pH-independent absorption, rendering them insensitive to gastric acid suppression by PPIs [216]. Although these agents are substrates for P-gp and undergo varying degrees of hepatic metabolism via CYP3A4, PPIs demonstrate negligible inhibitory activity against CYP3A4 and inconsistent effects on P-gp in clinical settings [210].

Randomised evidence further supports this interpretation. The COMPASS trial directly examined the gastroprotective effect of pantoprazole in patients receiving rivaroxaban for cardiovascular disease and found no significant reduction in the composite upper gastrointestinal endpoint, with a high number needed to treat to prevent a single gastroduodenal bleeding event [219].

Accordingly, protective bleeding associations observed in real-world studies of concurrent Factor Xa inhibitor–PPI exposure are unlikely to reflect a true pharmacological interaction. Rather, they are most plausibly explained by confounding by indication, whereby PPIs are selectively prescribed to patients at elevated baseline gastrointestinal bleeding risk. This interpretation is reinforced by large Asian cohort studies reporting modest reductions in gastrointestinal bleeding with PPI co-therapy among direct oral anticoagulant users, although these associations may reflect the same underlying confounding structure [221, 222]. The neutral association observed for treatment failure further supports minimal pharmacokinetic interaction, as one would expect either increased thrombosis (if PPIs reduced drug exposure) or decreased thrombosis (if confounding favoured patients at lower baseline risk), neither of which is observed.

4.4.4.4 Limitations of mechanistic inference without drug-concentration data

Interpretation of these findings is constrained by the absence of direct drug-concentration measurements, pharmacogenetic data, and detailed adherence information. Without such data, it is not possible to determine whether observed associations are mediated by altered drug exposure or arise entirely from residual confounding and selective prescribing. This limitation is particularly salient for dabigatran, where reduced drug concentrations in pharmacokinetic studies coexist with inconsistent clinical outcome associations in observational research. Similar constraints apply to warfarin in the absence of INR data, and to Factor Xa inhibitors without anti-Xa activity measurements. These limitations underscore the inherent constraints of observational pharmacoepidemiology and reinforce the need for integrated studies combining clinical outcomes with direct measurement of drug exposure and intermediate pharmacodynamic endpoints.

4.4.5 Alternative explanation and problem of confounding by indication

The interpretation of observed associations as indicative of causal pharmacokinetic drug–drug interactions is made difficult by evidence indicating that confounding by indication is the main explanation for most findings. This alternative interpretation suggests that PPIs are not prescribed randomly; rather, they are selectively initiated in patients identified by clinicians as having an increased risk of gastrointestinal bleeding, a history of peptic ulcer disease, polypharmacy, frailty, or other factors that independently affect both bleeding and thrombotic outcomes. Within this framework, the associations between PPI exposure and clinical outcomes are not driven by direct pharmacological interactions with anticoagulant drug exposure or activity, but rather from systematic variations in baseline risk profiles among patients receiving versus not receiving PPI therapy.

This interpretation is supported by multiple observations from the current analyses and the wider literature. First, baseline characteristics before applying IPTW indicated significant imbalances among exposure groups. Patients receiving PPIs exhibited a consistently higher burden of comorbidity, increased healthcare utilisation as indicated by longer hospital admission durations, and a higher prevalence of conditions linked to both bleeding and thrombotic risk, such as cardiovascular disease, musculoskeletal disorders, mental health conditions, respiratory disease, and gastrointestinal diagnoses. While IPTW successfully balanced measured covariates (all SMD < 0.10), it is unable to address unmeasured variables such as frailty, functional status, symptom burden, OTC medication use, or clinician-specific prescribing preferences, all of which may be related to both PPI initiation and clinical outcomes.

Second, the direction and magnitude of observed associations differ systematically from what would be predicted by pharmacokinetic mechanisms alone. For warfarin, the observed 2.13-fold increase in bleeding hazard with concurrent PPI exposure substantially exceeds the modest effects on INR and time in therapeutic range reported in pharmacokinetic studies of CYP2C9 inhibition. For dabigatran, the coexistence of reduced drug concentrations (22–33% lower with PPI co-therapy) and either neutral or protective bleeding outcomes in some

observational studies is pharmacologically inconsistent and suggests that observed associations are driven by patient selection rather than by altered dabigatran exposure. For Factor Xa inhibitors, protective bleeding associations (adjusted HR 0.55) are observed despite minimal theoretical grounds for pharmacokinetic interaction, again pointing to confounding by baseline gastrointestinal risk as the primary driver.

Third, evidence from randomised controlled trials provides a critical external validity check and consistently fails to support clinically meaningful drug–drug interactions. The COMPASS trial randomised 17,598 patients with stable cardiovascular disease to receive rivaroxaban, aspirin, or both, with or without pantoprazole gastroprotection [219]. Despite adequate statistical power, the trial found no significant reduction in the composite upper gastrointestinal endpoint with pantoprazole co-therapy, and the number needed to treat to prevent one gastroduodenal bleeding event was 982, indicating minimal absolute benefit. Similarly, a pre-specified subgroup analysis of the RE-DUAL PCI trial found no significant interaction between baseline PPI use and dabigatran efficacy or safety outcomes in patients with atrial fibrillation undergoing percutaneous coronary intervention [224]. The discordance between these null findings in randomised trials and the apparent gastroprotective associations reported in observational studies strongly suggests that observational associations are confounded.

Fourth, a recent methodologically rigorous observational study employed multiple advanced causal inference approaches to examine PPI–anticoagulant interactions using a large administrative dataset [11]. The authors conducted both a case-crossover analysis with self-matched controls to minimise time-invariant confounding and a time-dependent Cox proportional hazards model with inverse probability of treatment weighting. Across these complementary analyses, associations between PPI exposure and bleeding outcomes were substantially attenuated or reversed, suggesting that between-individual confounding drove crude associations.

4.4.5.1 The dabigatran paradox as evidence for confounding

The dabigatran findings represent a critical inconsistency with a simple causal pharmacokinetic interaction model. The pharmacological prediction is explicit: if

PPIs reduce dabigatran plasma concentrations by 22–33%, patients receiving concurrent dabigatran–PPI therapy should experience increased treatment failure (due to subtherapeutic anticoagulation) and decreased bleeding (due to reduced drug exposure). The present analysis observed increased treatment failure (adjusted HR 1.71, 95% CI 1.10–2.66; p=0.018), which is directionally consistent with pharmacokinetic predictions. However, large observational studies have reported reduced gastrointestinal bleeding with gastroprotective therapy among dabigatran users [220], and meta-analyses of observational data have estimated 32–47% reductions in bleeding with PPI co-therapy [217]. This pattern-wherein PPIs simultaneously reduce drug concentrations yet are associated with clinical gastroprotection or neutral bleeding effects-is pharmacologically inconsistent and cannot be reunited with a simple causal drug interaction model.

The tightest explanation is that patients receiving dabigatran plus PPIs are systematically different from those receiving dabigatran alone, with higher baseline gastrointestinal bleeding risk that prompts preventive PPI prescription. The observed gastroprotective associations in some studies may reflect successful risk stratification and appropriate clinical targeting of high-risk patients, rather than a pharmacological effect of PPIs on dabigatran-related bleeding. Conversely, the present finding of increased treatment failure may reflect either residual confounding (with PPIs prescribed to patients with greater overall clinical complexity and higher baseline thrombotic risk), or sparse data bias arising from very low concurrent exposure at baseline and few observed events in the concurrent exposure group. The wide confidence interval (1.10–2.66) and borderline statistical significance underscore the fragility of this estimate and the difficulty of drawing causal inferences from observational data with sparse exposure-outcome overlap.

4.4.5.2 Sparse concurrent exposure and statistical instability

An additional methodological concern that complicates interpretation is sparse concurrent exposure, particularly in the dabigatran cohort. At baseline and throughout follow-up, the proportion of patients concurrently exposed to dabigatran and PPIs was very small, reflecting clinical practice in which these agents are rarely co-prescribed. Although exposure status was time-varying and patients could transition into concurrent exposure during follow-up, the overall

person-time spent in the concurrent exposure state remained limited, and bleeding events occurring during concurrent exposure were insufficient to permit reliable hazard ratio estimation. This sparsity introduces substantial statistical uncertainty and potential for positivity violations wherein certain covariate patterns have near-zero probability of receiving concurrent exposure. Under such violations, IPTW may produce unstable estimates with extreme weights that inflate variance and bias results.

The inability to estimate bleeding associations for dabigatran concurrent exposure due to sparse data represents a meaningful limitation that prevents direct comparison with warfarin and Factor Xa inhibitor findings. It is unclear whether this sparsity reflects deliberate clinical decision-making to avoid co-prescribing dabigatran with PPIs due to awareness of potential pharmacokinetic interactions, or whether it arises from other prescribing dynamics unrelated to drug interaction concerns. Regardless of mechanism, the sparse data structure precludes definitive conclusions about dabigatran–PPI bleeding interactions and suggests that any observed associations for treatment failure should be interpreted with considerable caution.

4.4.5.3 Clinical implications of residual confounding

If confounding by indication is indeed the primary driver of observed associations, the clinical implications differ substantially from those that would follow from causal drug–drug interactions. Under a confounding interpretation, the observed associations do not indicate that PPIs cause harm or benefit through pharmacokinetic mechanisms, but rather that PPIs serve as markers of baseline gastrointestinal risk and clinical complexity. Protective associations for Factor Xa inhibitors would reflect appropriate risk stratification and successful gastroprotection in high-risk patients, while adverse associations for warfarin bleeding might reflect either incomplete confounding control or true pharmacological effects amplified by inadequate INR monitoring. For dabigatran, the observed association with increased treatment failure does not provide evidence in favour of avoiding PPI co-therapy, but instead suggests that greater attention should be paid to understanding the systematic differences between patients who receive concomitant PPI therapy and those who do not.

This interpretation supports a clinical strategy focused on selective, indication-driven PPI prescribing rather than either routine co-prescription or blanket avoidance. Guidelines already recommend gastroprotective therapy for patients at elevated bleeding risk, defined by prior gastrointestinal bleeding, peptic ulcer disease, concurrent antiplatelet therapy. The present findings do not challenge this approach but underscore that observational associations between PPI exposure and outcomes likely reflect the appropriateness of such risk-based prescribing rather than causal pharmacological effects.

4.4.6 Clinical implications and therapeutic considerations

This analysis indicates that clinical decision-making concerning concomitant PPI therapy in patients on oral anticoagulants should be customised based on the anticoagulant class and individual patient bleeding risk profiles, rather than relying on general recommendations for routine co-prescription or universal avoidance.

For patients receiving warfarin, the observed association between concurrent PPI exposure and increased bleeding risk (adjusted HR 2.13, 95% CI 1.25–3.63; p=0.005) warrants careful consideration of whether PPI co-therapy is clinically indicated. The finding supports selective rather than routine PPI prescribing, with gastroprotection reserved for patients at demonstrably elevated gastrointestinal bleeding risk, including those with prior peptic ulcer disease, concurrent antiplatelet therapy. When PPIs are prescribed alongside warfarin, clinicians should consider more frequent INR monitoring, particularly during PPI initiation. The choice of PPI agent may be relevant, as pantoprazole and rabeprazole demonstrate weaker CYP2C9 inhibition than omeprazole or esomeprazole.

For patients receiving dabigatran, the observed association between dabigatran-PPI co-therapy and increased treatment failure (adjusted HR 1.71, 95% CI 1.10–2.66; p=0.018) is most plausibly attributed to confounding by indication, given that observational studies have suggested gastroprotective effects of PPI co-therapy in dabigatran users. The inability to estimate bleeding associations due to sparse concurrent exposure prevents definitive conclusions. In the absence of clear evidence for clinically meaningful harm, the most defensible clinical approach is to prescribe PPIs to dabigatran users based on the same risk-

stratification criteria applied to other anticoagulants. Routine avoidance is not supported by available evidence.

For patients receiving Factor Xa inhibitors, the observed protective associations for bleeding (adjusted HR 0.55, 95% CI 0.43–0.69; p<0.001) and neutral associations for treatment failure (adjusted HR 0.99, 95% CI 0.90–1.08; p=0.785) suggest minimal pharmacokinetic interaction potential. These findings indicate that FXa inhibitors may be a reasonable option for patients requiring concurrent PPI therapy, although observational associations likely reflect patient selection rather than causal pharmacological effects.

Across all three anticoagulant classes, the evidence supports selective, indication-driven PPI prescribing. High-risk patients, defined by prior gastrointestinal bleeding, peptic ulcer disease, concurrent antiplatelet therapy are likely to benefit from gastroprotective therapy regardless of anticoagulant class, although warfarin users may require closer INR monitoring. Low-risk patients may not require routine PPI co-prescription, and unnecessary polypharmacy should be avoided. When gastroprotection is indicated, PPI therapy should be prescribed at the lowest effective dose.

4.4.7 Methodological strengths and limitations

This analysis utilised multiple methodological approaches to improve reliability and internal validity. The implementation of time-varying exposure classification effectively captured dynamic medication prescribing patterns and avoided immortal time bias. IPTW successfully balanced measured confounders among exposure groups, achieving SMD below 0.10 in weighted pseudo-populations. Simon-Makuch curves offered non-parametric visualisations that complement regression-based estimates. Separate cohort analyses for each anticoagulant class acknowledged established mechanistic differences, while large sample sizes (more than 25,000 patients per cohort) ensured sufficient statistical power.

Despite these strengths, several important limitations constrain causal interpretation. The most fundamental limitation is the potential for unmeasured confounding. Although propensity score models included comprehensive demographic characteristics, comorbidities, and medication exposures, they did

not capture frailty, functional status, symptom burden, OTC medication use, or clinician-specific prescribing preferences-all plausibly associated with both PPI initiation and clinical outcomes. Confounding by indication is particularly concerning for gastroprotective medications, as PPIs are prescribed specifically to patients judged to be at elevated gastrointestinal bleeding risk.

The overlap of the study period with the COVID-19 pandemic warrants particular attention in this cohort, because SARS-CoV-2 infection perturbs haemostasis in both directions relevant to the outcomes examined. COVID-19 is associated with a prothrombotic state that increases venous and arterial thromboembolism and, less commonly, with clinically significant bleeding [233], either could manifest as the treatment-failure or bleeding endpoints defined in this study. Infection was not ascertainable from the available records and thus represents an unmeasured confounder affecting both outcomes simultaneously. Furthermore, the well-documented reduction in hospital admissions during 2020 may have led to under-capture of both bleeding and thromboembolic admissions in the final study year, with an uncertain net effect on the estimated hazard ratios. Because anticoagulated patients were also a priority group for shielding and altered clinical monitoring during this period, differential changes in exposure classification and outcome ascertainment cannot be excluded. These considerations add a further layer of uncertainty to the interpretation of the 2020 data and reinforce the observational, associational nature of the conclusions.

The lack of direct measurements of drug concentration, pharmacogenetic information, or intermediate pharmacodynamic endpoints (such as INR or anti-Xa activity) prevents the assessment of whether the observed associations are due to changes in drug exposure or arise entirely from residual confounding. This constraint is particularly significant for dabigatran, as pharmacokinetic studies indicate decreased drug concentrations with PPI co-therapy, while clinical outcome data reveal a different pattern.

Administrative healthcare data introduce additional limitations. Bleeding and treatment failure events were identified through hospital admission records, capturing only events severe enough to require hospitalisation and potentially missing outpatient-managed episodes. PPI exposure was classified based on

prescription records, which do not guarantee adherence or account for OTC use. Medication dose, formulation, and timing relative to anticoagulant dosing were not captured.

The limited statistical power due to sparse concurrent exposure in the dabigatran cohort restricted the reliable estimation of bleeding hazard ratios. The observed sparsity accurately represents clinical practice patterns; however, it introduces uncertainty that prevents definitive conclusions regarding the interactions between dabigatran and PPIs.

Finally, the study population was restricted to adults aged 51 years and older receiving care within a single Scottish health system, which may limit generalisability to younger populations, different healthcare systems, or populations with different baseline risk profiles or genetic polymorphism frequencies.

The analytical approach censored competing events (treatment failure was censored in bleeding analyses and vice versa), which assumes that censoring is non-informative. However, patients who experience treatment failure may be systematically different from those who remain event-free, potentially introducing informative censoring bias. A formal competing risks framework, such as the Fine-Gray sub-distribution hazard model, would provide complementary estimates that account for the competing nature of bleeding and thrombotic outcomes, but was not implemented in the present analysis. The direction and magnitude of any bias from informative censoring is difficult to predict without additional modelling.

A further methodological limitation concerns derivation of the Both-versus-monotherapy contrast. Valid confidence intervals for the derived contrasts reported in Section 4.4.1 could not be estimated within the resources available for this analysis, and these contrasts are therefore reported as descriptive point estimates only, without formal statistical inference. Statistical inference and the conclusions based upon it are confined to the primary comparisons of each exposure group with the unexposed reference group.

Over-the-counter PPI use, which is not captured in prescription records, represents a further source of exposure misclassification. Patients classified as unexposed to PPIs may have been self-medicating with over-the-counter PPIs, which would attenuate the observed associations between PPI exposure and clinical outcomes by diluting the reference group. The prevalence of over-the-counter PPI use in this population is unknown, but a UK-based study estimated that approximately 10–15% of PPI use may be obtained without prescription [234]. This non-differential misclassification would bias results towards the null, potentially underestimating true associations.

Finally, this analysis did not assess dose-response relationships between PPI exposure and clinical outcomes. PPI dose, duration, and the specific agent prescribed may modify interaction magnitude, particularly for CYP2C9-mediated interactions with warfarin, where higher PPI doses would be expected to produce greater enzyme inhibition. The class-level PPI exposure definition, while pragmatic, may obscure clinically important dose-dependent or agent-specific effects.

4.4.8 Future research directions

The present findings identify several priorities for future research. Randomised controlled trials assessing PPI gastroprotection in users of warfarin and dabigatran, especially within high-risk subgroups, would yield conclusive evidence on causal effects. Trials should incorporate the measurement of drug concentrations and pharmacodynamic endpoints to clarify mechanisms.

Prospective cohort studies integrating clinical outcomes with direct measurement of anticoagulant drug concentrations, pharmacogenetic profiles (CYP2C9, CYP2C19, ABCB1 variants), and intermediate pharmacodynamic endpoints would enable mediation analyses to determine whether associations are mediated by altered drug exposure or arise from residual confounding. Such studies should capture detailed adherence data and validated measures of frailty to reduce unmeasured confounding.

Comparisons specific to agents within drug classes could clarify whether interaction effects differ based on PPI formulation or anticoagulant type.

Subgroup analyses that investigate effect modification by age, sex, renal function, and genetic polymorphisms will identify populations at elevated or diminished risk. Research in implementation science assessing deprescribing interventions and clinical decision support systems would aim to translate evidence into practical applications.

4.4.9 Conclusion

This analysis examined associations between PPI co-therapy and clinical outcomes in adults aged 51 years and older receiving oral anticoagulants for thromboembolic indications within NHS Greater Glasgow and Clyde. Findings differed substantially across anticoagulant classes, with warfarin showing increased bleeding risk, dabigatran showing increased treatment failure with uncertain bleeding effects due to sparse concurrent exposure, and Factor Xa inhibitors showing protective bleeding associations and neutral treatment failure effects. These patterns suggest that confounding by indication represents the most plausible explanation for most observed associations, although pharmacokinetic interactions may contribute to warfarin-related bleeding risk. Clinical practice should emphasise selective, indication-driven PPI prescribing based on individual bleeding risk assessment rather than routine co-prescription or universal avoidance, with particular attention to INR monitoring in warfarin users receiving concurrent PPI therapy.

Chapter 5 PPI Use and Bleeding Risk in Clopidogrel-Treated Patients Following Transient Ischaemic Attack or Ischaemic Stroke

5.1 Introduction

Transient ischaemic attack (TIA) and ischaemic stroke are significant cerebrovascular incidents that pose a substantial risk of early recurrence and long-term vascular complications, requiring immediate and ongoing antiplatelet medication for secondary prevention [77, 98]. Clopidogrel, an irreversible P2Y12 receptor antagonist, is commonly employed as the primary antiplatelet treatment for individuals intolerant to aspirin or at heightened risk of recurrent ischaemic episodes [85]. In standard clinical practice, populations following TIA and strokes are marked by advanced age, significant multimorbidity, and prevalent polypharmacy, all of which heighten susceptibility to recurrent ischaemic events and treatment-associated haemorrhagic complications [33, 98].

In order to reduce the risk of gastrointestinal bleeding, PPIs are frequently prescribed in conjunction with antiplatelet therapy in this population. This is especially true for older patients and those who have a history of gastrointestinal disorders, concurrent anticoagulant use, or exposure to other gastrotoxic medications [81]. The safety of simultaneous use of PPIs and clopidogrel has remained uncertain since a 2009 U.S. Food and Drug Administration safety communication warned against their combined use due to a potential pharmacokinetic interaction [103].

Clopidogrel is a prodrug that requires hepatic bioactivation to reveal its antiplatelet activity. Upon oral administration, most absorbed clopidogrel is quickly hydrolysed by carboxylesterase 1 into an inactive metabolite, with only a minor portion proceeding through a two-step oxidative activation pathway primarily facilitated by cytochrome P450 enzymes, particularly CYP2C19 [91, 95]. Ultimately, fewer than 2% of the supplied dose is transformed into the active thiol metabolite that irreversibly blocks the platelet P2Y12 receptor for the duration of the platelet's lifecycle [92, 96]. The restricted bioavailability, along with

significant inter-individual variability in CYP2C19 activity due to genetic polymorphisms, leads to variability in antiplatelet response among patients administered normal clopidogrel doses [97, 113].

Besides hepatic metabolism, the pharmacokinetics of clopidogrel are affected by intestinal P-gp, an ATP-dependent efflux transporter produced by the ABCB1 gene, which is expressed in enterocytes, hepatocytes, and renal tubular cells [99, 101]. Clopidogrel, being a P-gp substrate, undergoes active efflux during intestinal absorption, hence restricting its oral bioavailability [101]. Genetic diversity in ABCB1 expression and function has been linked to modified clopidogrel exposure and may further influence inter-individual variability in treatment response [99, 101]. Collectively, these metabolic and transport routes present numerous chances for clinically significant drug–drug interactions.

The mechanistic rationale for concern regarding PPI–clopidogrel co-prescribing centres on two potentially opposing pharmacokinetic effects. First, several PPIs, particularly omeprazole and esomeprazole, act as competitive inhibitors of CYP2C19 and could theoretically reduce formation of clopidogrel's active metabolite, thereby attenuating platelet inhibition [41, 235]. Pharmacodynamic studies have consistently demonstrated reduced ex vivo platelet inhibition when clopidogrel is administered concurrently with PPIs [236-238]. Second, some PPIs inhibit intestinal P-glycoprotein, which could increase clopidogrel absorption by reducing efflux from enterocytes [99, 101]. The net clinical effect of these competing mechanisms remains uncertain and may vary by individual PPI agent and patient susceptibility [239, 240].

Despite strong biological plausibility for a pharmacokinetic interaction, evidence linking PPI–clopidogrel co-prescription to adverse clinical outcomes has been inconsistent. Randomised trial sub-analyses and large observational studies in acute coronary syndrome and post–percutaneous coronary intervention populations have generally demonstrated reduced platelet inhibition with PPI use but have failed to show consistent associations with increased ischaemic events after adjustment for confounding [237, 240]. Conversely, some observational studies have reported increased cardiovascular risk among PPI users, although these findings have been widely criticised for confounding by indication and

residual bias [241]. Importantly, most existing studies have focused on ischaemic outcomes in cardiology populations, with limited attention to bleeding outcomes and minimal representation of patients with cerebrovascular disease [239, 240, 242].

Patients following TIA or ischaemic stroke constitute a clinically distinct population. Compared with acute coronary syndrome cohorts, stroke patients are typically older, more multimorbid, and at higher baseline risk of both bleeding and non-cardiovascular hospitalisation [33, 98]. Moreover, the clinically relevant question in this context differs fundamentally from that addressed in much of the prior literature. Rather than asking whether PPIs compromise clopidogrel's ischaemic protection, clinicians managing post-stroke patients must determine whether gastroprotection with PPIs alters bleeding risk in a population already vulnerable to haemorrhagic complications. Given the high prevalence of PPI use in older stroke patients and the frequent absence of definitive evidence specific to this group, outcome-based data addressing bleeding risk are critically needed to inform prescribing decisions.

5.1.1 Central research question and analytical approach

This study aimed to determine whether concurrent use of PPIs with clopidogrel in patients aged 51 years and older following TIA or ischaemic stroke is associated with altered risk of bleeding-related hospital admissions. We hypothesized that concurrent PPI-clopidogrel exposure would not be associated with increased bleeding risk, reasoning that any modest reduction in platelet inhibition resulting from CYP2C19 competition would be counterbalanced by the direct gastroprotective benefits of acid suppression, resulting in a neutral net effect on composite bleeding outcomes. To address this hypothesis, we employed a dynamic cohort design with time-varying exposure definitions, allowing patients to transition between four mutually exclusive medication states throughout a two-year follow-up period: (1) neither medication, (2) PPI monotherapy, (3) clopidogrel monotherapy, or (4) concurrent PPI-clopidogrel therapy. The primary comparison evaluated bleeding risk for concurrent exposure versus clopidogrel monotherapy, directly addressing the clinical decision faced by prescribers: "Should I add gastroprotection with a PPI for this stroke patient currently receiving clopidogrel?" This approach maintains independence from medication initiation

sequence, as patients could enter the concurrent exposure state by adding PPI to existing clopidogrel therapy or by initiating clopidogrel in patients already receiving PPI therapy.

We utilised time-dependent Cox proportional hazards regression within an IPTW framework to control for measured confounding by indication, recognising that PPI prescription is strongly influenced by gastrointestinal risk factors while clopidogrel prescription reflects cardiovascular risk stratification [144, 149, 178]. Time-varying exposure methodology prevented immortal time bias by appropriately allocating person-time to the exposure state experienced at each time point [185, 186]. Complementary Simon-Makuch survival curves provided non-parametric graphical representation of bleeding-free survival across exposure states, accounting for state transitions [180]. By examining a real-world National Health Service (NHS) Scotland cohort, this investigation provides pragmatic evidence directly applicable to routine stroke prevention practice in elderly, multimorbid population where balancing ischaemic and haemorrhagic risks represents a critical clinical challenge.

5.2 Methods

5.2.1 Study design and setting

This chapter comprises a single retrospective cohort study examining bleeding-related hospitalisation in clopidogrel-treated patients following TIA or ischaemic stroke. The data source (linked NHS Greater Glasgow and Clyde electronic health records, 2014–2020), the Safe Haven analytical infrastructure, the ethical approvals governing access, and STROBE-compliant reporting are described in Chapter 2 (Sections 2.2 and 2.3) and applied as in Chapter 3 (Section 3.2.1) and Chapter 4 (Section 4.2.1).

5.2.2 Study population and eligibility criteria

The source population for the clopidogrel cohort included all persons aged 51 and older who had a recorded prescription for clopidogrel and a documented diagnosis of at least one cerebrovascular indication between 1 January 2014 and 31 December 2020. Qualifying indications included transient ischaemic attack (ICD-10 code: G45.9) and ischaemic stroke (I63, I64).

Patients were included if they had a minimum of one documented clopidogrel prescription during the study period, indicating active antiplatelet medication. The exclusion criteria included: (1) missing baseline covariate data; (2) insufficient follow-up data; and (3) a previous bleeding-related hospitalisation prior to cohort entry. The final analytical cohort comprised 8,109 patients. The full ICD-10 code list applied across the thesis is presented in Chapter 2 (Table 2.2). Figure 5.1 presents the flowchart of cohort derivation and baseline exposure classification.

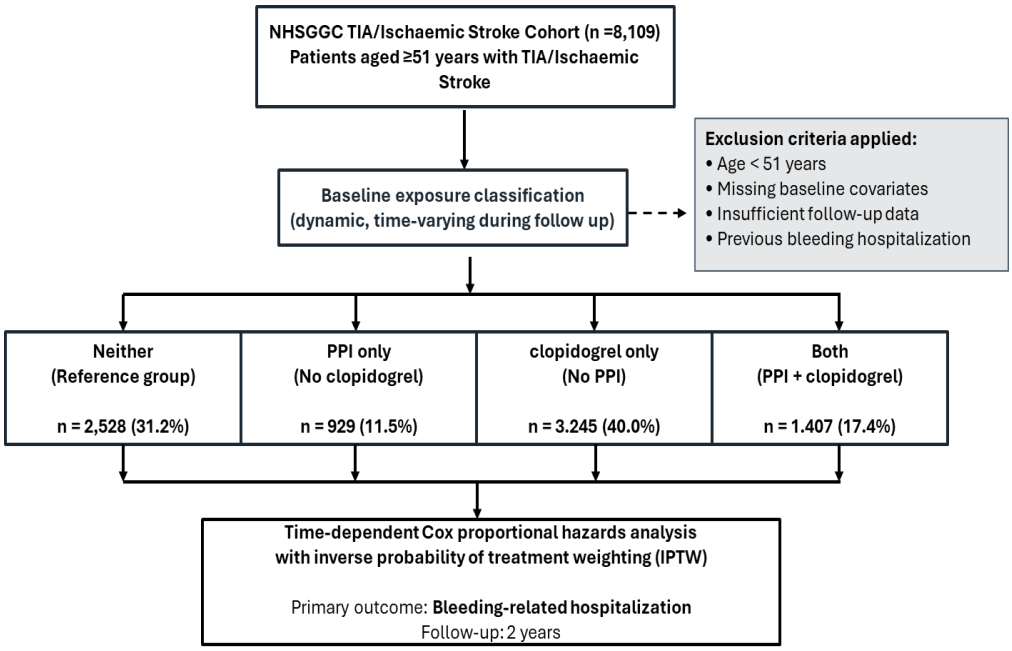


Figure 5.1 Cohort derivation and baseline exposure classification for clopidogrel-PPI analyses

Flowchart illustrating cohort selection from NHS Greater Glasgow and Clyde patients aged ≥51 years with transient ischaemic attack or ischaemic stroke. Baseline exposure groups represent concomitant PPI and clopidogrel use at cohort entry. Exposure status was modelled as time-varying during follow-up. Associations were estimated using time-dependent Cox proportional hazards models with IPTW over a maximum follow-up of 2 years.

5.2.3 Follow-up and censoring

Follow-up commenced at cohort entry (date of hospital discharge from the index TIA or ischaemic stroke admission, as defined in 5.2.2) and continued until the earliest occurrence of bleeding-related hospitalisation, death, loss to follow-up, or administrative censoring at two years. The general framework for follow-up, time scale (time since cohort entry), and the treatment of death as a censoring event in the primary analysis is described in Chapter 2 (Section 2.2.2) and applied as in Chapter 3 (Section 3.2.3) and Chapter 4 (Section 4.2.3).

5.2.4 Exposure definition and time-varying structure

Exposure to clopidogrel and PPIs was modelled as time-varying using the four-category framework described in Chapter 2 (Section 2.4) and applied as in Chapter 3 (Section 3.2.4) and Chapter 4 (Section 4.2.4). At any given time point, individuals were classified into one of four mutually exclusive exposure states: Neither (reference); PPI only; Clopidogrel only; or Both (concurrent clopidogrel and PPI). Individuals could transition between states throughout follow-up, with person-time allocated accordingly. The 7-day carry-over rule and the rationale for modelling PPIs as a therapeutic class are detailed in Chapter 2 (Sections 2.4.1 and 2.4.2).

5.2.5 Outcome definition

The primary outcome was bleeding-related hospitalisation, identified from inpatient admission records using ICD-10 codes for intracranial haemorrhage (I60–I62), gastrointestinal bleeding (K25–K28 sub-codes for haemorrhage and perforation; K920–K922), respiratory haemorrhage including haemoptysis (R040–R049), and other significant bleeding (R58). The full code list, the rationale for restricting outcomes to hospitalised events, and the implications for outcome misclassification are presented in Chapter 2 (Table 2.2; Sections 2.3.3 and 2.13.6) and applied as in Chapter 4 (Section 4.2.5). Recurrent ischemic outcomes, including recurrent ischemic stroke, TIA, and MI, were not examined in this study. Consequently, the analysis evaluates the association between concurrent PPI-clopidogrel exposure and bleeding-related hospitalisation but does not assess the principal potential effectiveness concern associated with PPI-clopidogrel co-prescription, namely recurrent ischaemic events. This limitation is considered further in the Discussion.

5.2.6 Covariates and confounding structure

Covariate selection followed the framework described in Chapter 2 (Section 2.8.1) and applied as in Chapter 3 (Section 3.2.6) and Chapter 4 (Section 4.2.6), using the disjunctive cause criterion [175] to identify pre-treatment causes of exposure or outcome. Measured covariates included demographics (age, sex, SIMD 2016 decile); binary comorbidity indicators identified from ICD-10 codes recorded prior to or at cohort entry - covering cardiovascular disease, prior gastrointestinal conditions (ulcer disease, reflux, gastrointestinal bleeding), hepatobiliary and pancreatic disease, renal and urinary-bladder disease, respiratory disease, diabetes mellitus, mental health conditions, and cancer; healthcare utilisation markers (cardiology, neurology, and gastroenterology consultations in the preceding year, and index hospitalisation duration); and concomitant medications modelled as binary indicators (aspirin; other antiplatelet agents - ticagrelor, prasugrel, dipyridamole; oral anticoagulants; and individual statins - simvastatin, atorvastatin, pravastatin, fluvastatin, rosuvastatin). Confounding by indication and residual unmeasured confounding (e.g., over-the-counter PPI use, alcohol consumption, frailty) are discussed in Chapter 2 (Sections 2.8.1 and 2.13.1) and revisited in Section 5.4.7.2.

5.2.7 Statistical analysis

The analytical strategy combined time-varying exposure modelling, IPTW, and time-dependent Cox proportional hazards regression to estimate, under stated assumptions, the contrast in the instantaneous hazard of bleeding-related hospitalisation between concurrent clopidogrel–PPI exposure and alternative exposure states (clopidogrel alone, PPI alone, or neither drug), conditional on observed clinical history. Effect estimates are reported as hazard ratios with 95% confidence intervals, with two-sided tests at an α level of 0.05. The full development of the survival framework, the causal and statistical estimand specification, IPTW implementation, Simon-Makuch curve construction, and the handling of missing data is set out in Chapter 2 (Sections 2.5–2.12) and applied as in Chapter 3 (Section 3.2.7) and Chapter 4 (Section 4.2.7) [130, 148]. This subsection records only the analytical choices specific to the present cohort.

Time-varying propensity scores were estimated using multinomial logistic regression on the covariates listed in Section 5.2.6, with stabilised weights

truncated at the 1st and 99th percentiles to limit the influence of extreme weights [203]. Covariate balance was assessed using absolute SMD before and after weighting, with values <0.10 considered acceptable [149]. The outcome model was an IPTW-weighted, time-dependent Cox proportional hazards regression with robust sandwich variance estimators to account for weighting and intra-individual correlation across exposure transitions [211]. The proportional hazards assumption was evaluated using Schoenfeld residuals and graphical diagnostics.

Because the primary model parameterises exposure groups against the "neither drug" reference, the clinically relevant contrast - concurrent clopidogrel–PPI therapy versus clopidogrel monotherapy - was derived from the fitted model coefficients (ß_Both − ß_Clopidogrel_only) and is reported alongside the primary estimates in Section 5.3.4. As noted in Chapter 2 (Section 2.4.2), a valid confidence interval for this contrast could not be estimated within the resources available for this analysis, and it is therefore reported as a descriptive point estimate only, without formal statistical inference.

All analyses were conducted in R (version 4.3.0) using the WeightIt package for IPTW, the survival package for Cox proportional hazards models, survminer for Simon-Makuch curves, and the tidyverse suite for data manipulation and visualisation.

5.3 Results

5.3.1 Study population and baseline characteristics

Figure 5.1 presents the STROBE flow diagram for cohort assembly. The final analytical cohort comprised 8,109 patients aged 51 years and older with a diagnosis of transient ischaemic attack or ischaemic stroke. At baseline, patients were distributed across four exposure states: neither medication (n=2,528; 31.2%), PPI monotherapy (n=929; 11.5%), clopidogrel monotherapy (n=3,245; 40.0%), and concurrent PPI-clopidogrel therapy (n=1,407; 17.4%), with exposure status subsequently modelled as time-varying during follow-up. Clopidogrel monotherapy was the most common baseline exposure state, consistent with guideline-recommended antiplatelet therapy for secondary stroke prevention.

Table 5.1 presents baseline characteristics stratified by exposure group. The overall cohort had a median age of 76.0 years (IQR 67.6–83.3) and was 51.5% female. Substantial differences in age distribution were observed across groups: patients receiving PPI monotherapy were oldest (median 80.2 years, IQR 72.3–85.2), while those receiving clopidogrel monotherapy were youngest (median 72.5 years, IQR 65.0–80.7). Patients in the concurrent exposure group had intermediate age (median 75.4 years, IQR 67.4–82.7). Groups receiving PPIs (PPI only and Both) had higher proportions of female patients (57.6% and 56.6%, respectively) compared with clopidogrel monotherapy (47.3%).

Comorbidity burden differed substantially across exposure groups, reflecting expected channelling consistent with clinical prescribing patterns. Cardiovascular disease was more prevalent among PPI-containing groups (82.1% for PPI only, 67.9% for Both) compared with clopidogrel monotherapy (52.3%). Similarly, gastrointestinal conditions, renal disease, and respiratory disease were more common in groups receiving PPIs. Mental health conditions were most prevalent in the concurrent exposure group (30.3%) and PPI monotherapy group (27.6%). These baseline imbalances motivated the use of IPTW to reduce confounding by indication.

The use of concomitant medications also differed among exposure groups. The co-prescription of aspirin was more prevalent in groups receiving proton pump inhibitors (22.0% for PPI only, 20.3% for both) compared to those on clopidogrel monotherapy (7.5%), indicating more aggressive antithrombotic strategies in patients assessed as having elevated cardiovascular risk. Statin use was prevalent across the cohort, with higher utilisation observed in PPI-containing groups; simvastatin use was 9.5%, 24.5%, 8.8%, and 15.8% and atorvastatin use was 8.2%, 17.5%, 9.9%, and 21.3% across the neither, PPI only, clopidogrel only, and concurrent groups respectively. The utilisation of direct oral anticoagulants was infrequent among all groups (<3%), aligning with the antiplatelet-centric treatment strategy in this cerebrovascular cohort. The duration of index hospitalisation was shortest in the concurrent exposure group (median 5.0 days, IQR 2.0–11.0) and longest in the neither group (median 16.0 days, IQR 4.0–52.0).

Table 5.1 Baseline characteristics of the study cohort by clopidogrel and PPI exposure

Data presented as n (%) for categorical variables and median (interquartile range) for continuous variables. Exposure groups: neither clopidogrel nor PPI (n=2,528; 31.2%), PPI only (n=929; 11.5%), clopidogrel only (n=3,245; 40.0%), and concurrent clopidogrel-PPI use (n=1,407; 17.4%). The table is summarising the demographic characteristics, comorbid conditions, and baseline medication use. Exposure groups were mutually exclusive at baseline but time-varying during follow-up, allowing patients to transition between states. SIMD, Scottish Index of Multiple Deprivation 2016 (decile 1 = most deprived).

label	levels	None	PPI only	Clopidogrel only	Both	Total
Total N (%)		2528 (31.2)	929 (11.5)	3245 (40.0)	1407 (17.4)	8109
Age	Median (IQR)	78.8 (70.8 to 85.3)	80.2 (72.3 to 85.2)	72.5 (65.0 to 80.7)	75.4 (67.4 to 82.7)	76.0 (67.6 to 83.3)
SEX	F	1312 (51.9)	535 (57.6)	1535 (47.3)	797 (56.6)	4179 (51.5)
	M	1216 (48.1)	394 (42.4)	1710 (52.7)	610 (43.4)	3930 (48.5)
SIMD_2016_DECILI	1	513 (20.3)	198 (21.3)	747 (23.0)	322 (22.9)	1780 (22.0)
	2	435 (17.2)	146 (15.7)	483 (14.9)	211 (15.0)	1275 (15.7)
	3	241 (9.5)	95 (10.2)	334 (10.3)	168 (11.9)	838 (10.3)
	4+	1339 (53.0)	490 (52.7)	1681 (51.8)	706 (50.2)	4216 (52.0)
Pravastatin	0	2511 (>99)	920 (99.0)	3231 (>99)	1398 (>99)	8060 (>99)
	1	17 (0.7)	9 (1.0)	14 (0.4)	9 (0.6)	49 (0.6)
Simvastatin	0	2288 (90.5)	701 (75.5)	2959 (91.2)	1184 (84.2)	7132 (88.0)
	1	240 (9.5)	228 (24.5)	286 (8.8)	223 (15.8)	977 (12.0)
Atorvastatin	0	2320 (91.8)	766 (82.5)	2925 (90.1)	1107 (78.7)	7118 (87.8)
	1	208 (8.2)	163 (17.5)	320 (9.9)	300 (21.3)	991 (12.2)
Edoxaban	0	2510 (>99)	907 (97.6)	3235 (>99)*	1400 (>99)*	8066 (>99)
	1	18 (0.7)	22 (2.4)	<5 (<1)	<5 (<1)	43 (0,5)
Apixaban	0	2452 (97.0)	859 (92.5)	3235 (>99)*	1402 (>99)	7955 (98.1)
	1	76 (3.0)	70 (7.5)	<5 (<1)	5 (0.4)	154 (1.9)
Aspirin	0	2323 (91.9)	725 (78.0)	3003 (92.5)	1122 (79.7)	7173 (88.5)
	1	205 (8.1)	204 (22.0)	242 (7.5)	285 (20.3)	936 (11.5)
Rivaroxaban	0	2508 (>99)	919 (98.9)	3235 (>99)*	1400 (>99)*	8077 (>99)
	1	20 (0.8)	10 (1.1)	<5 (<1)	<5 (<1)	32 (0.4)
Ticagrelor	0	2520 (>99)*	924 (>99)	3235 (>99)*	1400 (>99)*	8096 (>99)
	1	<5 (<1)	5 (0.5)	<5 (<1)	<5 (<1)	13 (0.2)
Dabigatran	0	2520 (>99)*	920 (>99)*	3235 (>99)*	1400 (>99)*	8102 (>99)
	1	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	7 (0.1)
CV	0	826 (32.7)	166 (17.9)	1549 (47.7)	451 (32.1)	2992 (36.9)
	1	1702 (67.3)	763 (82.1)	1696 (52.3)	956 (67.9)	5117 (63.1)
MSK	0	1782 (70.5)	515 (55.4)	2494 (76.9)	868 (61.7)	5659 (69.8)
	1	746 (29.5)	414 (44.6)	751 (23.1)	539 (38.3)	2450 (30.2)
Neurology	0	1803 (71.3)	474 (51.0)	2354 (72.5)	704 (50.0)	5335 (65.8)
	1	725 (28.7)	455 (49.0)	891 (27.5)	703 (50.0)	2774 (34.2)
KUB	0	1467 (58.0)	390 (42.0)	2322 (71.6)	792 (56.3)	4971 (61.3)
	1	1061 (42.0)	539 (58.0)	923 (28.4)	615 (43.7)	3138 (38.7)
Respiratory	0	2149 (85.0)	695 (74.8)	2798 (86.2)	1042 (74.1)	6684 (82.4)
	1	379 (15.0)	234 (25.2)	447 (13.8)	365 (25.9)	1425 (17.6)
MentalHealth	0	2127 (84.1)	673 (72.4)	2710 (83.5)	980 (69.7)	6490 (80.0)
	1	401 (15.9)	256 (27.6)	535 (16.5)	427 (30.3)	1619 (20.0)
Diabetes	0	2292 (90.7)	794 (85.5)	2919 (90.0)	1213 (86.2)	7218 (89.0)
	1	236 (9.3)	135 (14.5)	326 (10.0)	194 (13.8)	891 (11.0)
Endocrine	0	2337 (92.4)	826 (88.9)	3023 (93.2)	1262 (89.7)	7448 (91.8)
	1	191 (7.6)	103 (11.1)	222 (6.8)	145 (10.3)	661 (8.2)
Cancer	0	2282 (90.3)	808 (87.0)	3075 (94.8)	1283 (91.2)	7448 (91.8)
	1	246 (9.7)	121 (13.0)	170 (5.2)	124 (8.8)	661 (8.2)
Liver_GB_Panc	0	2467 (97.6)	878 (94.5)	3174 (97.8)	1360 (96.7)	7879 (97.2)
	1	61 (2.4)	51 (5.5)	71 (2.2)	47 (3.3)	230 (2.8)
GI	0	2493 (98.6)	901 (97.0)	3205 (98.8)	1368 (97.2)	7967 (98.2)
	1	35 (1.4)	28 (3.0)	40 (1.2)	39 (2.8)	142 (1.8)
Infection	0	2520 (>99)*	924 (>99)	3235 (>99)*	1400 (>99)*	8096 (>99)
	1	<5 (<1)	5 (0.5)	<5 (<1)	<5 (<1)	13 (0.2)
adm_duration	Median (IQR)	16.0 (4.0 to 52.0)	9.0 (3.0 to 29.0)	6.0 (2.0 to 21.0)	5.0 (2.0 to 11.0)	8.0 (3.0 to 28.0)

*Counts have been rounded to comply with Safe Haven Statistical Discluser Thershold. Dominant binary counted rounded down by ?5 to nearest 5 to prevent back-calculation of suppressed values. SIMD deciles 4-10 merged into 4+ to avoid suppression of individual small counts. Supressed counts (<5) have both count AND percentage supressed '<5(<1)'.

5.3.2 Propensity score estimation and covariate balance

Propensity scores for membership in each exposure state were estimated using multinomial logistic regression incorporating all baseline covariates. Figure 5.2 displays the Love plot illustrating absolute SMD before and after inverse probability of treatment weighting. Prior to weighting, substantial imbalances were observed across multiple covariates, with several SMD exceeding 0.20, reflecting the channelling bias identified in baseline characteristics. Following application of stabilised inverse probability weights with truncation at the 1st and 99th percentiles, all SMD were reduced to below 0.10, indicating adequate covariate balance in the weighted pseudo-population. This balance confirms that the IPTW approach successfully addressed measured confounding by indication.

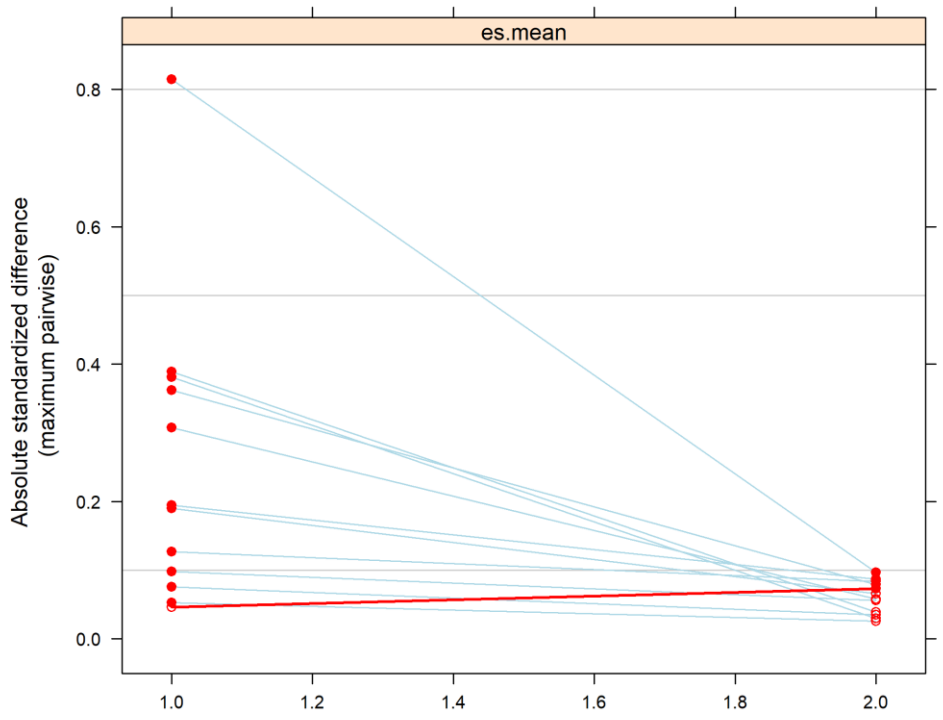


Figure 5.2 Standardised mean differences before and after IPTW – clopidogrel cohort

The plot displays the maximum pairwise absolute standardised mean differences (SMDs) across exposure groups for all covariates included in the propensity score model. Each line connects the pre-weighting (left) and post-weighting (right) SMD for a single covariate, with the horizontal reference line denoting the 0.10 balance threshold. Prior to weighting, several covariates exhibited substantial imbalance, with the largest exceeding 0.80. Following IPTW, all covariates achieved an SMD at or below 0.10, demonstrating substantial improvement in covariate balance and supporting the assumption of exchangeability across exposure groups.

5.3.3 Bleeding-related hospitalisations

During the two-year follow-up period, bleeding-related hospitalisations accrued across all four exposure states, with overall event rates remaining low throughout follow-up. Numbers at risk declined gradually and comparably across groups, consistent with the low absolute incidence of bleeding in this cohort. The Simon-Makuch survival curves (Figure 5.3) showed bleeding-free survival probabilities exceeding 0.95 in every exposure group across the full follow-up period. Visual inspection revealed no marked separation between the four curves, with bleeding-free survival tracking closely in parallel over time - a pattern consistent with the absence of a clinically meaningful difference in bleeding risk by exposure state.

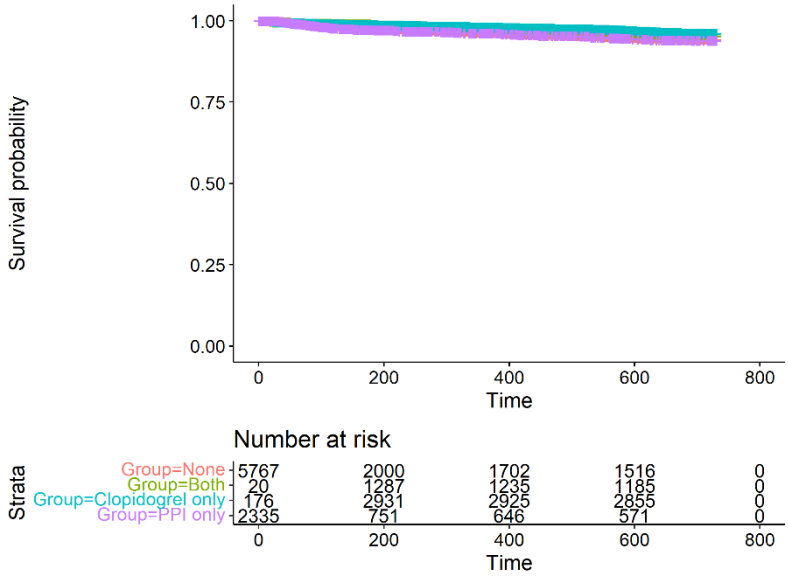


Figure 5.3 Time-varying bleeding-free survival by exposure state (clopidogrel cohort)

Simon-Makuch curves illustrating bleeding-free survival by time-varying exposure status over a 2-year follow-up (n=8,109). Unlike standard Kaplan-Meier curves, Simon-Makuch curves accommodate dynamic changes in exposure classification during follow-up, thereby avoiding immortal time bias that would arise from fixed baseline exposure assignment. Exposure categories: Neither clopidogrel nor PPI (red), PPI only (purple), Clopidogrel only (turquoise), and concurrent PPI-clopidogrel therapy (Both, green). All curves remain above 0.95 during follow-up, indicating low overall bleeding rates with no marked separation between groups.

5.3.4 Time-dependent Cox proportional hazards analysis

Table 5.2 presents hazard ratios for bleeding-related hospitalisation from the IPTW-weighted, time-dependent Cox proportional hazards model, using the neither medication group as the reference category. None of the exposure states demonstrated statistically significant associations with bleeding risk. Concurrent PPI-clopidogrel exposure was associated with a hazard ratio of 0.83 (95% CI 0.53–1.30, p=0.415), indicating no significant difference in bleeding risk compared with neither medication. Similarly, clopidogrel monotherapy (HR 0.73, 95% CI 0.50–1.05, p=0.089) and PPI monotherapy (HR 1.06, 95% CI 0.75–1.50, p=0.736) showed no statistically significant associations with altered bleeding risk.

The clinically relevant comparison - concurrent PPI-clopidogrel therapy versus clopidogrel monotherapy - was derived from the model coefficients. The hazard ratio for concurrent therapy relative to clopidogrel monotherapy, derived from the linear combination of model coefficients, was 1.14. As noted in Chapter 2 (Section 2.4.2), a valid 95% confidence interval for this derived contrast cannot be obtained from the separately reported estimates and could not be estimated within the resources available for this analysis. This derived contrast is therefore reported as a descriptive point estimate only, without formal statistical inference. The point estimate is numerically consistent with the marginal estimates for each exposure group versus the unexposed reference (HR 0.83 and HR 0.73 respectively, both with confidence intervals spanning unity), and with the Simon-Makuch survival curves, neither of which indicates a clinically meaningful increase in bleeding risk associated with PPI co-prescription.

Figure 5.4 presents the forest plot illustrating these exposure group comparisons. All confidence intervals crossed the null value of 1.0, consistent with no significant differences in bleeding risk across exposure states. The point estimates for clopidogrel-containing groups (clopidogrel only and Both) were below 1.0, while PPI monotherapy showed a point estimate marginally above 1.0, though none reached statistical significance.

Table 5.2 Hazard ratios for bleeding-related hospitalisation by exposure group from IPTW-weighted time-dependent Cox proportional hazards model

Exposure Group	HR	95% CI	P-value
Neither (reference)	1.00	—	—
PPI only	1.06	0.75–1.50	0.736
Clopidogrel only	0.73	0.50–1.05	0.089
Both (PPI + Clopidogrel)	0.83	0.53–1.30	0.415

HR, hazard ratio; CI, confidence interval; PPI, proton pump inhibitor. Reference category: Neither medication. Model adjusted for all baseline covariates using inverse probability of treatment weighting. Stabilised inverse probability weights were truncated at the 1st and 99th percentiles. Robust sandwich variance estimators were used to account for weighting and within-individual correlation. Reference category: Neither clopidogrel nor PPI. Model adjusted for age, sex, SIMD 2016 decile, comorbidities (cardiovascular, gastrointestinal, renal, respiratory, hepatobiliary, diabetes, mental health), concomitant medications (aspirin, other antiplatelets, anticoagulants, statins, NSAIDs, corticosteroids), specialist consultations, and index hospitalisation duration. HR, hazard ratio; CI, confidence interval; PPI, proton pump inhibitor.

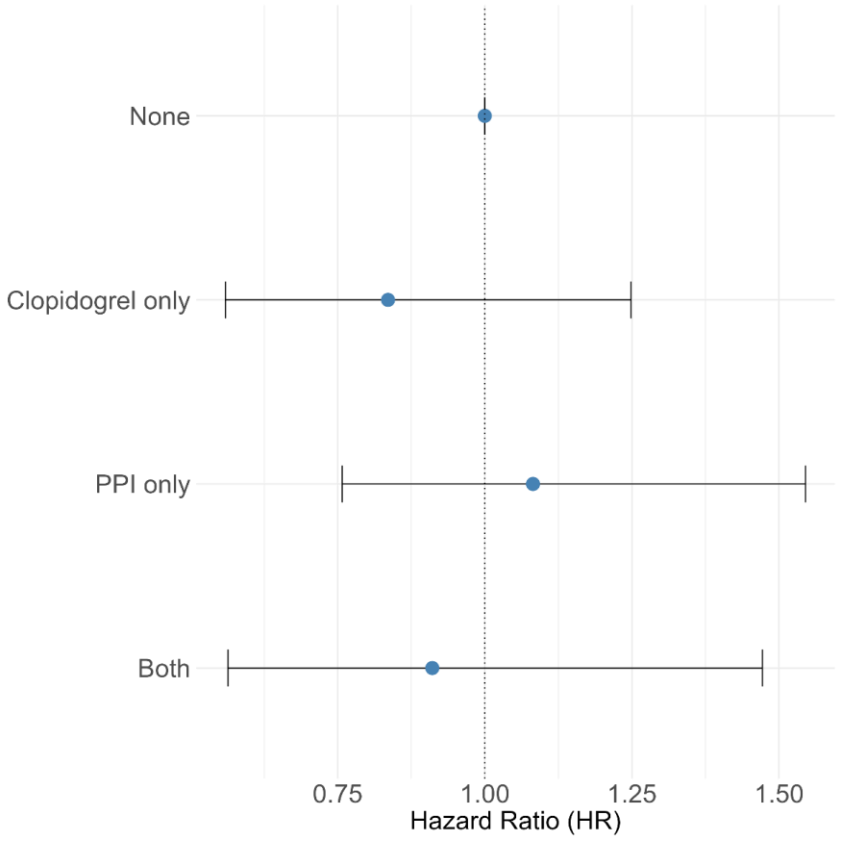


Figure 5.4 Clopidogrel cohort – forest plot of adjusted hazard ratios for bleeding outcomes

Forest plot of adjusted hazard ratios and 95% confidence intervals for bleeding outcomes by exposure group using IPTW-weighted, time-dependent Cox model. Reference group (Neither) is shown as a vertical line at HR=1.0. All confidence intervals cross the null, indicating no significant differences in bleeding risk.

5.3.5 Other predictors of bleeding risk

Table 5.3 displays hazard ratios for bleeding-related hospitalisation for all factors incorporated in the Cox proportional hazards model. Prior kidney disease (KUB; HR 1.45, 95% CI 1.09–1.95, p=0.012) and hepatobiliary/pancreatic diseases (HR 1.85, 95% CI 1.10–3.09, p=0.020) were significantly associated with bleeding-related hospitalisation. Age exhibited a marginally positive association with bleeding (HR 1.01 per year, 95% CI 1.00–1.03, p=0.076). Neither sex nor the majority of comorbidities had statistically significant associations with bleeding outcomes. In this model, estimates for fluvastatin and prasugrel were extreme and unstable, reflecting near-zero prevalence across exposure groups, and should not be interpreted as clinically meaningful associations, although confidence intervals were broad for certain medications with low prevalence.

Table 5.3 Clopidogrel cohort – multivariable Cox regression results for all covariates

Results of time-dependent Cox proportional hazards model showing hazard ratios for all covariates included in bleeding outcome analyses. Reference categories: Neither clopidogrel nor PPI (for exposure), male sex, SIMD decile 3 (for deprivation), absence of condition (for comorbidities and medications). HR, hazard ratio; CI, confidence interval. Significant associations (p<0.05) observed for renal disease (KUB) and hepatobiliary/pancreatic conditions.

Group	exp(coef)	lower .95	upper .95	P
Apixaban1	0.881	0.517	1.502	0.642
Dabigatran1	1.169	0.487	2.805	0.727
Edoxaban1	1.432	0.803	2.556	0.224
Rivaroxaban1	1.883	0.610	5.810	0.271
Aspirin1	1.115	0.805	1.544	0.512
Ticagrelor1	1.828	0.416	8.025	0.424
Atorvastatin1	0.879	0.628	1.229	0.451
Pravastatin1	1.237	0.317	4.827	0.759
Simvastatin1	0.949	0.671	1.344	0.768
Age	1.014	0.998	1.031	0.076
SEXM	1.141	0.846	1.539	0.387
SIMD_2016_DECILE1	1.234	0.757	2.013	0.399
SIMD_2016_DECILE2	0.755	0.451	1.264	0.285
SIMD_2016_DECILE4	0.712	0.360	1.409	0.330
SIMD_2016_DECILE5	0.914	0.516	1.619	0.758
SIMD_2016_DECILE6	0.610	0.294	1.267	0.185
SIMD_2016_DECILE7	0.494	0.250	0.976	0.042
SIMD_2016_DECILE8	0.498	0.248	0.999	0.050
SIMD_2016_DECILE9	0.687	0.388	1.215	0.197
SIMD_2016_DECILE10	0.582	0.313	1.080	0.086
Fluvastatin1	0.000	0.000	0.000	0.000
Prasugrel1	0.000	0.000	0.000	0.000
Dipyridamole1	20.567	6.635	63.751	0.000
MSK1	0.936	0.681	1.288	0.686
Neurology1	1.034	0.739	1.445	0.847
KUB1	1.454	1.086	1.946	0.012
Respiratory1	1.251	0.912	1.717	0.164
MentalHealth1	0.828	0.579	1.184	0.301
Diabetes1	0.903	0.566	1.442	0.670
Endocrine1	0.845	0.519	1.376	0.498
Cancer1	1.153	0.678	1.959	0.599
Liver_GB_Panc1	1.847	1.103	3.094	0.020
GI1	0.690	0.273	1.744	0.432
Infection1	1.320	0.168	10.393	0.792
adm_duration	1.000	0.998	1.002	0.813
GroupBoth	0.829	0.527	1.302	0.415
GroupClopidogrel only	0.726	0.502	1.050	0.089
GroupPPI only	1.062	0.749	1.504	0.736

5.3.6 Model diagnostics

The proportional hazards assumption was evaluated using Schoenfeld residuals and graphical diagnostics. No material violations were identified for the primary exposure variables or key covariates, supporting the validity of the time-dependent Cox regression approach. The distribution of stabilised inverse probability weights was examined following truncation at the 1st and 99th percentiles, and no evidence of extreme weight instability or meaningful positivity violations was identified. These diagnostics, combined with the covariate balance achieved (Section 5.3.2), support the validity of the IPTW approach in this cohort.

5.3.7 Summary of key findings

Among 8,109 patients following TIA or ischaemic stroke, bleeding-related hospitalisations were uncommon across all exposure groups during a maximum two-year follow-up. All hazard ratios reported here are estimated relative to the neither-medication reference group. Concurrent PPI–clopidogrel exposure (HR 0.83, 95% CI 0.53–1.30, p = 0.415), clopidogrel monotherapy (HR 0.73, 95% CI 0.50–1.05, p = 0.089), and PPI monotherapy (HR 1.06, 95% CI 0.75–1.50, p = 0.736) were each non-significant. It should be noted that the clinically relevant contrast between concurrent exposure and clopidogrel monotherapy is not directly given by these estimates; its approximate point estimate is 1.14, but a valid confidence interval requires the model's variance–covariance matrix and was not estimated here. Interpretation is therefore confined to comparisons against the unexposed reference group.

Prior renal disease (HR 1.45, 95% CI 1.09–1.95, p=0.012) and hepatobiliary/pancreatic conditions (HR 1.85, 95% CI 1.10–3.09, p=0.020) were the only covariates significantly associated with increased bleeding risk. These findings were consistent across the IPTW-weighted Cox model and the non-parametric Simon–Makuch survival curves (Figure 5.3), which showed no marked separation between exposure groups over time.

5.4 Discussion

5.4.1 Principal findings

This chapter examined whether concurrent prescribing of proton pump inhibitors and clopidogrel is associated with an increased risk of bleeding-related hospitalisation in a real-world cohort of adults following transient ischaemic attack or ischaemic stroke in NHS Greater Glasgow and Clyde. The principal finding was that concurrent exposure to clopidogrel and a PPI was not associated with a statistically significant elevation in bleeding-related hospitalisation compared with the unexposed reference group. The derived point estimate for concurrent therapy versus clopidogrel monotherapy is reported descriptively only, because a valid confidence interval could not be estimated within the resources available for this analysis.

For the clinically relevant comparison of concurrent PPI-clopidogrel therapy versus clopidogrel monotherapy, the derived point estimate (HR 1.14) is reported as a descriptive point estimate only, without formal statistical inference.

In the IPTW-weighted, time-dependent Cox proportional hazards model, hazard ratios for all exposure groups approximated unity when compared with the reference category of neither drug. PPI alone and clopidogrel alone showed no significantly elevated hazard relative to the unexposed group, suggesting that neither drug in isolation was associated with materially increased bleeding in this population.

The time-varying Simon–Makuch survival curves aligned with the regression results, indicating minimal distinction between exposure states during the approximately two-year follow-up period [180]. The four exposure groups consistently overlapped, with cumulative bleeding incidence gradually and uniformly increasing between groups. The visual alignment between the non-parametric survival estimates and the model-based hazard ratios enhances confidence in the robustness of the null finding.

The combination of neutral point estimates with overlapping confidence intervals supports a clinically reassuring interpretation: in this elderly, multimorbid cerebrovascular population, there is no evidence that concurrent PPI-clopidogrel

exposure, relative to neither medication, increases the overall risk of bleeding requiring hospitalisation. This finding aligns with prior clinical trial evidence suggesting that pharmacodynamic attenuation of clopidogrel by PPIs does not translate into clinically significant harm when appropriate confounding adjustment is applied [237, 239]. The low absolute event rate, while limiting precision for detecting small effects, provides adequate statistical power to exclude large, clinically meaningful increases in bleeding risk associated with PPI co-prescribing in this context.

Importantly, the internal coherence across all analytical displays - baseline characteristics demonstrating the need for adjustment, weighting diagnostics confirming adequate covariate balance, survival curves showing no separation, and adjusted estimates approximating the null - constitutes a methodologically robust foundation for interpreting these findings as a genuine absence of association with bleeding-related hospitalisation rather than a product of analytical approach.

5.4.2 Context within existing literature

The findings of this chapter must be interpreted within the broader landscape of evidence concerning the PPI–clopidogrel interaction, which has grown considerably since initial concerns emerged in 2009. Early observational studies and mechanistic investigations raised substantial alarm about the potential for PPIs to attenuate clopidogrel's antiplatelet efficacy through competitive inhibition of cytochrome P450 2C19 (CYP2C19), prompting regulatory warnings and clinical uncertainty that persists in some settings today.

Ho et al. (2009) [241] published one of the first large-scale observational analyses examining this interaction, reporting that concomitant use of clopidogrel and PPIs following acute coronary syndrome was associated with a higher risk of adverse outcomes, including rehospitalisation for acute coronary syndrome, compared with clopidogrel use without PPIs. This study, conducted in a Veterans Affairs population, generated considerable concern and contributed to the United States FDA issuing warnings against co-prescribing omeprazole with clopidogrel. Similarly, Kreutz et al. (2010) [240] demonstrated in a large retrospective cohort that PPI use with clopidogrel after coronary stent placement was associated with

increased risk of major adverse cardiovascular events over twelve months, with signals observed across multiple individual PPIs including omeprazole, esomeprazole, pantoprazole, and lansoprazole.

However, several important features of this early evidence base warrant consideration. First, the predominant signals in these observational studies were ischaemic rather than haemorrhagic-that is, the concern was that PPIs might reduce clopidogrel's protective effect against thrombotic events, not that they might increase bleeding [240, 241]. Second, these studies were vulnerable to confounding by indication, as clinicians frequently prescribe PPIs to patients perceived to be at higher baseline risk of gastrointestinal complications, who may also have greater overall morbidity and poorer prognosis [242]. Third, the populations studied were predominantly post-percutaneous coronary intervention cohorts, with limited representation of cerebrovascular disease.

Subsequent evidence from randomised controlled trials and more carefully adjusted observational analysis has significantly relieved initial concerns. The Clopidogrel and Optimisation of Gastrointestinal Events Trial (COGENT) randomised 3,627 patients (of a planned 5,000) on dual antiplatelet therapy to receive either omeprazole or placebo, finding no significant increase in cardiovascular events with omeprazole co-prescription. However, the trial was prematurely terminated due to loss of funding following sponsor bankruptcy after a median follow-up of only 133 days, leaving it underpowered for cardiovascular endpoints [117, 240]. O'Donoghue et al. (2009) [237] in a post-hoc analysis of the TRITON-TIMI 38 trial, indicated that the use of PPIs was not independently linked to an elevated risk of adverse clinical outcomes in patients administered either clopidogrel or prasugrel, a finding that remained consistent even among patients with reduced-function CYP2C19 alleles. The authors concluded that the pharmacodynamic interaction observed in platelet function studies did not translate into clinically significant harm after appropriate adjustment for confounding variables.

More recent evidence has supported this reassuring picture. Kim et al. (2024) [239] conducted a large propensity score-matched analysis in East Asian patients receiving clopidogrel-based dual antiplatelet therapy after drug-eluting stent

(DES) implantation and found that although PPI users demonstrated higher on-treatment platelet reactivity, this did not translate into significantly increased ischaemic or bleeding events at twelve months. This study is particularly relevant given the higher prevalence of CYP2C19 loss-of-function alleles in East Asian populations, which might be expected to amplify any PPI-mediated interaction. The Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) similarly found that adjusted bleeding outcomes were comparable between PPI users and non-users, despite PPI users being older and having higher baseline risk profiles [243].

Chandrasekhar et al. (2017) [242], in their analysis of data from the PARIS Registry, emphasised that the observed correlation between PPI usage and negative outcomes may largely originate from confounding factors, as PPI users represent a higher-risk population with increased comorbidities and a greater likelihood for therapy interruption. Upon suitable adjustment of these parameters, the independent impact of PPIs on unfavourable outcomes was significantly diminished. The finding highlights the essential necessity of strong confounding control in observational investigations of drug-drug interactions.

Several systematic reviews and meta-analyses have attempted to synthesise this heterogeneous evidence base. While some have concluded that PPI co-administration is associated with modestly increased cardiovascular risk [115, 240, 241], others have emphasised that this association is likely confounded and that no definitive causal relationship has been established [90, 244]. The most defensible interpretation of the totality of evidence is that any pharmacokinetic interaction between PPIs and clopidogrel at CYP2C19 is of modest magnitude and inconsistent clinical consequence, particularly when balanced against the established gastroprotective benefits of PPIs in patients receiving antiplatelet therapy.

First, this study expands the existing evidence base in numerous significant ways. This study focuses on a cerebrovascular cohort-patients post-TIA or ischaemic stroke-rather than the coronary artery disease groups found in previous work. Secondary stroke prevention is a primary indication for clopidogrel; nevertheless, information regarding the co-prescribing of PPIs in this setting has been limited.

Second, this investigation explicitly examines bleeding outcomes, investigating if the attenuation of clopidogrel's antiplatelet efficacy by PPIs may decrease bleeding risk, or if such an effect is clinically insignificant. Third, employing time-varying exposure definitions and IPTW addresses important biases that minimises significant biases found in prior observational studies.

The neutral finding observed in this chapter is consistent with the convergent evidence from pharmacodynamic experiments, randomised trials, and appropriately adjusted observational cohorts: co-prescribing a PPI alongside clopidogrel does not materially alter overall bleeding risk once confounding is addressed and exposure is modelled appropriately. The apparent pharmacokinetic interaction through CYP2C19, while demonstrable in platelet function assays, appears to be counterbalanced by protection of the upper gastrointestinal tract, yielding neutrality in composite bleeding outcomes where non-gastrointestinal events contribute substantially [81]. While genotype-specific effects and PPI-specific potency may still influence ischaemic responses in selected subgroups, there is no signal of excess haemorrhage in appropriately adjusted analyses across multiple populations and clinical contexts.

5.4.3 Methodological considerations and causal interpretation

The analytical framework employed in this chapter - time-varying exposure modelling, IPTW, and Simon–Makuch survival curves - has been described in detail in Chapters 3 and 4, where identical methods were used to examine PPI interactions with digoxin and oral anticoagulants respectively. The conceptual distinction between causal estimands and statistical estimands, the rationale for time-updated exposure definitions, and the role of IPTW in addressing confounding by indication are therefore not repeated here. Instead, this section focuses on aspects of causal interpretation that are specific to the clopidogrel–PPI–bleeding analysis.

The causal estimand motivating this analysis is the contrast in bleeding risk that would be observed if patients following TIA or ischaemic stroke were, at a given point in time, concurrently exposed to clopidogrel and a PPI compared with clopidogrel alone, under otherwise similar clinical conditions. This estimand is intrinsically time-varying, illustrating the dynamic characteristics of PPI

prescribing in standard post-stroke care, where gastroprotection may be initiated, discontinued, or returned in reaction to changing gastrointestinal risk, alterations in medication, or clinical assessment [130]. Modelling PPI exposure as fixed at baseline would misclassify substantial person-time and introduce bias; the time-updated approach ensures alignment between exposure status and risk time.

Because this causal estimand cannot be identified directly from observational data without assumptions, the analysis targets a statistical estimand defined as the weighted cause-specific hazard ratio estimated using a time-dependent Cox proportional hazards model. Under the assumptions of consistency, positivity, correct model specification, and conditional exchangeability given measured covariates, this estimand provides an approximation to the underlying causal contrast in a pseudo-population created through IPTW [211].

In this cohort, substantial baseline differences between exposure groups were observed, with PPI users being older, more comorbid, and more likely to have gastrointestinal disease and higher healthcare utilisation. The balance diagnostics demonstrate that IPTW substantially reduced these measured imbalances, with post-weighting SMD below 0.10 for nearly all covariates. This improvement supports the plausibility of exchangeability with respect to measured confounders and strengthens the internal validity of the weighted estimates.

The Simon–Makuch survival curves provide a complementary, non-parametric representation of the same time-varying estimand and showed no meaningful separation between exposure groups over follow-up. The concordance between these graphical results and the regression-based hazard ratios - both indicating no material association between PPI co-prescribing and bleeding - suggests that the null finding is not an artefact of model specification or analytical approach.

Nevertheless, important limits on causal interpretation remain. As with all observational analyses, IPTW cannot account for unmeasured or imperfectly measured confounders, such as frailty, functional status, clinician prescribing preferences, or patient adherence, which may influence both PPI use and bleeding risk in older stroke populations. Accordingly, the findings are best interpreted as robustly adjusted real-world evidence compatible with no clinically meaningful

increase in bleeding risk associated with concurrent PPI and clopidogrel use, rather than as definitive proof of absence of effect [147]. This interpretation is consistent with best practice in observational pharmacoepidemiology and complements existing trial-based and observational evidence.

5.4.4 Biological plausibility and mechanisms of interaction

The pharmacology of clopidogrel, including its bioactivation via hepatic cytochrome P450 enzymes and irreversible inhibition of the platelet P2Y12 receptor, has been described in Section 5.1. This section focuses on the mechanistic interpretation of the null finding for bleeding risk and considers why the observed epidemiological result is biologically coherent.

The mechanistic concern underlying the PPI–clopidogrel interaction centres on competitive inhibition of CYP2C19. Since CYP2C19 contributes substantially to clopidogrel's bioactivation, and PPIs are established substrates and inhibitors of this enzyme, concurrent use might reduce generation of clopidogrel's active metabolite and thereby attenuate antiplatelet efficacy [90, 96]. Pharmacokinetic and pharmacodynamic studies have confirmed this interaction at the laboratory level, demonstrating reduced plasma concentrations of the active metabolite and diminished inhibition of platelet aggregation with concurrent PPI therapy [235, 236].

However, several factors explain why this pharmacodynamic signal does not translate into increased bleeding risk and indeed, why a null finding is the biologically expected result.

First, and critically for interpreting the present findings, any reduction in antiplatelet efficacy would theoretically be expected to reduce rather than increase bleeding risk. Clopidogrel's therapeutic effect derives from platelet inhibition; if PPIs attenuate this effect, the pharmacological consequence would be relatively preserved haemostatic function. Notably, the clinical and regulatory concerns that emerged following initial observational studies focused predominantly on ischaemic outcomes - recurrent myocardial infarction, stent thrombosis, and major adverse cardiovascular events - rather than on haemorrhagic complications [237, 240, 241]. This reflects the mechanistic

expectation that reduced antiplatelet activity would increase thrombotic risk while potentially attenuating bleeding propensity. The neutral bleeding risk observed in the present study is therefore mechanistically coherent with the hypothesised interaction pathway.

Second, PPIs exert direct gastroprotective effects independent of any clopidogrel interaction. By suppressing gastric acid secretion, PPIs reduce peptic ulceration and upper gastrointestinal bleeding - the predominant bleeding site in patients receiving antiplatelet therapy [81]. This protective effect may offset any theoretical bleeding reduction from attenuated antiplatelet activity, yielding net neutrality. When upper gastrointestinal bleeding is combined with bleeding from other anatomical sites (intracranial, genitourinary) that PPIs do not influence, the composite outcome reflects this balance.

Third, there is significant variation in the degree of CYP2C19 inhibition between PPIs. Omeprazole and esomeprazole are more effective inhibitors compared to pantoprazole, lansoprazole, or rabeprazole [90, 238]. In practical application, when numerous PPIs are administered, the overall interaction impact within the class may be minimal. This study modelled PPIs as a category, aligning with clinical prescribing practices in NHS Scotland, and the neutral outcome likely indicates this variability.

Fourth, substantial interindividual variability exists in clopidogrel metabolism due to genetic polymorphisms in CYP2C19. Patients carrying loss-of-function genetic variants already have reduced capacity to generate the active clopidogrel metabolite; in these individuals, additional enzyme inhibition by PPIs may have proportionally less impact. Conversely, patients with normal or enhanced metabolic capacity may maintain adequate platelet inhibition despite concurrent PPI use. This genetic heterogeneity means that the population-level effect of PPIs on clopidogrel response is attenuated compared with predictions from pharmacokinetic models that assume uniform metabolism [92].

Finally, the relationship between on-treatment platelet reactivity and clinical outcomes is not linear. Risk appears to increase meaningfully only above certain thresholds of high platelet reactivity [239]. If PPI-mediated increases in platelet

reactivity remain below these thresholds for most patients, clinical consequences would not be expected.

The present study lacked serum drug concentrations, platelet function testing, and CYP2C19 genotype data, precluding direct confirmation of these mechanisms. Nevertheless, the null finding is biologically plausible and consistent with the pharmacological evidence. It should be noted that biological plausibility for neutral bleeding does not exclude the possibility of effects on ischaemic outcomes, which were not examined here and remain relevant to clinical decision-making.

5.4.5 Alternative explanations and problem of confounding by indication

While the null association between PPI co-prescribing and bleeding risk is consistent with both mechanistic expectations and prior clinical evidence, alternative explanations must be considered before concluding that the finding reflects a true absence of effect. Observational studies of drug-drug interactions are particularly vulnerable to confounding by indication and related biases that can mask or misrepresent causal relationships.

Confounding by indication occurs when the clinical circumstances that lead to the prescription of a medicine are correlated with the outcome of interest. In the context of PPI prescribing, this bias functions in a particular and possibly unexpected manner. Clinicians typically prescribe PPIs to patients perceived to be at elevated risk of gastrointestinal complications - those with prior peptic ulcer disease, gastrointestinal bleeding history, concurrent NSAID use, or advanced age [81]. These same patients may have higher baseline bleeding risk from multiple sources. If unadjusted, this channelling of PPIs toward higher-risk patients would create a false positive association between PPI use and bleeding, even if PPIs themselves confer protection. The observation of neutral rather than elevated bleeding risk in PPI users, despite their higher baseline risk profile, may therefore reflect true gastroprotective benefit offsetting underlying vulnerability.

Chandrasekhar et al. (2017) [242], analysing data from the PARIS Registry, demonstrated that PPI users represented a systematically higher-risk population

with more comorbidities and greater healthcare utilisation. When these baseline, differences were appropriately adjusted, much of the apparent association between PPI use and adverse outcomes was attenuated. Similarly, in the present study, PPI users were older, had more gastrointestinal comorbidity, and exhibited different patterns of medication use compared with non-users. The application of IPTW substantially reduced these measured imbalances, but residual confounding by unmeasured factors remains possible.

Protopathic bias represents a related concern, occurring when a medication is initiated in response to early symptoms of the outcome under study, creating a false impression of causation [187]. In the bleeding context, a patient experiencing prodromal gastrointestinal discomfort might be prescribed a PPI shortly before a bleeding event is diagnosed, artificially inflating the apparent association between recent PPI initiation and bleeding. The use of time-varying exposure definitions in the present analysis mitigates but does not entirely eliminate this bias, as the temporal granularity of prescription data may not capture very short-term symptom-driven prescribing.

Surveillance or detection bias may also influence observed associations. Patients administered both clopidogrel and PPIs may require enhanced clinical monitoring due to concerns over polypharmacy or the intricacy of their drug regimens. Improved monitoring may facilitate the early identification of bleeding incidents that could otherwise remain undetected, thereby increasing event rates in the dual-therapy cohort. Conversely, if PPI users exhibit greater engagement with healthcare facilities, minor bleeding episodes may be handled conservatively without hospitalisation, hence decreasing recorded incidents.

Finally, healthy users effects and selection bias warrant consideration. Patients who survive long enough to receive both medications and have adequate health to continue both therapies might represent a selected, healthier subgroup. This survival bias might mask harm if the most susceptible individuals discontinue therapy or die prior to accumulating significant concurrent exposure time.

Despite these potential biases, several features of the present analysis provide reassurance. The consistency of null findings across multiple analytical

approaches-unadjusted, IPTW-weighted, and time-varying argues against a single source of bias driving the results. The balance diagnostics confirm that measured confounders were adequately addressed through weighting. The direction of expected bias from confounding by indication (toward higher bleeding in PPI users) would work against the observed null finding, suggesting that if anything, the true protective or neutral effect of PPIs may be underestimated rather than overestimated.

5.4.6 Clinical implications and therapeutic considerations

The finding that concurrent PPI and clopidogrel use is not associated with increased bleeding risk in post-TIA and ischaemic stroke patients has direct relevance for clinical practice in secondary cerebrovascular prevention. These results, interpreted alongside the broader evidence base, support several practical conclusions for clinicians managing antiplatelet therapy in this population.

First, PPI co-prescription was not associated with increased bleeding-related hospitalisation in patients receiving clopidogrel. Clinical guidelines recommend consideration of PPI co-prescription for patients at elevated risk of gastrointestinal bleeding, including those of advanced age, with prior gastrointestinal events, or receiving concurrent therapies that increase bleeding risk such as aspirin, other antiplatelet agents, or anticoagulants [81, 91]. The present study confirms that in a representative real-world population of older adults following cerebrovascular events-precisely the demographic where gastroprotection is most frequently considered-PPI co-prescribing does not introduce a measurable bleeding hazard. These findings suggest that clinicians can prescribe PPIs for appropriate gastroprotective indications in clopidogrel-treated patients without strong concern about substantially increased bleeding risk, though the wide confidence intervals indicate that modest effects in either direction cannot be excluded from this study alone.

Second, while these findings address bleeding safety, they do not resolve ongoing uncertainty regarding potential effects on ischaemic outcomes. The mechanistic concern that PPIs might attenuate clopidogrel's antiplatelet efficacy through CYP2C19 inhibition remains theoretically valid, even if clinical translation has

proven inconsistent. The present study did not examine recurrent stroke, transient ischaemic attack, or other thrombotic endpoints. Clinicians should therefore continue to weigh the indication for gastroprotection against potential (though unproven) effects on antiplatelet efficacy, particularly in patients at very high thrombotic risk. Where gastroprotection is indicated, selection of PPIs with lower CYP2C19 inhibitory potential-such as pantoprazole or rabeprazole rather than omeprazole or esomeprazole-may represent a reasonable precautionary approach, although definitive evidence supporting this strategy from clinical outcome studies is lacking [90, 238].

Third, the findings support the principle of regular medication review and deprescribing where appropriate. Although PPI co-prescription with clopidogrel was not associated with increased bleeding-related hospitalisation in this study, PPIs are not without potential harms when used long-term, including associations with *Clostridioides difficile* infection, hypomagnesaemia, fracture risk, and possible renal effects [81, 90]. The decision to continue gastroprotection should be revisited periodically, particularly if the original indication has resolved or if the patient's bleeding risk profile has changed. In the post-stroke population, where polypharmacy is common and medication burden substantial, thoughtful deprescribing of PPIs no longer serving a clear purpose aligns with principles of patient-centred care.

Fourth, these findings have particular relevance for NHS Scotland and similar healthcare settings where clopidogrel remains the predominant P2Y12 inhibitor for secondary stroke prevention. Unlike in acute coronary syndrome management, where newer agents such as ticagrelor and prasugrel have gained prominence, clopidogrel remains first-line therapy for most cerebrovascular indications due to its favourable bleeding profile and established efficacy [91]. The absence of an association with bleeding-related hospitalisation in this context is consistent with current prescribing patterns, although the effect on ischaemic outcomes remains unexamined, while awaiting further evidence on optimal gastroprotection strategies.

Finally, the results highlight the value of real-world evidence in complementing trial-based findings. The COGENT trial, while providing important randomised

evidence on omeprazole and clopidogrel co-administration, was limited to cardiovascular populations and was terminated early after sponsor bankruptcy, enrolling 3,627 of the planned 5,000 patients with a median follow-up of only 133 days, leaving it underpowered for cardiovascular endpoints [117, 240]. Observational studies in broader populations, using rigorous methods to address confounding, extend the evidence base to patient groups underrepresented in trials-including older adults with cerebrovascular disease and multiple comorbidities. The convergence of findings across settings and methodologies strengthens the overall conclusion that PPI co-prescribing with clopidogrel is a safe practice from the perspective of bleeding risk.

5.4.7 Methodological strengths and limitations

The interpretation of findings from this study should be informed by consideration of both its methodological strengths and inherent limitations.

5.4.7.1 Strengths

This study has several notable strengths that enhance confidence in the findings. First, the analysis was conducted in a large, representative cohort of 8,109 patients following TIA or ischaemic stroke within NHS Greater Glasgow and Clyde, reflecting real-world prescribing patterns and patient characteristics encountered in routine clinical practice. Unlike trial populations, which often exclude older adults with multiple comorbidities, this cohort included the full spectrum of patients for whom clopidogrel and PPIs are commonly prescribed, enhancing external validity and generalisability to similar healthcare settings.

Second, the use of time-varying exposure definitions represents a significant methodological advantage over studies that classify exposure based solely on baseline status. PPI prescribing in post-stroke patients is dynamic, with frequent initiation, discontinuation, and re-initiation during follow-up. By updating exposure status throughout the observation period and allowing individuals to transition between exposure states, the analysis avoids immortal time bias and more accurately captures the relationship between concurrent medication use and outcomes [180].

Third, the application of IPTW effectively addressed the substantial baseline imbalances observed between exposure groups. Post-weighting SMD fell below 0.10 for nearly all covariates, indicating adequate balance and supporting the validity of causal inference from the weighted analysis. The consistency between IPTW-adjusted Cox model estimates and non-parametric Simon–Makuch survival curves provides additional reassurance that findings are robust to analytical approach.

Fourth, the study focused specifically on bleeding outcomes in a cerebrovascular population-an important gap in the existing literature, which has predominantly examined cardiovascular populations and ischaemic endpoints. This contribution addresses a clinically relevant question for stroke physicians and general practitioners managing secondary prevention.

Fifth, the study adhered to STROBE guidelines for reporting observational research, ensuring transparency in methods and results presentation [127].

5.4.7.2 Limitations

Several limitations must be acknowledged. A principal limitation of this study is that it examined only bleeding outcomes and did not analyse ischaemic events. The central clinical concern regarding PPI–clopidogrel co-prescription is not bleeding but the potential for CYP2C19 inhibition to attenuate clopidogrel bioactivation and thereby increase the risk of recurrent thrombotic events. By assessing bleeding alone, this study characterises only the bleeding-safety aspect of co-prescription and cannot, on its own, establish net clinical benefit or harm. The reassurance offered by the null bleeding finding must therefore be interpreted as conditional: it does not exclude an adverse association with ischaemic outcomes, which would require dedicated analysis of recurrent stroke and myocardial infarction. This represents the most significant single limitation of the chapter.

Second, bleeding events were identified through hospitalisation records using diagnostic codes, which captures only events of sufficient severity to require hospital admission. Minor bleeding episodes managed in primary care or self-limiting events would not be ascertained, as the study relied on hospital admission

records without linkage to general practitioner consultation or prescribing records for outcome identification. This potentially underestimates the total bleeding burden and limits the study to clinically severe episodes. Additionally, coding accuracy and completeness may vary, introducing potential misclassification.

Third, bleeding was examined as a composite outcome encompassing multiple anatomical sites. PPIs exert their gastroprotective effect specifically on upper gastrointestinal mucosa and would not be expected to influence bleeding from other sites such as intracranial, genitourinary, or soft tissue locations. The aggregation of bleeding events across sites may dilute any site-specific protective effect of PPIs, contributing to the observed neutral association. Statistical power was insufficient to examine site-specific bleeding separately.

Fourth, PPIs were modelled as a drug class rather than as individual agents. Given the established heterogeneity in CYP2C19 inhibitory potency across PPIs-with omeprazole and esomeprazole demonstrating stronger inhibition than pantoprazole or rabeprazole-class-level analysis may obscure agent-specific effects [238]. However, this approach reflects real-world prescribing patterns and maintains statistical power.

Fifth, related to the absence of genotype data, the thesis was unable to account for the ethnic composition of the cohort. Ethnicity was recorded as missing or not known for more than half of individuals (Chapter 2), which precluded both reliable description of the cohort's ethnic make-up and any stratified analysis. This is a material constraint in the specific context of clopidogrel, whose antiplatelet effect depends on CYP2C19-mediated bioactivation: the prevalence of reduced-function CYP2C19 alleles is substantially higher in East Asian populations, and for certain alleles in populations of African ancestry, than in those of European ancestry [140]. Because the theoretical basis for a clopidogrel–PPI interaction rests on competitive inhibition of CYP2C19, any population-level attenuation of clopidogrel efficacy would be expected to be more pronounced where loss-of-function alleles are more frequent. Had ethnicity been more completely recorded, it could have been used with due caution, and as no more than a coarse surrogate for genotype [245] to explore whether the null bleeding association, and the unexamined ischaemic risk, differed across ancestry groups. Its substantial

incompleteness here means the findings cannot be assumed to generalise to more genetically diverse populations, in which a greater proportion of patients begin from a position of reduced metabolic capacity. While ethnicity is at best a coarse surrogate for genotype and should not be equated with it [245], the incomplete recording of ethnicity means this study cannot speak to the interaction in those at greatest theoretical risk. Stratified analysis by ethnicity was precluded by the extent of missing ethnicity data, and this limitation should be addressed in more diverse cohorts or, preferably, through direct CYP2C19 genotyping.

Sixth, formal sensitivity analyses - such as variation of the 7-day carry-over period, restriction to incident clopidogrel users, alternative IPTW truncation thresholds, or calculation of E-values to quantify robustness to unmeasured confounding - were not conducted. These analyses would have provided additional reassurance regarding the stability of the primary findings under alternative assumptions. However, the consistency of the null association across the IPTW-weighted Cox model and the non-parametric Simon–Makuch survival curves provides indirect evidence of robustness, and the direction of expected bias from unmeasured confounding by indication (toward higher bleeding in PPI users) would work against the observed null finding.

Seventh, the confidence interval for the primary exposure comparison (HR 0.83, 95% CI 0.53–1.30) was wide, reflecting the relatively small number of bleeding events in this cohort. While the point estimate suggests no meaningful increase in bleeding risk, the upper confidence limit of 1.30 indicates that an increase of up to 30% cannot be excluded with 95% confidence. Conversely, the lower limit of 0.53 does not exclude a substantial protective effect. Future studies with larger sample sizes or longer follow-up would be required to estimate the association with greater precision and to detect smaller but potentially clinically important effects.

Eighth, a valid confidence interval for the derived Both vs clopidogrel contrast could not be estimated within the resources available for this analysis. This derived contrast is therefore reported as a descriptive point estimate only, without formal statistical inference. The conclusions drawn here rely on the

marginal inferential estimates for each exposure group and the convergent non-parametric survival analysis.

Ninth, despite achieving good balance on measured covariates through IPTW, residual confounding by unmeasured factors cannot be excluded. Variables such as frailty, functional status, alcohol consumption, *Helicobacter pylori* infection status, over-the-counter NSAID use, and clinician-specific prescribing preferences were not captured in the available data and may influence both PPI prescribing and bleeding risk.

Tenth, medication exposure was derived from prescription records, which may not perfectly reflect actual medication consumption. Patient adherence, over-the-counter PPI purchases, and inpatient medication administration may introduce exposure misclassification. The time-varying approach mitigates but does not eliminate this concern.

Eleventh, the approximately two-year follow-up period, while adequate to capture the majority of bleeding events in this population, may not detect very late effects or cumulative risks associated with prolonged concurrent exposure.

Finally, a further limitation concerns the coincidence of the study period with the COVID-19 pandemic, which is of particular relevance in this cerebrovascular cohort. SARS-CoV-2 infection is associated both with a prothrombotic state that may precipitate recurrent ischaemic events and with coagulopathic bleeding [246], and the pandemic substantially disrupted acute stroke and general hospital admission pathways during 2020 [207]. As bleeding outcomes were ascertained exclusively through hospital admission, and as infection status was not captured, the final study year is subject to both unmeasured confounding by infection and potential under-ascertainment of the outcome. The direction and magnitude of any resulting bias are uncertain; nonetheless, the overlap represents an uncontrolled influence on the data that qualifies the interpretation of results from 2020.

5.4.8 Conclusion

This real-world study of 8,109 patients following TIA or ischaemic stroke found no evidence that concurrent prescribing of proton pump inhibitors with clopidogrel is associated with increased risk of bleeding-related hospitalisation. The null association was consistent across time-varying survival analysis, IPTW-weighted Cox proportional hazards modelling, and Simon–Makuch curve visualisation, with hazard ratios approximating unity and confidence intervals comfortably spanning the null for all exposure comparisons.

These findings are biologically coherent with current understanding of the PPI-clopidogrel interaction. Any reduction of clopidogrel's antiplatelet effect through CYP2C19 inhibition would be expected to preserve rather than impair haemostatic function. Furthermore, the gastroprotective benefits of PPIs likely offset any theoretical bleeding reduction from diminished antiplatelet activity, yielding neutrality in composite bleeding outcomes. The results align with prior evidence from randomised trials and strictly adjusted observational studies demonstrating that the pharmacodynamic interaction observed in platelet function assays does not translate into clinically significant bleeding harm.

For clinicians managing secondary stroke prevention, these findings provide reassurance that PPI co-prescribing for appropriate gastroprotective indications does not introduce a measurable bleeding hazard in clopidogrel-treated patients. This is particularly relevant for older adults with cerebrovascular disease and multiple comorbidities - the population most frequently considered for gastroprotection and least well represented in prior trial evidence.

Several limitations must be borne in mind when interpreting these findings, including the restriction to hospitalised bleeding events, the composite bleeding endpoint that may mask site-specific effects, the class-level PPI analysis, all of which are discussed in detail in Section 5.4.7.2. Related to the absence of genotype data, incomplete information on the ethnic composition of the cohort constrains the generalisability of these findings. The prevalence of reduced-function CYP2C19 alleles varies across ancestry groups, with higher frequencies of relevant variants reported in some East Asian and African-ancestry populations than in populations of European ancestry.[140]. This is particularly relevant

because the theoretical basis for a clopidogrel-PPI interaction involves CYP2C19-mediated clopidogrel bioactivation and inhibition of this pathway by some PPIs. Ethnicity is, however, only a coarse population-level surrogate for genotype and should not be equated with individual genetic variation [245].The substantial incompleteness of ethnicity recording prevented reliable, stratified analysis in the present cohort. Future studies should therefore include more diverse populations and, preferably, direct CYP2C19 genotyping. The study did not examine ischaemic outcomes and therefore cannot address whether PPI co-prescription influences the risk of recurrent stroke or cardiovascular events - a question that remains clinically relevant and should guide personalised prescribing decisions.

Future research should examine both bleeding and ischaemic outcomes simultaneously to characterise net clinical benefit and evaluate individual PPI agents rather than the class as a whole. Linkage to primary care data would enable more complete ascertainment of medication exposure and minor bleeding events.

In conclusion, among patients following TIA or ischaemic stroke in NHS Scotland, concurrent use of PPIs and clopidogrel was not associated with increased bleeding-related hospitalisation. These findings suggest that gastroprotection does not increase bleeding-related hospitalisation in clopidogrel-treated cerebrovascular patients, although ischaemic outcomes were not examined, and contribute real-world evidence to guide clinical practice in this under-studied population.

Chapter 6 Overall Discussion

6.1 Introduction

The three empirical chapters of this thesis collectively address a clinically important question that has generated considerable uncertainty in cardiovascular medicine: do the pharmacokinetic interactions between proton pump inhibitors and cardiovascular medications, which are well-established at the mechanistic level, translate into meaningful clinical harm in real-world patient populations? This question has particular relevance in older multimorbid adults, where polypharmacy is the norm, gastroprotection is frequently indicated, and the competing risks of drug interactions must be balanced against the benefits of acid suppression [33, 194]. The findings from this thesis contribute substantially to this evidence base while also raising new questions about the gap between pharmacokinetic signals and clinical outcomes.

6.2 The Translation Problem: From Pharmacokinetics to Clinical Outcomes

A central theme emerging from this thesis is the inconsistent translation of pharmacokinetic interactions into clinical consequences. This phenomenon-whereby well-documented changes in drug exposure fail to produce proportionate effects on clinical outcomes-challenges simplistic assumptions about the relationship between drug concentrations and therapeutic effects [41, 72]. Understanding why this translation gap exists is essential for interpreting the findings and for developing a more sophisticated framework for evaluating drug-drug interactions.

The clopidogrel findings illustrate this phenomenon most clearly. Pharmacodynamic studies have consistently demonstrated that concurrent PPI use reduces formation of clopidogrel's active metabolite and diminishes ex vivo platelet inhibition [235, 236, 238], findings that generated substantial clinical concern and prompted regulatory warnings [241]. The US Food and Drug Administration issued a boxed warning in 2009 advising against concomitant use of clopidogrel and omeprazole [103], subsequently revised in 2010 to acknowledge uncertainty while maintaining caution. The European Medicines Agency issued

similar but less restrictive guidance [116]. These warnings had substantial clinical impact, leading to widespread avoidance of PPI co-prescription in patients receiving clopidogrel - a practice change driven primarily by pharmacokinetic and pharmacodynamic data rather than clinical outcome evidence [241, 244]. Yet this thesis found no association between PPI co-prescription and bleeding outcomes in post-stroke patients-a null finding that aligns with the COGENT trial [117] and several carefully adjusted observational studies [237, 244].

How can these apparently contradictory observations be reconciled? Several mechanisms explain this pharmacokinetic-clinical disconnect. First, the relationship between on-treatment platelet reactivity and clinical outcomes is not linear; risk appears to increase meaningfully only above certain thresholds of high platelet reactivity [92]. If PPI-mediated increases in platelet reactivity remain below these thresholds for most patients, clinical consequences would not be expected despite measurable pharmacodynamic changes. Second, substantial interindividual variability in clopidogrel metabolism due to CYP2C19 polymorphisms means that population-level effects are attenuated compared with predictions from pharmacokinetic models that assume uniform metabolism [92]. Third, any reduction in antiplatelet efficacy would theoretically reduce rather than increase bleeding risk-a prediction consistent with the neutral finding observed. The mechanistic concern regarding PPIs and clopidogrel was always about ischaemic outcomes, not haemorrhagic ones, yet the clinical literature has often conflated these distinct endpoints [244].

The dabigatran findings present a different interpretive challenge. Pharmacokinetic studies consistently demonstrate 22–33% reductions in dabigatran exposure with concurrent PPI use, attributable to impaired acid-dependent dissolution of the prodrug [231]. This thesis found that concurrent dabigatran-PPI exposure was associated with elevated treatment failure risk-a finding that superficially appears to confirm the clinical relevance of reduced drug exposure.

However, several observations argue strongly against a pharmacokinetic explanation. The same interaction would be expected to reduce bleeding risk, yet no corresponding bleeding reduction was observed. Randomised trial subgroup

analyses have not demonstrated significant interactions between PPI use and dabigatran efficacy [224].The sparse concurrent exposure at baseline (only 26 patients) introduces substantial statistical uncertainty.

On balance, the most plausible explanation for the dabigatran treatment failure finding is confounding by indication and channelling bias rather than a true pharmacokinetic effect. PPIs are selectively prescribed to patients with elevated gastrointestinal risk who typically have greater overall morbidity, more competing risks, and poorer prognosis [81, 226]. The observed association most likely reflects this channelling of higher-risk patients toward PPI therapy rather than a causal drug interaction. While a contribution from reduced dabigatran exposure cannot be excluded entirely, the weight of evidence favours confounding as the dominant explanation.

A further alternative explanation is depletion of susceptibles, a form of survivor bias. If patients most vulnerable to treatment failure on dabigatran experience events early in their treatment course and either discontinue therapy or die, the remaining dabigatran users at any given time point represent a selected, lower-risk subset. PPI users, who tend to be prescribed gastroprotection later in their treatment trajectory as gastrointestinal symptoms emerge, would disproportionately enter the concurrent exposure state during the period when susceptible individuals have already been depleted from the dabigatran monotherapy group. This differential timing of entry into the concurrent exposure state could produce an apparent excess of treatment failure events among concurrent users that reflects selection dynamics rather than pharmacological interaction. The time-varying analytical framework mitigates this bias to some extent by reassigning person-time as exposure status changes, but cannot fully eliminate it if the risk set composition changes systematically over time.

The warfarin findings present yet another pattern. The 2.13-fold increased bleeding risk associated with concurrent PPI use substantially exceeds predictions based on the modest CYP2C9-mediated pharmacokinetic effects documented in controlled studies [10, 41]. Two competing explanations merit consideration: amplified consequences of pharmacokinetic interaction in routine-care

populations with less intensive INR monitoring, or residual confounding by gastrointestinal bleeding risk factors.

While both mechanisms likely contribute, the weight of evidence suggests that a real pharmacological interaction is the primary driver. Unlike the dabigatran finding, the direction of effect aligns precisely with mechanistic predictions: enhanced anticoagulation produces increased bleeding. Studies demonstrating reduced time in therapeutic range among PPI users support this interpretation [10]. The effect size, while exceeding pure pharmacokinetic predictions, is plausible for a population receiving less intensive monitoring than clinical trial settings. However, the magnitude of association (HR 2.13) should be considered in light of potential unmeasured confounding. While a formal E-value analysis was not conducted, the E-value for this estimate would be approximately 3.7 [175], indicating that an unmeasured confounder would need to be associated with both PPI exposure and bleeding by a risk ratio of at least 3.7-fold, above and beyond measured covariates, to explain the association entirely. Given the substantial residual confounding plausible in this context - particularly from unmeasured gastrointestinal risk factors, frailty, and alcohol use - this threshold is not implausible, and caution is warranted in attributing the full magnitude of the observed association to a pharmacological interaction. On balance, the warfarin-PPI bleeding association is interpreted as reflecting a genuine, clinically relevant interaction that may be amplified-but is not created-by confounding.

The digoxin findings stand apart from these patterns and represent the exception that proves the rule. Unlike clopidogrel, where pharmacodynamic attenuation failed to produce clinical consequences, and unlike dabigatran, where the clinical signal most plausibly reflects confounding, the digoxin-PPI interaction demonstrates the scenario where pharmacokinetic changes genuinely translate into measurable clinical outcomes.

This distinction is not coincidental - it reflects unique pharmacological characteristics that render digoxin vulnerable to even modest changes in drug exposure. Digoxin has an exceptionally narrow therapeutic index, with toxic concentrations only marginally above therapeutic levels [191]. It is a substrate for P-gp, the efflux transporter inhibited by several PPIs [27, 225], and undergoes

minimal hepatic metabolism, meaning that changes in absorption or efflux directly impact systemic exposure without compensatory clearance mechanisms.

These characteristics-narrow therapeutic window, P-gp dependence, and limited metabolic buffering - create the conditions under which pharmacokinetic interactions produce clinical consequences. The modest but significant arrhythmia signal observed in this thesis is precisely what pharmacological principles predict. Importantly, the presence of this signal validates the methodology: if the analytical approach were biased toward detecting spurious interactions, positive findings would be expected across all drug combinations. Instead, the pattern-a signal for the drug with the narrowest therapeutic index, and null or confounded findings for drugs with wider margins - suggests appropriate discrimination between genuine effects and noise.

Taken together, these findings demonstrate that the translation from pharmacokinetic interaction to clinical outcome depends on drug-specific factors-therapeutic index, metabolic redundancy, and dose-response steepness-not simply the magnitude of pharmacokinetic change. Digoxin represents the scenario where pharmacokinetics matter; clopidogrel represents the scenario where they do not; and the anticoagulants occupy an intermediate position where class selection becomes clinically relevant.

Having established that the clinical consequences of pharmacokinetic interactions are drug-specific, the next critical question concerns how reliably these associations can be attributed to true pharmacological effects rather than systematic biases inherent in observational research.

6.3 The Problem of Confounding by Indication in Gastroprotective Drug Research

A fundamental interpretive challenge pervading all three empirical chapters-and indeed the broader PPI-cardiovascular drug interaction literature-is confounding by indication [147, 229]. PPIs are not prescribed randomly; they are selectively initiated in patients identified by clinicians as having elevated gastrointestinal bleeding risk, peptic ulcer disease history, polypharmacy, or frailty [81, 194]. These same characteristics are associated with adverse cardiovascular outcomes,

creating a systematic bias whereby PPI users appear to have worse outcomes even in the absence of true pharmacological interaction effects.

The baseline characteristics presented across all three studies clearly illustrate this phenomenon. PPI users were consistently older, more comorbid, more likely to have gastrointestinal disease, and had higher healthcare utilisation than non-users. Musculoskeletal disease, mental health conditions, neurological disease, and respiratory disease were all substantially enriched in PPI-containing exposure states. These patterns reflect the clinical reality that PPIs serve as markers for patient complexity and vulnerability [33, 194].

IPTW was employed throughout this thesis to address confounding by indication, following established methodological frameworks [144, 148, 178]. Balance diagnostics consistently demonstrated successful equilibration of measured confounders, with genuine effects and noise below the conventional 0.10 threshold [149].

However, IPTW can only address confounding from measured variables. Several important confounders were unavailable in the administrative data: frailty indices, functional status, disease severity, symptom burden, adherence to prescribed medications, and over-the-counter PPI use [201]. The extent to which residual confounding explains the observed associations cannot be determined from observational data alone [147, 229].

A related but distinct concern is protopathic bias, whereby early manifestations of the outcome prompt initiation of PPI therapy before the event is formally recorded [187]. In the context of this thesis, a patient experiencing early symptoms of gastrointestinal haemorrhage - such as dyspepsia, epigastric discomfort, or occult blood loss - may be prescribed a PPI as a therapeutic response. If the subsequent hospitalised bleeding event is then attributed to the concurrent PPI exposure period, the PPI would appear to be associated with increased bleeding risk when in reality it was prescribed in response to the evolving event. This form of bias is particularly relevant to the warfarin-PPI bleeding association, where the temporal relationship between PPI initiation and bleeding events cannot be fully disentangled using prescription-level data. The

time-varying exposure classification employed in this thesis mitigates protopathic bias to some extent by accurately assigning person-time, but cannot eliminate it entirely because the granularity of prescription dates may not capture the clinical sequence of symptom onset, PPI prescription, and hospitalisation.

The pattern of findings provides some reassurance that confounding does not entirely explain the observed associations. PPI monotherapy was consistently not associated with adverse outcomes across all three studies. If confounding were the sole explanation, one would expect PPI monotherapy to show elevated risk proportionate to the comorbidity enrichment in this group. The specificity of associations for concurrent exposure is compatible with an interaction effect, although, as all comparisons were made against the unexposed group, it cannot establish one and does not exclude interaction-specific confounding pathways.

What this section demonstrates is that confounding by indication contributes differently across drug combinations. For dabigatran, confounding appears to be the dominant explanation for the observed association. For warfarin, it likely amplifies a genuine pharmacological effect. For clopidogrel and factor Xa inhibitors, statistical adjustment yielded null or protective associations, suggesting that measured confounders accounted for the principal sources of bias in these drug combinations. This hierarchy of confounding contribution is essential for appropriate interpretation of the findings.

6.4 Rethinking the Risk-Benefit Framework for PPI Co-prescription

The findings from this thesis challenge simplistic approaches to PPI-cardiovascular drug interactions that focus solely on interaction risks without considering the benefits of gastroprotection [11, 81]. Clinical decision-making requires integration of multiple competing considerations: the magnitude and certainty of interaction risks, the benefits of acid suppression for gastrointestinal protection, the availability of alternative gastroprotective strategies, and patient-specific factors that modify the risk-benefit balance.

Consider the clinical scenario of a post-stroke patient requiring clopidogrel who has risk factors for gastrointestinal bleeding. The early observational evidence

suggesting harm with PPI co-prescription might discourage gastroprotection [241], leaving the patient vulnerable to upper gastrointestinal haemorrhage - the very complication PPIs are intended to prevent. Yet this thesis found no evidence that PPI co-prescription increases bleeding risk in this population, while the gastroprotective benefits of acid suppression are well-established [115]. The risk-benefit calculation clearly favours PPI use where gastrointestinal protection is indicated.

The oral anticoagulant findings present a more nuanced decision framework. The elevated bleeding risk associated with warfarin-PPI co-therapy might argue against gastroprotection in warfarin users-yet PPIs are often prescribed precisely because the patient is at elevated bleeding risk [219]. Avoiding PPIs does not eliminate the underlying gastrointestinal vulnerability; it merely substitutes one risk for another.

Notably, the protective association observed for treatment failure is consistent with the possibility that PPI-mediated enhancement of anticoagulation intensity may reduce thromboembolic risk, although this interpretation must be weighed against the broad confidence interval for this estimate (HR 0.19, 95% CI 0.04–0.86) and the potential for residual confounding to produce false protective associations. The clinical calculus therefore depends on the individual patient's relative priority of bleeding versus thrombotic prevention - a determination requiring shared decision-making rather than population-level prescribing rules.

The class-specific patterns observed for direct oral anticoagulants offer clearer guidance. Factor Xa inhibitors demonstrated protective bleeding associations and neutral treatment failure effects with concurrent PPI use, consistent with their pH-independent absorption and minimal interaction potential [72, 210]. This pattern suggests that factor Xa inhibitors should be the preferred anticoagulant class for patients requiring concurrent gastroprotection - a recommendation aligned with COMPASS trial evidence [219].

An important alternative explanation for the protective associations observed with factor Xa inhibitor–PPI co-therapy is healthy adherer bias. Patients who consistently take both an anticoagulant and a PPI may be systematically more

adherent to all prescribed medications, more engaged with healthcare services, and more likely to attend monitoring appointments than patients taking fewer medications. This general health-seeking behaviour, rather than a specific pharmacological interaction, could produce apparent protective associations for concurrent exposure [247]. While the inverse probability weighting employed in this thesis adjusts for measured markers of healthcare engagement (including comorbidity burden and co-medication use), it cannot fully capture the latent construct of adherence behaviour. The protective factor Xa inhibitor–PPI association should therefore be interpreted with caution and may partly reflect selection of adherent, lower-risk patients into the concurrent exposure group rather than a true gastroprotective benefit of the specific drug combination.

The digoxin findings require heightened caution rather than avoidance. The modest arrhythmia risk elevation is biologically plausible [27, 43] but small in absolute magnitude. The appropriate response is enhanced monitoring and attention to PPI indication, not reflexive discontinuation of gastroprotection [45, 191].

The overarching implication is that drug interactions should inform rather than dictate prescribing decisions. The findings support a framework of differential care - heightened monitoring for digoxin and warfarin, anticoagulant class selection for patients requiring gastroprotection, and clinical reassurance for clopidogrel users-rather than blanket avoidance of PPI co-prescription.

6.5 Implications for Anticoagulant Selection in Patients Requiring Gastroprotection

One of the most clinically actionable insights from this thesis concerns the differential safety profiles of oral anticoagulant classes when co-prescribed with PPIs. The divergent patterns observed - elevated bleeding with warfarin, elevated treatment failure with dabigatran, and protective/neutral associations with factor Xa inhibitors - have direct implications for anticoagulant selection [218].

The mechanistic basis for these differences is well-established. Warfarin is metabolised primarily by CYP2C9, with sensitivity to enzyme inhibition by PPIs [10, 41]. Dabigatran etexilate requires acid-dependent dissolution, making it

vulnerable to PPI-induced pH elevation [212, 231]. Factor Xa inhibitors have pH-independent absorption and metabolism primarily through CYP3A4, against which PPIs have negligible activity [72].

These mechanistic predictions align with the clinical findings. The elevated bleeding with warfarin-PPI co-therapy is consistent with reduced warfarin clearance, supported by studies showing reduced time in therapeutic range [10]. The neutral-to-protective associations with factor Xa inhibitors confirm minimal interaction potential [222].

The dabigatran findings, as established in Section 6.2, most plausibly reflect confounding rather than true pharmacokinetic interaction. However, the clinical recommendation remains unchanged: given available alternatives without either mechanistic concern (factor Xa inhibitors) or empirical uncertainty (dabigatran), factor Xa inhibitors emerge as the preferred choice for patients requiring concurrent gastroprotection.

For clinicians, these findings support preferential use of factor Xa inhibitors in patients requiring gastroprotection, aligning with broader prescribing trends favouring DOACs [69]. These findings align with the 2020 European Society of Cardiology guidelines on atrial fibrillation, which recommend DOACs in preference to warfarin for most patients and acknowledge that PPIs should be considered for patients at elevated gastrointestinal bleeding risk receiving anticoagulation [248]. Similarly, the 2023 NICE guideline on atrial fibrillation recommends DOACs as first-line and notes the importance of gastroprotection in high-risk patients [249]. However, neither guideline provides specific recommendations on anticoagulant selection based on anticipated PPI co-prescription, representing a gap that the present findings begin to address. The British National Formulary notes the potential for PPI-warfarin interactions but does not stratify anticoagulant recommendations by gastroprotective need [250]. The present findings suggest that integration of drug interaction profiles into anticoagulant selection algorithms could represent a clinically meaningful refinement of current guideline recommendations.

Where warfarin is necessary (mechanical valves, patient preference, cost), enhanced INR monitoring during PPI co-therapy is warranted. For dabigatran, while the observed signal likely reflects confounding, the residual uncertainty makes it a less attractive option when alternatives exist [223].

In summary, anticoagulant class selection should account for anticipated gastroprotective needs. The findings from this thesis, interpreted alongside the broader evidence base including trial data and pharmacokinetic considerations, are consistent with a hierarchy favouring factor Xa inhibitors for patients requiring concurrent gastroprotection, with warfarin as an acceptable alternative when accompanied by enhanced INR monitoring, and dabigatran as a less attractive option given the residual uncertainty surrounding its interaction profile. However, these recommendations should be considered hypothesis-generating rather than definitive, as they derive from observational data subject to the limitations discussed in Section 6.7, and require confirmation through appropriately designed comparative effectiveness studies.

6.6 Methodological Insights: The Importance of Time-Varying Exposure Analysis

A distinctive methodological feature of this thesis is the consistent application of time-varying exposure classification across all three studies. This approach addresses several important sources of bias that have compromised much of the prior literature on PPI-cardiovascular drug interactions [130, 186, 202].

The problem with baseline exposure classification is illustrated by the observation that concurrent PPI-cardiovascular drug exposure was rare at cohort entry. In the dabigatran cohort, only 26 patients (0.08%) were concurrently exposed at baseline. Had exposure been classified only at baseline, the vast majority of concurrent exposure person-time would have been misclassified, severely limiting statistical power [185].

Time-varying classification assigns person-time to the exposure state actually experienced at each time point [130]. This approach also avoids immortal time bias-the systematic error arising when pre-treatment person-time is incorrectly attributed to the treated group [185, 205]. In drug interaction research, where

medications may be initiated at different times, immortal time bias can severely distort effect estimates.

The concordance between Simon-Makuch survival curves and regression-based hazard ratios provides methodological reassurance [180]. Where hazard ratios approximated unity, survival curves showed overlapping trajectories. Where significant associations were detected, curves demonstrated visible divergence. This internal consistency suggests findings reflect genuine patterns rather than model artefacts.

Covariate balance through IPTW was consistently achieved (SMDs <0.10), supporting exchangeability assumptions [144, 149]. However, two important caveats apply. First, balance on measured covariates does not guarantee balance on unmeasured confounders [147]. Second, the positivity assumption - that all covariate patterns have a non-zero probability of receiving each exposure level - may have been violated in certain strata, particularly for the dabigatran cohort where concurrent PPI exposure was rare at baseline (n=26) and certain covariate combinations may have had near-zero probability of concurrent exposure [251]. Although weight truncation at the 99th percentile was employed to mitigate extreme weights arising from near-positivity violations, this approach trades reduced variance for potential bias, and the resulting estimates for sparse exposure groups should be interpreted with particular caution.

The methodological lesson is that drug interaction research requires analytical approaches matched to the complexity of real-world prescribing. Time-varying exposure classification, inverse probability weighting, and complementary survival visualisation together provide a robust framework for future pharmacoepidemiological studies.

6.7 Strengths of This Thesis

Before discussing limitations, it is important to acknowledge the substantive strengths of this work, which enhance the reliability and contribution of the findings.

First, the consistent methodological framework applied across all three empirical studies represents a significant strength. The uniform use of time-varying exposure classification, IPTW, and complementary Simon-Makuch survival visualisation enables direct comparison of findings across drug combinations within a common analytical architecture. This consistency avoids the interpretive difficulties that arise when different drug interaction studies employ heterogeneous methods, and provides a coherent basis for the integrative synthesis presented in Section 6.2.

Second, the time-varying exposure approach represents a methodological advance over the majority of prior studies in this field, which have classified PPI exposure at baseline only. As demonstrated by the observation that only 26 dabigatran patients (0.08%) were concurrently exposed at baseline, fixed exposure classification would have severely misclassified the substantial concurrent exposure that developed during follow-up, introducing exposure misclassification bias and loss of statistical power. The time-varying approach correctly assigns person-time to the exposure state actually experienced and avoids immortal time bias - a recognised source of error in drug interaction research [185, 205].

Third, the use of real-world administrative data from a defined population provides findings with high external validity for routine clinical practice. Unlike clinical trial populations, which are typically younger, less comorbid, and subject to stringent monitoring protocols, the study populations in this thesis reflect the older, multimorbid, polypharmacy patients in whom PPI-cardiovascular drug co-prescription most frequently occurs and in whom the clinical consequences are most relevant.

Fourth, the inclusion of PPI monotherapy as a separate exposure category across all three studies provides a valuable internal control. The consistent absence of adverse associations for PPI monotherapy argues against the hypothesis that PPIs independently increase cardiovascular risk - a claim that has generated considerable controversy in the broader literature [252] - and supports the specificity of associations observed for concurrent exposure states.

Fifth, the breadth of drug combinations examined within a single thesis enables cross-drug comparison that would not be possible from individual studies conducted in isolation. The demonstration that pharmacokinetic-clinical translation varies according to drug-specific pharmacological properties - therapeutic index, metabolic redundancy, and transporter dependence - represents a conceptual contribution that extends beyond any single drug combination.

Sixth, the study populations were large, with cohort sizes ranging from approximately 8,000 (clopidogrel) to over 30,000 (dabigatran), providing adequate statistical power for the primary analyses and enabling the detection of clinically meaningful associations where they existed.

Seventh, the analytical approach incorporated several safeguards against common biases: weight truncation at the 99th percentile to address extreme weights, balance diagnostics confirming successful covariate equilibration (SMD <0.10), proportional hazards assessment through Schoenfeld residuals, and robust sandwich variance estimators to account for weighting and repeated exposure transitions.

6.8 Limitations and Interpretive Boundaries

The findings must be interpreted within clear boundaries imposed by the observational design and administrative data sources, and analytical choices made throughout the three empirical studies [127]. The following limitations are discussed in order of their likely impact on the validity and interpretation of the findings.

6.8.1 Residual and unmeasured confounding

Despite the application of IPTW throughout this thesis, residual confounding remains the most fundamental threat to causal inference from observational data [147, 229]. IPTW can only address confounding from measured variables, and several clinically important confounders were unavailable in the administrative datasets. These include validated frailty indices, functional status and performance measures, disease severity within diagnostic categories, symptom burden and quality of life indicators, medication adherence, alcohol consumption,

body mass index, smoking status, *Helicobacter pylori* infection status, and dietary vitamin K intake for warfarin users [201]. Ethnicity and pharmacogenetic information were also not incorporated into the analyses. This is relevant because genetic variants affecting drug metabolism and transport may contribute to inter-individual variability in treatment response, and the frequencies of clinically relevant variants can differ between racial and ethnic populations [140]. Although ethnicity may provide an imperfect population-level proxy for such variation, it cannot substitute for individual genotyping. The absence of these data therefore represents an additional source of unmeasured heterogeneity across the study cohorts. The extent to which residual confounding explains the observed associations cannot be quantified from observational data alone. This limitation is particularly important for the warfarin-PPI bleeding association (HR 2.13), where the magnitude of association exceeds pharmacokinetic predictions and could be partially attributable to unmeasured gastrointestinal risk factors that drive both PPI prescription and bleeding events. It is also critical for the dabigatran-PPI treatment failure association (HR 1.71), where the discussion in Section 6.2 concluded that confounding by indication is the most plausible explanation for the observed signal. The mitigating factor is the internal consistency of findings: PPI monotherapy was not associated with adverse outcomes across any of the three studies, and the specificity of associations for concurrent exposure argues against confounding as the sole explanation. Nevertheless, this limitation means that all associations reported in this thesis should be interpreted as causally compatible rather than causally definitive.

A limitation common to all three studies arises from the overlap of the study period, which extended to December 2020, with the first year of the COVID-19 pandemic in Scotland. SARS-CoV-2 infection is independently associated with several of the outcomes examined across this thesis- arrhythmia, thromboembolism, and bleeding. This disproportionately affected the older, multimorbid populations under study [206]. Infection status could not be ascertained from the available administrative data and therefore constitutes an unmeasured confounder across all three cohorts. In parallel, the marked, non-random reduction in hospital admissions during 2020 [253] may have led to differential under-ascertainment of the hospitalisation-based outcomes used throughout this work. Because the majority of person-time and events accrued

before March 2020, these effects are unlikely to have driven the principal findings; however, they represent a genuine and uncontrolled source of both confounding and outcome misclassification. Where feasible, future replication should either exclude the pandemic period or incorporate laboratory-confirmed infection status as a time-varying covariate.

The choice of unexposed group (neither medication) as the reference category also limits the clinical interpretation of the hazard ratios. Although approximate contrasts between monotherapy and concurrent therapy were calculated, these did not include confidence intervals and should therefore be considered descriptive only. Accordingly, formal statistical inferences in this thesis are confined to comparisons against the unexposed reference group, and the reported hazard ratios should not be interpreted as estimating the effect of adding a PPI to cardiovascular-drug monotherapy.

6.8.2 Absence of drug concentration and laboratory data

The absence of drug concentration data represents the most important limitation for mechanistic interpretation. Without INR measurements for warfarin users, plasma dabigatran concentrations, platelet function testing for clopidogrel users, or serum digoxin levels, it is not possible to confirm that observed associations are mediated through altered drug exposure. This limitation is particularly salient for three reasons. First, for warfarin, INR data would permit direct assessment of whether PPI co-prescription is associated with supratherapeutic anticoagulation, thereby distinguishing genuine pharmacokinetic interaction from confounding. Second, for dabigatran, plasma concentration data would clarify whether the pharmacokinetically predicted 22–33% reduction in exposure [231] manifests in clinical practice. Third, for digoxin, serum levels would enable assessment of whether the observed arrhythmia signal correlates with supratherapeutic digoxin concentrations. The absence of electrolyte data (particularly magnesium and potassium) further limits mechanistic interpretation for digoxin, given the established role of electrolyte disturbances in digoxin toxicity and the association between long-term PPI use and hypomagnesaemia. Future studies integrating laboratory and clinical outcome data would substantially strengthen the mechanistic inferences that can be drawn.

6.8.3 PPI class-level analysis

The classification of PPIs as a single drug class throughout this thesis obscures established heterogeneity in interaction potential across individual agents. Omeprazole and esomeprazole are substantially more potent inhibitors of CYP2C19 than pantoprazole, lansoprazole, or rabeprazole [41], and omeprazole has demonstrated greater P-gp inhibitory activity than pantoprazole in vitro [43]. The class-level analysis was a deliberate methodological choice to preserve statistical power and reflect real-world prescribing patterns where PPI switching is common. However, this approach estimates an average class effect that may dilute agent-specific signals. If the interaction risk is concentrated among omeprazole and esomeprazole users, the class-level hazard ratios presented in this thesis will underestimate the true agent-specific interaction magnitude while overestimating risk for pantoprazole users. The direction of this bias is toward the null for high-potency agents and away from the null for low-potency agents, meaning that the class-level estimates reported here should be considered conservative for the most potent CYP2C19 inhibitors. Agent-specific analyses were not conducted due to insufficient numbers of events within individual PPI strata to permit stable estimation.

6.8.4 Outcome ascertainment bias

Outcome ascertainment relied exclusively on hospital discharge records coded using ICD-10, capturing only events of sufficient severity to require hospitalisation. This approach has important implications in both directions. Events managed in primary care, emergency departments without admission, or through outpatient adjustment of therapy would be missed, potentially underestimating the true burden of drug interaction-related adverse events. This is particularly relevant for warfarin, where supratherapeutic INR values may be managed through dose adjustment without hospitalisation, and for digoxin, where mild toxicity symptoms may be addressed through dose reduction in primary care. For the digoxin analysis, the outcome definition did not specifically capture bradyarrhythmia or atrioventricular block, which are clinically relevant manifestations of digoxin toxicity. The predominance of tachyarrhythmia outcomes also introduces potential confounding by indication because digoxin is prescribed for the management of tachyarrhythmias, limiting interpretation of the observed association. Conversely, hospitalisation-based ascertainment enhances

specificity for clinically meaningful events, reducing the noise associated with minor or self-limiting episodes. The net direction of this bias depends on the outcome: for bleeding events, restriction to hospitalised cases likely biases toward the null (as the most common PPI-preventable event - minor upper gastrointestinal bleeding - would be undercounted); for arrhythmia events, the direction is less clear but likely also toward the null. Administrative coding accuracy represents an additional concern. ICD-10 coding for bleeding events has been validated with reasonable sensitivity and high specificity in Scottish hospital data [254], but coding accuracy for arrhythmia subtypes is less well established, and misclassification of outcomes could introduce non-differential measurement error that would attenuate associations toward the null.

6.8.5 Exposure misclassification

Medication exposure was inferred from prescription records issued in primary care, which do not guarantee that medications were dispensed, collected, or consumed as prescribed [201]. Several sources of exposure misclassification warrant consideration. First, patient adherence to prescribed medications could not be assessed; non-adherence to either the cardiovascular drug or the PPI would bias associations toward the null through dilution of the exposed group with unexposed person-time. Second, over-the-counter PPI purchases - which are available without prescription in the United Kingdom - would result in misclassification of some truly exposed individuals as unexposed, again biasing toward the null. Third, inpatient medication administration was not captured in the community prescription data; patients may have received PPIs during hospital stays that were not reflected in their community prescription records. Fourth, the temporal resolution of prescribing data (prescription issue dates rather than dispensing or consumption dates) introduces imprecision in the timing of exposure transitions within the time-varying framework. The net effect of these misclassification sources is expected to be non-differential with respect to outcomes (as outcome events do not influence the accuracy of prior prescription records), and non-differential misclassification typically biases toward the null. Consequently, the true magnitude of associations may be larger than those reported.

6.8.6 Competing risks

The study populations comprised older, multimorbid adults with substantial mortality rates during follow-up. Death from non-study-related causes represents a competing risk that may have influenced the observed associations. The Cox proportional hazards models employed throughout this thesis estimate cause-specific hazard ratios, which quantify the instantaneous rate of the outcome among those still at risk. However, they do not account for the informative censoring that occurs when death precludes the occurrence of study outcomes. If PPI exposure is associated with reduced overall survival (through mechanisms unrelated to the study outcomes), differential depletion of the risk set could distort cause-specific hazard ratio estimates. Fine and Gray subdistribution hazard models, which account for competing risks by treating deaths as permanent members of the risk set, were not employed in this thesis and could be considered in future analyses [255]. The likely direction of competing risk bias in this context is toward the null: if PPI users are sicker and die earlier from non-study causes, they have less opportunity to experience study outcomes, potentially attenuating the observed associations.

6.8.7 Limited follow-up duration

The two-year follow-up period, while adequate to capture the majority of acute drug interaction-related adverse events, may not detect long-term or cumulative effects of concurrent PPI-cardiovascular drug exposure. Chronic PPI use has been associated with progressive magnesium depletion, altered gut microbiome composition, and other physiological changes that develop over extended time horizons [256]. These chronic effects could amplify drug interaction risks over periods exceeding the two-year observation window employed here. Conversely, the two-year period may overestimate risk for interactions whose clinical consequences are concentrated in the early period following co-initiation, before physiological adaptation or clinical monitoring adjustments occur. The findings therefore apply most directly to the medium-term risk window and cannot be extrapolated to longer-term concurrent exposure.

6.8.8 Single health board and generalisability

The findings derive from NHS Greater Glasgow and Clyde, a single Scottish health board serving approximately 1.2 million people. While the population is

demographically representative of older adults with cardiovascular disease in Scotland and broader UK settings, several features may limit generalisability. Ethnicity was missing for more than half of individuals (Section 2.3.5), so the ethnic composition of the cohorts could not be reliably characterised, and the results cannot be extrapolated to populations with different genetic backgrounds that influence drug metabolism - particularly CYP2C19 polymorphism frequencies, which vary substantially across ethnic groups and directly affect both PPI metabolism and clopidogrel bioactivation [257]. Prescribing patterns in NHS Scotland may differ from other healthcare systems; for example, the relative frequency of individual PPI agents, the threshold for initiating gastroprotection, and anticoagulant prescribing preferences may vary across settings. Additionally, the quality and completeness of administrative coding, which underpins both exposure and outcome ascertainment, may differ across healthcare systems and countries, limiting the transportability of findings to settings with different data infrastructure.

6.8.9 Absence of dose-response analysis

Drug interaction effects are expected to be dose-dependent: higher PPI doses producing greater enzyme or transporter inhibition and correspondingly larger effects on cardiovascular drug pharmacokinetics. This thesis did not examine dose-response relationships due to the complexity of modelling time-varying dose alongside time-varying exposure status, and because prescription data do not reliably capture actual consumed doses. The absence of dose-response analysis limits the ability to draw mechanistic inferences from the observed associations. A monotonic dose-response relationship would strengthen the argument for a pharmacological interaction, while its absence would support confounding as the dominant explanation. This limitation is particularly relevant for the warfarin-PPI association, where dose-dependent CYP2C19 inhibition would be expected to produce graded effects on INR and bleeding risk.

6.8.10 Potential for surveillance or detection bias

Patients receiving multiple medications, including concurrent cardiovascular drugs and PPIs, may be subject to more intensive clinical monitoring than those on fewer medications. Enhanced surveillance could lead to earlier detection and hospitalisation for events that might otherwise be managed conservatively or go

undetected, inflating event rates in the concurrent exposure group. Conversely, patients under closer monitoring may have events prevented or managed before they require hospitalisation, potentially deflating event rates. The net direction of surveillance bias is difficult to predict and may differ across outcomes. For digoxin, enhanced monitoring of patients on multiple medications could lead to earlier detection of arrhythmias, inflating the apparent association. For warfarin, closer INR monitoring in patients receiving PPIs could paradoxically reduce bleeding risk by enabling earlier dose adjustment, working against the observed positive association and suggesting the true pharmacological interaction effect may be even larger than estimated.

These limitations collectively define the interpretive boundaries of this thesis. The findings represent robust associational evidence from a well-characterised population, generated using state-of-the-art pharmacoepidemiological methods. They inform but cannot definitively resolve questions about PPI-cardiovascular drug interactions. Definitive mechanistic conclusions require future studies integrating pharmacokinetic, pharmacogenetic, and clinical outcome data in study designs that can address the specific limitations identified here.

6.9 Future Research Directions

The findings and limitations of this thesis define a structured research agenda. The following priorities are presented in order of their likely contribution to resolving the uncertainties identified in this work, with sufficient methodological detail to indicate feasibility.

6.9.1 Integration of laboratory data with clinical outcomes

The most important limitation of this thesis - the absence of drug concentration and laboratory data - should be the first priority for future investigation. Two complementary approaches merit consideration.

First, retrospective linkage of the existing cohort to laboratory information management systems could provide INR measurements for warfarin users and serum digoxin concentrations, where available from routine clinical monitoring. Within NHS Scotland, the SCI-Store clinical data repository holds laboratory results that could, in principle, be linked to the prescribing and hospitalisation data used

in this thesis. A study linking INR trajectories to bleeding events, stratified by PPI exposure status, would directly test whether the warfarin-PPI bleeding association observed in Chapter 4 (adjusted HR 2.13, 95% CI 1.25–3.63) is mediated through supratherapeutic anticoagulation. If PPI co-prescription is associated with prolonged time above therapeutic range, this would strongly support a pharmacokinetic mechanism; if INR patterns are similar regardless of PPI exposure, confounding becomes the dominant explanation. Similarly, linking serum digoxin levels to the arrhythmia outcomes examined in Chapter 3 would clarify whether the modest association observed (HR 1.195) correlates with supratherapeutic drug concentrations.

Second, prospective pharmacokinetic-clinical studies in patients initiating PPI therapy alongside established cardiovascular medications could provide definitive mechanistic data. A pragmatic design would recruit patients already receiving warfarin, digoxin, or dabigatran who are newly prescribed a PPI, measuring drug concentrations before and at intervals after PPI initiation while monitoring clinical outcomes. Such a study, although more resource-intensive than database linkage, would provide the causal evidence that observational analyses cannot.

6.9.2 Multi-site replication and external validation

The single health board setting (NHS Greater Glasgow and Clyde) identified in Section 6.7 as a limitation constrains the generalisability of the findings. Replication using multi-site or national-level datasets is essential. Within the United Kingdom, the Clinical Practice Research Datalink (CPRD) provides linked primary care prescribing, hospital admission, and mortality data for a representative sample of the UK population, and would support analyses with substantially larger sample sizes, greater ethnic diversity, and broader geographic coverage [258]. The Scottish Morbidity Record datasets linked through the electronic Data Research and Innovation Service (eDRIS) could provide national-level Scottish data.

International replication in populations with different CYP2C19 polymorphism distributions would be particularly informative. The frequency of CYP2C19 poor metaboliser phenotypes varies from approximately 2–5% in European populations to 12–23% in East Asian populations [257], with direct implications for PPI

metabolism, clopidogrel bioactivation, and the magnitude of PPI-mediated drug interactions. Studies in East Asian cohorts, where both PPI use and CYP2C19 loss-of-function alleles are more prevalent, could reveal interaction effects that are diluted in predominantly European-ancestry populations such as that studied here.

6.9.3 Agent-specific PPI analyses

The class-level PPI analysis employed throughout this thesis (Section 6.7) obscures established heterogeneity in CYP2C19 inhibitory potency and P-gp inhibition across individual PPI agents [197]. Omeprazole and esomeprazole are substantially more potent CYP2C19 inhibitors than pantoprazole, lansoprazole, or rabeprazole, and this differential potency has been demonstrated at the level of both in vitro enzyme kinetics and in vivo pharmacodynamic outcomes [238]. Agent-specific analyses would clarify whether the associations observed in this thesis are driven predominantly by high-potency CYP2C19 inhibitors, which would strengthen the pharmacokinetic interpretation, or are uniform across agents, which would favour confounding as the dominant explanation. Such analyses require either larger single-site cohorts or multi-site collaboration to achieve sufficient event counts within individual PPI strata. Emerging federated data analysis platforms, which enable analyses across multiple sites without transferring patient-level data, could facilitate this research while preserving data governance requirements [259].

6.9.4 Examination of ischaemic outcomes for clopidogrel users

This thesis examined bleeding outcomes for the clopidogrel cohort (Chapter 5) but did not assess ischaemic endpoints - recurrent stroke, transient ischaemic attack, or myocardial infarction - which represent the primary mechanistic concern motivating regulatory warnings about PPI-clopidogrel co-prescription [241, 244]. The null bleeding finding (adjusted HR 0.83, 95% CI 0.53–1.30) addresses one half of the clinical question; the ischaemic half remains unanswered in this specific post-stroke population. A study powered to detect a clinically meaningful difference in recurrent stroke rates (e.g., a 20% relative increase from an assumed baseline rate of 5% per year) would require a substantially larger cohort than the 8,109 patients studied here, further supporting the case for multi-site collaboration or national-level datasets. Such a study should examine both

bleeding and ischaemic outcomes simultaneously to characterise the net clinical benefit of PPI co-prescription in post-stroke clopidogrel users.

6.9.5 Target trial emulation

A methodological advance that could address several limitations of the present work is the application of the target trial emulation framework [186]. This approach would involve explicitly specifying the pragmatic randomised trial that would ideally address the clinical question - for example, a trial randomising anticoagulant users with gastroprotective indications to PPI versus H2-receptor antagonist versus no gastroprotection - and then designing the observational analysis to emulate that trial as closely as possible. Key features would include: an active comparator design (PPI versus H2-receptor antagonist) to mitigate confounding by indication more effectively than the PPI versus no-PPI comparison used in this thesis; a new-user design restricting to patients initiating gastroprotective therapy to avoid prevalent user bias; and explicit alignment of eligibility criteria, treatment strategies, and outcome definitions between the target trial and the observational emulation. This approach, applied to national-level linked datasets, could provide substantially stronger causal evidence than the current analyses while remaining feasible within existing data infrastructure.

6.9.6 Pharmacogenomic stratification

Finally, findings from a single Scottish health board may not generalise to populations with different prescribing patterns or demographic characteristics. Ethnicity was missing or recoded as ‘not known’ for more than half of individuals, limiting reliable characterisation of the ethnic composition of the cohort and preventing ethnicity-stratified analysis. This is particularly relevant to the clopidogrel-PPI analysis because the population frequency of the clinically relevant CYP2C19 variants differs across ancestry groups [140]. Ethnicity should not, however, be equated with genotype or genetic ancestry [245]. Consequently, replication in more diverse populations, ideally incorporating direct CYP2C19 genotype data, is a priority. CYP2C19 polymorphisms simultaneously influence PPI metabolism and clopidogrel bioactivation, creating the potential for gene-drug-drug interactions of a magnitude not captured by population-average estimates. A pharmacogenomic sub-study within a dataset containing both genotype data and linked prescribing and outcome records - such as UK Biobank linked to primary

care data - could stratify the PPI-clopidogrel and PPI-warfarin associations by CYP2C19 metaboliser status. If the PPI-cardiovascular drug interactions observed in this thesis are concentrated among CYP2C19 poor metabolisers, this would have direct implications for pharmacogenomics-guided prescribing. Similarly, ABCB1 genotyping could inform whether genetic variation in P-gp modifies the magnitude of the digoxin-PPI interaction observed in Chapter 3. These pharmacogenomic analyses would move the field from population-average risk estimates toward the personalised risk prediction that the heterogeneity of findings in this thesis clearly demands.

6.9.7 Competing risk and health economic analyses

Two analytical extensions of the present work warrant consideration. First, competing risk analyses using Fine and Gray subdistribution hazard models [255] would complement the cause-specific hazard ratios reported in this thesis by accounting for the informative censoring introduced when death from non-study causes precludes the occurrence of study outcomes. In the older, multimorbid populations studied here, competing mortality is substantial, and subdistribution hazard ratios may yield different estimates from the cause-specific hazard ratios reported, particularly if PPI exposure is associated with differential mortality.

Second, health economic evaluation of the differential prescribing strategies suggested by this thesis - particularly the preference for factor Xa inhibitors over warfarin or dabigatran in patients requiring concurrent gastroprotection - would inform implementation. While factor Xa inhibitors have higher acquisition costs than warfarin, the reduced monitoring requirements and the favourable interaction profile observed in this thesis may produce net cost savings when bleeding-related hospitalisations, INR monitoring visits, and treatment failure events are incorporated into cost-effectiveness models. Such analyses would strengthen the translation of the epidemiological findings into prescribing policy.

Chapter 7 Conclusions

This thesis examined the clinical consequences of proton pump inhibitor co-prescription with four cardiovascular drug classes - digoxin, warfarin, dabigatran, and factor Xa inhibitors, and clopidogrel - in over 90,000 older adults with cardiovascular disease treated in NHS Greater Glasgow and Clyde between 2014 and 2020. Using a consistent methodological framework of time-varying exposure classification, inverse probability of treatment weighting, and Simon–Makuch survival visualisation across all three empirical studies, the findings reveal that the translation from pharmacokinetic interaction to clinical outcome is neither automatic nor uniform.

In the digoxin cohort (n=23,351), concurrent PPI co-prescription was associated with a modest but statistically significant elevation in arrhythmia-related hospitalisation (adjusted HR 1.195, 95% CI 1.025–1.394; p=0.023), while neither digoxin monotherapy nor PPI monotherapy was associated with increased risk. The observed association is biologically compatible with a potential pharmacokinetic interaction; however, the outcome definition did not specifically capture characteristic manifestations of digoxin toxicity such as bradyarrhythmia or atrioventricular block, and residual confounding, including confounding by indication, cannot be excluded.

In the oral anticoagulant cohorts, the patterns varied markedly by drug class. Concurrent warfarin-PPI exposure was associated with a 2.13-fold increase in bleeding risk (95% CI 1.25–3.63; p=0.005) in a cohort of 29,765 patients, a magnitude exceeding pharmacokinetic predictions that may reflect amplification of a genuine interaction by routine-care monitoring conditions, residual confounding, or both. In the treatment failure analysis of the same warfarin population (n=25,721), concurrent warfarin-PPI exposure was associated with a pronounced protective effect (adjusted HR 0.19, 95% CI 0.04–0.86; p=0.031), although this estimate must be interpreted with considerable caution given the broad confidence interval spanning nearly a twenty-fold range and the limited number of patients in the concurrent exposure group at baseline. Concurrent dabigatran-PPI exposure was associated with elevated treatment failure risk (adjusted HR 1.71, 95% CI 1.10–2.66; p=0.018; n=30,985), although the weight of

evidence presented in this thesis favours confounding by indication as the dominant explanation rather than a true pharmacokinetic effect. Notably, the dabigatran-PPI bleeding association could not be reliably estimated due to sparse concurrent exposure (n=26 at baseline), illustrating the genuine rarity of this drug combination in clinical practice. In contrast, concurrent factor Xa inhibitor-PPI co-therapy was associated with lower bleeding risk (adjusted HR 0.55, 95% CI 0.44–0.69; p<0.001; n=27,713) and neutral treatment failure risk (adjusted HR 0.99, 95% CI 0.90–1.08; p=0.785), consistent with the minimal pharmacokinetic interaction potential of this drug class.

In the clopidogrel cohort (n=8,109), concurrent PPI co-prescription was not associated with altered bleeding risk in post-stroke patients (adjusted HR 0.83, 95% CI 0.53–1.30; p=0.415), a null finding that aligns with the COGENT trial [9] and supports the safety of gastroprotection in this population. This study did not examine ischaemic outcomes, and uncertainty regarding potential effects on recurrent stroke remains.

A cross-cutting finding of particular importance is that PPI monotherapy was consistently not associated with adverse outcomes across any of the three studies. This internal consistency argues against the hypothesis that PPIs independently increase cardiovascular risk. Because all comparisons were made against patients exposed to neither drug, the concurrent-exposure associations reported in this thesis cannot be interpreted as the effect of adding a PPI to index-drug therapy; estimates of that contrast are descriptive only.

7.1 Original contribution to knowledge

This thesis makes several original contributions to pharmacoepidemiology and cardiovascular therapeutics.

First, and most substantively, this thesis is among the first to apply a unified methodological framework - time-varying exposure classification with IPTW and complementary survival visualisation - to examine PPI interactions across multiple cardiovascular drug classes within a single, defined population. This cross-drug comparative approach, enabled by the consistent analytical architecture, reveals a pattern that would not be apparent from individual drug-pair studies conducted

in isolation: the clinical translation of pharmacokinetic interactions depends not on the magnitude of pharmacokinetic change, but on drug-specific pharmacological properties - therapeutic index, metabolic redundancy, transporter dependence, and dose-response steepness. Digoxin, with the narrowest therapeutic window and greatest dependence on P-glycoprotein-mediated clearance, is the drug for which pharmacokinetic perturbation most plausibly translates into clinical consequences. Clopidogrel, with threshold-dependent pharmacodynamic effects and substantial metabolic redundancy, is the drug for which it does not. The oral anticoagulants occupy an intermediate position where the pattern varies by class. This conceptual framework - that vulnerability to pharmacokinetic interaction is a drug-specific property predictable from pharmacological first principles - represents a contribution to how drug-drug interactions are evaluated and communicated, moving beyond simplistic assessments of pharmacokinetic magnitude toward clinically grounded risk stratification.

Second, this thesis provides the first comprehensive examination of PPI-cardiovascular drug interactions using real-world data from a defined Scottish population of older, multimorbid adults - the demographic in whom these drug combinations are most frequently prescribed and in whom clinical trial evidence is most sparse. The cohort sizes (ranging from 8,109 for clopidogrel to over 30,000 for dabigatran and warfarin), the two-year follow-up, and the use of hospitalisation-based outcomes provide evidence with direct applicability to routine clinical practice in settings comparable to NHS Scotland.

Third, the consistent demonstration that PPI monotherapy is not associated with adverse outcomes provides an internal methodological control that strengthens the credibility of the concurrent exposure findings. If the analytical approach systematically generated spurious associations through residual confounding, PPI monotherapy - which is prescribed to a population enriched for comorbidity and healthcare utilisation - would be expected to show elevated risk. Its consistent neutrality argues for appropriate discrimination between confounding and genuine interaction effects, and contributes to the broader debate regarding the cardiovascular safety of PPIs as a drug class.

7.2 Clinical implications

The clinical implications of this thesis should be interpreted within the boundaries imposed by the observational design and the specific limitations discussed in Section 6.7. With that caveat, the findings support several principles for clinical practice.

First, the results support a framework of differential vigilance rather than blanket avoidance of PPI co-prescription in patients receiving cardiovascular medications. The evidence does not justify withholding gastroprotection from patients with genuine indications, but suggests that the intensity of monitoring and the choice of co-prescribed cardiovascular agent should be informed by the interaction potential of the specific drug combination.

Second, for patients requiring concurrent gastroprotection and anticoagulation, the findings are consistent with preferential selection of factor Xa inhibitors where clinically appropriate, given their favourable interaction profile observed in this thesis and their established efficacy and safety in randomised trials. Where warfarin is necessary - as in patients with mechanical heart valves, certain valvular conditions, or healthcare systems where cost constraints limit DOAC access - enhanced INR monitoring during PPI co-therapy is warranted. For dabigatran, while the observed treatment failure association most plausibly reflects confounding, the residual uncertainty combined with the availability of alternatives without this concern makes it a less attractive option when gastroprotection is anticipated.

Third, for patients receiving clopidogrel for secondary stroke prevention, the findings provide reassurance that PPI co-prescription for appropriate gastroprotective indications does not introduce a measurable increase in bleeding risk. This is particularly relevant given that regulatory warnings regarding PPI-clopidogrel co-prescription have led to underuse of gastroprotection in populations at elevated gastrointestinal bleeding risk.

Fourth, for patients receiving concurrent digoxin and PPI therapy, the modest arrhythmia signal warrants awareness rather than alarm. The appropriate clinical response involves periodic medication review, attention to the ongoing indication

for PPI therapy, monitoring of renal function and electrolytes (particularly magnesium and potassium), and consideration of serum digoxin level measurement in patients exhibiting symptoms suggestive of toxicity.

These recommendations are hypothesis-generating rather than definitive prescribing mandates. They derive from observational data that, despite rigorous analytical methods, cannot fully exclude residual confounding or establish causal relationships. Confirmation through the methodological approaches outlined in Section 6.8 - particularly laboratory-linked analyses, multi-site replication, and target trial emulation - is required before these findings should be incorporated into formal clinical guidelines.

7.3 Closing statement

The clinical management of drug-drug interactions occupies an uneasy space between pharmacological theory and clinical pragmatism. Well-documented pharmacokinetic interactions generate concern, regulatory warnings, and prescribing restrictions - yet the translation from altered drug concentrations to patient harm is inconsistent, context-dependent, and frequently overestimated. This thesis provides evidence that the relationship between pharmacokinetic interaction and clinical consequence is mediated by drug-specific pharmacological properties, and that population-level data can distinguish the rare situations where pharmacokinetic perturbation plausibly matters from the more common situations where it does not. The goal of this work is not to minimise the importance of drug interactions, but to replace reflexive avoidance with informed, evidence-based prescribing - ensuring that patients receive the gastroprotection they need without unnecessary withholding of treatments that, on the available evidence, pose minimal additional risk. If this thesis contributes to a more nuanced clinical conversation about when drug interactions matter and when they do not, it will have served its purpose.

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