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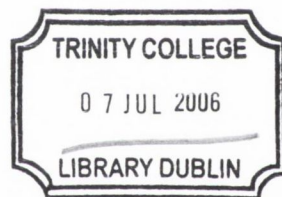
Modelling Compliance with Antihypertensives and Statins in Ireland, Using a National Prescription Claims Database.

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Ph. D.

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Declarations

This thesis has not been submitted as an exercise for a degree at this or any other University.

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Nicola Fitz-Simon

Acknowledgements

Summary

Hypertension and high cholesterol, especially in the middle-aged and elderly, are fairly common, and pharmacological therapy is often required to control them. In spite of substantial knowledge of the consequences of uncontrolled blood pressure and high cholesterol (for example cardiovascular and cerebrovascular disease) and the proven benefits of treatment for these conditions, many patients continue to have uncontrolled blood pressure and cholesterol levels. It has been demonstrated in large clinical trials that treatment with appropriate therapies substantially reduces the risk of morbidity and mortality. While lack of compliance is by no means the only reason for low control rates, many patients prescribed antihypertensives or lipid-lowering therapies do not continue to take them and therefore do not benefit. Previous studies of compliance have often not used the most appropriate methods to analyse drug discontinuations and thus have not been able to explore fully various characteristics of the problem – in particular the patterns of prescription claiming at the individual level, and their longitudinal dependencies. Determining appropriate models for the analysis of discontinuation and switching of statins and antihypertensives in the Irish population may help clinicians making decisions about what and how to prescribe.

In Irish patients eligible for free medical care under the General Medical Services (GMS) scheme, approximately one third of patients who start taking a statin or antihypertensive do not collect a prescription the following month. Of the remaining patients who continue to collect their prescriptions, more than half have discontinued by twelve months. The main

factor predicting discontinuation of therapy is duration, with most changes taking place in the first few months of an episode of claiming therapy.

Despite the large amount of literature on various aspects of the problem of non-compliance, the problem continues to persist. Various behavioural models have attempted to describe the factors that influence compliance. Why some patients continue taking their therapies while others do not is substantially affected by individual-level factors. For instance, some patients are more susceptible to adverse reactions to therapy, either at a physiological or psychological level, and therefore more likely to discontinue or switch therapy. For this reason a model allowing variation at the individual level is appropriate.

Modelling patterns of drug discontinuation has not been adequately addressed in previous studies and there have been no detailed studies of this in Ireland. This thesis aims to contribute to the knowledge and understanding of patterns of drug use in Ireland and suggests methods for more appropriate modelling of these patterns of drug claiming. These focus on the longitudinal aspect of claiming prescriptions, using repeated measures and event-history (or multistate) models. Dependencies between observations on the same patient are modelled by using both marginal (Generalised Estimating Equations) and conditional (random effects) approaches. The results of these modelling approaches suggest that not only should patients be supported in their early efforts to establish a habit of antihypertensive or statin use, but also that if a patient discontinues therapy, rapid intervention might be useful to ensure its resumption.

Abbreviations

ACE - Angiotensin converting enzyme inhibitors (antihypertensive)

ADR – Adverse drug reaction

AHT – Antihypertensives

AMI (or MI) - Acute myocardial infarction (death of an area of muscle due to local

ischaemia) or heart attack, ICD-9 410

AT2 - Angiotensin-II antagonists (antihypertensive)

ATC - Anatomical therapeutic chemical – drug classification system

BB - Beta-adrenergic receptor blockers (antihypertensive)

BP – Blood pressure

CCB - Calcium channel blockers (antihypertensive)

CHF - Heart Failure or Congestive Heart Failure – a condition arising from inadequate

output of blood from the heart.

CVD – Cardiovascular disease

DDD - Defined Daily Dose

ERHA - Eastern Regional Health Authority

GMS - General Medical Services

HDL – High density lipoprotein (good) cholesterol.

HT – Hypertension – blood pressure > 140/90 mmHg.

ICD-9 - International Classification of Diseases (9th revision)

IHD - Ischaemic heart disease ICD-9 410-413 (also coronary heart disease, CHD) - heart

muscle is damaged or works inefficiently due to poor blood supply - includes angina, AMI.

LLD – Lipid-lowering drugs

LDL – Low density lipoprotein (bad) cholesterol.

MEMS – Medical event monitoring system

MPR – Medication possession ratio (also PDC, proportion of days covered)

Statins (HMG-CoA reductase inhibitors) – hydroxymethyglutaryl-coenzyme A reductase inhibitors, cholesterol-lowering drugs.

1

5

List of Figures

10

11

List of Tables

Introduction

The aim of this thesis is to develop a quantitative understanding of the patterns of prescription claiming in an Irish population. The prescription claims of interest are for antihypertensive therapies and statins: in Ireland, these are the main pharmacological treatments for high blood pressure and high serum cholesterol respectively. These are early stages of diseases of the cardiovascular and cerebrovascular systems, which are the leading causes of mortality and morbidity in Ireland. The population is drawn from patients eligible for free health care under the General Medical Services (GMS) Scheme.

To reduce their risks of developing more serious diseases, people with high blood pressure and cholesterol may need to make changes to their lifestyles and take antihypertensive and lipid-lowering medicines. The benefits of these medicines have been established: they include reduced risks of developing more serious diseases of the cardiovascular and cerebrovascular systems and death. However, to achieve these benefits, the therapies must be used continuously and for a long period of time – perhaps lifelong. Stopping therapy can lead to an increase in blood pressure and/or serum cholesterol levels which remain risk factors for cardiovascular and cerebrovascular disease; and in some circumstances withdrawal of medicines can result in cardiovascular events and hospitalisation.

There has been vast research into patients' compliance – the extent to which patients follow prescribed treatments, including lifestyle modifications and therapies. There are many

dimensions to this research: how to define and measure and model compliance and assess its impact; the factors that affect it, and interventions to improve it. Analysing patterns of prescription claiming is one aspect of the study of patients' compliance.

It is difficult to quantify the extent to which non-compliance with antihypertensive therapies and statins leads to poor control of blood pressure and serum cholesterol levels, and to what extent morbidity and mortality rates may be attributed to this. There are many interacting factors at different levels (for instance, patient, treatment, environment, doctor, healthcare system) that affect blood pressure and serum cholesterol control; these factors also influence patients' patterns of prescription drug use. It is tempting to reduce the problem to the simple statement that drugs that are not taken can have no effect; however true this may be, it misses the essential point. Humans are individuals and have a tendency, either conscious or unconscious, to follow their own rules – in the decision to take treatments, in the way external factors affect these decisions, in their individual responses to illness and treatment, and in the way these things change over time. While the individual response may not make logical sense to (for instance) the doctor, it may make perfect sense to the patient. There is great variability from one individual to another.

So while it is acknowledged that failure to take treatment is a problem, this is generally quantified in vague terms: the World Health Organisation describes its magnitude as "striking".

This thesis sets out to improve the quantitative understanding of patient compliance in Ireland. It begins by setting the scene: the extent to which high blood pressure and high

cholesterol contribute to mortality and morbidity in general and in Ireland. High blood pressure and high serum cholesterol are described in terms of their characteristics, prevalence, consequences, treatment and control. Aspects of these factors that are relevant to assessing compliance using prescription claiming data are discussed – these include the effects of treatment, in particular expected levels of benefit, and the rates of treatment-related adverse events.

The second chapter is a discussion of patients' compliance – in particular, how it is defined and measured, the factors that influence it, and the evidence on the benefits of compliance in patients treated with antihypertensives and statins. Focusing on the assessment of compliance using prescription claims data, Chapter 3 reviews previous analyses of antihypertensive and statin prescription claiming histories. This concentrates particularly on the modelling methods used in previous research – their contribution and limitations - and makes suggestions for modelling methods that could give a more informative picture of prescription claiming patterns.

The remainder of this thesis deals with modelling the patterns of antihypertensive and statin claims in the GMS Scheme. Chapter 4 describes the data available from the GMS Scheme, and how patients were selected for this study. Chapter 5 describes the statistical models used to analyse prescription claiming patterns. Chapter 6 gives the results of modelling patterns of statin use in the GMS. Chapter 7 gives the results for antihypertensives: because there are five classes of antihypertensives and many patients change therapy over time, the models of Chapter 6 are extended to describe patterns of switching between different classes of antihypertensives.

Finally, Chapter 8 discusses the contribution these analyses make to the research, the implications of the results and suggestions for further work.

The original proposal for this thesis involved estimating compliance for both antihypertensives and statins. Each is interesting from a medical point of view; and as the characteristics of the conditions treated by both types of therapy are similar in some respects, it may be of interest to compare the patterns of claiming. However comparison of the study populations selected from the GMS database indicated that the statin group were more severely ill than the antihypertensive group, in that a higher proportion were at some point treated for Ischaemic heart disease (IHD). It is of substantive interest and a useful modelling extension to include time-varying covariates in the models, and while IHD status appeared a suitable candidate for the statin claiming data, there was no obvious time-varying covariate in the antihypertensive data. The antihypertensives, on the other hand, were interesting from a modelling perspective as the complexity of treatment lends itself to multistate and competing risks models; the simpler models used for the single drug class (statins) may be regarded as stepping stones in the development of appropriate models for antihypertensive claiming patterns.

1. Hypertension and Hyperlipidaemia:
Treatment and Control

Hypertension and hyperlipidaemia may be regarded as the early stages of cardiovascular and Cerebrovascular disease. I describe each condition – their characteristics, consequences, prevalence, treatment and rates of control in Ireland compared with other countries.

1.1 Hypertension and Hyperlipidaemia

1.1.1 Blood pressure

When blood leaves the heart it exerts a force on the walls of the arteries; the blood pressure is the force per unit area. As the blood travels further from the heart this pressure decreases. The pressure differential between the heart and the furthermost arteries causes the blood to flow around the circulatory system. What is commonly referred to as "blood pressure" is the pressure of the blood in the aorta and its branches. This is measured in both the systolic and the diastolic phases of the cardiac cycle and quoted in fractional form, the systolic pressure as numerator and the diastolic pressure as denominator.

Blood pressure is affected by four interacting factors, namely cardiac output (amount of blood per minute the heart pumps), blood volume, peripheral vascular resistance and viscosity, which is due to frictional forces within the blood which resist flow. In fact the blood pressure is equal to cardiac output (CO) * peripheral vascular resistance (PVR), and cardiac output is equal to heart rate * stroke volume (the amount of blood pushed into the aorta at each beat of the heart). The resistance is proportional to viscosity of the blood and length of the blood vessel, and inversely proportional to the fourth power of the inner radius of the blood vessel. Hence reducing the radius of a blood vessel increases resistance, and thus increases blood pressure. The arterioles - the smallest arteries - are the vessels that are primarily responsible for the resistance of the cardiovascular system to the flow of blood. Constriction or dilation of the arterioles affects the total peripheral resistance. Reduction of the blood volume, the heart rate, or the peripheral resistance can lead to a reduction in blood pressure.

The systolic pressure is mainly influenced by stroke volume, left ventricular ejection velocity and arterial stiffness. Diastolic pressure increases with an increase in total peripheral resistance. An increase in heart rate, which results in a shorter diastolic interval, can cause an increase in diastolic pressure.

The renin-angiotensin system is the main mechanism by which the body controls blood pressure. When blood volume falls, the kidneys release the enzyme renin which causes a plasma protein called angiotensinogen to split to form angiotensin I; the action of the angiotensin converting enzyme (ACE) causes this in turn to split to form the active substance angiotensin II. This is the most powerful natural vasoconstrictor made by the

body. Its action is to raise the blood pressure – this is achieved by constricting the blood vessels, thus increasing resistance, and by triggering the release of the hormone aldosterone, which induces the kidneys to retain salt and water, thus increasing blood volume. In normal circumstances this mechanism allows the body to maintain a stable blood pressure when the blood volume is decreased (for example after exercise). But if the renin-angiotensin system is overactive the blood pressure may become unnecessarily high.

An increase in blood pressure with age is due to changes in the structure of the large arteries. When the large arteries near the heart lose some of their flexibility the heart has to work harder for the blood to circulate around the body.

Blood pressure is measured in millimetres of mercury (mmHg). Hypertension or high blood pressure is defined as a systolic pressure of over 140 mm Hg and/or diastolic pressure of over 90 mm Hg (WHO 2003). High blood pressure causes damage to the heart and blood vessels, which can increase the risk of cerebrovascular and cardiovascular disease and kidney failure. However these risks are reduced if the blood pressure is controlled. Hypertension may be controlled by modification of lifestyle factors and/or pharmacological treatment.

While the causes of essential hypertension are unclear, there are associations with genetics and lifestyle factors. Lifestyle factors that may lead to an increase in blood pressure include stress, lack of physical exercise, excess weight and dietary intake. Salt intake increases the risk of hypertension. Excessive consumption of alcohol and smoking are also risk factors for hypertension (Aaronson and Ward 1999, Katzung 2001, Mancia et al 2002).

21

1.1.2   *Symptoms of high blood pressure*

Many people with mildly elevated blood pressures have no symptoms. However, hypertension not asymptomatic – headaches are more common under placebo than under drug treatment, suggesting that treatment alleviates symptoms in mild hypertension (Neaton et al 1993). Other symptoms of hypertension include exercise intolerance and fatigue (Mancia et al 2002).

1.1.3   *Cholesterol*

Cholesterol is a fatty substance that forms part of the cell membrane. It is necessary for the health of nerve cells and the production of certain hormones and bile acids. About two thirds of the cholesterol in the body is produced in the liver and transported via the circulatory system to the cells of the body. Cholesterol is transported by lipoproteins, of which there are two main types – high density (HDL) and low density (LDL). LDL transport cholesterol from the liver to the body's cells and tend to deposit cholesterol in the artery walls, while HDL, which transport cholesterol back to the liver, tend to remove it. An elevation of lipoproteins in the circulatory system is a physiological imbalance that may result in excessive deposit of cholesterol on the artery walls. This may over time lead to atherosclerosis, a disease whereby the formation of a plaque of cholesterol on artery walls causes them to thicken and the arteries to narrow. This makes it more difficult for blood to flow around the circulatory system, increasing the workload on the heart. It also increases

22

the risk of blood clots, which may result in myocardial infarction or stroke. There is evidence that a LDL cholesterol level of over 100 mg per 100ml (>2.6 mmol/L) increases the risk of atherosclerosis (NCEP 2002). The risk of high cholesterol is increased by the excessive consumption of foods high in saturated fat or cholesterol. Other risk factors include obesity, smoking, lack of physical exercise and excessive alcohol consumption.

1.1.4   Prevalence of hypertension

It is estimated that 27.6% of the adult population in North America (Canada and the US) has hypertension. The average prevalence of hypertension across six Western European countries (Germany, England, Sweden, Finland, Spain and Italy) is estimated at 44.1% (Wolf-Maier et al 2003). The prevalence of hypertension increases with age, so that while hypertension is relatively uncommon amongst young people, in some populations about half all people aged over 60 have high blood pressure (WHO 2004).

Table 1.1 give the prevalence of hypertension by age group and sex in the US, England and Ireland. In England it is estimated that 37.4% of men and 33.8% of women have high blood pressure (Great Britain Dept of Health, 2003). A study of a population of men and women aged 50-69 in primary care in Cork and Kerry found the prevalence of hypertension to be 47%. The prevalence of hypertension among men aged 55-64 was similar to the English but higher than the US estimates of prevalence for this group, while the prevalence of

hypertension among the Cork and Kerry women was lower than that for English and US women of the same age (Creagh et al 2002).

Table 1.1 Population rates of hypertension by age and sex

AGE	US Men (1)	US Women (1)	England men (2)	England women (2)	Cork/Kerry men (3)	Cork/Kerry women (3)
16-24			13.8	4.5		
25-34			16.6	6.1		
(20-34)	9.8					
35-44	17.1	16.0	24.3	12.5		
45-54	32.3	30.5	36.5	32.7		
(50-54)					39.7	25.4
55-64	44.1	53.0	53.4	52.5		
(55-59)					52.9	44.5
(60-64)					55.3	46.7
65-74	59.9	70.3	61.7	69.8		
(65-69)					55.0	57.4
75+	68.8	84.1	71.2	78.8		
total	33.1	32.1	37.4	33.8	50.7	43.5

Table 1.1 References (1) National Center for Health Statistics 2003, (2) Great Britain Department of Health 2003, (3) Creagh et al 2002.

1.1.5 Prevalence of hyperlipidaemia

Table 1.2 summarises the population prevalence of high cholesterol in the US, England, Ireland and France. US estimates were converted from mg/100ml to mmol/L. The population prevalence of high total cholesterol increases with age – in women in England it is estimated that 30.7% of those aged 16-24 have cholesterol over > 5.0 mmol/L and prevalence reaches its highest level at 83.7% in the 55-64 years age group – prevalence

decreases slightly in older age groups and 77.1% of women aged 65-74 have total cholesterol over 5.0 mmol/L (Great Britain Dept of Health, 1999). Total cholesterol levels are approximately normally distributed. Half all women in England have total cholesterol over 5.5 mmol/L and half all men have total cholesterol over 5.4 mmol/L.

Table 1.2 illustrates population rates of high cholesterol but the figures given are not intended for direct comparison due to differences in definitions and age ranges in different studies.

Table 1.2 Population rates of high cholesterol

	US Age>20	England Age > 16	Cork/Kerry Age 50-69	France/N. Ireland, age 35-55 (men)
Total cholesterol	>5.2 mmol/L	>5.0 mmol/L	>5.0 mmol/L	
		66% (men)		
	50.7% (1)	67% (women) (4)	82.2% (5)	
Total cholesterol	>6.2 mmol/L			>6.5 mmol/L or LDL > 4.2 mmol/L
	18.3% (2) (age-adjusted)			46% (France) 48% (NI) (6)
LDL	> 3.4 mmol/L 45.8% (3) (age-adjusted)		>3.0 mmol/L 74.6% (5)	
HDL	< 1.0 mmol/L 26.4% (3) (age-adjusted)			

Table 1.2 references (1) Ford et al 2003, (2) National Center for Health Statistics 2003, (3) American Heart Association 2004, (4) British Heart Foundation 2003, (5) Creagh et al 2002, (6) Marquez Vidal et al 1997.

1.1.6   Consequences of hypertension and hyperlipidaemia

Risk factors for cardiovascular diseases include a high level of low density lipoprotein (LDL) cholesterol in the blood, hypertension, diabetes, smoking, dietary and alcohol consumption patterns, being overweight, lack of exercise, psychosocial factors and genetic factors including family history, age, sex and race (Wilson et al 1998).

Any increase in systolic blood pressure above the theoretical minimum of 115 mmHg has been shown to increase the risk of cardiovascular and cerebrovascular mortality and morbidity (Kannel 1996). In patients who have had a myocardial infarction, after adjusting for other risk factors, an increase in systolic blood pressure of 25 mmHg increases the risk of mortality by 42% (Kannel et al 1980). Elevation of both systolic and diastolic blood pressures, and in older people, a large difference between systolic and diastolic pressures have been shown to increase the risk of cardiovascular-related mortality (Domanski et al 2002, Lee et al 1999)

Ischaemic heart disease (IHD) – also known as coronary heart disease (CHD) and coded under the International Classification of Disease, 9th revision as 410-414 (WHO 2004) - is a result of atherosclerosis, whereby the arteries leading to the heart are narrowed and hardened due to an accumulation of fatty deposits on their inner walls, leading to a reduced flow of blood and hence ischaemia (inadequate supply of oxygen to the heart). Types of IHD include angina pectoris, coronary thrombosis and myocardial infarction. Acute myocardial infarction (AMI) or heart attack is the death of part of the heart muscle due to a sudden loss

of blood supply, usually due to a blood clot in one of the coronary arteries. This is more likely if the coronary arteries are diseased. Angina pectoris is chest pain, usually due to insufficient blood supply to the heart because of disease of the coronary arteries. In the elderly (ie those aged over 65) the risk of IHD is 1.6 times greater in hypertensive men than men with normal blood pressure and the corresponding risk ratio for women is 1.9 (Kannel 1994).

Atherosclerosis of the arteries leading to the brain can result in cerebrovascular disease (otherwise known as stroke). The risk of stroke in hypertensive men aged over 65 is 1.9 times greater than those who are normotensive, and the corresponding rate for women is 2.3 (Kannel 1994).

Hypertension and other cardiovascular diseases, diabetes, obesity and smoking increase the risk of congestive heart failure (CHF) - a condition whereby the heart's function as a pump is impaired. This results in reduced flow of blood to the cells of the body so that the tissues do not get sufficient blood or oxygen. One of the body's responses to this is constriction of the peripheral blood vessels, so the overall volume of blood vessels is smaller. This leads to retention of sodium and thus water, resulting in an increase in blood volume and causing the heart to pump faster. It also leads to fluid retention in the lungs and body. The risk of heart failure among elderly people with hypertension is on average 1.9 times greater than for those with normal blood pressure (Kannel 1994).

Uncontrolled blood pressure also increases the risk of renal failure (Peterson et al 1995), dementia (Forette et al 2002), and blindness in people with diabetes (UK Prospective Diabetes Study Group 1998).

Poor control of blood pressure and cholesterol, resulting in morbidity and mortality, has economic implications – one study estimated the cost of hypertension to five European countries (France, Germany, Italy, UK and Sweden) at 1.26 billion euros (Hansson et al 2002).

1.1.7   Morbidity and mortality due to cardiovascular and cerebrovascular disease

World Health Organisation statistics identify IHD and cerebrovascular disease as the main causes of death worldwide. Global statistics for 2002 (Mathers et al 2003) attribute 12.6% of all deaths to IHD and 9.6% of all deaths to cerebrovascular disease. These factors are particularly important among adults aged over 60 years, amongst whom IHD is responsible for 20.1% of deaths and cerebrovascular disease is the primary cause in 16.2% of deaths. Mortality rates due to these two causes are especially high in developed countries (Global cardiovascular infobase).

Cardiovascular disease is the most common cause of death among Irish people (Irish Heart Foundation 2001). Data from the Central Statistics Office on causes of death in Ireland in 2001 show that 6,149 people died of coronary heart disease, 2,608 died of stroke and 3,157

died of other diseases of the circulation including heart failure and diseases of the arteries –

that is, a total of 11,941 deaths were due to diseases of the circulation. This represents 41%

of all deaths in Ireland; the next most common cause being cancer, to which is attributed

26% of all deaths (Central Statistics Office Ireland, 2002).

Ireland has the highest rate of mortality due to heart attack in the EU, at 176 per 100,000

people. The EU average is 108 per 100,000 people (WHO 1998). Ireland has the second-

highest rate of death due to IHD in the EU, at 175 per 100,000 (age-standardised rate) – the

highest being Finland at 189 per 100,000 (Cardiovascular Health Strategy Group 1999).

Irish data on morbidity due to cardiovascular disease is limited to the Hospital In-Patient

Enquiry (HIPE) system, which provides information on the number of discharges and

number of days spent in hospital. In 2001, of 543,141 discharges recorded, 61,325 (11.3%)

were due to vascular diseases. These accounted for 469,136 bed days, at 13.7% of all bed

days the leading disease burden in Irish public hospitals (Department of Health and Children

2002).

1.2   Treatment of Hypertension and Hyperlipidaemia

1.2.1   Treatment of hypertension

Hypertension may be controlled by lifestyle modifications and pharmacological therapy. Although the phenomenon of hypertension was first noted by the Chinese about 4000 years ago it was not until the 1950s with the introduction of diuretics that there was any pharmacological treatment for the condition.

1.2.2   Benefits of treatment for hypertension

Many studies have demonstrated the benefits of treating hypertension. These benefits include a reduction in the risk of stroke by 30-43% (Collins and Macmahon 1994) and myocardial infarction (MI) by 15% (Collins et al 1990). Treatment to lower blood pressure after MI and stroke reduces the risk of recurrence and mortality (MacMahon et al 1997).

Hypertensive patients with BP >140/90 mmHg are at higher risk of cardiovascular complications than those controlled to <140/90 mmHg (Benetos et al 2002). There is an increased risk of mortality in drug-treated hypertensives who have not achieved blood pressure <160/95 mmHg compared to normotensives. Klungel et al (2000) found that 32% of strokes in treated hypertensives could be attributed to uncontrolled BP. The risk of mortality in drug-treated hypertensives who have achieved blood pressure <160/95 mmHg compared to normotensives is also increased but not to the same extent. Compared to normotensives, hypertensive drug-treated women (men) are at 95% (82%) higher risk if BP>160/95 mmHg and at 30% (36%) higher risk if BP<160/95 mmHg (NCHS 2004).

1.2.3 Types of therapy for hypertension

In Ireland, five main classes of drugs are currently prescribed to treat hypertension: thiazide diuretics, beta blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin-II (ATII) antagonists (Weir 1999, Dictionary of Medicines 2000, Spence 2001, Williams 2003, National Medicines Information Centre 2004). Essential hypertension is a heterogeneous condition, affected by various mechanisms in the body: the different classes of antihypertensives target different aspects of hypertension. Because of this, monotherapy is often not sufficient to control hypertension – a combination of medications with different actions may have more success (Waeber 2002).

1.2.3.1 Diuretics

The first and oldest class of drugs are the diuretics. These act by increasing the elimination of water and salts from the system; reduction of the amount of fluid in the blood means the heart has a smaller volume of blood to pump around the body and therefore less work to do. Thiazide-type diuretics simultaneously cause the smooth muscles in the arterioles to dilate. The heart therefore does not have to pump so hard to get blood into the arteries and the blood pressure is decreased. Diuretics are often prescribed in combination with potassium if the effects of potassium loss are a problem for the patient. Alternatively a potassium-sparing diuretic may be prescribed – these do not cause the loss of potassium ions and do not worsen diabetes or gout. The thiazide diuretics achieve a moderate loss of fluid and are used

31

for the long term treatment of hypertension and oedema associated with heart failure. In the long term the diuretic effect decreases but the antihypertensive effect continues.

1.2.3.2 Beta Blockers

Beta blockers act against the beta1 receptors of the heart and, in the case of non-selective beta blockers, the beta2 receptors of the airways and blood vessels too. This reduces the heart rate and force of the heart muscle contraction. They also prevent vasodilation of the blood vessels; in spite of this their action on the heart is sufficient to reduce blood pressure. Beta blockers also suppress the release of renin and hence decrease the level of the vasoconstrictor angiotensin II.

1.2.3.3 Calcium Channel Blockers

Calcium channel blockers selectively inhibit the passage of calcium ions through specific ion channels of the cell membrane in muscle cells of the heart and arteries, causing the vascular smooth muscle to relax and hence producing a decrease in peripheral vascular resistance and a fall in blood pressure. There are three classes of calcium channel blocker – class I drugs (eg verapimil) act mainly on the heart to reduce the force of contraction and conduction of nerve impulses. Class II drugs (eg nifedipine) act mainly on the blood vessels and are used to treat angina and hypertension. Class III drugs (eg diltiazem) act mainly on the coronary arteries and are used to treat angina and (in longer acting formulations) hypertension.

1.2.3.4 ACE inhibitors

The synthesis of captopril, the first oral ACE inhibitor, arose from the observation that workers in Brazilian banana plantations who were bitten by the snake *Bothros jararaca* collapsed due to a sudden fall in blood pressure – the venom contained an ACE inhibitor. Captopril was licensed by the FDA for the treatment of hypertension in 1982. Angiotensin-converting enzyme (ACE) inhibitors work by suppressing the action of the enzyme that causes the conversion of angiotensin I to angiotensin II. Angiotensin II causes the blood vessels to narrow and blood volume to increase, which can contribute to high blood pressure. Thus the ACE-inhibitor is a vasodilator – by blocking the action of angiotensin-II it causes the arteries to dilate. ACE inhibitors also lower blood pressure by improving the blood supply to the kidneys and increasing the excretion of salt in urine. ACE inhibitors work better in younger people and whites than old people and blacks because the renin-angiotensin systems of the latter are more suppressed.

1.2.3.5 ATII antagonists

Angiotensin II antagonists work against the action of the vasopressor angiotensin II, hence blood vessels widen and the blood pressure decreases. The ATII antagonists are currently not widely prescribed in Ireland.

1.2.4   Classification System

The Anatomical Therapeutic Chemical (ATC) system is a hierarchical scheme whereby drugs are classified according to the organ or system upon which they act, and their therapeutic, pharmacological and chemical properties (WHO Collaborating Centre for drugs statistics methodology, 2004). Drugs acting on the cardiovascular system are firstly assigned the letter "C" and are divided into ten groups, C01-C10, according to therapeutic classification. Diuretics are coded C03, beta blockers C07, calcium channel blockers C08, drugs acting on the renin-angiotensin system C09 and lipid reducing agents C10. Each of these groups is further divided by pharmacological properties – thus plain ACE inhibitors are coded C09A, ACE inhibitor combinations are coded C09B and angiotensin II antagonists are coded C09C. The next level of classification is by chemical subgroup and the final level is by chemical substance. For instance ACE inhibitors in combination with diuretics are coded C09B A and captopril with a diuretic is coded C09B A01.

The majority of drugs with an ATC code have been assigned a defined daily dose (DDD), which is the assumed average maintenance dose per day for the drug used for its main indication in adults. This is not necessarily a reflection of the recommended or prescribed dose, which often differs according to individual patients' characteristics (eg age and weight), pharmacokinetic considerations, and stage of treatment (initial doses may be lower). While plain substances used to treat hypertension have been assigned DDDs as mass of the active agent, DDDs for combination treatments for hypertension are based on the average number of dosing intervals per day. Thus one tablet is the DDD for a combination taken once a day,

two tablets is the DDD for a combination taken twice a day, and so on. (See appendix for ATC and DDD for antihypertensives and statins).

1.2.5   Treatment guidelines for hypertension

Recent guidelines recommend initial treatment with a diuretic (WHO, 2003) or diuretic combination (Chobanian et al 2003) in hypertension with no compelling indications. If blood pressure control is not achieved either the dose is increased or a second antihypertensive is added. The European Society of Hypertension Guidelines suggest that any of the main classes of antihypertensives may be used to initiate therapy, either as monotherapy or a low-dose combination. If blood pressure control is not achieved, either the dose is increased or a different agent is substituted (in the case of initial monotherapy) or a third drug is added (if the initial therapy were a combination) (Guidelines Committee, 2003). The British Hypertension Society Guidelines aim to reduce blood pressure as much as possible (Laurent 2004).

The choice of medication depends on the severity and type of hypertension, comorbidities and contraindications. According to the Sixth Report of the Joint National Committee for the Detection and Control of High Blood Pressure the recommended practice for the treatment of patients newly diagnosed with uncomplicated hypertension and who have not responded sufficiently to lifestyle changes is to start pharmacological treatment with a low dose, once-daily diuretic or beta-blocker (Anonymous, 2003). The ALLHAT trial concludes that the preferred initial treatment is a thiazide diuretic (Appel 2002). There is evidence

from some trials that calcium channel blockers are less effective than other types of medicine in preventing myocardial infarction and congestive heart failure; however the ALLHAT trial concludes that the mortality rate is the same for calcium channel blockers as for ACE inhibitors, beta blockers and diuretics (ALLHAT Officers, 2003).

Most patients need at least two different antihypertensive drugs to achieve blood pressure below 140/90 mmHg. In the ALLHAT trial, 63% of patients were treated with two or more drugs. Blood-pressure lowering effects of different classes of antihypertensives in combination are additive (Law et al 2003).

1.2.6   *Inferring diagnoses from prescriptions*

Patients who are prescribed antihypertensive therapies may have been prescribed these drugs for hypertension and may have been prescribed them for more advanced stages of disease, for instance IHD and heart failure. Beta blockers are prescribed for hypertension, angina, arrhythmias, migraine and after heart attack as a secondary prevention. Calcium channel blockers may be used to treat arrhythmia and angina as well as hypertension. ACE inhibitors are used to treat heart failure and angina as well as hypertension.

In the absence of diagnostic information it is not possible to determine a diagnosis of hypertension simply from the prescribed medicines. Patients treated with antihypertensives are quite likely to have diagnoses other than hypertension. A recent study (Pittrow et al 2004) of antihypertensive drug utilization in primary care in Germany revealed that of 17,485 patients identified with a diagnosis of hypertension, 23.9% also had IHD, 29.2% had other

heart disease and 3.6% had cerebral infarction. Additionally, 5,204 (29.8%) of the hypertensive patients had diabetes. Patients with other diagnoses were more likely to be treated with antihypertensive drugs than were patients with a diagnosis of hypertension alone. 44.0% of the 9,416 patients with a diagnosis of hypertension alone were treated with antihypertensive monotherapy, representing 55.5% of all pharmacologically treated patients with this diagnosis. This is in contrast to the 26.0% of patients with a concomitant diagnosis of IHD who were prescribed antihypertensive monotherapy – that is 27.9% of all patients with these diagnoses and pharmacologically treated with antihypertensives.

Further analysis reveals that 61% of the patients treated with a single antihypertensive drug had a diagnosis of hypertension alone, while 17% of these patients on monotherapy also had diagnosed IHD. Meanwhile 46% of the patients treated with two, and 31% of the patients treated with three or more antihypertensive drugs had the single hypertension diagnosis, compared with 29% of patients on two drugs and 44% of patients on three or more drugs having hypertension and IHD.

Further analysis of the data provided in this study reveals that of all the pharmacologically treated patients with a diagnosis of hypertension, 49% had this diagnosis alone. 27% also have a diagnosis of IHD. 52% of beta blockers and 50% of AT1 antagonists were prescribed to the patients with a diagnosis of hypertension alone. 35% of the diuretics and 33% of the calcium channel blockers and ACE inhibitors were prescribed to the patients with hypertension and IHD. 26% of the patients who received ACE inhibitors, calcium channel blockers or diuretics had a diagnosis of hypertension and at least one comorbidity, not including IHD.

These utilization patterns may not be applicable to other populations. However they demonstrate that antihypertensives are often prescribed to patients with more advanced stages of disease than hypertension, and while it is more likely that a patient treated with antihypertensive monotherapy or a beta blocker has no diagnosis other than hypertension, this is by no means definite. In the German study, forty percent of patients prescribed monotherapy and half the patients prescribed beta blockers had comorbidities. It appears it is not correct to assume a diagnosis of hypertension knowing only that the patient was prescribed antihypertensives.

In reality the proportion of people treated with antihypertensive drugs who have a diagnosis of hypertension only may be lower than indicated here as this data did not include any patients who did not have a diagnosis of hypertension but were treated with antihypertensives. For instance, some patients are prescribed beta blockers to treat migraine.

It may be possible to identify patients with specific diseases from their prescription histories. For instance, treatment for heart failure includes ACE inhibitors, cardiac glycosides (digoxin) which improve the force of contraction and output of the heart, nitrates and diuretics (Davies et al 2000, Lonn and McKenzie 2000). There have been several attempts to validate the identification of patients with IHD from their prescription histories. Gray et al (2000), using a UK population, found that selecting patients with prescriptions for nitrate, aspirin, atenolol, statin and digoxin resulted in the identification of 89% (95% CI 81%-98%) of patients with IHD. However this method also identified a substantial number of patients without IHD - only 32% (95% CI 26%-38%) of patients thus identified actually had IHD.

A Dutch study found that 93% of patients who had repeat prescriptions for nitrates had at least possible angina pectoris (Maitland-van der Zee et al 2003).

1.2.7 *Adverse effects of pharmacological therapy for hypertension*

Antihypertensive drugs of all classes are known to cause adverse effects. The thiazide and thiazide-type diuretics can cause depletion of potassium (hypokalemia), muscle cramps, increased HDL/LDL, impaired diabetes control, hyperglycaemia (high glucose levels), hyperuricemia (high uric acid levels, which may cause gout) and sexual dysfunction. Most beta blockers can cause mild chronic fatigue, low exercise tolerance, nightmares, insomnia, difficulty breathing, sexual dysfunction, decreased HDL cholesterol and bradycardia (an abnormally slow heart rate). Side effects due to treatment with calcium channel blockers include tachycardia (a condition in which the heart rate exceeds 100 beats per minute), headaches, oedema (retention of fluid), flushing, dizziness and bradycardia. ACE inhibitors can cause hyperkalemia, rash, dry cough and angioneurotic oedema. ATII antagonists may cause hyperkalemia and impaired renal function. Adverse drug reactions for specific therapies are summarised in the Appendix.

Adverse drug reactions (ADR) are more likely to occur soon after initiation or changes in therapy. They may be related to dose, in particular for thiazides, beta blockers and calcium channel blockers (Law et al 2003). Elderly women may be especially vulnerable to adverse drug reactions due to excessive dose (Cohen 2002).

Concurrent treatment with other drugs increases the risk of adverse events due to interactions between drugs. However, in patients treated with combinations of different classes of antihypertensives the prevalence of ADR is less than additive (Law et al 2003).

The rate of ADR due to treatment with antihypertensives is quite low. Clinical trials indicate that the rate of discontinuation of antihypertensives due to ADR ranges from 3-15% and is not different to the rate reported under treatment with placebo (Ross et al 2001).

In a study of patients treated for one year with one of six antihypertensives or placebo, (Preston et al 2000) the rates of reported ADR were similar for the placebo and active treatment groups – in fact the highest rates of ADR were in the placebo group where 15.5% of patients reported headaches (compared to 7.9% of treated patients) and 16.6% reported joint pains (compared to 10.9% of treated patients). These could be symptoms of hypertension wrongly attributed to the treatment; for instance headaches are a symptom of hypertension (see Section 1.1.2).

In Preston's study, the rates of discontinuation due to ADR were 13% in the placebo group and 12% in the active treatment group, and the rates of discontinuation due to excessively high blood pressure were 14% in the placebo group and 7% in the active treatment group.

However the reported rates of adverse events attributed to antihypertensive medicines in community settings are much higher. A Japanese survey of patients treated with antihypertensives found that 49% of those with well-controlled BP and 61% of those with poorly controlled BP reported side effects (Toyoshima et al 1997). It appears that the

incidence of side effects varies by drug class. A Canadian study reported that 52.5% of patients treated with losartan, 60.2% of patients treated with an ACE inhibitor and 69.7% of patients treated with a CCB claimed they experienced side effects during the first 3 months of therapy (Gregoire et al 2001).

Discontinuation of antihypertensives can result in elevated blood pressure and increase the risk of cardiovascular events (Meredith 1996, Kostis et al 1998). Particular care must be taken in the withdrawal of beta blockers. (Psaty et al 1990)

There have been few studies of the withdrawal of antihypertensive therapy; a review found that 15%-50% of withdrawals were successful but concluded that in community settings many patients are unsuitable for withdrawal (Fletcher et al 1998). Factors predicting the return of high blood pressure include high pre-treatment blood pressure, obesity, short duration of treatment and left ventricular hypertrophy. The risk of a return to high blood pressure tends to be greater amongst men than women. In practice, it is recommended that patients may be considered for withdrawal of antihypertensive therapy if they have been normotensive for six to twelve months, are treated with a single antihypertensive therapy, had mildly elevated blood pressure prior to treatment, and have made lifestyle modifications (for example losing weight, increasing exercise, restricting alcohol and salt intake) (Andolsek et al 1998). It is recommended that patients who have withdrawn from therapy should be monitored every three to six months for the rest of their lives.

1.2.8 Treatment of hyperlipidaemia

High LDL cholesterol may be lowered by changes in lifestyle – for example, stopping smoking, losing weight if overweight, modifying the diet, limiting alcohol consumption and increasing physical activity. It may also be lowered by pharmacological therapies.

1.2.9 Benefits of treatment of elevated cholesterol levels

An elevated cholesterol level is a risk factor for ischaemic heart disease (IHD). Cholesterol levels may be reduced by treatment with statins (or HMG CoA reductase inhibitors). The evidence of several large clinical trials published between 1994 and 1998 (Anonymous 1994; Sacks et al 1996, Shepherd et al 1995, Anonymous 1998, Downs et al 1998) established the benefits of statin treatment in primary and secondary prevention of coronary heart disease. The clinical trials indicate that continuous treatment for at least one to two years is necessary before patients experience these benefits. Prevention of diseases of the circulatory system has economic benefits (Caro et al 1997).

1.2.10 Types of therapy for hyperlipidaemia

1.2.10.1 Statins

Hydroxymethyglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as statins, act on the enzyme that catalyses the conversion of HMG-CoA to mevalonic acid, which is an early precursor of cholesterol. This reduces cholesterol synthesis in the liver. Statins are the most effective drugs for reducing LDL cholesterol; depending on the particular statin and dose LDL cholesterol may be reduced by 18-55% (NCEP 2002).

1.2.10.2 Other drugs

The other main types of drug for the treatment of high cholesterol are niacin, fibrates and bile acid sequestrants. Niacin lowers LDL and total cholesterol and triglycerides and raises HDL cholesterol. Fibrates (gemfibrozel, fenofibrate, clofibrate) are useful for lowering serum triglycerides. Bile acid sequestrants (cholestyramine, colestipol, colesevelam) reduce LDL cholesterol and enhance the effects of other drugs (especially statins) in reducing LDL cholesterol (NCEP 2002).

1.2.11   Treatment guidelines for hyperlipidaemia

The most recent US guidelines identify LDL cholesterol as the target for intervention, and recommend that a level of less than 100 mg/dL (2.6 mmol/L) be achieved (Expert Panel, 2001). The European guidelines on cardiovascular disease prevention in asymptomatic patients suggest assessment of their overall risk (based on age, sex, smoking status, total cholesterol and systolic blood pressure) and treatment if, following lifestyle modifications, the total cholesterol is greater than 5.0 mmol/L or LDL cholesterol is greater than 3.0 mmol/L (De Backer et al, 2003).

1.2.12   Adverse events due to statins

Adverse events due to statins are relatively rare (Newman 2003). Rates of discontinuation of statin therapy due to adverse events are not significantly different to rates of discontinuation for placebo. Some people treated with statins may be at higher risk of adverse events involving skeletal muscle (for example myalgia and rhabdomyolysis). The reported incidence of myotoxic reactions in patients treated with statins ranges from 1-7% and varies by drug and is dependent on dose. The risk of these adverse reactions is increased by co-prescription of certain drugs that inhibit the metabolism of statins (for example itraconazole, cyclosporin, erythromycin and nefazodone) (Bellosta et al 2002). Factors that increase the risk of myotoxicity include electrolyte disturbances, infections, major trauma, hypoxia and abuse of drugs (Ucar et al 2000). The risk of adverse events involving skeletal muscle is higher during and after exercise (Singinger and O'Grady 2004).

44

There is some evidence that withdrawal of statins in patients with acute coronary syndromes may increase cardiovascular event rates (Heeschen et al 2002). Puccetti et al (2003) found platelet hyperactivity, which is associated with raised LDL cholesterol, in the second week after discontinuation of a statin.

1.3   Control of Hypertension and Hyperlipidaemia

1.3.1   *Control of hypertension – population rates*

Recent figures for US adults from the National Health and Nutrition Examination Surveys (NHANES) indicate that 29% of the population have hypertension, of whom 69% are aware of this, 58% are treated and 31% controlled (Hajjar and Kotchen 2003). This implies a rate of control amongst treated hypertensives of 53%. In England, where approximately 40% of women and 30% of men with hypertension are treated, the rate of control amongst treated hypertensives is 37% (Great Britain Department of Health 2003). In Ireland, the Cork/Kerry study found that of the people aged 50-69 identified with hypertension, 38% were pharmacologically treated and 15% controlled - so 41% of those treated had their blood pressures controlled to below 140/90 mmHg (Creagh et al 2002).

1.3.2   *Control of hypertension – evidence from clinical trials*

Many hypertensive patients do not achieve control of blood pressure to < 140/90mmHg in spite of adequate drug treatment and good compliance: in a study of recent trials only one quarter achieved systolic blood pressure < 140 mmHg (Mancia and Grassi 2002). Table 1.3 summarises the findings with respect to long-term control of blood pressure from three large clinical trials. Regardless of the treatment strategy for patients with high blood pressure, a significant proportion (in the medium term typically one third) of patients failed to achieve blood pressure control in the optimal setting of the clinical trial. Most patients required the addition or substitution of other antihypertensives to control blood pressure; in addition, those who did not respond to monotherapy had lower rates of blood pressure control when treated with combinations of therapies.

Table 1.3 Evidence on blood-pressure control in clinical trials

Trial	Initial treatment	Modifications	Time	Overall control rate
VALUE	Amlodipine or	40% initial mono		
(1)	Valsartan	27% + HCTZ	2.5 years	60.5%
		15%+HCTZ+other		
ALLHAT	Chlorthalidone or	27% monotherapy		
(2)	Amlodipine or	63% > 1 drug	5 years	66%
	Lisinopril			
CONVINCE	Atenolol or	25% initial mono		
(3)	Hydrochlorothiazide	50% + other AHTs	2.5 years	67%
	(HCTZ) or	25% other AHTs		
	Verapamil			

Table references (1) Julius et al 2003, (2) ALLHAT Officers 2003, (3) Black et al 2001.

In summary, about two thirds of patients achieve long-term blood pressure control when treated with antihypertensive therapies in the optimal setting of the clinical trial, and population control rates range from about 40-50% in treated hypertensives. If the blood pressure control rates achieved in the clinical trials were the maximum possible – that is, all patients were given appropriate treatments and used all treatments as they were prescribed – the gap in control rates must be partly due to differences in treatment strategies, partly due

to non-compliance and partly due to differences in other factors. There is insufficient evidence to assert that all or most treatment failures are due to non-compliance, as is sometimes done (see, for instance, Stephenson (1999)).

1.3.3   Factors affecting control of hypertension

Poor blood pressure control in treated hypertensive patients may be attributed to the healthcare system, the doctor, the patient or the treatment. Patients' compliance with the antihypertensive regimen may be influenced by all of these factors and their interrelationships (Egan and Basile 2003).

1.3.3.1 Implementation of treatment guidelines

According to a press release issued by the European Society of Cardiology (ESC Press & PR Office 19 Feb 2003), a significant proportion of doctors do not follow national cardiovascular disease prevention and treatment guidelines. Rates vary between countries: one fifth of doctors in France and Poland, one third of doctors in Germany and Italy and three quarters of doctors in Spain and the UK adhere to heart disease risk assessment guidelines (EUROASPIRE 2001). Reasons for these differences include a lack of support at Government level and financial constraints. Measures to ensure the implementation of the guidelines would be expected to improve cardiovascular outcomes (Feely 1999). Ebrahim et al (1998) in a thorough review of the control of hypertension for the prevention of stroke,

concluded that improving professional standards of detection and treatment would achieve greater benefits than taking measures to improve patients' compliance.

In the ALLHAT trial, blood pressure control was associated with geographic region (poorer control in the south-eastern US, better control in Canada and Puerto Rico than the US) and practice setting (poorer control in private patients). Differences in health care systems or in sociodemographic factors may explain the geographical and setting associations with blood pressure control (ALLHAT Officers, 2003).

1.3.3.2 Doctors

The doctor is not always aware of treatment guidelines and does not always prescribe appropriate therapy. In many cases it appears that hypertension is not treated aggressively enough and this may be the main reason for poor blood pressure control (Hyman and Pavlik 2002). The doctor has an important role in facilitating patients' compliance with lifestyle changes and pharmacological treatment.

1.3.3.3 Patients

An observational study of US hypertensive patients (Knight et al 2001) found that poor control of blood pressure was associated with increasing age (patients aged over 65 were more than twice as likely to have poorly controlled blood pressures as patients aged under 55), use of more than one antihypertensive drug, lack of knowledge of blood pressure targets

and reported drug side effects. Patients with angina were more likely to have controlled blood pressure.

Another study, based on Finnish patients (Jokisalo et al 2003), found that poor blood pressure control was associated with feelings of hopelessness towards hypertension, frustration with treatment and tension with blood pressure measurement. Frustration with treatment was indicated by agreement with the ideas that the antihypertensive medication was not effective and concerns that the treatment regimen involved interruptions to daily life and changes of habit. The authors suggest that these factors may be both causes and consequences of the level of blood pressure control achieved with therapy. This study also identified old age, monotherapy, and non-compliance in men as risk factors for poor control. It is interesting that non-compliance was associated with poor blood pressure control only in men; in fact women reporting non-compliance were the group most likely to achieve blood pressure control. This study is questionable in its analysis of compliance outcomes as it was measured by patient report, and has been established that a significant proportion of noncompliant patients report compliance (see section 2.2.2.1). The rate of uncontrolled blood pressure was very high (80%) and the rate of self-reported non-compliance rather low (14%).

An Italian study found that older patient age, older doctor age and presence of diabetes mellitus increased the risk of uncontrolled blood pressure and that the number of other medications taken and a history of MI reduced the risk of uncontrolled blood pressure. Patient gender, BMI, smoking, cholesterol level, family history of hypertension, previous visits for cardiologic, nephrologic or vascular surgery evaluation, hospitalisation for heart

failure, number of admissions for surgery, length of patient follow-up, type of antihypertensive, mean daily dose and adherence to the regimen were not associated with blood pressure control (Degli Esposti et al 2004).

The ALLHAT trial found that blood pressure control at 3 years after entry into the study was more likely in younger, male and non-black patients and those with lower baseline blood pressures. Patients with type 2 diabetes, with BMI>30, who had previously been treated for hypertension or who had left ventricular hypertrophy (LVH) were more likely to have uncontrolled blood pressure. Blacks, women and older patients were less likely to be treated with two or more drugs, which may contribute to the lower control rates in these groups.

Some types of patients may be more difficult to treat successfully than others. Patients with higher baseline blood pressures, renal insufficiency or obesity, and those who have hypertension due to secondary causes such as primary aldosteronism are more likely to have resistant hypertension. Concurrent use of certain other drugs, such as nonsteroidal anti-inflammatories and oral contraceptives may interfere with treatment for hypertension. (Calhoun et al 2002).

1.3.3.4 Treatment

It has been suggested that some patients respond better to one class of antihypertensive than another and the treatment strategy could involve sequential monotherapy to determine the best individual response. A trial of different antihypertensive drug classes in elderly patients

found that 6-15% achieved blood pressure control after one month on monotherapy and 29% achieved control on sequential monotherapy (Morgan et al 2001).

In another study 1,292 men were randomised to an initial therapy (one of six different antihypertensive drugs or placebo), and the initial treatment failed in about one third (410) of them, of whom 352 were randomised to a second treatment which was successful in 49.1%. (Materson et al 1995).

An alternative recommendation is low-dose combinations of antihypertensive therapies, as increasing the dose of a single drug does not result in a linear decrease in BP but does increase the risk of ADR, while adding another class of antihypertensive has an additive effect in terms of decreasing BP but the risk of ADR is less than additive (Law et al 2003)

1.3.3.5 The placebo effect

A study that examined the effects of placebo in comparison to active antihypertensive treatment (one of six different drugs) found that after one year 30% of the patients treated with placebo and 58% of patients treated with an antihypertensive had achieved DBP control. Interestingly an increase in dose of the placebo resulted in improved blood pressure control in some patients (Preston et al 2000). The placebo effect may be due to the natural history of the disease (it is possible that patients may experience spontaneous improvement or worsening of their hypertension during the course of the disease), regression to the mean, measurement error or random variation in individuals over time.

1.3.4   Control of hyperlipidaemia

With respect to control of high cholesterol, the issues are similar to those outlined above for control of hypertension. Population control rates of high cholesterol are quite low, in spite of treatment, and do not meet the levels achieved in clinical trials (Andrade et al 1999, Frolkis 2002). For instance, in a study of men aged 35-55 in France and Northern Ireland, 47% of the French and 43% of the Northern Irish men treated for high cholesterol were controlled to total cholesterol < 6.5 mmol/L and LDL cholesterol < 4.2 mml/L (Marquez-Vidal et al 1997). In contrast, in the 4S trial, 72% of patients had achieved total cholesterol < 5.2 mmol/L after one year of treatment with simvastatin (Anonymous 1994). Like hypertension, high cholesterol is a condition with generally mild symptoms that nevertheless requires long-term (possibly life-long) treatment to reduce the risks of cardiovascular and cerebrovascular morbidity and mortality. As in the case of antihypertensives, statin treatment has demonstrated benefits in terms of mortality, morbidity, and economics (Ebrahim et al 1999).

2. Patients' Compliance

This chapter is an introduction to the research on patients' compliance. It begins with a discussion of terminology and definitions, in the context of the historical research on the topic. This is followed by a description of the methods used to estimate compliance. The factors that influence compliance are also discussed; there are complex dependencies between these factors in relation to their effects on compliance. Section 2.4 is a discussion of the relationship between compliance with prescribed therapies to lower blood pressure and cholesterol and morbidity and mortality outcomes.

2.1. The Issue of Compliance

There have always been patients who are unwilling or unable to follow their doctors' instructions. Hippocrates (460-377BC) is attributed with advising doctors

"...to be alert to the faults of the patients which make them lie about their taking of the medicines prescribed and when things go wrong, refuse to confess that they have not been taking their medicine"

Compliance in the medical context is a complex problem. This is in part due to the fact that the definition is so broad; indeed there is disagreement on whether the word 'compliance'

55

should be used at all – it has been suggested that the words 'adherence' or 'concordance' or 'alliance' have more positive connotations, shifting the emphasis from passive obedience to active participation in the treatment process by patients. However, the term "compliance" is the one most often used in previous research (Blackwell 1996). Whichever word is used, the concept itself is open to interpretation, particularly in the context of quantitative estimation, where the exact definition depends on the context, the type of therapy and type of patient – and also to some extent upon the knowledge and preferences of the researchers. In the words of one author, the diversity of definitions for compliance reflect "ambiguity and ambivalence" (Metry 1999). In the absence of a clear definition, estimates of compliance are not necessarily comparable.

In 1973 Barry Blackwell published an article on patient compliance with drug therapy (Blackwell 1973). This was one of the earliest articles to use the term 'compliance' to describe the relationship between the prescribed medication regimen and the patient's pattern of medication use. In fact the commonly used definition of compliance in the medical context has a wider scope, encompassing several aspects of treatment regimens – for example, lifestyle changes, medical appointments and other advice or prescriptions. The first international conference on compliance took place at McMaster University in Canada in 1976 and the following definition of compliance was adopted: "the extent to which a patient's behaviour (in terms of taking medications, following diets, or executing other lifestyle changes) coincides with the clinical prescription" (Sackett 1976).

Blackwell's 1996 article, reviewing the previous 25 years' research, summarised various aspects of patients' compliance (Blackwell 1996). He noted that more than 12,000 articles,

covering almost every area of medicine, had been published on this topic in the previous 25 years. The aspects of compliance he reviewed were the history of research, terminology, necessity, definitions, measurement, sufficiency, models for compliance and types of intervention to improve it. Partly due to problems with definitions, measurements and responses, at least half the studies reviewed had failed to find a positive association between compliance and outcomes. But even though much of the research on compliance is limited by methodological problems, the magnitude of non-compliance is similar regardless of the condition, and certain characteristics of patients and treatments tend to be associated with compliance.

An article that reviewed the research published between 1975 and 1993 on patient compliance with treatment found that definitions of compliance are not always made explicit in the research (Vermeire et al 2001). Where they are, the focus may be on the process of medication use or on achievement of the desired outcome. This article points out that there are different types of compliance, in particular making a distinction between primary non-compliance, wherein a patient has a prescription but fails ever to have it made up at a pharmacy, and secondary non-compliance, wherein the patient collects the initial prescription but takes the wrong dose, or takes the medicine at the wrong times, or forgets to take doses, or stops the treatment too soon – for instance by failing to obtain a repeat prescription. Each type of non-compliance may be intentional or unintentional.

Recently there have been renewed efforts to highlight the issue of patients' compliance, with contributions by the WHO (2003) and conferences organised by the American Heart Association (AHA 2004). There have also been suggestions that in order to understand and

improve patients' compliance it should be thought of in a different way – for instance as a medical error (Barber 2002) or an ethical issue (Kahn 2001).

The idea that the term "compliance" is not satisfactory is not a new one; at the first McMaster symposium, 'the unfavourable connotation was discussed at length … and two alternative terms were briefly considered: "adherence" and "therapeutic alliance"'(Sackett 1976).

The definition of adherence adopted by the World Health Organisation in June 2001 is "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO 2003). Meanwhile, motivated by the idea of empowering the patient, the concept of concordance is "based on the notion that the work of the prescriber and patient in the consultation is a negotiation between equals and that therefore the aim is a therapeutic alliance between them" (Royal Pharmaceutical Society 1997).

For the purposes of this thesis, the McMaster definition and the WHO definition may be considered equivalent. I shall use the term "compliance" to denote the extent of agreement between what the patient was prescribed and what he or she actually used. When quoting from other studies, I shall use their terms.

2.1.1   *Magnitude of non-compliance*

Typically only half the patients treated for chronic conditions are classified as compliant with treatment (Haynes et al 2001). Low levels of compliance are common regardless of disease, treatment, or population. Multitudes of studies of compliance have been published – a few examples - chronic disease (Miller 1997, Dunbar-Jacob and Mortimer-Stephens 2001), heart failure (Roe et al 1999, Evangelista and Dracup 2000, Bobachik et al 2002), myocardial infarction (Butler et al 2002) and coronary heart disease (Kopjar et al 2003). Depending on the definition of compliance and method of assessment, 20-80% of patients treated for hypertension are considered "good compliers" (Costa 1996). Among patients treated for high cholesterol 15-78% have discontinued treatment one year after the initial prescription (Tsuyuki and Bungard 2001). The variability in these estimates reflect the ambiguity of the definition of compliance as much as the variability in actual compliance rates. The WHO describes poor adherence as "a worldwide problem of striking magnitude" (WHO 2003), a problem that is growing as the burden of chronic diseases increases worldwide.

2.2   Methods of Assessment

2.2.1   *Quantitative definitions of compliance*

The definitions of compliance are broad and methods of quantitative estimation vary. Compliance may be thought of as a comparison between two time series: the prescription and actual drug use, and has been described as "the extent to which the patient's dosing

59

history conforms to the prescribed regimen" (Urquhart 1997). This emphasises the importance of timing in taking medicines. Estimates of compliance often ignore the dimension of time, which simplifies the analysis, but at the expense of losing information. Simply calculating the percentage of drugs taken may not be an adequate measure of compliance and gives no information on the pattern of use. For instance, it is known that patients tend to miss entire doses rather than taking partial doses of their tablets at the prescribed times – that is, they are compliant with respect to the dose but not with respect to timing (Urquhart 1997). A study of compliance with antihypertensives found that 92% of doses prescribed were consumed though only 63% on time (Choo et al 1999).

Specific quantitative definitions of compliance vary and often seem to be in accordance with past practice rather than a base of evidence. Few studies attempt to validate their definitions of compliance. For instance, the medication possession ratio (MPR) – or equivalently the proportion of days covered (PDC) may be calculated, and "good compliance" is often ascribed to patients who take more than 80% of their medicines. Apart from the arbitrariness of this threshold, the concepts of good and bad compliance may be of little use in the context of a continuous dose-response relationship. Ignoring differences in bioavailability, the individual's response to a particular drug is a function of compliance and dose-response for that drug (Goldsmith 1976). The WHO report on adherence recommends that dose-response curves for real-life situations are necessary for defining adherence thresholds for different therapies (WHO 2003).

The evidence in support of an 80% MPR threshold for compliance with antihypertensives is not entirely convincing. This threshold makes no allowance for differences in the methods of compliance measurement or for the characteristics of the specific drug. The main supporting evidence appears to be a 1975 study of Canadian steel-mill workers whose compliance with their antihypertensive medicines was determined by pill count. (Sackett et al 1975). In a later randomised controlled trial, the same author found that 40% of the patients who took over 80% of their antihypertensives as assessed by pill count had their blood pressures stabilised after six months of treatment, whereas 28% of patients who took less than 80% of their pills had their blood pressures stabilised (Sackett et al 1978). It is quite striking that only 40% of the patients considered compliant had their blood pressures controlled: if 80% compliance is adequate for blood pressure control, presumably the remaining 60% were not adequately treated. This of course assumes the method of determining compliance levels was accurate. However, compliance as assessed by pill count tends to overestimate the actual level (see section 2.2.2.2) so that patients who were identified as taking 80% of their drugs may have actually been taking rather less, which may explain the low rate of blood pressure control. Using electronic monitoring (which is considered the most accurate method of measuring compliance) in a highly compliant population treated with a once-daily dose of the ACE inhibitor trandolapril for four weeks, Mallion et al found no relationship between the level of compliance and blood pressure reduction, with the exception that patients who were over-compliant (opened the pill bottle more times than needed) had a greater SBP reduction than patients who were good compliers (took 80-100% of prescribed doses) (Mallion et al 1996). The inability of this study to find a statistically significant relationship between compliance level and blood pressure reduction could have been because few patients were poor compliers; indeed one of

61

the limitations of electronic monitoring of compliance is that patients' awareness that their drug use is monitored tends to improve it (Burnier et al 2001).

In summary, it appears that the clinical evidence for a cut-off point in the level of compliance necessary for effective treatment of hypertension is not entirely convincing, and the choice of 80% is in accordance with past practice rather than based on evidence that 80% compliance with any antihypertensive regimen will reduce blood pressure and morbidity and mortality risks. It may be preferable to use a continuous measure of medication possession ratio, or choose drug-specific thresholds based on the dose-response. But preferable to any summary method across time is to use a measurement of compliance that incorporates timing. Evidence on the relationship between compliance with antihypertensives and statins and outcomes is discussed further in section 2.4.

2.2.2   *Methods of measurement*

Methods of measurement of compliance include questionnaires, pill-counts, biochemical markers, prescription claims data, and electronic monitoring (MEMS) (Metry 1999, Johnsrud 2002). There is no perfect method of measuring compliance: at present electronic monitoring is considered the most accurate method. It may be preferable to assess compliance by several methods – this is recommended by the WHO (2003). The limitations of the data collected by each method must be considered when drawing conclusions.

2.2.2.1 Subjective ratings

Doctors tend to overestimate the compliance of their patients (Jacobs 2002). A paper on the measurement of compliance in a clinical trial found that there was no correlation between the doctors' reports and any of the other measures of compliance - MEMs, pill count, patient report and urinary potassium excretion (Hamilton 2003). Assessment by patient self-report depends on the method used (diaries, interviews or questionnaires) and the framing of questions. Patients who admit to non-compliance tend to describe their behaviour accurately, whereas patients who claim compliance tend to include a large proportion who are in fact non-compliant (Choo et al 1999; Wang et al 2004). In other words, the sensitivity (number of patients correctly identified as compliant) of self-report is higher than its specificity (number of patients correctly identified as noncompliant). Choo et al (2001) found that high dosing frequency, low perceived health risks from non-compliance, and low income were associated with over-reporting compliance. Validated compliance questionnaires include the Brief Medication Questionnaire (BMQ), the Medical Outcomes Study (MOS) General Adherence Questionnaire and the Hill-Bone Compliance to High Blood Pressure Therapy Scale. (Kim et al 2000)

2.2.2.2 Objective ratings

Counts of remaining dosage at clinic visits tend to overestimate compliance levels and do not allow for any assessment of dose timing (Farmer 1999). Prescription claims databases

are useful to determine filling and discontinuation of prescriptions, but are only useful if complete (ie all prescriptions claimed are captured in the database); and using prescription claims to estimate compliance may lead to an overestimate as claiming a prescription does not necessarily imply it was used. However patients typically obtain less medication than prescribed; acquisition of oversupplies is rare (Steiner and Prochazka 1997). The use of prescription claims data to estimate compliance with antihypertensive therapies and statins is discussed in Chapter 3.

Electronic monitoring by the medical event monitoring system (MEMS) records the timing of each opening of the medication container. This is currently considered the best method of measuring compliance, but is more difficult and costly to implement than other methods. Compliance rates tend to improve if patients know their compliance is monitored (Burnier et al 2001).

Adding to the medication a biological marker that can be detected in blood or urine allows the ascertainment of recent use of the medication. However the presence of the marker may depend on rates of absorption and excretion and other individual characteristics and may not be accurate.

The association between medication use and serum drug levels or effects is relatively weak. This is due to other factors influencing drug effects. Patients who are highly compliant with their antihypertensive medications may have poor blood pressure control due to inadequate treatment. Patients' compliance behaviour cannot be inferred from outcomes.

That is not to say that compliance has no effect upon outcomes. The relationship between compliance with antihypertensive therapies and statins and outcomes is discussed further in Section 2.4.

2.2.2.3 Validity of compliance measures - antihypertensives

A study to evaluate the validity of measures of compliance with antihypertensives in comparison to electronic monitoring found that concurrent pill counts and previous refill compliance were correlated with electronic monitoring (Choo et al 1999). Patients' reports were accurate for noncompliance though not for compliance. This was based on 286 patients aged over 18, having prescription drug coverage and treated with monotherapy for hypertension. Patients were established users of antihypertensives. The patients' prescription refill compliance for the previous 12 months was determined from pharmacy dispensing records and compliance was assessed by a three month period of electronic monitoring, pill counts during this period and interviews at the start and end. These patients were highly compliant and results may not be generalisible.

2.3 Reasons for non-compliance with therapeutic regimens

There are many interacting factors that may influence drug-taking behaviour. The evidence on factors predictive of compliance is unclear and often contradictory, sometimes as a consequence of poor study design and analysis. Although Haynes et al (2001) found that certain factors tend to be associated with compliance, patient or disease attributes do not consistently predict refill compliance (Steiner and Prochazka 1997). Numerous studies have attempted to identify and quantify the factors associated with compliance with antihypertensives (see for instance Patel and Taylor (1992), Staffan et al (2000)) and lipid-lowering drugs (see for instance Kiortsis et al (2000)) and examine the effect of interventions (Schedbauer and Schroeder 2003).

2.3.1 Patient-related factors

Factors generally associated with good compliance with the prescribed treatment are that patients' expectations are met, they are supervised and provided with continuity of care, and they perceive the disease to be threatening. Long treatment, especially for asymptomatic disease, complicated regimens, side effects, social stress, isolation and alcoholism are associated with non-compliance (Blackwell 1996, Myers 1999, Busnello et al 2001). These factors may interact in complex ways to affect patients' compliance (Muehrer et al 2000).

2.3.1.1 Modelling Patients' Behaviour

An attempt to describe motivation to change behaviour, the transtheoretical model, (Prochaska et al 1997) groups people according to "stages of change" (SOC). The first stage is termed precontemplation and comprises those who are not interested in considering a change of behaviour; this is followed by the contemplation stage, which consists of those who are not certain about changing. Next come the preparation stage – those who are ready to change, the action stage – those who have started to change, and the maintenance stage – those who have changed. Among people with high-risk behaviours, it has been shown that about 40% are in the first stage and 40% in the second and only 20% are ready to change their behaviour (Prochaska et al 1997). Moving from one stage to another is related to the balance of costs and benefits of the particular change – for instance moving from precontemplation to contemplation occurs if the perceived benefits outweigh the costs and moving from contemplation to action depends on the costs of the change decreasing.

An application of the stages of change model to understanding why patients fail to adhere to their prescribed medicines found a significant association between SOC and previously validated measures of compliance in patients with HIV and hypertension (Willey et al 2000). Taking a convenience sample of 731 patients with hypertension, 29% were classified as precontemplators, 20% as contemplators, 12% were in the preparation stage, 7% in the action stage and 31% in the maintenance stage. SOC as assessed by two questions was compared with a Likert-scaled measure of medication compliance as used by the Medical Outcomes Study. The question asked of patients to assess compliance was "How often have you taken your prescribed medication in the past four weeks?" and there were six possible

responses – none of the time, a little of the time, some of the time, a good bit of the time, most of the time, and all of the time (the last two responses being grouped). Of the patients in the precontemplation and contemplation stages, 15.3% reported compliance most or all of the time. About half (52.3%) the patients in the preparation stage, 96% of patients in the action stage and 97% of patients in the maintenance stage reported compliance most or all of the time. The authors of this study suggest that patients with hypertension who are in the first two stages of change may need to have information on the benefits of therapy (for instance the prevention of stroke and heart attack) and to develop the perception that by adhering to their therapies they are protecting their health. For these patients focus should be shifted from the negative aspects of compliance with the regimen (for instance side effects and disruption of lifestyle). Patients who have begun to modify their behaviour may need different strategies, such as reminders, rewards and support from others. The SOC questions and the compliance questions are very similar and it would be quite inconsistent of patients to (for instance) claim "No, I do not take and right now am not considering taking my high blood pressure medication as directed" and thus be classified as precontemplators to then claim that in the last four weeks they had taken most or all of their medicines. The usefulness of this is that it gives a different way of thinking about the problem of non-compliance, by classifying patients according to their stages of motivation rather than by the amount of their prescriptions they use. In this study the SOC model was not extended to describe patients who stop taking their medicines. Are these primarily people who have never reached the action stages of change – or are they people who have reached this stage but for some reason abandoned the behaviour? Is it appropriate to assume that patients who reach the maintenance stage never further modify their behaviour? Another possible limitation to this approach is the unreliability of patients' reports of compliance – as noted in

Section 2.2.2.1, a comparison of patients' self-reported compliance with prescription availability found a very weak correlation between the two, as some non-compliant patients markedly overstated their compliance (Wang et al 2004).

2.3.1.2 Patients' reasons for compliance

Patients' perceptions of their illnesses and treatments have an effect on their compliance (Svensson and Lip 2003). Hypertensive patients have reservations about using drugs that may not be related to their drugs' pharmacology – for instance some patients are reluctant to take drugs because they see them as signifiers of ill-health, or they were brought up to avoid taking medicines (Benson and Britten 2002, Benson and Britten 2003). Benson and Britten found that the decision to take antihypertensive therapies is an individual one - most patients hold reservations about taking drugs but balance these against reasons to take them (for instance positive experiences of doctors and perceived benefits of treatment) in ways that make sense to them individually. That is, patients effectively weigh up the costs and benefits of treatment. It has been suggested that compliance rates would improve if patients were paid to take their drugs (Giuffrida and Togerson 1997).

A Swedish study (Svensson et al 2000) in which 33 patients were classified as adherent or non-adherent based on self-report found that the main reasons for compliance were confidence in the doctor, belief that medication issues should be handled by professionals, fear of the complications of hypertension and the desire to control their blood pressures and avoid the symptoms of hypertension. In the patients reporting non-compliance the main

reasons for this were the occurrence of side-effects, dislike for drugs in general, and being asymptomatic. The authors found that adherent patients gave less evidence of involvement in their treatment than non-adherent patients, whose decisions to stop taking their medicines were based on active reasoning. They suggest that the difference between the two groups may be attributable to personality, or may indicate that the option of following instructions requires little thought whereas the decision not to follow instructions requires some justification, or may be due to the fact that patients without reasons for non-compliance did not admit to this behaviour.

O'Donnell et al (2001) found that certain factors may influence some patients to comply and others to discontinue.

External factors also play a role: there is evidence that social and family support have a positive association with compliance (DiMatteo et al 1994, Lennon et al 2001, Marin-Reyes and Rodriguez-Moran 2001). Supervison may be positively associated with compliance (Roe et al 2000), particularly in patients who inadvertently forget to take their medicines. Monitoring of medication use (Burnier et al 2001) and self-monitoring of blood pressure while taking antihypertensive drugs (Vrijens and Goetghbeur 1997) are positively associated with medication compliance.

2.3.1.3 Psychological factors and compliance

The relationship between compliance with medication and control of blood pressure or cardiovascular morbidity and mortality is not clear. Some studies have demonstrated a relationship between adherence to placebo and blood pressure control (See Section 2.4). This has been variously explained by attributing to patients displaying compliant behaviour psychological characteristics that also influence cardiovascular health, and by explaining non-compliance as a consequence of psychological traits and conditions such as depression, which has been previously noted as having an adverse effect on survival in hypertensive patients (Zeigelstein et al 1998). A meta analysis of the effects of depression and anxiety on patient non-compliance with treatment found that depressed patients were three times more likely to be noncompliant than were non-depressed patients. (DiMatteo et al 2000) According to this study, it is estimated that depression of some degree occurs in 25% of medically treated patients, and is greater amongst more severely ill patients. This study suggests three reasons that depression might increase non-compliance: the depressed patient may be unable to hold a positive belief in the benefits of treatment, which is necessary for compliance (DiMatteo et al 1993), the depressed patient may be withdrawn from family and social support that have been demonstrated to enhance compliance (DiMatteo 1994), or the patient may have impaired cognitive functioning causing difficulty in remembering when to take their medicines (Salas et al 2001). The study demonstrates a correlation between depression and non-compliance but does not establish a causal relationship and as it notes the relationship may be mediated by a large number of interacting factors. It is possible that some underlying factor causes both depression and non-compliance.

71

A study of the relationship between psychiatric morbidity and episodes of antihypertensive drug intolerance resulting in discontinuation or dose reduction found that episodes of non drug-specific intolerance were significantly associated with panic attacks, anxiety and depression. Patients experiencing such episodes were more likely to have higher diastolic blood pressure. There was no correlation between psychiatric morbidity and drug-specific intolerance. (Davies et al 2003)

2.3.2 Doctors and the doctor-patient relationship

Positive experiences of doctors – namely trust in the doctor, willingness to take the doctor's advice and demonstrated improvement in blood pressure readings are among the reasons given by patients for taking antihypertensive therapies (Bensen and Britten 2002). Inadequacies in the relationships between patients and doctors may be the primary reason for failure to take medicines (Royal Pharmaceutical Society 1997). DiMatteo et al also studied the characteristics of the doctor that influence patients' adherence to medical treatment (DiMatteo et al 1993). They found that the doctor's job satisfaction and speciality, number of patients seen per week, and scheduling a follow-up appointment predicted patients' compliance.

Williams et al (1998) found that patients' motivation for compliance mediated the relationship between the perceptions they had of their physicians' support for their autonomy and their medication adherence.

2.3.3   Disease attributes

There is a widespread misperception that hypertensive patients are infrequently symptomatic (Flack et al 1996). This may contribute to non-compliance as patients attribute the symptoms of hypertension (headaches, fatigue, poor exercise tolerance) to their treatment. This may be especially true of treated hypertensives with poorly controlled blood pressures.

Gidron (1998) notes that patients with coronary (Ischaemic) heart disease are likely to be treated with a complex regimen including perhaps aspirin, nitrates and beta blockers. He writes "as patients with CHD are often more ill than those who suffer from HT, CHD-related symptoms and disability may motivate some patients to increase their adherence, and may be a barrier or a source of helplessness for others." Thus it is important to identify these patients in studies of compliance.

2.3.4   Treatment-related factors

Aspects of treatment that may be associated with compliance include the effectiveness of the drugs, the occurrence of drug-related adverse events, and the complexity of the treatment

regimen. Patients may discontinue their therapies because they are not (or are not perceived to be) effective. Unpleasant side effects increase the risk of non-compliance (Dusing 2001): both inefficacy and adverse events may be due to inappropriate dosing. Pharmacokinetics are thus useful for optimising compliance (Rudd and Lenert 1995)

A comparison of US recommendations for the treatment of hypertension revealed lower initial doses for 23 of 40 antihypertensive drugs according to the JNCVI guidelines than given in the *Physicians' Desk Reference*, suggesting that many patients may be initially prescribed too high a dose and thus exposed to the risk of dose-related adverse drug events and possible consequent discontinuation (Cohen 2001). Over 75% of adverse effects are dose-related: therefore the lower the dose the lower the risk of adverse events. First-dose reactions occur with the initial dose of the drug or when the dosage is increased, and have been documented in many antihypertensive drugs. These may result from a too abrupt lowering of blood pressure, resulting in hypotension, dizziness, synocope, headaches or tiredness. Many adverse events (and discontinuations) occur early in antihypertensive treatment and may indicate that the initial dose was too high. It may be useful to compare recommended initial dose with the typical initial dose and study the effect this has on the risk of discontinuation. Evidence of the influence of individual response on compliance constitutes an argument for the individualisation of therapy based on pharmacological response. Cohen suggests lower initial doses for elderly patients.

Treatment guidelines are based on the evidence of randomised trials where the analysis is usually by intention to treat – that is, outcomes are analysed regardless of compliance with the treatment protocol. If there are large numbers of noncompliant patients the effects of

treatment may be underestimated and the recommended dose might be an overestimate. (Vrijens and Goethebeur 1999). Thus patients who are compliant with the recommended dose may be over treated and at higher risk of discontinuation. Appropriate dosing guidelines are an essential aspect of patient compliance.

Compliance differences between drugs are common. Andrade et al (1995) found that the rate of discontinuation of lovastatin in long-term clinical trials (>one year) was 16% (95% CI 15%-17%). In the Treatment of Mild Hypertension Study (TOMHS) patients were randomised to lifestyle modifications plus placebo or one of five types of antihypertensive therapy (Neaton et al 1993). Differences in long-term compliance (defined as remaining on the initially prescribed monotherapy at 48 months) were observed across drug groups, with highest compliance rates observed for the CCB (amlodipine, 82.5%) compared to diuretic (chlorthalidone, 67.5%) or alpha-blocker (doxazosin, 66.1%) or placebo (58.5%). Approximately 6-15% of the patients withdrew from treatment and 10-20% switched treatment, with the exception of placebo where one third of the patients were prescribed an active treatment by 48 months. The study suggests there are long-term differences in compliance with drug therapy in patients with mild hypertension. The authors of this study state:

"Adherence to any drug therapy is, minimally, a result of the combined forces of blood-pressure lowering efficacy and patient tolerability of the prescribed drug. Patient tolerability will, to no small degree, relate to perceived side effects. Drugs that result in a high degree of therapeutic non-adherence can increase total healthcare costs, because patients taking these drugs will have a greater number of clinic visits triggered by perceived side-effects."

However, in observational studies it is not possible to conclude that differences in compliance between drugs are due to characteristics of the drug and not to the characteristics of the patients prescribed these drugs (Blandford et al 1999).

Complex regimens may be a barrier to compliance - compliance is better for drugs requiring fewer daily doses (Steiner and Prochazka 1997, Claxton Cramer and Peirce 2001, Iskedjan et al 2002). There is some evidence that this may be due to delays is dosing in patients who are prescribed twice-daily therapies rather than once-daily therapies (Andrejak et al 2000). One of the reasons fixed low-dose combinations may be better for compliance is that the dosing regimen is less complex (Neutel 2002, Waeber 2002).

2.4   Benefits of Compliance

Drugs that are not taken can have no therapeutic effect. Stopping therapy may cause rebound effects and re-starting at the full dose after a period without therapy can result in an overdose. Amongst hypertensive people, blood pressure elevations persist in spite of pharmacotherapy, due in part to non-compliance; a similar situation is seen in people treated for high cholesterol. Thus non-compliance contributes to the increased risk of morbidity and mortality in people treated for hypertension and elevated cholesterol levels. Non-compliance also has economic consequences.

2.4.1 Compliance and outcomes: antihypertensive therapies and statins

It is difficult to establish the extent to which non-compliance with pharmacological treatment is responsible for poor blood pressure control. The WHO report on adherence (WHO, 2003) states that the best available estimate - based on the sixth report of the Joint National Committee on the prevention, detection, evaluation and treatment of high blood pressure (1997) - is that poor adherence contributes to poor blood pressure control in more than two thirds of people with hypertension. According to Burt et al (1995), "poor adherence is the leading cause of uncontrolled blood pressure among treated patients".

Attempts to quantify the magnitude of this effect are problematic, as poor control of blood pressure and/or cholesterol levels in treated patients may be due to unsuitable treatment; even in the optimal setting of clinical trials a significant proportion of patients do not achieve control of blood pressure (Section1.3.2) or cholesterol levels (Section 1.3.4). There has been little attempt to determine the relative magnitude of the effect of non-compliance on blood pressure or cholesterol control; however Urquhart (2002) discusses the complexity of the problem, and Mar and Rodriguez–Artajelo (2001) estimate the relative effects of stage, efficacy and compliance on hypertension control.

In fact the relationship between blood pressure control and compliance is so weak that the former is considered a poor indicator of compliance (Section 2.2.2.2). This is further complicated by the observation that patients who are good compliers with a placebo regimen tend to have lower blood pressures than patients who are poor compliers with the placebo (Preston et al 2000). This might be explained in several ways: that the good motivation that

77

leads to good compliance has an independent effect on blood pressure, or that depressive symptoms may be the cause of poor compliance behaviour and independently affect blood pressure levels (DiMatteo et al 2000). The beneficial effect of compliance with a placebo has been noted for conditions other than hypertension – for instance, in the Beta Blocker Heart Attack trial it was found that patients who did not adhere well (that is, took less than 75% of their prescribed medicines, whether propanolol or placebo) were 2.6 (95% CI 1.2, 5.6) times more likely to die within one year (Horwitz et al 1990). The odds ratio for propanolol was 3.1 and for placebo was 2.5. Horwitz and Horwitz (1993) suggest that there are non-specific therapeutic factors that influence the outcomes of treatment over and above the action of the drug.

Additionally, it is difficult to separate the effects of compliance on medication response from the effects of response on compliance: there is some evidence that an adequate response may lead to better compliance which in turn leads to blood pressure control. These two aspects of the therapeutic process are thus in a constant cycle: the patient takes the drug and it is effective, so the patient continues to take the drug. But if the drug is not effective the patient may have less motivation to continue to take it. Undoubtedly there are some patients who are more affected by response or lack thereof than others. Thus there may be patients in whom the treatment is effective but are nevertheless noncompliant. Then there are the patients in whom the prescribed treatment is not effective. In fact a large proportion of patients who are complaint with the treatment do not have well-controlled blood pressure. It has been stated that blood pressure control can be achieved in almost all patients; however in recent clinical trials about two thirds of patients required treatment with two or more different antihypertensives (see section 1.3.1).

Compliance may be associated with initial treatment effectiveness. Benner et al (2004) investigated the influence of effectiveness of statin therapy in the first three months of treatment upon long-term adherence and found a significant association. Compliance with statin therapy in the first 3 months of treatment and recent coronary revascularisation were independently associated with long-term compliance.

A Swiss study (Burnier et al 2001) showed that one third of a group of patients with treatment-resistant hypertension could achieve control if their drug-taking were monitored. They found that patients who took less than 92% of their antihypertensive triple therapy over a period of 2 months had significantly higher diastolic blood pressures than those who took over 92% of their prescribed doses. This study suggests that in a substantial proportion of patients with uncontrolled blood pressure the main reason is non-compliance with treatment.

Reviews of the research have found that poor compliance is associated with poor control of blood pressure in hypertensives and hence with an increased risk of cardiovascular complications (Mallion and Schmitt 2001); Krousel-Wood et al (2004) highlight medication compliance as a "key factor" in achieving blood pressure control, and Neutel and Smith (2003) identify improvement of compliance as a major goal in the management of patients with hypertension.

The Systolic Hypertension in the Elderly Program (SHEP) pilot study showed that >80% compliance with either therapy or placebo was associated with a higher probability of

achieving target blood pressure (Black et al 1987). The fact that compliance with placebo had a positive influence on blood pressure control suggests that individual characteristics that influence persistence with therapy also influence control of blood pressure. Hershey et al (1980) found that hypertensive patients reporting good adherence were more likely to achieve blood pressure control than those reporting lower adherence. Good adherence has been associated with improved control of blood pressure (Luscher et al 1985) and reduced complications of hypertension. Burnier et al (2001) found that the patients with lowest compliance had significantly higher diastolic blood pressures.

On the other hand, many studies have failed to find any relationship between compliance with antihypertensives and blood pressure control – for example, Choo et al (2000) and Nuesch et al (2001). There were limitations to these studies that have implications for interpreting their results – the first was an observational study, not a controlled experiment (Urquhart 2000) and the second had possible problems with bias and sample size (Parenti et al 2001). Many studies of compliance are based on observational data and must be interpreted with this in mind.

Evidence for a relationship between good compliance with statins and reduced mortality risks has been found by Wei et al (2002), who found lower risks of a recurrent MI in patients who claimed over 80% of their prescribed statins, and by Howell et al (2004) who found reduced all-cause and IHD mortality in patients who claimed more than 80% of their prescribed statins (HR = 3.83, 95% CI 1.38, 10.63 for IHD).

DiMatteo et al (2002), in a random-effects meta analysis of the results of sixty-three studies of patients' compliance and outcomes, found an overall difference in outcome of 26% between high and low compliance. This study found the relationship between compliance and outcomes was especially apparent in chronic diseases, including hypertension and hyperlipidaemia.

What degree of compliance is adequate for blood pressure and cholesterol level control? Often good compliance is identified by evidence of taking eighty percent of medicines as prescribed. But considering the differences in individual patient response and treatment regimens, it seems that 80% may be too low in a lot of cases (non-responders) and more than adequate in others (for instance patients who are over-treated and patients whose compliance behaviour has an independent effect on blood pressure control). This assumes that the prescription is exactly what the patient needs to achieve a satisfactory outcome; thus choosing a compliance cut-off point is useful only if all prescribing is appropriate for the individual. In patients with hypertension, it assumes all the antihypertensive drugs have the same duration of action and same blood pressure response. Considering a standard cut-off point an adequate level of compliance for all drug classes (each of which target a different aspect of blood-pressure control) may obscure important issues.

It would be useful to establish the extent to which blood pressure and cholesterol level control depends on compliance. This could be determined by a study of patients who have been prescribed medicines that are known to be the necessary and sufficient medication for individual control. Variation of the compliance levels (by blinded introduction of a certain proportion of placebo) would indicate the minimum amount of medicine needed for

control. But this approach does not control for the negative effects of non-compliance behaviour, which may have an independent effect on outcomes. Such studies include comparisons of ACE inhibitors (Tan and Leenen 1999), beta blockers (Johnson and Whelton 1994), calcium channel blockers (Elliott et al 2002) and ATII receptor blockers (Mancia et al 1999). These studies showed the blood-pressure lowering effect of antihypertensive drugs do not last longer than several hours.

Some drugs have a longer duration of action on blood pressure than others. In a recent study (Girvin and Johnston 2004) 24 patients took part in a randomised crossover trial where they were treated sequentially with three different antihypertensives for four weeks each followed by one week with no treatment. The antihypertensives were 2.5mg bendroflumethiazide, 30mg nifedipine LA and 20mg enalapril. Blood pressure remained controlled for longest after stopping therapy with bendroflumethiazide. It has been suggested that drugs with longer duration of action are useful in patients who are partial compliers with their therapies – that is, they occasionally miss doses. However, this should be balanced against the increased risk of side effects due to the stronger formulation of these drugs, which increases the risk of treatment discontinuations (Urquhart and de Klerk 1998). Drugs with long duration of action are of little benefit in patients who are very compliant or in patients who are very non-compliant. Patients who miss doses may suffer rebound effects that could dispose them towards discontinuation (Urquhart 2000).

As a result of morbidity and mortality, non-compliance has negative economic consequences (Urquhart 1999, Urquhart 2001).

3. Studies of compliance with antihypertensives and statins using prescription claims

3.1 Introduction

Although collection of a prescription does not ensure its use, assessment of compliance with therapeutic regimens using prescription data has been validated by comparison with electronic monitoring (MEMS) (Choo et al 1999) and other measures of compliance and drug presence or effect (Steiner and Prochazka 1997). Steiner and Prochazka, in their assessment of refill compliance using pharmacy claims data concluded that in large populations, this type of data 'can provide an otherwise unobtainable information about the pattern and timing of drug exposure, and the determinants and consequences of adherence' (Steiner and Prochazka p 105). They also found that acquisition of drug oversupplies was rare.

To determine drug exposure patterns, it is necessary that all prescriptions received by the patient during the observation period are recorded in the database – that is, patients do not collect prescriptions from any other source, and the recording process is reliable. Given this,

prescription claims data can be used to estimate an upper bound for compliance, which may, depending on the patient population, be very close to the actual rate of drug use. How close cannot be known without other measures of compliance in the particular patient population. Indeed, the WHO recommend that compliance be measured by several methods (WHO 2003). But prescription data are especially useful to identify discontinuation and changes of treatment.

Because patients' actual compliance is closely related to prescription claiming patterns, predictive models for responses based on claiming patterns implicitly identify factors that predict compliance. Therefore appropriate strategies to model prescription claiming patterns are important – the results and interpretation of these models should help us understand patient compliance.

Methods for estimating and modelling compliance using prescription claims data vary, and results are often not directly comparable. The aim of this chapter is to examine previous approaches to estimating compliance with antihypertensive medicines and statins using data on patients' prescription claims. The majority of studies that use this type of data to estimate compliance are based on large prescription claims databases that were originally set up for other purposes, typically reimbursement of prescription claims. These data are a rich source of information – especially with respect to the type, dose, quantity and timing of prescription claims - but have limitations with respect to estimating and modelling compliance that must be borne in mind when interpreting the results. In particular, they give no information about many factors known to be associated with compliance. The data are observational,

not the result of randomised controlled trials to measure compliance – this has implications for the interpretation of the effects of explanatory variables.

In Section 3.2 I describe how I identified the relevant studies and in Section 3.3 I summarise and comment upon the criteria by which they selected their study populations. In Section 3.4 I discuss the measures they used to estimate compliance and in Section 3.5 I discuss their methods of analysis and results. For the most part, studies that estimate compliance with antihypertensives are discussed separately to studies that estimate compliance with statins.

For the purposes of this chapter, reference to a study's estimated compliance shall mean the estimate by whatever quantitative outcome measure was chosen by that study's authors for assessing compliance.

3.2   Identification of studies

I made comprehensive searches for articles published in the last ten years (1995-2004) that used prescription claims data to estimate compliance with antihypertensive therapies and statins. This included searches of PubMed, CINAHL and individual journals. For studies on compliance with antihypertensives the criteria for identification were the combination of terms for compliance with a term indicating hypertension and the term "prescription". For studies on compliance with statins the criteria for selection were the combination of terms for compliance with "statin" and "prescription". Articles thus identified were selected if

considered relevant. Further relevant references were identified from the bibliographies of these selected articles.

Based on these criteria, I found twenty relevant articles published between 1995 and 2004 that examined compliance with antihypertensive therapies, and eleven relevant articles on compliance with statins. Tables 3.1 and 3.4 summarise the origin of each study and characteristics of the study populations.

The studies on antihypertensives were all based on European or North American prescription databases, from which longitudinal prescription histories could be constructed for each patient. The majority of these studies used on US databases, including Medicaid and Medicare claims (Monane et al 1997, Rizzo and Simons 1997), the US Department of Defense United Services Personnel Drug Program (USPDP) (Okano et al 1997), Veterans' Health Administration (VHA) databases (Ren et al 2002, Wang et el 2002), and pharmacy benefits managers (PBM) databases (Bloom 1998, Benson et al 2000, Dezii 2000, Conlin et al 2001, Wogen et al 2003, Taylor and Shoheiber 2003). The Canadian studies were based on the Saskatchewan Health database (Caro et al 1999a, Caro et al 1999b, Bourgalt et al 2001, Marentette et al 2002). The European studies were based on the UK Mediplus automated primary care database (Jones et al 1995), an Italian prescription database for the Local Health Unit in Ravenna (Degli Esposti et al 2002a, Degli Esposti et al 2002b, Degli Esposti et al 2004), and the Mediplus data of IMS Health, an insurance system covering patients in France, Germany and the UK (Hasford et al 2002).

The studies on compliance with statins – of which seven of the eleven identified were published in or after 2002 – are similar in origin to the studies of antihypertensives – some sharing authors and databases. They include five North American studies, of which one used data from Health Management Organisations (HMOs) in Massachusetts (Andrade et al, 1995), two used Medicaid and Pharmaceutical Assistance to the Aged and Disabled (PAAD) databases in New Jersey (Avorn et al 1998, Benner et al 2002), and three used Canadian health databases in Ontario and Quebec (Avorn et al 1998, Catalan and LeLorier 2000, Jackevicius et al 2002). One of the earliest of the statin studies was based on patients' prescription claims for lipid-lowering drugs recorded by a network of pharmacies in Sydney (Simons et al 1996). A recent UK study was based on the prescription records from a single large GP practice in Liverpool. Other UK studies included one that followed the prescription histories of Scottish patients prescribed statins after a heart attack (Wei et al 2002), and one based on the UK General Practice Research Database (UKGPRD) (Yang et al 2003). There were two other European studies of statin compliance using large prescription databases – one from Denmark, which used the Odense University Pharmacoepidemiological Database (OPED) (Larsen et al 2002), and one from Italy, which used data from the Umbria Regional Government's Epidemiology Department (Abraha et al 2003).

Some of the study populations had characteristics known to influence compliance, for instance, insurance coverage - patients paying for their treatment may be more likely to adhere to therapy. Therefore, it may not be appropriate to extrapolate the conclusions of these studies to populations that do not share these traits.

Some studies included information on diagnoses or could be linked by patient to diagnoses codes (which, however, were sometimes available only in the event of a hospital discharge). Many of the prescription databases did not include information on diagnoses. All the prescription databases included a unique patient identifier, demographic information (minimally age and sex of the patient) and information on all prescriptions received, including date of prescription and type and quantity of the drug received (though information on daily dose was not always available). None included information on what was actually prescribed as opposed to what was claimed. Several of the smaller studies included data from patients' questionnaires or interviews.

3.3   Patient selection criteria

The characteristics of the populations chosen in each of the studies on compliance with antihypertensives are summarised in Table 3.1, and similarly for studies on compliance with statins in Table 3.4. Patients were selected based on diagnoses, evidence that they were (or were not) prescribed certain therapies, evidence that the therapy of interest was new (or the patient was new to therapy), and the duration of the prescription history. I comment firstly on the characteristics of the chosen populations for the studies of antihypertensives, then on the characteristics of the populations in the studies of statins. As all the factors that were used to select the study cohorts – particular medicine, co-prescriptions, number of drugs, duration of use, and age – may be associated with compliance with therapy (WHO 2003), it is necessary to interpret the results from a particular study in terms of patient selection.

3.3.1 Selection criteria – studies of antihypertensives

3.3.1.1 Identification of patients

Where diagnoses data were available the selection of the patient cohorts was based on this and prescription of selected drugs. Diagnoses varied between studies but all patients had hypertension. In three studies patients with the International Classification of Diseases – 9th Revision (ICD-9) codes 401, 401.1 and 401.9, referring to essential hypertension, benign and unspecified hypertension, were included (Rizzo and Simons 1997, Caro et al 1999a, Caro et al 1999b), while elsewhere patients with ICD-9 codes 401-405 were chosen (Jones et al 1995, Marentette et al 2002), or it was merely stated that patients had a diagnosis of hypertension (Wang et al 2002, Hasford et al 2002).

Where diagnoses data were not available patients were selected on the basis that they were prescribed certain drugs. The chosen antihypertensive drugs varied according to the study. They included some or all of the following: angiotensin-converting enzyme inhibitors (ACE), beta blockers (BB), calcium channel blockers (CCB), diuretics and angiotensin-II antagonists (ATII). Some studies chose patients prescribed particular drugs and others included patients prescribed all drugs in the class.

In some studies patients with diagnoses indicating cardiovascular and other comorbidities were excluded (Caro et al 1999a, Caro et al 1999b, Bourgault et al 2001); similarly the use of other drugs that could indicate certain conditions such as angina and heart failure were used as a basis for exclusion from the cohort (Bloom 1998, Bourgalt et al 2001, Conlin et al 2001). In other studies evidence of cardiovascular disease and other comorbidities was used to construct explanatory variables to be included in the predictive models for compliance (Rizzo and Simons 1997, Degli Esposti et al 2002a, Degli Esposti et al 2002b, Degli Esposti et al 2004, Wogen et al 2003).

To compare the compliance rates of different groups within the population it is necessary that the factors known to be associated with compliance – demographic factors, medical condition and type of therapy, and duration of therapy are determinable. Modelling compliance in a heterogeneous population with known characteristics may be more useful than an estimate based on a population with specific characteristics.

Individual patients' characteristics may change over time and these changes may affect their compliance. For instance, patients with hypertension are at increased risk of developing IHD and more serious forms of cardiovascular disease. A predictive model including the development of cardiovascular disease as a time-varying covariate may be a more informative than either excluding all patients with cardiovascular disease or including only time-invariant covariates indicating this.

3.3.1.2 Monotherapy and Combinations

Eight studies included only patients initiating antihypertensive monotherapy. In the other studies patients could be receiving prescriptions for single therapies or combinations. In some studies combinations of antihypertensives were treated as a separate drug class (Bourgalt et al 2001, Marentette et al 2002), while in others the prescription of other antihypertensives was controlled for by including appropriate explanatory variables in the model (Wogen et al 2003, Rizzo and Simons 1997). Two studies compared compliance to combinations in single-tablet or separate tablet forms (Dezii 2000, Taylor and Shoheiber 2003). Some studies appear to ignore or not specify how combinations of antihypertensive treatments were treated in their analysis.

3.3.1.3 New users of antihypertensives

Prescription claiming data usually gives no information on the dates of diagnosis or initiation of therapy. Therefore, patients' claiming histories are left-censored – that is, we do not know when the claiming histories began. Knowing the patients' total time on therapy allows the effect of therapeutic duration on the risk of stopping therapy to assessed or controlled for, and also allows the estimation of the effect of factors whose influence on compliance may change as duration of therapy increases. To allow for the known reduction of the risk of discontinuation as duration of therapy increases, (Sackett 1976) most studies used some

91

criteria to identify and exclude patients who may be considered established users of antihypertensives.

Most studies identified patients who were new users of antihypertensive drugs – three did not (Rizzo and Simons 1997, Ren et al 2002, Taylor and Shoheiber 2003). New users were determined in various ways - from diagnosis date in one study, but mostly by evidence of a period without therapy previous to the first prescription of an antihypertensive. The length of this period ranged from three to twelve months; however there was usually no attempt to justify this choice. A study based on the UK General Practice Research Database (UKGPRD) concluded that a four-month period without prescriptions was not sufficiently long to identify new users of antihypertensive drugs and that a twelve-month period would be more appropriate (Suarez et al 2000). This finding is not necessarily applicable to other databases, but it suggests that the studies choosing relatively short run-in periods may include a substantial number of patients who were not new to antihypertensive therapy. In the studies reviewed here, patients were variously considered new to therapy if they had received no antihypertensive prescriptions, no prescriptions for drugs in the same class, or no prescriptions of the particular drug during this period. Patients who have previously been prescribed a different antihypertensive are not new to therapy; they have been prescribed antihypertensives for an unknown duration and including them in the cohort means including a group with a lower risk of discontinuing at baseline. Three studies included such patients as new to the particular therapy. In principle the ideal inception cohort consists of recently diagnosed patients who are new to therapy, and given the evidence that twelve months without therapy is a sufficient period for identification of these, it appears that only half the studies of antihypertensives chose satisfactory inception cohorts.

92

3.3.1.4 Follow-up

For determination of compliance, it is necessary that all prescriptions received during the period of observation are recorded in the database – this requires that patients receive all their prescriptions under the scheme and that all claims are properly recorded. Many studies required continuous eligibility, excluding patients who died, moved away or otherwise became ineligible for the particular scheme. For instance, three quarters of initially identified patients from the US Department of Defence cohort (Okano et al 1997) were excluded because there were insufficient follow-up data. However, these patients could have been included if censoring techniques had been used – thus allowing patients who are observed for varying lengths of time from the date of the first prescription to be included in the study cohort (Caro et al 1999a, Caro et al 1999b, Bourgault at al 2001).

3.3.1.5 Patients' age

Many studies excluded patients based on age. Selected age groups ranged from a relatively young cohort aged 20-49 (Okano et al 1997) to elderly patients aged 65-99 (Monane et al 1997).

3.3.2 Selection criteria – statin studies

3.3.2.1 Identification of patients

The smaller studies on compliance with statins generally had access to patients' diagnoses, which were used in conjunction with prescription of selected therapies as the basis for inclusion in the cohort. Diagnoses included hyperlipidaemia/lipid disorder (Andrade et al 1995) and previous myocardial infarction (Wei et al 2002).

Most of the twelve studies identified focussed on patients prescribed statins, although several included patients prescribed other lipid-lowering drugs (LLDs) (Andrade et al 1995, Simons et al 1996, Yang et al 2003). If diagnoses data were not available patients were selected based on their prescriptions for chosen LLDs alone.

Obviously the patients prescribed statins may have had forms of cardiovascular disease more severe than hyperlipidaemia, just as antihypertensive therapies may have been prescribed to patients with cardiovascular diseases more severe than hypertension. Most studies of statins included explanatory variables indicating evidence of cardiovascular disease based on patients' diagnoses or prescription histories. For instance, Catalan and LeLorier (2002) identified patients with IHD, angina, heart failure and atherosclerosis by diagnosis. Catalan and LeLorier, who had access to both diagnoses and prescription histories, found that 24% of patients in their cohort were diagnosed with CVD and claimed prescriptions that they considered markers for this (nitrates for angina and digitalis with furosemide for heart failure), 9% were diagnosed with CVD but not prescribed the relevant drugs and 8% were

prescribed the relevant drugs but not diagnosed with CVD. Larsen et al (2000) identified patients with CVD or risk factors for CVD by co-prescription of drugs from classes C01, C02, C03, C07, C08, C09 and B01. Avorn et al (1998) identified patients with coronary artery disease (CAD) by diagnosis and/or prescription of nitrates, and patients with hypertension by prescription of thiazides or ACE inhibitors and beta blockers or calcium channel blockers if no evidence of CAD. Benner et al (2002) included evidence of cardiovascular events as a time-varying covariate.

3.3.2.2 New users of statins

Most of the studies of statins made an attempt to include only patients new to this type of therapy. Some studies with information on diagnosis dates used the first relevant prescription after diagnosis as the index prescription (Andrade et al 1995). Most studies identified patients as "new" if they had no evidence of prescriptions for their index therapy during a predetermined period before it was first prescribed. This period ranged from three to eighteen months, although in most cases was one year. There was little attempt to validate this choice. Some studies identified patients who were new to a particular therapy but not necessarily new to cholesterol-lowering treatment. Based on the evidence from the UKGPRD on antihypertensives that a one-year period is sufficient to identify patients new to therapy, and recognising the importance of identifying patients new to cholesterol-lowering therapy to avoid including patients who have been using other cholesterol-lowering drugs as new, it appears that six of the eleven study cohorts consisted only of patients new to statins.

3.3.2.3 Follow-up

Studies that excluded patients based on insufficient follow-up included the Italian one, where patients who died during the observation period were excluded (Abraha et al 2003). Yang et al (2003) excluded patients who received only one prescription; this was based on a review of 3000 patients of whom 336 discontinued in the first month, and it appeared that most of these had no valid reason for doing so and may never have used any of their statins. Patients who receive only their first prescription may be quite different to patients who make subsequent prescription claims – the first prescription could be thought of as an initial state, after which the patient moves to a states of claiming or non-claiming.

3.3.2.4 Patients' age

The studies of statin compliance often selected patients on the basis of age. For instance, Catalan and LeLorier (2000) selected patients aged 45-64, while Benner et al (2002) and Jackevicius et al (2002) chose patients aged over 65 (or 66).

3.4   Compliance Outcome Definitions

Table 3.2 gives the compliance outcome definitions and rates estimated for each study on antihypertensives, and Table 3.4 gives a similar summary for each study on statins. There was much variation in both the terms used for compliance outcomes and in their definitions. There were two main types of outcome – one that focussed on claiming of therapy, either at a certain point or accumulated over a period of time, and one that focussed on the length of time therapy was claimed.   Outcomes based on claiming of therapy were defined as dichotomous - for example compliant versus noncompliant - or continuous variables - for example proportion of days covered (PDC). These might be measured at one point in time or at multiple time points. Outcomes based on the length of time therapy was claimed were usually the starting point for survival (or event history) analysis – this gives estimates of the proportion of patients still on therapy over time. This type of outcome requires a definition of discontinuation of therapy.

With respect to discontinuation, it should be noted that patients prescribed treatments for hypertension (or high cholesterol) usually need to continue with therapy indefinitely to experience the benefits of reduced risk of morbidity and mortality.   Withdrawal of antihypertensive therapy after short duration is not usually successful (1.2.7) and may be assumed to be the decision of the patient rather than the doctor.

The broad definitions of compliance as adopted at the McMaster meeting and adherence as proposed by the WHO allow flexibility in the definition of quantitative measures (see

97

Chapter 2.2). This is useful as it encompasses the many aspects of compliance. However, because there is no standard quantitative definition care must be taken in the interpretation of studies that attempt to estimate compliance rates. A further complication is the use of the same term to mean different things in different studies. Quantitative studies of compliance should be interpreted in the light of the definitions they use and their justification of these definitions.

3.4.1 Outcome definitions – studies of antihypertensives

3.4.1.1 Proportion of prescriptions claimed

The term "compliance" was usually used for outcome measures based on the proportion of days covered (PDC) – also known as the medication possession ratio (MPR) - that is, the length of time the patient had a prescription available divided by the time the patient was observed. To determine availability, some studies included prescriptions for the initial therapy only, some included prescriptions for any drug in the initial class, and some included prescriptions for any antihypertensive. Some studies calculated the PDC as an estimate of the average level of compliance in the population at chosen time points (Rizzo and Simons 1997, Wogen et al 2003, Taylor and Shoheiber 2003). Several studies calculated the proportion of patients with PDC>80% to estimate the average rate of compliance at chosen time points (Monane et al 1997, Rizzo and Simons 1997, Okano et al 1997). It has been observed that patients receiving at least 80% of their medication are more likely to achieve

blood pressure control in both active treatment and placebo groups (Black et al 1997). However this does not make allowances for differences between antihypertensive drugs or differences in patients' responses to therapy (see Chapter 2). It often appears that the 80% cut-off point is chosen for convenience and to be in accordance with past practice rather than because it has any clinical significance.

The terms "adherence" and "continuous use" were also used for this type of measure. The term "persistent" was also used for patients collecting a certain proportion of prescriptions during the time observed. The use of different terms to mean the same thing, and the same terms in to mean different things, highlights the inconsistencies in the definitions of terms used in the literature.

3.4.1.2 Prescription claim at particular time point

In two studies patients were defined as persistent if they refilled their initial prescription on or within 3 months of the 1 year anniversary of the starting date (Bloom 1998, Conlin et al 2001); similarly in one study "continuous treatment" required a duration of over 273 days during a year of observation – that is, the patient had claimed at least one prescription in the last three months of the year (Degli Esposti et al 2002b). Elsewhere patients were considered persistent if their final prescription covered the period until the end of observation (Caro et al 1999a, Caro et al 1999b).

3.4.1.3 Duration of therapy

One type of outcome measure is based on the length of time during which patients claimed prescriptions. In some of the studies reviewed here this type of measure focussed on prescriptions for the initial therapy, in some on prescriptions for drugs from the initial class, in some on prescriptions for any antihypertensive therapy. The term used for this type of outcome was usually "persistence", although "continuation" was also used. Duration of prescription availability was calculated as time from the initial prescription until the date of discontinuation. Several studies classified patients as continuers, discontinuers or switchers and calculated rates for each outcome at chosen time points (Jones et al 1995, Dezii 2000, Degli Esposti 2001, Bourgalt Rainville and Suissa 2001, Degli Esposti et al 2002b).

3.4.1.4 Discontinuation

If the outcome is the length of time claiming prescriptions a definition of discontinuation is required. Discontinuation was generally defined as a gap in treatment exceeding some specified time ranging from one to three months. None of the studies of antihypertensives validated their choice of duration of the period without therapy. Clinical evidence from studies of withdrawal of antihypertensives indicates that the blood-pressure lowering effect does not last more than a few days, depending on the particular drug (see Section 2.4.1). Therefore patients who have no antihypertensive therapy available for one month or more cannot receive the benefits of treatment and considering them compliant during this period is incorrect in the clinical sense. However, this is not to say that these patients will not

resume treatment. Suarez et al, with their finding that four months was an insufficient period for identification of new users of antihypertensive therapies in the UKGPRD, showed that there were a large number of patients who although failing to collect their prescriptions for four months, returned to some form of antihypertensive therapy. If this finding holds true for other populations, it appears that many discontinuations could be more properly regarded as breaks in therapy. It is important to follow patients throughout the period of observation, rather than regarding gaps in therapy as final; however none of the studies of antihypertensives that used survival analysis methods included multiple episodes of claiming prescriptions

3.4.1.5 Change of therapy

Some studies considered changes of regimen as continuation of therapy (Monane et al 1997, Rizzo and Simons 1997, Okano et al 1997, Caro et al 1999a, Caro et al 1999b, Ren et al 2002, Delgi Esposti et al 2002a, Wang et al 2002), while others classified this as discontinuation of the initial therapy. The studies that focused on continuation of the initial therapy mostly ignored additional drugs (Jones et all 1995, Bloom 1998, Benson et al 2000, Dezii 2000, Conlin et al 2001, Degli Esposti et al 2002b, Wogen et al 2003), but in some instances classified these as modification of therapy (Bourgalt et al 2001, Hasford et al 2002).

3.4.2   Outcome definitions – studies of statins

3.4.2.1 Proportion of prescriptions claimed

Outcome measures based on the proportion of time with statins available were usually given the names "compliance" or "adherence". As in the studies of antihypertensives, this measure was often dichotomised with cut-off point 80%. For instance, Benner et al (2002) defined good adherence as PDC>80%; Wei (2002) called this outcome "good adherence", Howell (2004) called it "compliance", Avorn (1998) called it "good persistence" and Abraha (2003) called it "persistence". Larsen (2002) used the term "continuity" to describe PDC. Obviously the use of many different terms for the same measure can cause confusion, especially if these terms are also used for other measures of compliance.

3.4.2.2 Duration of therapy

Measures of time on therapy were used in some studies to determine the rates of continuation or persistence. For instance, Catalan and LeLorier (2000) defined persistence by the time from the first statin prescription until discontinuation, as did Larsen et al. (2002) Abraha et al (2003) defined continuity in patients who claimed at least one statin prescription per year, while Jackevicius (2002) uses the term "adherence" to denote at least one prescription every three months.

3.4.2.3 Discontinuation

To determine time on therapy, a definition of discontinuation is needed. This was usually identified as a period without statin therapy ranging from seven days to six months. Larsen et al (2000) justified their choice of discontinuation as a break of one month with no statin therapy, based on clinical evidence regarding the effect of withdrawing statin therapy on cholesterol levels. On this basis, studies defining discontinuation as a gap of three (Yang et al 2003) or six months (Andrade et al 1995, Howell et al 2004) implicitly define compliance in patients who have stopped taking their statins for long enough for their cholesterol levels to return to normal.

3.4.2.4 Change of therapy

A change of therapy was in some studies considered a discontinuation of the initial therapy (Andrade et al 1995) and in others considered a continuation of lipid-lowering treatment (Catalan and LeLorier 2002, Howell et al 2004). As switches between statins are comparatively rare, this does not have a huge effect on outcome measures in studies of statins only; however in studies that include other LLDs switching rates are higher – for instance Yang et al (2003) found that 16% of patients starting lipid-lowering therapy had switched to another type of lipid-lowering therapy (usually a statin) within one year.

3.5   Compliance Outcome Rates and Analysis

Table 3.3 shows the results on compliance rates in studies of antihypertensive prescription claiming according to individual study definitions, and includes associations with other variables. Table 3.6 shows similar results for the studies on statins.

3.5.1   Compliance outcome rates and analysis – studies of antihypertensives

3.5.1.1 Compliance rates for antihypertensives

The one-year compliance rate estimates for studies on antihypertensives are shown, if available, in Table 3.2. These are based on the outcome measures as defined in each study. They range from 33.8% of patients having made no modification of treatment at one year (Bourgalt et al 2001) to 78% of new users of antihypertensives persisting with treatment at one year (Caro et al 1999a). Interestingly these results were based on patient populations drawn from the same database - Saskatchewan Health - which emphasises the importance of patient selection and outcome definitions. Bourgalt et al included all patients who were new to antihypertensive therapy and observed for at least one month after the initial prescription (so that patients who left the scheme were treated as censored and included in the analysis)

and the outcome was any modification in treatment, which included treatment gaps, discontinuations and addition or substitution of drugs. Caro et al included patients who were new users of antihypertensives and were observed for at least one year from the inception date (that is, censored observations were excluded). These patients were considered persistent if their final prescription, which could be for any antihypertensive drug, covered the period until the end of the observation year. There are several reasons for the discrepancies between the results reported by the two studies. One is the possible selection bias in Caro's study resulting from the exclusion of patients who left the scheme during the observation year – patients who leave the scheme may be inherently less likely to claim their prescriptions. Another is the definition of the compliance outcome to include prescription of any antihypertensive drug at the end of the year - ie switches included (Caro et al 1999a) as opposed to the initial monotherapy - ie any type of modification classified as noncompliance with the initial therapy (Bourgalt et al 2001).

3.5.1.2 Models used in studies of antihypertensive compliance

Most of the earlier studies limited their measurement of outcomes to a single point in time. In several studies no modelling of the outcome in terms of covariates was attempted, the focus being on estimating the level of compliance as defined by the particular study at this point in time. However this approach effectively throws away a lot of data and may introduce bias – for instance estimating compliance at one year means excluding all patients who were observed for less than one year. A survival model, which allows for right-censored observations, is more appropriate.

105

Some of the studies that calculated patients' PDC (equivalently MPR) at a chosen point in time modelled this in terms of covariates by ordinary least squares (OLS) regression. For instance, Rizzo and Simons (1997) and Wogen et al (2003) modelled the PDC at one year in terms of covariates and Ren et al (2002) modelled the PDC at two years in terms of covariates. One problem with this approach, especially for short periods of time with a small number of monthly prescriptions, is that the PDC tends to have a bivariate distribution, with most patients receiving either all or none of their prescriptions after the first one. In the first month all patients (by definition) receive a prescription so have PDC equal to one. In the second month patients who claim a prescription will have PDC one and patients who do not receive a prescription will have PDC ½. At one year from the initial prescription, the PDC takes the values $\{1/12, 2/12, ..., 1\}$ – that is, a set of discrete values within a defined range not including zero, which tends to have a bivariate distribution with most patients either close to zero or close to one, although as time goes on more patients will tend to have partial PDC. OLS regression may not prove appropriate for this response – some of the model assumptions, such as Normally distributed residuals, may not hold. None of the studies that used OLS regression to model PDC made any comments on whether the modelling assumptions were met.

Because the PDC tends to have a bivariate distribution, it may be more appropriate to define a binary response. As previously mentioned, the cut-off point most usually chosen is 80% - and although the clinical evidence for this is questionable, it does separate the patients who never receive any further prescriptions from those who claim all their prescriptions, and these are the dominant groups in the earlier months.

A binary response at a single point in time may be modelled in terms of covariates using logistic regression (Hosmer and Lemeshow 2000). Monane et al (1997) used logistic regression to model good compliance (PDC>80%) at one year in terms of covariates. Wang et al (2003) constructed an ordinal response variable by dividing the PDC at one year into tertiles; this was modelled in terms of covariates using ordinal logistic regression. This type of outcome may be more informative than the binary response.

The other type of binary response, indicating whether the patient had a prescription at a certain point in time, may also be modelled by logistic regression. Bloom et al (1998) modelled persistence (at least one prescription claim within three months) at one year in terms of covariates, and Caro et al (1999a, 1999b) did likewise with a slightly stricter definition of persistence. However, none of the studies that used logistic regression made any comment on whether the modelling assumptions were met – in particular, the logistic regression model assumes Binomially distributed errors.

If the aim is to analyse the length of time with prescriptions available, survival analysis methods are appropriate. Some studies used Kaplan-Meier plots, showing the proportion of patients still taking their medications plotted against time, to illustrate how the risk of ceasing to claim prescriptions changed over time (Caro et al 1999a, Caro et al 1999b, Dezii 2000, Conlin et al 2001, Hasford et al 2002). Cox proportional hazards modelling - a regression method for modelling survival data (Hosmer and Lemeshow 1999) – was used by several studies to assess duration of therapy in terms of covariates. Bourgalt et al (2001), using a large Canadian prescription database, were the first of those I identified to model duration of

claiming antihypertensive prescriptions using Cox regression. Several subsequent studies used the same type of analysis (Degli Esposti et al 2002a, Gregoire et al 2002, Hasford et al 2002, Degli Esposti et al 2002b, Wogen et al 2003).

These studies did not all make full use of the capability of Cox regression to deal with patients who do not have complete follow-up data (that is, censored observations). Some of these studies excluded patients who did not have complete follow-up data – even though using the Cox regression method these patients could have been included in the analysis of duration of claiming. In the context of using Cox regression models for duration of claiming prescriptions, there are several problems with that were not adequately addressed. One is that it was assumed that none of the covariates were time dependent. The other is that where the data are available on a monthly basis, as is often the case with prescription claims, the model must be adapted to deal with the fact that durations of prescription claiming are discrete rather than continuous. Another limitation of the Cox regression models as used here is that these models were used to predict the time to the first discontinuation of therapy, which may be of limited use where patients have many episodes of claiming prescriptions, separated by gaps in therapy. Extension of survival analysis models to allow for multiple episodes of claiming prescriptions might provide a better reflection of actual claiming patterns.

3.5.1.3 Demographic factors affecting antihypertensive compliance

Table 3.3 shows significant and non-significant factors associated with compliance outcome measures used in the studies of antihypertenisves. There are some inconsistencies in the results, especially with regard to the association of demographic factors such as age and gender with outcomes. Some studies found women more persistent (Caro et al 1999b, Conlin et al 2001), two studies found men more persistent (Benson Vance-Bryan and Raddatz 2000, Wogen et al 2003) and some found no difference in outcome rates between men and women (Rizzo and Simons 1997; Degli Esposti et al 2002b). Some found no relationship with age, while others found older patients more likely to adhere with their antihypertensive therapies (Rizzo and Simons 1997, Bloom 1997, Caro et al 1999b, Conlin et al 2001, Ren et al 2002, Degli Esposti et al 2002b, Wogen et al 2003). Age was often dichotomised – a typical cut point being 65 years, though in some studies it was included as a linear variable (Degli Esposti et al 2002b, Wogen et al 2003). In any case, the effects of these factors on the compliance outcomes are relatively weak and should be interpreted with caution.

3.5.1.4 Other patient factors affecting antihypertensive compliance

A high chronic disease score (Wogen et al 2003) or evidence of two or more comorbidities (Degli Esposti et al 2002b) reduced the risk of discontinuation. Specifically, patients with evidence of heart disease and diabetes were found to be more persistent (Degli Esposti et al 2002b), as were patients with heart failure (Rizzo and Simons 1997).

Two of the studies of antihypertensives included patient interviews. One of these found an association between increasing depression symptom severity and compliance with anti-hypertensive therapy; however failed to find any association between health beliefs, knowledge of hypertension, social support or satisfaction with care and compliance (Wang et al 2002). The other found that patients who were involved in treatment decisions were more likely to be compliant (Ren et al 2002).

3.5.1.5 Health care system factors affecting antihypertensive compliance

Several studies investigated aspects of the relationship between patients and the health care system. The number of visits to the doctor was found to have a positive association with the compliace outcome (Jones et al 1995, Monane et al 1997, Caro et al 1999a). Two studies found that younger doctors tended to have more compliant patients (Ren et al 2002, Degli Esposti et al 2002a). One study found that patients treated by nurses or physicians' assistants were more likely to be compliant than patients treated by physicians (Ren et al 2002). Patients who had previously been hospitalised were found more likely to be persistent with antihypertensives in large Canadian and Italian studies (Caro et al 1999a, Degli Esposti et al 2002b), but an investigation using a smaller sample from the same Italian population found previous hospitalisation to have no association with persistence (Degli Esposti et al 2002a). One study found that patients who did not collect all their antihypertensive prescriptions from the same pharmacy were less likely to be compliant (Monane et al 1997).

3.5.1.6 Therapeutic regimen factors affecting antihypertensive compliance

Some authors used information on prescriptions for therapies other than the antihypertensives of interest either to select patients or to include as covariates in models for compliance. There was conflicting evidence on the association between co-prescriptions and compliance. Prescription of a large number of other medications was found to have a negative (large defined as more than eight medications) and also a positive (large defined as more than three medications) impact on compliance outcome rates (Monane et al 1997, Caro et al 1999a, Ren et al 2002).

Complexity of the therapeutic regimen is known to have a negative impact upon compliance. Two studies found that patients taking a medication as a combination tablet were more persistent with that treatment than patients who took two separate tablets (Dezii 2000, Taylor and Shoheiber 2003), while another found that taking more than one dose per day had a negative effect upon persistence (Bloom 1998).

Several studies set out to examine whether there were differences in compliance rates between drug classes. Although one study found no difference (Benson et al 2000) most concluded that patients were least likely to adhere with diuretic therapy, followed in various order by beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE)

inhibitors and angiotensin-II antagonists (Rizzo and Simons 1997, Bloom 1998, Conlin et al 2001, Caro et al 1999b, Degli Esposti et al 2002a, Hasford et al 2002, Degli Esposti et al 2002b, Wogen et al 2003). Care must be taken in interpreting these findings, as these were observational studies and it is not clear if the compliance rates observed are due to characteristics of the patients prescribed the drugs, or due to characteristics of the drugs themselves.

3.5.2 Compliance outcome rates and analysis in studies of statins

3.5.2.1 Compliance rates for statins

Table 3.5 gives for each study on statins, the one-year estimated compliance outcomes (where available). These range from 33% (Catalan and LeLorier 2002) to 85% (Andrade et al 1995). As with the studies of antihypertensives, differences in the estimated compliance rates can be partly attributed to differences in definitions of the outcome measure and methods of estimation, and partly attributed to the selection of patients and therapies.

3.5.2.2 Models for compliance with statins

The models used to predict the compliance outcome in terms of covariates in the studies of statins are summarised in Table 3.6. While the issues raised in modelling compliance outcomes in studies of statins are the same as for antihypertensives, the analysis methods used in the studies of statins were generally more advanced. In particular, survival analysis was used rather earlier – for instance, in 1995 Andrade et al plotted Kaplan-Meier curves for duration of claiming lipid lowering drugs (including a statin), and in the following year Simons et al used Cox regression to predict persistence with lipid-lowering therapies in terms of covariates. Following this, Canadian (Catalan and LeLorier 2002, Jackevicius et al 2002), Danish (Larsen et al 2002) and Italian (Abraha et al 2003) studies of statins used Cox regression in a similar way.

Many of the studies of statins modelled PDC>80% at one year in terms of covariates by logistic regression (Avorn et al 1998, Kim et al 2002, Larsen et al 2002, Abraha et al 2003, Yang et al 2003). Benner et al (2002) developed this approach by treating the PDC>80%, calculated over three or six months, as a repeated binary response, and used a generalised estimating equations logistic regression model to predict this in terms of the natural logarithm of time (months) and other covariates.

3.5.2.3 Demographic factors affecting statin compliance

Andrade et al (1995) found that women were more likely to stop claiming their statins than men, and noted that women were also more likely to report adverse drug reactions (ADRs). Yang (2003) also found women had lower rates of compliance. On the other hand, Jackevicius et al (2002) and Abraha et al (2003) found that men were more likely to stop claiming statin prescriptions. Other studies found no difference between men and women (Larsen et al 2002, Kim et al 2002, Benner et al 2002, Catalan and LeLorier 2002).

The effect of age on the compliance outcome also varied between studies, although this may be partly due to the different age distributions of the study populations. Benner et al (2002) found that patients aged over 75 years were less likely to claim over 80% of their statin prescriptions than patients aged 65-75 years. Jackevicius et al (2002), including age as a linear covariate, found lower compliance rates in older patients. Simons et al (1996) found lower persistence in patients aged under 65 than in older patients, and Kim et al (2002) found lower compliance rates in younger patients. Larsen et al (2002) and Abraha et al (2003) found lower persistence rates in patients aged under 45 years than in patients aged 45-75; however Larsen et al (2002) found no difference between these and patients aged over 75 years while Abraha et al (2003) found they were less persistent. Yang et al (2003) found that patients aged 60-69 years were most likely to continue to claim statin prescriptions, followed by patients aged 50-59, over 75 and under 50 years. In contrast, Catalan and Le Lorier (2002) found no effect of age on continuing to claim statin prescriptions – however their patient cohort was relatively young (45-64 years). Catalan and LeLorier suggest that age and gender may be confounded with pre-existing CVD, which has been shown in many studies to be associated with compliance.

3.5.2.4 Other patient factors affecting statin compliance

One study found that patients with high incomes were more persistent (Avorn et al 1998) and another found that patients with lower socio-economic score (SES) were less likely to have PDC>80% (Benner et al 2002). Wei et al (2002) found deprivation to have no association with the compliance outcome, and Simons et al (1996) found that prescription subsidies had no effect on continuing to claim LLD.

Andrade et al (1995) found that previous discontinuation predicted discontinuation of the index LLD. Simons et al (1996) found that patients who were a few days late collecting their prescriptions were more likely to discontinue. These findings support the idea that individuals' past behaviour can be used to predict their prescription claiming patterns. Similarly, Avorn et al (1998) found that long-term use of LLD predicted higher persistence. There have been attempts to model compliance in terms of patients' behaviour patterns (see Chapter 2) and the point has been made repeatedly in qualitative research that individual factors have a large influence on the decision to use medications as prescribed; none of the studies reviewed here however, attempted to quantify the effect of factors specific to individual patients upon their prescription claiming patterns.

Several studies examined the effect of evidence of co-morbidities on claiming statin prescriptions. Simons et al (1996) found that patients with depression or dementia were more likely to discontinue LLD, and Benner et al (2002) found that patients who collected prescriptions for antidepressants were more likely to discontinue statin therapy. Several studies found that patients with evidence of diabetes had higher estimated compliance rates

discontinuations due to poor efficacy were more likely at the sixth month, when patients were required to renew their prescriptions.

3.5.2.5 Healthcare system factors affecting statin compliance

Benner et al (2002) found that visits to hospitals and residence in nursing homes predicted higher compliance rates. Jackevicius et al (2002) found that having more than one doctor and few visits to the doctor predicted lower compliance, and Yang et al (2003) found that visits to the doctor were positively associated with compliance. Howell et al found that cholesterol monitoring was associated with higher compliance rates. The nature of the association between continuing to claim statin prescriptions and the patient-doctor relationship was further explored by Kim et al (2002). This study found that dissatisfaction with the doctor, smaller practice size, younger doctors and fewer patients with high cholesterol in the practice were individually predictive of lower compliance rates. However, they also found that in a multivariate model including all patient and doctor factors, none were statistically significant. It is possible that this study may have been underpowered – however this finding could point to dependencies between the patient and doctor factors. This would confirm other studies of compliance, which highlight the importance of individual relationships between the patient and the doctor.

Table 3.1. Characteristics of study populations (antihypertensive therapies)

Reference	Number subjects	follow-up	Diagnosis	Age	Antihypertensive Drugs	New	Required observation time	Other selection
Jones 1995 UK Mediplus	10,222	6 months	ICD-9 401-405	>40	ACE BB CCB diuretic	4 months that AHT	Visits for 6 month observation period	all new courses AHT
Monane 1997 New Jersey Medicaid Medicare	8,643	1 year	Hospital discharge only	65-99 Mean 75.6 (8.1)	Any AHT >= 1 month supply	12 months any AHT; new only	active use - at least 1 claim each 4 months	Hospital nursing home etc patients excluded
Rizzo 1997 Pennsylvania Medicaid	7,211	1 year	ICD-9 401 401.1 401.9	Mean 59.4 (13.9)	ACE BB CCB diuretic Monotherapy >= 1 month supply	Not identified	Continuous eligibility	Nursing home excluded Random sample selected
Okano 1997 US Dept Defense USPDP	771	1 year	No	20-49	ACE CCB	6 months selected AHT; new only	Continuous enrolment - claims at start & end	771/5947 enrolled continuously
Bloom 1998 Merck-Medco Managed care	21,723	1 year	No	Mean 56 Range 35-71	ACE BB CCB thiazide ATII monotherapy	12 months any AHT; new only	Not stated – drop outs considered to have stopped?	exclude nitrates antiarrhythmics digoxin wafarin loop diuretics migraine med
Caro 1999a Saskatchewan Health	74,181	5 years unless censored	ICD-9 401 401.1 401.9	>40 Median 65	ACE BB CCB diuretic combination other (All 56 AHTs in Saskatchewan formulary)	10 months any AHT; new v established	Patients observed min 1 yr 5,410 exclusions	Exclude other CVD, hepatic & renal disease & pregnant
Caro 1999b Saskatchewan Health	22,918	5 years unless censored	ICD-9 401 401.1 401.9	>40 Median 63	ACE BB CCB diuretic monotherapy	10 months any AHT; new only	Censoring after 6 month observation	Exclude other CVD, hepatic & renal disease & pregnant
Benson 2000 US HMO	7,490	1 year	No	>30	Amlodipine atenolol HCTZ/triamterene lisinopril losartan nifedipine quinapril	90 days any AHT; new only	Continuous eligibility	Discontinue in first year; Min 30 days therapy; max 1200 per drug
Dezii 2000 US PBM	3,942	1 year	No	Not given	Lisinopril or enalapril + HCTZ Single tablet or 2 separate tablets	6 months any AHT; new only	Continuous eligibility - some claim at 1 year	NA

Table 3.1 continued

Reference	Number	Follow-up	Diagnosis	Age	Antihypertensive drugs	New	Required observation time	Other selection
Bourgalt 2001 Saskatchewan Health	19,501	5 years unless censored	Hospital discharge diagnosis only	40-79 Mean 60	ACE BB CCB monotherapy or combination	12 months any AHT including diuretics, alpha-blockers etc; new only	Censored observations included	Exclude CVD (ICD-9 402 404 410-416 420-429 745.4-746.9) & anticoagulants, loop diuretics, cardiac thyroid & migraine medicines
Conlin 2001 Merck-Medco managed care	15,175	4 years, same cohort as Bloom	No	Mean 56 Range 35-71	ACE BB CCB diuretic ATII monotherapy	12 months any AHT; new only	continuous eligibility 6548 excluded from Bloom cohort	exclude nitrates antiarrhythmics digoxin wafarin loop diuretics migraine medicines
Ren 2002 Boston Veterans' Health	1,292 (59% response)	2 years	Not stated	Mean 65.2 (10.3)	Any AHT	Not identified	Observed 2 years complete	NA
Degli Esposti 2002a Ravenna LHU	7,312	3 years	Hospital discharge only	>20	ACE (C09A) BB (C07) CCB (C08) diuretic (C03) ATII (C09C); monotherapy	12 months any AHT; new only	Leave/die excluded 478	Exclude if< 7 days treatment
Marentette 2002 Saskatchewan Health	46,458	5 years	ICD-9 401-405	Mean 61 Range 1-95	ACE BB CCB ATII diuretic;- initial class only; diuretic+AHT classified with other AHT Mixed classes = >1 class	12 months any AHT; new only	4571 (9%) patients excluded as not observed entire period	Exclude patients receiving alpha-blockers alpha-agonists and vasodilators
Wang 2002 US HMO & Veterans' Health	496 (50% response)	1 year	Diagnosis HT in previous year	>40	Any AHT	180 days any AHT; new only	Continuous enrolment	Random sample eligible patients sent questionnaire
Hasford 2002 IMS Health Mediplus	2,416	1 year	New diagnosis HT	Mean 61 (12.7)	ACE BB CCB diuretic ATII monotherapy	New -exclude if HT diagnosis previous year	Lost to follow-up classed discontinued.	Patients matched to irbesartan group
Degli Esposti 2002b Ravenna LHU	16,783	1 year	No	>20 Mean 56.1 (18.3)	ACE (C09A) BB (C07) CCB (C08) diuretic (C03) ATII (C09C); monotherapy	12 months any AHT; new only	Leave/die excluded (660)	NA

Table 3.1 continued

Reference	Number	Follow-up	Diagnosis	Age	Antihypertensive drugs	New	Required observation time	Other selection
Wogen **2003** **US PBM**	142,945	1 year	No	Mean 63.1 (14.0)	Valsartan amlodipine lisinopril	12 months that class; new only	Continuous eligibility	NA
Taylor **2003** **US PBM**	5,732	1 year	Yes	18-64	Amlodipine/benazepril Or ACE+CCB	Not identified	Continuous eligibility	NA
Degli Esposti **2004** **Ravenna LHU**	14,062	1 year	No	>20	ACE BB CCB diuretic ATII monotherapy	12 months any AHT; new only	Leave/die excluded (817)	NA

Abbreviations: ACE angiotensin converting enzyme inhibitor, BB beta blocker, CCB calcium channel blocker, ATII angiotensin-II antagonist, AHT antihypertensive, HCTZ hydrochlorothiazide, ICD International Classification of Diseases, CVD cardiovascular disease, HT hypertension.

Table 3.2. Outcome Definitions & Rates from studies on claiming prescriptions (antihypertensive therapies)

Reference	Outcomes	Continuing rates	Switching rates
Jones 1995	Continuation = still taking initial therapy (class); not continuing if gap>60 days Switch = stop initial therapy & prescribed AHT from different class.	6 month (calculated monthly) Diuretic 41% BB 49% CCB 41% ACE 45%	6 month: Diuretic 49%, BB 43%, CCB 52%, ACE 48%
Monane 1997	Compliant = PDC>80% any AHT Switches included as compliant	Calculated at 1 year 20% patients compliant	
Rizzo 1997	Adherence = PDC averaged over all AHT classes Switches included as compliant	Calculated at 1 year: overall estimates Diuretic 15%, BB 29%, CCB 35%, ACE 35%	
Okano 1997	Continuous Use = PDC > 80% on any AHT Switches included as continuous use; tabulated for continuous users at 1 year.	At 1 year: continuous use any AHT- ACE 55.5%, CCB 49.4% initial therapy only (inc dose changes) ACE 35.4%, CCB 26.6%	1 year switches/additions of therapy ACE 20.1%, CCB 22.8%
Bloom 1998	Persistent = refill initial prescription at 12 (+3) months Switch is change of AHT class	Calculated at 1 year Diuretic 38% BB 43% CCB 50% ACE 58% ATII 64%	1 year Diuretic 6% BB 7% CCB 9% ACE 9% ATII 7%
Caro 1999a	Persistent (+cumulative rates) = last prescribed AHT covers period until end of observation, allowing for previous accumulation. Switches included as persistent.	1 year established 97% new 78%	
Caro 1999b	Persistent (+cumulative rates) = last prescribed AHT covers period until end of observation, allowing for previous accumulation. Switches included as persistent.	6 month diuretic 80% BB 85% CCB 86% ACE 89%	
Benson 2000	Duration = date last prescription+ days covered by this –start date Discontinued if initial AHT not available >30 days & no AHT within 90 days of end	Median duration: 90 days all drugs except HCTZ comb 80 days Note only patients who discontinued AHTs included	
Dezii 2000	Persistent (monthly) = initial AHT without missing > 3 prescriptions in year observed Not persistent if failing to renew 3 prescriptions during year	At 1 year (calculated monthly) lisinopril /HCTZ 1 tab 68.7% 2 tabs 57.8%	
Bourgalt 2001	Time to 1st modification = any change of initial therapy (drug titration allowed) Switch = change therapy (class) & stop initial AHT; maximum gap 90 days	1 year no modification 33.8%; 5 yrs no modification 11.5% BB 7.9% CCB 9.3% ACE 13.1% Combination 22.3%	1st modification: addition 20.1%, switch 14.3%, interruption (gap >90 days) 31.5%, discontinue 22.6%
Conlin 2001	Persistent = refill initial AHT at 12, 24, 36, 48 (+3) months Switch = no initial AHT & change AHT class in follow-up intervals	At 1 year (calculated yearly) Diuretic 20.8% BB 45.6% CCB 54.1% ACE 60.7% ATII 67.4%	1 year Diuretic18.8% BB 6.4% CCB 9.8% ACE 9.6% ATII 8.0%
Ren 2002	Adherence rates = PDC any AHT excluding last prescription Compliant = PDC>80% not including last prescription	At 2 years compliant 72.8%	
Degli Esposti 2002a	Adherence = duration 1st – last prescription any AHT; continuing if >1 AHT each year Switches include with continuers	3 years 57.9% continue	restart 7.6% >= 2 AHTs 1st & 3rd year & <2 AHTs 2nd year

Table 3.2 continued

Reference	Outcomes	Continuing rates	Switching rates
Marentette 2002	Adherence = prescription from initial class only within previous 90 days at 4 time points Switches included in "mixed" class	Calculated at days 180, 360,540, 720. 360 days overall 63.8% 180 days: diuretic 52.0% BB 67.2% CCB 69.8% ACE 75.1% ATII 87.8%	180 days mixed 79.7%
Wang 2002	Adherence = PDC any AHT tertiles (50% 80%) Switches included as compliant	Calculated at 1 year PDC>80% in 29% of patients	
Hasford 2002	Adherence = initially prescribed monotherapy; discontinue = gap > 30 days Switch = any change from initial monotherapy Duration on initially prescribed monotherapy (until switch/discontinue/end observation)	1 year overall 46.8% diuretic 34.4% BB 49.7% CCB 43.6% ACE 42.0% Other ATII 51.3% Irbesartan 60.8%	1 year add 23.8% change 12.9%
Degli Esposti 2002b	Adherence = continue with initial therapy after 9 months (continuers/switchers) Duration any AHT time covered 1st – last prescription	1 year overall 26.9% diuretic 23.1% BB 30.9% CCB 23.7% ACE 30.7% ATII 33.4%	1 year overall 8.2% diuretic 7.1% BB 6.7% CCB 7.6% ACE 9.4% ATII 24.6%
Wogen 2003	Adherence = remain on initial AHT no gaps > 60 days Switches not analysed. Duration = last prescr date – first prescr date (initial AHT).	1 year overall 54% valsartan 63% amlodipine 53% lisinopril 50%	
Taylor 2003	Adherence = PDC excluding last prescription 2 tablets: time is 1st prescr 2nd drug – last prescr last drug (ie sequential/combined)	Calculated at last prescription observed: Combination 80.8% ACE+CCB 73.2%	
Degli Esposti 2004	Adherence = continue with initial therapy after 9 months (continuers/switchers) Duration any AHT time covered 1st – last prescription	1 year overall 30.9% diuretic 25.9% BB 36.9% CCB 26.9% ACE 32.2% ATII 41.7%	1 year overall 8.8% diuretic 7.3% BB 6.5% CCB 8.6% ACE 10.6% ATII 13.2%

Abbreviations: ACE angiotensin converting enzyme inhibitor, BB beta blocker, CCB calcium channel blocker, ATII angiotensin-II antagonist, AHT antihypertensive, HCTZ hydrochlorothiazide, PDC proportion of days covered.

Table 3.3 Summary of results from studies on claiming prescriptions (antihypertensive therapies)

Reference	Survival analysis	Other analyses	Control	Significant	Non-significant	Comments
Jones 1995		ANOVA Compare continuers vs switch/discontinue		Continuers number GP visits↑ number AHT prescriptions↓ (Sig. levels not given)		Frequency of continuation ↓ with duration
Monane 1997		Logistic for good adherence at 1 year	Age (3 groups) Sex Race Start year	Odds ratios (95% CI) Thiazide 1.0, BB 1.4 (1.2,1.7), CCB 1.7 (1.5,2.1), ACE 1.9 (1.6,2.1), CHF/CAD 1.2, >8 GP visits 2.2, >8 other med 0.8, Redeem at >1 pharmacy 0.4	Thiazide dose	Analysis repeated for patients with > 1 prescription & with CHF/CAD - same
Rizzo 1997		OLS for 1 year adherence		Duration ↓, BB•duration ↑, CCB•duration ↑, ACE•duration ↑, Age ↑, White ↑, Medical resources ↑, CHF ↑.	Sex, Asthma, COPD Diabetes,Renal failure Angina, LVH, AMI, PAD,TIA	Significance level0.01 Also OLS regression for costs
Okano 1997		None				Tables for rates of adherence only
Bloom 1998		Logistic for adherence at 12 months		Odds ratios Thiazide 0.36 (0.30,0.43) , BB 0.56 (0.47,0.68) CCB 0.62 (0.51,0.74), ACE 0.81 (0.68,0.97), ATII 1.00 Age >65 1.00, Age >40-65 0.79, Age <40 0.32 >1 dose/day 1.40		Sex – OR is 1.08 (1.02-1.15) -Clinically uncertain & don't specify whether m v f or vice-versa.
Caro 1999a	Kaplan-Meier Log-rank test	Logistic for 12 months adherence		Odds ratios Age >60, 1.11, Female 1.16, Established HT 10.73, >3 other meds 1.29, >5 GP visits 1.59, hospital admission 0.75.		Log-rank test for new vs established HT significant p<0.001
Caro 1999b	Kaplan-Meier Log-rank test for Drug class	Logistic for 12 months adherence	Age, Sex, GP visits, other meds Hospitalisation	Odds ratios Diuretic 1.00, BB 1.25 (1.12-1.39) CCB 1.51 (1.36-1.69), ACE 1.92 (1.76-2.09)		Log-rank test for drug class significant p<0.001

Table 3.3 continued

Reference	Survival analysis	Other analyses	Control	Significant	Non-significant	Comments
Benson 2000		ANCOVA for median duration between drugs		Men significantly longer therapy overall & for atenolol, quinapril, HCTZ+triamterene	Drug type	Duration difference men vs women may not be clinically significant
Dezii 2000	% persistent plotted vs month			Test single tablet vs 2 separate drugs at 6 & 12 months test not stated but significant (p<0.05).		
Bourgalt 2001	Cox PH for time to 1st modification of initial therapy	Poisson regression for modification rates		Age ↑ Female ↑ BB vs others ↓ Combination vs others ↑		Hazard ratios not given in paper.
Conlin 2001	% persistent each 6 months plotted vs time	OLS regression for difference in adherence rate over time (12 – 48 months)		Predicted difference in adherence rates vs ATIIs thiazide –68.8%, BB –34.5%, CCB – 20.8%, ACE –10.1% P<0.001		Log transform adherence rate
Ren 2002		OLS regression for adherence (over 2 years)		Predictors of adherence: Age ↑, No. medications ↑, Input to treatment decisions ↑, Doctor age ↓, Speciality care resident vs primary care, Other health care provider vs doctor	Race Education >13yrs Doctor's sex Practice size	
Degli Esposti 2002a	Cox PH for duration 1st – last prescript.			Hazard ratios for discontinuation Age (1 yr) 0.976 (0.974, 0.978) ,Female 0.894 (0.832, 0.961) Diuretic 2.624 (1.992, 3.457), BB 1.869 (1.414, 2.472), CCB 2.073 (1.574, 2.731), ACE 1.577 (1.198, 2.076), ATII 1.00 GP age 1.006 (1.002, 1.011), GP female 0.911 (0.836, 0.992)	Comorbidity Previous hospitalisation District Practice size	Patient age then Drug class have most influence on adherence

Table 3.3 continued

Reference	Survival analysis	Other analyses	Control	Significant	Non-significant	Comments
Marentette 2002	Adherence plotted vs time for drug classes	Repeated measures ANCOVA for relationship between drug class and adherence.		Age, Female Drug class – all pairwise comparisons significant except CCB&BB Female*drug class, Age*drug class		Increasing age increases adherence - mainly due to younger patients esp taking BB, CCB, diuretics.
Wang 2002		Ordinal logistic regression for PDC tertiles	Age, sex, race, education, employment, treat site, thiazide use, comorbidities	Odds ratios Depression (1pt on 15 pt scale) 0.93 (0.87, 0.99) External locus of control (6pt scale) 1.15 (0.99, 1.33)	Health beliefs, Knowledge of HT, Social support, Satisfaction, Alcohol use, Smoking, Socially desirable responding, Depression diagnosis.	
Hasford 2002	Kaplan-Meier for differences in drug classes Cox PH for time on initial monotherapy			Hazard ratios not given. Patients on irbesartan significantly more likely to persist with initial therapy than all others		
Degli Esposti 2002b	Cox PH for time to discontinuing initial AHT (additions included) PH assumption tested	ANOVA To compare patient ages in continuers, switchers, discontinuers and in drug classes.		Hazard ratios for discontinuation Age (+1 yr) 0.982 (0.981, 0.983) ATII 1.00, Diuretics 2.442 (2.044,2.917), BB 1.525 (1.272,1.829) CCB 1.913 (1.602,2.284), ACE 1.695 (1.419, 2.025) Heart disease 1.531 (1.238, 1.894), Diabetes 1.509 (1.242, 1.834) Previous CVD hospitalisation 1.524 (1.394,1.667) 2 or more comorbidities 1.571 (1.334, 1.851)	Sex Asthma drugs	

Table 3.3 continued

Reference	Survival analysis	Other analyses	Control	Significant	Non-significant	Comments
Wogen 2003	Cox PH for time to discontinuation of any AHT	OLS regression for adherence (PDC)		Hazards ratios for discontinuation: P<0.0001 in all cases unless stated Age 0.933, Male 0.954 Valsartan 1.00, Amlodipine 1.333, Lisinopril 1.446 Diuretics 1.103, Diuretic combination 1.544, BB 1.131 Nitrates 1.137, LLDs 0.743, Chronic Disease Score 1.013 Digitalis 1.049 (p = 0.0012), Antiplatelets 1.032 (p=0.018)		
Taylor 2003		No modelling Chi square and t-tests	Stratified for Age group; morbidity score (Charlson index)	Amlodipine/benazepril vs ACE+CCB		Sequential prescripts of ACE, CCB considered for MPR
Degli Esposti 2004	Cox PH for time to discontinuing initial AHT	OLS regression for costs		Hazard ratios for discontinuation Age (+1 year) 0.978 Diuretic 1.853, CCB 1.663, ACE 1.386, ATII 1.00 Heart disease 1.666, Diabetes 1.394 Prev CVD hospitalisation 1.507 , 2 or more comorbidities 1.630	Sex Asthma drugs	

Abbreviations: ACE angiotensin converting enzyme inhibitor, BB beta blocker, CCB calcium channel blocker, ATII angiotensin-II antagonist, AHT antihypertensive, LLD lipid lowering drug, CVD cardiovascular disease, HF/CHF heart failure, CAD coronary artery disease, HT hypertension, COPD chronic obstructive pulmonary disease, LVH left ventricular hypertrophy, AMI acute myocardial infarction, PAD peripheral arterial disease, TIA transient Ischaemic attack, PDC proportion of days covered, MPR medication possession ratio, OLS ordinary least squares, PH proportional hazards, ANCOVA analysis of covariance, ANOVA analysis of variance.

Table 3.4. Characteristics of study populations (statins)

Reference	Number subjects	Follow-up	Diagnosis	Age	Lipid-lowering drugs	New	Required observation time	Other
Andrade **1995** **HMOs (2)** **Mass**	2,369 537 statins	Range 1-1093 days median 190 d	hyperlipidemia/ lipid disorder	mean 55/58	LLDs (only statin lovastatin)	1st prescr	Had prescription drug coverage throughout study time	
Simons **1996** **Pharmacies (138)** **Sydney**	610 521 statins	1 year	No	Mean 58	simvastatin pravastatin gemfibrozil	3 months		
Avorn **1998** **Medicaid/PAAD** **NJ & Quebec**	7,287 2650 statins	5 years	For CAD, HT, diabetes in previous year		LLDs	1 year (long-term users not excluded)	Died included but if not using program continuously excluded?	New and long-term users included US- nursing home residents excluded
Catalan **2000** **RAMQ** **Canada**	983	6 years	Hospital discharge diagnoses for CVD	45-64	statins	Range of antecedent period 79-2762 days, median 1761 days	Censored included	Alive at least 4 months after 1st statin
Benner **2002** **Medicaid/PAAD** **NJ**	34,501	5 years	No	>65	statins	18 months		

Table 3.4 continued

Reference	Number subjects	Follow-up	Diagnosis	Age	Lipid-lowering drugs	New	Required observation time	Other
Jackevicius 2002 Health databases Ontario	143,505	2 years	Hosp discharge diagnoses for ACS, CAD	>66	statins	1 year		ACS 22,379 CAD 36,106 PP 85,020 No hospital patients
Larsen 2002 OPED Denmark	3,623	5 years	No		statins	1 year	Censored included	
Wei 2002 Tayside hospital Scotland	427	6 years	previous MI		statins			study on patients who got statins after MI
Abraha 2003 Umbria Italy	39,222	4.5 years	Hospital admission/discharge diagnoses - CVD	Mean 62.9	statins	1 year	Died/moved away excluded	
Yang 2003 GPRD UK	22,408 15,488 statins	1 year	Yes not used for patient selection – diagnoses CHD, atherosclerotic disease, hyperlipidaemia		LLDs	1st prescr 1 year run in		excluded if only 1 prescription
Howell 2004 GP practice Liverpool UK	869	14 months			statins	1 year run-in		

Table 3.5. Outcome definitions and rates in studies of statin claims

Reference	Outcomes	Continue rate	Switches
Andrade 1995	Discontinuation – switch or > 6 month gap last prescription to end of observation or leave plan	lovastatin 85% 1 year all LLDs 56% 1 year	switch is discontinuation of initial LLD
Simons 1996	Discontinuation -1 month	40% 1 year median treatment time 3 mths	switch is discontinuation of initial LLD
Avorn 1998	Good persistence 80% PDC % days with prescription (PDC)	statin mean PDC 64.3% (+/-29.8%)	15% switched LLD
Catalan 2000	Discontinuation: break = max(7d, 0.5*presc time) Persistence = time 1st prescription to discontinuation	33% 1 year, 24% 2 years, 17% 3 years, 13% 5 years 20% discontinue after 1st prescription median persistence 173 days (155,204)	switches are continuation of therapy
Benner 2002	Good adherence PDC >80% (calculated quarterly year 1) partial adherence PDC 20-79% nonadherence PDC < 20%	Mean PDC 50% at 1 year (based on months 9-12) adherent 60% q1, 43% q2, 26% 5years, 32% 10 years	Switch of statin is continuation of therapy 4% of non adherent patients claimed different LLD in next interval
Jackevicius 2002	Adherence prescription at least every 3 mths	ACS 40.1% 2 years CAD 36.1% 2 years, PP 25.4% 2 years	Switch of statin is continuation of therapy
Larsen 2002	Discontinuation 1 month Persistence = discontinuation date-initial date (>2 prescr) continuity = PDC	50% persist 3 years, about 76% persist 1 year median persist 41 mths >2 presc continuity 80% in 95.1% in 1st period	
Wei 2002	Adherence PDC > 80%	Average PDC 64% (calculated over study period)	
Abraha 2003	Discontinuation 1 month Persistence PDC > 80% 1st treatment period Continuity at least 1 prescr/year	Persistence 12.8% Continuity 49.6% median pers. 5.3 months	Switch is continuation of therapy
Yang 2003	Discontinuation 3 months	69.8% 1 year (statins)	Switch is discont of initial LLD 16% switch 1 year (statins to other LLD)
Howell 2004	Discontinuation 6 months Compliance PDC>80%	91% continuing therapy 75% compliant	switch is continuation of therapy 182 switches

Table 3.6 Summary of results: compliance with statins using prescription data

Reference	Survival	Other analyses	Control	Significant predictors	NS	Comments
Andrade 1995	Kaplan-Meier			women previous discontinuation		women higher rate ADR
Simons 1996	Cox for non persistence			age < 65 gemfibrozil (vs simvastatin) antidepressants no other CVD, no analgesics late collecting prescriptions	pravastatin prev LLDs prescriber type subsidies Interactions between vars	reasons for discontinuing - questionnaire
Avorn 1998		logistic regression for persistence > 80%		hypertension diabetes, CAD long term use LLD, statin (vs other LLD) high income, younger, few hosp. visits	Gender Num. hospitalisations	
Catalan 2000	Cox for persistence			pravastatin, simvastatin vs lovastatin previous use nicotinic acid higher chronic disease score previous CVD	age, gender, interactions year start initial dose duration 1st presc	
Benner 2002		GEE logistic regression For PDC<80%		non-white, lower SES, > 75 years depression/dementia No HT, stroke, CHF, CHD, diabetes previous MI, earlier years hospital visit, lots drugs, nursing home residence	gender Number doctor visits	Time-varying covariates for CHD events
Jackevicius 2002	Cox for adherence			Older (age linear), men no diabetes, no HT > 1 doctor, few visits, many prescriptions CAD, Primary prevention vs ACS		

Table 3.6 continued

Reference	Survival	Other analyses	Control	Significant predictors	NS	Comments
Larsen 2002	Cox for persistence	Logistic for continuity <80%		age<45 (vs 45-75) insulin 1994 start no other CVD meds	sex age > 75 Oral antidiabetics	
Wei 2002				women	deprivation	
Abraha 2003	Cox for non-persistence	logistic for non-continuity		women; age < 45 (vs 45-75), age>75 not treated for: HT, CHF, MI, PTCA, CABG aspirin		
Yang 2003	Kaplan-Meier Log-rank tests For time to discontinuation/switch	logistic for continuation		men, age OR 50-59 1.32, 60-69 1.51, 75+ 1.26 vs <50 non smokers statins/fibrates vs others More GP visits diabetic, other CVD meds, no non-CVD meds	BMI	factors during treatment rather than baseline are important
Howell 2004		Chi square tests		cholesterol monitoring	Gender, age>60 Major CVD Diabetes Hypertension Smoker, BMI>30 Aspirin	

4. Patients' Compliance using the GMS Database

This chapter describes the data used to assess Irish patients' compliance with antihypertensive therapies and statins. The data were provided by the General Medical Services Payments Board (General Medical Services 2003). Section 4.1 is an introduction to this data: its extent, limitations and appropriateness to estimate aspects of the compliance problem. Section 2 explains the criteria by which subjects were identified for inclusion in the study cohorts, and gives the definitions of terms used. Figures depicting individual prescription histories illustrate how patients were selected and how events in their prescription histories were identified. This is followed by an explanation of how the GMS data were used to construct and select a set of prescription histories suitable for analysis, the aim of which is to give insights into patients' compliance with antihypertensives and statins. Section 4 discusses validity in the context of assessing compliance.

4.1   Introduction to the GMS Data

The General Medical Services (GMS) scheme provides free health services to approximately 31% of the population of Ireland and has been described in detail previously (Williams and Feely 2001). Eligibility for free health care is means tested, and is confined to those who are

unable, without undue hardship, to arrange general practitioner services for themselves and their dependants. All medicines are dispensed to such people without charge. The GMS population, (1.24M) comprising just over one third of the Irish population, cannot be regarded as representative of the general population as socially disadvantaged persons, children and the elderly are over-represented. However, they receive some 70% of all medicines prescribed in Irish general practice. Prescriptions are dispensed through community pharmacies operating within the scheme and a computer system is used for processing pharmacists' claims. All prescription items are coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system (see section 1.2.4). No information on dosing instructions, diagnoses or outcomes is recorded.

These data consist of all prescription claims under the GMS scheme. There is a separate file each month for each of the Health Board Areas. These files include information on each claimant: of particular importance for constructing longitudinal prescription histories, each claimant has a unique identifier. This identifier begins with a code indicating the Health Board Area. It also incorporates household information: all GMS card-holders in the same household have the same identifier with the exception of the final letter, which indicates position in the household - that is head of the household, spouse or dependent. Sex and age group of each claimant are recorded. Information on the prescriptions claimed by each person gives the ATC code, quantity and strength of each drug dispensed. There are also identifier codes for the pharmacist who dispensed the prescription and the doctor who prescribed it, and information on the costs of the drugs prescribed. At the time of this study, monthly prescription claims data were available between August 1999 and December 2002 – that is, forty-one months of prescription claims.

The Eastern Regional Health Authority (ERHA) provides health services for Dublin, Wicklow and Kildare. Demographic data files were available for people eligible for free medical care under the GMS scheme living in the ERHA area. GMS prescription data for the ERHA region may be matched by the unique patient identifier to demographic data. These demographic data include the dates each person joined and withdrew from the scheme. From these dates it is possible to distinguish people who are eligible for the scheme but not receiving prescriptions from those who have either not yet joined the scheme or have withdrawn. These are important for establishing prescription claiming histories: in particular for identifying patients who were new to therapy, and for differentiating between instances of discontinuation and censoring (ie leaving the scheme). Prescription claiming histories are left-truncated - there is no information on claims made before August 1999, or before the date the patient joined the GMS scheme if this was after August 1999 - and for this reason it is necessary to focus on patients who are new to therapy. For this reason the analysis of compliance presented in this thesis was restricted to ERHA patients.

The demographic data also provide date of birth, employment status, area of residence and a limited number of other factors that may be of use in characterising patterns of prescription drug use. Patients' ages were calculated using these dates of birth (age groups only were available in the monthly prescription files). Several of the variables available were not suitable for this analysis – for instance, while an area-level analysis might have proven interesting, only a subset of the addresses is currently coded to give the (small area) Electoral Division, and this subset could not be considered random. The data on occupational status were not considered reliable. The focus of this thesis was on development of models for

135

compliance; the addition of further covariates would be a theoretically simple extension to these models, and might be useful to answer questions of substantive interest.

4.2   Prescription Claiming Histories

From the GMS data, longitudinal prescription claiming histories may be constructed for each patient. From these histories, patients were selected for inclusion in the study cohort and events were identified. As prescription claims are monthly, and there is no information on dosing instructions, it is assumed that each prescription for an antihypertensive or a statin was intended to be used over the following month – as these drugs are used to treat chronic conditions, the assumption is reasonable. If there is evidence that the prescription was intended to be used over the following two months – that is, if there was a gap in therapy preceded by at least twice the normal monthly prescription (measured in DDDs) for that patient, this prescription is carried over to the next month. Thus the availability of antihypertensives and statins is determined for each patient for each month of observation. An example of a patient's prescription claiming history for a single therapy, showing (among other things) carry-over of prescriptions, is given in Figure 4.1. Prescription histories for each type of antihypertnesive or statin, identified by ATC code, were constructed for each patient. Although these were constructed for each drug, they were classified by class of antihypertensive in the working data sets. These prescription histories may be thought of as repeated measures of patients over time.

136

Figure 4.1 Prescription claiming history, showing identification of incident use and determination of drug availability each month

Prescription carried over to next month

12 months

| No prescription |

claim   claim   2xclaim no claim claim   claim   claim   no claim   no claim no claim noclaim

Start observation   Incident prescription   End of observation

Time
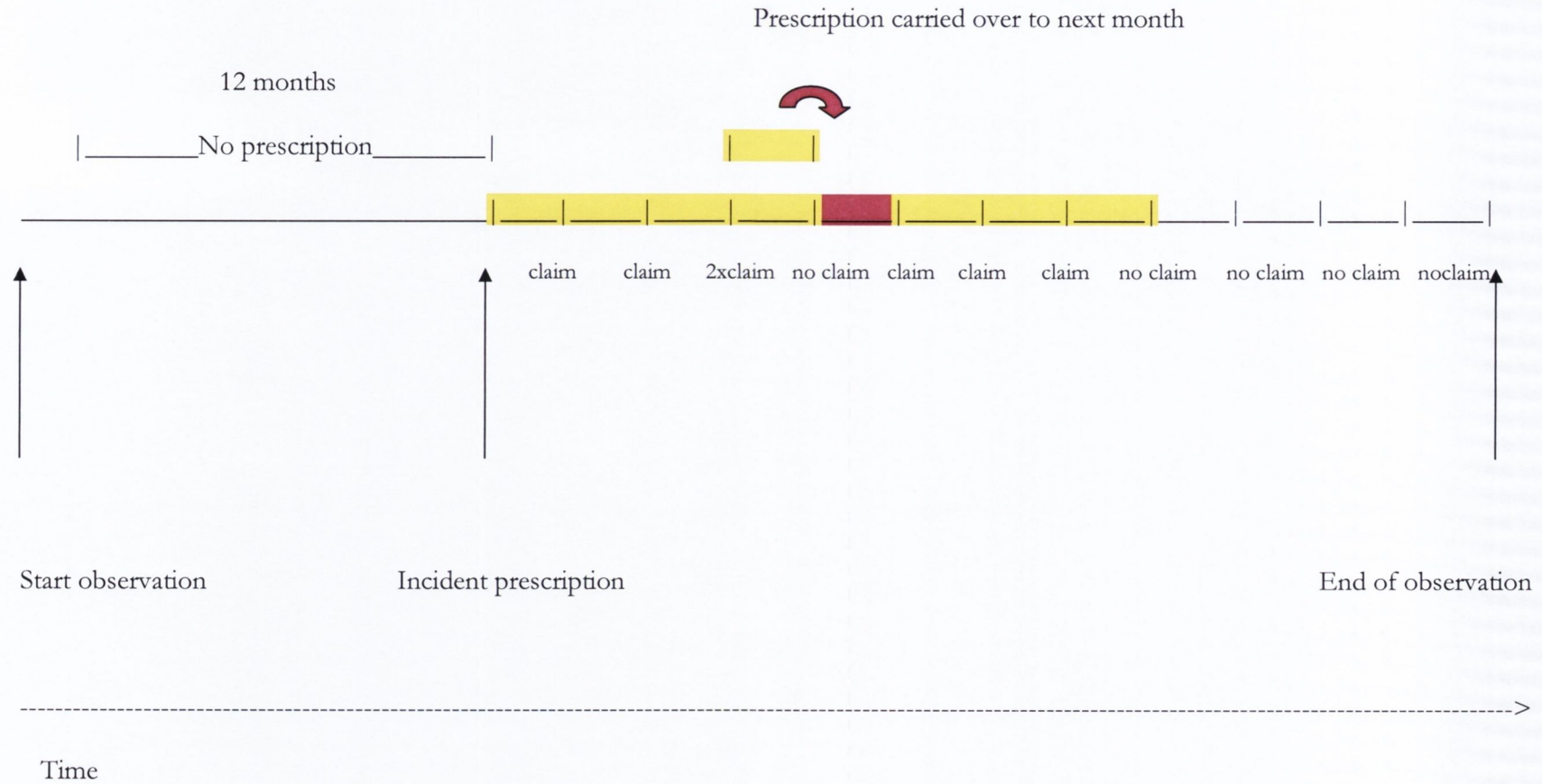
4.2.1   Selecting patients

As there are no records of diagnoses in the GMS database, identifying suitable subjects for inclusion in the analyses depends on the therapies they are prescribed. Thus it is possible to select patients who are prescribed any statin therapy rather than patients with high cholesterol, and patients prescribed any of the five classes of antihypertensive drugs rather than patients with hypertension. As noted in Section 1.2.6, a German study (Pittrow et al 2004) found that 49% of patients taking antihypertensives had a diagnosis of high blood pressure and no more severe diseases of the circulatory system; 27% also had a diagnosis of IHD and the remainder also had other (mainly cardiovascular) diseases. Patients treated with antihypertensive monotherapy were less likely to have diseases more severe than hypertension – though a substantial proportion (39%) of patients treated with antihypertensive monotherapy had more advanced stages of cardiovascular disease. Choosing patients prescribed antihypertensives means including a range of illnesses of varying severity. To a certain extent it may be possible to identify subgroups of patients who are probably being treated for conditions more severe than hypertension or high cholesterol alone. For instance, concurrent prescriptions for aspirin and nitrate, particularly if they are repeated, is a good marker for IHD (see Section 1.2.6).

4.2.2 Incident prescription claim

Including only patients who are new to therapy ensures baseline comparability – though how these new patients should be identified without dates of diagnoses and initial prescriptions is problematic. It is possible to identify patients who did not take a particular drug for a period of time before the initiation date – in previous studies this has been chosen as anything between 3 and 12 months for antihypertensive drugs and between 3 and 18 months for statins (See Tables 3.1 and 3.). There is evidence of some confusion in previous studies about whether baseline comparability is assured if the patients are new to a particular therapy, new to therapy for the specific condition (for example, new to blood-pressure lowering therapy) or new to any therapy for chronic conditions. Research on compliance has established the effect of previous drug use on current use (this research is summarised in Chapter 2).

The choice of drug-free duration antecedent to the initial prescription should be validated from the data. Based on a review of the literature (See Chapter 3, and Fitz-Simon et al (2005)), and analysis of the GMS data, I have chosen twelve months as drug-free run in period for both antihypertensives and statins. I have chosen patients new to any blood pressure-lowering therapy or new to any statin, as analysis of prescription histories of GMS patients new to a particular therapy shows that patients who had previously used antihypertensives (or statins) are at lower risk of discontinuation (See Section 4.4). So patients are identified as new to antihypertensive therapy if there is no evidence that they

139

claimed prescriptions for antihypertensives in the previous year (similarly for statins). It is possible that patients new to statins may have been switching from other lipid-lowering drugs. It is also possible that the selected patients may have been prescribed therapies for other chronic conditions in the previous year, and this may affect their compliance with statin and/or antihypertensive therapies.

The first use of a new therapy is known as the incident prescription and the new therapy is known as the index therapy. The identification of the incident prescription is illustrated in Figure 4.1.

4.2.3 Explanatory variables

Age and sex of each patient were determined and included in the data set. Age was calculated from date of birth at each month of observation; age at the start of each episode was also determined. Time (in months) since the index prescription was included in the data set. This is necessary for inclusion of functions (for instance polynomial and piecewise-constant functions) of duration as explanatory variables.

In light of the fact that patients diagnosed with hypertension and/or hyperlipidaemia and treated with antihypertenisves and statins respectively are at risk of developing more serious stages of disease during the course of observation, it is not appropriate to exclude patients with evidence of more severe disease. The data being prescription histories rather than

diagnoses histories, it is suitable to analyse patterns of prescription claiming in patients prescribed (say) statins rather than in patients with high cholesterol. To examine the effect of the evidence of developing more severe disease, this is best incorporated in models for compliance as time-varying covariates.

4.2.4   Prescription histories as event histories

Previous chapters have dealt with aspects of therapeutic compliance and the use of prescription claims data to assess this. One of the conclusions of reviewing previous research was that in the context of estimating levels of compliance, the most appropriate use of prescription databases is to focus on time to discontinuation – often termed "persistence". That is, to determine and analyse the duration of prescription claiming. Even though whether the patient is actually taking the claimed prescription is unknown, continued collection of prescriptions has been validated as a good measure for continued use of therapy (See Chapter 2). The focus on persistence is due not only to the nature of the data but also the patients' illnesses – hypertension and high cholesterol are chronic conditions requiring continuous long-term therapy. Control of these conditions requires continuation of the therapeutic regimen: therefore duration of therapy is of primary interest.

4.2.5   Discontinuation

To analyse persistence requires a definition of drug discontinuation: when the data are prescription histories this must be based on a period of time with no evidence of claiming

prescriptions for a particular drug. From a clinical point of view, discontinuation could be defined based on the length of time the therapy continues to have a lowering effect on blood pressure (or cholesterol level). Evidence points to the fact that a break in statin therapy of about a month will result in a substantial rise in cholesterol levels (Larsen et al 2002), while the effect of antihypertensive therapies on blood pressure is unlikely to last more than a week (See section 2.4.1). As GMS prescription claims are recorded monthly, the shortest break by which discontinuations may be identified is one month.

Analysis of the GMS data shows that many patients have periods of one month or more with no therapy available, after which they return to therapy. This might be considered an argument for choosing a longer break in claiming prescriptions to define a discontinuation. However, it is perhaps more appropriate to use a model which accommodates multiple episodes of prescription claiming (and non-claiming) – this describes the actual pattern of claiming prescriptions more closely, and reduces the possibility of classifying as compliant patients who have had no prescriptions for a long enough time that their blood pressure or cholesterol probably will have returned to pre-treatment levels.

Figure 4.2 illustrates an individual patient's antihypertensive prescription history, showing how discontinuations are identified. Having identified each discontinuation, it is possible to determine the duration of each episode of continuous claiming (and non-claiming). Note that discontinuation could be defined as a break in a particular therapy, or could be defined as a break in any therapy. However, ending a particular therapy and immediately claiming another type of therapy for the same purpose is perhaps better thought of as a switch.

142

4.2.6   Switching

Is discontinuation of a particular drug, or of any drug used to treat the same condition of interest?   A change of therapy may be considered a continuation of treatment, or a discontinuation of a particular treatment, but it would be perhaps more informative to think of this as a change of state.

Prescription claims data are particularly useful for identifying and analysing switches of therapy.   For the purposes of analysing changes of therapy, a switch is here defined as an alteration of therapy in the next month.   This includes any alteration of the type of drugs claimed between two successive months but does not include changes in dose.

Figure 4.3 shows a patient's antihypertensive prescription claiming history, including the type of antihypertensive drug claimed each month.   Switches are identified as changes of therapy with no break in claiming; and discontinuations are identified by a break of at least one month with no therapy.   Episodes of claiming and non-claiming are indicated.

Figure 4.2 Prescription claiming history as event history, showing discontinuation & defintion of episodes

DRUG   A   A   B   B   B   AD   AD   AD

claim   claim   2xclaim   no claim claim claim   claim no claim   no claim no claim noclaim

|_____No prescription_____| |_____Episode 1 _____|_____Episode 2_____|

12 months   Claiming   Non-claiming

Start observation   Incident prescription   Discontinuation   End of observation

Time
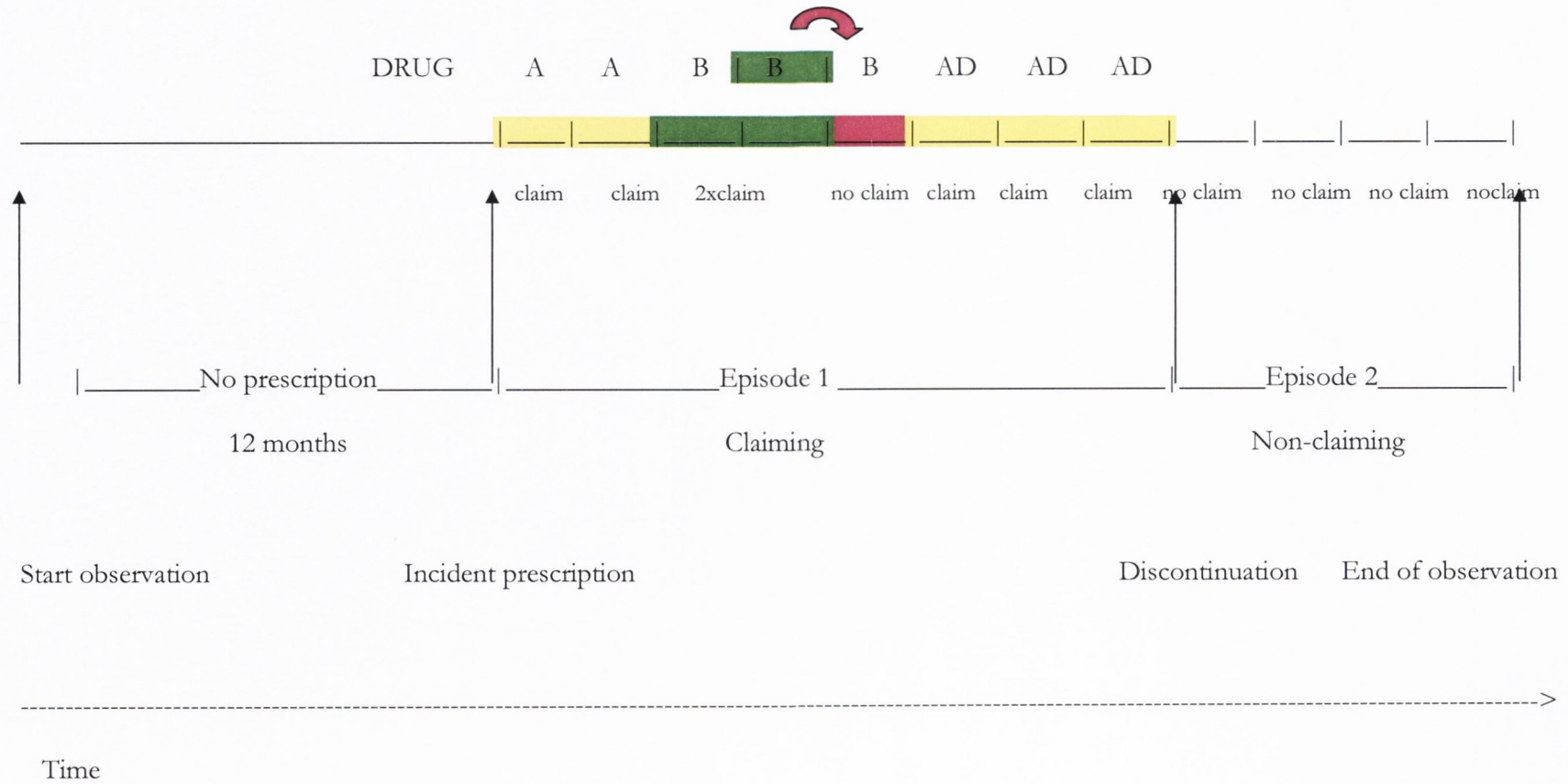
A = ACE inhibitor, B = Beta blocker, AD = ACE inhibitor + diuretic

Figure 4.3 Prescription claiming history as event history, showing switching and definition of episodes

DRUG   A   A   B   B   B   B   AD   AD   AD

claim   claim   2xclaim   no claim   claim   claim   claim   no claim   no claim   no claim   noclaim

|_____No prescription_____||_Episode 1 _||_____Episode 2____||___Episode 3_____||_____Episode 4_____|

12 months   Claiming   Claiming   Claiming   Non-claiming

Start observation   Incident   Switch   Switch   Discontinuation   End observation

-->

Time

A   =   ACE   inhibitor,   B   =   Beta   blocker,   AD   =   ACE   inhibitor   +   diuretic
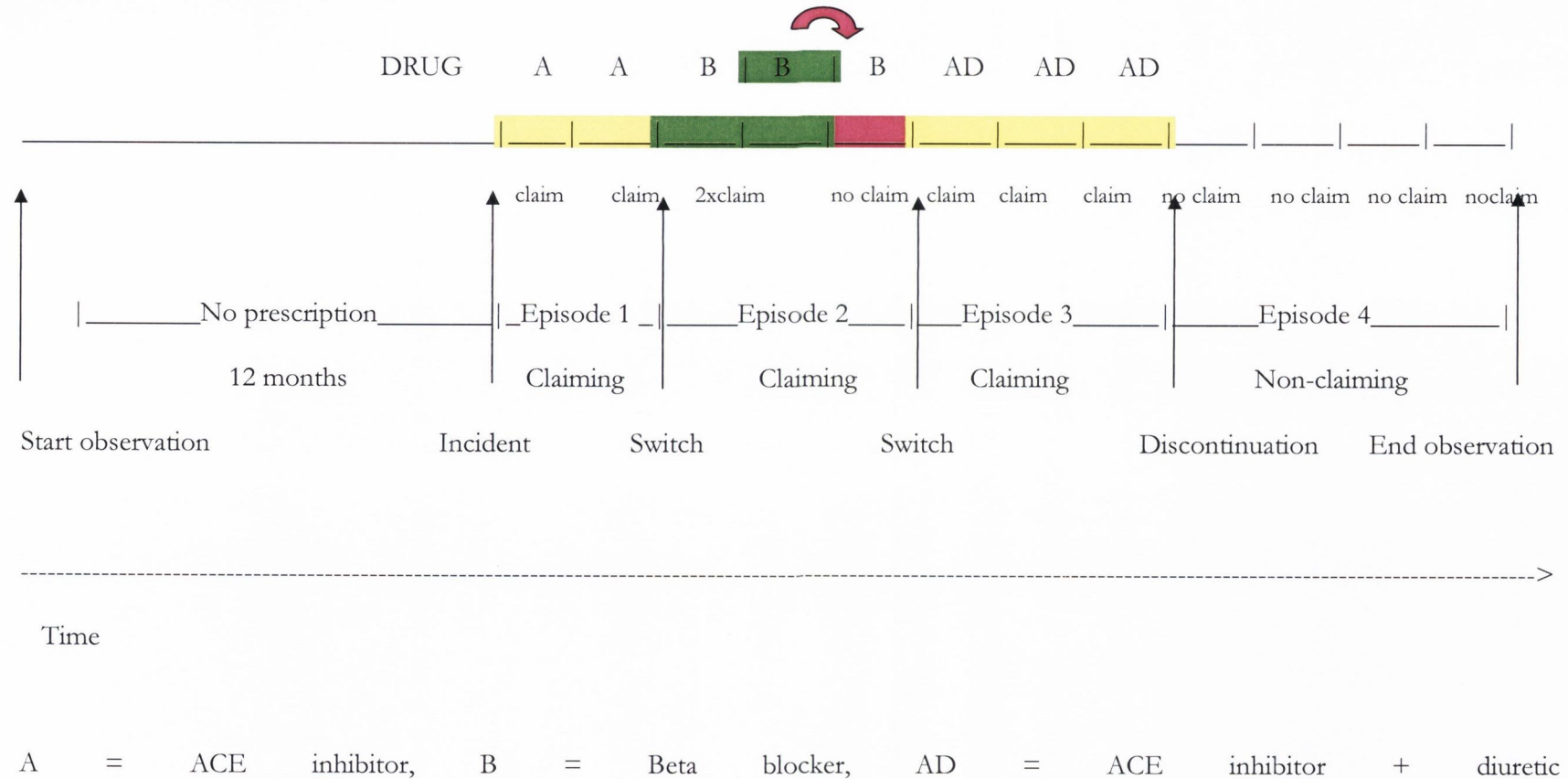
4.3 Selection of Patients using GMS Data

This section describes in detail the selection of patient cohorts from the GMS data. The initial patient cohort described includes patients who were new to a particular antihypertensive therapy (within specific dates). This cohort includes patients who were changing their antihypertensive regimen. It is used to illustrate the differences in baseline characteristics between patients new to any therapy and patients who had been using a different therapy previously to treat the same condition (See Section 4.4), and to illustrate the differences in claiming patterns between these groups in Chapter 7. Choosing patients new to therapy from this cohort is simply a matter of excluding those who claimed antihypertensives in the previous 12 months.

4.3.1 *New to particular antihypertensive therapy*

ERHA GMS patients were selected on the basis that they were new users of a single antihypertensive agent between August 2000 and July 2001 - that is, they had not received any prescription for that particular drug in the previous twelve months. They may, however, have been receiving a different antihypertensive therapy in the previous twelve months and prescribed the new therapy as a switch or addition to an existing antihypertensive regimen. To allow the determination of previous antihypertensive and other drug use, patients who were new to the scheme during the antecedent period (August 1999-July 2000) were excluded. Antihypertensive therapies of interest were ACE inhibitors, beta blockers, calcium

146

channel blockers, diuretics (but not loop diuretics or spironolactone) and angiotensin II antagonists. Patients who claimed prescriptions from pharmacies in the ERHA area but were residents of other areas were excluded, together with a small number of patients who could not be matched to demographic data. Analysis showed that most of these made single claims (that is, not repeated monthly claims). Given that patients who lived outside the ERHA area claimed prescriptions within it, the reverse may be the case – so we do not observe the full prescription histories of some ERHA GMS patients who claimed some or all of their prescriptions outside the ERHA area, thus underestimating prescription availability in some patients.

The prescription history of each patient in the cohort was constructed between twelve months prior to the incident antihypertensive prescription and December 2002. From the date of the incident prescription, this gave a minimum of 17 months and a maximum of 29 months follow-up for patients who remained in the scheme. Patients who withdrew from the scheme were censored at the date of withdrawal. There were a relatively small number of withdrawals. Patients who were still receiving their prescriptions at the end of observation were considered censored at this date.

The twelve-month antecedent period was used to determine baseline characteristics – patients were classified as new to any antihypertensive therapy, adding a new antihypertensive to an existing regimen, or changing the therapeutic regimen.

Information on any other drugs received each month by these patients, including statins, aspirin, nitrates, anti-depressants and diabetes medicines was retained in the data set. Doses were calculated as number of defined daily doses prescribed per month.

4.3.1.1 Selecting the patient cohort

Figure 4.4 (below) illustrates the process of selecting a patient cohort in which to analyse the patterns of antihypertensive drug use after starting a new antihypertensive monotherapy. The initial data set was a merged file of all the relevant antihypertensive prescriptions between August 2000 and July 2001. This was merged by patient identifier and drug with the monthly prescription files for August 1999 to July 2000. From this were selected the first antihypertensive prescriptions that each patient claimed after the 1st July 2000, provided they had made no claim for this particular drug in the previous twelve months (that is, incident claims for particular therapies). Merging with the demographic file allowed exclusion of patients who had not been sufficiently long in the scheme based on the dates of joining.
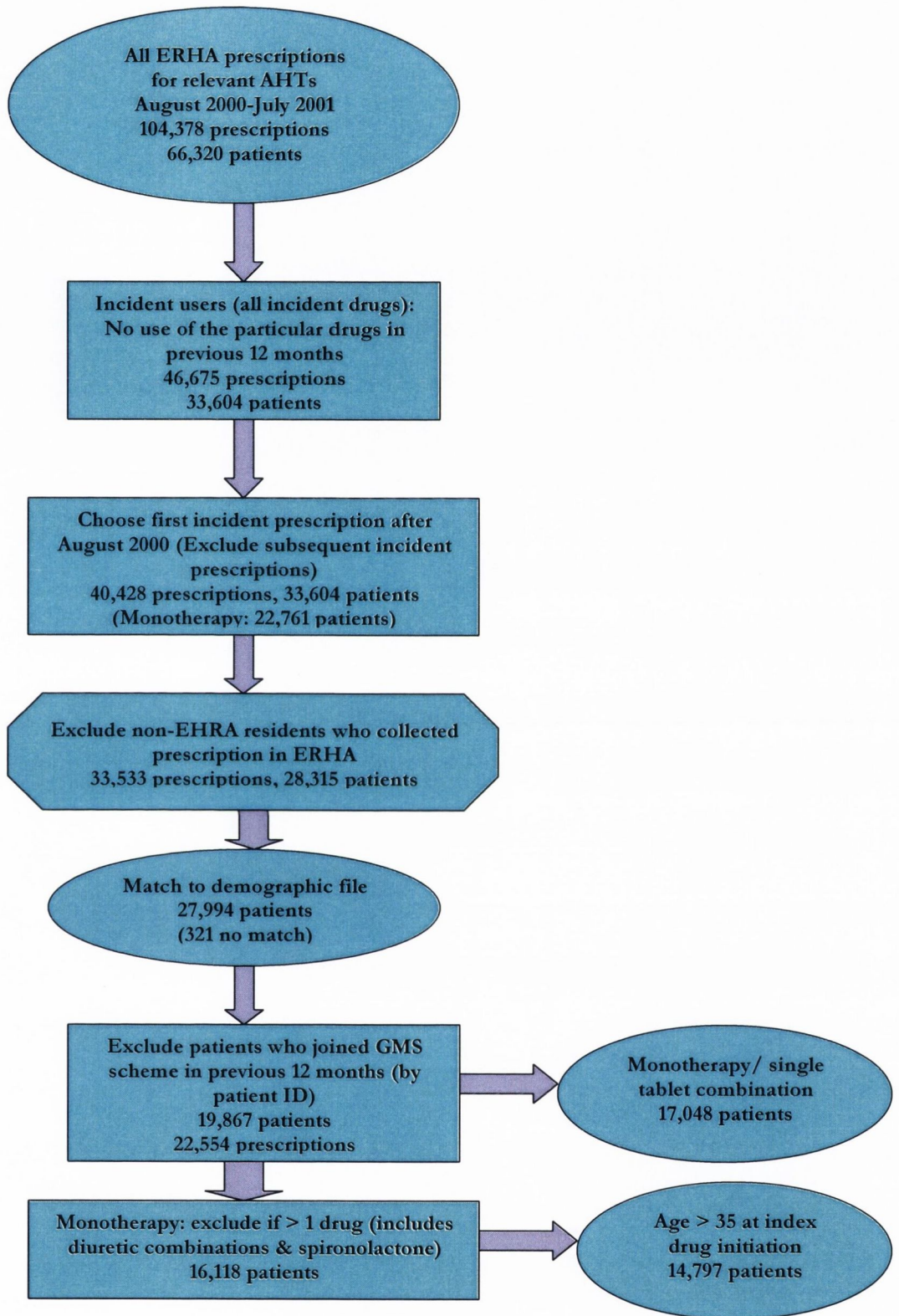
Figure 4.4. Cohort Identification

The result of this process is a file consisting of 14,797 uniquely identified individuals.

Patients aged less than 35 years were excluded: prevalence of hypertension (and high cholesterol) is low in younger people, treatment regimes may be different and younger people may have particular problems with treatment compliance (Temple and Nahata 2000, Staples and Bravender 2002).

The individual patients' prescription histories for their index therapies were constructed by merging by selected patients' identifiers with prescription files for all months until December 2002. The data set thus constructed consists of longitudinal prescription claiming histories for patients who were new to a particular course of therapy but may have been prescribed other antihypertensives in the previous twelve months. These prescription claiming histories may be re-cast as event histories as described above.

4.3.2   *New to any antihypertensive therapy*

Another data file similarly constructed excludes patients who were prescribed any antihypertensive therapies in the twelve months previous to the index period, taken to be the eighteen months from August 2000 to January 2002. Patients aged 30 years or more initiating any single antihypertensive therapy or combination of therapies during the index period were included. These patients may be considered new to any form of pharmacological therapy for hypertension. A data set consisting of prescription claiming

histories for 10,830 new users of antihypertensives was constructed, and re-cast as event histories for event history analysis.

4.3.3   New to any statin therapy

A data set consisting of the prescription histories of 7,027 new users of statin therapy aged over 30 years was similarly constructed. The construction of this data set was identical to that for new users of antihypertensive therapies described above.

Table 4.1 Baseline characteristics of GMS patients initiating a new antihypertensive monotherapy or single-tablet combination between August 2000 and July 2001

PATIENT CHARACTERISTICS	NUMBER OF PATIENTS (%)						
	DIURETICS	BETA BLOCKER	CC BLOCKER	ACE-I	ATII	COMBINATION	TOTAL
NUMBER	3893	4328	3120	4176	815	716	17048
AGE, MEAN (SD)	66.1 (16.5)	61.2 (17.8)	66.1 (16.3)	67.3 (15.9)	66.1 (14.2)	65.7 (15.3)	65 (17)
AGE RANGE							
<50	631 (16.2)	1068 (24.7)	476 (15.3)	529 (12.7)	110 (13.5)	101 (14.1)	2915 (17.1)
50-80	2513 (64.6)	2746 (63.4)	2132 (68.3)	2825 (67.6)	598 (73.4)	524 (73.2)	11338 (66.5)
80+	749 (19.2)	514 (11.9)	511 (16.4)	822 (19.7)	107 (13.1)	91 (12.7)	2794 (16.4)
WOMEN	2742 (70.4)	2567 (59.3)	1864 (59.7)	2379 (57.0)	520 (63.8)	443 (61.9)	10515 (61.7)
PREVIOUS ANTIHYPERTENSIVES							
NONE	2091 (53.7)	2495 (57.6)	1401 (44.9)	1914(45.8)	248 (30.4)	244 (34.1)	8393 (49.2)
SWITCH	669 (17.2)	796 (18.4)	641 (20.5)	1089 (26.1)	255 (31.3)	243 (33.9)	3693 (21.7)
ADDITION	1133 (29.1)	1037 (24.0)	1078 (34.6)	1173 (28.1)	312 (38.3)	229 (32.0)	4962 (29.1)
OTHER DRUGS previously							
DIABETIC	168 (4.3)	236 (5.5)	305 (9.8)	644 (15.4)	89 (10.9)	36 (5.0)	1478 (8.7)
ASPIRIN	1084 (27.8)	1357 (31.4)	1180 (37.8)	1628 (39.0)	295 (36.2)	237 (33.1)	5781 (33.9)
STATIN	321 (8.2)	576 (13.3)	477 (15.3)	656 (15.7)	140 (17.2)	86 (12.0)	2256 (13.2)
NITRATE	365 (9.4)	789 (18.2)	615 (19.7)	840 (20.1)	129 (15.8)	75 (10.5)	2813 (16.5)
ANTIDEPRESSANT	760 (19.5)	866 (20.0)	610 (19.6)	752 (18.0)	152 (18.7)	119 (16.6)	3259 (19.1)

Note: Patients may be prescribed their new antihypertensives as first antihypertensive therapy ("NONE") or as a switch ("SWITCH") or addition ("ADDITION") to an existing antihypertensive regimen. Patients in the "NONE" category are the new-to-therapy patients selected for further analysis.

4.4   Validation

4.4.1   Using observational data

Therapies are not randomly assigned to patients – characteristics of the patients such as severity of their diseases, comorbidities and demographic factors such as age and sex may influence the likelihood of being prescribed a particular drug. Table 4.1 gives the baseline characteristics for all patients initiating a new antihypertensive monotherapy or single-tablet combination between August 2000 and July 2001 (17,048 patients). The identification of this group is shown in Figure 4.4. This group includes patients who may have been claiming other antihypertensives prior to the prescription for the new antihypertensive therapy. The new antihypertensive therapy may be either the first antihypertensive of any type, or a switch or addition to an existing therapeutic regimen.

Diuretics are more commonly prescribed to women, older patients, people who have not been taking any antihypertensive agents in the previous twelve months, and people who have not been taking nitrates, statins, aspirin or diabetes medicine during the antecedent period. Beta blockers are more likely to be prescribed to younger patients (this is especially the case for non cardioselective beta blockers) and patients who have not taken any antihypertensives previously. Calcium channel blockers are more commonly prescribed to patients who have been taking aspirin or nitrates previously (that is, patients with evidence of IHD), and are relatively likely to be prescribed as an addition to an existing antihypertensive regimen. ACE inhibitors are more likely to be given to older patients, men, patients prescribed statins,

153

nitrates, and medicine for diabetes, and patients switching from another antihypertensive drug rather than new users. Angiotensin–II antagonists are more likely to be prescribed to patients in the middle of the age range, women, and patients who have taken antihypertensive drugs before and are either switching or adding to an existing regimen. These patients are more likely to have been taking aspirin, statins and diabetes medicines. The patients who are prescribed a single tablet combination (diuretic + either ACE-I, ATII or beta blocker) have similar characteristics to the patients prescribed ATII antagonists except that they are equally likely to be men as women and they are less likely to have been taking a nitrate previously.

Younger patients are less likely to have previously taken an antihypertensive – 79% of patients aged less than 50 years have not taken an antihypertensive in the previous 12 months, whereas 57% of patients over 50 are taking their new antihypertensive as a switch or addition to an existing regimen.

Therefore, to investigate the effect of drug class on the compliance outcome, age, sex and previous drug use must be controlled for. However this will probably not control for all confounding factors. There are factors not reported in the GMS database that influence the prescription of particular drug classes – for instance the severity of the disease, comorbidities, and preferences of the prescribing doctors. The factors that influence prescription of a particular drug class have been shown in previous research to be associated with patients' compliance (see Chapter 2). Compliance differences between drug classes should be interpreted as differences in compliance between patients prescribed each type of drug rather than as differences between the drugs.

4.4.2 Identification of patients new to therapy

Analysis of the cohort of 17,048 patients new to a particular AHT therapy shows that less than 4% of patients will take any antihypertensive therapy in the next 6 months after a gap of 12 months or more with no therapy. After a gap of 6 months with no therapy, less than 8% of patients will resume treatment in some form during the next 12 months. Most patients who have had 12 months with no antihypertensive therapy may be considered new to therapy. This is in agreement with the results found by Suarez et al (2000) for the UK General Practice Research Database.

4.4.3 Discontinuation

Because here I do not consider discontinuations as final, but rather as breaks between episodes of claiming, validation of the discontinuation definition from the data (that is, comparing results from models for this outcome using different periods of time without therapy to define discontinuation) is not necessary. Because many patients have multiple episodes of claiming (and non-claiming) prescriptions, it seems more appropriate to use models that allow for this rather than regard the first discontinuation as final.

4.4.4   Claiming prescriptions and compliance

As the data available consist of prescription claims, all that can be determined is whether patients received a prescription or not - there is no way of determining whether the patients actually took their drugs as prescribed.   However, these data show when patients discontinued or switched therapies.   It has been found that claiming prescriptions consistently is a good indicator of secondary compliance – that is, taking the drug as recommended (see Chapter 2); however considering all patients who continuously collect their prescriptions to be compliers must to some extent overestimate their true number.   The results based on this assumption may be thought of as an upper bound for compliance.

While continuous claiming of prescriptions has been validated as a good indicator of secondary compliance, it is unclear if claiming a single monthly prescription (ie never claiming another) may be taken to indicate that therapy was used for one month.   A recent UK study of compliance with LLDs, which reviewed reasons for discontinuation in patients who only ever claimed a single LLD prescription during the observation period, found no recorded reason for discontinuation in most cases and concluded that it was uncertain that these patients ever actually used their medicines (Yang et al 2003).   There may be a case for excluding patients who only claim a single prescription on the basis that these are unlikely to have ever used any of their therapy and are therefore not comparable with patients who did use their therapy.   However there is no known quantification of the extent of this problem in GMS patients, and excluding them would mean ignoring a major feature of the data, namely the substantial number of discontinuations at some point during the first month of claiming.

156

It is possible, as noted in Section 4.2, that some prescription claims may not have been recorded in the data set if patients went to pharmacies outside the ERHA area. This effect has not been quantified, but is assumed to be quite small, based on analysis of claims by patients resident in other areas claiming prescriptions in the ERHA – most of these are single claims.

Previous research has validated the use of prescription claims data as a measure of compliance (See Chapter 2). The WHO recommends that several measures should be used to estimate compliance. However, at the time of this study there was no other means of measuring compliance with antihypertensives and statins in the GMS population as a whole. Prescription claims data are the most suitable way (sometimes the only way) of measuring compliance in large populations.

5. Statistical Methods

5.1   Modelling strategy

5.1.1   Introduction

The choice of modelling strategy to analyse patients' claiming of antihypertensive therapies and statins depends on two things: the data and the question of how this can be used to extend our understanding of patients' compliance. The data comprises many series of monthly observations on individual subjects. These may be viewed as repeated measures or as event histories. However, to analyse, for example, the monthly availability of prescriptions as if they were independent observations would not be appropriate as collection of prescriptions by the same patient are clearly not independent. The data are clustered in a natural hierarchy (collection of prescriptions by patients). This chapter describes the development of models for prescription claiming patterns, beginning with a simple repeated measures model, which is extended to allow for dependencies between

successive observations of patients. This is followed with a description of a simple event history model, which is developed to allow for repeated events within patients, and complex patterns of claiming and non-claiming prescriptions. Ultimately the aim of fitting these models is to develop an understanding of compliance in the GMS population.

5.1.2   *The prescription claims history*

Consider the individual prescription claiming history illustrated in Figure 4.3, starting with the incident claim and continuing to the final observation. This prescription history may be viewed in various ways. The simplest way to view these data is as a series of binary responses Y_t, indicating whether the patient had a prescription claim available at time (month) t, where $Y_t = 1$ if the patient had a prescription available that month and $Y_t = 0$ if not. This may be illustrated as follows:

Figure 5.1 Prescription history as series of binary responses (repeated measures)

Month (t)	1	2	3	4	5	6	7	8	9	10	11	12
Y_t	1	1	1	1	1	1	1	1	0	0	0	0

Here time begins with the incident claim and continues to the final observation.

The simplest way to analyse these data is by fitting a logistic regression model to the response. However there is correlation between observations on the same patient and this

160

should be allowed for in the model. This can be done by either a marginal (5.3.4) or conditional (5.3.5) approach.

An alternative way to view these data is as a series of events. An event of particular interest is discontinuation of all therapy, where the response for each month during which a prescription was available is determined by the availability of a prescription in the next month (if discontinuation is defined as a break of at least one month with no therapy). The definition of discontinuation is described in Section 4.2.5.

This amounts to a discrete-time event history or survival model, where the event of interest is discontinuation. The pattern of responses may be illustrated as follows:

Figure 5.2 Prescription history as single-episode event history

Month (t)	1	2	3	4	5	6	7	8	-	-	-	-
Y_t	0	0	0	0	0	0	0	1	-	-	-	-

Here $Y_t = 1$ if the patient discontinued all therapy at month t , and $Y_t = 0$ if the patient did not discontinue therapy at month t . Time begins at the start of the episode of claiming and ends with discontinuation. Months where the patient had no prescription are excluded.

This model may be elaborated by including other features of the claiming history, for example repeated episodes of claiming a specific therapy:

161

Figure 5.3 Prescription history as event history with repeated episodes

Episode (j)	1	1	2	2	2	3	3	3				
Month (t)	1	2	1	2	3	1	2	3	-	-	-	-
Y_{tj}	0	1	0	0	1	0	0	1	-	-	-	-

Here time re-starts at the start of each episode of claiming a specific therapy and ends with the end of the episode (discontinuation or final observation). As in the case of the repeated-measures approach, correlations between repeated episodes from the same individual should be allowed for in the model.

Switching of therapy may be explicitly modelled by a multinomial approach. Because in this case there are three possible responses for each subject currently claiming prescriptions, the term "competing risks" is used. Let $Y_t = 1$ if the patient continued therapy, $Y_t = 2$ if the patient discontinued therapy and $Y_t = 3$ if the patient switched to a different type of therapy at month t . Now the pattern of responses may be illustrated as follows:

Figure 5.4 Prescription history as event history with multinomial response

Episode (j)	1	1	2	2	2	3	3	3	-	-	-	-
Month (t)	1	2	1	2	3	1	2	3	-	-	-	-
Y_{tj}	1	3	1	1	3	1	1	2	-	-	-	-

We can think of patients' patterns of claiming prescriptions in terms of movement from one state to another – for example a patient may move from claiming one type of drug, to having no drugs available, to claiming a different type of drug. This modelling approach allows for complex event histories. It is often referred to as multistate modelling.

A simple multistate model allows us to include all observations of each patient, by bringing episodes of non-claiming into the model. The patient may be considered to be in one of two states: claiming (U) and not claiming (N). Episodes of claiming may end with a discontinuation of all therapy $Y_{tU} = 2$ (ie transition to the state of non-claiming) or switch $Y_{tU} = 3$, and episodes of non-claiming may end with a resumption of claiming $Y_{tN} = 2$ (ie transition to the state of claiming).

163

Figure 5.5 Prescription history as a multistate model with multinomial response

State (s)	U	U	U	U	U	U	U	U	N	N	N	N
Episode (j)	1	1	2	2	2	3	3	3	1	1	1	1
Month (t)	1	2	1	2	3	1	2	3	1	2	3	4
Y_{tjs}	1	3	1	1	3	1	1	2	1	1	1	1

Now all months are included in the event-history analysis, as for the repeated-measures analysis. However the data are structured quite differently. Using the repeated-measures approach we may estimate the probability of having a prescription available in terms of time (and other covariates), whereas using the event-history approach we may estimate the probability of an event after a given duration, during which no event has occurred.

Suppose interest lies in estimating the hazards of transitions between specific drug classes. As a further development of the multistate model, different types of drugs may be considered as different states. Here (for simplicity) we define four states: ACE inhibitor (A), ACE+ other drug (A+), other drug (B) and no prescription (N). All transitions between different classes are allowed – thus (including transitions to the same state) there are sixteen types of transition (see Figure 5.10 for allowed transitions between states). Time starts at the beginning of claiming and continues until the final observation. Here we consider the current state of the process X_t, which takes the values A, B, A+ and N.

Figure 5.6 Prescription history as general multistate model

Month (t)	1	2	3	4	5	6	7	8	9	10	11	12
X_t	A	A	B	B	B	A+	A+	A+	N	N	N	N

Here rather than modelling a multinomial response (as in the previous diagram), which would require sixteen categories (four possible transitions from each of the four states) and may cause estimation difficulties, it would appear to be simpler to model the stochastic process directly, although this structure may not be amenable to longitudinal modelling, which introduces further complexity to an already complex model.

5.1.3   Discrete versus continuous time in event-history models

For event history models where time to events is continuous, the usual data structure is a single observation for each patient giving the duration until the event of interest occurs (for instance, the first discontinuation). Using duration of therapy as a response, and including information on whether the subject is still under observation (ie a censoring variable), continuous-time survival methods may be used. Kaplan-Meier plots may be used to give a population-level overview of the relationship between prescription availability and time since the initial prescription. Cox regression (Hosmer and Lemeshow 1999) has been used in previous studies of compliance with antihypertensives and statins (summarised in Tables 3.3

and 3.6). However this method is designed for continuous time and when time is measured in discrete units there can be problems with ties.

In the GMS prescription claiming data prescription claims are recorded monthly – that is, time is discrete - appropriate models allow for this (Allison 1982). Rather than modelling duration directly, the response indicating occurrence of the event of interest is modelled with explanatory time variables. This requires that the data be expanded to give an observation for each patient each month. Discrete-time models are more suitable for discrete-time data, and also can be naturally adapted to allow for complex data structures. Advantages are that these models accommodate censored observations in a natural way, and inclusion of time-varying covariates is straightforward

5.1.4   Covariates

In the discrete-time formulation, it is straightforward to include time-varying and time-invariant covariates. Interactions between time covariates and other explanatory variables may be included to test whether the effect of covariates changes with time. Age of the patient, IHD status, and type of prescription claimed may change with time, whereas sex is time-invariant.

5.2 Models for Repeated Measures

For subject i observed for T months we have a response vector $(Y_{i1},...,Y_{iT})'$ and a vector of covariates $(x_{i1},...,x_{iT})'$, which may be time-varying or time-invariant. Suppose this response vector indicates prescription availability at each month t the subject is observed – that is,

$$Y_{it} = \begin{cases} 1 & prescription \\ 0 & no\_prescription \end{cases}$$

5.2.1 Generalised linear models

The simplest way to analyse these data is to fit a logistic regression model to the response. For independent observations Y_i, $i = 1,..., N$, a link function $g(\bullet)$ of the expectation of the response $E[Y_i]$ may be modelled as a linear function of the covariates x_i (McCullagh and Nelder, 1989). For independent Bernoulli observations, that is, $Y_i \sim binomial(\pi_i, 1)$ where we define $\pi_i = E[Y_i] = \Pr(Y_i = 1)$, the usual link function chosen is the logit:

$$\log it(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right) = x_i\beta \qquad (1)$$

where x_i is a $p\times1$ vector of explanatory variables, and β is a $p\times1$ vector of (unknown) regression coefficients, and for a Bernoulli distributed response the variance is given by $\pi_i(1-\pi_i)$.

Alternatively, a complementary log-log or probit link may be used.

A series of observations on one subject cannot be considered independent of one another (Burton et al 1998, Cook and Lawless 2002), which is one of the assumptions of the model above. One of the main modelling issues in the present context is to apply suitable methods to deal with this. The remainder of this section describes the methods used to model dependencies in the data.

5.2.2   *Models for longitudinal data with categorical response*

Dependencies between responses contributed by the same subject may be dealt with by a marginal or a conditional approach (Fitzmaurice 1998).

5.2.3   *Marginal Models*

Marginal models are appropriate if the focus is on population averages or rates. The marginal expectation of each response, $E[Y_{it}]$, is modelled. The first step is to choose an appropriate link function and correctly specify the distribution of the response. We choose a suitable function of the marginal expectation that is linear in the covariates; for instance for a binary response the logit link is a standard choice. The marginal expectation is modelled separately to time dependence or within-subject association.

To model time dependence within subjects we need to consider the joint distribution of all responses – this is a multinomial distribution, which requires a large number of parameters.

The regression parameters may be interpreted in terms of change in the prevalence of an event in the population given a unit change in the covariate.

For binary response data Generalised Estimating Equations (GEE) regression models are appropriate.

5.2.3.1 Generalised Estimating Equations (GEE)

In estimating a marginal model by generalised estimating equations (GEE) the issues to address are the choice of an appropriate family of distributions for the data (eg Bernoulli response), the choice of a suitable link function (eg logistic), the choice of a reasonable specification for correlations between observations, the choice of an appropriate model for the mean, and choice of the variance estimator.

5.2.3.2 Estimating marginal models by GEE

Generalised estimating equations (GEE) were developed to extend generalised linear models to allow for correlated observations within subjects (Liang and Zeger 1986, Zeger and Liang 1986). GEE are used to express the marginal expectation (that is, the average response for

169

observations with the same covariates) of a set of responses as a function of explanatory variables.

We relate the marginal response $\mu_{it} = E[Y_{it}]$ to a linear combination of the covariates

$$g(\mu_{it}) = x_{it}\beta \qquad (2)$$

where Y_{it} is the response for subject i ($i=1\ldots N$) at time t ($t=1\ldots T_i$), x_{it} is a $p\times1$ vector of explanatory variables, β is a $p\times1$ vector of (unknown) regression coefficients, and $g(\bullet)$ is the link function. We assume observations on different subjects are independent, but allow for correlations between outcomes observed on the same subject.

We describe the variance of response Y_{it} as a function of the mean

$$V(Y_{it}) = V(\mu_{it})\phi \qquad (3)$$

where ϕ is a scale parameter (possibly unknown) and $V(\bullet)$ is the variance function.

Analogously to Equation (1), for a binary response we define $\pi_{it} = E[Y_{it}] = \Pr(Y_{it} = 1)$ and we may use the logit link; assuming the responses follow a Bernoulli distribution, we have

$$g(\pi_{it}) = \log\left(\frac{\pi_{it}}{1 - \pi_{it}}\right) = x_{it}\beta \qquad (4)$$

170

$$V(\pi_{it}) = \pi_{it}(1 - \pi_{it})$$ (5)

We choose the form of the TxT working correlation matrix $R_i(\alpha)$ for each Y_{it} such that the (t,t') element of the working correlation matrix is the correlation between Y_{it} and $Y_{it'}$. The correlations may be known, hypothesised or estimated.

The working correlation matrix may depend on a vector of unknown parameters α, assumed the same for each subject. We usually use a working correlation matrix that approximates the average dependence among repeated observations over subjects. In practice we should choose the working correlation matrix to be consistent with empirical correlations. Choice of the correlation structure should be guided primarily by theoretical considerations – for instance if there is reason to believe the correlations between successive observations are time-dependent a correlation matrix allowing for autocorrelation should be used. Types of correlation structure are given in Section 5.4.2 below.

The GEE method gives consistent estimates of regression coefficients and their variances even if the structure of the covariance matrix is mis-specified. However if the specified correlation structure does not incorporate all information on the correlations the parameter estimates may be inefficient (Fitzmaurice 1995). If the number of subjects is large the loss of efficiency due to an incorrect specification of the covariance structure is lessened (Liang and Zeger 1986).

$$V_i(\alpha) = \phi A_i^{1/2} R_i(\alpha) A_i^{1/2} \qquad (6)$$

The estimate of β is the solution of

$$\sum_{i=1}^{N} D_i'[V_i(\hat{\alpha})]^{-1}(Y_i - \mu_i) = 0, \qquad (7)$$

where $\hat{\alpha}$ is a consistent estimate of α and $D_i' = \partial \mu_i / \partial \beta$.

The GEE are solved by iterating between quasi-likelihood methods for estimating β and a robust method for estimating α as a function of β. That is, given the working correlation matrix and the scale parameter, calculate updated estimates of β using iterative quasi-likelihood methods. Then given the estimate of β, calculate the Pearson residuals $r_{it} = (y_{it} - \mu_{it})/[V_i]_{it}^{1/2}$, which are in turn used to consistently estimate α. These steps are repeated until convergence.

The square roots of the diagonal elements of the matrix $V(\hat{\beta})$ give standard errors for the regression coefficients.

5.2.3.5 *The variance estimator*

The model-based estimate of the variance is given by

173

$$V(\hat{\beta}) = \hat{\sigma}^2 \left[\sum_{i=1}^{N} D_i' \hat{V}_i^{-1} D_i \right]^{-1} \tag{8}$$

which is consistent when the mean and covariance structure are correctly specified. The empirical estimate (robust) for the variance is preferred if the number of clusters is large as in general the covariance structure is not known. The empirical estimate of the variance is given by

$$V(\hat{\beta}) = \left[\sum_{i=1}^{N} D_i' \hat{V}_i^{-1} D_i \right]^{-1} \left[\sum_{i=1}^{N} D_i' (y_i - \hat{\mu}_i)(y_i - \hat{\mu}_i)' \hat{V}_i^{-1} D_i \right] \left[\sum_{i=1}^{N} D_i' \hat{V}_i^{-1} D_i \right]^{-1} \tag{9}$$

Note that the estimates are the same when $\hat{\sigma}^2 = (y_i - \hat{\mu}_i)(y_i - \hat{\mu}_i)'$

For the purposed of defining a goodness of fit statistic in 5.2.3.7, we denote the model-based estimate of the variance by Γ and the empirical estimate by Ψ.

5.2.3.6   Modelling issues

The testing of models estimated by GEE is an underdeveloped area and statistical tests of goodness of fit and modelling assumptions are not yet available in standard statistical software procedures.

5.2.3.7 *Goodness of fit*

Response variables in a model estimated by GEE are generally not independent – therefore the model's residuals are not independent and not appropriate for developing goodness-of-fit statistics (Zorn 2001). Alternative goodness-of-fit statistics for models estimated by GEE have been proposed by Zheng (2000) – the marginal R-square – and Pan (2001) – the quasilikelihood information criterion (QIC). However these are not available in standard statistical software implementations of GEEs (for example SAS and Stata, see Section 5.6).

Zheng's marginal R^2 is a measure of the improvement in fit between the estimated model and the null model and is interpreted as the amount of variance in the response variable that is explained by the estimated model. The working correlation matrix is not explicitly included in the estimate of the marginal R^2.

Pan's QIC allows the comparison of models estimated by GEE with different correlation structures to the model with independent correlation matrix. The QIC is a modification of Akaike's information criterion (AIC), with the likelihood replaced by the quasilikelihood obtained by GEE with a working correlation matrix with independent structure (ie the identity) and the penalty term adjusted. It may be written

$$QIC = -2Q(\beta) + 2trace(\Gamma^{-1}\Psi) \qquad (10)$$

where Γ and Ψ are respectively the model-based and empirical variance estimators (5.2.3.5), and $Q(\beta)$ is the quasilikelihood estimate with independent working correlation matrix. Thus the QIC is minimised when the difference between the model-based and empirical estimates of the variance is smallest (that is, the working correlation matrix is closest to the true correlation matrix).

However this applies only to comparisons between independent and other structures, and as Ballinger (2004) points out, relying on this test for model selection limits one of the strengths of the GEE approach, namely flexibility of the modelling process.

5.2.3.8 Residuals

Residuals may be checked for outliers that might have inordinate influence on the results. For instance, DFBETA measures the change in the fitted coefficient vector when a single subject is omitted (Ballinger 2004). Residual versus fitted values plots for each subject may give a good visual test of independence – residuals should be randomly distributed, with no evidence of clustering – however this is practical only if the number of subjects is small.

5.2.3.9 Interpreting and testing parameter estimates

In the GEE approach the correlation structure is considered a nuisance and the focus is on estimating parameters for the mean response with correct standard errors. We interpret parameter estimates as population average values. If interest lies in the correlation structure, developments of the GEE approach (eg GEE 2) – (Zhao and Prentice 1990), or a random-effects approach should be used.

Harrison (2002) has demonstrated that if the parameter estimates are large the standard errors may be over-estimated.

5.2.3.10   Missing data

If the assumption that missing data are missing completely at random (MCAR) is true than GEE give correct parameter estimates. However if the data are missing depending on previous values of the response, the parameter estimates may not be correct (Zorn 2001). Where there is attrition, the model estimates may not be interpretable if the attrition process is dependent on previous values of the response or covariates.

5.2.3.11   Example: use of GEE in assessing rate of antipsychotic monotherapy

Faries et al (2005) analysed initial treatment group (3 different antipsychotic therapies) differences in the percentage of patients on monotherapy each day over a 1-year period. The repeated response within each patient (monotherapy versus not monotherapy) was modelled using a generalised linear model for binary response, by generalised estimating equations with an exchangeable correlation matrix to allow for dependence between repeated observations. Covariates included in the model were treatment, time, treatment by time interaction, and socio-demographic and medication history variables. From the parameter estimates of this model the odds ratios for monotherapy for specified covariate values were calculated. Similarly the percentage of patients on monotherapy, given covariates, were estimated.

5.2.4   *Conditional Models*

The alternative to modelling the marginal expectation is to model the conditional expectation of each response given values of previous responses or a set of unobserved random variables. The mean and time dependence are modelled simultaneously (unlike marginal models). There are two types of conditional model: transitional and random effects.

For transitional models, $E\left[Y_{it} \mid Y_{i1}, Y_{12}, ..., Y_{i,t-1}\right]$ is modelled. That is, we model (logit of) the conditional expectation as a function of previous responses (and other covariates). An

important subclass is Markov chain models, which allow only a fixed number of previous responses as covariates. The parameter estimates may be interpreted in terms of changes in an individual's response probability conditional on values of the previous responses. That is, holding response history and other covariates fixed and changing the value of a covariate by one unit, the estimated regression parameter can be used to calculate the change in the probability of a positive response. Interpretation varies according to the number of previous responses included as covariates and on the functional form of the dependence (Fitzmaurice 1998).

In the case of random effects (or multilevel) models, $E[Y_{it} \mid u_i]$ (u_i random effects) is modelled. Estimates of the fixed effects are interpreted as the change in the probability of event for a unit change in the covariate for a specific individual with underlying propensity to experience the event u_i. These estimates are, in general, not equal to marginal regression parameter estimates. In general the effects of covariates are greater in absolute magnitude in the random effects model than in the marginal model. Indeed, the conditional distribution of the response may not be the same as the marginal distribution.

5.2.4.1 Multilevel models: introduction

This section previously discussed the marginal models; multilevel (or random-effects) models take a different approach to data with hierarchical (or clustered, or nested) structure. Units (at level 1) within the same group (level 2) may share characteristics that make them

179

more similar to one another than units from another group. Groups tend to be different and both the group and the units within it affect and are affected by group membership.

Ignoring the hierarchical structure of the data and analysing at unit level can lead to attributing group-level effects to the unit, resulting in over-estimation of the standard errors for unit-level factors and thus finding them significant when they are not if the contribution of group-level variation is taken into account. On the other hand, aggregating unit-level covariates to group level means losing information about unit variability.

Longitudinal data can be thought of as observations within subjects. By using multilevel models (Goldstein 2003, Hox 1995) for longitudinal data we allow for correlations within individuals who are repeatedly observed over time. An advantage of using multilevel methods for longitudinal data analysis is that there is no requirement that all individuals must be observed at the same time points – any pattern of measurements is allowed and provides efficient estimation of the model parameters (Hedeker and Mermelstein 2000).

Models for time spent in different states (event history models) have a similar multilevel formulation to that for longitudinal repeated measures – here the structure of the data is conceptualised as time periods within individuals.

5.2.4.2 Unobserved factors affecting compliance

There are certain factors specific to the patients and their behaviour that are not observed in the data. These include knowledge and information available to the patients, their perceptions of the need for therapy and their perceptions of side effects (see Chapter 2). These factors at patient level are clearly important at in influencing the decision to continue with therapy. Modelling individual patients' propensities to continue to collect their prescription allows the identification of any patient-specific tendencies. Here the interest is in modelling patient-level heterogeneity and establishing to what extent some patients are more likely than others to continue collecting their prescriptions. This information potentially could be used to determine the likelihood of an individual patient continuing with a prescription, given covariates.

5.2.4.3 Multilevel model for prescription availability

For the repeated binary response indicating monthly prescription availability I initially used a logistic model with random intercepts for patients. This is similar to a GEE logistic regression model with an exchangeable correlation matrix. However, the assumption that responses are independent conditional on the patient may not be justified. For instance, there may be dependence between successive responses within individual patients. The assumption that the errors are binomially distributed should be tested.

The multilevel approach allows the correlation of outcomes at each level to be modelled. The second level of the multilevel model accounts for the clustering of prescription collections by patients (those with more than one month of continuous claiming since August 2000). That is, it treats collection of each prescription as independent events given the patient-level effects. This gives a direct way of looking at the influence of patients' unobserved characteristics on the collection of prescriptions and hence a direct measure of the unobserved effects. It also ensures that the standard errors of the parameters in the model are correctly estimated. Unlike marginal models (GEE) where the dependence between responses from the same patient is considered a nuisance, this approach allows the assessment of within-patient dependence in the response.

As for the marginal regression model by GEE, the multilevel model is an extension of the generalised linear model for binary responses. In its simplest form, a random intercept is included for each subject.

The response Y_{it} has two possible values (collection versus non-collection of monthly prescription t nested in patient i). The probability of collection of a prescription is expressed as $\pi_{it} = E[Y_{it}] = \Pr(Y_{it} = 1)$ and $V(Y_{it} \mid \pi_{it}) = \pi_{it}(1 - \pi_{it})$. The response is assumed to follow the Bernoulli distribution $Y_{it} \sim \text{binomial}(\pi_{it}, 1)$, and the logit link is chosen: (compare with Equation (4))

$$\log\left(\frac{\pi_{it}}{1 - \pi_{it}}\right) = x_{it}\beta + u_i \qquad (11)$$

182

where $u_i \sim N(0, \sigma_u^2)$. The term u_i allows for the clustering of prescription claiming within patients – it is the effect of patient i on the logit hazard after controlling for the covariates. This model assumes that, given the clustering of the data, monthly observations are independent Bernoulli trials where the probability of collecting a prescription, π_{it}, depends on the characteristics of the month and the patient. Within each patient the decision to collect a prescription each month is independent. We can examine this assumption by including variation at the level of month. If the variance (or extra-binomial) parameter is unconstrained and therefore estimated we can check our assumption that it is equal to 1 (independent Bernoulli trials). If the estimated variance is significantly less than 1 this implies underdispersion, which suggests correlation between outcomes after controlling for the effect of patient (that is, the monthly observations are not independent given the patient). If the estimated variance is significantly greater than 1 this implies overdispersion of the data at the level of month, possibly due to omission of an important explanatory variable from the model or unaccounted clustering at higher levels.

The assumption that the random effects at patient level are Normally distributed may be examined by a Normal probability plot.

5.2.4.4 Extra-binomial and extra-multinomial variation

One solution to underdispersion is transitional models, which allow for dependence between successive outcomes to the same subject. For example, Curtis and Steele (1996) used

random-effects with a first-order transitional model for mortality - however for prescription claiming a first-order transitional model may not be sufficient to explain the correlations within each patient, and higher orders may be necessary. This because the decision to collect a prescription may not be independent given the patient and the decision in the previous month only.

An alternative is a multivariate multilevel model. Here for a patient the response Y_{it} for each month is one component of a multivariate binary response at the patient level i rather than a univariate response at the month level t. This approach was used by Yang et al (2000) and by Griffiths et al (2004) as an alternative to the univariate logistic model specified above. This model does not assume conditional independence of individual responses and specifies a correlation structure between prescriptions to the same patient. The variance parameters are constrained to equal 1 and the covariance terms estimated from the data and represent the clustering of responses for a patient and the fact that the outcomes are not independent of one another given the patient. However this approach requires the estimation of a large number of parameters if the patients are observed over a long period of time – for instance for 12 months the variance is a 12x12 matrix, which requires estimation of 60 covariance parameters. The approach would be more feasible for a short series of correlated observations on the same subject.

The multinomial model is a generalisation of the binomial model to more than two response categories and the extra-multinomial parameter is analogous to the extra-binomial parameter. Fielding and Yang (2002) suggest that estimating the extra-multinomial parameter may improve the estimation of other model parameters – stating that this 'seems to take up any

184

features of the data that make the imposition of multinomial variation over-rigid' (section 4).

In a small simulation study on multinomial data, they found that when the multinomial variance was constrained to 1 the random-effects variances were underestimated by 15-25%, whereas when the multinomial variance was unconstrained it was estimated close to 1 and the random-effects variances were underestimated by 2-9%.

Misspecification of the conditional probability may result in extra-multinomial variation, which is provided for by the introduction of the extra-multinomial parameter. Extra-multinomial variation may also arise if data are sparse, or may be due to missing levels in the data structure. However interpretation of this parameter may be difficult.

5.2.4.5 Variance partition coefficients

The variance partition coefficient gives the proportion of the variance ascribed to each level of the data hierarchy (Goldstein et al 2002). This is useful to establish the relative importance of different levels in the model. For binary data, one method suggested by Goldstein is to assume that the binary response is a realisation of an underlying continuous response variable, in which case the proportion of variance at level 2 is given by

$$\frac{\sigma^2}{\sigma^2 + \pi^2/3},$$ where σ^2 is the level-2 variance.

Browne et al (2005) extended the methods of Goldstein et al (2002) to calculate the variance partition coefficients for data with a binary response that is possibly overdispersed.

5.2.4.6 Multilevel modelling issues

Data are assumed missing at random (MAR) – that is, the data may be missing depending on observed variables (previous responses or covariates) (Little and Rubin 1987). Due to attrition being possibly dependent on previous responses, the random effects approach may be more suitable than the GEE approach (see Section 5.2.3.8). Marginal models assume data are missing completely at random (MCAR) – marginal models may run into problems where there is a high rate of attrition and the attrition process is not independent of the previous values of the response. Comparison of estimates from both approaches may give further insights.

Langford and Lewis (1998) discuss model fit in multilevel models with Normal response variables. Tests of model fit for categorical response multilevel models are underdeveloped. Distributional assumptions (for instance, the assumption that random effects are Normally distributed) may be examined by residual plots at level 2. As discussed in Sections 5.2.4.3 and 5.2.4.4, the binomial assumption may be examined by fitting an extra-binomial parameter – however the interpretation of this parameter may be difficult.

5.2.4.7 Example: Random effects model for compliance in diabetes

A study on adherence to medication for type 2 diabetes (Balkrishnan et al 2003) implemented a random effects regression model. The authors were interested in exploring the idea that poor health status in diabetic patients at baseline was associated with poor

186

adherence to diabetes medications (and consequently greater use of health services). They fit a generalised least squares regression model with yearly medication possession ratio (MPR) (a skewed variable) as the response and a random effect to allow for baseline variability between patients. The covariates found to have a significant association with MPR were use of an oral antidiabetic (which had a positive effect on MPR), the comorbidity severity index and having had an emergency room (ER) visit in the previous year (both had a negative effect on MPR). Age, sex, depressive symptoms, alcohol consumption, smoking, physical activity, hospitalisation in previous year, a quality of life score and year had no significant association with MPR. This is one of the few studies related to compliance to use a random effects model. Apart from noting that there was evidence of unobserved between-patient differences over time, the authors made no comment upon the patient-level variance.

5.2.5   *Comparison between marginal and random effects models*

The parameter estimates for the fixed effects in marginal and random effects models are not in general equal – the estimates from the random effects model are larger than the marginal model estimates and the discrepancy increases if the random-effects variance is large.

The interpretation of parameter estimates is different for marginal and random effects models. We consider the example of the logistic model for prescription claiming. For the marginal model the interpretation is population averaged – that is, parameter estimates

compare the log odds of claiming a prescription in one population group to another (for example women versus men, or patients who have IHD versus those who do not at some point in time). For random effects models the interpretation is subject-specific, being conditioned on the individual's random effects – that is, the parameter estimates give the log odds of claiming a prescription in a specific patient given a change in the covariate. Obviously this interpretation only applies to within-subject effects – for example IHD status – which may change within an individual. Between-subject effects, such as gender, are interpreted differently: the parameter estimate gives the average patient-specific intercept for one group (for example women) compared to another (for example men). In this example if the parameter estimate is larger for women than for men this suggests that women have a higher propensity to claim prescriptions.

In logistic models the estimated probabilities from the random effects model are not mean probabilities due to the nonlinearity of the transformation (Goldstein 2003). These may however be viewed as median probability estimates and show the pattern of responses.

The choice between marginal and random effects models is dependent not on the data but on the objectives of modelling. If the objective is to make inferences about the population then the marginal model is the appropriate choice; if the objective is to make inferences about individuals then the random effects model should be selected.

The missing data assumptions of the marginal model are more stringent than those of the random-effects model. The marginal model requires that the process of missingness is not

dependent on previous responses – a random-effects model does not require this for consistent estimation of the parameters.

In the random effects model for longitudinal data is each subject has an individual random intercept based on all their observed responses. One of the advantages of the random-effects approach is that these observations need not be made at the same time points nor does the model require the same number of observations from each patient for efficient estimation of the parameters (Hedeker and Mermelstein 2000).

5.3 Models for discontinuation

5.3.1 Event history data with binary response

An alternative to the repeated measures approach is to model the duration of prescription availability, using discrete-time event history models. For instance, the outcome of interest may be discontinuation of therapy.

We consider the probability that first discontinuation occurs. The data set includes all months that each patient had therapy available until their first discontinuation. Thus patients who discontinued in the first month and never resumed therapy contribute only one observation to the data set, whereas patients who had prescriptions available every month until the end of the observation period contribute a large number of observations. For a patient i at time (month) t with response vector $(Y_{i1}, ..., Y_{it})$ and covariates x_{it} the conditional probability of first discontinuation at time t may be expressed as $\Pr(Y_{it} = 1 | Y_{i1}, ..., Y_{i(t-1)} = 0, x_{it})$. This is also known as the hazard rate, $h_i(t)$. We can model the logit hazards as a function of the covariates

$$\log it[h_i(t)] = x_i(t)\beta + \alpha(t) \qquad (12)$$

where $\alpha(t)$ is the antilogit of the baseline hazard function and may be modelled as a polynomial or fractional polynomial (Royston and Altman 1994) function of time, or any smooth nonparametric curve, for instance cubic splines (Reinsch 1967), or by fitting a step

190

function which may be constant for each month or for suitably grouped time intervals (by including time dummy variables as covariates). Interactions between $\alpha(t)$ and $x(t)$ allow the effects of the covariates to change over time.

This may be extended to include multiple episodes j of prescription claiming for each patient. As described in Chapter 4, an episode may be defined as a continuous period during which therapy was continuously available. The model may be written $\log it[h_{ij}(t)] = x_{ij}(t)\beta + \alpha_j(t)$, allowing the covariates to vary with time and be defined at episode or individual level, and allowing the baseline hazard function to vary for first and subsequent events. This model is essentially the same as above and is estimated in the same way.

As for repeated measures data, dependencies due to clustering within subjects must be allowed for. If there are subject-specific unobserved factors that affect the hazard, the observed form of the hazard function at population level will tend to be different to observed forms at individual level. This is because of a selection effect – high-risk individuals tend to experience the event early, and over time the population consists mainly of people not likely to experience the event. The selection is on unobservables and the variation between individuals in the risk of the event occurring is usually referred to as unobserved heterogeneity. The population hazard decreases, even if individuals' hazards are increasing or constant. In survival analysis, this is known as "frailty".

5.3.2 Marginal event-history models for discontinuation

Dependencies within subjects may be modelled using either a marginal or random effects approach. The marginal model is estimated by generalised estimating equations, which are described in detail above. This requires the choice of a working correlation structure to model the average dependencies between successive durations. The exchangeable correlation structure makes a similar assumption to the random effects model with random intercepts – that is, the correlations between all observations of the same patient are assumed to be equal.

The random effects model for a discrete-time event history for discontinuation is described in more detail in the next section.

5.3.3 Multilevel event-history models for discontinuation

One way to allow for dependencies between observations within patients is to model the outcomes of episodes of claiming within individual patients.

The equation for this model looks very similar to Equation 11 but here we model hazards of discontinuation rather than probability of claim, and only the months where the patient was at risk of discontinuation are included in the data set – that is, months when the patient had a prescription.

The hazard of first discontinuation may be modelled by including monthly observations on patients up to the point at which the first discontinuation occurred or until the end of the observation period. Similarly the hazard of any discontinuation may be modelled by including all episodes j of claiming within patients i.

$$\log it\left[h_{ij}\left(t\right)\right] = x_{ij}\left(t\right)\beta + \alpha_j\left(t\right) + u_i \qquad (13)$$

where $u_i \sim N\left(0, \sigma_u^2\right)$.

With no random effect in the model $\exp(\beta)$ is an odds ratio – the interpretation is population-averaged. With a random effect, the interpretation is an odds ratio only if the random effect is held constant – that is, if we compare two hypothetical subjects with the same random effect. The interpretation is subject-specific.

Episodes of claiming, nested within patients, are defined as continuous claiming of the same therapy. Durations of episodes within the same patient may be correlated because of unobserved individual characteristics that influence the duration of each of an individual's episodes. A multilevel hazards model, with random effects to allow for unobserved heterogeneity between patients, allows for correlations between repeated durations. For example, the individual risk of discontinuation of the therapy prescribed due to adverse events varies due to an individual's response to therapy. There may be correlations between durations of claiming within individuals due to unobserved factors (for example patients

193

who find it hard to establish the habit of drug use or who suffer adverse reactions to their therapies may contribute a series of short episodes).

5.4   Models for competing risks

5.4.1   Multinomial response

There may be more than one way of ending an episode of prescription claiming.   For instance, consider the probability that the first discontinuation or switch occurs at time t. In this case we construct a monthly response variable coding continue (ie receive the same prescription the next month) = 1, discontinue (ie had no prescription available the next month) = 2 and switch (ie receive a different prescription the next month) = 3. We model the risks that the first discontinuation and the first switch occur at time t:

$$\Pr\left(Y_{it} = 2 \mid Y_{i1}, ..., Y_{i(t-1)} = 1, x_{it}\right)$$

$$\Pr\left(Y_{it} = 3 \mid Y_{i1}, ..., Y_{i(t-1)} = 1, x_{it}\right) \tag{14}$$

A competing-risks model may be used to differentiate between the different kinds of therapy change (eg switching or discontinuation). To model the duration to the first change, after experiencing one kind of change an individual is removed from observation – for example, if an episode ends in a switch then time to discontinuation is right-censored. In this case the

194

minimum of time to switch and time to discontinuation only is observed. This may be extended to model the durations of all episodes of prescription claiming observed within patients.

The hazard that event of type d has occurred in interval t is the probability of event of type d in interval t given no events (of any type) have occurred in the previous intervals. The log-odds of the hazard may be modelled using a multinomial logit model. This may be extended to include repeated episodes of prescription claiming for each patient. The hazard ratio of an event of type d to event of type 1 may be written:

$$\log\left(\frac{h_{ij}^{(d)}(t)}{h_{ij}^{(1)}(t)}\right) = \alpha_j(t)^{(d)} + x_{ij}^{(d)}(t)\beta^{(d)} \qquad (15)$$

5.4.2   *Example: marginal model for discontinuation of contraception*

Ali et al (2001) modelled the cause-specific probability of discontinuation of contraception by time t, in the presence of competing risks. Cause-specific hazards were simultaneously modelled as log-linear functions of the covariates in a semi-parametric proportional hazards model. Multiple episodes of contraceptive use within women were accounted for by calculating the standard errors by double bootstrap, which allows for the clustering of the data. The interpretation is marginal: parameter estimates give population average cause-specific hazards and cumulative incidence.

5.4.3   Multilevel models for competing risks

Steele et al (1996) suggested a discrete-time competing risks model to analyse the duration of contraception use in China.

For episode j patient i the log-odds of the probability of an event of type d taking place in interval t versus no event may be modelled as a linear function of time and other covariates with random effects for individuals and for each type of outcome.

$$\log\left(\frac{h_{ij}^{(d)}(t)}{h_{ij}^{(1)}(t)}\right) = \alpha_j^{(d)}(t) + x_{ij}^{(d)}(t)\beta^{(d)} + u_i^{(d)} \tag{16}$$

The $u_i^{(d)}$ allow for unobserved subject-specific factors. Each subject has a random intercept for each type of outcome. It is assumed these follow a multivariate normal distribution with variance Ω_u. By allowing random intercepts to be correlated across different types of therapeutic change, the presence of unobserved risk factors that influence both types of change may be accommodated. That is, there may be unobserved factors at patient level that affect their propensity to both switch and discontinue their medicines. A negative correlation between the random intercepts for switching and discontinuation would indicate that patients whose unobserved characteristics tend to influence them to continue with therapy also tend to influence them not to switch and vice-versa. A positive correlation would indicate that patients whose unobserved characteristics give them a propensity to

discontinue are also likely to switch and patients with a propensity to continue are not likely to switch.

It is also possible to include random effects at episode level. However, Steele et al (2004) suggest that it may be preferable to model episode-level variation by including random slopes for individual-level factors.

In practice, data must be in discrete-time format, with one record per month using therapy. The initial step is to model the log hazard for change of type d, episode j in patient i in terms of time t. We then model the log hazard in terms of time (baseline log hazard) and other covariates. To add random effects for each outcome category, the intercepts are allowed to vary randomly across patients. The between-patient variance in the log hazard of discontinuation versus continuation, the between-patient variance for the log hazard of switching versus continuation, and the covariance between the cause-specific random effects are estimated. If patients with a high risk of discontinuing all therapy have a low risk of switching to another therapy a negative covariance estimate is expected.

5.5 Multistate models

5.5.1 Multistate models for event histories

A multistate model focuses on the transitions of an individual between a finite set of states (Hougaard 1999). It can be thought of as an extension of event history or survival models, where there are several possible states. Multistate models give a useful way of analysing complex event histories. An event history is a stochastic process, which at any time t occupies one of a discrete set of values (states), and where an event is a change of state (Andersen and Keilding, 2002). The stochastic process is denoted by X_t, $t \in [0, \infty)$ such that $X_t = s$, where $s \in S = \{1, ..., q\}$ denotes the state space, if the process is in state s at time t.

One of the attractive features of a multistate model is the specification of a graphical representation of the state structure. This shows the states and possible transitions between them. States may be absorbing or transient, and we may choose to allow only a subset of all possible transitions. The graphical depiction makes our assumptions apparent.

We consider the models above as multistate models and give their graphical depictions: these illustrate the states defined from the data and the allowed transitions. In the simplest case, we can illustrate the transition from the initial state of drug claiming to non-claiming.

Here the states are first episode of claiming and first episode of non-claiming, and the event is discontinuation (Figure 5.7).

Figure 5.7 Multistate model: episodes of claiming and non-claiming

Competing risks may be thought of as a multistate model, as illustrated in Figure 5.8 (Anderson 2002).

Figure 5.8. Competing risks as a multistate model
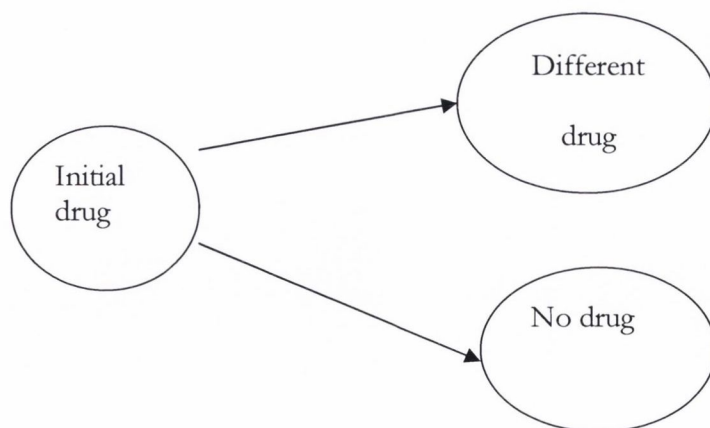
Repeated measures can be formulated as a multistate model – for instance, repeated episodes of claiming prescriptions (Figure 5.9):

Figure 5.9. Repeated episodes of claiming as a multistate model

| 1st claiming episode (No discont) | → | 2nd claiming episode (1 discont) | → | 3rd claiming episode (2 discont) |
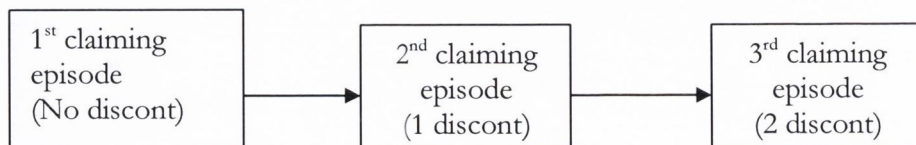
Given that all the prescriptions claimed each month are known, we could define separate states for claiming particular combinations of drugs – however this would lead to a very large number of states and a very complex structure. Illustrated below is a four-state model with the four states being claiming initial drug, claiming initial+other drug, claiming a different drug (or combination), and not claiming any drug (Figure 5.10). In this model all states are potentially transient, as indicated by the arrows showing allowable transitions.

Figure 5.10. General four-state model for prescription claiming
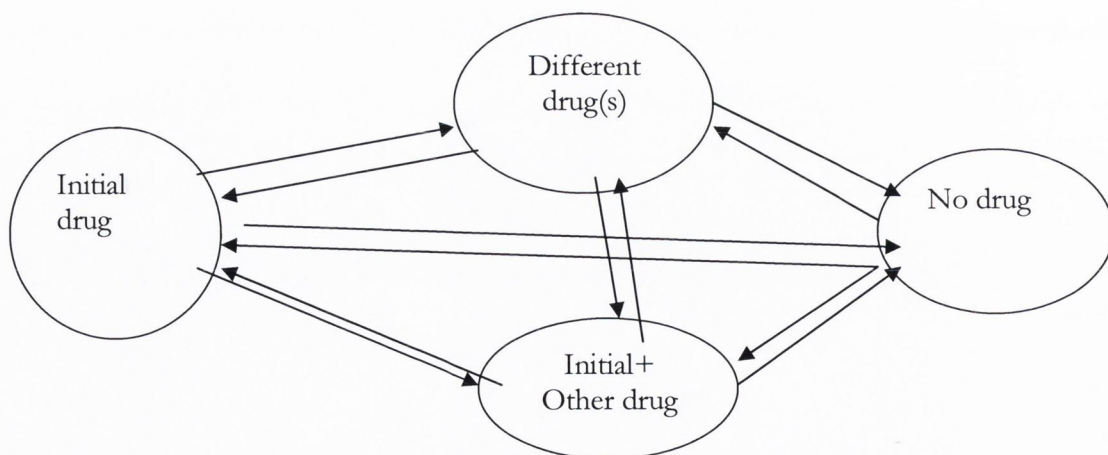
The multistate model specifies the state structure and the hazard (or transition intensity) for each possible transition. For the model illustrated in Figure 5.10, a 4x4 matrix of transition intensities is required. The transition intensities are the instantaneous probabilities that the process X_t makes a transition between states (given covariates $x(t)$).

$$h_{rs}(t, x(t)) = \Pr(X_{t+\delta t} = s \mid X_t = r) / \delta t \qquad (17)$$

5.5.2   Multistate models for claiming and non-claiming

An individual patient may experience episodes of different types during the observation period. For instance, the patient might start on one drug, take it for three months, have a gap of two months, start another therapy, add a third therapy two months later, and so on.

We may think of claiming and non-claiming as separate states. Using a simple logistic regression model, we can model the hazards of ending states of claiming (u) by discontinuation and non-claiming (n) by resumption of therapy.

$$\log it[h_{iju}(t)] = x_{iju}(t)\beta_u + \alpha_{ju}(t)$$

$$\log it[h_{ijn}(t)] = x_{ijn}(t)\beta_n + \alpha_{jn}(t) \qquad (18)$$

Where there is heterogeneity between individuals, random effects models are appropriate. One of the benefits of formulating the model in this way is that it is relatively simple to incorporate random intercepts at patient level. In the next section I discuss a multistate model for claiming and non-claiming that allows for individual heterogeneity.

5.5.3   *Multilevel multistate models for claiming and non-claiming*

Goldstein et al (2004) describe a multilevel multistate discrete time model for repeated episodes within individuals.

Here interest is in the modelling durations of claiming and non-claiming of therapies at the individual level. As above, claiming and non-claiming are considered to be separate states. An episode of claiming is defined as a continuous period using any therapy (ie any AHT, or any statin), and an episode of non-claiming is defined as a continuous period with no prescription claims. The outcome of interest is discontinuation of the episode of claiming or non-claiming.

The data are structured in discrete-time format, with one record per month during each episode of claiming and one record per month during each episode of non-claiming. A logistic model may be fit with dummies for the separate states multiplied by the covariates (duration, age, sex). To add random effects for each state, the coefficients of the state dummies are allowed to vary randomly across patients. This allows for dependencies

between durations of episodes within the same individual and for correlation between state-specific random effects. For patient i, episode j, in state u (claiming) and state n (non-claiming) the logit hazards of an event at time t are modelled:

$$\log it\left[h_{ijn}(t)\right] = x_{ijn}(t)\beta_n + \alpha_{jn}(t) + u_{in}$$

$$\log it\left[h_{iju}(t)\right] = x_{iju}(t)\beta_u + \alpha_{ju}(t) + u_{iu} \qquad (19)$$

The between-patient variances in the log-odds of discontinuation show the significance of unobserved patient-level effects for claiming and non-claiming therapy. The covariances between state-specific random effects are also estimated. If patients with a high risk of discontinuing an episode of claiming also have a low risk of discontinuing an episode of non-claiming, or vice versa, a negative covariance estimate is expected.

5.5.4 Multilevel models for competing risks and multiple states

Steele et al (2004) proposed an extension of the discrete-time multilevel model for competing risks to allow for multiple states.

$$\log\left(\frac{h_{ijs}^{(d)}(t)}{h_{ijs}^{(1)}(t)}\right) = z_s^{(d)}(t)\alpha_{js}^{(d)} + x_{ijs}^{(d)}(t)\beta_s^{(d)} + u_{is}^{(d)} \tag{20}$$

For each state $s = 1,\ldots, S$ the possible outcomes are denoted d_s, where $d_s = 1,\ldots D_s$. Each subject has a random effect for each type of outcome from each state. The random effects are assumed to follow a multivariate normal distribution.

To fit this model the data must be structured to give a response for each time interval in each episode. This means a very large data set if the number of episodes is large and the duration of episodes is long relative to the width of time interval used. Time intervals may be aggregated without affecting the number of episodes. Aggregation may be appropriate if transitions between states are unlikely to occur during the aggregated interval.

In the previous multistate model (Section 5.5.3) an episode was defined as a continuous period of claiming any drug - now an episode is defined as continuous claiming of a specific therapy. Transitions from claiming are by either discontinuation to non-claiming or switch to an alternative therapy.

The first step in the modelling process is to fit a model including duration effects only. Transitions from the state of claiming may be modelled by a multinomial logit model, with random effects for each type of transition. For transitions from the state of non-claiming a binomial logit model is used to model the risk of resuming therapy. The two models are estimated jointly, allowing for correlation between random effects.

A separate set of random effects is estimated for each transition type. The size of the random effects covariances gives evidence of unobserved heterogeneity in hazards of each type of transition. Positive correlation estimates between discontinuation and switching (or resuming therapy) indicate that patients at high risk of discontinuing episodes of claiming are also at high risk of switching (or resuming therapy).

The type of drug and other factors may be included as possibly time-varying covariates.

5.5.5   A general multistate model

More generally, suppose individual i is observed at times $\left(t_{i1},...,t_{in_i}\right)$ to be in states $\left(S(t_{i1}),...,S(t_{in_i})\right)$. Between each pair of states, r and s, the transition intensity or hazard $h_{rs}(t,x(t))$ gives the instantaneous risk of moving from state r to state s, where $x(t)$ are possibly time-varying covariates (see Equation 17). The transition probability matrix for a specified time t is given by the matrix exponential $P(t) = \exp(tH)$, where H is the matrix of transition intensities between each pair of states. Instead of considering states of claiming and non-claiming, we could define episodes of claiming different types or combinations of drugs as different states – in the case of antihypertensives the number of possible states could be very large.

In this model the probabilities of moving between any pair of states are assumed to depend only on the current state and not on previous states. In other words, it is assumed that the transitions follow a Markov process. Under the Markov assumption, the hazards for each

transition depend on the history of the process only via the current state. That is, in discrete time, the probability of a transition between state r and state s is given by

$$P_{rs}(t, t+1) = \Pr(Y_{t+1} = s \mid Y_t = r)$$ (21)

Transition intensities (hence probabilities) may be estimated by maximising the likelihood. They may be allowed to depend on covariates, which may be time-varying.

5.6 Software

The GEE regression models were fit using SAS Version 8 proc genmod (SAS Institute, 1999) and Stata xtlogit command with option "pa" (population average) (StataCorp, 2001). Comparison between the results of modelling in SAS and Stata was made as a check of model estimates, and to examine the different statistics reported by each package. Stata gives a Wald χ^2 statistic, which is a test of whether all the parameter estimates are different to each other and to zero (this is not a goodness-of-fit statistic). It is not interpretable when an autoregressive correlation structure is specified. Stata provides higher orders of autoregressive correlation matrices than SAS, which provides only AR(1). Software for fitting GEE regression models is reviewed by Horton and Lipsitz (1999).

Random effects models were fit using MLwiN 2.0 (Rasbash et al 2003), with estimates based on both penalised quasi-likelihood and Markov Chain Monte Carlo (MCMC) methods. As it has been shown that quasi-likelihood methods give biased parameter estimates for binary response data, estimates were based on MCMC methods where possible (Browne and Draper, 2000). To check if convergence has been achieved, the trajectories of each parameter may be inspected. A chain with good mixing should not show any trend – the estimates should fluctuate randomly. It may be necessary to increase the burn-in and the monitoring chain length to achieve convergence. Interval estimates for each parameter may be obtained based on the samples in the MCMC chain. A 95% interval estimate is given by the 2.5% and 97.5% points of the simulated distribution. If in the initial models fitted the quasi-likelihood estimates were close to MCMC estimates, the former were used to reduce the time that would be needed for a sufficient number of MCMC iterations.

It is also possible to fit simple random effects models using Stata's xtlogit command with option "re" (random effects), but MLwiN was preferred as is can be used to fit more general competing risks and multistate models and (unlike in Stata) MCMC estimation is available.

Multistate Markov models were fit in R, using version 0.5.1 of the msm package (Jackson 2005).

6. Patterns of Claiming Statin Prescriptions

in the GMS Scheme

6.1 Introduction

The primary aim of this chapter is to describe and characterise the patterns of claiming statin prescriptions under the GMS scheme. In particular, models are developed for the following:

1. Statin availability in the population over time since the initiation of therapy, adjusting for age, sex and evidence of IHD.

2. Subject-specific statin availability over time since the initiation of therapy, adjusting for age, sex and evidence of IHD. This includes an estimate of the importance of the variability due to unobserved subject-specific factors, conditional on previous responses.

3. The hazard of ending a continuous period of claiming statin prescriptions in the population, in terms of duration of the period and other covariates.

4. The subject-specific hazard of ending a continuous period of claiming statin prescriptions in terms of duration of the period and other covariates.

5. The subject-specific hazards of ending continuous periods in one of two states: claiming and not claiming statin prescriptions, in terms of time spent in the state and other covariates.

A sequential modelling strategy was followed, as outlined below. To gain insight into patterns of claiming statin prescriptions, two types of data structure were considered: repeated measures on individuals (where the response was availability of a statin prescription each month) and discrete-time event history (the main event of interest being discontinuation of statins). Dependencies between responses from the same patient were accounted for by the GEE and random effects approaches, and transitional terms were included where appropriate.

Section 6.2 presents some preliminary analyses of the cohort of new users of statin therapy, which was first described in Chapter 4.3.

Section 6.3 gives the results of fitting logistic regression models to the binary response indicating statin availability. The first model ignores the dependencies between repeated observations of patients, but is useful to indicate the form of the relationships between the response variable and covariates, in particular time. This model was extended to allow for the dependencies between responses contributed by the same patient, using marginal and conditional approaches. Model fit and interpretation of the parameter estimates of the conditional (random effects) model in comparison to the corresponding marginal model by GEE are also discussed.

The event-history model with outcome discontinuation of statin claiming is described in Section 6.4; the model is extended by a GEE approach to allow for dependencies between repeated episodes within patients. This section then reports the results of fitting multilevel discrete-time hazards models. The first of these is a model for the time to first discontinuation, with a random intercept for each patient to allow for the unobserved patient-level factors that influence discontinuation. This model is extended to allow for multiple episodes of claiming statin prescriptions within each patient; the parameter estimates of this model are compared with the corresponding GEE estimates. Random coefficients for the duration covariates are included in the model to allow for differences over time in unobserved heterogeneity at patient level. Finally, section 6.5 gives the results of a multilevel multistate model for the hazards of ending episodes of claiming and not claiming statin prescriptions.

6.2   Preliminary results

6.2.1   Introduction

Presented here are some preliminary results on patterns of claiming of statin prescriptions in the cohort introduced in Section 4.3.3.

The cohort consists of 7,207 people from the ERHA region who were newly prescribed a statin under the GMS scheme between August 2000 and January 2002. Statins prescribed

were atorvastatin, simvastatin, pravastatin and fluvastatin. Patients selected had not received any prescription for that particular statin (ie the index statin) in the previous twelve months. People aged under 30 years were excluded from the cohort. The mean age was 65.5 years (SD 11.1 years) and 3,996 (55%) of the cohort were women. 74% were concurrently prescribed antihypertensives at some point during observation, and 23% were concurrently prescribed nitrate and aspirin (a marker for IHD). 24% of monthly statin prescriptions were for less than one DDD per day, 49% of prescriptions were for one DDD per day and 27% were for more.

Figure 6.1 shows, at patient level, the distribution of the proportion of months with a statin prescription available during the time each patient was observed, and thus illustrates one of the salient features of this data set: that there are groups of patients who collect either only one prescription (ie the first), or all their prescriptions, leading to clusters in the distribution of this response at 0 and 1. This indicates a high degree of consistency in claiming patterns within particular patient groups. The implications of this for modelling are explored further in Section 6.3.
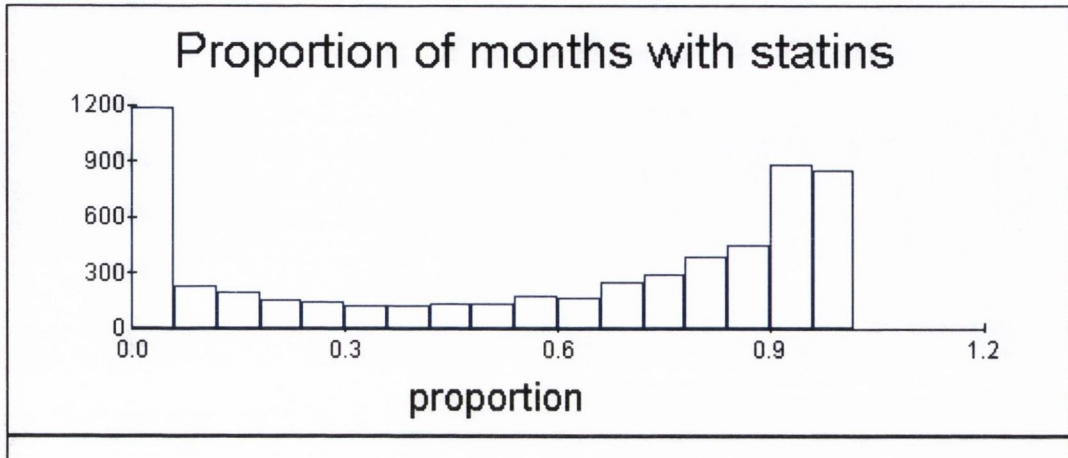
Figure 6.1 Distribution of statin availability at patient level

6.2.2. *Prescription histories*

Longitudinal prescription histories were constructed for each patient, with follow-up until December 2002 unless the patient withdrew from the GMS scheme at an earlier date. Prescription histories included a time variable, giving each month since the incident prescription (also referred to as the index prescription), and a variable indicating whether the patient had claimed a statin prescription to cover that month. If there was evidence that a patient had received a double prescription, this was carried over to the next month (see Chapter 4.2). Age of the patient was included as a time-varying covariate, and sex as time-invariant. Evidence of IHD was included as a time-varying covariate (see Section 6.2.5).

213

6.2.3   Event histories

For the purposes of the event history analyses, discontinuation was defined, based on clinical evidence, as a gap of one month with no prescription available (Sampietro et al 1995). Switching was defined as a change in the type of statin without any gap in therapy.

Two definitions of an episode may be considered – one based on continuous availability of any statin (switches ignored), and the other based on continuous availability of the same statin. The selected patients contributed 12,409 episodes ending in discontinuation, 836 ending in a switch and 4,091 ongoing at the end of observation. As switches of the type of statin therapy were quite rare, these were classified as continuation of therapy – that is, episodes of the first type only (continuous claiming of any statin) were considered. Using this definition, patients contributed a total of 16,500 episodes, of which 75% ended in a discontinuation during the observation period. The distribution of episode lengths was positively skewed, with a large number of short episodes and small numbers of longer episodes. This is illustrated in Figure 6.2 for the duration of the first episode and duration of subsequent episodes separately. The first episode tends to be of shorter duration than later episodes, with a higher proportion of first episodes ending during the first month. Across all episodes, 32% lasted one month (or less). The median length of an episode of statin claiming was 2 months. 61% of patients contributed more than one episode of statin claiming.
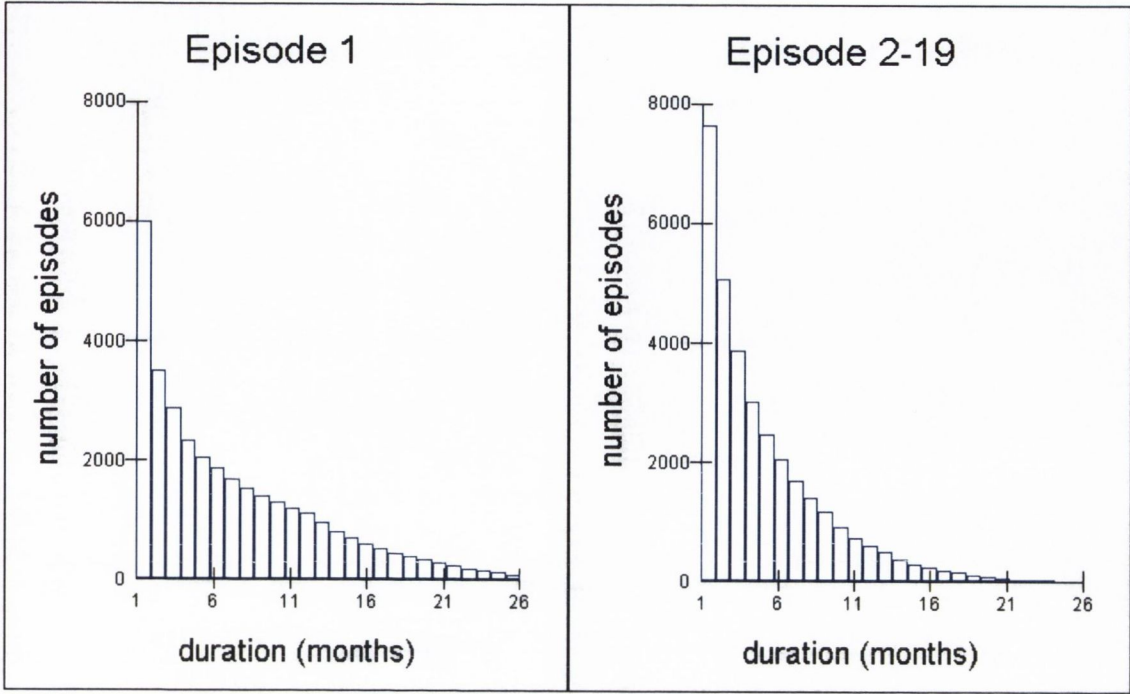
Figure 6.2. Distribution of duration of episodes of statin claiming.

Figure 6.3 illustrates the distribution of the number of episodes of claiming and non-claiming by patient. Most patients contributed 1-2 episodes of claiming and 2-3 episodes of non-claiming.
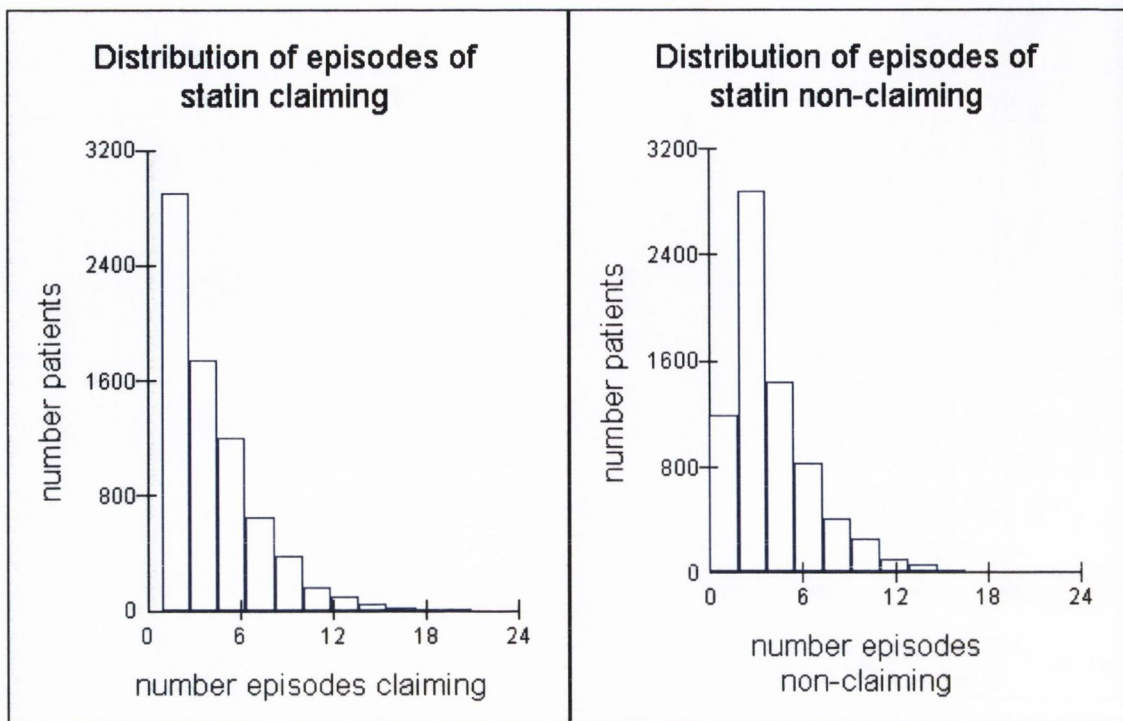
Figure 6.3. Distribution of number of episodes of claiming statins and non-claiming, by patient.

6.2.4 New patients

Of this cohort of 7,207 patients, those who had in the previous twelve months been prescribed a statin therapy different to their index therapy were classified as previous statin users. This left 6,094 patients new to statin therapy of any type – that is, they had not received any statins under the GMS scheme during the previous twelve months, although they had been eligible to claim prescriptions under the scheme during this time. 103 people who claimed statin therapy more than twelve months before their index therapy and no statins in the intervening period were classified as new. Figure 6.4 is a plot of the observed

216

proportions of patients who claimed statin prescriptions over time since the start of the new

therapy, with patients classified as new to any statin (6,094) or recently prescribed a different

statin (1,113). This shows that the proportion of new patients claiming statin therapy is

slightly lower than that of previous patients in the first few months, but the situation is

reversed after about fifteen months. For the purposes of subsequent analyses I shall

concentrate on new patients – this ensures baseline comparability. Also, because few

patients were observed for more than two years, observations up to a maximum time of two

years were included in the data set.
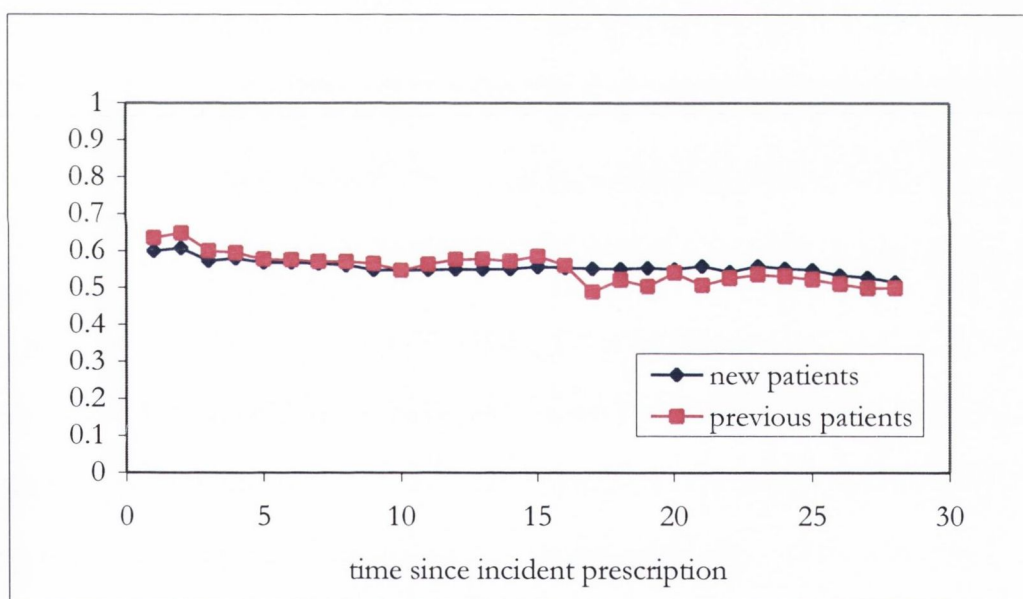
Figure 6.4 Observed proportions with statin therapy

6.2.5 Ischaemic heart disease

For the purposes of these analyses, evidence of IHD was determined by at least two prescriptions of aspirin and nitrate together. The patients thus identified were classified as IHD patients from the time of the first such prescription until the end of observation – previously they were considered not to be IHD patients. There were 977 (16%) such patients in the cohort of new statin users. IHD status is a time-varying covariate as a patient may change from being IHD-free to having IHD at some point during the observation period – this covariate changes over time.

6.2.6 Attrition

The rate of attrition is quite high after twelve months of observation, as this is the point at which the patients initiating therapy in January 2002 were no longer observed – from this point the cohort loses about 400 subjects each month. The rate of attrition before this point is rather lower – about 30 patients each month – this is due only to withdrawals from the GMS scheme. The models used here to analyse statin prescription histories are able to handle certain types of missing data – it is only if the patients who withdrew from the scheme or those who started their therapies in more recent months had different patterns of statin prescription whilst in the scheme that missing observations may pose a problem, for the GEE approach in particular (see Section 5.2.3.7). The implications of missing data are discussed more fully as part of the analyses.

218

6.3   Repeated measures models

6.3.1   *Prescription availability assuming independence within patients*

Figure 6.5 shows the proportion of patients new to any statin therapy having a prescription available against time in months since the incident prescription. Clearly the probability of claiming a statin prescription decreases over time, and the decrease in this probability is most rapid in the first few months after the first prescription. After nine months about 55% of the patients still observed claimed a prescription each month, and this remained fairly constant until the end of the observation period.

Here I model the binary response indicating monthly statin availability after the initial prescription by assuming a Bernoulli distribution for the response and using a logit link function. The month the first statin prescription was claimed is excluded, as availability in the first month is by definition equal to one for all patients. This resulted in a slight reduction in the size of the cohort, to 5,850 patients - some patients were observed for only one month before withdrawing from the GMS scheme. These patients contributed 104,548 monthly observations. Dependencies between responses from the same patient are initially ignored. To investigate the relationship between claiming a prescription and time since the first statin was prescribed, one method is to include a separate dummy variable for each of the 24 months of follow-up (and no intercept term). The parameter estimates, which give the log odds of statin availability each month, can be used to calculate the monthly probabilities of statin availability, as illustrated in Figure 6.7.
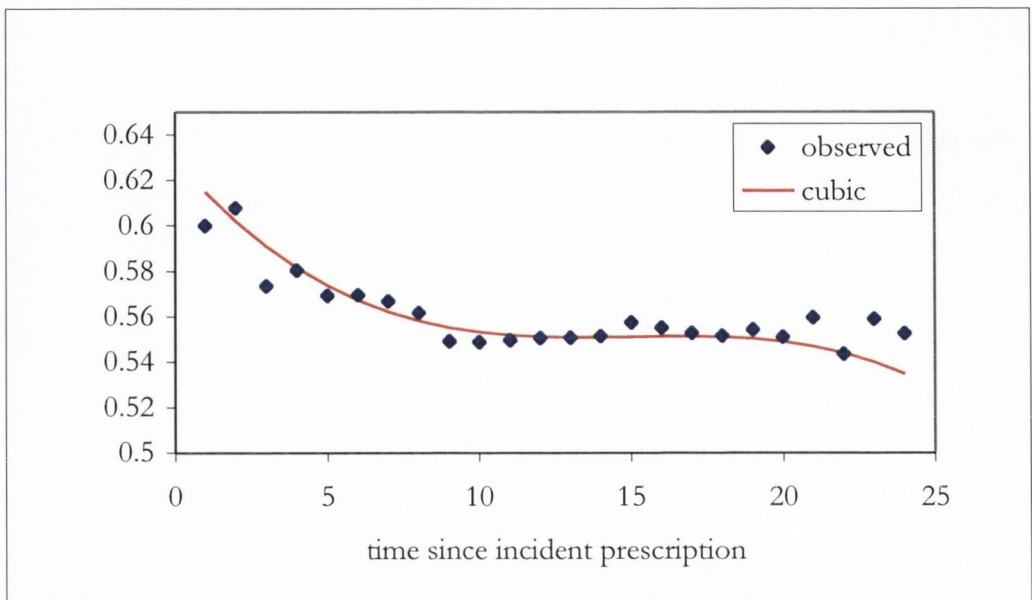
Figure 6.5 Observed proportions with statin therapy and cubic model

This plot is useful to help choose a functional form for the relationship between prescription availability and time. A smooth function of time, either parametric or non-parametric, may be fitted. One of the advantages of this is that if an appropriate model can be found, the number of parameters to be estimated is reduced: this consideration, however, is not vital in such a large data set. Figure 6.5 shows a cubic model for the dependence of the probability of claiming a statin prescription on time since the first statin was prescribed. For the purposes of fitting this model, time was centred on 12 months. Higher order polynomial terms in time were tested but found to be non-significant. The model does not appear to fit particularly well in the last few months; however due to attrition the observed proportions at these months may not be representative of the population in any case. In subsequent

analyses of the availability of statin prescriptions, I shall model the relationship with time by

a) including a dummy variable for each month and b) a cubic polynomial.

Fitting a logistic regression model for monthly statin availability with a cubic model for time since initial prescription (centred), a quadratic model for patients' age (also centred) and patients' gender and IHD status included as covariates, but making no allowance for dependencies between observations on the same patient, gives a log-likelihood of − 69281.2309. The scaled deviance (1.33) and scaled χ^2 (1.00) are both close to 1, indicating that the assumption that the marginal responses follow a Bernoulli distribution is reasonable.

However, as the responses are due to repeated observations of patients, it is not to be expected that they are independent. To illustrate the dependency of the responses as a function of lag time between observations, an empirical lorelogram (Heagarty and Zeger 1998) is estimated and plotted in Figure 6.6. This shows the log odds ratio between pairs (on the same patient) of observations separated by a given lag time. It clearly illustrates a large dependency between observations on the same patient, which is consistent with individual patients having an underlying propensity to claim their prescriptions. This decreases as the time between pairs of observations increases. Log odds ratios at the longest lags are not estimated precisely as they are based on relatively few pairs of observations.
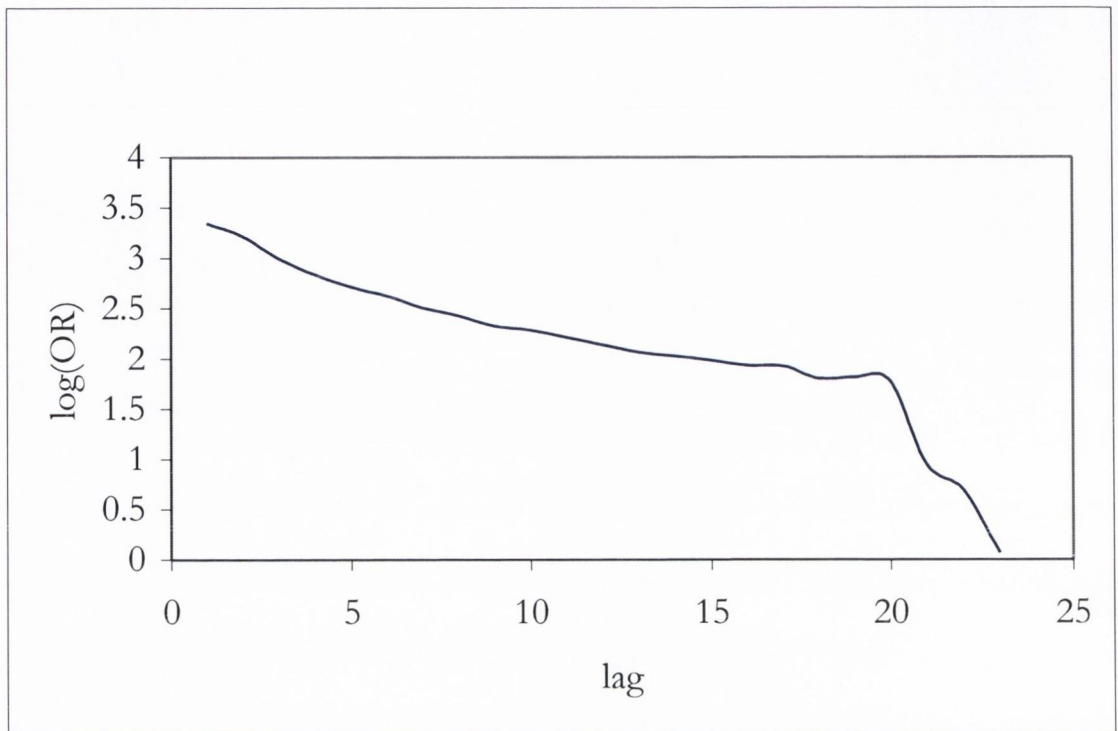
Figure 6.6 Estimated log odds ratio by lag time

6.3.2   *Repeated measures by GEE*

Here I consider statin availability in the 5,850 new patients who were observed for more
than one month. I give the results of fitting a logistic regression model to predict availability
of a prescription for any statin. To model the change over time I a) include a dummy
variable for each month of observation, and b) fit a cubic polynomial.   To allow for
correlations between the responses contributed by each patient, I use a marginal model

estimated by the GEE approach, choosing firstly an unstructured correlation matrix (Section 5.2.3). All marginal models were fit using SAS and Stata (See Section 5.6).

Table 6.1 gives the parameter estimates and standard errors for the GEE approach for each type of correlation structure. Here the dependence of the response on time is modelled as a cubic polynomial, and the covariates age, age squared, female and IHD are included. Parameter estimates for the models with dummy variables for time are not shown.

Table 6.1 Parameter estimates (standard errors) for marginal models using cubic model for time and different correlation structures

VARIABLE	WORKING CORRELATION STRUCTURE					
	independent	unstructured	exchangeable	Autoregressive(1)	Autoregressive(2)	Autoregressive(3)
intercept	0.1313 (0.0131)	0.0986 (0.0986)	0.1495 (0.0385)	0.1158 (0.0387)	0.0997 (0.0381)	0.1009 (0.0380)
Time	-0.0039 (0.0024)	-0.0021 (0.0024)	-0.0009 (0.0025)	-0.0041 (0.0028)	-0.0024(0.0026)	-0.0024 (0.0025)
time^2	0.0012 (0.0002)	0.0012 (0.0012)	0.0013 (0.0002)	0.0011 (0.0002)	0.0012 (0.0002)	0.0012 (0.0002)
time^3	-0.0001 (0.00002)	-0.0001 (0.00002)	-0.0001 (0.00002)	-0.0001 (0.00002)	-0.0001 (0.00002)	-0.0001 (0.00002)
Age	-0.0035 (0.0006)	-0.0025 (0.0018)	-0.0032 (0.0019)	-0.0037 (0.0019)	-0.0036 (0.0019)	-0.0035 (0.0019)
age^2	-0.0016 (0.0000)	-0.0014 (0.0001)	-0.0016 (0.0001)	-0.0015 (0.0001)	-0.0015 (0.0001)	-0.0015 (0.0001)
Female	0.2737 (0.0129)	0.2882 (0.0408)	0.2863 (0.0423)	0.2778 (0.0426)	0.2863 (0.0421)	0.2884 (0.0419)
Ihd	0.8907 (0.0194)	0.9519 (0.0546)	0.7572 (0.0652)	1.0043 (0.0548)	1.0344 (0.0542)	1.0166 (0.0550)

Selection of an appropriate correlation structure is based on theoretical considerations rather than statistical tests, which are not available in the standard procedures in SAS and Stata; as noted in Section 5.2.3.8, the QIC, which has been proposed to examine the appropriateness of models using various correlation structures, is only available for certain comparisons which limits the flexibility of modelling using GEE. In agreement with the logelogram (Figure 6.6), the estimated unstructured correlation matrix (not shown – a 24x24 matrix) implies a structure where dependencies between the responses decrease as time between the responses increases; I therefore fitted a model with an autoregressive structure of order one and compared the results of this with the results from using the unstructured correlation matrix (shown in Table 6.1). While the parameter estimates are similar, and the significance of covariates in the model is unchanged, it appears from inspection of the estimated correlation matrix that the autoregressive structure of order one does not adequately describe the correlation between successive observations within each patient. An autoregressive structure of higher order, which allows for dependencies between more widely spaced months, may be more appropriate. In fact, an autoregressive structure of order two is found to give predictions very close to the estimates from the model with an unstructured correlation matrix; while an autoregressive structure of order three offers no substantial improvement. Estimates using the exchangeable correlation structure appear too large, especially for longer durations. Estimated probabilities of claiming a statin prescription over time for each type of correlation structure are illustrated in Figure 6.7. For the purposes of this analysis I proceed with an autoregressive correlation structure of order two. In theory, if the model for the expected value of the response is correctly specified, the parameter estimates are not affected by choice of the correlation structure, though the efficiency of estimation may be compromised (see Section 5.2.3.2).

225
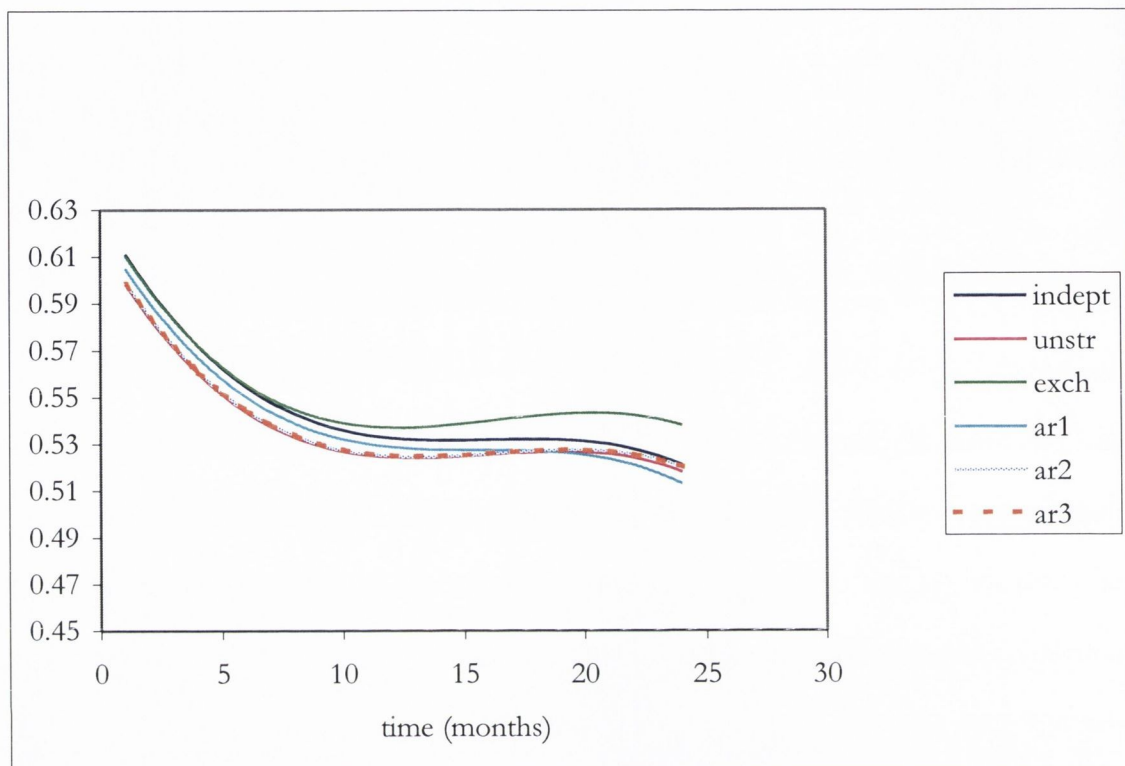
Figure 6.7 Comparison of predicted probabilities of claiming statins for marginal models by GEE with different correlation structures

The parameter estimates given in Table 6.1 are log odds ratios. For instance, using the model with unstructured correlation, the odds ratio for claiming a statin prescription one year after the first claim in the population of patients with IHD compared to the population of patients without IHD is the exponent of 0.9519, that is 2.59 (95% CI 2.33-2.88). Using the autoregressive structure of order two, this odds ratio is estimated as 2.81 (95% CI 2.53, 3.13). In fact it appears that claiming patterns over time are different for patients with

evidence of IHD, and without allowing for this in our model for the expected response, the autoregressive structure of order two does not give as good fit for patients with IHD as for those without.

I tested interactions between the covariates and found the interaction between IHD status and time to be significant. The parameter estimates for this model are shown in Table 6.2. To explore the nature of this interaction, the estimated probabilities of claiming a statin prescription are plotted against time for IHD and non-IHD patients in Figure 6.8. Estimates are adjusted for age and sex, and the estimates using a dummy variable for each month are plotted (as points) in comparison to the estimates using a cubic polynomial for time (as smooth lines). Estimates using an unstructured correlation matrix or autoregressive structure of order two are not distinguishable.

Table 6.2 Comparison of parameter estimates (SE) for marginal logistic regression models

by GEE, with time interactions

Variable	GEE cubic unstructured	GEE cubic AR(2)	GEE dummies for time unstructured
Intercept	0.1202 (0.0374)	0.1247 (0.0383)	0.1214 (0.0516)
Time	-0.0009 (0.0026)	-0.0021 (0.0028)	
time^2	0.0010 (0.0002)	0.0010 (0.0002)	
time^3	-0.0001 (0.00003)	-0.0007 (0.0003)	
IHD	0.7997 (0.0606)	0.8304 (0.0598)	0.7472 (0.1221)
Time*IHD	-0.0030 (0.0076)	0.0083 (0.0091)	
time^2*IHD	0.0025 (0.0006)	0.0034 (0.0001)	
time^3*IHD	-0.0002 (0.0001)	-0.0004 (0.0001)	
age	-0.0026 (0.0018)	-0.0035 (0.0019)	-0.0025 (0.0018)
age^2	-0.0014 (0.0001)	-0.0015 (0.0001)	-0.0014 (0.0001)
female	0.2877 (0.0408)	0.2834 (0.0421)	0.2887 (0.0408)
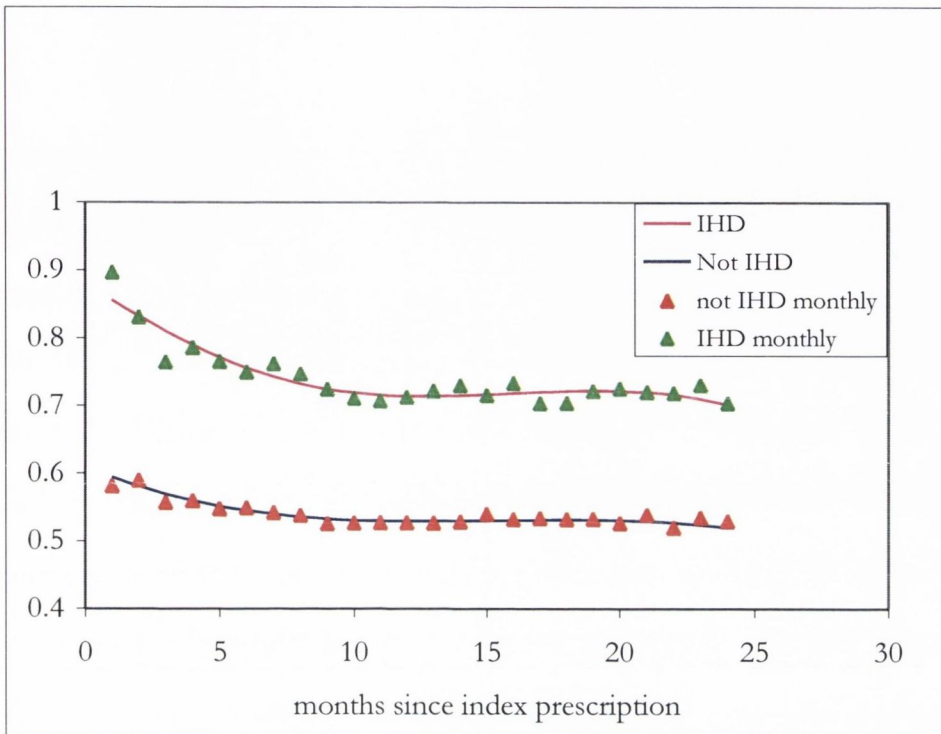
Figure 6.8 Predicted population proportions of (male, age 65.5) patients claiming statins

We can see from Figure 6.8 that the decline in the proportion of patients with a statin prescription who have IHD is more dramatic in the early months than for patients without IHD. The relationship with time is relatively constant in both groups after about nine months from the initial statin prescription. Using the autoregressive order two correlation matrix estimates, one year after the first statin prescription, the odds of claiming a statin in the population of IHD patients is 2.29 (95% CI 2.04, 2.58) times that of the population of non-IHD patients. The corresponding odds ratio using the unstructured correlation matrix

is 2.22 (95% CI 1.97, 2.50). Choosing an appropriate correlation structure is dependent on correct specification of the model for the expected response.

IHD status is a time-varying covariate (see 6.2.5) – patients are classified as having evidence of IHD from the point during statin claiming at which they are prescribed the first of at least two prescriptions for aspirin and nitrate together. Thus the proportion of IHD patients increases through the observation period, so there is more variability in estimates for this covariate in the early months of the observation period. The effect of evidence of IHD is to increase the probability that patients will claim prescriptions. This was strongest in the first few months, when the IHD patients were either previously treated for IHD or newly treated for IHD (in comparison to patients newly treated for high cholesterol). Later in the observation period the comparison is between patients treated with statins and patients who had initiated statins and were subsequently prescribed nitrates and aspirin (together with the original IHD patients). The effect of adding nitrate and aspirin during treatment does not have as large an impact on the prescription claiming probability as the effect of starting on statin, aspirin and nitrate.

6.3.2.1 GEE approach and missing data

What are the consequences of observing subjects for different lengths of time? Some patients contribute more observations to the data set than others. The marginal model parameter estimates and correlations between repeated observations at later time points are

based on observations of a subset of the cohort. If the attrition can be considered random, different numbers of observations of each patient do not pose a problem, as the GEE allow for clusters of different sizes. However, if missing data cannot be considered random, the estimates at later time points will be biased. This would occur if the claiming patterns of patients who started their therapy towards the end of the initiation period were different to the claiming patterns of patients who started their therapies early in this period.

However, the duration this period was only 18 months – a short timespan, during which it is unlikely that there would have been a major shift in claiming patterns. Of greater cause for concern in terms of differences in claiming patterns are the patients who withdrew from the GMS scheme before December 2002. These patients may be inherently less likely to collect their prescriptions than patients who remain eligible for the scheme, leading to over-estimates of the rates of prescription claiming in later months. A relatively small number of statin patients withdrew from the scheme before the end of the observation period – about 30 each month. However, the cumulative effect of attrition may mean that differences in claiming patterns in withdrawing patients could lead to biases in the parameter estimates at later time points. These estimates should therefore be interpreted with caution.

6.3.3 Multilevel logistic model for prescription availability

To analyse patients' monthly collection of prescriptions as if they are independent observations using standard logistic regression is not appropriate due to the dependence between responses from the same patient.   Here I consider a different approach to modelling dependencies between repeated responses from individual patients, by including a random intercept for each patient. This effectively allows each patient to have a unique underlying risk of collecting a prescription in any given month.

As for the marginal logistic regression model by GEE for statin availability (6.3.2), I modelled the response in terms of time, age, sex and evidence of IHD. A random intercept was included for each patient to allow for unobserved heterogeneity at patient level. The model parameters were estimated in MLwiN by 2nd order PQL methods as simpler models indicated the estimates by PQL were similar to MCMC and the former method saved a considerable amount of time. These results may be compared with the corresponding GEE estimates.

To check the fit of the model I tested the assumption that the errors are binomially distributed by re-fitting the model with the binomial variance not constrained to equal one. From this we see that the binomial variance is estimated to be 0.757 (SD 0.004) – that is, significantly less than one. This suggested underdispersion – observations within each patient remain correlated after conditioning on the patient. This especially throws into question the estimate of the random effects variance at patient level and hence the

232

interpretation of the influence of unobserved heterogeneity at patient level. Parameter estimates for the model with constrained and unconstrained variance are shown in the first two columns of Table 6.3.

6.3.3.1 Including lagged responses as covariates

To model the time dependencies between observations that may be contributing to the observed underdispersion, I included lagged responses for the previous month, the previous two months and the previous three months in the model. The parameter estimates for these models are also shown in Table 6.3. Each of the models were fit with constrained and unconstrained binomial variance. As can be seen from the table, the binomial variance estimate is reduced in the models with lagged responses as explanatory variables – that is, some of the dependence between observations of the same patient may be explained by conditioning on previous responses; however evidence of underdispersion remains. Choosing the model with three lagged responses, the random effects variance at patient level is clearly large and significant (estimate 2.229, SD 0.056). A tentative interpretation of this is that conditional on claiming patterns in the previous three months and other covariates, unobserved patient-level factors have a large and significant influence on the probability of claiming a statin prescription. However this interpretation of the random effects at patient level may not be valid due to the problem of underdispersion.

Table 6.3. Parameter estimates (SE) for multilevel model for statin availability, conditional on previous responses.

variable	No lag unconstrained	constrained	1 lag unconstrained	constrained	2 lags unconstrained	constrained	3 lags unconstrained	constrained
Intercept	0.159 (0.065)	0.162 (0.065)	-0.594 (0.056)	-0.640 (0.055)	-1.102 (0.051)	-1.215 (0.048)	-1.286 (0.05)	-1.461 (0.047)
time	-0.003 (0.003)	-0.003 (0.004)	-0.015 (0.003)	-0.017 (0.004)	0.003 (0.004)	0.003 (0.004)	0.013 (0.004)	0.016 (0.004)
$time^2$	0.0029 (0.0002)	0.003 (0.000)	0.001 (0.0002)	0.001 (0.0002)	0.001 (0.0002)	0.001 (0.0002)	1.83e-3 (2.41e-4)	1.68e-3 (2.67e-4)
$time^3$	-0.0002 (0.00004)	-0.0002 (0.00001)	-0.0002 (0.00001)	-0.0002 (0.00001)	-0.0002 (0.00001)	-0.0002 (0.00001)	-2.58e-4 (3.95e-5)	-2.79e-4 (4.97e-5)
Female	0.460 (0.076)	0.461 (0.076)	0.397 (0.064)	0.385 (0.061)	0.343 (0.056)	0.319 (0.051)	0.326 (0.053)	0.294 (0.045)
Age	-0.005 (0.003)	-0.005 (0.003)	-0.004 (0.003)	-0.004 (0.003)	-0.004 (0.003)	-0.004 (0.002)	-0.004 (0.002)	-0.004 (0.002)
age^2	-0.003 (0.0002)	-0.003 (0.000)	-0.002 (0.000)	-0.002 (0.000)	-0.002 (0.000)	-0.002 (0.000)	2.1e-3 (1.5e-4)	1.87e-3 (1.35e-4)
IHD	1.377 (0.062)	1.374 (0.068)	1.210 (0.060)	1.181 (0.063)	1.069 (0.057)	1.008 (0.057)	1.028 (0.055)	0.942 (0.055)
lag 1	-	-	1.428 (0.019)	1.535 (0.022)	1.36 (0.020)	1.492 (0.022)	1.334 (0.020)	1.476 (0.022)
lag 2	-	-	-	-	0.958 (0.019)	1.060 (0.022)	0.904 (0.020)	1.005 (0.022)
lag 3	-	-	-	-	-	-	0.376 (0.021)	0.474 (0.023)
patient-level variance	6.601 (0.149)	6.402 (0.148)	4.624 (0.105)	4.128 (0.097)	3.404 (0.080)	2.701 (0.066)	3.055 (0.073)	2.229 (0.06)
binomial variance	0.759 (0.003)	1	0.782 (0.004)	1	0.797 (0.004)	1	0.799 (0.004)	1

In Figure 6.9 are plotted the random effects model estimates for the probability of claiming a statin prescription conditional on the claiming patterns over the previous three months (for a male patient, aged 65.5 with no evidence of IHD). These predicted probabilities were calculated with the random effects fixed at zero. These are not mean probabilities due to the non-linear logistic transformation and are therefore not comparable to the predictions from a marginal model. However they are useful to illustrate the predicted patterns of claiming conditional on previous responses, clearly showing the strong predictive effect of previous claiming patterns on current statin use.
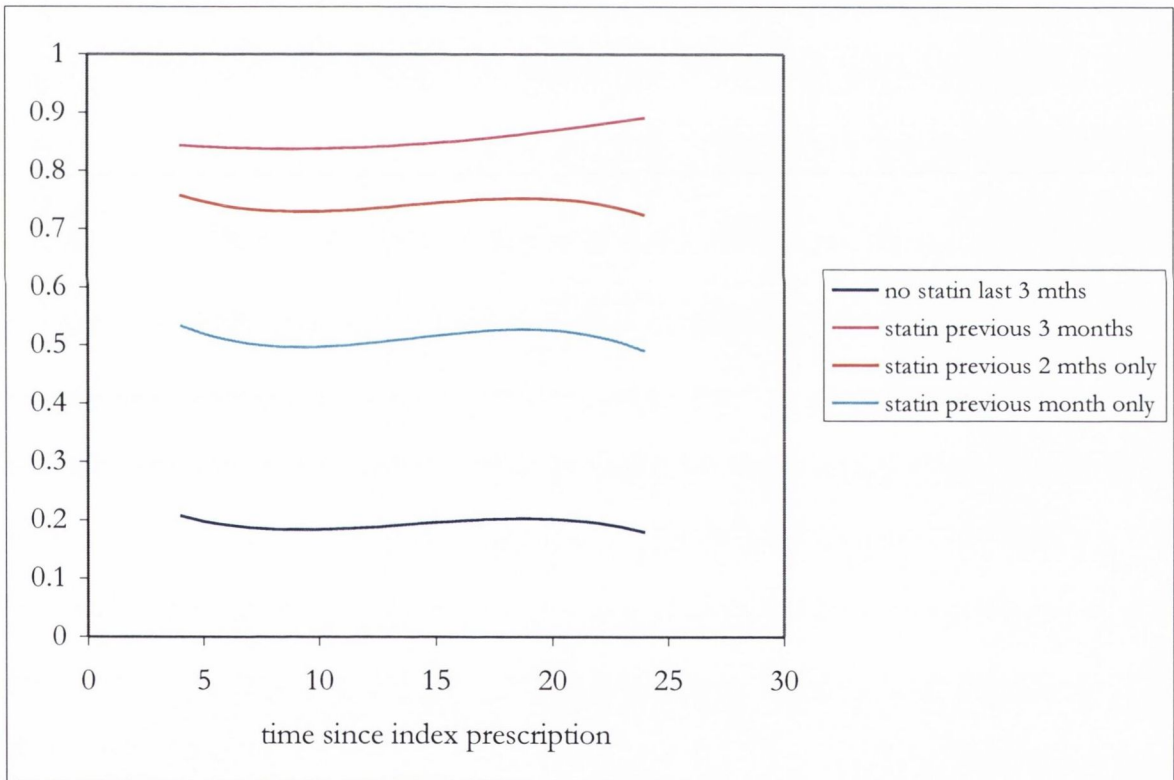
Figure 6.9 Predicted proportion of (male, age 65.5, non-IHD) patients claiming statins by previous 3 months' responses (RE model)

6.3.3.2 *Previous medication possession ratio as a covariate*

The models described in the previous section give a useful insight into the influence of previous claiming patterns on the probability of collecting the next prescription. However, the problem of underdispersion is unresolved, and as the modelling assumption of binomially distributed errors is therefore in doubt, interpretation of the parameter estimates is questionable. In particular, it can be seen from Table 6.3 that by fitting each model with the binomial variance unconstrained the patient-level random effects variance is increased. As interest here is in quantifying the variance due to unobserved factors at patient level, what is needed is a model where the binomial assumption is not violated.

I consider the variable previous medication possession ratio, denoted MPR, which is defined as the proportion of months with a statin prescription up to the previous month, but not including the index prescription. Thus the MPR for the first month after the index prescription is not calculated as it is by definition equal to one for all patients. If the previous first month is included in the calculation of MPR, no patients will ever have MPR zero and the variable cannot separate the patients who take no further prescriptions from those who do, which is a large part of the reason why there is clustering in the monthly claiming patterns. The MPR variable is calculated for months 2-24, so the responses for the first month are excluded (5850 observations).

Figure 6.10 shows the distribution of MPR. This is categorised into three levels indicating no previous prescriptions, some previous prescriptions, or all previous prescriptions had been claimed. For 21,478 (21.8%) observations the MPR was zero, for 51,298 (52.0%) observations the MPR lay between zero and one, and for 25,922 (26.3%) observations the MPR was one.
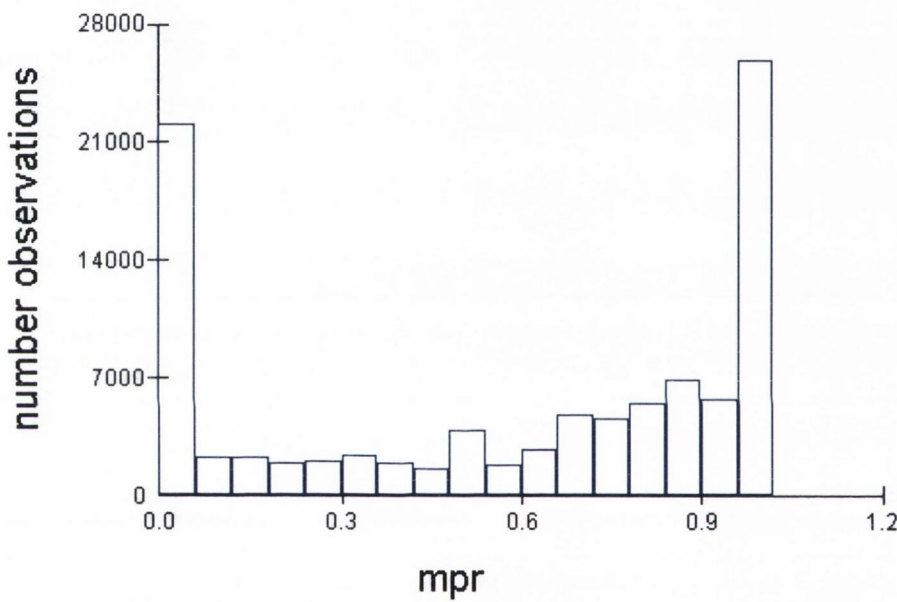
Figure 6.10 Distribution of statin possession ratio

As clustering within patients over time is important, I included as covariates MPR and interactions between MPR and the time covariates. The parameter estimates for this model are shown in Table 6.4 and the estimated probabilities of claiming statins by MPR category over time are plotted in Figure 6.11. The binomial variance is estimated at 0.984 (SD 0.005),

which although is significantly less than one by a Chi –squared test is in effect quite close – it has been observed that estimates for this parameter tend to be less than one even when the data have the correct variance structure (Fielding and Yang 2002).

Agreement with the assumption of Binomial variance when MPR is included as a covariate may be a reflection of the fact that this variable determines the form of the distribution of the response. Incorporating it as a covariate may not be the best approach. Indeed, as illustrated in Figure 6.14, the residuals at patient level do not conform to the Normal distribution.

Table 6.4 Parameter estimates (SE) for random-effects model with MPR and time interactions, with binomial variance constrained and unconstrained.

Variable	constrained	unconstrained
Intercept	-2.898 (0.113)	-2.854(0.112)
time	0.0366 (0.020)	0.0374 (0.020)
time^2	0.0089(0.0021)	0.0088 (0.0020)
time^3	-0.0017 (0.0003)	-0.0017 (0.0002)
Female	0.287 (0.059)	0.2900 (0.0598)
Age	-0.0059 (0.0027)	-0.0059 (0.0027)
age^2	-0.0021 (0.0002)	-0.0021 (0.0002)
IHD	0.9313 (0.0650)	0.9397 (0.0653)
mpr0	0	0
mpr1	3.466 (0.107)	3.422 (0.015)
mpr2	4.149 (0.121)	4.071 (0.120)
mpr1*time	-0.0350 (0.0211)	-0.036 (0.021)
mpr1*time^2	-0.0066 (0.0021)	-0.0065 (0.0020)
mpr1*time^3	0.0016 (0.0003)	0.0015 (0.0003)
mpr2*time	-0.0820 (0.0243)	-0.0853 (0.0240)
mpr2*time^2	-0.0074 (0.0023)	-0.0073 (0.0023)
mpr2*time^3	0.0019 (0.0003)	0.0019 (0.0003)
patient-level variance	3.529 (0.087)	3.624 (0.090)
binomial variance	1	0.984 (0.005)

238
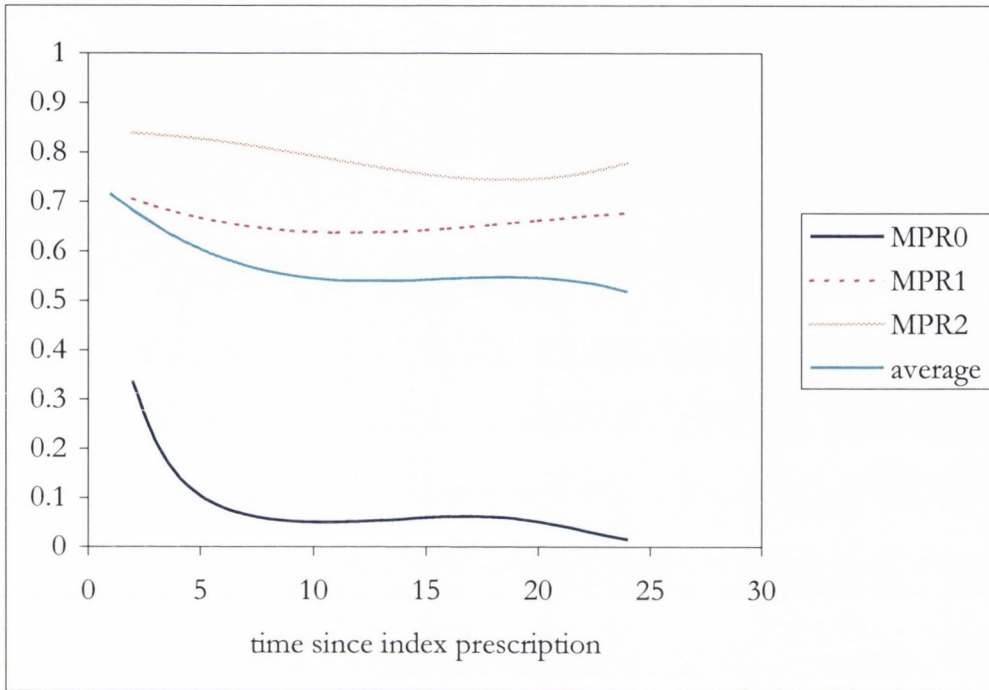
Figure 6.11 Subject-specific estimated probability of claiming statins by previous MPR

(baseline patient male, age 65.5, no IHD)

Figure 6.11 gives an insight into subject-specific claiming patterns over time, in terms of previous MPR. It shows that patients who have claimed at least one prescription after the initial one are considerably more likely to continue to claim prescriptions than patients who have not collected another prescription after the first. Indeed, patients in the latter group who have not claimed another prescription within six months of the initial one are extremely unlikely to claim another statin over the next 18 months. (As in Figure 6.9, these are not

mean probabilities but the plot serves to illustrate claiming patterns in terms of covariates over time).

It is important to note that conditional upon time, MPR and other covariates, there is large and significant variance at patient level in the probability of claiming statins (estimate 3.529, SD 0.087). This is due to the effect of unobserved factors at patient level. Using the method described in 5.2.4.5, assuming the binary response we are modelling is due to an underlying continuous response, the proportion of variance accounted for by unobserved factors at patient level is 52%.

6.3.4   Comparison of random effects and GEE estimates

The parameter estimates for the random effects model with unconstrained binomial variance and no transitional terms (Table 6.3, column 1) are compared with the estimates from the marginal model by GEE with exchangeable correlation matrix (Table 6.1). The patient-level random effects variance is very large (estimate 6.601) and the estimates for the fixed effects for the random-effects model are larger in magnitude than the estimates for the corresponding marginal model parameters. This could be a consequence of the large between-subject variability, where large groups of subjects have the same response every month (see below). This may be due to incorrect distributional assumptions, which limits the interpretability of the random-effects estimates.

The estimated probabilities for our baseline patient (male, aged 65.5, no IHD) are plotted against time in Figure 6.12. Estimated probabilities for the GEE approach with both unstructured correlation matrix (which is closer to the observed data) and exchangeable correlation matrix (where the assumed correlation structure is equivalent to the random intercepts model) are plotted. As in Figure 6.9, the probability estimates from the random effects model are not mean probabilities and direct comparison with marginal model estimates is therefore inappropriate.
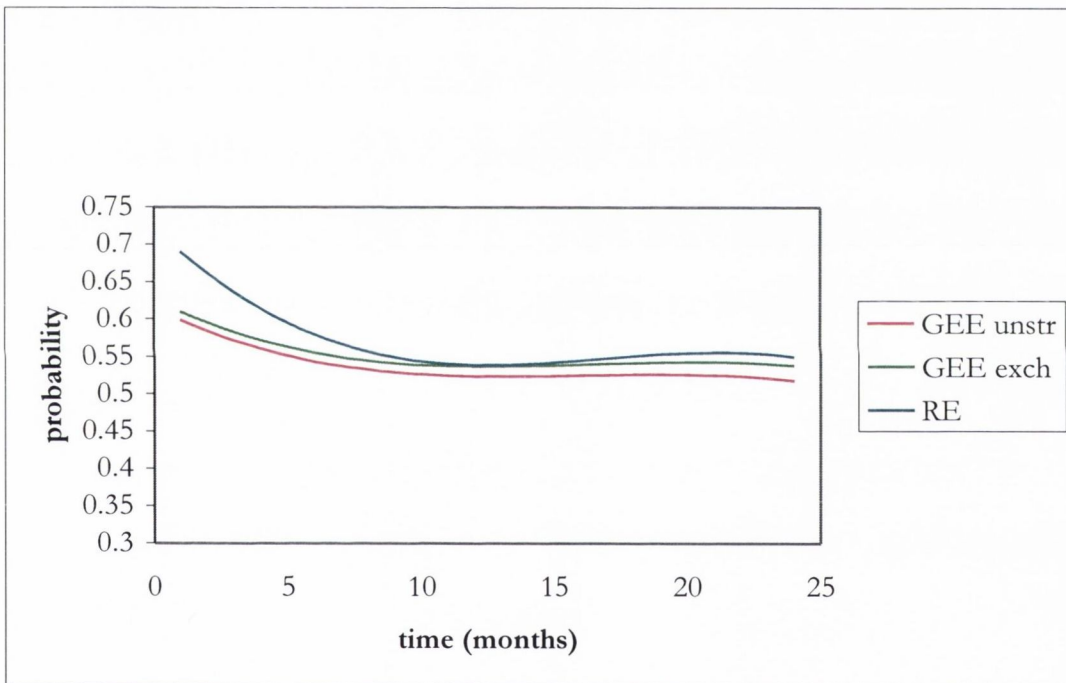
Figure 6.12 Comparison of predicted probabilities for Marginal and Random Effects models

6.3.5 *Distributional assumptions*

As some patients consistently fail to claim their statins, and some patients always claim their statins, there are two groups with constant responses 0 and 1. Figure 6.13 shows the distribution of the proportion of months with statins available on the original and log odds scales. The response is not Normal on the log-odds scale, having clusters at $\pm\infty$. It could be that the large estimates of the random-effects variances (see Tables 6.4 and 6.5) are the way the model captures the distribution of the response (that is, via wide dispersion of the random intercepts). This also explains why the parameter estimates for the random effects models are so much larger than for the corresponding marginal models. It is possible that the response may be better modelled by a mixture distribution that estimates the probabilities of never claiming another prescription and claiming every prescription.
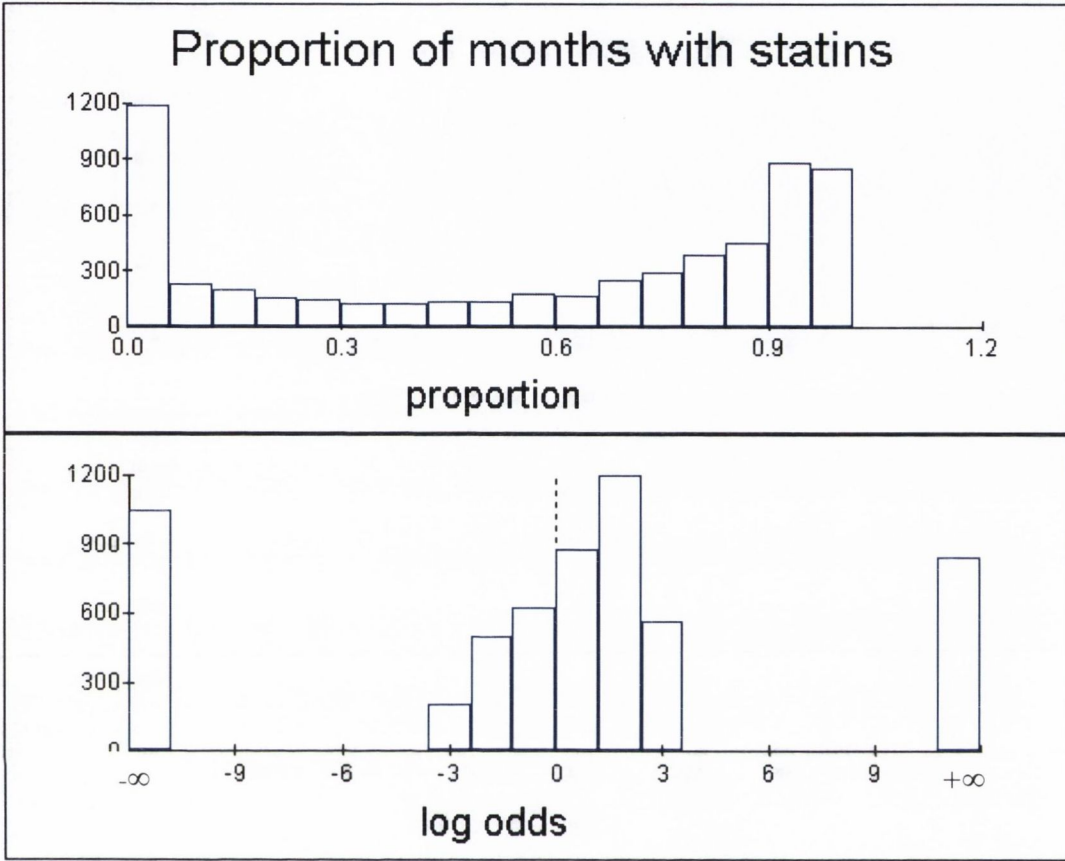
Figure 6.13 Distribution of statin availability at patient level on (1) original and (2) log odds

scales

Figure 6.14 shows the Normal probability plot for the residuals for the final random effects model at patient level. These are clearly not Normally distributed, thus violating one of the assumptions of the multilevel logistic model. As mentioned above, a mixture model may be more appropriate. However this may not make any difference to the parameter estimates for

243

the fixed or random effects in this model. Carlin and Wolfe (2001), who fit a mixture model to a similar but simpler data set, where repeated observations were made of a binary response on a group of subjects and a large number of these consistently gave the same response, found that the subject-specific time effects were very similar in the mixture and logistic-Normal models, suggesting these are mainly determined by the strength of persistence of a positive response in subjects who had at least one positive response. Carlin and Wolfe suggest that these parameter estimates cannot be given the usual interpretation as the relative odds at one time point compared to a previous one within an individual. Clearly, subjects who have the same response at every time point do not contribute any information about rates of change across time. The underlying model may not be adequate to deal with this. Carlin and Wolfe note that neither the mixture model nor the logistic-Normal model reproduced the observed proportions, and although the mixture model was theoretically more appealing than the logistic-Normal model its fit was little better.
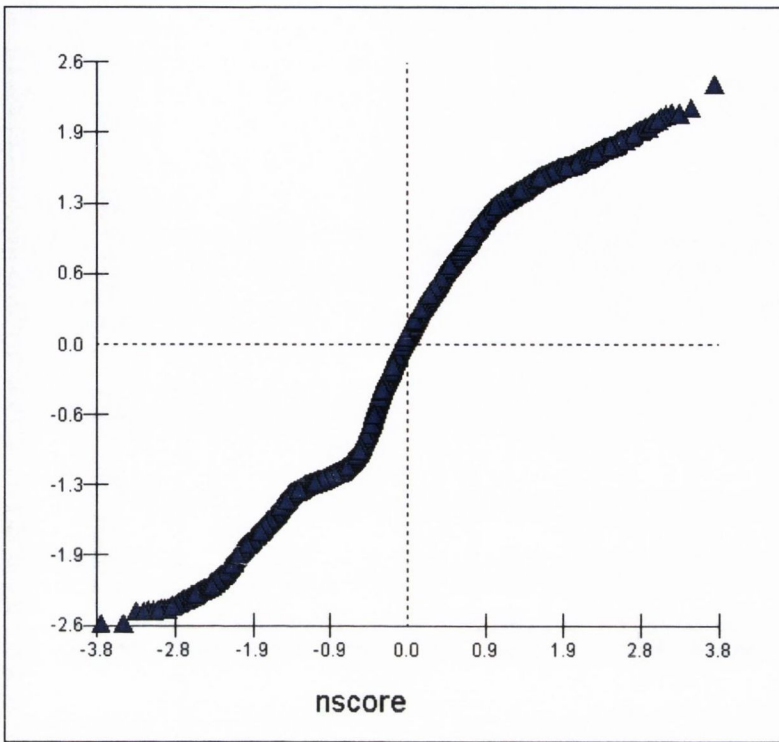
Figure 6.14 Normal probability plot for patient-level residuals in random-effects logistic model for statin availability

6.4 Models for discontinuation

6.4.1 Event history model

For the initial simple event-history model for statin claiming, the data set includes observations on each patient only up to the first discontinuation, which is identified as the

first gap of one month (or more) with no therapy. The month during which the index therapy was initially claimed is included, in contrast to the data set of Section 6.3.1. The model is, again, a logistic regression. Here I model the hazard of first discontinuation of the index therapy in terms of duration of therapy, including a dummy variable for each month and no intercept term. Figure 6.14 shows how the hazard of first discontinuation changes with time.

In subsequent analyses of the hazards of discontinuation, I shall use a piecewise constant model, in which the baseline hazard is modelled as constant in month 1, months 2-3, months 4-6, months 7-12, months 13-18 and months 19-25. A continuous parametric fit will not be used as suitable functional forms of the required flexibility are complex and therefore not straightforward to interpret. The piecewise constant model gives a better fit to the data and is easier to interpret. The fit of the piecewise constant model is discussed for antihypertensives in Section 7.5.1.
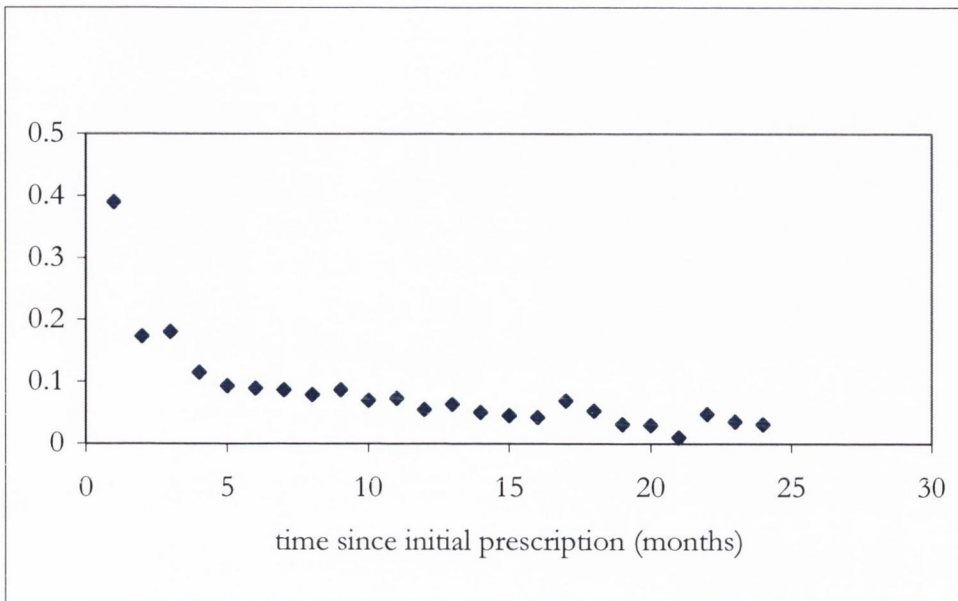
Figure 6.15 Hazards of first discontinuation of statin

Similarly, by fitting a logistic model for the hazard of discontinuation with a dummy variable for each year of age, we can see the relationship between the hazard of first discontinuation and the age of the patient (Figure 6.16). It appears that the hazard of first discontinuation is quadratic in age; I shall test the significance of an age squared term in subsequent models. It is to be noted that the age and age squared terms will be centred on the mean age (65.5 years) in subsequent models.
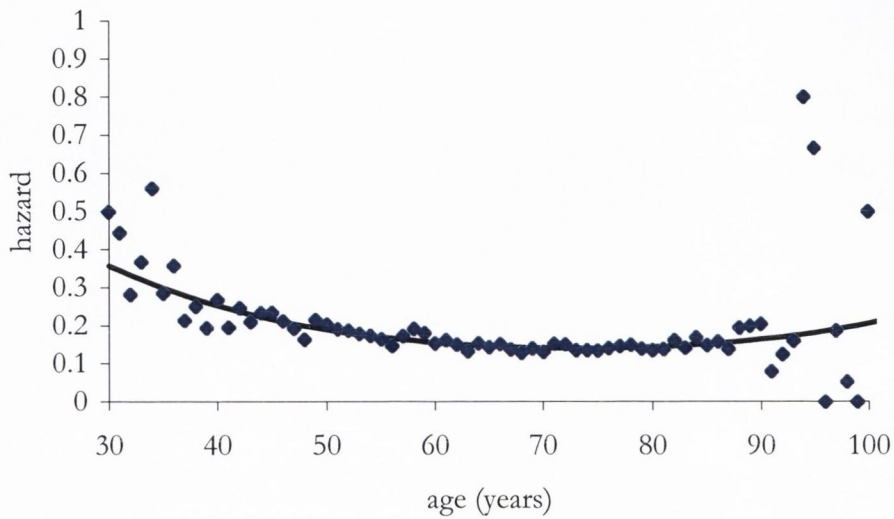
Figure 6.16 Hazard of discontinuing statins by age

6.4.2 *Marginal model for discontinuation*

Here I consider a GEE approach to the discrete-time model for the hazard of discontinuation of statin therapy. The binary response indicating discontinuation is modelled by logistic regression (as in Section 6.3.2), and the dependencies between repeated responses from the same patient are dealt with by the GEE approach. I included as covariates a piecewise constant baseline hazard function, age and sex of the patient and evidence of IHD. The effect of IHD refers to the population of IHD versus non-IHD

248

patients at a given point in time. I assume an exchangeable correlation structure for repeated episodes of statin therapy within patients. The exchangeable correlation structure is equivalent to fitting a random-effects model with a random intercept for each patient – correlations between any pair of observations from the same patient are assumed equal. The random intercepts approach can be thought of as attributing to each patient a unique (time-invariant) underlying risk of discontinuation.

The parameter estimates are shown in Table 6.5 (Model 1). Estimates are interpreted as population-average hazards ratios. So the hazard of discontinuation in the population of IHD patients is the exponent of –0.3056, which is 0.737 times that of the population of non-IHD patients. The parameter estimates can be used to calculate the population-average risks of discontinuing an episode by duration. In the first month of an episode of claiming statins, the model predicts 31.5% of (male, age 65.5, non-IHD) patients will discontinue. The hazard of discontinuation declines over time, so that for the baseline patient the hazard of discontinuing therapy during months 13-18, given continuous claiming during the previous year, is 8%.

Table 6.5. Parameter estimates (standard errors) for Marginal Hazards Models by GEE

Variable	Model 1	Model 2
intercept	-2.7365 (0.0748)	-2.8179 (0.0815)
month1	1.9619 (0.0749)	2.0704 (0.0821)
month2-3	1.2370 (0.0752)	1.3186 (0.0828)
month4-6	0.8059 (0.0757)	0.8681 (0.0833)
month7-9	0.6223 (0.0779)	0.6925 (0.0858)
month10-12	0.4360 (0.0815)	0.4629 (0.0899)
month13-18	0.3086 (0.0807)	0.3852 (0.0888)
month18-25	0	0
Age	-0.0044 (0.0012)	-0.0044 (0.0012)
Age^2	0.0006 (0.0001)	0.0006 (0.00008)
female	-0.0726 (0.0264)	-0.0723 (0.0266)
IHD	-0.3056 (0.0345)	0.2372 (0.1595)
IHD*month 1		-0.9291 (0.1776)
IHD*month 2-3		-0.5352 (0.1703)
IHD*month 4-6		-0.3815 (0.1723)
IHD*month 7-9		-0.3922 (0.1771)
IHD*month 10-12		-0.1620 (0.1841)
IHD*month 13-18		-0.3641 (0.1831)

To investigate how the effects of covariates change with time, I included interactions between the duration periods and other covariates. Significant parameter estimates are shown in Table 6.4 (Model 2). It appears that IHD patients have different risks of stopping therapy over time in comparison to non-IHD patients – they are significantly less likely to stop claiming prescriptions in the first few months, but the difference is quite small after 3 months. For instance, after 18 months of continuous claiming of prescriptions the hazard ratio for discontinuation in the population of IHD patients versus non-IHD patients is $\exp(0.237) = 1.27$ (95% CI 0.93, 1.73) – that is, there is no significant difference at this time. In the first month, however, the same hazard ratio is 0.500 and this is significant. Figure

250

6.17 shows how the estimated risk of discontinuation changes as duration of the episode of claiming statins increases for IHD and non-IHD patients.
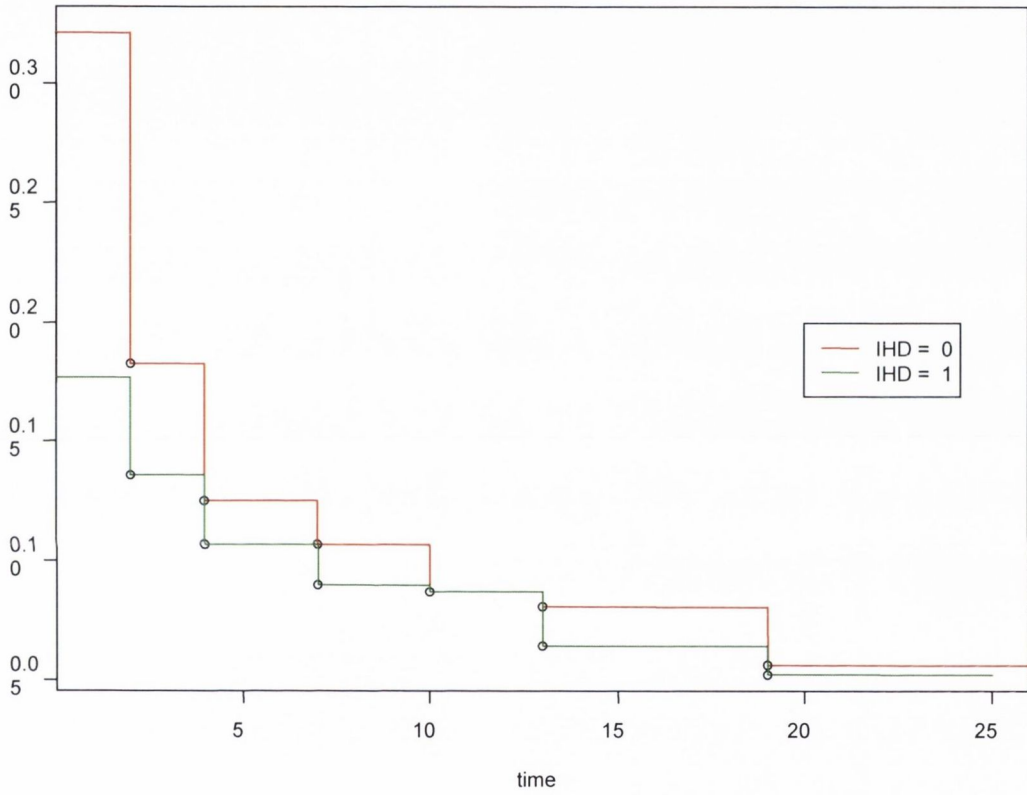
Figure 6.17 Estimated population-average hazards of discontinuation of statins (GEE approach)

6.4.3.1 Multilevel discrete-time hazards model for first discontinuation

Here I present the results of fitting models to predict the subject-specific hazards of discontinuing the first episode during which statin prescriptions were continuously collected. Two data sets were constructed: one consisting of observations on each patient until first discontinuation of statin claiming (5,991 patients, 32,851 months), and the other consisting of observations until first discontinuation of the subset of patients who did not discontinue in the first month (3,512 patients, 26,860 months). The model is the same as that used in Section 6.4.2, except that instead of allowing for the dependencies between repeated observations of patients using a GEE approach, a random intercept was included for each patient. Covariates included were dummy variables for time intervals (see Section 6.3.2), a quadratic model for age, sex and IHD status. Parameter estimates for the hazards of first discontinuation are shown in Table 6.6.

Table 6.6 PQL parameter estimates (SE) for hazards of first discontinuation of statin claiming (random effects model)

Variable	all patients	Omit patients who stop in mth 1
Intercept	-2.670 (0.072)	-2.503 (0.083)
Month1	2.132 (0.073)	
Month 2-3	1.160 (0.074)	0.719 (0.079)
Month 4-6	0.603 (0.079)	0.315 (0.083)
Month 7-9	0.486 (0.085)	0.309 (0.089)
Month 10-12	0.287 (0.095)	0.190 (0.098)
Month 13+	0	0
Female	-0.073 (0.038)	0.061 (0.057)
Age	-0.003 (0.002)	-0.006 (0.003)
Age^2	0.001 (0.0002)	0.001 (0.0002)
IHD	-0.200 (0.064)	-0.223 (0.074)
Patient-level variance	0.281 (0.033)	0.733 (0.059)

The Normal probability plot of the residuals at patient level for the model for all patients shows extreme departures from Normality (not shown). This is largely due to the substantial number of patients who discontinue their statins at some point during the first month, and thus contribute a single observation to the model. The Normal probability plot for the model based on the subset of patients who do not discontinue therapy in the first month also shows major departures from Normality, though not as marked as for the total population. The models with binomial variance unconstrained do not converge, probably due to the high level of clustering in the data.

Bearing in mind the evidence that the distributional assumptions of the model do not hold, the parameter estimates show (as expected) that patients are at greatest risk of discontinuing during the first few months of therapy; and the risk decreases as duration of therapy increases. This appears more pronounced in the full patient group than in the subset. There is no significant difference between men and women in the risk of stopping their first episode of statin therapy, though interestingly the direction of this effect changes direction in the subset. Younger and older patients are more likely to stop than those in the middle of the age range. Patients with IHD are less likely to discontinue than those without. The most striking difference between the two models is that the patient-level variance in the subset model accounts for a rather larger proportion of the total variance than it does in the total population model. Due to the violation of the distributional assumptions about patient-level residuals, it may be that this parameter is capturing the non-Normality of the residuals and cannot be interpreted as a measure of patient-level variance.

6.4.3.2 Multilevel discrete-time model for hazards of any discontinuation

The multilevel model of Section 6.4.3.1 is easily extended to allow for multiple episodes (during each of which prescriptions were continuously collected) within each patient. The model is the same as that used in the previous section – the difference being that all episodes of prescription claiming are included in the data set (5,991 patients, 65,582 months). Parameter estimates are given in Table 6.7. Model 1 gives the parameter estimates for the main effects only, and Model 2 includes parameter estimates for significant interactions. In particular, this indicates that patients with IHD are at an especially low risk of discontinuing

compared to patients without IHD in the first few months of an episode of statin use (ie, when patients are at highest risk of discontinuation) – however after the first few months the subject-specific risk of discontinuation does not depend on IHD status. This supports previous evidence that patients who are more seriously ill (or perceive themselves to be more seriously ill) may have greater motivation to establish the habit of compliance (See Section 2.3). Model 3 is the same as Model 2, except that the Binomial variance is allowed to be unconstrained. The effect of this is to decrease the magnitude of the fixed effect estimates and increase the estimate of the patient-level variance. It has been suggested that allowing the variance to be unconstrained in multinomial models gives better parameter estimates (Fielding and Yang 2002).

The random-effects model is equivalent to a marginal model by GEE with exchangeable correlation structure (Section 6.4.2) and parameter estimates may be compared with those in Table 6.5. As was noted in the comparison of random effects and GEE estimates for statin availability, the absolute magnitudes of the parameter estimates for the random effects Model 2 are greater than those for the marginal model. This may be partly due to violation of the assumptions about the distribution of the conditional responses in the random effects model – distributional assumptions are discussed further below. Most of the estimates of Model 3 are also greater than the GEE estimates, though some of them are smaller and it appears that Model 3 may be closer to the marginal model than Model 2. However there is no straightforward interpretation of the random effects variance at patient level in the situation where the assumption that the variance is Normally distributed is incorrect. A Normal probability plot the random effects variance at patient level for Model 3 illustrates that these are not Normally distributed (Figure 6.18).

Table 6.7. PQL parameter estimates (SE) for hazards of any discontinuation (random effects model)

Variable	Model 1	Model 2	Model 3
constant	-2.9714 (0.1333)	-3.1220 (0.1616)	-2.7666 (0.1562)
month1	2.0920 (0.1359)	2.2764 (0.1620)	1.8480 (0.1555)
month2-3	1.4196 (0.1335)	1.5676 (0.1620)	1.2238 (0.1560)
month4-6	1.0182 (0.1323)	1.1407 (0.1631)	0.8798 (0.1569)
month7-9	0.8354 (0.1334)	0.9626 (0.1658)	0.7680 (0.1593)
month10-12	0.6234 (0.1374)	0.6956 (0.1715)	0.5588 (0.1645)
month13-18	0.4540 (0.1388)	0.5740 (0.1731)	0.4999 (0.1655)
month18-25	0	0	0
age	-0.0051 (0.0014)	-0.0050 (0.0014)	-0.0058 (0.0015)
age^2	0.0007 (0.0001)	0.0007 (0.0001)	0.0008 (0.0001)
female	-0.0912 (0.0303)	-0.0891 (0.0301)	-0.1239 (0.0342)
IHD	-0.3547 (0.0417)	0.3719 (0.2870)	0.3180 (0.2777)
IHD*month 1		-1.1524 (0.2966)	-1.2100 (0.2873)
IHD*month 2-3		-0.7305 (0.2938)	-0.7727 (0.2844)
IHD*month 4-6		-0.5674 (0.2957)	-0.5999 (0.2859)
IHD*month 7-9		-0.5763 (0.3030)	-0.5972 (0.2925)
IHD*month 10-12		-0.3088 (0.3130)	-0.3139 (0.3014)
IHD*month 13-18		-0.5492 (0.3198)	-0.5467 (0.3067)
Binomial variance	1.000	1.000	0.8862 (0.0051)
patient variance	0.3885 (0.0212)	0.3832 (0.0216)	0.7439 (0.0291)
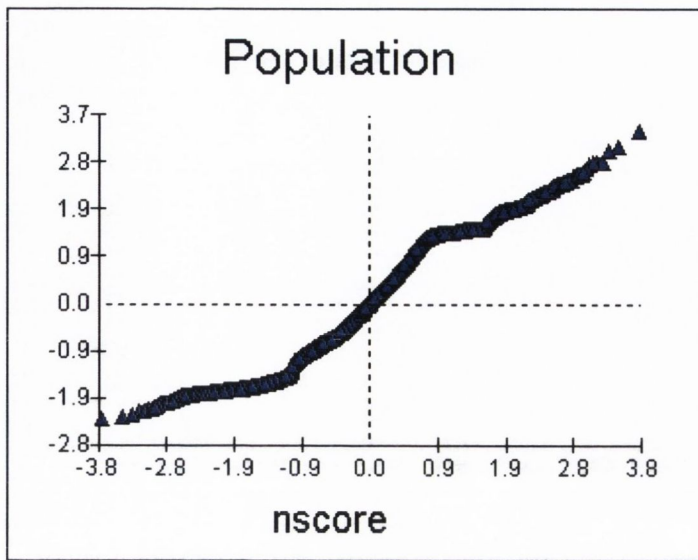
Figure 6.18 Normal probability plot for Model 3
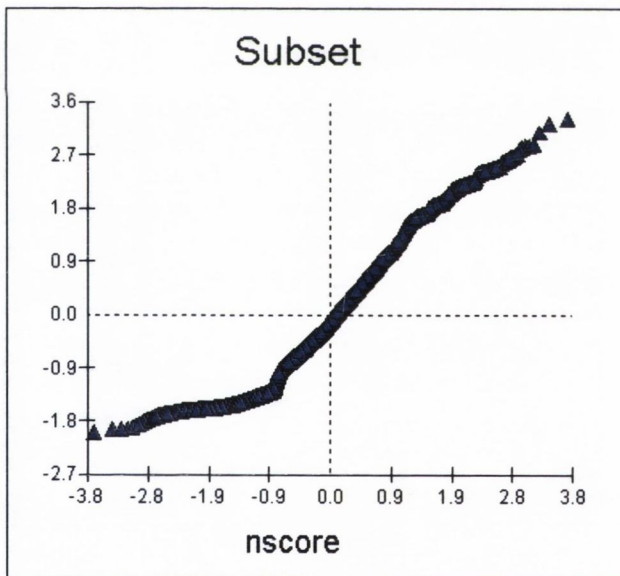
Figure 6.19 Normal probability plot for Model 3 for subset of population who claim statins

for 2 months or more

Figure 6.19 illustrates the Normal probability plot for the residuals at patient level that is obtained after fitting Model 3 to the subset of the population that claims at least two statin prescriptions during the observation time (4,805 patients, 59,591 observations). While there remains a departure from Normality, these data appear to approach more closely the required distributional assumptions of the model than the cohort including patients who only claim a single statin prescription during the time under observation (and whose use of this is questionable – which supports the case for analysing patterns of claiming only in patients for whom there is evidence of some degree of drug use, namely those who claim at least one repeat prescription) – compare with Figure 6.18.

To investigate the relationship between patient-level variability and duration of therapy, the coefficients of the first three duration variables in Model 2 (above) were set to be random at patient level (binomial variance constrained to equal one). The estimates of the random-effects variances for this model are given in Table 6.8. It is apparent that the variability in the effect of unobserved patient-level factors on the hazards of discontinuation are greatest in the first month of a new episode, and this variability decreases as duration of the episode increases. The estimates of the random-effects covariances suggest that patients who contributed episodes longer than six months tended not to contribute shorter episodes, but that some patients tended to have several short periods of claiming prescriptions. The variance functions may be estimated from this matrix to give the patient-level variance in the risk of discontinuation at different time periods. After month six, this is simply the intercept variance (0.399). During month 1 the patient-level variance is equal to $0.399 + 2*(-0.695)+1.379 = 0.388$. During months 2-3 this variance can be calculated to be 0.518 and

258

during months 4-6, 0.643. Thus it appears that the variability in the risk of discontinuation initially increases with time, but after six months decreases.

Table 6.8. Random effects variance-covariance (SE)

	intercept	Month 1	Month 2-3	Month 4-6
intercept	0.399 (0.066)			
Month 1	-0.695 (0.091)	1.379 (0.143)		
Month 2-3	-0.456 (0.087)	1.143 (0.118)	1.031 (0.142)	
Month 4-6	-0.428 (0.090)	0.902 (0.124)	0.760 (0.122)	1.100 (0.164)

6.5   A multilevel multistate model for statin claiming and non-claiming

A multistate model, which jointly estimates the hazards of stopping periods during which statin prescriptions were continuously claimed and re-starting after periods with no therapy, may throw further light on the patterns of prescription claiming. Now all observations are included – in previous hazards analyses episodes of no therapy were excluded. The data require re-structuring to give an observation for each patient at each time in each state. For details of the data structure see Goldstein et al (2004).

The binomial response "change", which indicates exiting the state of claiming or non-claiming, is modelled in terms of dummy variables to indicate each state and interactions

259

between these and the chosen covariates. The transition from claiming to non-claiming is discontinuation and from non-claiming to claiming is resumption. To allow for patient-specific factors that affect the hazards of leaving each state I included two random effects for each patient- one for episodes of claiming prescriptions and one for episodes of not claiming prescriptions. To examine the relationship at patient level between the hazards of leaving each state, the random effects covariance was estimated. This indicates the effect of unobserved factors at patient level on the risks of ending episodes of both claiming and non-claiming.

As in previously fitted models, I firstly modelled the baseline hazards as piecewise constant in duration of the episode, then included other covariates and random effects at patient level. The model parameters and standard errors, estimated by 2nd order PQL, are shown in Table 6.9.

Table 6.9 Parameter estimates (SE) for multilevel multistate model for statin claiming and

non-claiming

Variable	Claiming->non-claiming	Non-claiming->claiming
Intercept	-2.4779 (0.0769)	-2.2843 (0.1073)
Month 1	1.3491 (0.0564)	2.6632 (0.0991)
Month 2-3	0.8739 (0.0568)	1.5561 (0.1010)
Month 4-6	0.4660 (0.0588)	0.8833 (0.1061)
Month 7-9	0.3023 (0.0636)	0.3915 (0.1204)
Month 10-12	0.1461 (0.0721)	0.2504 (0.1347)
Month 13+	0	0
Female	-0.1280 (0.0339)	0.3206 (0.0600)
Age	-0.0065 (0.0016)	-0.0099 (0.0027)
age^2	0.0010 (0.0001)	-0.0020 (0.0002)
Random effects		
Claiming->non-claiming	3.3833 (0.0960)	
Non-claiming-> claiming	-1.7087 (0.0460)	1.0443 (0.0317)

The parameter estimates given in Table 6.9 indicate that women are more likely than men to resume therapy after a break and less likely to discontinue, and that patients in the middle of the age range are less likely to discontinue an episode and more likely to re-start. The relationship with the duration of the episode is modelled as piecewise constant for the episodes of claiming and non-claiming, as previously in this chapter.

The random effects variances are large and significant after allowing for the effects of duration, age and sex, indicating that unobserved factors at patient level affect the hazards of both discontinuing episodes of claiming prescriptions and re-starting statins after a break in therapy. The random-effects covariance is negative and significant. This indicates that patients who are at high risk of ending episodes of collecting prescriptions are at low risk of

261

re-starting after breaks in therapy, and vice versa. That is, patients might be classified as high risk of discontinuing/low risk of resuming and low risk of discontinuing/high risk of resuming.

As for previous models, there are violations of the assumptions about the distribution of the data – Normal probability plots (not shown, but similar to those in Section 6.4), indicate that the distributions of responses for both states, claiming and non-claiming, are non-Normal. This is not unexpected – the previous plots show that responses for episodes of claiming statins are not Normally distributed, and the pattern for responses in episodes of non-claiming is similar. Furthermore, re-fitting the model given in Table 6.9 with the binomial variance unconstrained gives evidence of underdispersion (Binomial variance = 0.7650, SE = 0.0031) and substantially decreases the parameter estimates for the duration effects and increases the random effects estimates. It may not be appropriate to interpret the estimates of the random effects variances, in particular, as a measure of subject-specific variability, as the assumption of Normality may be incorrect.

6.6   Summary of models for statin claiming in the GMS

This chapter has presented the results of several approaches to modelling statin claiming patterns in the GMS, and described the strategies used to deal with various problems encountered during this process.

Perhaps the main consideration in choosing between modelling strategies is the objective of the analysis, rather than the data. For instance, does interest lie in the probability of claiming a prescription over time, or in the risk of discontinuing over time? In the former case a repeated measures approach is appropriate, and in the latter case an event-history approach. If patterns of non-claiming together with claiming are of interest, a generalisation of the event-history model – the multistate model - is a suitable approach. Is the focus on the behaviour of the individual or the population – for instance, if the outcome of interest is discontinuation of therapy, does interest lie in the population risk (marginal model) or the subject-specific risk (random effects model)? There are several very appealing aspects to the random-effects models – they allow the modelling and quantification of patient-level heterogeneity, which is of particular interest in the context of compliance, where the decision to continue (or discontinue) therapy for chronic illness is largely due to the individual, and certain factors, for instance disease severity, may have quite different influences in different patients. In all the models described above, the patient-level variance is large and significant, suggesting substantial variability at this level and highlighting the issue of compliance as an individual-specific phenonomen. The main problem with the random-effects models appears to be that the distributional assumptions of the binomial models used here are not met. This may limit the interpretation of random-effects parameter estimates; an interesting question for further research could be to determine the extent to which this violation affects parameter estimates. A mixture model may be more appropriate; however it has previously been shown that although this type of model may meet distributional assumptions for this type of data, the parameter estimates are little different to those from a logistic model (Carlin and Wolfe 2001). This is not an issue with the marginal model, where distributional assumptions are met. The parameter estimates from the marginal models give population-

average effects, which while interesting to characterise overall patterns of population prescription claiming, may be of less interest when studying the phenonomen of compliance.

This chapter on patterns of statin claiming has highlighted and explored several characteristics of note. For instance, repeated measures models with transitional terms show that recent previous statin claiming patterns have a strong predictive effect on current and future use; this is illustrated in Figure 6.9. This is mirrored in event history models, where the risks of both discontinuation and resumption of therapy decrease substantially as the duration of consistent behaviour increases. The final multistate model fitted (Section 6.5) provides evidence that individuals tend to have long periods of statin claiming and short periods of non-claiming, or vice-versa. It appears that individuals who stop claiming therapy are extremely unlikely to resume unless this takes place within the first few months of discontinuation. There may be identified as a suitable point for interventions designed to improve compliance.

The model estimates show that women tend to be slightly less likely to discontinue therapy / have a higher probability of collecting prescriptions over time than men, and that those in the middle of the age range (mean age 65.5. years) tend to be less likely to discontinue than both older and younger people. However these effects are quite small in comparison to the effect of the length of time claiming therapy previously. Of perhaps greater interest is the effect of the time-varying covariate indicating IHD status on compliance, which decreases as time from the first prescription (in the repeated measures model) or duration (in the event history model) increases.

The following chapter on the patterns of antihypertensive claiming begins with a similar modelling strategy to that followed for statins. However as prescription claiming patterns are rather more complex due to the various treatments available for hypertension, the simple models for antihypertensive claiming do not provide the full picture. To address questions about compliance with statins these simpler models are suitable; they may be seen as stepping stones in developing models to address questions about compliance with antihypertensives.

7.   Patterns of Claiming Antihypertensive

Prescriptions in the GMS Scheme

7.1   Introduction

This chapter presents the results of the analyses of patterns of antihypertensive claiming by GMS patients living in the ERHA area.   Although the diseases treated with statins and antihypertensives are similar in the sense that they are both chronic conditions with relatively minor symptoms, the control of which reduces the risk of morbidity and mortality, in some respects the problems posed in analysing patterns of prescription claiming for each type of treatment are quite different.   For one thing the study populations are different - the statin group have a much higher level of treatment for more serious cardiovascular disease, in particular IHD, which is known to affect compliance rates.   Patterns of claiming are different due to the fact that hypertension is affected by several different mechanisms which may be targeted by different drugs – the majority of patients require a combination of therapies to control their hypertension, and changes to their initial prescription, which is usually monotherapy and most commonly a diuretic, may be necessary for control and to minimise ADR (See Chapter 1).   Switches of therapy, which require a decision by the doctor,

267

are a result of quite a different underlying process to discontinuation, where the decision to stop collecting prescriptions is often made by the patient. It is not recommended practice to withdraw antihypertensive therapy, especially after short duration. Here we may model two competing processes, one based on doctors' treatment decisions, and the other based on patients' ongoing choice to continue therapy.

The chapter begins with an analysis of the time to first discontinuation of antihypertensives, typical of the approach used in previous studies (as reviewed in Chapter 3). This includes a discussion of the insights this approach gives, and its limitations in the context of assessing and understanding patients' compliance. The remainder of the chapter is concerned with developing models to make more use of the data available from the GMS Board and gain a better understanding of patients' compliance.

Section 7.3 gives baseline information on the patient cohort selected for analysis of antihypertensive claiming patterns. Aspects of the data relevant to each modelling approach used in this chapter are summarised.

Section 7.4 begins by fitting a logistic regression model for the response antihypertensive availability (repeated measures model), making no allowance for dependencies between responses from the same patient. The initial model shows how the probability of antihypertensive availability changes with time and age, which is helpful to choose functional forms for these covariates. It is important at the initial stages of modelling to (1) choose a suitable link function, and the logit is standard and easy to interpret for binary responses, and (2) choose an appropriate family of distributions so that the estimates of standard errors

can be correctly interpreted– the binomial distribution is usually assumed for binary responses.

Subsequently the binary response indicating antihypertensive availability is modelled in terms of covariates by logistic regression, and the dependencies between repeated observations of the same patient dealt with by using Generalised Estimating Equations (GEE). This is followed by a similar model that allows for dependencies between observations on the same patient by including a random intercept for each patient. Issues of extra-binomial variation are also explored, and the random effects model parameter estimates compared with the corresponding GEE estimates.

Section 7.5 begins with a simple discrete time event-history model for antihypertensive discontinuation. This is developed to allow for dependencies between observations of the same patient by using a multilevel discrete-time hazards model; that is, a random intercept is included for each patient to allow for unobserved factors at patient level that influence the hazards of discontinuation. The model is extended to allow for repeated episodes of prescription claiming within patients. The parameter estimates are interpreted as the effect of the covariate within a specific patient.

In Section 7.6 a multilevel multinomial discrete-time hazards model is used to predict the subject-specific hazards of switching and discontinuing versus continuing episodes of prescription claiming.

269

In Section 7.7 a multilevel multistate model is used to predict the subject-specific hazards of making transitions from the state of claiming to non-claiming (discontinuation) and non-claiming to claiming (resumption).

In Section 7.8 this is extended to predict the hazards of ending episodes of claiming by switch or discontinuation and ending episodes of non-claiming by resuming therapy.

Section 7.9 introduces a multistate model of more complex structure, but with no random intercepts for patients. This model analyses patterns of claiming prescriptions after starting a course of angiotensin-II antagonists.

In view of the potentially complex structure of antihypertensive claiming patterns, this chapter focuses on multistate and competing risks models. In these models a multilevel approach is used to allow for factors at patient level that affect their claiming patterns: a subject-specific interpretation of the factors affecting therapeutic changes being potentially more useful in understanding compliance than a population-average interpretation.

7.2   A Typical Analysis

I begin with an analysis of time to first discontinuation in patients new to a particular antihypertensive. This analysis is typical of previous studies that modelled patterns of prescription claims to estimate patients' compliance with antihypertensives (reviewed in Fitz-Simon et al 2005). I based this analysis on the patient population selected as described in Chapter 4.3 – this consists of 17,048 patients who claimed at least one prescription for a new antihypertensive as a single tablet (either monotherapy or diuretic combination). The baseline characteristics of this population are given in Table 4.1.

For the purposes of the following example of a typical analysis, discontinuation was defined, as has been common in previous studies (see Section 3.4.1.4), by a period of three months with no claims for the index therapy; the first discontinuation was identified and time to first discontinuation was calculated for each patient. Switches were considered discontinuation of the index therapy.

6,641 (39%) of these patients received only one month's prescription of antihypertensives before their first discontinuation. Thus for the purposes of this analysis, nearly two fifths of patients in the cohort were observed for only one month, although many of these may have recommenced claiming antihypertensives after a break, or switched to a different type of antihypertensive therapy. By twelve months 64% of patients had discontinued their index

antihypertensives. The median time claiming the index therapy was four months. Time to the first discontinuation is illustrated by a Kaplan-Meier plot in Figure 7.1 (see Section 5.1.3).
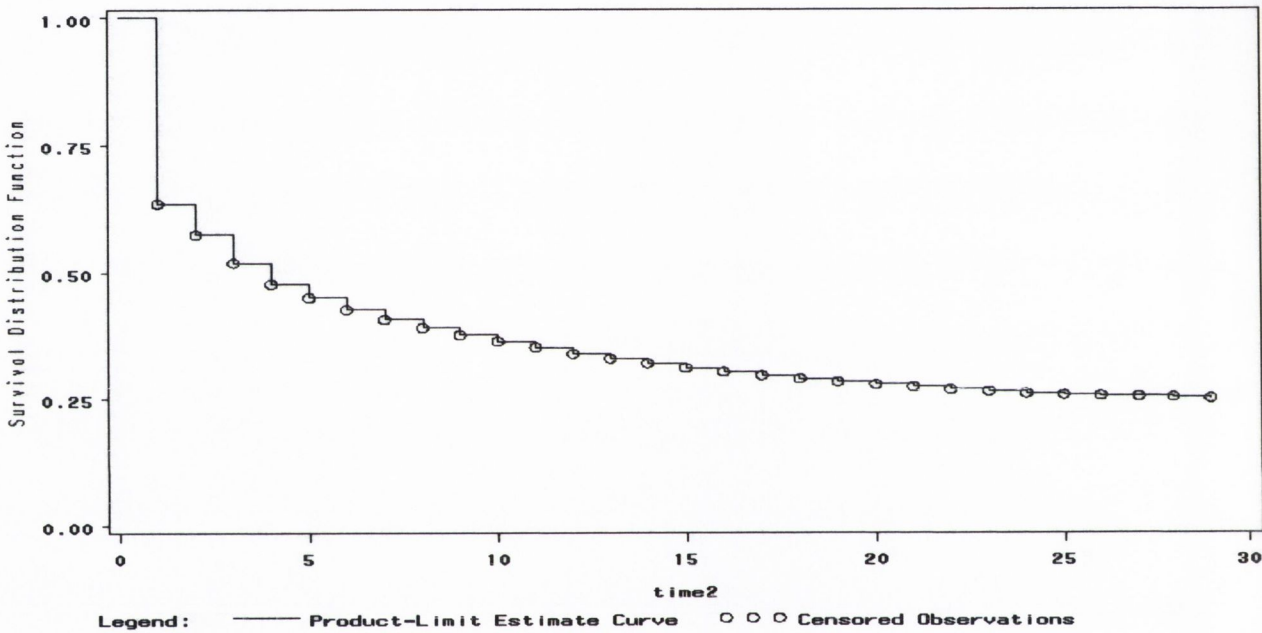
Figure 7.1 Time to first discontinuation

Although all these patients were newly prescribed their index therapies, they may have been taking a different antihypertensive at some time during the previous twelve months. The patients who were not previously prescribed any antihypertensive are referred to as "new antihypertensive patients", and those who were prescribed a different antihypertensive in the

year antecedent to the first prescription of the index therapy are termed "established antihypertensive patients". Figure 7.2 illustrates the difference in time to first discontinuation for new and established antihypertensive patients, and indicates that new antihypertensive patients (n=8,393) are at higher risk of discontinuing their therapy, especially in the first few months, than patients who have been prescribed their index therapy as either a switch (n=3,693) or an addition (4,962) to an existing therapeutic regimen. 48% of new antihypertensive patients received only one prescription, and their median claiming duration was two months, whereas for established patients, whether they were switching therapy or adding the new antihypertensive to an existing regime, 30% claimed only one prescription and the median time to discontinuation was six months. As noted in Chapter 2.5, selecting patients who are new to therapy ensures baseline comparability, which is an important point when analysing the dependence of the risk of discontinuation on time.
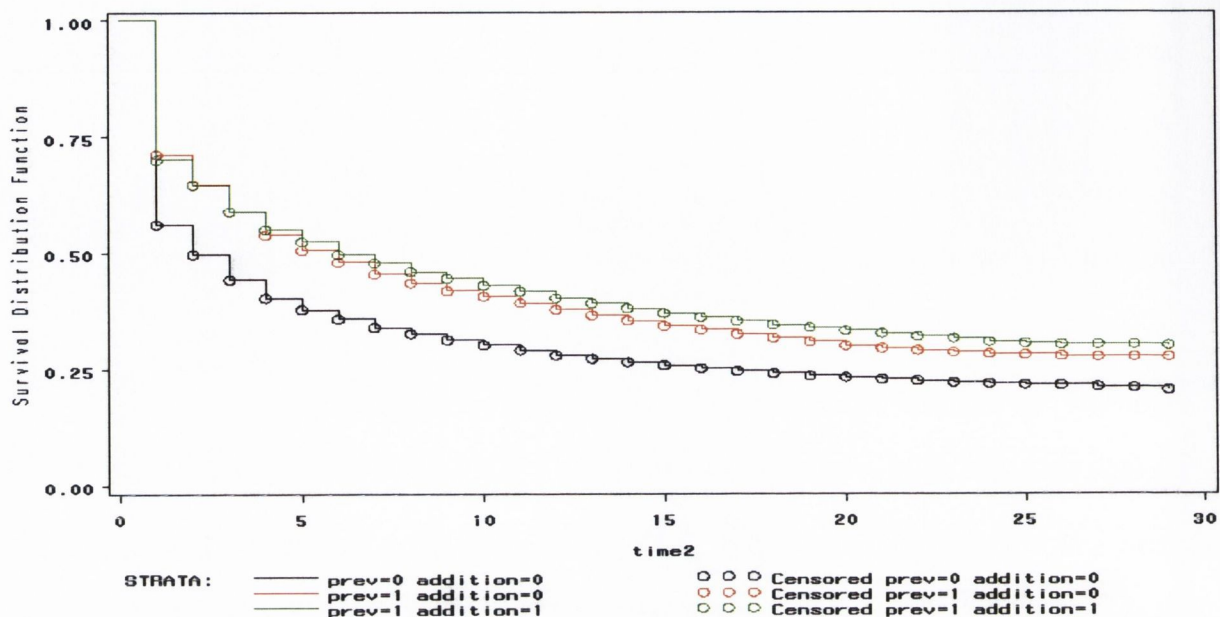
Figure 7.2 Time to first discontinuation for new and established patients

(Black = new patient, red = new therapy is a switch, green = new therapy is an addition)

Figure 7.3 is an illustration of the time to discontinuation for patients starting a new therapy from each of the antihypertensive classes. This indicates that patients who were prescribed an ATII antagonist were at the lowest risk of discontinuing this, followed by patients prescribed ACE inhibitors, calcium channel blockers, beta blockers and diuretics. However, this result must be interpreted with care: this is an observational study wherein therapies are not randomly allocated to patients – the result cannot be interpreted as an effect of the differences in drug class characteristics, as there may be a selection bias whereby particular patients are prescribed particular drugs based on their characteristics, characteristics of their condition and prescribing behaviour of their doctors.

274
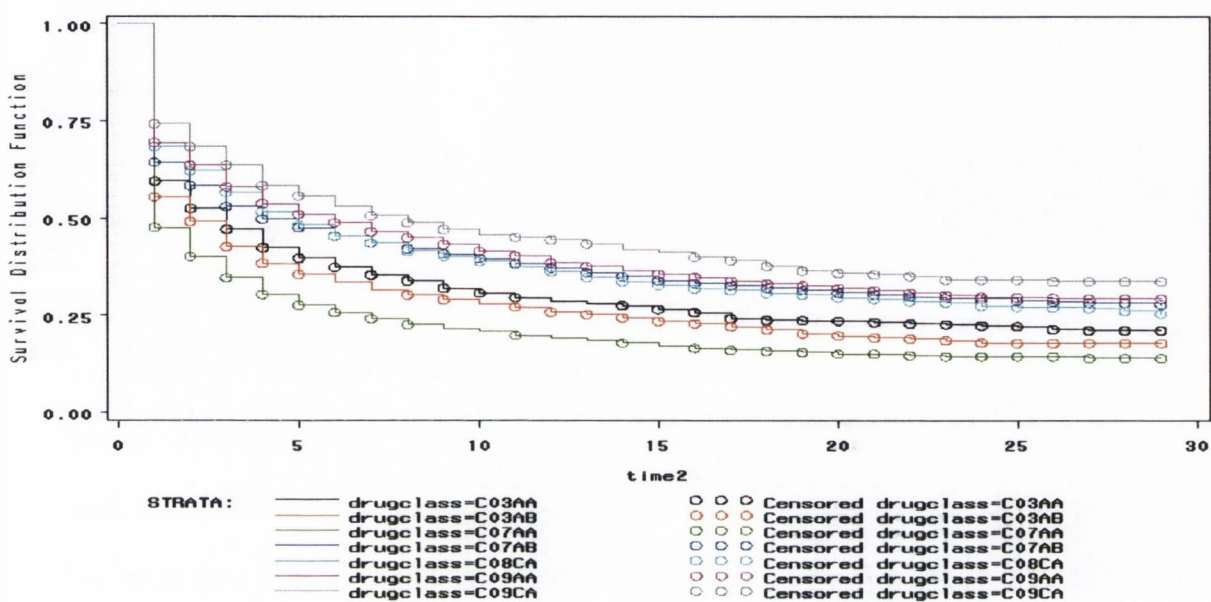
Figure 7.3 Time to first discontinuation by drug class

(see Appendix for ATC codes)

A typical study would proceed to model the time to first discontinuation in terms of covariates using Cox regression (Section 5.1.3; see also Chapter 3 for modelling approaches of previous studies). The limitations of Cox regression for analysing this type of data were discussed in Chapter 3. This example highlights some inadequacies in the definitions and the way the data are structured - alternative approaches may yield greater insight in assessing compliance, and therefore I do not here proceed with this approach.

Analysing the time to first discontinuation is inadequate where patients have multiple episodes of claiming different therapies and multiple discontinuations. Analysing the time to

275

first discontinuation of a particular drug gives only a partial picture of what is happening. This approach is useful to demonstrate the very high rate of discontinuation in the first month: it should be noted that many of these patients are never observed to claim another prescription, and research has indicated that it is unclear whether patients who claim only one prescription in total ever actually take their drugs (Yang et al 2003). However, modelling prescription claiming in this way gives no information on patients who resume claiming prescriptions after a break of more than three months. Choosing three months to define discontinuation may obscure actual claiming patterns in patients who have several short breaks in claiming prescriptions – these patients are obviously different in their behaviour and (it is assumed) in their blood pressure response than patients who claim and use prescriptions consistently – however defining discontinuation in this way does not allow differentiation between patients who claim consistently and those who have any number of gaps of less than three months duration in their claiming patterns.

Choosing the outcome of interest to be discontinuation of therapy entails ignoring switches of therapy – this approach is not informative where interest is in compliance for control of blood pressure. Most antihypertensives will ultimately reduce blood pressure to the same extent (Neaton et al 1993; see Chapter 2.4.2); switches are decided by the doctor to achieve blood pressure control.

It would be more appropriate to model multiple episodes of claiming (and non-claiming) within each patient.

The remainder of this chapter is concerned with developing modelling approaches that give further insights into patterns of antihypertensive prescription claiming, and, thereby, patients' compliance.

7.3   The Patient Cohort

To ensure baseline comparability, I selected patients new to any antihypertensive. The process by which the patient cohort was chosen is described in Section 4.3. 10,830 patients were included in the sample and their prescription histories constructed. Their age range at the time of the initial antihypertensive prescription was 31-101 years, mean age 64.4 years (SD 14.7 years), and 6,377 (59%) of them were women. The quartiles of the number of defined daily doses (DDD) per month for all antihypertensives combined were calculated to be 15, 28 and 37.33 DDD.

Because few patients were observed for more than 24 months, observations only until this point were included in the prescription claiming histories. This gave a total of 204,755 monthly observations (not including the first month, when all patients received a prescription by definition). Of these monthly observations, 85,588 (42%) were classified as months with antihypertensive prescriptions available and the remainder were classified as months with no antihypertensive prescriptions available.

Looking at antihypertensive prescription claiming histories over the first year after the initial prescription, it is apparent that patients might be classified into several groups. Considering patients who were observed for twelve months after the initial prescription (that is, excluding patients who withdrew from the scheme) 3,225 (31.4%) patients claimed no further prescriptions after the initial one – on the other hand, 1,293 (12.6%) of patients claimed an antihypertensive prescription every month, and 1,118 (10.9%) of patients claimed all prescriptions bar one. Including observations on all patients up to and including the 24th month after the initial prescription claim, 3,129 (28.9%) of patients never claimed another prescription and 1,006 (9.29%) claimed a prescription each month observed. The remaining patients claimed at least one and missed at least one prescription during the observation time. Of these 934 (8.6% of the total) missed only one prescription.

Event-history analysis requires data in the form of episodes in defined states (for example, continuous claiming of antihypertensive prescriptions) with defined outcomes (for example, discontinuation or switch) – see Sections 4.2.5 and 4.2.6 for definitions. These 10,830 patients contributed 28,898 episodes of continuous claiming a specific antihypertensive therapy and 18,291 episodes of non-claiming. Spells of both claiming and non-claiming were usually short, with 20,710 (73%) of episodes of claiming and 10,829 (59%) of episodes of non-claiming lasting three months or less. The median length of an episode of claiming a particular antihypertensive was one month and the 75th percentile four months, with 5% of episodes lasting more than one year. Treating switches as continuation of therapy, the median duration of continuous therapy was two months, and 10% of episodes of antihypertensive therapy lasted more than one year. Meanwhile 45% of episodes of non-

claiming lasted one month, and 25% of such episodes lasted more than one year. Considering the 28,898 episodes of claiming a particular antihypertensive, 6,232 (21.6%) ended with a switch and 18,378 (63.6%) ended with a discontinuation; the remaining episodes were ongoing at the end of observation. For the episodes of non-claiming, 11,953 (65.4%) ended when the patient resumed therapy.

All patients, by definition, contributed at least one episode of claiming. 4,427 (59.1%) contributed more than one episode of claiming; the maximum number of episodes of claiming observed was fifteen. 9,811 patients contributed at least one episode of non-claiming – of these 5,417 (55.2%) contributed a single episode of non-claiming and the maximum number of episodes of non-claiming was nine.

Covariates at episode level are summarised in Table 7.1.

Table 7.1. Summary of covariates at episode level

Episode-level variables		
age group	number episodes	% episodes
30-56	11,395	23.9%
56-69	12,287	25.8%
69-76	10,819	22.7%
>76	13,091	27.5%
drug type (for episodes of claiming)		
A	5,376	18.5%
B	6,013	20.6%
C	3,641	12.5%
D	5,400	18.5%
ATII	1,021	3.5%
A+B	1,144	3.9%
A+C	714	2.5%
A+D	1,229	4.2%
A+ATII	107	0.4%
B+C	610	2.1%
B+D	1,286	4.4%
B+ATII	218	0.7%
C+D	548	1.9%
C+ATII	120	0.4%
D+ATII	403	1.4%
2 drugs total	6,379	21.9%
3+ drugs	1,294	4.4%
previous drug (episodes of non-claiming)		
A	3,616	19.6%
B	4,243	23.0%
C	2,608	14.1%
D	3,956	21.4%
ATII	622	3.4%
2 drugs	2,938	15.9%
3+	485	2.6%

7.4 Repeated measures models

One of the aims of the modelling process is to incorporate all the observed information on claims for antihypertensives in the data set. As for the models for statin claiming, two types of data structure were considered – repeated measures, giving the monthly availability of antihypertensive therapies, (described in this section) and a discrete-time event history approach (Section 7.5).

7.4.1 Prescription availability

Here I illustrate the results of modelling the binary response indicating monthly antihypertensive availability by logistic regression. The first month, during which all patients (by definition) received a prescription, was not included in the data set. Dependencies between responses from the same patient were initially ignored. To investigate the relationship between the probability of having a prescription and time since the incident prescription, I included in the model as covariates a separate dummy variable for each month and did not fit an intercept term. Figure 7.4 is a plot of the probability of having a prescription available against time in months since the incident prescription. This plot is useful to help choose a functional form for the relationship between prescription availability and time. A smooth function of time, either parametric or non-parametric, might be considered. Here polynomial and logarithmic functions were considered, and a cubic

polynomial chosen (illustrated in Figure 7.4). Under Akaike's Information Criterion (AIC) (Akaike 1973) the model with a dummy variable for each month is preferred overall (AIC=277,819), but the cubic model (AIC=277,834) gives a better fit than the logarithmic model (AIC=277,847). Adding further polynomial terms does not improve the model under AIC. The form of the functional dependence illustrated here is very like that seen for statins (Figure 6.5), although the overall rate of claiming is lower for antihypertensives.
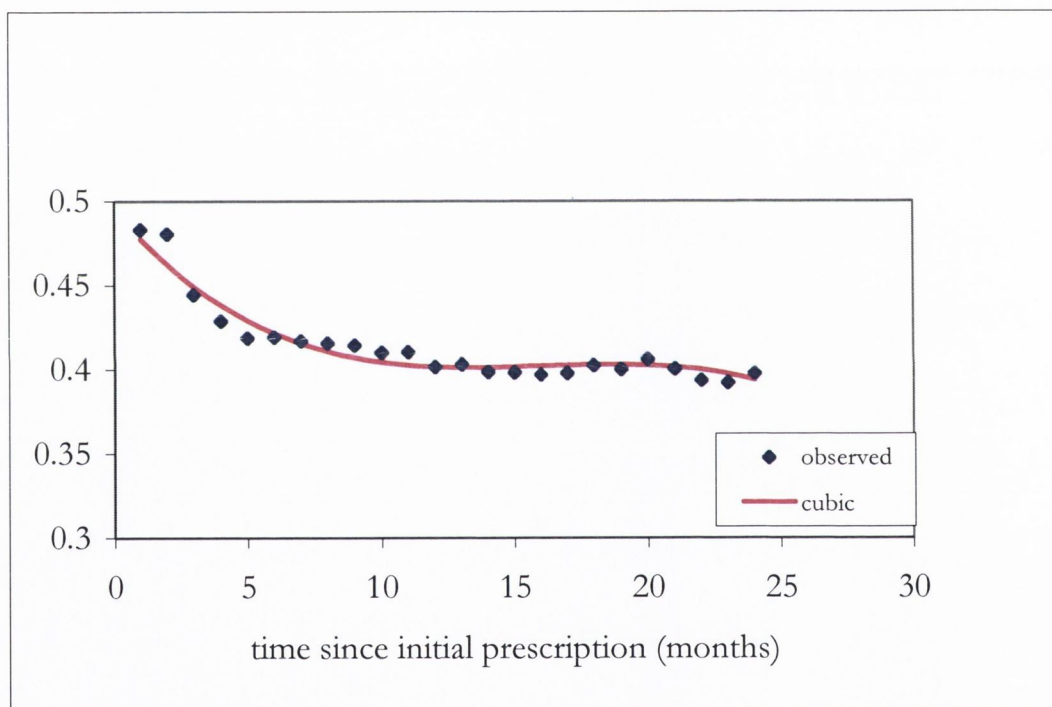
Figure 7.4 Observed proportions claiming antihypertensive therapy and cubic model for time

7.4.2 *Marginal logistic regression model for prescription availability*

Here I give the results of fitting a logistic regression model to predict availability of any antihypertensive prescription. To model the change over time I included as covariates centred cubic polynomial terms for time since the initial prescription, and to allow for correlations between the responses contributed by each patient, I used a GEE approach, choosing firstly an unstructured correlation matrix (see Section 5.4).

As the estimated 24x24 correlation matrix (not shown) implies a structure where dependencies in the responses decrease as time between the responses increases, I fitted a model with an autoregressive structure of order one and compared the results of this with the results using the unstructured correlation matrix. While the parameter estimates are similar, and the significance of covariates in the model is unchanged, it appears from inspection of the estimated correlation matrices that the autoregressive structure of order one does not adequately describe the correlation between successive observations within each patient. An autoregressive structure of higher order, which allows for dependencies between more widely spaced months, may be more appropriate. This issue was explored in greater detail in the chapter on statins, Section 6.4.1. For the purposes of this analysis I proceed with the unstructured correlation matrix. In theory, if the model for the expected value of the response is correctly specified, the parameter estimates are not affected by choice of the correlation structure (see Section 5.2.3).

Table 7.2. Parameter estimates for marginal logistic regression model with unstructured correlation matrix for antihypertensive availability

Variable	Estimate	Standard Error	p
intercept	-0.4632	0.0461	<0.0001
time	0.0018	0.0023	0.4204
time²	0.0012	0.0002	<0.0001
time³	-0.0001	0.0000	<0.0001
First ACE	0.3965	0.0460	<0.0001
First ATII	0.4319	0.0949	<0.0001
First BB	0.2475	0.0447	<0.0001
First CCB	0.2026	0.0513	<0.0001
First diuretic	0		
First 2 drugs	0.0340	0.0532	0.5227
First 3+ drugs	-0.1861	0.1156	0.1073
female	0.2893	0.0419	<0.0001
age	0.2422	0.0296	<0.0001
age²	-0.3126	0.0282	<0.0001
Female*age	0.1439	0.0338	<0.0001
Female* age²	-0.0261	0.0312	0.4029
Time*age	0.0068	0.0011	<0.0001
Time*age²	-0.0064	0.0010	<0.0001

Table 7.2 gives the parameter estimates and standard errors for the marginal logistic regression model (by GEE) for antihypertensive prescription availability. Here age was standardised by subtracting the mean and dividing by the standard deviation. The relationship between the probability of having a drug available and age is quadratic, with the older and, more particularly, younger patients being least likely to claim prescriptions. Women in the middle of the age range (mean = 64.4 years) are more likely to claim prescriptions than men, and there is an interaction with age whereby this difference becomes larger as age increases (and smaller as age decreases). With respect to the effects of age and sex, it has been pointed out that these are often confounded with cardiovascular

comorbidities which may also affect compliance (Catalan and LeLorier 2002, reviewed in Chapter 3). However the direction of this effect may be dependent on the individual patient, as comorbidities may serve as a motivation to some and a barrier to others with respect to compliance (Section 2.3.3). I have not included evidence of cardiovascular comorbidities as covariates in this model, so the effects of age and sex should be interpreted with caution.

The group of patients prescribed diuretics was less likely than any other to claim their prescriptions in the month after this was initially prescribed, after which the functional relationship of claiming probability with time mirrors that of patients prescribed other classes of antihypertensives (interactions between antihypertensive class and time covariates were tested and found to be non-significant – see below). Whether this is due to the characteristics of the patient groups prescribed each type of drug or due to the drugs themselves cannot be determined. Are patients starting diuretics at higher risk of adverse drug reactions (ADR) than patients starting other classes of antihypertensives? Clinical trials have shown that of all the classes of antihypertensive, diuretics may be attributed with one of the lowest rates of ADR (Neaton et al 1993). Maybe there is a selection bias whereby patients who have relatively low blood pressures are more likely to be prescribed diuretics: patients whose disease is not severe may decide not to continue with therapy. As has been noted previously, patients make individual decisions about the necessity to continue with treatment based on a large number of interacting factors (Section 2.3.1). Table 4.1 indicates that patients prescribed diuretic monotherapy were less likely to be treated for cardiovascular comorbidities than were patients prescribed any other type of antihypertensive (monotherapy or combination).

Interactions between time covariates and the initially prescribed drug were tested but found to be non-significant – that is, the effect of the initial treatment group is apparent in the first month and the pattern of availability of antihypertensive therapy over time is no different thereafter, regardless of which drug was initially prescribed. Figure 7.5 illustrates how the availability of any antihypertensive prescription changes with time since initiation in a population of baseline patients (that is male, aged 64.4), by class of initial therapy.
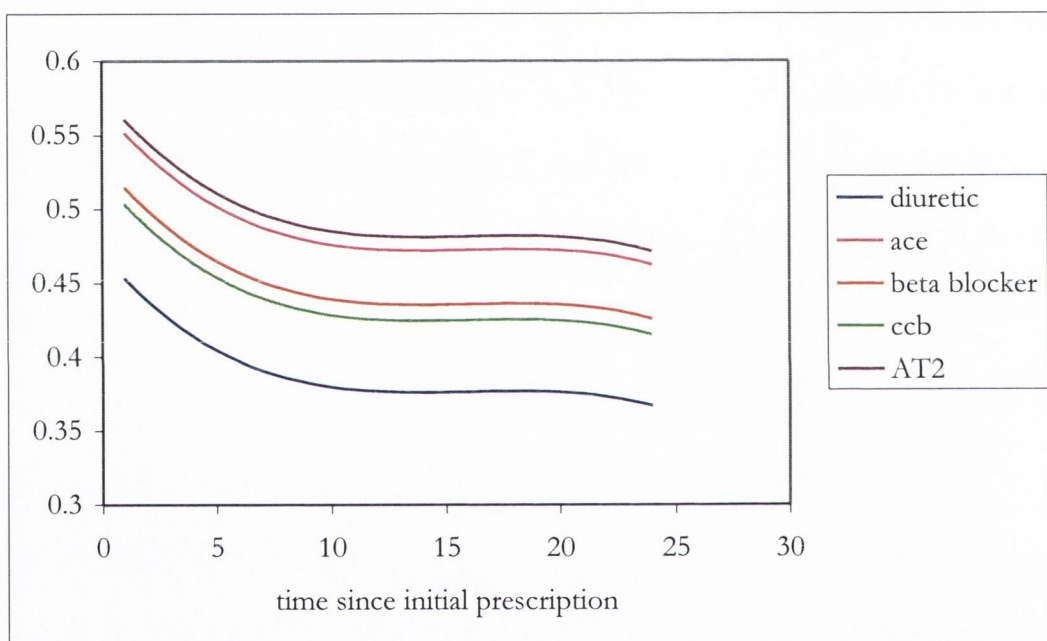
Figure 7.5 Marginal model predicted proportions of patients (Male, age 64.4) claiming antihypertensive therapy by initial class

As noted previously, the pattern of prescription availability over time closely mirrors the patterns seen for patients new to statin therapy. This suggests that behavioural

characteristics over time of patients treated for chronic illnesses may be similar regardless of the specific condition or treatment.

In this marginal model by GEE the correlation structure is considered a nuisance and the focus is on estimating parameters for the mean response with correct standard errors. The interpretation of parameter estimates is in terms of population average values. If interest lies in the correlation structure, developments of the GEE approach (eg GEE 2), or a random-effects approach should be used (Section 5.2.3.9).

7.4.3 Multilevel logistic model for prescription availability

A logistic model with random intercepts for each patient is equivalent to the GEE with clusters defined by patients and exchangeable correlation structure. In the random intercepts approach we are allowing each patient to have a unique underlying risk of claiming his or her prescription, and this risk does not change over time. The equivalent GEE assumption is that all the correlations between repeated measures on the same patient are equal – that is, there is no time structure. However, using the GEE approach with unstructured correlation matrix in the previous section indicated that there is a time structure, with greater dependencies between responses close in time than in responses widely separated in time. It is apparent that patients are more likely to collect a prescription if they have been doing so during the previous months.

Here I give the results of fitting a random intercepts logistic regression model for prescription availability. I test whether the Binomial assumption is met by checking for extra-binomial variation, and fit further models to account for dependencies between successive responses from the same patient. The issues are explored in more detail in the chapter on statins (6.3.3).

As in the case of the multilevel logistic model for statin availability, when the response for antihypertensive availability is modelled in terms of covariates (duration, age, sex, and interactions) with a random intercept for each patient, there is a problem with underdispersion. The Binomial variance is estimated as 0.685 (SE 0.002) – that is, significantly less than one. This is because even when allowing each patient to have a unique underlying risk of claiming prescriptions, there remains clustering in the responses within each patient. In particular, a large group of patients are not observed to claim another antihypertensive prescription after the first one; another group of patients are observed to claim a prescription every month. The patients in both these groups have a constant response of 0 (no further claims) or 1 (claim every month), and therefore the value of the linear predictor in the logistic model is $\pm\infty$.

As for the model for statin availability, I included the previous medication possession ratio (MPR), categorised to denote claims in none (MPR0), some (MPR1) and all (MPR2) previous months, as a covariate. When previous MPR is included as a covariate the Binomial variance is no longer significantly different to one (estimate = 0.997, SE = 0.003, p = 0.381). Interactions with time (modelled as a cubic polynomial) are also included – these are significant, but not necessary to deal with underdispersion. Estimates for the random

288

effects logistic regression model, and, for comparison, the corresponding marginal logistic regression model by GEE with exchangeable correlation structure are given in Table 7.3. The random effects model was estimated in MLwiN using 2nd order penalised quasi-likelihood and the marginal model estimated in SAS using proc genmod (see 5.6).

Table 7.3 Random-effects and marginal model estimates for AHT availability

Variable	RE estimate	RE SE	GEE (exch) estimate	GEE SE	GEE p
Intercept	0.5073	0.0883	0.2058	0.0519	<0.0001
Time	-0.0173	0.0109	-0.0039	0.0031	0.2180
time^2	0.0030	0.0009	0.0018	0.0002	<0.0001
time^3	-0.00025	0.00013	-0.0001	0.0000	0.0001
MPR0 (none)	-3.8460	0.0824	-1.7013	0.0449	<0.0001
MPR1 (some)	-0.8126	0.0536	-0.4306	0.0312	<0.0001
MPR2 (all)	0		0		
Time*MPR0	0.0780	0.0168	0.0357	0.0036	<0.0001
Time*MPR1	0.0125	0.0115	0.0017	0.0041	0.6832
T^2*MPR0	0.0043	0.0015	0.0008	0.0002	0.0006
T^2*MPR1	-0.0021	0.0010	-0.0012	0.0003	0.0003
T^3*MPR0	-0.0013	0.0002	-0.0003	0.0000	<0.0001
T^3*MPR1	0.00018	0.00001	0.0001	0.0001	0.0628
female	0.3650	0.0688	0.2651	0.0425	<0.0001
age	0.3105	0.0449	0.2221	0.0313	<0.0001
age^2	-0.4494	0.0419	-0.2970	0.0306	<0.0001
Female*age	0.2110	0.0555	0.1374	0.0367	0.0002
Female*age^2	-0.0373	0.0512	-0.0247	0.0350	0.4798
Time*age	0.0154	0.0016	0.0081	0.0014	<0.0001
Time*age^2	-0.0166	0.0014	-0.0079	0.0013	<0.0001
Diuretic	0				
ACE	0.4921	0.0758	0.3244	0.0472	<0.0001
BB	0.2967	0.0734	0.1868	0.0454	<0.0001
CCB	0.2323	0.0842	0.1475	0.0524	0.0049
ATII	0.5966	0.1548	0.3494	0.0943	0.0002
2 drugs	0.0176	0.0879	-0.0012	0.0545	0.9820
3+ drugs	0.1080	0.1845	0.0801	0.1124	0.4761

The random effects model indicates large and significant unobserved heterogeneity at patient level (Variance 4.575, SE 0.086). Thus approximately 58% of the variance in antihypertensive claiming probability may be attributed to unobserved factors at patient level (see 5.2.4.5). The marginal model was fit using an exchangeable correlation structure for comparison with the random-effects estimates – the working correlation (an estimate of the average correlation between any pair of responses from the same patient) was 0.4953 (see 5.2.3.3).
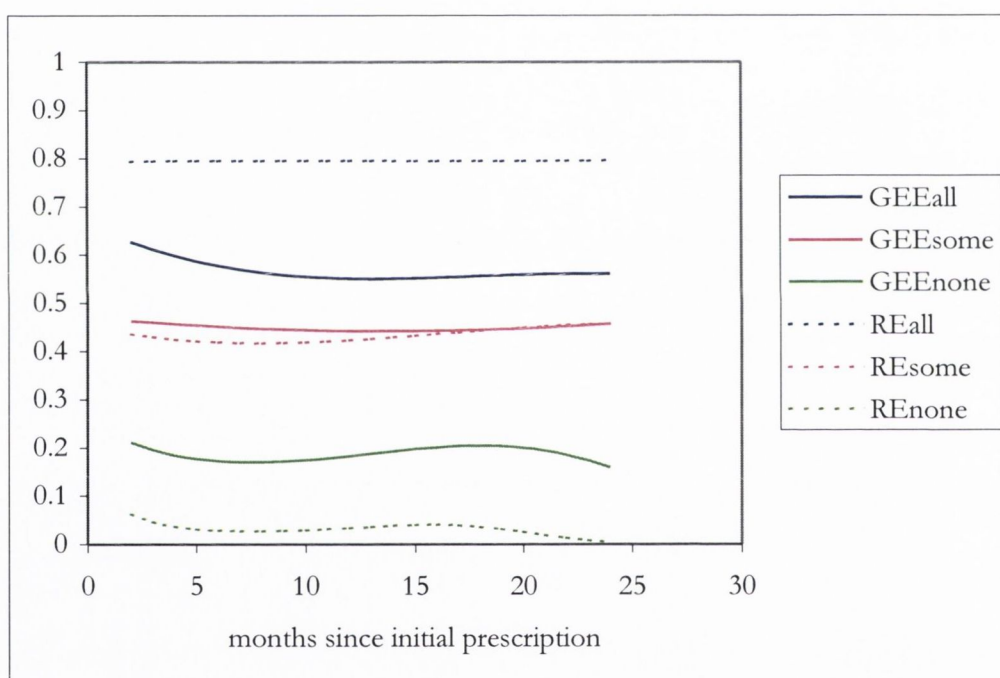
Figure 7.6 Predicted antihypertensive claiming by previous MPR – comparison of marginal and Random Effects models

Figure 7.6 shows the predicted probabilities for antihypertensive prescription claiming over time for patients who have claimed all, some or none of their previous prescriptions. The estimates from both the random-effects model and the marginal model by GEE with exchangeable correlation structure are shown. The random effects estimates may be interpreted as the median probability of a specific patient claiming the next prescription, and the GEE estimates give the mean probability of this population of patients claiming the next prescription. The subject-specific probability of continuing to claim prescriptions if all previous prescriptions were claimed is rather higher than the population-average estimate, while the subject-specific probability of continuing to claim prescriptions if no previous prescriptions were claimed is rather lower than the population-average estimate. The large differences between GEE and random effects estimates might be attributed to the high variance at patient level – that is, much of the variability in responses is explained by unobserved patient-level factors. However this does not explain why the random effects and GEE estimates are so different (in the opposite directions) for both groups of patients with constant responses, but the random effects and GEE estimates are quite similar for the patients who do not have constant responses. It is possible that this occurs because the distributional assumptions of the random effects model are incorrect. It should, however, be noted that the random-effects probability estimates are not mean values and therefore should not be directly compared with GEE estimates.

Table 7.3 gives parameter estimates for different classes of antihypertensive therapy (in comparison to diuretics). It should however be noted that these cannot be interpreted as the effect of the drugs. In the marginal model the interpretation is in terms of differences in claiming in groups of patients prescribed each therapy. In the random-effects models the

291

explanatory variables indicating drug class may be correlated with the patient-level random effects, thus violating an assumption of the random effects model. A multiprocess model, jointly modelling the processes of antihypertensive class and claiming, would be more appropriate if interest lies in estimating the effect different types of therapy at patient level, as it would allow for the fact that patient characteristics may have an effect upon the type of therapy they are prescribed (Steele et al 2005).

7.5 Event-history models for antihypertensive discontinuation

7.5.1 The event-history model

The model is the same as above (that is, a logistic regression model), but here the response is discontinued (versus did not discontinue) and observations on patients only until their first discontinuations, defined as a gap of one month with no therapy, are included. I modelled the hazard of first discontinuation of the index therapy in terms of time, including a dummy variable for each month and no intercept term. Figure 7.7 shows how the hazard of first discontinuation changes with the duration of claiming. Here a piecewise constant model was chosen for the hazard of discontinuation as a function of duration of the first episode of claiming. Constant baseline hazards were fit for month 1, months 2-3, months 4-6, months 7-9, months 10-12, months 13-18 and months 19-24. Using Akaike's Information Criterion (AIC), the model with a dummy variable for each month gave the best fit (AIC=40,217), followed by the stepwise constant model (AIC=40,231). The cubic model provided the worst fit of those considered (AIC=40,745), followed by the logarithmic (AIC=40,552),

quartic (AIC=40,526) and quintic (AIC=40,425) models. Another advantage of the stepwise

constant model is its ease of interpretation.
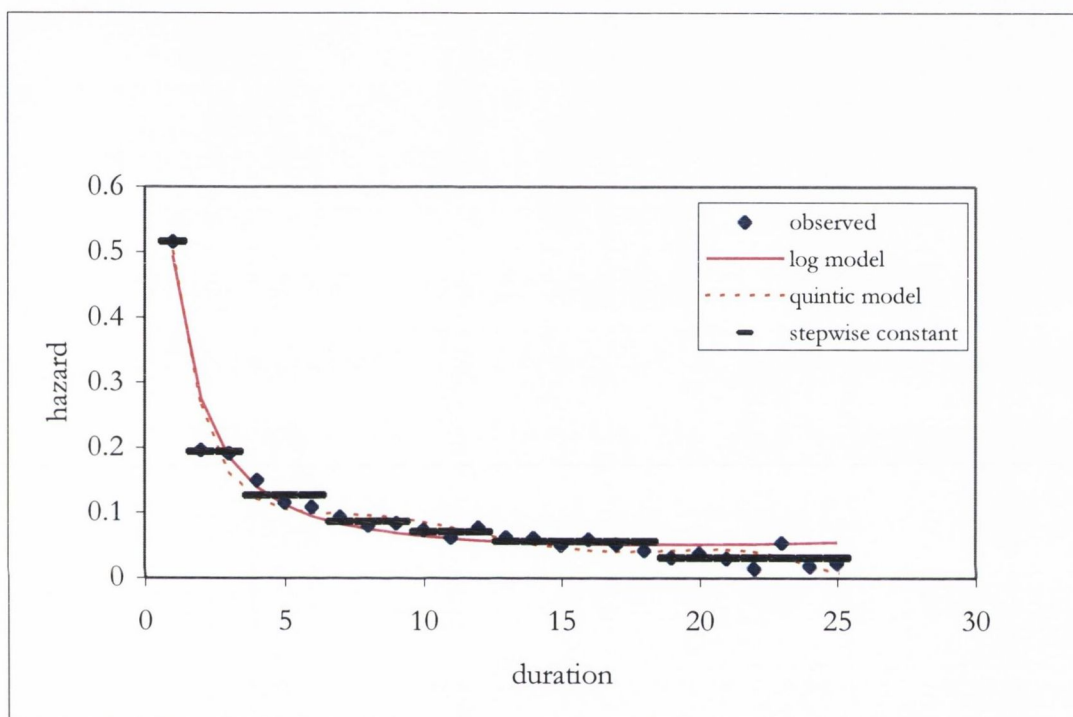
Figure 7.7 Hazard of first discontinuation of continuous claiming of antihypertensive

therapy

Similarly, by including a dummy variable for each year of age, we can see the relationship

between the hazard of first discontinuation and the age of the patient (Figure 7.8). It

appears that the hazard of first discontinuation is quadratic in age; I shall test the significance of an age squared term in subsequent models.

As for statins, dependencies between events contributed by the same patient should be allowed for in the model. A marginal or random-effects model may be used: for the remainder of this chapter the focus is on developing the random effects model with the aim of achieving a better understanding of patient-specific antihypertensive claiming patterns.
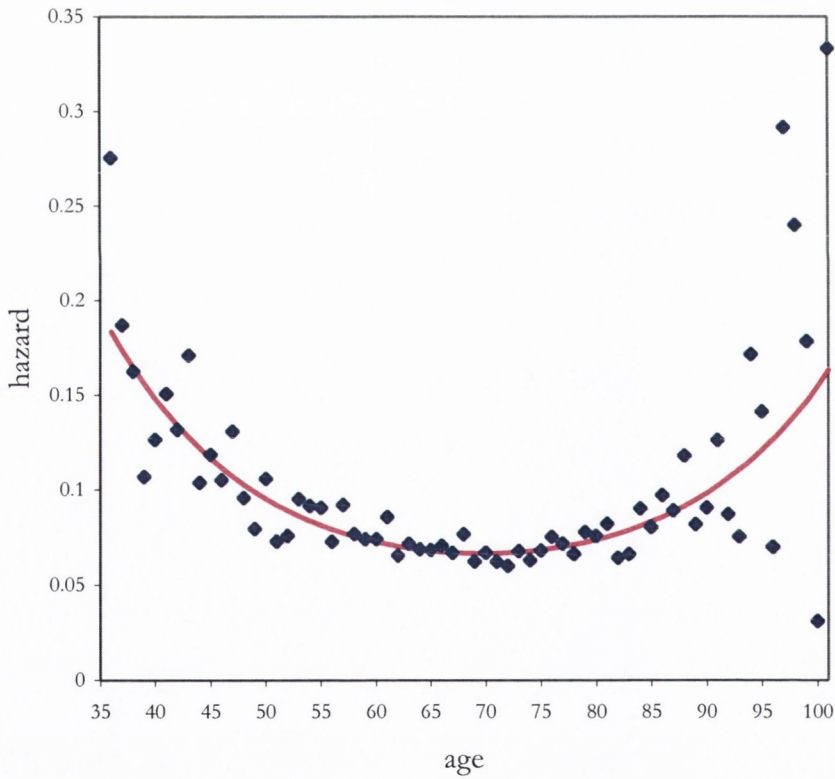
Figure 7.8 Quadratic model for hazard of antihypertensive discontinuation by age

7.5.2 *Multilevel discrete-time hazards model for antihypertensive discontinuation*

Here I give the results of fitting models for the hazard of discontinuing to claim antihypertensive prescriptions in the population of 10,830 antihypertensive patients (96,557 months) and in the subset of 7,701 patients (93,424 months) who claimed at least two prescriptions during the observation period. Repeated episodes of claiming are included in the data set, as in Section 6.7. Covariates included in the models are time (modelled as piecewise constant in the hazard of discontinuation), age and age squared (centred on the mean), sex, class of antihypertensive, use of statins and IHD status. A random intercept is included for each patient, so that each has a unique baseline hazard of discontinuation. This is to allow for unobserved factors at patient level that affect the risk of discontinuation. Parameter estimates are shown in Table 7.5 (column 1, "population constrained").

Parameter estimates are subject-specific. Men have a greater underlying propensity to discontinue than women. If a patient not previously treated for IHD is treated for this his risk of discontinuation substantially decreases; the same is true of statin treatment. The parameter estimates for different drug classes are difficult to interpret as there may be correlations between the random effects and these explanatory variables, as the prescription of particular drugs may be partly determined by patients' characteristics that also may effect the risk of discontinuation. If there were no such correlations between explanatory variables and random effects, the patient-specific adjusted hazard ratios for discontinuation for each drug class in comparison to thiazide diuretics may be calculated from the parameter estimates (Table 7.4). However these estimates may not be interpretable as hazards ratios

due to possible violation of the random effects model assumptions: a multiprocess model, allowing for correlations between random effects and explanatory variables, may be more appropriate (Steele et al 2005).

Table 7.4. Hazard ratios for discontinuation by antihypertensive class

DRUG CLASS	Discontinue versus continue
Thiazide	1.0
Beta blocker	0.81
Calcium channel blocker	0.83
ACE inhibitor	0.69
ATII antagonist	0.62
2 drug classes	0.72
3+ drug classes	0.73

Unobserved patient-level factors have a significant effect on the risk of discontinuation. The variance due to unobserved patient-level factors in the population is 0.4814 (SE = 0.0189). This can be used to calculate the proportion of the variance that may be ascribed to the patient level. Making the assumption that there is a continuous underlying response, the proportion of variance explained by the patient level is about 9%. It is apparent that unobserved patient-level factors have an influence on the hazards of discontinuation.

Table 7.5 PQL parameter estimates (SE) for multilevel discrete-time hazards model with repeated episodes within patients

Variable	Population constrained	Subset unconstrained
Intercept	-2.4211 (0.1163)	-2.0818 (0.1144)
Month 1	2.2669 (0.1119)	1.3838 (0.1078)
Month 2-3	1.3035 (0.1124)	0.8871 (0.1080)
Month 4-6	0.9786 (0.1131)	0.6559 (0.1086)
Month 7-9	0.7372 (0.1155)	0.4963 (0.1107)
Month 10-12	0.5863 (0.1194)	0.4138 (0.1142)
Month 13-18	0.4332 (0.1211)	0.3412 (0.1153)
Month 19+	0	0
Female	-0.2083 (0.0334)	-0.1915 (0.0405)
Age	-0.0120 (0.0015)	-0.0086 (0.0019)
Age^2	0.0007 (0.0001)	0.0004 (0.0001)
Female*age	-0.0056 (0.0019)	-0.0056 (0.0023)
Female*age^2	0.0002 (0.0001)	0.0004 (0.0001)
Diuretic	0	0
ACE	-0.3650 (0.0361)	-0.3833 (0.0419)
Beta blocker	-0.2053 (0.0354)	-0.2240 (0.0415)
Calcium channel blocker	-0.1835 (0.0400)	-0.1737 (0.0464)
ATII antagonist	-0.4849 (0.0666)	-0.4762 (0.0746)
2 drugs	-0.3330 (0.0382)	-0.4288 (0.0436)
3+ drugs	-0.3086 (0.0741)	-0.4512 (0.0850)
IHD	-0.4130 (0.0611)	-0.3018 (0.0669)
statin	-0.2867 (0.0329)	-0.3081 (0.0362)
Random variance	0.4814 (0.0189)	0.8772 (0.0259)
Binomial variance	1.000	0.8781 (0.0042)

Care must be taken, however, in interpreting these results. As mentioned previously, the data are observational and one cannot therefore attribute higher rates of claiming particular therapies to characteristics of the drugs only. There are also issues with regards to the

adequacy of the model given that the conditional distribution of the responses are often constant. As was found for a similar model for statins, the residuals at patient level are not Normally distributed, although the approximation to Normality is probably closer than for the statin models (see Figure 7.9). Model 1 was re-fit with the binomial variance unconstrained, and this indicated underdispersion (estimate = 0.879, SE = 0.004). The model with unconstrained variance also has different estimates for the fixed effects – smaller in magnitude for the duration covariates and larger in magnitude for the drug class effects than for the constrained model (these estimates may be better, see Fielding and Yang 2002). The patient-level variance is rather larger than for the unconstrained model (var = 1.005, SE = 0.0272). Given that the model may not give a good fit to these data, the interpretation of the random-effects variance is problematic.

To further explore some of the modelling issues, the same model was fit for a subset of patients who were observed to claim at least one further prescription after the first. The parameter estimates for this model, with binomial variance unconstrained, are given in Table 7.5. The Normal probability plot of the residuals at patient level are shown is shown in Figure 7.10 – this is probably closer to Normality than the residuals for the population model, though is still noticeably non-Normal. The Binomial variance is significantly less than one, but the increase in the variance at patient level, from 0.524 for the constrained model to 0.877 for the unconstrained model is not as pronounced as was seen for the population model. Thus the random-effects variance can be interpreted with a little more confidence as a measure of the variance (at patient level) in a response that is very approximately Normally distributed on the log-odds scale.

298
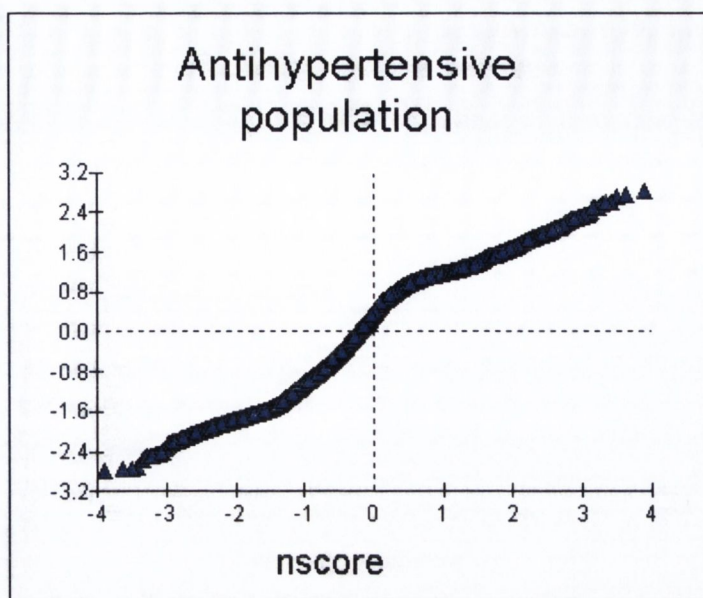
Figure 7.9 Normal probability plot for population model
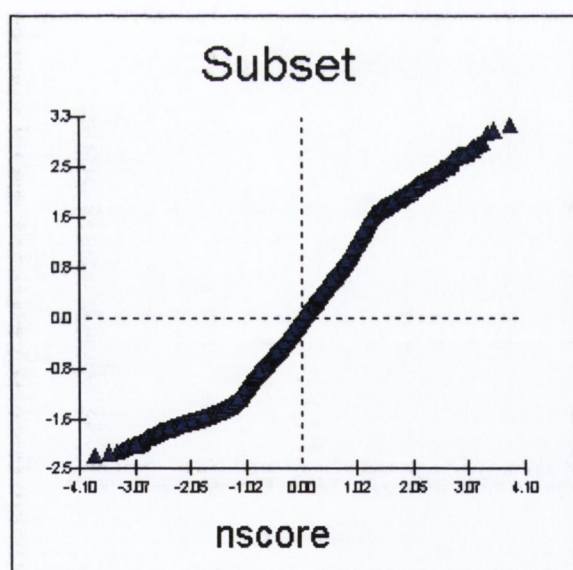
Figure 7.10 Normal probability plot for subset model

7.6 Multilevel competing-risks model for switching and discontinuing antihypertensives

I now consider a different type of episode of claiming within patients, where an episode is defined as a continuous period claiming the same therapy (regardless of changes of dose). Episodes of prescription claiming end when a patient either discontinues or changes to a different therapeutic regimen, whether by adding or subtracting antihypertensive drugs (as long as some antihypertensive is available). As there are a large number of antihypertensive drugs, there are many possible combinations of therapy. For instance, not differentiating between drugs within classes, there are 25 possible combinations of antihypertensive classes, ranging from monotherapies to a drug from each class.

Once again basing analysis on the cohort of 10,830 new users of antihypertensive therapies, discontinuation is defined as a break of one month with no therapy, and any change in drug prescription without discontinuation as a switch. Each patient may contribute multiple episodes of claiming. Patients may continue claiming their drugs, discontinue, or change the type of drug taken. Over the course of observation of this cohort, patients claimed 97,979 monthly prescriptions, of which 18,444 were the last prescription prior to discontinuation, and 6,263 were the last prescription prior to a switch.

Switching and discontinuation may be thought of as competing risks. I modelled the hazards of discontinuation and switching versus continuation using a multinomial model. These hazards are modelled in terms of duration of therapy and other covariates – age and

sex of the patient and type of antihypertensive drug. To allow for unobserved factors at patient level that influence the hazards of discontinuation and switching, random intercepts are included for each patient.

The model was estimated by penalised quasi-likelihood (PQL) and MCMC methods. After 200,000 iterations, the MCMC estimates appeared stable and were quite close to the PQL estimates. This indicates that the PQL estimates are not biased, which is useful as MCMC takes a long time to converge.

Table 7.6 gives the parameter estimates and standard errors for each type of outcome. Interpretation, as explained previously, is tentative, given possible problems with distributional assumptions.

Table 7.6 Parameter estimates (SE) for multilevel multinomial model for competing risks

	DISCONTINUE	SE	SWITCH	SE
VARIABLE				
constant	-2.159	0.050	-3.976	0.107
1 month	2.047	0.043	2.334	0.095
2-3 months	1.085	0.044	1.260	0.097
4-6 months	0.690	0.046	0.755	0.101
7-9 months	0.412	0.051	0.408	0.113
10-12 months	0.132	0.067	0.223	0.145
>12 months	0.000		0.000	
diuretic	0.000		0.000	
ACE	-0.404	0.032	-0.275	0.062
B-Blocker	-0.256	0.032	-0.217	0.062
CCB	-0.215	0.036	-0.320	0.072
ATII	-0.439	0.056	-0.190	0.106
A+D	-0.389	0.055	0.472	0.087
A+B	-0.792	0.058	0.174	0.091
A+C	-0.494	0.067	0.186	0.112
A+ATII	-1.070	0.228	1.299	0.203
B+C	-0.489	0.075	0.508	0.113
B+D	-0.304	0.075	0.294	0.088
B+ATII	-0.587	0.126	0.433	0.179
C+D	-0.436	0.077	0.393	0.119
C+ATII	-0.556	0.156	0.057	0.255
D+ATII	-0.526	0.092	0.393	0.143
> 3 drugs	-0.659	0.077	0.676	0.107
Female	-0.155	0.022	-0.008	0.042
Age	-0.212	0.012	-0.033	0.024
Age^2	0.189	0.011	-0.086	0.022

The random effects variance for discontinuation was estimated at 0.328 (SE 0.014) and the random effects variance for switching was estimated at 1.279 (SE 0.050). These are large and significant, indicating there is considerable variation between patients in the risk of

discontinuing and this is even more apparent for switching. The random effects covariance between the hazards of discontinuation and switching was –0.413 (SE 0.020). This indicates that the patients who are at high risk of switching are at low risk of discontinuing (and vice-versa). Switching and discontinuation are due to different underlying processes, being based on the choice of the doctor and the patient respectively.

Table 7.7 gives the conditional probabilities for discontinuation and switching by duration of the episode of claiming the same therapy. Patients are most likely to discontinue their therapies in the first few months of the episode. The probability of discontinuation in the first month is 0.37, while the probability of discontinuation after taking the drug for one year is quite low (0.08).

Table 7.7 Conditional probabilities of discontinuing and switching by duration

duration	Conditional Probabilities	
	discontinue	switch
1 month	0.372	0.045
2-3 months	0.194	0.022
4-6 months	0.143	0.015
7-9 months	0.115	0.011
10-12 months	0.096	0.010
13-18 months	0.081	0.008
19+ months	0.063	0.008

The risk of switching is quite small in comparison to the risk of discontinuation. Most switches occur during the first three months of an episode of claiming antihypertensive prescriptions.

303

As was found in previous models, men were at higher risk of discontinuing than women. However the risks of switching were no different between men and women. It is difficult to interpret these estimates as subject-specific effects, as an individual cannot change sex; they may be interpreted however as differences in the underlying propensities of men and women to discontinue. The higher risk of discontinuation in men may be because men are less likely to visit their doctors than women after they have been prescribed antihypertensives, or they may be less willing to follow treatment. However, there is no difference in switching rates between men and women, which may indicate that although men are more likely reject treatment, doctors are more likely to prescribe changes of therapy to those who seek to continue treatment for hypertension.

The relationships between age and the hazards of discontinuation and switching were quadratic, with patients in the middle of the age range being at lowest risk of discontinuing and at highest risk of switching. Younger and older patients were less likely to switch and more likely to discontinue. This may be due to less contact with doctors in younger and older age groups.

As previously, the parameter estimates for the explanatory variables indicating class of antihypertensives prescribed may not be interpretable due to correlations with the random effects. If this were not the case, we might say that patients claiming ACE inhibitors, beta blockers, calcium channel blockers and angiotensin-II antagonists were at lower risk of switching than if they had been claiming diuretics. Patients claiming combinations of drugs

were more likely to switch and less likely to discontinue than if they had been claiming single therapies.

Patients who discontinue are different to those who switch – that is, those who discontinue are unlikely to switch, and those who switch are unlikely to discontinue. Some patients appear particularly at risk of repeated switching, while others discontinue early and do not resume therapy. A large number of patients received only one prescription and thus contributed one episode of length one month with outcome discontinuation – these patients contributed no switches. The patients who were observed to switch therapy changed therapy without any break and were thus consistently claiming prescriptions of antihypertensives.

Sections 7.7 and 7.8 aim to throw more light on patterns of claiming antihypertensive prescriptions by including episodes of non-claiming in the prescription histories.

7.7   A multilevel multistate model for episodes of claiming and non-claiming antihypertensives.

Patients may be considered to move between states of claiming and non-claiming antihypertensive prescriptions. Here I jointly model the hazards of ending episodes of claiming (ie discontinuation of all antihypertensives) versus continuing claiming and ending episodes of non-claiming (ie re-starting) versus continuing in the state of non-claiming. As previously, discontinuation is defined by a break of one month with no antihypertensive

available. Hazards are modelled in terms of duration of the episode and other covariates (age, sex, and first drug claimed in the episode). Figure 7.11 illustrates how the hazards of claiming and non-claiming change over time. This shows that the hazard of re-starting declines more rapidly than the hazard of discontinuing. The hazard of re-starting is less than 0.05 after five months and continues to decrease thereafter. That is, patients who start a new therapy after a break are most likely to do so within the first few months of discontinuing. The same is true of discontinuation: most discontinuations occur within the first few months of an episode of claiming and the hazard of stopping to claim prescriptions quite small after a year of continuous antihypertensive claiming.
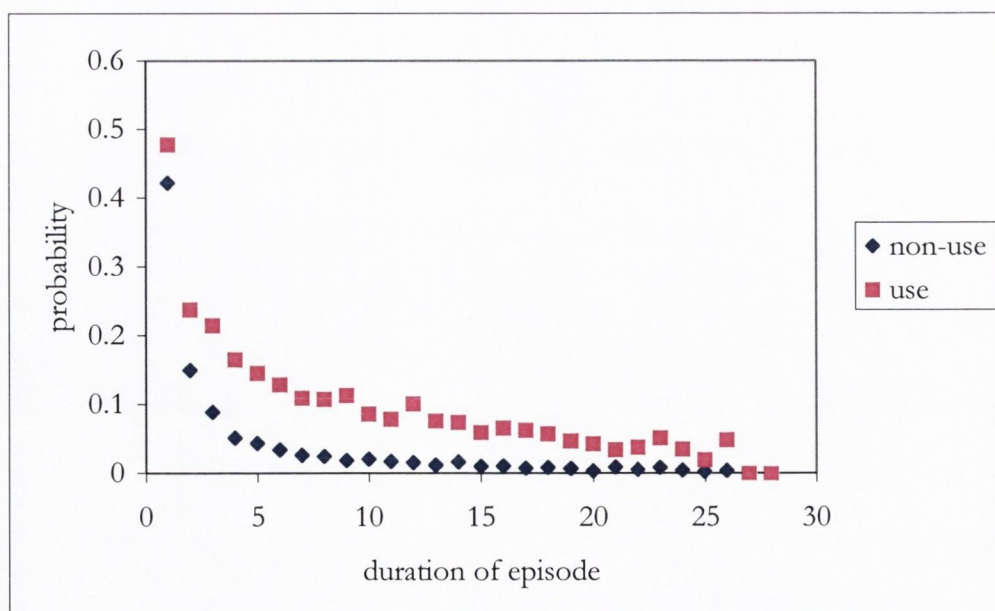
Figure 7.11 Observed hazards of ending episodes of claiming and non-claiming

antihypertensives

Here I give the results of fitting a multistate model for stopping episodes of claiming and resuming therapy after episodes of non-claiming in terms of covariates (Section 5.5.4). To allow for factors at patient level that influence the hazards of discontinuing and re-starting, I included random intercepts at patient level. Each patient has one random effect for episodes of claiming and one for episodes of non-claiming. The random-effects correlation models the within-patient dependencies between each type of risk. Parameter estimates for the multilevel multistate model are shown in Table 7.8. As previous sections have indicated that the distribution of the responses for the subset of patients who claim at least two prescriptions is closer to the distributional assumptions of the logistic model, I fit the multilevel multistate to this subset, with Binomial variance unconstrained.

Table 7.8 Parameter estimates for multilevel multistate model for transitions from claiming ->non-claiming and non-claiming->claiming for antihypertensives

	Claiming->non-claiming		Non-claiming->claiming	
VARIABLE	Estimate	SE	Estimate	SE
Intercept	-2.116	0.053	-2.466	0.068
Month 1	1.748	0.052	2.405	0.066
Month 2-3	1.006	0.053	1.205	0.068
Month 4-6	0.645	0.054	0.457	0.072
Month 7-9	0.412	0.059	0.412	0.059
Month 10-12	0.266	0.066	0.134	0.088
Month 13+	0			
Female	-0.059	0.024	0.213	0.038
Random				
Claiming	0.453	0.016		
Non-claiming	-0.565	0.020	1.168	0.038
Binomial	0.934	0.003		

The Binomial variance is quite close to one, thus giving little evidence for underdispersion as a result of clustering of the responses within patients. Thus the random-effects variances can be interpreted as a quantification of the influence of factors at patient level on their propensities to discontinue episodes of claiming and resuming therapy after episodes of non-claiming. The variance of the random effect for resuming therapy is particularly large, indicating the substantial influence that patient-level factors have on the propensity to resume therapy. The negative random-effects covariance indicates that patients who are likely to discontinue are unlikely to resume therapy and vice-versa – in other words, that patients tend to have long episodes of continuous claiming (and short episodes with no therapy) or long episodes without therapy (and short episodes with therapy).

7.8   A multilevel multistate competing-risks model for episodes of claiming and non-claiming antihypertensives

In the multistate model of the previous section an episode was defined as a continuous period of claiming (or non-claiming) any antihypertensive – that is, switches of therapy were ignored.   To gain a better understanding of the actual patterns of claiming including switching between antihypertensive classes, an episode is here taken (as in Section 7.6) to be a continuous period claiming the same antihypertensive therapy.   Any change of the type of claim, including addition, substitution or subtraction of drugs is now considered a switch, and the duration of each episode of claiming is calculated accordingly.   The identification of switches is illustrated in Figure 4.3.   Transitions from states of claiming and non-claiming are defined as in the previous section.

Thus there are two possible ways of ending an episode of claiming (switch or discontinue) and one way of ending an episode of non-claiming (resuming therapy).   The model for these joint responses is described in Section 5.5.4.   Here time is modelled as logarithmic, due to convergence problems with the stepwise model.   Parameter estimates, based on MQL methods, are given in Table 7.9.   While MQL estimates are evidently biased downwards for such models (Goldstein and Rasbash 1996), neither the PQL nor MCMC methods converged.

Table 7.9 Parameter estimates (SE) for multilevel multistate competing-risks model for

antihypertensive claiming patterns

VARIABLE	CLAIM->NO CLAIM (DISCONTINUE)	CLAIM->CLAIM OTHER THERAPY (SWITCH)	NO CLAIM -> CLAIM (RESUME)
Intercept	0.001 (0.034)	-1.846 (0.065)	-0.646 (0.039)
Duration	0.045 (0.005)	0.081 (0.001)	0.066 (0.005)
Log duration	-0.880 (0.021)	-1.259 (0.046)	-1.530 (0.026)
Female	-0.170 (0.022)	-0.018 (0.042)	0.276 (0.026)
Age 30-56	0.680 (0.030)	0.114 (0.061)	-0.668 (0.035)
Age 56-69	0.074 (0.029)	0.110 (0.055)	0.014 (0.035)
Age 69-76	-0.037 (0.029)	0.166 (0.054)	0.176 (0.036)
Age 76+	0	0	0
Statin	-0.330 (0.026)	-0.149 (0.049)	-0.056 (0.061)
ACE	-0.407 (0.032)	-0.300 (0.064)	
BB	-0.236 (0.032)	-0.209 (0.063)	
CCB	-0.206 (0.035)	-0.324 (0.073)	
ATII	-0.448 (0.055)	-0.235 (0.109)	
2 drug classes	-0.431 (0.031)	0.336 (0.057)	
3 drug classes	-0.477 (0.055)	0.648 (0.086)	
Diuretic	0	0	
Previous ACE			0.345 (0.038)
Previous BB			0.165 (0.037)
Previous CCB			0.188 (0.042)
Previous ATII			0.423 (0.071)
Previous 2 class			0.318 (0.040)
Previous 3 class			0.255 (0.077)
Previous diuretic			0
RANDOM:			
DISCONTINUE	0.480 (0.015)		
SWITCH	-0.468 (0.022)	1.401 (0.053)	
RESUME	-0.579 (0.016)	0.237 (0.028)	0.619 (0.022)

Duration of the episode has a significant effect on the risk of any type of outcome. The predicted probabilities of each type of event are plotted against time for the baseline patient

(male, aged over 76 years, treated with diuretic, not claiming statins) in Figure 7.12. Note these are not mean probabilities but the plot is useful to illustrate the pattern of the response. As can be seen from this plot, the risk of each type of event is highest in the first few months of the episode, but declines rapidly thereafter and reaches a fairly constant value of about 0.16 after twelve months for discontinuation and about 0.02 for switching and resuming therapy. The probabilities of switching therapy while in a state of claiming and resuming therapy from a state of non-claiming are very low after the first few months of the episode.
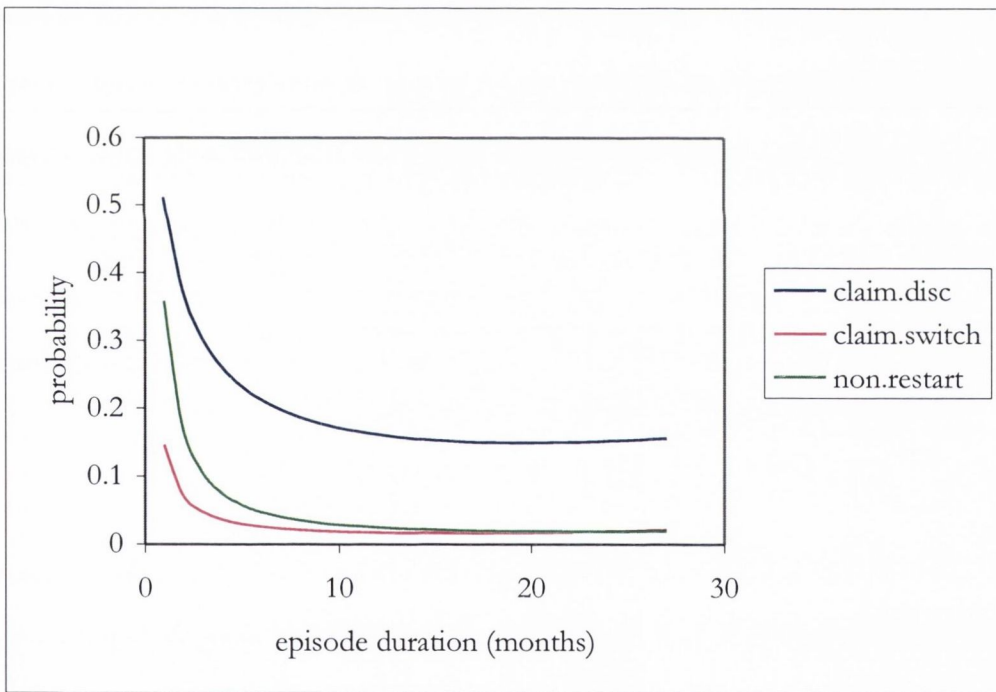
Figure 7.12 Predicted hazards of discontinuing, switching and resuming therapy for baseline patient (male, age>76, diuretic) (Random effects model)

A patient claiming statins was less likely to either discontinue or switch episodes of antihypertensive claiming than if he or she had not been claiming statins, but claiming statins had no effect on the subject-specific risk of resuming antihypertensive therapy after a break. Women were less likely to discontinue than men and more likely to resume therapy; however as in Section 7.6 there was no difference in switching rates. Younger patients were more likely to discontinue and less likely to resume therapy. The oldest age group (>76 years) was the least likely to switch therapy. A patient who was claiming ACE inhibitors, beta blockers, calcium channel blockers, ATII antagonists or a combination of drugs was less likely to discontinue than if claiming diuretics. However a patient claiming diuretics was more likely to switch than if claiming any other monotherapy. A patient claiming more than one therapy was more likely to switch than if claiming monotherapy – although switching could include discontinuing some class or classes of a combination, as long as at least one therapy were still claimed. A patients who had stopped claiming prescriptions and whose last claim had been an ACE, beta blocker, calcium channel blocker, ATII antagonist or a combination of drugs was more likely to resume therapy than if previously claiming diuretics.

Previous analysis (competing risks model) indicated that interactions between duration and type of prescription claimed were not significant, so these were not tested in this model.

Switching, discontinuing and resuming therapy are different processes. A change in prescription requires the involvement of a doctor, as does a resumption of therapy if this requires a new prescription. It is possible that resumption of therapy after short breaks might be entirely due to the patient (for instance failing to collect one or more monthly

312

prescriptions of a series and then resuming – it is common practice for doctors to write prescriptions to cover six months). Discontinuation could be the decision of either the patient or the doctor, but is more likely to be due to the patient, as withdrawal of antihypertensive therapy is not recommended, especially after short durations. In the multilevel model, a further level in the hierarchy, where patients are nested within GPs, could be included to estimate the GP-level and patient-level heterogeneity separately.

There are unobserved factors at patient level that have significant effects on the risks of stopping or switching episodes of claiming antihypertensives and resuming after breaks in therapy. The positive covariance between resuming therapy and switching indicates that patients who switch therapy are also likely to resume if they have breaks in therapy and vice-versa. That is, there are unobserved factors at patient level that affect the risks of both switching and resuming therapy after a break. The negative covariances of both switching and resumption of therapy with discontinuation indicates that patients who discontinue episodes of claiming are unlikely either to switch or resume therapy (and vice-versa). This supports the observation that many patients can be classified into one of two groups: they either have short episodes of claiming (ending in discontinuation) and long episodes with no therapy, or long episodes of claiming (and short episodes of non-claiming). Another group of patients have multiple short episodes of claiming different types of therapy, perhaps interspersed with short periods with no therapy available.

7.9 A multistate model for claiming ATII antagonists

The aim of this section is to model the transitions between different states of monthly antihypertensive drug prescriptions, where states are defined by being prescribed a specific drug (as monotherapy), prescribed different drugs, prescribed the specific drug as part of a combination, or prescribed no drugs.

A subset of patients initiating an ATII antagonist was selected and their subsequent prescriptions observed. This model may equally be applied to patients initiating any drug but here for simplicity a single drug was selected.

I identified patients in the ERHA area receiving prescriptions for ATII antagonists under the GMS scheme between August 1999 and December 2002. All such patients were included provided they could be matched to ERHA demographic data (giving dates of birth, dates of entry into and withdrawal from scheme, etc). Patients were excluded if they were observed for less than two months after taking their first ATII antagonist during the period August 1999-December 2002 (these patients made no transitions between states). Each patient contributed at least one monthly transition and up to 40 monthly transitions to the data set. These patients were not necessarily new to antihypertensive therapy. Rather than following new patients over the first few years of claiming antihypertensives, this model analyses

patterns of movement between different states of antihypertensive use in the population of patients with hypertension as a whole.

There were 3,547 patients identified who started an ATII antagonist with no other antihypertensives and 4,600 patients started an ATII antagonist with other antihypertensives. Other antihypertensives are ACE inhibitors, beta blockers, calcium channel blockers and thiazide diuretics.

A longitudinal prescription history was constructed for each patient showing monthly prescriptions during the observation period. Each patient was followed as long as observed after the first ATII antagonist (based on dates of entry into and withdrawal from the GMS scheme). Here the focus is on the patients starting an ATII antagonist alone.

The multistate model is illustrated in Figure 7.13. The ovals represent each of the four states in the model, and the arrows indicate transitions between states. In this model all possible transitions between states are allowed. There are no absorbing states (as may be analogous with death).

315

Figure 7.13 Multistate model for ATII claiming
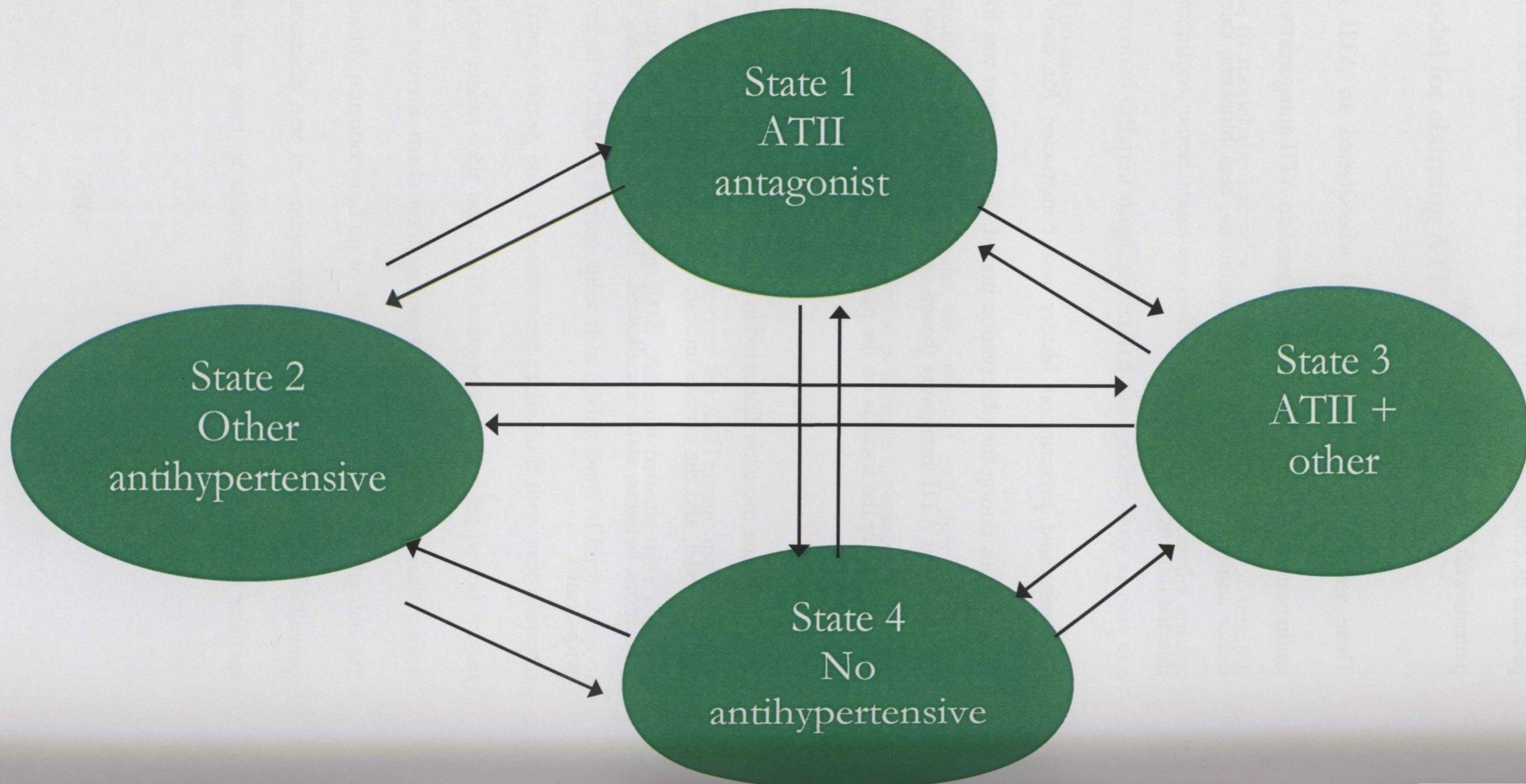
Figure 7.14 shows the numbers and proportions of transitions between each pair of states. The individual intensities given in Figure 7.15 are the instantaneous risks of moving from one state to another. This 4x4 transition intensity matrix is estimated by maximum likelihood. Transition intensities (at any point in time) are estimated given the Markov assumption that the current state determines the transition – that is, transitions are independent of the development of the process previous to the current state.

TO STATE ⟍ ⟍ FROM STATE	1 ATII	2 OTHER AHT	3 ATII +OTHER	4 NONE	TOTAL
1 ATII	22,915 (0.78)	426 (0.01)	1,041 (0.04)	5,139 (0.17)	29,521
2 OTHER AHT	124 (0.02)	4,864 (0.77)	278 (0.04)	1,059 (0.17)	6,325
3 ATII+OTHER	452 (0.06)	339 (0.04)	6,261 (0.78)	959 (0.12)	8,011
4 NONE	3,826 (0.19)	1,141 (0.06)	964 (0.05)	14,609 (0.71)	20,540

Figure 7.14 Numbers (and proportions) making transitions between states

Most monthly transitions were to the same state (70-80%). Of patients who had received no prescription, nearly 20% of monthly transitions were back to an ATII antagonist. Among patients claiming drugs, 16% of transitions were to no antihypertensive drugs. There were very few transitions from ATII to other antihypertensives or back to ATII after switching to other antihypertensives.

TO STATE FROM STATE	1 ATII	2 OTHER AHT	3 ATII +OTHER	4 NONE
1 ATII	-0.344 (0.004)	0.014 (0.001)	0.079 (0.002)	0.251 (0.004)
2 OTHER AHT	0.009 (0.002)	-0.429 (0.010)	0.145 (0.006)	0.274 (0.008)
3 ATII+OTHER	0.094 (0.004)	0.100 (0.004)	-0.342 (0.007)	0.148 (0.005)
4 NONE	0.304 (0.005)	0.083 (0.003)	0.022 (0.003)	-0.408 (0.005)

Figure 7.15 Estimated transition intensity matrix (SE)

318

The transition intensities may be interpreted as a comparison of risks of transitions to other states. Patients in state 1 (ATII antagonist) are more than three times as likely to receive no prescription the next month as receive ATII + other antihypertensives (0.251/0.079 = 3.18). Patients in state 2 (other antihypertensives, having started by taking an ATII) are nearly twice as likely to receive no prescription the following month as receive ATII + other antihypertensives (0.274/0.145 = 1.89).

The intensity ratio may be estimated between any pair of states. For instance, the ratio of progression rate from state 4 (no antihypertensives) to state 1 (ATII antagonist) to progression rate from state 1 to state 4 is 1.21 (SE 0.02) – that is, transition from no antihypertensives back to ATII is 1.2 times as likely as transition from ATII to no antihypertensives.

The probability matrix at a given time after the initial claim may be calculated as the matrix exponential of the intensity matrix multiplied by time. Table 7.10 gives the estimated probabilities of being in other states at three and six months after starting an ATII antagonist.

Table 7.10 Estimated probabilities of being in other states for patients starting ATII

	3 months	6 months
State1 (ATII)	0.50	0.40
State 2 (Other AHT)	0.06	0.10
State 3 (ATII+Other)	0.12	0.14
State 4 (None)	0.32	0.36

Duration in each state may be calculated by integrating the probability function over time. Table 7.11 shows the estimated duration in each state at given times (having started with an ATII antagonist). On average, in the first year after starting an ATII antagonist a patient will receive a prescription for an ATII antagonist for seven months and no prescription for four months. On average, in the first two years after starting an ATII antagonist a patient will receive a prescription for an ATII antagonist for thirteen months and no prescription for eight months. On average, in the first three years after starting an ATII antagonist a patient will receive a prescription for an ATII antagonist for twenty months and no prescription for twelve months.

Table 7.11 Estimated duration in each state at given times from initial claim

STATE	12 months	24 months	36 months
1 (ATII)	5.65	10.03	14.39
2 (other AHT)	1.00	2.43	3.85
3 (ATII+other)	1.52	3.40	5.29
4 (NONE)	3.84	8.14	12.47

The average length in months of a single stay in each state may be calculated. The average length of an episode in state 1 (ATII) was 2.91 months (SE 0.04), in State 2 (other drugs) 2.33 months (SE 0.05), in State 3 (ATII+other drugs) 2.93 months (SE 0.06) and State 4 (no antihypertensives) 2.45 months (SE 0.03).

Covariates may be included in the model (for example age, sex, daily dose, and these may be time-varying). Hazard ratios, odds ratios and mean duration times for fixed covariate values may then be estimated. The model may be extended to allow a larger number of possible states. States may be absorbing, that is transitions are not permitted from this state (for example define an absorbing discontinuation state by more than a year with no prescriptions). It may simplify the model estimation if certain transitions between transient states are not allowed – typically when observed number of transitions is small, for example between states 1 (ATII) and 2 (other drugs) in the model above.

The modelling approach introduced in this section provides an interesting way of visualising the data and of analysing specific claiming patterns. Here, for instance, we see that patients prescribed ATII antagonists are quite likely to continue claiming this drug, either alone or as part of a combination. They are, however, quite unlikely to be prescribed therapies that do not include an ATII antagonist. Further development of this approach may usefully answer other research questions about claiming patterns of interest.

7.10 Summary of models for antihypertensive claiming in the GMS

The initial models fitted in this chapter were very similar to those fitted in the chapter on statins; however as there are several different types of antihypertensive treatment a more informative model for patterns of claiming different drug classes was developed. As compliance is largely affected by the individual, the focus in this chapter was on developing multilevel models, allowing for multiple states and different types of transitions between states.

Many of the same problems encountered in modelling patterns of statin claiming were met here: for instance meeting the conditional distributional assumptions of the model; as for statins a binomial model may not be adequate – a mixture model may better describe the underlying distribution in a data set where many of the conditional responses do not change.

The models fitted for antihypertensives became increasingly complex, to allow for transitions from different states (claiming and non-claiming) in different ways (for instance by discontinuing or switching from claiming and by resuming therapy from non-claiming). In the multilevel multistate model there were problems with convergence and the only estimation method that produced results (MQL) is known to give biased estimates for this type of model. Further complexity – for instance by a multiprocess model to allow for the fact that there are factors at patient level that influence the type of drug prescribed and also influence the risk of discontinuation – or by including a further level in the model to allow for the fact that patients are nested within doctors – might answer substantive questions.

However it appears that these should be developed independently rather than included as extensions to an already complex model, thus adding to estimation difficulties.

The final model described in this section did not include random effects at patient level as this would have proven quite difficult to estimate using currently available software. It included because it gives a useful overview of claiming patterns for a specific class of antihypertensive; while for completeness it would be nice to determine the level of patient-level variability in these patterns this was not attempted due to problems estimating simpler models.

8.   Discussion

8.1   Medical background

Hypertension and high cholesterol are common conditions, the prevalence of which increase with age. They may be thought of as the initial stages of more serious cardiovascular and cerebrovascular diseases. They may be controlled by lifestyle modifications and/or treratment, which must be maintained indefinitely. Hypertension is influenced by several different mechanisms, and there are different types of drugs to control it – the main classes being ACE inhibitors, beta blockers, calcium channel blockers, thiazide diuretics and angiotensin-II antagonists. Indeed, the majority of cases of hypertension are controlled with combinations of therapies. High cholesterol may be controlled by treatment with statins or other lipid-lowering drugs.

There is a large base of evidence that demonstrates the benefits of controlling hypertension and cholesterol levels with pharmacological treatments. Treatment substantially and significantly reduces the risks of mortality and morbidity in people with hypertension and high cholesterol. However, population rates of control of these conditions are low, and rates of the consequential morbidity and mortality remain high – for instance, cardiovascular disease is the major cause of death in Ireland, and it is responsible for more bed-days in Irish hospitals than any other cause.

There are many factors that may explain the low rates of control of hypertension and high cholesterol. These may be divided into healthcare-system, patient, doctor and treatment factors; these factors interact to influence rates of control. Treatment guidelines or their implementation may be inadequate, and patients may fail to respond to treatment due to inefficacy or poor compliance. It is difficult to quantify the extent to which these factors affect control rates. Lack of compliance with treatment is often assumed to be the major contributing factor to low control rates, and while it is obvious that drugs that are not taken can have no effect, it has been suggested that improvements in the implementation of treatment guidelines would have a larger impact upon hypertension control rates and subsequent morbidity and mortality than would improvements in patients' compliance.

8.2   Estimating compliance

Many people, it would seem, are with Macbeth on medicines –

Throw physic to the dogs, I'll none o it

Failure to take prescriptions for whatever reason is very common. There has been a vast amount of research into all aspects of patients' compliance. Any attempt to estimate compliance must address certain issues. Foremost, is the study is observational or experimental – that is, a randomised controlled trial. Randomised controlled trials are often neither possible nor appropriate in studies of compliance. Observational studies have limitations due to differences in baseline characteristics do not make allowances for placebo

326

effects; these must be borne in mind when interpreting the results of the study (Grobbee and Hoes 1997, Grimes and Schulz 2002, Laupacuis and Mamdani 2004).

The next issue to address is the selection of patients. Patients should be comparable at baseline with respect to factors known to affect compliance. If patients are selected based on treatment (rather than, for instance, diagnosis) this must be borne in mind when interpreting the results. It is of particular importance to identify patients new to therapy to ensure baseline and subsequent comparability (duration of therapy is known to affect compliance). Other factors – for instance, evidence of comorbidities, should be controlled for by including them as possibly time-varying covariates in predictive models for compliance. This may not always be possible in observational studies. Once patients have been selected the study should include all patients on whom therapy was initiated to avoid selection bias.

The next issue to address is the measurement of compliance. All medicines that were taken should be observed and recorded. If possible, the method of measurement chosen should be validated by comparison with other methods. Outcome definitions (for instance medication possession ratio, persistence, and discontinuation) should be validated for the study population.

Ideally, analysis of the timing aspect of medication compliance should be incorporated in the definition of the response. Statistical methods are available to analyse outcomes within individuals over time.

Once compliance has been estimated and modelled in terms of covariates, interpretation of the findings should be made in terms of the type of study (experimental or observational), selection of the population, definitions, measurement, and method of analysis. It may not be appropriate to extrapolate the conclusions to other populations.

8.3   Previous studies

The review of studies that estimated compliance with antihypertensives and statins using prescription claims data showed that there is a wide variability in rates of non-compliance. Much of this variability is due to differences in definitions of the outcome measures and methods of analysis.

Due to the lack of comparability no meta-analysis, combining results from the various studies, was attempted. Some of the study populations had specific characteristics known to be associated with compliance (such as insurance cover). Compliance outcome measures were defined differently and estimated at different points in time. Some studies estimated the proportion of patients compliant, others estimated the proportion of compliance (generally based on the medication possession ratio). There were not a sufficient number of comparable studies to allow a standard meta-analysis. It is to be noted that DiMatteo et al (2002) carried out a meta-analysis of compliance and outcomes using a random-effects model to allow for the variability in the methods used by individual studies to estimate compliance.

328

Prescription databases give no information on the daily pattern of drug use. They only provide information on drug availability; patients are unlikely to continue collecting prescriptions if they have stopped taking their medicines, though without further measures of compliance in the particular problem the extent of this cannot be quantified. Prescription databases provide information on prescriptions collected but not what was actually prescribed by the doctor or consumed by the patient, so that for the assessment of compliance the assumption is that the medicine type and quantity received is exactly what was prescribed. In particular, it may not be valid to assume the daily dose prescribed.

When attempting to quantify compliance, the most appropriate use of these type of data is to ascertain discontinuations and changes of therapy. To do this, it is necessary that all prescriptions collected by the patient during the time of observation are included in the database. Analysis methods that allow for censored observations can be used to include information on patients who leave the scheme before the end of the observation period. There is less justification for using prescription databases to estimate percentage levels of patient compliance at a fixed time point. As it is typically estimated over a year, a percentage estimate of compliance takes no account of the longitudinal structure of the data – this approach effectively discards information about prescription claiming patterns over time. For example, an estimate of the compliance of a patient who fails to collect a prescription in the third, fifth and ninth months will be the same as for one who collects prescriptions continuously for nine months and then stops. The other problem with this approach is that patients who were not continuously observed until the chosen time point are excluded, which may lead to biased estimates.

Previous reviews of the assessment of compliance using prescription databases have made some important observations on the scope and limitations of this approach, which have often not been adequately addressed in subsequent studies (Steiner and Prochazka 1997; Payne and Esmonde-White 2000). Since these reviews were published further studies on the analysis of antihypertensive and statin prescription claims have been published and there have been advances in modelling of the data, notably the use of more sophisticated survival techniques such as the Cox proportional hazards model.

Methods of analysis that choose a single point in time for the outcome and require that all patients must be observed until this point may introduce selection bias and do not allow for any modelling of patterns of prescriptions claimed over time. Survival analysis methods model the time it takes for events (for example discontinuation of claiming therapy) to take place. An example of this is the Cox proportional hazards model, which was used in several of the studies reviewed here. An advantage of this method is that patients who were not observed over the entire follow-up time need not be excluded. But as noted in Chapter 3, the Cox model assumes proportionality of baseline hazards, which leads to problems in dealing with time-dependent covariates. Yang et al (2003) noted that factors during treatment rather than at baseline are important; however none of the studies that used Cox regression to model duration of prescription claiming in terms of covariates attempted to model the change in the effect of covariates over time. The Cox regression model also assumes continuous time, so that where prescriptions are dispensed monthly - that is, on a discrete-time basis - there may be problems dealing with multiple ties in the survival times – once again, all of the studies reviewed in Chapter 3 appear to have assumed prescription

times were continuous. A model allowing for discrete survival times is more appropriate for discrete-time data. Another limitation of this approach as used in the studies reviewed in Chapter 3 is that predicting the time to first discontinuation is of limited use where patterns of prescription claiming often include multiple episodes. Survival analysis methods can be extended to allow for this.

Many of the studies that estimate and analyse compliance with therapies using prescription claims data seem to rework the same ground without providing new insight and perhaps perpetuating the same flaws in design, analysis and interpretation. The contribution they make is to reinforce the point that non-compliance rates in many patient populations are very high. In future studies it would be useful to focus on appropriate design and analysis methods. The analyses used in previous studies do not make full use of the data available, and, in some cases, modelling strategies do not appear to be appropriate and the conclusions drawn may be unjustified.

One particular problem is that these studies analyse observational data and there are inherent biases associated with this - for example individual characteristics that may affect drug compliance may also have an association with the type of drug prescribed. This is not considered in most studies – for instance, the better compliance rates for ATII antagonists are attributed to characteristics of the drug rather than to characteristics of the patient who was prescribed the drug. In particular, the tolerability of ATII antagonists is used to explain higher rates of compliance in patients prescribed this rather than other antihypertensives. But the relationship between side effects and discontinuation is not fully understood and appears to depend upon context. According to a meta-analysis of clinical trials

approximately 3.1% of patients treated with ATII antagonists or diuretics will discontinue therapy due to adverse effects (Ross et al 2001); however in the observational studies examined in Chapter 3, 33%-67% of patients starting an ATII antagonist and 62%-79% of patients starting a diuretic had discontinued their initial treatment by the end of the first year. A Canadian study that followed 682 patients who were newly prescribed antihypertensives found that 62% reported side effects and 50% of these discontinued their initial therapy, in comparison with a 31% discontinuation rate amongst patients who did not report side effects (Gregoire et al 2002). A Japanese questionnaire-based study found 49% of patients with well-controlled blood pressure reported side effects with their antihypertensive medicines and found a statistically significant relationship between the number of reported side effects and noncompliance (Toyoshima et al 1997). But it has been observed elsewhere that patients who discontinue are less likely to respond to questionnaires (Suarez et al 2000), so that the results of this study should be interpreted with caution. Certainly it is known that polypharmacy increases the risk of adverse effects due to increased risk of drug interactions. It has been observed that patients who are more ill, and therefore prescribed more drugs, are also more likely to adhere with their treatment. This suggests a relationship between patients' level of illness and their perception of side-effects and willingness to endure them. There are many complex interacting factors that affect patient compliance; quantification of these remains a problem.

The results reported in the observational studies tabulated in Chapter 3 should be interpreted carefully in terms of context, patient and regimen selection, and definitions of compliance. There is a need for more sophisticated statistical modelling appropriate to the discrete-time longitudinal structure of the data. Given that prescription refills are effectively

332

repeated measures on individual patients, random effects models, incorporating patient-specific variability, may give further insights into the patterns of antihypertensive and statin prescription claiming at the individual level (Goldstein 2003).

8.4   Modelling approaches and results

Data from the General Medical Services Board were used to construct longitudinal antihypertensive and statin prescription claiming histories between August 1999 and December 2002 for patients in the Eastern region. Analyses were based on cohorts of 10,830 patients newly prescribed antihypertensives and 6,094 patients newly prescribed statins.

In view of the limitations of previous research on compliance using prescription claiming data, this thesis set out to develop suitable modelling strategies to describe compliance.

The data may be viewed as either repeated measures – that is, monthly observations of prescription claims, or as event histories – that is, duration to an event, for instance discontinuation of therapy. Marginal models give an overview of the average response in terms of covariates, but do not model the dependencies between responses from individual patients. Multilevel (or random effects) models quantify the variance in the response due to unobserved patient-level factors. However interpreting the estimated random effects variance can be problematic if the distributional assumptions of the model are not

appropriate. In all the models fitted in Chapters 6 and 7 the patient-level variance was found to be significant, after controlling for time, age, sex and other covariates.

An understanding of patterns of claiming statin prescriptions at patient level may be useful in devising strategies to enhance continuous use of therapy. Identification of individual patients at high risk of discontinuation would enable the timely targeting of strategies to enhance their compliance.

For efficient use of resources in promoting the continuous use of statin therapy by patients with high cholesterol levels, we need to be able to characterise the individual patients who are most likely to give up. The findings of the multilevel models reveal that even after controlling for patient-level variables that are available in the GMS data, unobserved factors at patient level have a large effect on the patterns of claiming statin prescriptions.

The multilevel models show that after allowing for covariates, typically one half of the variance in the probability of claiming statin prescriptions is due to unobserved patient-level factors. This highlights the importance of identifying individual factors that increase the risk of stopping therapy. Research has identified patient, doctor and treatment factors as barriers to continued use of statins (See Chapter 2). The findings of these multilevel models suggest that resources to encourage the continued collection of prescriptions should be targeted at patients who show early signs of discontinuation and these resources should address the issues identified that might be preventing individual patients from continuing to claim (and use) their prescriptions.

It may be useful to compare the results of modelling statin claiming patterns with those of modelling antihypertensives. In some ways these patterns appear very similar; and similar modelling strategies are appropriate. For instance, the pattern of statin availability over time appears very similar to what is seen for antihypertensives, although the rate of statin claiming is higher.

It is evident that consistent previous claiming of antihypertensive prescriptions in individuals is perhaps the strongest predictor of continued claiming. From Section 7.4.3, an individual who has previously claimed a prescription every month since the one after the incident prescription will have a high probability of claiming the next antihypertensive prescription, regardless of how long it is since therapy was initiated. Missing one or more months' claims at any time, though still claiming at least one prescription after the incident one, approximately halves the probability of making a claim the following month – this, too, remains fairly constant over time. If the patient has claimed no antihypertensives since the first then the probability he or she ever claims another prescription during the next two years is always close to zero. The message, perhaps, is that patients who establish the habit of claiming repeat prescriptions by claiming during the month after they were initially prescribed antihypertensives are much more likely to continue claiming (and using therapy).

There are several limitations to this study, partly due to the nature of the data and the task attempted, and partly due to the models chosen. Compliance is notoriously difficult to assess and using prescription claims to do this is open to question, despite the fact that this has been validated in comparison to other forms of measurement (for example electronic monitoring). The data are observational and interpretation should be made bearing this in

mind – in particular, therapies are not randomly assigned to patients and it is therefore inappropriate to attribute better compliance solely to the attributes of different classes of drugs. Another limitation is due to the fact that responses are mostly binary – patients who continuously claim their therapies (or continuously fail to claim them) repeatedly have the same response, effectively contributing no information about variability at the individual level and perhaps invalidating distributional assumptions of the random effects logistic model. In this case it would appear that the marginal model by GEE, which makes no distributional assumptions at individual level, would be preferable, although this runs into difficulties if data are missing conditional on the values of previous responses – a situation that can easily occur in longitudinal studies. It might seem appropriate to fit a random-effects mixture distribution to allow for individuals who repeatedly have the same response. However in practice such models may have problems with convergence and their estimates may be quite similar to the estimates from the standard logistic model.

Any model is merely a representation – some may describe and simplify the problem in a better way than others. This thesis aimed to use models for compliance that may better describe the patterns of drug claiming, at both population and patient levels, than have previously been used in this context. There are many possible further refinements and developments of the models used here. Further factors and relationships might be usefully explored. Mixture models and further development of the hierarchical structure via introduction of random effects at higher levels (for instance at the level of the doctor) may be two of the most appealing developments.

Appendix: ATC codes, indications, ADR

ATC	name	treat	side effects
B01AC06	**aspirin low dose (75-100 mg)** post MI or stroke		irritate lining of stomach, causing indigestion, stomach pain, nausea and vomiting, and (rarely) gastrointestinal bleeding. Rashes, wheezing, or breathing problems may develop in people who are allergic to NSAIDs
C01AA	**cardiac glycosides**		
C01AA05	**digoxin**	CHF, atrial fibrillation	nausea, vomiting, loss of appetite, diarrhoea, confusion, visual disturbance, and arrhythmias
C01DA	**organic nitrates**		
C01DA02	glyceryl trinitrate	angina	headache, flushing, and dizziness, fainting
C01DA05	pentaerythritol tetranitrate	angina	headache, flushing, and dizziness, fainting
C01DA08/14	isosorbide (mono+dinitrate)	angina, CHF (with diuretics+cardiac glycosides)	headache, flushing, and dizziness, fainting
C03AA	**Thiazides**		
C03AA01	bendroflumethiazide	oedema, hypertension	weakness, lethargy, cramps, dizziness, gastrointestinal upsets, rashes, photosensitivity, anorexia, reversible impotence, blood disorders, and pancreatitis
C03AA02	hydroflumethiazide	oedema, hypertension (with spironolactone)	see bendroflumethiazide
C03AA03	hydrochlorothiazide	oedema, hypertension, recurrence of kidney stones	see bendroflumethiazide
C03AA04	chlorothiazide	oedema, hypertension	see bendroflumethiazide
C03AA05	polythiazide	oedema, hypertension	see bendroflumethiazide
C03AA07	cyclopenthiazide	oedema, hypertension	see bendroflumethiazide
C03BA	**Other low-ceiling diuretics**		
C03BA04	chlorthalidone	oedema, hypertension	see bendroflumethiazide
C03BA05	mefruside	oedema, hypertension	see bendroflumethiazide
C03BA08	metolazone	oedema, hypertension	see bendroflumethiazide
C03BA10	xipamide	oedema, hypertension, more potent than most thiazide	see bendroflumethiazide
C03BA11	indapamide	hypertension	headache, dizziness, fatigue, and muscle cramps due to K loss

ATC	name	treat	side effects
C03D	**Potassium-sparing diuretics**		
C03DA01	spironolactone	oedema, CHF, kidney disorders,primary hyperaldosteronism	nausea, vomiting, muscle weakness and numbness, in men breast enlargement and reversible impotence. Menstrual irregularities, diarrhoea, headache, confusion, rash
C03DB01	amiloride	oedema, hypertension	muscle weakness and abnormal heartbeat. Nausea and gastrointestinal upsets
C03DB02	triamterene	oedema	
C07AA	**beta blockers (noncardioselective)**		
C07AA02	oxprenolol	arrhythmias, angina, anxiety, hypertension (modified release)	see acebutolol
C07AA03	pindolol	angina, hypertension	see acebutolol
C07AA05	propanolol	arrhythmias, angina, hypertension, migraine, after MI	see acebutolol
C07AA06	timolol	arrhythmias, angina, glaucoma, migraine, after MI	see acebutolol
C07AA07	sotalol	arrhythmias (noncardioselective); also class III anti-arrhythmic	see acebutolol
C07AA12	nadolol	arrhythmias, angina, migraine, hypertension (with diuretic)	see acebutolol
C07AA16	tertatolol		
C07AB	**beta blockers (cardioselective)**		
C07AB02	metoprolol	arrhythmias, hypertension, angina, after MI	see acebutolol
C07AB03	atenolol	arrhythmias, angina, hypertension	see acebutolol
C07AB04	acebutolol	arrhythmias, angina, hypertension	reduced tolerance of exercise, tiredness, cold hands/feet, impotence, strange dreams, constrict airways.
C07AB05	betaxolol	hypertension, glaucoma	see acebutolol
C07AB07	bisoprolol	angina	see acebutolol
C07AB08	celiprolol	hypertension	see acebutolol
C07AB09	esmolol	arrhythmias, hypertension intravenous post surgery	see acebutolol
C07AB12	nebivolol		

ATC	name	treat	side effects
C07AG	**alpha and beta blockers**		
C07AG01	labetalol	hypertension (alpha + beta blocker)	low blood pressure on standing, tiredness, weakness, headache, rash, tingling of the scalp, difficulty in passing urine, stomach pain, nausea, vomiting, and liver damage
C07AG02	carvedilol	hypertension, angina, chronic HF (alpha + beta blocker)	low blood pressure on standing, dizziness, headache, fatigue, gastrointestinal upsets, and a slow heart rate
C08CA	**Selective calcium channel blockers, vascular effects**		
C08CA01	amlodipine	angina, hypertension	see nifedipine
C08CA02	felodipine	hypertension	see nifedipine
C08CA03	isradipine	hypertension	see nifedipine
C08CA04	nicardipine	stable angina, hypertension	see nifedipine
C08CA05	nifedipine	angina, hypertension, Raynaud's condition	dizziness, fainting, headaches, flushing, ankle oedema, palpitations
C08CA06	nimodipine	prevent spasm of arteries after subarachnoid haemorrhage	low blood pressure, flushing, headache, gastrointestinal upset
C08CA07	nisoldipine	stable angina, hypertension	see nifedipine
C08CA09	lacidipine	hypertension	see nifedipine
C08CA10	nilvadipine		
C08CA13	lercanidipine	hypertension	see nifedipine
C08D	**Selective calcium channel blockers, cardiac effects**		
C08DA01	verapamil	angina, hypertension, supraventricular tachycardia	constipation,dizziness, fainting, headaches, flushing
C08DB01	diltiazem	angina; hypertension in long-acting formulation	dizziness, fainting, headaches, flushing
C09AA	**ACE inhibitors**		
C09AA01	captopril	heart failure (+diuretics), hypertension, kidney disease in diabetics	blood pressure drops too fast, headache, skin rash, dry cough. Nausea, muscle cramps, sore throat, impaired kidney function
C09AA02	enalapril	heart failure (+diuretics), hypertension	see captopril
C09AA03	lisinopril	heart failure (+diuretics), hypertension, after MI reduce recurrence	see captopril
C09AA04	perindopril	heart failure (+diuretics), hypertension	see captopril
C09AA05	ramipril	heart failure (+diuretics), hypertension, after MI	see captopril

ATC	name	treat	side effects
C09AA06	quinapril	heart failure (+diuretics), hypertension	see captopril
C09AA07	benazepril		
C09AA08	cilazapril	heart failure (+diuretics), hypertension	see captopril
C09AA09	fosinopril	heart failure (+diuretics)	see captopril
C09AA10	trandolapril	heart failure (+diuretics), hypertension, after MI	see captopril
C09AA13	moexipril	hypertension	see captopril
C10AA	**statins**		
C10AA01	simvastatin	primary hypercholesterolaemia, atherosclerosis in CAD	
C10AA03	pravastatin	primary hypercholesterolaemia, atherosclerosis in CAD	
C10AA04	fluvastatin	primary hypercholesterolaemia	
C10AA05	atorvastatin	primary hypercholesterolaemia	reversible muscle inflammation and rhabdomyolysis, headache, abdominal pain, nausea, and vomiting
C10AA06	cerivastatin	primary hypercholesterolaemia	

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343

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