"Contrasting the effect of Ramipril on the time to combinations of various heart events including death in patients with acute myocardial infarction (using AIRE study data)"

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To

my parents, my husband
and two lovely children

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Summary

This research is designed to study the effect of the Ramipril on different 'survival times' of survivors of acute myocardial infarction with heart failure. These different survival times, correspond to different defined end points. The data which is used in this research was gathered under the AIRE study.

The AIRE Study tested the hypothesis that patients with acute myocardial infarction complicated by clinical evidence of heart failure would live longer if they received long-term ramipril treatment, initiated between the second and ninth days after infarction. The AIRE study was a multicentre, multinational, double-blind, randomised, placebo-controlled study. 2006 patients with acute myocardial infarction and clinical evidence of heart failure were recruited in 144 centres in 14 countries. The start date of the AIRE study was 7 April 1989 and the end date was 28 February 1993. All patients aged at least 18 years admitted to coronary care, intensive care, or general medical units with a definite AMI and clinical evidence of heart failure, were potentially eligible.

The study found that Ramipril had a significant effect on time to death.

The study also had a secondary endpoint namely a validated re infarction which was a rigorously defined endpoint(see later). The conclusion was that the drug had no effect on time to this endpoint.

It is the purpose of this thesis to explore the consistency of these conclusions across a variety of further endpoints since studies on other drugs have exhibited different conclusions for various but similar endpoints.

So in this research a variety of 'survival' times were considered for each patient for a variety of endpoints. In particular the following adverse events were considered; time to 'death', 'first re infarction after treatment' and 'first stroke after treatment'. Then, in later stages, we tried to combine or to change the definition of the end event. An example of these changes, is to define an adverse event to be 'either sudden death or first re infarction or chest pain'. A complete list of end points are presented in chapter 4-1. The time origin for all survival times is the same and that is the date of registration which identifies the time when a patient has been entered in to the study.

In chapter 1 we outline background information.

In chapter 2 we introduce survival models and some of their key aspects. Then we introduce the various types of these models including hazard models and the Cox proportional hazards model in particular.

In chapter 3 the Kaplan-Meier approach was used to estimate the survival curves of those patients who were treated by Ramipril and those who were treated by the placebo. These survival curves were estimated for different adverse events and for each adverse event, the survival curve

of the patients treated by Ramipril and the survival curve corresponding to those who were treated by the placebo, were compared using the Generalised Savage (Manted_Cox) test statistic. These analyses and tests were performed by using the BMDP program 1L.

In chapter 4 we fit 12 different Cox Proportional Models (2 for each endpoint) to the various end points. Six models (one for each endpoint) included a single covariate, namely: "Treatment". These potentially offer a simple comparison between the effects of Ramipril and of the Placebo. In fact all these models, except one of them fitted well. The proportionality of hazards assumption corresponding to most endpoints, was valid. This makes it easier to believe that the results of these models are reliable. All these well fitting models suggest that Ramipril increases the corresponding 'survival' time. Among the above mentioned models, the numerically largest coefficient occurs in the model which is corresponding to endpoint "death". In this endpoint the patient's survival time is defined as the time interval between his/her registration date and his/her death. Recall that the other endpoints are mixtures of "death" and some other events such as validated or non validated re infarction or chest pain (except one endpoint). This indicates that Ramipril postpones the occurrence of "Death" but it may not postpone the occurrence of other adverse events such as re infarction (validated or non validated) or chest pain.

It is difficult to come to any overall conclusion in the light of the fitted Cox models including several covariates. In all these models several covariates (all significant covariates) are included in the Cox proportional

Hazards model. While the proportionality of hazards assumption is valid in all these models none of them fits well. This is based on our investigation of residuals which only appeared to have the required Ex(1) distribution in some cases.

In chapter 5 we discuss how it may be possible to derive a new baseline hazard function from the previously estimated baseline, in that the model based on the new baseline hazard function fits well i.e. its residuals have Ex(1) distribution.

Chapter 1

1-1 : Introduction :

Cardiac disease is one of the primary causes of death in the western world despite advances in medical care. Whilst many die with little warning of heart disease, a substantial proportion develop the syndrome of congestive heart failure (CHF). Patients with heart failure carry a heavy burden of symptoms and have a poor life expectancy. Until recently, no mode of therapy other than heart transplantation had been shown to improve the survival of patients with heart failure, despite great efficiency shown by some treatments in improving morbidity (Packer 1987).

Improved understanding of pathophysiological mechanisms involved in heart failure has led to the development and use of vasodilator drugs, and more recently, Angiotensin Converting Enzyme (ACE) inhibitors.

The most common aetiology of heart failure is ischaemic heart disease, in particular, Acute Myocardial Infarction (AMI). The earliest indication of mechanical cardiac dysfunction following AMI may occur within days or even hours. Ventricular enlargement is observed in 40-50% (Warren 1988, Jeremy 1989) of patients following transmural myocardial

infarction, resulting in increases in both diastolic and systolic left ventricular volume, strong predictors of subsequent mortality and morbidity (White 1987, Feild 1974). The main renin-angiotensin-aldosterone system (RAAS) is also stimulated during myocardial infarction which may be important in the development of heart failure.

The role of ACE inhibitors after myocardial infarction has now been the subject of intensive investigation. Several large studies have been conducted (Swedberg 1992, Pfeffer 1992, The TRACE study 1993) or are currently in progress (Ambrosioni 1991, ACE1-AMI 1992, Gruppo 1992, ISIS-4 Collaborative Group 1991) to investigate the effect of early treatment with ACE inhibitors following myocardial infarction on subsequent mortality. In some of these studies (Swedberg 1992, Gruppo 1992, ISIS-4 Collaborative Group 1991) all patients were treated within 24 hours of acute myocardial infarction and in some others (Pfeffer 1992), patients with evidence of left ventricular dysfunction based on a radionuclide measurement of ejection fraction but without overt clinical evidence of heart failure at the time of randomisation were selected.

The rationale for the AIRE (Acute Infarction Ramipril Efficacy) Study differed from that chosen in the above mentioned studies. The aim of the AIRE Study was to select a high risk group of patients based on overt, even if only transient, clinical evidence of heart failure (an excellent predictor of prognosis, The Mullticentre postinfarction Research Group 1983) using simple criteria in order to parallel normal clinical practice. A measure of ejection fraction was not required. The patients

were to be haemodynamically stable and study treatment was to start no sooner than two days after the acute myocardial infarction.

Ramipril was the ACE inhibitor which is used in the AIRE Study. Ramipril is an orally active, non-sulphydryl ACE inhibitor which is effective in low doses and is well tolerated. Acute haemodynamic studies in patients with Congestive Heart Failure (CHF) have shown trends towards a reduction in pulmonary capillary wedge pressure and an increase in cardiac index (DE Graeff 1987, Grozier 1987) suggesting a favourable role in the management of heart failure. Additionally, physical, chemical and enzyme kinetic properties of ramipril differ from those of other ACE inhibitors, and may have special significance for the post-infarct myocardium. Ramipril shows excellent tissue penetration, has a high affinity for, and binds tightly to, ACE both in the circulation and locally in different tissues, and has a stronger bradykinin-potentiating effect, compared with other ACE inhibitors (Bunning 1987, Linz 1990, Linz 1986, Linz 1992).

1-2 : Background of the Study :

Congestive heart failure is a major and growing public health problem. About 2 million patients have congestive heart failure in the United States, and the number is expected to increase substantially in the next few decades (see The SOLVD investigators 1991). The one-year mortality rate ranges from 15 percent among relatively unselected patients

(the SOLVD investigators 1991) to 50 percent among those in New York Heart Association functional class IV (The SOLVD investigators 1991). About 35 percent of all patients with a diagnosis of congestive heart failure are hospitalised every year.

In 1985 the Veterans Administration Cooperative Vasodilator Heart Failure Trial (The SOLVD investigators 1991) reported a lower mortality in patients with congestive heart failure treated with combined hydrazine and isosorbide dinitrate than in patients receiving placebo (P=.093). No benefit was observed in the group randomly assigned to prazosin. Angiotensin-converting-enzyme inhibitors appeared to be particularly promising in improving hemodynamic indexes (The SOLVD investigators 1991) and symptoms (The SOLVD investigators 1991 and Ball 1993) .

More recently, the Cooperative Scandinavian Enalapril Survival (CONSENSUS) Study Group showed that treatment with enalapril, an ACE inhibitor, in addition to diuretics, digitalis and directly-acting vasodilator drugs, significantly reduced total mortality in patients with severe CHF, compared with placebo (by 40% at six months, P=.002; by 31% at one year, P=.001; and by 27% at study close, P=.003) (CONSESUS 1987).

The benefit of ACE inhibitor therapy on the survival of patients with less severe but symptomatic mild to moderate chronic heart failure selected on the basis of reduced ejection fractions has been demonstrated in two recently reported trials, V-HEFT II (Vasodilator Heart Failure Trail) (Cohn 1991) and SOLVD (Studies of Left ventricular dysfunction)

(The SOLVD investigators 1991). V-HeFT II showed that enalapril reduced mortality to a greater extent (by 28% at a two-year preselected time point) than the combination of hydralazine and isosorbide denigrate in patients already receiving diuretics and digitalis (Cohn 1991). The SOLVD treatment trial showed that treatment with enalapril significantly reduced both mortality (by 16%) and hospitalisation for worsening heart failure (by 26%), compared with a placebo (The SOLVD investigators 1991). As a result of these findings, ACE inhibitors have now become accepted as standard long-term therapy in chronic heart failure. However, despite optimal care, mortality from heart failure remains high. The five-year mortality for patient with newly diagnosed heart failure is approximately 50% (Packer 1987).

1-3 : AIRE Study :

The Acute Infarction Ramipril Efficacy (AIRE) Study was designed to study the effect of Ramipril on the mortality of survivors of acute myocardial infarction with heart failure. The AIRE Study tested the hypothesis that patients with acute myocardial infarction complicated by clinical evidence of heart failure would live longer if they received long-term Ramipril treatment, initiated between 3 and 10 days after infarction. The rationale, design, organisation, and outcome definition of the AIRE Study were described prospectively (Hall 1991). Here we just mention some important aspects of the AIRE Study. The AIRE study was a multicentre, multinational, double-blind, randomised, placebo-controlled study. 2006 patients with acute myocardial infarction and clinical evidence of heart failure were recruited in 144 centres in 14 countries. A list of these countries is presented in section 1-2-5. The start date of study was 7 April 1989 with an end date of 28 February 1993. All patients aged at least 18 years admitted to coronary care, intensive care, or general medical units with a definite AMI and clinical evidence of heart failure, were potentially eligible.

The AIRE Study included 2006 patients with acute myocardial infarction (during the course of study they removed 20 patients from one centre (Belgium) because the data were inconsistent). These are the patients who subsequently developed transient or persistent clinical evidence of heart failure, a group at high risk of subsequent death.

Between days 3 and 10 after acute myocardial infarction, patients were randomised to treatment with either placebo or the angiotensin-converting enzyme (ACE) inhibitor Ramipril. Patients were followed for a minimum of 6 months and a mean of 15 months. Recruitment was completed on August 27, 1992. subsequently the official study closed on February 28, 1993 (Ball 1993).

The treatment was initiated in hospital between 3 and 10 days after AMI. Patients initially received 2.5 mg of Ramipril or placebo twice daily. Those who tolerated this dose received it for 2 days and then were given 5 mg of ramipril or the placebo twice daily thereafter. Patients who could not tolerate the higher 5 mg dose were discharged on 2.5 mg or placebo twice daily. Ramipril at 1.25 mg or the Placebo was provided for those patients who could not tolerate the initial 2.5 mg dose. These patients began again on the lower dose 1.25 mg twice daily for 2 days before increasing to 2.5 mg twice daily and then 5 mg twice daily. When therapy was started or dosage was changed, blood pressure was monitored before and at 2, 4, and 6 hours after, all adverse events being recorded. If a patient was unable to tolerate Ramipril at least 2.5 mg twice daily or matching the Placebo doses he or she was withdrawn from the study treatment but followed at the prescribed visit intervals for intention-to-treat analysis. The protocol did not allow discharge of a patient on the low dose of 1.25 mg twice daily.

- Follow up :

In the AIRE Study patients' follow up was designed to minimise any interference with usual clinical practice. All patients, including those withdrawn from randomised treatment, were seen at 4 and 12 weeks after randomisation and thereafter every 12 weeks until study close. At each visit, the occurrence of adverse events, compliance, and concomitant therapy were recorded. Renal function (serum electrolytes, creatinine, and urea) was reviewed in accordance with the investigator's normal clinical practice. Patients could continue or begin any other necessary treatment except an ACE inhibitor while on randomised treatment. Monitoring of serum potassium was strongly advised, particularly if potassium-sparing diuretics or potassium supplements were judged necessary. The last day included in the analysis of the mortality data was Feb. 28, 1993, six months after the 2000th patient had been recuited. As soon as possible after this date, the final status of all patients was assessed.

- Sample size :

On the following assumptions the trial was estimated to require about 2000 patients: predicted average patient follow-up 15 months; predicted the Placebo mortality 20% at 15 months; a 'clinically relevant improvement' defined as a 25% reduction in all-cause mortality, resulting in an expected mortality of 15% in the active treatment group at 15 months; and statistical power of at least 80% at a significance level of 5% (two-tailed test, log rank test).

- Study Organisation :

An Independent Adjudicating Panel (IAP) acted as the overall ethical supervisory body and had access to the randomisation code. The IAP performed the interim analysis. The IAP was also responsible for transmitting data on serious adverse events to the relevant regulatory authorities. An international steering committee met regularly to review progress and was responsible, inter alia, for the clinical definition of the secondary endpoints. The executive committee, chaired by the principal investigator and including representatives of the sponsor, the study managers, and the data manager, was responsible for the day-to-day decisions on the conduct of the study and the operation of the AIRE Study Co-ordinating centre. All endpoints were validated by a subcommittee of the international steering committee. An independent group was responsible for conducting a series of prospective audits of study procedures, to ensure that the study conduct adhered closely to the European Guidelines for good Clinical Research Practice

In the AIRE Study the primary outcome was total mortality. The secondary outcome was time to first validated outcome, that is the time to death or progression to severe/resistant heart failure, reinfarction or stroke.

Validation of reinfarction was hampered by the fact that the Subcommittee relied on the Investigator's interpretation of ECGs, often made difficult by the presence of severe baseline abnormalities. In contrast, the presence of chest pain and elevated enzyme levels were more easily defined, although the use of a uniform enzyme test would have

further improved the validation process. Patients with chest pain and minor increase in cardiac enzymes did not fulfil validation criteria, but this group deserves further study. The number of autopsies was small; therefore, autopsy evidence that could not be clinically validated was not accepted (Cleland 1993).

In validation of stroke, the Subcommittee did not rigidly apply the requirement to exclude other diseases that may cause neurological deficit in cases in which there was no clinical suspicion of a process other than a vascular event.

1-4 : Results of AIRE Study :

- Baseline demographic data

1004 patients were randomised to Ramipril and 982 to the Placebo; randomisation to drug or the Placebo was well balanced within the 14 countries. Some 22.6% of the patients had received treatment for a previous myocardial infarction but only 8.2% had a history of previous heart failure. The mean time to randomisation was 5.4 (SD 2.1) days after AMI for Ramipril and 5.4 (SD 2.2) for the Placebo. The groups were well matched in all aspects at baseline. Overall, 58% of patients received thrombolytic treatment. Concomitant medication was similar in the two groups.

- Follow-up :

The average time of follow-up was 15 months with a minimum of 6 months. Only 1 patient was lost to follow-up being last seen 12 weeks after randomisation, at which time the data for this patient were censored.

There were 170 deaths (17%) in the Ramipril group and 222 (23%) in the Placebo group, with overall a 27% reduction in the risk of death (95% C1 11% to 40%), which was highly significant statistically (P=0.002).

- Secondary endpoints :

For the formal analysis they used only the findings for the first validated event in any individual patient-namely, death, reinfarction, stroke, or development of severe/resistant heart failure. Again the reduction, 19% (95% CI 5% to 31%), was highly significant statistically (P=0.008).

- Withdrawal from study medication :

There were 352 premature withdrawals from the Ramipril group and 318 from the Placebo group. Intolerance was given as the primary or contributory factor in 126 of the Ramipril withdrawals and in 68 of the Placebo withdrawals, whereas progression to severe/resistant heart failure was the stated reason for 58 Ramipril withdrawals and 92 the Placebo withdrawals.

- Serious adverse events :

There were fewer patients with reported serious adverse events on Ramipril, 581 (58%), than on the Placebo, 625 (64%). Serious adverse events included the endpoints of the trial (death, progression to severe/resistant heart failure, reinfarction, and stroke) as well as possible adverse effects of treatment. Syncope was reported for 24 (2.4%) patients on Ramipril and 17 (1.7%) on the Placebo with a similarly increased occurrence of hypertension in the Ramipril treated group-42 (4.2%) compared with the Placebo-23 (2.3%). Renal failure occurred with a similar frequency in the two groups: 15 (1.5%) on the drug and 12 (1.2%) on the Placebo. Angina which it was thought might be worsened in some

patients prescribed an ACE inhibitor, was reported as a serious adverse event in 181 patients (18%) taking Ramipril and 171 (17%) taking the Placebo.

1-5 : Particulars and objectives of our research :

1-5-1 : Data set

The data set which is used in our research, is exactly the AIRE study data set. It contains the 2006 patients and data from one centre which apparently recruited 20 patients subsequently found to be inconsistent and were censored. The main analyses were based on the remaining 1986. Of these 982 were randimised to the Placebo and 1004 to Ramipril. The difference between the AIRE Study and our research is in the definition of the secondary endpoint which will be defined in section 1-5-2.

1-5-2 : End Points :

As was mentioned before, the difference between the AIRE Study and our research is in the definition of secondary end points. Initially we consider 26 endpoints and then reduce these numbers to 6. These 6 end points and the corresponding survival times are defined as follow :

1- End Point No. 1 :

Time from registration date to time of death.

2- End Point No. 2 :

Time from registration date to time of first validated reinfarction.

3- End Point No. 3 :

Time from registration date to time of sudden death or first validated reinfarction.

4- End Point No. 4 :

Time from registration date to time of sudden death or first non validated reinfarction.

5- End Point No. 5 :

Time from registration date to time of sudden death or first validated reinfarction or chest pain.

6- End Point No. 6 :

Time from registration date to time of sudden death or first non validated reinfarction or chest pain.

Since these response variables are time measurements we wish to model these distribution using survival methods.

1-5-3 : Objectives :

1- Investigating the effect of Ramipril on the time to occurrence of the various endpoints described above. Different survival times are defined for each patient. Each of these survival times is defined as the time interval between the patient's registration date and the date of a particular end point. The Cox Proportional hazards model is used to carry out these investigations.

2- Investigating the goodness of fit of fitted Cox proportional hazards models to assess the precision of results.

3- Including more covariates (in addition to treatment which is either Ramipril or the placebo) in the Cox proportional hazard model to investigate the relationship between any of the survival times and Ramipril when the effect of other covariates is fixed.

1-5-4 : Definition of variables :

A complete list of variables, which have been collected at baseline for each patient in the AIRE Study, is presented in the Ball SG et al's reports (1994). Here we just mention and define those variables which will be used in our research.

- **Age :** Is defined as age of patient (in years) at the date of randomisation
- **Sex :** Is coded as 1 if the patient is male and 0 if patient is female.

- Site of index infarction:

1- Anterior; includes anteroseptal and anterolateral infarcts.

2- Inferior; includes posterior and inferolateral infarcts.

3- Unclassified; includes previous myocardial infarction at the same or an unknown site, left bundle branch block (LBBB), right bundle branch block (RBBB) hemiblocks, pacemakers and illegible or non-available ECG.

This covariate is included in models by using two dummy variables named as Site_d1 (Anterior, Yes or No) and Site_d2 (Inferior, Yes or No). Note that the basic category is the Unclassified site.

-New Q wave :

This variable has three levels which are defined as below :

Code (1) : New Q wave; A pathological Q wave was defined as one with ≥ 2mm amplitude in any two associated leads in the absence of same unknown territory.

Code (2) : No new Q wave; No new Q wave was observed.

Code (3) : Unclassified; As for site infarction but with the caution that pacemaker spikes may resemble Q waves.

This covariate is included in models using 2 dummy variables, wave_d1 (code 1, Yes or No) and wave_d2 (code 2, Yes or No). Note the basic category is code 3.

- Hypertension : This variable has two levels which are coded as 1 or 0 according to whether the patient has a history of treated hypertension .

- **Diabetes Mellitus :** This variable has two levels which are coded as 1 or 0 according to whether or not the patient has a history of treated Diabetes Mellitus.
- **Previous Myocardial Infarction :** This variable has two levels which are coded as 1 or 0 according to whether the patient has or has not previous myocardial infarction. In Cox models it is named as 'PMI'.
- **Angina Pectoris :** This variable has two levels which are coded as 1 or 0 according to whether or not the patient has a history treated Angina Pectoris.
- **Cardiac Arrhythmia :** This variable has two levels which are coded as 1 or 0 according to whether the patient has or has not Cardiac Arrhythmia. In Cox models, it is named as 'Cardiac'.
- **ac4a :**Is coded as 1 or 0 according to whether Bibasilar post_tussive crackles is checked or not .
- **ac4b :**Is coded as 1 or 0 according to whether Pulmonary venous congestion is checked or not
- **ac4c :**Is coded as 1 or 0 according to whether Third heart sound with pers is checked or not .
- **NYHA :** This variable has 4 classes or levels which are defined as :

  Code (0) : No previous cardiac disease. (Class I)

  Code (1) : Resulting limitations of physical activity.Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain(class II).

  Code (2) : Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest.

Ordinary physical activity results in fatigue, palpitation, dyspnoea anginal pain(class III).

Code (3) : Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain(class IV).

This covariate is included in models by using 3 dummy variables nyha_d1 (Class I, Yes or No), nyha_d2 (Class II, Yes or No) and nyha_d3 (Class III, Yes or No). Note the basic category is Class IV.

-List of countries and number of centers in each country :

Argentina(11), Austria(5), Belgium(15), Denmark(10), Finland(8), Germany(8), Great Britain(34), Ireland(17), Italy(5), Luxembourg(2), Netherlands(16), South Africa(8), Sweden(11), Switzerland(1).

Chapter 2

An Introduction to Survival Models

In this chapter we introduce survival models and some of their key aspects. Then we introduce the various types of these models including hazards based models and the Cox Proportional Hazards model in particular. Finally we will give some reasons for using the Cox Proportional Hazards model in analysing our data.

2-1: Introducing Survival Models:

Survival models are those types of models which are used for analysing failure times. These models have as the response variable the length of time to 'end events'. Such events may be, for example, between birth and death, between marriage and divorce, between start of treatment and death or between start of treatment and 'cure' of a particular disease. The length of time between such events, which is actually the response variable, is called 'survival time', 'life time' or 'failure time'. Note that to determine the failure time precisely, there are requirements:

a) A time origin must be unambiguously defined. It is the time which the subject (or the individual) enters the study or begins to be observed or gets a particular treatment.

b) A scale for measuring the passage of time must be considered. In medical research, which usually deals with actual life times , this scale could be for example, hours, days, weeks, months or even years.

C) The meaning of failure should be clearly defined. This means we should identify what we mean by a failure event.

In survival analysis, sometimes we are interested in only the distribution of failure times, for example, in a group of patients. More often we may be interested in comparing the failure times of two (or more) groups of individuals or patients, say one group treated by a Placebo and the other by a new medicine. We wish to investigate the influence of the new medicine in prolonging the patients' survival time. Alternatively, values of potential explanatory variables may be available for each individual from which a model for survival time may be formed. In some survival analyses the researcher may wish to investigate the relation between the explanatory variables and the survival times as well.

2-2: Censoring :

An important reason for using specialised statistical models and methods for survival data is to accommodate a problem which arises in recording failure times. In survival data there is the possibility that some individuals or patients may not be observed for the full time to failure. Note, for example, it is impossible or at least very difficult to follow up a group of patients for tens of years to observe their death and record their survival time. In some types of survival analyses it may be impossible to observe the failure event for all individuals or patients. Such a situation happens, for example, when the failure event is death from a particular disease (e.g. heart attack) but there are several other diseases which could cause death. Note someone who has died from Lung Cancer could not have died from the Heart Attack as well. This implies that in survival models, the problem of not being able to record the actual or whole survival time can not be neglected.

The above mentioned difficulty in recording individuals' or patients' survival time is known as a censoring problem. Censoring has led statisticians to develop some particular methods to analyse survival or failure times. Note that when the failure time of a patient is censored, this implies that his/her actual failure time is more than the observed time.

2-3 : Failure time distributions :

Let T be a non-negative continuous random variable representing the failure time of an individual from a homogeneous population. The probability model of T can be specified in many ways, three of which are particularly useful in survival applications: the survivor function, the probability density function, and the hazard function. Interrelations between these three representations are given below for both discrete and continuous distributions.

The survival function is defined as the probability that T is at least as great a value as t; that is,

$$S(t)=P(T \geq t), \qquad 0<t<\infty,$$

where t is a possible survival time and S(.) is the survival function and gives the probabilities in the right tail of the distribution. Clearly S(t) is a monotone non-increasing left continuous function with

$$S(0)=1,$$

and,

$$\lim_{t\to\infty} S(t)=0.$$

The probability density function (p.d.f) of T is

$$f(t)=\lim_{\Delta t\to 0^+} [P(t\leq T<t+\Delta t)/ \Delta t]$$

$$= -dS(t)/dt.$$

Conversely, $S(t)=\int_t^{\infty} f(s)ds$ and $f(t)\geq 0$ with $\int_0^{\infty} f(t)dt=1$. The range of T as should be the case over $(0, \infty)$.

The hazard function specifies the instantaneous rate of failure at T=t

$$h(t)= \lim_{\Delta t \to o+}[P(t \leq T < t+\Delta t \mid T \geq t)/ \Delta t]$$

$$=f(t)/S(t).$$

It is easily seen that h(t) specifies the distribution of T since, from the previous equation,

$$h(t)=-d\log S(t)/dt$$

So that integrating and using S(0)=1, we obtain

$$S(t)= \exp(-\int_0^t h(u)du).$$

The p.d.f can then be written as

$$f(t)=h(t) \exp(-\int_0^t h(u)du).$$

2-4: Different types of survival models :

Different types of survival models have been introduced in the last two decades. Here we do not intend to mention or to discuss all of them. In this section we just mention two main groups of survival models and then in the next section we will introduce more precisely the (survival) model which is intended to be used in this research. As was said before, two main types of survival models are usually considered. These are parametric and non parametric survival models. Parametric survival models are those for which some assumptions about the distribution of the failure (survival) times are made in advance; for example, that the failure times are exponentially distributed or that they have a Weibull distribution. Accelerated failure time models and Log duration survival models are two examples of parametric survival models. The other type of survival models are those under which no assumption is made about the distribution of survival times i.e. we do not assume that the distribution of failure times is a particular distribution.

One of the most famous survival models is the Cox Proportional Hazards model. Since in this research we use this particular model, therefore we introduce this model in the next section in more detail than the other models.

2-5 :Cox Proportional Hazards Model :

As was said, the Cox Proportional Hazards Model or simply the Cox Regression Model is a nonparametric proportional hazards based (survival) model. As is clear from its name, the assumption of "proportional hazards" is a basic assumption in the Cox model. It is a strong assumption which needs to be checked. Later in section 4-5-1 a method for investigating the proportionality of hazards assumption will be introduced.

The Cox Proportional Hazards model proposed by Cox can be written in several different ways of which the most usual is :

$$h(t)=h_0(t)\exp(\underline{\beta}^T \underline{X}),$$

where $h_0(t)$ is an unknown function and is called the baseline hazard function, $\underline{X}$ is a particular set of levels of explanatory variables, $\underline{\beta}$ is the vector of coefficients of the explanatory variables and h(t) is the hazard function which shows the instantaneous hazard of failure at time T= t. Both $h_0(t)$ and $\underline{\beta}$ are estimated from the data. The baseline survival function, the survival function and the density function of the survival time T can be, respectively, written as :

$$S_0(t) =\exp\{-\int_0^t h_0(t)\}$$

and

$$S(t) = [S_0(t)]^{\exp(\underline{\beta}^T \underline{X})} \quad \text{or} \quad S(t) = \exp\{-\int_0^t h(u)du\}$$

and

$$f(t)=h(t)\,[S_0(t)]^{\exp(\underline{\beta}^T \underline{X})} \quad \text{or} \quad f(t) =h(t)\exp\{-\int_0^t h(u)du\}.$$

Different approaches can be used to estimate the coefficient $\underline{\beta}$ but the most usual approach is the one which is known as the method of partial likelihood as proposed by Cox. We do not write down the partial likelihood here. Instead some concepts of the Cox proportional Hazards model will be discussed.

To illustrate what the assumption of proportional hazards really means, suppose that a Cox Proportional Hazards model is fitted to the hazard of failure, using only one explanatory variable, say the sex of patients. Then the proportionality of hazards of failure means that the ratio of the hazards of failure for male and female (two levels of sex) is constant over time. As was mentioned before, this is quite a strong assumption on which to base estimation of hazard functions. Hence it is necessary to check this assumption in respect of any fitted Cox Proportional Hazards model.

2-5-1: Checking The Proportional Hazards Assumption :

As was mentioned before, one of the assumptions of a Cox regression model is that for any two cases (e.g. for any two patients), the ratio of the estimated hazard across time is a constant. For example if we have two patients who are similar in all values of the explanatory variables except sex and one of them is male and the another is female, then the proportionality assumption of hazards of failure in respect f sex for these two patients means, the ratio of their estimated hazard rates across all time points is the constant value of e^{β}, where β is the regression coefficient of sex in the fitted Cox Regression model. This is not an assumption to be made lightly.

A useful plot for assessing whether the proportional hazards assumption is valid or not, is the Log-Minus-Log (LML) of the survival function plot. If the hazards of failure for two levels of one explanatory variable, say for male and female, is proportional, then the plot of the logarithm of minus the logarithm of the survival functions corresponding to different levels of the estimated explanatory variable (e.g. for male and females) against survival times should be more or less proportional . The survival function at each level of the explanatory variable can be estimated using the Kaplan-Meier method. The mathematical expression for this property is as follows:

We show the property only for the case when a single explanatory variable is included in the Cox Proportional hazards model. Suppose a Cox Proportional Hazards model is fitted to the survival time T (T is a non negative random variable) of some individuals, using an explanatory variable X for two possible levels are which $X= x_1$ and $X= x_2$ (say code zero for male individuals and code 1 for females). Then the fitted Cox model could be written as,

$$h(t)=h_0(t)\exp(\beta X),$$

where $h_0(t)$ is the baseline hazard function (the hazard at X=0), β is the coefficient of the explanatory variable X in the model, X is either x_1 or x_2 and h(t) is the hazard function which shows the instantaneous hazard of failure at time T= t. Note that the hazard functions for those individuals whose value of the explanatory is x_1 or x_2 could be written, respectively, as

$$h(t|x1)=h_0(t)\exp(\beta x_1),$$

$$h(t|x2)=h_0(t)\exp(\beta x_2),$$

and the related survival functions to each of the above hazard functions could be written as,

$$\begin{aligned} S(t|x1) &= \exp\int_0^t h_{x1}(u)du \\ &= \exp\{-\int_0^t h_0(u)\exp(\beta x_1)du\} \\ &= \{\exp\{-\int_0^t h_0(t)\}\{\exp(\beta x_1)\} \end{aligned}$$

since $\exp\{-\int_0^t h_0(t)\}$ is known as $S_0(t)$ then,

$$S(t|x1) = [S_0(t)]^{\exp(\beta x_1)}.$$

Similarly for the survival function of those individuals whose value of explanatory variable is x_2, could be written as

$$S(t|x2)\ (t) = [S_0(t)]^{\exp(\beta x_2)}.$$

Note then,

$$\text{Log}[S(t|\ x1)] = \text{Log}\ \{[S_0(t)]^{\exp(\beta x1)}\}$$

$$= \exp(\beta x1)\ .\ \text{Log}\ [S_0(t)]$$

Since $S(t|\ x1)$ is always less than 1 we multiple it by a minus sign in order to take logs again to give

$$\text{Log}\ \{-\text{Log}[S(t|\ x_1)]\} = \text{Log}\ -\{\exp(\beta x_1)\ .\ \text{Log}\ [S_0(t)]\}$$

$$= \beta x_1 + \text{Log}\{-\ \text{Log}\ [S_0(t)]\}.$$

Similarly it can be shown that,

$$\text{Log}\ \{-\text{Log}[S(t|\ x_2)]\} = \beta\ x_2 + \text{Log}\{-\ \text{Log}\ [S_0(t)]\}.$$

Note that the difference between

$$C = \text{Log}\ \{-\text{Log}[S(t|\ x_1)]\}$$

and

$$D\ = \text{Log}\ \{-\text{Log}[S\ (t|\ x_2)]\}$$

is $\beta(x_1-x_2)$. Since x_1 and x_2 are constant over time, therefore the difference between C and D is always constant i.e. the two functions

$$C = \text{Log}\ \{-\text{Log}[S\ (t|\ x_1)]\}$$

and

$$D\ = \text{Log}\ \{-\text{Log}[S\ (t|\ x_2)]\}$$

are parallel over time t. Note that this result is obtained from a Cox Proportional Hazards model for which the proportionality assumption of hazards is adopted. This implies that if it is discovered that the Log Minus Log (LML) plot of the survival functions corresponding to two or more levels of an explanatory variable are parallel (over time t) then it can be assumed that the hazards of failure for the individuals at different levels of

the explanatory variable, at any particular time, is proportional. In this research the Log Minus Log plot of survival functions against the survival times (LML plot), has been used to investigate the validity of the proportional hazards assumption. For this purpose survival functions will be estimated by the Kaplan-Meier method.

2-5-2 : Methods for Checking The Goodness of Fit of The Cox Proportional Hazards Model :

In this research it is also intended to investigate the goodness of fit of all fitted Cox Proportional Hazard models by studying residuals. One definition is:

$$H(t \mid \underline{x}) = H_0(t)\, e^{\underline{\beta}^T \underline{X}} \qquad (1)$$

this should have a unit exponential distribution. We will explain why this is the case then how we will investigate whether the estimated residuals, which are defined as above, have or have not the unit exponential distribution. But before going through this, we introduce the Cox-Snell residuals. Note that in the above quantity, $H(t \mid \underline{X})$ is the cumulative hazard function for an individuals with the vector of explanatory variables of $\underline{X}$, while $\underline{\beta}$ is the vector of parameters.

a) Residuals in General. (Cox-Snell Residuals in particular)

Residuals are usually defined in connection with linear models. Here a general definition of residuals which proposed by Cox and Snell (Cox,

Snell 1968), and is known as the Cox-Snell residuals, will be presented. In the context of normal-theory linear model, an n×1 vector of random variables $\underline{Y}$ is assumed to have the form

$$\underline{Y}= X\underline{\beta}+\underline{\varepsilon},$$

where X is a known matrix, β a vector of unknown parameters and ε an n ×1 vector of unobserved random variables of zero mean, independently normally distributed with constant variance. If $\hat{\beta}$ is the vector of least-squares estimates of β, the residuals R* are defined by

$$R^*=\underline{Y}-X\underline{\hat{\beta}} \qquad (2)$$

Provided that the number of parameters is small compared with n, most of the properties of R* are nearly those of ε, i.e. R* should have approximately the properties of a random sample from a normal distribution.

In keeping with (2), a more general definition of residuals are defined below (Cox and Snell1968). Consider a model expressing an observed vector random variable Y in terms of a vector β of unknown parameters and a vector ε of independent and identically distributed unobserved random variables. More particularly we assume that each observation Y_i depends on only one of the ε's, so that we can write

$$Y_i =g_i(\beta,\varepsilon_i) \quad (i=1, 2, ..., n). \qquad (3)$$

This assumption excludes applications to time series and also to component of variance problems in which several random variables enter into each observation.

To define the residuals (i.e. Cox-Snell residuals) , let $\hat{\beta}$ be the maximum likelihood estimate of β from Y. It would be possible to work

with other asymptotically efficient estimates, or even with inefficient estimates. Now suppose that the equation

$$Y_i = g_i(\hat{\beta}, \varepsilon_i)$$

has a unique solution for ε_i, namely

$$e_i = h_i(Y_i, \hat{\beta}). \qquad (4)$$

Note that

$$\varepsilon_i = h_i(Y_i, \beta).$$

We take (4) as defining the residuals corresponding to Y_i and the model (3). It is known as a crude residual or Cox-Snell residual.

Note that according to the above definition,

$$\varepsilon_i = H_0(t_i) e^{\underline{\beta}^T \underline{X}_i} \qquad i=1, 2, ..., n$$

is a generalised residual for individual i (Lagakos 1980). Hence ε_i can be estimated by

$$e_i = \hat{H}_0(t_i) \exp(\underline{\hat{\beta}}^T \underline{X}_i) \qquad i=1, 2, ..., n \quad (5)$$

where $\underline{\hat{\beta}}$ is the maximum likelihood estimator of β and $\hat{H}_0(t_i)$ is the estimated cumulative baseline hazard function for individual i with covariate values $\underline{Xi}$. Note that e_i is right-censored when T_i is right-censored.

B) Distribution of e_i :

We now show that under the Cox proportional hazards model the Cox Snell residuals have a unit exponential distribution

$$e_i = \hat{H}_0(t_i) \exp(\underline{\hat{\beta}}^T \underline{Xi})$$

Suppose the random variable T has the density function f(t), distribution function F(t) and survival function S(t) with S(0)=1 let

$$h(t)=f(t)/S(t)$$
$$= -S'(t)/S(t)$$
$$= -d\{\ln[S(t)]\}/dt.$$

Hence,

$$H(t)=\int_0^t h(u)\,du$$
$$=\int_0^t (-d\{\ln[S(u)]\}/du)\,du$$
$$= \{-\ln[S(u)]\}_0^t$$
$$= -\ln[S(t)] - [-\ln[s(0)]]$$

and since $[-\ln[s(0)]] = 0$, therefore

$$H(t)= - \ln[S(t)].$$

Now consider the cumulative distribution of H=H(T)

$$F_H(h)=P(H\leq h),$$

Take U=S(T). Then we have H=-ln(U). Hence

$$F_H(h)=P(-\ln(U)\leq h)$$
$$=P(\ln(U)\geq -h)$$
$$=P(U\geq \exp(-h))$$
$$=1-P(U\leq \exp(-h))$$
$$=1-P(U\leq u), \text{ where } u=\exp(-h).$$

and since U= S(T) is uniform (0 , 1) then it implies $P(U\leq u)=u$, therefore

$$F_H(h)=1-u$$

where u=exp(-h). This implies

$$=F_H(h)=1-\exp(-h).$$

This is the cumulative distribution of unit exponential distribution. Hence

$$f_H(h)=F'_H(h)$$
$$=d[1-\exp(-h)]/dh$$
$$=e^{-h}$$

Which is the Ex(1) p.d.f.

This argument extends to $e_i=H(T_i \mid \underline{X}_i)=H_0(T_i)\exp(\underline{\beta}^T\underline{x}_i)=-\ln s(T_i \mid \underline{X}_i)$

c) Use of $e_i = \hat{H}_0(t_i) \exp(\hat{\underline{\beta}}^T \underline{Xi})$ in investigating the goodness of fit of the Cox Proportional Hazards model :

Hence the overall fit of the Cox Proportional Hazards model can be assessed by investigating whether the estimated values of the e_1, e_2, ..., e_n have the unit exponential distribution or not. Note that the estimation of e_i can be obtain by

$$e_i = \hat{H}_0(t_i) \exp(\hat{\underline{\beta}}^T \underline{Xi}).$$

Since $\hat{e}_i$ can be either complete or censored therefore the above mentioned assessment can be done by using the tools developed for survival analyses. It is necessary to estimate the log 'survival' function or the cumulative hazard function of the residuals $\hat{e}_i$. If $\hat{e}_i$ has an unit exponential distribution then the plot of the log survival function of the residuals or the cumulative hazard function of the residuals against the residuals itself should illustrate , respectively, a straight line having an inverse relation with the residuals(slope of -45^0) or a straight 45^0 degree line through the origin. This idea comes from the fact that for the unit exponential distribution we have

$$S(e)=\exp(e)$$

and therefore,

$$\text{Log } S(e)=e$$

D) Comparisons with covariates :

In this research, the goodness of fit of all fitted Cox Proportional Hazard models will be investigated by the above mentioned properties (Kay 1997, Lagakos 1980).

The e_i can, in principle, be used to assess the explanatory variables by checking for the possibility that the residuals corresponding to different levels of an important explanatory variable may have different distributions. A good fit might be indicated if the distribution of the e_i 's corresponding to different levels of an explanatory variable do not have different distributions. This idea has been used in this research to evaluate model fits in relation to those explanatory variables included in the fitted Cox Proportional Hazards models. There are some opinions that the e_i are not ideally suited for this purpose. The reason is that they depend explicitly on the times of failure, and neither they nor their ranks are invariant to monotone transformations of the time scale or to the choice of intervals (Lagakos 1980).

Chapter 3

Ramipril and Placebo survival functions (estimated by Kaplan Meier method) compared for various endpoints

In this chapter it is intended to discover whether or not there is any difference in the effect of Ramipril and the Placebo on the time to a variety of events. In particular the following adverse events were considered; time to 'death', 'first reinfarction' after treatment or 'first stroke' after treatment. Then, in later stages, we tried to combine or to change the definition of the end event. An example of these changes, is to define an adverse event to be either sudden death or first reinfarction or chest pain.

To obtain the above aims, the Kaplan-Meier approach was used to estimate the survival curves of those patients who were treated by Ramipril and those who were treated by the placebo. These survival curves were estimated for 26 different adverse events. For each case, the survival curve of the patients treated by Ramipril and the survival curve corresponding to those treated by the Placebo, were compared using the generalised Savage (Mantel_Cox) test statistic. These analyses and tests were performed by using the BMDP program 1L.

Tables 3-1 to 3-3 show the survival functions for two groups of patients; namely, those treated by Ramipril and those treated by the

Placebo when, respectively, the survival time is, ' time to death', 'time to first validated reinfarction' and 'time to first validated stroke'.

Table 3-1 indicates that those patients who were treated by Ramipril had significantly longer survival time (to death) than those who were treated by the Placebo (Mantel_Cox P=0.0021) while table 3-2 and table 3-3 indicates that there is no difference on the 'time to first validated reinfarction' or 'time to first validated stroke' between the patients who were treated by Ramipril or the Placebo. As a primary result, these three tables indicate that using Ramipril only increases the life time of patients but it has no effect on the time to reinfarction or to stroke. Similar analyses indicated that the above result is achieved when non validated reinfarction is included (tables 3-4, P=0.8622 and 3-5, P=0.6864). Note non validated reinfarctions which are considered in table 3-4 are suspected by the investigators but rejected by the sub committee and while those considered in table 3-5 are all suspected infarctions whether or not validated by sub committee.

Table 3-6 shows the survival functions for 'time to sudden death or validated reinfarction' for the two treatments. Those patients who were treated by Ramipril had significantly longer survival times than those who were treated by the Placebo (Mantel_Cox, P=0.0289).

Table 3-7 shows survival functions for 'time to chest pain or validated reinfarction' for the two treatments. There is no difference between the patients who were treated by Ramipril or the Placebo (Mantel_Cox, P=0.3395).

Table 3-8 shows a further analysis for patients who had died with chest pain . Here the survival time is defined as the time between

registration and chest pain ending in death or first validated reinfarction. It showed that there is no difference in the survival times of patients treated by Ramipril or the Placebo (Mantel_Cox, P=0.2517).

Table 3-9 shows survival functions for 'time to sudden death or validated reinfarction or chest pain' for the two treatments. Those patients who were treated by Ramipril had significantly longer survival times than those who were treated by the Placebo (Mantel_Cox, P=0.0197).

Table 3-10 shows the same analysis for patients who had died with chest pain. Here the survival time is defined as the time between registration and sudden death with chest pain or first validated reinfarction. The same result as for the previous table was achieved (Mantel_Cox, P=0.0236).

Table 3-11 shows survival functions for 'time to death or non validated reinfarction(whether or not validated by sub committee)' Those patients who were treated by Ramipril had significantly longer survival times than those who were treated by the Placebo (Mantel_Cox, P=0.0297).

Table 3-12 shows survival functions for 'time to chest pain or first non validated reinfarction(whether or not validated by sub committee)' for the two treatments. There is no difference between patients who were treated by Ramipril or the Placebo (Mantel_Cox, P=0.2736).

Table 3-13 shows a further analysis for patients who had died with chest pain. It showed that there is no difference in the survival times of the patients treated by Ramipril or the Placebo (Mantel_Cox, P=.5104). Here the survival time is defined as time between registration date and date of chest pain or first non validated reinfarction.

Table 3-14 shows survival functions for 'time to sudden death or non validated reinfarction(whether or not validated by sub committee) or chest pain' for the two treatments. Those patients who were treated by Ramipril have significantly longer survival times than those who were treated by the Placebo (Mantel_Cox, P=0.0110).

Table 3-15 shows the same analysis for patients who had died suddenly with chest pain. Note here the end point is sudden death with chest pain or first non validated reinfarction(whether or not validated by sub committee). The same conclusion as for the previous table was achieved (Mantel_Cox, P=0.0432).

Tables 3-16 shows survival functions for 'time to sudden death or first non validated reinfarction(suspected by investigators but rejected by sub committiee)' for the two treatments. Those patients who were treated by Ramipril have significantly longer survival times than those who were treated by the Placebo (Mantel-Cox,P=0.0163).

Table 3-17 shows survival functions for 'time to chest pain or first non validated reinfarction(suspected by investigators but rejected by sub committiee) for the two treatments. There is no difference between patients who were treated by Ramipril or the Placebo (Mantel-Cox0.5607).

Table 3-18 shows a further analysis for patients who had died with chest pain . Here the survival time is defined as the 'time between registration and chest pain ending in death or first validated reinfarction(suspected by investigators but rejected by sub committiee)'. It shows that there is no difference in the survival times of patients treated by Ramipril or the Placebo (Mantel_Cox, P=0.8960).

Table 3-19 shows survival functions for 'time to sudden death or non validated reinfarction (suspected by investigators but rejected by sub committiee) or chest pain' for the two treatments. Those patients who were treated by Ramipril have significantly longer survival times than those who were treated by the Placebo (Mantel_Cox, P=0.0152).

Table 3-20 shows the same analysis for patients who had died suddenly with chest pain. Note here the end point is 'sudden death with chest pain or first non validated reinfarction(suspected by investigators but rejected by sub committiee)'. The same conclusion as for the previous table was rachedachieved (Mantel_Cox, P=0.0398).

Tables 3-21 to 3-22 show the survival functions for time to sudden death and for time to chest pain for the two treatments. For 'time to sudden death', those patients who were treated by Ramipril had significantly longer survival times than those who were treated by the Placebo (Mantel_Cox, P=0.0108). Meanwhile table 3-22 indicates that there is no difference for chest pain between patients who were treated by Ramipril or the Placebo (Mantel_Cox, P=0.9351)

Here the survival time was considered as the time from the registration date to one type of death which was taken from the adverse event's file. This type of death was labelled as sudden death. Actually in the adverse events file, those deaths which could not be labelled otherwise were called sudden death. There were 45 patients whose death were labelled as sudden death.

Tables 3-23 to 3-26 show the survival functions for those patients who were treated by Ramipril or Placebo when the survival time is defined as the time from the registration date to, respectively, 'sudden death or first

validated reinfarction', 'sudden death or first non validated reinfarction', 'sudden death or chest pain or first validated reinfarction', 'sudden death or chest pain or non validated first reinfarction'. All these tables indicate that there is no significant difference between the survival function of those patients who were treated by Ramipril and the survival function of those who were treated by the Placebo, when the survival time is taken as any of the above mentioned times.

Table 3-27 contains a summary of results which we got in tables 3-1 to 3-26.

All the above mentioned tables (3-1 to 3-26) indicate that there is basically a significant effect for endpoints involving "sudden death" (as well as that which involved death). There are 11 such endpoints. In contrast, according to these tables, Ramipril has no significant effect in postponing other adverse events. The conclusions about the endpoints involving "death" show that Ramipril increases real life times i.e. Ramipril significantly postpones the occurrence of a "death" event. Therefore we go on to study selected endpoints involving "death" in order to model, with the Cox Proportional Hazard models if possible, the difference between the Placebo and Ramipril and to explore the possible effect of other factors. In choosing these we were guided by the interests of those involved in the AIRE study. These interests included the 4 endpoints: "sudden death or first validated reinfarction", "sudden death or first validated reinfarction or chest pain", "sudden death or first non validated reinfarction" and finally "sudden death or first non validated reinfarction or chest pain". Recall that non validated reinfarctions are those reinfarctions which were reported by the investigators but have not been confirmed by the sub committee. For

the purposes of comparisons with the AIRE study results we also study the two endpoints considered by that study namely : "death" and "first validated reinfarction".. Hence, in total, we move on to study 6 endpoints.

Table 3-1 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
Placebo	982	222	760	0.77
Ramipril	1004	170	834	0.83
Total	1986	392	1594	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	9.47	1	0.0021	

Table 3-2 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to first validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
Placebo	980	88	892	0.9102
Ramipril	1004	81	923	0.9193
Total	1984	169	1815	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.459	1	0.4982	

Table 3-3 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to first validated stroke.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
Placebo	9982	17	965	0.983
Ramipril	1004	24	980	0.976
Total	1986	41	1945	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.137	1	0.286	

Table 3-4 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to first non validated* reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	981	58	923	0.941
Ramipril	1003	61	942	0.939
Total	1984	119	1865	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.30	1	0.8622	

Table 3-5 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to first non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	146	834	0.851
Ramipril	1003	142	861	0.858
Total	1983	288	1695	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.163	1	0.687	

Table 3-6 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death or first validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	195	785	0.801
Ramipril	1004	162	842	0.839
Total	1984	357	1627	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	4.773	1	0.029	

Table 3-7 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain or first validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	979	150	829	0.847
Ramipril	1004	142	862	0.859
Total	1983	292	1691	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.912	1	0.339	

Table 3-8 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain ending to death or first validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	113	867	0.885
Ramipril	1004	101	903	0.899
Total	1984	214	1770	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.314	1	0.252	

Table 3-9 : Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death or first validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	979	250	729	0.745
Ramipril	1004	791	791	0.788
Total	1983	463	1520	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.5.442	1	0.0197	

Table 3-10: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death with chest pain or first validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	203	777	0.793
Ramipril	1003	168	836	0.833
Total	1984	371	1613	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	5.126	1	0.0236	

Table 3-11: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death or first non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	221	759	0.774
Ramipril	1003	186	817	0.815
Total	1983	407	1576	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	4.727	1	0.0297	

Table 3-12: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain or non validated reinfarction+.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	979	202	777	0.794
Ramipril	1003	191	812	0.810
Total	1982	393	1589	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.199	1	0.274	

Table 3-13: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain ending to death or first non validated reinfarction+.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	155	825	0.842
Ramipril	1003	150	853	0.850
Total	1983	305	1678	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.433	1	0.510	

Table 3-14: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death or non validated reinfarction+ or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	979	271	708	0.723
Ramipril	1003	228	775	0.773
Total	1982	499	1483	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	6.468	1	0.0110	

Table 3-15: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to
sudden death or first non validated* reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	980	221	759	0.775
Ramipril	1003	189	814	0.812
Total	1983	410	1573	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	4.088	1	0.0432	

Table 3-16: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death or first non validated* reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	982	146	836	0.851
Ramipril	1003	113	890	0.887
Total	1985	259	1726	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	5.773	1	0.0163	

Table 3-17: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain or first non validated reinfarction*.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	981	120	861	0.878
Ramipril	1003	118	885	0.882
Total	1984	238	1746	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.338	1	0.561	

Table 3-18: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain ending to death or first non validated reinfarction*.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	982	89	893	0.9094
Ramipril	1003	91	912	0.9094
Total	1985	180	1805	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.0170	1	0.896	

Table 3-19: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death or first non validated* reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	981	199	782	0.797
Ramipril	1003	163	840	0.838
Total	1984	362	1622	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	5.894	1	0.0152	

Table 3-20: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death (with chest pain) or first non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	982	163	819	0.834
Ramipril	1003	134	869	0.866
Total	1985	297	1688	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	4.227	1	0.0398	

Table 3-21: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to sudden death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	982	121	861	0.878
Ramipril	1004	89	915	0.911
Total	1986	210	1776	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	6.5	1	0.0108	

Table 3-22: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
Placebo	981	68	913	0.9307
Ramipril	1004	69	935	0.9313
Total	1985	137	1848	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.007	1	0.935	

Table 3-23: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to non validated sudden death or first validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
Placebo	980	112	868	0.886
Ramipril	1004	99	905	0.901
Total	1984	211	1773	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.492	1	0.222	

Table 3-24: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to first non validated sudden death or non validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
Placebo	980	166	814	0.831
Ramipril	1003	158	845	0.842
Total	1983	324	1659	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	.690	1	0.406	

Table 3-25: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to non validated sudden death or first validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	979	172	807	0.824
Ramipril	1004	159	845	0.842
Total	1983	331	1652	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.524	1	0.217	

Table 3-26: Result of Generalised Savage (Mantel-Cox) test for comparing the survival functions of patients who were treated by Ramipril or placebo for time to non validated sudden death or first non validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
Placebo	981	91	890	0.907
Ramipril	1004	88	916	0.912
Total	1985	179	1806	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.429	1	0.5122	

Table 3-27 : Summary results of tables 2-1 to 2-26.

	Survival time: Time from registration to : (end point)	Statistic	d.f.	P-value
1	Death	9.477	1	0.0021
2	First validated reinfarction	0.459	1	0.4982
3	First validated stroke	1.137	1	0.2863
4	First non validated reinfarction*.	0.030	1	0.8622
5	First non validated reinfarction+.	0.163	1	0.6864
6	Sudden death or first validated reinfarction*.	4.773	1	0.0289
7	Chest pain or first validated reinfarction.	0.912	1	0.3395
8	Chest pain ending to death or first validated reinfarction.	1.314	1	0.2517
9	Sudden death or first validated reinfarction or chest pain.	5.442	1	0.0197
10	Sudden death with chest pain or first validated infarction .	5.126	1	0.0236
11	Sudden death or first non validated reinfarction+.	4.727	1	0.0297
12	Chest pain or first non validated reinfarction+.	1.199	1	0.2736
13	Chest pain ending to death or first non validated reinfarction +.	0.433	1	0.5104
14	Sudden death or first non validated reinfarction + or chest pain.	6.463	1	0.0110
15	Sudden death with chest pain or first non validated reinfarction+.	4.088	1	0.0432
16	Sudden death or first non validated reinfarction*.	5.773	1	0.0163
17	Chest pain or non validated reinfarction*.	0.338	1	0.5607
18	Chest pain ending to death or first non validated reinfarction*.	0.017	1	0.8960
19	Sudden death or first non validated reinfarction* or chest pain.	5.894	1	0.0152
20	Sudden death with chest pain or first non validated reinfarction*.	4.227	1	0.0398
21	Sudden death.	6.500	1	0.0108

Chapter 4

Survival Models for Investigating the Effect of Ramipril on Prolonging the Patients' Life time or Delaying time of Reinfarction

In the previous chapter the Kaplan-Meier method was used to estimate the survival and the cumulative hazard functions for a particular end point. We remind the reader that several end points were defined and for each end point we produced separate survival and cumulative hazard functions for the patients who had been treated by either Ramipril or the placebo.

In this chapter we intend to use the well known Cox Proportional Hazards Model to investigate the effect of Ramipril on survival times. We will carry out this investigation by comparing the survival or hazard function of those patients who have been treated by Ramipril with of those who were treated with the placebo. Once again we remind the reader that, to be able to investigate the effect of the Ramipril on prolonging the patients' life, we have treated a group of patients with the Placebo.

Continued : table 3-27

	Survival time: Time from registration to : (end point)	Statistic	d.f.	P-value
22	Chest pain.	0.007	1	0.9351
23	Non validated sudden death or first validated reinfarction.	1.492	1	0.2219
24	Non validated sudden death or first non validated reinfarction+.	0.690	1	0.4061
25	Non validated sudden death or first validated reinfarction or chest pain.	1.524	1	0.2171
26	Non validated sudden death or first non validated reinfarction+ or chest pain.	0.429	1	0.5122

*These are suspected infarctions reported by the investigators, but rejected by the sub committee i.e. not validated by the sub committee.
+ These are suspected infarctions , whether or not validated by the sub committee.

At the beginning we introduce the Cox Proportional Hazards Model and then some of its important properties will be discussed. Later we fit different Cox Proportional Models to the various end points. Finally for each fitted Cox model we will discuss the precision of assumptions made and also the goodness of fit of the model. At this stage we show some plots to confirm the goodness of fit of the model or carry out some tests to investigate whether the covariates are significantly related to the hazard of failure or not. We will fit two Cox Proportional Hazards Models to the responses of each end point. One model includes only one covariate and that is "Treatment" which identifies whether the patient has been treated by Ramipril or the Placebo. Another model contains all significant covariates including the covariate "Treatment". For both of these models we will investigate both the proportionality assumption and goodness of fit of the models.

4-1 : Introducing Different Response Variables According to Different Assumed End points :

As was said before , in this chapter we intend to fit different Cox Proportional Hazards models to different life time response variables. These response variables are actually the outcome of considering different end points. The time origin for all these response variables is the same and that is the date of registration which identifies the time when a patient has been entered in to the study. It is the start time for all response variables. We have considered 6 different end points for each patient i.e. each patient has 6 different end points or 6 different response variables. The main objective which we are going to carry out in this whole research is to investigate the effect of the treatments on these 6 response variables in order to judge whether Ramipril is or is not significantly important in prolonging a patients' 'life time'. Recall that The end points are as follows:

1- Event No. 1 :

Time from registration date to time of death.

2- Event No. 2 :

Time from registration date to time of first validated reinfarction.

3- Event No. 3 :

Time from registration date to time of sudden death or first validated reinfarction.

4- Event No. 4 :

Time from registration date to time of sudden death or first non validated reinfarction.

5- Event No. 5 :

Time from registration date to time of sudden death or first validated reinfarction or chest pain.

6- Event No. 6 :

Time from registration date to time of sudden death or first non validated reinfarction or chest pain.

Since these response variables are time measurements to model their distribution using survival methods.

4-2 : Cox Proportional Hazards Models Fitted to "Time from Registration Date to Time of Death" (Event No. 1) :

4-2-1 : Entering A Single Covariate (Event No. 1) :

Here we fit a Cox Proportional Hazards model to survival time when the response is the time interval from registration to death. This model is presented in table 4-2-1-1. The covariate "Treatment" is the only covariate which is entered in to this model. This covariate is entered as a dummy variable and is coded "1" if the patient has been treated by Ramipril and is coded "0" if only the placebo has been used to treat him/her. The model shows that 'Treatment's' coefficient is -0.3122 with a standard error of 0.1019. The standard error indicates that the 'Treatment's' effect (i.e. the effect of Ramipril) is significant. The fact that "Treatment" is coded 1 for those patients who were treated by Ramipril together with the fact that the sign of coefficient is negative, implies those patients who have been treated by Ramipril have significantly longer survival times compared to those who were treated by the Placebo. The model suggests the fitted baseline hazard function, for those patients who have been treated by Ramipril, is 0.7318 times that of the fitted baseline hazard function of those patients who were treated by Placebo. It implies the hazard of failure for the patients who were treated by Ramipril is

always (i.e. over time) less than the hazard of failure of those who were not treated by the drug. We remind the reader that in the Cox Proportional Hazards model it is assumed the hazard functions due to, say two levels of one covariate, are always parallel. This is the reason why we claim that one fitted hazard function is always 0.7318 times of the other one. The mathematical expression of this property of the Cox Proportional Hazards model was explained before in chapter 2.

Plot 4-2-1-1 shows the baseline survival function for the fitted model (of table 4-2-1-1). This plot indicates that the chance of still being alive decreases in the first days after registration very rapidly. Since the covariate "Treatment" is coded as "0" or "1" for those patients who were treated, respectively, by the Placebo or Ramipril, then this baseline survival function stands for the survival function of those patients who were treated by the Placebo. The survival function of those patients who were treated by Ramipril can be obtained by raising every value of baseline survival function to the power of

$e^{-0.3122} = 0.7318$. The mathematical expressions are :

$$S(t) = [S_\circ(t)]^{\exp(\beta^T Z)}$$

where $S_\circ(t)$ is the baseline survival function, B is the estimated coefficient and Z is the covariate's value which is 0 if the patient is treated by the Placebo and 1 if treated by Ramipril. Note for the group of patients who were treated by the Placebo, all Z's are zero and in this case :

$$\begin{aligned} S(t|_{placebo}) &= [S_\circ(t)]^{\exp(\beta^T Z)} \\ &= [S_\circ(t)]^{\exp(\beta^T * 0)} \\ &= [S_\circ(t)]^{\exp(0)} \end{aligned}$$

$$= [S_{\circ}(t)]^{1}$$

$$= [S_{\circ}(t)] .$$

Note that for the group of patients who were treated by Ramipril, all Z's are 1 and in this case :

$$S(t|_{Ramipril}) = [S_{\circ}(t)]^{\exp(\beta^{T}Z)}$$

$$= [S_{\circ}(t)]^{\exp(\beta^{T}*1)}$$

$$= [S_{\circ}(t)]^{\exp(\beta^{T})}$$

$$= [S_{\circ}(t)]^{\exp(-0.3122)}$$

$$= [S_{\circ}(t)]^{0.71318}$$

Plot 4-2-1-2 shows the cumulative baseline hazard function for the model of table 4-2-1-1. Since the covariate (i.e. treatment) which is included in the model, was coded as "0" and "1" respectively for those who were treated by the Placebo or Ramipril), therefore this cumulative baseline hazard function is for those patients who were treated by the Placebo. Note that the fitted cumulative hazard function for those patients who were treated by Ramipril could be estimated by multiplying the cumulative baseline hazard function by number 0.7318. The mathematical expression is :

The assumed fitted model :

$$h(t|z) = h_{\circ}(t)e^{\beta z}$$

where $h_{\circ}(t)$ is the baseline hazard function and,

Z= 0 if patient is treated by Placebo and,

1 if patient is treated by Ramipril.

Then,

$$h(t|_{Placebo}) = h_{\circ}(t)\, e^{\beta*0} = h_{\circ}(t)\, e^{-0.3122*0} = h_{\circ}(t)$$

and,

$$h(t|_{Ramipril}) = h_o(t)\, e^{\beta * 1} = h_o(t)\, e^{-0.3122 * 1} = 0.7318 * h_o(t)$$

Plot 4-2-1-2 indicates that hazard of failure for both groups of patients increase very rapidly at first days of registration.

So far in this section we have fitted a Cox Proportional model to the time interval from registration to death (event No. 1) and it was shown that the use of Ramipril increases the chance of surviving significantly. In the rest of this section we investigate how reliable the given results are i.e. we check the goodness of fit of the model. To investigate the validity of the fitted model, two important things should be checked. First we should check how valid the assumed proportionality assumption (of hazards) is. Second, suppose the proportionality assumption is correct; Then we need to investigate the goodness of fit of the model.

As was fully explained in chapter 2 the correctness of the proportionality assumption of the hazard functions (for the two groups of patients) could be checked by plotting Log Minus Log plots of survival functions. These two curves (plots of survival functions for the Placebo and Ramipril groups) will be shown in one plot. Hence if these two curves are more or less parallel then it is logical to believe that the hazards of failure are proportional (over the time interval from the registration date) for the Placebo and Ramipril groups. The full mathematical expression and an explanation of how the parallel relationship of these two curves could lead to proportionality of the hazard function, was discussed in chapter 2.

We estimated the survival functions for those patients who were treated by the Placebo and those who were treated by Ramipril by using the Kaplan-Meier method and then the logarithm of minus the logarithm of these survival functions were calculated and finally they were plotted against the survival times. Plot 4-2-1-3 shows the LML plot of the survival functions for both groups of patients. Since for most part these two curves are not clearly separated, plot 4-2-1-4 was prepared. In this new plot some extremely small values are deleted in order to see the remaining values on a bigger scale. The new plot indicates that the LML curves of the two survival functions are more or less parallel. This implies that the hazard functions are more or less parallel i.e. the hazards of failure (hazard of death in the case of this end point), at any particular value of time interval from the registration date, for the two groups is proportional (note we discovered the constant of proportionality to be 0.7318). Hence in this case the Cox Proportional Hazards model can be assumed with some justification.

In chapter 2 we showed that the goodness of fit of the Cox Proportional model can be checked by investigating whether the Cox-Snell residuals of the model are or are not exponentially distributed with parameter 1. This is a task for which we might normally use the Kolmogorov-Smironov test which would involve estimating the distribution function of the residuals by their empirical distribution function, i.e. we estimate $F_R(r)=P(R<r)$ where R is a random residual by the observed proportion of residuals below r. Note that we then have an estimate of $S_R(r)=P(R>r)=1-F_R(r)$. We then compare this estimate with the

Ex(1) distribution function via the test Kolmogorov Smironov statistic. It is also informative to plot one function against the other. However when a 'survival' time is censored so is its residual. Hence the residuals are subject to censoring. Nevertheless it is still possible to calculate an empirical estimate of $F_R(r)$ or more directly of $S_R(r)$ namely the Kaplan Meier estimate of $S_R(r)$. Hence it is convenient to exploit the tools developed for survival data in analysing residuals. See Kay (1976) and Lankakos (1980). These describe this activity as a 'survival analysis' of the residuals. We investigated the distribution of two kinds of residuals: namely 'our residuals' by which we mean the residuals which we have calculated and 'BMDP's residuals' which means residuals reported in BMDP's output. In theory 'our residuals' and 'BMDP's residuals' should be similar but they are not. We could not find any reason for the difference.

Plots 4-2-1-5 and 4-2-1-6 show, respectively, the logarithm of the 'survival function' of BMDP's residuals and our residuals against the relevant residuals. Once again we remind the reader that to show the residuals have an exponential distribution with parameter 1, we need to show

$$\text{Log } S_R(r) = -r$$

,where r is the residual and $S_R(r)$ is the 'survival function' of the residuals. Hence one easy way to show the above relation is to plot the logarithm of the 'survival function' of the residuals against residual values. We should have a straight line (through the origin) having an inverse relation with the residuals to justify the claim that the distribution of residuals is

exponential with parameter 1. Both plots 4-2-1-5 and 4-2-1-6 show this property. It implies that, whichever of the residuals is the correct one, they have an exponential distribution with parameter 1. This indicates that the fitted model to end point number 1 (time to death) is well fitted to the data. Hence it implies that our conclusions in respect of the results which we have got in comparing the survival times of the two groups of patients are reliable.

4-2-2 : Entering Several Covariates (Event No. 1) :

In this section we intend to enter several covariates to the Cox Proportional Hazards model to achieve several objectives. The most important objective is to investigate whether entering the new covariates, will or will not change conclusions. Note we are interested in investigating the effect of these covariates on survival time (i.e. on the response variable). We would like to investigate whether there is any improvement in results (i.e. in judgements about the effect of Ramipril on survival time) when the other covariates are included in the model. Actually in this part we are interested to enter the other significant covariates in the model to control that part of the variability in the response variable which is due to these covariates. Note it helps to have a better judgement about the effectiveness or ineffectiveness of Ramipril. For example it is possible to appear to have an effect due to Ramipril on the response variable while the effect is really due to age of patients and not really due to use of Ramipril. This could happened if those patients who were treated by Ramipril were younger and therefore probably more resistant to death or any other type of failure and those treated by the Placebo were older. This type of misleading result can happen with other significant covariates as well although randomisation should avoid such confounding and there is no reason to believe it is a problem here. For example age is well matched between the two groups. A very important point is that in linear models almost certainly one could believe that

entering more significant covariates in the model, will improve the quality of judgement (see Ford et al 1995) i.e. entering more significant covariates in the model will improve the goodness of fit of the model, but in non-linear models it is not really clear what is going to happen when more covariates are entered in a model. This suggests we should check the goodness of fit of the new model (the model with several covariates) to make sure the new included covariates have improved the goodness of fit of the model. If this investigation suggests the new included covariates have not improved the goodness of fit of the model or the model is not, at least, as well fitted as the previous model (the model with a single covariate, "Treatment") then there is no reason to believe the new model shows more reliable results than the previous one.

Table 4-2-2-1 shows the results of fitting the Cox regression model to the time interval between registration and death (end point No. 1), using all covariates which could be candidates for entering the model i.e. those suggested by Dr Gordon Murray. These are the covariates used in other analyses of this same data by the original organised investigators. Dr Gordon Murray advised on the choice of the candidate covariates. Table 4-2-2-1 reports the results of fitting all candidate covariates. We call this method the exhaustive method. In this model all covariates are represented by dummy variables, some covariates by more than one in order to define all categories of such covariates. The model suggests that the covariates Treatment, age, diabetes, angina, nyha_d2 (i.e. class II, Yes or No), ac4b (Pulmonary venous congestion, Checked or Not) and ac4c

(Third heart Sound with pers, Checked or Not) are significantly related to the time interval between the registration date and the date of death.

Table 4-2-2-2 shows the results of fitting the Cox Proportional Hazards model to the same data, but the Stepwise Method has been used to enter the candidate covariates in the model. In the Stepwise Method at each step only one covariate, given the model from the previous step, is entered into the model and at each step a test for removing the covariates which are already in the model is carried out. The stepwise method, in constructing the model, has the very important advantage that it constructs the model in such way that the best set of covariates in respect of decreasing the log likelihood are chosen. Note carefully that the Stepwise Method does not necessarily enter all covariates which would be marginally significant in a model including all covariates. Thus it is the reason that the previous model (that of table 4-2-2-1) was fitted. Actually we fitted the previous model to see if all significant covariates are included by the stepwise approach in the next model.

The model of table 4-2-2-2 which is constructed by the Stepwise Method, suggests, in addition to the covariates which were entered in the model 4-2-2-1, the covariates site_d2 (i.e. Inferior, Yes or No) and ac4a (i.e. Bibasilar post-Tussive, Checked or Not) are also included into the model. The model of table 4-2-2-2 suggests that the age of patients is the most important covariate in respect of the time interval between the registration date and the date of death. The covariates Diabetes, ac4c (i.e. Third heart Sound with pers, Checked or Not), Angina, ac4b (i.e. Venous Congestion, Checked or Not) and treatment are the next important

covariates. The model of table 4-2-2-2 suggests that those patients who are older or have Diabetes or have Angina or whose Bibasilar post-Tussive or Pulmonary Venous Congestion or Third heart Sound with pers are checked, are more at risk of failure than those who do not have any of these characteristics. On the other hand, those patients who have been treated by Ramipril or are in Class II of Nyha or their site has been identified as Inferior Site, are at less risk of failure than those who do have not these characteristics.

A very important result of table 4-2-2-2 is that the coefficient of the covariate "Treatment" is not so different from that of model 4-2-1-1 in which "Treatment" was the only covariate : -0.2975 (in model 4-2-2-2) compare to -0.3122 (in model 4-2-1-1). This implies that the other covariates do not affect results of section 4-2-1 in the sense that we can still believe that those patients who were treated by Ramipril have longer survival times than those who were treated by the Placebo. Both models (the model with the single covariate and the model with multiple covariates) suggest less hazard of failure for those who were treated by Ramipril compared to those who were treated by the Placebo, but the model with the single covariate (model of table 4-2-1-1) shows that Ramipril is more effective than does the model with multiple covariates (model of table 4-2-2-2). To discover which conclusion is the more reliable and also to asses the reliability of the results of the model of table 4-2-2-2 we need to investigate the correctness of the proportionality assumption as well as the goodness of fit of the model. Since the model of

table 4-2-2-2 depends on covariates we must conduct these investigations for a selection of combinations of the levels of the covariates.

Plot 4-2-2-1 shows the baseline survival function arising from the model of table 4-2-2-2. It drops to 0.95 in two weeks and further drops to 0.70 by two years.

It is difficult to calculate the survival function due to the model of table 4-2-2-2 from the baseline one or at least it is not as easy as we did in section 4-2-1 where we got the survival function just by taking the baseline survival function to a power. When a Cox Proportional Hazards model depends on several covariates i.e. several covariates are included in the model, both the survival and the cumulative hazard functions are functions of these covariates and so values for these must be chosen. So to obtain the survival or the cumulative hazard function we need to ask ourselves that for what values (or which levels) of the included covariates do we wish to estimate the survival or the cumulative hazard function. Since in our model (of table 4-2-2-2) many of sets of values can be chosen for the covariates it is practically impossible to show all possible survival functions or cumulative hazard functions.

Plot 4-2-2-2 shows the estimated baseline cumulative hazard function for model of table 4-2-2-2. The Plot shows a very sharp increase in the first days after registration and also towards the end of the first 200 days.

So far we have fitted a Cox Proportional Hazards model to the time interval between the registration date and the date of death (model of table 4-2-2-2) and we have discussed the effect of Ramipril in decreasing the

hazard of death. In the rest of this section we will investigate the goodness of fit of the model by illustrating some plots and carrying out some tests.

First we illustrate some plots to investigate the validity of the proportionality assumption which we have made in using the Cox Proportional Hazards model. Just as a reminder, when several covariates are included in a Cox Proportional Hazards model, by proportionality of hazards we mean that the hazards of failure at the different levels of any particular covariate (at a given time point after registration) are proportional i.e. all hazard functions are parallel. Such hazard functions are obtained by multiplying the baseline hazard function by different constants. In the model of table 4-2-2-2 several covariates are included. Therefore the proportionality assumption of the hazards should be checked for all of them i.e. we should prepare several Log Minus Log plots (one for each covariate) to investigate the validity of the proportionality assumption for all covariates included in the model. Plots 4-2-2-3 to 4-2-2-18 are the LML plots prepared for this purpose. There are 16 plots, two for each covariate which was included in model of table 4-2-2-2. We have prepared two LML plots for each covariate because it was required to delete some small values to be able to see the pattern of LML plots clearly. Hence no LML plot due to the covariate age is included. The reason is that the covariate age is a continuos covariate and it is not possible to consider it as a stratification variable unless we define age categories. We have not pursued this. We remind the reader that the LML plot is actually the plot of "log of minus log of survival function" (where the survival function is estimated by the Kaplan-Meier method)

against the survival time. None of the plots 4-2-2-3 to 4-2-2-18 show any serious departure from the proportional hazards assumption certainly in the first year or two from the registration date. This implies that the proportionality of hazards (except for the covariate age for which no LML plot has been prepared) is a valid assumption for all covariates and the model of table 4-2-2-2 has no difficulty with it.

To investigate the goodness of fit of the model of table 4-2-2-2, Plots 4-2-2-19 to 4-2-2-22 were prepared. Plots 4-2-2-19 and 4-2-2-20 show, respectively, the log survival function and cumulative hazard function of BMDP's residuals against those residuals. Plots 4-2-2-21 and 4-2-2-22 are the same plots as 4-2-2-19 and 4-2-2-20 but they have been prepared for our residuals. The difference between the BMDP's residuals and our residuals was discussed earlier. There we gave reasons why we use two types of residuals to investigate the goodness of fit of the model.

Plots 4-2-2-19 and 4-2-2-20 which are due to BMDP's residuals, both suggest that the model of table 4-2-2-2 fits well i.e. these plots indicate that BMDP's residuals are exponentially distributed with parameter 1. Unfortunately plots 4-2-2-21 and 4-2-2-22 do not imply same result. These plots suggest that our residuals are exponentially distributed but the parameter of the distribution is not 1. We have used the formulas of $H(t|X)=H_0(t)e^{\underline{\beta}^T\underline{X}}$ (we discussed in chapter 2). It is not clear why our calculations are different from BMDP's calculations. In these circumstances it is hard to know whether the model of table 4-2-2-2 fits well or not but considering that we are sure about the correctness of our residuals, we conclude the model does not fit well.

Some further tests were carried out to investigate whether the model of table 4-2-2-2 fitted well or not. A usual method for investigating the goodness of fit of a model (e.g. a usual linear regression model) is to prepare some plots which may show a pattern in residuals against a covariate included in the model. Such plots should not show any particular pattern. When some of the responses are censored the situation is not as easy as for complete data and plots like those which were mentioned can mislead the researcher in judgements about the goodness of fit of the model. Note we are dealing with a response variable which could be censored and the only thing which we know about the survival time of a censored observation is that his/her survival time is greater than the censored value i.e. for patients with the censored response we do not know the actual value of survival time. This implies that for a patient with a censored response, the estimated residual is actually a censored residual. Therefore for some patients we do not have the complete or the actual residuals. Hence if in this case we were to use the usual methods, we would treat censored residuals as complete residuals which certainly is not correct. However there is a method for investigating the goodness of fit of a Cox Proportional Hazards model for a particular covariate. In this method for each level of a covariate which is included in the model, the survival function of the estimated residuals are estimated by the Kaplan-Meier method and then a test will be carried out to investigate whether these survival functions are or are not significantly different. If the survival functions of the residuals (corresponding to different levels of the covariate) are not significantly different this suggests that the model fits

well for that particular covariate. Otherwise we claim the model does not fit well.

Tables 4-2-2-3 to 4-2-2-10 (8 tables) show the result of comparing the survival functions of our residuals. In each of these tables, the survival functions of our residuals corresponding to different levels of a particular covariate have been compared. One table for each covariate which is included in model of table 4-2-2-2. These tables indicate that the survival functions, corresponding to different levels of a particular covariate, are not significantly different from each other i.e. our residuals implies that model of table 4-2-2-2 fits well.

Tables 4-2-2-11 to 4-2-2-18 show the result of comparing the survival functions of BMDP's residuals. In each of these tables, the survival functions of our residuals corresponding to different levels of a particular covariate have been compared. These cover the same set of covariates as tables 4-2-2-3 to 4-2-2-10. These tables indicate that none of the survival functions, corresponding to different levels of a particular covariate, are significantly different from each other i.e. BMDP's residuals implies that model of table 4-2-2-2 fits well. Note both "our residuals" and "BMDP's residuals" suggest that the model of table 4-2-2-2 fits well. Previously we came to the conclusion that "our residuals" suggest that the model of table 4-2-2-2 does not fit well. So there is a contradiction in results. We discuss this contradiction in chapter 5. An important point is that whether we choose the model of table 4-2-2-2 (the model with all significant covariates) or the model of table 4-2-1-1 (the model with the single covariate "treatment"), there is no considerable change in our

judgement. The reasons are, first, both models suggest that the use of Ramipril significantly decreases the hazard of death. Secondly, the amounts of decrease in the hazard of death as reported by each of the models, are not very different. Model 4-2-1-1 reports a greater decrease in the hazard of death when Ramipril is used compared to that of model of 4-2-2-2.

Table 4-2-1-1 : Cox Proportional Hazard model fitted to time from registration date to death. (single treatment covariate)

```
Log Likelihood = -2845.8568
Global Chi-Square = 9.46  d.f. = 1  P-value = 0.0021
```

Variable	Coeeficient	Standard Error	Coeff./S.E.	Exp(Coeff.)
Treatment	-0.3122	0.1019	- 3.0628	0.7318

Table 4-2-2-1 : Cox Proportional Hazard model fitted to time from registration date to death. (all candidate covariates)

```
   LOG LIKELIHOOD = -2754.9644
GLOBAL CHI-SQUARE = 184.61  D.F.= 18 P-VALUE =0.0000
```

VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF)
treatment	-0.2893	0.1027	-2.8180	0.7488
age	0.0369	0.0058	6.3511	1.0376
sex	0.1364	0.1137	1.1995	1.1462
hyperten	0.0656	0.1118	0.5869	1.0678
diabet	0.5504	0.1292	4.2608	1.7340
pmi_n_y	0.1462	0.1228	1.1902	1.1574
angina	0.2398	0.1191	2.0126	1.2710
cardiac	0.2584	0.1742	1.4829	1.2948
nyha_d1	-0.2310	0.2316	-0.9972	0.7938
nyha_d2	-0.4065	0.2023	-2.0096	0.6659
nyha_d3	-0.1683	0.1993	-0.8442	0.8451
site_d1	-0.5202	0.4210	-1.2356	0.5944
site_d2	-0.7854	0.4248	-1.8491	0.4559
wave_d1	0.4193	0.4649	0.9018	1.5208
wave_d2	0.2218	0.4606	0.4816	1.2483
ac4a	0.3164	0.1632	1.9383	1.3722
ac4b	0.2841	0.1059	2.6829	1.3285
ac4c	0.4242	0.1115	3.8042	1.5284

Table 4-2-2-2: Cox Proportional Hazard model fitted to time from registration date to death. (Stepwise method)

```
LOG LIKELIHOOD = -2760.9388
GLOBAL CHI-SQUARE = 165.94 D.F.= 9 P-VALUE =0.0000
```

Step No.	Variable	df	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF)
1	age	1	0.0399	0.0055	7.2295	1.0407
2	diabet	2	0.6162	0.1259	4.8930	1.8519
3	ac4c	3	0.4395	0.1106	3.9736	1.5520

4	angina	4	0.3202	0.1039	3.0803	1.3774
5	ac4b	5	0.3076	0.1043	2.9502	1.3602
6	treatment	6	-0.2975	0.1022	-2.9112	0.7426
7	site_d2	7	-0.3095	0.1105	-2.8011	0.7338
8	nyha_d2	8	-0.2412	0.1040	-2.3190	0.7857
9	ac4a	9	0.3277	0.1627	2.0139	1.3877

Table 4-2-2-3 :Comparing the distributions of our residuals for two levels of ac4a (Bibasilar post-Tussive, Checked or Not) for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	271	44	227	0.84
level 2	1687	347	1340	0.79
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.007	1	0.9338	

Table 4-2-2-4 :Comparing the distributions of our residuals for two levels of ac4b (Pulmonary Venous Congestion, Checked or Not) for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	939	158	781	0.83
level 2	1019	233	786	0.77
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.003	1	0.9585	

Table 4-2-2-5 : Comparing the distributions of our residuals for two levels of ac4c (Third heart Sound with pers, Checked or Not) for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1488	265	1223	0.82
level 2	470	126	344	0.73
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.42	1	0.8377	

Table 4-2-2-6 : Comparing the distributions of our residuals for two levels of Angina for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1254	205	1049	0.84
level 2	704	186	518	0.74
Total	1958	391	1567	
	Statistic	d.f.	P-value	
Generalised Savage test	0.067	1	0.7960	

Table 4-2-2-7 : Comparing the distributions of our residuals for two levels of Diabetes for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1721	310	1411	0.82
level 2	237	81	156	0.66
Total	1958	391	1567	
	Statistic	d.f.	P-value	
Generalised Savage test	0.078	1	0.7795	

Table 4-2-2-8 :Comparing the distributions of our residuals for two levels of nyha_d2 (i.e. class II, Yes or No) for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1040	233	807	0.776
level 2	918	158	760	0.8297
Total	1958	391	1567	
	Statistic	d.f.	P-value	
Generalised Savage test	0.112	1	0.7384	

Table 4-2-2-9 : Comparing the distributions of our residuals for two levels of site_d2 (Inferior, Yes or No) for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1227	272	955	0.78
level 2	731	119	612	0.84
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.002	1	0.9613	

Table 4-2-2-10 : Comparing the distributions of our residuals for two levels of treatment for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	968	221	747	0.77
level 2	990	170	820	0.83
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.001	1	0.9779	

Table 4-2-2-11 : Comparing the distributions of BMDP residuals for two levels of ac4a (Bibasilar post-tussive crackers, Checked or Not) for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	271	44	227	0.84
level 2	1687	347	1340	0.79
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	4.36	1	0.0368	

Table 4-2-2-12 : Comparing the distributions of BMDP residuals for two levels of ac4b (Pulmonary venous congestion, Checked or Not) for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	939	158	781	0.83
level 2	1019	233	786	0.77
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.586	1	0.2079	

Table 4-2-2-13 : Comparing the distributions of BMDP residuals for two levels of ac4c (Third heart sound with pers, Checked or Not) for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1488	265	1223	0.82
level 2	470	126	344	0.73
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	7.341	1	0.0067	

Table 4-2-2-14 : Comparing the distributions of BMDP residuals for two levels of Angina for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1254	205	1049	0.84
level 2	704	186	518	0.74
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	10.295	1	0.0013	

Table 4-2-2-15 : Comparing the distributions of BMDP residuals for two levels of Diabetes for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1721	310	1411	0.82
level 2	237	81	156	0.66
Total	1958	391	1567	
	Statistic	d.f.	P-value	
Generalised Savage test	14.646	1	0.0001	

Table 4-2-2-16 : Comparing the distributions of BMDP residuals for two levels of nyha_d2 (i.e. class II, Yes or No) for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1040	233	807	0.78
level 2	918	158	760	0.83
Total	1958	391	1567	
	Statistic	d.f.	P-value	
Generalised Savage test	2.153	1	0.1423	

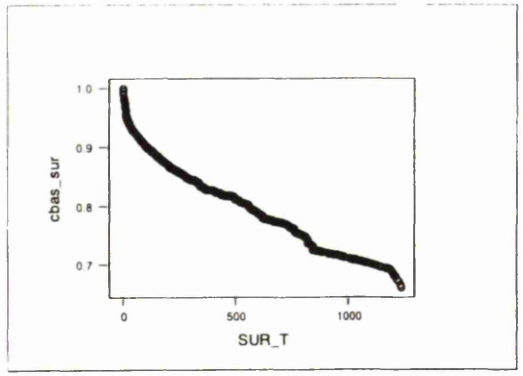
Table 4-2-2-17 : Comparing the distributions of BMDP residuals for two levels of site_d2 (Inferior, Yes or No) for time to death.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1227	272	955	0.78
level 2	731	119	612	0.84
Total	1958	391	1567	
	Statistic	d.f.	P-value	
Generalised Savage test	4.701	1	0.0301	

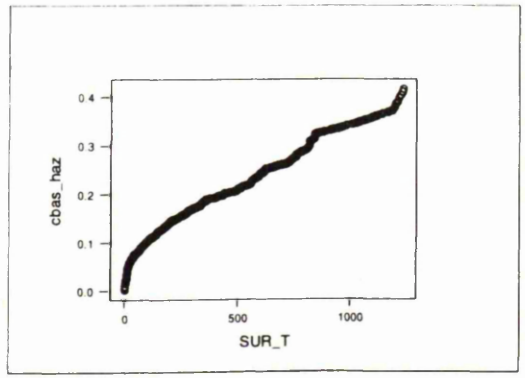
Table 4-2-2-18 : Comparing the distributions of BMDP residuals for two levels of treatment for time to death.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	968	221	747	0.77
level 2	990	170	820	0.83
Total	1958	391	1567	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	3.019	1	0.0823	

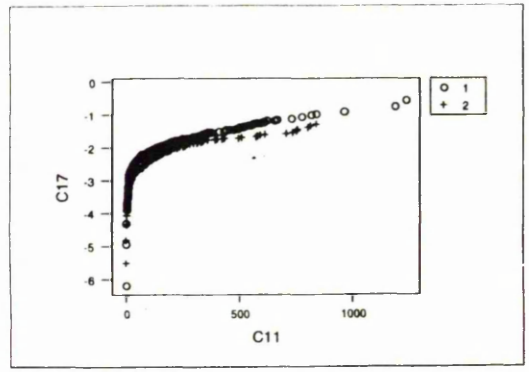
Plot 4-2-1-1: Estimated baseline survival function for model of table 4-2-1-1.



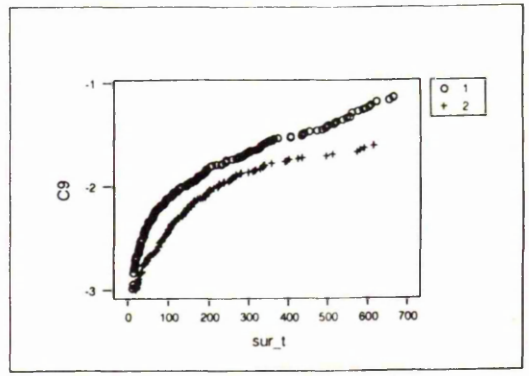
Plot 4-2-1-2: Estimated baseline cumulative hazard function for model of table 4-2-1-1.



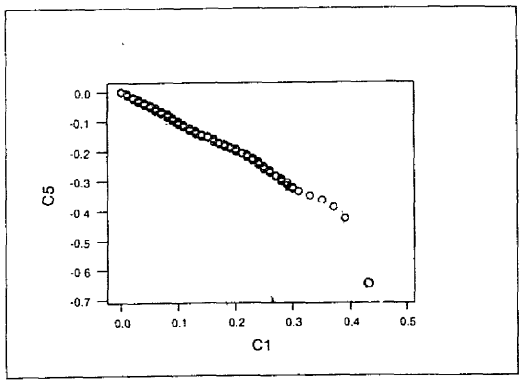
Plot 4-2-1-3: log minus log of survival functions for each treatment under model of table 4-2-1-1. (1:Placebo 2:Ramipril)



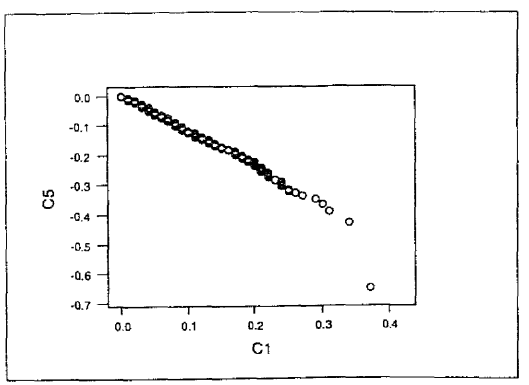
Plot 4-2-1-4: log minus log of survival function for each tratment under model of table 4-2-1-1(small values are deleted).1:Placebo 2:Ramipril



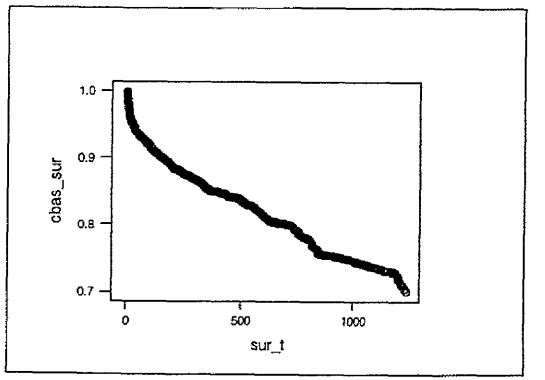
Plot 4-2-1-5: log 'survival' function of BMDP residuals against residuals for model of table 4-2-1-1.



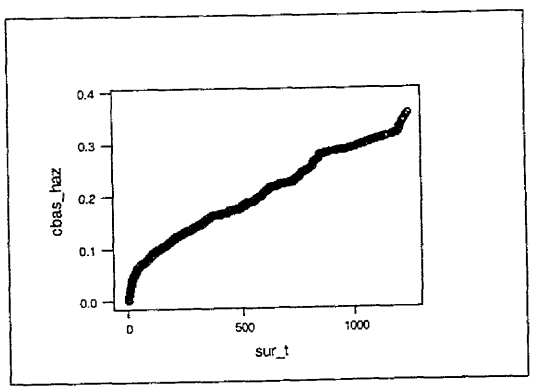
Plot 4-2-1-6: log 'survival' function of our residuals against these residuals for model of table 4-2-1-1.



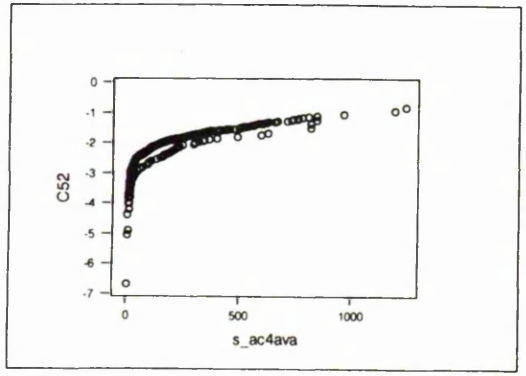
Plot 4-2-2-1: estimated baseline survival function for model of table 4-2-2-2.



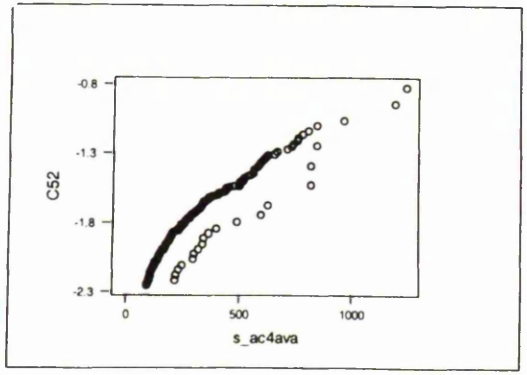
Plot 4-2-2-2: estimated baseline cumulative hazard function for model of table 4-2-2-2.



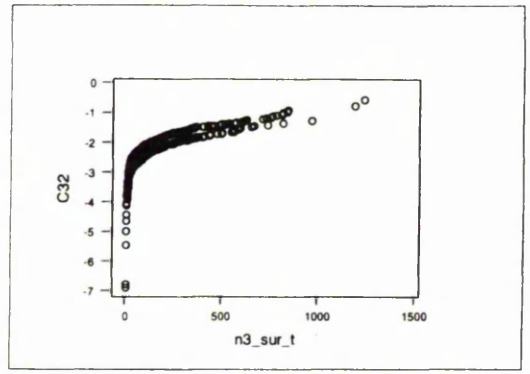
Plot 4-2-2-3: log minus log of survival functions under model of table 4-2-2-2 when Bibasilar post-tussive crackles defines a two level stratification (checked or not).



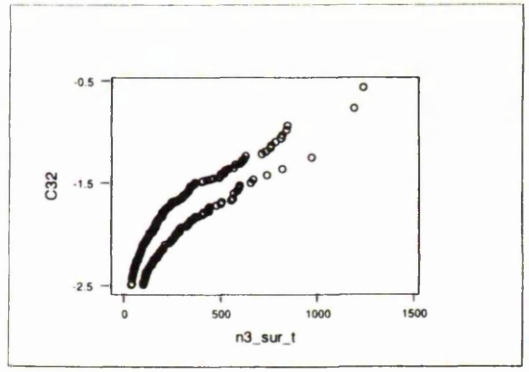
Plot 4-2-2-4: log minus log of survival functions under model of table 4-2-2-2 when Bibasilar post-tussive crackles defines a two level stratification(checked or not).Small values are deleted.



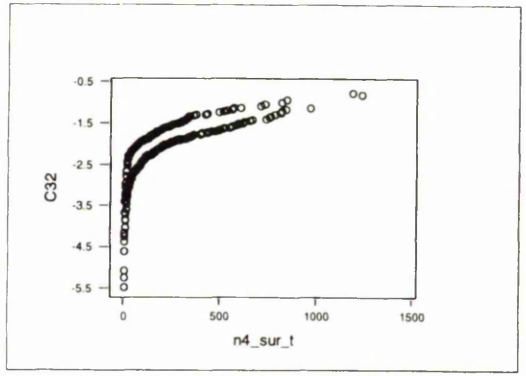
Plot 4-2-2-5: log minus log of survival functions under model of table 4-2-2-2 when Pulmary venous congestion defines a two level stratification (checked or not).



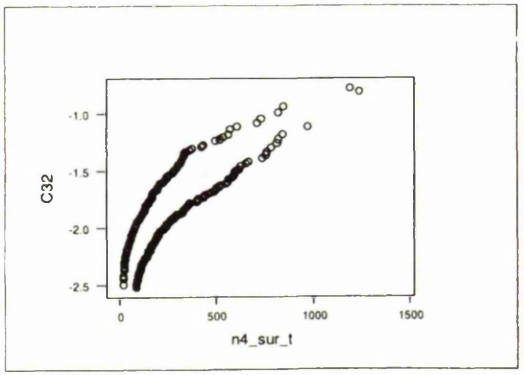
Plot 4-2-2-6: log minus log of survival functions under model of table 4-2-2-2 when Pulmary venous congestion defines a two level stratification(checked or not). Small values are deleted.



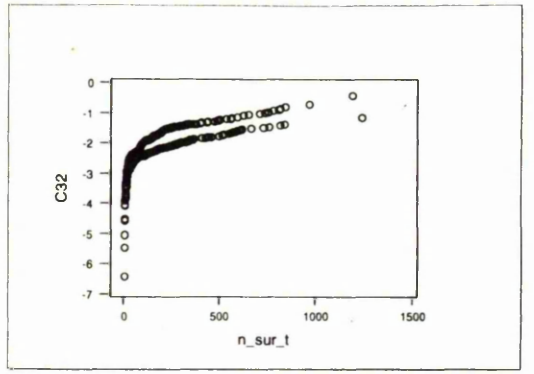
Plot 4-2-2-7: log minus log of survival functions under model of table 4-2-2-2 when Third heart sound with pers is defines a two level stratification(checked or not).



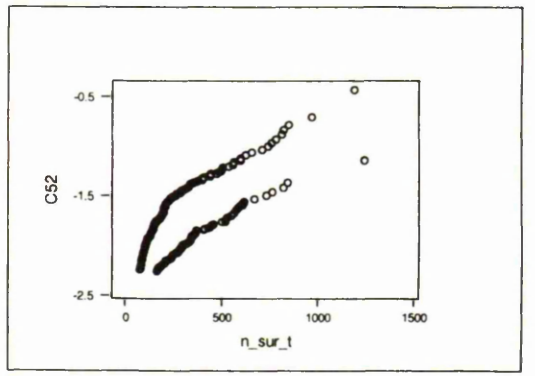
Plot 4-2-2-8: log minus log of survival functions under model of table 4-2-2-2 when Third heart sound with pers defines a two level stratification (checked or not). Small values are deleted.



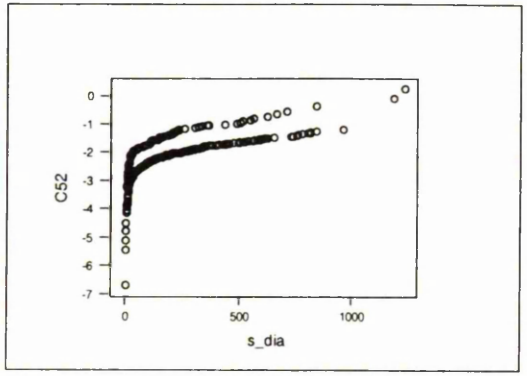
Plot 4-2-2-9: log minus log of survival functions under model of table 4-2-2-2 when Angina defines a two level stratification(yes or no).



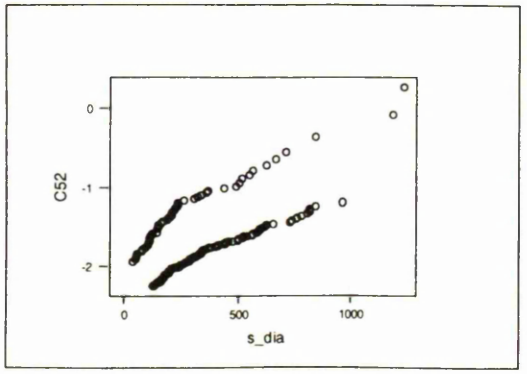
Plot 4-2-2-10: log minus log of survival functions under model of table 4-2-2-2 when Angina defines a two level stratification.(yes or no) Small values are deleted.



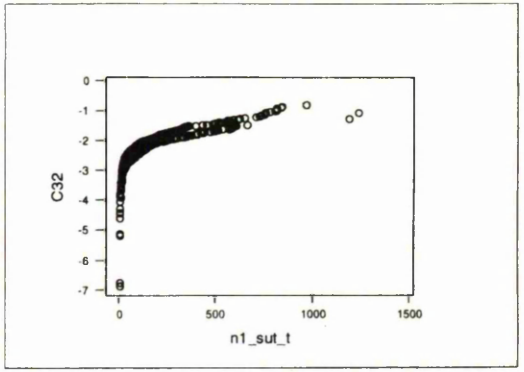
Plot 4-2-2-11: log minus log of survival functions under model of table 4-2-2-2 when Diabetes is defines a two level stratification.(yes or no)



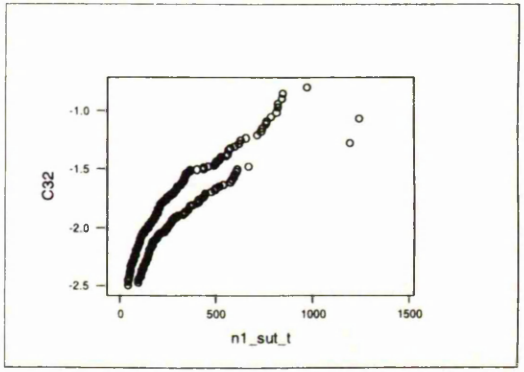
Plot 4-2-2-12: log minus log of survival functions under model of table 4-2-2-2 when Diabetes is defines a two level stratification.(yes or no) Small values are deleted.



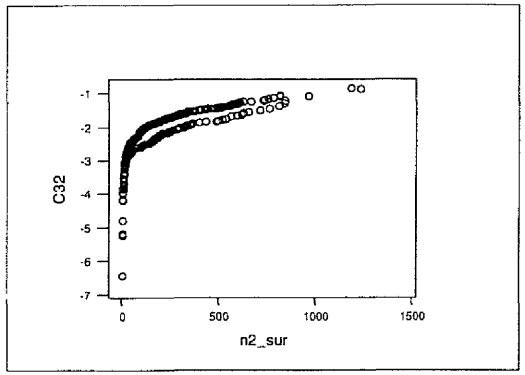
Plot 4-2-2-13: log minus log of survival functions under model of table 4-2-2-2 when Nyha defines a two level stratification (class III or not).



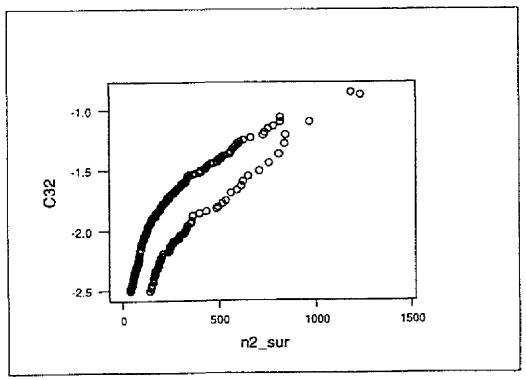
Plot 4-2-2-14: log minus log of survival functions under model of table 4-2-2-2 when Nyha defines a two level stratification (class III or not).Small values are deleted.



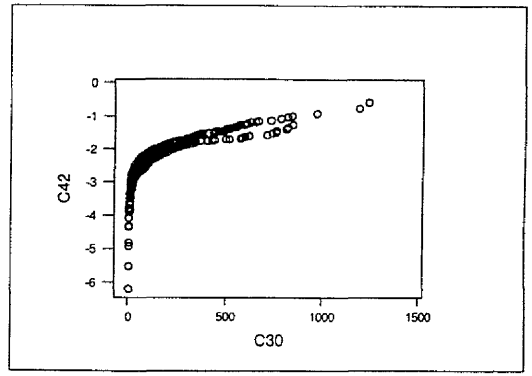
Plot 4-2-2-15: log minus log of survival functions under model of table 4-2-2-2 when Site defines a two level stratification (Inferior or not).



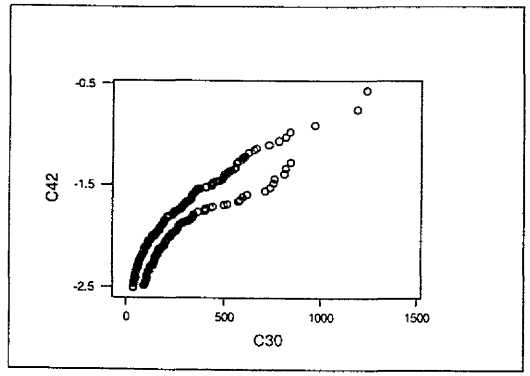
Plot 4-2-2-16: log minus log of survival functions under model of table 4-2-2-2 when Site defines a two level stratification (Inferior or not). Small values are deleted.



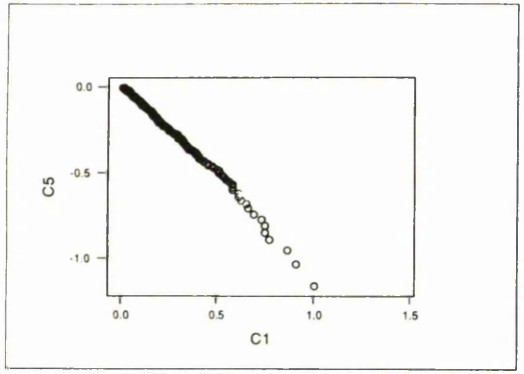
Plot 4-2-2-17: log minus log of survival functions under model of table 4-2-2-2 when'treatment' defines a two level stratification(Placeboor Ramipril).



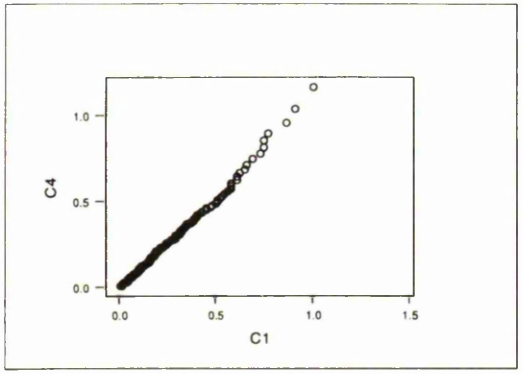
Plot 4-2-2-18: log minus log of survival functions under model of table 4-2-2-2 when 'treatment' defines a two level stratification(Placebo or Ramipril). Small values are deleted.



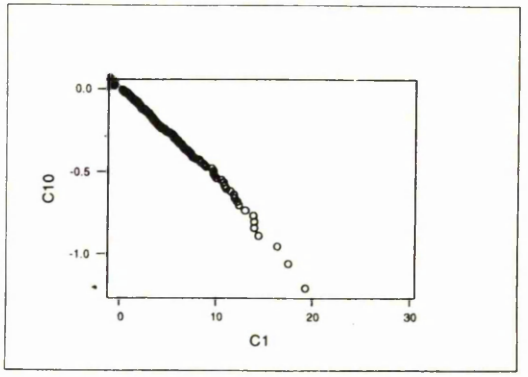
Plot 4-2-2-19: log 'survival' function of BMDP residuals against these residuals for model of table 4-2-2-2.



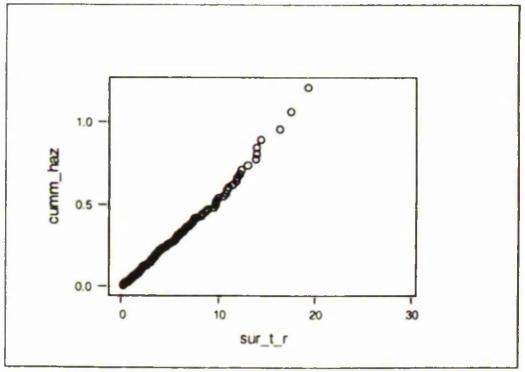
Plot 4-2-2-20: cumulative hazard function of BMDP residuals against these residuals for model of table 4-2-2-2.



Plot 4-2-2-21: log 'survival' function of our residuals against these residuals for model of table 4-2-2-2.



Plot 4-2-2-22: cumulative hazard function of our residuals against these residuals for model of table 4-2-2-2.



4-3 : Cox Proportional Hazards Models Fitted to "Time from Registration Date to Time of First Validated Reinfarction" (Event No. 2) :

4-3-1 : Entering A Single Covariate (Event No. 2) :

In this section we fit a Cox Proportional Hazards model in respect of event No. 2. We remind the reader that for this the survival time is the time interval between the date of registration and date of occurrence of the first validated reinfarction. We enter only a single covariate "Treatment" to the model. As a brief reminder we mention that a validated reinfarction is a heart event which has had been confirmed by the committee as a reinfarction .

Table 4-3-1-1 shows the Cox Proportional Hazards model fitted to the above mentioned survival time. The coefficient of the covariate treatment in the fitted model is -0.1043 with a standard error of 0.154 which strongly suggests the coefficient is not significantly different from zero. The coeff/s.e. rate is -0.6770.

This implies that whether the patient is treated by Ramipril or by the Placebo, there is no significant difference between responses. Note this suggests that Ramipril is not an effective treatment in delaying the occurrence of a validated reinfarction (first reinfarction).

Plot 4-3-1-1 shows the estimated baseline survival function (according to the Cox Proportional Hazards model). Note since the covariate "Treatment" is coded as "0" and "1" and code "0" corresponds to the patients who were treated by the Placebo, therefore this baseline survival function stands for the survival function corresponding to the time interval from registration date to first validated reinfarction for those patients who were treated by the Placebo. This baseline survival function suggests that the chances of not having a validated reinfarction (as the first one) decreases very rapidly in the first days after registration. It also shows that the probability it has not yet occurred by 2 years is at least 90 %.

Plot 4-3-1-2 shows the estimated cumulative baseline hazard function for the model of table 4-3-1-1. Once again, since the covariate "Treatment" is coded as "0" and "1" and the code "0" stands for those patients who have been treated by Placebo, therefore this cumulative baseline hazard function stands for the cumulative hazard function of having a first validated reinfarction for those patients who were treated by the Placebo. Note since the model indicated the effect of "Treatment" is not significant therefore this cumulative baseline hazard function can be used as the cumulative hazard function of having a validated reinfarction for those patients treated by Ramipril as well.

To investigate the validity of the proportionality assumption of the model 4-3-1-1, plot 4-3-1-3 was prepared. This plot shows the Log Minus Log of both survival functions (those patients who were treated by Ramipril and for those who were treated by the Placebo) against time.

Since the LML of both survival functions are very close together it was difficult to make any comment about proportionality of hazards therefore the plot 4-3-1-4 was prepared. This plot shows the two curves crossing, indicating that the hazards of having a validated reinfarction (the first one) for those patients who were treated by the Placebo and those who were treated by Ramipril are not proportional over the time interval from the registration date to the time of first the validated reinfarction. This suggests the proportionality assumption of hazards for model of table 4-3-1-1 is not valid.

Plots 4-3-1-5 and 4-3-1-6 show, respectively, the logarithm of the 'survival' function of BMDP's residuals and our residuals against the residuals. Both of these plots suggest that the relation between the log survival function of residuals (either BMDP's residuals or our residuals) and the residuals is a straight line (through the origin) having an inverse relation with the residuals. It seems to imply that the distribution of the residuals (either BMDP's or our residuals) is exponential with parameter 1(except for the last few patients). It indicates that the fitted model to end point number 2 (time to first valid reinfarction) is well fitted to the data. This implies that our results in respect of comparing the survival times of the two groups of patients are reliable.

4-3-2 : Entering Several Covariates (Event No. 2) :

Table 4-3-2-1 shows the fitted Cox regression model to the time interval between the registration date and the date of first validated reinfarction. The exhaustive method was used to construct this model and the same set of covariates were candidates to enter the model. This model indicates that four covariates age, Angina, ac4a (Bibasilar post-Tussive, Checked or Not) and ac4b (Pulmonary Venous Congestion, Checked or Not) are the only covariates which are significantly related to the specified mentioned 'survival time'. Note the model suggests that the use of Ramipril has no effect in delaying the time of first validated reinfarction. This result is the same as the previous one obtained from the model of table 4-3-1-1.

Table 4-3-2-2 shows another Cox Proportional hazards model fitted to the time interval between the registration date and the date of first validated reinfarction. In this new model the stepwise method has been used to enter the covariates into the model. The differences between the exhaustive method and stepwise method in constructing a model was explained in section 4-2-2. The model of table 4-3-2-2 indicates that the same set of covariates as in model 4-3-2-1, are significantly related to the specified survival time. This model suggests that the age of patients is a risk factor in respect of the time to a first validated reinfarction and older patients are more likely to have this sooner than younger patients. The model suggests also that for any time point those patients who has a

history of Angina or Bibasilar post-tussive has been Checked for them, have greater hazard of the occurrence of a first validated reinfarction.

Plot 4-3-2-1 and 4-3-2-2 show, respectively, the estimated baseline survival function and the estimated baseline cumulative hazard function corresponding to the model of table 4-3-2-2. These plots indicate that a large proportion of patients survive (i.e. a validated reinfarction does not occur for them) at the end of study (aprox. 88%).

Plots 4-3-2-3 to 4-3-2-5 were prepared to investigate the validity of the proportional hazards assumption in the model of table 4-3-2-2. Each of these plots show the Log Minus Log of the survival functions for different levels of a particular covariate. These are the covariates included in the model. We remind the reader that 4 covariates were included in the model of table 4-3-2-2, namely age, ac4a (Bibasilar post-tussive, Checked or Not), ac4b (Pulmonary Venous Congestion, Checked or Not) and Angina. Plots 4-3-2-3 to 4-3-2-5 are, respectively, for ac4b, ac4a, ac4b and Angina. In each of these plots we examine whether the proportionality of hazards assumption for the relevant covariate, is or is not valid. We remind the reader that the survival functions have been estimated by the Kaplan-Meier method and that the survival time is defined as the time interval between the registration date and the date of the first validated reinfarction. These plots suggest that the assumption of proportionality of hazards assumption is valid for all covariates which are included in the model.

To investigate the goodness of fit of the model 4-3-2-2, plots 4-3-2-6 to 4-3-2-9 were prepared. Plots 4-3-2-6 and 4-3-2-7 show,

respectively, the logarithm of survival function of the residuals and the cumulative hazard function of the residuals(our residuals and BMDP's residuals). Clearly the above plots look linear but not with slopes of -1 or 1 respective. The residuals would appear to be exponentially distributed but not with parameter 1. So both types of residuals (our residuals and BMDP's residuals) suggest that the Cox Proportional Hazards model fitted to the time interval between the registration date and the date of first validated reinfarction does not actually fit well.

Some further tests were carried out to investigate the fit of the model of table 4-3-2-2. In these further tests we test whether the 'survival functions' of the residuals (either our residuals or BMDP's residuals) at different levels of a particular covariate are or are not significantly different. Note to have a good fit, these survival functions (of the residuals) should not be significantly different. Tables 4-3-2-3 to 4-3-2-5 show, respectively, the results of the comparing the survival functions of our residuals corresponding to different levels of covariates whic are included in model of table 4-3-2-2. These tables suggest that those survival functions (of our residuals) are significantly different. It implies, once again that the model of table 4-3-2-2 does not fit the relevant survival time (i.e. the time interval between the registration date and the date of first validated reinfarction). Tables 4-3-2-6 to 4-3-2-8 are similar to tables 4-3-2-3 to 4-3-2-5 but have been prepared for BMDP's residuals. These new tables suggest that the survival functions of BMDP's residuals corresponding to different levels of each of the covariates ac4a (Bibasilar post-Tussive, Checked or Not), ac4b (Pulmonary Venous Congestion,

Checked or Not) and Angina, are not significantly different i.e. the model of table 4-3-2-2 does fit well. Hence we have a contradiction in results. However, since we are sure about the validity of our residuals (and not about BMDP's residuals) we conclude that the Cox proportional hazards model does not fit the specified survival time.

Table 4-3-1-1 : Cox Proportional Hazard model fitted to time from registration date to validated re infarction. (single treatment covariate)

Log Likelihood = -1248.5661
Global Chi-Square = 0.46 d.f. = 1 P-value = 0.4982

Variable	Coefficient	Standard Error	Coeff./S.E.	Exp(Coeff
Treatment	-0.1043	0.1540	- 0.6770	0.9010

Table 4-3-2-1 : Cox Proportional Hazard model fitted to time from registration date to validated re infarction. (all candidate covariates)

LOG LIKELIHOOD = -1216.8426
GLOBAL CHI-SQUARE = 62.97 D.F.= 16 P-VALUE =0.0000

VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF)
treatment	-0.1175	0.1545	-0.7607	0.8891
age	0.0285	0.0086	3.3257	1.0290
sex	0.0378	0.1754	0.2155	1.0385
hyperten	-0.0472	0.1731	-0.2727	0.9539
diabet	-0.0821	0.2385	-0.3441	0.9212
pmi	0.2414	0.1828	1.3209	1.2731
angina	0.5291	0.1854	2.8541	1.6975
cardiac	-0.2852	0.3175	-0.8984	0.7518
nyha_d1	-0.4572	0.3607	-1.2675	0.6330
nyha_d2	-0.4544	0.3071	-1.4800	0.6348
nyha_d3	-0.3179	0.3043	-1.0446	0.7277
site_d1	0.5843	0.4235	1.3797	1.7937
site_d2	0.4269	0.4319	0.9885	1.5325
ac4a	0.6784	0.3067	2.2118	1.9706
ac4b	-0.4136	0.1607	-2.5745	0.6613
ac4c	0.0692	0.1891	0.3659	1.0716

Table 4-3-2-2: Cox Proportional Hazard model fitted to time from registration date to validated re infarction. (Stepwise method)

LOG LIKELIHOOD = -1221.0441
GLOBAL CHI-SQUARE = 53.28 D.F.=4 P-VALUE =0.0000

STEP NO	VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF)
1	angina	0.6559	0.1574	4.1682	1.9269
2	age	0.0286	0.0082	3.4938	1.0290
3	ac4b	0.6415	0.3027	2.1192	1.8993
4	ac4a	-0.3879	0.1577	-2.4599	0.6784

Table 4-3-2-3 : Comparing the distributions of our residuals for two levels of ac4b (Pulmonary venous congestion, Checked or Not) for time to validated re infarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	264	12	252	0.95
level 2	1664	157	1507	0.91
Total	1928	169	1759	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.001	1	0.9819	

Table 4-3-2-4 : Comparing the distributions of our residuals for two levels of ac4c (Third heart sound with pers, Checked or Not) for time to validated re infarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	929	98	831	0.89
level 2	999	71	928	0.93
Total	1928	169	1759	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.002	1	0.9668	

Table 4-3-2-5 : Comparing the distributions of our residuals for two levels of Angina for time to validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1233	78	1155	0.94
level 2	695	91	604	0.87
Total	1928	169	1759	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.015	1	0.9031	

Table 4-3-2-6 : Comparing the distributions of BMDP residuals for two levels of ac4b (Pulmonary venous congestion, Checked or Not) for time to validated re infarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	264	12	252	0.95
level 2	1664	157	1507	0.91
Total	1928	169	1759	
	Statistic	d.f.	P-value	
Generalised Savage test	5.101	1	0.0239	

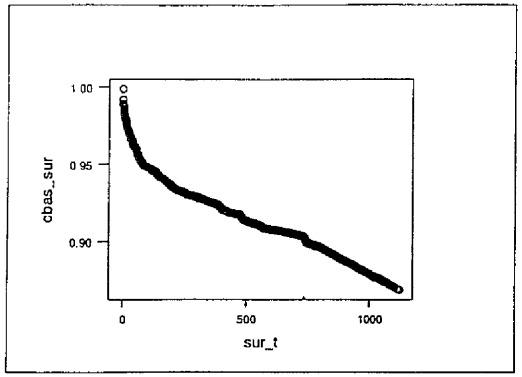
Table 4-3-2-7 : Comparing the distributions of BMDP residuals for two levels of ac4c (Third heart sound with pres, Checked or Not) for time to validated re infarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	929	98	831	0.89
level 2	999	71	928	0.93
Total	1928	169	1759	
	Statistic	d.f.	P-value	
Generalised Savage test	4.544	1	0.033	

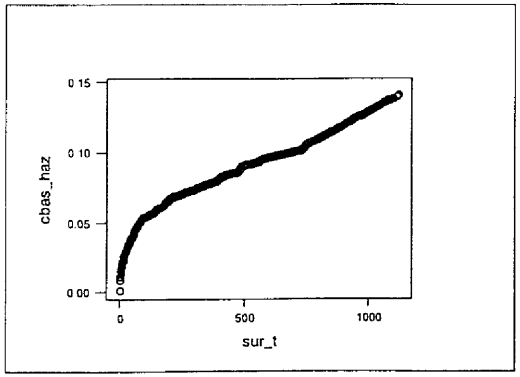
Table 4-3-2-8 : Comparing the distributions of BMDP residuals for two levels of Angina for time to validated re infarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1233	78	1155	0.94
level 2	695	91	604	0.87
Total	1928	169	1759	
	Statistic	d.f.	P-value	
Generalised Savage test	12.747	1	0.0004	

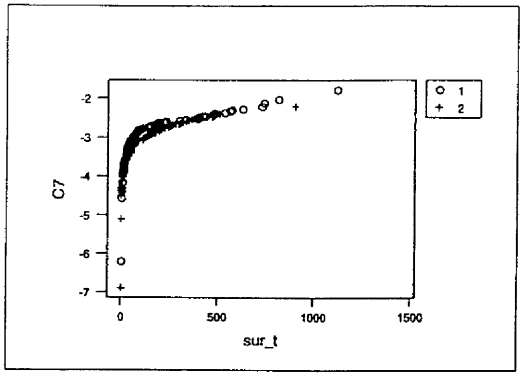
Plot 4-3-1-1: estimated baseline survival function for model of table 4-3-1-1.



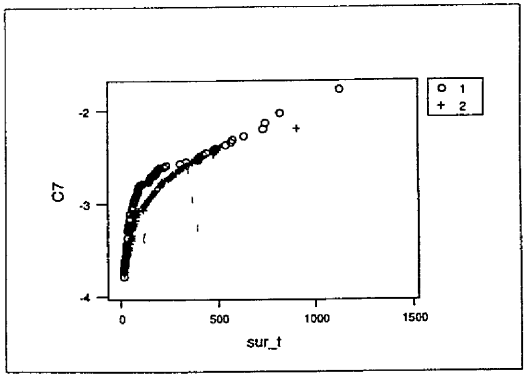
Plot 4-3-1-2: estimated baseline cumulative hazard function for model of table 4-3-1-1.



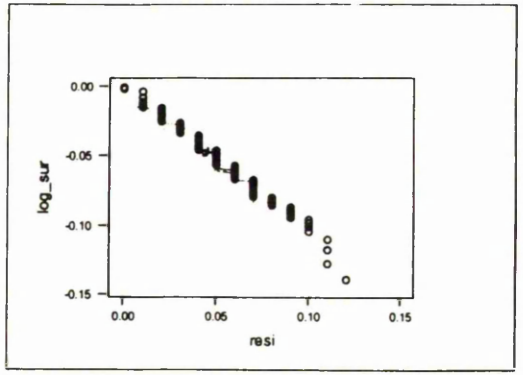
Plot 4-3-1-3: log minus log of survival functions for each 'treatment' under model of table 4-3-1-1. (1:Placebo 2:Ramipril)



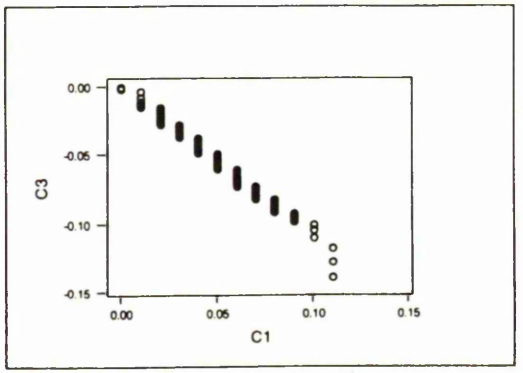
Plot 4_3-1-4: log minus log of survival functions for each 'treatment' under model of table 4-3-1-1.(small values are deleted). 1:Placebo 2:Ramipril



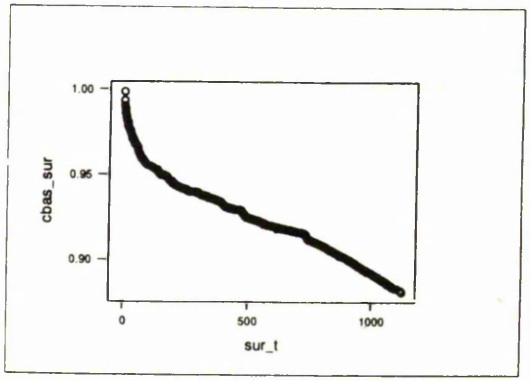
Plot 4-3-1-5: log 'survival' function of BMDP residuals against these residuals for model of table 4-3-1-1.



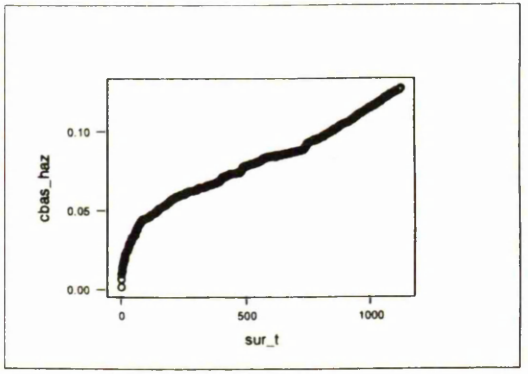
Plot 4-3-1-6: log 'survival' function of our residuals against these residuals for model of table 4-3-1-1.



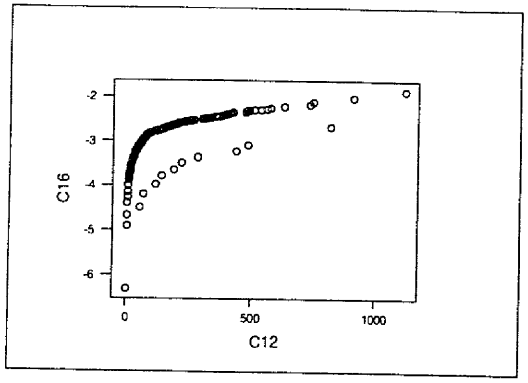
Plot 4-3-2-1:estimated baseline survival function for model of table 4-3-2-2.



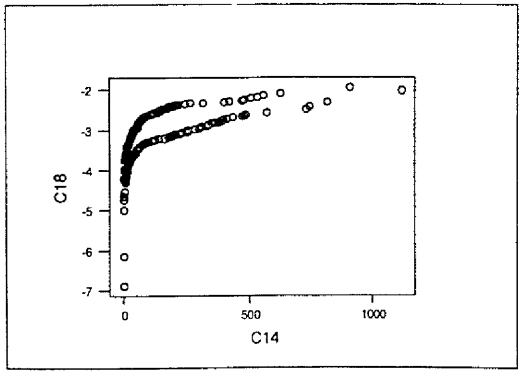
Plot 4-3-2-2: estimated baseline cumulative hazard function for model of table 4-3-2-2.



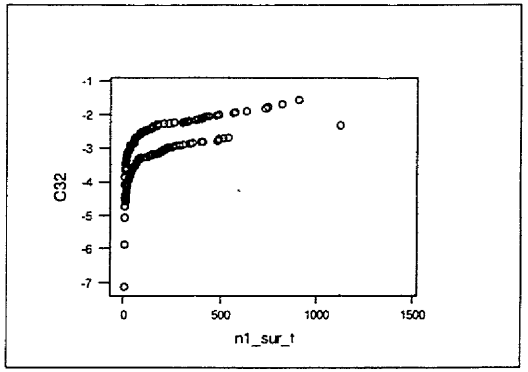
Plot 4-3-2-3: log minus log of survival functions under model of table 4-3-2-2 when Bibasilar post-tussive defines a two level stratification(checked or not).



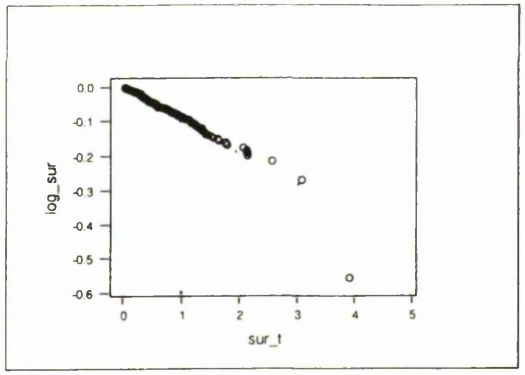
Plot 4-3-2-4: log minus log of survival functions under model of table 4-3-2-2 when Pulmonary venous congestion defines a two level stratification(checked or not).



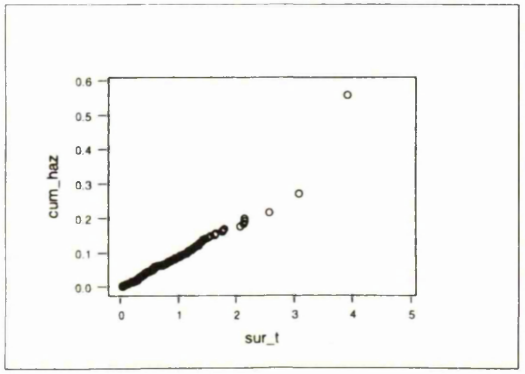
Plot 4-3-2-5: log minus log of survival functions under model of table 4-3-2-2 when Angina is defines a two level stratification (yes or no).



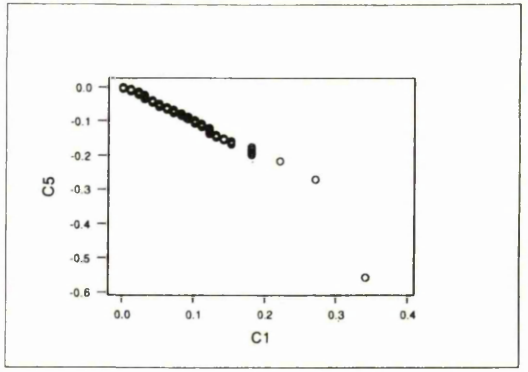
Plot 4-3-2-6: log 'survival' function of our residuals against these residuals for model of table 4-3-2-2.



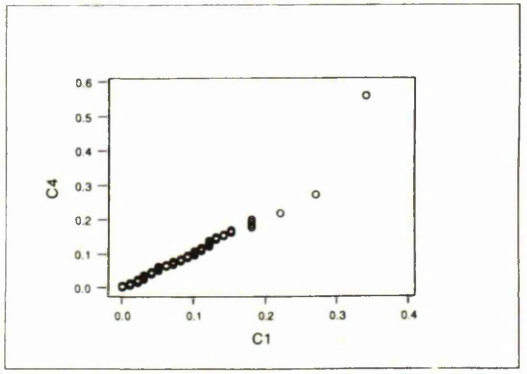
Plot 4-3-2-7: cumulative hazard function of our residuals against these residuals for model of table 4-3-2-2.



Plot 4-3-2-8: log 'survival' function of BMDP residuals against these residuals for model of table 4-3-2-2.



Plot 4-3-2-9: cumulative hazard function of BMDP residuals against these residuals for model of table 4-3-2-2.



4-4 : Cox Proportional Hazards Models Fitted to "Time from Registration Date to Time of Sudden Death or First Validated Reinfarction" (Event No. 3) :

4-4-1 : Entering A Single Covariate (Event No. 3) :

In this section we fit a Cox Proportional Hazards model to the time interval between the registration date and the date of either sudden death or first validated reinfarction. This endpoint is labelled endpoint No. 3. Sudden deaths are those deaths which have been recognised by the committee as sudden deaths. Here we will enter only a single covariate to the model and that is the covariate "Treatment".

Table 4-4-1-1 shows the Cox Proportional hazards model fitted to the above 'survival' times in respect of the covariate "Treatment". The Model shows that the coefficient of the covariate is -0.2317 with a standard error of 0.1063. This implies that the coefficient is significantly different from zero. Hence since the covariate "Treatment" is coded as "0" and "1", "0" if the patient has been treated by the Placebo, the model suggests that the use of Ramipril has prolonged (note that the coefficient of "Treatment" is negative) the time from the registration date to the time of sudden death or first validated reinfarction. The model also shows that the hazard of failure for those patients who were treated by Ramipril, at

any particular time point from the registration date, is 0.7932 times the hazard of failure of those patients who were treated by Placebo.

Plot 4-4-1-1 shows the baseline survival function for the model of table 4-4-1-1. This plot stands for the survival function of those patients who were treated by the Placebo. To obtain the survival function of those patients who were treated by Ramipril, every value of this baseline survival function should be raised to the power of 0.7932. The mathematical reason was discussed in section 2-2-1. Plot 4-4-1-1 shows that the probability of failure, for those patients who were treated by the Placebo, decreases in the first days after registration very rapidly to .90 but those patients who survive these critical days have good survival prospects, the probability of survival beyond years after registration being about 0.70.

Plot 4-4-1-2 shows the commulative baseline hazard function of the Cox Model fitted to the time interval between the registration date and the date of either sudden death or first validated reinfarction. Since the covariate "Treatment" is coded as "0" if the patient is treated by the Placebo therefore this function is the cumulative hazard function of these patients. The cumulative hazard function of those patients who were treated by Ramipril can be estimated by multiplying this function by the number 0.7932.

To investigate the validity of the assumption of proportionality between the hazards of those patients who were treated by the Placebo with the hazards of those who were treated by Ramipril, Plot 4-4-1-3 was prepared. This plot shows the LML of survival functions of the patients

who were treated by the Placebo and Ramipril. These survival functions were estimated by the Kaplan-Meier method. Unfortunately the values of these LML plots of the survival functions are very close to each other and it is not possible to make any comment about a parallel relationship between them. So plot 4-4-1-4 is presented, this being plot 4-4-1-3 but with the extreme small values deleted to be able produce a plot in a reasonable scale. This plot suggests that the hazard of the two groups of patients are more or less parallel. Hence the proportionality of hazards assumption is valid.

Plots 4-4-1-5 and 4-4-1-6 show, respectively, that the logarithm of the survival function of BMDP's residuals and our residuals against the relevant residuals. Both of these plots suggest that the relation between the logarithm of the residuals and the residuals is a straight line (through the origin). This implies that the distribution of the residuals (either BMDP's or our residuals) is exponential with parameter 1(except possibly for the last patient). This suggests that the fitted model in respect of end point number 3 (sudden death or first validated reinfarction) fits well so that the conclusions we have reached about the effect of Ramipril are reliable.

4-4-2 : Entering Several Covariates (Event No. 3) :

In this section we fit a similar model as in section 4-4-1 (i.e. Cox Proportional Hazards model) to the time interval between the registration date and the date of sudden death or first validated reinfarction but with the difference that here we entered all significant covariates in the model.

Table 4-4-2-1 shows the Cox regression model fitted to the time interval between the registration date and the date of sudden death or first validated reinfarction. The exhaustive method was used to construct this model. The model indicates that six covariates treatment, age, Diabetes, Angina, Nyha_d2 (i.e. class II, Yes or No) and ac4c (Third heart Sound with pers, Checked or Not) are the covariates which are significantly related to the specified 'survival' time. Note the model suggests that the use of Ramipril is significantly effective in decreasing the hazard of failure. This result is the same as that obtained from the model of table 4-4-1-1 (the model with the single covariate, "Treatment").

Table 4-4-2-2 shows another Cox Proportional hazards model fitted to the time interval between the registration date and the date of sudden death or first validated reinfarction. In this new model the stepwise method has been used to enter the covariates into the model. The model of table 4-4-2-2 indicates that in addition to the previous covariates included in the model of table 4-4-2-1, the covariate Site_d2 (i.e. Inferior, Yes or No) is also significantly related to the specified 'survival' time. This model suggests older patients are more likely to experience sudden

death or have a reinfarction earlier than younger patients. The model suggests also that those who were treated by Ramipril are less at risk of failure than those patients who were treated by the Placebo. The covariates Diabetes, Angina, Site_d2 (i.e. Inferior, Yes or No), Nyha_d2 (i.e. class II, Yes or No) and ac4c (Third heart Sound with pers Checked or Not) are the other covariates which are significantly related to the time interval between the registration date and the date of sudden death or first validated reinfarction.

Plots 4-4-2-1 and 4-4-2-2 show, respectively, the estimated baseline survival function and the estimated baseline cumulative hazard function corresponding to model of table 4-4-2-2.

Plots 4-4-2-3 to 4-4-2-14 (12 plots) enable investigation of the validity of the proportional hazards assumption in the model of table 4-4-2-2. Each of these plots show the Log Minus Log of the survival functions at different levels of a particular covariate. These are the covariates included in the model. For each covariate two plots were prepared. The reason is usually that the values of the LML of the 'survival' functions are too close early on. So it was necessary to delete some small LML values to illustrate the parallel relationship of the LML of survival functions. We remind the reader that 7 covariates were included in the model of table 4-4-2-2. Therefore 14 plots were prepared. These are plots 4-4-2-3 to 4-4-2-14. In each of these plots we examine whether the proportionality of hazards assumption for the relevant covariate, is or is not valid. We remind the reader that the survival functions have been estimated by the Kaplan-Meier method and the survival time is defined as the time interval

between the registration date and the date of sudden death or first validated reinfarction. These plots show that the assumption of proportional hazards is valid.

To investigate the goodness of fit of the model 4-4-2-2, plots 4-4-2-15 to 4-4-2-18 were prepared. Plots 4-4-2-15 and 4-4-2-16 show, respectively, the logarithm of the survival function of our residuals and the cumulative hazard function of our residuals. Clearly both the plots look linear but not with slopes of -1 or 1 respectively. The residuals would appear to be exponentially distributed but not with parameter 1. This indicates that the model of table 4-4-2-2 does not fit well. Plots 4-4-2-17 and 4-4-2-18 are same plots as plots 4-4-2-15 and 4-4-2-18 but they have been prepared for BMDP's residuals. Once again, these two plots look linear but not with slopes -1 or 1 respectively. The residuals would appear to be exponentially distributed but not with parameter 1. This indicates also that the model of table 4-4-2-2 does not fit well Note both types of residuals (our residuals and BMDP's residuals) suggest that the Cox Proportional Hazards model does not fit well to the time interval between the registration date and the date of the first validated reinfarction.

Further tests were carried out to investigate the fit of the model of table 4-4-2-2. In these further tests we tested whether the distributions of the residuals (either our residuals or BMDP's residuals) corresponding to different levels of a particular covariate are or are not significantly different. To have a good fit, these distributions (of the residuals) should not be significantly different. Note that in the previous paragraph we showed that the model of table 4-4-2-2 does not fit well. These further

tests may provide some explanation as to why this is the case if they detect differences in the distribution of the residuals between different levels of a covariate. If they don't detect such differences, then we are left with the conclusion that the residuals have a common distribution across the levels of the relevant covariate but that common distribution according to the previous results is not exponential 1. Moreover it would seem that the influence of the covariate has been adequately captured by the model. Tables 4-4-2-3 to 4-4-2-8 show the results of comparing the survival functions of our residuals corresponding to different levels of the covariates which are included in the model of table 4-4-2-2. These tables suggest that these survival functions (of our residuals) are not significantly different. This implies that the residuals do not show any significant pattern between different levels of any of the covariates i.e. as far as the pattern of residuals at different levels of any of the covariates concerned, the model of table 4-4-2-2 fits reasonably. But note that we previously discovered that the residuals (our residuals) show that the model of table 4-5-2-2 does not fit well. Tables 4-4-2-9 to 4-4-2-14 are similar to tables as 4-4-2-4 to 4-4-2-8 but have been prepared for BMDP's residuals. These new tables suggest that the distribution of BMDP's residuals corresponding different levels of the covariate Angina are significantly different while those corresponding to different levels of the other covariates are not different.

Table 4-4-1-1 : Cox Proportional Hazard model fitted to time from registration date to sudden death or validated re infarction . (single treatment covariate)

```
Log Likelihood = -2603.5129
Global Chi-Square = 4.77  d.f. = 1  P-value = 0.0290
```

Variable	Coeeficient	Standard Error	Coeff./S.E.	Exp(Coeff.)
Treatment	-0.2317	0.1063	- 2.1790	0.7932

Table 4-4-2-1 : Cox Proportional Hazard model fitted to time from registration date to sudden death or validated re infarction. (all candidate covariates)

```
   LOG LIKELIHOOD =  -2549.7010
GLOBAL CHI-SQUARE =    114.59  D.F.=  18  P-VALUE =0.0000
NORM OF THE SCORE VECTOR=   0.296E-04
```

VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF.)
age	0.0273	0.0059	4.6284	1.0277
treatment	-0.2420	0.1067	-2.2670	0.7851
sex	0.0568	0.1209	0.4701	1.0585
hyperten	0.0838	0.1169	0.7169	1.0874
diabet	0.3768	0.1432	2.6312	1.4577
pmi	0.0864	0.1290	0.6696	1.0902
angina	0.4229	0.1263	3.3482	1.5263
cardia	-0.0188	0.2019	-0.0932	0.9814
nyha_d1	-0.3982	0.2417	-1.6476	0.6715
site_d1	0.5571	0.7157	0.7783	1.7455
site_d2	0.2796	0.7178	0.3895	1.3226
nyha_d2	-0.5320	0.2099	-2.5345	0.5874
nyha_d3	-0.2695	0.2069	-1.3029	0.7637
wave_d1	-0.4015	0.7545	-0.5321	0.6693
wave_d2	-0.4455	0.7505	-0.5936	0.6405
ac4a	0.3091	0.1719	1.7985	1.3622
ac4b	0.0372	0.1092	0.3407	1.0379
ac4c	0.3254	0.1207	2.6964	1.3846

Table: 4-4-2-2 : Cox Proportional Hazard model fitted to time from registration date to sudden death or validated re infarction. (Stepwise method)

```
LOG LIKELIHOOD =  -2554.1555
GLOBAL CHI-SQUARE =    102.11  D.F.=7  P-VALUE =0.0000
```

Step No.	VARIABLE	df	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF.)
1	age	1	0.0298	0.0056	-5.3471	1.0303
2	angina	2	0.5065	0.1089	4.6520	1.6594
3	diabet	3	0.4146	0.1400	2.9606	1.5138
4	site_d2	4	-0.2785	0.1141	-2.4415	0.7569
5	treatment	5	-0.2417	0.1064	-2.2714	0.7853
6	ac4c	6	0.2886	0.1180	2.4466	1.3345
7	nyha_d2	7	-0.2529	0.1087	-2.3263	0.7766

Table 4-4-2-3 : Comparing the distributions of our residuals for two levels of ac4c (Third heart sound with pers, Checked or Not) for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1483	253	1230	0.83
level 2	469	104	365	0.78
Total	1952	357	1595	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.013	1	0.9077	

Table 4-4-2-4 : Comparing the distributions of our residuals for two levels of Angina for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1249	177	1072	0.86
level 2	703	180	523	0.74
Total	1952	357	1595	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.22	1	0.6391	

Table 4-4-2-5 : Comparing the distributions of our residuals for two levels of Diabetes for time to sudden death or validated reinfarction

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1716	294	1422	0.83
level 2	236	63	173	0.73
Total	1952	357	1595	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.089	1	0.7655	

Table 4-4-2-6 : Comparing the distributions of our residuals for two levels of nyha_d2 (i.e. class II, Yes or No) for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1037	213	824	0.79
level 2	915	144	771	0.84
Total	1952	357	1595	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.099	1	0.7533	

Table 4-4-2-7 : Comparing the distributions of our residuals for two levels of side_d2 (Inferior, Yes or No) for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1222	244	978	0.80
level 2	730	113	617	0.85
Total	1952	357	1595	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.002	1	0.965	

Table 4-4-2-8 : Comparing the distributions of our residuals for two levels of treatment for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	963	195	768	0.80
level 2	989	162	827	0.84
Total	1952	357	1595	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.002	1	0.9653	

Table 4-4-2-9 : Comparing the distributions of BMDP residuals for two levels of ac4c (Third heart sound with pers, Checked or Not) for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1483	253	1230	0.83
level 2	469	104	365	0.78
Total	1952	357	1595	
	Statistic	d.f.	P-value	
Generalised Savage test	3.126	1	0.077	

Table 4-4-2-10 : Comparing the distributions of BMDP residuals for two levels of Angina for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1249	177	1072	0.86
level 2	703	180	523	0.744
Total	1952	357	1595	
	Statistic	d.f.	P-value	
Generalised Savage test	12.916	1	0.0003	

Table 4-4-2-11 : Comparing the distributions of BMDP residuals for two levels of Diabetes for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1716	294	1422	0.83
level 2	236	63	173	0.73
Total	1952	357	1595	
	Statistic	d.f.	P-value	
Generalised Savage test	6.805	1	0.0091	

Table 4-4-2-12 : Comparing the distributions of BMDP residuals for two levels nyha_d2 (i.e. class II, Yes or No) for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1037	213	824	0.79
level 2	915	144	771	0.84
Total	1952	357	1595	
	Statistic	d.f.	P-value	
Generalised Savage test	2.907	1	0.0882	

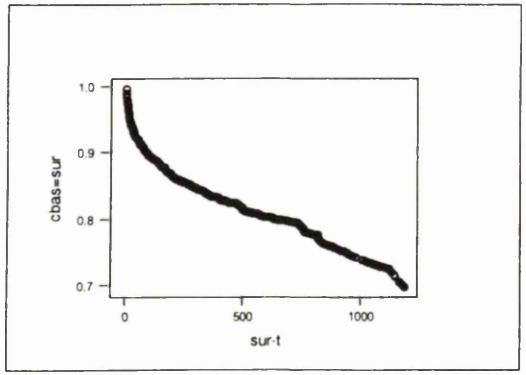
Table 4-4-2-13 : Comparing the distributions of BMDP residuals for two levels of site _d2 (Inferior, Yes or No)for time to sudden death or validated reinfarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1222	244	978	0.80
level 2	730	113	617	0.86
Total	1952	357	1595	
	Statistic	d.f.	P-value	
Generalised Savage test	2.316	1	0.1281	

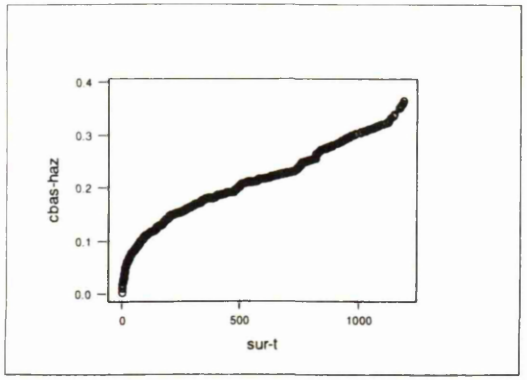
Table 4-4-2-14 : Comparing the distributions of BMDP residuals for two levels of treatment for time to sudden death or validated re infarction.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	963	195	768	0.80
level 2	989	162	827	0.84
Total	1952	357	1595	
	Statistic	d.f.	P-value	
Generalised Savage test	2.040	1	0.1533	

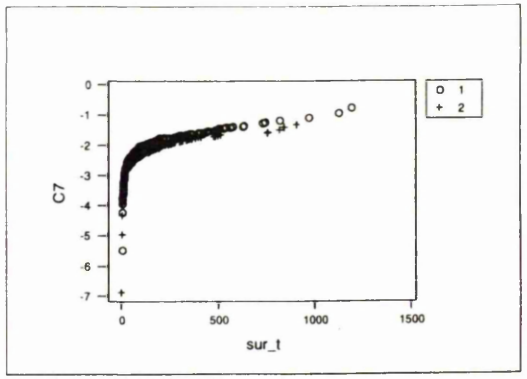
Plot 4-4-1-1: Estimated baseline survival function for model of table 4-4-1-1.



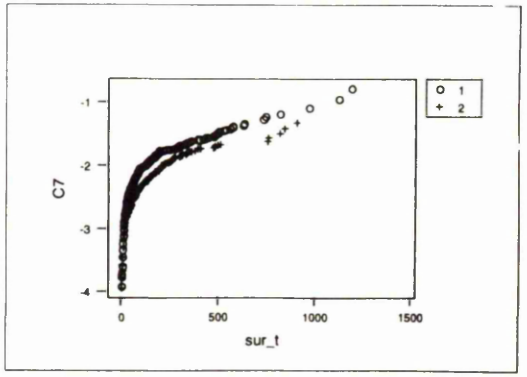
Plot 4-4-1-2: Estimated baseline cumulative hazard function for model of table 4-4-1-1.



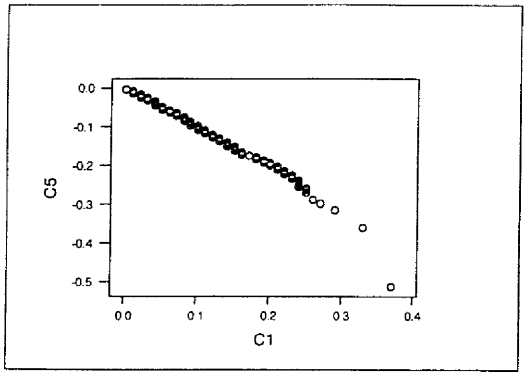
Plot 4-4-1-3: log minus log of survival functions for each treatment under model of table 4-4-1-1. (1:Placebo 2:Ramipril)



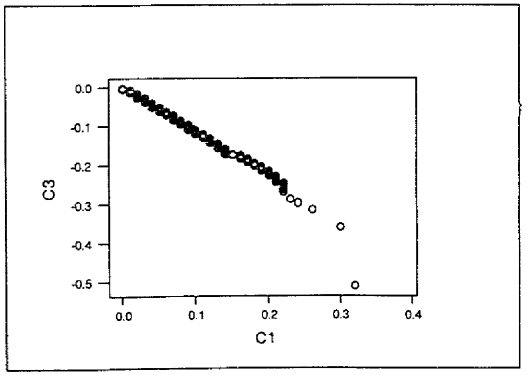
Plot 4-4-1-4: log minus log of survival function for each tratment under model of table 4-4-1-1(small values are deleted).1:Placebo 2:Ramipril



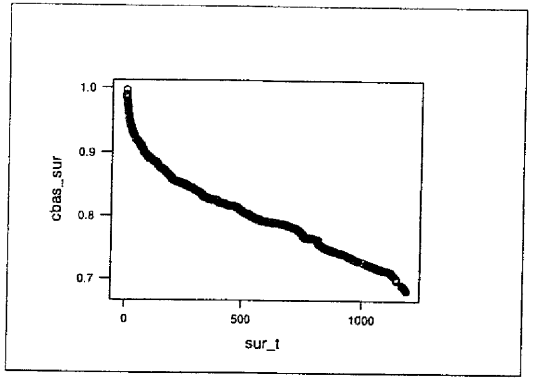
Plot 4-4-1-5: log 'survival' function of BMDP residuals against these residuals for model of table 4-4-1-1.



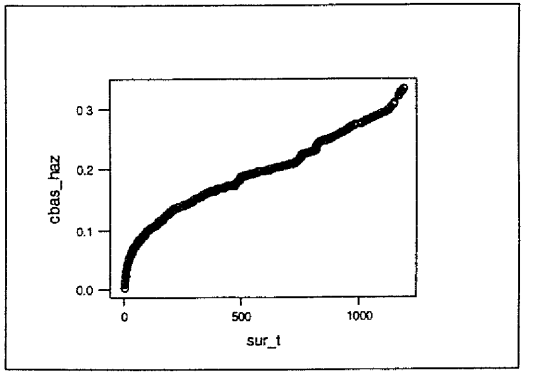
Plot 4-4-1-6: log 'survival' function of our residuals against these residuals for model of table 4-4-1-1.



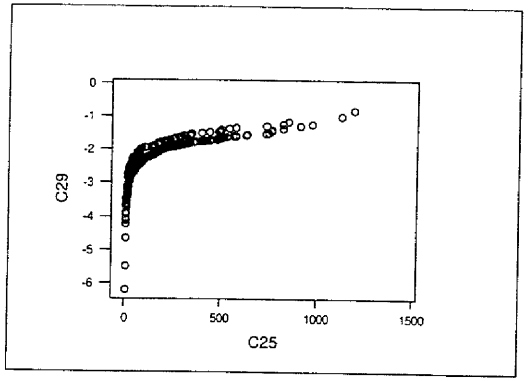
Plot 4-4-2-1: estimated baseline survival function for model of table 4-4-2-2.



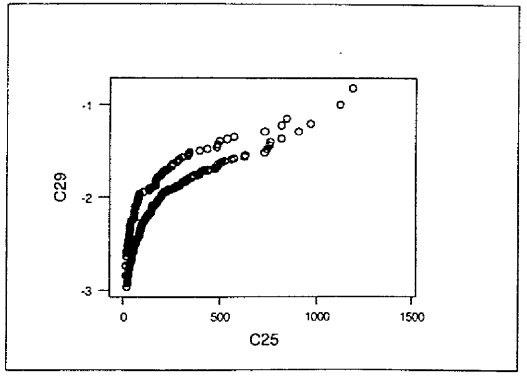
Plot 4-4-2-2: estimated base line cumulative hazard function for model of table 4-4-2-2.



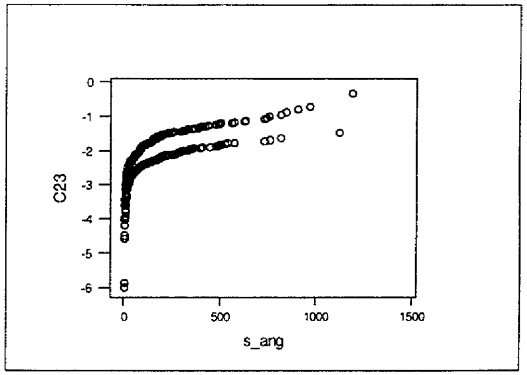
Plot 4-4-2-3: log minus log of survival functions under model of table 4-4-2-2 when Third heart sound with pers defines a two level stratification(checked or not).



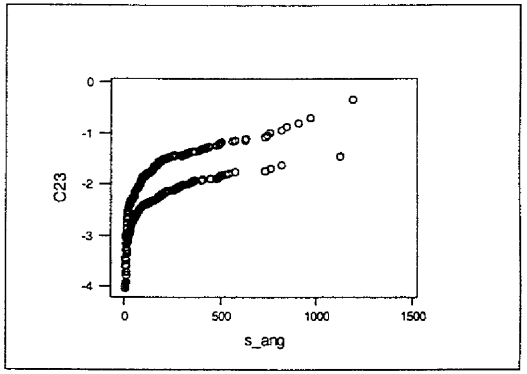
Plot 4-4-2-4: log minus log of survival functions under model of table 4-4-2-2 when Third heart sound with pers defines a two level stratification(checked or no). Small values are deleted.



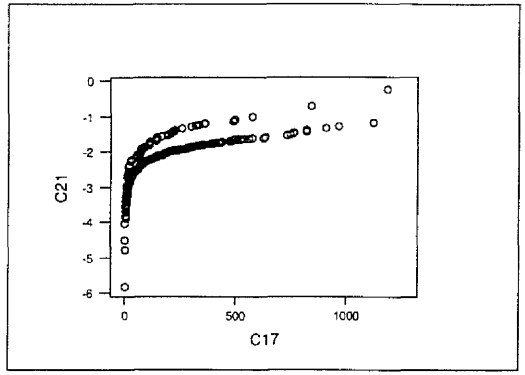
Plot 4-4-2-5: log minus log of survival functions under model of table 4-4-2-2 when Angina defines a two level stratification(yes or no).



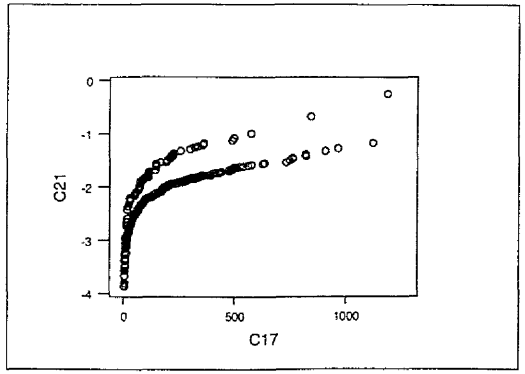
Plot 4-4-2-6: log minus log of survival functions under model of table 4-4-2-2 when Angina define a two level stratification(yes or no). Small values are deleted.



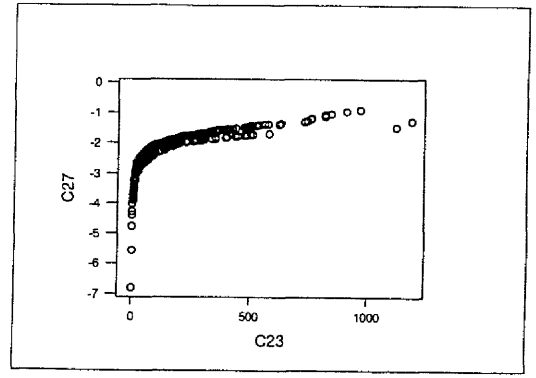
Plot 4-4-2-7: log minus log of survival functions under model of table 4-4-2-2 when Diabetes defines a two level stratification(yes or no).



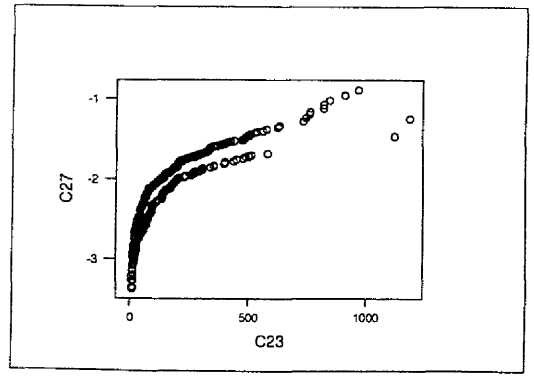
Plot 4-4-2-8: log minus log of survival functions under model of table 4-4-2-2 when Diabetes defines a two level stratification(yes or no). Small values are deleted.



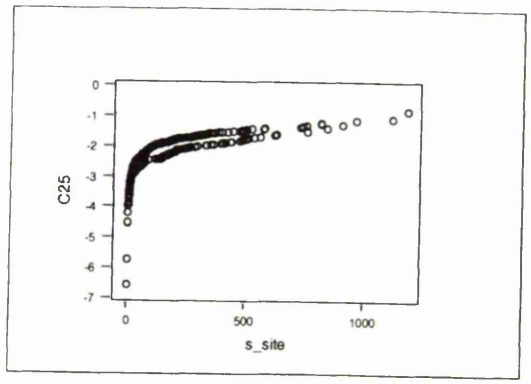
Plot 4-4-2-9: log minus log of survival functions under model of table 4-4-2-2 when Nyha is defines a two level stratification(class III or not).



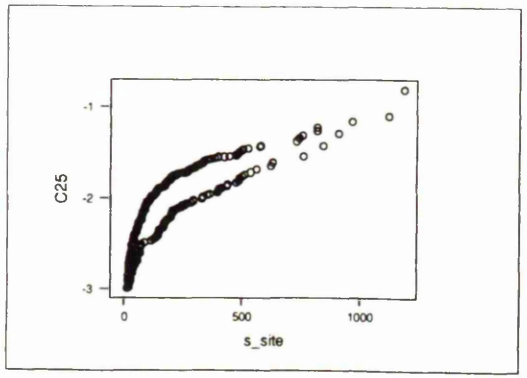
Plot 4-4-2-10: log minus log of survival functions under of table model 4-4-2-2 when Nyha defines a two level stratification(class III or not). Small values are deleted.



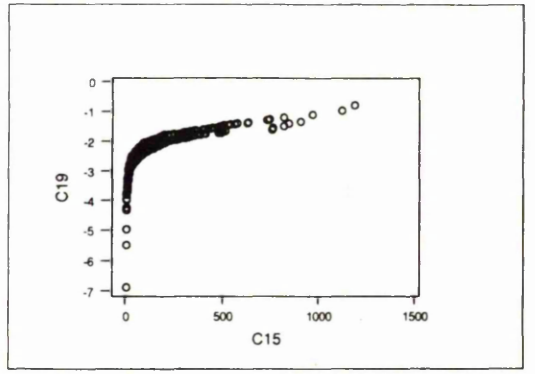
Plot 4-4-2-11: log minus log of survival functions under model of table 4-4-2-2 when Site defines a two level stratification(unclassified or no).



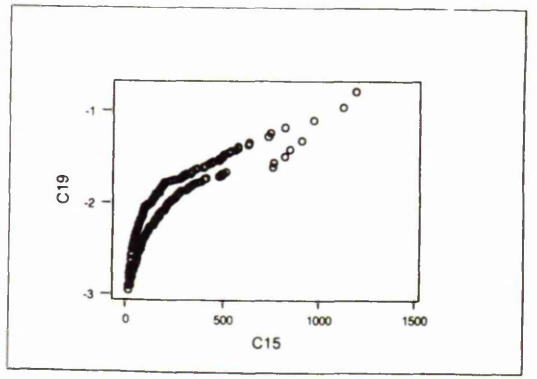
Plot 4-4-2-12: log minus log of survival functions under model of table 4-4-2-2 when Site defines a two level stratification(unclassified or no). Small values are deleted.



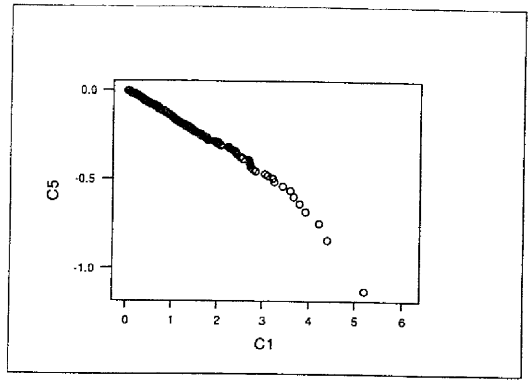
Plot 4-4-2-13: log minus log of survival functions under model of table 4-4-2-2 when 'Treatment' defines as a two level stratification(Placebo or Ramipril).



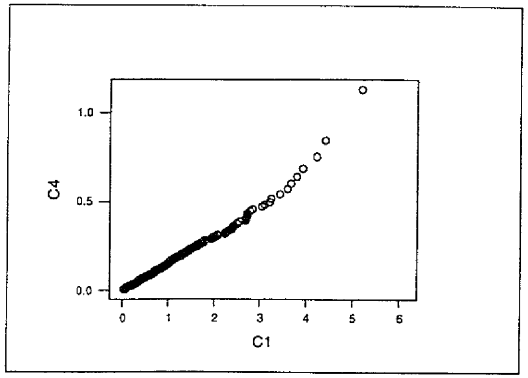
Plot 4-4-2-14: log minus log of survival functions under model of table 4-4-2-2 when Treatment defines a two level stratification(Placebo or Ramipril).Small values are deleted.



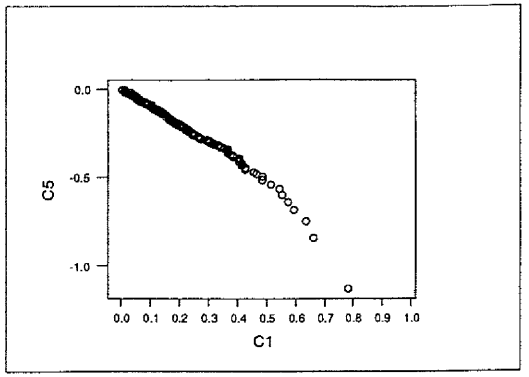
Plot 4-4-2-15: log 'survival' function of our residuals against these residuals for model of table 4-4-2-2.



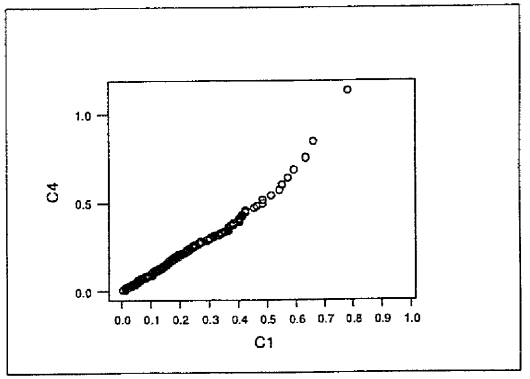
Plot 4-4-2-16: cumulative hazard function of our residuals against these residuals for model of table 4-4-2-2.



Plot 4-4-2-17: log 'survival' function of BMDP residuals against these residuals for model of table 4-4-2-2.



Plot 4-4-2-18: cumulative hazard function of BMDP residuals against these residuals for model of table 4-4-2-2.



4-5 : Cox Proportional Hazards Models Fitted to "Time from Registration Date to Time of Sudden Death or First Non validated Reinfarction" (Event No. 4) :

4-5-1 : Entering A Single Covariate (Event No. 4) :

In this section we fit another Cox Proportional Hazards model to a new 'survival' time which we label as end point number 4. Here the survival time is defined as the time interval between the registration date and the date of either sudden death or first non validated reinfarction. A non validated reinfarction is a heart event diagnosed by the other doctors in charge of a patient as a reinfarction but not confirmed as such by the committee.

Table 4-5-1-1 shows the Cox regression model fitted to this 'survival' time depending only on the covariate "Treatment". The coefficient of the "Treatment" in the model is -0.2158 with a standard error of 0.0995. Since the "Treatment" is coded as "0" or "1", respectively for those patients who were treated by the Placebo or Ramipril, and since the coefficient of "Treatment" in the fitted model is negative therefore it implies that the use of Ramipril has at any time point decreased the hazard of death or of having a non validated reinfarction. The model of table 4-5-1-1 suggests that the hazard of death or having a non validated

reinfarction for those patients treated by Ramipril is 0.8059 times that of those treated by the Placebo.

Plot 4-5-1-1 shows the estimated baseline survival function for the model of table 4-5-1-1. Note that this function stands for the survival function of those patients who were treated by the Placebo. To estimate the survival function for those patients who were treated by Ramipril, every value of the baseline survival function should be raised to the power of 0.8059. The reason is that

$$S(t) = [S_{\circ}(t)]^{\exp.(\beta Z)}$$

where $S_{\circ}(t)$ is the baseline survival function and we have $e^{\beta Z} = 0.8059$, $(Z=1)$.

Plot 4-5-1-2 shows the estimated cumulative baseline hazard function corresponding to the model of table 4-5-1-1. This function stands for the cumulative hazard function of those patients who were treated by the Placebo. To obtain the estimated cumulative hazard function of those patients who were treated by Ramipril, we should multiply the values of the baseline hazard function by the constant 0.8059.

To check the proportionality assumption in the model of table 4-5-1-1 we prepared plot 4-5-1-3. This shows the Log Minus Log of the estimated survival functions of those patients who were treated, respectively, by the Placebo and by Ramipril. These survival functions were estimated by using the Kaplan-Meier method. The values of LML of these two survival functions are too close to make any comment on the proportionality of hazards. Plot 4-5-1-4 shows the LML of the survival functions when extremely small values are deleted. This plot indicates that

the hazards of failure (i.e. hazard of sudden death or having a non validated reinfarction) for those patient who were treated by the Placebo and for those who were treated by Ramipril are reasonably proportional.

Plots 4-5-1-5 and 4-5-1-6 show, respectively, the logarithm of the survival function of BMDP's residuals and our residuals against the relevant residuals. Both of these plots suggest that the relation between the logarithm of the survival function of the residuals (either BMDP's residuals or our residuals) and the residuals is a straight line (through the origin) having an inverse relation with the relevant residuals. It implies that the distribution of the residuals (either BMDP's or our residuals) is exponential with parameter 1 and in turn indicates that the fitted model to end point number 4 (sudden death or first non validated reinfarction) fits well.

4-5-2 : Entering Several Covariates (Event No. 4) :

In this section it is intended to construct a Cox Proportional Hazards model depending on all significant covariates and the time interval between the registration date and the date of sudden death or first non validated reinfarction (end point 4).

Table 4-5-2-1 shows the fitted Cox regression model to the time interval between the registration date and the date of sudden death or first non validated reinfarction (end point 4). The exhaustive method was used to construct this model. The model indicates that six covariates treatment, age, Diabetes, Angina, Nyha_d2 (i.e class II, Yes or No) and ac4c (Third heart Sound with pers checked or Not) are the covariates which are significantly related to the specified survival time. Note that these are exactly the covariates which were significantly related to the time interval between the registration date and the date of first validated reinfarction (end point 3). The fitted model (of table 4-5-2-1) suggests that the use of Ramipril is significantly effective in decreasing the hazard of failure. This result is the same as that obtained from the model of table 4-5-1-1 (depending on the single covariate, "Treatment").

Table 4-5-2-2 shows another Cox Proportional hazards model fitted to the time interval between the registration date and the date of sudden death or first validated reinfarction. In this new model the stepwise method has been used to enter the covariates into the model. The differences between the exhaustive method and stepwise method in

constructing a model were explained in section 4-2-2. The model of table 4-5-2-2 indicates that in addition to the previous covariates which were included in the model of table 4-5-2-1, the covariate Site_d2 (i.e. Inferior, Yes or No) is also significantly related to the specified survival time. In this new model the covariate ac4c (Third heart Sound with pers, Checked or Not) was not entered into the model. This model suggests that older patients are more at risk of sudden death or of having a first non validated reinfarction than younger patients. The model suggests also that those who were treated by Ramipril are less at risk of failure than those patients who were treated by the Placebo. The covariates Diabetes, Angina, Site_d2 (i.e. Inferior, Yes or No) and Nyha_d2 (i.e. class II, Yes or No) are the other covariates which were entered by the Stepwise method.

Plots 4-5-2-1 and 4-5-2-2 show, respectively, the estimated baseline survival function and the estimated baseline cumulative hazard function corresponding to the model of table 4-5-2-2.

Plots 4-5-2-3 to 4-5-2-12 (10 plots) are available to investigate the validity of the proportional hazards assumption in the model of table 4-5-2-2. Each of these plots show the Log Minus Log of the survival functions at different levels of a particular covariate. These are the covariates which are included in the model. For each covariate two plots were prepared. The reason is that usually the values of LML of survival functions were too close and it was needed to delete some small hazard values to illustrate the parallel relationship of LML of survival functions. Plots 4-5-2-3 to 4-5-2-12 correspond, respectively , to Angina, Diabetes, Nyha_d2 (i.e. class II, Yes or No), Site_d2 (i.e. Inferior, Yes or No) and

treatment. In each of these plots we examine whether the proportionality of hazards assumption for the relevant covariate, is or is not valid. We remind the reader that the survival functions have been estimated by the Kaplan-Meier method and that the survival time is defined as the time interval between the registration date and the date of sudden death or first non validated reinfarction. These plots show that the proportionality of hazards assumption is a valid one .

To investigate the goodness of fit of the model 4-5-2-2, plots 4-5-2-13 to 4-5-2-16 were prepared. Plots 4-5-2-13 and 4-5-2-14 show, respectively, the logarithm of the survival function of our residuals and the cumulative hazard function of our residuals. Clearly both plots look linear but not with slopes -1 or 1 respectively. The residuals would appear to be exponentially distributed but not with parameter 1. This indicates that the model of table 4-5-2-2 does not fit well. Plots 4-5-2-15 and 4-5-2-16 are same plots as 4-5-2-13 and 4-5-2-14 but they have been prepared for BMDP's residuals. Once again, these two plots also look linear but not with slopes of -1 or 1 respectively. So both types of residuals (our residuals and BMDP's residuals) suggest that the Cox Proportional Hazards model fitted to the time interval between the registration date and the date of first non validated reinfarction does not fit well. This implies that there is doubt about the validity of the results obtained from the model of table 4-5-2-2.

Further tests were carried out to investigate whether the model of table 4-5-2-2 fits well or not. In these further tests we tested whether the distributions of the residuals (either our residuals or BMDP's residuals) at

different levels of a particular covariate are or are not significantly different. To have a good fit, these distributions (of the residuals) should not be significantly different. Note that in the previous paragraph we showed that the model of table 4-5-2-2 does not fit well. These further tests may provide some explanation as to why this is the case if they detect differences in the distribution of the residuals between different levels of a covariate. If they don't detect such differences then we are left with the conclusion that the residuals have a common distribution across the levels of the relevant covariate but that common distribution according to the previous results is not exponential. This situation might suggest that the influence of the covariate has been adequately captured by the model. Tables 4-5-2-3 to 4-5-2-7 show, respectively, the results of comparing the distributions of our residuals corresponding to different levels of the covariates which are included in model of table 4-5-2-2.These tables suggest that these distributions (of our residuals) are not significantly different. This implies that the residuals do not show any significant different pattern between in different levels of any of the covariates. So as far as the pattern of residuals at different levels of any of the covariates concerned, the model of table 4-5-2-2 fits reasonably. But note that we previously discovered that the residuals (our residuals) show that the model of table 4-5-2-2 does not fit well. Tables 4-5-2-8 to 4-5-2-12 are similar to tables as 4-5-2-3 to 4-5-2-7 but have been prepared for BMDP's residuals. These new tables suggest that the distribution of the BMDP's residuals corresponding different levels of the covariate Angina and Diabetes are significantly different while those corresponding to

different levels of the other covariates are not different. So the model could possibly be improved by the changing its dependence in some way on the significant covariates. However since we are more confident about our residuals and since there were no significant covariates in relation to them we conclude that the influence of the covariates has been adequately captured by the model.

Table 4-5-1-1 : Cox Proportional Hazard model fitted to time from registration date to sudden death or non validated re infarction. (single treatment covariate)

```
Log Likelihood = -2966.5987
Global Chi-Square = 4.72  d.f. = 1  P-value = 0.0298
```

Variable	Coeeficient	Standard Error	Coeff./S.E.	Exp(Coeff.)
Treatment	-0.2158	0.0995	- 2.1688	0.8059

Table 4-5-2-1 : Cox Proportional Hazard model fitted to time from registration date to sudden death or non validated re infarction. (all candidate covariates)

LOG LIKELIHOOD = -2909.0883
GLOBAL CHI-SQUARE = 121.31 D.F.= 18 P-VALUE =0.0000

VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF.)
treatment	-0.2239	0.0999	-2.2405	0.7994
age	0.0274	0.0055	4.9602	1.0278
sex	0.0964	0.1124	0.8577	1.1012
hyperten	0.0722	0.1094	0.6597	1.0748
diabet	0.4037	0.1331	3.0325	1.4974
pmi	0.1136	0.1207	0.9411	1.1203
angina	0.3902	0.1180	3.3071	1.4772
cardiac	-0.0832	0.1939	-0.4291	0.9202
site_d1	0.2641	0.5866	0.4503	1.3023
site_d2	0.0447	0.5885	0.0760	1.0458
wave_d1	-0.1639	0.6267	-0.2615	0.8489
wave_d2	-0.1774	0.6225	-0.2850	0.8374
nyha_d1	-0.3758	0.2292	-1.6398	0.6868
nyha_d2	-0.4542	0.1991	-2.2814	0.6349
nyha_d3	-0.2254	0.1967	-1.1458	0.7982
ac4a	0.2910	0.1605	1.8125	1.3377
ac4b	0.0469	0.1023	0.4579	1.0480
ac4c	0.2499	0.1145	2.1821	1.2839

Table 4-5-2-2 : Cox Proportional Hazard model fitted to time from registration date to sudden death or non validated re infarction. (Stepwise method)

LOG LIKELIHOOD = -2915.5207
GLOBAL CHI-SQUARE = 105.4 D.F.= 6 P-VALUE =0.0000

STEP NO	VARIABLE	DF	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF.)
1	age	1	0.0295	0.0052	5.6787	1.03300
2	angina	2	0.4797	0.1018	4.7133	1.6156
3	diabet	3	0.4653	0.1299	3.5829	1.5925
4	treatment	4	-0.2227	0.0996	-2.2873	0.7963
5	site_d2	5	-0.2302	0.1056	-2.1805	0.7944
6	nyha_d2	6	-0.2002	0.1014	-1.9753	0.8185

Table 4-5-2-3 : Comparing the distributions of our residuals for two levels of Angina for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1249	205	1044	0.84
level 2	701	201	500	0.71
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.417	1	0.2339	

Table 4-5-2-4 : Comparing the distributions of our residuals for two levels of Diabetes for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1716	335	1381	0.80
level 2	234	71	163	0.70
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	2.736	1	0.0981	

Table 4-5-2-5 : Comparing the distributions of our residuals for two levels of nyha_d2 (class II, Yes or Not) for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1037	237	800	0.77
level 2	913	169	744	0.81
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.705	1	0.4012	

Table 4-5-2-6 : Comparing the distributions of our residuals for two levels of Site_d2 (Inferior, Yes or no) for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1222	273	949	0.78
level 2	728	133	595	0.82
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.981	1	0.3219	

Table 4-5-2-7 : Comparing the distributions of our residuals for two levels of treatment for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	962	220	742	.077
level 2	988	186	802	0.81
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.835	1	0.3608	

Table 4-5-2-8 : Comparing the distributions of BMDP residuals for two levels of Angina for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1249	205	1044	0.84
level 2	701	201	500	0.71
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	20.419	1	0.0000	

Table 4-5-2-9 : Comparing the distributions of BMDP residuals for two levels of Diabetes for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1716	335	1381	0.80
level 2	234	71	163	0.70
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	8.191	1	0.0042	

Table 4-5-2-10 : Comparing the distributions of BMDP residuals for two levels of nyha_d2 i.e. class II, Yes or No) for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1037	237	800	0.77
level 2	913	169	744	0.81
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	3.87	1	0.0492	

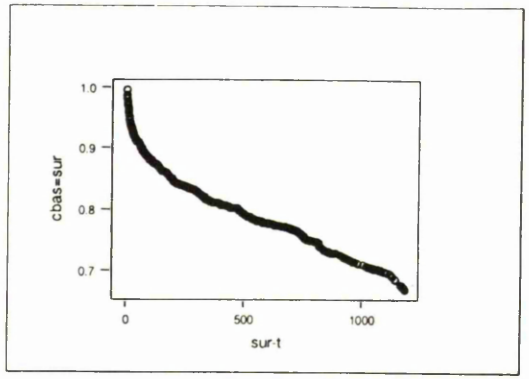
Table 4-5-2-11 : Comparing the distributions of BMDP residuals for two levels of Site_d2 (Inferior, Yes or No) for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1222	273	949	0.78
level 2	728	133	595	0.82
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.455	1	0.2277	

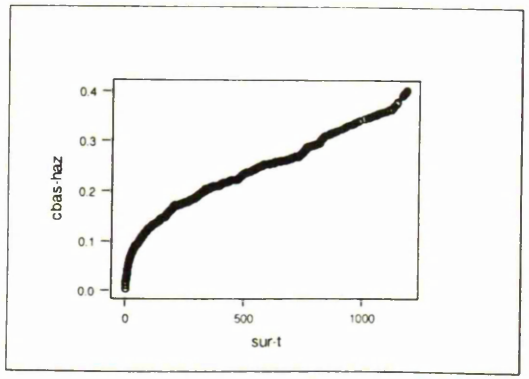
Table 4-5-2-12 : Comparing the distributions of BMDP residuals for two levels of treatment for time to sudden death or non validated reinfarction.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	962	220	742	.077
level 2	988	186	802	0.81
Total	1950	406	1544	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.683	1	0.1945	

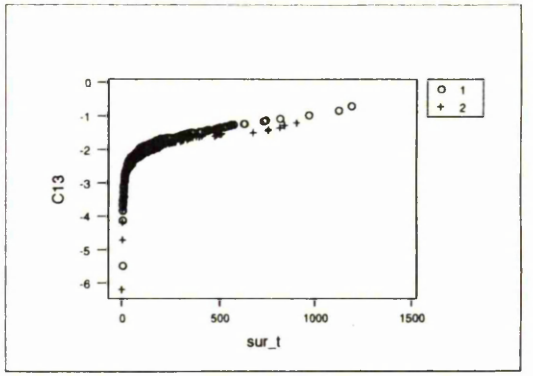
Plot 4-5-1-1: Estimated baseline survival function for model of table 4-5-1-1.



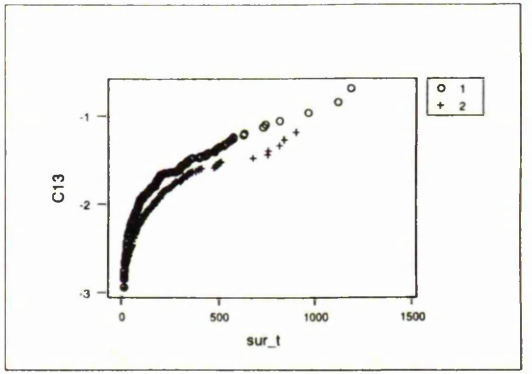
Plot 4-5-1-2: Estimated baseline cumulative hazard function for model of table 4-5-1-1.



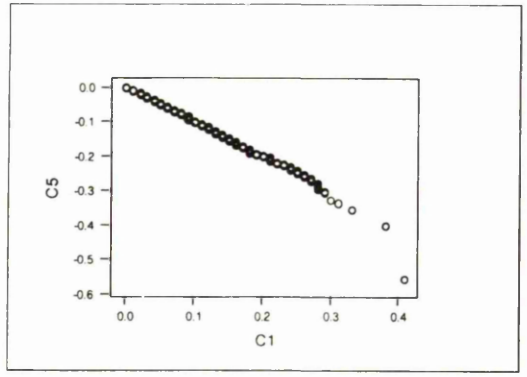
Plot 4-5-1-3: log minus log of survival functions for each treatments under model of table 4-5-1-1. (1:Placebo 2:Ramipril)



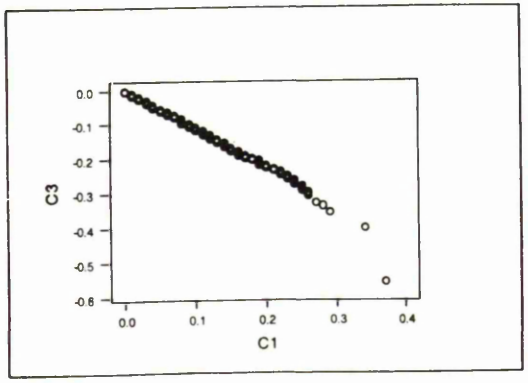
Plot 4-5-1-4: log minus log of survival function for each tratment under model of table 4-5-1-1(small values are deleted).1:Placebo 2:Ramipril



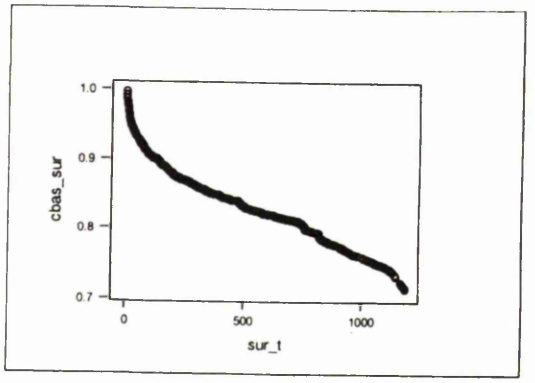
Plot 4-5-1-5: log 'survival' function of BMDP residuals against these residuals for model of table 4-5-1-1.



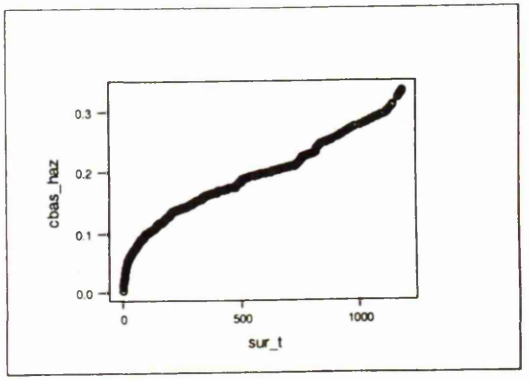
Plot 4-5-1-6: log 'survival' function of our residuals against these residuals for model of table 4-5-1-1.



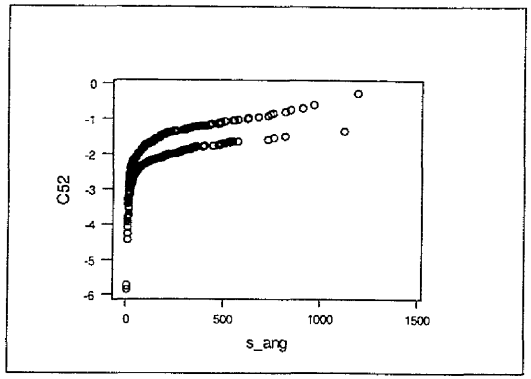
Plot 4-5-2-1: estimated baseline survival function for model of table 4-5-2-2.



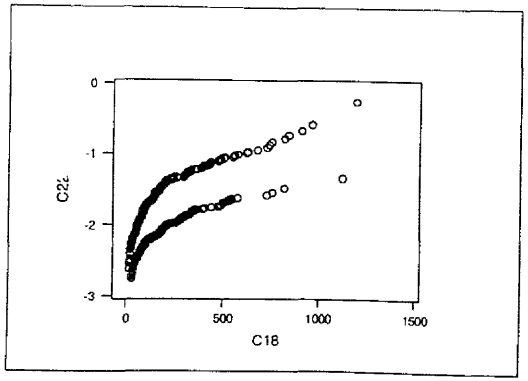
Plot 4-5-2-2: estimated baseline cumulative hazard function for model of table 4-5-2-2.



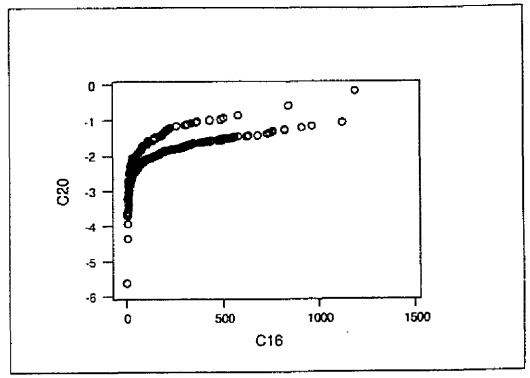
Plot 4-5-2-3: log minus log of survival functions under model of table 4-5-2-2 when Anginais defines a two level stratification(yes or not).



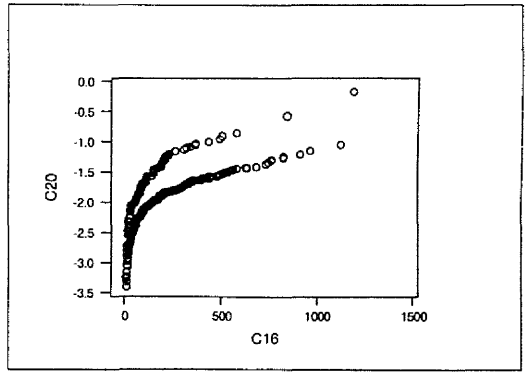
Plot 4-5-2-4: log minus log of survival functions under model of table 4-5-2-2 when Angina defines a two level stratification(yes or no). Small values are deleted.



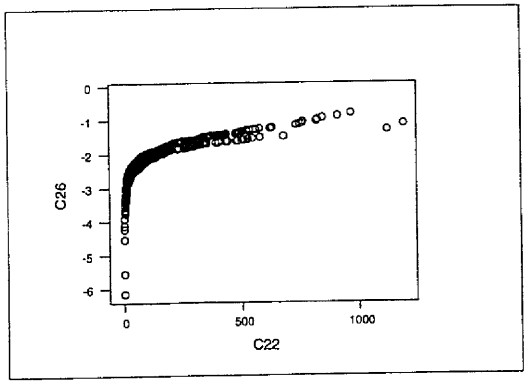
Plot 4-5-2-5: log minus log of survival functions under model of table 4-5-2-2 when Diabetes define a two level stratification(yes or not).



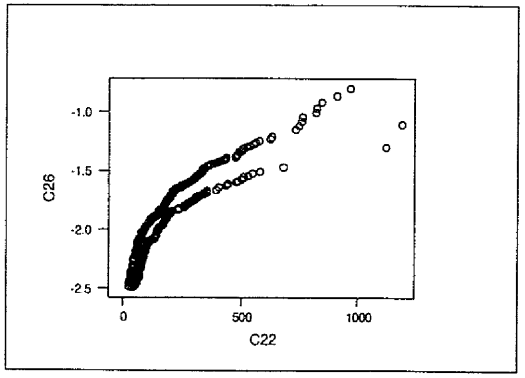
Plot 4-5-2-6: log minus log of survival functions under model of table 4-5-2-2 when Diabetes defines a two level stratification(yes or not). Small values are deleted.



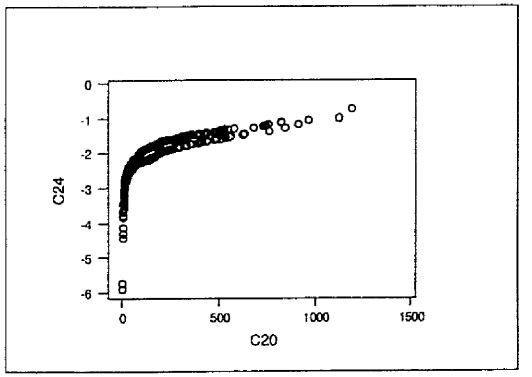
Plot 4-5-2-7: log minus log of survival functions under model of table 4-5-2-2 when Nyha defines a two level stratification(class II or not).



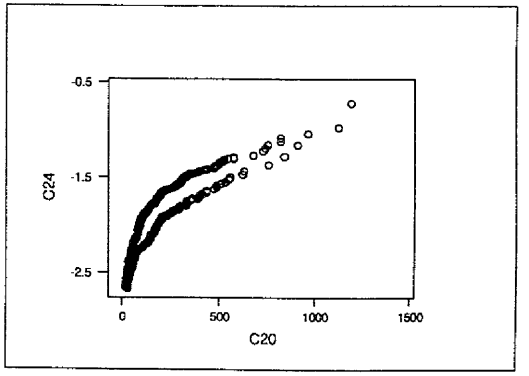
Plot 4-5-2-8: log minus log of survival functions under model of table 4-5-2-2 when Nyha defines a two level stratification(class II or not). Small values are deleted.



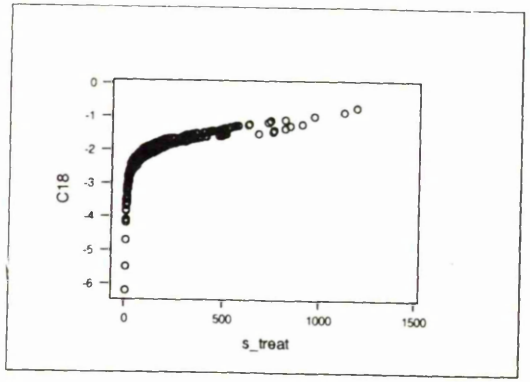
Plot 4-5-2-9: log minus log of survival functions under model of table 4-5-2-2 when Site defines a two level stratification(Inferior or not).



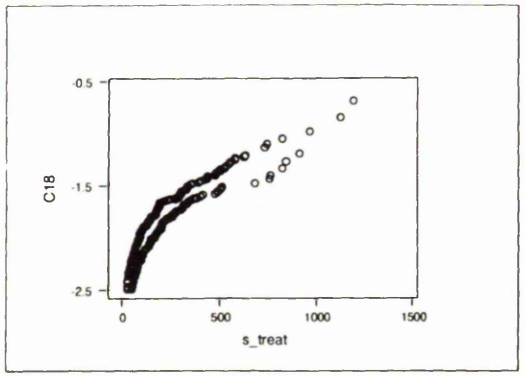
Plot 4-5-2-10: log minus log of survival functions under model of table 4-5-2-2 when Site defines a two level stratification.(Inferior or not) Small values are deleted.



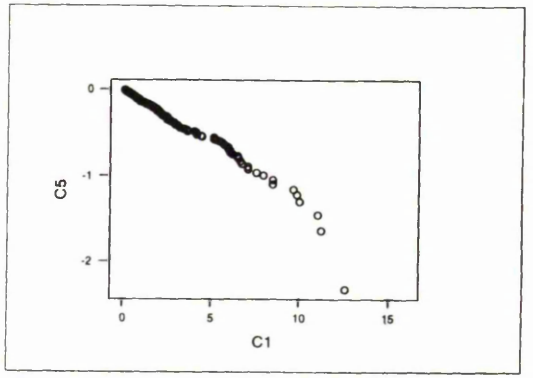
Plot 4-5-2-11: log minus log of survival functions under model of table 4-5-2-2 when treatment defines a two level stratification(Placebo or Ramipril).



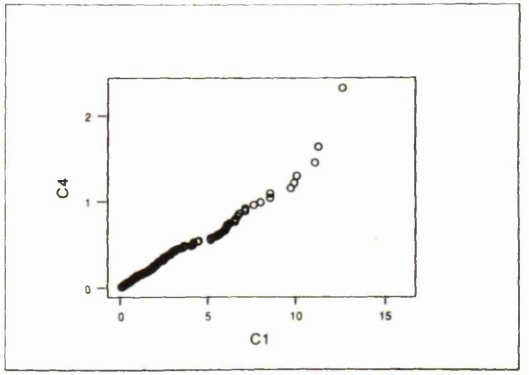
Plot 4-5-2-12: log minus log of survival functions under model of table 4-5-2-2 when treatment defines a two level stratification(Placebo or Ramipril).Small values are deleted



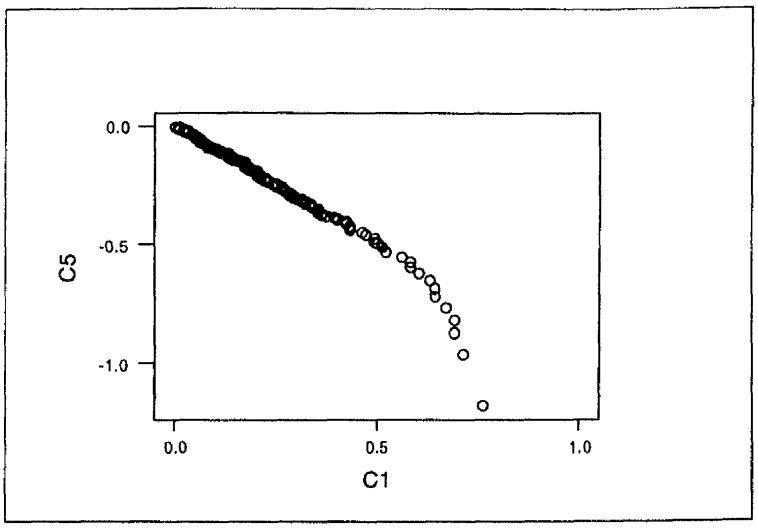
Plot 4-5-2-13: log 'survival' function of our residuals against these residuals for model of table 4-5-2-2.



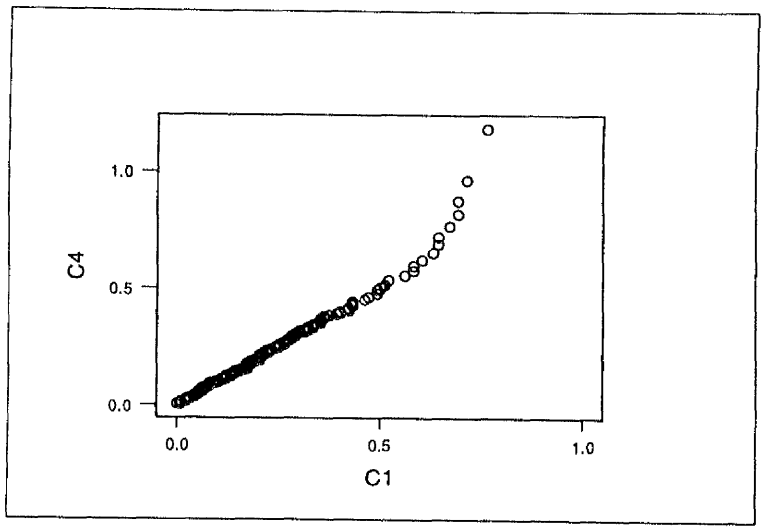
Plot 4-5-2-14: cumulative hazard function of our residuals against these residuals for model of table 4-5-2-2.



Plot 4-5-2-15: log 'survival' function of BMDP residuals against these residuals for model of table 4-5-2-2.



Plot 4-5-2-16: cumulative hazard function of BMDP residuals against these residuals for model of table 4-5-2-2.



4-6 : Cox Proportional Hazards Models Fitted to "Time from Registration Date to Time of Sudden Death or First validated Reinfarction or Chest Pain " (Event No. 5) :

4-6-1 : Entering A Single Covariate (Event No. 5) :

In this section we fit a Cox regression model depending on the single covariate "Treatment" to the time interval between the registration date and the date of sudden death or first validated infarction or chest pain. The fitted Cox Proportional model is shown in table 4-6-1-1. The coefficient is -02172 with a standard error of .0933 since the coefficient of the model is negative and those patients treated by the Placebo have been coded as "0" (and those treated by Ramipril were coded as "1"), therefore we can claim that the use of Ramipril has prolonged survival time. The model suggests that the hazard of those patients who were treated by Ramipril is always 0.8048 times the hazard of those treated by the Placebo. Note this suggests that, at any time point, those patients who were treated by Ramipril have less chance of failure than those who were treated the by Placebo.

Plot 4-6-1-1 shows the estimated baseline survival function under this model. This function stands for the survival function of those patients who were treated by the Placebo. To obtain the survival function of those

patients who were treated by Ramipril, every value of this baseline survival function should be raised to the power of 0.8048. The mathematical reason was discussed in section 4-2-1. Plot 4-6-1-1 shows that the probability of failure, for those patients who were treated by the Placebo, decreases in the first days after registration very rapidly to .90 but those patients who survive in these critical days have good survival prospects the probability of survival beyond 2 years after registration being about 0.60.

Plot 4-6-1-2 shows the cumulative hazard function estimated under this model. Since those patients who were treated by the Placebo are coded as "0", therefore plot 4-6-1-2 shows the cumulative hazard function of such patients. To obtain the cumulative hazard function of the patients treated by Ramipril, we should multiple every value of the baseline cumulative hazard function by the constant 0.8048. Plot 4-6-1-2 suggests that the rate of increase in the hazard of failure in the first days after registration date is very sharp, and then this rate levels off until about 2 years after registration. After two years from the registration date, once again the rate of increase in the hazard of failure changes sharply.

To investigate the validity of the proportionality of hazards assumption between those patients who were treated by the Placebo with that of those who were treated by Ramipril plot 4-6-1-3 was prepared. This plot shows the LML of the survival functions of the patients who were treated by the placebo and by Ramipril. These survival functions were estimated by Kaplan-Meier method. Unfortunately the values of the LML of these survival functions are too close to make any comment about

any parallel relationship. Plot 4-6-1-4 is actually the same plot as 4-6-1-3 but with extremely small LML values deleted. This plot suggests that the hazard of the two groups of patients are more or less parallel (they have not crossed each other). Hence the proportionality of hazards assumption is valid.

Plots 4-6-1-5 and 4-6-1-6 show, respectively, the logarithm of the survival function of BMDP's residuals and of our residuals (both residuals should be Cox-Snell residuals) against the relevant residuals. Both plots 4-2-1-6 and 4-2-1-7 indicate that the log survival function of the Cox-Snell residuals is linear. This property implies, whichever of the residuals is the correct one, that the residuals have an exponential distribution with parameter 1(except possibly for the last patients). This indicates that the model of table 4-6-1-1 fits well to the time interval from the registration date to the date of sudden death or first validated reinfarction or chest pain (End point No. 5). This implies that our conclusion regarding comparisons between the survival times of the two groups of patients are reliable.

4-6-2 : Entering Several Covariates (Event No. 5) :

In this section it is intended to construct a Cox Proportional Hazards model depending on additional covariates for the time interval between the registration date and the date of sudden death or first validated reinfarction or chest pain (end point 5).

Table 4-6-2-1 shows the Cox regression model fitted to this time interval. The exhaustive method was used to construct this model. The model indicates that six covariates treatment, age, Angina, Nyha_d1 (i.e. class I, Yes or Not), Nyha_d2 (i.e. class II, Yes or Not) and ac4c (Third heart Sound with pers, Checked or Not) are the covariates which are significantly related to the specified survival time. The fitted model (that of table 4-6-2-1) suggests that the use of Ramipril is significantly effective in decreasing the hazard of failure. This result is the same as that obtained from the model of table 4-6-1-1 (the model with the single covariate, "Treatment").

Table 4-6-2-2 shows another Cox Proportional hazards model fitted to the time interval between the registration date and the date of sudden death or first validated reinfarction or chest pain. In this new model the stepwise method has been used to enter the covariates into the model. The differences between the exhaustive method and stepwise method in constructing a model was explained in section 4-2-2. Comparing this new model with the model of table 4-6-2-1, the covariates Nyha_d1 (i.e. class I, Yes or Not), Nyha_d2 (i.e. class II, Yes or No) are

not entered in the new model instead of them the two covariates Nyha_d3 (i.e. class III, Yes or No) and Site_d1 (i.e. Anterior, Yes or No) are included. This model (of table 4-6-2-2) suggests that, at any time point, older patients are more at risk of sudden death or having first validated reinfarction or of having chest pain than younger patients. The model suggests also that those who were treated by Ramipril are less at risk of 'failure' than those patients treated by the Placebo.

Plots 4-6-2-1 and 4-6-2-2 show, respectively, the estimated baseline survival function and the estimated baseline cumulative hazard function corresponding to the model of table 4-6-2-2.

Plots 4-6-2-3 to 4-6-2-12 (10 plots) are prepared to investigate the validity of the proportional hazards assumption of the model of table 4-6-2-2. Each of these plots show the Log Minus Log of the survival functions at different levels of a particular covariate. These are the covariates which are included in the model. For each covariate two plots were prepared. The reason is that usually the values of LML of survival functions were too close and it was needed to delete some small LML values to explore for a parallel relationship of the LML of the survival functions. Plots 4-6-2-3 to 4-6-2-12 are, respectively , corresponding to ac4c (Third heart Sound with pers, Checked or Not), Angina, Nyha_d3 (i.e. class III, Yes or No), Site_d1 (i.e. Anterior, Yes or No) and treatment. In each of these plots we examine whether the proportionality assumption of the hazards for one of these covariates, is or is not valid. We remind the reader that the survival functions have been estimated by the Kaplan-Meier method and that the survival time is defined as the time interval between the

registration date and the date of sudden death or first validated reinfarction or chest pain. These plots show that the proportionality of hazards assumption is a valid one .

To investigate the goodness of fit of the model 4-6-2-2, plots 4-6-2-13 to 4-6-2-16 were prepared. Plots 4-6-2-13 and 4-6-2-14 show, respectively, the logarithm of survival function of our residuals and the cumulative hazard function of our residuals. Clearly both plots look linear but not with slopes 1 or -1 respectively. The residuals would appear to be exponentially distributed but not with parameter 1. This indicates that the model of table 4-6-2-2 does not fit well. Plots 4-6-2-15 and 4-6-2-16 are the same plots as 4-6-2-13 and 4-6-2-14 but they have been prepared for BMDP's residuals. Once again, these two plots also look linear but not with slopes 1 or -1 respectively. i.e. the model of table 4-6-2-2 does not fit well. So both types of residuals (our residuals and BMDP's residuals) suggest that the Cox Proportional Hazards model fitted to the time interval between the registration date and the date of first validated reinfarction or chest pain does not fit well.

Further tests were carried out to investigate whether the model of table 4-6-2-2 fits well to survival times or not. In these further tests we tested whether the distributions of the residuals (either our residuals or BMDP's residuals) corresponding to different levels of a particular covariate are or are not significantly different. To have a good fit, these distributions should not be significantly different. Note that in the previous paragraph we showed that the model of table 4-6-2-2 does not fit well. These further tests may provide some explanation as to why this is

the case if they detect differences in the distributions of the residuals between different levels of a covariates. If they don't detect such differences then we are left with the conclusion that the residuals have a common distributions across the levels of the relevant covariate but that common distribution according to the previous results is not exponential. This situation might suggest that the influence of the covariate has been adequately captured by the model. Tables 4-6-2-3 to 4-6-2-7 show, respectively, the results of comparing the survival functions of our residuals corresponding to different levels of the covariates which are included in model of table 4-6-2-2. These tables suggest that these distributions of our residuals are not significantly different. This implies that the residuals do not show any significant relationship with the levels of the covariates and the model of table 4-6-2-2 fits well in this respect. But note that we previously discovered that the residuals (our residuals) show that the model of table 4-6-2-2 does not fit well. Tables 4-6-2-8 to 4-6-2-12 are similar to tables 4-6-2-3 to 4-6-2-7 but have been prepared for BMDP's residuals. These new tables suggest that the distributions of BMDP's residuals corresponding to different levels of the covariate Angina and Nyha_d3 (i.e. class III, Yes or No) are significantly different while those which are due to different levels of the other covariates are not different. So the model could possibly be improved by the changing its dependence in some way on the significant covariates.. However since we are more confident about our residuals and since there were no significant covariates in relation to them we conclude that the influence of the covariates has been adequately captured by the model.

Table 4-6-1-1 : Cox Proportional Hazard model fitted to time from registration date to sudden death or validated re infarction or chest pain. (single treatment covariate)

Log Likelihood = -3349.0521
Global Chi-Square = 5.45 d.f. = 1 P-value = 0.0196

Variable	Coeeficient	Standard Error	Coeff./S.E.	Exp(Coeff.)
Treatment	-0.2172	0.0933	- 2.3291	0.8048

Table:4-6-2-1 : Cox Proportional Hazard model fitted to time from registration date tosudden death or validated re infarction or chest pain. (all candidate covariates)

LOG LIKELIHOOD = -3297.2193
GLOBAL CHI-SQUARE = 109.68 D.F.= 18 P-VALUE =0.0000

VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF.)
age	0.0202	0.0051	3.9675	1.0204
sex	0.0709	0.1073	0.6605	1.0734
treatment	-0.2317	0.0937	-2.4723	0.7932
hyperten	-0.0033	0.1044	-0.0317	0.9967
diabet	0.1879	0.1350	1.3919	1.2067
pmi	0.0929	0.1145	0.8120	1.0974
angina	0.2989	0.1110	2.6935	1.3484
cardiac	-0.0660	0.1850	-0.3568	0.9361
nyha_d1	-0.5785	0.2227	-2.5978	0.5607
nyha_d2	-0.5670	0.1952	-2.9043	0.5672
nyha_d3	-0.1613	0.1909	-0.8451	0.8510
site_d1	0.3002	0.5856	0.5127	1.3502
site_d2	0.0943	0.5872	0.1606	1.0989
wave_d1	0.0990	0.6318	0.1566	1.1040
wave_d2	0.0077	0.6284	0.0123	1.0077
ac4a	0.2645	0.1478	1.7893	1.3028
ac4b	-0.0711	0.0956	-0.7435	0.9314
ac4c	0.2453	0.1075	2.2812	1.2780

Table:4-6-2-2 : Cox Proportional Hazard model fitted to time from registration date to sudden death or validated re infarction or chest pain. (Stepwise method)

LOG LIKELIHOOD = -3305.7126
GLOBAL CHI-SQUARE = 89.58 D.F.=6 P-VALUE =0.0000

Step No.	VARIABLE	df	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF.)
1	age	1	0.0232	0.0048	4.8290	1.0235
2	angina	2	0.3835	0.1014	3.7833	1.4675
3	nyha_d3	3	0.3338	0.1069	3.1234	1.3962
4	treatment	4	-0.2436	0.0934	-2.6065	0.7838
5	site_d1	5	0.2367	0.0963	2.4580	1.2671
6	ac4c	6	0.2115	0.1046	2.0231	1.2356

Table 4-6-2-3 : Comparing the distributions of our residuals for two levels of ac4c (Third heart sound with pers, Checked or Not) for time to sudden death or validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1480	346	1134	0.77
level 2	464	117	347	0.75
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.621	1	0.2029	

Table 4-6-2-4 : Comparing the distributions of our residuals for two levels of Angina for time to sudden death or validated re infarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1240	264	976	0.79
level 2	704	199	505	0.72
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	2.011	1	0.1561	

Table 4-6-2-5 : Comparing the distributions of our residuals for two levels of nyha_d3 (i.e. class III, Yes or No) for time to sudden death or validated re infarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1492	327	1165	0.78
level 2	452	136	316	0.70
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.552	1	0.2128	

Table 4-6-2-6 : Comparing the distributions of our residuals for two levels of Site_d1 (Anterior, Yes or No) for time to sudden death or validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	820	174	646	0.79
level 2	1124	289	835	0.74
Total	1124	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.000	1	0.9932	

Table 4-6-2-7 : Comparing the distributions of our residuals for two levels of treatment for time to sudden death or validated re infarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	958	250	708	0.74
level 2	986	213	773	0.78
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.075	1	0.7839	

Table 4-6-2-8 : Comparing the distributions of BMDP residuals for two levels of ac4c (Third heart sound with pers, Checked or Not) for time to sudden death or validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1480	346	1134	0.77
level 2	464	117	347	0.75
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.052	1	0.8203	

Table 4-6-2-9 : Comparing the distributions of BMDP residuals for two levels of Angina for time to sudden death or validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1240	264	976	0.79
level 2	704	199	505	0.72
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	11.150	1	0.0008	

Table 4-6-2-10: Comparing the distributions of BMDP residuals for two levels of nyha_d3 (i.e. class III, Yes or no) for time to sudden death or validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1492	327	1165	0.78
level 2	452	136	316	0.70
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	7.376	1	0.0066	

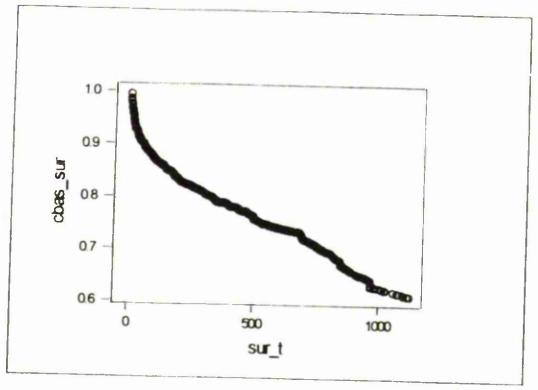
Table 4-6-2-11 : Comparing the distributions of BMDP residuals for two levels of site_d1 (Anterior, Yes or No) for time to sudden death or validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	820	174	646	0.79
level 2	1124	289	835	0.74
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	2.664	1	0.1026	

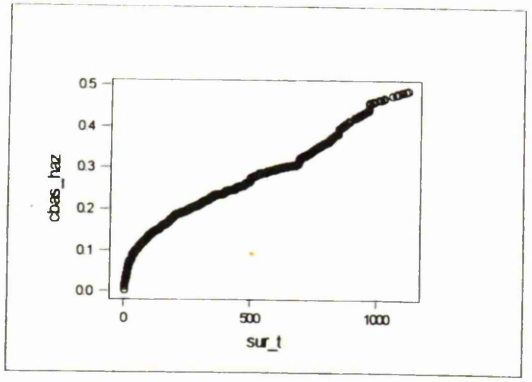
Table 4-6-2-12 : Comparing the distributions of BMDP residuals for two levels of treatment for time to sudden death or validated re infarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	958	250	708	0.74
level 2	986	213	773	0.78
Total	1944	463	1481	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	2.001	1	0.1572	

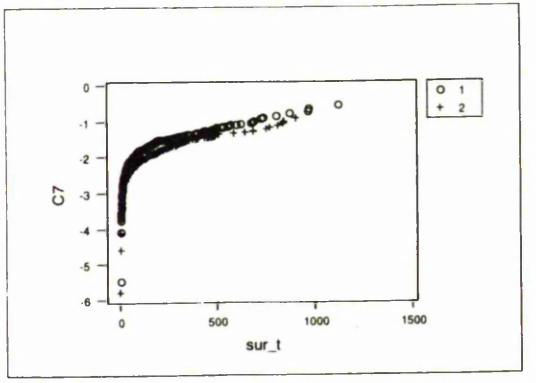
Plot 4-6-1-1: Estimated baseline survival function for model of table 4-6-1-1.



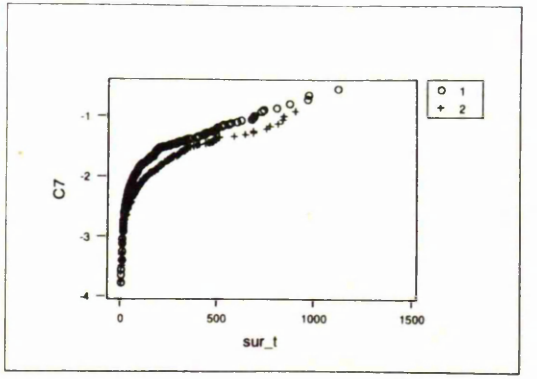
Plot 4-6-1-2: Estimated baseline cumulative hazard function for model of table 4-6-1-1.



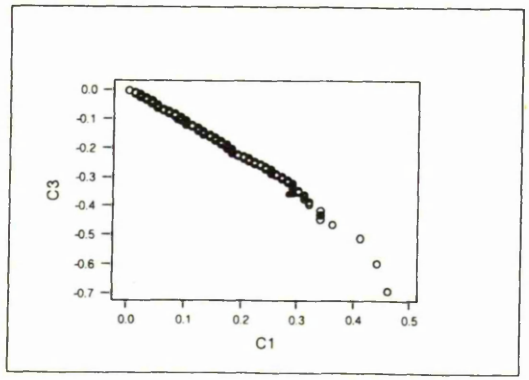
Plot 4-6-1-3: log minus log of survival functions for each treatment under model of table 4-6-1-1. (1:Placebo 2:Ramipril)



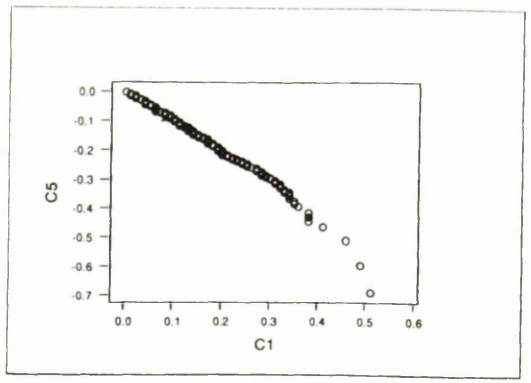
Plot 4-6-1-4: log minus log of survival function for each tratment under model of table 4-6-1-1(small values are deleted).1:Placebo 2:Ramipril



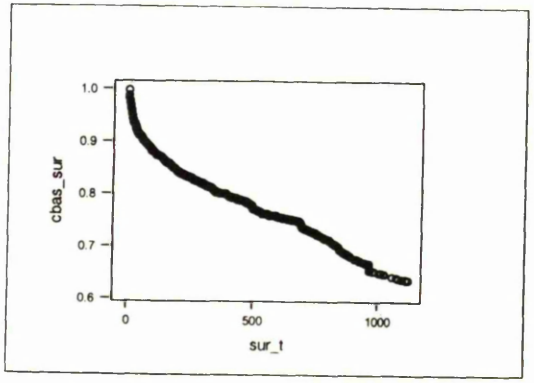
Plot 4-6-1-5: log 'survival' function of BMDP residuals against these residuals for model of table 4-6-1-1.



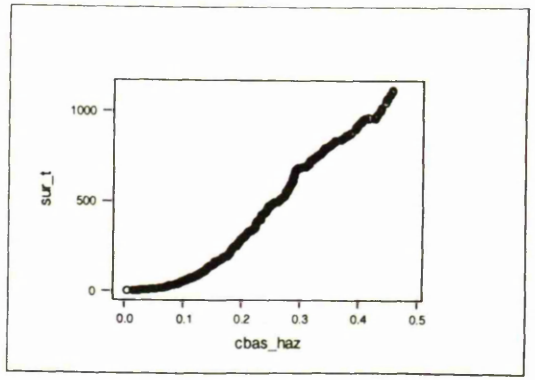
Plot 4-6-1-6: log 'survival' function of our residuals against these residuals for model of table 4-6-1-1.



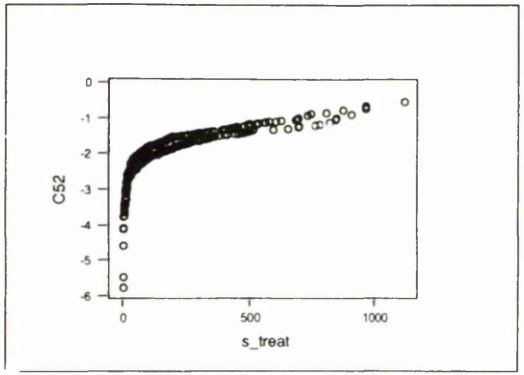
Plot 4-6-2-1: estimated baseline survival function for model of table 4-6-2-2.



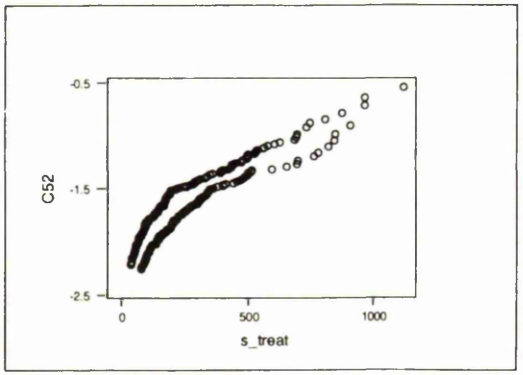
Plot 4-6-2-2: estimated baseline cumulative hazard function for model of table 4-6-2-2.



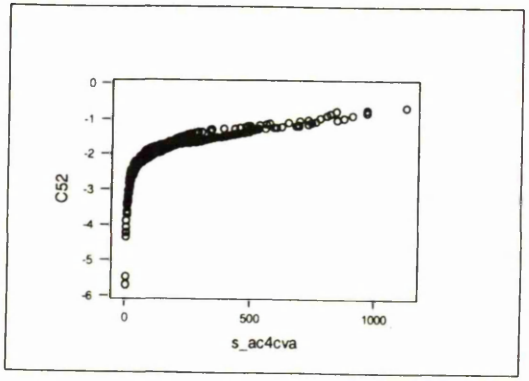
Plot 4-6-2-3: log minus log of survival functions under model of table 4-6-2-2 when treatment defines a two level stratification. (Placebo or Ramipril)



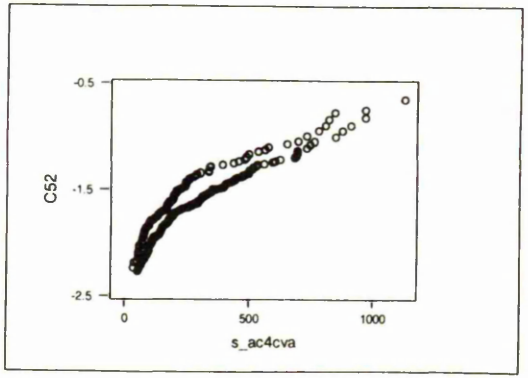
Plot 4-6-2-4: log minus log of survival functions under model of table 4-6-2-2 when treatment defines a two level stratification(Placebo or Ramipril). Small values are deleted.



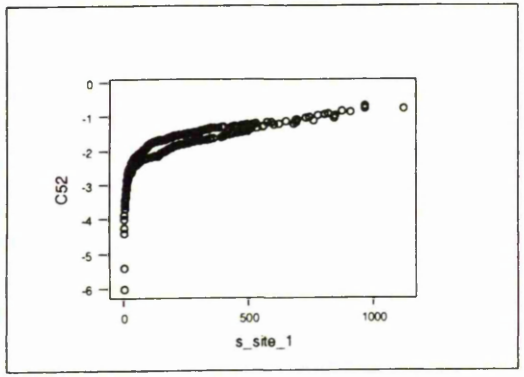
Plot 4-6-2-5: log minus log of survival functions under model of table 4-6-2-2 when Third heart sound with pers defines a two level stratification(checked or not).



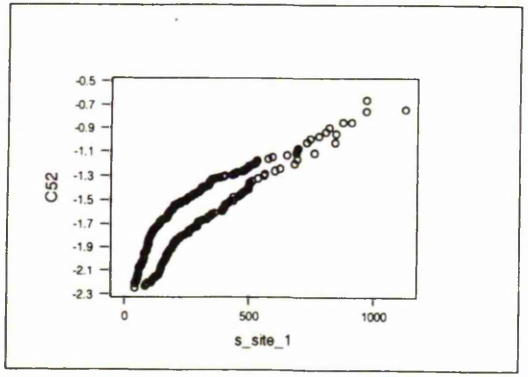
Plot 4-6-2-6: log minus log of survival functions under model of table 4-6-2-2 when Third heart sound with pers defines a two level stratification(checked or not).Small values are deleted.



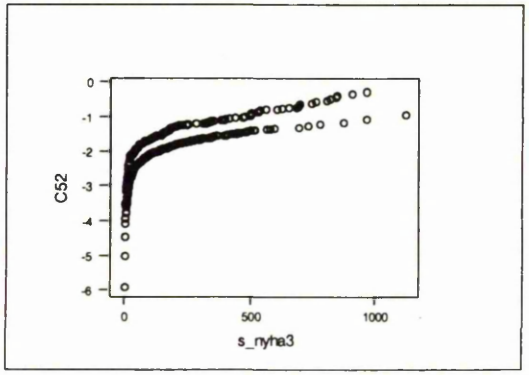
Plot 4-6-2-7: log minus log of survival functions under model of table 4-6-2-2 when Site defines a two level stratification(Anterior or not).



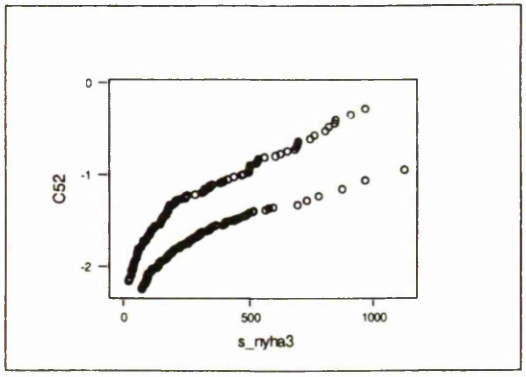
Plot 4-6-2-8: log minus log of survival functions under model of table 4-6-2-2 when Site defines a two level stratification(Anterior or not). Small values are deleted.



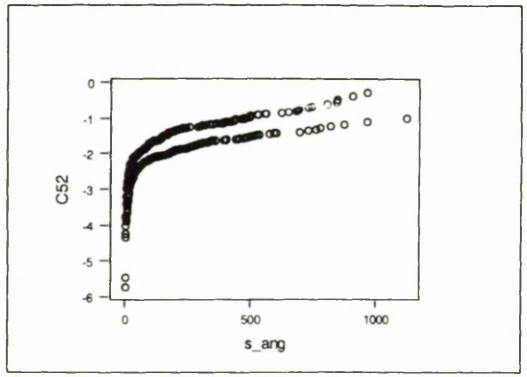
Plot 4-6-2-9: log minus log of survival functions under model of table 4-6-2-2 when Nyha defines a two level stratification(class I or not).



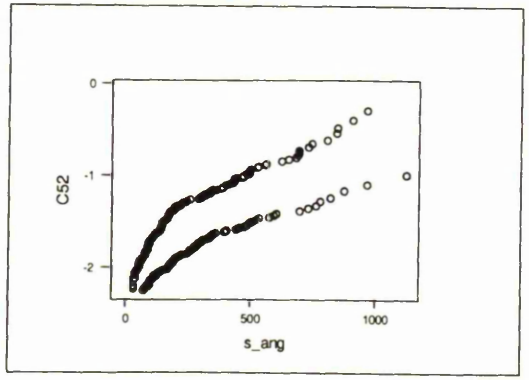
Plot 4-6-2-10: log minus log of survival functions under model of table 4-6-2-2 when Nyha defines a two level stratification(class I or not) Small values are deleted.



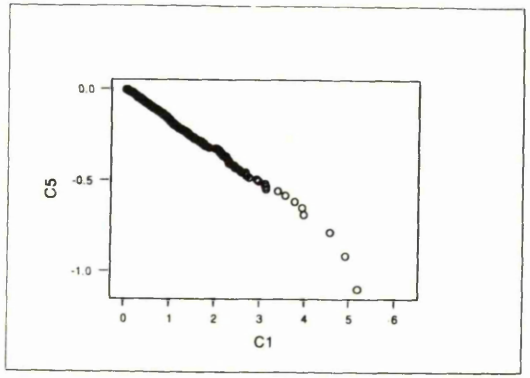
Plot 4-6-2-11: log minus log of survival functions under model of table 4-6-2-2 when Angina defines a two level stratification.(yes or no).



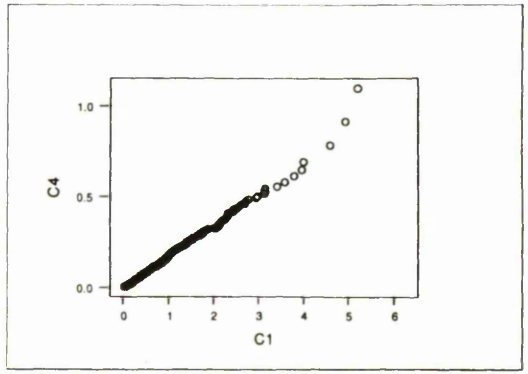
Plot 4-6-2-12: log minus log of survival functions under model of table 4-6-2-2 when Angina defines a two level stratification(yes or no). Small values are deleted



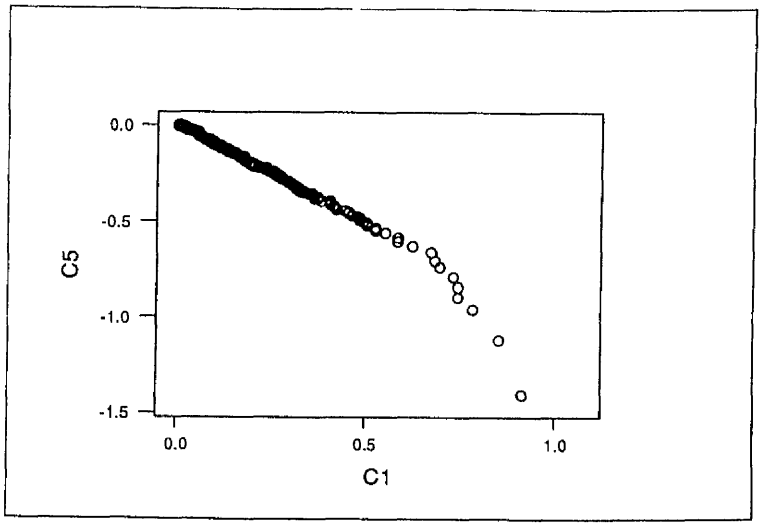
Plot 4-6-2-13: log 'survival' function of our residuals against these residuals for model of table 4-6-2-2.



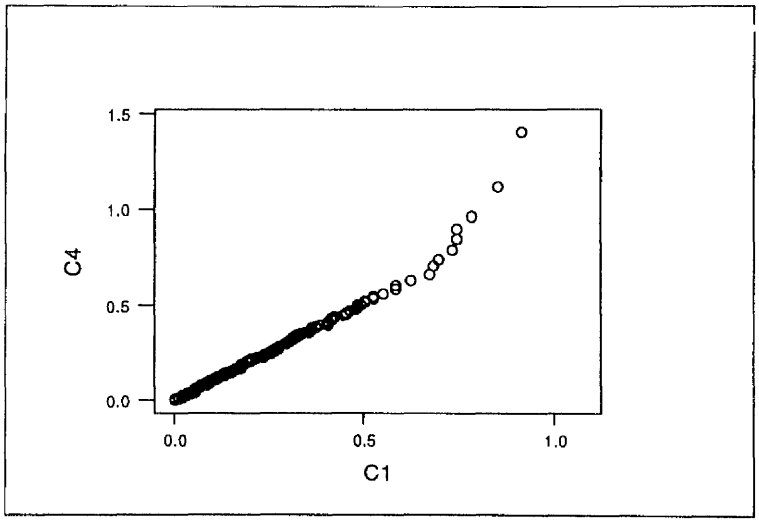
Plot 4-6-2-14: cumulative hazard function of our residuals against these residuals for model of table 4-6-2-2.



Plot 4-6-2-15: log 'survival' function of BMDP residuals against these residuals for model of table 4-6-2-2.



Plot 4-6-2-16: cumulative hazard function of BMDP residuals against these residuals for model of table 4-6-2-2.



4-7 : Cox Proportional Hazards Models Fitted to "Time from Registration Date to Time of Sudden Death or First non validated Reinfarction or Chest Pain " (Event No. 6) :

4-7-1 : Entering A Single Covariate (Event No. 6) :

Here we fit a Cox Proportional Hazards model depending on the covariate "Treatment" to the time interval from the registration date to the date of sudden death or first non validated reinfarction or chest pain (end point No. 6). Table 4-7-1-1 shows the fitted model. of sudden death or first non validated reinfarction or chest pain .The coefficient of the model is -0.228 with a standard error of 0.0899. Considering the fact that those patients who were treated by the Placebo are coded as "0", this implies that the hazard of failure, at a any time point, for those patients treated by Ramipril is significantly less than those who were treated by the Placebo i.e. those patients who were treated by Ramipril are less at risk of failure than those who were treated by the Placebo. Note Ramipril has been effective in prolonging survival times. The model suggests that at each particular time interval from the registration date, the hazard of failure for those patients who were treated by Ramipril is 0.7961 times the hazard of those treated by the Placebo.

Plot 4-7-1-1 shows the estimated baseline survival function (according to the Cox Proportional Hazards model). Note that since the covariate "Treatment" is coded as "0" and "1" and code "0" corresponds to the patients treated by the Placebo, therefore this baseline survival function stands for the survival function of those patients who were treated by the Placebo. This baseline survival function suggests that the chance of still 'surviving' i.e. the probability of not being dead or having a non validated reinfarction (as the first one) or chest pain decreases very rapidly in the first days after registration. The plot suggests that nearly 90% of patients pass these critical days. It also shows that at 2 years after registration, death or first non validated reinfarction or chest pain has not occurred yet for more than 65% of the patients.

Plot 4-7-1-2 shows the estimated cumulative baseline hazard function for model of table 4-7-1-1. Once again, since the covariate "Treatment" is coded as "0" and "1" and the code "0" stands for those patients who have been treated by the Placebo. Therefore this cumulative baseline hazard function stands for the cumulative hazard function for those patients who were treated by the Placebo. The cumulative hazard function of those patients who were treated by Ramipril can be obtained by multiplying the baseline hazard function by the constant 0.7961.

To investigate the validity of the proportionality of hazards assumption of the model 4-7-1-1, plot 4-7-1-3 was prepared. This plot shows the Log Minus Log of both survival functions (of those patients who were treated by Ramipril and of those who were treated by the Placebo) against survival times. Since the LML of both survival functions

are too close together it was difficult to make any comment about proportionality of hazards. Therefore plot 4-7-1-4 was prepared. This plot indicates that the hazards of having a non validated reinfarction (as the first one) for those patients who were treated by the Placebo and those who were treated by Ramipril are more or less parallel. This implies that the proportionality of hazards assumption is valid for the model of table 4-7-1-1.

Plots 4-7-1-5 and 4-7-1-6 show, respectively, the logarithm of the survival function of BMDP's residuals and our residuals against the relevant residuals. Both plots suggest that the relation between the logarithm of survival function of the residuals (either BMDP's residuals or our residuals) and the relevant residuals is a straight line (through the origin) . This implies that the distribution of the residuals (either BMDP's or our residuals) is exponential with parameter 1(except possibly for few last patients). It indicates the fitted model to end point number 6 (time to sudden death or first non validated reinfarction or chest pain) fits well to the data.

4-7-2 : Entering Several Covariates (Event No. 6) :

Table 4-7-2-1 shows the Cox regression model fitted to the time interval between the registration date and date of sudden death or first non validated reinfarction or chest pain (end point No. 6). The exhaustive method was used to construct this model. This model indicates that five covariates; treatment, age, Angina, Nyha_d1 i.e. (class I, Yes or No) and Nyha_d2 (i.e. class II, Yes or No) are the only covariates which are significantly related to the specified survival time. The fitted model (the model of table 4-7-2-1) suggests that the use of Ramipril is significantly effective in decreasing the hazard of failure. This result is the same as that obtained from the model of table 4-7-1-1 (the same model with a single covariate, "Treatment").

Table 4-7-2-2 shows another Cox Proportional hazards model fitted to the specified time interval. In this new model the stepwise method has been used to enter covariates into the model. The differences between the exhaustive method and stepwise method in constructing a model was explained in section 4-2-2. Comparing this new model with the model of table 4-7-2-1, the covariates Nyha_d1 (i.e. class I, Yes or No), Nyha_d2 (i.e. class II, Yes or No) are not entered in to the new model. Instead the two covariates Nyha_d3 (i.e. class III, Yes or No) and Site_d1 (i.e. Anterior, yes or No) are included. This model (of table 4-7-2-2) suggests that older patients are more at risk of sudden death or of having a first non validated reinfarction or chest pain than younger patients. The

model suggests also that those who were treated by Ramipril are less at risk of failure than those patients who were treated by the Placebo.

Plot 4-7-2-1 and 4-7-2-2 show, respectively, the estimated baseline survival function and the estimated baseline cumulative hazard function corresponding to the model of table 4-7-2-2.

Plots 4-7-2-3 to 4-7-2-8 are prepared to investigate the validity of the proportional hazards assumption of the model of table 4-7-2-2. Each of these plots show the Log Minus Log of the survival functions at different levels of a particular covariate. These are the covariates included in the model. For some covariates two plots were prepared. The reason is that sometimes the values of LML of survival functions were too close and it was needed to delete small LML values to investigate for a parallel relationship between the LML of the survival functions. Plots 4-7-2-3 to 4-7-2-8 are, respectively, for Angina, Nyha_d3 (i.e. class III, Yes or No), Site_d1 (i.e. Anterior, Yes or No) and treatment. In each of these plots we examine whether the proportionality of hazards assumption for one of the covariates, is ,or is not, valid. We remind the reader that the survival functions have been estimated by the Kaplan-Meier method and that the survival time is defined as the time interval between the registration date and the date of sudden death or first non validated reinfarction or chest pain. For one of the covariates Site_d1 (i.e. Anterior, Yes or No) the proportionality of hazards assumption is possibly doubtful but for the other the assumption seems reasonable.

To investigate the goodness of fit of the model 4-7-2-2, plots 4-7-2-9 to 4-7-2-12 were prepared. Plots 4-7-2-9 and 4-7-2-10 show,

respectively, the logarithm of the survival function of our residuals and the cumulative hazard function of our residuals. Clearly both plots look linear but not with slopes 1 or -1 respectively. The residuals would appear to be exponentially distributed but not with parameter 1. This indicates that the model of table 4-7-2-2 does not fit well. Plots 4-7-2-11 and 4-7-2-12 are the same plots as 4-7-2-9 and 4-7-2-10 but they have been prepared for BMDP's residuals. Once again, these two plots also look linear but not with slopes 1 or -1 respectively. So both types of residuals (our residuals and BMDP's residuals) suggest that the Cox Proportional Hazards model fitted to the time interval between the registration date and the date of first non validated reinfarction or chest pain does not fit well. We remind the reader that the model of table 4-7-1-1, the Cox model was constructed for this end point depending on the single covariate treatment, did fit well. So it is possibly unwise to use the results of the new model(of table 4-7-2-2) to report or to interpret any relationship between the use of Ramipril and the time interval between the registration date and the date of sudden death or first non validated reinfarction or chest pain while we can be more confident that the model of table 4-7-1-1 can be used to claim that Ramipril is effective in prolonging the specified survival time.

Further tests were carried out to investigate whether the model of table 4-7-2-2 fits well to survival times or not. In these further tests we tested whether the distributions of the residuals (either our residuals or BMDP's residuals) at different levels of a particular covariate are or are not significantly different. To have a good fit, these distributions (of the residuals) should not be significantly different. Note that in the previous

paragraph we showed that the model of table 4-7-2-2 does not fit. Tables 4-7-2-3 to 4-7-2-6 show, respectively, the results of the comparing the distributions of our residuals due to different levels of covariates Angina, Nyha_d3 (i.e. class III, Yes or No), Site_d1 (i.e. Anterior, Yes or No) and treatment. These tables suggest that these distribution of our residuals are not significantly different. This implies the residuals do not show any significant pattern in relationship to the levels of any of the covariates. Thus there is no reason to doubt the fit of the model of table 4-7-2-2 in this respect. This would suggest that the model of table 4-7-2-2 adequately accounts for the influence of these covariates. Tables 4-7-2-7 to 4-7-2-10 are similar to tables 4-7-2-3 to 4-7-2-6 but have been prepared for BMDP's residuals. These new tables suggest that the distributions of the BMDP's residuals corresponding to different levels of the covariate Angina and Nyha_d3 (i.e. class III, Yes or No) are significantly different while those which are due to different levels of the other covariates are not different. So the model could possibly be improved by changing its dependence in some way on the two significant covariates. However since we are more confident about our residuals and since there were no significant covariates in relation to them we conclude that the model has adequately accounted for the influence of these covariates.

Table 4-7-1-1 : Cox Proportional Hazard model fitted to time from registration date to sudden death or non validated re infarction or chest pain. (single treatment covariate)

Log Likelihood = -3611.4408
Global Chi-Square = 6.46 d.f. = 1 P-value = 0.011

Variable	Coeeficient	Standard Error	Coeff./S.E.	Exp(Coeff.)
Treatment	-0.2280	0.089	- 2.536	0.7961

Table:4-7-2-1: Cox Proportional Hazard model fitted to time from registration date to sudden death or non validated re infarction or chest pain.(all candidate covariates)

LOG LIKELIHOOD = -3559.3038
GLOBAL CHI-SQUARE = 110.55 D.F.= 18 P-VALUE =0.0000

VARIABLE	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF
age	0.0207	0.0049	4.2320	1.0209
sex	0.1157	0.1025	1.1288	1.1227
hyperten	-0.0158	0.1006	-0.1572	0.9843
diabet	0.1942	0.1300	1.4935	1.2144
pmi	0.1076	0.1107	0.9720	1.1136
angina	0.2510	0.1068	2.3495	1.2853
cardiac	-0.1092	0.1815	-0.6016	0.8965
nyha_d1	-0.5807	0.2138	-2.7162	0.5595
nyha_d2	-0.5403	0.1874	-2.8827	0.5826
nyha_d3	-0.1743	0.1838	-0.9481	0.8401
site_d1	0.3637	0.5850	0.6217	1.4386
site_d2	0.1657	0.5865	0.2824	1.1802
wave_d1	-0.0536	0.6248	-0.0858	0.9478
wave_d2	-0.1343	0.6217	-0.2161	0.8743
ac4a	0.2723	0.1438	1.8937	1.3130
ac4b	-0.0599	0.0922	-0.6502	0.9418
ac4c	0.1680	0.1051	1.5986	1.1829
treatment	-0.2398	0.0903	-2.6548	0.7868

Table:4-7-2-2: Cox Proportional Hazard model fitted to time from registration date to sudden death or non validated re infarction or chest pain.(Stepwise method)

LOG LIKELIHOOD = -3569.7173
GLOBAL CHI-SQUARE = 86.46 D.F.=5 P-VALUE =0.0000

Step No.	VARIABLE	df	COEFFICIENT	STANDARD ERROR	COEFF./S.E.	EXP(COEFF
1	age	1	0.0239	0.0046	5.1737	1.0242
2	angina	2	0.3379	0.0977	3.4599	1.4019
3	nyha_d3	3	0.3032	0.1035	2.9294	1.3542
4	treatment	4	-0.2531	0.0900	-2.8117	0.7764
5	site_d1	5	0.2257	0.0923	2.4450	1.2532

Table 4-7-2-3 : Comparing the distributions of our residuals for two levels of Angina for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1240	265	975	0.79
level 2	702	233	469	0.67
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.405	1	0.5247	

Table 4-7-2-4 : Comparing the distributions of our residuals for two levels of nyha_d3 (i.e. class III, Yes or No) for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	1491	332	1159	0.78
level 2	451	166	285	0.63
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.094	1	0.7590	

Table 4-7-2-5 : Comparing the distributions of our residuals for two levels of site_d1 (i.e. Anterior, Yes or No) site for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	No. of complete times	No. of censored times	Proportion of censored times
level 1	820	193	627	0.76
level 2	1122	305	817	0.73
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.000	1	0.9831	

Table 4-7-2-6 : Comparing the distributions of our residuals for two levels of treatment for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	957	270	687	0.72
level 2	985	228	757	0.77
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	0.001	1	0.9724	

Table 4-7-2-7 : Comparing the distributions of BMDP residuals for two levels of Angina for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1240	265	975	0.79
level 2	702	233	469	0.67
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	9.952	1	0.0016	

Table 4-7-2-8 : Comparing the distributions of BMDP residuals for two levels of nyha_d3 (i.e. class III, Yes or No) for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	1491	332	1159	0.78
level 2	451	166	285	0.63
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	7.836	1	0.0051	

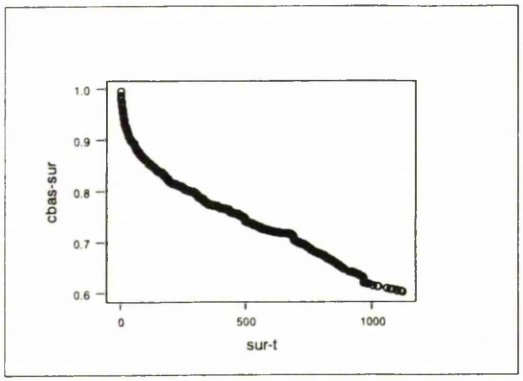
Table 4-7-2-9 : Comparing the distributions of BMDP residuals for two levels of Site_d1 (Anterior, Yes or No) for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	820	193	627	0.76
level 2	1122	305	817	0.73
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.204	1	0.2726	

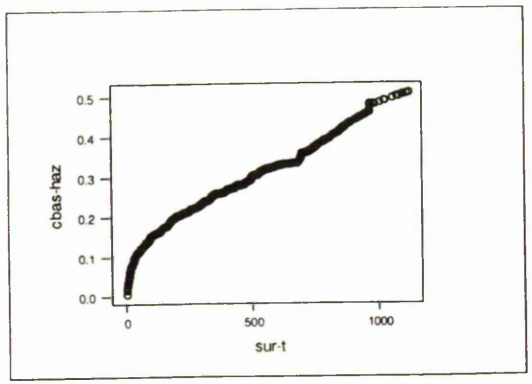
Table 4-7-2-10 : Comparing the distributions of BMDP residuals for two levels of treatment for time to sudden death or non validated reinfarction or chest pain.

	Total no. of patients	**No. of complete times**	**No. of censored times**	**Proportion of censored times**
level 1	957	270	687	0.72
level 2	985	228	757	0.77
Total	1942	498	1444	
	Statistic	**d.f.**	**P-value**	
Generalised Savage test	1.798	1	0.18	

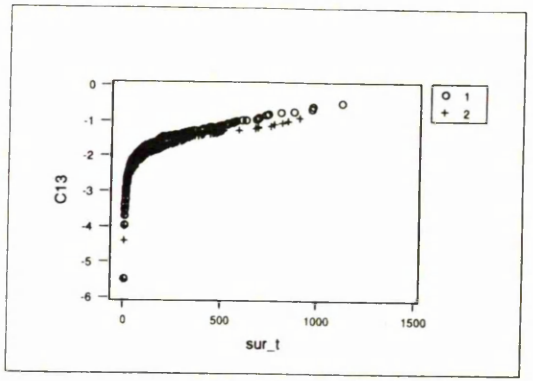
Plot 4-7-1-1: Estimated baseline survival function for model of table 4-7-1-1.



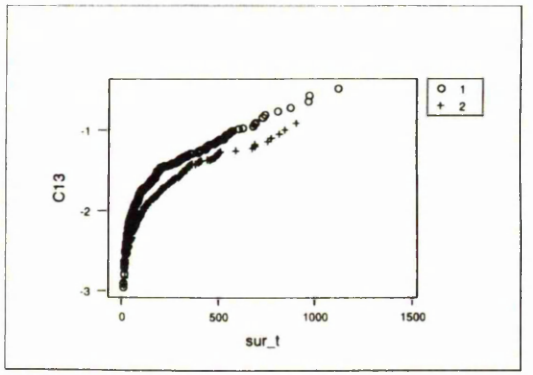
Plot 4-7-1-2: Estimated baseline cumulative hazard function for model of table 4-7-1-1.



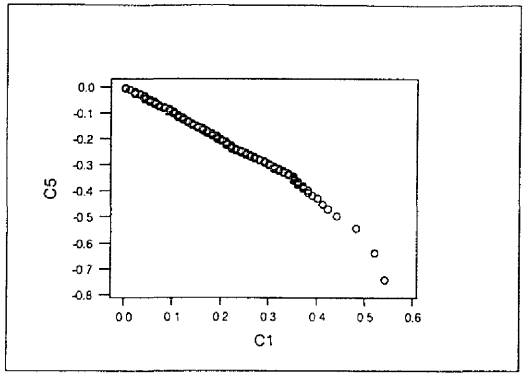
Plot 4-7-1-3: log minus log of survival functions for each treatment under model of table 4-7-1-1. (1:Placebo 2:Ramipril)



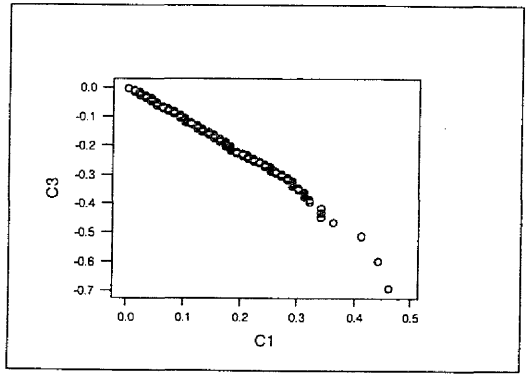
Plot 4-7-1-4: log minus log of survival function for each tratment under model of table 4-7-1-1(small values are deleted).1:Placebo 2:Ramipril



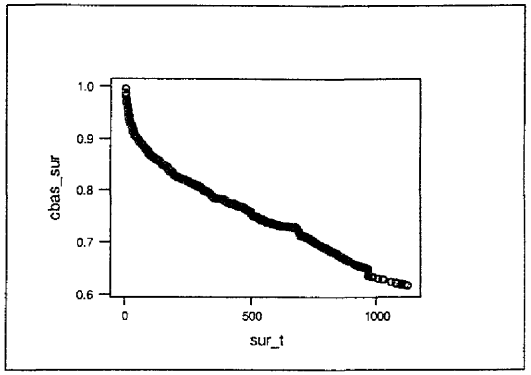
Plot 4-7-1-5: log 'survival' function of BMDP residuals against these residuals for model of table 4-7-1-1.



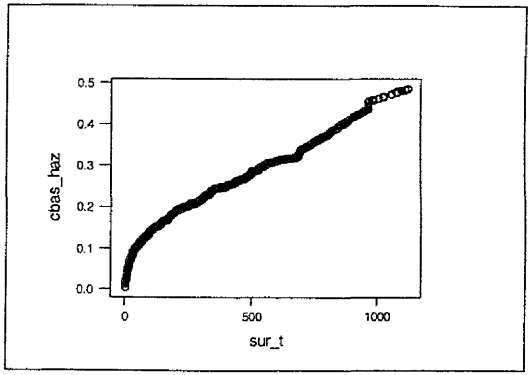
Plot 4-7-1-6: log 'survival' function of our residuals against these residuals for model of table 4-7-1-1.



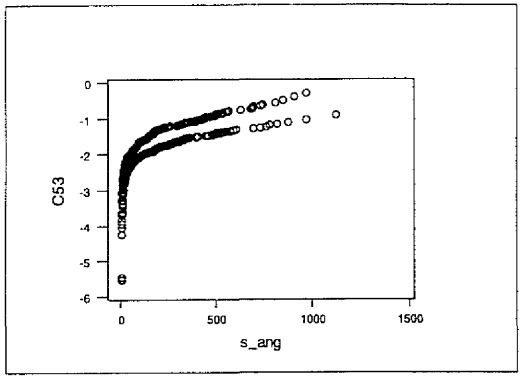
Plot 4-7-2-1: estimated baseline survival function for model of table 4-7-2-2.



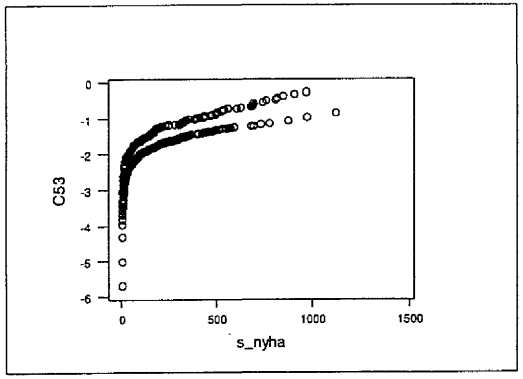
Plot 4-7-2-2: estimated baseline cumulative hazard function for model of table 4-7-2-2.



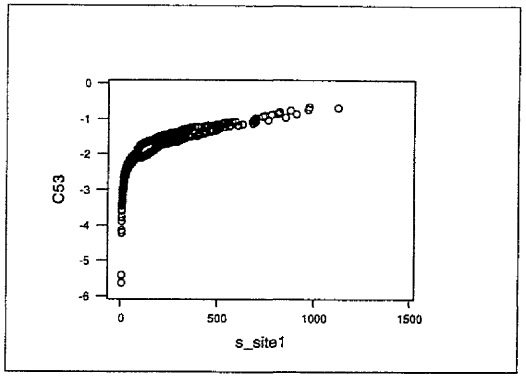
Plot 4-7-2-3: log minus log of survival functions under model of table 4-7-2-2 when Angina defines a two level stratification (yes or no).



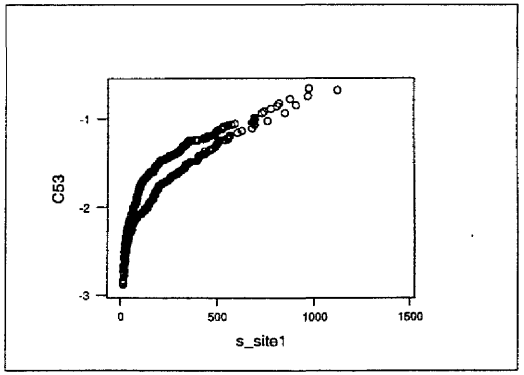
Plot 4-7-2-4: log minus log of survival functions under model of table 4-7-2-2 when Nyha defines a two level stratification.(class III or not).



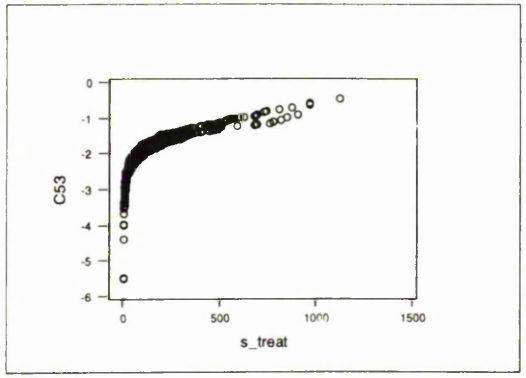
Plot 4-7-2-5: log minus log of survival functions under model of table 4-7-2-2 when Site defines a two level stratification(Anterior or not).



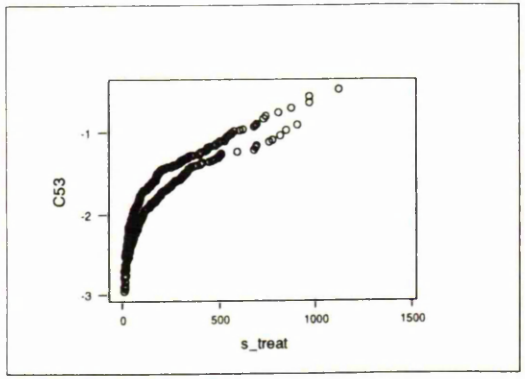
Plot 4-7-2-6: log minus log of survival functions under model of table 4-7-2-2 when Site defines a two level stratification.(Anterior or not) Small values are deleted.



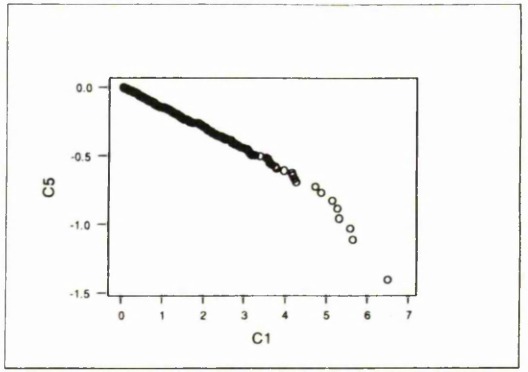
Plot 4-7-2-7: log minus log of survival functions under model of table 4-7-2-2 when'treatment' is defines a two level stratification(Placeboor Ramipril).



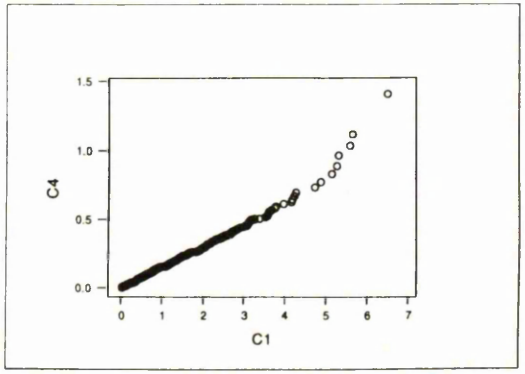
Plot 4-2-7-8: log minus log of survival functions under model of table 4-7-2-2 when 'treatment' defines a two level stratification(Placebo or Ramipril). Small values are deleted.



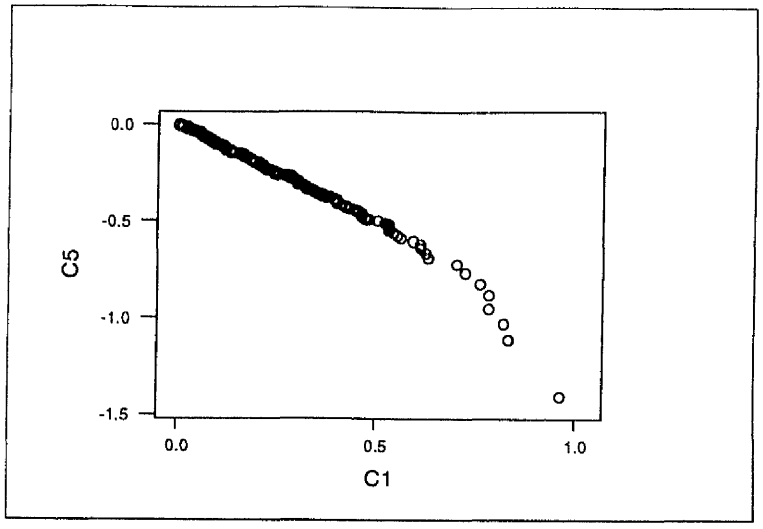
Plot 4-7-2-9: log 'survival' function of our residuals against these residuals for model of table 4-7-2-2.



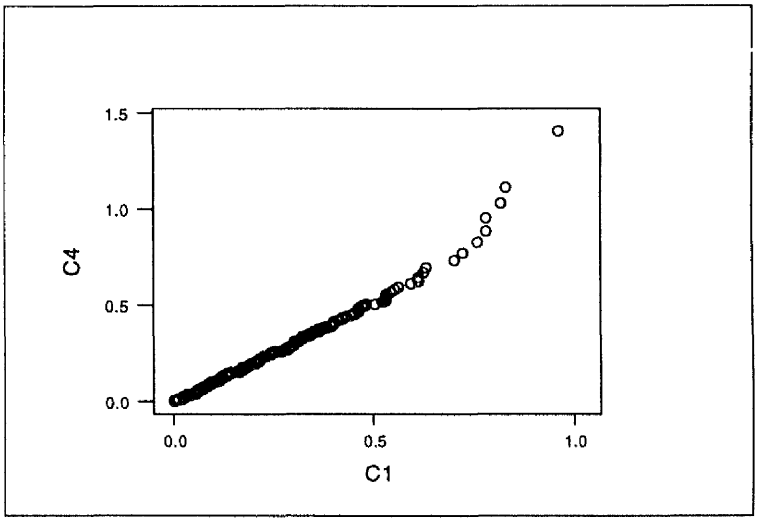
Plot 4-7-2-10: cumulative hazard function of our residuals against these residuals for model of table 4-7-2-2.



Plot 4-7-2-11: log 'survival' function of BMDP residuals against these residuals for model of table 4-7-2-2.



Plot 4-7-2-12: cumulative hazard function of BMDP residuals against these residuals for model of table 4-7-2-2.



4-8: Summary of Cox Proportional Hazards Model Fitting :

So far in sections 4-2 to 4-7, 12 different Cox Proportional Hazards models were fitted to 6 different end points, 2 models for each end point. It is quite useful to have an overall idea about how well these models fitted and how effective the use of Ramipril has been.

Six models included a single covariate, namely: "Treatment" (one for each endpoint) These potentially offer a simple comparison between the effects of Ramipril and of the Placebo. In fact all these models, except model 4-3-1-1 which corresponds to end point No. 2, fitted well (see sections 4-2-1 to 4-7-1). Note that the proportionality of hazards assumptions corresponding to all endpoints, except the one which is due to endpoint No. 2, seem valid. This makes it easier to believe that the results of these models are reliable. All these models suggest that Ramipril increases the corresponding 'survival' time.

Note that, among the above mentioned models, the numerically largest coefficient occurs in the model for endpoint No. 1. This endpoint is "death" i.e. the patient's survival time is defined as the time interval between his/her registration date and his/her death. Having the least coefficient together with the fact that those patients who were treated by Ramipril were coded as 1, imply for this end point that Ramipril has been more effective, than for the other endpoints, in prolonging the corresponding 'survival' time. Recall that the other endpoints are mixtures

of "death" and some other events such as validated or non validated reinfarction or chest pain (except endpoint no 2). This indicates that Ramipril postpones the occurrence of "Death" but it may not postpone the occurrence of other adverse events such as reinfarction (validated or non validated) or chest pain. This is consistent with conclusions obtained in chapter 2, where the separate survival functions (corresponding to these adverse events i.e. time from registration to validated or non validated reinfarction or chest pain) which were estimated by the Kaplan-Meier method for the Ramipril and Placebo groups were found to be not significantly different. In effect the coefficient of "Treatment" in the Cox Proportional Hazards model decreases numerically when any of these adverse end points together with "Death" is considered as the terminal event. Note that this numerical decrease in the coefficient of "Treatment" in the Cox Proportional Hazards models implies that when other adverse events are taken as the terminal event then the corresponding survival function is lower than the survival function when only the event "Death" is the terminal event. Hence the results in sections 4-2-1, 4-3-1, 4-4-1, 4-5-1, 4-6-1 and 4-7-1 (together with the results in chapter 3) confirm that Ramipril only postpones the occurrence of "Death" and not of other adverse events.

It is difficult to come to any overall conclusion in the light of the fitted cox models including several covariates. These are the models of sections 4-2-2, 4-3-2, 4-4-2, 4-5-2, 4-6-2 and 4-7-2. In all these sections several covariates (all significant covariates) are included in the Cox proportional Hazards model. Note that while the proportionality of

hazards assumption seems valid in all these models none of them fitted well. This is based on our investigation of residuals which only appeared to have the required Ex(1) distribution. Further tests also were carried out to investigate if there is any difference in the distribution of the residuals between different levels of a covariate. We saw for most of them that there is a common distribution across the levels of the relevant covariate. This will be more discussed in the next chapter.

Chapter 5

Discussion

In this chapter it is intended to summarise the results of chapter 3 and 4. Recall that in chapter 3, the Kaplan_Meier method was used to estimate the survival functions of those patients who were treated by Ramipril or the Placebo. This was done for various end points. Later, in chapter 4, the Cox Proportional Hazards model was used to model survival times, corresponding to various end points, using different sets of covariates.

In chapter 3, in total, 26 different end points were considered and for each of them the survival functions of the patients who were treated by Ramipril or the Placebo were estimated (by Kaplan-Meier method). The Log Rank test was used to compare the two survival functions for each end point. In this chapter, we discovered that there is basically a significant effect for endpoints involving "sudden death" (as well as that which involved death). According to these results, Ramipril has no significant effect in postponing other adverse events. The conclusions about the endpoints involving "death" show that Ramipril increases real life times i.e. Ramipril significantly postpones the occurrence of a "death" event.

In chapter 4, 6 of the 26 end points were chosen and the survival times corresponding to each of them were modelled by a Cox Proportional Hazards model. The reasons for the choice of 6 end points from 26 was fully described at end of chapter 3. For each of these 6 end points, two Cox Models were fitted, one including the single covariate "Treatment" and one by including all significant covariates. In total, in this chapter, 12 different Cox models were constructed. Six models included a single covariate, namely: "Treatment" (one for each endpoint). These potentially offer a simple comparison between the effects of Ramipril and of the Placebo. In fact all these models fitted well (see sections 4-2-1 to 4-7-1). Note that the proportionality of hazards assumptions seems valid for all endpoints, except endpoint no 2. This makes it easier to believe that the results of these models are reliable. All these models suggest that Ramipril increases the corresponding 'survival' time.

Note that, among the above mentioned models, the numerically largest coefficient occurs in the model for endpoint No. 1. This endpoint is "death" i.e. the patient's survival time is defined as the time interval between his/her registration date and his/her death., So for this end point Ramipril has been more effective, than for other endpoints, in prolonging the corresponding 'survival' time. Recall that the other endpoints are mixtures of "death" and some other events such as validated or non validated reinfarction or chest pain (except endpoint no 2). This suggests that Ramipril postpones the occurrence of "Death" but it may not postpone the occurrence of other adverse events such as reinfarction (validated or non validated) or chest pain. This is consistent with

conclusions obtained in chapter 3, where the separate survival functions (corresponding to these adverse events i.e. time from registration to validated or non validated reinfarction or chest pain) which were estimated by the Kaplan-Meier method for the Ramipril and the Placebo groups were found to be not significantly different. In effect the coefficient of "Treatment" in the Cox Proportional Hazards model decreases numerically when any of these adverse end points together with "Death" is considered as the terminal event. Note that this numerical decrease in the coefficient of "Treatment" in the Cox Proportional Hazards models implies that when other adverse events are taken as the terminal event then the corresponding survival function is lower than the survival function when only the event "Death" is the terminal event. Hence the results in sections 4-2-1, 4-3-1, 4-4-1, 4-5-1, 4-6-1 and 4-7-1 (together with results in chapter 3) confirm that Ramipril only postpones the occurrence of "Death" event and not other adverse events.

It is difficult to come to any overall conclusion in the light of the fitted Cox models including several covariates. These are the models of sections 4-2-2, 4-3-2, 4-4-2, 4-5-2, 4-6-2 and 4-7-2. In all these sections several covariates (all significant covariates) are included in the Cox proportional Hazards model. Note that while the proportionality of hazards assumption seems valid in all these models none of the models fitted well. This is based on our investigation of residuals which did not have the required Ex(1) distribution in any of these models whereas they did in the case of the single covariate models. This will be discussed in more detail later.

Further tests also were carried out to investigate if there is any difference in the distribution of the residuals between different levels of a particular covariate and we saw in most cases that there is a common distribution across the levels of the relevant covariate. To carry out these tests, the distributions of the residuals (of each model) corresponding to different levels of a particular covariate (in the model) were estimated by the Kaplan_Meier method and then the Log Rank test was used to compare them.

It was mentioned before that the Cox models of sections 4-2-2, 4-3-2, 4-4-2, 4-5-2, 4-6-2, 4-7-2 did not fit well. These are the models which were fitted to survival times corresponding to end points 2 to 6 with several covariates included in them. The goodness of fit of these models was investigated by comparing the 'survival' function of the (Cox-Snell) residuals with the Ex(1) distribution. Recall that all the Cox models, corresponding to different end points, based on the single covariate "Treatment" fitted well. So we have discovered that for particular endpoints, it is possible that the Cox model which includes a single covariate fits well but entering more covariates in the model disturbs the goodness of fit of the model. It can be referred to inconsistency in the Cox Proportional Hazard model (Ford et al 1995).

It is seen that in comparing two types of treatments, for data arising from non-normal distributions there is the possibility that models adjusting for covariates (models 4-2-2, 4-3-2, 4-4-2, 4-5-2, 4-6-2, 4-7-2) and those not adjusting for covariates (4-2-1, 4-3-1, 4-4-1, 4-5-1, 4-6-1, 4-7-1) will be inconsistent; that is, at most one of the models can be valid.

Alternatively, even if conditional and unconditional models are valid, parameters in each model may have different interpretations. Note this presents difficulties for the interpretation of this analysis. So model validation is critical.

So far we have noticed that most of the Cox models which include several covariates do not fit well i.e. the distribution of the Cox-Snell residuals of theses models was not exponentially distributed with parameter 1. These numerical values did however appear to be distributed as Ex(θ) random variables. There is also the above conclusion that the residuals seemed to have common distributions across the levels of the covariates in the model. One possible interpretation of these conclusions is that the effects of the covariates have been captured with sufficient accuracy and, if the model still does not fit well, it must be that estimation of the base line survival function has been distorted. We now suggest one idea for correcting this estimate based on the result that if a random variable X ~Ex (θ) then Y=θx ~Ex(1).

Suppose $e_1, e_2, \ldots, e_n$ are the initial estimated Cox-Snell residuals which are defined as :

$$e_i = H_0(t) \exp(\underline{\beta}^T \underline{x_i})$$

where $H_0(t)$ is the estimated cumulative baseline hazard at time T=t $\underline{\beta}$ is the vector of estimated coefficients and finally e_i is the estimated Cox-Snell residual for the i-th patient.

Suppose $e_1\ e_2 \ldots e_n$ are distributed Ex(θ) $\theta>0$.

Let

$$f_i = \theta\, e_i$$

Then $f_i \sim Ex(1)$

Further

$$f_i = H_0(t)\, \alpha_0 \exp(\underline{\beta}^T \underline{x})$$

$$= H_0(t) \exp(\underline{\beta}^T \underline{x} + \alpha) \text{ where } \theta = e^{\alpha} \text{ (i.e. } \alpha = \ln\theta)$$

$$= H_0(t) \exp(\underline{\beta}^T \underline{x} + \alpha z) \text{ where } z=1 \ \forall \ i$$

$$= H_0(t) \exp(\sum_{j=0}^{k} \beta_j x_j)$$

where $\beta_0 = \alpha$,

$\underline{x}_0 = 1$,

k : is the number of covariates included in the model,

β_j : is the coefficient of j-th. covariate in the model and

x_j : is the value of the j-th. covariate for i-th patient.

Thus f_i is like a residual under a Cox regression model with covariates $\underline{X}$ and z where z=1 and cumulative baseline hazard function $H_0(t)$.

The corresponding survival function is :

$$S^*(t \mid \underline{x}) = S^*_0(t)^{\exp(\underline{\beta}^T \underline{X})}$$

where

$$S^*_0(t) = S_0(t)^{\exp(\alpha)}$$

$$= [S_0(t)]^{\exp(\sum_{j=0}^{k} \beta_j x_j)} \text{ where } \beta_0 = \alpha \text{ and } x_0 = 1).$$

$$= [S_0(t)]^{\exp(\alpha + \underline{\beta}^T \underline{X})}$$

$$= [S_0(t)]^{[\exp(\alpha) + \exp(\underline{\beta}^T \underline{X})]}$$

This $S^*(t \mid \underline{x})$ is a survival function under Cox regression Model with baseline survival function $[S^*_0(t)]$.

We suggest estimation of θ on the basis of assuming the residuals to be a censored sample of independent observations from $Ex(\theta)$. The independence assumption is, of course, strictly speaking not justified.

Suppose $r_1, r_2, \ldots, r_m$ are the uncensored residuals and $r^*_1, r^*_2, \ldots, r^*_n$ are the censored residuals. Then, under the Ex(θ) assumption the likelihood is :

$$\text{Likelihood} = \{\pi_{i=1}^{m} (\theta e^{-\theta r_i})\} \{\pi_{j=1}^{n} (e^{-\theta r^*_j})\}$$
$$= \theta^m e^{-\theta T} \qquad \text{where } T = \sum r_i + \sum r^*_j$$

$l = \text{Log(likelihood)} = m \ln(\theta) - \theta T,$

$\partial l/\partial\theta = m/\theta - T = 0.$ if $\theta = m/T$

So $\hat{\theta} = m/T$ where m= number of complete residuals and $T = \sum r_i + \sum r^*_j$ is a maximum likelihood estimate of θ. Thus the new baseline survival function is

$$S^*_0(t) = [S_0(t)]^{\exp(m/T)}$$

and in effect residuals under this version of the fitted model are the original residuals multiplied by m/t. Approximately they should be distributed as Ex(1) variables. Further their distributions will not vary across levels of covariates if this is true of the original residuals. We have not explored this idea in practice. It is one that would require empirical investigation, especially simulation studies.

Chapter 6

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