Demographics, Epidemiology and Prognostic Factors in Pulmonary Arterial Hypertension

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ABSTRACT

Prevalent patients were over-represented in many pulmonary hypertension registries and clinical trials. These patients have better survival compared with incident patients. As pulmonary hypertension (PH) is diagnosed and managed in designated pulmonary hypertension centres only in the United Kingdom (UK) and Ireland, this provides a unique opportunity to define the demographics, epidemiology and outcomes of a large cohort of purely incident, treatment-naive idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension (PAH) patients.

We included all newly diagnosed, treatment naive patients diagnosed in all eight PH centres in the UK and Ireland between January 2001 and December 2009 in our study. We used the same inclusion criteria used in the French and Scottish registries to define our idiopathic, heritable and anorexigen-associated PAH patients. We further refined our criteria for idiopathic, heritable and anorexigen-associated PAH by excluding patients with evidence of parenchymal lung disease on thoracic CT. These excluded patients (refer as Pre-capillary pulmonary hypertension co-existing lung disease in this thesis) were managed as idiopathic PAH by their PH physicians and otherwise satisfied the usual haemodynamic and pulmonary function criteria used to define idiopathic PAH in many PH registries and clinical trials.

We divided our idiopathic, heritable and anorexigen-associated PAH patients into two age subgroups according to their median age to study the effect of age on their phenotypes and survival. We also divided our idiopathic, heritable and anorexigen-associated PAH patients into three subgroups according to their year of diagnosis to study the changing epidemiology of the disease over the past decade. We also compared the baseline characteristics and outcomes of our idiopathic, heritable and anorexigen-associated PAH patients with PAH with ‘co-existing lung disease’ patients.

Firstly, we confirmed that the demographics, epidemiology and survival of incident idiopathic, heritable and anorexigen-associated PAH has changed compared with patients from the pre-disease targeted therapy era of the 1980s,

and continued to evolve in the UK and Ireland over the past decade. The incidence of idiopathic PAH continued to increase over the past decade in the UK and Ireland, most likely reflecting increased referral to the pulmonary hypertension centres. Patients were still referred late with severe functional and haemodynamic impairment. Greater education is needed to raise awareness amongst the non-pulmonary hypertension community of the changing epidemiology of the disease.

We have used our incident study cohort of idiopathic, heritable and anorexigen-associated PAH to validate currently available survival prediction models in PAH. Our results suggested that some survival prediction models performed better than others.

We observed different phenotypic characteristics and survival between younger and older idiopathic, heritable and anorexigen-associated PAH patients. Baseline variables with prognostic significance were also different between younger and older idiopathic, heritable and anorexigen-associated PAH patients. Interestingly, obesity was associated with better survival in older patients but the contrary in younger patients.

We also explored the prognostic significance of short term improvement in six minute walk distance and functional class in response to treatment in incident idiopathic, heritable and anorexigen-associated PAH. Change in six minute walk distance after three months of pulmonary hypertension treatment was associated with improved survival in patients with low baseline six minute walk distance. Change in functional class at six months was also predictive of survival in our idiopathic, heritable and anorexigen-associated PAH patients.

Finally, we observed that pre-capillary pulmonary hypertension with co-existing lung disease patients who otherwise satisfied the usual haemodynamic and pulmonary function criteria for idiopathic PAH had significantly different demographics and worse survival compared with idiopathic PAH patients. Better characterisation of this subgroup of PH patients will avoid bias from inclusion of these patients as idiopathic PAH in future clinical trials.

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AUTHOR'S DECLARATION

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature _____

Printed Name _____

ABBREVIATIONS

Δ6MWD	change in six minute walk distance
6MWD	six minute walk distance
ALK-1	activin receptor-like kinase-1
BMI	body mass index
BMPR2	bone morphogenetic protein type 2 receptor
BNP	brain natriuretic protein
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CCB	calcium channel blockers
cGMP	cyclic guanosine monophosphate
CTEPH	chronic thromboembolic pulmonary hypertension
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CT	computerised tomography
CTD-PAH	connective tissue disease associated pulmonary arterial hypertension
DL_{CO}	diffusion capacity for carbon monoxide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ERA	endothelin receptor antagonists
ERS	European Respiratory Society
ESC	European Society of Cardiology
ET-A	endothelin receptor A
ET-B	endothelin receptor B
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FC	functional class
FVC	forced vital capacity
HIV	human immunodeficiency virus
HR	hazard ratio
IQR	interquartile range
IHD	ischaemic heart disease
IT	information technology

IV	intravenous
LV	left ventricle
mPAP	mean pulmonary arterial pressure
MRI	magnetic resonance imaging
NIH	National Institute of Health Registry
NO	nitric oxide
NT-proBNP	N-terminal pro brain natriuretic peptide
O_2	oxygen
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PAOP	pulmonary artery occlusion pressure
PD5	phosphodiesterase type 5
PD5i	phosphodiesterase type 5 inhibitor
PDGF	platelet derived growth factors
PH	pulmonary hypertension
PHC	Pulmonary Hypertension Connection
PVR	pulmonary vascular resistance
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RV	right ventricle
SC	subcutaneous
SMR	Scottish morbidity record
SPVU	Scottish Pulmonary Vascular Unit
SvO_2	mixed venous oxygen saturations
TAPSE	tricuspid annular planar systolic excursion
TGF-ß	transforming growth factor ß
TLC	total lung capacity
TPG	transpulmonary gradient
UK	United Kingdom
V/Q	ventilation/perfusion scan
WHO	World Health Organisation
WU	Woods unit

1 Chapter 1: Introduction

1.1 The Normal Pulmonary Circulation

The normal adult pulmonary vascular bed is a low pressure, low vascular resistance, highly distensible system capable of accommodating large increases in blood flow with minimal elevation in pulmonary artery pressure. The most important factors influencing pulmonary artery pressure are the hydrostatic pressure, intra-alveolar pressure, left atrial pressure and the alveolar gas. Normally, sixty percent of the resistance of the pulmonary circulation is in the arterial component; the capillaries and venous system account for the remaining forty percent (1). Systemic circulation, in contrast, is a high pressure system. As a result the left ventricle is larger and more muscular than the right.

Kovacs et al (2) reviewed published right heart catheterisation studies data on 1187 healthy individuals from forty seven studies in thirteen countries and concluded that normal mean pulmonary artery pressure (mPAP) at rest is 14 ± 3 mmHg and is independent of sex and ethnicity. Using the customary approach to define the upper limit of normal as mean plus two standard deviations, the upper limit of normal for mPAP is around 20 mmHg. The significance of mPAP at rest between 21 to 24 mmHg is currently unclear. At rest, there are negligible differences in mPAP between the different age groups. In contrast, mPAP during exercise is largely age-dependent, presumably as a result of increasing stiffness of the left ventricle and the pulmonary vessels (3). During mild exercise, mPAP is 19 ± 5 mmHg in subjects aged < 50 years compared with mPAP 29 ± 8 mmHg in subjects ≥ 50 years (2).

1.2 Definition of Pulmonary Hypertension

Pulmonary arterial hypertension is characterised by chronically elevated pulmonary artery pressure and pulmonary vascular resistance, leading to right ventricular failure and ultimately death. Pulmonary Hypertension is defined as

mPAP ≥ 25 mmHg at rest as assessed by right heart catheterisation (Table 1.1). This value was used for selecting patients in randomised controlled trials and registries of pulmonary arterial hypertension. Exercise and pulmonary vascular resistance criteria were removed from the latest definition of pulmonary hypertension (4).

Pulmonary hypertension can be found in multiple clinical conditions. The subgroup of pulmonary hypertension known as pulmonary arterial hypertension (WHO Group 1) is a clinical condition characterised haemodynamically by the presence of pre-capillary pulmonary hypertension in the absence of other causes of pre-capillary pulmonary hypertension (5). Current guidelines recommend using pulmonary artery occlusion pressure (PAOP) or left ventricular end-diastolic pressure ≤ 15 mmHg to define pre-capillary PH (4, 5) . A normal PAOP does not however rule out the presence of heart failure with preserved ejection fraction. Exercise or fluid challenge during right heart catheterisation may help to unmask the presence of left heart disease but lack standardisation and is not currently use routinely in the diagnostic work-up of patients. A comprehensive assessment taking into account past medical history, risk factors, echocardiographic and cardiac MRI parameters will provide a more reliable diagnosis of pulmonary arterial hypertension than a single PAOP measurement.

Table 1.1. Haemodynamic definitions of pulmonary hypertension (5).

Definition	**Characteristics**	**Clinical Group as per Dana Point Classification**
Pulmonary Hypertension	mPAP ≥ 25 mmHg	All
Pre-capillary PH	mPAP ≥ 25 mmHg PCWP ≤ 15 mmHg CO normal or reduced	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanism
Post –capillary PH Passive Reactive (out of proportion)	mPAP ≥ 25 mmHg PCWP > 15 mmHg CO normal or reduced TPG ≤ 12 mmHg TPG > 12 mmHg	2. PH due to left heart disease

Definition of abbreviations: CO = cardiac output, mPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PH = pulmonary hypertension, TPG = transpulmonary gradient.

1.3 Classification of Pulmonary Hypertension

The initial classification of pulmonary hypertension, proposed at the 1st World Symposium on pulmonary hypertension in Geneva (1973) designated only two categories: primary pulmonary hypertension when no underlying cause for pulmonary hypertension could be identified, and secondary pulmonary hypertension when an underlying cause or risk factor did exist (6). This WHO-sponsored conference was triggered by the previous epidemic of pulmonary hypertension associated with aminorex. Since then, the clinical classification of pulmonary hypertension has gone through a series of changes. At the second World Symposium on pulmonary hypertension held in Evian, France (1998), clinical conditions with pulmonary hypertension were classified into five groups ('Evian classification') based on shared pathophysiology, clinical features and treatment characteristics (7). This was further refined at the third World Symposium held in Venice, Italy in 2003 (8). At this meeting, the term idiopathic PAH was substituted for primary pulmonary hypertension, new associations with other rare conditions were recognised and the conditions of pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis were classified under PAH.

The fourth World Symposium on pulmonary hypertension took place in Dana Point, California 2008 (4). Familial PAH was replaced with heritable PAH, which included idiopathic PAH with germline mutations and familial cases with or without identified germline mutations. This new category of heritable PAH does not mandate genetic testing in patients with idiopathic PAH or in familial cases of PAH because this would not change the clinical management. Schistosomiasis and chronic haemolytic anaemia associated pulmonary hypertension were included among the 'associated PAH' category. Congenital heart disease causing PAH was updated to include a clinical and anatomical-pathophysiological version. Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis were felt to be distinct but not completely separable from the other subgroups of PAH and was therefore designated as clinical group 1'. No substantial changes were made to the other groups of pulmonary hypertension.

The Dana Point clinical classification of pulmonary hypertension is summarised in Table 1.2.

Table 1.2. Clinical classification of pulmonary hypertension (Dana Point classification 2008).

1. Pulmonary arterial hypertension (PAH) 1.1 Idiopathic 1.2 Heritable 1.2.1 BMPR2 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia) 1.2.3 Unknown 1.3 Drugs and toxins induced 1.4 Associated with PAH 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.4.6 Chronic haemolytic anaemia 1.5 Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2. Pulmonary hypertension due to left heart disease 2.1 Systolic dysfunction 2.2 Diastolic dysfunction 2.3 Valvular disease
3. Pulmonary hypertension due to lung disease and/or hypoxaemia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation 3.6 Chronic exposure to high altitudes 3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumour obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Definition of abbreviations: ALK-1 = activin receptor-like kinase 1 gene, BMPR2 = bone morphogenetic protein receptor type 2, HIV = human immunodeficiency virus, PAH = pulmonary arterial hypertension.

1.4 Pathology and Pathobiology of Pulmonary Arterial Hypertension

Pathological lesions in PAH affect the distal muscular pulmonary arteries (< 500μm of diameter). Pulmonary veins, capillaries, bronchial circulation, airways and the systemic vasculature are classically unaffected. Regardless of the underlying aetiology, all forms of PAH share the same spectrum of histopathological lesions characterised by medial hypertrophy, intimal proliferation, fibrotic changes (concentric and/or eccentric) and adventitial thickening with moderate perivascular inflammatory infiltrates. In advanced stages of pulmonary hypertension, cells originating from within the vessel wall (smooth muscle cells, endothelial cells and fibroblast) assemble in a 'plexiform' (9). These 'plexiform' lesions are often located downstream from the occluded arteries and express transcription and growth factors typically seen in angiogenesis. These angioproliferative 'plexiform' lesions are not found in other pulmonary hypertension categories.

Excessive vasoconstriction has been related to abnormal function or expression of potassium channels in the smooth muscle cells and to endothelial dysfunction. Endothelial dysfunction leads to chronically impaired production of vasodilator and antiproliferative substances such as thromboxane A_2 and endothelin-1. Complex molecular and cellular abnormalities result in vascular remodelling in which fibroblasts, smooth muscle cells, endothelial cells, inflammatory infiltrates (macrophages, lymphocytes and dendritic cells) and platelets all appear to play a role in PAH through a combination of migration, hypertrophy and proliferation (5, 10, 11). In the adventitia, there is increased production of extracellular matrix including collagen, elastin, fibronectin and tenascin. Prothrombotic abnormalities have been demonstrated in PAH patients and thrombi are present in both the distal pulmonary arteries and the proximal elastic pulmonary arteries. Together with the associated vasoconstriction and development of in-situ thrombosis, this proliferative and obstructive remodelling of pulmonary blood vessels lead to reduced capacity for vasodilatation and a decrease in cross sectional area of the pulmonary vascular bed. The progressive increase in pulmonary vascular resistance leads to increase in pulmonary artery

pressure, reduced exercise tolerance, right heart failure and in many advanced cases, premature death.

1.5 Pathophysiology of Pulmonary Arterial Hypertension

As described in the earlier section, the normal pulmonary circulation is a low pressure system with little or no resting vascular tone. Any increase in mean pulmonary artery pressure can be passive (due to increase in downstream pressure), hyperkinetic (due to increase in cardiac output through the lungs) or due to increase in pulmonary vascular resistance. Increase in pulmonary vascular resistance (PVR) occurred following reduction in the cross sectional area of proximal (mainly capacitive) and /or distal (mainly resistive) pulmonary arterioles. According to the Poiseuille's law, PVR is inversely related to the fourth power of the radius. PVR is therefore sensitive to small changes in the calibre radius. Increases in PVR may be fixed or potentially reversible. Arterial obstruction, obliteration and remodelling are responsible for the fixed component. Vasoconstriction, the reversible component is likely to be prevalent in a small group of patients responding to acute vasoreactivity test.

Poiseuille's law: $\text{Resistance} = \Delta P/Q = 8l\eta/\pi r^4$

where

P = pressure drop

Q = Flow

l = length

η = viscosity constant

r = internal radius

PVR = (mPAP – downstream pressure)/cardiac output

where

PVR = pulmonary vascular resistance, measured in Wood Units

mPAP = mean pulmonary arterial pressure

1.6 Genetics of Pulmonary Arterial Hypertension

Dresdale reported on cases of primary pulmonary hypertension from three members of the same family in 1954 and recognised that there may be a genetic component to PAH (12). Since then, significant advances have been achieved in understanding the genetic aspects of PAH. In 2000, the DNA sequence variations of the bone morphogenetic protein type II receptor (BMPR2) gene were reported by two separate groups of investigators (13, 14) . Heterozygous germline mutations in the BMPR2, a receptor from the transforming growth factor ß (TGF-ß) superfamily were detected in 70% - 80% of familial cases of PAH, and in up to 20% of sporadic cases (15, 16). TGF-ß superfamily comprises a large series of cytokine growth factors that control a host of cellular functions, amongst them, proliferation, migration, differentiation, apoptosis and extracellular matrix secretion and deposition (15).

Germline BMPR2 mutation is inherited as an autosomal dominant trait with incomplete penetrance, with multiple unaffected generations in a family pedigree (17). Only ~20% of BMPR2 mutation carriers will develop PAH, suggesting a 'second hit', either genetic or environmental, may be required to cause disease (11).

Genetic anticipation has also been reported in heritable PAH, where the disease occurs at earlier and earlier ages in subsequent generations (17). The usual mechanisms for genetic anticipation, namely trinucleotide repeat expansion and progressive telomere shortening have however failed to explain the apparent genetic anticipation in families with PAH. An alternative explanation is statistical artefact, where family members are diagnosed earlier and at a younger age through progressive improvement in clinical and genetic screening.

BMPR2 mutation carriers with PAH present approximately 10 years earlier than non-carriers, with more severe haemodynamic compromise at diagnosis but similar overall survival (16). BMPR2 mutation carriers are also less likely to demonstrate acute vasoreactivity in response to short-acting vasodilator such as inhaled nitric oxide (15, 18).

In addition to BMPR2 mutation, several other genotypes have been associated with the occurrence of PAH. Mutations in the two genes that cause Hereditary Haemorrhagic Telangiectasia (activin A receptor type II like kinase-1 [ACVRL1, also known as ALK1] and the endoglin gene) have both been reported to lead to heritable PAH (5, 19). Compared with other patients with PAH, ACVRL1 mutation carriers are younger at diagnosis (even younger than BMPR2 carriers), with less severe haemodynamics compromise but more rapid disease progression (20).

1.7 Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

Definition

Idiopathic PAH corresponds to sporadic disease in which there is neither a family history nor an identified risk factors for PAH (8). Heritable PAH includes sporadic idiopathic PAH with germline mutations and clinically familial cases with or without identified germline mutations (8). A number of drugs and toxins have been identified as risk factors for PAH (Table 1.3). Amongst these drugs, aminorex, fenfluramine, dexfenfluramine and benfluorex are definite risk factors for PAH. Patients with idiopathic, heritable and anorexigens-associated PAH shared similar clinical, functional and haemodynamic characteristics and overall survival (21) and are often studied together as a group (22, 23).

Table 1.3. Risk level of drugs and toxins known to induce PAH (5).

Definite	**Possible**
Aminorex Fenfluramine Dexfenfluramine Benfluorex Toxic rapeseed oil	Cocaine Phenylpropanolamine St John's Wort Chemotherapeutic agents Selective serotonin reuptake inhibitors Pergolide
Likely	**Unlikely**
Amphetamines L-tryptophan Methamphetamines	Oral contraceptives Oestrogens Cigarette smoking

1.8 Pulmonary Hypertension Registries and Epidemiology of Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

Disease registries describe the population characteristics (phenotypes and genotypes), disease frequencies (incidence and prevalence), outcomes (mortality and morbidity) and risk factors for that outcomes (24). In rare diseases like PAH, registries allow comparison of characteristics and outcomes in different patients population over time. Data from registries can also be used to predict outcomes of patients, generate hypotheses and develop prognostic equations. A number of pulmonary hypertension registries have existed over the past few decades. These registries differ in patient population and size, study design, period (before or after the availability of modern disease targeted therapies), duration of recruitment and geographical sites.

<u>The NIH registry:</u>

Information from the Division of Lung Disease of the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health registry on primary pulmonary hypertension (the Patient Registry for the Characterisation of Primary Pulmonary Hypertension, commonly referred to simply as the NIH registry) provided comprehensive data on the natural history of primary pulmonary hypertension. Primary pulmonary hypertension referred to patients now classified as idiopathic, heritable and anorexigen-associated PAH according to the latest updated Dana Point classification system (Table 1.2). The NIH registry was a multicentre, prospective registry where 194 patients from thirty two medical centres in the United States with the diagnosis of primary pulmonary hypertension were enrolled from between 1st July 1981 and 30th Sept 1985 and followed through to 8th August 1988 (25, 26). Baseline demographics, clinical characteristics, haemodynamics parameters and survival were reported for primary pulmonary hypertension in an era before the availability of pulmonary hypertension disease targeted therapies.

In the NIH registry, pulmonary hypertension was defined as mPAP > 25 mmHg at rest or >30mmHg with exercise at right heart catheterisation. Pulmonary capillary wedge pressure in excess of 12mmHg was considered as pulmonary venous hypertension and was excluded from the NIH registry.

The mean age of the NIH cohort was 36.4 years, with female to male ratio of 1.7:1. Female to male preponderance was much higher in the black population (4.3:1). Nine percent of the patients were diagnosed at the age of 60 or later. The incidence of familial cases in the NIH registry was 6.4%, with no distinctive features except shorter intervals from the onset of symptoms to diagnosis. 5% of patients in the NIH registry had histories of appetite suppressant drug use. The mean interval from onset of symptoms to diagnosis was 2.0 years (median 1.3 years) with a median survival of 2.8 years after diagnosis. Patients in the NIH registry had severe pulmonary hypertension with mPAP of 60mmHg, cardiac index of 2.3 $L.min^{-1}.m^{-2}$ and pulmonary vascular resistance index of 26 $WU.m^{-2}$. Estimated 1, 3 and 5 year survival rates were 68%, 48% and 34% respectively. 36% of patients in the NIH registry were 'prevalent' cases who had their diagnosis of primary pulmonary hypertension made prior to the establishment of the registry. Newly diagnosed ('incident') patients in the NIH registry also had a shorter survival compared with 'prevalent' patients (median survival of 2.6 years vs. 3.2 years) although the result was not statistically significant.

Variables associated with poor survival in the NIH registry included New York Heart Association functional class of III or IV, presence of Raynaud's phenomenon, elevated mean right atrial pressure, elevated mean pulmonary artery pressure, decreased cardiac index and decreased diffusion capacity for carbon monoxide (DL_{CO}). Gender was not associated with survival in the NIH registry. Data from the NIH registry was used to develop a prognostic equation (commonly referred as the NIH equation) that estimates the probability of survival of primary pulmonary hypertension over a three year period (26).

<u>International Primary Pulmonary Hypertension Study:</u>

The NIH registry was followed by the International Primary Pulmonary Hypertension Study which recruited 95 newly diagnosed primary pulmonary

hypertension patients aged between 18 to 70 years from two hundred and twenty centres in the United Kingdom, France, Belgium and Netherlands between 1st September 1992 and 30th September 1994 (27). This was a prospective case-control study designed to explore the relationship between various risk factors, especially anorexigens and primary pulmonary hypertension. The mean age of primary pulmonary hypertension patients were 44.7 years with female: male ratio of 2.3:1. This study confirmed the strong association between primary pulmonary hypertension and the use of appetite suppressants, primarily the fenfluramine derivatives. In nearly two third of patients, the diagnosis was not established until more than a year after the onset of symptoms. This registry also provided the first estimates of incidence of idiopathic PAH (1.7 cases per million population per year in Belgium).

The Swiss Registries:

The first Swiss registry was a retrospective analysis of 106 pulmonary hypertension patients diagnosed in Switzerland from 1991 to 1999 (28). Disease subtypes other than idiopathic PAH were included (primary pulmonary hypertension 37%, venous thromboembolism 15%, collagen vascular disease 22%, congenital heart disease 4% and HIV/anorexigens/portal hypertension 22%). In that study, a significant minority (16%) had no right heart catheterisation and prostacyclin was the only disease targeted therapy available.

This was followed by a prospective Swiss registry from January 1999 to December 2004 where a total of 250 patients with pulmonary hypertension (defined as mPAP of >25mmHg at rest or >30mmHg on exercise) were followed up for median of 18.8 months (29). Other subtypes of PAH were included, with idiopathic and familial PAH comprising 28% (n=70) of the whole cohort. 10% of all patients were lost to follow up and a significant number (28%) were diagnosed without right heart catheterisation in the later Swiss Registry. In the later Swiss registry, patients were also older compared with the earlier Swiss registry. Further subgroup analysis of idiopathic PAH in the later Swiss registry found 64% of idiopathic PAH being female, 66% were over age 50 years old and 90% presented late in functional class III and IV. Estimated incidence of idiopathic PAH in Switzerland was 0.8 patients per million adult in 1999 and 1.2 per million

in 2004. The estimated prevalence of idiopathic PAH in Switzerland in 2004 was 8.6 per million adult inhabitants.

The Chinese Registries:

Information on pulmonary hypertension in the developing countries is relatively sparse. The first Chinese registry reported on outcomes of 72 patients with idiopathic or familial PAH who were followed at two institutions in China from January 1999 to Oct 2004 (30). PAH was defined as mPAP>25 mmHg at rest by right heart catheterisation or systolic pulmonary arterial pressure >40 mmHg by echocardiography. Only 28% (n=20) of patients had their initial diagnosis confirmed by right heart catheterisation and a similar number of patients were lost to follow up. The mean age was 35.9 years with female: male ratio of 2.4:1. Mean duration of symptoms to diagnosis was 2.2 years. Only conventional treatment such as calcium channel blockers, diuretics, digoxin and anticoagulation were available during the study period. Not surprisingly, the survival data from this study (1 year survival of 68.0% and 3 year survival of 38.9% in idiopathic and heritable PAH) was worse compared to other more recent registries but comparable to the NIH data.

After 2006, several types of PAH targeted therapies, including bosentan, sildenafil and epoprostenol became available in China. Data on demographics, haemodynamic characteristics and survival of idiopathic PAH in the modern treatment era in China was recently updated in a retrospective observational study (31). In this second later Chinese registry, PAH was defined as mPAP ≥ 25 mmHg at rest or ≥ 30 mmHg on exercise, pulmonary capillary wedge pressure ≤ 15 mmHg and PVR > 3 WU. 173 incident idiopathic PAH patients were diagnosed between 2007 and 2009 at five national referral pulmonary vascular centres in China. Patients had severe haemodynamic impairment (mPAP 63 mmHg, cardiac index 2.5 $L.min^{-1}$, PVR 17 Wood units) and presented late after mean delay of 3.4 years after onset of symptoms. In contrast to contemporary pulmonary hypertension registries from Europe and United States where the average age of patients was around 50 years old (32-35), Chinese idiopathic PAH patients in this second later Chinese registry were much younger, with mean age of 33.4 years. The age discrepancy for Chinese patients compared with contemporary European

and United States data may be partly explained by referral bias. Symptoms of older Chinese patients may be attributed to other co-morbid conditions and therefore less likely to be referred for suspicion of PAH. Healthcare coverage are uneven or inadequate and the tremendous cost of PAH targeted therapies posed a significant economic burden to many Chinese patients. Majority of patients were treated with a phosphodiesterase type 5 inhibitor (31.2% received sildenafil, 30.0% vardenafil; 17.3% bosentan and 0.2% iloprost). Despite these challenges, Zhang et al reported a significant improvement in survival of patients in the later Chinese registry compared with the earlier 2007 Chinese registry (31). In the modern treatment era, 1- and 3- year survival estimates of idiopathic PAH in China had improved to 92.1% and 75.1% respectively.

Multivariate analysis of the whole cohort in the second later Chinese registry (173 idiopathic PAH and 103 connective tissue-associated-PAH[CTD-PAH] found the diagnosis of CTD-PAH, WHO functional class III and IV, DL_{CO} < 80% predicted and the presence of pericardial effusion to be independent predictor of survival. Age, gender, six minute walk distance and mPAP were not predictive of survival in multivariate analysis.

The Israeli Registry:

A small registry was reported from Israel on primary pulmonary hypertension diagnosed between the years 1988-1997 (36). The study was retrospective and numbers were small (44 patients in total), reflecting the rarity of the condition. The mean age was 42.8 years with female: male ratio of 3.4:1. The treatment received was mostly vasodilator (mostly nifedipine) and only 6 patients (13%) received prostacyclins and 3 received transplantation. Median survival time was 4 years with 1, 3 and 5 year survival rates of 82%, 57% and 43% respectively. Duration of symptoms and haemodynamic variables (mean pulmonary artery pressure, right atrial pressure and cardiac index) were associated with survival whereas gender and age at diagnosis were not. The estimated incidence and prevalence of idiopathic PAH in Israel were 1.4 and 8 patients per million population respectively.

The Scottish Registry:

The Scottish registry reported on the epidemiological features of PAH in Scotland, using hospitalisation data from the Scottish Morbidity Record (SMR) scheme (1986 to 2001) and separate data from the Scottish Pulmonary Vascular Unit (SPVU) to provide estimations of incidence and prevalence (32). The study was retrospective in design. Prevalence estimates of PAH was higher from the SMR data. The hospitalisation data from the SMR may over-estimate the disease prevalence as data from the SMR scheme relied on accurate coding of hospital admissions and the assumption of recorded diagnoses being accurate. Based on the SPVU data, estimated incidence and prevalence of idiopathic PAH in the Scottish population were 2.6 and 9 cases per million in 2005. Despite similar inclusion and exclusion criteria, estimates of incidence and prevalence of PAH and idiopathic PAH from the Scottish registry were higher compared with estimates from all other registries.

The French Registry:

In the early 2000s, the French Network on Pulmonary Hypertension registry (commonly referred as the French registry) was established (33). This was the first major multicentre registry of pulmonary hypertension since the availability of pulmonary hypertension disease targeted therapies. PAH was defined as mPAP > 25 mmHg at rest and pulmonary capillary wedge pressure < 15 mmHg at right heart catheterisation. Patients with severe pulmonary function abnormalities (defined as % predicted FEV_1, % predicted FVC or % predicted total lung capacity <60%) were excluded from the French registry.

A total of 674 cases of PAH presented at seventeen University pulmonary vascular centres in France between October 2002 and October 2003 were prospectively enrolled and followed up for three years. Delay between onset of symptoms and diagnosis for the whole PAH cohort was 2.3 years. 39% of the French registry were idiopathic, heritable and anorexigen-associated PAH (n=354) with the rest comprising of connective tissue disease associated PAH (15.3%), congenital heart disease PAH (11.3%), portopulmonary hypertension (10.4%), HIV associated PAH (6.2%) and two co-existing risk factors (4.3%). The

mean age of idiopathic PAH was 52 years, with 62% female and 81% presenting late in NYHA class III and IV.

The French registry included patients who were newly diagnosed during the recruitment phase of the registry (incident cases, 18%) as well as patients with established diagnosis of PAH before enrolment in the registry (prevalent cases, 82%). Not all patients with pulmonary hypertension in France may be included as some patients may have good response to oral treatment outside the study centres and were never referred. There was a wide variation of prevalence, with the highest prevalence seen in Paris (the region with the best known and largest pulmonary hypertension centre). In fact, 64% of all cases in the French registry come from one Paris Centre alone, suggesting an element of selection bias. The prevalence of idiopathic PAH was estimated at 5.9 cases per million population.

Recently, combined 3 year follow-up data on idiopathic, heritable and anorexigen-associated PAH from the same cohort was reported. There was clear distinction between incident and prevalent idiopathic, heritable and anorexigen-associated PAH patient, with incident patients displaying worse overall survival (37). In prevalent idiopathic, familial and anorexigen-associated PAH, 1-, 2- and 3-year survival rates were 89%, 77% and 69%. In incident patients, 1-, 2- and 3-year survival rates were 89%, 68% and 55% respectively. Moreover, within the prevalent population, patients in whom the diagnosis of PAH were most recently made had worse survival when compared with those with longer duration of disease prior to inclusion in the study (37).

The survival of idiopathic, heritable and anorexigen-associated PAH in the French registry was lower compared with the survival from other pulmonary hypertension registries in the disease targeted therapy era. This may be partly explained by the availability of treatment in France during the duration of the French registry. Bosentan became available only around late 2002, inhaled iloprost around late 2003/early 2004 and sildenafil around late 2005/early 2006 in France.

Multivariate analysis showed female gender, greater 6MWD and higher cardiac output were associated with better survival in idiopathic, heritable and

anorexigen-associated PAH (22). Outcome data from 56 incident patients and 134 prevalent patients with idiopathic, heritable and anorexigen-associated PAH who were diagnosed < 3 years prior to enrolment to the French registry were combined to develop a survival prediction equation (commonly referred as the French equation) (37).

The Pulmonary Hypertension Connection Registry:

The Pulmonary Hypertension Connection (PHC) registry was initiated in 2004 in Chicago, United States and comprised of 578 patients with group I PAH from 1982 to 2006 (23, 34). Patients were entered retrospectively from 1982 to 2004 and prospectively thereafter. There are a few limitations to that registry. It was based on patients referred to the authors' practice at a single tertiary centre. It was largely an observational, retrospective study and standardised diagnostic procedures were not followed (eg use of exercise threadmill testing instead of six minute walk test), making comparisons with other registries difficult and may not reflect routine clinical practice.

Baseline right heart catheterisation data was available in 90% of patients. Only 14% of the whole study cohort was incident cases (defined in that study as patients diagnosed between 2004 and 2006). Idiopathic and heritable PAH made up 49.0% (n=282) of all cases (23). Patients were older compared with the NIH registry (mean age of idiopathic, heritable and anorexigen-associated PAH in the PHC registry was 46 years vs 36 years in the NIH registry). Data from the PHC registry also suggested PAH can occur at a relatively later age, with 8.5% of all PAH patients diagnosed after 70 years of age (individual results for idiopathic, heritable and anorexigen-associated PAH were not reported). Female: male ratio of idiopathic, heritable and anorexigen-associated PAH was 3:1 in the PHC registry. The female preponderance of idiopathic, heritable and anorexigen-associated PAH was much higher in the PHC registry compared with the NIH (25) (female: male ratio 1.7:1), the Scottish (32) (female: male ratio 1.7:1) and the French (22) (female: male ratio 1.5:1) registries. 1-, 3- and 5- year survival of idiopathic, heritable and anorexigen-associated PAH from the PHC registry were 91%, 75% and 65% respectively (23). Patients diagnosed after 2002 exhibited better survival than those diagnosed before 2002. Age, functional class, mean

right atrial pressure and cardiac index were independent predictors of survival in idiopathic, heritable and anorexigen-associated PAH. Survival data from the idiopathic, heritable and anorexigen-associated PAH subgroup was used to develop a new survival prediction equation (commonly referred as the Pulmonary Hypertension Connection equation) (23).

The REVEAL registry:

The Registry to Evaluate Early and Long-term PAH Disease Management (commonly referred as the REVEAL registry) is the largest to date on-going registry in the United States on PAH (35, 38). Group 1 PAH patients were enrolled from fifty four centres in the United States between March 2006 and December 2009, with follow-up planned until 2014. Diagnosis was assigned by the investigators enrolling subjects into the registry, based upon their impression of the most likely cause of a patient's PAH. Patients were classified as newly diagnosed (incident cases) PAH in the REVEAL registry if the diagnostic right heart catheterisation occurred within the previous 90 days.

PAH was defined as mPAP > 25 mmHg at rest or > 30 mmHg with exercise, pulmonary capillary wedge pressure < 15 mmHg and pulmonary vascular resistance > 3 Wood Units. The REVEAL registry also included an expanded criteria for patients with pulmonary capillary wedge pressure of 16-18 mmHg.

The mean time from onset of symptoms to diagnostic right heart catheterisation amongst patients who met traditional haemodynamic criteria for PAH (n=2525) were 34.1 months (median 13.6 months). Amongst the 1166 patients with idiopathic PAH, only 15% were incident patients. Mean age of idiopathic PAH at diagnosis in the REVEAL registry was 50 years. This was older compared with the NIH registry but comparable to the more recent cohorts of idiopathic PAH from the French, Scottish and PHC registries. Female: male ratio of idiopathic PAH was 4.1:1 in the REVEAL registry. This female preponderance was even more marked amongst the blacks (female: male ratio of 5.2:1) and Hispanic (female: male ratio of 5.6:1) idiopathic PAH populations in the REVEAL registry (38). The greater female preponderance in the REVEAL registry is not fully understood. It may be partly due to its large prevalent population. Female: male ratio in the

REVEAL registry increases with survival post diagnosis, with 3.3:1 within a year of diagnosis to 4.3: 1 at > 5 years after diagnosis.

Idiopathic PAH in the REVEAL registry also have multiple co-morbidities including hypertension (42%), obesity (38%), sleep apnoea (27%), obstructive airway disease (23%), thyroid disease (20%), diabetes (14%) and ischaemic cardiovascular event (10%) (35). Interestingly, nearly 10% of idiopathic PAH in the REVEAL registry also had an associated connective tissue or collagen vascular disease. Despite older age at diagnosis and higher female preponderance, haemodynamic parameters at the time of diagnostic right heart catheterisation in the REVEAL registry have not changed substantially compared with patients from the NIH era (38). 1-, 3- and 5-year survival rates of idiopathic and heritable PAH patients in the REVEAL registry were 91%, 74% and 65% respectively (39).

Based on data from the REVEAL registry, the low estimate for incidence of idiopathic and familial PAH in the United States was 1.1 cases per million. The true incidence of PAH is likely to be higher as patients seen outside pulmonary hypertension centres or seen in centres not participating in the REVEAL registry were not included.

Data from group 1 PAH in the REVEAL registry was also used to derive a new survival equation (commonly referred as the REVEAL equation) and a simplified survival score (commonly referred as the REVEAL risk score).

<u>The Spanish Registry:</u>

The recently published Spanish REHAP (Spanish Registry of Pulmonary Arterial Hypertension) registry provided further insights into the epidemiology of PAH (40). A total of 866 PAH and 162 chronic thromboembolic pulmonary hypertension patients evaluated in thirty one Spanish hospitals between 1998 and 2008 were included. 30% of patients in the REHAP registry (n=314) were idiopathic PAH. Three centres contributed 61% of patients in this registry. Patients diagnosed in the period 1998 – 2006 were entered retrospectively and prospectively thereafter. Patients were classified as newly diagnosed (incident) if the diagnostic right heart catheterisation took place between July 2007 and

June 2008. 16.2% of all cases were incident patients. Patients were also diagnosed late in the course of their disease, with delay of 2.2 years after onset of symptoms in incident PAH patients. In the idiopathic PAH population, observed survival was 89% at 1 year and 77% at 3 year. Male gender, functional class, mean right atrial pressure and cardiac index were independent predictors of survival in PAH. Estimated incidence and prevalence of idiopathic PAH in Spain were 1.2 and 5.6 per million population. The applicability of the NIH equation, French equation, PHC equation and REVEAL equation were also tested in this study. Observed survival of this Spanish cohort was similar to survival predicted from the PHC equation. The French equation slightly underestimated survival whereas the REVEAL equation over-estimated survival of the Spanish cohort.

Each pulmonary hypertension registry was defined by its unique strengths and weaknesses. The NIH registry was a landmark accomplishment, but the data may no longer be applicable to real life patients seen in current day to day practice. A few of the smaller registries were set up from the late 1980s to the early 20th century had small patient numbers and were done in an era where current disease targeted therapy were not readily available or affordable to the patients. Direct comparison of baseline demographics and characteristics of patients from different registries was also complicated by the changing definition of PAH. Inclusion of prevalent subjects in many registries may lead to underestimation of mortality. Very few pulmonary hypertension registries were truly national studies, inclusive of all pulmonary hypertension patients within a single country or region. This may potentially introduce further selection bias and underestimate incidence and prevalence of the disease.

To summarize, results from pulmonary hypertension registries to date suggest idiopathic PAH is increasingly been recognised and diagnosed in older population. This may be the result of more elderly patients been referred as better modern treatments are now available and increased awareness of PAH as a potential contributing cause of elderly patients' symptoms. However, striking differences in certain baseline demographic characteristics were observed between the NIH, REVEAL, French and other US and European registries. The

underlying cause for such differences is not clear. Despite recent advances in diagnosis and treatment over the past 30 years, there remained significant delay between the onset of symptoms and diagnosis, with majority of patients presenting in advance state with severe haemodynamic and functional compromise. On a positive note, overall survival of idiopathic PAH has significantly improved in the era of modern therapy.

Table 1.4. Epidemiology of PAH and idiopathic PAH.

Registry	Country	Year	Incidence per million per year		Prevalence per million population	
			Idiopathic PAH	PAH	Idiopathic PAH	PAH
IPPHS	Belgium	1992-1994	1.7	-	-	-
Israeli	Israel	1988-1997	1.4	-	8	-
Swiss	Switzerland	1999 2004	0.8 1.2	1.2 3.5*	- 8.6	- 15.5*
French	France	2002-2003	-	2.4	5.9	15
Scottish	Scotland	2005	2.6	-	9	-
REVEAL	United States	2006-2007	1.1	2.3	-	12.4
Spanish	Spain	2007-2008	1.2	3.7	5.6	16

Definition of abbreviations: IPPHS = International Primary Pulmonary Hypertension Study Group, PAH = pulmonary arterial hypertension, REVEAL = The Registry to Evaluate Early And Long-term PAH disease management.

* includes group 1 PAH, pulmonary hypertension with chronic lung disease, chronic thromboembolic pulmonary hypertension and pulmonary hypertension due to miscellaneous disorders.

Table 1.5. Baseline characteristics and survival of idiopathic pulmonary arterial hypertension in major pulmonary hypertension registries.

Registry	NIH	French	PHC	REVEAL	Spanish
Year of recruitment	1981-1985	2002-2003	1982-2006	2006-2007	2007-2008
% incidence	64%	16%	14%	15%	16%
No of idiopathic PAH patients	187	354	282	1166	314
Age, years	36	52	46	50	46
% female	63%	62%	76%	80%	73%
% in FC III and IV at diagnosis	71%	81%	82%	55%*	70%
6MWD at diagnosis	-	328	-	374*	382
Haemodynamics					
RAP	9	8§	11	10	8
mPAP	60	52§	55	52	55
CI	2.3	2.2§	2.0	2.2	2.4
PVR	-	-	14	-	12
PVRI	-	21.9§	-	23	-
Survival of IPAH					
1 year	68%	89%§	91%	91%	89%
3 year	48%	55%§	75%	74%	77%
5 year	34%	-	65%	65%	68%

Definition of abbreviations: 6MWD = 6-minute walk distance, CI = cardiac index, FC = WHO functional class, mPAP = mean pulmonary artery pressure, PAH = pulmonary arterial hypertension, PVR = pulmonary vascular resistance, PVRI = pulmonary vascular resistance index, RAP = right atrial pressure

*at enrolment, §incident idiopathic, heritable and anorexigen-associated PAH cohort of the French registry.

1.9 Clinical Presentation of Pulmonary Arterial Hypertension

The most common initial symptom of PAH is breathlessness on exertion (25, 27). Other common initial symptoms include fatigue, chest pain, near syncope, syncope, leg oedema and palpitation (25). Clinical signs consistent with pulmonary hypertension such as loud second pulmonary heart sound, right-sided third heart sound, left parasternal lift, pansystolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary regurgitation may be present. Evidence of right heart failure such as elevated jugular venous pressure, peripheral oedema, ascites, hepatomegaly, systemic hypotension and cool extremities may be seen in more advanced state. Clinical signs may be subtle despite the presence of significantly elevated pulmonary hypertension.

1.10 Investigations of Pulmonary Arterial Hypertension

The evaluation process of a patient with suspected pulmonary arterial hypertension requires a series of investigations to confirm the diagnosis, to clarify the clinical diagnosis group and the specific aetiology within the PAH group, and to evaluate the severity of functional and haemodynamic impairment.

Pulmonary function tests

Pulmonary function tests are useful to exclude chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease. Screening overnight oximetry or polysomnography is useful in patients where significant obstructive sleep apnoea/hypopnoea is suspected. In the NIH registry, idiopathic PAH patients had mild restrictive pattern (forced vital capacity was 82% of predicted) with reduced diffusion capacity for carbon monoxide (mean 69% of predicted) and hypoxaemia with hypocapnia (25).

Electrocardiography

The electrocardiogram (ECG) in idiopathic PAH may show evidence suggestive of pulmonary hypertension: right atrial dilatation, right axis deviation, right ventricular hypertrophy and strain. A normal ECG does not exclude the presence of pulmonary hypertension or presence of significant haemodynamic abnormalities (5). Most patients are in sinus rhythm (25). Supraventricular arrhythmias such as atrial flutter or atrial fibrillation may be present in advanced stages and usually leads to further clinical deterioration (5).

Chest X ray

Typical chest X ray findings in PAH include central pulmonary arterial dilatation, prominent hila from enlarged pulmonary arteries, enlarged right heart and pruning of the peripheral vessels due to reduced blood flow in the lung periphery secondary to high peripheral resistance. Chest X ray may also show evidence suggestive of chronic lung diseases and pulmonary venous hypertension.

Echocardiography

Echocardiogram is the definitive screening test for the presence of pulmonary hypertension (Table 1.6). It allows non-invasive assessment of the cardiac size and function. The peak pressure gradient of tricuspid regurgitation can be estimated based on the simplified Bernouli equation, where pressure gradient of the tricuspid regurgitation = 4 x (tricuspid regurgitation velocity)^2. Pulmonary

artery systolic pressure can then be estimated after taking into account the right atrial pressure: Pulmonary artery systolic pressure = tricuspid regurgitation pressure gradient + estimated right atrial pressure. A fixed value of 5 or 10 mmHg is often assumed for the right atrial pressure. Although a useful screening test, echocardiogram may be inaccurate in estimating the pulmonary artery pressure in nearly 50% of cases (41). Other echocardiographic variables suggestive of pulmonary hypertension include increased velocity of pulmonary valve regurgitation, short acceleration time of RV ejection into the pulmonary artery, increased dimensions of right heart chambers, increased RV wall thickness and dilated main pulmonary artery. Additionally, a poor outcome can also be predicted by the presence of pericardial effusion, increased right atrial size and reduced tricuspid annular planar systolic excursion (TAPSE) (5).

Table 1.6. Arbitrary criteria for estimating the presence of pulmonary hypertension based on tricuspid regurgitation peak velocity and Doppler-calculated pulmonary arterial systolic pressure at rest (assuming a normal right atrial pressure of 5mmHg) (5).

Echocardiographic findings:	
Tricuspid regurgitation velocity ≤ 2.8 m/s, PA systolic pressure ≤ 36 mmHg, and no additional echocardiographic variables suggestive of PH	PH unlikely
Tricuspid regurgitation velocity ≤ 2.8 m/s, PA systolic pressure ≤ 36 mmHg, but presence of additional echocardiographic variables suggestive of PH Tricuspid regurgitation velocity 2.9 – 3.4 m/s, PA systolic pressure 37 - 50 mmHg, With or without additional echocardiographic variables suggestive of PH	PH possible
Tricuspid regurgitation velocity >3.4 m/s, PA systolic pressure > 50 mmHg, With or without additional echocardiographic variables suggestive of PH	PH likely

Definition of abbreviations: PA = pulmonary arterial, PH = pulmonary hypertension

Isotope ventilation perfusion scan

The ventilation/perfusion (V/Q) scan is used to distinguish chronic thromboembolic pulmonary hypertension (CTEPH) from other causes of pulmonary hypertension. In CTEPH, the V/Q scan shows multiple mismatched segmental or larger perfusion defects. A normal V/Q scan effectively excludes CTEPH. In idiopathic PAH, the V/Q scan is usually normal or shows heterogeneous perfusion (42).

Computed Tomography (CT)

An absolute pulmonary artery (PA) diameter of > 29 mm or ratio between PA and ascending aorta >1 is supportive of pulmonary hypertension (42). Cardiac abnormalities may also be demonstrated on CT. In pulmonary hypertension of any cause, dilatation of the right heart chambers, right ventricular hypertrophy, flattening or reversal of the interventricular septum, presence of pericardial effusion and reflux of contrast into the inferior vena cava may be seen. Left atrial and ventricular dilatation may be seen in pulmonary hypertension secondary to left heart disease. High resolution CT is useful in assessing the lung parenchyma and contrast CT pulmonary angiography is helpful to exclude thromboembolic disease.

Cardiac Magnetic Resonance Imaging (MRI)

Cardiac MRI allows accurate quantification of the right ventricle (RV) geometry, RV mass, RV function and assessment of pulmonary artery flow and distensibility. RV end-diastolic volume, stroke volume and left ventricular end-diastolic volume at baseline are predictive of mortality in idiopathic PAH (43). There are also increasing evidence to support the role of MRI in monitoring the effects of PAH treatment on the RV over time (43).

Exercise testing

The six minute walk test and cardiopulmonary exercise testing are the two most common tests used in clinical practice and research trials to assess exercise capacity in patients with pulmonary hypertension.

i. Six minute walk test

The six minute walk test is an unencouraged, self-paced test that determines submaximal exercise capacity. Patients are asked to walk on a flat surface for 6 minutes, covering as much distance as possible at their own pace. It is non-invasive, easy to perform and reproducible. Improvement in 6MWD over a treatment period of three to four months has been used as the primary endpoint in majority of randomised controlled trials studying novel PAH treatments.

The 6 minute walk distance (6MWD) can be affected by many factors, including age, gender, height, weight, learning effect, patient motivation, general fitness, and musculoskeletal conditions. Its use may be limited in young paediatric patients and in patients with milder or early disease who may have a relatively high baseline 6MWD (the 'ceiling' effect) (44). Degano et al studied 49 patients with idiopathic, heritable and anorexigen-associated PAH who walked > 450m at the time of diagnosis and found treatment improved haemodynamics and functional class but had no significant effect on 6MWD in these group of patients with 'high' baseline walk (45).

Baseline 6MWD is predictive of survival in idiopathic PAH, and also correlates with WHO functional class and haemodynamic parameters (33, 46). Higher 6MWD on treatment has also been associated with better survival (46-48). In a study of 178 primary pulmonary hypertension patients treated with long term epoprostenol therapy, absolute values of 6MWD > 380 m correlated with better survival whereas change in 6MWD from baseline did not (48).

Although widely used to assess response to treatment, no randomised clinical trial for PAH has ever shown that the change in 6MWD had any relationship with survival. A recent meta-analysis of 16 randomised controlled trials in PAH has also not found any correlation between change in 6MWD and survival (49). Another meta-analysis of 22 randomised controlled trials in PAH studied the

relationship between change in 6MWD and outcomes and found improvement in 6MWD did not reflect benefits in clinical outcomes (50).

There is also currently no consensus view on what constitutes a clinically important or relevant change in 6MWD. Mathai et al analysed data from the Pulmonary Hypertension Response to Tadalafil trial and found an improvement in 6MWD of 33 metres was associated with improvement in quality of life measures (51). Another study that pooled results from ten randomised clinical trials of PAH-targeted therapy found clinically meaningful change of 6MWD to be 42 metres (52). The magnitude of improvement in 6MWD is also greater in treatment naive patients compared with patients already receiving background therapy.

Despite its shortcomings, it is currently the only Food and Drug Administration(FDA) and European Agency for the Evaluation of Medicinal Products accepted exercise end-point for studies evaluating treatment effects in PAH.

ii. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is another non-invasive assessment of cardiopulmonary and metabolic adaptation to exercise. Gas exchange and ventilation are continuously recorded throughout incremental exercise. CPET can be performed on a cycle ergometer or a treadmill. Impaired O_2 transport and ventilation/perfusion mismatching contribute to impaired exercise tolerance in PAH. Typical CPET findings in PAH patients include reduced O_2 uptake at anaerobic threshold and peak exercise, reduced peak O_2 pulse (VO_2/HR), peak work rate, peak heart rate and ventilatory efficiency. Wensel et al showed peak VO_2 < 10.4mL/min/kg and peak systolic blood pressure below 120 mmHg to be independent predictors of poor outcome in idiopathic PAH (53). One major limitation of CPET is the lack of standardisation in the determination of key CPET parameters.

<u>Right heart catheterisation</u>

Right heart catheterisation is required to confirm the diagnosis of pulmonary arterial hypertension. It allows appropriate classification of the disease, provides accurate assessment of the severity of the disease and allows selection of appropriate therapy. This is performed using a Swan-Ganz thermodilution catheter. The catheter is inserted into a central vein and floated through the right heart chambers into the pulmonary artery. The following variables are measured during right heart catheterisation: right atrial pressure, right ventricular pressure, pulmonary artery pressure and pulmonary capillary wedge pressure. Pulmonary vascular pressures are measured at end-expiration when the lungs are at functional residual capacity. Cardiac output is measured by thermodilution or by the Fick method. Sampling of oxygen saturations from different sites will help to identify any 'step-up' or 'step-down' in oxygen saturation to detect and quantify shunting. Transpulmonary gradient (TPG) and pulmonary vascular resistance are derived from the following equations:

TPG = mPAP – pulmonary capillary wedge pressure

PVR = TPG/CO

where

TPG = transpulmonary gradient

mPAP = mean pulmonary artery pressure

PVR = pulmonary vascular resistance

CO = cardiac output

Acute vasoreactivity testing should be performed at the time of right heart catheterisation in PAH to identify patients who may benefit from long term calcium channel blockers. Acute vasoreactivity is most commonly performed using inhaled nitric oxide. A positive acute response is defined as a reduction of mPAP ≥ 10 mmHg to reach an absolute value of mPAP ≤ 40 mmHg with increased or unchanged cardiac output. Only ~10% of idiopathic PAH are acute responders and about half of these acute responders are also positive long term responders to calcium channel blockers.

1.11 **Treatment of Pulmonary Arterial Hypertension**

Conventional (supportive) therapies

These include oral anticoagulants, diuretics, digoxin and oxygen, in addition to general measures to help alleviate symptoms (5). Patients with idiopathic PAH should avoid pregnancy. In-flight oxygen is recommended for pulmonary hypertension patients in functional class III and IV (54).

Calcium channel blockers

Acute vasoreactivity testing performed during right heart catheterisation identified patients who may benefit from long term therapy with calcium channel blockers (CCB). Long term therapy with CCB should only be started in positive acute responders (~10% of patients with idiopathic PAH). The choice of CCBs is based on patient's heart rate at baseline, with a relative bradycardia favouring nifedipine and a relative tachycardia favouring diltiazem. About half of the positive acute responders are also positive long term responders to calcium channel blockers (55) and only in these patients is the continuation of long term CCBs as a single agent warranted.

Disease targeted therapies

In the United Kingdom and Ireland, there are currently seven approved PAH targeted drugs with different routes of administration (Table 1.7). The approval of additional drugs is expected in the near future. The currently approved disease targeted treatments fall into 3 classes: prostacyclin and its analogues that target the prostacyclin pathway, phosphodiesterase 5 inhibitors that target the nitric oxide pathway and endothelin receptor antagonists that target the endothelin-1 pathway. Each of these classes of drugs has demonstrated benefits in randomised controlled trials to show benefit in haemodynamics, 6MWD and functional class.

No randomised controlled trials in PAH have been designed with mortality as a primary endpoint because of the limited number patients that can be recruited into clinical trials worldwide. Most randomised clinical trials of PAH targeted therapies were of three to four months duration only. Survival benefit was

observed in only one randomised controlled trial of intravenous (IV) epoprostenol in severe idiopathic PAH. Based on this result, IV epoprostenol is used as a rescue therapy (47) and subsequent randomised controlled trials assessing mortality as endpoint could not ethically be performed. Clinical trials also included mainly prevalent patients with stable disease resulting in low mortality in the study population. Nevertheless, meta-analysis of 23 randomised controlled trials suggest that treatment with disease targeted therapies (after an average treatment period of 14.3 weeks) improved survival in PAH, with 43% reduction in mortality and 61% reduction in hospital stays (56). Data from pulmonary hypertension registries also suggested improved survival of PAH in the modern era of treatment compared with historical cohorts (22, 33, 57).

Table 1.7. Currently available PAH disease targeted therapies in the UK and Ireland.

Treatment	Route of administration
Epoprostenol	IV
Treprostinil	Inhaled, IV, SC
Iloprost	Inhaled, IV
Bosentan	oral
Ambrisentan	oral
Sildenafil	oral
Tadalafil	oral

Definition of abbreviations: IV = intravenous, SC = subcutaneous.

Prostacyclins and analogues:

Prostacyclin (epoprostenol, PGI_2) is an arachidonic acid derivative that is abundantly expressed in the pulmonary vascular endothelium and exerts potent vasodilator, antithrombotic and antiproliferative activity by acting on the cyclic adenosine monophosphate pathway. In the pivotal randomised controlled trial of epoprostenol, 81 idiopathic PAH (known as primary pulmonary hypertension at the time of the study) patients in functional class III and IV were randomised to epoprostenol plus conventional therapy vs. conventional therapy alone (47). At 12 weeks, the epoprostenol treated group had improved quality of life scores, improved functional class, increased 6MWD and improved haemodynamic parameters compared with the conventional group. Eight patients died during the 12 weeks study period, all of whom had been in the conventional therapy group. The result of this study led to FDA approval of epoprostenol for idiopathic PAH in 1995. Data from longer term observational studies also suggested improved long term outcomes in idiopathic PAH treated with epoprostenol (48, 58, 59).

Epoprostenol has a short half life (approximately 5 minutes) and is given as a continuous long term infusion via a tunnelled, cuffed central venous catheter. Patients usually begun on a low dose (1 to 2 ng/kg/min) and gradually titrated upward in increments of 1 to 2 ng/kg/min, limited by the side effects and tolerance. Typical side effects associated with prostanoids treatment include hypotension, flushing, jaw aches, headaches, nausea and diarrhoea.

More stable prostacylin analogues such as treprostinil and iloprost with similar pharmacodynamic effects are now available for the treatment of idiopathic PAH.

Treprostinil is a chemically stable, tricyclic benzidene analog of prostacyclin. It has a longer half-life than epoprostenol and can be administered via a continuous subcutaneous infusion. In a pivotal, twelve week double-blind placebo-controlled study of treprostinil, a total of 470 patients with PAH (of which n=270 were idiopathic PAH) were randomised to receive subcutaneous (SC) treprostinil or placebo (60). Patients randomised to SC treprostinil showed greater improvement in 6MWD (between-group difference in median 6MWD = 16

metres, p-value = 0.006), Borg dyspnoea index score, signs and symptoms of pulmonary hypertension and haemodynamics compared with patients randomised to placebo. Long term persistence of efficacy of SC treprostinil has also been confirmed in idiopathic PAH. In a large, open-label, observational study of SC treprostinil, total of 860 patients with PAH (of which n = 412 were idiopathic PAH) were followed up to 4 years. For the idiopathic PAH subset, 1-, 2-, 3- and 4-year survival rates were 91%, 82%, 76% and 72% respectively (61). Treatment with inhaled treprostinil also resulted in improvement in 6MWD in patients already on oral monotherapy with either bosentan or sildenafil in the TRIUMPH study (62). The long term effects of inhaled treprostinil were confirmed in the TRIUMPH study open-label extension (63).

Iloprost is a stable, synthetic analog of prostacyclin and can be administered by the intravenous and aerosolised route. The AIR study (The Aerosolized Iloprost Randomised Study) was a twelve week placebo-controlled study that evaluated the efficacy of daily repetitive iloprost inhalations (64). A total of 203 patients with PAH or chronic thromboembolic pulmonary hypertension (of which n = 102 were idiopathic PAH) were included. This study showed inhaled iloprost improved exercise capacity, functional class, level of dyspnoea, quality of life and haemodynamics.

Phosphodiesterase type-5 inhibitors:

Endothelial nitric oxide synthase is the principal mediator of endothelium dependent vasodilation in the pulmonary circulation. Endothelium derived nitric oxide (NO) diffuses into pulmonary smooth muscle cells, where it stimulates soluble guanylate cyclase to produce cyclic guanosine monophosphate (cGMP). cGMP activates cGMP-dependent protein kinase G, which in turn, promotes vascular smooth muscle relaxation. Degradation of the cGMP is regulated via the production of several distinct phosphodiesterase inhibitors. Within the pulmonary circulation, phosphodiesterase type 5 (PD5) is the most abundantly expressed isoform. Inhibiting the activity of PD5 has been shown to augment nitric oxide vasodilatation. Currently available PD5 inhibitors used to treat PAH include sildenafil and tadalafil, with sildenafil being the most commonly prescribed. In the pivotal twelve week double blind, placebo-controlled SUPER

trial which included 278 patients with PAH (of which n = 175 were idiopathic PAH), sildenafil improved 6MWD, symptoms and haemodynamics over placebo (65). Patients in the original SUPER trial were entered into an open labelled extension study (SUPER-2). Results of the SUPER-2 study confirmed safety, tolerability and efficacy of long term sildenafil with 60% of all patients improved or maintained their functional status and 46% improved or maintained their 6MWD after 3 years (66).

Endothelin receptor antagonists:

Endothelin 1 is a vasoconstrictor that acts via two receptors, endothelin receptor A (ET-A) and endothelin receptor B (ET-B), to regulate vascular tone and cell proliferation. Lung and circulating endothelin 1 levels are increased in idiopathic PAH. Endothelin receptor antagonists (ERA) cause significant but modest improvement in pulmonary haemodynamics, exercise capacity and symptoms. Patients treated with ERA require monthly liver function tests.

The non selective ET-A/ET-B receptor antagonist bosentan is the first orally active agent to be granted regulatory approval in the treatment of PAH. In the BREATHE-1 trial, 213 patients (of which n = 150 were idiopathic PAH) in functional class III and IV were randomised to bosentan (at dose of 125mg or 250mg twice daily) or placebo. At 16 weeks, a placebo corrected 6MWD improvement of 44 metres was noted (67). Bosentan was also assessed in less functionally impaired patients (WHO functional class II) in the EARLY trial and demonstrated benefit in reducing pulmonary vascular resistance and preventing clinical worsening at 6 months (68). The long term efficacy of bosentan in idiopathic PAH was confirmed in a long term observational study of 169 idiopathic PAH patients with estimated one and two year survival of 96% and 89% respectively in patients on first line bosentan therapy (69).

Ambrisentan is a selective ET-A receptor antagonist. There is no data to suggest selective ET-A antagonism is superior to combined ET-A and ET-B antagonism. In the ARIES 1 and 2 trials, ambrisentan improved exercise capacity, haemodynamics and time to clinical worsening of idiopathic PAH patients (70). Sustained improvement in exercise capacity after two years of ambrisentan was

confirmed in patients who were followed in the long term extension study (ARIES-E study) (71).

Other novel treatments:

Platelet derived growth factors (PDGF) have the ability to induce proliferation and migration of smooth muscle cells and fibroblast, and the PDGF and its receptors are over-expressed in human and experimental models of PAH. Novel therapeutic agents, such as imatinib that inhibit tyrosine kinases are currently been evaluated in phase III clinical trials. Efficacy of soluble guanylate cyclase stimulator riociguat in PAH is also currently been studied in a phase III clinical trial (PATENT trial).

1.12 Survival Prediction Equations in Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

Although epidemiological studies suggested survival has improved compared with historical survival from the NIH era, outcomes of idiopathic, heritable and anorexigen-associated PAH remain unacceptably poor. None of the currently approved therapies represents a cure for this progressive and often fatal disease.

Outcomes of Group 1 PAH subsets depend on the aetiology. Patients with congenital heart disease associated PAH have better survival whereas those with connective tissue associated PAH have worse survival compared with idiopathic PAH (5, 72). Idiopathic PAH patients who responded to acute vasoreactivity testing had the best survival (55, 73). Survival is also worse for incident (newly diagnosed) patients compared with prevalent patients (37).

Currently, no single parameter has been shown to accurately predict survival of PAH when considered alone. The pulmonary hypertension literature is also dominated by many small, often retrospective single centre studies with limited power to properly assess the effects of treatment, compare multiple outcomes and draw meaningful conclusion (74). Many parameters were reported to be

associated with mortality in only a few studies or were not reproducible in other studies. However, analyses from major registries and clinical trial datasets have repeatedly identified a number of clinical, physical and haemodynamic parameters to have prognostic significance in PAH. These parameters include age, gender, six minute walk distance, functional class, heart rate, presence of pericardial effusion, and haemodynamic parameters (right atrial pressure, cardiac index, mean pulmonary artery pressure, stroke volume index, pulmonary vascular resistance and mixed venous oxygen saturation) (22, 23, 26, 46, 57, 74, 75).

Currently, five prognostic equations have been developed from existing datasets to predict outcomes of PAH patients.

<u>NIH registry equation</u> (26):

The NIH equation was derived using survival data of 194 primary pulmonary hypertension patients from the NIH Registry.

$$P(t) = [H(t)]^{A(x,y,z)}$$

where

P(t) indicates the patient's chances of survival,

t = 1, 2 or 3 years

$H(t) = [0.88\text{-}0.14t + 0.01t^2]$

$A(x,y.z) = e^{(0.007325x + 0.0526y - 0.3275z)}$

where

X = mean pulmonary artery pressure

Y = mean right atrial pressure

Z = cardiac index

<u>French registry equation</u> (37):

The French equation was derived using survival data from a combined cohort of 56 incident and 134 prevalent idiopathic, heritable and anorexigen-associated PAH patients diagnosed 3 years prior to entry into the French Registry. In order to remove survivor bias that results from inclusion of prevalent patients, survival

estimates and a Cox proportional hazards model from time to diagnosis were adjusted for the left truncation arising from the delay between diagnosis and study entry (37). Patients were only in the risk setfrom their time of study entry (37).

The probability of survival of a patient at t years post diagnosis is:

$$P(t;x,y,z) = \exp(-0.02 - 0.28t)^{\exp(-(0.004x + 0.98y + 0.28z))}$$

where

t = years post diagnosis

x = 6 minute walk distance at diagnosis – 280 m

y = 1 if female, y = 0 if male

z = cardiac output at diagnosis – 4.0 $L.min^{-1}$

Pulmonary Hypertension Connection registry equation (PHC equation) (23):

The PHC equation was derived from 247 patients with a diagnosis of idiopathic, familial and anorexigen-associated PAH.

The probability of survival of a patient at t years post diagnosis is:

$$P(t) = e^{-A(x,y,z)t}$$

$$A(x,y,z) = e^{(-1.270 - 0.0148x + 0.0402y - 0.361z)}$$

where

P(t) = probability of survival

t = time in years after diagnosis

x= mean pulmonary artery pressure

y = mean right atrial pressure

z = cardiac index

REVEAL equation (57) and REVEAL risk score (76):

Predictors of 1-year survival were determined using data from 2716 Group 1 PAH patients enrolled in the REVEAL Registry. 19 independent predictors of survival were identified and used to generate a prognostic equation based on the Cox proportional hazard multivariate analysis.

Predicted 1 year survival = $S0(1)^{\exp(Z'ß\gamma)}$

where

S0(1) is the baseline survivor function 0.9698

Z'ß is the sum of the patient's individual characteristics multipled by the ß coefficients for each of the 19 parameters in the equation

γ is the shrinkage coefficient (0.939)

Starting with a base value of 0, the linear component is increased or decreased according to the variable coefficients summarised in Table 1.8.

Table 1.8. Variable Coefficients for the linear component of the REVEAL equation.

	Additions and subtractions to linear component of equation	
WHO group 1 subgroup	Familial PAH, +0.7737	Po-PAH, +1.2801 CTD-PAH, +0.4624
Demographics and comorbidities	Male > 60 years, +0.7779	Renal insufficiency, +0.6422
WHO FC	FC I, -0.8749	FC III, +0.3454 FC IV, +1.1402
Vital signs	Systolic BP <110mmHg, -0.5128	Heart rate > 92 beats.min^{-1}, +0.3322
6MWD	6MWD ≥ 440 metres, -0.5455	6MWD < 165 metres, +0.5210
BNP	BNP < 50 pg/mL or NTproBNP < 300pg/mL, -0.6922	BNP > 180 pg/mL or NTproBNP > 1500 pg/mL, +0.6791
Echocardiogram	Pericardial effusion, +0.3014	
PFT	% predicted DL_{CO} ≥ 80%, -0.5317	% predicted DL_{CO} ≤ 32%, +0.3756
RHC	mRAP > 20mmHg within 1 year, +0.5816	PVR > 32 Wood units, +1.4062

Definition of abbreviations: 6MWD = six minute walk distance, BNP = brain natriuretic peptide, BP = blood pressure, CTD-PAH = connective tissue disease associated PAH, DL_{CO} = diffusion capacity for carbon monoxide, FC = functional class, mRAP = mean right atrial pressure, NTproBNP = N-terminal-proBNP, PAH = pulmonary arterial hypertension, PFT = pulmonary function tests, Po-PAH = portal pulmonary hypertension, PVR = pulmonary vascular resistance, RHC = right heart catheterisation, WHO = World Health Organisation.

Based on the REVEAL equation, the simplified REVEAL risk score was developed. For a given test, a point value of zero was assigned if it was either unmeasured or if it did not fall above or below the threshold used in the calculator. Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk).

The REVEAL risk score is an ordinal scale calculated as a baseline number of 6 to which qualifiers are added or subtracted based on available data, as follows:

1. WHO group I	+1 point	CTD-PAH
subgroup:	+2 points	Po-PAH
	+2 points	familial PAH
2. Demographics:	+1 point	renal insufficiency
	+2 points	male and > 60 years
3. WHO FC :	-2 points	functional class I
	+1 point	functional class III
	+2 points	functional class IV
4. Vital signs	+1 point	systolic blood pressure < 110 mmHg
	+1 point	heart rate > 92 beats per minute
5. 6MWD	-1 point	≥440 metres
	+1 point	<165 metres
6. BNP	-2 points	<50 pg/mL
	+1 point	>180 pg/mL
7. Echocardiogram	+1 point	pericardial effusion
8. PFT	-1 point	%predicted DL_{CO} ≥ 80%
	+1 point	% predicted DL_{CO} ≤ 32%
9. RHC	+1 point	mRAP > 20mmHg within 1 year
	+2 points	PVR > 32 Wood Units
Sum of above	_____	
	+ 6 points	
	= REVEAL risk scores	

Scottish Composite Score (77):

The Scottish Composite Score was derived from 182 incident, treatment naive WHO Group 1 PAH who were diagnosed and treated at the Scottish Pulmonary Vascular Unit between November 2000 and September 2009. Multivariate Cox analysis showed age, sex, aetiology, right atrial pressure, cardiac output and 6-minute walk distance to be independent predictor of mortality. These variables were used to derive the Scottish Composite Score. The Scottish Composite Score was designed as a simple point-based risk score to stratify patients into prognostic groups whereas all the other equations were developed to compute predicted survival probabilities at certain time points post-diagnosis.

Table 1.9. The Scottish Composite Score

Variables	Categories	Points
Age, years	≥ 70	1
	< 70	0
Sex	Male	1
	Female	0
Aetiology	CTD-PAH-SSc or Group 1 PAH others*	1
	Idiopathic, heritable, anorexigen-associated PAH or CTD-PAH-non-SSC	0
Six minute walk distance, metres	< 50	3
	50 – 149	2
	150 -299	1
	≥ 300	0
Right atrial pressure, mmHg	≥ 10	1
	< 10	0
Cardiac output, $L.min^{-1}$	< 3	1
	≥ 3	0

Definition of abbreviations: CTD-PAH = connective tissue disease associated pulmonary arterial hypertension, SSc = systemic sclerosis, others* = includes portopulmonary hypertension, HIV and pulmonary veno-occlusive disease.

Scottish Composite Score risk groups:

High risk = score 4 – 8
Intermediate risk = score 2 – 3
Low risk = score 0 – 1

The Scottish Composite Score was validated in a separate cohort of incident and treatment naive idiopathic, heritable and anorexigen-associated PAH diagnosed and treated in the Pulmonary Vascular Disease Unit at Papworth Hospital (Cambridge, UK) between January 2001 and December 2009. The Scottish Composite Score also provides further risk stratification in WHO functional class III patients. When compared with the French and PHC equation, the Scottish Composite Score was more accurate than the French equation at predicting 1 and 2 year survival and not inferior to the PHC equation (77). The validation cohort raw data came from parts of the data collected for this MD thesis.

1.13 Limitations of Pulmonary Hypertension Registries and Survival Prediction Equations

All pulmonary hypertension registries and their derived survival prediction equations have limitations. Each describes the survival of their specific population. Currently available survival equations are useful research tools and can provide clinical guidance but are not yet ready to replace clinical judgement. Further assessment is needed to determine whether any of the currently available equations confidently predict individual patient outcomes or whether their utility is restricted to cohort analysis.

The NIH equation was the first survival prediction equation in primary pulmonary hypertension (which at that time included patients now classified as idiopathic, heritable and anorexigen-associated PAH in the latest Dana Point classification) and for many years formed the basis of comparison for studies of outcomes, including many long term clinical drug studies (58, 61, 78, 79). This equation was derived from a predominantly incident cohort. On the other hand, patients in randomised controlled trials were usually stable prevalent patients who are known to have better outcomes than incident patients. In addition, important differences in the diagnosis, disease classification and treatment of PAH between the early 1980s and the current era meant that the NIH equation is likely to perform poorly when applied to contemporary idiopathic PAH populations from the modern treatment era. Indeed, the NIH equation underestimated survival by around 16-18% when applied to the more recent

idiopathic PAH cohorts from the French, REVEAL and Spanish Registries (33, 39, 40).

The study period of the PHC registry also spanned both pre- and post-modern treatment era (1991-2007) and this may potentially have an impact on the performance of the PHC equation.

The REVEAL equation, REVEAL risk score and the Scottish Composite Score are applicable to all WHO Group 1 PAH. On the other hand, the NIH, French and PHC equations apply only to patients with idiopathic, heritable and anorexigen-associated PAH.

With the exception of the REVEAL equation and the REVEAL risk score, all the other survival prediction equations were derived using baseline parameters obtained at the time of diagnosis. The REVEAL equation and risk score were developed to be applicable at any time point in the course of a patient's disease.

The Scottish Composite Score was derived from a purely incident cohort. The PHC registry excluded patients who were already on approved PAH therapy at the time of referral (n=52), which in effect probably excluded prevalent patients. All other equations were derived from a mixed incident and prevalent cohort and are therefore limited by survival and immortal time bias. Newly diagnosed patients with severe rapidly progressive disease may not survive long enough to be enrolled into registries, potentially leading to underestimation of mortality in these survival prediction equations. Definition of incident patient was also variable amongst the registries. The French Registry defined incident cases as patients who were newly diagnosed within the 1- year recruitment phase whereas the REVEAL Registry defined incident cases as any patients who received a diagnosis of PAH within 90 days prior to study enrollment.

The REVEAL risk score and Scottish Composite Score have the added advantage of simplicity to use. Both REVEAL equation and risk score also allow calculation of probability of survival even if certain data are unavailable for all predictive factors in the model.

Missing data is a limitation in all pulmonary hypertension registries, and many other known prognostic predictors of outcomes are not captured. Serial assessment was not performed and thus prediction of disease trajectory over time could not be assessed. Finally, none of the survival equations accounted for the influence of modern PAH therapies on future mortality risk.

2 Chapter 2: Methods

2.1 Pulmonary Hypertension Service in the United Kingdom and Ireland

The diagnosis, treatment and long term management of all adult pulmonary hypertension patients in the United Kingdom (UK) and Ireland are centralised to eight designated pulmonary hypertension centres (Table 2.1). Formal designation of centres was undertaken by the National Specialist Commissioning Advisory Group (replaced by National Commissioning Group in 2007) of the Department of Health in England in 2001, the National Service Division of the Scottish Parliament in Scotland in 1998, and the Health Service Executive in Ireland (80). Wales and Northern Ireland refer patients to the UK centres. The centralisation of management of patients with pulmonary arterial hypertension (PAH) to designated centres only provides a unique opportunity to perform this study that aim to investigate the epidemiology, characteristics, long term survival and treatment outcomes of all idiopathic PAH patients within a single region. All pulmonary hypertension centres in the UK and Ireland met the minimum standards for specialist unit. In the UK and Ireland, the prescription of PAH specific therapies (endothelin receptor antagonists, phosphodiesterase 5 inhibitors and prostanoids) are limited to designated pulmonary centres only. There is therefore no indiscriminate use of PAH drugs as occurred in some other countries where PAH drugs may be used in classes of pulmonary hypertension with inadequate clinical evidence or even potential harm.

Table 2.1. Eight designated pulmonary hypertension centres in the UK and Ireland.

Designated centre locations	Details
Glasgow, Scotland.	Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital.
Newcastle-Upon-Tyne, England.	Northern Pulmonary Vascular Unit, Freeman Hospital.
Sheffield, England.	Sheffield Pulmonary Vascular Unit, Royal Hallamshire Hospital.
Cambridge, England.	Pulmonary Vascular Diseases Unit, Papworth Hospital.
London, England.	National Pulmonary Hypertension Service, Hammersmith Hospital.
London, England.	Royal Brompton Pulmonary Hypertension and Adult Congenital Heart Disease Centre.
London, England.	Pulmonary Hypertension Unit, Royal Free Hospital.
Dublin, Ireland.	National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital.

2.2 Study Design and Methods

This was a retrospective, longitudinal cohort study. Professor Andrew Peacock, the director of the Scottish Pulmonary Vascular Unit, had previously obtained permission from the other pulmonary hypertension centres in the UK and Ireland to share data. I wrote to the West of Scotland Research Ethics Committee outlining my study proposal. As this study was designed and conducted to define current care, formal ethics approval was deemed unnecessary by the West of Scotland Research Ethics Committee (Appendix 2).

Only anonymised and non-identifiable data were collected. I first performed a pilot study on patients from our own centre (Scottish Pulmonary Vascular Unit). The data collection proforma was modified accordingly prior to travelling to the other pulmonary hypertension centres. I visited each site to examine the local database and patient records. The diagnosis was confirmed in all cases. An encrypted laptop was used to store all data collected. Prior to my visit, I contacted the personnel department to obtain honorary contract with the individual hospital, the IT department to obtain approval and passwords to access hospital computerised records and liaised with staffs in each pulmonary hypertension centre to arrange workspace.

Data were collected on all consecutive, newly diagnosed (incident), treatment-naive cases of idiopathic, heritable and anorexigen-associated PAH diagnosed between 1st January 2001 and 31st December 2009 in all eight pulmonary hypertension centres in the UK and Ireland.

Problems encountered during data collection:

1. Quality of local database:

The information recorded in local databases was highly variable across the various centres. In a number of centres, data recorded may include only the basic demographics and diagnosis. To avoid missing cases, all patients on the local database were screened and where appropriate the medical case notes were retrieved and reviewed.

2. Misclassification of diagnosis:
The diagnosis recorded in local databases may not be accurate or fully satisfied my study's definition of idiopathic PAH. For example, a patient was recorded and managed as idiopathic PAH by the treating physician but had abnormal pulmonary function tests and/or evidence of co-existing parenchymal lung disease on chest CT.

3. Data collection:
The retrieval of the relevant data from the medical records was very time consuming. Clinic letters, discharge summaries and many investigation results were stored electronically in most centres, mostly under different IT systems or software packages. I examined each of these individually and extracted the data of interest. Some results were stored in different hospital departments and involved further liaisons with colleagues from other departments to access these data. For example, in one centre, I was only able to access the pulmonary function results stored in the pulmonary physiology lab when one of the staffs was working on a half-day. Although it was possible to extract a lot of data from various electronic sources, in majority of patients, the hospital paper medical records were needed for the remaining missing data. Request for paper medical records was time consuming (took approximately 2 weeks per request) and only limited number of records could be requested at any one time. In one hospital, to avoid delay, I pulled the medical records from the shelves in the records department myself. All centres involved at least two separate visits before data collection was fully completed.

2.3 Inclusion and exclusion criteria

Inclusion criteria:

PAH was defined as mPAP ≥ 25mmHg at rest and pulmonary artery occlusion pressure (or pulmonary capillary wedge pressure) ≤ 15mmHg with normal or reduced cardiac output. Idiopathic PAH was defined as PAH with no identifiable secondary causes of pulmonary hypertension or associated risk factors. Patients

with heritable and anorexigen-associated PAH have similar baseline characteristics and outcomes to idiopathic PAH (21) and were therefore analysed together in this thesis.

The definition of idiopathic PAH in this thesis was based on the same haemodynamic and pulmonary function criteria used to define idiopathic PAH in the French (33) and the Scottish (32) registries. We refined our criteria for the definition of idiopathic PAH by further excluding patients with radiological evidence of parenchymal lung disease from our idiopathic PAH cohort. These excluded patients with CT evidence of parenchymal lung disease who otherwise satisfied the standard haemodynamic and pulmonary function criteria for idiopathic PAH were classified in this thesis as PAH with 'co-existing lung disease' (Figure 2.1).

The date of diagnosis was taken as the date of initial right heart catheterisation. If this cannot be located in the hospital records, then the date of first visit to the pulmonary hypertension centre was used. The diagnosis of idiopathic, heritable and anorexigen-associated PAH was made by experienced pulmonary vascular physicians in all pulmonary hypertension centres following systematic assessment with multiple modalities in a multidisciplinary setting. In all patients classified as PAH with 'co-existing lung disease' in this thesis, the underlying lung disease was considered by their treating pulmonary hypertension specialists to be either insignficant or unlikely to be the main contibuting cause of the individual's pulmonary hypertension.

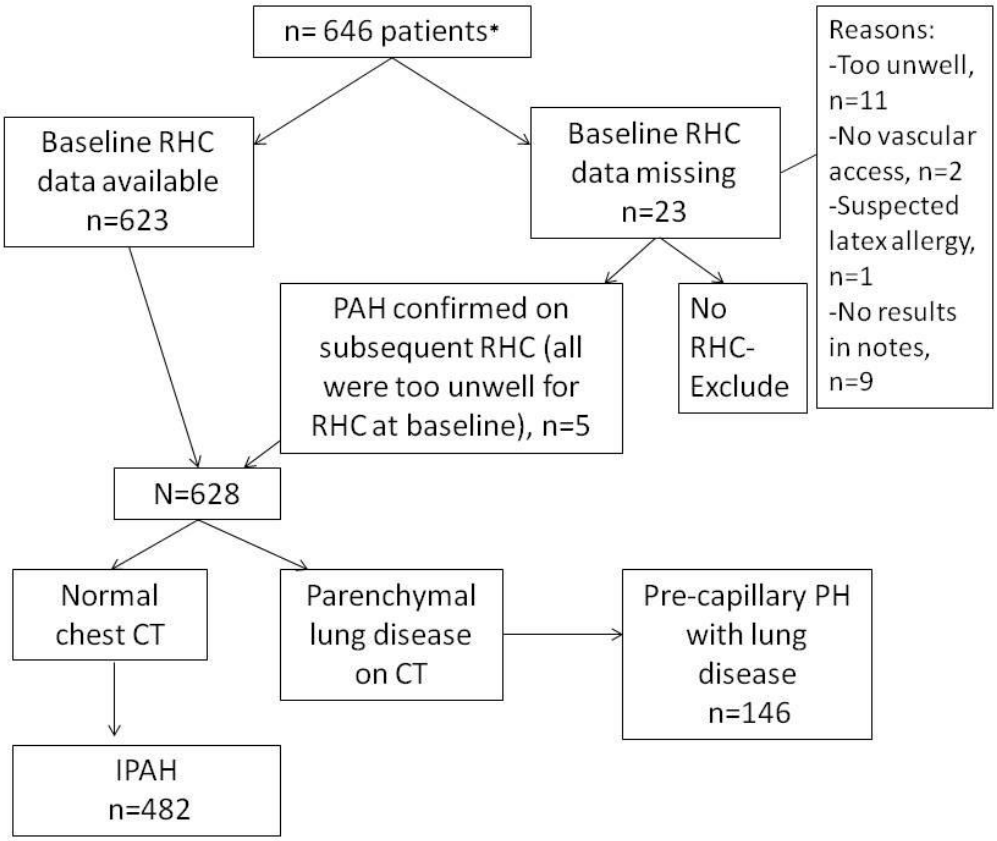


Figure 2.1. Flow diagram showing inclusion of patients.

*646 patients satisfying the traditional haemodynamic and pulmonary function criteria of idiopathic, heritable and anorexigen-associated PAH were diagnosed in all eight pulmonary hypertension centres in the UK and Ireland between January 2001 and December 2009. In all patients, mPAP ≥ 25mmHg, pulmonary artery occlusion pressure ≤ 15mmHg, cardiac output was normal or reduced and pulmonary function (FEV_1, FVC and TLC) were ≥ 60% predicted.

Definition of abbreviations: IPAH = idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension, n= number, PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, RHC = right heart catheterisation.

Parenchymal disease = emphysema (n=88), pulmonary fibrosis (n=35), emphysema and pulmonary fibrosis (n=16) and others (n=7). Others include bronchiectasis (n=3), old TB changes (n=1), respiratory bronchiolotis (n=1), bilateral ground glass opacities (n=1), and cystic lung disease (n=1).

Exclusion criteria:

Patients with mPAP at rest of <25 mmHg or pulmonary arterial occlusion pressure >15 mmHg were excluded. Patients were also excluded if known to have connective tissue/collagen vascular disease, portal hypertension, haemolytic anaemia, HIV, sarcoidosis, congenital heart disease and pulmonary veno-occlusive disease. Patients who may have pulmonary hypertension secondary to significant hypoxic lung disease were excluded by abnormal pulmonary function test (defined as FEV_1, FVC or TLC <60% predicted) (32, 33).

All patients were started on conventional therapy (long term warfarin, oxygen and/or diuretics) unless otherwise contraindicated. No specific nationwide treatment algorithm was used. PAH specific therapies were commenced as felt appropriate at each centre, in accordance with contemporary pulmonary hypertension commissioning guidelines and national and European pulmonary hypertension guidelines (5, 80, 81). Combination therapies were used when allowed and clinically indicated. Patients were followed-up as per clinical need.

2.4 **Data collection**

Baseline data on demographics, right heart catheterisation results, 6 minute walk distance, pulmonary function test and WHO functional class were collected. Follow up data were collected at 3 ± 1 month and 6 ± 2 months for 6 minute walk distance and functional class. Co-morbidities, presenting symptoms and chest CT findings at diagnosis, treatment started at diagnosis and subsequent follow-up were also collected. Table 2.2 listed all the variables collected in this study.

Table 2.2. Study variables collected for all patients.

1. Baseline variables:
Demographics:
Age
Gender
Ethnicity
Height
Weight
Date of right heart catheterisation
Pulmonary hypertension centre
Duration of symptoms
Presenting symptoms
Functional class
Co-morbidities
Smoking history
Chest CT findings
Exercise capacity:
6 minute walk distance
Incremental shuttle walk distance
Biomarkers:
BNP and NT-proBNP
Quality of life:
CAMPHOR score
Pulmonary function test:
% predicted forced expiratory volume in one second
% predicted forced vital capacity
% predicted total lung capacity
% predicted diffusion capacity for carbon monoxide
Pulmonary haemodynamics:
Right atrial pressure
Systolic pulmonary artery pressure
Diastolic pulmonary artery pressure
Mean pulmonary artery pressure

Pulmonary artery occlusion pressure (wedge pressure) Cardiac output Cardiac index Mixed venous oxygen saturations Pulmonary vascular reisstance Pulmonary vascular resistance index
2. Treatment started after diagnosis: First line treatment All subsequent treatment Lung transplantation Atrial septostomy
3. Variables at follow-up (3-months and 6-months): 6 minute walk distance Functional class Pulmonary function test Treatment
4. Date of death

2.5 Epidemiology of Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

Idiopathic, heritable and anorexigen-associated PAH patients were divided into younger and older subgroups according to their median age at the time of diagnosis. Patients were also divided into three groups based on the year of diagnosis (2001-2003, 2004- 2006 and 2007-2009) to identify any changing trends in the epidemiology, baseline characteristics, treatment and outcomes over the course of the study period. The incidence and prevalence of idiopathic, heritable and anorexigen-associated PAH were calculated as the ratio of newly diagnosed (incidence) or all living patients (prevalence) and the total population of the United Kingdom and Ireland for the respective year.

2.6 Survival and Prognostic Factors in Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

Prognostic factors were assessed for the whole cohort of idiopathic, heritable and anorexigen-associated PAH and then separately for the two age subgroups (younger and older patients, divided according to the median age at the time of diagnosis). All cause mortality was used for survival analyses. Patients were followed-up until their date of death or the censoring date of 31st December 2009 if still alive. Mortality was confirmed using pulmonary hypertension centres records, with the general practitioners' records and NHS strategic tracing services. Survival from the time of diagnosis was estimated using the Kaplan Meier method and survival curves compared using log-rank test. Multivariate Cox regression was used to evaluate the prognostic significance of various baseline parameters.

2.7 Validation of Survival Prediction Equations

Patients with idiopathic, heritable and anorexigen-associated PAH in this thesis were used to validate five currently available survival prediction equations in

pulmonary arterial hypertension. The Brier score was used to assess the overall performance of individual survival prediction model.

2.8 Prognostic Significance of Short Term Change in Six Minute Walk Distance and Functional Class

The prognostic significance of change in six minute walk distance and functional class after three and six months of disease targeted therapies were studied in idiopathic, heritable and anorexigen-associated PAH patients. Patients were divided into high and low baseline walk according to the median baseline six minute walk distance.

In order to assess the prognostic significance of change in functional class, the patients were also divided into 4 groups according to their baseline and follow-up functional class:

Group 1: Baseline functional class I and II; Follow-up functional class I and II

Group 2: Baseline functional class III and IV; Follow-up functional class I and II

Group 3: Baseline functional class I and II; Follow-up functional class III and IV

Group 4: Baseline functional class III and IV; Follow-up functional class III and IV

Survival was assessed using the Kaplan Meier method and survival curves compared using the log rank test.

2.9 Characteristics and Outcomes of Pulmonary Arterial Hypertension with 'Co-existing Lung Disease'

The baseline characteristics and outcomes of patients with PAH with 'co-existing lung disease' were assessed and compared with patients with idiopathic, heritable and anorexigen-associated PAH diagnosed concurrently

in all eight pulmonary hypertension centres in the UK and Ireland. Short term response to treatment in both groups of patients was assessed by the functional class and the change in six minute walk distance after three months of pulmonary hypertension disease targeted therapies.

3 Chapter 3: Changing Demographics, Epidemiology and Survival of Incident Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

3.1 Summary

Rationale:

Incident pulmonary arterial hypertension was under-represented in most pulmonary hypertension registries and may have a different disease profile to prevalent disease.

Objectives:

To determine the characteristics and outcomes of a purely incident, treatment-naive cohort of idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension and to determine the changes in presentations and survival over the past decade in the UK and Ireland.

Methods:

All consecutive, incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension diagnosed in all eight pulmonary hypertension centres in the UK and Ireland between 1st January 2001 and 31st December 2009 were included. Patients with parenchymal lung disease (of any severity) on chest CT were excluded.

Results:

A total of 482 consecutive patients (93% idiopathic, 5% heritable and 2% anorexigen-associated pulmonary arterial hypertension) were newly diagnosed

over the study period, giving rise to an estimated incidence of 1.1 cases/million/year and prevalence of 6.6 cases/million in 2009. Younger patients (age ≤ 50) had shorter duration of symptoms, less co-morbidities, better functional and exercise capacity, higher % DL_{CO}, more severe haemodynamic impairment but better survival compared with older patients. In comparison with the earlier cohorts, patients diagnosed in 2007-2009 were older, more obese, had lower % $DL_{CO,}$ more co-morbidities but better survival.

Conclusions:

This study highlights the influence of age on the phenotypes of incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension and has shown the changes in demographics and epidemiology over the past decade in a national setting. The results suggest that there may be two subtypes of patients: the younger subtype with more severe haemodynamic impairment but better survival compared with the older subtype who has more comorbidities.

3.2 Introduction

Pulmonary arterial hypertension (PAH) is a rare, debilitating disorder of the pulmonary vasculature characterised by progressive increase of the pulmonary vascular resistance, right ventricular afterload, right-sided cardiac failure and in advanced cases, death. In rare diseases such as PAH, registries provide valuable information on the baseline characteristics and outcomes of the disease. In some of the earlier pulmonary hypertension registries, definition and assessment of PAH were not standardised, numbers were small and a significant number of patients did not have right heart catheterisation to confirm the diagnosis (28-30, 36) . In addition, most pulmonary hypertension registries were composed of a mixture of incident and prevalent patients (25, 26, 33-35). However, prevalent patients have better prognosis compared with incident patients (37). We are concerned that current knowledge of pulmonary arterial hypertension based on data obtained from a mixed population may be biased. Patients with severe or rapidly progressive disease may die early and never live long enough to be enrolled in registries. Conversely, patients with stable disease for a number of years have better survival and may be over-represented in pulmonary hypertension registries. In addition, patients outside registry participating centres were not included, potentially introducing further selection bias.

Recent reports from contemporary registries (22, 23, 34, 35) suggested that the typical idiopathic PAH patients are now older and have better survival when compared with patients from the NIH era (25, 26). However, it is unclear whether younger and older patients in the current treatment era differ in their baseline characteristics and long term outcomes. We are also interested to know whether the demographics, baseline characteristics and survival of incident idiopathic PAH have changed over the past decade since the availability of disease targeted therapies. Since 2001, the diagnosis, initiation of treatment and long term management of all adult pulmonary hypertension patients in the UK and Ireland has been centralised to eight designated pulmonary hypertension centres (80). This set up also provides an opportunity to study the demographic and survival trends of virtually all newly diagnosed, treatment-naïve patients within a single region with a similar healthcare system.

The objectives of this study were:

1. To determine the epidemiology, baseline characteristics and outcomes of an incident cohort of idiopathic, heritable and anorexigen-associated PAH.
2. To determine whether younger and older incident idiopathic, heritable and anorexigen-associated PAH patients differ in baseline characteristics and outcomes.
3. To determine whether the demographics and epidemiology of incident idiopathic, heritable and anorexigen-associated PAH have changed over the past decade in the UK and Ireland.

3.3 **Methods**

This was a longitudinal observational study. Data were collected on all consecutive treatment-naive, incident cases of idiopathic, heritable and anorexigen-associated PAH diagnosed between 1st January 2001 and 31st December 2009 in all eight pulmonary hypertension centres in the UK and Ireland. Only anonymised and non-identifiable data were collected. This study was designed and conducted to define current care and hence formal ethics approval was deemed unnecessary by the West of Scotland Research Ethics Committee.

The diagnosis of idiopathic PAH was made at each pulmonary hypertension centre following systematic assessment with multiple modalities in a multidisciplinary setting. Idiopathic PAH was defined as PAH with no identifiable causes or risk factors of pulmonary hypertension. Patients with heritable and anorexigen-associated PAH have similar baseline characteristics and outcomes to idiopathic PAH (21) and were therefore analysed together in this study. PAH was defined as mean pulmonary arterial pressure ≥ 25 mmHg at rest and pulmonary artery occlusion pressure (PAOP) ≤ 15 mmHg with a normal or reduced cardiac output. The date of diagnostic right heart catheterisation was taken as the date of diagnosis. If this could not be located in the hospital records, then date of first visit to the pulmonary hypertension centre was used.

Patients with mPAP at rest of <25 mmHg or PAOP >15 mmHg were excluded. Patients with missing PAOP were excluded if echocardiogram and/or cardiac MRI suggested evidence of left heart disease. Patients were also excluded if known to have connective tissue/collagen vascular disease, portal hypertension, haemolytic anaemia, HIV or congenital heart disease. Patients with significantly abnormal pulmonary function test (FEV_1, FVC or TLC <60% predicted) (32, 33) were excluded. Patients with radiological evidence of co-existing parenchymal lung disease (of any severity) on chest CT were also excluded from this study.

<u>Incidence and Prevalence:</u>

The incidence and prevalence of idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension were calculated as the ratio of newly diagnosed (incidence) or all living patients (prevalence) and the total population of the United Kingdom and Ireland for the respective year. Patients lost to follow up were assumed to be dead for the purpose of the prevalence count. Patients who were diagnosed prior to 1st January 2001 and were still alive on the 31st December 2009 were noted and used in the prevalence count only.

Statistical Analysis:

Statistical analyses were performed using SPSS 19 (SPSS Inc, Chicago, IL). Mean ± standard deviation or median (interquartile ranges) were used to describe quantitative variables. Comparisons between 2 independent groups were performed using Student's t test or Mann-Whitney U test. For multiple comparisons of quantitative data, one way analysis of variance (ANOVA) or Kruskal-Wallis test were used. Categorical variables were described by frequencies and percentages and comparisons between groups performed using x^2 or Fisher's exact tests. Patients were divided into younger (age ≤ 50) and older (age > 50) subgroups by the median age at diagnosis. Patients were also divided into three cohorts based on the year of diagnosis (2001-2003, 2004-2006 and 2007-2009) to identify any changing trends over the course of the study period.

Survival endpoint was taken as either date of death or censoring. Patients were censored if they were transplanted, lost to follow up (date of last visit to PH centre was used as censor date) or if they were alive on the 31st December 2009. Mortality was confirmed using PH centre and general practitioner records and NHS strategic tracing services. Survival was estimated using the Kaplan Meier method and survival curves compared using the log-rank test.

Multivariate Cox regression was used to evaluate the prognostic significance of year of diagnosis after adjusting for variables known to have prognostic significance (age, functional class, 6 minute walk distance, % predicted diffusion capacity for carbon monoxide, mean right atrial pressure and cardiac index) (22, 23, 26, 33, 57).

Handling of missing data:

For descriptive statistics, only patients with available data were analysed. For multivariate Cox regression analysis of prognostic significance of year of diagnosis, a missing data category (ie, data available, data not available) was created for each covariate to enable evaluation of patients with missing data.

P-value<0.05 was considered significant throughout.

3.4 Results

Incidence and prevalence 2001 - 2009:

The combined population of the UK (http://www.statistics.gov.uk) and Ireland (http://www.cso.ie) in 2001- 2003, 2004 - 2006 and 2007 - 2009 were estimated to be 61, 62 and 64 million respectively. 121, 159 and 202 patients were diagnosed in the period 2001 - 2003, 2004 - 2006 and 2007 - 2009 respectively. This gave rise to estimated incidence (per million per year) of idiopathic, heritable and anorexigen-associated PAH in the UK and Ireland of 0.7, 0.9 and 1.1 in 2001 - 2003, 2004 - 2006 and 2007 - 2009 respectively. The estimated prevalence in 2009 was 6.6 cases/million population.

Baseline characteristics at the time of diagnosis:

482 patients satisfied the inclusion and exclusion criteria of idiopathic, heritable and anorexigen-associated PAH of this study. Out of the 482 patients, 92.9% (n=448) were idiopathic, 5.4%(n=26) heritable and 1.7% (n=8) anorexigen-associated PAH. Baseline characteristics of the whole study cohort of idiopathic, heritable and anorexigen-associated PAH are shown in Table 3.1. Selective baseline variables were compared across four age-quartiles subgroups in Table 3.2.

Table 3.1. Baseline characteristics of all idiopathic, heritable and anorexigen-associated PAH (n=482) and according to age subgroups (age ≤ 50 and age > 50 subgroups).

Baseline characteristics	All cases	Age ≤ 50	Age > 50	p-value*
Age, years (n=482)	50.1(17.1)	36.5(9.3)	65.1(8.3)	<0.001
Gender, % female (n=482)	69.9%(337)	73.2%(180)	66.5%(157)	0.112
Ethnicity, % non-white (n=424)	12.3%(52)	15.4%(34)	8.9%(18)	0.041
Symptoms: (n=437)				
Breathlessness	98.9%(432)	98.5%(218)	99.1%(214)	1.0
Chest pain	29.1%(127)	31.7%(70)	26.3%(57)	0.212
Peripheral oedema	30.9%(135)	23.5%(52)	38.4%(83)	0.001
Syncope	22.7%(99)	33.5%(74)	11.6%(25)	<0.001
Dizziness	19.7%(86)	20.4%(45)	19.1%(41)	0.735
Presyncope	11.9%(52)	14.9%(33)	8.8%(19)	0.048
Fatigue	13.5%(59)	14.5%(32)	12.5%(77)	0.545
Cough	13.1%(57)	13.1%(29)	13.0%(28)	0.976
Palpitation	8.9%(39)	8.6%(19)	9.3%(20)	0.808
Haemoptysis	3.9%(17)	5.0%(11)	2.8%(6)	0.238
Weight loss	4.8%(21)	3.6%(8)	6.0%(13)	0.237
Ascites	2.5%(11)	1.8%(4)	3.3%(7)	0.376
Duration of symptoms, months, median (IQR) (n=404)	18.0 (9.0-36.0)	12.0 (6.0-24.0)	24.0 (12.0-36.0)	<0.001
Functional class: (n=456)				
I/II	15.5%(72)	19.7%(45)	11.9%(27)	
III	66.7%(304)	65.9%(151)	67.4%(153)	0.031
IV	17.5%(80)	14.4%(33)	20.7%(47)	
Smoking history: (n=361)				
Current smoker	14.4%(52)	16.0%(28)	12.9%(24)	
Ex-smoker	41.3%(149)	30.9%(54)	51.1%(95)	<0.001
Never smoker	44.3%(160)	53.1%(93)	36.0%(67)	

Baseline characteristics	All cases	Age ≤ 50	Age > 50	p-value*
Co-morbidities: (n=455)				
IHD	12.1%(58)	1.3%(3)	24.2%(55)	<0.001
Hypertension	26.6%(121)	11.0%(25)	42.3%(96)	<0.001
Atrial fibrillation	5.3%(24)	0%(0)	10.6%(24)	<0.001
Diabetes	14.3%(65)	5.3%(12)	23.3%(53)	<0.001
Hypothyroidism	11.6%(53)	7.5%(17)	15.9%(36)	0.005
6MWD, metres (n=260)	292.4(123.0)	330.0(118.7)	246.1(112.2)	<0.001
ISWD, metres (n=120), median	190.0(82.3-340.0)	260.0(130.0-360.0)	140.0(70.0-255.0)	0.001
Pulmonary Function:				
%FEV_1 (n=350)	85.3(14.7)	85.5(13.6)	85.1(15.8)	0.785
%FVC (n=346)	94.0(16.4)	91.2(14.6)	96.7(17.6)	0.002
%TLC (n=204)	95.4(13.9)	96.3(13.4)	94.4(14.3)	0.324
%DL_{CO} (n=331)	62.0(20.9)	67.0(17.6)	56.7(22.8)	<0.001
Haemodynamics:				
mRAP, mmHg (n=439)	10.1(6.0)	10.0(5.8)	10.2(6.1)	0.738
PASP, mmHg (n=427)	86.2(21.1)	88.7(22.6)	83.8(19.2)	0.016
PADP, mmHg (n=424)	34.7(12.3)	38.6(12.9)	31.1(10.5)	<0.001
mPAP, mmHg (n=457)	54.1(13.9)	57.2(14.9)	51.0(12.2)	<0.001
PAOP, mmHg (n=408)	9.2(3.5)	8.8(3.5)	9.5(3.5)	0.035
TPG, mmHg (n=404)	44.4(13.7)	47.8(14.5)	41.3(12.2)	<0.001
SvO_2, % (n=395)	61.5(9.5)	62.5(10.3)	60.0(8.6)	0.053
CO, $L.min^{-1}$ (n=410)	4.0(1.5)	4.0(1.5)	4.0(1.5)	0.830
CI, $L.min^{-1}m^{-2}$ (n=366)	2.1(0.7)	2.1(0.7)	2.1(0.7)	0.683
PVR, WU (n=395)	12.8(6.3)	13.9(6.7)	11.8(5.8)	0.001
PVRI, $WU.m^2$ (n=355)	23.1(10.3)	24.8(11.2)	21.5(9.1)	0.003

Data expressed as % (n) or mean (SD) unless otherwise stated.

*Comparisons are for age ≤ 50 vs. age > 50 years.

Definition of abbreviations: 6MWD = 6 minute walk distance, CI= cardiac index, CO= cardiac output, % DL_{CO} = % predicted diffusion capacity for carbon monoxide, %FEV_1 = % predicted forced expiratory volume in 1 second, %FVC = % predicted forced vital capacity, IHD = ischaemic heart disease, IQR = interquartile range ISWD = incremental shuttle walk distance, mPAP = mean

pulmonary artery pressure, mRAP= mean right atrial pressure, PADP = pulmonary artery diastolic pressure, PAOP= pulmonary artery occlusion pressure, PASP = pulmonary artery systolic pressure, PVR= pulmonary vascular resistance, PVRI= pulmonary vascular resistance index, SvO_2= mixed venous oxygen saturation, %TLC= % predicted total lung capacity, TPG= transpulmonary gradient, WU= Wood Units.

Table 3.2. Selective baseline characteristics of incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension according to age quartile subgroups.

Variables	Age ≤ 36 years	Age 37-50 years	Age 51-65 years	Age >65 years	p-value*
Gender, % female (n=482)	71.9%(92)	74.6%(88)	68.3%(84)	64.6%(73)	0.373
Duration, months, median(IQR)	12.0 (6.0-24.0)	12.0 (8.0-24.0)	24.0 (12.0-36.0)	22.0 (12.0-36.0)	<0.001
6MWD, metres (n=260)	362.8 (105.2)	299.2 (123.2)	286.7 (103.1)	208.9 (107.9)	<0.001
$\%D_{LCO}$ (n=331)	66.7(15.9)	67.2(19.4)	61.4(21.1)	51.0(23.5)	<0.001
mPAP, mmHg (n=457)	58.9(17.7)	55.5(11.2)	53.6(10.9)	48.1(13.0)	<0.001
PAOP, mmHg (n=408)	8.8(3.5)	8.8(3.5)	9.5(3.3)	9.5(3.8)	0.218
TPG, mmHg (n=404)	49.2(17.1)	46.5(11.3)	43.9(10.7)	38.2(13.0)	<0.001
PVRI, $WU.m^2$ (n=355)	25.0(12.6)	24.6(9.6)	22.9(8.6)	19.9(9.6)	0.005

Data expressed as % (n) or mean (SD) unless otherwise indicated

Definition of abbreviations: see Table 3.1.

*Comparisons are for the 4 age-quartile groups. P-values relate to overall difference between the 4 age-quartile subgroups.

Age and gender:

The median age of incident idiopathic, heritable and anorexigen-associated PAH in this study was 50.0 years (IQR 36.0-65.0) and was similar between males and females. There was no statistically significant difference in gender ratio across the 4 age quartiles. 13.5%(n=65) of patients were over 70 years of age at the time of diagnosis.

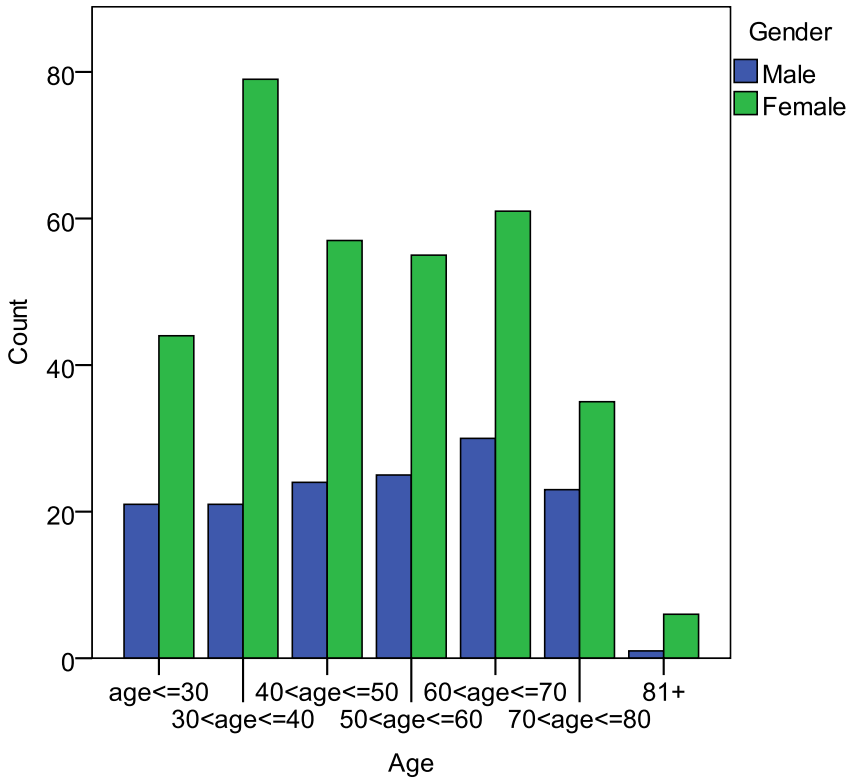


Figure 3.1: Distribution of age of incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension by gender.

Ethnicity:

Ethnicity data were available in 424 patients of which 12.3% were of non-white ethnic origin. Compared with whites, non-whites were younger (39.5 years [IQR 32.0-59.8] vs 50.0 years [IQR 36.0-65.0], p=0.015), had greater female predominance (% female 84.6% vs. 68.3%, p=0.016) and lower proportion of current and/or ex-smoker (34.2% vs 58.6%, p=0.007). There was no statistically significant difference in body mass index (BMI), functional class, exercise capacity or haemodynamics between whites and non-whites. Patients with missing ethnicity data had similar baseline characteristics to the white ethnic group.

Body mass index (BMI):

Mean BMI was 28.3 ± 6.3 kg/m^2 and was higher in females (females: 28.8 ± 6.6 kg/m^2 vs. males: 27.3 ± 5.5 kg/m^2, p=0.02). 37.9% of females and 24.8% of males were obese.

Symptoms:

Presenting symptoms were available in 437 patients . The median duration of symptoms (n=404) was 18.0 months (IQR 9.0-36.0) and was similar in males and females. Dyspnoea was the most common symptom (98.9%, n=432) at the time of diagnosis. Other less common symptoms included peripheral oedema (30.9%, n=135), chest pain (29.1%, n=127), syncope (22.7%, n=99), light-headedness (19.7%, n=86), fatigue (13.5%, n=59), cough (13.1%, n=57), pre-syncope (11.9%, n=52), palpitation (8.9%, n=39), weight loss (4.8%, n=21) and haemoptysis (3.9%, n=17).

Older (age > 50 years) patients were more likely to present with peripheral oedema whereas younger (age ≤ 50 years) patients were more likely to present with syncope and presyncope (Table 3.1).

Baseline exercise capacity and functional class:

Baseline exercise capacity was evaluated with 6 minute walk test in 260 patients and incremental shuttle walk test in 120 patients. Mean 6MWD and median incremental shuttle walk distance at the time of diagnosis were 292.4 ± 123.0 metres and 190.0 metres (IQR 82.3-340.0) respectively.

The majority of patients had severe symptoms by the time of diagnosis, with 66.7% and 17.5% in functional class III and IV respectively. Distribution of functional class was similar between males and females. A greater proportion of younger patients were in functional class I/II compared with older patients (Table 3.1).

Smoking History:

14.4% (n=52) and 41.3% (n=149) of patients were current and ex-smokers respectively. History of smoking was more prevalent in older (table 3.1) and male patients (11.4% of male patients were current and 57.9% ex-smoker compared with 15.8% and 33.6% of female patients were current and ex-smoker respectively, $p<0.001$).

Pulmonary function:

Patients had preserved spirometry and lung volumes but disproportionately reduced % DL_{CO} (Table 3.1). Older patients had lower %DL_{CO} compared with their younger counterparts (Table 3.1 and Table 3.2).

When compared across smoking history subgroups, ex-smoker had lower %DL_{CO} (55.9% ± 20.8%) compared with never (65.9% ± 20.2%, $p=0.001$) and current smoker (64.6% ± 21.3%, one way ANOVA $p=0.001$).

Pulmonary haemodynamics:

Patients had severe haemodynamic compromise (Table 3.1) and this was similar for males and females. Younger patients had significantly higher mean pulmonary artery pressures and transpulmonary gradient, lower pulmonary artery occlusion pressures, similar cardiac indices, and higher pulmonary

vascular resistance indices compared with older patients (Table 3.1 and Table 3.2)

Treatment:

First line treatment data were available in 479 patients. 44.3% (n=212) of patients were started on an endothelin receptor antagonist, 29.2% (n=140) phosphodiesterase type 5 inhibitor, 18.8% (n=90) prostaglandins, 5.0% (n=24) calcium channel blocker, 2.1%(n=10) combination therapy and 0.6% (n=3) patients received no treatment.

46.3% (n=222) and 6.0% (n=29) of patients received combination and triple therapy respectively at some point of their disease. A higher proportion of younger patients received sequential combination therapy (57.6% vs 34.5%, $p<0.001$), triple therapy (10.6% vs 1.3%, $p<0.001$), prostaglandins (51.8% vs 28.1%, $p<0.001$), calcium channel blocker (10.2% vs 3.0%, $p=0.002$) and transplantation (5.3% vs 0.4%, $p=0.002$) compared with their older counterparts. There was no statistically significant difference in treatment between males and females .

14 patients received heart-lung or bilateral lung transplantation and 12 patients had atrial septostomy over the study period.

Comparison of baseline characteristics according to year of diagnosis: 2001-3 vs 2004-6 vs 2007-9.

In the later cohort (2007-2009), patients were older, more obese, had more co-morbidities and lower $\%DL_{CO}$ (Table 3.3). There was no statistically significant difference in gender, distribution of functional class, exercise capacity or pulmonary haemodynamics over the three time periods.

Table 3.3. Baseline characteristics and treatment of the study cohort according to the year of diagnosis.

Baseline characteristics and treatment	2001 - 2003	2004 - 2006	2007 - 2009	p-value*
Age, years, median (IQR) (n=482)	45.0 (34.5-59.0)	52.0 (36.0-65.0)	52.0 (37.8-68.0)	0.003
Duration, months, median (IQR) (n=404)	18.0 (8.0-39.0)	18.0 (8.5-30.0)	18.0 (10.0-30.0)	0.883
BMI, kg/m^2 (n=398)	28.1(6.4)	26.9(5.8)	29.8(6.5)	<0.001
% obese (n=398)	31.2%(29)	25.5%(37)	43.1%(69)	0.004
Co-morbidities (n=455)				
IHD	5.8%(7)	11.4%(18)	16.3%(33)	0.018
Diabetes	5.7%(6)	15.0%(23)	18.3%(36)	0.012
%DL_{CO} (n=331)	68.6(21.8)	61.8(19.0)	59.2(21.3)	0.009
First line treatment (n=479)				
PD5i	7.6%(9)	20.8%(33)	48.8%(98)	
ERA	51.3%(61)	57.9%(92)	29.4%(59)	
Prostaglandins	31.1%(37)	17.0%(27)	12.9%(26)	<0.001
CCB	7.6%(9)	3.1%(5)	5%(10)	
Combination	2.5%(3)	0.6%(1)	3.0%(6)	
None	0%(0)	0.6%(1)	1.0%(2)	

Definition of abbreviations: BMI = body mass index, CCB = calcium channel blockers, %DL_{CO} = % predicted diffusion capacity for carbon monoxide, ERA = endothelin receptor antagonists, IHD = ischaemic heart disease, PD5i = phosphodiesterase 5 inhibitors.

Survival:

129 patients died over the study period with observed 1, 2, 3 and 5 year survival of 92.7%, 84.0%, 73.3% and 61.1% respectively. Younger patients (aged ≤ 50 years) had better survival with 1, 2, 3 and 5 year survival of 94.7%, 91.0%, 87.2% and 74.7% compared with 1, 2, 3 and 5 year survival of 90.0%, 75.5%, 57.1% and 43.7% in patients aged >50 years (Figure 3.3, log- rank, p<0.001). Patients aged >50 years were more likely to die compared with patients aged ≤50 years (unadjusted hazard ratio 3.0, p<0.001).

There was no difference in overall survival for the 3 time periods (Figure 3.2). However, after adjusting for age, functional class, 6 minute walk distance, % diffusion capacity for carbon monoxide, mean right atrial presssure and cardiac index, patients diagnosed in 2001 -2003 were more likely to have a shorter survival time compared with patients diagnosed in 2007-2009 (hazard ratio 1.96, p=0.019).

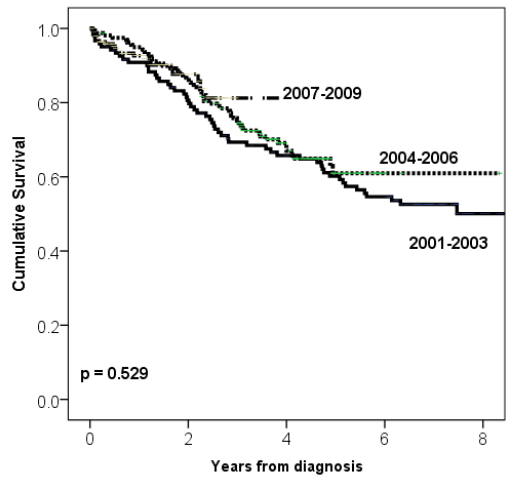
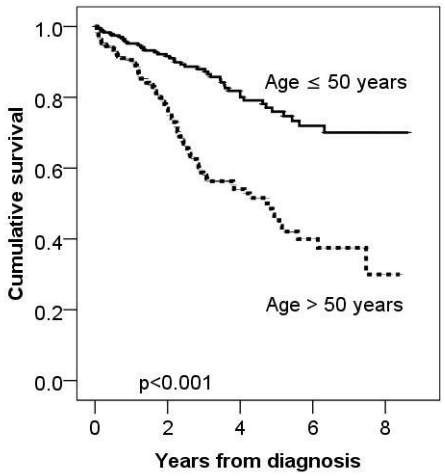


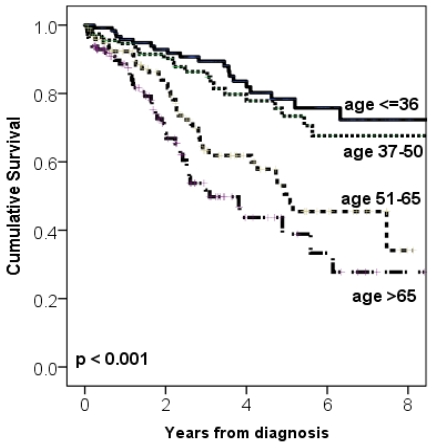
Figure 3.2. Kaplan meier survival curves according to year of diagnosis (2001-2003, 2004-2006, 2007-2009) in incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension.

Years from diagnosis	0	2	4	6	8
No at risk					
2001-2003	121	93	70	58	8
2004-2006	159	135	65	1	0
2007-2009	202	53	0	0	0

3.3a



3.3b



Years from diagnosis	0	2	4	6	8	Years from diagnosis	0	2	4	6	8
No at risk						No at risk					
≤50	246	163	91	44	7	≤36	128	87	49	24	3
>50	236	120	45	18	2	37-50	118	74	41	19	3
						51-65	123	73	31	11	0
						>65	113	46	12	5	0

Figure 3.3. Kaplan Meier survival curves according to age in incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension. Figure 3.3a. Patients ≤ 50 years old (corresponding to median age) had better survival compared with patients >50 years old. Figure 3.3b. Patients were divided into 4 groups according to age quartiles.

3.5 Discussion

Our study described the largest series so far reported of incident, treatment-naive, idiopathic, heritable and anorexigen-associated PAH patients. This was a national study encompassing all patients diagnosed with idiopathic, heritable and anorexigen-associated PAH in the UK and Ireland. Firstly, we found age influenced the phenotypic characteristics of patients. Secondly, we found despite the aging demographics over the past decade, survival of idiopathic, heritable and anorexigen-associated PAH patients in the UK and Ireland have improved. On the other hand, there was no change in duration of symptoms before diagnosis. Patients were still diagnosed late with severe functional and haemodynamic impairment.

Our study showed age influenced the phenotypic characteristics of incident idiopathic, heritable and anorexigen-associated PAH. Although we dichotomised our study cohort into the younger and older subgroups and showed significant differences between the two, in real-life these are likely to represent the two ends of a continuous spectrum of the same disease. When the study cohort was divided into 4 groups by age quartile, similar relationship was observed between these variables and aging. Co-morbidities in the older patients may partly explain their worse functional capacity despite their less severe haemodynamic impairment. Although Shapiro et al also reported similar age related findings with lower 6-minute walk distance, transpulmonary gradient and pulmonary vascular resistance in elderly patients with pulmonary hypertension, 28% of all patients and 56% of the elderly group in that study had pulmonary artery occlusion pressure ≥ 15mmHg and thus did not meet the haemodynamic criteria for idiopathic PAH (82). Although a normal pulmonary artery occlusion pressure does not exclude pulmonary venous hypertension (83), especially in older patients with comorbidities, we believe it is unlikely many patients in this study were misclassified . All patients were diagnosed by multidisciplinary teams of pulmonary vascular experts at each centre in accordance with contemporary national and international pulmonary hypertension guidelines (5, 80, 81). Routine work-up of all new patients include ECG, echocardiogram and cardiac

MRI. Results of these assessment were taken into consideration in a multidisciplinary setting before a final diagnosis was made in any new patient.

Younger patients in this study had a significantly higher frequency of syncope and presyncope whereas older patients were more likely to present with peripheral oedema. Syncope and presyncope were also common in childhood idiopathic PAH whereas oedema was rare (84). Younger patients with their better functional class and exercise capacity may exert themselves further leading to presyncope or syncope. The onset of peripheral oedema may reflect right ventricular failure. Interestingly, even in patients with similar mean right atrial pressure, older patients are still more likely to present with oedema compared with younger patients in this study (results not shown). Older patients, despite their less severe haemodynamic impairment appeared to have less physiological reserve than their younger counterparts to cope with the progressive pulmonary hypertension and subsequent failing right ventricle. This needs to be taken into account when deciding the choice of treatment for individual patient.

Older patients in this study had lower %DL_{CO} compared with their younger counterparts. Most reference equations for DL_{CO} use age, height and gender in a linear equation to predict DL_{CO} (85). However, the rate of decline of DL_{CO} accelerates with aging (86). This may therefore potentially result in overprediction of predicted DL_{CO} in older patients. A higher proportion of current/ex-smoker observed in older patients in this study may also explain their lower % DL_{CO} due to the presence of co-existing smoking related lung disease. However, we have excluded patients with any co-existing parenchymal lung disease from this study. As parenchymal lung abnormalities on chest CT are difficult to quantify objectively, we therefore excluded abnormalities of all severity from this study of idiopathic, heritable and anorexigen-associated PAH patients.

The demographics, epidemiology and survival of idiopathic, heritable and anorexigen-associated PAH have changed in the UK and Ireland between 2001 and 2009. We observed that over the nine year study period, patients were older, more obese, and had more co-morbidities in the later years. We speculate

that these changing demographics are largely due to changes in the referral pattern rather than an actual change in the disease. Alternatively, this may indicate that we are dealing with two possible subtypes of patients: younger patients similar to the primary pulmonary hypertension cohort of the NIH era (25) versus older patients characterised by the presence of co-morbidities. The incidence of idiopathic, heritable and anorexigen-associated PAH also appeared to increase year on year, largely due to rising number of referrals to PH centres. Although there was no difference in overall survival between the three time periods, when survival was adjusted for age and other known prognostic factors, it is encouraging to observe that the survival of incident idiopathic, heritable and anorexigen-associated PAH in the UK and Ireland has improved over the past decade. On the other hand, delays in diagnosis persist. Not only was the delay unchanged within the UK and Ireland over the past decade, there was no improvement when compared with patients in the NIH registry from the 1980s (25). We believe the persistent delay in diagnosis over time is largely due to the increasing proportion of elderly PAH patients. We found older patients have longer duration of symptoms before diagnosis. It is possible that the non-specific pulmonary hypertension symptoms were more commonly attributed to their old age or other more common illnesses before PAH was suspected. More education is therefore needed outside the pulmonary hypertension community to recognise that idiopathic PAH is no longer a disease affecting young patients only.

The main limitation of our study is the unavoidable incompleteness in our dataset due to its observational nature, with a small amount of missing data and uneven frequency of follow-up and investigations performed at each visit. Future studies looking into the relationship between age and right heart function at baseline and on treatment may help to understand the phenotypic and survival differences observed between the younger and older patients.

3.6 Conclusion

The current UK and Ireland study is the largest incident series of treatment-naive idiopathic, heritable and anorexigen-associated PAH patients to date. We have shown that younger patients have different phenotype and survival compared with their older counterparts. The demographics and epidemiology of incident idiopathic, heritable and anorexigen-associated PAH have changed and survival has improved between 2001 and 2009. However, patients still presented in advanced stages. Awareness of the changing demographics and epidemiology of idiopathic, heritable and anorexigen-associated PAH as reported in this study is imperative to the early diagnosis and treatment of this otherwise rare and fatal disease.

4 Chapter 4: Validation of Pulmonary Hypertension Survival Prediction Equations

4.1 Summary

Rationale:

The NIH equation, French equation, Pulmonary Hypertension Connection (PHC) equation, REVEAL equation and REVEAL risk score are currently available to predict prognosis in pulmonary arterial hypertension (PAH). It is unclear whether these survival prediction models that were all derived from a mixed incident-prevalent cohort are applicable to a purely incident PAH population.

Objectives:

To test the applicability of currently available PAH survival prediction equations in a purely incident cohort of idiopathic, heritable and anorexigen-associated PAH patients.

Methods:

482 patients with incident idiopathic, heritable and anorexigen-associated PAH diagnosed in all eight centres in the UK and Ireland between 2001 and 2009 were included in this study to validate the survival prediction equations. Patients with parenchymal lung disease (of any severity) on chest CT were excluded from this study. Observed survival was estimated using life table analysis and compared with predicted survival in the same patients calculated using the NIH equation, French equation, PHC equation, REVEAL equation and REVEAL risk score.

Results:

The NIH equation underestimated survival of our study cohort. Although the REVEAL equation, REVEAL risk score and Pulmonary Hypertension Connection

equation were derived from mixed incident-prevalent cohorts, all three models accurately predicted survival of our incident cohort at 1 year.

Conclusion:

Some survival equations more accurately predicted survival of our incident study cohort than others.

4.2 Introduction

Five survival prediction equations or models are currently available to predict prognosis in pulmonary arterial hypertension (PAH): National Institute of Health (NIH) equation (26), French equation (37), Pulmonary Hypertension Connection (PHC) equation (23), REVEAL equation (57) and REVEAL risk score (76). These survival prediction equations were individually derived from pulmonary hypertension registries that differ in size, duration and period of recruitment, patient population, length of follow-up, timing of assessment of prognostic variables, geographical region and healthcare system. It is also recognised that previously diagnosed 'prevalent' patients have better survival compared with newly-diagnosed 'incident' patients. The NIH, French and PHC equations were derived from idiopathic, heritable and anorexigen-associated PAH population. On the other hand, both REVEAL models' derivation population included group I PAH patients with diagnosis other than idiopathic, heritable and anorexigen-associated PAH. It is unclear whether any of these five models that were all derived from a mixed incident-prevalent cohort are applicable to a purely incident PAH population.

The aim of this study was to validate the five currently available PAH survival prediction equations using a purely incident cohort of idiopathic, heritable and anorexigen-associated PAH patients diagnosed in the UK and Ireland between 2001 and 2009.

4.3 **Methods.**

The study cohort included all consecutive, newly diagnosed (incident), treatment–naive cases of idiopathic, heritable and anorexigen-associated PAH (n=482) diagnosed in all eight pulmonary hypertension centres in the UK and Ireland between 1st January 2001 and 31st December 2009. Patients with radiological evidence of co-existing parenchymal lung disease (of any severity) on chest CT were excluded from this study. Inclusion and exclusion criteria of idiopathic, heritable and anorexigen-associated PAH used for validation of survival equations in this study were described in details in the methods section of chapter 3.

Statistical Analysis:

Analyses were performed using SPSS 18 (SPSS Inc, Chicago, IL) and SAS v9.2 (SAS Institute, Cary, NC). Survival endpoint was taken as either date of death or censoring. Patients were censored if they were transplanted, lost to follow up (date of last visit to pulmonary hypertension centre was used as censor date) or if they were alive on the 31st December 2009.

Expected survival was calculated for each patient for each of the survival prediction equations and compared with observed survival of the same patient estimated using the Kaplan Meier method. To assess the overall performance of each prediction model, Brier score with a weighted function that takes censoring into consideration was used. At each time point, the Brier score is the average of squared difference between observed and predicted survival for each patient. The Brier score for a model (survival prediction equation or risk score) can range from 0 to 1, with lower score representing higher accuracy. For example, if a model predicts survival probability of 70% and the patient survived, then the Brier score is $(0.7\text{-}1)^2$=0.09. Conversely, if a model predicts survival probability of 70% and the patient died, then the Brier score is $(0.7\text{-}0)^2$= 0.49. The differences in Brier score between the five survival prediction models were compared in matched patient groups. The upper and lower 95% confidence intervals were obtained from 50,000 bootstrap re-samples.

Handling of missing data:

As not all patients have a calculable probability of survival for all five survival prediction models, Brier scores were derived from patients where probability of survival from all five models were all available. The results were similar when analyses were repeated on all patients with available probability of survival.

P-value<0.05 was considered significant throughout.

4.4 **Results**

Comparisons of survival prediction equations (all patients):

The baseline characteristics of the validation cohort (n=482 incident idiopathic, heritable and anorexigen-associated PAH) have been described in the previous chapter (chapter 3, Table 3.1). Some survival prediction equations performed better (i.e, lower brier score) than others at predicting survival of our study population (Table 4.1). At 1 year, there was no difference in accuracy between the two REVEAL models and the PHC equation (Table 4.2). Both REVEAL equation and REVEAL risk score performed better than the French equation at predicting survival of our study cohort at 1 year (Table 4.2). At 2 and 3 year, both the PHC and French equations performed better than the NIH equation (Tables 4.3 and 4.4). There was no statistically significant differences in Brier scores between the French equation and the PHC equation at predicting survival at 2 and 3 year (Tables 4.3 and 4.4). The accuracy of all survival equations (NIH, French and PHC) decreased with time from diagnosis (Table 4.1).

Figure 4.1 shows the survival curves of actual observed survival of our UK and Ireland validation cohort versus predicted survival of the same patients calculated using the NIH, French, PHC and REVEAL equations. Predicted survival from the REVEAL and PHC equations were comparable to the observed survival of our UK and Ireland incident idiopathic, heritable and anorexigen-associated PAH study cohort. The NIH and French equations under-estimated survival of our study cohort.

Table 4.1. Brier scores of survival prediction models (all patients).

	Brier scores via bootstrap (95% Confidence interval)		
Survival prediction models	**1 year prediction**	**2 year prediction**	**3 year prediction**
NIH equation	0.1231 (0.1034-0.1448)	0.2103 (0.1836-0.2384)	0.2799 (0.2437-0.3137)
French equation	0.0642 (0.0413-0.0919)	0.1206 (0.0918-0.1539)	0.1831 (0.1458-0.2251)
PHC equation	0.0499 (0.0214-0.0851)	0.1015 (0.0651-0.1439)	0.1691 (0.1263-0.2181)
REVEAL equation	0.0462 (0.0177-0.0815)		
REVEAL risk score	0.0468 (0.0193-0.0809)		

Table 4.2. Brier scores differences via bootstrapping for 1-year prediction for all patients.

Survival prediction models	Brier score differences	95% Confidence Interval	p-value
French equation – REVEAL equation	0.0181	0.0019 to 0.0331	0.031
NIH equation – REVEAL equation	0.0769	0.0509 to 0.1004	<0.001
PHC equation – REVEAL equation	0.0038	-0.0027 to 0.0119	0.296
REVEAL risk score – REVEAL equation	0.0007	-0.0050 to 0.0055	0.763
French equation – PHC equation	0.0143	-0.0046 to 0.0314	0.124
NIH equation – PHC equation	0.0731	0.0484 to 0.0959	<0.001
REVEAL risk score – PHC equation	-0.0031	-0.0106 to 0.0030	0.373
French equation – NIH equation	-0.0588	-0.0774 to -0.0393	<0.001
REVEAL risk score – NIH equation	-0.0762	-0.0985 to -0.0518	<0.001
French equation – REVEAL risk score	0.0174	0.0023 to 0.0315	0.026

Table 4.3. Brier scores differences via bootstrapping for 2-year prediction for all patients.

Survival prediction models	Brier score differences	95% Confidence Interval	p-value
French equation – PHC equation	0.0191	-0.0144 to 0.0513	0.244
NIH equation – PHC equation	0.1087	0.0681 to 0.1469	<0.001
French equation – NIH equation	-0.0896	-0.1195 to -0.0587	<0.001

Table 4.4. Brier scores differences via bootstrapping for 3-year prediction for all patients.

Survival prediction models	Brier score differences	95% Confidence Interval	p-value
French equation – PHC equation	0.0140	-0.0297 to 0.0562	0.521
NIH equation – PHC equation	0.1088	0.0512 to 0.1623	<0.001
French equation – NIH equation	-0.0949	-0.1371 to -0.0499	<0.001

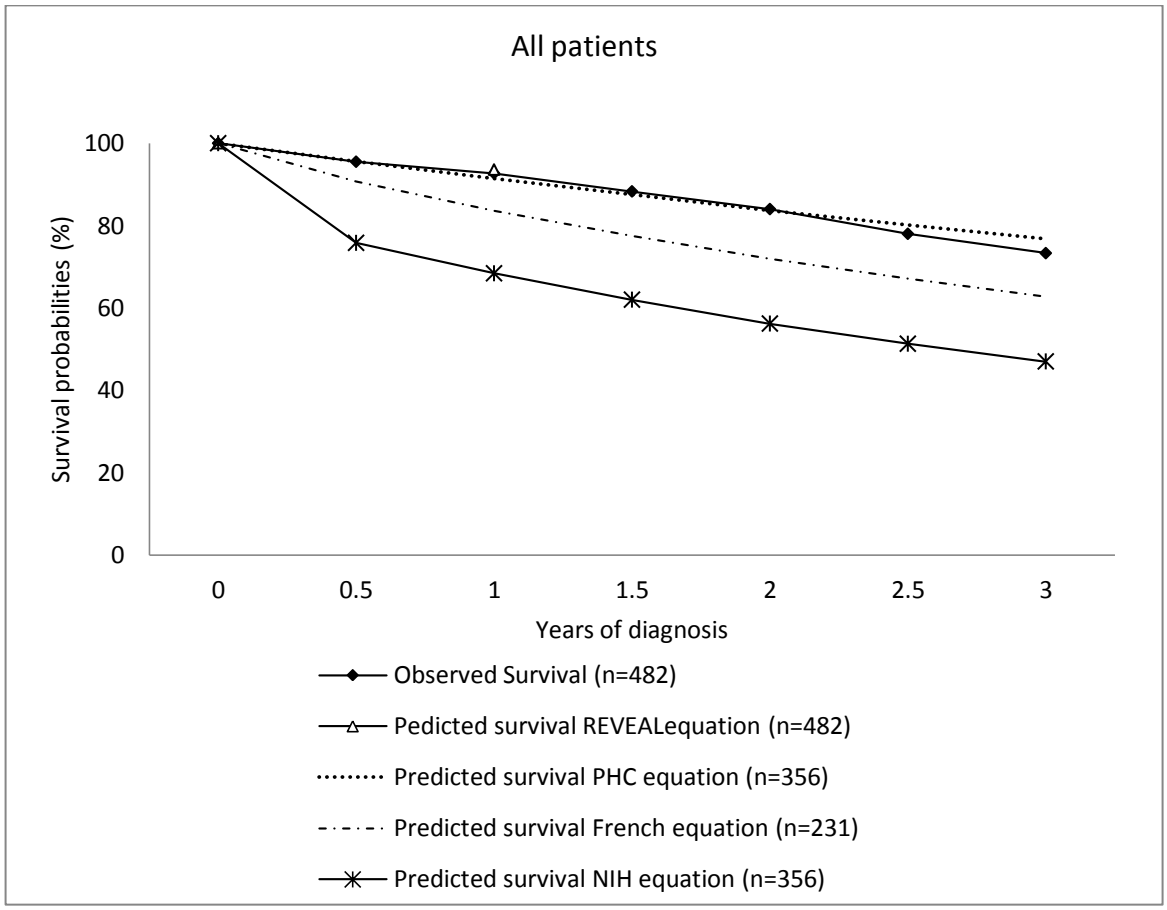


Figure 4.1. Observed versus predicted survival using the NIH equation, French equation, PHC equation and REVEAL equation for all patients. Only 1-year predicted survival was calculated for the REVEAL equation.

Comparisons of survival prediction equations in female patients:

The above analyses were repeated within gender subgroups. In female patients, the NIH equation had higher Brier scores compared with all other survival prediction models. There were no statistically significant differences between the French equation, PHC equation, REVEAL equation and REVEAL risk scores at predicting survival of our female incident patients (Tables 4.5, 4.6, 4.7 and 4.8). Figure 4.2 shows the survival curves of actual observed survival of our female subgroup versus predicted survival of the same patients calculated using the NIH, French, PHC and REVEAL equations.

Table 4.5. Comparison of survival prediction models using the Brier scores in female idiopathic, heritable and anorexigen-associated PAH patients.

Females patients	**Brier scores via bootstrap (95% Confidence interval)**		
Survival prediction models	**1 year prediction**	**2 year prediction**	**3 year prediction**
NIH equation	0.1209 (0.1005–0.1433)	0.2057 (0.1796-0.2335)	0.2731 (0.2391-0.3096)
French equation	0.0547 (0.0305-0.0847)	0.1117 (0.0831-0.1442)	0.1679 (0.1324-0.2071)
PHC equation	0.0488 (0.0212-0.0846)	0.1006 (0.0640-0.1430)	0.1708 (0.1268-0.2208)
REVEAL equation	0.0477 (0.0182-0.0848)		
REVEAL risk score	0.0465 (0.0182-0.0815)		

Table 4.6. Brier scores differences via bootstrapping for 1-year prediction in female idiopathic, heritable and anorexigen-associated PAH patients.

Survival prediction models (female patients)	Brier score differences	95% Confidence Interval	p-value
French equation – REVEAL equation	0.0070	-0.0037 to 0.0159	0.180
NIH equation – REVEAL equation	0.0731	0.0485 to 0.0957	<0.001
PHC equation – REVEAL equation	0.0011	-0.0043 to 0.0059	0.658
REVEAL risk score – REVEAL equation	-0.0012	-0.0066 to 0.0025	0.671
French equation – PHC equation	0.0059	-0.0055 to 0.0152	0.270
NIH equation – PHC equation	0.0721	0.0495 to 0.0935	<0.001
REVEAL risk score – PHC equation	-0.0023	-0.0079 to 0.0027	0.382
French equation – NIH equation	-0.0661	-0.0835 to -0.0484	<0.001
REVEAL risk score – NIH equation	-0.0744	-0.0956 to -0.0516	<0.001
French equation – REVEAL risk score	0.0082	-0.0016 to 0.0160	0.089

Table 4.7. Brier scores differences via bootstrapping for 2-year prediction in female idiopathic, heritable and anorexigen-associated PAH patients.

Survival prediction models (female patients)	Brier score differences	95% Confidence Interval	p-value
French equation – PHC equation	0.0111	-0.0131 to 0.0334	0.359
NIH equation – PHC equation	0.1051	0.0664 to 0.1413	<0.001
French equation – NIH equation	-0.0940	-0.1224 to -0.0652	<0.001

Table 4.8. Brier scores differences via bootstrapping for 3-year prediction in female idiopathic, heritable and anorexigen-associated PAH patients.

Survival prediction models (female patients)	Brier score differences	95% Confidence Interval	p-value
French equation – PHC equation	-0.0029	-0.0371 to 0.0304	0.866
NIH equation – PHC equation	0.1024	0.0459 to 0.1552	<0.001
French equation – NIH equation	-0.1053	-0.1467 to -0.0629	<0.001

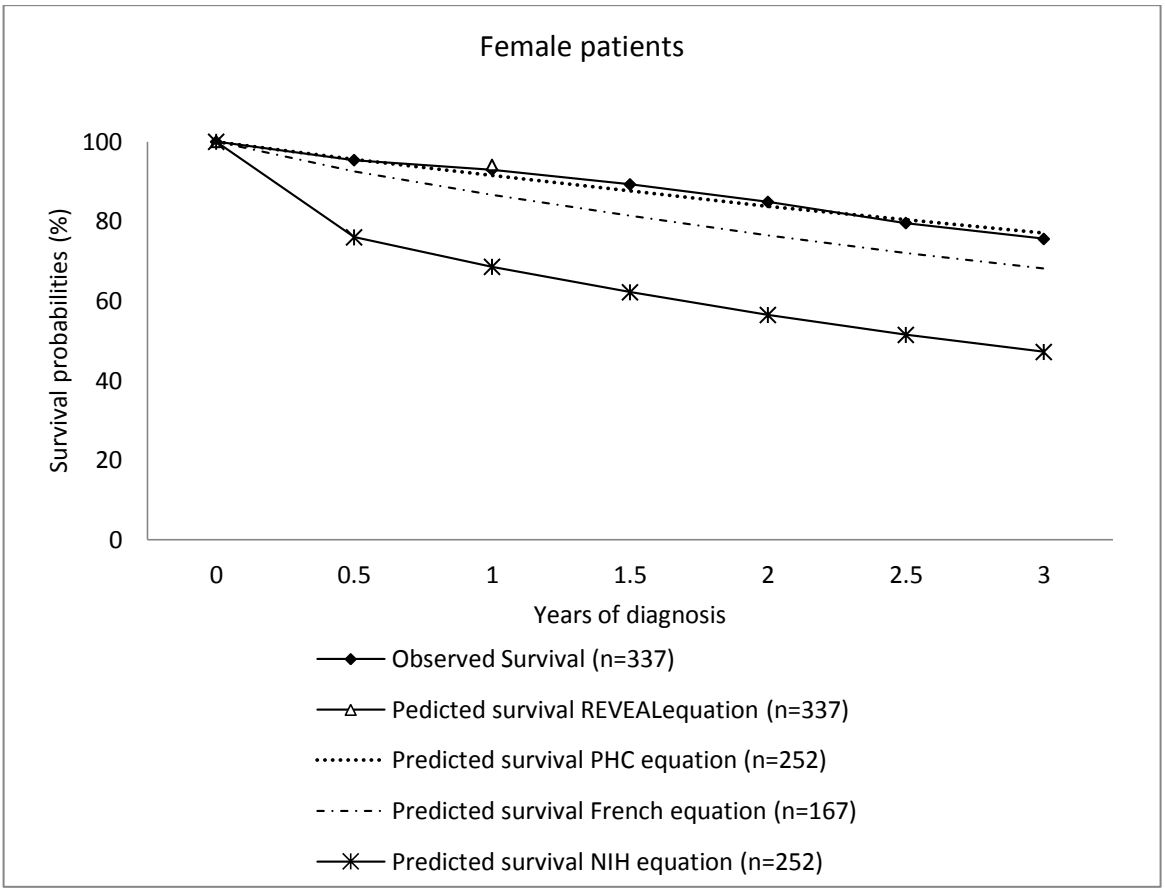


Figure 4.2. Observed versus predicted survival using the NIH equation, French equation, PHC equation and REVEAL equation for female idiopathic, heritable and anorexigen-associated PAH patients.

Comparisons of survival prediction equations in male patients:

In male idiopathic, heritable and anorexigen-associated PAH patients, the Brier score of the NIH equation was significantly higher compared with all other survival prediction models (Table 4.9). There was no difference in Brier scores between the REVEAL equation and REVEAL risk score in predicting 1 year survival of our male patients (Table 4.10). However, unlike in the female patients, the French equation also had higher Brier score compared with the PHC equation, REVEAL equation and REVEAL risk score for predicting 1-year survival of our male patients (Table 4.10). At 2 and 3 year, Brier score of the French equation for predicting survival of our male patients was significantly lower than the NIH equation but higher compared with the PHC equation (Tables 4.11 and 4.12). Figure 4.3 shows the survival curves of actual observed survival of the male patients versus predicted survival of the same patients calculated using the NIH, French, PHC and REVEAL equations.

Table 4.9. Comparison of 5 survival prediction models using the Brier scores for male idiopathic, heritable and anorexigen-associated PAH patients.

Males patients	**Brier scores via bootstrap (95% Confidence interval)**		
Survival prediction models	**1 year prediction**	**2 year prediction**	**3 year prediction**
NIH equation	0.1288 (0.1114 to 0.1474)	0.2240 (0.1956 to 0.2531)	0.2945 (0.2607 to 0.3295)
French equation	0.0892 (0.0706 to 0.1097)	0.1502 (0.1204 to 0.1828)	0.2396 (0.1982 to 0.2858)
PHC equation	0.0531 (0.0252 to 0.0880)	0.1045 (0.0683 to 0.1453)	0.1650 (0.1223 to 0.2147)
REVEAL equation	0.0418 (0.0163 to 0.0727)		
REVEAL risk score	0.0475 (0.0232 to 0.0768)		

Table 4.10. Brier scores differences via bootstrapping for 1-year prediction in male idiopathic, heritable and anorexigen-associated PAH patients.

Survival prediction models (male patients)	Brier score differences	95% Confidence Interval	p-value
French equation – REVEAL equation	0.0474	0.0229 to 0.0712	<0.001
NIH equation – REVEAL equation	0.0870	0.0565 to 0.1129	<0.001
PHC equation – REVEAL equation	0.0113	0.0016 to 0.0238	0.011
REVEAL risk score – REVEAL equation	0.0057	-0.0011 to 0.0128	0.102
French equation – PHC equation	0.0361	0.0060 to 0.0642	0.018
NIH equation – PHC equation	0.0757	0.0444 to 0.1029	<0.001
REVEAL risk score – PHC equation	-0.0056	-0.0162 to 0.0036	0.261
French equation – NIH equation	-0.0396	-0.0613 to -0.0161	0.002
REVEAL risk score – NIH equation	-0.0813	-0.1063 to -0.0524	<0.001
French equation – REVEAL risk score	0.0417	0.0185 to 0.0641	0.001

Table 4.11. Brier scores differences via bootstrapping for 2-year prediction in male idiopathic, heritable and anorexigen-associated PAH patients.

Survival prediction models (male patients)	Brier score differences	95% Confidence Interval	p-value
French equation – PHC equation	0.0457	-0.0053 to 0.0955	0.081
NIH equation – PHC equation	0.1194	0.0743 to 0.1618	<0.001
French equation – NIH equation	-0.0738	-0.1078 to -0.0360	<0.001

Table 4.12. Brier scores differences via bootstrapping for 3-year prediction in male idiopathic, heritable and anorexigen-associated PAH patients.

Survival prediction models (male patients)	Brier score differences	95% Confidence Interval	p-value
French equation – PHC equation	0.0747	0.0085 to 0.1403	0.027
NIH equation – PHC equation	0.1295	0.0671 to 0.1863	<0.001
French equation – NIH equation	-0.0549	-0.1051 to 0.0013	0.055

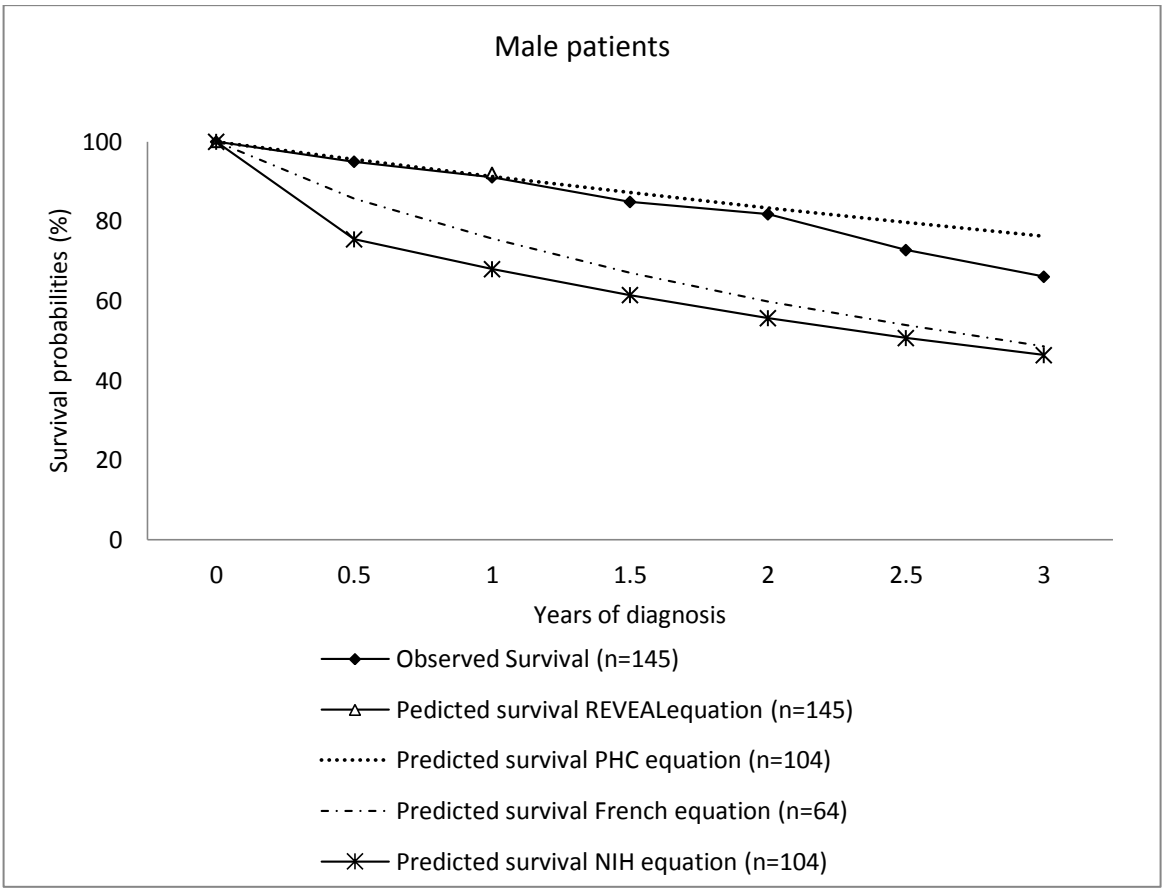


Figure 4.3. Observed versus predicted survival using the NIH equation, French equation, PHC equation and REVEAL equation for male idiopathic, heritable and anorexigen-associated PAH patients.

4.5 Discussion

We validated five PAH survival prediction equations with our incident cohort of idiopathic, heritable and anorexigen-associated PAH and demonstrated superiority of some prediction equations over others.

The ability to predict prognosis helps to guide treatment decisions. This includes selection of patients for prostacyclins and/or combination treatment and early consideration of lung transplantation. The NIH equation (26) was derived from a cohort of 194 patients with primary pulmonary hypertension (equivalent to idiopathic or heritable PAH in the latest Dana Point Classification) from the 1980s in the pre-disease targeted therapy era. This NIH equation was used in many clinical trials to suggest survival benefit of the study drug. The mean age of patients in the NIH registry was 36 years compared with 50 years in our patients. As discussed in Chapter 3, the epidemiology of idiopathic PAH has evolved and survival has improved since the NIH registry era. The NIH equation also underestimated survival when applied to cohorts of idiopathic PAH derived from participants of pulmonary hypertension clinical trials or other contemporary pulmonary hypertension registries (33, 40, 87). Our results confirmed that the NIH equation under- estimated survival of incident idiopathic, heritable and anorexigen-associated PAH in the UK and Ireland and should no longer be used in the current age of modern PAH therapies.

The French equation (37) also under-estimated survival of our study cohort. We believe there are three possible explanations. Firstly, the French equation may simply reflect outcomes of patients in France in 2002-2006, at a time when several currently approved PAH therapies were not yet available (37). Secondly, patients with less severe disease and/or those who remained stable on oral therapies may not be referred to one of the French University Hospitals. In contrast, our study is a truly national study inclusive of all idiopathic PAH patients of all severity in the UK and Ireland. Finally, in addition to using the same pulmonary function criteria as the French registry, we have also excluded patients with any radiological evidence of co-existing parenchymal lung disease from our study. These patients with co-existing lung disease (refers to as

precapillary PH with ‘co-existing lung disease’ in Chapter 7 of this thesis) otherwise fit the ‘standard’ haemodynamic criteria for idiopathic PAH and may be included in the French registry. However, despite similar short term improvement in 6 minute walk distance in response to PAH disease targeted therapies, these patients with ‘co-existing lung disease’ had worse survival compared with idiopathic PAH patients (see Chapter 7 for details). Interestingly, the French equation more accurately predicted survival of our female patients and significantly underestimated survival of our male patients. The male gender was also independently associated with worse survival in the French registry despite similar baseline characteristics and management between male and female patients.

Although the PHC equation and both REVEAL survival prediction models were derived from a mixed incident and prevalent population, they accurately predicted survival of our purely incident study cohort. The derivation cohort of both REVEAL survival models also included group I PAH patients with diagnosis other than idiopathic PAH. That did not appear to affect the performances of both REVEAL models in predicting survival of our patients which comprised of purely idiopathic, heritable and anorexigen-associated PAH patients only. Although some of the parameters in the REVEAL models were missing or not routinely performed in our patients, the REVEAL models were designed to handle missing data and did not appear to affect the performance of both REVEAL models. Although both REVEAL equation (57) and REVEAL risk score (76) had lower Brier scores than the PHC (23) equation, the differences were not statistically significant. In addition, analyses of REVEAL equation and risk score were limited to 1 year prediction only. As there was no difference in accuracy between the REVEAL equation (57), REVEAL risk score (76) and the PHC equation (23), user-friendliness of an survival prediction model may also influence its applicability in daily clinical practice.

All survival prediction models were better at predicting survival at 1 year than at longer terms. This is not unexpected as the course of disease of a patient can be highly variable. Any deteriorations and/or changes to treatment during follow-up may have an impact on their subsequent outcome.

The Scottish Composite Score was also developed recently to predict survival of incident PAH patients. A significant majority of the derivation cohort of the Scottish Composite Score came from patients in this study. The performance of the Scottish Composite Score was therefore not validated in this study.

The main limitation of our study is the unavoidable incompleteness in our dataset due to its observational nature, with a small amount of missing data and uneven frequency of follow-up and investigations performed at each visit.

4.6 Conclusion

Some survival prediction equations more accurately predict survival of incident idiopathic, heritable and anorexigen-associated PAH patients in the UK and Ireland than others. Differences in baseline characteristics, treatment practice and time period between our patients and survival equations derivation populations need to be taken into account when applying these equations in daily clinical practice.

5 Chapter 5: Effect of Age on Prognostic Factors in Incident Idiopathic, Heritable and Anorexigen-associated Pulmonary Arterial Hypertension

5.1 Summary

Rationale:

Younger and older idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension patients have different phenotypic characteristics and survival and may also have different prognostic predictors.

Objectives:

To determine the baseline prognostic factors associated with survival in idiopathic pulmonary arterial hypertension and to evaluate whether these prognostic predictors are different between younger and older patients.

Methods:

We studied 482 consecutive, incident, idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension diagnosed in all eight pulmonary hypertension centres in the UK and Ireland between 2001-2009. Patients with parenchymal lung disease (of any severity) on chest CT were excluded from this study. Patients were divided into younger (age ≤ 50 years) and older (age >50 years) subgroups by the median age at diagnosis.

Results:

Univariate survival analyses were performed in the age ≤ 50 and age > 50 subgroups. Body mass index (BMI) ≥ 30, lower 6 minute walk distance (6MWD), lower % predicted diffusion capacity for carbon monoxide (%DL_{CO}), higher mean pulmonary artery pressure and lower mixed venous oxygen saturations (SvO_2)

were markers of poor prognosis in the age ≤ 50 subgroup. In the age > 50 subgroup, male gender, BMI < 30, functional class IV, low 6MWD, low $\%DL_{CO}$, low SvO_2 and low cardiac index were associated with worse survival. Age, 6MWD and $\%DL_{CO}$ were independent predictors of survival of the whole cohort in multivariate analysis. Significant interactions were observed between age and BMI. BMI ≥30 was associated with better survival in the age > 50 subgroup but worse survival in the age ≤ 50 subgroup.

Conclusion:

Our results suggest prognostic variables in incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension may be different in younger and older patients. In addition, obesity may have a protective effect in older idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension patients.

5.2 Introduction

Numerous registries and clinical trials have reported on prognostic factors in idiopathic pulmonary arterial hypertension (22, 26, 36, 57, 74, 88). However, prevalent patients are over-represented in many of these studies, and prevalent patients have better outcomes when compared with incident patients (37). We have shown in the previous chapter of this thesis (Chapter 3) that younger (age ≤ 50 years) and older (age > 50 years) incident idiopathic, heritable and anorexigen-associated PAH patients have different phenotypes and survival (89). We hypothesised that prognostic factors other than age itself may also be different in younger versus older incident idiopathic, heritable and anorexigen-associated PAH patients. All patients with idiopathic, heritable and anorexigen-associated PAH are diagnosed and treated in designated pulmonary hypertension centres in the UK and Ireland. This provides a unique opportunity to study the prognostic significance of various variables in a large national, purely incident cohort of patients. Potential survival bias introduced by prevalent patients is avoided as our study included only incident cases. Furthermore, unlike the highly selected patients in clinical trials, our patients are representative of real life patients seen in day to day practice.

5.3 **Methods**

This was a longitudinal observational study of all consecutive, newly diagnosed, treatment-naive idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension (PAH) patients diagnosed in all eight pulmonary centres in the UK and Ireland between 1st January 2001 and 31st December 2009. Details of inclusion and exclusion criteria of idiopathic, heritable and anorexigen-associated PAH have been described in the previous chapter (Chapter 3.3: Methods). The date of diagnostic right heart catheterisation was taken as the date of diagnosis. Body mass index (BMI) values were calculated using height and weight values at the time of diagnostic right heart catheterisation. All patients were treatment naive prior to their diagnosis of idiopathic, heritable and anorexigen-associated PAH. The choice of pulmonary hypertension treatment started at diagnosis was at the discretion of the treating pulmonary hypertension specialist and in accordance with contemporary pulmonary hypertension guidelines (5, 80, 90). Patients were divided into younger (age ≤ 50) and older (age > 50) subgroups according to the median age at the time of diagnosis. This study was designed and conducted to describe current care and hence formal ethics approval was deemed unnecessary by the West of Scotland Research Ethics Committee.

Statistical analysis:

Statistical analysis was performed using SPSS 19 (SPSS Inc, Chicago, IL). Continuous variables were described by mean ± standard deviation and categorical variables described by frequencies and percentages unless otherwise indicated. Continuous variables were compared using student t-test or Mann Whitney U test. Categorical variables were compared using x^2 or Fisher exact test. Paired t-test was used to compare the difference between mean values of 6-minute walk distance (6MWD) at baseline and follow-up. Survival was estimated from the time of diagnosis and survival endpoint taken as either the date of death or date of censoring. Patients were censored if they were transplanted (n=14), lost to follow up (date of last visit to pulmonary hypertension centre was used as censor date) or if they were alive on the last

day of the study (31st December 2009). All cause mortality was used for survival analysis.

Patients were divided into younger (age ≤ 50) and older (age > 50) subgroups according to the median age at diagnosis. Univariate Cox regression analyses were performed to identify baseline variables that predicted survival in the whole cohort, and in the younger and older subgroups. Variables considered were as follows: age, gender, ethnicity, BMI, duration of symptoms, functional class, 6MWD, diffusion capacity for carbon monoxide (DL_{CO}) and haemodynamics parameters. BMI was re-coded as non-obese (BMI <30) and obese (BMI ≥ 30). Variables with $p < 0.1$ in the univariate analyses were entered into the multivariate Cox regression analysis. To allow inclusion of all patients in survival analyses, a missing data category (data available or data missing) was created for each covariate and included in the multivariate model when that covariate was analysed.

The analyses of age-variable interactions were used to investigate whether the effect of variables on survival depended on the age of patients. The product of the two variables was included in the model to describe the interaction. Two variables were said to interact in the effect on survival if the effect of the first variable was significantly different at the different levels of the second variable. Results of all Cox regression analyses were expressed as hazard ratios with 95% confidence interval. The survival analyses were repeated with time from onset of symptoms as the start of follow-up to account for potential lead time bias introduced by differential delay in diagnosis between younger and older patients. P-value <0.05 were considered significant throughout.

5.4 **Results**

Baseline characteristics, treatment and survival of study cohort:

A total of 482 idiopathic, heritable and anorexigen-associated PAH patients fulfilled the inclusion criteria and were included in the analyses. Selective baseline characteristics of patients and first-line treatment started at the time of diagnosis are shown in table 5.1. Detailed descriptions of baseline characteristics of the study cohort can be found in previous chapter (Chapter 3). Kaplan Meier survival estimates at 1, 2, 3 and 5 years were 92.7%, 84.0%, 73.3% and 61.1% respectively.

Table 5.1. Baseline variables and first line treatment started at diagnosis for study cohort (n=482).

	Mean (SD) or %(n)
Age, years (n=482)	50.1(17.1)
Gender (n=482):	
% female	69.9%(337)
WHO functional class (n=456):	
I/II	15.5%(72)
III	66.7%(304)
IV	17.5%(80)
BMI ≥ 30 (n=398)	33.9%(135)
6MWD, metres (n=260)	292.4(123.0)
% DL_{CO} (n=331)	62.0%(20.9)
Haemodynamics:	
mPAP, mmHg (n=457)	54.1(13.9)
SvO_2, % (n=395)	61.5(9.5)
Cardiac index, $L.min^{-1}.m^{-2}$ (n=366)	2.1(0.7)
PVRI, $WU.m^2$ (n=355)	23.1(10.3)
Treatment started at the time of diagnosis: (n=479)	
Endothelin receptor antagonist	44.3%(212)
Phosphodiesterase 5 inhibitor	29.2%(140)
Prostaglandins	18.8%(90)
Calcium channel blocker	5.0%(24)
Combination therapy	2.1%(10)
None	0.6%(3)

Definition of abbreviations: 6MWD= 6 minute walk distance, BMI = body mass index, % DL_{CO}= % predicted diffusion capacity for carbon monoxide, mPAP= mean pulmonary artery pressure, mRAP= mean right atrial pressure, PAOP= pulmonary artery occlusion pressure, PVR= pulmonary vascular resistance, PVRI= pulmonary vascular resistance index, SvO_2= mixed venous oxygen saturation, WU= Wood Units.

Predictors of survival at baseline:

Univariate Cox regression analyses (Table 5.2) showed BMI ≥ 30, lower 6MWD, lower $\%DL_{CO}$, higher mean pulmonary artery pressure (mPAP) and lower mixed venous oxygen saturation (SvO_2) as markers of poor prognosis in the age ≤ 50 subgroup. In the age >50 subgroup, male gender, BMI < 30, functional class IV, low 6MWD, low $\%DL_{CO}$, low SvO_2 and low cardiac index were associated with worse survival.

The results of first order interaction between age-BMI and age-mPAP in the whole cohort were shown in Table 5.3. Interaction terms between age and all other variables were not significant at $p<0.05$. Regardless of the BMI or mPAP, patients in the age > 50 subgroup had poorer survival. In the age > 50 subgroup, patients with BMI ≥ 30 had a lower risk of death whereas in the age ≤ 50 subgroup, patients with BMI ≥ 30 had a higher risk of death. The test for an age-BMI interaction on survival indicated a highly statistically significant risk difference. Similarly, the test for an age-mPAP interaction on survival also indicated a statistically significant risk difference.

As significant first order interaction was found between age-BMI and age-mPAP, a multivariate Cox regression model containing interaction terms between age and these two variables (in addition to variables that were significant in the univariate analyses) were considered. The interaction term between age-mPAP was no longer significant in the final model. The final model with both interactions terms is shown in Table 5.4. Age, 6MWD, $\%DL_{CO}$ and SvO2 were independent predictors of survival. In patients aged > 50, BMI ≥ 30 were associated with better survival (hazard ratio = 0.326, p = 0.016). The interaction between age and BMI remained significant when survival analysis was repeated using time from onset of symptom as the start of follow-up (Table 5.5, Table 5.6 and Table 5.7).

Table 5.2. Univariate Cox proportional hazard regression analyses of baseline variables predictive of survival in the whole cohort and by age subgroups (age ≤50 years and age > 50 years).

Univariate analyses	All patients		Age ≤ 50 years subgroup		Age > 50 years subgroup	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Age ≤ 50 Age >50	<0.001	1 3.012 (2.078–4.366)		N/A		N/A
Female Male	0.131	1 1.326 (0.919-1.914)	0.924	1 0.967 (0.486-1.925)	0.048	1.556 (1.003-2.412)
White Non-white	0.037	1 0.442 (0.205-0.953)	0.072	1 0.161 (0.022-1.181)	0.429	1 0.712 (0.308-1.650)
BMI < 30 BMI ≥ 30	0.931	1 0.982 (0.649-1.486)	0.030	1 2.170 (1.078-4.368)	0.012	1 0.512 (0.303-0.865)
WHO FC I+II III IV	0.019 0.010 0.006	1 2.368 (1.230-4.558) 2.816 (1.339-5.921)	0.055 0.053 0.988	1 3.216 (0.983-10.521) 1.014 (0.169-6.074)	0.045 0.147 0.019	1 1.794 (0.815-3.950) 2.808 (1.188-6.639)
6MWD	<0.001	0.994 (0.992-0.996)	0.015	0.995 (0.991-0.999)	0.002	0.995 (0.993-0.998)
$\%DL_{CO}$	<0.001	0.974 (0.964-0.985)	<0.001	0.967 (0.949-0.985)	0.027	0.986 (0.973-0.998)
mRAP	0.012	1.037 (1.008-1.067)	0.092	1.047 (0.993-1.103)	0.113	1.027 (0.994-1.062)
mPAP	0.462	1.005 (0.992-1.018)	0.001	1.031 (1.012-1.051)	0.637	0.997 (0.982-1.011)

Univariate analyses	All patients		Age ≤ 50 years subgroup		Age > 50 years subgroup	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
S_VO_2	<0.001	0.955 (0.937-0.974)	0.004	0.954 (0.924-0.985)	0.002	0.958 (0.933-0.984)
CI	0.013	0.669 (0.487-0.919)	0.442	0.812 (0.477-1.382)	0.007	0.562 (0.371-0.852)

N/A = not applicable

Definition of abbreviations: 6MWD = six minute walk distance, BMI = body mass index, CI = cardiac index, $\%DL_{CO}$ = % predicted diffusion capacity for carbon monoxide, HR = hazard ratio, mPAP = mean pulmonary artery pressure, RAP = mean right atrial pressure, SvO2 = mixed venous oxygen saturations, WHO FC = World Health Organisation functional class.

Table 5.3. First order interaction between age and baseline variables.

	p-value	Hazard ratio	95% confidence interval
Model 1.			
Age > 50	<0.001	5.012	2.992 – 8.396
BMI ≥ 30	0.031	2.154	1.071 – 4.332
Age > 50 * BMI ≥ 30	0.001	0.240	0.100 – 0.574
Model 2.			
Age > 50	<0.001	20.789	4.545 - 95.090
mPAP	0.001	1.031	1.012 – 1.050
Age > 50 * mPAP	0.008	0.996	0.942 – 0.991

Age ≤ 50 and BMI < 30 were the reference groups.

Definition of abbreviations: See Table 5.2.

Table 5.4. Multivariate Cox proportional hazard regression analysis of baseline variables predictive of survival of the whole cohort (with interaction terms).

Multivariate analysis	All patients	
	p-value	HR (95% CI)
Age > 50	<0.001	3.784 (2.152-6.653)
Non-white	0.084	0.502 (0.230-1.096)
Functional class III	0.242	1.508 (0.758-3.001)
Functional class IV	0.533	1.291(0.579-2.877)
6MWD	0.013	0.997 (0.994-0.999)
$\%DL_{CO}$	0.002	0.982 (0.971-0.994)
mRAP	0.404	1.015 (0.980-1.052)
S_VO_2	0.057	0.976 (0.951-1.001)
CI	0.292	0.810 (0.548-1.198)
BMI ≥ 30	0.096	1.862 (0.895-3.874)
mPAP	0.601	1.004 (0.989-1.019)
Interactions:		
Age > 50 * BMI ≥ 30	0.016	0.327 (0.132-0.872)
Age > 50 * mPAP	0.632	0.584 (0.065-5.275)

Definition of abbreviations: See Table 5.2.

Table 5.5. Univariate Cox proportional hazard regression analyses of baseline variables predictive of survival in whole cohort using time from onset of symptoms as 'times zero' for survival analyses.

Univariate analyses	All patients		Age ≤ 50 years subgroup		Age > 50 years subgroup	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Age ≤ 50 Age >50	<0.001	1 2.788 (1.842-4.222)				
Female Male	0.205	1 1.307 (0.864-1.977)	0.852	1 0.874 (0.379-2.016)	0.145	1 1.435 (0.883-2.330)
White Non-white	0.044	1 0.393 (0.159-0.973)	0.119	1 0.204 (0.028-1.509)	0.513	1 0.711 (0.256-1.975)
BMI < 30 BMI ≥ 30	0.811	1 0.946 (0.600-1.491)	0.080	1 2.003 (0.920-4.364)	0.029	1 0.530 (0.299-0.938)
WHO FC I+II III IV	0.059 0.019 0.039	1 2.397 (1.156-4.969) 2.448 (1.046-5.728)	0.037 0.045 0.828	1 4.323 (1.031-18.134) 0.766 (0.069-8.454)	0.210 0.371 0.103	1 1.475 (0.629-3.459) 2.207 (0.852-5.715)
6MWD	0.001	0.996 (0.994-0.998)	0.176	0.997 (0.993-1.001)	0.144	0.998 (0.994-1.001)
$\%DL_{CO}$	<0.001	0.978 (0.967-0.988)	0.002	0.971 (0.952-0.989)	0.080	0.988 (0.974-1.001)
mRAP	0.008	1.044 (1.011-1.077)	0.056	1.062 (0.999-1.128)	0.179	1.025 (0.989-1.062)
mPAP	0.820	1.002 (0.988-1.016)	0.047	1.021 (1.000-1.043)	0.897	1.001 (0.981-1.022)

Univariate analyses	All patients		Age ≤ 50 years subgroup		Age > 50 years subgroup	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
S_VO_2	<0.001	0.952 (0.932-0.972)	0.003	0.946 (0.912-0.982)	0.006	0.962 (0.936-0.989)
CI	0.008	0.610 (0.424-0.878)	0.243	0.678 (0.354-1.301)	0.005	0.518 (0.327-0.820)

Definition of abbreviations: See Table 5.2.

Table 5.6. First order interaction between age and body mass index using time from onset of symptoms as 'times zero' for survival analyses. Interaction terms between age and all other variables were not significant.

Model	p-value	Hazard ratio	95% confidence interval
Age > 50	<0.001	4.641	2.584-8.337
BMI ≥ 30	0.060	2.112	0.969-4.603
Age > 50 * BMI ≥ 30	0.005	0.253	0.096-0.665

Age ≤ 50 and BMI < 30 were the reference groups.

Table 5.7. Multivariate Cox proportional hazard regression analysis of baseline variables predictive of survival in the whole cohort (with interaction terms) using time from onset of symptoms as 'times zero' for survival analyses.

Multivariate analysis	All patients	
	p-value	Hazard ratio (95% CI)
Age > 50	0.003	2.650 (1.404-5.000)
Non-white	0.209	0.547 (0.214-1.401)
Functional class III	0.272	1.544 (0.711-3.351)
Functional class IV	0.480	1.406 (0.547-3.613)
6MWD	0.173	0.998 (0.995-1.001)
$\%DL_{CO}$	0.004	0.982 (0.969-0.994)
mRAP	0.420	1.015 (0.979-1.053)
SvO_2	0.174	0.980 (0.953-1.009)
CI	0.087	0.681 (0.438-1.057)
BMI ≥ 30	0.157	1.787 (0.800-3.993)
Interactions:		
Age > 50 * BMI ≥ 30	0.028	0.327 (0.121-0.885)

Definition of abbreviations: See Table 5.2.

Age, body mass index and survival:

BMI had a normal distribution in our patients (Figure 5.1). Compared with non-obese patients, obese patients were older, more likely to be female, had higher right atrial and pulmonary artery occlusion pressure and were more likely to have systemic hypertension and diabetes. When analysed within age-subgroups, the above differences between non-obese and obese patients remained significant in the older (age > 50) subgroup only (Table 5.8). There were no significant differences in duration of symptoms, functional class, haemodynamic impairment (mPAP, SvO_2 and pulmonary vascular resistance index), choice of first line treatment and proportion who received combination therapy between non-obese and obese patients when analysed within age-subgroups.

Figure 5.2 showed the Kaplan Meier survival curves of incident idiopathic, heritable and anorexigen-associated PAH according to age and BMI. Unadjusted mean survivals of patients with different BMI are shown in Figure 5.3. In the younger subgroup (age ≤ 50), the best survival was observed in those with normal BMI. In the older subgroup (age > 50), underweight patients had the worst survival, followed by normal weight patients, with mildly obese patients having the best survival.

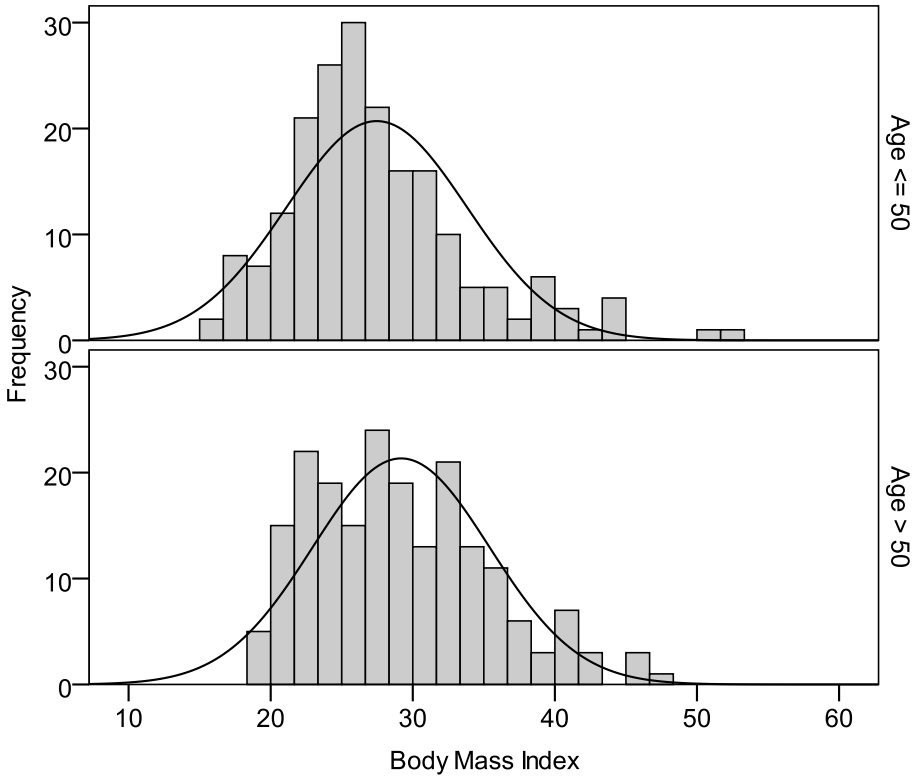
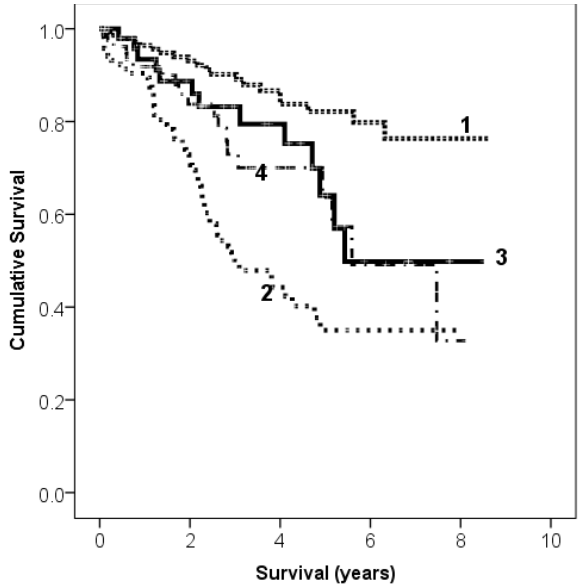


Figure 5.1. Distribution of BMI values displayed a bell-shaped, normal distribution in both younger (age ≤ 50) and older (age > 50) subgroups.



Years from diagnosis	0	2	4	6	8
No at risk					
1	144	103	59	28	4
2	119	63	22	7	0
3	54	32	18	5	0
4	81	38	14	5	0

Figure 5.2. Kaplan Meier survival curves of obese versus non-obese patients according to age subgroups.

IPAH refers to patients with idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension, BMI = body mass index.

1 = Younger subgroup and non obese (Age ≤ 50 and BMI < 30),

2 = Older subgroup and non obese (Age > 50 and BMI < 30),

3 = Younger subgroup and obese (Age ≤ 50 and BMI ≥ 30) and

4 = Older subgroup and Obese (Age > 50 and BMI ≥ 30).

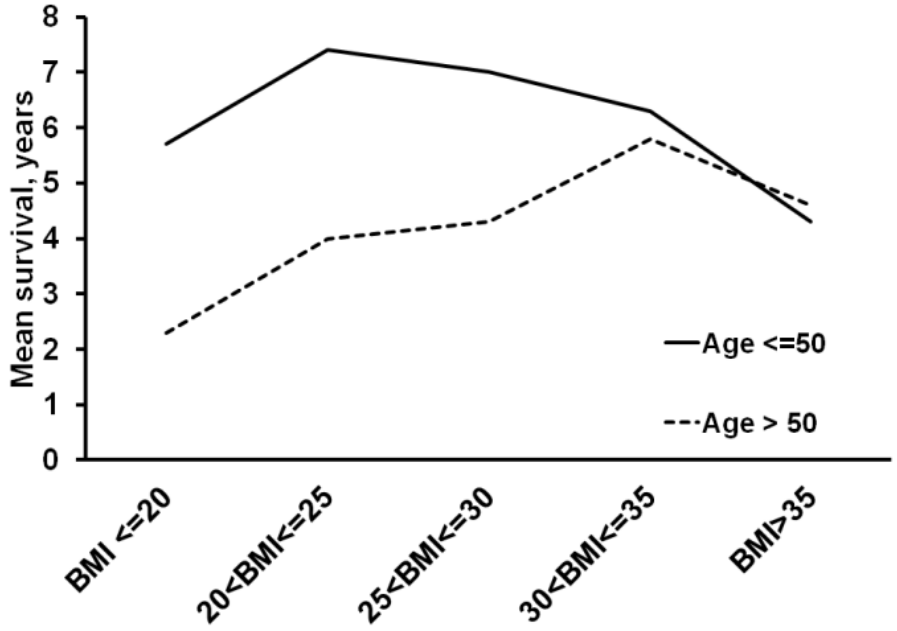


Figure 5.3. Survival of idiopathic, heritable and anorexigen-associated PAH according to age and body mass index.

In the older idiopathic, heritable and anorexigen-associated PAH subgroup (age > 50), underweight patients had the worst survival, followed by normal weight patients, with mildly obese patients having the best survival. In the younger subgroup (age ≤ 50), patients with normal BMI had the best survival.

Table 5.8. Comparison of baseline characteristics of obese (BMI ≥ 30) and non obese (BMI < 30) incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension in younger (age ≤ 50) and older (age > 50) age subgroups.

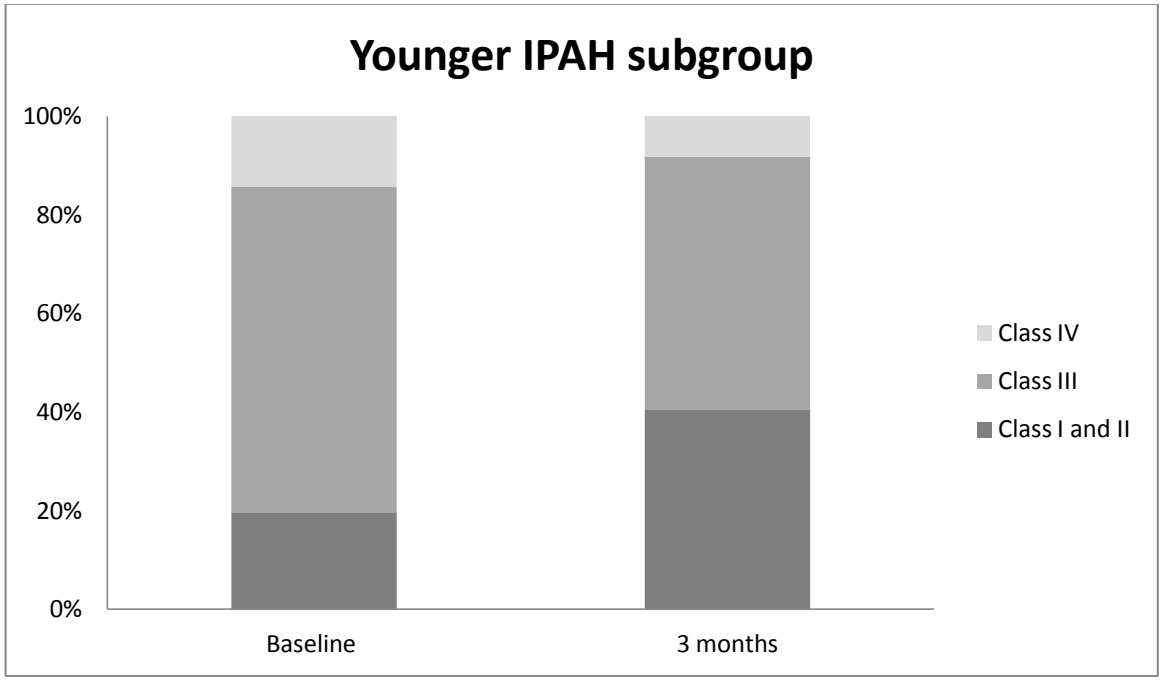
	Younger subgroup (age ≤50)			Older subgroup (age >50)		
	BMI<30	**BMI≥30**	**p-value**	**BMI<30**	**BMI≥30**	**p-value**
% female	68.8%(99)	81.5%(44)	NS	61.3%(73)	75.3%(61)	0.039
Median duration, months	12.0 (6.0-24.0)	13.0 (8.0-24.0)	NS	24.0 (12.0-6.0)	24.0 (12.0-6.0)	NS
WHO FC I/II III IV	 20.1%(27) 69.4%(93) 10.4%(14)	 13.7%(7) 72.5%(37) 13.7%(7)	 NS	 11.1%(13) 71.8%(84) 17.1%(20)	 11.8%(9) 67.1%(51) 21.1%(16)	 NS
6MWD	355.3 (101.7)	278.4 (121.1)	<0.001	249.7 (109.2)	249.4 (112.7)	NS
%DLCO	66.6 (17.7)	67.2 (19.9)	NS	54.0 (20.8)	59.9 (24.3)	NS
RAP	9.1(5.4)	10.7(6.0)	NS	8.9(5.3)	11.5(6.7)	0.003
mPAP	57.4 (16.1)	55.0 (11.7)	NS	50.4 (12.7)	50.8 (11.8)	NS
PAOP	8.6(3.4)	8.9(3.7)	NS	8.9(3.3)	10.3(3.8)	0.008
CI	2.2(0.8)	2.0(0.7)	0.024	2.1(0.7)	2.1(0.7)	NS
S_vO_2	63.6(10.1)	61.1(9.9)	NS	60.8(8.3)	61.1(8.4)	NS
PVRI	24.8 (11.7)	25.3 (10.2)	NS	21.7 (9.3)	21.1 (9.1)	NS
Comorbidities: IHD Hypertension Diabetes	 0.7%(1) 7.4%(10) 2.2%(3)	 3.7%(2) 17.0%(9) 17.0%(9)	 NS 0.050 0.001	 22.7%(27) 38.6%(44) 14.0%(16)	 24.7%(20) 45.6%(36) 38.0%(30)	 NS NS <0.001

Definition of abbreviations: IHD = ischaemic heart disease, NS = not significant, PAOP = pulmonary artery occlusion pressure, PVRI = pulmonary vascular resistance index and see Table 5.2.

Age and response to treatment:

Two types of walk tests (6-minute walk and incremental shuttle walk) are used to assess exercise capacity in the UK and Ireland. Patients whose exercise capacity were assessed using the incremental shuttle walk test were not included in the analysis of 6MWD. Paired baseline and 3 months 6MWD data were available in 158 patients. The mean increase in 6MWD at 3 months was 39.5 m (95% CI = 28.1 - 51.0 m) from baseline. The magnitude of change in 6MWD at 3 months in response to treatment was not statistically different between younger (age ≤ 50) and older (age > 50) patients. In the younger subgroup, after 3 months of treatment, 40.4% (n= 59), 51.4% (n=75) and 8.2% (n=12) were in functional class I/II, III and IV respectively (Figure 5.4a). In the older subgroup, after 3 months of treatment, 23.9% (n=28), 67.5% (n=79) and 8.5% (n=10) were in functional class I/II, III and IV respectively, p=0.016 (Figure 5.4b).

5.4a



5.4b

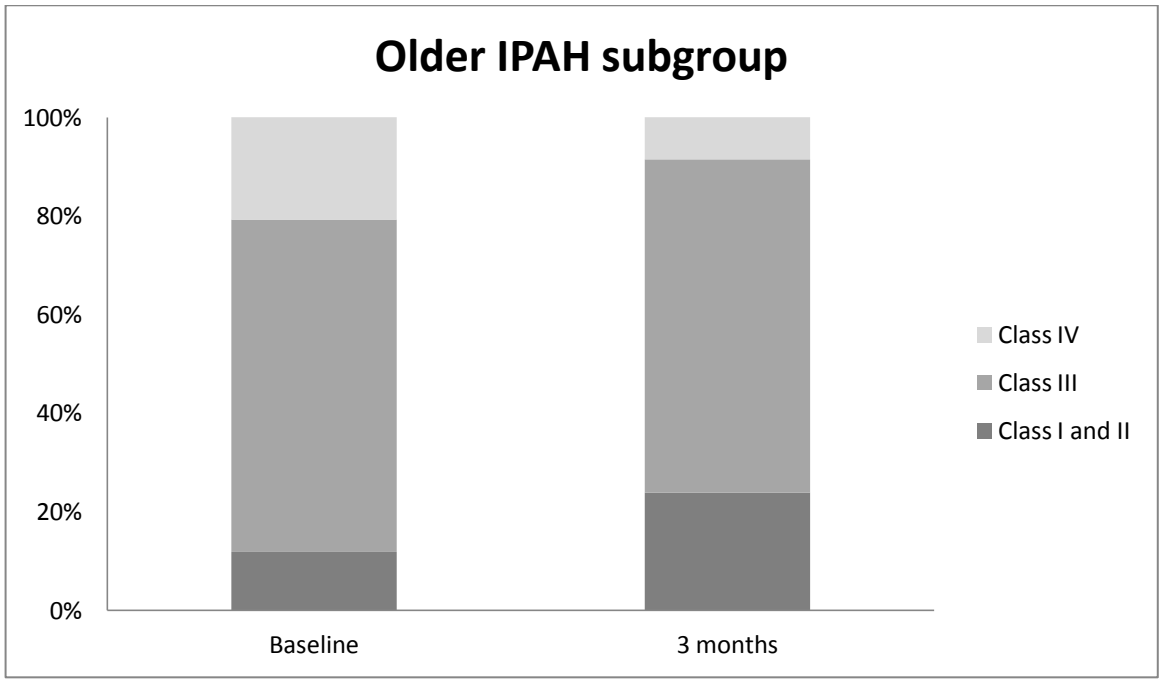


Figure 5.4. Distribution of functional class at baseline and at 3-month follow up according to age subgroups.

IPAH refers to patients with idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension.

5.5 Discussion

We have shown in the previous chapter of this thesis (Chapter 3) that there was a difference in overall survival between idiopathic, heritable and anorexigen-associated PAH patients who were younger and older than 50 years old (89). In this chapter, we further explored the hypothesis that variables predictive of patients' outcomes may also be different between younger and older idiopathic, heritable and anorexigen-associated PAH patients. Our results suggested that prognostic variables may be different in younger and older incident idiopathic, heritable and anorexigen-associated PAH patients. Obesity was associated with better survival in older patients but worse survival in younger patients.

The present study demonstrated that age, 6MWD, $\%DL_{CO}$ and SvO_2 were independent predictors of survival in the whole incident idiopathic, heritable and anorexigen-associated PAH cohort. This is consistent with results from previously published studies (22, 46, 57, 91). Although prognostic baseline variables of idiopathic PAH have been reported from registries and clinical trials, very few large studies had focused on purely incident, treatment-naive idiopathic PAH patients only. Contrary to results from the French (33) and REVEAL (57) registries that were comprised predominantly of prevalent patients, gender was not predictive of survival in multivariate analysis in our study. One possible explanation may be the over-representation of lower risk female patients in prevalent patients in the French and REVEAL registries. That potential bias is avoided in our study which comprised wholly of incident patient. Gender was also not predictive of survival in the NIH (26) registry (64% incident patient), Chinese registry (31) (100% incident patient) and the Israeli (36) registry (100% incident patient) that comprised predominantly or wholly of incident patients. The reason for the survival advantage of female idiopathic PAH patients observed in the French and REVEAL registries is unclear as male and female patients have similar baseline characteristics and received similar treatment. Baseline demographics and haemodynamics parameters of idiopathic PAH patients in the French (22) registry were similar to our study cohort whereas female preponderance was more marked in the REVEAL idiopathic PAH

population (female:male ratio 4.1:1)(35) compared with our study cohort (ratio 2.3:1).

We found prognostic parameters independently associated with survival are different in younger and older patients. This is not surprising as younger and older incident idiopathic PAH patients have different characteristics and survival (89). As discussed in Chapter 3, compared with younger incident idiopathic, heritable and anorexigen-associated PAH patients, older patients had longer duration of symptoms, more co-morbidities (ischaemic heart disease, hypertension, atrial fibrillation, diabetes and hypothyroidism), worse functional class and exercise capacity, lower $\%DL_{CO}$, lower mPAP and lower PVRI. Another possible explanation may be the difference in treatment between younger and older patients. In our study cohort, higher proportion of younger patients received combination therapy compared with their older counterparts.

The association between obesity and mortality in younger patients but survival in older patients as observed in our study has not been reported previously in idiopathic, heritable and anorexigen-associated PAH. In our study, younger idiopathic, heritable and anorexigen-associated PAH patients with normal body mass index (BMI 20-25) have the longest survival, with excess mortality at both extremes of BMI. This U-shaped relationship between mortality and BMI is also noted in the general population (92). On the contrary, older patients in our study who were overweight or obese (BMI>25) have better survival compared with those who were normal or under-weight. Similar to findings from the REVEAL registry (93), obese idiopathic, heritable and anorexigen-associated PAH patients in our study were also older, had more co-morbidities and higher right atrial pressure compared with non-obese. To avoid the confounding effect of age, we compared baseline characteristics and survival of obese versus non-obese patients in two different age-subgroups divided according to the median age. We found no significant differences in delay before diagnosis, severity of pulmonary hypertension or treatment to explain the discrepancy in survival between obese and non-obese patients.

Although several recent studies have reported on the protective effect of obesity in pulmonary hypertension (88, 94, 95), no studies to date have examined the

relationship between age, obesity and survival. In addition, the population studied were heterogeneous, comprising of patients in different PAH aetiologies, a mixture of pre-and post capillary pulmonary hypertension or highly selective patients participating in clinical trials (88, 94, 95). However, baseline characteristics and outcomes are different according to the PAH aetiologies and grouping various PAH aetiologies together may introduce bias. Idiopathic PAH patients had higher BMI and percentage of obese patients whereas PAH associated with connective tissue disease, congenital heart disease and HIV had lower BMI compared with the general population (93).

The 'obesity paradox' of older idiopathic, heritable and anorexigen-associated PAH patients as observed in this study has also been reported in the general elderly population and in patients with heart failure, cancer, after cardiac surgery, percutaneous coronary intervention and in patients on haemodialysis (96-99). Several hypotheses have been proposed to explain the apparent improved survival of obese patients. Obese patients may be younger and 'healthier' than their leaner counterparts. That does not appears to be the case in our patients. Adipose tissue has been shown to produce soluble tumour necrosis factor receptor, thought to neutralise the deleterious effects of tumour necrosis factor-α on the myocardium (100, 101). Obese patients have higher lipoprotein concentrations that may bind and remove circulating endotoxins that play a role in stimulating the release of inflammatory cytokines (97, 102).

The relationship between obesity and all cause mortality appears conflicting between younger and older patients in our study. However, BMI may not be the optimal parameter for assessing the relationship between age, obesity and health outcomes. Age-dependent height decreases may induce a false BMI increase in elderly patients despite minimal changes in body weight. Older patients may have different body fat and lean muscle composition and distribution compared with younger patients despite similar BMI. Older obese patients may also have better preservation of cognitive function, protection from oesteoporosis and better energy reserve compared with their non-obese counterparts (96).

The strength of this study is the inclusion of only incident, treatment-naive idiopathic, heritable and anorexigen-associated PAH. Our study population is homogeneous, and potential survival bias introduced by the inclusion of prevalent patients was avoided. As pulmonary hypertension is diagnosed and treated in designated pulmonary hypertension centres only in the UK and Ireland, it is likely we have included nearly all cases of idiopathic, heritable and anorexigen-associated PAH diagnosed and treated over the study period in the region. In the UK and Ireland, all PAH patients were diagnosed in designated centres by PH specialists in a multidisciplinary setting. We therefore believe it is unlikely many patients in this study were misclassified.

The main limitation of our study is the observational nature of the study. There may be unseen confounding factors that may influence survival results. Many variables such as biomarkers or quality of life scores that may have additional prognostic values were not collected or had too many missing data. We have not controlled for treatment. Finally, our results are not generalisable to patients with other PAH aetiologies.

Our results should be considered as hypothesis-generating. Future studies looking into the effect of aging, obesity, insulin resistance and metabolic syndrome on the pulmonary vasculature and right ventricle may provide insights to explain this survival discrepancy between younger and older idiopathic PAH patients. In addition to BMI, additional measures of adiposity such as mid arm circumference, waist circumference or waist to hip ratio should also be considered when examining the relationship between obesity and survival.

5.6 Conclusion

Our data suggest prognostic variables may be different in younger and older incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension. Obesity may have a protective effect in older idiopathic, heritable and anorexigen-associated PAH patients.

6 Chapter 6. Prognostic Significance of Change in Six Minute Walk Distance and Functional Class in Incident Idiopathic, Heritable and Anorexigen associated Pulmonary Arterial Hypertension.

6.1 Summary

Rationale:

Pulmonary arterial hypertension treatment has been approved based on changes in six minute walk distance (6MWD) after 12-16 weeks of treatment. However, previous work has suggested that improvement in 6MWD with treatment does not impact on survival.

Objectives:

To evaluate whether short term changes in 6MWD and functional class in response to treatment translates into long term survival difference.

Methods:

482 consecutive, incident, treatment-naive idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension diagnosed in all eight pulmonary hypertension centres in the UK and Ireland between 2001-2009 were included.

Results:

Patients with more severe exercise limitations (6MWD ≤ 318 m) and worse functional class (III/IV) at baseline had greater improvement in 6MWD in response to treatment. Change in 6MWD >36 m at 3 months was associated with better survival but only in patients with baseline 6MWD ≤ 318 m. At 6 months follow-up, patients who improved from baseline functional class III/IV to I/II

have similar survival, whereas patients who deteriorated from baseline functional class I/II to III/IV have worse survival compared with patients who remained in functional class I/II at baseline and follow-up.

Conclusions:

Change in 6MWD after 3 months of treatment predicts survival in patients with more impaired baseline exercise tolerance. Change in functional class after 6 months of treatment also has prognostic implication.

6.2 Introduction

Despite recent advances in diagnosis and treatment, idiopathic pulmonary arterial hypertension (PAH) remains largely a progressive disease with a fatal outcome. Knowledge of adverse predictors of outcome at the time of diagnosis and subsequent follow up helps to identify patients who may benefit from early aggressive treatment and from closer monitoring. Change in six minute walk distance (6MWD) after 12-16 weeks of treatment has been used as the primary endpoint in many pivotal clinical trials. However, the consensus view is that although baseline 6MWD predicts survival, change in 6MWD may not. There is also recent evidence suggesting interval change in variables other than 6MWD in response to treatment may have additional prognostic values (103, 104). However, the course of disease of each individual idiopathic PAH patient is highly variable whereas the optimal tools and timing of follow up remain uncertain. In the United Kingdom (UK) and Ireland, all newly diagnosed, treatment naive patients with idiopathic, heritable and anorexigen-associated PAH were diagnosed and treated in designated pulmonary hypertension centres. This provides a unique opportunity to study the prognostic significance of various variables in a large national, purely incident cohort of patients.

The aim of this study was to evaluate the prognostic significance of short term changes in 6MWD and functional class (FC) in response to treatment in patients with idiopathic, heritable and anorexigen-associated PAH.

6.3 **Methods**

We performed a longitudinal observational study of all consecutive, newly diagnosed, treatment naive idiopathic, heritable and anorexigen-associated PAH patients diagnosed in all eight pulmonary hypertension centres in the UK and Ireland between 1st January 2001 and 31st December 2009. Details of inclusion and exclusion criteria of idiopathic, heritable and anorexigen-associated PAH have been described in previous chapter (Chapter 3.3: Methods). The date of diagnostic right heart catheterisation was taken as the date of diagnosis. Data were collected for 6MWD and FC assessment performed at fixed time points (baseline, three and six months) from the time of diagnosis. The choice of pulmonary hypertension treatment started at diagnosis was at the discretion of the treating pulmonary hypertension specialist and in accordance with contemporary pulmonary hypertension guidelines (5, 80, 81). This study was designed and conducted to describe current care and hence formal ethics approval was deemed unnecessary by the West of Scotland Research Ethics Committee.

Statistical analysis:

Statistical analysis was performed using SPSS 19 (SPSS Inc, Chicago, IL) and SAS (SAS institute, Cary, NC). Continuous variables were described by mean ± standard deviation and categorical variables described by frequencies and percentages unless otherwise indicated. Survival was estimated from the time of diagnosis and survival endpoint taken as either date of death or censoring. Patients were censored if they were transplanted (n=14), lost to follow up (date of last visit to pulmonary hypertension centre was used as censor date) or if they were alive on the last day of the study (31st December 2009). All cause mortality was used for survival analysis. P-value <0.05 were considered significant throughout.

Two types of walk tests (six minute walk and incremental shuttle walk) are used to assess exercise capacity in the UK and Ireland. For analyses that determined the prognostic significance of 6MWD, patients who had incremental shuttle walk

test (n=120) were excluded. Paired t-test was used to compare the difference between mean values of 6MWD at baseline and follow-up. 6MWD at baseline, at 3 months, and change in 6MWD at 3 months were dichotomised according to their median values and the Kaplan Meier survival curves compared using the log-rank test. The prognostic significance of change in 6MWD at 3 months was also assessed using univariate Cox regression analysis.

To evaluate the prognostic significance of change in FC from baseline to 3 months follow-up, patients were categorised into 4 groups:
Group 1- FC I/II at baseline and FC I/II at follow-up,
Group 2- FC III/IV at baseline and FC I/II at follow-up,
Group 3- FC I/II at baseline and FC III/IV at follow-up and
Group 4- FC III/IV at baseline and FC III/IV at follow-up.

Kaplan Meier survival curves of the 4 groups of change in FC were compared using the log rank test. The same analysis was repeated for 6 months follow-up.

6.4 **Results**

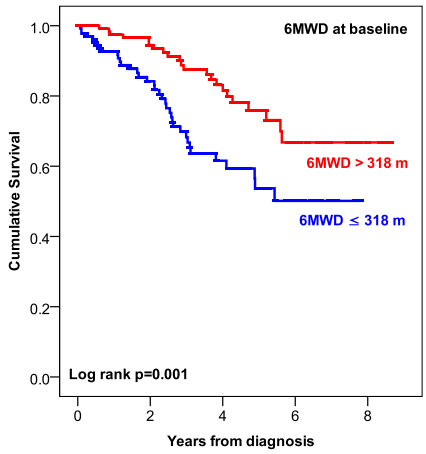
Absolute values and change in 6MWD at 3 month:

Paired baseline and 3 months 6MWD data were available in 158 patients. The mean increase in 6MWD at 3 months was 39.5 m (95% CI 28.1-51.0) from baseline (baseline 6MWD was 304.2 ± 115.5 m, increasing to 343.7 ± 115.6 m at 3 months). The magnitude of change in 6MWD at 3 months in response to treatment was not statistically different between younger vs. older patients or different gender. Patients with baseline 6MWD of ≤ 318 m (corresponding to the median 6MWD at diagnosis) had greater magnitude of change in 6MWD at 3 months in response to treatment (Δ6MWD at 3 months = 59.1 m) compared with patients with baseline 6MWD of > 318 m (Δ6MWD at 3 months = 20.9 m, p=0.001). Patients in baseline FC III/IV also had greater magnitude of change in 6MWD at 3 months in response to treatment (Δ6MWD at 3 months = 48.6 m) compared with patients in baseline FC I/II (Δ6MWD at 3 months = 15.8 m, p= 0.022).

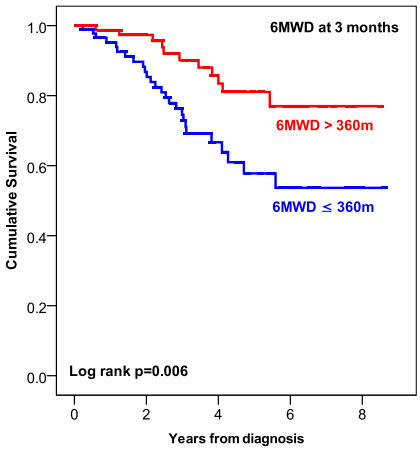
Figure 6.1 shows Kaplan Meier survival curves according to baseline 6MWD (Figure 6.1a), 6MWD at 3 months (Figure 6.1b), change in 6MWD at 3 months for patients with baseline 6MWD ≤ 318 m(Figure 6.1c) and change in 6MWD at 3 months for patients with baseline 6MWD >318m (figure 6.1d). Patients with baseline 6MWD of >318 m (p=0.001) and 3 months 6MWD of >360 m (p=0.006) had better survival. Change in 6MWD >36 m(corresponding to median Δ6MWD at 3 month) was also associated with better survival but only in patients with baseline 6MWD ≤318 m. Change in 6MWD at 3 months was not associated with survival in those with baseline 6MWD of > 318 m.

Result from univariate Cox regression showed that patients with greater change in 6MWD from baseline to 3 months had better post 3 months survival (hazard ratio 0.579 per 100 m, 95% CI 0.349-0.960, p=0.0343).

6.1a



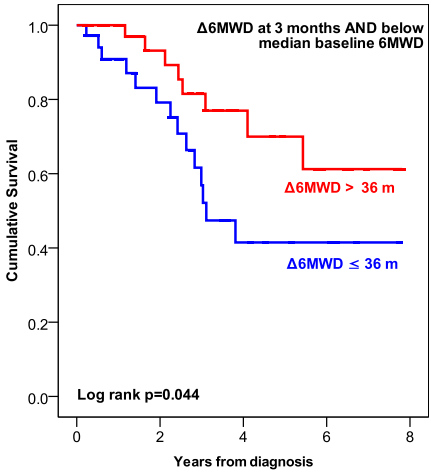
6.1b



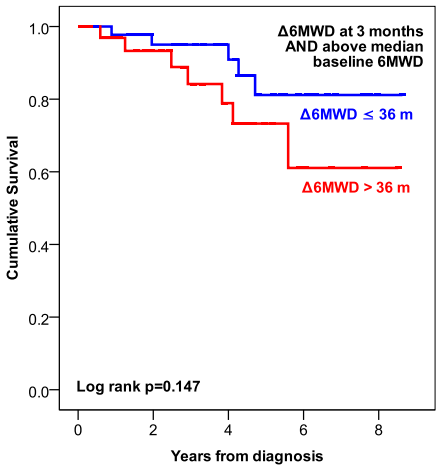
Years from diagnosis	0	2	4	6	8
No at risk					
6MWD>318	129	89	50	17	2
6MWD≤318	131	67	27	10	0

Years from diagnosis	0	2	4	6	8
No at risk					
6MWD>360	86	56	35	15	0
6MWD≤360	94	59	23	10	0

6.1c



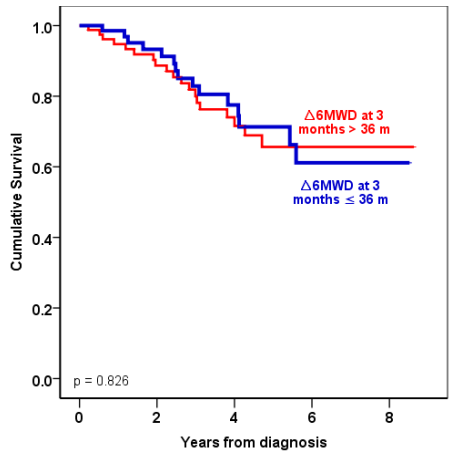
6.1d



Years from diagnosis	0	2	4	6	8
No at risk					
6MWD>36	42	23	10	4	0
6MWD≤36	35	19	6	3	0

Years from diagnosis	0	2	4	6	8
No at risk					
6MWD>36	46	34	22	9	0
6MWD≤36	35	22	13	3	0

6.1e



Years from diagnosis	0	2	4	6	8
No at risk					
6MWD>36	81	47	24	8	0
6MWD≤36	77	54	29	13	0

Figure 6.1. Kaplan Meier survival curves according to 6MWD at baseline and follow-up and Δ6MWD at 3 months.

6.1a) Patients who walked >318 m at the time of diagnosis (corresponds to median 6MWD at baseline) have better survival than those who walked ≤ 318 m.

6.1b) Patients who walked > 360 m at 3 months (corresponds to median 6MWD at 3 months) have better survival than those who walked ≤ 360m.

6.1c) In patients with below median baseline walk (≤ 318 m), Δ6MWD at 3 months of > 36 m (corresponds to median Δ6MWD at 3 months) was associated with better survival compared to those with Δ6MWD ≤ 36 m).

6.1d) In patients with above median baseline 6MWD (>318 m), Δ6MWD at 3 months was not associated with survival.

6.1 e) Δ6MWD at 3 months was not associated with survival in the whole cohort.

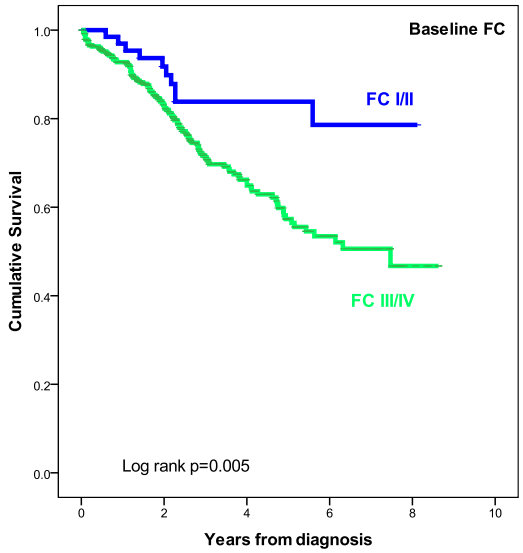
Absolute values and change in 6MWD at 6 months:

Paired baseline and 6 months 6MWD data were available in 136 patients. The mean increase in 6MWD at 6 months was 50.7 m (95% CI 35.2 – 66.1 m) from baseline (baseline 6MWD was 304.5 ± 114.1 m increasing to 355.2 ± 117.2 m at 6 months). The magnitude of change in 6MWD at 6 months in response to treatment was not statistically significant between younger vs. older patients, between gender or between patients in baseline FC III/IV vs. baseline FC I/II. Patients with baseline 6MWD of ≤ 318 m (corresponding to median baseline 6MWD) had greater magnitude of change in 6MWD at 6 months in response to treatment (Δ6MWD at 6 months = 77.5 m) compared with patients with baseline 6MWD of > 318 m (Δ6MWD at 6 months = 27.5 m, p=0.002). Change in 6MWD at 6 months was not associated with survival.

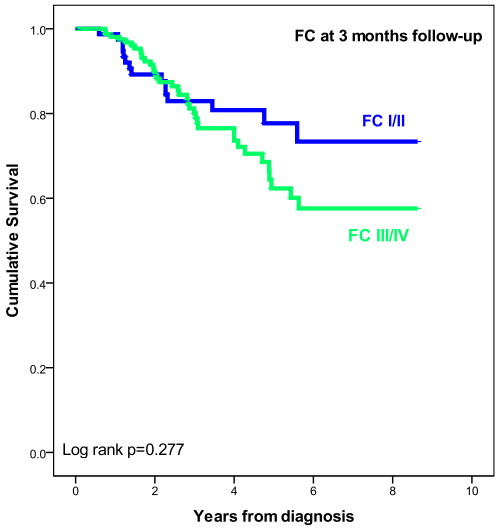
Functional Class at 3 months:

Out of 482 patients, 15 patients died before 3 months. In the remaining patients, paired baseline and 3 months FC data were available in 260 patients. FC at 3 months was not associated with survival (Figure 6.2b). However, patients with missing FC data at baseline and/or 3 months (n=207) had worse survival compared with those with available data (Log rank, p=0.009). Change in FC group at 3 months was not associated with survival (Log rank, p=0.650, Figure 6.3a). There was no change in the result when a missing data category was added to include patients with missing baseline and/or 3 months FC (Log rank, p=0.086).

6.2a



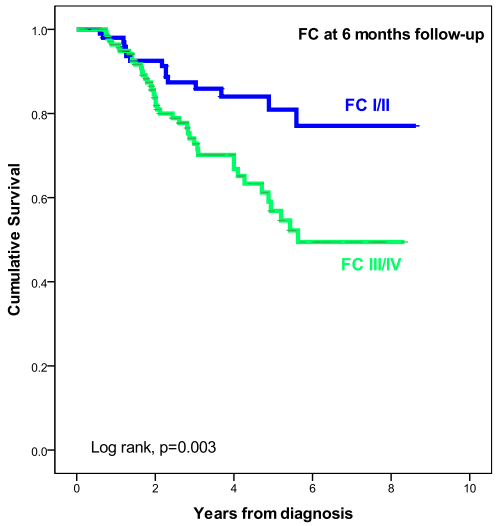
6.2b



Years from diagnosis	0	2	4	6	8
No at risk					
FC I/II	72	46	24	11	0
FC III/IV	384	218	101	43	4

Years from diagnosis	0	2	4	6	8
No at risk					
FC I/II	87	56	29	15	0
FC iii/IV	176	109	51	20	1

6.2c



Years from diagnosis	0	2	4	6	8
No at risk					
FC I/II	105	74	36	17	1
FC III/IV	147	89	41	16	0

Figure 6.2 . Kaplan Meier survival curves according to baseline FC (Figure 6.2a), functional class at 3 months (Figure 6.2b) and functional class at 6 months follow-up (Figure 6.2c).

Functional class at 6 months:

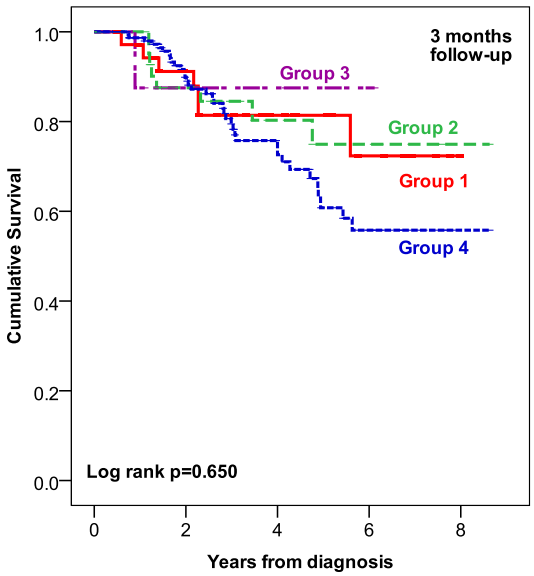
Out of 482 patients, 20 patients died before 6 months. In the remaining patients, paired baseline and 6 months FC data were available in 249 patients. Patients with missing FC data at baseline and/or 6 months (n=213) had similar survival to those with available data (Log rank, p=0.240). Patients in FC I/II at 6 months had better survival compared with patients in FC III/IV (Figure 6.2c). Patients who improved from baseline FC III/IV to FC I/II after of 6 months of treatment (Group 2) had similar survival to patients who were in FC I/II at baseline and remained in FC I/II (Group 1) after 6 months of treatment (Table 6.1). Conversely, patients who deteriorated from baseline FC I/II to FC III/IV at 6 months (Group 3) had worse survival compared with patients who remained at FC I/II at baseline and at 6 months (Group 1). Kaplan Meier survival curves for change in FC group after 6 months of treatment are shown in Figure 6.3b (Log rank, p=0.018).

Table 6.1. Univariate and multivariate Cox proportional hazard models to determine the prognostic significance of change in functional class at 6 months.

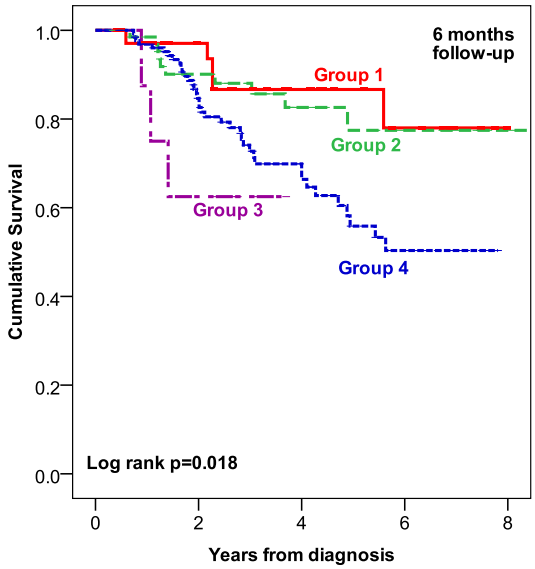
Change in functional class at 6 months	Univariate analysis		Multivariate analysis*	
	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)
Group 1	0.025	1	0.034	1
Group 2	0.727	1.211 (0.414-3.545)	0.293	1.899 (0.574-6.282)
Group 3	0.035	4.740 (1.119-20.081)	0.003	9.669 (2.113-44.236)
Group 4	0.045	2.600(1.022-6.616)	0.135	2.183 (0.784-6.075)

* Adjusted for age, mixed venous oxygen saturations and pulmonary vascular resistance index.

6.3a



6.3b



Years from diagnosis	0	2	4	6	8
No at risk					
Group 1	36	27	13	6	0
Group 2	51	28	15	8	0
Group 3	8	4	2	0	0
Group 4	165	102	47	18	0

Years from diagnosis	0	2	4	6	8
No at risk					
Group 1	36	27	15	7	0
Group 2	69	46	20	9	2
Group 3	8	4	0	0	0
Group 4	136	81	39	15	0

Figure 6.3. Kaplan Meier survival curves according to change in functional class from baseline to follow-up.

6.3a) 3 months follow-up: Change in functional class at 3 months from baseline is not associated with survival.

6.3b) 6 months follow-up: Patients who improved from FC III/IV at baseline to FC I/II at 6 months (Group 2) have similar survival as patients who remained stable at FC I/II from baseline to 6 months (Group 1). Patients who deteriorated from FC I/II at baseline to FC III/IV at 6 months (Group 3) have similar survival to patients who started in FC III/IV at baseline and remained in FC III/IV at 6 months (Group 4). At 6 months follow-up, Group 1 and 2 patients have better survival than Group 3 and 4 patients.

Out of the whole cohort, baseline, 3 and 6 months FC data were all available in 215 patients. 4 out of 34 (11.8%) patients with FC I/II at baseline and at 3 months subsequently deteriorated to FC III/IV at 6 months. 24 out of 143 (16.8%) patients with FC III/IV at baseline and at 3 months subsequently improved to FC I/II at 6 months. 7 out of 34 (20.6%) patients with FC III/IV at baseline and improved to FC I/II at 3 months had subsequently deteriorated again to FC III/IV at 6 months.

6.5 Discussion

In this chapter, we reported on the prognostic significance of change in 6MWD and functional class of idiopathic, heritable and anorexigens-associated PAH in response to treatment. Change in 6MWD after 3 months of treatment was associated with survival in patients with below median baseline 6MWD. Change in functional class at 6 months but not at an earlier time of follow-up in response to treatment also predicted survival.

Change in 6MWD and survival:

Change in invasive pulmonary haemodynamics in response to treatment has been shown to predict survival in PAH (48, 58, 104, 105). However, right heart catheterisation is expensive and invasive. On the other hand, 6MWD is non-invasive, cheap to perform and reproducible. Baseline 6MWD correlates with functional class and haemodynamics variables and predicts survival (46, 106). Change in 6MWD has been used as the primary endpoint in many pivotal PAH clinical trials. It is however unclear what constitutes a clinically meaningful change of 6MWD in PAH (107). Mathai et al found improvement of 33 m was associated with improvement in quality of life measures (51). The majority of randomised clinical trials in PAH were 12-16 weeks in duration. We have therefore chosen 3 months follow-up as a fixed time point to evaluate whether short term improvement in 6MWD has any long term prognostic implications.

The magnitude of change in 6MWD at 3 months in this study of 39.5 m was similar to pooled results of 19 randomised clinical trials from a recent meta-analysis (56). We observed that patients with more severe functional impairment (lower baseline 6MWD and FC III/IV) had bigger magnitude of change in 6MWD after 3 months of treatment. Our results are consistent with findings from the clinical trials that showed bigger increases in 6MWD in advanced, severe patients and no significant change of 6MWD in less ill patients (68).

We found absolute baseline 6MWD > 318m, absolute 3 months 6MWD > 360 m and change in 6MWD at 3 months > 36 m were all associated with better survival.

Each 100 metre improvement in 6MWD after 3 months of PAH treatment was associated with 42% reduction in mortality in our study population. The association between improvement in 6MWD at 3 months and survival appears to be stronger in the more compromised patients (those with lower baseline 6MWD < 318 m). Provencher et al also found increase in 6MWD after 4 months of treatment was associated with improved survival (105) That was a single centre study and was restricted to idiopathic PAH patients in functional class III and IV who were started on first-line bosentan. Better prognostic value of change in 6MWD in more compromised patients was recently reported in the SUPER-2 study (66). Unlike patients in our study, patients recruited in the SUPER-2 study were highly selected and may be not representative of real-life patients seen in daily clinical practice.

Patients with higher baseline walk may need a bigger change in 6MWD to translate into survival difference. The ceiling effect of 6MWD (44) may also mean there is less scope for 6MWD improvement in those with high baseline walk. Our study demonstrated short term improvement in 6MWD in response to treatment has prognostic significance albeit only in those with severe functional impairment. Change in 6MWD is not a good surrogate marker to assess response to treatment in those with less functional impairment.

Change in functional class and survival:

FC at baseline and on treatment have been shown to be associated with survival (58). In this study, no association was found between FC at 3 months or change in FC at 3 months and survival. Patients with missing FC data at 3 months have worse survival than those at 3 months and this may explain the lack of significance of FC at 3 months follow up. It is also possible that 3 months may be too early for any real response to treatment to be translated into FC improvement. A bigger improvement may be needed to change a patient from FC III to II compared with a change of FC from IV to III.

Change in functional class became prognostically significant at 6 months follow-up. Irrespective of baseline FC, patients who were in FC I/II at 6 months have better survival than those who either deteriorated or remained at FC III/IV.

Nickel et al (104) also found changes in FC influenced outcomes. In that study, timing of follow-up was variable and defined as the date of the first follow-up right heart catheterisation after initiation of PAH therapy.

The clinical relevance of any variables used to monitor response to treatment may also depend on the timing of their measurement following diagnosis. In our study, change in 6MWD translated into better survival (at least in those with low baseline walk) at 3 months, which was the length of most clinical pulmonary hypertension randomised clinical trials. Change in FC translated into survival difference at 6 months but not at earlier time of follow-up in the current study. The course of disease may also be highly variable in the first few months after diagnosis. A significant proportion of our patients who improved initially after 3 months of treatment subsequently deteriorated at 6 months.

Limitations:

There are several limitations to our study. Not all tests were done in all centres at predefined follow-up time points leading to unavoidable missing data. Patients who died before the predefined follow-up time points were excluded from survival analysis. This may potentially bias the results although the numbers of such patients were small. Patients with missing data may have worse outcome and their exclusion may systematically bias our findings. For example, 6MWD at follow-up may be missing because a patient was too ill to perform the test. However, similar conclusions were found using missing 6MWD data imputation (Table 6.2) suggesting that the relationship between change in 6MWD at 3 months and survival is likely to be true. 25% of this study population came from a single centre that used incremental shuttle walk test to assess exercise capacity and were therefore exluded from the 6MWD analyses. These excluded patients were otherwise similar in baseline characteristics and managed similarly according to contemporary UK and European pulmonary hypertension guidelines. Similarly, patients with missing data for change in FC at 3 months had worse survival compared with those with available data. This may therefore account for the lack of prognostic significance of change in FC at 3 months. Other factors such as change in NT-pro BNP or Quality of life scores at follow-up may also have prognostic significance but had too many missing data and were thus not

included in the analysis. We have not controlled for the type of treatment in this study. Nevertheless, it is possible patients who persisted in FC III/IV at 3 months may have changes to their treatment which may subsequently alter their outcome. Finally, our results are not generalisable to patients with other PAH aetiologies.

Table 6.2. Univariate Cox regression and missing data imputation on change in six-minute walk distance at 3 months.

Method	p-value	Hazard ratio*	95% confidence interval
1	0.0343	0.579	0.349-0.960
2	0.0898	0.651	0.397-1.069
3	0.0807	0.654	0.406-1.053
4	0.0567	0.671	0.445-1.011
5	0.0030	0.496	0.312-0.789
6	0.0116	0.555	0.352-0.877
7	0.0042	0.519	0.331-0.813

*6MWD per 100 metres

Method 1 corresponds to a complete case analysis.

Method 2 incorporates a missing data indicator.

Method 3 assumes no change in the case of missing 3-month assessments.

Method 4 assumes a 20% reduction from baseline in the case of missing 3-month assessments.

Method 5 uses linear interpolation to estimate 3 month 6MWD in patients who had 3- or 6-month assessments.

Method 6 is based on method 5, but assumes an average increase of 38 metres to 3 month 6MWD for those patients with missing 3-, 6- or 12-month assessments. The increase in 6MWD of 38m was the observed mean change in patients with 3 month data.

Method 7 is based on method 6, but uses a linear regression equation as follow: 3 month 6MWD = 1.02727-0.21016x(baseline 6MWD). The equation was developed following a regression analysis of 3 month 6MWD on baseline 6MWD in patients with 3 month data.

6.6 Conclusion

Change in 6MWD at 3 months was associated with better survival in patients with more compromised exercise impairment. Improvement as well as deterioration of FC in response to treatment at 6 months but not 3 months follow-up has long term prognostic implications.

7 Chapter 7. Pre-capillary Pulmonary Hypertension with Co-existing Lung Disease: Response to Treatment and Survival.

7.1 Summary

Rationale:

Patients with preserved pulmonary function who otherwise satisfied the standard haemodynamic criteria used to define idiopathic pulmonary arterial hypertension (PAH) in pulmonary hypertension registries and clinical trials may have some evidence of co-existing lung disease on thoracic CT. It is unclear how the response to treatment and survival in this group of patients (refers as Pre-capillary pulmonary hypertension with co-existing lung disease or 'pre-capillary PH-LD' in this study) differ from idiopathic PAH.

Objectives:

To describe and compare the baseline characteristics and survival of pre-capillary PH-LD with idiopathic, heritable and anorexigen-associated PAH.

Methods:

All consecutive, newly diagnosed patients with PAH with pre-capillary PH-LD were compared with idiopathic, heritable and anorexigen-associated PAH diagnosed concurrently between 2001 and 2009 in all eight pulmonary hypertension centres in the UK and Ireland. Both groups of patients had preserved pulmonary functions (% FEV_1, % FVC and/or %TLC > 60%). However, patients with pre-capillary PH-LD also had evidence of parenchymal lung disease (of any severity) on thoracic CT.

Results:

Compared with idiopathic, heritable and anorexigen-associated PAH (n=482), pre-capillary PH-LD (n=146) patients were older, predominantly male current and/or ex-smoker, and had lower six minute walk distance (6MWD), % predicted diffusion capacity for carbon monoxide, mean pulmonary arterial pressure and pulmonary vascular resistance index. After 3 months of pulmonary hypertension targeted treatment, 6MWD improved by 51.7m in pre-capillary PH-LD and by 39.6 m in idiopathic, heritable and anorexigen-associated PAH (p=0.361). However, 1 year survival of pre-capillary PH-LD was only 73.8% compared with 92.7% in idiopathic, heritable and anorexigen-associated PAH.

Conclusion:

Pre-capillary pulmonary hypertension with co-existing lung disease patients had different phenotype compared with idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension patients. Despite similar short term improvement in 6MWD in response to treatment, survival of pre-capillary pulmonary hypertension with co-existing lung disease was worse compared with idiopathic, heritable and anorexigen-associated PAH.

7.2 Introduction

The development of pulmonary hypertension (PH) in patients with COPD and interstitial lung disease is associated with poor outcome (108-110). Patients with advanced lung diseases have been excluded from randomised controlled trials in the field of pulmonary arterial hypertension (PAH). Although PH targeted therapies have been used in selective patients outside the context of clinical trials, there is currently no consensus on the definition of the group of patients whose PH appears to be out of proportion to their underlying lung disease. There is also no evidence to date to support the use of PH targeted therapies in patients with PH secondary to chronic lung disease (Dana Point Group III patients) (5).

In the United Kingdom (UK) and Ireland, the diagnosis and initiation of PH targeted therapies are centralised to eight PH centres. Between the period 2001 to 2009, 628 patients who satisfied the traditional haemodynamic (mPAP ≥ 25mmHg, pulmonary artery occlusion pressure ≤ 15mmHg, cardiac output was normal or reduced) and pulmonary function criteria (FEV_1, FVC and TLC ≥ 60% predicted) used to define idiopathic, heritable and anorexigen-associated PAH in PH registries and clinical trials were diagnosed in all eight pulmonary hypertension centres in the UK and Ireland. We further refined our study exclusion criteria by excluding patients with evidence of co-existing lung diseases on thoracic CT from our idiopathic, heritable and anorexigen-associated PAH cohort. The baseline characteristics and outcomes of our idiopathic, heritable and anorexigen-associated PAH patients (n= 482) were discussed in Chapter 3 of this thesis and published as the Pulmonary Hypertension Registry of the United Kingdom and Ireland (89). Patients with evidence of co-existing lung disease on thoracic CT (n=146) who were excluded from this idiopathic PAH registry otherwise satisfied the traditional haemodynamic and pulmonary function criteria used to define idiopathic PAH in PH registries and clinical trials(32, 33) and were managed in a similar fashion to idiopathic PAH by their PH specialists in accordance with contemporary PH guidelines (5, 80, 81). It is however unclear whether the response to treatment and survival of this excluded group of patients (refers as pre-capillary pulmonary hypertension with

co-existing lung disease or ‘pre-capillary PH – LD’ in this study) are affected by the co-existence of modest lung disease.

The objective of this study was to describe and compare the clinical characteristics, haemodynamics and outcomes of this selective group of incident, treatment-naive pre-capillary PH – LD patients with idiopathic PAH diagnosed concurrently in the UK and Ireland.

The flow diagram of patients selection for idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension and pre-capillary PH – LD has been described in Chapter 2, Figure 2.1.

7.3 **Methods**

We included all consecutive, treatment-naive, incident cases of pre-capillary PH – LD diagnosed between 1st January 2001 and 31st December 2009 in all eight pulmonary hypertension centres in the UK and Ireland. PAH was defined as mean pulmonary arterial pressure (mPAP) ≥ 25mmHg and pulmonary artery occlusion pressure ≤ 15mmHg with a normal or reduced cardiac output. All patients underwent CT of the thorax as part of their multimodality assessment for pulmonary hypertension. For the purpose of this study, the presence of co-existing lung disease was defined based on the reports of the thoracic CT performed at the time of diagnosis of PAH and included parenchymal abnormalities of all severity.

The following patients were excluded from pre-capillary PH – LD: family history of PAH, previous anorexigens exposure, connective tissue/collagen vascular disease, portal hypertension, haemolytic anaemia, HIV, congenital heart disease and sarcoidosis. Patients who may have pulmonary hypertension secondary to significant hypoxic lung disease were excluded by abnormal pulmonary function test (defined as FEV_1, FVC or TLC < 60% predicted) (32, 33).

We compared the baseline characteristics, treatments started at the time of diagnosis, and functional class and 6 minute walk distance at 3 months follow up between idiopathic, heritable and anorexigen-associated PAH versus pre-capillary PH – LD. The date of diagnostic right heart catheterisation was taken as the date of diagnosis. Due to the nature of the study, ethical approval was deemed unnecessary by the West of Scotland Research Ethics Committee.

Statistical Analysis:

Analysis was performed using SPSS version 19 (SPSS, Chicago, IL). For quantitative variables, mean ± standard deviation was used to describe parametric data, whereas median and interquartile range (IQR) was used for non-parametric data. Comparisons between two independent groups were performed using Student's t test or Mann-Whitney U test. Categorical variables

were described by frequencies and percentages and comparisons between groups performed using x^2 or Fisher's exact tests. Survival endpoint was taken as either date of death or censoring. Patients were censored if they were transplanted (n=14), lost to follow up (date of last visit to pulmonary hypertension centre was used as censor date) or if they were alive on the last day of the study (31st December 2009). Mortality was confirmed using pulmonary hypertension centres and general practitioners' records and NHS strategic tracing services. All-cause mortality was used in survival analysis. Survival from time of diagnosis was estimated using the Kaplan Meier method and survival curves compared using log-rank test. Multivariate Cox regression was used to determine the independent predictors of survival in pre-capillary PH – LD. Variables with $p < 0.1$ in univariate analyses were entered into multivariate analysis. Multivariate Cox regression was also used to compare the survival of pre-capillary PH – LD versus idiopathic, heritable and anorexigen-associated PAH after adjusting for potential confounders. P-values <0.05 were considered to be significant.

7.4 **Results**

A total of 146 patients satisfied the inclusion criteria for pre-capillary PH – LD. The types of parenchymal abnormalities reported on thoracic CT were as follow: emphysema only (n=88), pulmonary fibrosis only (n=35), emphysema and pulmonary fibrosis (n=16) and others (n=7).

Demographics, pulmonary function and haemodynamics:

Baseline characteristics of pre-capillary PH – LD patients were compared with idiopathic, heritable and anorexigen-associated PAH patients diagnosed over the same period in the UK and Ireland (Table 7.1). Compared with idiopathic, heritable and anorexigen-associated PAH, pre-capillary PH – LD patients were older, had lower body mass index and were predominantly male (Figure 7.1) current or ex-smoker. Like idiopathic, heritable and anorexigen-associated PAH, patients with pre-capillary PH – LD also had long delay in diagnosis with median symptom duration of 18 months before diagnosis. Despite similar functional class distribution, pre-capillary PH – LD patients had lower mean six minute walk distance (6MWD) at the time of diagnosis. Mean values of spirometry and lung volumes were within normal limits whereas $\%DL_{CO}$ were severely impaired in pre-capillary PH – LD (Figure 7.2). Pre-capillary PH – LD patients had severe precapillary pulmonary hypertension. However, mPAP and PVRI were significantly lower in pre-capillary PH – LD compared with idiopathic, heritable and anorexigen-associated PAH (Table 7.1). This differences in baseline characteristics remained significant when pre-capillary PH – LD was compared with the older (age > 50) subgroup of idiopathic heritable and anorexigen-associated PAH patients. (Table 7.2).

Table 7.1. Comparison of baseline demographics, pulmonary function tests and haemodynamics between patients with pre-capillary pulmonary hypertension with co-existing lung disease and idiopathic, heritable and anorexigen-associated PAH.

	pre-capillary PH – LD **(n=146)**	**IPAH (n=482)**	**p-value**
Age, years	67.7(11.6)	50.1(17.1)	<0.001
% female	41.8%(61)	69.9%(337)	<0.001
Ethnicity, % non white	1.6%(2)	12.3%(52)	<0.001
BMI≥30	17.1%(22)	33.9%(135)	<0.001
BMI, $kg.m^{-2}$	26.1(6.0)	28.3(6.3)	<0.001
6MWD, metres	209.2(118.0)	292.4(123.0)	<0.001
Current/ex-smoker	89.7%(113)	55.7%(201)	<0.001
Median duration of symptoms, months	18.0(11.0-36.0)	18.0(9.0-36.0)	N.S
Functional class: I/II III IV	 10.5%(15) 69.9%(100) 19.6%(28)	 15.8%(72) 66.7%(304) 17.5%(80)	 N.S
FEV_1%	88.8(18.0)	85.3(14.7)	N.S
FVC %	102.2(20.6)	94.0(16.4)	<0.001
TLC %	95.4(15.2)	95.4(13.9)	N.S
DL_{CO}%	37.9(20.0)	62.0(20.9)	<0.001
RAP, mmHg	9.4(5.1)	10.1(6.0)	N.S
mPAP, mmHg	48.6(9.0)	54.1(13.9)	<0.001
PAOP, mmHg	9.3(3.3)	9.2(3.5)	N.S
SvO_2, %	62.0(9.2)	61.5(9.5)	N.S
CI, $L.min^{-1}.m^{-2}$	2.1(0.7)	2.1(0.7)	N.S
PVRI, $WU.m^2$	20.6(8.2)	23.1(10.3)	0.007

Definition of abbreviations: 6MWD = 6 minute walk distance, BMI = body mass index, CI = cardiac index, DL_{CO}% = % predicted diffusion capacity for carbon monoxide, FEV_1% = % predicted forced expiratory volume in 1 second, FVC% = % predicted forced vital capacity, IPAH = idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension, mPAP = mean pulmonary artery pressure, N.S = not significant, pre-capillary PH – LD = pre-capillary pulmonary hypertension with co-existing lung disease, PAOP = pulmonary artery occlusion pressure, PVRI = pulmonary vascular resistance index, RAP = mean right atrial pressure, S_vO_2 = mixed venous oxygen saturations, TLC% = % predicted total lung capacity, WU = Woods Unit.

Data were presented as mean (standard deviation) or % (number) unless otherwise stated.

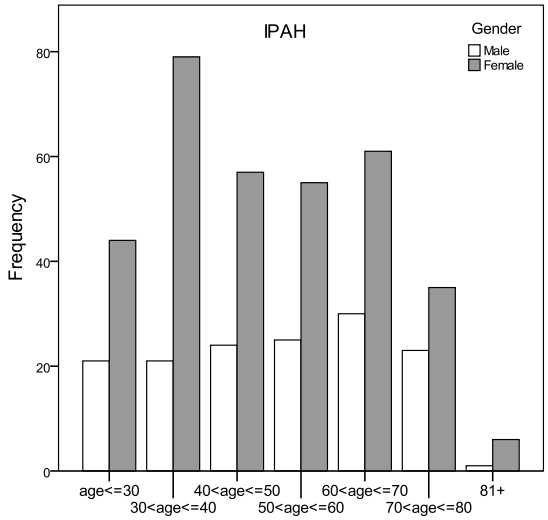
Table 7.2. Comparison of baseline characteristics between pre-capillary PH – LD and idiopathic, heritable and anorexigen-associated PAH age > 50 years old.

	pre-capillary PH – LD **(n=146)**	**Older IPAH subgroup*(n=236)**	**p-value**
Age, years	67.7(11.6)	65.1(8.3)	0.016
% female	41.8%(61)	66.5%(157)	<0.001
Ethnicity, % non white	1.6%(2)	8.9%(18)	0.008
BMI≥30	17.1%(22)	40.5%(81)	<0.001
BMI, $kg.m^{-2}$	26.1(6.0)	29.2(6.2)	<0.001
6MWD, metres	209.2(118.0)	246.1(112.2)	0.029
Current/ex-smoker	89.7%(113)	64.0%(119)	<0.001
Median duration of symptoms, months	18.0(11.0-36.0)	24.0(12.0-36.0)	N.S
Functional class: I/II III IV	 10.5%(15) 69.9%(100) 19.6%(28)	 11.9%(27) 67.4%(153) 20.7%(47)	 N.S
FEV_1%	88.8(18.0)	85.1(15.8)	N.S
FVC %	102.2(20.6)	96.7(17.6)	0.015
TLC %	95.4(15.2)	94.4(14.3)	N.S
DL_{CO}%	37.9(20.0)	56.7(22.8)	<0.001
RAP, mmHg	9.4(5.1)	10.2(6.1)	N.S
mPAP, mmHg	48.6(9.0)	51.0(12.2)	0.028
PAOP, mmHg	9.3(3.3)	9.5(3.5)	N.S
SvO_2, %	62.0(9.2)	60.6(8.6)	N.S
CI, $L.min^{-1}.m^{-2}$	2.1(0.7)	2.1(0.7)	N.S
PVRI, $WU.m^2$	20.6(8.2)	21.5(9.1)	N.S
Median survival, years (95% CI)	2.5(1.4-2.6)	4.8(4.2-5.3)	0.001

See Table 7.1 for definition of abbreviations

* IPAH patients were divided into younger and older subgroups according to the median age. Older IPAH refers to the subgroup of IPAH patients who were more than 50 years old.

7.1a



7.1b

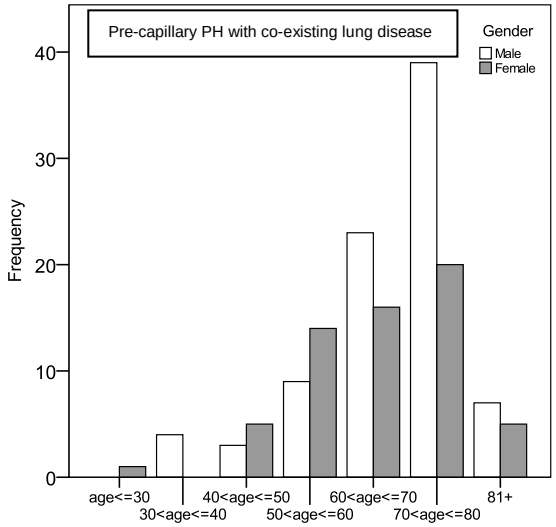
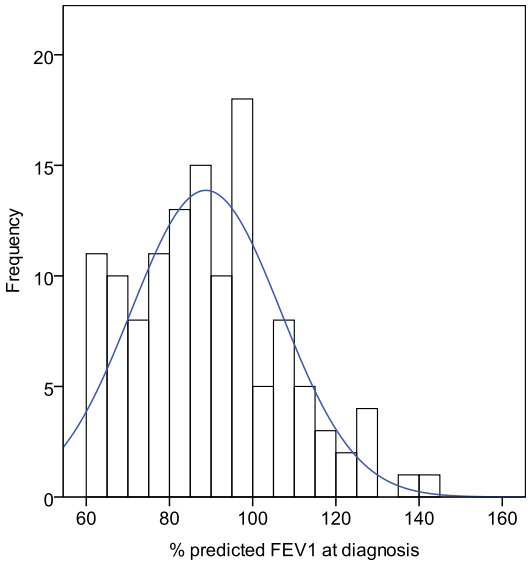


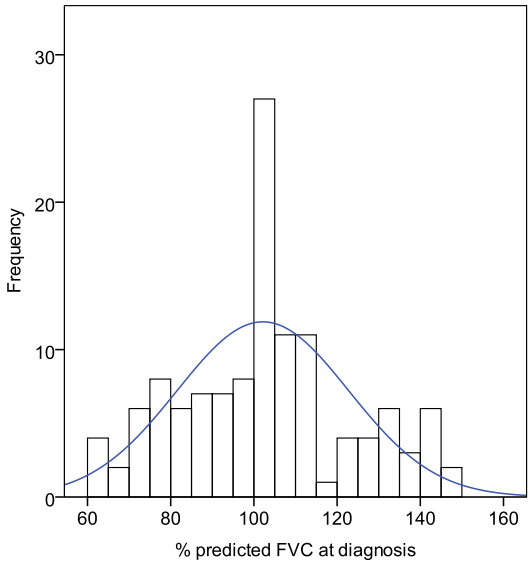
Figure 7.1. Distribution of age by gender in idiopathic, heritable and anorexigen-associated PAH (7.1a) and pre-capillary PH – LD (7.1b).

IPAH refers to patients with idiopathic, heritable and anorexigen associated PAH.

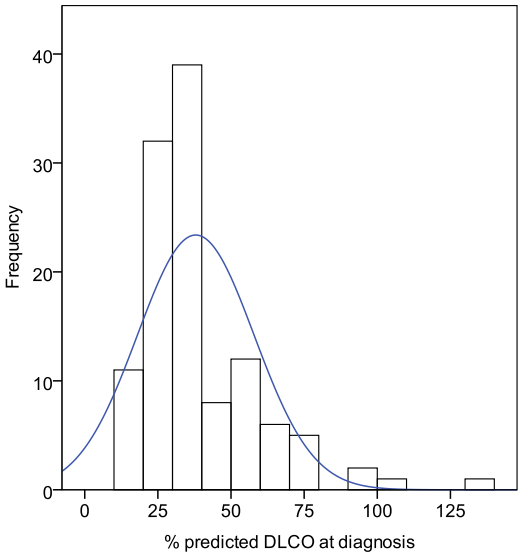
7.2a



7.2b



7.2c



7.2d

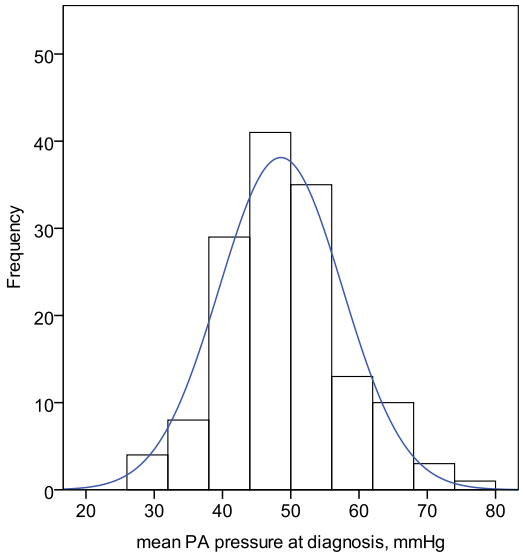


Figure 7.2. Frequency distributions of selective baseline parameters in pre-capillary PH – LD patients.

See table 7.1 for definition of abbreviations.

Co-morbidities:

pre-capillary PH – LD patients had more non-respiratory co-morbidities compared with idiopathic, heritable and anorexigen-associated PAH (Table 7.3).

Table 7.3. Comparisons of co-morbidities in pre-capillary PH – LD pre-capillary PH – LD and idiopathic, heritable and anorexigen-associated PAH.

Co-morbidities	pre-capillary PH – LD **(n=146)**	**IPAH (n=482)**	**p-value**
IHD	29.7%(43)	12.1%(58)	<0.001
Hypertension	25.9%(37)	26.6%(121)	N.S
Diabetes	21.0%(30)	14.3%(65)	0.056

Definition of abbreviations: COPD = chronic obstructive pulmonary disease, IHD = ischaemic heart disease and ILD = interstitial lung disease, and see table 7.1.

Treatment:

All patients were treatment-naive prior to the diagnosis of PAH. First line pulmonary hypertension treatment started at the time of diagnosis for patients with pre-capillary PH – LD was as follow: phosphodiesterase 5 inhibitors 52.1% (n=76), endothelin receptor antagonists 32.9% (n=48) and prostanoids 7.5% (n=11). 29.0% (n=42) of pre-capillary PH – LD patients received combination therapy over the study period compared with 46.3% (n=222) in idiopathic, heritable and anorexigen-associated PAH. No pre-capillary PH – LD patient received lung transplantation.

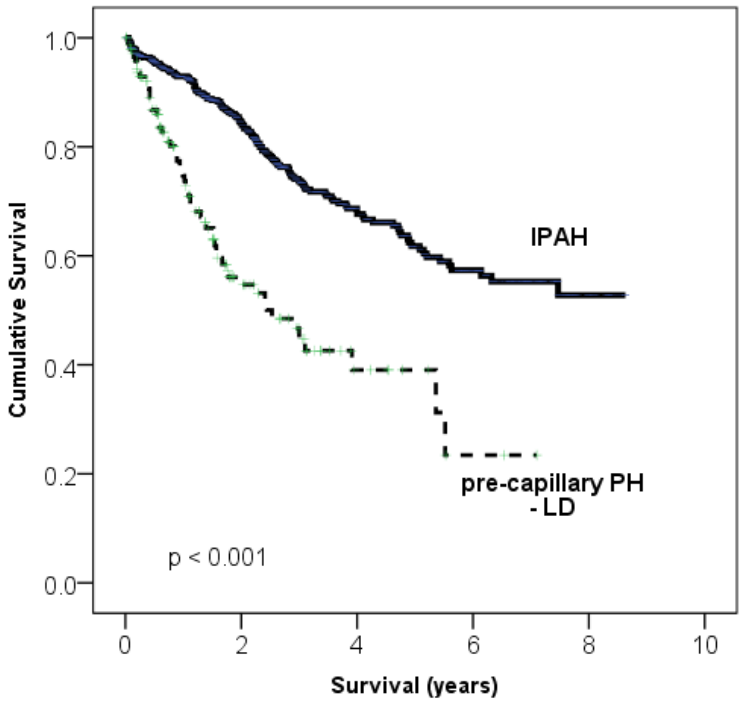
6MWD and functional class at 3 months:

6MWD improved by 51.7 ± 85.6 m after 3 months of disease targeted therapies in pre-capillary PH – LD compared with 39.6 ± 73.1m in idiopathic, heritable and anorexigen-associated PAH (p= N.S). After 3 months of PAH treatment, 73.6% (n=64) and 9.2% (n=8) of pre-capillary PH – LD patients remained in functional class III and IV respectively. This was significantly less compared with idiopathic, heritable and anorexigen-associated PAH patients. After 3 months of pulmonary hypertension treatment, 58.6% (n=154) and 8.4% (n=22) of idiopathic, heritable and anorexigen-associated PAH remained in functional class III and IV respectively (p=0.018).

Survival:

Out of the 146 pre-capillary PH – LD patients, 61 died by the end of the study. The mean follow-up period was 1.6 years. Kaplan Meier survival estimates at 1, 2 and 3 years were 73.8%, 54.7% and 42.6% respectively. Pre-capillary PH – LD had worse survival compared with idiopathic, heritable and anorexigen-associated PAH (Figure 7.3). Compared with idiopathic, heritable and anorexigen-associated PAH, patients with pre-capillary PH – LD were more likely to die after adjusting for age, gender and smoking history (hazard ratio 1.669, 95% CI 1.130-2.464, p = 0.010).

Age, smoking history, $\%DL_{CO}$, mean right atrial pressure, mixed venous oxygen saturations, cardiac index and pulmonary vascular resistance index were associated with survival in univariate analyses (Table 7.4). Age, smoking history, mean right atrial pressure were independent predictors of survival in pre-capillary PH – LD in multivariate analysis (Table 7.5).



Years from diagnosis	0	2	4	6	8
No at risk					
IPAH	482	283	136	62	9
Pre-capillary PH-LD	146	40	9	1	0

Figure 7.3. Survival curves of pre-capillary PH – LD and IPAH.

Pre-capillary PH – LD refers to pre-capillary pulmonary hypertension with co-existing lung disease and IPAH refers to idiopathic, heritable and anorexigen-associated PAH.

Table 7.4. Univariate Cox proportional hazard regression analyses of baseline variables in pre-capillary PH – LD.

	p-value	Hazard ratio	95% confidence interval
Age, years	<0.001	1.062	1.031-1.094
Male gender	0.108	1.535	0.911-2.587
Smoking history:			
Never smoke		1	
Current/ex-smoker	0.029	4.845	1.173-20.010
Duration of symptoms, months	0.896	1.001	0.990-1.012
Functional class-			
I and II	0.331	1	
III	0.179	2.237	0.692-7.232
IV	0.138	2.579	0.738-9.016
Systemic hypertension	0.537	0.818	0.434-1.545
Ischaemic heart disease	0.373	1.281	0.743-2.210
Diabetes	0.062	1.733	0.972-3.088
%FEV1	0.469	1.005	0.991-1.021
%FVC	0.176	1.010	0.996-1.024
%TLC	0.521	0.991	0.966-1.018
%DLCO	0.038	0.980	0.962-0.999
RAP, mmHg	0.002	1.083	1.030-1.139
mPAP, mmHg	0.969	1.000	0.976-1.026
PAOP, mmHg	0.686	0.984	0.908-1.065
SvO2, %	0.030	0.970	0.943-0.997
CI, L.min-1.m-2	0.002	0.431	0.253-0.732
PVRI, WU.m-2	0.061	1.026	0.999-1.054

See table 7.1 for definition of abbreviations.

Table 7.5. Multivariate Cox proportional hazard regression analysis of selected baseline variables in pre-capillary PH – LD.

	p-value	Hazard ratio	95% confidence interval
Age, years	0.001	1.064	1.025-1.104
Smoking history: Never smoke Current/ex-smoker	 0.035	 1 4.111	 1.102-15.339
Diabetes	0.165	1.634	0.817-3.268
$\%DL_{CO}$	0.051	0.983	0.967-1.000
RAP, mmHg	0.018	1.093	1.106-1.176
SVO2, %	0.879	1.004	0.958-1.052
CI, $L.min^{-1}.m^{-2}$	0.434	0.651	0.222-1.908
PVRI, $WU.m^{-2}$	0.746	1.011	0.948-1.077

See table 7.1 for definition of abbreviations.

7.5 **Discussion**

We report on the baseline characteristics and outcomes of a selective group of PAH patients with radiological evidence of lung disease who otherwise satisfied the traditional haemodynamic and pulmonary function criteria used to define idiopathic pulmonary arterial hypertension in PH registries and clinical trials. This selective group of pre-capillary PH – LD patients had preserved spirometry and lung volumes but severely reduced $\%DL_{CO}$, and had significant precapillary pulmonary hypertension that appeared disproportionate to their underlying lung disease. Our results show that despite similar baseline haemodynamic impairment, demographics of these pre-capillary PH – LD patients were different compared with idiopathic, heritable and anorexigen-associated PAH patients. Furthermore, despite similar short term improvement in 6MWD in response to PH disease targeted therapies, survival of pre-capillary PH – LD patients appeared significantly worse compared with idiopathic, heritable and anorexigen-associated PAH patients.

Pre-capillary PH – LD patients described in our study had normal spirometry and lung volumes. Most of the parenchymal abnormality in our study cohort was emphysema. Emphysema on CT may be noted in otherwise asymptomatic healthy smokers and may not be associated with airflow obstruction on spirometry (111) . Interstitial changes were also frequently seen on the CT of asymptomatic elderly patients and may not be of any clinical relevance (112). It is possible this selective group of pre-capillary PH – LD as reported in our study simply represents a subgroup of 'idiopathic PAH' patients where the predominant disease is idiopathic PAH and the parenchymal abnormality is an incidental insignificant finding noted on thoracic CT done as part of the standard assessment of PH. However, the differences in phenotypes and the worse survival of this selective group of patients compared with idiopathic PAH suggested that may not be the case.

Although mPAP and PVR were lower than idiopathic PAH patients, pre-capillary PH – LD patients in our study still had significantly impaired pulmonary haemodynamics and depressed cardiac function. On the other hand PH that

complicates stable COPD usually occurs when airflow limitation is severe and associated with chronic alveolar hypoxia and tends to be mild to moderate in severity, with relatively preserved right ventricular function (108) . A subgroup of COPD patients with severe out of proportion PH and significantly worse survival had also been described. These patients had moderate to severe PH, severe hypoxaemia and markedly reduced DL_{CO} (113, 114). However, these patients also had mild- to moderate airflow obstruction with FEV_1 of ~50%, whereas spirometric values were within normal limits in our study cohort.

A recent case report of 3 patients also described similar phenotype to our study cohort: elderly male smokers with normal spirometry and lung volumes, emphysema on CT, severely reduced DL_{CO} and severe precapillary PH (115). With our larger number of patients, our study not only confirmed the presence of this rare phenotype of PAH but also allowed comparison of this selective group of pre-capillary PH – LD patients with idiopathic PAH diagnosed and managed concurrently by PH physicians with similar practice within a single region (UK and Ireland).

The normal spirometry and lung volumes noted in pre-capillary PH – LD patients in our study may also be similar to the mechanism of opposing effect of fibrosis and hyperinflation noted in the combined pulmonary fibrosis and emphysema syndrome (116). The combined pulmonary fibrosis and emphysema syndrome described a group of patients who were predominantly male current or ex-smokers with relatively normal spirometry and lung volumes, significant dyspnoea and exercise limitation and higher prevalence of PH (117-119). However, the combination of pulmonary fibrosis and emphysema was only observed in 11% of our study cohort.

One of the main features that differentiated pre-capillary PH – LD patients in our study from idiopathic PAH was the grossly reduced DL_{CO}. DL_{CO} was 38% in pre-capillary PH – LD compared with 62% in idiopathic PAH in our study. The lower DL_{CO} in pre-capillary PH – LD may be secondary to a combination of factors including obliteration of small pulmonary arterioles, reduced cardiac output, local thrombosis, pulmonary alveolar-capillary membrane thickening from

fibrotic and/or proliferative process, ventilation-perfusion mismatching and loss of pulmonary capillaries in emphysema.

Demographics of pre-capillary PH – LD in our study was different compared with idiopathic PAH diagnosed concurrently in the UK and Ireland. In this study, pre-capillary PH – LD was significantly older, predominantly male with current or previous smoking history, less obese, worse exercise capacity and had more co-morbidities compared with idiopathic PAH. We have recently reported that older idiopathic PAH patients had different phenotype compared with their younger counterparts (89). Older idiopathic PAH patients had more co-morbidities, worse exercise and functional impairment, more impaired DL_{CO}, less severe haemodynamic impairment and worse survival compared with younger idiopathic PAH patients. However, the differences in demographic characteristics described above remained significant when we compared pre-capillary PH – LD patients with the older idiopathic PAH subgroup.

Response to treatment as measured by change in 6MWD after 3 months of PAH specific therapies in pre-capillary PH – LD patients in this study was comparable to the improvement observed in concurrent idiopathic PAH patients. This improvement in exercise capacity was not observed in randomised controlled trials of PAH specific therapies in COPD and pulmonary fibrosis. Sildenafil had no effect on 6MWD in a study of 15 COPD patients, 5 of which had PH at rest (120). In another study of 30 patients with severe COPD, bosentan had no effect on exercise capacity (121) . Median pulmonary systolic pressure assessed by echocardiography was 32mmHg in the bosentan arm in that study. In BUILD-1 trial, effect of bosentan on 6MWD was no better than placebo. However, patient with echocardiographic evidence of severe PH were excluded from the BUILD-1 trial (122). Pulmonary haemodynamic data was not available in the STEP-IPF trial which showed no benefit in 6MWD with sildenafil in advanced IPF (123). Cottin et al studied the characteristics and outcome of 40 patients with combined pulmonary fibrosis and emphysema syndrome and severe pulmonary hypertension (mean pulmonary artery pressure was 40mmHg) (117). No significant effect on functional class or 6MWD was noted after 3 to 6 months of PAH specific therapies in that study. Currently, it remains unclear whether patients with so called disproportionate PH may benefit from PAH therapies.

The survival of idiopathic PAH patients has improved in the modern era of PAH disease targeted therapies (22, 26, 89). However, the short term improvement in 6MWD observed in pre-capillary PH – LD in our study cohort did not appear to translate into similar survival benefit observed in idiopathic PAH. 1 year survival of pre-capillary PH – LD in our study was only 74% compared with 93% (89) in idiopathic PAH diagnosed and managed concurrently in the UK and Ireland. PAH specific therapies have vasodilatory and antiproliferative properties and may help to unload the right ventricle to account for the short term improvement in exercise capacity. However, other factors such as older age and associated co-morbidities, and the effect of smoking may contribute to the worse survival of pre-capillary PH – LD compared with idiopathic PAH. In addition, higher proportion of idiopathic PAH (89) received combination therapy compared with pre-capillary PH – LD.

The pre-capillary PH – LD patients described in this study otherwise satisfied the traditional haemodynamic and pulmonary function criteria of idiopathic PAH (32, 33) and could have been recruited into clinical trials of PAH. Despite short term improvement in 6MWD, the primary endpoint of many pivotal PAH clinical trials, survival of this selective group of patients was poor, and even worse than idiopathic PAH despite treatment with PAH specific therapies. Our study may help to inform the design and better selection of patients for future PAH clinical trials.

The strengths of this study included confirmation of PAH by right heart catheterisation in all patients. Only incident, treatment-naive patients were included. All patients were diagnosed and treated by PH specialist in designated centres only in the UK and Ireland. Patients were assessed by a multidisciplinary team and alternative causes of PH were excluded.

Our study has several limitations. This was an observational study and we have not controlled for treatment. CT images were not reviewed by independent reviewer. We defined the presence of parenchymal lung disease based on what was recorded on the CT report. Data was not collected for hypoxaemia or use of long term oxygen therapy. Our study population comprised of a heterogenous

group of patients with different types, severity and combination of parenchymal lung diseases. However, the relatively small number of patients did not permit further subgroup analysis.

7.6 Conclusion

Pre-capillary pulmonary hypertension with co-existing lung disease patients had different phenotype compared with idiopathic pulmonary arterial hypertension. Despite similar baseline haemodynamic impairment and short term response to treatment, survival of pre-capillary pulmonary hypertension with co-existing lung disease appeared worse compared with idiopathic pulmonary arterial hypertension. Age, the effect of smoking and the presence of age-related co-morbidities may account for the difference in long term outcome between these two groups of patients.

8 Chapter 8. Conclusion

The unique set up of the pulmonary hypertension service in the UK and Ireland allowed us to study a truly incident, treatment-naive cohort of PAH patients in a national setting over a nine year period. In this thesis, we studied the demographics, epidemiology and prognostic outcomes of idiopathic, heritable and anorexigen-associated PAH. We also identified a new phenotype of pre-capillary pulmonary hypertension with co-existing lung disease in this thesis.

Our main findings are as follow:

1. The demographics and epidemiology of incident idiopathic, heritable and anorexigen-associated PAH has changed compared with the NIH era in the 1980s and continue to evolve over the past decade in the UK and Ireland.

2. Age influenced the phenotypic characteristics, prognostic predictors and survival of incident idiopathic, heritable and anorexigen-associated PAH.

3. Some of the survival prediction equations derived from non UK and Ireland patients cohorts more accurately predicted the survival of incident idiopathic, heritable and anorexigen-associated PAH patients in the UK and Ireland than others.

4. Short term improvement in six minute walk distance and functional class in response to treatment have prognostic implications in incident idiopathic, heritable and anorexigen-associated PAH.

5. Pre-capillary pulmonary hypertension with co-existing lung disease patients had different phenotypic charateristics and worse survival compared with idiopathic, heritable and anorexigen-associated PAH patients.

The results presented in this thesis will help to improve our current knowledge of idiopathic, heritable and anorexigen-associated PAH. The identification of a separate phenotype of pre-capillary pulmonary hypertension with co-existing

lung disease will also help to inform the design and better selection of patients for future clinical trials.

9 Appendix

1. Classes of recommendations (5).

Classes of recommendations	Definitions
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class II b	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

2. Levels of evidence (5).

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomised clinical trial or large non-randomised studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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Dear Dr Ling

Full title of project: **Characteristics & Outcome of Pulmonary Arterial Hypertension**

You have sought advice from the West of Scotland Research Ethics Service Office on the above project. This has been considered by the Scientific Officer and Committee Administrator and you are advised that it does not need ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK. The advice is based on the following.

- The project is an audit using only data obtained as part of usual care but note the requirement for Caldicott Guardian approval to permit sharing or publication of anonymised data obtained from patients under the care of NHS Scotland.

If during the course of your project the nature of the study changes and starts to generate new knowledge and thereby inadvertently becoming research then the changing nature of the study would necessitate REC review at that point, before any further work was undertaken. A REC opinion would be required for the new use of the data collected.

Note that this advice is issued on behalf of the West of Scotland Research Ethics Service Office and does **not** constitute a favourable opinion from a REC. It is intended to satisfy journal editors and conference organisers and others who may require evidence of consideration of the need for ethical review prior to publication or presentation of your results.

However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS. This letter has been copied to the R&D Manager at the Golden Jubilee National Hospital for their information.

Kind regards

Dr Judith Godden
WoSRES Scientific Officer/Manager

10 List of References

1. Fung Y and R Yen. 1986. A new theory of pulmonary blood flow in zone 2 condition. J Appl Physiol 60:1638-1650.

2. Kovacs G, Berghold A and Olschewski A. 2009. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systemic review. Eur Respir J 34:888-894.

3. Hoeper M. 2009. The new definition of pulmonary hypertension. Eur Respir J 34:790-791.

4. Badesch DB, Champion HC, Sanchez MAG, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, and Torbicki A. 2009. Diagnosis and Assessment of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology 54(1):S55-S66.

5. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M and Simmonneau G. 2009. Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS), endorsed by the international society of heart and lung transplantation (ISHLT). European Heart Journal 30:2493-2537.

6. Hatano S and Strasser T. 1975. Primary pulmonary hypertension. Report on a WHO meeting. October 15-17, 1973. Geneva: World Health Organization.

7. Fishman A. 2001. Clinical classification of pulmonary hypertension. Clin Chest Med 22:385-91.

8. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S and Fishman A. 2004. Clinical classification of pulmonary hypertension. Journal of American College of Cardiology 43:5S-12S.

9. Tuder RM, Abman SH, Braun T, Capron F, Stevens T, Thistlethwaite PA, and Haworth SG. 2009. Development and Pathology of Pulmonary Hypertension. Journal of the American College of Cardiology 54(1):S3-S9.

10. Dorfmuller P and Humbert M. 2012. Progress in Pulmonary Arterial Hypertension Pathology: Relighting a Torch Inside the Tunnel. American Journal of Respiratory and Critical Care Medicine 186(3):210-212.
11. Humbert M. 2008. Update in pulmonary arterial hypertension 2007. American Journal of Respiratory and Critical Care Medicine 177(6):574-579.
12. Dresdale DT, Michtom RJ, and Schultz M. 1954. Recent studies in primary pulmonary hypertension including pharmacodynamic observations on pulmonary vascular resistance. Bull N Y Acad Med 30(3):195-207.
13. Deng Z, Morse JH, Slager SL, Cuervo N, Moore KJ, Venetos G, Kalachikov S, Cayanis E, Fischer SG, Barst RJ, Hodge SE, and Knowles JA. 2000. Familial primary pulmonary hypertension gene (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 67:737-744.
14. Lane KB, Machado RD, Pauciulo MW, Thomson JR, Phillips JA, Loyd JE, Nichols WC and Trembath RC. 2000. Heterozygous germline mutations in BMPR2, encoding a TGF-B receptor, cause familial primary pulmonary hypertension. Nature Genetics 26:81-84.
15. Machado RD, Eickelberg O, Elliott CG, Geraci MW, Hanaoka M, Loyd JE, Newman JH, Phillips JA, Soubrier F, Trembath RC, and Chung WK. 2009. Genetics and Genomics of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology 54(1):S32-S42.
16. Sztrymf B, Coulet F, Girerd B, Yaici A, Jais X, Sitbon O, Montani D, Souza R, Simonneau G, Soubrier F and Humbert M. 2008. Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. American Journal of Respiratory and Critical Care Medicine 177(12):1377-1383.
17. Fessel JP, Loyd JE, and Austin ED. 2011. The genetics of pulmonary artertal hypertension in the post-BMPR2 era. Pulm Circ 1:305-319.
18. Elliott CG, Glissmeyer EW, Havlena GT, Carlquist J, McKinney JT, Rich S, McGoon MD, Scholand MB, Kim M, Jensen RL, Schmidt JW, and Ward K. 2006. Relationship of BMPR2 mutations to vasoreactivity in pulmonary arterial hypertension. Circulation 113(21):2509-2515.
19. Durrington HJ and Morrell NW. 2009. What we know and what we would like to know about genetics and pulmonary arterial hypertension. The International Journal of Clinical Practice 63(Suppl 161):11-16.
20. Girerd B, Montani D, Coulet F, Sztrymf B, Yaici A, Jais X, Tregouet D, Reis A, Drouin-Garraud V, Fraisse A, Sitbon O, O'Callaghan DS, Simonneau G, Soubrier

F and Humbert M. 2010. Clinical Outcomes of Pulmonary Arterial Hypertension in Patients Carrying an ACVRL1 (ALK1) Mutation. American Journal of Respiratory and Critical Care Medicine 181(8):851-861.

21. Souza R, Humbert M, Sztrymf B, Jais X, Yaici A, Le Pavec J, Parent F, Herve P, Soubrier F, Sitbon O and Simonneau G. 2008. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. Eur Respir J 31:343-348.

22. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jais X, Montani D, Souza R and Simonneau G. 2010. Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era. Circulation 122(2):156-163.

23. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL and Gomberg-Maitland M. 2010. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. European Respiratory Journal 35(5):1079-1087.

24. Benza RL, Gomberg-Maitland M, Frost AE, Frantz RP, Humbert M and McGoon MD. 2012. Development of prognostic tools in pulmonary arterial hypertension: Lessons from modern day registries. Thrombosis and Haemostasis 108(6):1049-1060.

25. Rich S, Dantzker D, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, Levy PC, Reid LM, Vreim CE and Williams GW. 1987. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 107(2):216-223.

26. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, Levy PS, Pietra GG, Reid LM, Reeves JT, Rich S, Vreim CE, Williams GW and Wu M. 1991. Survival in Patients with Primary Pulmonary-Hypertension - Results from a National Prospective Registry. Ann Intern Med 115(5):343-349.

27. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simmonneau G and Begaud B. 1996. Appetite-suppressant drugs and the risk of primary pulmonary hypetension. N Eng J Med 335:609-616.

28. Stricker H, Domenighetti G, Popov W, Speich R, Nicod L, Aubert JD and Soler M. 2001. Severe pulmonary hypertension: data from the Swiss Registry. Swiss Medical Weekly 131(23-24):346-350.

29. Tueller C, Stricker H, Soccal P, Tamm M, Aubert JD, Maggiorini M, Zwahlen M and Nicod L. 2008. Epidemiology of pulmonary hypertension: new data from the Swiss registry. Swiss Medical Weekly 138(25-26):379-384.

30. Jing ZC, Xu XQ, Han ZY, Wu Y, Deng KW, Wang H, Wang ZW, Cheng XS, Xu B, Hu SS, Hui RT and Yang YJ. 2007. Registry and survival study in chinese patients with idiopathic and familial pulmonary arterial hypertension. Chest 132(2):373-379.

31. Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, Yuan P, Jiang X, He J, Humbert M and Jing ZC. 2011. Survival of chinese patients with pulmonary arterial hypertension in the modern treatment era. Chest 140(2):301-9.

32. Peacock AJ, Murphy NF, McMurray JJV, Caballero L and Stewart S. 2007. An epidemiological study of pulmonary arterial hypertension. Eur Respir J 30(1):104-109.

33. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jais X, Montani D, Souza R and Simonneau G. 2006. Pulmonary arterial hypertension in France - Results from a national registry. Am J Respir Crit Care Med 173(9):1023-1030.

34. Thenappan T, Shah SJ, Rich S, and Gomberg-Maitland M. 2007. A USA-based registry for pulmonary arterial hypertension: 1982–2006. Eur Respir J 30(6):1103-1110.

35. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP and McGoon MD. 2010. Pulmonary Arterial Hypertension Baseline Characteristics From the REVEAL Registry. Chest 137(2):376-387.

36. Appelbaum L, Yigla M, Bendayan D, Reichart N, Fink G, Priel. S, Schwartz Y, Richman P, Picard E, Goldman S and Kramer MR. 2001. Primary Pulmonary Hypertension in Israel: A National Survey. Chest 119:1801-1806.

37. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jais X, Montani D, Souza R

and Simonneau G. 2010. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 36(3):549-555.

38. Frost AE, Badesch DB, Barst RJ, Benza RL Ellott G, Farber HW, Krichman A, Liou TG, Raskob GE, Wason P, Feldkircher K, Turner M and McGoon MD. 2011. The Changing Picture of Patients With Pulmonary Arterial Hypertension in the United States How REVEAL Differs From Historic and Non-US Contemporary Registries. Chest 139(1):128-137.

39. Benza R L, Miller DP, Barst RJ, Badesch DB, Frost AE and McGoon MD. 2012. An Evaluation of Long-term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry. Chest 142(2):448-456.

40. Escribano-Subias P, Blanco I, Lopez-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gomez-Sanchez MA and Barbera JA. 2012. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. European Respiratory Journal 40(3):596-603.

41. Rich JD, Shah SJ, Swamy RS, Kamp A and Rich S. 2011. Inaccuracy of Doppler Echocardiographic Estimates of Pulmonary Artery Pressures in Patients With Pulmonary Hypertension Implications for Clinical Practice. Chest 139(5):988-993.

42. Sproule M. 2011. Imaging: Chest radiography, ventilation/perfusion scintigrahy and computed tomography. In: Peacock AJ, Naeije R, Rubin LJ, eds. Pulmonary circulation diseases and their treatment. Hodder & Stoughton 3rd edition:115-127.

43. Vonk-Noordegraaf A. 2011. Imaging: Emerging modalities (MR, PET and others) In: Peacock AJ, Naeije R, Rubin LJ, eds. Pulmonary circulation diseases and their treatment. Hodder & Stoughton(3rd edition):128-137.

44. Frost AE, Langleben D, Oudiz R, Hill N, Horn E, McLaughlin V, Robbins IM, Shapiro S, Tapson VF, Zwicke D, DeMarco T, Schilz R, Rubenfire M and Barst RJ. 2005. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: Demonstration of a ceiling effect. Vascular Pharmacology 43(1):36-39.

45. Degano B, Sitbon O, Savale L, Garcia G, O'Callaghan DS, Jais X, Humbert M and Simonneau G. 2010. Characterization of Pulmonary Arterial Hypertension Patients Walking More Than 450 m in 6 Min at Diagnosis. Chest 137(6):1297-1303.

46. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N and Miyatake K. 2000. Clinical correlates and prognostic significance

of six-minute walk test in patients with primary pulmonary hypertension - Comparison with cardiopulmonary exercise testing. American Journal of Respiratory and Critical Care Medicine 161(2):487-492.

47. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D and Crow JW. 1996. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. New England Journal of Medicine 334(5):296-301.

48. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, and Simonneau G. 2002. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension - Prognostic factors and survival. Journal of the American College of Cardiology 40(4):780-788.

49. Macchia A, Marchioli R, Tognoni G, Scarano M, Marfisi R, Tavazzi L and Rich S. 2010. Systemic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. Am Heart Journal 159:245-57.

50. Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, Musella F, Gargiulo P, Marciano C, and Perrone-Filardi P. 2012. Do Changes of 6-Minute Walk Distance Predict Clinical Events in Patients With Pulmonary Arterial Hypertension? A Meta-Analysis of 22 Randomized Trials. Journal of the American College of Cardiology 60(13):1192-1201.

51. Mathai SC, Puhan MA, Lam, D and Wise RA. 2012. The Minimal Important Difference in the 6-Minute Walk Test for Patients with Pulmonary Arterial Hypertension. American Journal of Respiratory and Critical Care Medicine 186(5):428-433.

52. Gabler NB, French B, Strom BL, Palevsky HI, Taichman DB, Kawut SM, and Halpern SD. 2012. Validation of 6-Minute Walk Distance as a Surrogate End Point in Pulmonary Arterial Hypertension Trials. Circulation 126(3):349-56.

53. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, Sharma R, Hummel M, Hetzer R and Ewert R. 2002. Assessment of survival in patients with primary pulmonary hypertension importance of cardiopulmonary exercise testing. Circulation 106(3):319-324.

54. Ahmedzai S, Balfour-Lynn IM, Bewick T, Buchdahl R, Coker RK, Cummin AR, Gradwell DP, Howard L, Innes JA, Johnson AOC, Lim E, Lim WS, McKinlay KP, Partridge MR, Popplestone M, Pozniak A, Robson A, Shovlin CL, Shrikrishna D,

Simonds A, Tait P and Thomas M. 2011. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. Thorax 66:1-30.

55. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P and Simonneau G. 2005. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 111(23):3105-3111.

56. Galie N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML and Branzi A. 2009. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. European Heart Journal 30(4):394-403.

57. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG and McGoon MD. 2010. Predicting Survival in Pulmonary Arterial Hypertension Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 122(2):164-72.

58. McLaughlin VV, Shillington A and Rich S. 2002. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation 106:1477-1482.

59. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann J, Georgiou D, Mandayam S, Ginzton LE and Brundage BH. 1997. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am Coll Cardiol 30:343-349.

60. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW and Rubin LJ. 2002. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension - A double-blind, randomized, placebo-controlled trial. American Journal of Respiratory and Critical Care Medicine 165(6):800-804.

61. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C and Rubin LJ. 2006. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. European Respiratory Journal 28(6):1195-1203.

62. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M and Seeger W. 2010. Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension A

Randomized Controlled Clinical Trial. Journal of the American College of Cardiology 55(18):1915-1922.

63. Benza RL, Seeger W, McLaughlin VV, Channick RN, Voswinckel R, Tapson VF, Robbinsm IM, Olschewski H and Rubin LJ. 2011. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: The TReprostinil sodium Inhalation Used in the Management of Pulmonary arterial Hypertension (TRIUMPH) study open-label extension. Journal of Heart and Lung Transplantation 30(12):1327-1333.

64. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Siedentop H and Seeger W. 2002. Inhaled iloprost for severe pulmonary hypertension. New England Journal of Medicine 347(5):322-329.

65. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M and Simonneau G. 2005. Sildenafil citrate therapy for pulmonary arterial hypertension. New England Journal of Medicine 353(20):2148-2157.

66. Rubin LJ, Badesch DB, Fleming TR, Galie N, Simonneau G, Ghofrani HA, Oakes M, Layton G, Serdarevic-Pehar M, McLaughlin VV and Barst RJ. 2011. Long-term Treatment With Sildenafil Citrate in Pulmonary Arterial Hypertension The SUPER-2 Study. Chest 140(5):1274-1283.

67. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M and Simonneau G. 2002. Bosentan therapy for pulmonary arterial hypertension. New England Journal of Medicine 346(12):896-903.

68. Galie N, Hoeper MM, Jansa P, Al-Hiti H, Meyer GMB, Chiassi E, Kusic-Pajic A and Simonneau G. 2008. Treatment of patients with midly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. The Lancet 371:2093-2100.

69. McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galle N, Rainisio M, Simonneau G and Rubin LJ. 2005. Survival with first-line bosentan in patients with primary pulmonary hypertension. European Respiratory Journal 25(2):244-249.

70. Galie N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL and

Rubin LJ. 2008. Ambrisentan for the treatment of pulmonary arterial hypertension - Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. Circulation 117(23):3010-3019.

71. Oudiz RJ, Galie N, Olschewski H, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Harrison BC, Despain D, Dufton C and Rubin LJ. 2009. Long-Term Ambrisentan Therapy for the Treatment of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology 54(21):1971-1981.

72. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicolls MR and Zamanian RT. 2010. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL. Identifying systemic sclerosis as a unique phenotype. Chest 138:1383-1394.

73. Rich S, Kaufmann E and Levy PS. 1992. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. New England Journal of Medicine 327(2):76-81.

74. Swiston J, Johnson SR and Granton JT. 2010. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: A systematic review of the literature. Respiratory Medicine 104(11):1588-1607.

75. Kane GC, Maradit-Kremers H, Slusser JP, Scott CG, Frabtz RP and McGoon MD. 2011. Integration of clinical and haemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. Chest 139(6):1285-1293.

76. Benza RL, Gomberg-Maitland M, Miller DP, Frost A, Frantz RP, Foreman AJ, Badesch DB and McGoon MD. 2012. The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest 141(2):354-362.

77. Lee WTN, Ling Y, Sheares KK, Pepke-Zaba J, Peacock AJ and Johnson MK. 2012. Predicting survival in pulmonary arterial hypertension in the UK. European Respiratory Journal 40(3):604-611.

78. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA and Levy PS. 1994. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 121:409-415.

79. Kuhn KP, Byrne DW, Arbogast PG, Doyle TP, Loyd JE and Robbins IM. 2003. Outcome in 91 consecutive patients with pulmonary arterial hypertension

receiving epoprostenol. American Journal of Respiratory and Critical Care Medicine 167(4):580-586.

80. National pulmonary hypertension centres of the UK and Ireland 2008. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Heart 94(Suppl 1):i1-i41.

81. British Cardiac Society guidelines and medical practice committee and approved by the British Thoracic Society and the British Society of Rheumatology. 2001. Recommendations on the management of pulmonary hypertension in clinical practice. Heart 86:i1-i13.

82. Shapiro BP, McGoon MD and Redfield MM. 2007. Unexplained pulmonary hypertension in elderly patients. Chest 131:94-100.

83. Halpern SD and Taichman DB. 2009. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest 136:37-43.

84. Moledina S, Hislop AA, Foster H, Schulze-Neick I and Haworth SG. 2010. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 96:1401-1406.

85. Crapo RO, Hankinson JL, Irvin C, MacIntyre NR, Zoter KZ and Rise RA. 1995. Single-breath carbon monoxide diffusion capacity (transfer factor). Recommendations for a standard technique- 1995 update. American Journal of Respiratory and Critical Care Medicine 152:2185-2198.

86. Sherrill DL, Enright PL, Kaltenborn WT and Lebowitz MD. 1999. Predictors of longitudinal change in diffusion capacity over 8 years. American Journal of Respiratory and Critical Care Medicine 160:1883-1887.

87. Thenappan T, Cherlyanne G and Gomberg-Maitland M. 2012. Validation of the Pulmonary Hypertension Connection Equation for Survival Prediction in Pulmonary Arterial Hypertension. Chest 141(3):642-650.

88. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, and Lang IM. 2011. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. Journal of Heart and Lung Transplantation 30(9):982-989.

89. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, Howard LS, Pepke-Zaba J, Sheares KK, Corris PA, Fisher AJ, Lordan JL, Gaine S, Coghlan JG, Wort SJ, Gatzoulis MA and Peacock AJ. 2012. Changing demographics,

epidemiology and survival of incident pulmonary arterial hypertension. Am J Respir Crit Care Med 186(8):790-796.

90. British Cardiac Society guidelines and Medical Practice Committe, and approved by the British Thoracic Society and British Society of Rheumatology. 2001. Recommendations on the management of pulmonary hypertension in clinical practice. Heart 86:i1-i13.

91. Chandra S, Shah SJ, Thenappan T, Archer SL, Rich S and Gomberg-Maitland M. 2010. Carbon monoxide diffusing capacity and mortality in pulmonary arterial hypertension. Journal of Heart and Lung Transplantation 29(2):181-187.

92. Calle EE, Thun MJ, Petrelli JM, Rodriguez C and Heath CW. 1999. Body mass index and mortality in a prospective cohort of US. adults. New England Journal of Medicine 341(15):1097-1105.

93. Burger CD, Foreman AJ, Miller DP, Safford RE, McGoon MD and Badesch DB. 2011. Comparison of Body Habitus in Patients With Pulmonary Arterial Hypertension Enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management With Normative Values From the National Health and Nutrition Examination Survey. Mayo Clinic Proceedings 86(2):105-112.

94. Poms AM, Turner M, Farber HW, Meltzer LA and McGoon MD. 2013. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. Chest 144(1):169-176.

95. Zafrir B, Adir Y, Shehadeh W, Shteinberg M, Salman N and Amir O. 2013. The association between obesity, mortality and filling pressures in pulmonary hypertension patients; the 'obesity paradox'. Respiratory medicine 107:139-146.

96. Oreopoulos A, Kalantar-Zadeh K, Sharma AM and Fonarow GC. 2009. The obesity paradox in the elderly: Potential mechanisms and clinical implications. Clin Geriatr Med 25:643-659.

97. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD and Horwich TB. 2005. Survival advantages of obesity in dialysis patients. Am J Clin Nutr 81:543-54.

98. Lavie CJ, Milani and Ventura HO. 2009. Obesity and cardiovascular disease. J Am Coll Cardiol 53:1925-32.

99. Doehner W, Clark A and Anker SD. 2010. The obesity paradox: weighing the benefit. Eur Heart J 31:146-148.

100. Mohamed-Ali V, Goodrick S, Bulmer K, Holly JMP, Yudkin JS and Coppack SW. 1999. Production of soluble tumour necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am J Physiol 277:E971-5.

101. Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY and McTiernan C. 2000. The role of tumour necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol 35:537-44.

102. Rauchhaus M, Coats A and Anker SD. 2000. The endotoxin-lipoprotein hypothesis. Lancet 356:930-3.

103. Mauritz GJ, Rizopoulos D, Groepenhoff H, Tiede H, Felix J, Eilers P, Bosboom J, Postmus PE, Westerhof N and Vonk-Noordegraaf A. 2011. Usefulness of serial N-terminal Pro-B-type natriuretic peptide measurements for determining prognosis in patients with pulmonary arterial hypertension. Am J Cardiol 108(11):1645-50.

104. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T and Hoeper MM. 2012. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. European Respiratory Journal 39(3):589-596.

105. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X and Simonneau G. 2006. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. European Heart Journal 27(5):589-595.

106. Peacock A, Keogh A and Humbert M. 2010. Endpoints in pulmonary arterial hypertension: the role of clinical worsening. Curr Opin Pulm Med 16(suppl 1):S1-S9.

107. Peacock AJ, Naeije R, Galie N and Rubin L. 2009. End-points and clinical trial design in pulmonary arterial hypertension: have we made progress? European Respiratory Journal 34(1):231-242.

108. Minai OA, Chaouat A and Adnot S. 2010. Pulmonary Hypertension in COPD: Epidemiology, Significance, and Management Pulmonary Vascular Disease: The Global Perspective. Chest 137(6):39S-51S.

109. Hamada K, Nagai S, Tanaka S, Handa T, Shigematsau M, Nagao T, Mishima M, Kitaichi M and Izumi T. 2007. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest 131(3):650-656.

110. Shorr AF, Wainright JL, Cors CS, Lettieri CJ and Nathan SD. 2007. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. European Respiratory Journal 30(4):715-721.
111. Clark KD, Wardrobe-Wong N, Elliott JJ, Gill PT, Tait NP and Snashall PD. 2001. Patterns of lung disease in a 'normal' smoking population. Are emphysema and airflow obstruction found together? Chest 120:743-747.
112. Copley SJ, Wells AU, Hawtin KE, Gibson DJ, Hodson JM, Jacques AET and Hansell DM. 2009. Lung morphology in the elderly: Comparative CT study of subjects over 75 years old versus those under 55 years old. Radiology 251:566-573.
113. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, Ehrhart M, Kessler R and Weitzenblum E. 2005. Severe pulmonary hypertension and chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 172(2):189-194.
114. Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R and Mal H. 2005. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest 127(5):1531-1536.
115. Adir Y, Shachner R, Amir O and Humbert M. 2012. Severe pulmonary hypertension associated with emphysema. A new phenotype? Chest 142(6):1654-1658.
116. Munson JC. 2010. Combined pulmonary fibrosis and emphysema: a high pressure situation. Eur Respir J 35:9-11.
117. Cottin VJ, Le Pavec J, Prevot G, Mal H, Humbert M, Simonneau G and Cordier JF. 2010. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. European Respiratory Journal 35(1):105-111.
118. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D and Cordier JF. 2005. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. European Respiratory Journal 26(4):586-593.
119. Mejia M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso D, Barrientos E, Gaxiola M, Navarro C and Selman M. 2009. Idiopathic Pulmonary Fibrosis and Emphysema Decreased Survival Associated With Severe Pulmonary Arterial Hypertension. Chest 136(1):10-15.
120. Rietema H, Holverda S, Bogaard HJ, Marcus JT, Smit HJ, Westerhof N, Postmus PE, Boonstra A and Vonk-Noordegraaf A. 2008. Sildenafil treatment in

COPD does not affect stroke volume or exercise capacity. European Respiratory Journal 31(4):759-764.

121. Stolz D, Rasch H, Linka A, Di Valentino M, Meyer A, Brutsche M and Tamm M. 2008. A randomised, controlled trial of bosentan in severe COPD. European Respiratory Journal 32(3):619-628.

122. King TE, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S and Raghu G. 2008. BUILD-1: A randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine 177(1):75-81.

123. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR and Hunninghake GW. A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis. New England Journal of Medicine 363(7):620-628.