ADHERENCE TO SECONDARY PREVENTION MEDICINES BY CORONARY HEART DISEASE PATIENTS

R. KHATIB

DPharm

2012

ADHERENCE TO SECONDARY PREVENTION MEDICINES BY CORONARY HEART DISEASE PATIENTS

First **R**eported **A**dherence vs. **N**on-adherence **I**nvestigation (**RANI-1**)

Rani KHATIB

Submitted for the degree of
Doctor of Pharmacy

Pharmacy Department

University of Bradford

2012

Abstract

Adherence to Secondary Prevention Medicines by Coronary Heart Disease Patients
Rani Khatib, Doctor of Pharmacy

Keywords: Patient compliance, concordance, heart disease, angina, self-reported medicines adherence, medicines adherence assessment, shared decision making.

Background
Non-adherence to evidence based secondary prevention medicines (SPM) by coronary heart disease (CHD) patients limits their expected benefits and may result in a lack of improvement or significant deterioration in health. This study explored self-reported non-adherence to SPM, barriers to adherence, and the perception that patients in West Yorkshire have about their medicines in order to inform practice and improve adherence.

Methods
In this cross-sectional study a specially designed postal survey (The Heart Medicines Survey) assessed medicines-taking behaviour using the Morisky Medicines Adherence 8 items Scale (MMAS-8), a modified version of the Single Question Scale (SQ), the Adherence Estimator (AE), Beliefs about Medicines Questionnaire(BMQ) and additional questions to explore practical barriers to adherence. Patients were also asked to make any additional comments about their medicines-taking experience. A purposive sample of 696 patients with long established CHD and who were on SPM for at least 3 months was surveyed. Ethical approval was granted by the local ethics committee.

Results
503 (72%) patients participated in the survey. 52%, 34% and 11% of patients were prescribed at least four, three and two SPMs respectively. The level of non-adherence to collective SPM was 44%. The AE predicted that 39% of those had an element of intentional non-adherence. The contribution of aspirin, statins, clopidogrel, beta blockers, angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) to overall non-adherence as identified by the SQ scale was 62%, 67%, 7%, 30%, 22% and 5%, respectively. A logistic regression model for overall non-adherence revealed that older age and female gender were associated with less non-adherence (OR = 0.96, 95% CI: 0.94, 0.98; OR = 0.56, 95% CI: 0.34, 0.93; respectively). Specific concern about SPM, having issues with repeat prescriptions and aspirin were associated with more non-adherence (OR = 1.12, 95% CI: 1.07, 1.18; OR = 2.48, 95% CI: 1.26, 4.90, OR = 2.22, 95% CI: 1.18, 4.17). Other variables were associated with intentional and non-intentional non-adherence. 221 (44%) patients elaborated on their medicines-taking behaviour by providing additional comments about the need for patient tailored information and better structured medicines reviews.

Conclusions
The Medicines Heart Survey was successful in revealing the prevalence of self-reported non-adherence and barriers to adherence in our population. Healthcare professionals should examine specific modifiable barriers to adherence in their population before developing interventions to improve adherence. Conducting frequent structured medicines-reviews, which explore and address patients' concerns about their medicines and healthcare services, and enable them to make suggestions, will better inform practice and may improve adherence.

Acknowledgements

I would like to thank all the patients who made it possible for this study to be conducted.

I am also indebted to all members of the Cardiovascular Research Unit at the Leeds Teaching Hospitals NHS Trust, for their generous help and support in conducting this study. My clinical supervisor Professor Alistair Hall has been an inspiration and taught me a great deal about passion for research.

My supervisors Professor Kay Marshall and Dr. Jon Silcock have provided invaluable support which I am most grateful for.

I would also like to thank the Pharmacy Department at the Leeds Teaching Hospitals NHS Trust for giving me the opportunity to undertake this work. My thanks also go to my colleagues at the Medicines Management Academic Unit, University of Leeds.

My words can never express thankfulness to my wife Asmaa for her endless love, support and patience throughout my DPharm and beyond.

This work is dedicated to my parents who always drove me to excel in my studies, my beloved wife Asmaa and my beautiful children Uns, Marjan, Jana and Raihana.

Dissemination

This research and various aspects of it have been published and presented at the following conferences and meetings:

- Khatib R & A Hall. 2012. *Adherence to Secondary Prevention Medicines by Coronary Artery Disease Patients - Exploring Barriers to Inform Interventions.* Moderated Poster Presentation at The American College of Cardiology Conference. March 2012. Chicago, USA.

- Khatib R & A Hall. 2012. Adherence to Secondary Prevention Medicines by Coronary Artery Disease Patients - Exploring Barriers to Inform Interventions*. Journal of American College of Cardiology* 59(13); A358.

- Khatib R, A. Hall, C. Morrell, C. Forrest, J. Silcock and K. Marshall. 2012. *Adherent and Non-adherent Coronary Heart Disease Patients' Perceptions About Medicines and Healthcare Services*. Moderated Poster Presentation at The European Society of Cardiology – European Society of Cardiology, EuroPRevent 12 Conference. May 2012. Dublin, Ireland.

- Khatib R, A. Hall, C. Morrell, C. Forrest, J. Silcock and K. Marshall. 2012. Adherent and Non-adherent Coronary Heart Disease Patients' Perceptions About Medicines and Healthcare Services. *European Journal of Cardiovascular Prevention & Rehabilitation* 19(Supp1); S59.

- Khatib R, Waterman E, Acomb C, Lad J, Moran J and Y Tariq Y. 2011. Assessment of Medicines Adherence by Primary and Secondary Care Pharmacists in Yorkshire and Humber – a survey. *Clinical Pharmacist* Supplement 2; S42 – S43.

- Khatib R. 2012. *Keynote Lecture on Factors Affecting Patient Adherence – The Patient Perspective, The medicines-taking behaviour of coronary heart disease patients*. International Patient Adherence Conference, Abu Dhabi, United Arab Emirates. 18th Feb 2012. Invited International Speaker.

- Khatib R. 2012. *Workshop on Assessing Adherence*. West Yorkshire Pharmacy Practice Conference, Brighouse, UK. 26th Feb 2012. Invited Expert Speaker.

This research also informed the following scholarly activities:

- Khatib R. 2011. *United Kingdom Clinical Pharmacy Association Stake Holder Feedback on Review of National Institute for Health and Clinical Excellence (NICE) Clinical Guideline (CG76) – Medicines Adherence*. Aug 2011.

- Khatib R. 2011. *Seminar on Assessing Adherence in Practice*. Developing partnerships with medicine-takers (HECS 5150M) Module. Postgraduate Masters in Pharmacy Practice. University of Leeds. 11th May 2011.

Table of Contents

List of Tables and Figures

TABLES

FIGURES

Glossary of Abbreviations

AACTG	Adult AIDS Clinical Trial Group
ACEI	Angiotensin Converting Enzyme Inhibitors
ADHERE study	Adherence to Drugs Having Evidence of Real Effectiveness
AE	Adherence Estimator ™
ARBs	Angiotensin Receptor Blockers
ARMS	Adherence to Refills and Medications scale
ASRQ	Adherence Self-Report Questionnaire)
BEMIB	Brief Evaluation of Medication Influences and Beliefs scale
BHF	British Heart Foundation
BMQ	Belief about Medicines Questionnaire
BrMQ	Brief Medication Questionnaire
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CHD	Coronary heart disease
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
ENCOURAGE	Epidemiology of Northern Cardiovascular Outcomes and Underlying Risk of Atherosclerosis due to Genes and Environment
GP	General Practitioner
HF	Heart Failure
HIV	Human Immunodeficiency Virus
LDL	Low Density Lipoproteins
HLT	Hosmer and Lemeshow Test
LTHT	Leeds Teaching Hospitals NHS Trust
LVD	Left Ventricular Dysfunction
MARS	The Medication Adherence Report Scale
MEMS®	Medication Events Monitoring System
MI	Myocardial Infarction
MMAS-8	The 8-item Morisky
MOS	Medical Outcome Study
MPK	Medical Prescription Knowledge questionnaire
MTQ	Medication-Taking Questionnaire
MUAH	Maastricht Utrecht Adherence in Hypertension questionnaire
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
PACTG	Paediatric AIDS Clinical Trial Group
PCI	Percutaneous Coronary Intervention
Q	Quartile – Q1 = first quartile, Q3 = third quartile
Qn	Question
RANI-1	First Reported Adherence vs. Non-adherence Investigation
r_p	Pearson's correlation coefficient
r_s	Spearman's correlation coefficient
SE	Standard Error
SQ	The Single Question Scale by Gehi et al. (2007).
VAS	Visual Analogue Scale
WHO	World Health Organisation
κ	kappa coefficient

1 Introduction

This chapter will set the scene for this research and elaborate on the rationale behind choosing medicines adherence to secondary prevention medicines in coronary heart disease.

1.1 Setting the scene for this research

One of the most common interventions in healthcare is the prescribing of medicines. The total cost of dispensed prescriptions for the National Health Service (NHS) in England in 2010 was £12.9 billion and around 32% of this use was in hospitals (The Health and Social Care Information Centre, 2010). Nearly 927 million prescription items were dispensed in the community in England in 2010 (The Health and Social Care Information Centre, 2011). Optimal use of this intervention requires the appropriate prescribing of evidence-based medicines with the aim of maximising patient benefit and minimizing harm. However, for medicines to deliver benefit they need to be taken in accordance with agreed directions according to best available evidence. The term used to describe patients' medicines-taking behaviour is called *medicines adherence* and is defined as: the extent to which a person's behaviour – of taking medicines – corresponds with agreed recommendations from a healthcare provider (WHO: World Health Organisation, 2003; Horne et al., 2005; NICE: National Institute for Health and Clinical Excellence, 2009). In the last decade there has been a transition from the use of the term 'compliance' to 'adherence' to reflect the patient involvement and agreement with the recommendations made by the prescriber (NICE, 2009). While

some literature distinguishes between taking medicines as agreed and prescribed e.g. *40mg twice a day* (adherence), and continuing to take it as prescribed (persistence) others consider adherence to mean both (Ho et al., 2009). In the UK, the term adherence is the currently recommended term (NICE, 2009).

In recent years, many reports and publications have targeted the topic of medicines adherence. This interest is due to the association of medicines non-adherence with: increased health care spending, high readmission and hospitalisation rates, higher morbidity and mortality (Sherbourne et al., 1992; Osterberg & Blaschke, 2005). In 2009, the National Institute for Health and Clinical Excellence (NICE) issued its guidance on medicines adherence in which it estimated that between a third and a half of all medicines prescribed for patients with long-term conditions are not used as recommended (NICE, 2009). Non-adherence to evidence-based medicines limits the potential benefits and so may result in a lack of improvement or significant deterioration in health. Deterioration of patients' health necessarily increases the demands for healthcare, which together with wasted medicines, also has significant economic consequences. The current cost of unused or unwanted medicines is estimated to exceed £300 million per year in England alone (Traueman et al., 2010). Non-adherence is cited as one of the reasons for this avoidable cost (Traueman et al., 2010). Non-adherence is therefore an important issue that needs to be considered and addressed during the provision of healthcare services.

Healthcare professionals have the responsibility of ensuring that patients continue to derive the best from their medicines after they are prescribed and therefore the review of medicines adherence and factors that can influence it should be integrated

into healthcare practice and specifically medicines reviews or pharmaceutical care (Clyne et al., 2008; NICE, 2009). This is particularly important to patients with chronic conditions who are expected to take their medicines long term, and in most cases for the rest of their lives.

Of all the long-term conditions, cardiovascular disease (CVD) is the main cause of death in the UK and almost half of CVD deaths are from coronary artery disease (CAD)[*] (BHF: British Heart Foundation, 2010). In England, around 266 million prescriptions were issued for the treatment of CVD in 2008 (BHF, 2010). The increase of mortality and morbidity due to medicines non-adherence in patients with CVD has been demonstrated in several studies (Horwitz et al., 1990; Blackburn et al., 2005; Rasmussen et al., 2007).

The Leeds Teaching Hospitals NHS Trust (LTHT) cardiology service is one of the largest in the country providing secondary and tertiary care to the West Yorkshire region (LTHT, 2011). Large numbers of patients with CAD visit the LTHT on a daily basis. This provides healthcare professionals, including clinical pharmacists, with an excellent opportunity to optimise patients' medicines. One aspect of medicines optimisation not formally addressed at LTHT is the issue of medicines non-adherence. The most frequently prescribed cardiovascular medicines are CAD secondary prevention medicines (see Section 1.3). These medicines tend to be prescribed for life and their benefit in reducing mortality and morbidity are well established (NICE, 2007; Gibbons et al., 2007).

[*] The terms Coronary Artery Disease (CAD) and Coronary Heart Disease (CHD) are used interchangeably in this thesis and are assumed to mean the same, although CHD can be due causes other than atherosclerosis (CAD) such as coronary vasospasm.

As experts on medicines, clinical pharmacists have a central role to play in medicines optimisation. A research project was developed to explore adherence to CAD secondary prevention medicines, to design interventions to address non-adherence and to test their effectiveness in a randomised controlled trial. This project was later called the ADHERE study (**A**dherence to **D**rugs **H**aving **E**vidence of **R**eal **E**ffectiveness - A randomised controlled trial of structured pharmacist-led review of heart medicines as compared to usual-care for patients with established coronary artery disease). See Figure 1.1 for a summary which describes the stages of the ADHERE study.

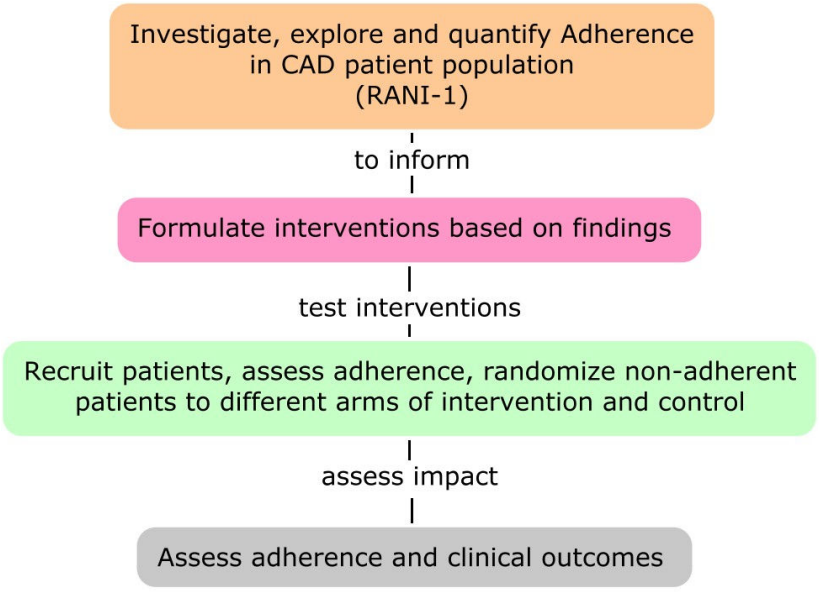

Figure 1.1 – Description of the stages of the ADHERE study (Adherence to Drugs Having Evidence of Real Effectiveness) and how the research idea came about. **CAD** = Coronary Artery Disease, **RANI-1** = First Reported Adherence vs. Non-adherence Investigation.

NICE and World Health Organisation (WHO) reviews of medicines adherence highlight the complexity and multidimensionality of the causes of non-adherence (WHO, 2003; NICE, 2009). They emphasise that addressing the issue of non-adherence requires an understanding of patients' perspectives of medicines and the reasons behind why they may not want or are unable to use them effectively (NICE, 2009). Therefore, stage one

of the ADHERE study was designed to explore non-adherence behaviour among the LTHT's CAD population and to quantify the level of non-adherence to inform any future interventions. In order to be able to measure the impact of any intervention, it was necessary to identify suitable tools to assess adherence.

After conducting a full literature review and following discussions with various health professionals in the cardiology team, it was identified that non-adherence to secondary prevention medicines among our CAD population in West Yorkshire had not been explored previously. With regards to adherence assessment tools, none were in use in the Trust. The researcher also surveyed current practice around adherence assessment in Yorkshire and Humber in primary and secondary care in order to identify any assessment tools in use. Fourteen out of sixteen hospital NHS Trusts in Yorkshire and Humber completed the questionnaire and 28 out of approximately 150 community pharmacies (Khatib et al., 2011). Despite good awareness of the NICE guidelines on adherence among respondents, none of them reported the formal use of validated tools to measure adherence in routine practice (Khatib et al., 2011).

Based on the above findings the First Reported Adherence vs. Non-adherence Investigation (RANI-1) was conducted (ADHERE Stage 1). The investigation of medicines non-adherence to secondary prevention medicines by CAD patients in West Yorkshire and nearby areas will be reported in this research study in order to inform practice and enable the design of suitable interventions that can be tested in later stages of the ADHERE study.

1.2 Why coronary artery disease?

CAD or coronary heart disease (CHD) is an obstruction or narrowing in the arteries supplying blood to the heart muscle due to, mainly, atherosclerosis (deposits of plaque inside the arteries) (Kumar & Clark, 2009; Nabel & Braunwald, 2012). Patients with CAD may be diagnosed with, for example, angina pectoris, myocardial infarction (MI), unstable angina or silent myocardial ischaemia. In addition to medical treatment, some patients may have additional interventions for their CAD such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

CAD is a major cause of death and disability in the developed world and despite the decrease in the death rate from CAD over the last 4 decades, the UK death rate from CAD remains high compared to other Western European Countries, with nearly 88,000 deaths per year (NICE, 2007; BHF 2010). In England around 2 million people have or have had angina and around 62,000 men and 39,000 women suffer a heart attack every year (BHF, 2010; NICE, 2011). Every six minutes someone dies of a heart attack in the UK (BHF, 2010). Based on the Framingham Heart Study, at the age of 40 years, it is estimated that the life-time risk for developing CAD is 1 in 2 for men and 1 in 3 for women (Lloyd-Jones et al. 1999). Apart from the high risk of death, CAD negatively impacts on patients' quality of life, employment and personal relationships (DoH: Department of Health, 2000).

It is estimated that CAD costs the UK economy approximately £9billion a year (BHF, 2010). This total cost can be divided as follows: 36% due to direct healthcare costs, 43% due to productivity losses and 21% due to the informal care of patients with CAD

(BHF, 2010). The magnitude of health and cost burden of CAD makes it an appropriate target condition for this research. In 2000 the National Service Framework on Coronary Heart Disease stated the following about CAD:

> "*It is a condition that makes a significant impact on every aspect of an individual's life including their quality of life, future employment and personal relationships, as well as increasing the risk of their dying early. Much can be done to reduce the suffering caused by CHD and to stop it developing in the first place. The Government sees this as a major priority*" (DoH, 2000).

1.3 Why CAD secondary prevention medicines?

While the primary prevention of CAD is very important, the main focus of the study will be on secondary prevention of CAD using medicines. This is because of the secondary care nature of the setting of the study and the healthcare professionals involved. In addition, the evidence of the mortality and morbidity benefits of secondary prevention medicines for CAD is much more established and robust than primary prevention.

As mentioned in Section 1.2, deaths from CAD have declined from 174,000 deaths per year in 1970s to 88,000 in 2008 (NICE, 2007; BHF, 2010). This decline in death rate is consistent across the developed world and largely attributable to better healthcare; particularly, the development and use of medicines such as lipid lowering and antihypertensive medicines, and certain life style changes such as smoking cessation (Ker, 2010; Unal et al., 2004). The prescribing of secondary prevention medicines after

MI had the largest contribution and it is estimated that each death avoided by treating a patient with CAD can yield an additional 7.5 years of life (Ker, 2010).

Medicines for the secondary prevention of CVD that have a proven benefit in reducing mortality and morbidity include: antiplatelets (aspirin or/and clopidogrel), statins; and (in patients with MI or heart failure) beta blockers and angiotensin converting enzyme inhibitors (ACEI) (NICE, 2007; NICE, 2011). NICE (2007) makes it clear that all patients who have suffered an MI should be prescribed all these 4 classes of medicines unless they are contraindicated. Similar recommendations are made by NICE (2011) about antiplatelets and statins for patients with stable angina. In addition, there is some evidence to support the use of ACEI in stable CAD patients without MI or heart failure (Fox, 2003; Teo et al., 2004). The American and European guidelines on the management of stable angina recommend the use of beta blockers as first line in patients without MI or heart failure (Fox et al., 2006; Gibbons et al., 2007). Patients who cannot tolerate ACEI can be offered angiotensin receptor blockers (ARBs) instead, though the evidence for their use is not as robust as for ACEI (NICE, 2007).

Optimal medical treatment post MI with all these 4 classes of medicines (5 medicines including aspirin and clopidogrel) was associated with a 74% reduction in total mortality compared to patients receiving only one or none of these medicines (Bramlage et al., 2010). Recent trials have also shown that PCI does not improve cardiovascular outcomes in patients receiving optimal medical treatment (with these 4 classes of medicines) (Boden et al., 2007). This has led to renewed emphasis on the need to utilise these classes of medicines optimally. Table 1.1 summarises the evidence and benefits for the use of these 4 classes of medicines in CAD. Economic analysis has also shown that secondary prevention medicines are relatively cheap and cost effective (Fidan et al., 2007).

Consequently, these classes of medicines were specifically targeted by this research and every effort should be made to ensure that they are utilised optimally.

Table 1.1 – Summary of the evidence and benefits for the use of the 4 classes of CVD secondary prevention medicines in CAD patients.

Antiplatelets
A meta-analysis of 12 randomized controlled trials of antiplatelet treatment in patients with established CAD found that long term treatment with aspirin reduced vascular death (14 fewer per 1000 treated, standard error (SE) 4, $p < 0.0006$) and non-fatal MI (18 fewer per 1000 treated, SE 3, $p < 0.001$) (Antithrombotic Trialists' Collaboration, 2002). Clopidogrel was slightly better than aspirin in reducing mortality and cardiovascular events in patients with CAD (CAPRIE Steering Committee, 1996).
Statins
A meta-analysis of 14 placebo-controlled trials in which all participants at study entry had CAD found that long term treatment with statins was associated with a reduction in all-cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), non-fatal MI (RR 0.69, 95% CI 0.59 to 0.79), hospitalization for unstable angina (RR 0.90, 95% CI 0.84 to 0.97), and need for coronary revascularization (RR 0.77, 95% CI 0.69 to 0.85) (NICE, 2006).
ACEI
Long-term treatment of patients with CAD (with preserved left ventricular dysfunction (LVD)) post MI with ACEIs was associated with a reduction in total mortality (RR 0.87, 95% CI 0.81 to 0.94), non-fatal MI (RR 0.84, 95% CI 0.75 to 0.94), and coronary revascularization (RR 0.93, 95% CI 0.85 to 1.00) (Al-Mallah et al., 2006). In CAD patients with LVD, long term treatment with ACEI was associated with substantial reductions in all-cause mortality (OR 0.74, 95% CI 0.66 to 0.83), recurrent MI (OR 0.80, 95% CI 0.69 to 0.94) and re-admission for heart failure (OR 0.73, 95% CI 0.63 to 0.85) (Flather et al., 2000). ACEI were also found to reduce the risk of the composite of sudden death or non-fatal cardiac arrest in high-risk individuals who did not have an MI in two major studies (Fox, 2003; Teo et al., 2004).
Beta Blockers
Long-term treatment of CAD patients post MI with a beta-blocker was associated with reduction in all-cause mortality (OR 0.77, 95% CI 0.69 to 0.85) (Freemantle et al., 1999). In patients who had LVD, long term treatment with ACEI and BB was associated with reduction of all-cause mortality (HR 0.77, 95% CI 0.60 to 0.98) and non-fatal MI (HR 0.59, 95% CI 0.39 to 0.90) (Dargie, 2001). Some weak evidence suggests that in people with severe CAD without MI or LVD, beta blockers may reduce the risk of all-cause death, but not the risk of future non-fatal MI (Bunch et al., 2005).

1.4 Medicines adherence in CAD

For evidence based medicines to work they need to be taken by patients in accordance with the evidence and as C. Everett Koop said “Drugs don’t work in patients who don’t take them” (Osterberg & Blaschke, 2005). Non-adherence limits the maximum benefit that patients can derive from medical treatment which can in turn lead to poor health outcomes, lower quality of life and increased demands for healthcare, which together with wasted medicines, also has significant economic consequences (NICE, 2009). NICE (2009) estimates the level of non-adherence to medicines in patients with long-term conditions to be between 33 to 50%. Various levels of non-adherence, ranging from 25% to 50% were reported by patients with chronic obstructive pulmonary disease (COPD), asthma, psychiatric disorders, arthritis, CVD, HIV and cancer (DiMatteo, 2005; Cramer & Rosenheck, 1998). Therefore, non-adherence is a growing concern to clinicians and healthcare systems.

As mentioned in Section 1.3, a large number of clinical trials have demonstrated the efficacy of antiplatelets, beta blockers, ACEI and statins for secondary prevention of CAD. National and international guidelines and quality improvement initiatives have incorporated prescription of these medications as important quality of care measures in secondary and primary care (NICE, 2007; NICE, 2011; DoH, 2000; Gibbons et al., 2007; Fox et al., 2006; BMA, 2011). This has improved the level of prescribing of these secondary prevention medicines in both primary and secondary care, though there is still room for further improvement (DeWilde et al., 2008). However, even with these improvements in the prescription rates of secondary prevention medicines, a gap still exists between the efficacy shown in clinical trials and the effectiveness of these

medicines in clinical practice (Ho et al., 2008). One possible explanation for this is the level of adherence to these secondary prevention medicines.

Many studies support this explanation and show that there is a significant level of non-adherence to secondary prevention medicines by CHD patients. Jackevicius et al. (2008) reported that almost a quarter of post-acute MI patients did not fill their prescription 7 days after discharge. Several authors suggest that as many as 50% of patients with recurrent MI were not taking their prescribed aspirin, beta blockers, or lipid-lowering medications - at the time of readmission (Majumdar et al., 1999; Krumholz et al., 1995; Rathore et al., 2003; Burwen et al., 2003). Sung et al. (1998) reported that only about one-third of patients took at least 90% of their lipid-lowering treatment. Others have estimated the discontinuation rates in this context to be 50% after one year and 85% after two years (Insull, 1997). A study which assessed self-reported adherence to evidence-based medicines used in secondary prevention of CAD found that adherence was highest for aspirin (83%); followed by lipid-lowering agents (63%), beta blockers (61%), both aspirin and a beta blocker (54%); the lowest measured adherence rate was for joint use of all 3 medications (39%) (Newby et al., 2006). In another study, the rates of non-adherence among patients with established CAD were 28.8% for beta blockers, 21.6% for ACEI, and 26.0% for statins (Ho et al., 2008).

Despite reports of some improvement, adherence rates remain suboptimal for secondary prevention medicines. In 2003 levels of adherence by post MI Medicare patients in the USA, compared to 1995, increased from 38.6% to 56.2% for statins and 29.1% to 46.4% for all three secondary prevention medicines (statin, beta-blocker, and

ACEI/ARB) (Choudhry et al., 2008). Though there was an increase in adherence rates for statins and beta-blockers, there was no change in the rate of adherence to ACEIs/ARBs which remained around 50% (Choudhry et al., 2008). On the other hand, some longitudinal studies show that non-adherence to secondary prevention medicines decreases among the same population over time. For example, Chodick et al. (2008) reported that the mean levels of adherence to statin therapy among Israeli patients with CAD (initiated between 1998 and 2006) was 59% and more than 75% of patients stopped their statins within 2 years of the initial prescription.

The above studies clearly demonstrate that non-adherence to secondary prevention medicines by patients with established CHD is a real problem which needs addressing. A Cochrane review on "interventions for enhancing medication adherence" concluded that improving adherence may have a far greater impact on clinical outcomes than an improvement in treatments (Haynes et al., 2008). This statement can be better understood when one considers the impact and consequences of non-adherence to these secondary prevention medicines. CAD patients who had primary non-adherence (not filling prescriptions) by 120 days after MI in comparison with those who filled their prescriptions had an 80% increased risk of mortality (Jackevicius et al., 2008). Post MI patients in the Beta Blocker Heart Attack Trial who took 75% or less of their prescribed medicines were 2.5 times more likely to die than were those who were more adherent to treatment (Horwitz et al., 1990). Ho et al. (2008) reported that non-adherence to secondary prevention medicines (beta blockers, statins, ACEI) by patients with established CAD was associated with a 10–40% relative increase in risk of cardiac hospitalisations and a 50–80% relative increase in mortality. These findings further emphasise that non-adherence should be investigated to develop quality improvement

interventions which can maximise the outcomes of patients with CAD. This is why medicines adherence has been described as the "next frontier in quality improvement" (Heidenreich, 2004).

1.4.1 Level of adherence required to gain benefit

In order for patients to derive the benefits seen in clinical trials, they need to have a high adherence to the treatment plan. Though there is no agreement as to what constitutes an adequately high level of adherence, several trials consider rates of greater than 75% to be acceptable (Osterberg & Blaschke, 2005; Silcock & Standage 2007). Pharmacy refill data and dosage counts are the most commonly used methods in the literature to quantify the level of adherence and patients with medications available greater than 75% of the time are considered adherent (Ho et al., 2009). The percentage is worked out by calculating the number of doses absent in a given time period divided by the number of doses prescribed by the doctor in that same time period (Brown & Bussell, 2011). Though this cut off point is somewhat arbitrary, it has been used for a majority of the observational and randomized, controlled clinical trials on medicines adherence and has been associated with both intermediate and hard outcomes (Ho et al., 2009).

Recent literature suggests that patients might be missing on additional benefits by using this cut off point. For example, adherence levels beyond 80% were associated with better reduction in Low Density Lipoprotein (LDL) cholesterol and blood pressure, which can lead to better outcomes (Bryson et al., 2007). The use of 75% as a cut-off point is considered very low for other medicines such as HIV medicines. In order to

establish better understanding of adherence benefits beyond 75%, future studies should report outcomes for different dichotomous cut-offs (Ho et al., 2009).

1.4.2 Causes of medicines non-adherence

In order to address the problem of non-adherence, it is necessary to understand the underlying causes of this behaviour. Non-adherence should not be perceived as a patient's problem but as a limitation in the delivery of healthcare (NICE, 2009). The causes of medicines non-adherence are complex, multifactorial and cannot be explained by single fixed factors such as the type or severity of the disease and sociodemographics of patients (Horne et al., 2005). A large proportion of the research into causes of non-adherence attempts to identify factors distinguishing adherent from non-adherent patients such as sociodemographic and clinical factors (Horne, 2005; Brown & Bussell, 2011). Many of these factors, however, are fixed (e.g. gender, age, race) and others, although they can be modified, they cannot be addressed in a clinical practice setting (e.g. financial status). The WHO summarised the different factors that can contribute to non-adherence in 5 categories as can be seen in Table 1.2 with examples (WHO, 2003). It is important to emphasise that not all of these factors have been consistently associated with patient non-adherence (Brown & Bussell, 2011). The level of contribution of each one of these factors towards non-adherence is not consistent and depends on interactions with other factors. For example, patients with good knowledge and strong belief that they need their medicines may still be non-adherent because they cannot afford the prescription charges, if applied, or are unable to swallow them. So it cannot be said that clear information about medicines, although

essential, can guarantee adherence to medicines because of the presence and absence of other factors which contribute to non-adherence (Horne, 2005).

Adherence is a behaviour and various research studies investigating causes of non-adherence have used psychosocial approaches to conceptualise adherence (Horne & Weinman, 1999). This type of research identifies that adherence and non-adherence behaviours are best understood in terms of patient's motivation and capacity to follow therapeutic recommendations (Horne et al., 2005). Therefore, the patient's medicines-taking behaviour is determined by their beliefs, perceptions about illness and treatment, preferences and resources (Horne et al., 2005). With a better understanding of the patient's perceptions and role in their non-adherence to medicines, the health professional can have a better understanding of the causes of non-adherence and possibly a positive impact on patients' medicine-taking behaviour.

Horne (2003) identifies two types of adherence: intentional and unintentional. *Intentional non-adherence* is when the patient decides to stop or change their agreed treatment regimen and their decision is often made through active reasoning, where the perceived benefits of the medicine are balanced against the perceived risks. Addressing this type of non-adherence requires interventions to address motivational and perceptual barriers (Horne et al., 2005). *Unintentional non-adherence* is when the patient wants to follow the treatment, but barriers beyond their control stop them from doing so (e.g. forgetfulness, lack of understanding, difficulty swallowing) (Horne, 2003; Lowry et al., 2005; NICE, 2009). This type of non-adherence would require interventions targeting practical barriers and capacity and resources (Horne et al., 2005). Patients may display both types of non-adherence behaviour simultaneously.

Furthermore, a patient may be intentionally non-adherent to one medicine and unintentionally non-adherent to another.

Horne et al. (2005) mapped the determinants of adherence behaviour in an attempt to improve understanding of how patients approach the taking of medicines. As can be seen in Figure 1.2, the decision to take medicines and continue taking them is a complex behaviour. There are internal and external factors and influences on medicines-taking behaviour. These factors interact, which further shows the complex nature of causes behind non-adherence behaviour (NICE, 2009). The internal factors reflect the beliefs that the patient holds about their illness and medicines in general and specifically about their own condition and medicines. These beliefs about the necessity (or personal need/benefit), concern and the harm (or risk) that can be caused by medicines, heavily influence patients' motivation and intention to take or not take their medicines (Horne et al., 2005). External factors such as communication with healthcare professionals, family and friends, feed into the patient's own internal appraisal process and influence the decision making process of taking medicines (NICE, 2009).

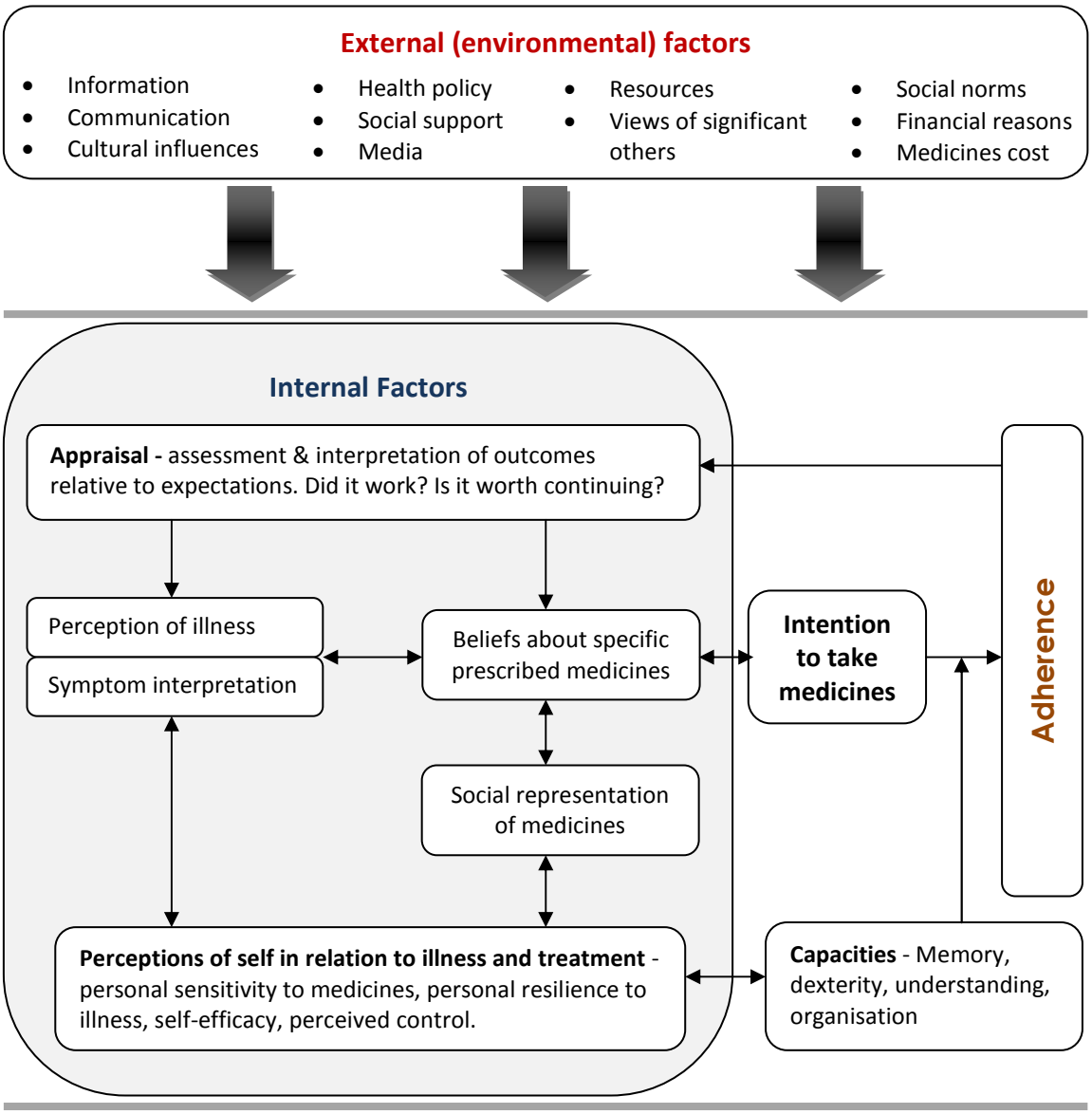

Figure 1.2 – Map of determinants of adherence which conceptualises non-adherence as unintentional and intentional behaviours with internal and external determinants. The internal factors influence motivation, and capacities may be moderated by external variables, (Adapted from Horne et al. 2005).

It is clear that reasons behind non-adherence are complex and require considering multiple factors. However, in this research the main focus will be on actual and perceived causes which can be modified in clinical practice. The main interest will be in factors in any of the 5 domains identified by the WHO (see Table 1.2) which are related to medicines or medicines related processes (e.g. repeat prescriptions).

It is noteworthy that non-adherence is usually a hidden problem which is under - recognised by prescribers and not necessarily disclosed by patients (Horne et al., 2005). Patients do not often disclose their reluctance or disagreement with the prescriber's recommendations and it is therefore expected that healthcare professionals would assess, elicit and explore patients' beliefs and experiences with their medicines to help them make an informed choice on whether to take or not to take a medicine (NICE, 2009).

Table 1.2 – The WHO five categories of factors that can contribute to medicines non-adherence with examples for each factor.

1)	**Socioeconomic Factors**
•	Financial burden (cost of medicines)
•	Lack of transportation
•	Low levels of patient education and/or literacy
•	Language barriers
•	Lack of effective social support networks (e.g. family helping with medicines)
•	Unstable living conditions (problems at home, patients who travel frequently, homeless)
•	Attitudes associated with poverty (lower levels of self-efficacy, learned helplessness, low levels self-determination)
2)	**Healthcare team and system factors**
•	Health professionals' lack of time (to identify & address patient medicine taking behaviour)
•	Healthcare professionals lack of involvement of patients & addressing their specific needs
•	Fragmented healthcare systems leading to lack of continuity of care & access to care
•	Inter-professional collaboration (important for better treatment plans and a better overview of patient adherence)
•	On-going communication after initiation of medicine (monitor progress & overall health)
•	Poor medicine distribution and costs (rural areas, repeat prescriptions)
•	Failing to recognise the non-adherence problem
3)	**Disease – related factors**
•	Permanent or chronic disease (e.g. CAD, HF)
•	Co-morbidities (e.g. depression)
•	No symptoms/no severe symptoms (e.g. hypertension)
•	Rate of progression and severity of the condition (e.g. HF progressive + potential gradual aggravation)
4)	**Therapy – related factors**
•	Regimen complexity and how it fits into the patient's routine
•	Side-effects and pharmaceutical properties of the medicine (e.g. taste, size of tablet etc.)
•	Frequent changes in treatment (example titrating ACEI)
•	Poor instructions, complex process of ordering refills
•	Lack of immediacy of beneficial effects (effect not immediate, or impact not apparent)
•	Reduced access to medicines and/or medical support (rural and remote areas, cost, access)
5)	**Patient-related factors**
•	Lack of understanding of the disease.
•	Lack of involvement in treatment decision-making process.
•	Language or literacy barriers
•	Actual or perceived side-effects
•	Own health beliefs and attitude towards medicines
•	Rejection of the diagnosis (lack of symptoms)
•	Limited understanding of the importance of medicines (asymptomatic conditions)
•	Previous experience and loss of faith in medicines
•	Poor sight, poor memory, inability to swallow
•	Lack of self-efficacy (lack of confidence to make recommended behavioural changes)
•	Poor mental health (e.g. depression and anxiety in CAD patients)

(WHO, 2003; Horne et al., 2005; Brown & Bussell, 2011)

1.4.3 Interventions to Improve Adherence

After discussing the complex nature of the reasons behind non-adherence the interventions that have been tested to improve adherence will be considered to inform the direction of this research.

Several systematic reviews and meta-analyses evaluated the effectiveness of interventions to enhance medicines adherence (Roter et al., 1998; Horne et al., 2005; Kripalani et al., 2007). Some focused only on randomised controlled trials (e.g. Kripalani et al., 2007), while others included trials with controlled designs which were not necessarily randomised (e.g. Roter et al., 1998).

The interventions can be summarised as follows (Roter et al., 1998; Horne et al., 2005; Kripalani et al., 2007; Dulmen et al., 2007):

Informational or educational interventions – which provide the patients with intensive educational materials using different methods (written information, face to face educational sessions etc.). The methods used were very diverse and it was difficult to compare findings due to different methods.

Behavioural interventions (skills) – help patients to deal with practicalities of taking medicines e.g. most common was dosage simplification, memory aids (reminders including using telephone etc.), monitoring, enhancing self-efficacy, self-training, providing repeated assessment of medicines use with feedback and reward. These interventions were generally effective and stemmed from behavioural theories e.g. incentives and reminders. Though there was evidence that "technical interventions"

such as simplifying medication dosage schedules led to improved adherence, the effects of this simplification seem to become less the longer the treatment lasts and no theoretical explanation was always provided of the operating mechanisms for these interventions. Others included specialised packaging, directly observed therapy and cognitive behaviour therapy, but these did not significantly improve adherence.

Combined interventions – most studies included both informational and behavioural components and others had joined social support strategies with either informational or behavioural components. There were variable outcomes with these interventions.

Though there was evidence to support some of these interventions, not all trials within the same category were effective and it was not possible to establish why the same intervention worked in one trial and did not in the other (Roter et al., 1998; Kripalani et al., 2007). There was also a lack of consistency in reporting the type of interventions used and the type of outcomes and adherence measurements (Kripalani et al., 2007).

The interventions can also be categorized into two approaches based on their purpose (Horne et al., 2005): *Perceptual (motivational)* interventions which are aimed at changing motivation by influencing knowledge, beliefs, or attitudes and *practical (capacity and resources)* interventions which are aimed at changing specific patient behaviours (e.g. reminder or skill building) and removing barriers to performance.

Interventions with a combined purpose can also be used. The augmented review by Horne et al. (2005) concluded that interventions to promote adherence were broadly efficacious and increased adherence by 4 – 11%. However, the interventions

consumed considerable resources and effort with small impact and considerable room for improvement.

A Cochrane systematic review of "Interventions for enhancing medication adherence" included interventions with randomised controlled design and had a clinical outcome measure (Haynes et al., 2008). It identified that only 36 of 83 interventions reported in 70 trials were associated with improvements in adherence in long-term treatments and only 25 interventions led to improvement in at least one treatment outcome (Haynes et al., 2008). However, the improvements were not large and even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. Those interventions that were effective were complex and included various combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care (Haynes et al., 2008).

In their critique of the interventions, Horne et al. (2005) listed the following limitations in the interventional studies to improve adherence:

(1) Narrow focus of the intervention and lack of comprehensiveness. Very few interventions address both the practical and the perceptual barriers to adherence.

(2) One size fit all approach. Very few of the interventions could be classed as patient-centred in their approach. They broadly seem to fail to identify the reasons behind non-adherence in the population before designing the intervention.

(3) Little information was provided about the content of the intervention which made it difficult to evaluate what worked and what did not work.

(4) Lack of theoretical framework and specific targeting of determinants of adherence.

(5) Studies which used complex interventions did not evaluate the impact of each element on adherence.

(6) Lack of evaluation of the changes in the antecedents of adherence and the extent to which the interventions were correctly implemented.

The reviews seem to show that interventions to improve medicines non-adherence produced only modest success and uni-modal interventions were less successful than multi-modal interventions (Ho et al., 2009). Due to the often multifactorial nature of the reasons behind non-adherence, multimodal interventions are generally considered to be more likely to be successful than uni-modal approaches (Baroletti & Dell'Orfano, 2010). It is most important that the development of any intervention need to target patient or population specific barriers rather than the "one size fit all" approach.

1.5 The direction of this research

To optimise the medical treatment of CHD patients and maximise their opportunity to benefit from secondary prevention medicines, their medicines-taking behaviour needs to be understood by healthcare professionals and patient specific interventions need to be deployed to address barriers to adherence. The review of evidence about interventions to improve adherence emphasises the need to study the target population before implementing any intervention in order to tailor the intervention(s) to the needs of the population. This helps in building individualised or patient-centred interventions. This study will explore the medicines-taking behaviour of CHD patients to inform practice and enable us to address non-adherence which in turn should

contribute to an increase in the benefits patient derive from secondary prevention medicines.

As explained earlier, non-adherence is usually a hidden and under–recognised problem. Therefore, there is a need to have appropriate practical assessment tools which enable identifying non-adherence in practice. Indeed NICE (2009) and the WHO (2003) recommend that patients' level of adherence should be assessed routinely as whenever one prescribes, dispenses and reviews medicines. It would be very useful if these assessment tools could also identify the specific barriers that prevent patients from adhering to their secondary prevention medicines.

Despite its importance and its significant negative impact on patients and healthcare systems the assessment of patients' non- adherence and use of interventions to improve adherence remain rare in routine clinical practice (Ho et. al., 2009). This research attempts to help inform and change practice in the LTHT and possibly wider context.

In the next chapter, the literature will be comprehensively reviewed to identify the best ways of assessing and investigating medicines-taking behaviour among CHD patients. Any tools identified need to serve the following requirements:

(1) The tool(s) needs to enable quantifying the level of non-adherence in order to be able to measure the impact of any interventions in the future.
(2) The tool(s) needs to be practical and can be easily used in clinical practice to enable the assessment of adherence in routine practice

(3) The tool(s) needs to provide information about barriers to adherence to inform the design of interventions which are tailored to patients' needs and specific barriers.

2 Literature Review

Hippocrates observed over 2500 years ago that *"(Physicians should) keep watch also on the faults of patients which often make them lie about the taking of things prescribed"* (Horne, 2001)

As identified in Chapter 1 the assessment of adherence behaviour is essential for optimising medical therapy. The purpose of the assessment is to measure non-adherence levels and more importantly to reveal barriers to adherence. These findings are needed for effective and efficient treatment planning, ensuring that changes in health outcomes can be attributed to the recommended regimen and informing the development of patient-tailored adherence improvement interventions, which are more likely to be effective (WHO, 2003; NICE, 2009). The assessment of adherence is not about monitoring patients *per se*. Its fundamental purpose is to find out if patients need help and support in taking their medicines to optimise their therapy (NICE, 2009).

Most health professionals overestimate their patients' adherence and patients generally do not volunteer information about their non-adherence to medicines (Hansen et al., 2009). Therefore, health professionals need to make specific efforts to assess adherence. Healthcare professionals need to screen individual patients for perceptual and practical barriers to adherence. This should be not only at the time of prescribing but also during medicines reviews, because adherence may change over time (NICE, 2009). Therefore, there is a need for near patient adherence assessment tools that are practical, simple, accurate, valid and reliable. Tools should identify and measure non-adherence including its types and causes so that interventions to

improve adherence can be formulated and assessed (Horne et al., 2005; Hansen et al., 2009). Such tools need to be non-judgmental and easy to use when prescribing, dispensing, reviewing medicines or discussing a patient's health (Horne et al., 2005; NICE, 2009).

This chapter will summarise an extensive literature review which attempted to identify the different tools that can be used to measure and assess adherence as described above. The main focus will be on practical tools that can be used in clinical practice specifically while providing care to CHD patients in secondary care setting.

2.1 Direct and indirect methods to assess adherence

Various adherence assessment strategies have been reported in the literature but there is no *"gold standard"* tool for measuring adherence behaviour and no single tool to detect all types of non-adherence (WHO, 2003; Osterberg & Blaschke, 2005; Simoni et al., 2006). The assessment of adherence can be carried out using direct and indirect methods (Osterberg & Blaschke, 2005). *Direct methods* include observing patients taking their medicines and the measurement of drug or metabolite levels in the blood or urine. *Indirect methods* of assessment include self-reporting (using questionnaires, interviews, surveys or patient diaries), rates of repeat prescription ordering, refill rates, dose counting, assessment of a patient's clinical response or therapeutic outcomes (e.g. lipid levels, blood pressure), electronic monitoring devices, and measuring serum or urine markers (Horne, 2001; Osterberg & Blaschke, 2005; Ho et al., 2009).

Direct methods are considered to be more robust than indirect methods because they directly assess medicines-taking rather than relying on proxy indicators (Ho et al.,

2009). However, their major limitation is that they are expensive and not practical for routine clinical use in daily practice (Osterberg & Blaschke, 2005; Ho et al., 2009). They can also be prone to error and manipulation. For example, there may be inter-individual variations in metabolism that can affect serum levels, or patients can hide doses in their mouth and discard them later. The therapeutic outcome approach assumes a close relationship between adherence to treatment and clinical benefit. While this might be true for certain effective treatments, adherence does not guarantee benefit and its relationship with health outcome is rarely linear (Horne, 2001). The identification and measurement of non-adherence behaviour are far from easy and each available method has its own advantages and disadvantages (Horne, 2001; Hansen et al., 2009). Table 2.1 summarises some examples of direct and indirect methods of assessing adherence including the advantages and disadvantages of these methods.

Adherence is assessed by each of these methods at different stages of the prescribing and medicines-use time line. Therefore, they have the potential to identify different adherence behaviours e.g. adhering to ordering the prescription but not filling the prescription. They also differ in terms of the gap between adherence assessment and the actual medicines-taking behaviour (Hansen et al., 2009). Some methods may be good for acute or recent medicine-taking e.g. serum levels. Others may reflect a pattern of behaviour over a certain period e.g. prescription refill data over 6 or 12 months. Self-report methods may ask questions about medicines-taking behaviour at a time and place which are distant from the actual event and the answer, therefore, can be affected by the ability of recall (Horne, 2001). People can experience the "*golden*

halo" effect of recalling the "good" rather than the "bad" in relation to an event (Horne, 2001).

Table 2.1 – Examples of direct and indirect adherence assessment methods including their advantages and disadvantages.

Tool	Description	Advantages	Disadvantages
Direct			
Measurement of the level of medicine or metabolite in the blood or Urine	Depending on the type of drug and its pharmacokinetics, samples are taken and drug levels or metabolites are measured at specific intervals.	• Objective • Individualised	• Variations can be due to factors other than non-adherence. • White-coat adherence • Expensive • No information about reasons for non-
Directly observed therapy	Patients are observed when taking the prescribed medicines on specific times.	• Most accurate	• Not practical for routine use • Patients can hide dose in mouth • Contrary to the concept of informed adherence
Indirect			
Repeat Prescription Ordering Data	The frequency of ordering repeat prescription from GP over a defined period and checking if amount of medicines ordered covers that period.	• Practical • Non-invasive • Inexpensive • Ability to measure adherence rate • Good as a scanning tool for potential non-adherers • Can identify potential non-adherence to specific medicines	• Reports rates only • Patients do not always "cash" their prescription • Patient may still be not taking their medicines despite ordering repeat prescriptions. • No information about reasons for non-adherence
Medication Events Monitoring System (MEMS®)	The cap of the medicines bottle is fitted with a special microprocessor which records number of times of bottles opening.	• Accurate • Non-invasive • Ability to measure adherence rate • Can observe behaviour pattern • Suitable for studies • Provide a profile of medication taking rather than simply detailing how much was taken.	• Not practical (not all medicines are in bottles) • Expensive. • Patients may still not take their medicines. • No information about reasons for non-adherence • Can enhance adherence by acting as a behavioural intervention

(Horne, 2001; Osterberg & Blaschke, 2005; Ho et al., 2009)

As non-adherence is a behaviour, the act of measurement itself can influence the behaviour. When patients are aware that their medicines-taking behaviour is being monitored, their adherence might be stimulated simply by drawing their attention to it (Horne, 2001). Therefore, the findings may be less likely to reflect routine medicines-taking behaviour.

It is apparent that the most practical and commonly used methods in the literature to measure adherence are: patient self-report, repeat prescription data, pharmacy refill records, or use of electronic lids to measure doses e.g. medication event monitoring systems (MEMS®) (WHO, 2003; Horne et al., 2005; NICE, 2009; Hansen et al., 2009). The latter three are most relied on to quantify adherence especially in research. They are also useful to identify patients who may need additional support with their medicines. Patients with low levels of adherence can also be identified by monitoring return of unused medicines (NICE, 2009). However, while these tools are useful for screening, research and audit purposes, they are very limited in identifying barriers to adherence that would enable the formulation of individualised interventions. Their findings need to be examined to identify complementary information they provide to enable healthcare professionals to do something about non-adherence (Steiner & Prochazka, 1997; Hansen et al., 2009; NICE, 2009).

Asking patients to describe their medicines-taking behaviour is the simplest and most commonly used method to assess adherence (Horne, 2001). Some researchers undermined this approach due to its tendency to overestimate adherence, but it is a valid, practical and useful indicator of non-adherence and sheds more light on barriers to adherence than many other tools (Horne, 2001). In routine clinical practice and to

involve patients in decision making, self-report methods are considered most appropriate (NICE, 2009). They are also probably the closest the researcher can get to the actual medicines-taking behaviour of the patient. NICE (2009) identifies self-report as the most suitable method for reporting adherence in clinical context. Therefore, the rest of this review will focus on self-report methods.

2.2 Self-reporting adherence assessment tools

Patients' self-reports are an inexpensive and pragmatic method to assess adherence in clinical practice. Their reliability is limited by several factors including memory and social desirability, that is, patients not admitting to non-adherence to avoid the disappointment of the prescriber (Horne, 2001). However, despite their limitations, generally reported non-adherence behaviour, in particular, using this method is considered reliable and accurate (Graber et al., 2004; Dimatteo, 2004; Shi et al., 2010; Shi et al., 2010a). Each method to measure adherence has its own advantages and failings which limit accuracy, reliability or practical application. Available tools are generally indicators of adherence rather than exact, quantitative measures of medicines-taking behaviour (Horne et al., 2005). Self-report methods represent a fair compromise in which accuracy and comprehensiveness is balanced against practicality, reactivity, ethical and cost implications (Horne et al., 2005). It is widely accepted that reports of low adherence by self-report scales are usually useful in practice and more accurate than reports of high adherence (Morisky et al., 1986). Table 2.2 summarises some of the advantages and disadvantages of self-report adherence assessment tools.

Table 2.2 – A summary of the advantages and disadvantages of using self-report to assess adherence.

Advantages	Disadvantages

• Simple
• Inexpensive
• Identifies non-adherence
• Validated tools can be used to measure levels of adherence
• Practical and easy to administer
• Suitable for clinical settings
• Truthfulness of those reporting non-adherence
• Gathers important information which can inform the support needed (e.g. situational and behavioural factors)
	• Overestimates adherence
	• Patients may exaggerate their adherence if they believe that reports of non-adherence will disappoint their clinician
	• Inaccurate self-reporting due to:
	  ○ Recall bias
	  ○ Social desirability bias
	  ○ Errors in self-observation
	• Remembering can be a problem (specifying time period can help)
	• The wording and the way the questions are asked can influence outcome.
	• Inadequate reliability and poor distributional properties (i.e. restricted range and skewness).

(Horne et al., 2005; Osterberg & Blaschke, 2005; Bangsberg, 2006; NICE, 2009)

Self-reported adherence is usually an overestimation when compared to other indirect methods such as MEMS® or repeat prescription data (Bangsberg, 2006; Simoni et al., 2006). It is thought that adherence rates identified by self-reported methods are usually 10 to 20% higher than the rates obtained with other methods (Bangsberg, 2006; Simoni et al., 2006). These often cited disadvantages to self-reported adherence measures could have possibly arisen from inadequate attention to administration and measurement issues as will be discussed in Section 2.2.3 (Voils et al., 2011).

Patients' self-reports can effectively measure adherence in a very simple and practical way and readily identify adherence-related behaviours at the point of care (Osterberg & Blaschke, 2005). Self-report measures include questionnaires, diaries and interviews and they are considered the most appropriate for use in clinical practice to continuously monitor medicines-taking behaviour (Horne et al., 2005; NICE, 2009). Self-reporting methods should enable better understanding of the type of non-adherence (intentional vs. unintentional) as well as possible barriers to adherence. This

should in turn provide a better picture about an individual patient's adherence support needs.

Some studies argue that the use of self-report daily diary methods might be most accurate for certain conditions such as cystic fibrosis (Modi et al., 2006). While this is correct for study purposes, for long-term use such methods are costly in terms of clinicians' time and increase the burden on patients (Daniels et al., 2011). Interviews are also less practical, time consuming and cannot be easily administered.

Valid and reliable scales, questionnaires or surveys are the most frequently reported type of self-report tools in the literature (Graber et al., 2004; Dimatteo, 2004; NICE, 2009; Shi et al., 2010; Shi et al., 2010a). They offer the advantage of assessing adherence in 'naturalistic' studies (e.g. following up a group of chronically ill patients) and have the highest potential for widespread application in clinical practice (Garber et al., 2004; Horne et al., 2005; NICE, 2009). A number of validated medication adherence scales have been described in the literature (see Section 2.2.3 and Appendix 1 for a full description of sample of these tools). However, no gold standard exists, and no single scale is appropriate for every scenario as will be detailed in Section 2.2.3 (Horne 2001; NICE 2009; Shi et al., 2010; Shi et al., 2010a).

There is increasing interest in combining information from self-report with other adherence indicators such as repeat prescription data or prescription-redemption rates to produce amalgamated assessments of adherence and cross-check self-report methods (Horne, 2001; Horne et al., 2005). Such an approach is particularly important in interventional studies to enhance adherence.

Self-reporting of medicines-taking behaviour has many advantages. The most relevant to this research is that it is easy and practical to use in clinical settings and can gather useful information to inform the formulation of individualised interventions to improve adherence. Selecting the right self-report adherence assessment questionnaire requires understanding of validity, reliability and other basic characteristics of these tools.

2.2.1 Validity and reliability of self-report adherence assessment questionnaires

The *validity* of the self-report questionnaires establishes whether the instrument measures what it is supposed to measure (Braker et al., 1994). This is often established by checking the tool against other measures of adherence such as MEMS®, dosage counts and clinical markers (e.g. blood pressure). The MEMS® is considered by some as the 'imperfect gold standard' that self-report adherence assessment questionnaires are often checked against (Shi et al., 2010a). The association and agreement between adherence levels identified by self-report questionnaires and other measures such as MEMS® is reported using correlation coefficients such as the Pearson's correlation coefficient (r_p), the Spearman's correlation coefficient (r_s) or kappa coefficient (κ) (Krousel-Wood et al., 2009; Shi et al., 2010a).

Reliability of an assessment tool refers to the degree of consistency or reproducibility of the measurement and acceptability to the respondent (Barker et al., 1994). This is usually assessed using tests like the "test-retest reliability" where the questionnaire is administered twice and the findings are compared (Barker et al., 1994). The other most commonly used statistic is Cronbach's α (Barker et al., 1994; Machin et al., 2007;

Field, 2009). It measures the internal consistency and content validity of the questionnaire and assesses the degree to which individual items in the questionnaire represent the construct being measured (Machin et al., 2007; Field, 2009). A Cronbach's α value of 1 indicates a perfect correlation between the items that make up the scale, whereas, a value of 0 indicates no correlation between those items (Machin et al., 2007). For research purposes a Cronbach's α value of 0.60 is considered marginal, and values should be higher than 0.7 to 0.8 (Braker et al., 1994; Bland & Altman, 1997). Further details are in Appendix 15. Complete correlation (α =1) could indicate that most of the questions can be discarded as all the information is contained in one of them (Machin et al., 2007). Studies also report: sensitivity of the instrument which is the proportion of true positives (predicted non-adherent and found to be non-adherent) and specificity which is the proportion of true negatives (predicted adherent and found to be adherent) (Marston, 2010).

A systematic review examined the concordance of self-report methods (interviews (57%), questionnaires (27%), and diaries (17%)) with other measures of medicines adherence (Garber et al., 2004). The self-report measures showed higher adherence rates compared to other tools in most non-concordant cases. Concordance varied substantially by type of self-report measures. Questionnaires and diaries were more concordant with other methods compared to interviews (Garber et al., 2004). Generally, self-report questionnaires concorded with other electronic measures, although some variation in the level of agreement was found (Garber et al., 2004).

Another recent meta-analysis examined the correlation between adherence rates measured by MEMS® and self-reported questionnaires (Shi et al., 2010). The mean

adherence levels identified by MEMS® were 75% (range 53%-93%) versus 84% by self-reported questionnaires (range 68%-95%). The correlation between the two approaches ranged from 0.24 to 0.87. The pooled correlation coefficient for the 11 studies was 0.45 (p = 0.001, 95% CI: 0.34-0.56). The authors concluded that self-reported questionnaires give a good estimate of medication adherence because they at least moderately correlated with adherence measured by MEMS® (Shi et al., 2010).

Shi et al. (2010a) reviewed the association between medication adherence self-report questionnaires and medication monitoring devices. The review identified that the majority of articles (68%) reported significant to high correlation between self-report questionnaires and monitoring devices. Therefore, self-report can be used to measure patient-reported adherence. Most of the trials used the MEMS® monitoring system as a comparator. The most commonly used self-report questionnaires were the Adult/Pediatric AIDS Clinical Trial Group (AACTG /PACTG) (24%), the 4-item Morisky (10%), Brief Medication Questionnaire (BrMQ) (10%) and the Visual Analogue Scale (VAS) (7%) (Shi et al., 2010a). Generally self-report questionnaires appeared to report on average 15% higher rate of medicines adherence than electronic monitoring devices (Shi et al., 2010a). Self-report questionnaires used for assessing adherence in patients with cardiovascular disease were: 4 item Morisky, VAS, BrMQ, ASRQ (adherence self-report questionnaire) and another two unnamed tools which were not described clearly in the original sources (Rudd et al., 1993; Hope et al., 2004; Shi et al., 2010a). More details about these tools can be found in Appendix 1 and in Section 2.3.

Hansen et al. (2009) compared the three most commonly used adherence assessment tools in practice: self-report, prescription refill records and electronic lids. Factors that

might impact on measurement agreement were explored. The review focused on two similarly designed intervention trials to examine agreement among these adherence assessment tools. The self-report methods were a single question (did you take medications as intended (i.e., on schedule and regularly) during the past 4 weeks?) and the 4-item Morisky. All three methods provided similar estimates of overall adherence levels. However, refill and electronic measures were in highest agreement (Hansen et al., 2009).

2.2.2 Improving self-report measures

Different considerations and approaches can be used to reduce some of the limitations of self-report questionnaires. The first limitation of social-desirability can be addressed by diminishing the social pressure on patients to report high adherence (Rand & Wise, 1994; NICE, 2009). Questions should be phrased in a non-threatening manner and without blaming the patient for non-adherent behaviour (NICE, 2009). Assuring confidentiality, anonymity and explaining that there are no right or wrong answers can also minimise social-desirability bias (Rand & Wise, 1994; NICE, 2009). Incorrect wording of the questionnaire items can exacerbate this problem such as the use of the word 'careless' in the 4-item Morisky or the Adherence to Refills and Medications scale (ARMS) (Morisky et al., 1986; Kripalani et al., 2009). Such use describes non-adherence as a 'careless' behaviour which might be misinterpreted as judgmental and make patients reluctant to report their non-adherent behaviour truthfully (Horne et al., 2005). The use of statements to preface the items in the tool can also be very useful to minimise social-desirability. Various tools use this approach e.g. the 8-item Morisky (MMAS-8) and The Medication Adherence Report Scale (MARS) (Horne &

Weinman, 2002; Morisky et al. 2008). Here is an example of a preface statement (Horne & Weinman, 2002):

'Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines. For each statement, please tick the box which best applies to you'

The recall bias can be reduced by mentioning a specific time period (e.g. in the last month) to make it easier for the patient to remember (Horne, 2001; NICE, 2009). Tools which explore a wide range of possible medicines-taking behaviours are more likely to capture non-adherent behaviour than those which focus on one aspect (e.g. forgetfulness, reducing dose, stopping a medicine etc.) (NICE, 2009).

It is recommended that the patient should be asked to answer questions in the form of scale items with a range of responses rather than a Yes/No responses (Horne, 2001; NICE, 2009). This should improve the quality of information obtained from this method of assessment as patients are being graded according to their relative standing on the adherence dimension, not as an exact measure of when and how they took their medicines (Horne, 2001). The Likert scales answers can also give the opportunity to learn about the frequency of non-adherent behaviour rather than just the presence of non-adherence.

Horne et al. (2005) argues that if the questionnaire items combine reports of non-adherence with reasons for non-adherence it can lead for further problems. A statement like *'I take less medication if I am feeling better'* might be difficult for

patients to interpret in certain circumstances such as if they take less medicines, but not because they feel better (Horne et al., 2005). The importance of making this distinction was also highlighted by Voils et al. (2011) when they reviewed the various self-reported measures of medicines non-adherence in the context of hypertension. It was identified that these measures can be improved by using *"effect indicators"* to assess the extent of non-adherence and *"causal indicators"* to assess reasons for non-adherence. Voils et al. (2011) also emphasises the need to assess adherence longitudinally. This is to establish if the extent to which medication non-adherence is transient or stable. They conclude that paying attention to these issues can improve the assessment of self-reported non-adherence and allow more accurate conclusions to be made about medicines taking behaviour (Voils et al., 2011). This will undoubtedly inform the design of patient-tailored interventions to improve adherence.

2.2.3 Characteristics of self-reporting assessment questionnaires

The review of literature clearly identifies various types of self-report assessment tools with different features. The tools differ in length; some tools have a single question, and others have more than 30 questions. Some tools quantify or measure non-adherence and shed some light on barriers to adherence. Others mainly explore possible barriers with no quantification of non-adherence. The intentional and unintentional types of non-adherence are not covered by all tools. Some focus mainly on unintentional non-adherence, others explore mainly intentional non-adherence and few explore both elements. Certain questionnaires explore current or recent non-adherence behaviour and others attempt to "predict" the likelihood of non-adherence behaviour based on the exploration of beliefs and other psychological aspects such as

self-efficacy. Certain scales were developed for specific conditions and are not generic. Table 2.3 summarises a sample of the wide range of self-report tools that were frequently reported in the literature and their main features. Full details about some of these tools can be seen in Appendix 1.

The tools also varied in terms of their validity and reliability in different contexts. For example: the VAS and ASRQ had poor correlation with MEMS® for identifying non-adherent patients with cardiovascular disease (Zeller et al., 2008). However, VAS showed good correlation with MEMS® in HIV patients (Oyugi et al., 2004). The MARS scale has been used in several studies and in various settings to assess self-report of medicines adherence such as in bipolar disorder, renal transplant and respiratory disease (Butler et al., 2004; George et al., 2005; Bowskill et al., 2007 Mahler et al., 2010). However, it exists in a few versions with a range of four to nine items (Horne & Weinman, 1999; Horne et al., 2001; Horne & Weinman, 2002). Different versions were used in different studies, though the five item version is the more commonly used and validated (Ediger et al., 2007; Mahler et al., 2010). The internal consistency (Cronbach's α) of MARS ranged from 0.60 to 0.90 and the test–retest reliability (r_p) also ranged from 0.61 to 0.97 in different studies (Mahler et al., 2010).

Table 2.3 – Summary of some of the most frequently mentioned self-report adherence assessment tools and their main features.

Self-report Tool	Disease Specific / Generic	Quantify adherence	Screening for barriers to adherence	Intentional / unintentional aspect	Beliefs / psychological aspects
4 and 8 -items **Morisky**	Generic (wide range of conditions)	Yes (scores & different levels)	Yes, some. (Current behaviour)	Yes, brief, both.	Behaviour more than belief
The Medication Adherence Report Scale (**MARS**)	Generic (different versions, 5-9 items)	Yes	Yes, some. (Current behaviour)	Yes, brief, both.	Behaviour more than belief
ASK-20 adherence barrier survey	Generic (Asthma, depression & diabetes, 20 items)	No	Yes, extensive. (Current behaviour / possible future impact)	Yes, both.	Yes, (not as detailed as other tools).
Adherence Estimator™ (**AE**)	Generic (3 items)	Yes (Likelihood of future adherence)	Yes. (Predictive tool)	Intentional only	Yes. (Benefit, harm)
Belief about Medicines Questionnaire (**BMQ**)	Generic (18 items)	No.	Yes.	Mainly Intentional	Yes. (4 aspects of belief)
Brief Medication Questionnaire (**BrMQ**)	Generic (9 items)	Yes.	Yes.	Yes, both.	No.
Medication-Taking Questionnaire (**MTQ**)	Hypertension (12 item)	No.	Yes.	Mainly intentional	Yes (hypertension & treatment)
Medical Prescription Knowledge questionnaire (**MPK**)	Diabetes type 2 (4 item)	No.	Limited (Mainly issues with specific anti-hyperglycaemics)	Mainly knowledge.	No.
Maastricht Utrecht Adherence in Hypertension questionnaire (**MUAH**)	Hypertension (40 items)	Yes	Yes	Yes	Yes
Brief Evaluation of Medication Influences and Beliefs (**BEMIB**) scale	schizophrenia (& related psychotic disorders) (8 items)	Yes	Yes	Yes, both.	Yes

(Morisky et al., 1986; Morisky et al., 2008; Horne & Weinman, 1999; Hahn et. al., 2008; McHorney, 2009; Horne et al., 1999; Svarstad et.al, 1999; Johnson &Rogers, 2006; Prado-Aguilar et al., 2009; Wetzels et al., 2006; Dolder et al., 2004)

Some of the tools might be more appropriate in specific settings. For example: the BrMQ tool was validated against MEMS® with good correlation (Svarstad et al., 1999; Shi et al., 2010a). The sensitivity was reported to be 90% and its specificity was 100% (Svarstad et al., 1999). But it is rather a lengthy tool for patients who are on large number of medicines as the tool expects the patient to provide full detail about every single medicine and this could explain its lack of popularity (McHorney, 2009). Such a tool may be useful in a comprehensive medicines review settings, rather than a routine assessment or screening setting.

2.3 Self-report adherence assessment tools in cardiology patients

A literature review was carried out to identify self-report adherence assessment tools used in patients with CAD. The following databases were searched: Ovid Medline (1946 to June 2009), EMBASE (1980 to June 2009), British Nursing Index and Archive (1985 to June 2009), PsycINFO (1806 to June 2009) and Pharmline (1978 to June 2009). The initial search used the following combinations of keywords: (medication, medicines, drug), (compliance, adherence, persistence), (self-report), (questionnaire, survey, scale, measure, assess) and (coronary heart disease, coronary artery disease). The search was limited to articles in English and all repeated references were excluded.

The research strategy revealed two self-report adherence assessment tools that were used in CAD: the Single question tool by Gehi et al. (2007) and the ARMS tool by Kripalani et al. (2009).

These tools did not cover all aspects of barriers to adherence and were not thoroughly investigated except in one trial each. Therefore, a second literature search was conducted for all self-report adherence assessment tools used in patients with Cardiovascular Disease (CVD). The broadening of the search captured tools which had been used in cardiology patients. The tools had to be transferable and adaptable to CAD patients. All disease specific tools were, therefore, excluded.

Seven different tools were identified. The content of all tools were compared including validity and reliability data. It was clear at this stage that the element of intentional non-adherence, specifically beliefs about medicines, was not covered by these tools. Therefore, a third search identified two generic tools which could be used to explore patients' beliefs about medicines and intentional non-adherence in specific. Tables 2.4, 2.5 and 2.6 summarise these findings.

Table 2.4 – Self-report adherence assessment tools used in patients with CAD as identified by the literature review.

Self-report Tool	Description	Conditions Used In	Outcome	Practical issues	Validity and Reliability
Adherence to Refills and Medication Scale (**ARMS**)	12 item, Likert scale No time period over which adherence measured	Coronary heart disease and Hypertension	• Rate • Some intentional • Barriers Forgetting Prescription Refill	Designed for use in patients with low literacy 12 items + uses words like "careless" Covers few barriers.	Checked against 4 items Morisky (r_s=0.651) and Prescription Refill with significant correlation (r=0.323), Cronbach's α = 0.814.
Single Question (**Gehi et al.**)	1 item, Likert scale Assesses adherence over the last month	Coronary heart disease	• Rate • No barriers	No barriers Can adapt to report for single medicines	Checked against mortality, significant association (p=0.03).

(Kripalani et al., 2009; Gehi et al., 2007)

Table 2.5 - Self-report adherence assessment tools used in patients with cardiovascular disease as identified by the literature review.

Self-report Tool	Description	Conditions Used In	Outcome	Practical issues	Validity and Reliability
Adherence Self Report Questionnaire (**ASRQ**)	6 item Participants indicate which of the 6 items describe their medication compliance. No time period over which adherence measured	Hypertension, diabetes or dyslipidaemia	• Rate • Very limited info about barriers	Short, can be adapted to CAD. Patients could have more than one statement describing their behaviour	Checked again MEMS® in different trials. With both significant and insignificant associations were reported. Sensitivity = 46% Specificity = 66%
Medical Outcome Study (**MOS**)	5 item, Likert scale Assesses adherence over the last month	Hypertension, diabetes, Dyslipidaemia	• Rate • Very limited info about barriers	Not consistent with current thinking about Adherence and concordance	Checked against prescription refill records with some association (r_s=0.261, p=0.05)
4-item **Morisky**	4 item, Dichotomous scale No time period over which adherence measured	Outpatient hypertension, patients taking ACEI or lipid lowering agents + other conditions (e.g. HIV, Crohn's)	• Rate • Barriers forgetting • Intentional element	Uses terminology like "careless" Limited information on barriers	Checked against blood pressure with significant correlation r_p=0.58 (p<0.01), sensitivity = 81% Specificity = 44% Cronbach's α = 0.61
8-item Morisky (**MMAS-8**)	8 item, Dichotomous and one Likert scale item One item previous day, previous 2 weeks.	Hypertension	• Rate • Barriers forgetting, different context Intentional element	Removed terminology like "carless" More info on barriers Still concise	Checked against blood pressure control with significant association (p<0.05), Cronbach's α = 0.83 Sensitivity = 93% Specificity = 53% Checked against prescription refill data with significant association (Concordance was 75% or higher).
Brief Medication Questionnaire (**BrMQ**)	9 item, Continuous Asks about previous week.	Hypertension, diabetes, dyslipidaemia	• Rate • Barriers Forgetting, beliefs, access to medicines Regimen, belief, recall & access screen.	Can be lengthy as it asks about each medicine in detail. Belief screen mainly looks at side-effects and bothersome	Prescription refill records, poor correlation: belief screen (r_s= 0.213), regimen (r_s=.091) Regimen Screen against MEMS® good correlation r_p=0.67. Sensitivity = 90% Specificity = 100% for >80% adherence
Visual Analogue Scale (**VAS**)	1 item, Continuous Previous month	Hypertension, diabetes and dyslipidaemia	• Rate • No barriers	Very limited info. But can use to measure adherence for each medicine.	1 month scale checked against MEMS®, significant correlation (r_s = 0.77)

(Zeller et al., 2008; Hamilton, 2003; Morisky et al., 1986; Morisky et al., 2008; Svarstad et al., 1999; Cook et al., 2005)

Table 2.6 - Self-report adherence assessment tools to assess beliefs about medicines as identified by the literature review

Self-report Tool	Description	Conditions Used In	Outcome	Practical issues	Validity and Reliability
Adherence Estimator ™ (**AE**)	3 item Likert scale Predicting intentional non-adherent behaviour	Generic, patients had different chronic conditions including cardiovascular disease, diabetes, osteoporosis, asthma and dyslipidaemia.	• Rate • Barriers around belief in benefit worry about harm and cost.	Very practical to use. Transferrable. Validated in America where cost issues are more relevant.	Validated in an already identified intentionally non-adherent patients. Sensitivity was 88% – of the non-adherers. Specificity was 59%. Predictive validity against pharmacy refills over 9 months. Significant associations were observed 0.655, 0.598, and 0.484 in the low-, medium-, and high-risk groups.
Beliefs about Medicines Questionnaire (**BMQ**)	18 items Likert scale No time scale. Explores beliefs. Two scales: BMQ-Specific scale (specific necessity + specific concern) BMQ-General scale (General overuse + general harm)	Wide range of conditions	• No direct rates of adherence • Possible predictions • Assesses participants' beliefs about medicines that they are currently using or prescribed • Assesses participants' beliefs and attitudes to medicines in general.	Very useful information about understanding people's beliefs & perceptions about medicines. Beliefs about medicines are more likely to be associated with intentional non-adherence Lengthy (18 items)	Various studies showed that non-adherent patients had one or more of the following when they completed the BMQ: Low necessity score, high concern scores, high overuse score, high general harm score, compared to adherent patients.

(McHorney, 2009; McHorney et al., 2009; Horne et al., 1999; Horne & Weinman, 1999)

It became apparent from the literature review that there was no single self-report adherence assessment tool that covers all dimensions and aspects of non-adherence behaviour. Therefore, it is more likely that an amalgamation of several tools will be needed to be used to be able to explore the medicines-taking behaviour in enough depth to inform the formulation of interventions. Supplementing these tools and

combining some of them may be the best way to achieve an accurate assessment of adherence and enable tailoring to patient needs (Hawkshead & Krousel-Wood, 2007).

2.3.1 Selecting a self-report adherence tool for CAD patients

Several factors should be considered when selecting an adherence scale. These include: the administration length of the tool, reliability and validity, ability to detect barriers to adherence, the type of non-adherence (intentional vs. unintentional) detected, transferability, generalizability, ability to assess beliefs about medicines, sensitivity and specificity, as well as the diseases in which it has been validated (NICE, 2009; Lavsa et al., 2011). All points considered in Sections 2.2.1 and 2.22 relating to validity, reliability and improving self-report tools should also be taken into account.

Only two tools were validated in CAD patients; the Single Question (SQ) and ARMS tools (Gehi et al., 2007; Kripalani et al., 2009). The SQ tool is practical and had good validity against cardiovascular events. However, it only reports the rate of non-adherence. It is very similar to the VAS tool which had good validity against MEMS®. The advantage of this tool is that it can be adapted to ask the same question for every single CAD secondary prevention medicine without burdening the patients with many questions as was seen in the BrMQ (Svarstad et al., 1999). This can help in identifying adherence levels to individual medicines. The SQ will be a good tool to use to quantify the level of non-adherence, but is insufficient on its own to explore barriers to adherence.

Despite its good validity against the 4-item Morisky scale, the ARMS tool is lengthy and uses terminology which may be misunderstood by patients and increase social-

desirability (Kripalani et al., 2009). It builds on the older version of Morisky which has been revised to a much improved 8-item version (Morisky et al. 2008). It covers barriers to repeat prescriptions, which should be included while screening for barriers.

The ASRQ and MOS had poor validity and sensitivity compared to other tools e.g. MMAS-8 (Hamilton, 2003; Zeller et al., 2008). The MOS also seems to check for compliance rather than adherence and it portrays the patient as someone who has to follow the orders of the prescriber (Hamilton, 2003).

The Morisky adherence assessment scales are among the most widely used self-reported medication adherence measures (Gao & Nau, 2000; Erickson et al., 2001; Shalansky et al., 2004; Sakthong et al., 2009). Despite its popularity the 4-item Morisky has poor psychometric properties, and measures the presence of non-adherent behaviour without taking its frequency into account (Morisky et al., 1986). It also uses terminology which can increase social-desirability (Morisky et al., 2008). The MMAS-8 is a much improved newer version with better psychometric properties compared to the old version and addresses previous limitations (Sakthong et al., 2009). Non-adherence is explored with a non-threatening and non-judgmental way to tackle the social-desirability and encourage patients to answer truthfully. It has good validity and reliability and is useful for quantifying non-adherence levels and identifying some barriers. However, it does not explore enough barriers to adherence (e.g. swallowing).

The BrMQ is good for extensive medicines review as it screens for regimen, belief, recall, and access to medicines (Svarstad et al., 1999). Its overall scoring system is not simple and it can be very lengthy if the patient takes many medicines. The belief

screen only explores "side-effects" and "medicine(s) bothersome". The access screen is very good as it explores several barriers to adherence including: ability to open medicines bottles, reading the label, swallowing, and ordering repeat prescriptions (Svarstad et al., 1999). These are very important barriers that should be included when exploring patient's medicines-taking behaviour.

Exploring patients' beliefs about medicines is very important to understanding medicines-taking behaviour (Horne & Weinman, 1999). None of the tools explore this aspect in enough depth like the BMQ. Therefore, it would be a good tool to use, though it is rather lengthy. The AE is a good short, practical, validated and reliable tool in detecting intentional non-adherence (McHorney, 2009). Its predictive feature is attractive in clinical practice as it can be used to identify patients who are likely to need adherence support in advance. The tool was developed in the United States of America, where the paying for medicines is different to that in the United Kingdom. However, cost of medicines for patients who are not exempt from paying prescription charges in the UK may be similar and therefore worth exploring.

Based on the above findings, in this research a number of adherence assessment and exploratory tools will be used to enable better exploration of the various dimensions of medicines-taking behaviour. This will also enable comparison of the different tools and inform practice. Those tools will include:

- SQ - a modified version, asking about each CAD secondary prevention medicine
- The MMAS-8
- The BMQ
- The AE

Full details about these tools are provided in the following sections.

As discussed earlier in relation to the BrMQ, the assessment of access to medicines is essential. Therefore, there should also be screening for problems in opening bottles or blister packs, reading labels, swallowing and issues with ordering repeat prescription.

2.3.1.1 The MMAS-8 assessment tool

The MMAS-8 scale contains 8 items and was built on the theory that there are many causes to medicines non-adherence (see Figure 2.1) (Morisky et al., 2008). So it asks the patients questions around these causes. For example, questions around remembering such as *"Do you sometimes forget to bring medications with you when travelling?"*, questions around the complexity of the regimen such as "*Do you feel hassled by sticking to your treatment plan?"*. The MMAS-8 items measure specific behaviours and are not each a determinant of adherent behaviour (Morisky et al., 2008). The scale uses the following preface to minimise social-desirability:

> *"You indicated that you are taking medication for your (identify health concern). Individuals have identified several issues regarding their medication-taking behaviour and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your (health concern) medication. Interviewers may self-identify regarding difficulties they may experience concerning medication-taking behaviour."*

Patients answer yes or no to items 1–7 and choose one of 5 options to answer questions 8. Items 1,2,3,4,6 and 7 score "1" if the patient answers "no" and "0" if they answer "yes". This is reversed in question 5. Question 8 scores "1" for "Never" and "0" for "Always". "Almost never" scores "0.75", "Sometimes" scores "0.5" and "Quite often" scores 0.25 (Morisky et al., 2008; Morisky, 2009, pers. comm.).

Question				Please Tick Box	
1. Do you sometimes forget to take your heart medicines ?				Yes	No
2. Over the past 2 weeks, were there any days when you did not take your heart medications ?				Yes	No
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it ?				Yes	No
4. When you travel or leave home, do you sometimes forget to bring along your medications?				Yes	No
5. Did you take your heart medications yesterday ?				Yes	No
6. When you feel like your heart condition is under control, do you sometimes stop taking your medications ?				Yes	No
7. Do you ever feel hassled about sticking to your heart treatment plan ?				Yes	No
8. How often do you have difficulty remembering to take ALL your heart medications ?	Never	Almost Never	Sometimes	Quite often	Always
PLEASE TICK BOX	☐	☐	☐	☐	☐

Figure 2.1 – The MMAS-8 scale (Morisky et al., 2008).

The total score ranges from 0 to 8, where higher scores indicate higher adherence. The ranges are classified and interpreted as can be seen in Table 2.7.

Table 2.7 – Interpretation of the MMAS-8 total scores

Total MMAS-8 Score	Interpretation
8	patient is likely to be adherent
6 to <8	medium adherence
< 6	low adherence

2.3.1.2 The Adherence Estimator ™ (AE)

The AE is a brief three item proximal screener for the likelihood of intentional non-adherence to medicines used in chronic disease (McHorney, 2009). The tool contains three proximal drivers of adherence: perceived concerns about medicines, perceived need for medicines, and perceived affordability of medicines. The tool was designed with the involvement of intentionally non-adherent population. These drivers were identified and cross-validated in nearly 2000 adult patients using two rounds of psychometric approaches (McHorney, 2009). The researchers used a synthesis of psychometric results obtained from classical and modern psychometric test theory (McHorney, 2009).

As can be seen in Figure 2.2 each one of the three questions has a weighted Likert scale. Each response to each question is given a weight. The summation of these weights produces a total score which can be easily interpreted to categorise the patients into one of three groups:

1) Low risk for adherence problems, >75% probability of adherence (Score=0)
2) Medium risk for adherence problems, 32-75% probability of adherence (Score=2-7)
3) High risk of for adherence problems, <32% probability of adherence (Score ≥ 8)

Statements	Agree completely	Agree mostly	Agree somewhat	Disagree somewhat	Disagree mostly	Disagree completely
I am convinced of the importance of my prescription medication	**0**	**0**	**7**	**7**	**20**	**20**
I worry that my prescription medication will do more harm than good to me	**14**	**14**	**4**	**4**	**0**	**0**
I feel financially burdened by my out-of-pocket expenses for my prescription medication	**2**	**2**	**0**	**0**	**0**	**0**

Figure 2.2 - The Adherence Estimator self-scoring algorithm (McHorney, 2009). The total number of points are added up from each ticked box and interpreted as explained above.

The tool was also validated for its ability to predict non-adherent patients against pharmacy claims (cashed prescriptions) in nearly 1600 patients (McHorney et al., 2009). The study showed that patients' propensity to adhere to their medicines using the AE was statistically associated with several measures of adherence as derived from pharmacy claims over a 9-month period (McHorney et al., 2009).

2.3.1.3 The Single Question scale

The SQ adherence assessment tool was used in the Heart and Soul Study by Gehi et al. (2007). In this study patients with stable CAD were asked in an outpatient setting to answer one question "In the past month, how often did you take your medications as the doctor prescribed?". Patients were given a Likert scale to answer this question and the possible responses were: "All of the time" (100%), "Nearly all of the time" (90%), "Most of the time" (75%), "About half the time" (50%), or "Less than half the time" (50%) (Gehi et al., 2007). The cut-off point for non-adherence was defined as 75% by the authors. They cited that the reason for this was that the small number of

participants in the latter categories (75% and 50%), non-adherence was defined as 75% of the time or less. The study found that patients who were classed to be non-adherent by this SQ scale (≤75%) had a greater than 2-fold increased rate of subsequent cardiovascular events, including coronary heart disease death, myocardial infarction, and stroke (Gehi et al., 2007). The tool can be modified to make it measure adherence to individual secondary prevention medicines.

2.3.1.4 Beliefs about Medicines Questionnaire (BMQ)

Beliefs about medicines are powerful predictors of adherence to medicines' behaviour and exploring patients' beliefs is therefore very important for the purpose of this study (Horne & Weinman, 1999). The BMQ was developed by Horne et al. (1999) to understand the beliefs and perceptions that patients have about medicines. The BMQ has two different scales and each scale has two subscales as follows (Horne et al., 1999):

- **The BMQ-Specific scale** - assesses participants' beliefs about medicines that they are currently using or prescribed (e.g. Secondary prevention medicines for CAD)
    - The ***specific necessity*** **subscale** – measures the level of belief that a patient has about the necessity of their medicines.
    - The ***specific concern*** **subscale** – measures the level of concern that a patients have about their medicines.
- **The BMQ-General scale** – assesses participants' beliefs and attitudes to medicines in general.
    - The ***general overuse*** **subscale** – measures the level of beliefs participants have about over prescribing or over using medicines by doctors.

- The ***general harm*** **subscale** – measures the level of beliefs participants have about the harmfulness of medicines in general.

The first 2 subscales contain 5 questions each. The latter two subscales contain 4 questions each. Each question has a 5 items Likert scale ranging from "strongly agree" to "strongly disagree".

Various studies have shown association between one or more of the BMQ subscales and adherence to medicines (Horne & Weinman, 1999; Ross et al., 2004; Khanderia et al., 2008). For example hypertensive patients who believe in the necessity of medication were more likely to be adherent (odds ratio 3.06; 95% CI: 1.74-5.38; $p<0.001$) (Ross et al., 2004). A similar finding was seen in haemophilia patients (Llewellyn et al., 2003). However, perceptions of the necessity of treatment were not always associated with adherence to treatment in patients. This was found in patients with diabetes whose concerns regarding the use of treatments outweighed the benefits of regularly taking medicines (Horne et al., 1999). Strong concern about potential medicines adverse effects scores on the BMQ were found to be associated with higher self-reported non-adherence (Bane et al., 2006).

Following coronary artery bypass graft (CABG), non-adherent patients were in stronger agreement on the *General Overuse* (p = 0.01) and *General Harm* (p = 0.04) scales (Khanderia et al., 2008). The adjusted odds of adherent behaviour were significantly lower, with an increasing *General Overuse* score (odds ratio 0.83; 95% CI: 0.72 - 0.95; p = 0.007) (Khanderia et al., 2008).

2.4 Aims and objectives of the study

This study is conducted to investigate medicines-taking behaviour among patients with CAD. The main focus was on adherence to CAD secondary prevention medicines. The study's primary aim is:

To investigate the prevalence and possible factors contributing to self-reported non-adherence to secondary prevention medicines in patients living within West Yorkshire and nearby areas who have a well-established diagnosis of CAD.

The following were the primary objectives of this study:

- Assess self-reported non-adherence to collective and individual secondary prevention medicines.
    - Aspirin, clopidogrel, statins, beta-blockers, ACEI, ARBs.
- Compare the findings, practicality, sensitivity and reliability of three different instruments (questionnaires) which assess self-reported non-adherence; MMAS-8, Adherence Estimator™, and the Single Question approach.
- Identify barriers contributing to non-adherence to inform and change practice.
- Survey the prevailing individual beliefs and attitudes to use of medication among patients with established CAD.

The secondary objectives were:

- Identify the level of secondary prevention medicines prescribing and use in patients with stable CAD.
- Develop a practical approach to address non-adherence among this population.

3 Methodology

This chapter will describe how this research was designed and conducted based on the findings of the literature review and the stated aims and objectives. The methods used to conduct this study will be detailed together with the rationale, approach and tools used to interpret and analyse the results.

3.1 Study design and rationale

This was a cross-sectional study designed to understand the current medicines-taking behaviour among a selected patient population with established CAD. It was also a prevalence and hypothesis generating study which attempted to explore the levels of non-adherence to CAD secondary prevention medicines and the factors influencing the medicines-taking behaviour of CAD patients. A quantitative method was used in order to quantify the levels of self-reported non-adherence to secondary prevention medicines and reasons for non-adherence. The study included multiple self-report adherence assessment and exploratory tools to capture wider aspects of non-adherence behaviour and compare the tools' performance and findings. To enable the administration of these tools a special questionnaire, "The Heart Medicines Survey", was developed for data collection (see Appendix 2). The questionnaire method is widely used in cross-sectional studies. Compared to other methods that can be used to administer self-report questionnaires, such as interviews and telephone calls, this was the most practical and efficient approach, as discussed in Section 3.1.2.

The analysis of the findings of the survey intends to generate hypotheses to enable better ways of identifying non-adherent patients and tackle contributing factors to non-adherence in practice.

The time line for designing and conducting this study can be seen in Figure 3.1. The Heart Medicines Survey was designed based on the findings of the literature review to answer the primary and secondary aims and objectives of the study. This is discussed in Section 3.2. The target population was identified from the on-going West Yorkshire ENCOURAGE (Epidemiology of Northern Cardiovascular Outcomes and Underlying Risk of Atherosclerosis due to Genes and Environment) programme database (see Section 3.3). Full protocols and necessary documentation were prepared as discussed in Section 3.4 and can be seen in Appendices 3, 4, 5, 6 and 7. As the study was taking place in the NHS, a full application to the NHS Research & Ethics Committee (NHS REC) was made. Applications were also made to the Leeds Teaching Hospitals Research and Development (R&D) unit and the University of Bradford Research Ethics committee. All relevant bodies approved the study as can be seen in Appendix 9. A special *Microsoft Access®* database, called RANI-1, was built to hold the data electronically before the study started. Full description of the RANI-1 data base can be seen in Appendix 11. Patients who met the inclusion criteria of the study were identified as detailed in Section 3.3. The study was started in Jan 2010. Patients were contacted by post in groups of 20-40. All returned questionnaires were entered into the RANI-1 database. Detailed examination of each single questionnaire was carried out in patches after data was entered into the database as described in Section 3.7. Last entry into the database was made in January 2011. Complete analysis of data was completed by September

2011. Thank you letters were sent to all patients participating in the study with suitable information leaflets in Oct 2011 (see Appendices 10 and 13).

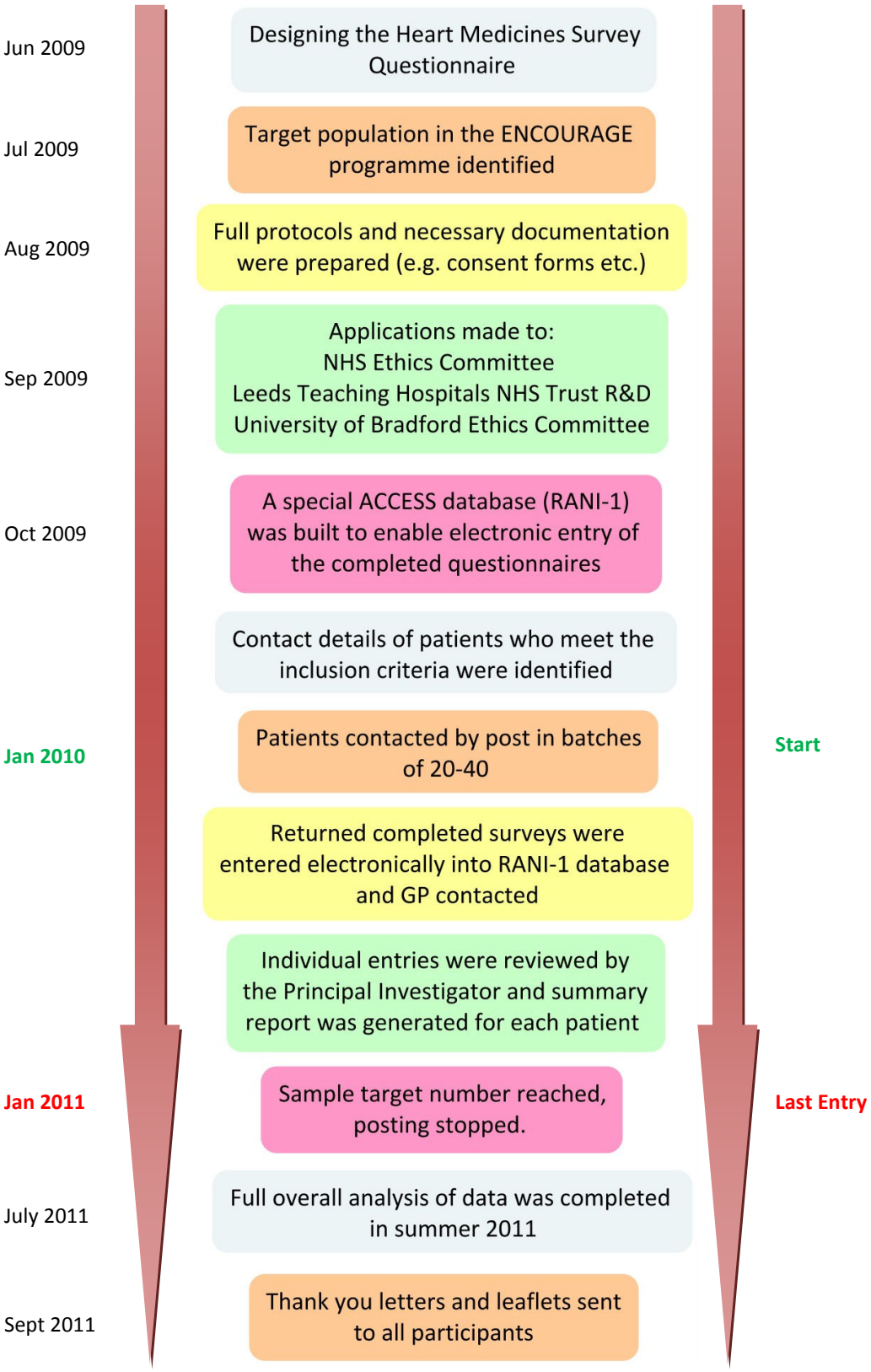

Figure 3.1 – Summary of the major steps in designing and conducting the study.

3.1.1 Advantages of the questionnaire tool and approaches used to improve limitations

The study employed self-report postal questionnaires for data collection. This is an efficient method of data collection from large number of patients. It is also a very practical tool and can be easily replicated in practice. As this research was intended to inform practice, approaches that could be duplicated and used in practice were selected. Questionnaires have the flexibility to be designed to meet the research question and provide an organised data gathering tool which can easily be entered in a database and analysed (Matthews & Ross, 2010). Compared to other self-report methods, such as interviews, questionnaires enable quicker data collection in a short period of time.

The questionnaire method gave participants the chance and time to consider the questions on their own. They could look up their medicines in their own time, complete parts of the questionnaire or all of it as it suited them. As participants were completing the questionnaire on their own, they probably would have been more likely to feel comfortable expressing their opinions about their medicines on paper than to share it face to face with healthcare professionals (Braker et al., 1994).

One of the main problems that survey - or questionnaire-based studies - face is low response rate. It was demonstrated by various researchers that non-responders may differ from responders in important ways which can result in study bias (Matthews & Ross, 2010). Therefore, it was important to maximise the response rate to reduce such potential bias. If high response rate was not achieved, the sample would be viewed as

self-selecting (Smith, 2010). Various measures were employed in advance to address this limitation. A covering letter which summarised the purpose of the study, what it involved and the benefits gained from the information provided by participants was enclosed with the first communication (see Appendix 5). A patient information leaflet was also enclosed to clarify frequently asked questions and explain the relevance of the study to patients with CAD (see Appendix 6). A full explanation of confidentiality and reassurance were provided and it was made clear to potential participants that they would be able to withdraw from the study at any time. This could reduce reluctance to take part in the study (Smith, 2010). A free phone number was also provided to enable patients to contact the researcher if they had any questions or queries about the study. To eliminate any ambiguities in the questionnaire it was piloted among a number of healthcare professional colleagues. Table 3.1 summarises some of the other limitations of self-reporting questionnaires and suggested possible approaches to minimise these limitations.

Table 3.1 – Further limitations of postal questionnaires and considerations to reduce these limitations.

Limitation	Considerations
• Postal questionnaires may take long time to be returned or patients may forget about them. • Limited access for the researcher to in-depth experience. • Certain people might be excluded. Example, patients unable to read or write and those with a language barrier. • Costs – including printing, envelops, administration time, postage (posting and return envelopes), data entry time.	• Send patients a reminder • Provide patients the opportunity to provide extra comments • Identify patients with literacy or language barriers in advance and offer alternatives (e.g. translations) • Cost is still acceptable compared to other methods (e.g. interviews). Use 2nd class stamps or free post scheme.

(Content adopted from Matthews & Ross, 2010; Smith, 2010)

More details on the limitations and ways to improve self-report questionnaires were provided in Section 2.2.

3.1.2 Other methods that could have been used

Other methods could have been used in this study to collect the data. *The interview method* using a structured or a non-structured questionnaire style would have had some advantages. This method would have enabled further exploration of interesting responses and the collection of more in-depth data about the reasons for non-adherence. Participants would also have been able to clarify with the researcher any issues that they would prefer to talk about rather than write down in a questionnaire. Interview methods, however, are very labour intensive, time consuming, more costly and may require more resources. Such methods would have needed several researchers to be able to interview big number of patients.

Collecting the data using *telephone calls* would have been another option. This method would have had the advantage of collecting data in a shorter time, if resources were available, rather than waiting for patients to return the questionnaires. The researcher would have had the opportunity to discuss with patients adherence related issues or explore further interesting answers. Patients would have had the opportunity to ask questions and clarify any ambiguous issues. Such a method can be cheaper and enable contacting more patients compared to the interview method. However, with the limited resource available the researcher would have needed to spend longer time collecting the data, and would have needed to make two phone-calls at least to enable patients to prepare themselves for the interview. In addition, contacting patients during a suitable time would have been another challenge. The frankness of the responses could have been influenced by the time of the call and the presence and absence of other people around the participant (Smith, 2010). It would also have been necessary to contact

patients in advance and provide them with all the necessary documentation (e.g. information about the study, consent form).

The use of *electronic questionnaires* was another method which was explored by the researcher. Such a method would have been a very efficient way of conducting the research in terms of time, data collection, data entry and contacting patients. Such an approach would have required the participants to have internet access and ability to use e-mails and web browsers. Furthermore, the researcher would have needed the e-mail addresses of all participants and such information was not available. Due to confidentiality issues the researcher would have needed to develop a special secure website which enabled patients to access it and enter their personal details and answers to the questionnaire. This was not practical at this stage. However, this approach will be explored for future research related to this area.

3.2 The structure and design of the Heart Medicines Survey questionnaire

The Heart Medicines Survey questionnaire was designed to answer the primary and secondary research questions. The design and content of the questionnaire are a very important part of the research as they determine the questions and the answers that the researcher will be working with (Matthews & Ross, 2010). Based on the findings of the literature review four adherence assessment and exploratory tools were included to understand the various aspects of medicines-taking behaviour and enable comparison of the tools (see Section 2.3.1). The MMAS-8 and SQ tools estimate levels of self-reported non-adherence. The MMAS-8 also explores possible reasons for non-

adherence. The AE screens for likelihood of levels and reasons of intentional non-adherence. The BMQ explores in more detail patients' beliefs about medicines. Figure 3.2 shows the overall structure of the Heart Medicines Survey (see also Appendix 2).

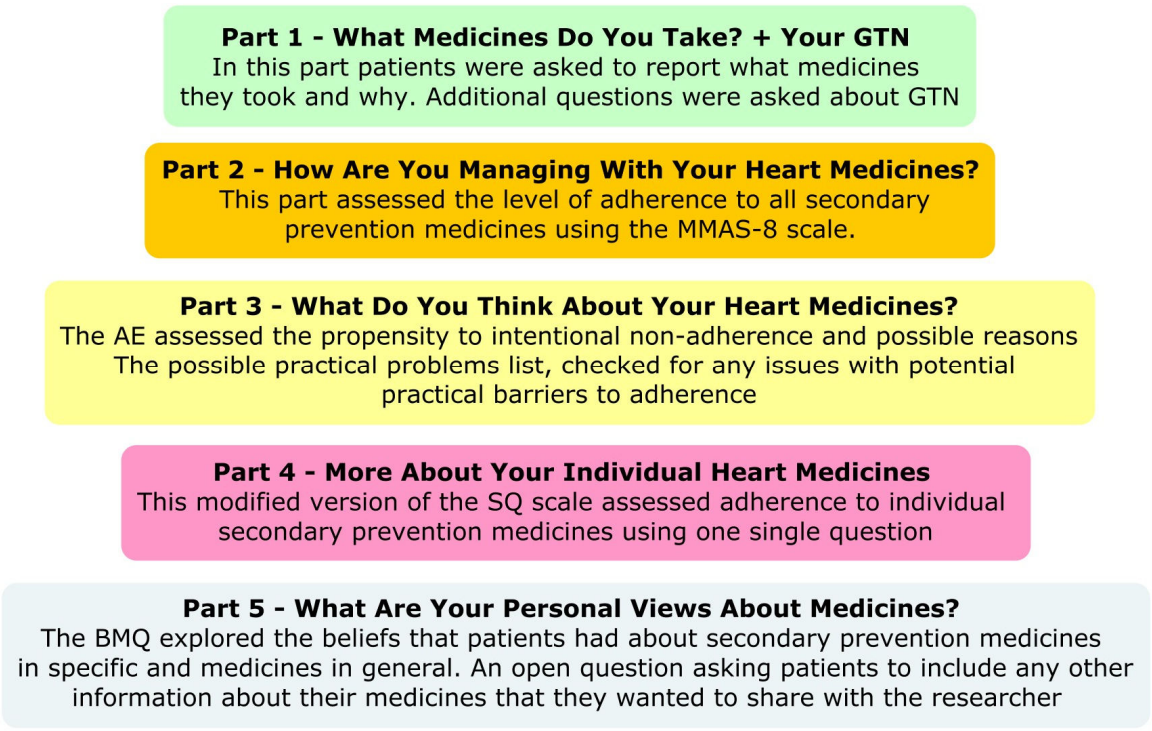

Figure 3.2 – The structure of the Heart Medicines Survey.

The questionnaire was composed of 5 parts. Part 1 aimed to identify what medicines the patient was taking and assess their basic knowledge of the indication of each secondary prevention medicine. This was of value when analysing the results of the survey in terms of the number, types, frequency and knowledge of the indication for the medicines prescribed. This part also asked about GTN use as it could be an indicative of how well patient's angina was controlled. Parts 2, 3 and 4 used the pre-validated self-report adherence assessment tools to evaluate adherence to CAD secondary prevention medicines. Part 3 also explored four potential or possible barriers to adherence based on the BrMQ (see Section 2.3.1). These were practical problems that patients might

have faced when handling medicines and could have contributed to non-adherence. They included: opening medicine bottles or blister packs, reading the label, swallowing the medicine and ordering repeat prescriptions. Patients were asked to identify any issues with these *"Possible Practical Problems"* using a Likert scale to give them a better chance to express the extent of the problem, if present. This also helped the researcher better distinguish between respondents according to the scale.

The SQ in Part 4 was modified to explore levels of non-adherence to individual CAD secondary prevention medicines. The single question nature of this tool made it easier to utilise for this purpose without burdening the patient with a lengthy survey. The modification involved the listing of the different classes of secondary prevention medicines in a table as can be seen in Appendix 2. The patient was asked to estimate their level of adherence in the previous month to each one of these medicines. This approach enabled the collection of additional information about non-adherence to individual secondary prevention medicines.

Part 5 included the BMQ and an open question to enable the respondents to answer in their own way and add any other issues that they wished to share with the researcher about their medicines. An open question at the end of the questionnaire sends a message to the respondents that their opinions were valued (Matthews & Ross, 2010).

Each part of the questionnaire began with a statement explaining the purpose of the questions and providing instructions on how to answer them. Jargon was avoided and language used was familiar to patients whenever possible. The introductory statement and the questions were worded in a way to minimise them coming across as judgmental

or insensitive which could have made patients feel embarrassed or ashamed to report their medicines-taking behaviour (Matthews & Ross, 2010).

More details about the 4 tools used in the questionnaire can be seen in Sections 2.3.1.1 to 2.3.1.4.

3.2.1 Agreement with authors of adherence assessment tools.

The researcher sought permission from the developers of these tools. The MMAS-8 tool is copyrighted and the author was contacted and permission was granted. The AE was also copyrighted and the author requested a signed agreement for using the tool. The developer of the BMQ, Prof. Rob Horne, was informed of the intentions of the researcher to use this tool. No official agreements were requested. The SQ tool was not copyrighted. See Appendix 14 for communications with authors and use agreement.

3.3 Target population

The study targeted patients with established CAD in West Yorkshire and nearby areas who had been prescribed a minimum of one CAD secondary prevention medicine for at least three months. The study ran in conjunction with the ENCOURAGE programme which is managed by the Cardiovascular Research Unit at the Yorkshire Heart Centre, Leeds. The programme frequently invites patients in the region to take part in various cardiovascular studies. Over the years it built a database of patients who have given consent allowing the unit to contact them whenever needed to offer them the opportunity of participating in cardiovascular research studies. Patients on the database

regularly receive the ENCOURAGE Newsletter to update them on recent developments in heart disease.

The ENCOURAGE database provided a practical and convenient way to access patients with CAD in the region with the limited resources and time frame of the study. Because the Yorkshire Heart Centre at the Leeds General Infirmary is one of the largest in the country and provides secondary care for Leeds and also tertiary care for West Yorkshire and part of North Yorkshire, there was a good representation of the different parts of the region (LTHT, 2011). In prevalence studies it is important that the sample is representative of the relevant population in order to be able to make inferences (Marston, 2010).

3.3.1 Sampling

Eight hundred patients within the ENCOURAGE cohort expressed specific interest after the April 2009 Newsletter mail shot in assisting in heart related health-care improvement projects. A purposive sample of 696 patients was chosen by screening respondents to check if they met the inclusion criteria of the study as detailed in Table 3.2. All patients who met the criteria were contacted in batches of 20-40 inviting them to participate in the study. Patients were sent a covering letter explaining what patients needed to do to participate, a study patient information leaflet, consent form, the Heart Medicines Survey and prepaid envelope. Patients were asked to sign the consent form, complete the survey and post it back using the prepaid envelope if they were interested in taking part in the study. Those who were not interested did not need to do anything. Forms are found in Appendices 2, 4, 5 and 6.

Table 3.2 – Inclusion and exclusion criteria of the study.

Inclusion criteria
1. Individual patients within the ENCOURAGE cohort who have recently expressed a specific interest in being involved in heart related healthcare improvement projects.
2. Well-established CAD (CAD defined as documented or reported MI, CABG, PTCA, or angina (positive exercise test))
3. Prescription of at least one secondary prevention medicine for at least 3 months. (Secondary prevention medicines are: aspirin / clopidogrel, statins, beta blockers, ACEI / ARBS).
4. Able to independently give informed consent.
Exclusion criteria
1. Patients who did not want to be contacted for further studies.
2. Patients who are not part of the ENCOURAGE programme.

If it had been feasible with the number of patients available a random sampling approach would have been adopted. The advantage of random sampling is that all members of the population have an equal probability of being a member of the selected sample and bias is reduced (Marston, 2010). It is important to emphasise, however, that all sampling frames have their own potential problems and measures should be taken to minimise bias as much as possible.

3.3.2 Sample size

The decision on the sample size for this study was based on two factors:

Better representation and practicalities - The sample size for surveys should ensure sufficient numbers of the groups that needed to be compared (if sample is not random) (Matthews & Ross, 2010). Generally, the larger the sample in survey research, the more accurate the estimates when applied to the wider population and the narrower the confidence intervals (Smith, 2010). Other factors which influenced the sample size were time, practicality, availability of resources, and the ease of access to the sampled cases

(Matthews & Ross, 2010). The researcher considered the time scale for completing this study and the resources available and decided based on these factors, that 500 patients would be reasonable.

A follow up study - The design of this study was part of the ADHERE Study (see Section 1.1). The power calculations used to determine the sample size for the ADHERE study determined the sample size for RANI-1. A statistician was consulted on the design and the power of the ADHERE study. The sample size needed to conduct the study was 40 – 60 patients for each arm (of 3 arms). That is a total of 120 – 180 patients. That is a power of 90% and an alpha of 0.05 to be able to detect 1 unit change in the MMAS-8 score. Because the levels of non-adherence in the literature are estimated to be around 30 – 50%, it was estimated that screening 500 patients for non-adherence would be sufficient to identify around 150 – 250 non-adherent patients to take part in the ADHERE study.

3.4 Ethical considerations

This healthcare research study needed a formal ethics approval because it was conducted on NHS premises and involved contacting patients and retaining identifiable patient information. Any ethical appraisal of a study should consider three different perspectives according to the Foster Framework (Smith, 2010):

1. The worthiness and value of the study and whether the aims are likely to be achieved.
    a. The importance of the study
    b. Are the methods chosen the best way of answering the research question
    c. How beneficial will the findings be to patients and the healthcare system

2. Is what the study is asking participants to do reasonable and justified.
    a. The time and effort required from the participants
    b. The risk the participants are exposed to by enrolling in the study
    c. Are the needs / special needs of participants taken into account?

3. Respecting the rights of the participants
    a. Full information provided to participants to enable them to have full understanding and opportunity to ask questions.
    b. Genuine informed consent to participate and ability to withdraw from the study easily. Enough time to consider their decision.
    c. Anonymity and confidentiality of data

As can be seen from the detailed NHS REC and R&D application forms, all the above issues were addressed (see Appendix 8). Full ethical approval documents are in Appendix 9. The University of Bradford Ethics Committee also approved this study. All relevant documents (e.g. protocol, consent form, patient information leaflet, covering letter, thank you letter etc.) are in Appendices 3 to 10.

3.5 Conducting the study

After the study was granted NHS REC and R&D approvals it was started in Jan 2010. As described in the sampling section, a purposive sample was selected from the ENCOURAGE database. The mortality status of those patients was checked on the NHS Patient Summary Records before they were contacted (i.e. patients were still alive according to the system). Figure 3.3 is a flow diagram which describes how the study was conducted. An entry was made in the RANI-1 database (see Appendix 11) of all the patients who were contacted (see Section 3.3.1). All returned questionnaires and consent forms were examined. If the consent form was not completed correctly or was

missing, the patient was contacted to address any queries about consent or missing documentation. Once consent was established the patient's GP was contacted by post to inform them of their patient's participation in the study. See Appendix 7 for GP letter.

All returned forms were handled with full confidentiality. The paper version was stored in a safe cabinet within the research unit. The cabinet was securely locked and accessed only by the research team as per protocol (see Appendix 3). The data were then entered electronically into the database on the secure server by the support clerk. The patient's progress in the study was marked accordingly.

The researcher carried a detailed examination of each single questionnaire in batches after data were entered into the database. The last entry into the database was made in Jan 2011. The review of all returned questionnaires was completed in June 2011. During the review of the questionnaires the researcher considered the following:

1) The accuracy of data entry.
2) Level 1 medicines review (see Appendix 12).
3) Assessment of patient's knowledge.
4) Examination of the overall adherence status of the patient according to the scores of the different scales and considering any missing data.
5) Reviewed the comments made by patients.
6) Completed the analysis summary on the RANI-1 database (see Appendix 11).

From June 2011 to Sept 2011 a full analysis of the overall findings of the survey were conducted as described in the data interpretation and analysis Section 3.6. Thank you letters were sent to all patients participating in the study with suitable information leaflets in Oct 2011. For more information about the leaflets that were provided see Appendix 13.

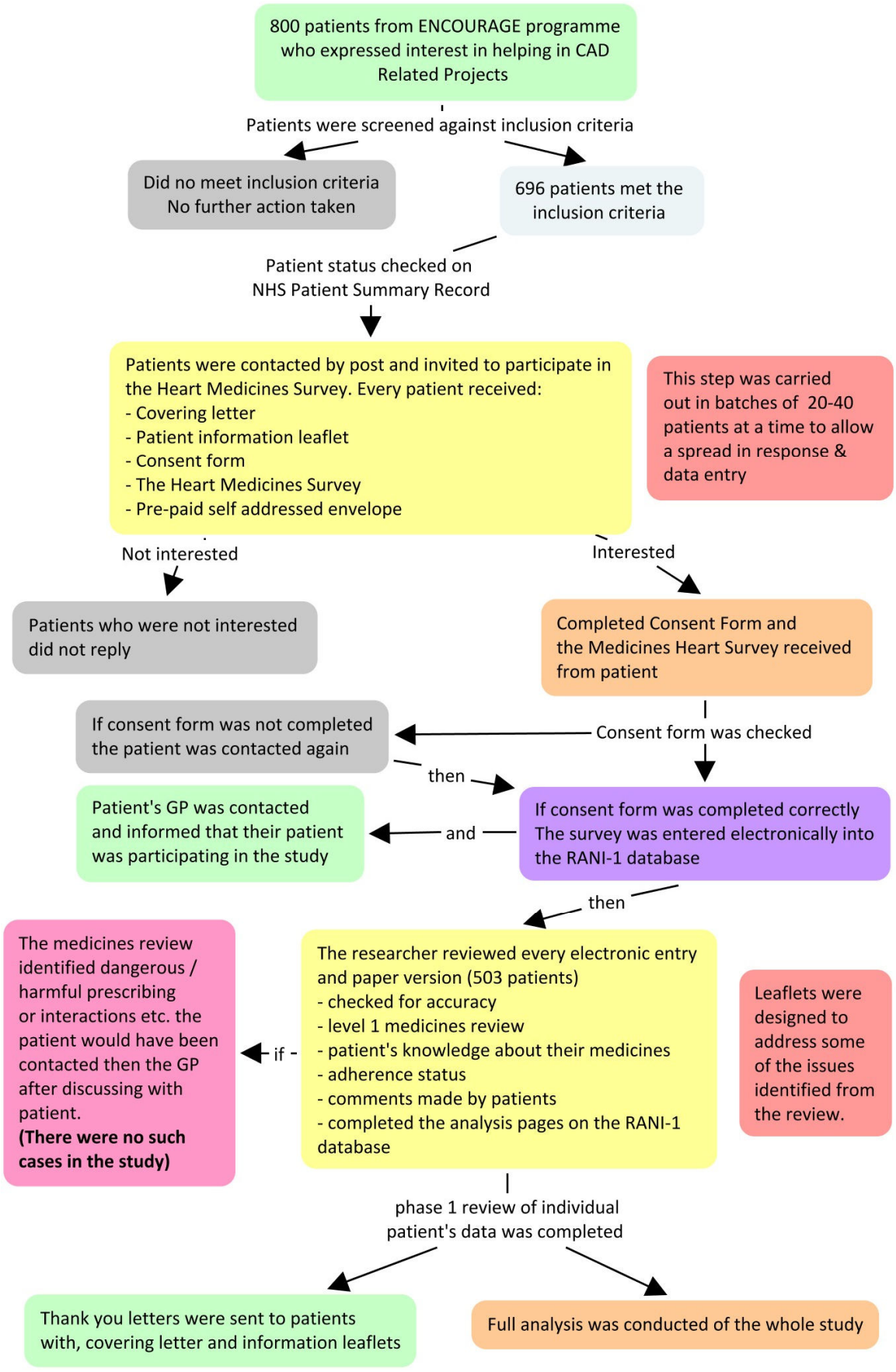

Figure 3.3 – A flow diagram which describes how the study was conducted.

3.6 Data interpretation and analysis

This section will detail the assumptions and approaches used while interpreting and analysing the findings of study. Full statistical analysis was conducted on the dataset. Statistical analysis included the use of simple descriptive statistics which enabled the presentation and understanding of the characteristics of the dataset. Bivariate statistical investigations were used to identify any associations between variables. Multivariate analysis was followed mainly by using logistic regression. The full detail of statistical tools and principles used can be found in Appendix 15. Detailed statistical output and analysis can be found in Appendix 16. Frequency and categorisation analysis was also carried out on the last part of the questionnaire and will be detailed in Section 3.6.7. The RANI-1 *Microsoft Access®* database was used to code all questions and answers and various reviews of overall data was conducted using the functions in the database to establish familiarity with the dataset. *Microsoft Excel® 2010* was also used to conduct various frequencies and interpretative analysis. The *SPSS v.19 (IBM, Chicago IL)* was employed to conduct all statistical analyses. The mind mapping software *IHNC CmapTools* was used during exploration of patients' comments, thematic and frequency analysis.

3.6.1 Organising and presenting the data and using descriptive statistics

3.6.1.1 Demographics

The demographics of the sample according to age, gender, post code, ethnicity and marital status were described. The data on ethnicity and marital status were obtained from the ENCOURAGE database. Patients were grouped according to their post codes.

Post codes were also grouped according to the following categories: Leeds, West Yorkshire (other than Leeds) and outside West Yorkshire. This grouping aimed to explore the geographical spread of the sample.

The patients' marital status was incomplete, as around 45% of patients did not identify their current marital status in the database. This was only identified after the analysis. Therefore, the marital status analysis was conducted by collapsing the categories into two; married vs. non-married during bivariate analysis. This produced larger cell counts to see if the chi-square test assumptions hold (Marston, 2010; Smith, 2010).

3.6.1.2 Comorbidities and cardiac history

All available information about patients' cardiac history, medicines, identifiable comorbidities relevant to CHD was identified, grouped and presented. These variables were used in the exploratory analysis comparing groups of adherent and non-adherent patients. Patients identified their angina, MI, angioplasty and bypass (CABG) procedure when they expressed interest in being contacted. No exact dates were provided of when the events or procedures took place. None of these claims were verified against the medical notes as it was not practical to review the medical records of 503 patients.

Patients' medicines were reviewed and two comorbidities relevant to CAD and/or medicines taking analysis were identified. These were diabetes (controlled with medicines) and hypothyroidism (controlled by levothyroxine). Patients who were prescribed anti-diabetic medicines were assumed to have diabetes. Those who were prescribed levothyroxine were assumed to have hypothyroidism.

Patients recruited into this study participated in the past in various studies conducted in the Cardiovascular Research Unit. Patients' participation in previous studies was identified. This information shed light on the cardiac history of the sample. This will be elaborated on in the Results and Discussion Chapters.

3.6.1.3 Number and frequency of prescribed medicines

Descriptive statistics were presented of the number of medicines prescribed according to patients' reporting in Part 1 of the questionnaire. The descriptive statistics presented for the purpose of exploring the dataset were for the following variables: number of medicines prescribed, number of individual daily doses and the number of daily administrations. *The number of daily doses* was calculated in order to account for medicines with more than once a day doses and enable comparing the impact of the frequency of medicines taking on adherence. *The number of daily administrations* represented the total number of times the patient had to take a medicine regardless of the number of medicines taken at the point of administration. More than one medicine may have been taken at each administration time.

3.6.1.4 Secondary prevention medicines

Special attention was paid to the secondary prevention medicines because they were at the centre of this study. The frequency of each single class of secondary prevention medicines and all prescribed combinations were explored. The total number of doses and the total number of administration times per day were also presented.

3.6.1.5 Patients' knowledge of secondary prevention medicines indications

The patients' knowledge about the indication of their secondary prevention medicines was divided into 3 categories: *"specific"* knowledge if the patient reported the indication and gave a correct description which distinguished the class of medicine e.g. antiplatelets, *"general"* knowledge if the patient identified that the drug is for the heart, and *"none"* if the patient was unsure about the indication, provided incorrect information or left blank. The researcher decided on these categories as part of the review of the returned questionnaires. For the purpose of analysis the categories about knowledge were also grouped into two categories: *"knowledgeable"* which included patients who reported "specific" knowledge about the secondary prevention medicines and *"not knowledgeable"* which included patients who were identified to have "general" or "none" level of knowledge about secondary prevention medicines.

The overall patients' knowledge about ***all*** the secondary prevention medicines that they were prescribed was calculated as follows: after allocating each secondary prevention medicine with a score of 1 to 3 (1 = having "specific" knowledge about the medicine, 2 = "general", and 3 = no knowledge was reported), all scores were added and the average was calculated for each patient. This was used to compare overall knowledge of secondary prevention medicines between different groups.

3.6.1.6 GTN

Patients were asked to report if they had GTN spray or tablets used to manage their angina. Those who reported that they did possess GTN were also asked to report the frequency of GTN use. Descriptive statistics were used to summarise these data.

Because patients reported the frequency of GTN use in different ways; as number of times per day, per week and per month, a cumulative monthly description of GTN use was calculated and presented to enable easier comparison. Daily and weekly frequencies were converted into monthly frequencies.

3.6.1.7 Possible practical problems

The four possible practical problems that could impact on adherence were examined. The frequencies of the results were summarised under each one of the 4 Likert scale options. The results were also presented by grouping the 4 categories into the following categories: *"There is a problem"* included patients who identified the barrier to be always or sometimes a problem and *"Need a solution / alternative"* included patients who identified that the barrier was not a problem but preferred an alternative or the barrier was sometimes or always a problems and a solution was needed. The associations between the four barriers and non-adherence identified by various scales were examined.

3.6.1.8 Descriptive statistics used

Descriptive statistics were used to summarise the data. Frequencies on each variable were reported and presented in different formats e.g. tables, bar charts, pie charts as can be seen in the Results Chapter. Depending on data type (nominal, ordinal, scale), appropriate summary statistics were chosen to describe each set of data (variable). For central tendencies: mean was used for normally distributed variables and median for data which was not normally distributed. In normally distributed data the mean equals median (Marston, 2010). To describe the spread of normally distributed data, standard

deviation was used. For variables which were not normally distributed interquartile range (lower quartile, and upper quartile), minimum and maximum were reported. Because the second quartile equals the median, it was not reported (Marston, 2010). The normal distribution of continuous parametric data was tested using the Probability–Probability plot (P-P plot), Kolmogorov-Smirnov test (K-S test) and a histogram. These data can be seen in Appendix 16. Wherever missing data was identified and valid percentages were reported.

3.6.2 Adherence assessment tools – scoring and exploration

The MMAS-8 and AE scales were scored in accordance with the described scoring systems in Sections 2.3.1.1 and 2.3.1.2. However, additional considerations for these scales are highlighted here. The SQ and BMQ scoring considerations are described below.

3.6.2.1 The MMAS-8

The internal consistency and uni-dimensionality of the construct of the MMAS-8 scale was examined using Cronbach's α statistics and Factorial Analysis. This aimed to identify any problems in any of the 8 questions used by the scale which could impact on the findings.

3.6.2.1.1 Reliability and consistency of the MMAS-8

Cronbach's α statistic was used to measure the internal consistency, reliability and content validity of the MMAS-8. This aimed to explore any problematic questions in this

tool and assess the degree to which individual items in the questionnaire represented the construct being measured (Field, 2009). As discussed in Section 2.2.1 the value of Cronbach's α varies from zero to 1. A value of 1 indicates a perfect correlation between the items that make up the scale, whereas, a value of 0 indicates no correlation between those items (Machin et al., 2007). Cronbach's α indirectly indicates the degree to which a set of questions in the instrument measures a single **unidimensional** latent construct (Field, 2009). If there is a suspicion that an instrument is capturing several dimensions (i.e. different constructs), then *factorial analysis* is used to investigate the internal structure of the instrument (Barker et al., 1994).

Question 5 was a reverse-phrased item used to reduce response bias, and had to be reversed before conducting the analysis (Field, 2009). For research purposes a Cronbach's α value of 0.60 was considered marginal, and more than 0.7 to 0.8 was preferred for good internal consistency (Braker et. al., 1994; Bland & Altman, 1997). If there are several subscales within a questionnaire, one should calculate Cronbach's α for each subscale individually (Field, 2009). All cases of missing values in any one of the 8 questions were excluded by the analysis. Full SPSS output can be seen in Appendix 16. The researcher evaluated the impact of each item in the scale on the value of Cronbach's α. Items which increased the value of Cronbach's α were removed and Cronbach's α was recalculated. The process was repeated until the largest Cronbach's α value was achieved. If the removal of an item caused insignificant increase in Cronbach's α value, it was retained (see Results Chapter).

3.6.2.1.2 Factor analysis (Principal Component Analysis (PCA))

The aim of this analysis was to explore the dimensions or constructs in the MMAS-8 scale. Factor analysis is useful to explore the data and generate hypotheses (Dytham, 2011). Subsets of variables with large correlation coefficients between them indicate that such variables may be measuring aspects of the same underlying dimension (factor, latent variables) (Field, 2009).

Full interpretation can be seen in Appendix 15 and full SPSS output can be seen in Appendix 16. Multicolinearity, sampling adequacy (Kaiser-Meyer-Olkin (KMO) statistic), and identity matrix (the Bartlett's test of sphericity) were all considered. Please see Appendices 15 and 16 for more detail.

Factorial analysis uses eigenvalues associated with the factors. The eigenvalue associated with each item before extraction, after extraction and after rotation were generated. The eigenvalues associated with each factor represented the variance explained by that particular linear component and was displayed as a percentage of variance (Field, 2009). Eigenvalues showed how evenly (or otherwise) the variances of the matrix were distributed. The dimensions of the data were examined by looking at all the eigenvalues for the dataset. The eigenvalue associated with a variate indicated the substantive importance of that factor. Factors with large eigenvalues were retained. Kaiser's criterion of retaining factors with eigenvalues >1 was used.

To discriminate between factors, *orthogonal factor rotation* was used (factors are rotated while keeping them independent or unrelated). Any factor loading of >0.29 was considered important. Reverse phrasing questions give a negative factor loading and

therefore need to be reversed (Field, 2009). Therefore, question 5 was reversed. Full SPSS output was presented in Appendix 16 and only a table of the main findings will be shown in the Results Chapter

3.6.2.2 Adherence Estimator

Further analysis of item 3, which is related to cost of medicines, was conducted. This was because patients over 60 and those with certain medical conditions were at the time of the study exempt from paying prescription charges. This item was analysed taking age and co-morbidities into account. It was not possible to establish for certain all those patients who were under 60 **and** were exempt from paying prescription charges. However, all identifiable reasons available to the researcher were used in the analysis.

3.6.2.3 Single Question scale

The original and modified SQ scale asked patients to answer the "single question" using a Likert scale (Gehi et al., 2007). No percentages were included on the questionnaire. The answers were converted to percentages as described earlier in Section 2.3.1.3. Frequencies of the answers for each class of the secondary prevention medicines were calculated. The medicines list provided by patients in Part 1 of the questionnaire was compared to their answers in Part 4. All calculations were based on the number of patients who answered the SQ part and listed these medicines in Part 1 of the questionnaire. All patients who answered the SQ part about a medicine that they did not include in Part 1 were excluded unless their comments clarified the discrepancy. Please see Appendix 16.

The original authors of the SQ tools used 75% ("most of the time") as a cut-off point in identifying their non-adherent group. The cut-off point of 75% in the SQ scale was not validated or chosen based on comparing it to a "gold standard" adherence assessment method. Furthermore, these Likert scale assigned percentages were subjective and not necessarily a true representation of the percentage of adherence. So "most of the time" could mean a different percentage to different people. These assigned percentages were not tested or verified by the researchers. Every patient who selected any choice other than "All of the time" (100%) had some kind of non-adherence. Therefore, the analysis will consider two cut-off points; 75% which was used in the original study and found to correlate with mortality and 90% which represents any kind of non-adherence. No sensitivity or specificity tests were reported for the SQ scale. Hence, both cut-off points were explored.

3.6.2.4 The Beliefs about Medicines Questionnaire

In Part 5 of the survey patients were asked 18 questions related to 4 categories of beliefs about medicines. The questions were grouped under the 4 categories: *specific necessity*, *specific concern*, *general harm*, and *general overuse*. The first 2 categories contained 5 questions each. The latter two categories contained 4 questions each.

Each question had a Likert scale ranging from "strongly agree" to "strongly disagree". Each option in the Likert scale was assigned a number as follows:

- Strongly disagree = 1
- Disagree = 2
- Uncertain = 3
- Agree = 4
- Strongly agree = 5

The frequency of answers, total score for each question, average score for each question, total score for each category and average for each category were calculated and reported. All these values were also calculated for adherent and non-adherent patients and compared using appropriate statistical methods to identify any statistically significant differences. Horne & Weinman (2002) used a similar approach in their studies and limitations in using parametric statistics to analyse Likert scales are discussed below.

3.6.2.4.1 Analysing Likert scales using parametric statistics

Frequency analysis is usually the first tool used in reporting Likert scale answers. Some authors question the validity of assigning numerical values (1-5) due to the non-linearity of the Likert scale (Smith, 2010). Such self-reported data should probably be treated as ordinal because the intervals between values cannot be presumed equal, though many scientists do analyse it as if it was continuous (Field, 2009). It has become common practice in literature to assume that Likert type data can be analysed using statistics for interval level measurement (e.g. mean, standard deviation) (Jamieson, 2004). Such use is justified by arguing that sample size and distribution are more significant than level of measurement to determine if it is appropriate to use parametric statistics (Jamieson, 2004). Norman (2010) argues that though the use of parametric tests on Likert scales can, strictly speaking, increase the chance of "wrong conclusions", one needs to ask the question "by how much?". He affirms that if the chance of such error is not much (or none at all) then such violation of using parametric statistics on ordinal data can be justified and that it is not more than an issue of robustness (Norman, 2010). He conducted various parametric statistical tests on Likert scale data and showed that

fearing to come to the "wrong conclusions" is almost non-existent and therefore the use of parametric statistics on Likert scale data is fully acceptable (Norman, 2010).

Due to the large sample size of the study and the above discussion, parametric statistics were occasionally used in the analysis of the Likert scale data. However, the researcher did also conduct non-parametric statistical analysis of the findings and any major differences were pointed out. For the BMQ non-parametric statistics were presented in the Results Chapter. Parametric statistics of the scale were calculated for comparison and can be found in Appendix 16.

3.6.3 Missing data

Identifying missing data is very important and therefore the approach adopted to handle missing data is described here. The analysis of missing data can reveal various issues related to the questionnaire, patients and the area being investigated in general. For example: patients may miss questions that they did not know how to answer them or felt uncomfortable to answer, questions which were not clear could also have been intentionally missed (Smith, 2010). However, a full analysis of missing data will not be presented in this write up as it is beyond its scope.

Patients who did not answer a whole part of the questionnaire were excluded from the analysis of that part. Below is a description of how partially answered parts of the questionnaire were handled. Excluding all patients who had partial answers would have wasted valuable information.

MMAS-8 scale – In cases where patients partially answered this part, the researcher assumed *best case scenario* and the missing response was given a score in favour of adherence, so all missing questions were scored "1". This approach is similar to the "intention to treat" approach, where the analysis was testing how the overall findings would look, if the patients were assumed adherent in any partially missing data. The alternative approach was to score the answered items and adjust to a scale of 0 – 8. So for example a patient who answered 7 questions and had a total score of 7, their adjusted score would (7x1.144) = 8. However, this approach was unlikely to produce any different results to the earlier approach except that some patients may be ranked differently in the non-adherence categories. The levels of adherence according to MMAS-8 were also calculated with adjusting partial responses in favour of non-adherence and non-adherence to compare the significance of the approach on changing outcome.

Adherence Estimator - Patients who answered at least one question in the scale were assigned a score of zero for every missing response (i.e. in favour of adherence).

BMQ - As some patients missed some questions in the BMQ, the "n" for each question was calculated. For ease of comparison and analysis the mean and standard deviation of the answers for each question and the overall category were calculated.

3.6.4 Comparing groups

The attributes of the adherent and non-adherent groups according to various scales were compared according to the set of variables identified to describe the sample population. The three main categories used in the comparison were as follows:

- Demographics of the adherent vs. non-adherent groups
    - Age, gender, post code, ethnic origin and marital status.
- Co-morbidities and cardiac history of both groups
    - Diabetes, angina, MI, angioplasty, CABG and trial background.
- Medicines related variables
    - Number of overall medicines, doses per day, administration per day, GTN possession, GTN use, GTN monthly use, the type of secondary prevention medicines, number of secondary prevention medicines, number daily doses and number of daily administrations of secondary prevention medicines, and overall and individual knowledge about secondary prevention.

Appropriate statistical tests were used to identify if differences were statistically significant as described below. Detailed comparisons of all variables were tabulated in Appendix 16. Only statistically significant differences were reported in the relevant sections in the Results Chapter.

3.6.4.1 Bivariate analysis statistics

Bivariate analysis was used to explore relationships between variables. Cross-tabulations were used to look at categorical variables and explore possible associations between the variables and adherence. Two sided tests were used. The null hypothesis was that there was no difference between the adherent and non-adherent groups in regards to the variable being tested. The following tests were applied:

- **chi-square test** (χ^2 test) for categorical data.

- **Fisher's exact test** was used when the assumptions of the chi-square test were violated (i.e. if less than 5 cases were expected in any of the cells).
- **Independent samples t-test** to compare the means of parametric variables which had normal distribution.
- **Mann-Whitney U test** is the equivalent of the independent samples t-test for non-parametric or not normally distributed data.
- **Kruskal-Wallis H test** is a non-parametric test which is similar to Mann-Whitney U test, but was used when more than two groups were being compared.

p-values (2-sided) were calculated using the above various statistical methods. *p*-values of <0.05 were considered statistically significant and indicated that the null hypothesis of no difference or no association was rejected. All *p*-values <0.001 were reported as <0.001 rather than the actual value (Marston, 2010). All *p*-values reported were two-sided because both directions of the effect or trend were considered possible. This was based on non-directional hypotheses, where it was assumed that the effect of the variables on adherence could have gone either way (i.e. increase or decrease adherence) (Howitt & Cramer, 2011).

3.6.5 Comparing scales

The results of the survey were further analysed to compare the consistency and differences between the 3 adherence measurement tools (MMAS-8, AE and SQ). This should inform future studies on best tools to use to assess adherence among CAD patients.

In the absence of a "gold standard" to compare the tools to, the findings of the AE and SQ tools were compared to the MMAS-8 and any Factors identified within it. The *sensitivity* and *specificity* of the SQ was calculated against the MMAS-8 findings using cross-tabulation. Because the AE *predicted* intentional non-adherence behaviour, its "prediction" was compared to the findings of both the MMAS-8 and SQ. The *positive predictive value* and *negative predictive values* were calculated for the AE. The sensitivity and specificity of AE were calculated using the findings of both the MMAS-8 and SQ. More details are provided in Appendix 15.

3.6.5.1 Kappa statistic

Kappa statistic (Cohen's Kappa) was used to quantify the level of agreement between the 3 adherence assessment scales. The 95% confidence interval (CI) for this statistic was calculated manually using the equation (Estimate ± 1.96 x SE) where SE is standard error. The interpretation and conclusion about the kappa statistic outcome was in accordance with the recommendations made by Landis and Koch (1977) for all statistically significant Kappas:

$\kappa < 0$ Poor agreement
$\kappa = 0.0 – 0.20$ Slight agreement
$\kappa = 0.21 – 0.40$ Fair agreement
$\kappa = 0.41 – 0.60$ Moderate agreement
$\kappa = 0.61 – 0.80$ Substantial agreement
$\kappa = 0.81 – 1.00$ Almost perfect agreement

It is usually desirable to have a kappa statistic >0.60. The *p*-value for kappa is not always reported since the null hypothesis of no association is not always logical (Marston, 2010).

3.6.6 Interpreting overall results

Three adherence scales were used to measure levels of non-adherence. The MMAS-8 and SQ scales identified current behaviour and any underway non-adherence to secondary prevention medicines. The AE explored propensity to non-adherence based on the major drivers of intentional non-adherence. All three scales findings were brought together and all patients who were identified to be non-adherent by the MMAS-8 or the SQ scales were explored to identify the reasons for their non-adherence. Where data was missing for one of the two scales the conclusion on level of adherence was used based on the other scale. The AE scores for the non-adherent patients identified by the MMAS-8 or SQ were also explored. A summary of the reasons for non-adherence was generated. The percentage of non-adherent patients due to the cost of medicines was calculated separately taking into account patients who did not seem to be exempt from paying for their prescriptions. The BMQ of the non-adherers was also compared to the adherers.

3.6.6.1 Building a regression model

Regression analysis is one of the most commonly used multivariate statistical methods in the analysis of quantitative data. The aim was to identify variables (independent) that can be predictive of the dependent variable (non-adherence). To further explore the relationships between the different variables and patients' adherent and non-adherent status *multiple logistic regression* was used. The null hypothesis in the logistic regression model for each variable would be that there is no relationship between the dependent variable and the independent variable being examined in the model (Marston, 2010). Full description of this statistic is in Appendix 15.

Independent variables were systematically included in the logistic regression model. Based on the researcher's clinical knowledge, literature review, and the bivariate comparisons which were carried out to compare the adherent and non-adherent groups the following variables were **individually** tested using the SPPS logistic regression function to check for the relationship between them and the probability of non-adherence:

- Age
- Gender
- Diabetes
- Angina Status
- MI Status
- Bypass Status
- Angioplasty Status
- Trial background
- *Specific Necessity* Score
- *Specific Concern* Score
- *General Overuse* Score
- *General Harm* Score
- Number of medicines
- Number of doses per day
- Number of administrations per day
- GTN use
- GTN monthly use
- Being on any one of the 6 secondary prevention medicines
- Number of secondary prevention medicines per day
- Number administrations of secondary prevention medicines per day
- Knowledge about individual secondary prevention medicines
- Overall average knowledge about secondary prevention medicines
- Needing solution or alternative to the four possible barriers to adherence.

Three regression models were built for the following dependent variables: Non-adherence according to MMAS-8 (excluding Qn5) or SQ, non-adherence according to Factor 1, and non-adherence according to Factor 2. Details on the variables included in each of the three models after univariate analysis can be found in Appendix 15.

The following variables had a *p*-value of <0.25 in the univariate analysis for non-adherence according to MMAS-8 (excluding Qn5) or SQ and were retained to include in the multivariate model:

- Age
- Gender
- Diabetes
- Bypass Status
- Angioplasty Status
- *Specific Necessity* Score
- *Specific Concern* Score
- *General Overuse* Score
- *General Harm* Score
- Number of doses per day
- Number of administrations per day
- Being on statins, ACEI, aspirin
- Number administrations of secondary prevention medicines per day
- Knowledge about aspirin, ACEI, BB
- Overall average knowledge about secondary prevention medicines
- Needing solution or alternative to reading labels, getting repeat prescriptions.

A correlation matrix (using Spearman's co-efficient) for all variables considered for the model was created and reviewed for any evidence of collinearity. The variables related to the *knowledge about certain secondary prevention medicines* were excluded as patients who were not on that specific medicine could not be judged as if they knew or did not know about that medicine which would create vast number of missing values which would limit the data available for model estimation. However, the average of overall knowledge about the indication of secondary prevention medicines was retained.

The literature does not support the theory testing of each single variable in this study. Therefore, three various approaches of model building were used to enable further exploration of associations and missing any independent variables (see Appendix 15 and 16). The model which was considered more comprehensive, clinically meaningful, and explained more of the observed data was used and presented in the Results Chapter. The dependent variable was coded as 0 and 1 and the category most important (non-adherence) was coded as 1 (Marston, 2010). Variables with non-significant p-values (>0.05) were removed. Important statistics were reported for the overall model such as the model's χ^2 and *p*-value which indicated whether the model was significant or not (*p*-value needs to be <0.05), the Hosmer and Lemeshow Test (HLT) *p*-value to explain the

overall goodness-of-fit of the model (*p*-value needs to be >0.05) and the overall prediction ability of the model (the higher the percentage the better) (Field, 2009; Marston, 2010).

Logistic regression reports odds ratios. The dependent variable is more likely to occur when the odds ratio is greater than one, and less likely to occur when less than 1 (Marston, 2010). In continuous independent variables the odds ratio is for one unit of change (Marsden, 2010). The confidence intervals were quoted with each odds ratio. When they did not include 1 then the difference is statistically significant.

Only relevant values from the final table of the logistic regression were reported and the rest of the output was populated in Appendix 16. The tables in Appendix 16 contained the log odds ratio (B), standard error for log odds ratio (SE), the Wald statistic, degrees of freedom (df), *p*-value (Sig.), odds ratio (Exp(B)), and 95% confidence interval for the odds ratio. The summary tables in the Results Chapter will only contain odds ratios, 95% confidence intervals and *p*-values.

3.6.6.1.1 Interactions

An interaction effect is the effect of two or more variables in combination on the outcome. The independent variables interact if the effect of one of the variables on the outcome differs depending on the level of the other variable (Field, 2009). Interaction is also known as a conditional relationship in which the relationship between two variables depends on the specific values of a third variable (Argyrous, 2011). Interactions were explored wherever the researcher suspected the existence of such effect. For example, gender, age and adherence.

3.6.7 Analysis of patients' comments

Due to the qualitative nature of patients' comments and answers to the last question in the questionnaire a different analytical method was used. Frequency analysis of patients' comments was identified to be most suitable for this purpose. The content and frequency of comments were reviewed in order to identify key ideas or themes using segmentation, categorisation and re-linking of aspects of the data (Matthews & Ross, 2010).

All comments made by patients were studied thoroughly because data familiarization is key to analysing qualitative data (Howitt & Cramer, 2011). A list of topics or issues identified by patients was generated and grouped together to examine for initial themes. All comments were charted and further analysis was carried out to identify themes, categories and sub-categories. Links between all these components were also examined and established. The overarching themes were checked to see if they were inclusive. The IHMC CmapTools software v. 5.03 was used to assist in mapping the initial themes and other emerging categories and subcategories. The software was invaluable in grouping the various emerging themes and linking relevant topics / issues. After the major themes, categories and subcategories were presented; the researcher identified comments made by adherent and non-adherent patients and made them distinguishable for the benefit of the analysis.

As the data generated by this part of the questionnaire were not collected in a structured way such as an interview or structured questions, the analysis was a categorisation and frequency analysis of patients' comments. These comments were useful in providing complementary and explanatory detail for the quantitative analysis.

4 Results

In this chapter data from the constituent sections of the study will be presented in order to facilitate the interpretation of the results. Basic descriptive statistics will be used first to illustrate the quantitative elements of the results, followed by more analytical statistics to explore associations, correlations and relationships. Chapter 3 contains more detail on data interpretation and analysis. Figure 4.1 summarises how the results are presented and analysed in this chapter. Detailed description of the statistical tools used can be found in Appendix 15. Further detailed statistical analysis is presented in Appendix 16.

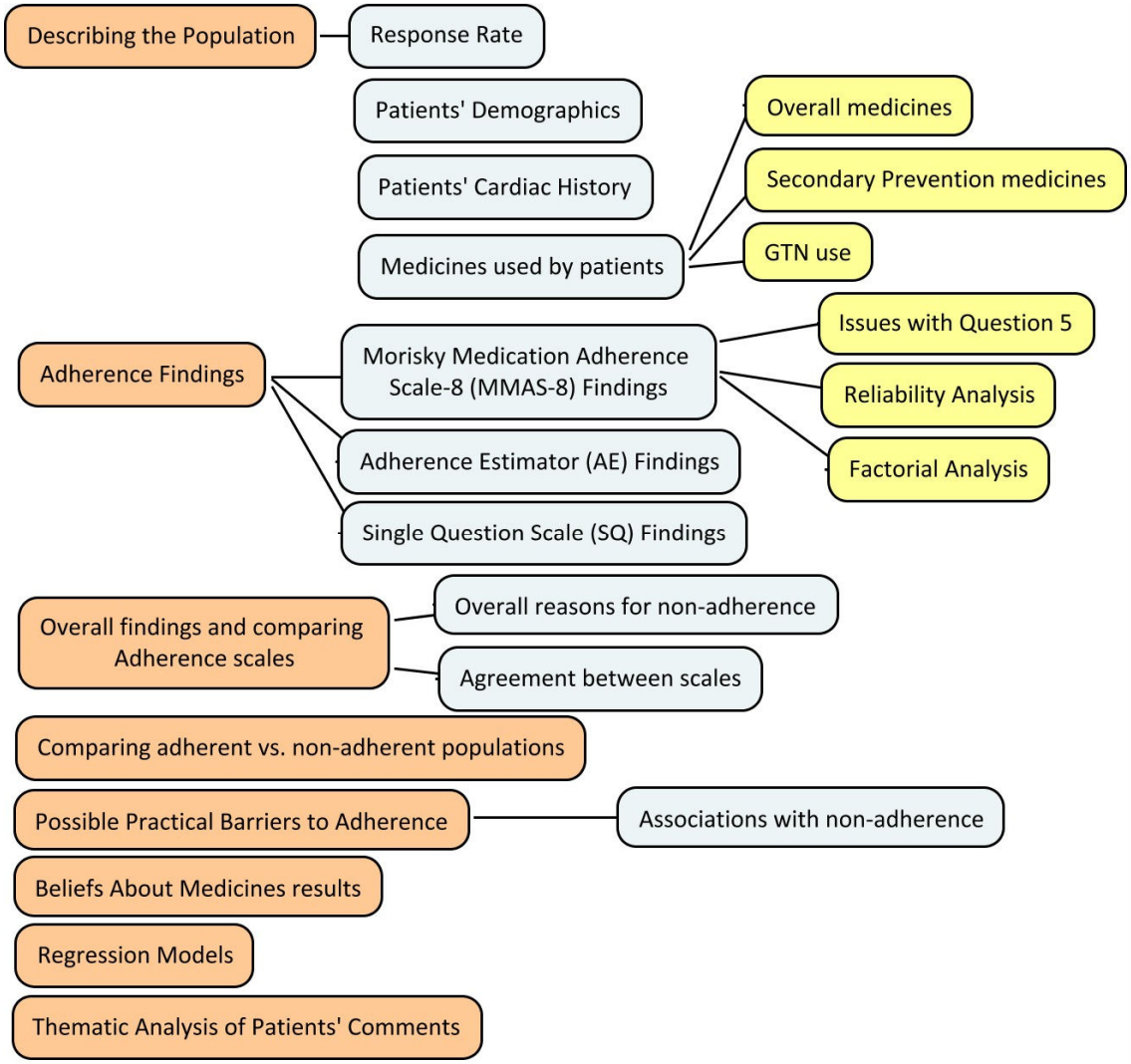

Figure 4.1 – Chapter overview to demonstrate the structure and organisation of the data.

4.1 Response rate

Out of the 696 questionnaires posted to patients from the ENCOURAGE data base, 503 were completed and returned. The response rate was 72%. All questionnaires were reviewed by the principal investigator as described in Chapter 3. Respondents were older than non-respondents (median age in years (Q1, Q3) = 70 (64, 74) versus 67 (61, 74), respectively. *p*-value (2-sided) = 0.001 (Mann-Whitney U test)). The distribution of gender was the same among respondents and non-respondents.

4.2 Patient demographics

Table 4.1 describes the demographic profile of the participants according to age, gender, post code (of residence), ethnicity and marital status. The median age of the participants was 70 years. Males constituted 80% of the sample. Approximately 43% of the sample was from Leeds, 47% were from the rest of West Yorkshire (excluding Leeds) and 11% were from outside West Yorkshire. The majority of the participants were white (92%). Information about patients' marital status was incomplete as discussed in Section 3.6.1.1.

The age distribution of the sample is shown in Figure 4.2. The age of around 75% of the patients falls in the 6^{th} and 7^{th} decade. Fifty percent of participants were 70 years or older.

Table 4.1 – Demographics of the participants according to age, gender, post code, ethnicity and marital status (N=503).

	Number	Percentage
Age(years)		
Median (Q1, Q3)	70 (63, 75)	
Min, Max	38, 92	
Gender		
F	100	20%
M	403	80%
Post Code		
Leeds (LS)	214	**42.5%**
WF	108	21.5%
BD	63	12.5%
HD	38	7.6%
HX	27	5.4%
West Yorkshire (excluding LS)	**236**	**47%**
YO	38	7.6%
HG	9	1.7%
BB	2	0.4%
DN	2	0.4%
HU	1	0.2%
OL	1	0.2%
Other (outside of WY)	**53**	**10.5%**
Ethnicity		
White	462	91.8%
South Asian	2	0.4%
Mixed Race	1	0.2%
Unknown	38	7.6%
Marital Status		
Single	10	2%
Married	247	49.1%
Widow / Widower	10	2%
Divorced/Separated	10	2%
Not Known	226	44.9%

Q1 = Lower quartile, **Q3 =** upper quartile, **LS**=Leeds, **WF**=Wakefield, **BD**=Bradford, **HD**=Huddersfield, **YO**=York, **HX**=Halifax, **HG**=Harrogate, **BB**=Blackburn, **DN**=Doncaster, **HU**=Hull, **OL**=Oldham, **WY**=West Yorkshire

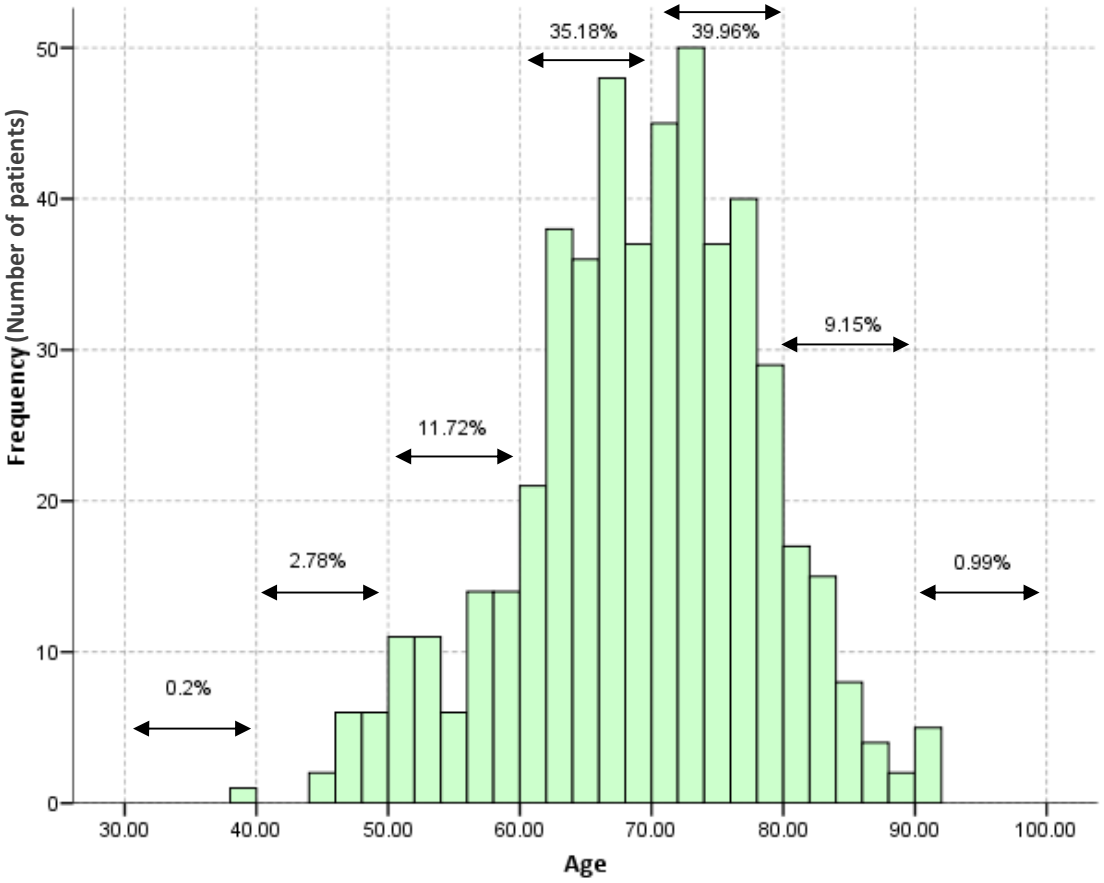

Figure 4.2 – Age distribution of the sample (N=503). The percentages on the graph represent the patients in each age decade.

4.3 Patients' cardiac history and comorbidities

The cardiac history and comorbidities relevant to CHD and medicines-taking analysis are described in Table 4.2. This information was based on the details provided by patients when they expressed interest in taking part in the study (see Sections 3.6.1.2 and 3.6.1.3 for more detail). Table 4.3 summarises studies conducted in the Cardiovascular Research Unit that participants were enrolled on in the past. Ninety three percent of the sample participated in the Family Heart Study or OPERA which indicates that they should have been on secondary prevention medicines for more than 5 years.

Table 4.2 – Cardiac history and procedures as reported by patients prior to completing the survey and relevant comorbidities identified from review of patients' medicines (N=503).

Condition / procedure	Status	Number of patients	Percentage (N=503)
Angina	Yes	65	13%
	No	188	37%
	Unknown	250	50%
MI	Yes	349	69%
	No	154	31%
Angioplasty	Yes	286	57%
	No	217	43%
CABG	Yes	192	38%
	No	311	62%
Diabetes (on anti-diabetics)	Yes	62	12%
	No	441	88%
Controlled by:			
PO (only)		40	
INJ (only)		9	
Both		13	
Age less than 60 years		8	
Hypothyroidism (on levothyroxine)	Yes	32	6%
	No	471	94%
Age less than 60 years		6	

MI=Myocardial Infarction, **CABG** = Coronary artery bypass grafting, **Diabetes**= controlled with anti-diabetic medicines, **PO**=oral anti-diabetic medicines, **INJ**=injectable anti-diabetic medicines (insulin and other).

Table 4.3 – Description of the trials that patients had participated in and associated information about patients' cardiac history (N=503).

Trial	No. of patients (percentage)	Relevant Cardiac History
Family Heart Study (Samani et. al., 2005)	285 (56.7%)	Launched 2001. Patients with CAD defined as MI, CABG, PTCA, or angina (positive exercise test), with validated onset before the age of 66.
OPERA Study (Sainsbury et. al., 2005)	183 (36.4%)	Launched 2005. Patients undergoing acute or elective PTCA at the Leeds General Infirmary.
Candidates for SIGNIFY study (Ferrari, 2009)	35 (7.0%)	Launched 2009. Documented stable CAD without clinical signs of heart failure. CAD based on previous documented MI, PCTA, CABG, or imaging evidence and positive exercise test positive at least 3 months before enrolment.

CAD=Coronary artery disease, **MI**=Myocardial Infarction, **CABG**= Coronary artery bypass graft, **PTCA**= Percutaneous transluminal coronary angioplasty. **OPERA** = Markers of myocardial injury in patients undergoing percutaneous angioplasty, **SIGNIFY= S**tudy assess**I**n**G** the morbidity–mortality be**N**efits of the **If** inhibitor ivabradine in patients with coronar**Y** artery disease

4.4 Medicines used by patients in the sample

This section reports the number of medicines used by patients, the number of daily doses and administrations, GTN use, and secondary prevention medicines use.

4.4.1 Number of medicines

The median (Q1, Q3) number of different medicines reported in Part 1 of the questionnaire by patients was 7 (5, 9). Figure 4.3 is a histogram showing the distribution of the overall number of medicines used by patients in the study. Approximately 55% of patients were prescribed 4 to 7 medicines and 81 (16%) patients were on 5 medicines.

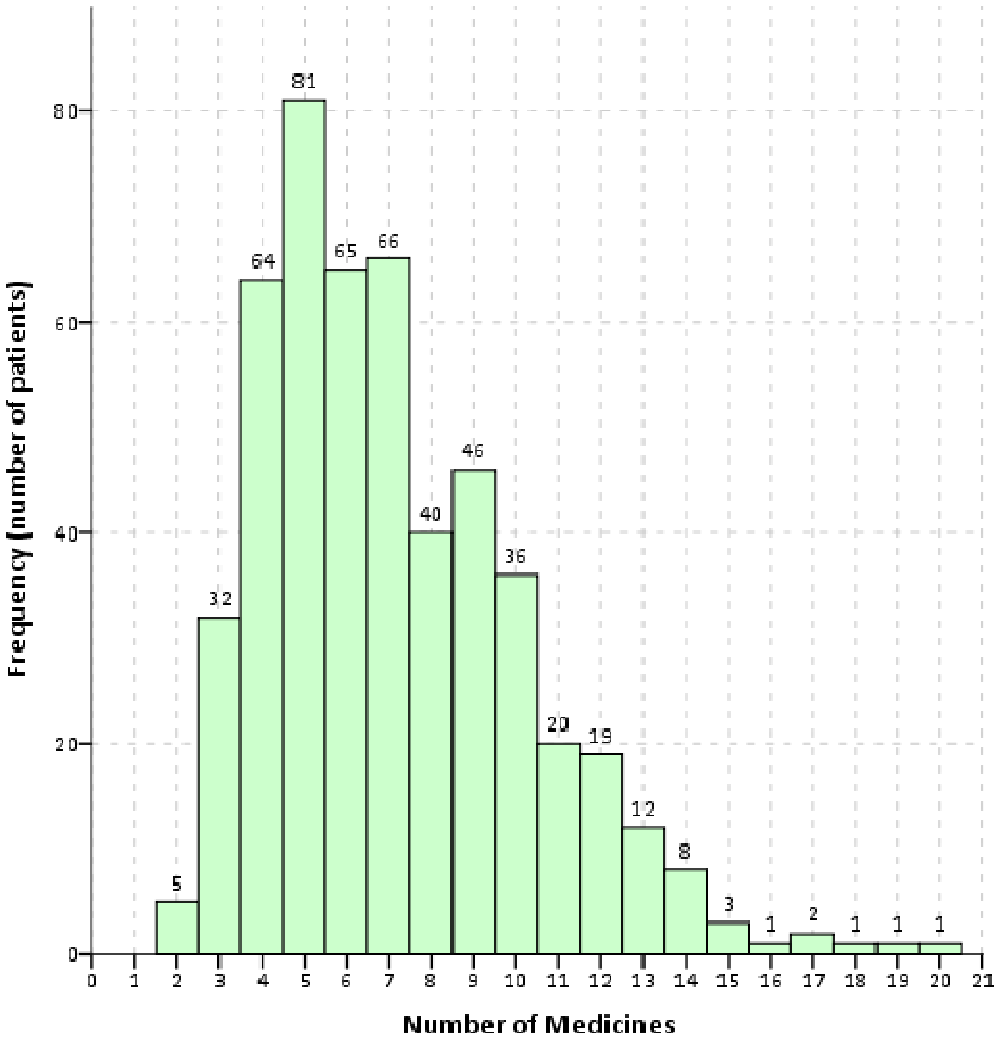

Figure 4.3 – The frequency and distribution of the overall number of medicines prescribed to patients in the study according to their reporting in Part 1 of the questionnaire (N = 503).

4.4.2 Frequency of daily medicines doses and administrations

Table 4.4 shows the medicines administration reported by patients in the study categorised according to daily frequencies. Fifty percent of patients were prescribed all their medicines for once daily administration, and 37% reported taking at least one of their medicines twice daily (and none more than twice daily). The total number of daily doses is presented in Figure 4.4. The median number of individual doses per day was 6. Figure 4.5 highlights the total number of administration times per day with a median of 2 (see Section 3.6.1.3).

Table 4.4 – Frequency of daily medicines administration as reported by participants (N= 503).

Description	No. of patients who meet the criteria	Percentage (N=503)
Takes all medicines Once Daily (OD) only	250	50%
Takes at least one medicine Twice Daily (BD) (But not >BD)	189	37%
Takes at least one medicine more than BD	64	13%
Total	**503**	**100%**

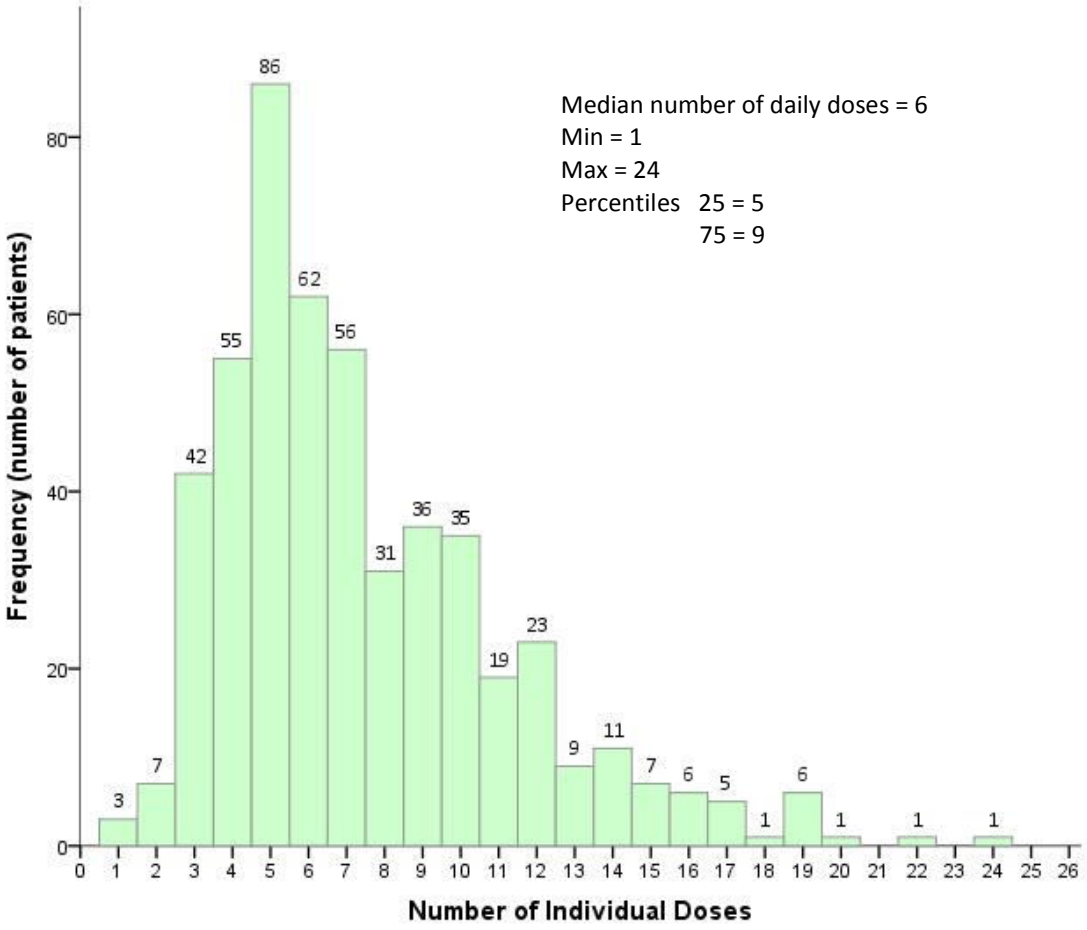

Figure 4.4 – Frequency and distribution of individual daily doses (N = 503).

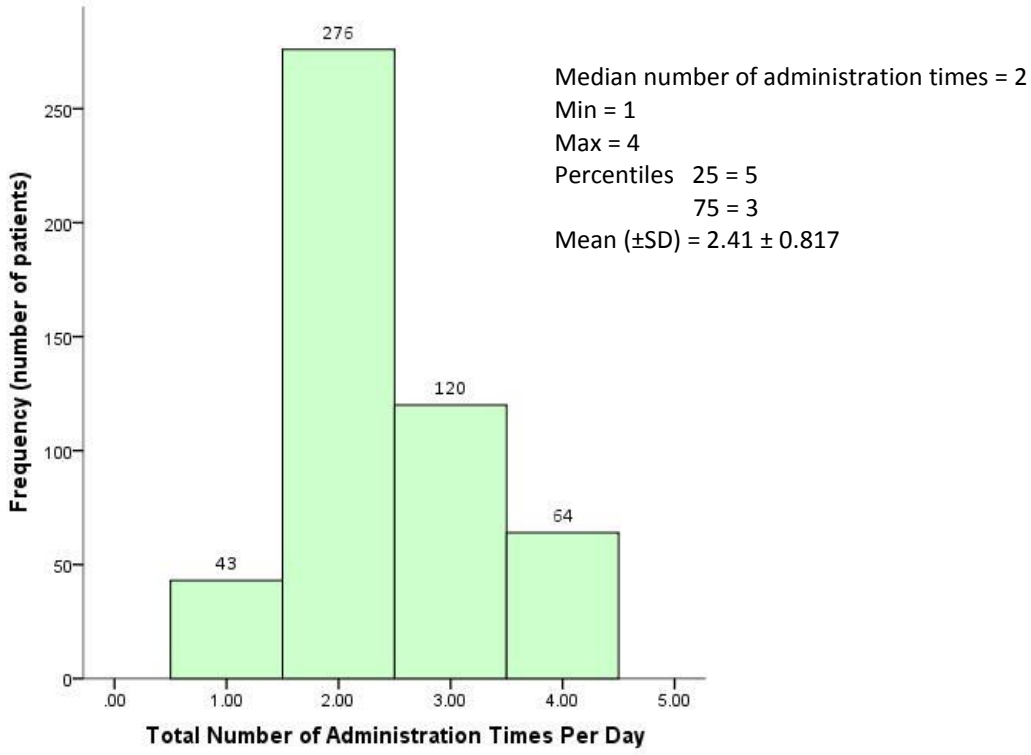

Figure 4.5 – Frequencies and distribution of the total number of daily administrations of medicines as reported by patients in the sample (N = 503).

4.4.3 Secondary prevention medicines

The number of patients prescribed each class of secondary prevention medicines is shown in Table 4.5. The number of individual daily doses of secondary prevention medicines is shown in Figure 4.6. Figure 4.7 shows the number of daily administration times. The different combinations are described in Tables 4.6 and 4.7. Only 263 (52%) patients were prescribed at least four of the secondary prevention medicines. One hundred and seventy (34%) patients were prescribed three secondary prevention medicines and 53 (11%) were prescribed only two secondary prevention medicines. Table 4.8 shows that 15 (3%) patients were prescribed only one secondary prevention medicine. One patient reported that they were not on any secondary prevention medicines. Another patient indicated that they no longer take their secondary prevention medicines without identifying which ones they were prescribed.

Table 4.5 – Secondary prevention medicines prescribed for patients in this sample; ranked according to the most commonly prescribed (N=503).

Name of Heart Medicine	No. of patients on the drug	Percentage
Statin	476	94.6%
Aspirin	439	87.3%
BB	356	70.8%
ACEI	293	58.3%
ARBs	104	20.7%
Clopidogrel	59	11.7%

BB = beta blockers, **ACEI** = angiotensin converting enzyme inhibitors, **ARBs** = angiotensin receptor blockers

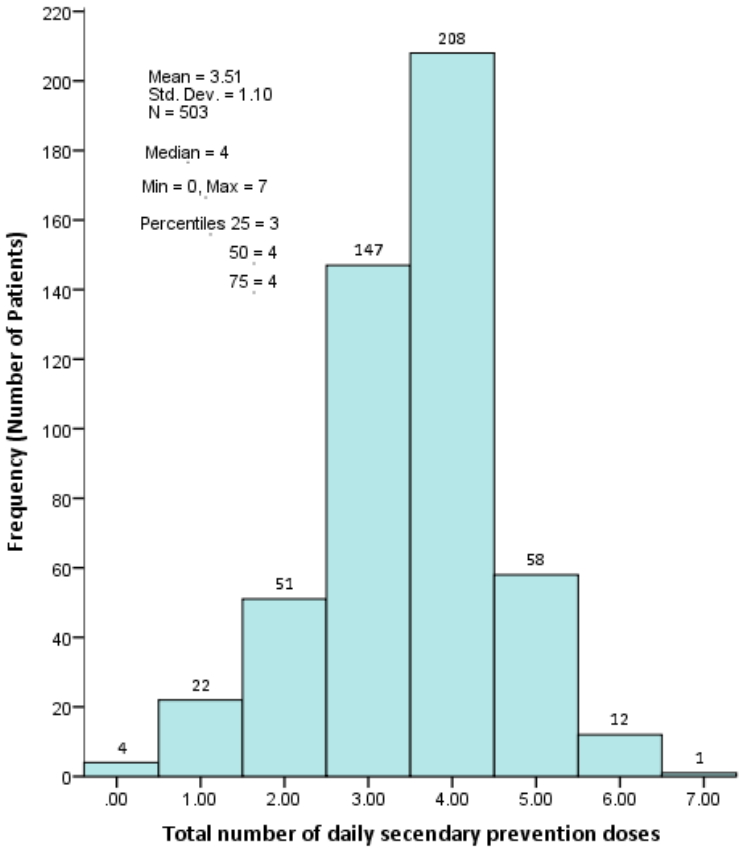

Figure 4.6 – Frequency and distribution of the number of individual daily doses of secondary prevention medicines as reported by patients in the sample (N = 503).

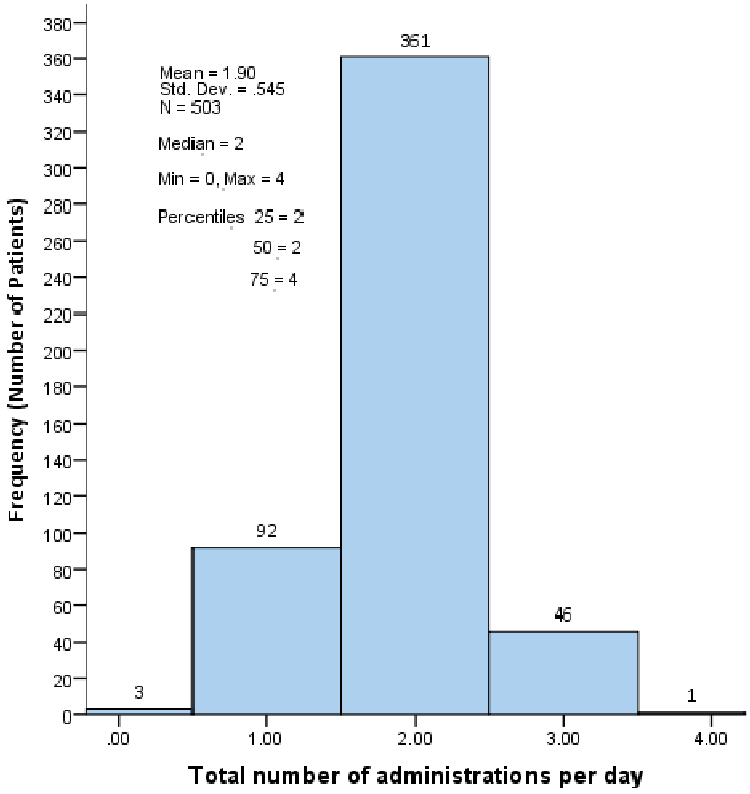

Figure 4.7 – Frequency and distribution of the number of daily administration times for secondary prevention medicines reported by participants (N = 503).

Table 4.6 – Frequency of the different combinations of secondary prevention medicines prescribed for patients in this sample (N = 503).

Combination	No. of patients
Number of patients on **FIVE** secondary prevention medicines. • Aspirin **&** Clopidogrel • ACEI **or** ARBs • BB • Statin	27 (5.4%)
Number of patients on **FOUR** secondary prevention medicines. • Aspirin **or** Clopidogrel • ACEI **or** ARBs • BB • Statin	236 (46.9%)
Total (on at least four medicines)	**263 (52.3%)**
Number of patients on **THREE** secondary prevention medicines. **Combination 1 (No BB)** • Aspirin **or** Clopidogrel • ACEI **or** ARBs • Statin	82 (16.3%)
Combination 2 (No ACEI or ARBs) • Aspirin **or** Clopidogrel • BB • Statin	60 (11.9%)
Combination 3 (No Aspirin or Clopidogrel) • Statin • BB • ACEI	22 (4.4%)
Combination 4 (No Statin) • Aspirin **or** Clopidogrel • BB • ACEI	6 (1.2%)
Total (on three only, any combination)	**170 (33.8%)**
Number of patients on **TWO** secondary prevention medicines. **Combination 1 (No BB & ACEI)** • Aspirin **or** Clopidogrel • Statin	33 (6.6%)
Combination 2 (No BB & Aspirin or Clopidogrel) • ACEI **or** ARBs • Statin	9 (1.8%)
Combination 3 (No BB & Statin) • Aspirin **or** Clopidogrel • ACEI **or** ARBs	7 (1.4%)
Combination 4 (No Statin & ACEI) • Aspirin OR Clopidogrel • BB	3 (0.6%)
Combination 5 (No Aspirin or Clopidogrel & ACEI) • Statin • BB	1 (0.2%)
Total (on two only, any combination)	**53 (10.6%)**

BB = beta blockers, **ACE I** = angiotensin converting enzyme inhibitors, **ARBs** = angiotensin II receptor antagonists

Table 4.7 – Number of patients prescribed only ONE of the secondary prevention (N=503).

Name of Heart Medicine	No. of patients on the drug	Percentage
Statin	6	1.2%
Aspirin	5	1%
BB	1	0.2%
ACEI	2	0.4%
ARBs	1	0.2%

BB = beta blockers, **ACE I** = angiotensin converting enzyme inhibitors, **ARBs** = angiotensin II receptor antagonists

4.4.3.1 Knowledge of secondary prevention medicines indication

Table 4.8 summarises participants' level of knowledge of secondary prevention medicines indications as described in Section 3.6.1.5.

Table 4.8 – Patients' level of knowledge about the indication of each of the prescribed secondary prevention medicines on a scale of 1 – 3 (N=503).

Name of Heart Medicine	No. of patients on the drug	Level of Knowledge of Indication						
		Specific (1)		General (2)		None (3)		n
Aspirin	439	230	52.4%	144	32.8%	63	14.4%	439
Statin	476	316	66.7%	77	16.2%	83	17.5%	474
Clopidogrel	59	28	47.5%	17	28.8%	14	23.7%	59
BB	356	128	36.4%	139	39.5%	85	24.1%	352
ACEI	293	110	37.8%	106	36.4%	75	25.8%	291
ARBs	104	46	44.2%	25	24.0%	34	32.7%	104

BB = beta blockers, **ACE I** = angiotensin converting enzyme inhibitors, **ARBs** = angiotensin II receptor antagonists
1=have "specific" knowledge about indication, 2 = have "general" knowledge and 3 = have "none" knowledge reported.

The "knowledgeable" vs. "not knowledgeable" categorisation as explained in Section 3.6.1.5 is shown in Table 4.9. This classification is used later in the comparative analysis. The overall patients' knowledge about the indications of all the secondary prevention medicines that they were prescribed was calculated as described in Section 3.6.1.5. The sample's overall knowledge of secondary prevention medicines' indication is as follows: mean ± SD = 1.7 ± 0.65, median (Q1, Q3) = 1.6 (1, 2).

Table 4.9 – Patients' knowledge about the indication of each of the secondary prevention medicines they were prescribed (N=503).

Name of Heart Medicine	No. of patients on the drug	Level of Knowledge of Indications				
		Knowledgeable		Not Knowledgeable		n
Statin	476	316	66.7%	160	33.8%	474
Aspirin	439	230	52.4%	207	47.2%	439
Clopidogrel	59	28	47.5%	31	52.5%	59
ARBs	104	46	44.2%	59	56.7%	104
ACEI	293	110	37.8%	181	62.2%	291
BB	356	128	36.4%	224	63.6%	352

BB = beta blockers, **ACE I** = angiotensin converting enzyme inhibitors, **ARBs** = angiotensin II receptor antagonists
"knowledgeable" = reported indication and gave accurate description to distinguish the class of medicine, "not knowledgeable" = not reported indication, wrong indication, unsure about indication, or said it is for the heart.

4.4.4 GTN use

Seventy three percent of patients were prescribed a GTN spray or tablet and 49% of them used their GTN as shown in Table 4.10. The frequency of GTN use was not reported by 38% of those who reported using it. The median (Q1, Q3; min, max) number of times GTN used was 3 times per day (2, 4; 1, 8) among those who reported GTN use daily, 3 times per week (2, 4; 1, 6) among weekly users and 2 usages per month (1, 3; 1, 10) among monthly users. Cumulative Monthly GTN is shown in Figure 4.8.

Table 4.10 – Summary of the GTN possession and use among patients in the study (N=503).

Possession of a GTN			n = 503
	Yes	366	73%
	No	128	25%
	Missing	9	2%
	Total	**503**	
GTN use *(for those who possess GTN)*			n = 366
	Yes	180	49%
	No	178	49%
	Missing	8	2%
	Total	**366**	
Frequency of reported GTN use			n = 180
	Daily	15	8%
	Weekly	41	23%
	Monthly	56	31%
	Missing	68	38%
	Total	**180**	

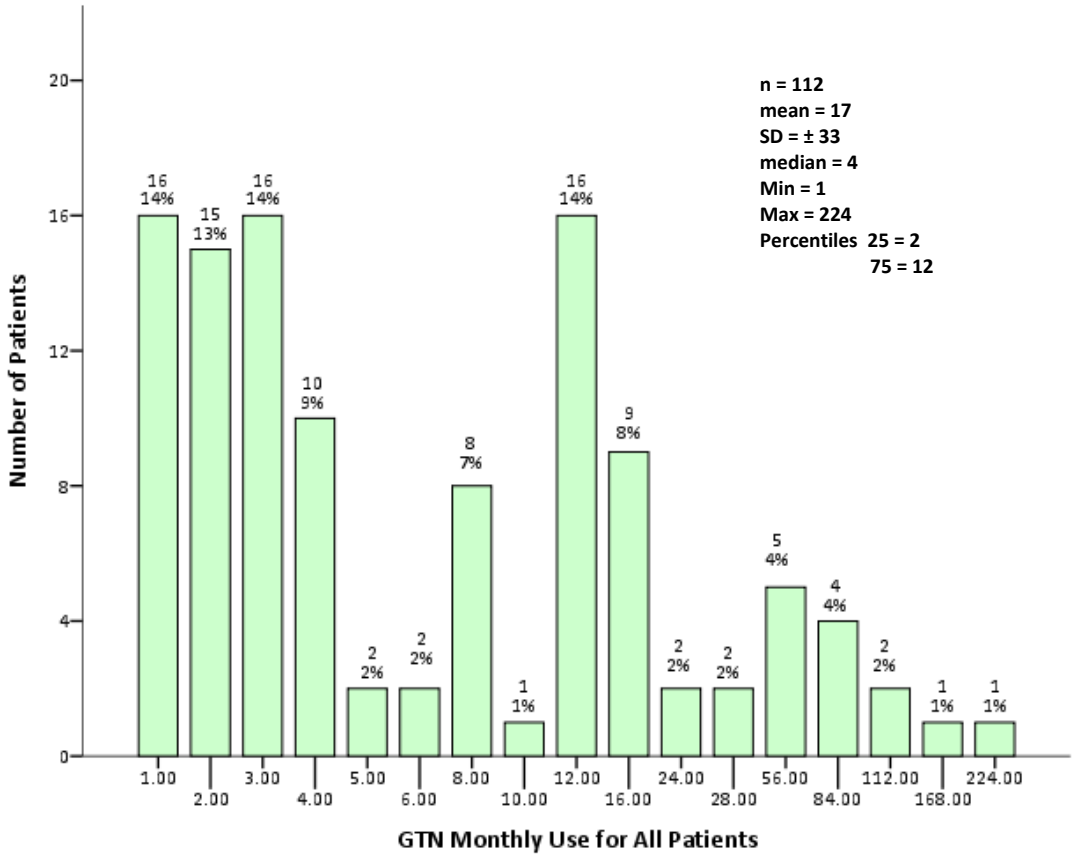

Figure 4.8 – Cumulative Monthly GTN use by all patients who reported frequency of their GTN use (n = 112). Daily and weekly use was aggregated to monthly use.

There was no statistically significant correlation between cumulative monthly GTN use and number of secondary prevention medicines prescribed, reported angina status, MI, angioplasty or CABG.

4.5 Levels of adherence according to the adherence scales

In this section the findings of each of the adherence assessment scales will be presented.

4.5.1 Results of the Morisky Medication Adherence Scale – 8 (MMAS-8)

This part of the questionnaire was completed by 500 patients. Missing data were handled as described in Section 3.6.3. Three patients did not answer any question on the MMAS-8 scale and will therefore be excluded from the analysis. Table 4.11 shows the overall results of the MMAS-8 including individual item responses. As can be seen from Table 4.12, the level of adherence was 49%; 40% of patients had medium adherence and 11% had low adherence. These levels were calculated after adjusting partial responses in favour of non-adherence. The overall summary of responses for the non-adherent patients is shown in Table 4.13. After adjusting missing data in favour of adherence, only 8 patients shifted from being classed non-adherent to the adherent category. Other changes can be seen by comparing Table 4.12 to Table 4.14 which shows the levels of non-adherence according to the MMAS-8 after adjusting missing responses in favour of adherence.

Table 4.11 – Overall results for MMAS-8 for both adherent and non-adherent patients (n = 500) (3 patients did not answer any of the scale's questions).

Question	Yes	No	n
1. Do you sometimes forget to take your heart medicines?	92 (18.4%)	405 (81.0%)	497
2. Over the past 2 weeks, were there any days when you did not take your heart medications?	29 (5.8%)	470 (94.0%)	499
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	31 (6.2%)	465 (93.0%)	496
4. When you travel or leave home, do you sometimes forget to bring along your medications?	26 (5.2%)	469 (93.8%)	495
5. Did you take your heart medications yesterday?	450 (90.0%)	48 (9.6%)	498
6. When you feel like your heart condition is under control, do you sometimes stop taking your medications?	5 (1%)	492 (98.4%)	497
7. Do you ever feel hassled about sticking to your heart treatment plan?	41 (8.2%)	456 (91.2%)	497

8. How often do you have difficulty remembering to take ALL your heart medications?	Never	Almost Never	Sometimes	Quite often	Always	n
	323	136	33	5	0	497
	64.6%	27.2%	6.6%	1%	0%	

Table 4.12 – The levels of adherence and non-adherence according to the MMAS-8 Score after adjusting missing data in favour of non-adherence i.e. unanswered question scored 0 (n = 500).

Morisky Adherence Status	
Adherent (MS = 8)	245 (49%)
Non-adherent (MS <8)	255 (51%)
n	500
Level of Adherence	
High Adherence (MS = 8)	245 (49%)
Medium Adherence (MS - 6 to 8)	202 (40%)
Low Adherence (MS <6)	53 (11%)
n	500

MS = Morisky Score

Table 4.13 – MMAS-8 results for non-adherent patients after adjusting missing answers in favour of adherence (n=247) (Green shading indicates response considered non-adherence).

	Yes	No	n* (missing)
1. Do you sometimes forget to take your heart medicines?	92 (37.3%)	155 (62.7%)	245(2)
2. Over the past 2 weeks, were there any days when you did not take your heart medications?	29 (11.7%)	218 (88.3%)	246(1)
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	31 (12.6%)	216 (87.4%)	244(3)
4. When you travel or leave home, do you sometimes forget to bring along your medications?	26 (10.5%)	221 (89.5%)	245(2)
5. Did you take your heart medications yesterday?	198 (80.2%)	49 (19.8%)	246(1)
6. When you feel like your heart condition is under control, do you sometimes stop taking your medications?	5 (2%)	242 (98%)	244(3)
7. Do you ever feel hassled about sticking to your heart treatment plan?	41 (16.6%)	206 (83.4%)	246(1)

8. How often do you have difficulty remembering to take ALL your heart medications?	Never	Almost Never	Sometimes	Quite often	Always	n* (missing)
	73	136	33	5	0	245 (2)
	29.5%	55.1%	13.4%	2%	0%	

***n** = number of patients who answered this question before adjusting.

Table 4.14 – Adherence levels according to MMAS-8 Score after adjusting for partial responses and scoring them in favour of adherence (n=500).

Morisky Adherence Status	
Adherent (MS = 8)	253 (51%)
Non-adherent (MS <8)	247 (49%)
n	500
Level of Adherence	
High Adherence (MS = 8)	253 (51%)
Medium Adherence (MS - 6 to 8)	195 (39%)
Low Adherence (MS <6)	52 (10%)
n	500

MS = Morisky Score

Figure 4.9 shows the distribution of MMAS-8 scores for non-adherent patients after adjusting for missing responses in favour of adherence. Twenty three percent of non-adherent patients had a score of 7.75 which indicates that they only answered "almost never" to Question 8 instead of "never".

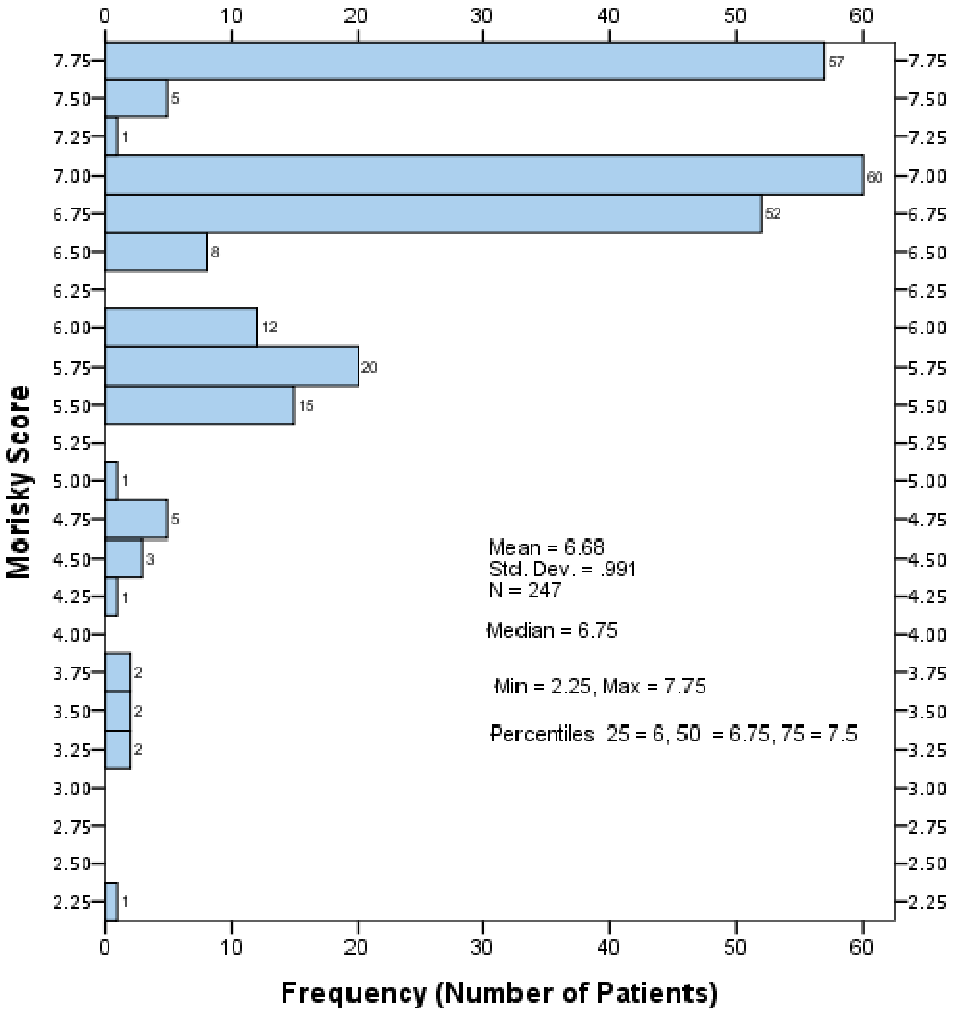

Figure 4.9 – Distribution of MMAS-8 scores among **Non-adherent** patients identified by the MMAS-8 scale after adjustments in favour of adherence (n= 247).

The MMAS-8 scale explores various types of reasons for non-adherence. Questions 1, 4 and 8 (Qn1, Qn4 and Qn8) mainly address forgetfulness. Questions 2 and 5 (Qn2 and Qn5) can be due to forgetfulness or other intentional non-adherence reasons. In Table 4.15 responses were grouped, where possible, to understand reasons behind non-adherence according to the MMAS-8 scale. The most common reason for non-

adherence was forgetfulness. Seventeen percent of patients were hassled about their medicines and 13% stopped their medicines after feeling worse on them without informing their doctor.

Table 4.15 – The reasons for non-adherence among non-adherent patients who were identified by the MMAS-8 scale (n=247).

Reason	Frequency
(1) Forgetfulness of any type (questions 1,4,8)	182 (74%)
Forgetfulness when travelling (question 4)	26 (11%)
(2) Did not take medicine in the last 2 weeks OR yesterday. (forgetfulness or other reason) (questions 2, 5)	75(30%)
Not taken in the last 2 weeks (question 2)	29 (12%)
Not taken yesterday (question 5)	49 (20%)
(3) Hassled about medicines	41 (17%)
(4) Stopped medicine(s) after feeling worse on medicine (without telling doctor)	31 (13%)
(5) Stopped medicine(s) after feeling condition under control	5 (2%)

4.5.1.1 Issues with Question 5 in the MMAS-8 scale

Qn5 in the MMAS-8 was reversed (i.e. if the patient answered no = non-adherence, yes = adherence) with respect to Qn1, Qn2, questions3 (Qn3), Qn4 and question 7 (Qn7). This sometimes caused confusion and certain patients may have answered it incorrectly. An account of the number of patients who could have been wrongly classified as non-adherent based ***only*** on Qn5 of the MMAS-8 is as follows:

> The number of patients who answered Qn5 with "No" was 49. Of those patients 14 answered "Yes" to at least one of the other questions in the MMAS-8 scale. This means that 35 patients were classed to be non-adherent based only on Qn5. To reduce the risk of incorrectly classifying those patients as non-adherent, Qn5 will be excluded from further analysis.

After excluding Qn5, the scoring of MMAS-8 was recalculated. The number of non-adherent patients was found to be **211 (42%)** as opposed to 247 (49%) (adjusted in

favour of adherence) without excluding Qn5. The levels of non-adherence were: medium adherence 162 (32%) and low adherence 49 (10%). Before excluding Qn5 the levels were: 195 (39%) and 52 (10%) respectively.

4.5.1.2 Reliability of MMAS-8 - Cronbach's α

Cronbach's α (alpha) was calculated for MMAS-8 to check for internal consistency in identifying non-adherent patients in the sample as described in Section 3.6.2.1.1 and Appendix 15. Full statistical SPSS output can be seen in Appendix 16. As can be seen in Table 4.16 the calculated Cronbach's α for all 8 items was 0.495, which reflects low internal consistency and *"unidimensionality"*. It is noteworthy that n for this calculation was 486 and 17 cases were excluded from the analysis because the reliability test employs *"listwise deletion"* i.e. the case is excluded if any data is missing in the tested variables (any of the 8 questions). Table 4.16 also shows the correlation between each item in the scale and the overall scale. Any question with a correlation of <0.3 indicates lack of consistency with the rest of the questionnaire. A negative value indicates a negative correlation with the total score of the questionnaire. Qn3, Qn5, question 6 (Qn6) and Qn7 have poor correlation with the overall finding of the scale. Qn5 negatively correlates with the overall scale.

Table 4.16 – The correlation between each item in the MMAS-8 scale and the total score for the scale and Cronbach's α for all 8 items (n = 486).

MMAS- 8 Question	Correlation with the total score
Question (1)	0.408
Question (2)	0.373
Question (3)	**0.182***
Question (4)	0.308
Question (5)	**- 0.108†**
Question (6)	**0.172***
Question (7)	**0.193***
Question (8)	0.546
Cronbach's α (N items = 8)	**0.495**

*correlation value is <0.3, † negative correlation.

Table 4.17 shows the predicted change to Cronbach's α if any one of the 8 items was excluded from the scale. Removing Qn5 increases Cronbach's α value significantly from 0.495 to 0.602. This means that removing Qn5 improves the reliability of this scale. The correlation of each question to the overall scale and Cronbach's α were recalculated after removing Qn5 (see Table 4.18).

Table 4.17 – Changes in Cronbach's α for the MMAS-8 scale if any item was excluded (n=486).

MMAS- 8 Question	Cronbach's α if Item Excluded
Question (1)	0.362
Question (2)	0.410
Question (3)	0.477
Question (4)	0.434
Question (5)	**0.602**
Question (6)	0.487
Question (7)	0.476
Question (8)	0.384

Table 4.18 – The correlation between each item in the MMAS-8 scale and the total score for the scale and Cronbach's α for all 7 items after removing Qn5 (n = 487).

MMAS- 8 Question	Correlation with the total
Question (1)	0.484
Question (2)	0.399
Question (3)	**0.195***
Question (4)	0.343
Question (6)	**0.163***
Question (7)	**0.205***
Question (8)	0.601
Cronbach's α (N items = 7)	**0.602**

*correlation value is <0.3

A Cronbach's α value of <0.7 indicates reduced internal consistency and this could be explained by the diverse themes covered by the scale. Qn3, Qn6 and Qn7 have a correlation of <0.3 which indicates lack of consistency with the rest of the questionnaire. However, as can be seen in Table 4.19 removing Qn3, Qn6 and Qn7 individually will cause negligible increases in Cronbach's α value.

Table 4.19 - Changes in Cronbach's α for the MMAS-8 scale if any item of the 7 remaining was excluded (n=486).

MMAS- 8 Question	Cronbach's α if Item Excluded
Question (1)	0.500
Question (2)	0.538
Question (3)	**0.604**
Question (4)	0.557
Question (6)	**0.606**
Question (7)	**0.608**
Question (8)	0.504

The MMAS-8 scale had medium reliability after removing Qn5 (Cronbach's α = 0.602). Due to the poor correlation between Qn3, Qn6 and Qn7 with the overall score of the questionnaire, Cronbach's α value was recalculated in the absence of all of these three questions. Cronbach's α for MMAS-8 for Qn1, Qn2, Qn4, and Qn8 was increased to the value of **0.681** (n=493). Any further item deletion reduced Cronbach's α value to <0.681. If all missing values were replaced with a score in favour of adherence to make n= 500. Cronbach's α (including Qn5) = 0.501, Cronbach's α (excluding Qn5) = 0.610, Cronbach's α (excluding Qn5, Qn3, Qn6 and Qn7) = 0.678.

Due to these findings further exploration by conducting a factorial analysis is needed to identify if the scale is "unidimensional" or contains other constructs that should be considered when analysing the results.

4.5.1.3 Factor analysis of MMAS-8

An exploratory factorial analysis was conducted on the 8 questions as described in Section 3.6.2.1.2 and Appendix 15. The analysis was carried on 486 patients following the principle of *listwise deletion*. Full SPSS output can be seen in Appendix 16. The determinant of the correlation matrix was 0.345 which means that multicolinearity is not a problem for this data (Field, 2009). The questions correlate and none of the

correlation coefficients were particularly large (>0.9), so there was no need to eliminate any questions. The KMO was 0.698 indicating good sampling adequacy and factor analysis should yield distinct and reliable factors (Field, 2009). Bartlett's test of sphericity results were $\chi^2 = 518.204$, $p < 0.001$ and therefore the original matrix is not an identity matrix (Field, 2009).

Initial eigenvalues identified 8 components (equal to the number of questions). Kaiser's criterion of retaining factors with eigenvalues >1 was used. The extraction identified two constructs or factors. The communilaties table (see Appendix 16) indicates the proportion of variance explained by the underlying factors. Qn1 has a common associated variance of 72.5% whereas Qn5 had only 8.9%. Before rotating: Qn1, Qn2, Qn4, and Qn8 load highly onto the first factor; and Qn3, Qn6 and Qn7 load highly onto the second factor. Qn5 does not seem to load onto either of the factors.

SPSS used the extraction method of principal component analysis and the rotation method of Varimax with Kaiser Normalization. Rotation converged in 3 iterations and the same questions were loaded onto the same factors. However, the values of loading for most of the questions were bigger. Table 4.20 shows factor loading after rotation. The two constructs identified were as follows: **Factor 1** - includes Qn1, Qn2, Qn4 and Qn8 which focus mainly on non-intentional i.e. forgetfulness, and **Factor 2** – includes Qn3, Qn6 and Qn7 which focus more on intentional non-adherence. While Qn3 and Qn6 reflect intentional non-adherence, Qn7 possibly has both intentional and non-intentional components.

Table 4.20 - Summary of exploratory factor analysis results for MMAS-8 scale (n=486). The green shaded areas are the questions with high factor loading (>0.4).

Item	Factor 1 (Unintentional / Forgetfulness non-adherence)	Factor 2 (Intentional / Hassle non-adherence)
1. Do you sometimes forget to take your heart medicines?	**0.85**	0.05
2. Over the past 2 weeks, were there any days when you did not take your heart medications?	**0.69**	0.02
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	0.05	**0.67**
4. When you travel or leave home, do you sometimes forget to bring along your medications?	**0.50**	0.26
5. Did you take your heart medications yesterday?	-0.27	0.13
6. When you feel like your heart condition is under control, do you sometimes stop taking your medications?	-0.13	**0.63**
7. Do you ever feel hassled about sticking to your heart treatment plan?	0.10	**0.65**
8. How often do you have difficulty remembering to take ALL your heart medications?	**0.80**	0.18
Eigenvalues	2.17	1.38
% of variance	27.15	17.19
Cronbach's α	0.681	0.324

The calculation of Cronbach's α for Factor 2 shows very low internal consistency among the 3 questions. Removing item 6 from Factor 2 would increase Cronbach's α to 0.329. Removing either item 3 or item 7 would reduce Cronbach's α to <0.180. This will be discussed further in the Discussion Chapter.

4.5.1.4 Adherence levels according to the two Factors

Factor 1 (unintentional / forgetfulness non-adherence) includes all patients who answered “yes” to one or more of the following questions: Qn1, Q2, Qn4 or Qn8 in the

MMAS-8 scale. Factor 2 (intentional / hassle non-adherence) includes those who answered "yes" to one or more of Qn3, Qn6 or Qn7. In Factor 2 six patients had one missing response to one of the three questions. Those were adjusted in favour of adherence. Figure 4.10 shows the distribution of the non-adherent group identified by MMAS-8 (excluding Qn5) (211 patients) according to Factor 1 and Factor 2. Forty (19%) of non-adherent patients had both elements of non-adherence (Factor 1 and Factor 2).

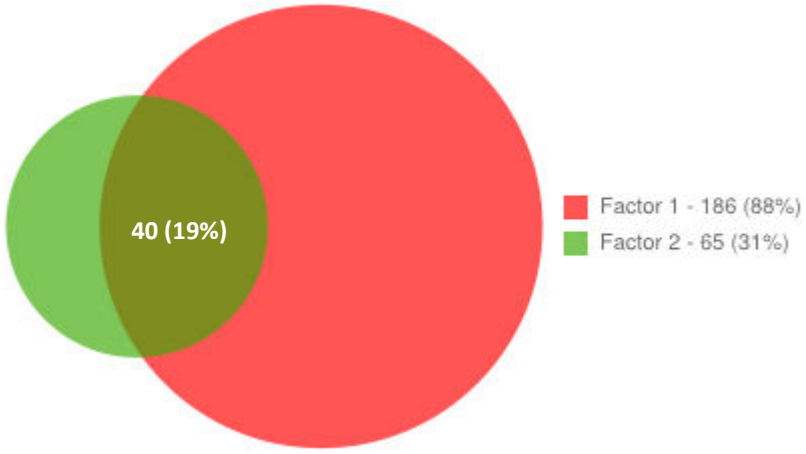

Figure 4.10 – Venn diagram of non-adherent patients identified by the MMAS-8 and distributed to Factor 1 and Factor 2 (n = 211).

4.5.2 Results of the Adherence Estimator scale

Table 4.21 describes the overall results for the scale. Table 4.22 is an analysis for Item 3 which is related to cost of medicines. As patients over 60 and those with certain medical conditions are exempt from paying prescription charges, the item was analysed taking age and relevant identifiable co-morbidities into account. It was not possible to establish for certain which patients who were both under 60 and exempt from paying for their medicines. However, all identifiable reasons available to the researcher were used in the analysis.

Table 4.21 – Overall results for the Adherence Estimator (n=498).
(Five patients did not answer any question of the AE (one was <60 years old). Green cells are significant according to the AE scale (weight > 0))

	Agree Completely	Agree Mostly	Agree Somewhat	Disagree Somewhat	Disagree Mostly	Disagree Completely	n
1. I am convinced of the importance of my prescription medication	386 (77.8%)	83 (16.7%)	19 (3.8%)	6 (1.2%)	0 (0%)	2 (0.4%)	496
2. I worry that my prescription medication will do more harm than good to me	16 (3.4%)	22(4.7%)	47 (10.0%)	39 (8.3%)	96 (20.5%)	248 (53.0%)	468
3. I feel financially burdened by my out-of-pocket expenses for my prescription medication	18 (3.6%)	3 (0.6%)	17 (3.4%)	13 (2.6%)	8 (1.6%)	441 (88.1%)	496

Table 4.22 – Overall results for question 3 for Adherence Estimator ™ score for patients <60. (n=71)

	Agree Completely	Agree Mostly	Agree Somewhat	Disagree Somewhat	Disagree Mostly	Disagree Completely	n
I feel financially burdened by my out-of-pocket expenses for my prescription medication	16 (22.5%)*	3 (4.2%)	13 (18.3%)*	7 (9.5%)*	5 (7.0%)*	27 (38.0%)	71

* 15 patients ≥ 60 answered item 3 with other than “Disagree Completely”. Two aged 72 and 71 said “Agree completely” and the rest said “Agree Somewhat” or less. Four had just turned 60 – so they could have been recently paying for their prescription and have just become exempt. Nine were older than 60. Only one patient of the 9 gave a reason for answering this question. He commented that “erectile dysfunction medication should be free for a non-earning pensioner”. The other 8 made no comment.

Table 4.23 shows the probability of the level of intentional adherence and non-adherence to secondary prevention medicines according to the AE. All missing cases were handled as was discussed in Section 3.6.3. Thirty percent of patients were predicted by the AE to have low to medium probability of adherence. The AE estimated that 10% of patients should have low probability of adherence.

Table 4.23 – Probability of adherence levels according to the AE.
(Assuming best case scenario – i.e. missing responses were converted in favour of adherence)

AE Adherence Status	
Adherent (AES = 0)	351 (71%)
Non-adherent (AES> 0)	147 (30%)
n	498
Level of Adherence	
High probability of adherence (>75%) (AES = 0)	351 (71%)
Medium probability of adherence (32 – 75%) (AES = 2 to 7)	96 (19%)
Low probability of adherence (<32%) (AES ≥ 8)	51 (10%)
n	498

AES = Adherence Estimator score.

The distribution of scores for the non-adherent patients is presented in Figure 4.11. It is notable that the scores in the AE suggest possible reasons for non-adherence as summarised in Table 4.24.

Table 4.24 – Summary of the interpretation of various AE scores in terms of the reasons underlying propensity to intentional non-adherence.

	Possible reason for propensity to intentional non-adherence		
AE Score	*Cost*	*Worried about harm*	*Not convinced of importance*
2	✓		
4		✓	
6	✓	✓	
7			✓
11		✓	✓
14		✓✓	
16	✓	✓✓	
20			✓✓
21		✓✓	✓
23	✓	✓✓	✓
34		✓✓	✓✓

✓✓ = indicates a stronger contribution from this element (Possible range 0 – 36)

Sixty eight percent of the predicted non-adherent group are only worrying that their medicines can cause more harm than good (scored 4 or 14 as in Figure 4.11).

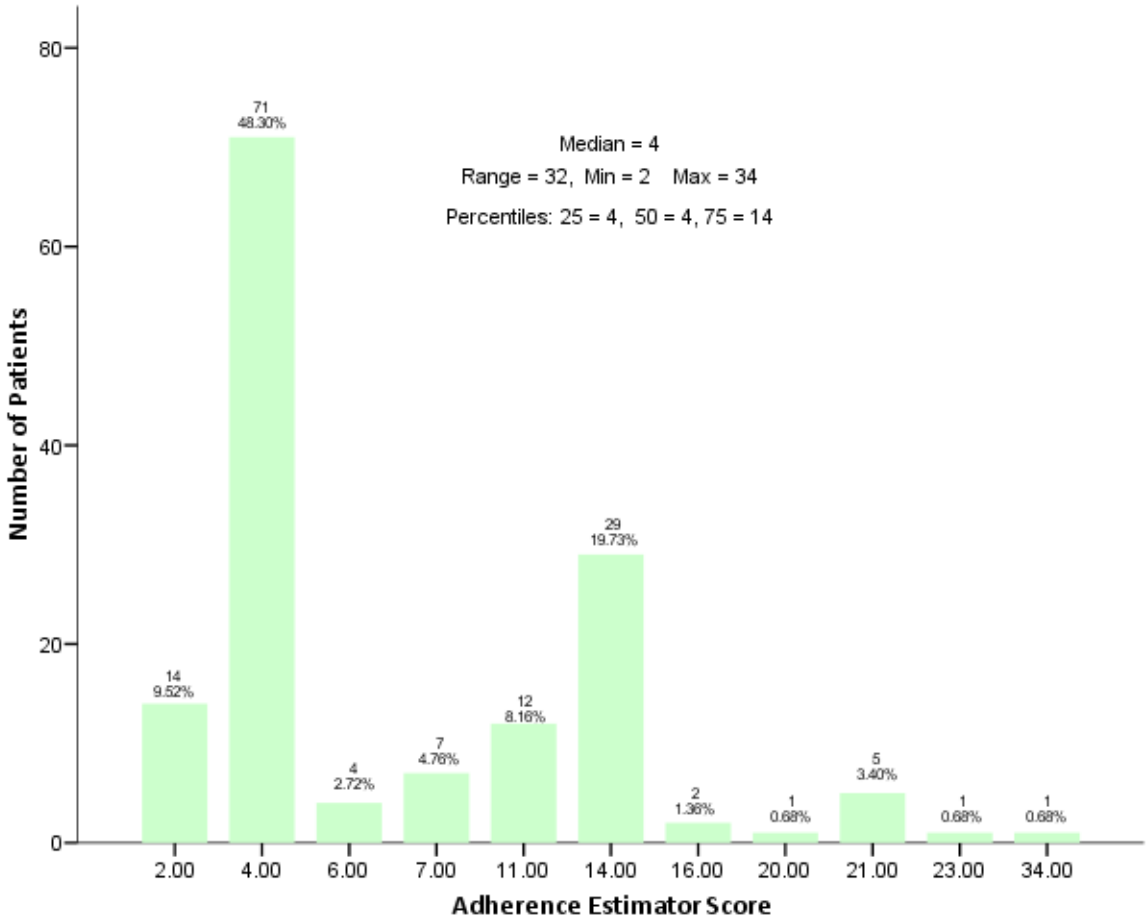

Figure 4.11 – Distribution of AE scores among probable non-adherent patients according to AE (n = 147).

The reasons for propensity to intentional non-adherence according to the AE findings are shown in Table 4.25. Worrying about the harm of medicines ranked first. The analysis of cost of medicines' impact on adherence is shown in Table 4.26.

Table 4.25 – Reasons for probable non-adherence according to AE (overall) Ranked according to higher frequency (n=147).

Reason	Frequency
Worry that their medicines will do more harm than good	124 (84.4%)
Not convinced enough about the importance of their medicines	27 (18.4%)
Feel financially burdened by cost of medicines	See Table 4.27

Table 4.26 – Analysis of question 3 in AE (cost of medicines being reason for non-adherence) by identifying the number of patients who are not exempt from paying a prescription charge. (Only patients aged <60 were included)

	Number of patients
Patients <60 yrs old in the sample **AND** who answered Q3 in AE	71
Patients <60 yrs old who are not exempt (not diabetic or hypothyroid)	58
Adherent patients according to question 3 in AE (and are not exempt)	41 (71% of 58)
Non-adherent patients according to question 3 in AE	17* (29% of 58)

One way Chi square test (assuming 50:50) *p*-value = 0.002

*Two patients were excluded because they were exempt (one is diabetic and the second has hypothyroid) and still answered that cost is an issue. It is unclear why they identified cost as an issue.

Fourteen of those none adherent according to AE had a score of 2, i.e. no other reason under the AE to be non-adherent except cost of medicines. One of those patients was a diabetic and therefore should have not identified cost as an issue. This means that 22% (13/58) of patients who pay a prescription charge identified cost as the only possible barrier to their adherence according to the AE. Seven of them were found to be non-adherent by the MMAS-8 (excluding Qn5) scale. Four had both elements of non-intentional (forgetfulness) and intentional (medicines related) non-adherence. Two patients had only non-intentional (forgetfulness) reasons and one patient had only intentional (medicines related) non-adherence. Their median number of medicines was 5.

4.5.3 Results of the Single Question scale

Table 4.27 summarises the final findings of the SQ after addressing discrepancies between this part and Part 1 of the questionnaire. The overall "raw" results of this part are presented in Appendix 16. See Section 3.6.2.3 for more details. Only patients who

answered the SQ part and listed the secondary prevention medicine(s) in Part 1 of the questionnaire were included.

Overall 482 out of 503 patients answered this part of the questionnaire. Table 4.28 shows the level of adherence and non-adherence to individual secondary prevention medicines as reported by patients who responded to the SQ scale. Patients who were non-adherent to at least one of the secondary prevention medicines were classed as non-adherent. The original SQ scale used 75% as a cut-off point in identifying the non-adherent patients. Accordingly, statins are the most non-adhered to medicines (3% non-adherence). However, patients who chose 90% also have some level of non-adherence. Therefore, examining any non-adherence to the secondary prevention medicines (≤90%) shows that aspirin is the most non-adhered to secondary prevention medicine (9%) followed by statins (8%). The researcher introduced an additional cut-off point of 90% to identify patients with medium adherence vs. those with low adherence (≤75%). For the purpose of this analysis two categories of non-adherence were created; **SQ Medium adherence** = non-adherence of 90% to at least one of the secondary prevention medicines and in the absence of any non-adherence of <90% to any of the other secondary prevention medicines. **SQ Low adherence** = non-adherence of ≤75% to any of the secondary prevention medicines. Table 4.29 describes the overall levels of adherence according to the SQ scale. The estimated level of non-adherence according to the SQ scale if the 75% cut-off point was used is **5% (25/482)**. If the 90% cut-off point was used the level of reported non-adherence would be **13% (60/482)**. The contribution of aspirin, statins, clopidogrel, beta blockers, ACEI and ARBs to the SQ scale non-adherence was 62%, 67%, 7%, 30%, 22% and 5%, respectively.

Table 4.27 – Summary of patients' answers to the modified Single Question Scale (n = 482).
(21 patients did not answer this part of the questionnaire)

	In the past month, how often did you take your medications as the doctor prescribed?					
Name of Heart Medicine	**All of the time 100%**	**Nearly all of the time 90%**	**Most of the time 75%**	**About half the time 50%**	**Less than half the time <50%**	**n***
Aspirin	370 (90.9%)	27 (6.6%)	2 (0.5%)	5 (1.2%)	3 (0.7%)	**407**
Clopidogrel	53 (93.0%)	3 (5.3%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	**57**
ACE Inhibitor	262 (95.3%)	9 (3.3%)	3 (1.1%)	0 (0.0%)	1 (0.4%)	**275**
BB	321 (94.7%)	14 (4.1%)	2 (0.6%)	0 (0.0%)	2 (0.6%)	**339**
Statin	409 (91.1%)	26 (5.8%)	7 (1.6%)	3 (0.7%)	4 (0.9%)	**449**
ARBs	87 (96.7%)	3 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**90**

ACE = Angiotensin Converting Enzyme, **BB =** Beta Blockers, **ARBs =** Angiotensin Receptor Blockers
*__n__ = the number of patients who answered this part of the questionnaire and listed the drug in Part 1 OR declared intentional non-adherence

Table 4.28 – Levels of adherence and non-adherence to individual secondary prevention medicines according to the SQ scale (n = 482).

Secondary Prevention Medicine	n	Adherence according to SQ scale							
		100%		90%		≤75%		≤90%	
Aspirin	407	370	91%	**27**	**7%**	10	2%	**37**	**9%**
Clopidogrel	57	53	93%	3	5%	1	2%	4	7%
ACEI	275	262	95%	9	3%	4	1%	13	4%
BB	339	321	95%	14	4%	4	1%	18	5%
Statin	449	409	91%	26	6%	**14**	**3%**	40	8%
ARBs	90	**87**	**97%**	3	3%	0	0%	3	3%

ACEI = Angiotensin Converting Enzyme Inhibitors**, BB** = Beta Blockers**, ARBs** = Angiotensin Receptor Blockers

Table 4.29 – Overall levels of adherence and non-adherence according to the modified SQ scale (n = 482).

SQ Adherence Levels	Number of Patients
Number of patients with SQS of 100% for all their secondary prevention medicines	422 (87.5%)
Number of Patients with SQS of 90% for at least one of their secondary prevention medicines (none of the other medicines <90%) - **Medium Adherence**	35 (7.3%)
Number of Patients with SQS of ≤75% for at least one of their secondary prevention medicines (none of the other medicines <90%) – **Low Adherence**	25 (5.2%)
Total	**482 (100%)**
Missing (SQ part not answered at all from the 503)	21

SQ = Single Question, **SQS** = Single Question Score

Table 4.30 is a cross-tabulation of the number of the secondary prevention medicines prescribed as reported by patients and the number of the secondary prevention medicines not adhered to in each category. The total number of non-adherent patients was 60. Fifty three percent (32/60), 18% (11/60), 12% (7/60) and 17% (10/60) of non-adherent patients did not adhere to 1, 2, 3 and 4 of their secondary prevention medicines respectively.

Table 4.30 – The number of secondary prevention medicines not adhered to, according to the number of secondary prevention medicines taken by patients.

No. of Sec Prev Medicines Taken by Patient	No. of Secondary Prevention Medicines NOT adhered to										Total
	0		1		2		3		4		
1	17	89%	**2**	**11%**	0	0%	0	0%	0	0%	19
2	46	87%	4	8%	**3**	**6%**	0	0%	0	0%	53
3	150	87%	12	7%	3	2%	**7**	**4%**	0	0%	172
4	186	87%	13	6%	5	2%	0	0%	**10**	**5%**	214
5	**23**	**96%**	1	4%	0	0%	0	0%	0	0%	24
Total	422	88%	**32**	**7%**	11	2%	7	1%	10	2%	482

4.6 Overall findings and comparing the adherence scales

The MMAS-8 and SQ scales identified current behaviour and any contemporaneous non-adherence to secondary prevention medicines. The AE, on the other hand, explored propensity to non-adherence based on the major drivers of intentional non-adherence. In this section the findings of all three scales will be brought together and compared. Agreement between the scales will also be explored.

As can be seen in Figure 4.12, the level of non-adherence identified by MMAS-8 (excluding Qn5) or SQ scale was approximately 44%. Where data was missing for one scale the conclusion on level of adherence was used based on the other scale. Only one patient could not be classified according to either scale. Figure 4.13 describes the number of patients who were predicted by the AE to be non-adherent and were identified to be non-adherent by the MMAS-8 (excluding Qn5) or the SQ scale. It also identifies the proportion of patients who had propensity to non-adherence according to the AE and were not identified by other scales to be non-adherent.

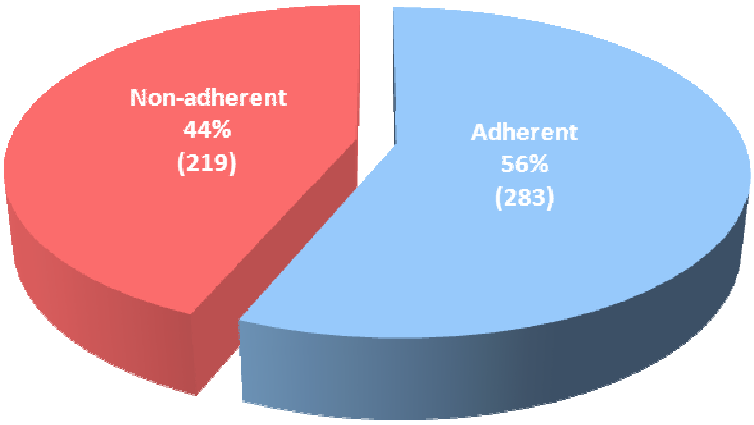

Figure 4.12 – Overall identified adherence vs. non-adherence according to MMAS-8 (excluding Qn5) or SQ scale (n=502).

Only 39% of non-adherent patients were predicted by the AE. Forty two percent of patients who were predicted to be non-adherent by the AE were not identified to be so by any of the scales.

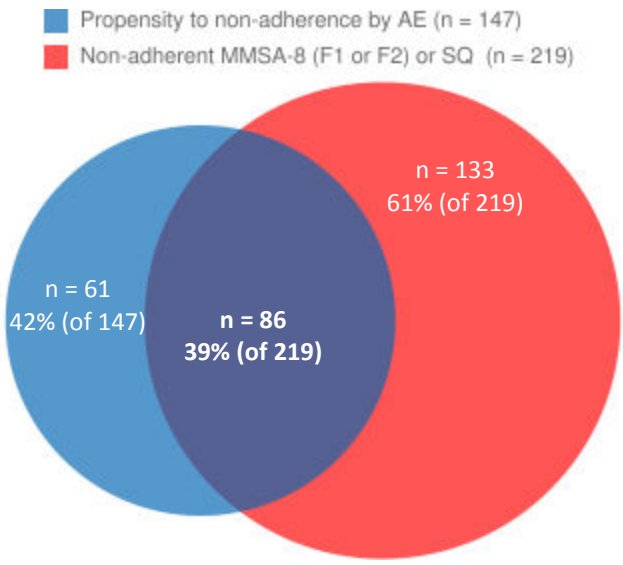

Figure 4.13 – Venn diagram of non-adherent patients identified by the MMAS-8 (excluding Qn5) or the SQ scale and those patients who were identified by the AE to have propensity to non-adherence.

Figure 4.14 shows the distribution of AE scores for the 86 patients who were identified by the AE to have propensity to non-adherence and were detected by the MMAS-8 (excluding Qn5) or the SQ scale to be non-adherent.

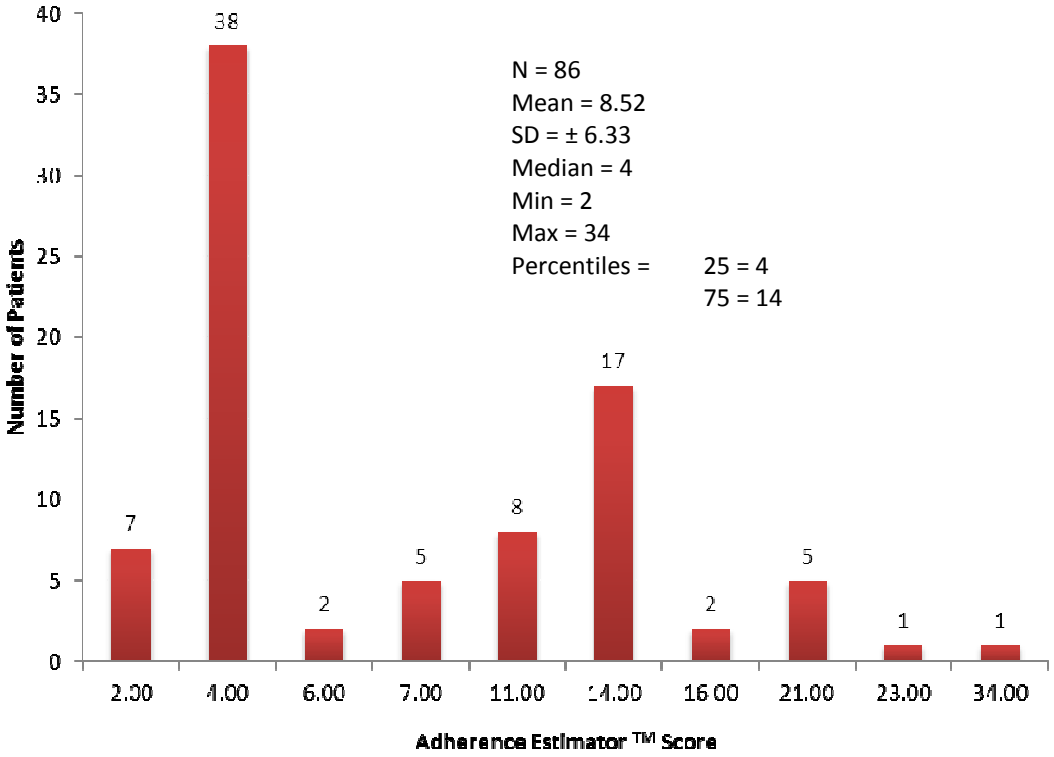

Figure 4.14 – Distribution of AE scores for non-adherent patients who were identified by AE to have propensity to non-adherence and were detected by the MMAS-8 (excluding Qn5) or SQ scale.

Table 4.31 summarises the possible cumulative reasons for non-adherence in those 86 patients based on the AE. The main reason for predicted intentional non-adherence among non-adherent patients was worrying that the medicines will cause harm (86%). Not being convinced about the importance of medicines was cited by 23% of patients. Cost was identified as a reason by 12 patients. All those patients were less than 60 years old and did not have diabetes or hypothyroidism (except for one patient). One patient did have hypothyroidism and it is unclear why he cited cost as a reason (as they would be exempt from prescription charges).

Table 4.31 – Reasons for propensity to non-adherence according to AE in patients who were identified to be non-adherent by the MMAS-8 (excluding Qn5) or SQ scales.

Factor	Number of Patients (n=86)
Worry that their medicines will cause harm	74 (86%)
Not convinced enough about the importance of their medicines	20 (23%)
Feel burdened by the cost of their medicines*	12 (14%)

*All patients in this category were <60 years old and not exempt, except for one patient who has hypothyroidism.

4.6.1 Reasons for non-adherence according to the findings of various scales

Table 4.32 summarises the overall reasons for non-adherence in the non-adherent group identified by MMAS-8 (excluding Qn5) or SQ scale. The biggest cause of non-adherence was forgetfulness (83%). Worrying that medicines will do more harm than good was reported by nearly 34% of the non-adherers. Approximately 19% of non-adherents were hassled with their medicines and nearly 14% stopped taking their medicines because they felt worse. The percentage of non-adherent patients due to the cost of medicines was calculated separately as can be seen in the table (30%). Though 12 patients were identified to have cost of medicines as a cause for non-adherence, one patient was excluded because of his exemption status (hypothyroidism).

Table 4.32 – Overall reasons of non-adherence among the non-adherent group identified by MMAS-8 (excluding Qn5) and SQ scale (n = 219).

	n = 219
Forgetfulness of any type (questions 1,4,8)	182 (83%)
General forgetfulness (question 1 and 8)	179 (82%)
Forgetfulness when travelling (question 4)	26 (11%)
Worry that their medicines will do more harm than good	74(34%)
Hassled about medicines	41 (19%)
Stopped medicine(s) after feeling worse on medicine (without telling doctor)	31 (14%)
Did not take medicine in the last 2 weeks (due to forgetfulness or other reason)	29(13%)
Not convinced enough about the importance of their medicines	20(9%)
Stopped medicine(s) after feeling condition under control	5 (2%)
	n = 37*
Feel financially burdened by cost of medicines*	11 (30%)

*Total non-adherent patients <60 and not exempt = 37. Percentage = 11/37 = 30% of those paying charges

4.6.2 Comparing AE findings with MMAS-8 (excluding Qn5) scale and SQ

The AE identified 30% of patients to have a medium to a high probability of non-adherence. The predictions of the AE are compared to the findings of MMAS-8 (excluding Qn5) scale, and Factor 1 and 2 elements (see Table 4.33).

Only 39% of patients identified by MMAS-8 (excluding Qn5) to be non-adherent had been predicted by the AE. A similar percentage (37%) was found for Factor 1 findings. However, 63% of non-adherent patients who were identified by the Factor 2 element (intentional / hassle non-adherence) had been predicted by AE to be non-adherent. This could be explained by the intentional non-adherence element in Factor 2.

Table 4.33 - Cross-tabulation of predicted adherent and non-adherent findings of the AE against identified adherent and non-adherent findings of the MMAS-8 (excluding Qn5), Factor 1, and Factor 2 (n=496).

	Adherence Estimator			
	Probably Adherent (n=350)	Probably non-adherent (146)	χ^2	*p*-value* (2-sided)
MMAS-8 (Excluding Qn5) (n=496)				
Adherent	223 (78%)	64 (22%)	16.697	<0.001
Non-adherent	127 (61%)	82 (39%)		
Factor 2 (intentional / hassle) MMAS-8 (n=496)				
Adherent	326 (76%)	105(24%)	40.758	<0.001
Non-adherent	24 (37%)	**41 (63%)**		
Factor 1 (unintentional) MMAS-8 (n=496)				
Adherent	234 (75%)	78 (25%)	7.966	0.005
Non-adherent	116 (63%)	68(37%)		

* *p*-values were calculated using Chi-square test

As explained in Sections 2.1, 2.2.1 and 3.6.5 there is no "gold standard" tool for measuring actual adherence behaviour and no single tool to detect all types of non-adherence. To evaluate the performance of self-report adherence assessment tools researchers in this field often select an 'imperfect gold standard' tool to check against (e.g. MEMS® or other self-report tool). Therefore, the reported sensitivity, specificity, positive predictive and negative predictive values for a specific self-report tool is only relative to the 'imperfect gold standard' chosen[**]. If the findings of the MMAS-8 (excluding Qn5) or SQ scale were used as a "gold standard" in identifying non-adherent patients, it is possible to calculate the positive and negative predictive values of the AE (as a screening tool). Table 4.34 is a breakdown of the predicted estimated level of

[**] And therefore somewhat imprecise compared to their use in other healthcare fields. In diagnostics, for example, they would only be calculated with regard to a definitive final outcome (i.e. whether the patient developed the disease according to a completely accurate diagnostic test). However, reporting these "imprecise" values is standard in the adherence literature, and in this thesis, as they are useful for comparing the performance of adherence assessment tools. This impreciseness should always be taken into account when interpreting and reporting these values.

adherence according to the AE and the number of patients who were identified to be adherent or non-adherent by the gold standard tools. Based on these figures the **positive predictive value** of the AE is **59%** (86/147). That is the portion of patients who were found to be non-adherent of those who were predicted by the AE to have medium (52) to high (34) risk of adherence problems. More patients who were predicted in the high risk category were identified to be non-adherent than those in the medium risk category (67% vs. 54% respectively). The **negative predictive value** for the AE was **63%** (220/351). That is the proportion of patients who were found to be adherent of those predicted to have low risk of adherence problems. The **sensitivity** of the AE in predicting patients who are likely to be non-adherent in this sample was **40%** (86/217 (two were missing)).The **specificity** of the AE in predicting adherent patients was **78%** (220/281).

Table 4.34 – Comparing the risk levels of propensity to adherence by the AE to the findings of self-reported adherence scales (n=498).

AE estimate for adherence	Identified to be non-adherent	Identified to be adherent	Total
Low risk of adherence problems (>75% prob of adherence)	131 (37%)	220 (63%)	351
Medium Risk of adherence problems (32%- 75% prob of adherence)	52 (54%)	44 (46%)	96
High risk of adherence problems (<32% prob of adherence)	34 (67%)	17 (33%)	51
Total	**217**	**281**	**498**

χ^2 =21.023 , *p* = <0.001 (2-sided), prob = probability

4.6.3 Comparing SQ findings with MMAS-8 (excluding Qn5) and AE

Table 4.35 compares the findings of the SQ scale with other scales. The table shows that the SQ has lower sensitivity compared to the MMAS-8 (excluding Qn5) scale. The

SQ **sensitivity** was 25% (52/206). The SQ **specificity** was 97% (266/274). This lack of sensitivity is apparent for example in that 131 patients who said that they sometimes forgot to take their secondary prevention medicines according to Factor 1 findings were classed as adherent by the SQ scale. The intentional element of non-adherence (Factor 2) was seen more in the *low adherence* category of the SQ scale (20% in SQ low adherence vs. 11% in SQ medium adherence); whereas the unintentional element (Factor 1) was seen more in the *medium adherence* category (18% in SQ medium adherence vs. 10% in SQ low adherence).

Table 4.35 - Comparing adherent and non-adherent findings of the SQ with the MMAS-8 (excluding Qn5), Factor 1 and Factor 2 of MMAS-8, and Adherence Estimator.

	Level of Adherence According to SQ scale			
	Adherent	Medium Adherence	Low Adherence	*p*-value* (2-sided)
MMAS-8 (excluding Qn5) (n=480)				
Adherent	266 (97%)	3 (1%)	5 (2%)	<0.001
Non-adherent	154 (75%)	**32 (15%)**	20(10%)	
Factor 2 (intentional / hassle) MMAS-8 (n=480)				
Adherent	376 (90%)	28 (7%)	12 (3%)	<0.001
Non-adherent	44 (69%)	7 (11%)	**13 (20%)**	
Factor 1 (unintentional) MMAS-8 (n=480)				
Adherent	289 (97%)	3 (1%)	6 (2%)	<0.001
Non-adherent	131 (72%)	**32 (18%)**	19 (10%)	
Adherence Estimator (n=478)				
Adherent	301 (89%)	24 (7%)	12 (4%)	0.037
Non-adherent	117 (83%)	11 (8%)	**13 (9%)**	

* *p*-values were calculated using Chi-square test OR Fisher's Exact test

Table 4.36 focuses on the non-adherent patients identified by the scales and excludes the adherent patients according to any scale. The earlier discussion about the distribution of the intentional and non-intentional elements of non-adherence in the SQ scale becomes more apparent. Higher percentage of patients who were non-adherent due to non-intentional cause (forgetfulness) was classified by the SQ as "medium adherers" (63% vs. 37% in the "low adherers" category). The intentional /

medicines related non-adherers or those who have high propensity to be intentionally non-adherent were found more among the SQ low adherence category (65% and 54% respectively).

Table 4.36 - The distribution of non-adherent patients identified by both scales; the SQ scale and comparator scales.

	Level of Adherence According to SQ scale		
	Medium Adherence	Low Adherence	**Total non-adherent according to both scales**
MMAS-8 (excluding Qn5) Non-adherent	**32 (62%)**	20(38%)	52
Factor 2 (intentional / hassle) MMAS-8 Non-adherent	7 (35%)	**13 (65%)**	20
Factor 1 (non-intentional) MMAS-8 Non-adherent	**32 (63%)**	19 (37%)	51
Adherence Estimator TM Non-adherent	11 (46%)	**13 (54%)**	24

4.6.4 Kappa statistic to examine agreement between scales.

The Kappa statistic was used to examine the agreement between scales as described in Section 3.6.5.1 and Appendix 15. Full SPSS statistical results can be seen in Appendix 16. All findings are summarised in Table 4.37. Overall the agreement between the scales was poor. The highest agreement was seen between Factor 1 and the SQ scale. Factor 2 had a fair agreement with the SQ scale when the 75% cut off point was used, and with the AE. This emphasises the intentional element of non-adherence in Factor 2 and the SQ findings with a score of <90%. The agreement between the scales in their ranking was also explored and the calculations are presented in Table 4.38. The overall agreement was also poor.

Table 4.37 – Agreement between the scales (including Factor 1 and Factor 2) in detecting or identifying possible adherent vs. non-adherent patients.

Comparison	n	Value of *κ*	95% CI	*p*-value	Conclusion
MMAS-8 & SQ	480	0.192	0.133, 0.251	< 0.001	Slight agreement
MMAS-8 (excluding Qn5) & SQ	480	0.245	0.176, 0.314	< 0.001	Fair agreement
Factor 1 (MMAS-8) & SQ	480	**0.288**	0.212, 0.364	<0.001	Fair agreement
Factor 2 (MMAS-8) & SQ	480	0.222	0.104, 0.340	<0.001	Fair agreement
MMAS-8 (excluding Qn5) & SQ75	480	0.088	0.039, 0.137	<0.001	Slight agreement
Factor 1 (MMAS-8) & SQ75	480	0.101	0.044, 0.158	<0.001	Slight agreement
Factor 2 (MMAS-8) & SQ75	480	**0.235**	0.110, 0.360	<0.001	Fair agreement
MMAS-8 (excluding Qn5) & AE	496	0.177	0.093, 0.261	<0.001	Slight agreement
Factor 1 (MMAS-8) & AE	496	0.125	0.037, 0.213	0.005	Slight agreement
Factor 2 (MMAS-8) & AE	496	**0.253**	0.165, 0.341	<0.001	Fair agreement
AE & SQ	478	0.076	-0.008, 0.160	0.056	No agreement
AE & SQ75	478	**0.074**	0.007, 0.141	0.011	Slight agreement

AE = Adherence Estimator, **SQ** = Single Question, **SQ75** = Single Question with 75% cut off point, ***κ*** = Kappa, **CI** = Confidence Interval. **Bolded** values are best agreement within each set of comparisons.

Table 4.38 - Agreement between the scales in ranking the identified or possible level of non-adherence among patients.

Comparison	n	Value of *κ*	95% CI	*p*-value	Conclusion
MMAS-8 (excluding Qn5) rank & AE rank	496	0.103	0.029, 0.155	0.002	Slight agreement
MMAS-8 (excluding Qn5) rank & SQ rank	480	0.169	0.112, 0.226	<0.001	Slight agreement
SQ rank & AE rank	478	0.080	0.018, 0.104	0.010	Slight agreement

AE = Adherence Estimator, ***κ*** = Kappa, **CI** = Confidence Interval

4.7 Comparing groups of adherers vs. non-adherers according to findings

The attributes of the adherent and non-adherent groups were compared as described in Sections 3.6.4 and 3.6.4.1. Detailed comparisons of all variables will be tabulated in Appendix 16. Only statistically significant differences will reported in this section and will be discussed later in the discussion chapter.

4.7.1 Comparing groups of adherent vs. non-adherent according to MMAS-8 scale (excluding Qn5)

When comparing the demographics of the adherent vs. non-adherent groups, only the difference in age was statistically significant. Overall the non-adherent group was younger than the adherent (see Table 4.39). All differences in other variables were not statistically significant. When comparing co-morbidities and cardiac history, the differences in patients' angioplasty and CABG history were statistically significant. CABG patients were less likely to be non-adherent, whereas patients who had angioplasty were more non-adherent. The differences between the medicines related variables were statistically non-significant except for being prescribed aspirin and the knowledge about beta blockers. Patients who were prescribed aspirin were more likely to be non-adherent. Non-adherent patients were more knowledgeable about beta blockers than adherers.

Table 4.39 – Statistically significant differences between the adherent vs. non-adherent groups according to the MMAS-8 (excluding Qn5).

Variable		Adherent (n=289)	Non-adherent (n=211)	n
Age*	***Median (Q1, Q3)***	71 (65, 76)	67 (63, 73)	500
	Min, Max	45, 92	38, 92	
CABG **	*Yes*	122 (42%)	68 (32%)	500
	No	167 (58%)	143 (68%)	
Angioplasty**	*Yes*	153 (53%)	132 (63%)	500
	No	136 (47%)	79 (37%)	
On the following secondary prevention medicines	*Aspirin***			
	Yes	241 (83%)	196 (93%)	500
	No	48 (17%)	15 (7%)	
		Adherent (n=206)	**Non-adherent (n=144)**	**n**
Knowledge about secondary prevention medicines	BB**			
	K	63(30%)	64 (44%)	350†
	N	143(70%)	80 (56%)	
(K = " Knowledgeable" vs. N = "not-knowledgeable")				

*p-value (2-sided) <0.05 (Mann-Whitney), **p-value (2-sided) <0.05 (Chi-square test), **CABG** = Coronary artery bypass grafting, **BB** = beta blocker, †not all patients were on BB and 2 did not complete the MMAS-8 part, hence n=350

4.7.2 Comparing groups according to factor analysis findings

Table 4.40 compares the groups of the adherers and none-adherers based on Factor 1 (unintentional / forgetfulness). Non-adherent patients were younger with a median age 67 compared to a median age of 71 among the adherent group. Females were more adherent than males. Patients who had diabetes controlled with anti-diabetics were more likely to be adherent than non-diabetics. Patients with a history of CABG were more likely to be adherent. The number of medicines that patients were prescribed was higher among adherers. Adherent patients had also higher number of medicines doses and administrations per day. Patients who were prescribed aspirin were more likely to be non-adherent. More non-adherent patients, prescribed beta blockers, were classified as "knowledgable" about beta blockers than adherent.

Table 4.40 – Comparison of various variables in the adherent vs. non-adherent groups according to Factor 1 (unintentional) in the MMAS-8 (n=500).

Variable		Adherent (n=314)	Non-adherent (n=186)	n
Age*	***Median(Q1, Q3)***	71 (65, 76)	67 (63, 73)	500
	Min, Max	45, 92	38, 92	
Gender**	*Male*	242 (77%)	160 (86%)	500
	Female	72 (23%)	26 (14%)	
Diabetes**	*Yes*	48 (15%)	14 (8%)	500
	No	266 (85%)	172 (92%)	
CABG **	*Yes*	134 (42.7%)	56 (30.1%)	500
	No	180 (57.3%)	130 (69.9%)	
Number of Medicines*	***Median (Q1, Q3)***	7 (5, 9)	6 (4, 9)	500
	Min, Max	2, 19	2, 20	
Number of doses per day*	***Median (Q1, Q3)***	7 (5, 10)	6 (5, 9)	500
	Min, Max	1, 24	2, 22	
Total number of daily administrations*	***Mean (SD)***	2.47 (± 0.86)	2.31 (± 0.74)	500
	Median (Q1, Q3)	2 (2, 3)	2 (2, 3)	
	Min, Max	1, 4	1, 4	
On the following secondary prevention medicines	*Aspirin***			500
	Yes	265 (84%)	172 (92%)	
	No	49 (16%)	14 (8%)	
		Adherent (n=221)	**Non-adherent (n=129)**	**n**
Knowledge about individual secondary prevention medicines **(K = " Knowledgeable" vs. N = "not-knowledgeable")**	BB**			350†
	K	68 (31%)	59 (46%)	
	N	153 (69%)	70 (54%)	

p*-value (2-sided) <0.05 (Mann-Whitney OR Independent samples t-test), ***p*-value (2-sided) <0.05 (Chi-square or Fisher's Exact test), **BB = beta blockers, †not all patients were on BB and 2 did not complete the MMAS-8 part, hence n=350

Further analysis was carried out on the interactions between gender and marital status, and age and gender among the Factor 1 adherent vs. non-adherent groups. These can be found in Appendix 16. The analysis showed no statistically significant difference in adherence behaviour between married vs. non-married males or females. The distribution of the age of females was the same across the categories of adherent and non-adherent groups and the difference in the median age (72 vs. 68.5 respectively) was not statistically significant. However, among males the median age of non-adherers was lower than that for adherers (66.5 vs. 71 respectively). This difference was statistically significant (*p*-value (2-sided) < 0.05).

The average overall knowledge of indication(s) of prescribed secondary prevention medicines among non-adherers was higher than that for adherers (mean ± SD = 1.6 (±0.63) vs. 1.8 (±0.63) respectively, median (Q1, Q3) = 1.5 (1, 2) vs. 1.7 (1.3, 2) respectively). The difference was statistically significant (*p*-value (2-sided) <0.05, Mann-Whitney &Independent samples *t*-test), n = 498 (2 patients did not list any prescribed secondary prevention medicines).

Tables 4.41 compares the adherent vs. non-adherent groups based on Factor 2 (intentional/ hassle). The median age of non-adherers was lower than the adherers. Compared to adherers, non-adherers were more likely to have reported suffering from angina. Contrary to the previous findings non-adherent patients had a higher median of number of medicines. Patients who were prescribed aspirin were more likely to be non-adherent as seen previously and those who were prescribed beta blockers were more likely to be adherent.

Table 4.41 – Comparison of various variables in the adherent vs. non-adherent groups according to Factor 2 (intentional / hassle) in the MMAS-8 (n=500).

Variable		Adherent (n=435)	Non-adherent (n=65)	n
Age*	***Median (Q1, Q3)***	70 (64, 76)	67 (58, 72)	500
	Min, Max	45, 92	38, 92	
Number of Medicines*	***Median (Q1, Q3)***	6 (5, 9)	7 (5, 10)	500
	Min, Max	2, 20	3, 19	
On the following secondary prevention medicines	*Aspirin***			500
	Yes	375 (86%)	62 (95%)	
	No	60 (14%)	3 (5%)	
	*BB***			500
	Yes	315 (72%)	39 (60%)	
	No	120 (28%)	26 (40%)	
Variable		**Adherent (n=217)**	**Non-adherent (n=34)**	**n**
Angina Status**	*Yes*	49 (23%)	15 (44%)	251†
	No	168 (77%)	19 (56%)	

**p*-value (2-sided) <0.05 (Mann-Whitney OR Independent samples t-test), ***p*-value (2-sided) <0.05 (Chi-square or Fisher's Exact test, †not all patients reported whether they have angina or not, hence n=251.

4.7.3 Comparing groups of adherence vs. non-adherence according to AE

Five patients did not complete this part of the questionnaires and therefore n=498. As can be seen in Table 4.42 the median age among the predicted non-adherent group was lower than the adherent. CABG patients were less likely to be identified among the non-adherent, whereas angioplasty patients were more likely to be non-adherent. Predicted non-adherers were more likely to be experiencing angina.

Table 4.42 – Comparison of various variables in the adherent vs. non-adherent groups according to the findings of the AE (n=498).

Variable		Adherent (n=351)	Non-adherent (n=147)	n
Age*	***Median (Q1, Q3)***	70 (64, 76)	67 (59, 74)	498
	Min, Max	44, 92	38, 92	
CABG **	*Yes*	145 (41%)	45(31%)	498
	No	206 (59%)	102(69%)	
Angioplasty**	*Yes*	189(54%)	94(64%)	498
	No	162(46%)	53(36%)	
Variable		**Adherent (n=177)**	**Non-adherent (n=73)**	**n**
Angina Status**	*Yes*	39 (22%)	25 (34%)	250†
	No	138 (78%)	48 (66%)	

**p*-value (2-sided) <0.05 (Mann-Whitney OR Independent samples t-test), ***p*-value (2-sided) <0.05 (Chi-square or Fisher's Exact test, †not all patients reported whether they have angina or not, hence n=250.

4.7.4 Comparing groups of adherence vs. non-adherence according to SQ

The cut-off point of 90% is used to identify all non-adherent patients according to the SQ scale. The findings are summarised in Table 4.43. The median age of the non-adherent patients was lower than the adherent. The number of medicines and doses per day was lower among the non-adherent patients compared to the adherent. No other statistically significant differences were identified.

Table 4.43 – Comparison of various variables in the adherent vs. non-adherent groups according to the SQ scale (n=482). Patients with any level of non-adherence according to the SQ scale were classed as non-adherent.

Variable		Adherent (n=422)	Non-adherent (n=60)	n
Age*	***Median (Q1, Q3)***	70 (64, 76)	65 (59, 70)	482
	Min, Max	38, 92	44, 84	
Number of Medicines*	***Median (Q1, Q3)***	7 (5, 9)	5 (4, 8)	482
	Min, Max	2, 20	2, 13	
Number of doses per day*	***Median (Q1, Q3)***	7 (5, 10)	5 (4, 7)	482
	Min, Max	1, 24	2, 15	

**p*-value (2-sided) <0.05 (Mann-Whitney), ***p*-value (2-sided) <0.05 (Chi-square or Fisher's Exact test.

4.7.5 Comparing groups of adherence vs. non-adherence according to overall findings

The characteristics of all non-adherent patients identified by MMAS-8 (excluding Qn5) or SQ scales were compared. As can be seen from Table 4.44 the non-adherent group was younger than the adherent. CABG patients were less likely to be non-adherent, whereas patients who had angioplasty were more non-adherent. The differences between the medicines related variables were statistically insignificant except for being prescribed aspirin and the knowledge about BB. Patients who were prescribed aspirin were more likely to be non-adherent. Non-adherent patients were more knowledgeable about BB than the adherent.

The average overall knowledge of indication(s) of prescribed secondary prevention medicines among non-adherers was higher than that for adherers (mean ± SD = 1.6 (±0.62) vs. 1.8 (±0.66) respectively, median (Q1, Q3) = 1.5 (1, 2) vs. 1.7 (1.3, 2) respectively). The difference was statistically significant (*p*-value (2-sided) <0.05, Mann-Whitney &Independent samples t-test), n = 498 (2 patients did not list any prescribed secondary prevention medicines).

Table 4.44 – Comparison of various variables in the adherent vs. non-adherent groups according MMAS-8 (excluding Qn5) or SQ scales (n=502).

Variable		Adherent (n=283)	Non-adherent (n=219)	n
Age*	***Median(Q1, Q3)***	71 (65, 71)	67 (62, 73)	
	Min, Max	45, 92	38, 92	502
CABG**	*Yes*	119 (42%)	72 (33%)	502
	No	164 (58%)	147 (67%)	
Angioplasty**	*Yes*	150 (53%)	136 (62%)	502
	No	133 (47%)	83 (38%)	
On the following secondary prevention medicines	*Aspirin***			
	Yes	237 (84%)	202 (92%)	502
	No	46 (16%)	17 (8%)	
		Adherent (n=202)	**Non-adherent (n=150)**	**n**
Knowledge about individual secondary prevention medicines	BB**			
(K = " Knowledgeable" vs. N = "not-knowledgeable")	K	61 (30%)	67 (45%)	352†
	N	141(70%)	83 (55%)	

p*-value (2-sided) <0.05 (Mann-Whitney OR Independent samples t-test), ***p*-value (2-sided) <0.05 (Chi-square or Fisher's Exact test), **BB = beta blockers, †not all patients were on BB and 2 did not complete the MMAS-8 part, hence n=352

4.8 Possible practical barriers to adherence

The four possible practical problems or barriers to adherence are examined as described in Section 3.6.1.7. Table 4.45 summarises the results for all patients who answered this part of the questionnaire. The answers were grouped in Table 4.46 to identify those patients who want an alternative for one or more of these four barriers; answers which indicate that one or more of these barriers are sometimes or always problematic are also grouped together. Having a problem opening bottles or blister packs was reported by 18% of patients, and 22% of those patients who answered this question want a solution or an alternative. Seven percent of patients have a problem reading the label, and similar percentages have problems swallowing medicines and getting repeat prescriptions.

Table 4.45 – Results of the possible practical barriers which can affect adherence.

Possible Problem	Always a problem for me	Sometimes a problem for me	Not a problem prefer alternative (solution)	Not a problem to me at all	n
Opening the medicines bottle or blister pack	16 (3%)	70 (14%)	24 (5%)	382 (78%)	492
Reading the label on the medicines bottle or box	9 (2%)	25 (5%)	6 (1%)	449 (92%)	489
Swallowing my medicines	4 (1%)	30 (6%)	8 (2%)	449 (925%)	491
Getting my repeat prescription	4 (1%)	31 (6%)	16 (3%)	441 (90%)	492

Table 4.46 – Patients who have a problem (always OR sometimes) with the four practical barriers and those who need a solution or an alternative.

Possible Problem	There is a problem	Need a solution / alternative	Total number of patients who answered this question
Opening the medicines bottle or blister pack	86 (18%)	110 (22%)	492
Reading the label on the medicines bottle or box	34 (7%)	40 (8%)	489
Swallowing my medicines	34 (7%)	42 (9%)	491
Getting my repeat prescription	35 (7%)	51 (10%)	492

4.8.1 The effects of barriers to adherence on non-adherence identified by different scales

The association of the four barriers with adherence was examined in Tables 4.47 and 4.48. Patients who have problems with their repeat prescriptions or ask for a solution or an alternative are more likely to be non-adherent. Those asking for an alternative to reading the labels are also more likely to be non-adherent.

Table 4.47 – Adherent and non-adherent patients who have possible problems (always or sometimes) with the four practical categories.

Possible Problem	This is a problem	MMAS-8 (excluding Qn5) or SQ		*p*-value (2-sided)
		Adherent	Non-Adherent	
Opening the medicines bottle or blister pack	Yes = 86 No = 406	45 (16%) 233 (84%)	41 (19%) 173 (81%)	NS
Reading the label on the medicines bottle or box	Yes = 34 No = 455	15 (5%) 261 (95%)	19(9%) 194 (91%)	NS
Swallowing my medicines	Yes = 34 No = 457	18(7%) 256 (93%)	16 (7%) 201 (93%)	NS
Getting my repeat prescription	Yes = 35 No = 457	11(4%) 265(96%)	24(11%) 192(89%)	**0.002**

NS = not significant, Chi-Square test was used to calculated p-values

Table 4.48 – Adherent and non-adherent patients who need a solution or an alternative with one or more of the four categories of possible barriers to adherence.

Possible Problem	Need an alternative	MMAS-8 (excluding Qn5) or SQ		*p*-value (2-sided)
		Adherent	Non-Adherent	
Opening the medicines bottle or blister pack	Yes = 110 No = 382	57 (20%) 221(80%)	53 (25%) 161 (75%)	NS
Reading the label on the medicines bottle or box	Yes = 40 No = 449	16 (6%) 260 (94%)	24(11%) 189 (89%)	**0.029**
Swallowing my medicines	Yes = 42 No = 449	20(7%) 254(93%)	22(10%) 195(90%)	NS
Getting my repeat prescription	Yes = 51 No = 441	15(5%) 261(95%)	36(17%) 180(83%)	**<0.001**

NS = not significant, Chi-Square test was used to calculated *p*-values

The association of these four barriers with non-adherence identified by Factor 1 and Factor 2 was also explored. Patients who need an alternative or a solution to getting repeat prescription were more likely to be non-adherent according to Factor 1 (see Table 4.49). Non-adherent patients according to Factor 2 were more likely to identify all four barriers as a problem or needing an alternative (see Table 4.50).

Table 4.49 – Possible barriers which were found to have a statistically significant effect on adherence vs. non-adherence according to the Factor 1.

Possible Problem	Need an alternative	Factor 1 (MMAS-8) – forgetfulness		*p*-value (2-sided)
		Adherent	Non-Adherent	
Getting my repeat prescription	Yes = 51 No = 439	22(7%) 285(93%)	29(16%) 154(84%)	**0.002**

Chi-Square test OR Fisher's Exact test were used to calculate *p*-values

Table 4.50 - Possible barriers which were found to have a statistically significant effect on adherence vs. non-adherence according to the Factor 2.

Possible Problem	This is a problem	Factor 2 (MMAS-8) – intentional / hassle		*p*-value (2-sided)
		Adherent	Non-Adherent	
Opening the medicines bottle or blister pack	Yes = 86 No = 404	66 (15%) 362 (85%)	20 (32%) 42 (68%)	**0.001**
Swallowing my medicines	Yes = 34 No = 455	23(5%) 401(95%)	11(17%) 54 (83%)	**0.002**
Getting my repeat prescription	Yes = 35 No = 455	22(5%) 403(95%)	13(20%) 52(80%)	**<0.001**
Possible Problem	**Need an alternative**	**Factor 2 (MMAS-8)**		***p*-value (2-sided)**
		Adherent	**Non-Adherent**	
Opening the medicines bottle or blister pack	Yes = 110 No = 380	87 (20%) 341(80%)	23 (37%) 39 (63%)	**0.003**
Reading the label on the medicines bottle or box	Yes = 40 No = 447	30 (7%) 395(93%)	10(16%) 52(84%)	**0.015**
Swallowing my medicines	Yes = 42 No = 447	30(7%) 394(93%)	12(19%) 53(81%)	**0.002**
Getting my repeat prescription	Yes = 51 No = 439	33(8%) 392(92%)	18(28%) 47(72%)	**<0.001**

Chi-Square test OR Fisher's Exact test were used to calculate *p*-values

4.9 Beliefs about medicines results

The method of analysis of this section was described in Section 3.6.2.4. Table 4.51 summarises the overall answers. The highest percentage of answers for each question

is bolded. For example: approximately 48% of the sample strongly agrees that their "health at the moment depends on their medicines". In the *specific concern* (SC) category 30% of the sample agrees that they "sometime worry about the long-term effects of their medicines". In the *general overuse* (GO) category approximately 41% of patients are uncertain if "doctors use too many medicines". Only 491 patients answered this part of the questionnaire. However, not all the questions in this tool were answered by each patient. Therefore, "n" is different for each question. For ease of comparison and analysis the mean and standard deviation of the answers for each question and the overall category were calculated as seen in Table 4.51.

Table 4.52 compares the beliefs about medicines among the adherent and non-adherent groups identified by MMAS-8 (excluding Qn5) or SQ scales. The answers to some questions within each category do not seem to differ between groups. However, the overall total score medians indicate that there is a difference in all four categories. Non-adherent patients agree less with the *specific necessity* (SN) category than adherers. On the other hand, they disagree less with the SC and GO categories than adherers. The biggest difference between adherent and non-adherent patients is in the SC category. This indicates that they have more concern about their medicines.

Table 4.51 – The overall results of the Beliefs about Medicines Questionnaire (BMQ).

		Strongly Agree (5)	Agree (4)	Uncertain (3)	Disagree (2)	Strongly Disagree (1)	Median	Q1, Q3	n
Specific Necessity	My health, at present, depends on my medicines	**233 (47.6%)**	186 (38.0%)	55 (10.9%)	13 (2.6%)	2 (0.4%)	4	4, 5	489
	My life would be impossible without my medicines	111 (23.7%)	111 (23.7%)	**193 (41.2%)**	45 (9.6%)	9 (1.8%)	3	3, 4	**469**
	Without my medicines I would be very ill	104 (21.4%)	119 (24.5%)	**206 (42.5%)**	47 (9.7%)	9 (1.9%)	3	3, 4	485
	My health in the future will depends on my medicines	156 (32.7%)	**214 (44.9%)**	81 (17.0%)	19 (4.0%)	7 (1.5%)	4	4, 5	477
	My medicines protect me from becoming worse	177 (36.0%)	**231 (47.0%)**	71 (14.5%)	6 (1.2%)	6 (1.2%)	4	4, 5	491
			Median (Q1, Q3) SN totals = 19 (16, 22)			**Overall SN median**	**4**	**3.5, 5**	
Specific Concern	Having to take medicines worries me	24 (5.0%)	71 (14.9%)	59 (12.4%)	**171 (35.8%)**	152 (30.2%)	2	1, 3	477
	I sometimes worry about long-term effects of my medicines	51 (10.5%)	**151 (30.1%)**	89 (18.4%)	119 (24.5%)	75 (15.5%)	3	2, 4	485
	My medicines are a mystery to me	27 (5.6%)	79 (16.3%)	78 (16.1%)	**204 (42.1%)**	96 (19.8%)	2	2, 3	484
	My medicines disrupt my life	9 (1.9%)	29 (6.0%)	26 (5.4%)	**211 (43.5%)**	210 (43.3%)	2	1, 2	485
	I sometimes worry about becoming too dependent on my medicines	28 (5.9%)	80 (16.8%)	71 (14.9%)	**165 (34.7%)**	131 (27.6%)	2	1, 3	**475**
			Median (Q1, Q3) SC totals = 11 (8, 14)			**Overall SC median**	**2**	**1.38, 3**	
General Harm	People who take medicines should stop their treatment for a while every now and again	8 (1.6%)	17 (3.5%)	97 (19.8%)	168 (34.4%)	**199 (40.7%)**	2	1, 2.5	489
	Most medicines are addictive	9 (1.9%)	30 (6.3%)	160 (33.6%)	**165 (34.7%)**	112 (23.5%)	2	2, 3	**476**
	Medicines do more harm than good	8 (1.7%)	6 (1.2%)	70 (14.6%)	**209 (43.5%)**	188 (39.1%)	2	1, 2	481
	All medicines are poisons	7 (1.4%)	17 (3.5%)	104 (21.4%)	168 (34.6%)	**190 (39.1%)**	2	1, 3	486
			Median (Q1, Q3) GH totals = 8 (6, 10)			**Overall GH median**	**2**	**1, 2**	
General Overuse	Doctors use too many medicines	16 (3.4%)	51 (10.9%)	**191 (40.9%)**	136 (29.1%)	73 (15.6%)	3	2, 3	**467**
	Natural remedies are safer than medicines	5 (1%)	12 (2.5%)	**200 (41.1%)**	138 (28.3%)	132 (27.1%)	2	1, 3	487
	Doctors place too much trust on medicines	6 (1.3%)	45 (9.5%)	146 (30.7%)	**175 (36.8%)**	103 (21.7%)	2	2, 3	475
	If doctors had more time with patients they would prescribe fewer medicines.	19 (4.0%)	89 (18.5%)	**177 (36.8%)**	123 (25.6%)	73 (15.2%)	3	2, 3	481
			Median (Q1, Q3) GO totals = 10 (8, 12)			**Overall GO median**	**2.5**	**2, 3**	

SN = *Specific Necessity*, SC = *Specific Concern*, GH = *General Harm*, GO = *General Overuse*

Table 4.52 – Comparing beliefs about medicines in the adherent vs. non-adherent group identified by the MMAS-8 (excluding Qn5) or SQ scales.

		Adherence MMAS-8 (excluding Qn5) or SQ scale						
		Adherent			Non-adherent			
		Median	Q1, Q3	n	Median	Q1, Q3	n	*p*-value (2 sided)
Specific Necessity	My health, at present, depends on my medicines	5	4, 5	277	4	4, 5	212	0.002
	My life would be impossible without my medicines	4	3, 5	265	3	3, 4	204	0.005
	Without my medicines I would be very ill	3	3, 4	271	3	3, 4	214	NS
	My health in the future will depends on my medicines	4	4, 5	269	4	3, 4.75	208	0.002
	My medicines protect me from becoming worse	4	4, 5	274	4	4, 5	217	0.017
	Overall SN Median	**4**	4, 5	281	**4**	3, 5	218	**0.013**
	Overall SN score	**20**	17, 22	281	**18**	16, 21	218	**0.004**
Specific Concern	Having to take medicines worries me	2	1, 3	266	2	2, 4	211	<0.001
	I sometimes worry about long-term effects of my medicines	3	2, 4	275	4	2, 4	210	<0.001
	My medicines are a mystery to me	2	1, 3	270	2	2, 3	214	0.023
	My medicines disrupt my life	1	1, 2	273	2	1, 2	212	<0.001
	I sometimes worry about becoming too dependent on my medicines	2	1, 3	268	2	2, 4	**207**	<0.001
	Overall SC Median	**2**	1, 2	278	**2**	2, 3	216	**<0.001**
	Overall SC score	**10**	7.75, 13	278	**12.5**	10, 16	216	**<0.001**
General Harm	People who take medicines should stop their treatment for a while every now & again	2	1, 2	275	2	1, 3	214	<0.001
	Most medicines are addictive	2	1, 3	266	2	2, 3	210	NS
	Medicines do more harm than good	2	1, 2	271	2	1, 2	210	0.035
	All medicines are poisons	2	1, 3	272	2	1, 3	214	NS
	Overall GH Median	**2**	1, 2.5	276	**2**	1.5, 2.5	216	**0.024**
	Overall GH score	**8**	6, 9	276	**8**	6, 10	216	**0.014**
General Overuse	Doctors use too many medicines	2	2, 3	266	3	2, 3	201	<0.001
	Natural remedies are safer than medicines	2	1, 3	275	2	1, 3	212	NS
	Doctors place too much trust on medicines	2	1, 3	266	2	2, 3	209	0.015
	If doctors had more time with patients they would prescribe fewer medicines.	3	2, 3	270	3	2, 4	211	0.004
	Overall GO Median	**2.5**	2, 3	276	**3**	2, 3	215	**<0.001**
	Overall GO score	**9**	7, 11	276	**10**	8, 12	215	**0.001**

NS = not significant. The non-parametric Mann-Whitney test was used to calculate the 2-sided *p*-value.

4.10 Building a regression model

The regression models described in this section were built as described in Section 3.6.6.1 and Appendix 15. SPSS output can be seen in Appendix 16. A model will be built for the non-adherent group identified by the MMAS-8 (F1, F2) or SQ scale. Another two models will be built to look at non-adherent patients identified by the Factor 1, and those identified by Factor 2 in the MMAS-8 scale.

4.10.1 Building a logistic regression model for the MMAS-8 (excluding Qn5) or SQ scale non-adherence.

In accordance with the criteria described in Section 3.6.6.1, the best model identified by the researcher is reported. The final model had the following statistics: the model's χ^2 = 65.408, p <0.001 which means that the model was significant. The Hosmer and Lemeshow Test (HLT) *p*-value = 0.169 indicating the overall goodness-of-fit of the model. The overall prediction was 67.4%. Table 4.53 is a summary of the final model.

Table 4.53 – Final model, variables with significant association with non-adherence identified by MMAS-8 (excluding Qn5) or SQ scale. Multivariate logistic regression Analysis (*p*-values <0.05) (n=484).

Variable	Odds Ratio	95% CI	
		Lower	Upper
Age	0.96	0.94	0.98
Gender (Male – Female)	0.56	0.34	0.93
Specific Concern about SPM (score)	1.12	1.07	1.18
Issues with Repeat Prescriptions	2.48	1.26	4.90
Aspirin (Prescribed)	2.22	1.18	4.17

CI = confidence interval, SPM = Secondary Prevention Medicines

Interpretation of the model:

- Every one year increase in age was associated with a 4% reduction in the risk of being non-adherent.
- Being female was associated with 44% reduction in the risk of being non-adherent.

- Every one unit increase in the *specific concern* score was associated with 12% increase in the risk of being non-adherent.
- Having a problem or needing alternatives with repeat prescriptions was associated with a 2.5 times increase in the risk of being non-adherent.
- Being on aspirin was associated with a 2.2 times increase in the risk of being non-adherent.

4.10.2 Building a logistic regression model for various non-adherent groups

The final model for Factor 1 had the following statistics: the model's χ^2 = 57.013, p <0.001 which means that the model was significant. The HLT *p*-value = 0.871 indicating good overall goodness-of-fit of the model. The overall prediction was 69.1%. The final model can be seen in Table 4.54.

Table 4.54 – Final model, variables with significant association with non-adherence identified by Factor 1. Multivariate logistic regression Analysis (*p*-values <0.05) (n=492).

Variable	Odds Ratio	95% CI	
		Lower	Upper
Age	0.96	0.94	0.98
Gender (Male – Female)	0.50	0.29	0.82
Diabetic (No – Yes)	0.44	0.23	0.85
CABG (No – Yes)	0.60	0.40	0.90
Aspirin (Prescribed)	2.00	1.05	3.85
Specific Concern about SPM (score)	1.08	1.03	1.13

CI = confidence interval, SPM = Secondary Prevention Medicines

Interpretation of the model:

- Every one year increase in age was associated with reduction in the risk of being non-adherent due to forgetfulness by 4%.
- Being a female was associated with a reduction in the risk of being non-adherent due to forgetfulness by 50%.
- Being diabetic was associated with a reduction in the risk of being non-adherent due to forgetfulness by 56%.
- Having CABG was associated with a reduction in the risk of being non-adherent due to forgetfulness by 40%.
- Being on aspirin was associated with two fold increase in the risk of being non-adherent.

- Every one unit increase in the score of *specific concern* was associated with increase in the risk of non-adherence by 8%.

The final model for Factor 2 is presented in Table 4.55 and had the following statistics: the model's χ^2 = 90.585, p <0.001 which means that the model was statistically significant. HLT *p*-value = 0.820 indicating good overall goodness-of-fit of the model. The overall prediction was 86%.

Table 4.55 – Final model, variables with significant association with non-adherence identified by Factor 2. Multivariate logistic regression analysis (*p*-values <0.05). (n=480)

Variable	Odds Ratio	95% CI	
		Lower	Upper
Age	0.96	0.93	0.99
Specific Necessity for SPM (score)	0.90	0.82	0.99
Specific Concern about SPM (score)	1.16	1.07	1.27
General Overuse of Medicines (score)	1.16	1.03	1.32
Beta Blocker (Prescribed)	0.48	0.25	0.90
Aspirin (Prescribed)	4.60	1.25	16.96
Issues with Repeat Prescriptions	3.68	1.75	7.74
No. of Prescribed Medicines	1.18	1.07	1.31

CI = confidence interval, SPM = Secondary Prevention Medicines

Interpretation of the model:

- Every one year increase in age was associated with a 4% reduction in being intentionally non-adherent.
- Every one unit increase in the score of *specific necessity* was associated with a decrease in the risk of intentional non-adherence by 10%.
- Every one unit increase in the score of *specific concern* was associated with an increase in the risk of intentional non-adherence by 16%.
- Every one unit increase in the score of *general overuse* was associated with an increase in the risk of intentional non-adherence by 16%.
- Being on beta blockers was associated with reducing the risk of being intentionally non-adherent almost by 50%.
- Being on aspirin was associated with almost a 5 times increase in the risk of being intentionally non-adherent.
- Having a problem or needing an alternative / solution to repeat prescriptions was associated with approximately 4 times increase in the risk of intentional non-adherence.
- Every one unit increase in the number of medicines was associated with a 14% increase in the risk of intentional non-adherence.

4.11 Additional comments by patients

A total of 221 patients provided extra comments. There were 85 comments made by 82 adherent patients and around 225 comments made by non-adherent patients. In this section the analysis of these comments will be presented and summarised.

4.11.1 Analysis of patients' comments

Frequency and categorisation analysis was conducted as described in Section 3.6.7. The full analysis can be seen in the spider diagram presented in Figure 4.15. Comments of adherent and non-adherent patients (according to MMAS-8 (excluding Qn5) or SQ scale) were clearly separated in order to learn more about the reasons behind non-adherence to medicines. Seven major themes were identified from the analysis and they are as follows:

1) Specific concerns about secondary prevention medicines
2) General concerns about medicines
3) General concern about healthcare professionals
4) General concern about sexual health
5) Satisfaction and happiness related to medicines and services
6) Favouring alternative therapies
7) Suggestions related to medicines and medicines related services

Table 4.56 summarises the number and percentage of comments made under each theme by adherent and non-adherent patients. The majority of the comments made under the "specific concerns about secondary prevention medicines" were by non-adherent patients (87%). This was the same for all other themes except for the "satisfaction and happiness related to medicines and services" theme where most comments were by adherent patients.

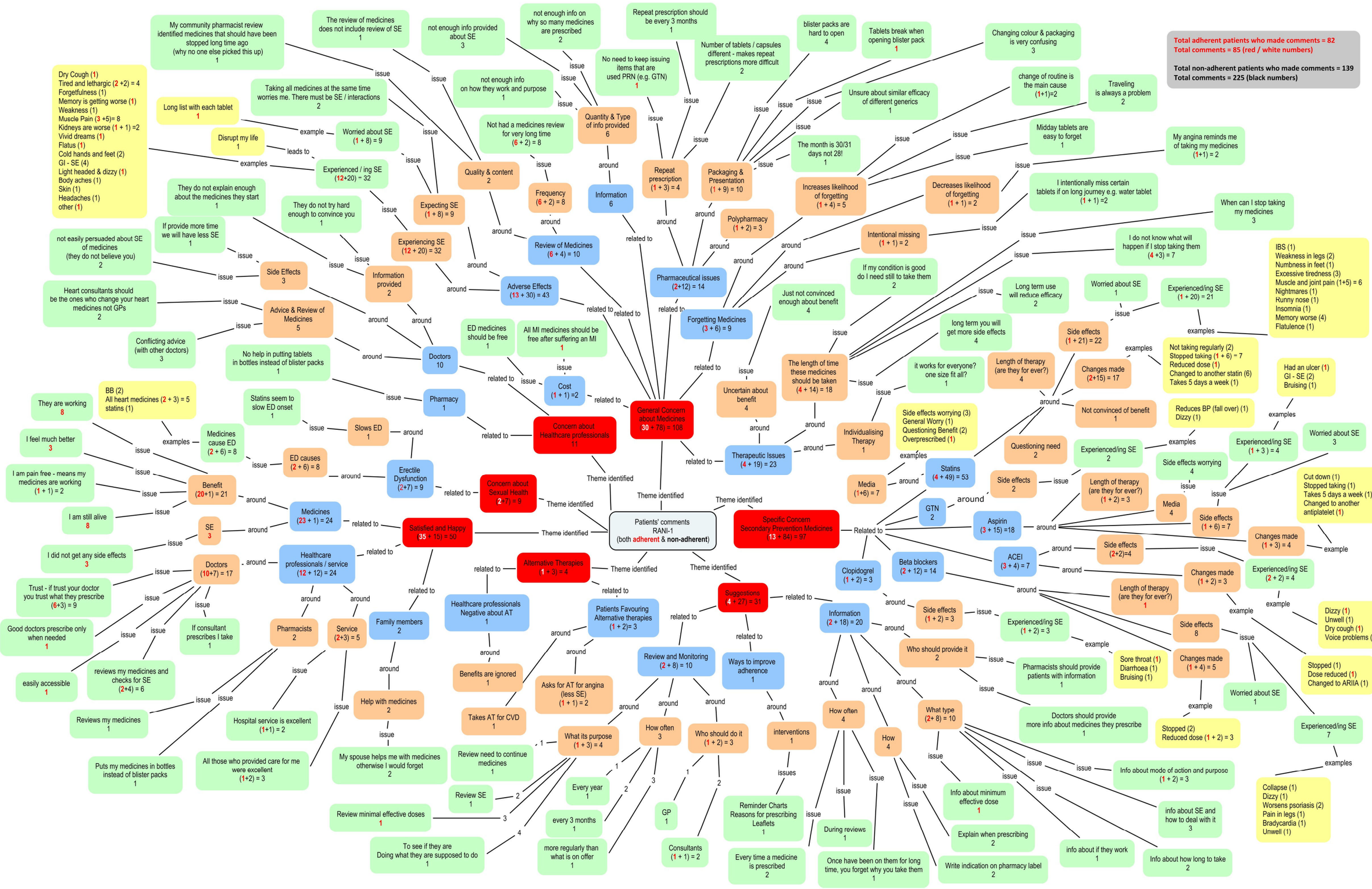

Figure 4.15 – Spider diagram representing the full analysis of patients' comments

Table 4.56 – Summary of the number of comments made under each theme by adherent and non-adherent patients. (Total number of comments = 310)

Themes	Number of comments	Adherent	Non-adherent
1) Specific concerns about secondary prevention medicines	97	13 (13%)	**84 (87%)**
2) General concerns about medicines	108	30 (28%)	**78 (72%)**
3) General concern about healthcare professionals	11	0 (0%)	**11 (100%)**
4) General concern about sexual health	9	2 (22%)	**7 (78%)**
5) Satisfaction and happiness related to medicines and services	50	**35 (70%)**	15 (30%)
6) Favouring alternative therapies	4	1 (25%)	**3 (75%)**
7) Suggestions related to medicines and medicines related services.	31	4 (13%)	**27 (87%)**

Figures 4.16 and 4.17 show the distribution of the comments made by both groups across the seven themes identified. The majority of the comments made by adherers were about "satisfaction and happiness" and "general concern about medicines". The non-adherers commented most on "specific concerns about secondary prevention medicines" and "general concern about medicines". Adherent patients had very few suggestions compared to those who were non-adherent (5% vs. 12%, respectively).

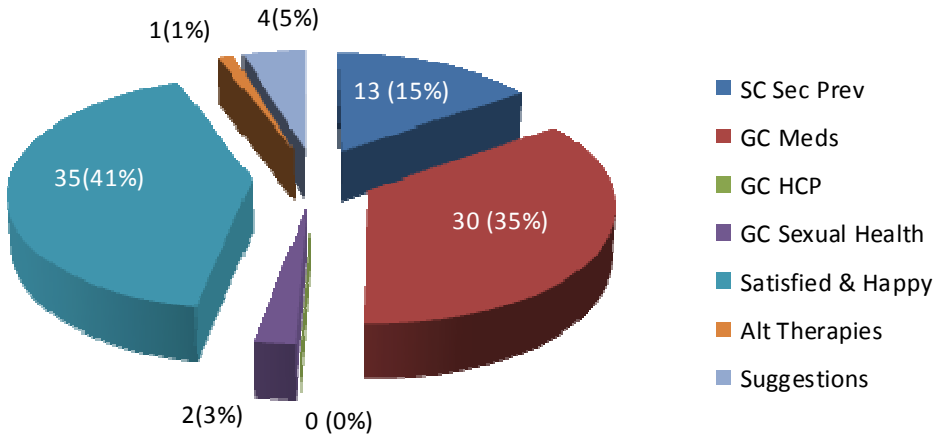

Figure 4.16 – Distribution of **adherent** patients' comments between the seven themes identified in the analysis. (Total number of comments = 85)

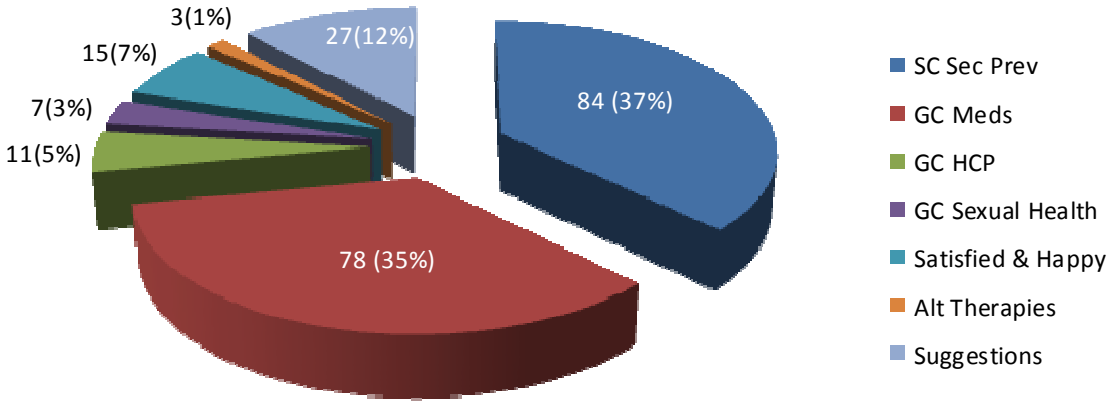

Figure 4.17 - Distribution of **non-adherent** patients' comments between the seven themes identified in the analysis. (Total number of comments = 225)

Tables 4.57 to 4.63 summarise in groups of categories and sub-categories the issues highlighted by adherent and non-adherent patients under each one of the seven themes. Most comments under the **"specific concerns about secondary prevention medicines"** theme were about statins, aspirin, and beta blockers (55%, 19%, and 14% respectively). The sub-categories show a great number of comments from patients about the side-effects of these medicines.

Table 4.58 shows that the three top concerns that patients raised about medicines in general related to adverse effects, therapeutic issues (mainly around the length of time they should continue on this therapy), and pharmaceutical issues (mainly around packaging and presentation of medicines) (40%, 21%, and 13% respectively).

Table 4.57 – Breakdown of comments under the theme of **"specific concerns about secondary prevention medicines"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments = 97)

Theme, categories and sub-categories	No. of comments	Adherent		Non-adherent	
1) Specific concerns about secondary prevention medicines	97	13	(13%)	84	(87%)
a. Statins	53	4	(8%)	49	(92%)
i. Side-effects - worried about or experiencing SE	22	1	(5%)	21	(95%)
ii. Questioning Need or Benefit	3	0	(0%)	3	(100%)
iii. Length of therapy - are they forever?	4	0	(0%)	4	(100%)
iv. Media - instilled doubt / created worry	7	1	(14%)	6	(86%)
v. Made changes – with/without doctor's knowledge	17	2	(12%)	15	(88%)
b. Aspirin	18	3	(17%)	15	(83%)
i. Side-effects - worried about or experiencing SE	7	1	(14%)	6	(86%)
ii. Length of therapy - are they forever?	3	1	(33%)	2	(67%)
iii. Media - instilled doubt / created worry	4	0	(0%)	4	(100%)
iv. Made changes - with/without doctor's knowledge	4	1	(25%)	3	(75%)
c. Clopidogrel	3	1	(33%)	2	67%
i. Side-effects – experienced/ing SE	3	1	(33%)	2	67%
d. ACEI	7	3	(43%)	4	57%
i. Side-effects - worried about or experiencing SE	4	2	(50%)	2	50%
ii. Made changes – with/without doctor's knowledge	3	1	(33%)	1	33%
e. Beta Blocker	14	2	(14%)	12	86%
i. Side-effects - worried about or experiencing SE	8	0	(0%)	8	100%
ii. Length of therapy - are they forever?	1	1	(100%)	0	0%
iii. Made changes – with/without doctor's knowledge	5	1	(20%)	4	80%
f. GTN	2	0	(0%)	2	100%
i. Side-effects – experienced/ing SE	2	0	(0%)	2	100%

The theme of "General concern about healthcare professionals" (Table 4.59) was mainly focused on the information and the attitude doctors have about medicines, doctors' medicines review and pharmacists not being helpful in putting tablets into bottles. All patients who commented under this theme were non-adherent. The "General concern about sexual health" theme (Table 4.60) was mainly about erectile dysfunction and which medicines contribute to this.

Table 4.58 – Breakdown of comments under the theme of **"General concerns about medicines"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments =108)

Theme, categories and sub-categories	No. of comments	Adherent	Non-adherent
2) General concerns about medicines	108	30 (28%)	78 (72%)
a. Adverse effects	43	13 (30%)	30 (70%)
i. Experienced / experiencing Side-effects	32	12 (38%)	20 (63%)
ii. Worried about SE	9	1 (11%)	8 (89%)
b. Review of Medicines	10	6 (60%)	4 (40%)
i. Frequency	8	6 (75%)	2 (25%)
ii. Quality and content	2	0 (0%)	2 (100%)
c. Information about Medicines	6	0 (0%)	6 (100%)
i. Quality and type of information (SE, mode of action, purpose of multiple therapies)	6	0 (0%)	6 (100%)
d. Pharmaceutical Issues	14	2 (14%)	12 (86%)
i. Repeat Prescriptions (Freq, synchronising no. & type of meds issued)	4	1 (25%)	3 (75%)
ii. Packaging and presentation of medicines	10	1 (10%)	9 (90%)
iii. Polypharmacy	3	1 (33%)	2 (67%)
e. Forgetting Medicines	9	3 (33%)	6 (67%)
i. What increases the likelihood of forgetting	5	1 (20%)	4 (80%)
ii. What decreases the likelihood of forgetting	2	1 (50%)	1 (50%)
iii. Intentional forgetting	2	1 (50%)	1 (50%)
f. Therapeutic Issues	23	4 (17%)	19 (83%)
i. Uncertain about benefit	4	0 (0%)	4 (100%)
ii. Length of time of therapy	18	4 (22%)	14 (78%)
iii. Individualising therapy	1	0 (0%)	1 (100%)
g. Cost	2	1 (50%)	1 (50%)
i. Medicines should be free esp. post MI and Medicines for ED	2	1 (50%)	1 (50%)

Table 4.59 – Breakdown of comments under the theme of **"General concern about healthcare professionals"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments =11)

Theme, categories and sub-categories	No. of comments	Adherent	Non-adherent
3) General concern about healthcare professionals	11	0 (0%)	11 (100%)
a. Doctors	10	0 (0%)	10 (100%)
i. Information provided	2	0 (0%)	2 (100%)
ii. Attitude and approach of Side-effects	3	0 (0%)	3 (100%)
iii. Advice & review of medicines (quality & who)	5	0 (0%)	5 (100%)
b. Pharmacists	1	0 (0%)	1 (100%)
i. Help with putting tablets in bottles	1	0 (0%)	1 (100%)

Table 4.60 – Breakdown of comments under the theme of **"General concern about sexual health"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments =9)

Theme, categories and sub-categories	No. of comments	Adherent	Non-adherent
4) General concern about sexual health	9	2 (22%)	7 (78%)
a. Erectile Dysfunction	9	2 (22%)	7 (78%)
i. Medicines that cause ED	8	2 (25%)	6 (75%)
ii. Medicines that protect against ED	1	0 (0%)	1 (100%)

In Table 4.61, patients' comments under the "Satisfaction and happiness related to medicines and services" theme mainly highlighted what makes patients feel satisfied with their medicines (48%), healthcare professionals and the healthcare service (48%). Patients also highlighted the role of family members in managing their medicines.

Table 4.61– Breakdown of comments under the theme of **"Satisfaction and happiness related to medicines and services"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments =50)

Theme, categories and sub-categories	No. of comments	Adherent	Non-adherent
5) Satisfaction and happiness related to medicines and services	50	35 (70%)	15 (30%)
a. Medicines	24	23 (96%)	1 (4%)
i. Can feel benefit	21	20 (95%)	1 (5%)
ii. Did not get Side-effects	3	3 (100%)	0 (0%)
b. Healthcare Services / Professionals	24	12 (50%)	12 (50%)
i. Doctors - (trust, prescribe when needed, accessible, reviews meds, checks for SE)	17	10 (59%)	7 (41%)
ii. Pharmacists – (review meds, help with tablets in bottles)	2	0 (0%)	2 (100%)
iii. Service in general was excellent	5	2 (40%)	3 (60%)
c. Family members	2	0 (0%)	2 (100%)
i. Help with medicines	2	0 (0%)	2 (100%)

Comments under the theme of "Favouring alternative therapies" mainly focused on patients' interest in alternative therapies (75%) and that healthcare professionals usually ignore the benefits of alternative therapies (25%) (see Table 4.62).

Table 4.62 – Breakdown of comments under the theme of **"Favouring alternative therapies"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments = 4)

Theme, categories and sub-categories	No. of comments	Adherent	Non-adherent
6) Alternative therapies (AT)	4	1 (25%)	3 (75%)
a. Healthcare professionals & AT	1	0 (0%)	1 (100%)
i. Healthcare professionals ignore benefits of AT	1	0 (0%)	1 (100%)
b. Patients favour AT	3	1 (33%)	2 (67%)
i. Take AT for cardiovascular disease	1	0 (0%)	1 (100%)
ii. Asking for AT for angina	2	1 (50%)	1 (50%)

In Table 4.63, the suggestions made by patients under the "Suggestions related to medicines and medicines related services" mainly focused on the information that should be provided about medicines with some details on how and when (65%), and the need for the review and monitoring of medicines (32%).

Table 4.63 – Breakdown of comments under the theme of **"Suggestions related to medicines and medicines related services"** grouped in categories and sub-categories as identified by adherent and non-adherent patients. (Total number of comments = 31)

Theme, categories and sub-categories	No. of comments	Adherent	Non-adherent
7) Suggestions related to medicines and medicines related services.	31	4 (13%)	27 (87%)
a. Review and monitoring of medicines	10	2 (20%)	8 (80%)
i. Identified specific purpose (need to continue, SE, efficacy, minimal effective dose)	4	1 (25%)	3 (75%)
ii. Frequency	3	0 (0%)	3 (100%)
iii. Who should do it?	3	1 (33%)	2 (67%)
b. Ways to improve adherence	1	0 (0%)	1 (100%)
i. Interventions - (reminder chart, reason for prescribing, leaflets)	1	0 (0%)	1 (100%)
c. Information about medicines	20	2 (10%)	18 (90%)
i. How often and when to provide info	4	0 (0%)	4 (100%)
ii. Methods to communicate information	4	0 (0%)	4 (100%)
iii. What type of info needed - (SE & what to do, how do we know they work, purpose &mode of action, how long to take, min effective dose)	10	2 (20%)	8 (80%)
iv. Who should provide it	2	0 (0%)	2 (100%)

5 Discussion

The main aim of this study was to investigate the prevalence and possible factors contributing to self-reported non-adherence to secondary prevention medicines in patients who have a well-established diagnosis of CAD. This chapter discusses the findings of this research, its implications for practice, policy, further research and evaluation. The following is a summary of how the different sections of this chapter relate to the aims and objectives of the study:

- The primary aim was to investigate the prevalence and possible factors contributing to self-reported non-adherence to secondary prevention medicines in patients living within West Yorkshire and nearby areas who have a well-established diagnosis of CAD.
    - **This was covered in Sections 5.1, 5.2 and 5.4.**

- Objective 1: assess self-reported non-adherence to collective and individual secondary prevention medicines. Aspirin, clopidogrel, statins, beta-blockers, ACEI, ARBs.
    - **This was covered in Sections 5.1.3.1 and 5.2.**

- Objective 2: compare the findings, practicality, sensitivity and reliability of three different instruments (questionnaires) which assess self-reported non-adherence; MMAS-8, Adherence Estimator™, and the Single Question approach.
    - **This was covered in Section 5.3.**

- Objective 3: identify barriers contributing to non-adherence to inform and change practice.
    - **This was covered in Section 5.4.**

- Objective 4: Survey the prevailing individual beliefs and attitudes to use of medication among patients with established CAD.
    - **This was covered in Section 5.4.2.6.**

- Secondary objective 1: Identify the level of secondary prevention medicines prescribing and use in patients with stable CAD.
    - **This was covered in Section 5.1.3.1.**

- Secondary objective 2: Develop a practical approach to address non-adherence among this population.
    - **This was mainly covered in Sections 5.6 and 5.7 and also in other various sections in this chapter.**

5.1 The participants

This section discusses how representative the sample was, if the findings can be generalised, and the possible reasons for the high response rate and its implication for practice. Aspects related to the prescribed medicines and relevant to later discussions will be highlighted.

5.1.1 Representativeness of the sample

The sample contained a good regional representation of CHD patients who accessed the LTHT cardiology services. Approximately 90% of the participants were from West Yorkshire and 10% from nearby regions. The median (Q1, Q3) age (years) of participants was 70 (63, 75) with 99.8% of the sample aged 40 years or older. This is consistent with the prevalence of cardiovascular disease which increases significantly after the age of 40 years (BHF, 2010; SEPHO: South East Public Health Observatory, 2011). The age spread of the participants was similar to that seen nationally. In 2006, the prevalence of CHD in England was 6.5% in men and 4% in women (total of 10.5%) (BHF, 2010). Approximately 30% of those were 65 – 74 years old and 48% were 75 years and older (BHF, 2010). In our study 80% of the participants were males. The prevalence of CHD is higher among men in England and is estimated to account for 60 – 65% of patients with CHD (BHF, 2010). The low representation of females in our study could be explained by the fact that CHD is underdiagnosed, undertreated and under-researched among females. In recent years there has been more interest in addressing this gap (Mikhail, 2005).

White people represented approximately 92% of the sample. There was an underrepresentation of Black and other ethnic minorities, which was estimated to be around 13% in 2009 in West Yorkshire (ONS: Office of National Statistics, 2011). This reflected the patient population in the ENCOURAGE database which did not have high representation of non-whites. Concerns about the low representation of ethnic groups in clinical trials has been reported in the literature and mainly attributed to lack of interest, language barriers and lower socio-economic status (Jolly et al., 2005). This

should be taken into account when interpreting and applying the findings of this research. It also highlights the need for researching medicines-taking behaviour of ethnic minorities with CHD. CHD is more prevalent at a younger age among South Asian men who also have higher rates of myocardial infarction (SEPHO, 2011; BHF, 2010a). Minority ethnic groups also have a lower participation in cardiac rehabilitation programmes compared to the white population which could possibly make them at higher risk of non-adherence (BHF, 2010a).

Patients with diabetes are three times more likely to suffer an MI and an estimated 15% of MIs in Western Europe are due to diagnosed diabetes (BHF, 2010). In our study, a similar percentage (12%) of participants was identified to have diabetes controlled with medicines.

5.1.2 The response rate and its implications for practice

The response rate for postal questionnaires is usually around 25% (Matthews & Ross, 2010). The high response rate (72%) achieved in this study could be attributed to several factors. Various measures were taken to improve the low response rate limitation of postal questionnaires (see Section 3.1.1). These advance considerations were possibly a contributing factor. In addition, the patients in the sample were probably more motivated than the average population to participate in research as they had already expressed their willingness to take part in future research opportunities (see Section 3.3). Another possible factor is the topic of this research: medicines. This was evident from the number of comments made by patients (221 out 503 patients made comments) where they had many medicines related issues that

they wanted to discuss. Several patients clearly indicated their dissatisfaction with the frequency and quality of medicines reviews. They could, therefore, have taken this opportunity to highlight their experiences and issues related to their secondary prevention medicines, medicines in general, healthcare professionals and the healthcare system. This suggests the need to provide more frequent opportunities for patients to talk about their medicines with their healthcare professionals. Pharmacists have a major role to play in this field. Clinical pharmacists can enhance their medicines reconciliation service during in-patient admissions to give opportunities to raise any issues about medicines. Community pharmacists are frequently visited by patients with chronic conditions and can seize these opportunities to offer patients the chance to discuss their medicines (e.g. Medicines Use Reviews, the New Medicine Service and Repeat Dispensing). However, criticism of the way medicines reviews were conducted has been reported in the literature (Latif et al., 2011). One of the main findings was that the format of the review (e.g. asking closed questions, very brief session) did not give patients enough chance to ask questions and express their concerns (Latif et al., 2011). Therefore, there is a need to take on board the suggestions made by patients about medicines reviews in our study (see Section 5.4.2.7).

5.1.3 Overall Prescribed medicines

The median (Q1, Q3) number of the overall medicines prescribed for patients was 7 (5, 9). The frequency of daily medicines administration was once a day for 50% of patients and 37% of the participants had at least one medicine with a twice a day frequency. Patients with chronic conditions and co-morbidities are likely to be on a large number of medicines as evidence based guidelines recommend several drugs in the treatment

of a single condition (see Section 1.3). This is often referred to as *polypharmacy*. The definition of polypharmacy is variable and it has been defined as the concurrent use of multiple drugs (usually more than 4) (Fulton & Allen, 2005). Polypharmacy can be further exacerbated by multiple daily dosing regimens as it can increase the daily burden of medicines-taking. This makes drug treatment particularly challenging and more likely to contribute to non-adherence (Avorn, 2004). See Section 5.4.2.1 for the association of polypharmacy with non-adherence in this study.

5.1.3.1 Secondary prevention medicines

The level of individual secondary prevention medicines prescribing was highest for statins (95%). Aspirin or clopidogrel monotherapy were prescribed in 94% of cases. This is above the target of 80% set by the CHD National Service Framework (DoH, 2000, BHF, 2010). Beta blockers were below the 80% target and prescribed for only 71% of patients. The prescribing of ACEI (or ARBs) was 78%. All these results were below England's national average in 2008/2009 (97% for statins, 98% for aspirin, and 93% for beta blockers) (BHF, 2010). Capewell et al. (2006) suggested that consistently hitting the 80% target when prescribing secondary prevention medicines might result in some 20,000 fewer CHD deaths each year in England and Wales. This highlights the level of benefit that could be potentially gained from prescribing optimal levels of secondary prevention medicines that are adhered to.

Only 52% of patients were prescribed at least four secondary prevention medicines as recommended by NICE (NICE, 2007; NICE, 2011) and 34% were only prescribed three. These results indicate that there is room for optimising secondary prevention

medicines therapy in the absence of specific clinical contraindications. Patients need to be reviewed individually to identify reasons for omission of indicated individual secondary prevention medicines. DeWilde et al. (2008) reported that under half of patients in the UK in 2005 were receiving all four secondary prevention medicines. The results of this research show that despite higher levels of statins and antiplatelets prescribing, there is still room for increasing the benefits of secondary prevention medicines through the wider use of combined treatments. This area should be explored further to identify reasons behind low levels of prescribing secondary prevention medicines.

Knowledge about secondary prevention medicines was assessed by asking patients in Part 1 of the questionnaire to identify the indication for each one of their medicines. This was used as a proxy for the level of knowledge patients had about the medicine. Patients were classed as "knowledgeable" and "not knowledgeable" as described in the Section 3.6.1.5. This approach is not sufficient to assess patients' overall knowledge about the medicine (e.g. side-effects). However, knowing why one was prescribed a certain medicine is a good starting point, which reflects minimum understanding.

Patients' knowledge, as defined in this study, about why medicines were prescribed was the highest for statins (67%) compared to other secondary prevention medicines. This was followed by aspirin (52%). Participants knew very little about why they were prescribed beta blockers (36%). One explanation for this difference in levels of knowledge could be that it is easier to explain the mode of action of statins and antiplatelets than that of beta blockers or ACEI. While patients may understand that

both beta blockers and/or ACEI are for their hearts, they do not necessarily understand the difference between them compared to antiplatelets and statins. In addition, both statins and aspirin were frequently mentioned in the media which may have made patients more aware of their use and mode of action (see Section 5.4.2.2). This is consistent with patients who mentioned the impact of the media on their perception about these medicines (see Figure 4.15 and Table 4.57). The lack of understanding of the difference between these classes of medicines was possibly reflected in patients asking for more information about the reasons behind prescribing multiple therapies post MI (See Figure 4.15 and Table 4.58).

Overall the sample had a tendency towards not knowing the indications for the secondary prevention medicines they were prescribed (mean ± SD = 1.7 ± 0.65, median (Q1, Q3) = 1.6 (1, 2) – where 1 = full knowledge and 3 = no knowledge).

5.1.3.2 GTN

Patients with symptomatic CAD should be prescribed sublingual GTN spray or tablets unless contraindicated (NICE, 2011). Evaluating the frequency for needing to use GTN can reflect how well patients' angina is controlled and if there is a need to modify therapy (NICE, 2011). Only 73% of participants reported that they were prescribed GTN, which could indicate that the rest had asymptomatic CAD. Of those who were prescribed GTN, 49% reported using it which could indicate that the rest of them had well controlled stable CAD. However, studies have shown that prescribers erroneously omitted GTN from 38% of CAD patients' prescriptions (Zimmerman et al., 2009). This issue could be addressed during a medicines review session. When asked to indicate

the frequency of use, only 62% of those who reported using their GTN provided the information. The majority of these used their GTN monthly or weekly. The low number of patients who reported frequency of GTN use made the analysis limited to 112 patients.

While information about GTN use can in principle be used to screen for patients who are likely to be non-adherent, this study showed that such an approach is not generally reliable. There was no statistically significant association between GTN use or frequency of use and non-adherence to secondary prevention medicines and anti-anginals. This could be due to the small number of patients who reported the frequency of GTN use. However, it is more likely to be explained by the complex relationship between symptomatic CAD and use of GTN to alleviate the pain. Not all patients who experience angina necessarily use their GTN to control it. The researcher conducted various interviews and surveys with patients prescribed GTN to assess their knowledge and use of GTN (Khatib & Keenan, 2011). Patients were reluctant to use GTN for their angina due to side-effects (headaches and hypotension) or due to their perception that it should only be used when symptoms are very serious (Khatib & Keenan, 2011). This makes the Angina – GTN – Non-adherence relationship more complicated as not all patients who are non-adherent and experience angina necessarily use their GTN more frequently.

5.2 Levels of non-adherence

Adherence to collective and individual secondary prevention medicines was assessed using the MMAS-8 and SQ scale. The level of collective self-reported non-adherence

according to the MMAS-8 scale (before excluding Qn5) was 49%. Medium adherence was identified in 39% of the sample and 10% had low adherence. After excluding Qn5, the level of non-adherence was 42%, medium adherence 32% and low adherence 10%. Reviewing the scores of the MMAS-8 revealed that 57 patients had a score of 7.75. This indicates that their only reason for being classified as non-adherent was that they "almost never" had difficulty remembering to take all their medicines as opposed to "never". While this is classed as non-adherence according to the MMAS-8, one can argue that "almost never" is acceptable. However, 38% of the patients would still be classed as non-adherent according to the scale. This is consistent with non-adherence levels of a third to a half reported in the literature for patients with long term conditions (WHO, 2003; NICE, 2009). Non-adherence related to Factor 1 (unintentional/ forgetfulness) and 2 (intentional / hassle non-adherence) highlighted that 69% of patients were non-adherent due to forgetfulness only, 12% due to intentional/medicines related hassle only and 19% due to an element of both.

The levels of non-adherence according to the SQ scale were lower and estimated to be 13% when 90%[‡] was used as a cut-off point and 5% when 75%[‡] was used. As discussed in Section 3.6.2.3, the original authors use of 75% ("most of the time") as a cut-off point was not validated or chosen with reference to a "gold standard" adherence assessment method. Therefore, patients who said that they took their medicines "nearly all of the time" (90% cut-off point) did still have an element of non-adherence.

[‡] It should be noted that the 90% and 75% cut-off points used in the SQ scale are arbitrary (see Section 3.6.2.3) and they should not be confused with the cut-off points used to define acceptable non-adherence which does not impact on benefits derived from prescribed medicines as discussed in Section 1.4.1.

The modified SQ scale identified that the levels of non-adherence to aspirin, statins, clopidogrel, beta blockers, ACEI and ARBs were 9%, 8%, 7%, 5%, 4% and 3% respectively. Their contribution to SQ scale non-adherence was 62%, 67%, 7%, 30%, 22% and 5% respectively. Aspirin and statins were least adhered to and contributed to most of the non-adherence identified by the SQ scale. This is contrary to previously reported non-adherence to individual secondary prevention medicines, where aspirin had the highest adherence (Newby et al., 2006). This further emphasises that patient populations with similar chronic conditions may have different medicines-taking behaviour. An increase in the number of secondary prevention medicines included in the various combinations was not necessarily associated with an increase in non-adherence. Patients chose to adhere to certain secondary prevention medicines and not adhere to others. This confirms that non-adherence behaviour is not *"all or none"* and a patient could be adherent to one medicine and not the other (McHorney, 2009). For example: 214 patients were concomitantly prescribed four secondary prevention medicines; 6% did not adhere to only one of the four medicines, 2% did not adhere to two and 5% did not adhere to all four prescribed secondary prevention medicines.

The AE estimated that 30% of the participants had low to medium probability of adherence and were likely to be intentionally non-adherent.

The combined findings of the MMAS-8 (excluding Qn5) and SQ scale showed a level of non-adherence of 44%. Only 39% of these were predicted by the AE to have an element of intentional non-adherence.

5.3 Performance of the self-report adherence assessment tools

Three self-reported adherence assessment tools were used in the study. There was no "gold standard" adherence measure to compare them against. Therefore, the performance of each individual tool on its own and as compared to other tools within the study will be discussed.

5.3.1 The MMAS-8

The MMAS-8 was simple and easy to administer. The calculation of the scores was also relatively straightforward. Qn5 in the MMAS-8 was reversed, possibly to reduce bias. However, the analysis of the MMAS-8 results revealed a problem with this question as it was the only reversed question and sometimes caused confusion and certain patients may have answered it incorrectly. Reliability analysis using Cronbach's α confirmed this problem. Despite reversing the scores of Qn5 it had a negative correlation with the overall scale and its removal brought a significant increase in the value of Cronbach's α. This indicated that the removal of this question increased the reliability of the scale. The factor analysis revealed that Qn5 did not load onto either factor and had a very low common associated variance of 8.9%. The researcher contacted the original inventor of the scale who stated that he had never encountered this problem before (Morisky, 2001, pers. comm.).

This error could be explained by the concept of *"acquiescence"*. It is estimated that around 10% of a questionnaire's participants may experience acquiescence, where they would agree or disagree with statements without considering the contents of the

statements or questions (McBurney & White, 2007). This could have been seen with the MMAS-8 Qn5 problem. One suggestion to address this problem would be to have an equal number of positively and negatively scored items in a questionnaire (Barker et. al., 1994).

MMAS-8 (excluding Qn5) had a marginal Cronbach's α of 0.602 indicating low consistency and possibly the presence of more than one construct in the scale. Indeed factorial analysis revealed two constructs or factors within the scale. These findings are contrary to the original validation of this scale which showed a very good Cronbach's α of 0.83 and a single-factor scale using factor analysis to assess its dimensionality (Morisky et al., 2008). Sakthong et al. (2009) reported a Cronbach's of 0.61 and factor analysis revealed three factors within the scale when tested in patients with diabetes. The two factors identified in this research included: Factor 1 (Questions 1, 2, 4 and 8), which is mainly about forgetfulness, with a Cronbach's α of 0.681; and Factor 2 (Questions 3, 6 and 7), which is mainly about intentional non-adherence and complexity of regimen, with a Cronbach's α of 0.324. Though, Qn2 could have an element of intentional non-adherence as well, it seems that the majority of those who answered it were mainly considering forgetfulness. The low Cronbach's α value for Factor 2 can be explained by the low number of patients who answered yes to Qn6 and the possibility of the non-intentional element found in Qn7, which mainly asks about the complexity of the regimen. Patients on complex regimens may be hassled about sticking to their treatment; but this can be intentional or non-intentional.

The MMAS-8 scale should be used with caution and tests of internal validity and dimensionality should always be conducted to inform the analysis of data. A modified

version of the scale which uses an equal number of positively and negatively scored items might perform better. Despite these limitations, the MMAS-8 was able to detect non-adherent behaviour which was confirmed by the SQ scale, AE or comments made by patients.

5.3.2 The Adherence Estimator

The AE was also a simple tool to administer and was very useful in exploring the underlying drivers of some of the non-adherence behaviour. It mainly looked at propensity to intentional non-adherence. Despite concerns about the applicability of question 3 about cost of medicines to the NHS in England, it proved very useful and relevant and will be elaborated on in Section 5.4.2.4. Of the 147 patients who were identified by the AE to have low or medium probability to be adherent, 86 were classed by MMAS-8 (excluding Qn5) or SQ scale to be non-adherent. There are three potential explanations for this:

1) The non-adherence behaviour of those who had propensity was not yet apparent.
2) The MMAS-8 (excluding Qn5) and the SQ failed to detect the non-adherence behaviour.
3) The AE was incorrect in its classification of those patients.

Whatever the reason, the information provided by the AE is clinically relevant and should be acted upon by healthcare professionals. If a patient is adherent and having concerns or worries about his or her medicines, then these concerns should be addressed regardless of the adherence status. It is also possible that if concerns are

genuine (e.g. suspecting a medicine to be causing a harmful side effect) then adherence might be inappropriate.

The sensitivity of the AE was 40%. This is almost 50% lower than the reported 88% by the author of this tool (McHorney, 2009). The specificity was 78% and higher than the 59% reported by McHorney (2009). This could be explained by the fact that the "gold standard" used in this study was MMAS-8 (excluding Qn5) or SQ scale. Those scales detect both intentional and unintentional non-adherence, whereas, the values reported by McHorney (2009) were for patients who were already identified to be intentionally non-adherent. In addition, the sociodemographic characteristics of the patients in the McHorney (2009) study were different to our study. For example: the median age was 58 and females constituted approximately 65% of the sample.

This argument is substantiated by comparison between the AE and Factor 1 and 2 (see Table 4.33). Only 37% of patients identified by Factor 1 to be non-adherent had been predicted by the AE. However, almost twice this percentage (63%) of patients were found by Factor 2, which represents more the intentional element of non-adherence. In the Kappa statistic analysis, the AE had more agreement with Factor 2 than Factor 1 or MMAS-8 (excluding Qn5). These findings highlight two further issues:

First, the presence of two dimensions (intentional vs. un-intentional) in the MMAS-8 (excluding Qn5) scale as found by the factor analysis, is more likely to be true.

Second, forgetfulness is affected to some extent by underlying beliefs about medicines and it is not purely unintentional. This is evident from the fact that 37% of non-adherent patients according to Factor 1 were predicted by the AE. The multivariate analysis for Factor 1 also showed a strong association between *specific concern* about secondary prevention medicines score and non-adherence according to Factor 1. Every one unit increase in the score of *specific concern* was associated with 8% increase in the risk of non-adherence due to forgetfulness. This increase in risk was 16% for Factor 2 non-adherence. Therefore, *specific concern* about medicines increases the risk of non-adherence due to both elements, though it is a stronger driver of intentional non-adherence.

Unni and Farris (2011) investigated this relationship between beliefs about medicines and forgetfulness to take medicines. They found that concerns about medicines were a significant predictor of forgetfulness in taking medicines (Unni & Farris, 2011). This could partially explain why interventions to address non-adherence due to forgetfulness were not always successful. The underlying beliefs should also be addressed.

5.3.3 The SQ scale

The SQ scale was the easiest to administer. Before modification the scale provided no information or detail about the reasons or the type of non-adherence behaviour. Therefore, it is best used as a screening tool to identify patients who may need further investigation into their medicines-taking behaviour. However, the SQ scale had very

low sensitivity (25%) compared to the MMAS-8 which means it is unable to identify many non-adherent patients. However, its very high specificity (97%) shows that patients identified by this scale almost certainly have issues that need exploring around their medicine-taking behaviour. In the Heart and Soul Study by Gehi et al. (2007) the SQ scale identified 8.3% of patients to be non-adherent using the 75% cut-off point. They did not report the level of non-adherence for the 90% cut-off point (Gehi et al., 2007).

The modification of the tool by the researcher provided useful information about the medicines-taking behaviour relating to individual secondary prevention medicines. Patients were able to comment on individual medicines, which proved to be invaluable during the analysis and interpretation of the findings. Based on participants' responses, the modification does not seem to have made answering the tool burdensome.

The introduction and exploration of the 90% (medium adherence) and 75% (low adherence) cut-off points in the tool provided additional information that can be used by healthcare professionals who use this tool. Patients classed as medium adherers (90%) correlated better with Factor 1 non-adherers. Whereas those who were classified as low adherers (≤75%) had a better agreement with the findings of Factor 2 and the AE. The Kappa statistic showed better agreement between SQ75 and Factor 2 than Factor 1 or MAAS-8. Users of this scale may find that patients who score 75% or less (low adherence) are more likely to have a greater element of intentional non-adherence compared to those who score 90% (medium adherence). The latter are more likely to have a greater tendency of forgetfulness non-adherence.

5.4 Barriers to adherence and factors associated with non-adherence

There is a plethora of literature on the barriers and factors that are likely to be associated with non-adherence (WHO, 2003; Horne et al., 2005; NICE, 2009). The causes of medicines non-adherence are complex, multifactorial and cannot be explained by single fixed factors such as the type or severity of the disease and sociodemographics of patients (Horne et al., 2005) (see Section 1.4.2). Non-adherence is not necessarily related to sociodemographic factors such as age, gender, level of education or race (Horne, 2005; Brown & Bussell, 2011). Many of these factors are non-modifiable (e.g. gender, age) and should be mainly used for screening and for targeting resources. However, these can vary from one population to another. The modifiable factors should be targeted by interventions. It is important to emphasise that not all of these factors have been consistently associated with patient non-adherence (Brown & Bussell, 2011). Both modifiable and non-modifiable factors had a different direction and level of association with medicines adherence depending on the studied population. The findings of this research concur with this (see Sections 5.4.1 and 5.4.2).

5.4.1 Non-modifiable Associations

5.4.1.1 Age

Comparing the adherent and non-adherent groups (according to all scales) identified that non-adherers were younger. The median (Q1, Q3; Min, Max) age of non-adherers

was 67 (62, 73; 38, 92) and for the adherers 71 (65, 71; 45, 92). The multivariate analysis showed that every one year increase in age was associated with a 4% reduction in the risk of being non-adherent regardless of the type of non-adherence (intentional or unintentional). Age is known to influence health related behaviour including the perception of risk (Deeks et al., 2009). Older patients are more likely to participate in health checks, read health promotion materials and have plans in place for future health and wellbeing compared to younger patients (Deeks et al., 2009). This may also translate into an effect on their medicines-taking behaviour.

Several adherent elderly patients made comments like *"I am still alive"* when they wanted to explain their satisfaction with their medicines and others highlighted how much they trusted their prescribers *"If you trust your doctor you trust what they prescribe"* (see Figure 4.15). These findings are consistent with an exploratory study which investigated older patients' perceptions of medication importance and worth (Lau et al., 2008). The study identified that medication importance was influenced by three factors: drug-related (indications, side-effects, and alternatives); patient-related (knowledge, attitudes, and health); and external (the media, healthcare and family carers) (Lau et al., 2008). In the absence of detailed adequate knowledge about their medicines, patients relied on their personal experience of medicines or complete trust in their healthcare providers' advice, to assign importance ratings (Lau et al., 2008).

It can be argued that our findings are specific to this study, as in the literature older age has been associated with higher non-adherence, lower non-adherence and also a neutral impact (Gehi et al., 2007; Granger et al., 2009; Doggrell, 2010; Rolnick et al., 2011). The evidence about these factors could be contradictory due to the complexity

of the interactions of the factors that can contribute to non-adherence (see Section 1.4.2). Therefore, the findings may only be applicable to the population being studied.

5.4.1.2 Gender

Females were more likely to be adherent than males according to the multivariate logistic regression analysis of overall non-adherence. The analysis of non-adherence according to Factor 1 and Factor 2 showed that gender was only important in Factor 1 (unintentional / forgetfulness). An interaction analysis showed that this was not dependent on age.

Various studies have shown that gender is associated with health related behaviour (Davidson & Freudenburg, 1996; Deeks et al., 2009). Females were more likely than males to indicate preparedness to have an annual health check, have a greater willingness to seek advice from a healthcare professional and attend educational sessions (Deeks et al., 2009). The literature also suggests that females are more likely than males to report poor self-rated health, which could explain their higher adherence to medicines (Lim et al., 2007). However, these findings were not consistent in all studies and gender health behaviour was also influenced by cultural, ethnic and social factors (Lim et al., 2007). This could explain why, contrary to our research's findings, Gehi et al. (2007) and Granger et al. (2009) found that females were more likely to be non-adherent than males in their studies. This is another example of why non-modifiable factors associated with non-adherence need to be considered in the population that is being studied and not over-generalised. This underlines one of the

main conclusions of this thesis that individual patient profiling is essential for the success of any planned intervention.

5.4.1.3 Cardiac history and co-morbidities

Patients who had angioplasty were more likely to be non-adherent than those who did not have angioplasty according to the overall non-adherence findings and the AE. Those who had CABG were more likely to be adherent according to overall non-adherence, AE and Factor 1 non-adherence than those who did not have CABG. A prior CABG was associated with a reduction in the risk of being non-adherent due to forgetfulness by 40%. This difference in medicines-taking behaviour might be due to the perception patients have about these procedures. The expected treatment benefits perceived by patients undergoing angioplasty is usually exaggerated (Ozkan et al., 2008; Chandrasekharan & Taggart, 2011). Post angioplasty patients took their heart disease less seriously, had the expectation that they would not get chest pain or MI, and had less fear of death (Ozkan et al., 2008). A review of patient perceptions about CABG and angioplasty found that 71% of those who had angioplasty erroneously believed that angioplasty would prevent future MIs (Chandrasekharan & Taggart, 2011). CABG patients were better informed and their expectations were more realistic compared to angioplasty patients (Chandrasekharan & Taggart, 2011). Patients should be better educated about the outcomes of angioplasty to make their expectations more realistic. This could reduce their erroneous expectations and cause them to take their heart disease more seriously, which would be expected to possibly improve adherence and outcomes.

Patients with diabetes were less likely than those without diabetes (not on anti-diabetic medicines) to be non-adherent according to Factor 1. Having diabetes was associated with a reduction in the risk of being non-adherent due to forgetfulness by 56%. This is perhaps not surprising as patients with diabetes tend to ensure a good routine for taking their medicines as the consequences of missing their medicines are usually felt.

5.4.2 Modifiable Associations

5.4.2.1 Polypharmacy and forgetfulness

In this study, polypharmacy was not associated with overall non-adherence in the bivariate or multivariate analyses (See Table 4.44 and Table 4.53). The frequency of daily medicines administration and number of individual daily doses were not associated with higher levels of overall non-adherence either. This is contrary to other studies which found that the complexity of the regimen (as the number of daily administrations of individual drugs) was negatively associated with adherence (Corsonello et al., 2009; Claxton et al., 2001). However, the systematic review identified no significant differences in levels of adherence between once daily and twice-daily regimens or between twice daily and 3 times daily regimens (Claxton et al., 2001). The majority of our participants were on once or twice a day regimens, which could explain this difference. Exploring the association of polypharmacy with adherence according to Factor 1 and Factor 2 provides additional explanation.

Adherent patients according to Factor 1 (unintentional / forgetfulness) were more likely to have polypharmacy than non-adherers. Patients on multiple therapies are

more likely to need to be organised with their medicines and fit them into their daily routine. Once this is established it should reduce the likelihood of forgetfulness. In Figure 4.15 (see also Table 4.58) both adherent and non-adherent patients said that a change of routine was the main cause of forgetting to take medicines. Midday doses and travelling were other causes. Though it was not assessed in this study, patients with polypharmacy are often offered multidose compliance aids which can help them better plan their medicines-taking. Shalansky and Levy (2002) studied the levels of non-adherence among patients with CVD and identified that taking more medicines was associated with higher adherence. They also reported that the adherent group used more compliance aids and in the multivariate analyses using a compliance aid was associated with adherence (Shalansky & Levy; 2002).

In Figure 4.15 (see also Table 4.61), patients cited the help of their family members as invaluable in reminding them to take their medicines. This could have been an important factor in improving adherence and reducing forgetfulness.

In addition, polypharmacy can be a proxy for more advanced disease and co-morbidities that can become more symptomatic. In Figure 4.15 (see also Table 4.58) patients reported that their *"angina reminds them to take their medicines"*. Some trials suggest that patients with greater illness severity may be more motivated to take their medicines (Balkrishnan, 1998; Billups et al., 2000). This can be further supplemented by the results of the BMQ which identified that adherent patients had a stronger belief (higher score) in the necessity of their medicines to maintain their health (see Table 4.52). Every one unit increase in the score for *specific necessity* was associated with a 10% reduction in the risk of being intentionally non-adherent (see Table 4.55). This

means that polypharmacy *per se* is not necessarily sufficient to lead to non-adherence, other factors which make the patient favour adherence might be more important (e.g. how well the treatment fits in with the individual patient's routine, expectations and preferences).

Non-adherent patients according to Factor 2 (intentional / hassle) were more likely to be on more medicines in both bivariate and multivariate analyses (see Table 4.41 and Table 4.55). Being on multiple therapies causes patients more *"hassle"* and concern about adverse drug reactions which can make them become non-adherent. In Figure 4.15 (see also Table 4.58) patients raised concerns about polypharmacy and non-adherent patients asked for more information on "why so many medicines are prescribed". They also expressed a clear concern that taking so many medicines at the same time could lead to side-effects and interactions. While the most frequent interventions used to address polypharmacy involve compliance aids, the findings of this research indicate that a different approach should be adopted. After establishing the need for the medicines that a patient is prescribed, healthcare professionals should first evaluate and clarify why these multiple therapies are needed and address any specific concerns that patients have about their regimen.

When analysing the association between different variables and non-adherence, it is recommended to distinguish between intentional and non-intentional non-adherence as they may differ. This in turn would have different implications for the interventions that should be employed to address non-adherence.

5.4.2.2 Secondary Prevention Medicines

There was no correlation between the number of secondary prevention medicines prescribed, the number of daily doses or number of administrations per day and adherence in both bivariate and multivariate analysis (see Tables 4.40, 4.41, 4.44, 4.53, 4.54 and 4.55). This could possibly indicate that non-adherence to secondary prevention medicines is not associated specifically with secondary prevention medicines' polypharmacy. However, individual secondary prevention medicines were associated with an increase or a decrease in the level of non-adherence.

Aspirin was positively associated with overall non-adherence, Factor 1 and Factor 2 non-adherence in both bivariate and multivariate analyses (see Tables 4.40, 4.41, 4.44, 4.53, 4.54 and 4.55). This was consistent with the findings of the SQ scale where aspirin was the secondary prevention medicine most non-adherence (see Table 4.28). This is contrary to previous studies, which showed that patient adherence to aspirin was usually the highest (Newby et al., 2006; Ho et al., 2008). In Figure 4.15 and Table 4.57, patients cited high levels of concern about the side-effects of aspirin. This could have been a major contributing factor to aspirin non-adherence. Patients indicated that *"media"* added more concern about taking aspirin. Searching the BBC (British Broadcasting Corporation) website (www.bbc.co.uk) revealed 4 articles about aspirin in heart disease between 1/1/2009 and 1/1/2011. The reports were mainly around the increased risk of gastrointestinal bleeding and lack of evidence that aspirin was useful in primary prevention of MIs. The headlines were very confusing such as "*Warning for healthy aspirin users"* and possibly few patients would distinguish between primary and secondary prevention use of aspirin. These findings may reflect the impact the media could have on adherence to secondary prevention medicines. "Media" was also

mentioned by patients in relation to statins indicating that it increased their worry about side-effects. A similar search of the BBC website revealed two articles about the side-effects of statins. One of the major articles started by claiming: *"GPs should think more carefully about prescribing cholesterol-busting drugs say researchers who highlighted a range of 'unintended' side-effects"*. In this study statins were the second most non-adhered to secondary prevention medicine. The bivariate and multivariate analyses failed to identify any association between being prescribed a statin and non-adherence possibly due to the lack of variation in statin prescribing (95% of participants were on statins).

Similar searches were conducted for ACEI, beta blockers, clopidogrel and ARBs. No main headlines were identified about any of these classes of medicines in CAD.

Beta blockers were associated with higher Factor 2 adherence (see Table 4.41 and 4.55). This means that patients were less likely to intentionally not adhere to secondary prevention medicines if they were on a beta blocker. Though some patients reported modifying the dose of beta blockers (see Figure 4.15 and Table 4.57) due to side-effects, fewer patients were non-adherent to beta blockers compared to aspirin, statins and clopidogrel (see Table 4.28). This could possibly be explained by the advice that is repeatedly given to patients prescribed beta blockers and included in patient information leaflets and on the medicines label: *"Warning: Do not stop taking this medicine unless your doctor tells you to stop"*. During cardiac rehabilitation sessions this advice is emphasised and explained in detail. This, together with the lack of knowledge (hence lack of confidence) about this class of medicines could have made patients less likely to intentionally stop this medicine.

5.4.2.3 Knowledge about the indication of secondary prevention medicines

Knowledge about the indications for the secondary prevention medicines that each patient was prescribed was variable and not associated with adherence. Despite the participants overall high level of knowledge about statins and aspirin, they still reported the highest non-adherence to these two classes of medicines.

The overall knowledge of prescribed secondary prevention medicines among overall non-adherers was higher than adherers and was statistically significant (mean ± SD = 1.6 (±0.62) vs. 1.8 (±0.66) respectively, median (Q1, Q3) = 1.5 (1, 2) vs. 1.7 (1.3, 2) respectively). This means that knowing the indication of secondary prevention medicines is not necessarily sufficient to increase adherence. Patients who know more about a medicine may read more about it and become concerned about its side-effects. This concern may lead patients to non-adherence. This is supported by the findings of Karaeren et al. (2009) who investigated the effect of patients' knowledge about their antihypertensives on adherence. They found that knowing the side-effects of medicines had a negative effect on adherence to antihypertensive therapy (Karaeren et al., 2009). This is possibly due to the way the information about side-effects was presented and the absence of healthcare professionals' contribution to address patients concerns about side-effects. While information about side effects is a priority to many patients, a lot of them express dissatisfaction and lack of understanding with the way information about risk of harm and side-effects are presented in written information leaflets (Raynor et al., 2007). Healthcare professionals should also accept the possibility that patients may decide not to take a

medicine after receiving satisfactory information and weighing the benefits against the risks of taking that medicine (Raynor et al., 2007; NICE, 2009).

In Figure 4.15 (see Tables 4.57, 4.58, 4.63) patients frequently mentioned that the information available through various sources (media, information leaflets and healthcare professionals) added to their concern about the medicines' side-effects or did not answer their questions and worries about side-effects. Patients who had more knowledge about a medicine might also have felt more confident to change it. If patients suspected that healthcare professionals were likely to disagree or not listen to them, then they could act without consulting them. Some patients commented about healthcare professionals: *"It is not easy to persuade them about the side-effects of medicines, they do not believe you"*. A similar trend was seen in Factor 2 adherence. However, the difference was not statistically significant.

In the bivariate analysis, patients who had less knowledge about beta blockers were more likely to be adherent (see Table 4.44, Table 4.40). This means that knowing why beta blockers were prescribed does not necessarily increase adherence. However, this was not statistically significant in the Factor 2 adherence assessment.

While providing patients with information is recommended, it does not necessarily improve adherence. This conclusion is consistent with other studies (Horne et al., 2005). Patients are clearly interested in more information about their medicines as can be seen in Figure 4.15 and Table 4.63. However, they were not satisfied with the information provided and made suggestions about the type they need. There is a significant demand for clearer information about side-effects as expressed in Tables

4.58, 4.59 and 4.63. This research recommends that healthcare professionals provide tailored patient information, which answers patients' specific concerns and questions about their medicines. Such information may have a different impact on adherence as patients are more likely to find it satisfactory (Raynor et al., 2007). Further research is needed on the impact of tailored patient information on adherence.

5.4.2.4 Prescription costs

The AE identified that 21 patients had a propensity to be non-adherent because of the cost of prescriptions. Two of those patients were over 60 years of age and would be exempt from paying for their prescriptions. However, they commented that *"erectile dysfunction medication should be free for a non-earning pensioner"*. This indicates that they were referring to medicines that needed a private prescription (see Section 5.4.2.6 for more about erectile dysfunction in CAD patients). Of the 19 patients under the age of 60, two identified cost as an issue. They could also have been referring to private prescriptions. There were 58 patients in the whole study who were possibly exempt from prescription charges and 37 of them were non-adherent. Of the 37 non-adherers, 11 identified prescription charges as a reason.

In Figure 4.15 and Table 4.58 cost was mentioned as a concern for both adherent and non-adherent patients. "*All MI medicines should be free after suffering an MI"* one of the patients commented. Prescription charges are per item and post MI patients are likely to be on at least 4 – 5 items (£29.6 - £37 per month or per three months depending on the quantity prescribed for each item in 2011). A 12 months prescription

prepayment certificate can save patients money, but it still costs £104 a year (DoH, 2012).

Though the majority of patients are exempt from paying NHS prescription charges, a substantial minority still have to pay for their prescriptions. It is estimated that patients in England paid prescription charges for 11.4% of items dispensed in 2007 (4.1% through pre-payment certificates) (Information Centre, 2011). Furthermore, some medicines are prescribed on private prescriptions and can be expensive. For example the cost of 8 tablets of 100mg of sildenafil is £46.99 excluding additional dispensing costs (Joint Formulary Committee, 2011). While cost of medicines is considered to be a barrier to adherence, the majority of the evidence around this comes from the US and is not necessarily relevant to NHS settings (Horne et al., 2005; NICE, 2009). A few studies have been done in the UK to explore this issue (Schafheutle, 2009; NICE, 2009). However, it is known that cost is an important external factor which influences patients' adherence (Lexchin & Grootendorst, 2004). Though this might be true, its impact on patients is not the same and possibly dependent on the patient's socioeconomic background. Schafheutle et al. (2004) showed that prescription charges may act as a stronger barrier to the use of prescribed among non-exempt patients on lower incomes. A recent American randomised study which eliminated all costs for medicines for post MI patients improved adherence by only 4 to 6 percentage points indicating that other factors contributing to non-adherence were still present (Choudhry et al., 2011). Nevertheless, even this small increase in the percentage of adherence is evidence for its impact.

The findings of our research add to the scarce evidence around this topic and suggest that prescription charges can be a barrier to adherence here in England. 18% of those who pay for prescription charges were found to be non-adherent due to cost.

5.4.2.5 Practical barriers

Opening medicine bottles or blister packs was a problem for 18% of patients and 22% needed a solution or an alternative (see Section 4.8). Patients complained about blister packs and that they were hard to open and others mentioned that tablets break when opening the blister pack (see Figure 4.15 and Table 4.58). Though this was not associated with overall non-adherence, patients with Factor 2 non-adherence (intentional / hassle) were more likely to have issues with opening medicines' bottles and blister packs (see Table 4.50). This could be explained by the *"hassle"* element in Factor 2. Patients also wanted solutions or alternatives to reading labels on medicines bottles, swallowing medicines, and getting repeat prescriptions (8%, 9%, and 10%, respectively). Barber et al. (2004) described that 7% of patients with chronic diseases reported difficulties with the practical aspects of taking medicines. However, they did not provide enough detail about these practical issues. Problem swallowing tablets was listed as one of these difficulties (Barber et al., 2004).

Getting repeat prescriptions had a strong association with non-adherence and patients who had issues with repeat prescriptions and needed a solution or alternative were nearly 2.5 times more likely to be overall non-adherent and 4 times non-adherent according to Factor 2. As seen in Figure 4.15 and Table 4.58 patients complained about the lack of synchrony between the number of medicines ordered and the short periods

of supply. When certain medicines are supplied for 28 days and others for 56 days the patient would need to remember to order repeat prescriptions every month for different medicines. Patients seem to favour three monthly supply as it causes them less hassle as well. The lack of smoothness in repeat prescription ordering can lead to forgetting medicines and hassle patients as it would require them to spend more time and effort sorting out their medicines.

Though some of these barriers were not associated with non-adherence, they should still be addressed as they could be causing patients inconvenience and can cause patients to become non-adherent at a later stage. The pharmaceutical industry has a major role to play in ensuring that medicines packaging is suitable for patients and tablets/capsules are easy to swallow. Currently, there are no regulatory requirements or guidelines in Europe to test medicines during their manufacturing process for *ease of opening* of blister packs or *swallowing medicines* (MHRA : The Medicines and Healthcare products Regulatory Agency, 2012; MHRA, 2012, pers. comm). The MHRA, European Medicines Agency (EMA) and the pharmaceutical industry should address this issue. Furthermore, pharmacists and GPs have a major role to play in assessing and overcoming these barriers.

5.4.2.6 Beliefs about medicines

In the bivariate analysis non-adherent patients scored less for *specific necessity* and higher for *specific concern* and *general overuse*. The biggest difference in score was for *specific concern,* which indicates that it possibly had the biggest influence. This is confirmed by the multivariate logistic regression analysis, which showed that every

one unit increase in *specific concern* about secondary prevention medicines score was associated with a 12% increase in the risk of non-adherence. This association was found in both Factor 1 and Factor 2 elements. However, it had a stronger association with Factor 2 non-adherence indicating that it is a stronger driver of intentional non-adherence than forgetfulness non-adherence. *Specific necessity* was only associated with intentional non-adherence but it had a weaker association than *specific concern* and *general overuse* of medicines. These findings highlight the areas that should be addressed and targeted with interventions.

Though various studies have shown association between one or more of the BMQ subscales and adherence to medicines, the associations were different depending on the population studied (Horne & Weinman, 1999; Ross et al., 2004; Khanderia et al., 2008). While hypertensive patients who believed in the necessity of medication were more likely to be adherent (Ross et al., 2004), this was not the case in patients with diabetes whose concerns regarding the use of treatments outweighed the benefits of regularly taking medicines (Horne et al., 1999). In another study CABG non-adherent patients were in stronger agreement on the *general overuse* and *general harm* scales (Khanderia et al., 2008).

This re-emphasises the need to tailor interventions to the needs and characteristics of the targeted patient population. Our research also shows the benefit of the Factor 1 and Factor 2 analysis, which revealed additional associations between beliefs and different types of non-adherence.

The analysis of patients' comments revealed that patients were concerned about the following issues in relation to their secondary prevention medicines:

1) Side-effects
2) Lack of understanding of need and benefit
3) Length of therapy

Some of these elements were also raised as a general concern about all medicines. Those who were satisfied with their medicines reported fewer side-effects and *"feeling"* the benefits. Examples of the statements used were: *"I do not get any side-effects"*, *"I am pain free, means they are working"*, *"I feel much better"*, *"I am still alive"*. It is also clear that the concern about side-effects was either "experienced" or "expected". Some patients were concerned about side-effects that they were actually experiencing or had experienced and associated them with a specific medicine(s). Others, were not experiencing side-effects but were concerned that they might experience them either because of what they had read, heard in the media or simply because they had been on these medicines for long time. Patients are generally less likely to adhere to therapies that have / or are expected to have significant side-effects and these issues need to be addressed (Elwyn et al., 2003). However, the complexity of these scenarios reflects the need for suitable interventions. Patients who are experiencing side-effects will need different information and advice to those who are just worrying about side-effects happening. Those who are associating the increased likelihood of side effect and reduced benefit with the length of time they have been on a specific medicine would also need a different approach. Karaeren et al. (2009) reported that patients who knew about the duration of use of antihypertensive medicines were more likely to be adherent than those who did not know.

One of the main themes of concern identified by patients was *"concern about sexual health"*. Erectile dysfunction is very common in heart disease patients (38 - 78% after a MI) and is caused by organic causes (e.g. atherosclerosis), psychological issues and commonly prescribed secondary prevention medicines such as beta-blockers and statins (Sainz et al., 2004). Almost all non-adherent patients in that category identified all heart medicines to cause erectile dysfunction. This is an important concern that should be addressed as it can also lead to non-adherence (if it has not already). It needs addressing regardless of adherence as it could have an impact on patients' quality of life. Patients should be offered opportunities to discuss any concerns they have about erectile dysfunction and they should be provided with the appropriate advice.

5.4.2.7 Healthcare Professionals and Healthcare Services

The Heart Medicines Survey did not have specific questions about healthcare professionals and healthcare services except for some questions mentioned in the BMQ. However, patients made many comments about healthcare professionals and services which became apparent from patients' comments. Adherent patients generally expressed satisfaction with healthcare professionals and healthcare services (see Figure 4.15 and Table 4.61). Non-adherent patients spoke of concerns about various aspects of the healthcare service and healthcare professionals. However, non-adherent patients made almost all the suggestions on how to improve healthcare services related to medicines and adherence. This suggests that if non-adherent patients are given opportunities to raise their concerns about their medicines (e.g. in a

medicines review), healthcare professionals would be more likely to know their needs and address non-adherence with targeted interventions.

Satisfied patients identified the following reasons for their satisfaction:

1) Trusted and accessible prescriber who prescribes only when necessary.
2) Review of medicines and checking for side-effects.
3) Help with access to medicines (puts medicines in bottles instead of blister packs).

Unsatisfied patients cited the following reasons for their dissatisfaction:

1) Lack of information at the point of prescribing medicines.
2) Generally lack of information on side-effects, rationale behind multiple therapies, and length of time they should be taken for.
3) Prescribers lack of acknowledgment of the side-effects patients experience ("*not easy to persuade them about the side-effects of medicines – they do not believe you*").
4) No help in accessing medicines (e.g. bottles instead of blister packs).
5) Lack of medicines reviews (e.g. not had a medicines review for a long time).
6) Medicines reviews lacked review of side-effects.
7) Prescribers sometimes give conflicting advice.

Most of the suggestions made by non-adherent patients were around the need for more frequent medicines reviews which assess efficacy, side-effects and patients' experience and satisfaction. They also asked for better quality information which answers their questions and refreshes their memory during medicines reviews. There also was a clear request for healthcare professionals to initiate questions about side-effects, show more sympathy towards patients who experience them and offer solutions. In a study which assessed how physicians responded when patients presented with possible adverse drug reactions, it was found that in at least 86% of

cases physicians did not ask about any side-effects and they were more likely to deny than affirm the possibility of a connection between a side effect and a medicine despite high likelihoods (Golomb et al., 2007).

These findings also clearly indicate the need for more frequent and structured medicines reviews which involve the patients. Despite the publication of a guide to medication review in 2008 (Clyne et al., 2008), there seems to be a need to implement these recommendations in both primary and secondary care settings so that patients can start to feel the benefits of such service. Pharmacists have a major role to play in the delivery of medicines review. Clinical pharmacists can conduct reviews on the ward and run medicines review clinics. Community pharmacists can revisit, restructure and better utilise their Medicines Use Reviews (MURs). The recent New Medicine Services in primary care is another opportunity that should not be missed (PSNC: Pharmaceutical Services Negotiating Committee, 2011). Pharmacists need to be trained and equipped with the right tools and time to conduct these reviews in the most clinically effective manner. There is also a clear need to revisit the current structure and format of the GP medicines review under the Quality and Outcomes Framework (QoF) of the General Medical Services (GMS) contract (BMA, 2011). They should be redefined to include patients in the review and conducted in a structured format that meets patients' needs.

5.5 Limitations of the study

The limitations of using the questionnaire based method in cross-sectional studies were discussed in Chapter 3. The findings were undoubtedly limited by the cross-sectional approach as adherence to medicines is dynamic and a longitudinal study would have revealed more findings about patients' medicines taking behaviour. However, such a study would have needed more resources and time to conduct. Currently, the Medicines Heart Survey is being used in the longitudinal EMMACE-3 study (Evaluation of the Methods and Management of Acute Coronary Events - 3: Investigating variation in hospital acute coronary syndrome outcomes) which aims to recruit 5000 patients and follow them for at least 1 year (UKCRN: United Kingdom Clinical Research Network, 2012).

The use of self-reporting to measure adherence has its own limitations as was discussed in Chapter 2. Such tools usually under-estimate non-adherence and patients may feel inhibited from disclosing their real medicines- taking behaviour to healthcare professionals. Significant effort was made to draft the study documentation in a non-judgmental way that made the patients feel comfortable with volunteering such information.

"Questionnaire fatigue" is another factor which could have contributed to lower quality in the answers provided and missing data. Due to the length of the survey, respondents could have developed questionnaire fatigue towards the end of the questionnaire. Respondents usually would be more likely to make faster, more uniform answers and miss questions towards the end of the survey (Galesic & Bosnjak,

2009). This could have been overcome by rotating some of the sections/parts in the questionnaire. However, this approach could also raise problems.

Despite the small amount of missing data, it can be considered a limitation. As discussed in Section 3.6.3, missing data arose mainly from patients not answering certain questions in the questionnaire. Patients may have been unsure about these questions, or chose not to share that information with the researcher. In very few cases, whole parts of the questionnaire were missed, possibly because the page was missed. Providing clear signposts in the questionnaire indicating the next question could have reduced such occurrences (Marston, 2010). The approach used by the researcher of scoring missing data by assuming the best case scenario (in favour of adherence) could have further reduced the true levels of non-adherence in the target population.

One of the other limitations of the study was the potential bias in the sample. The sampling frame (ENCOURAGE database) could have contributed to that. The patients in this sample were people who had already participated in other cardiac related studies (which had their own inclusion and exclusion criteria) and had more exposure and input from healthcare professionals than the "real" targeted population. This created limitations and selectiveness in the type of patients included in the database. The patients' ethnic distribution was also not fully representative of the ethnic diversity of the targeted population which can limit the generalizability of the study's findings. However, the diversity of the chosen patients in terms of their geographical location and the different clinical trials they participated in previously could have reduced some of this bias. The trial backgrounds of patients were diverse, which

meant that patients came from different trials rather than one trial. This may have improved the diversity and the representation of the population in the sample.

The participants from the database were also more likely to have been better informed and more interested in their heart medicines. However, understanding the medicines related needs of this part of the population would undoubtedly still have been of great value and can inform practice. Furthermore, if levels of non-adherence were high among this sample, then this would probably indicate that the reality of the levels of non-adherence in the target population would be even lower. The findings are still valuable in informing a better approach to addressing non-adherence to secondary prevention medicines.

Comparing respondents to non-respondents can be used to show if the characteristics of the respondents were very different to the non-respondents. However, this was not possible due to the lack of information or lack of up-to-date information about the non-respondents. Most of the information about medicines was derived from self-report and not the database. However, as mentioned in Section 4.1 there was no difference in the distribution in gender between respondents and non-respondents. Higher participation might have revealed more non-adherence behaviour as non-respondents were younger and this study showed that younger patients were more likely to be non-adherent.

The study lacked a “gold standard” to compare all three adherence scales to objective reports such as MEMS® or repeat prescription data. This was not feasible and would have needed more resources and time to conduct. In addition, this was not the main aim of the study.

5.6 General summary and conclusions

The Heart Medicines Survey was successful in fulfilling its aims and objectives. The self-reported level of non-adherence to secondary prevention medicines by patients with established CHD in West Yorkshire and nearby areas was found to be 44% according to the MMAS-8 (excluding Qn5) or SQ scale. Of those 39% had an element of intentional non-adherence that was predicted by the AE. Only 52% of patients were prescribed at least four secondary prevention medicines. The levels of non-adherence to individual secondary prevention medicines were as follows (starting with the most non-adhered to): aspirin, statins, clopidogrel, beta blockers, ACEI and ARBs. The contribution of each one of those medicines to overall non-adherence as identified by the SQ scale was 62%, 67%, 7%, 30%, 22% and 5% respectively.

The amalgamated use of all the tools proved very useful in identifying barriers to adherence. Single use of any of the tools would not have been sufficient to identify all the barriers uncovered by the Heart Medicines Survey. The MMAS-8 identified more non-adherence behaviour than the other two scales. However, Qn5 was problematic and the scale had low internal consistency which revealed a lack of unidimensionality. Exploration of the tool with factor analysis identified Factor 1 (unintentional / forgetfulness non-adherence) and Factor 2 (intentional/hassle related non-adherence) which enriched the data analysis and enabled better understanding of the findings. The MMAS-8 will need modification before use in the future to prevent the Qn5 problem. The use of any of the self-reported tools should be with caution and by testing their performance in the population in question. Interpretation of results should always consider that the association between different variables and non-

adherence behaviour seems to depend on the type of non-adherence. This should better inform the types of interventions deployed to address factors contributing to non-adherence.

The AE estimator had a low sensitivity (40%) and high specificity (78%). However, its findings were relevant to clinical practice even when the predicted non-adherence behaviour was not apparent. The modified SQ scale was good for screening and providing details about individual secondary prevention medicines. It had very low sensitivity (25%) and excellent specificity (97%). The additional questions introduced by the researcher about practical barriers and the open question at the end of the survey were very useful in informing about patients' needs and population specific interventions.

Younger age, male gender and angioplasty had some positive association with non-adherence. Patients who had CABG or diabetes were less likely to be non-adherent. These non-modifiable associations were mainly useful for screening and resource targeting purposes. However, healthcare professionals need to better inform patients about angioplasty to ensure that their expectations are realistic.

Interventions to address non-adherence by CAD patients in West Yorkshire and nearby areas need to consider the following modifiable barriers that were found to be associated with non-adherence:

- Polypharmacy was associated with intentional/hassle non-adherence and therefore the interventions need to address patients' concerns about polypharmacy after establishing that the prescribed medicines are appropriate.

- The interventions should also address any perception of *general overuse* of medicines because belief in *general overuse* of medicines was positively associated with intentional non-adherence.
- Non-adherence to secondary prevention medicines seems to have been largely driven by concerns about their side-effects. Interventions need to alleviate these specific concerns (for statins and aspirin in particular).
- Problems and difficulties surrounding repeat prescriptions had a strong positive association with non-adherence and should be addressed.
- Specific concerns about medicines had a strong positive association with both unintentional and intentional non-adherence. However, it had a stronger association with intentional non-adherence.
- Belief in the *specific necessity* of medicines was negatively associated with intentional non-adherence only. However, it had an association weaker than that of *specific concern* about medicines.

In addition to the above, the interventions should take into consideration that better knowledge about the indication of secondary prevention medicines was not associated with better adherence. Tailoring the information provided to the needs of patients may have a different impact. Patients wanted more information about side-effects, the rationale for multiple therapies, and the length of time they should continue taking their medicines. In addition, 30% of patients who paid prescription charges cited it as at least one of the reasons for their non-adherence. Therefore, this barrier should be explored and alternative options offered where it is identified as a problem. Though opening medicine bottles / blister packs, reading labels and difficulty swallowing were not associated with non-adherence (except for some cases in bivariate analysis) they should be addressed because they cause patients inconvenience and may lead to non-adherence in the future.

Healthcare professionals need to ask patients about how they are managing their medicines and specifically ask about side-effects during their consultations. They should show sensitivity and co-operation with patients while discussing possible side-effects experienced by patients. Every effort should be made to address practical barriers to medicines-taking. Interprofessional communication is essential to reduce contradictions that can confuse patients, improve access and collectively address problems and difficulties that patients are experiencing.

There is a clear demand from patients for better structured medicines reviews which involve them and are carried out at least once a year. This setting should give the opportunity for patients to share their medicines-taking experience, share their concerns about their medicines and ask any questions they want.

This study clearly identified that rather than depending on extrapolations from the literature when developing interventions to address non-adherence, healthcare professionals need to frequently examine specific modifiable barriers to adherence in their patients in order to individualise interventions. This is thought to be more likely to improve adherence as discussed in Section 1.4.3.

5.7 Recommendations and future work

Based on the findings of this research the following recommendations can be made for practice, policy makers and future research:

- Interventions to address adherence should always be preceded by exploring the medicines-taking behaviour of the population in question. The investigation should

inform the interventions. Extrapolations from literature and assumptions should not be the main driver of the interventions.

- Since adherence is a behaviour that changes depending on circumstances, it should be frequently assessed using appropriate tools. The aim of the screening should not only be to identify non-adherent behaviour. It should explore the patients' **medicine-taking experience** and address *actual* and *potential* barriers to adherence. Though some of these barriers were not associated with non-adherence, they should still be addressed as they could be causing patients inconvenience and could cause patients to become non-adherent in the future.

- Self-report assessment tools should be used for the purpose of assessing non-adherence more than other tools because they are more likely to reveal actual and potential modifiable barriers to adherence. Amalgamation of tools exploring different aspects of medicines-taking behaviour, similar to the Heart Medicines Survey, is more effective than a single tool. At least one open question should be included to enable the respondents to answer in their own way and add any other issues that they wish to share about their **medicines-taking experience**.

- The performance of any tools used should be examined in the targeted population and modified according to their performance in the population in question rather than in relation to other populations from the literature.

- More opportunities should be made for patients to talk about their medicines with their healthcare professionals. Such opportunities should be preceded by

completing a **medicines-taking experience** questionnaire, similar to the Heart Medicines Survey, which is more likely to make the consultation tailored to the patient's needs. This area should be researched further to examine its impact on adherence.

- Pharmacists have a major role to play in this field. Clinical pharmacists can enhance their medicines reconciliation service during in-patient admission to give opportunities to raise any issues about medicines. They can also conduct medicines review clinics. Patients attending outpatient clinics can also be assessed and if necessary referred for a full medicines review. Community pharmacists are frequently visited by patients with chronic conditions and can seize these opportunities to offer patients the chance to discuss their medicines. The Medicines Use Reviews (MURs) and the recent New Medicine Services by community pharmacists should take on board the findings of this study of how to approach the assessment of adherence and the formulation of interventions. Further research is also needed to assess the impact of these proposed changes in clinical practice on patients' experience and adherence.

- There is a clear demand from patients for better structured medicines reviews which involve them and are carried out at least once a year. There is a need to revisit the current structure and format of the GP medicines review under the Quality and Outcomes Framework (QoF) of the General Medical Services (GMS) contract. Patients should be consulted during these medicines reviews and a new approach, as suggested in this research, should be considered. If GPs cannot, due to time constraints, conduct such more comprehensive reviews, then other

healthcare professionals (e.g. community pharmacists) should be offered the chance to contribute to this service at least once a year. The impact of the current and a modified version of the service need to be researched further.

- Healthcare professionals should provide patients with tailored information, which answers their concerns and questions about their medicines. This is more likely to be beneficial than a "one-size fits all" information provision.

- It is evident from the findings of this research that the cost of prescriptions is an added actual or potential barrier to adherence. The Department of Health should consider exempting patients who are prescribed secondary prevention medicines from prescription charges. The impact of prescription charges and any suggested exemptions, on adherence of CHD patients should be researched further.

- The pharmaceutical industry has a major role to play in ensuring that medicines packaging is suitable for patients and tablets/capsules and other formulations available are easy to swallow. The MHRA, EMA and the pharmaceutical industry should incorporate into their manufacturing process ***"ease of opening packaging"*** and ***"ease of swallowing"*** tests as these seem to be actual or potential barriers to adherence that patients encounter frequently.

- Pharmacists and GPs need to work together to simplify, synchronise and rationalise the repeat prescription ordering and supply system. This has major benefits for patients and is likely to improve adherence. Further research to explore this should be undertaken.

- Concerns about medicines side-effects seem to be a major driver of non-adherence. Information about medicines' side-effects need to be simplified and made clearer for patients. The MHRA, pharmaceutical companies and healthcare professionals need to work together to address this issue. Healthcare professionals need to be trained to ask, acknowledge and address patients' concerns about the adverse effects of medicines. Research into how to do that is needed.

- The assessment of sexual health should be part of the services provided to patients with CAD, not only during cardiac rehabilitation but at once a year reviews. The impact of sexual health on non-adherence needs further exploring.

- The media needs to be made aware of the impact it has on patients' adherence to medicines. It needs to be more responsible and accurate when presenting information about medicines and take into account any confusion that it can cause patients. Specialist healthcare professionals should be consulted on presenting the information before breaking the news to the public.

6 References

Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, et al. 2006. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. *Journal of the American College of Cardiology* 47(8); 1576-1583.

Antithrombotic Trialists' Collaboration. 2002. Collaborative meta-analysis of randomised trials of antiplatelet therapy for the prevention of death, myocardial infarction and death in high risk patients. *British Medical Journal* 324(7329); 71-86.

Argyrous G. 2011. *Statistics for research – with a guide to SPSS*. London: Sage Publications Ltd.

Avorn J. 2004. Polypharmacy - A New Paradigm for Quality Drug Therapy in the Elderly? *Arch Intern Med* 164; 1957 – 1959.

Balkrishnan R. 1998. Predictors of medication adherence in the elderly. *Clin Ther* 20; 764-771.

Bane C, Hughes CM and JC McElnay. 2006. The impact of depressive symptoms and psychosocial factors on medication adherence in cardiovascular disease. *Patient Educ Couns* 60(2); 187-193.

Bangsberg D. 2006. Monitoring adherence to HIV antiretroviral therapy in routine clinical practice: the past, the present, and the future. *AIDS Behav* 10; 249-251.

Barber N, Parsons J, Clifford S, et al. 2004. Patients' problems with new medication for chronic conditions. *Qual Saf Health Care* 13; 172–175

Baroletti S & H Dell'Orfano. 2010. Medication Adherence in Cardiovascular Disease. *Circulation* 121; 1455 – 1458.

Berry DC, Michas IC, Gillie T, et al. 1997. What do patients want to know about their medicines and what do doctors want to tell them? A comparative study. *Psychol Health* 12; 467–480.

BHF (British Heart Foundation). 2010. *Coronary Heart Disease Statistics*. Online. Available from www.hearstats.com. Accessed 2nd Nov 2011.

BHF (British Heart Foundation). 2010a. *Ethnic Difference in Cardiovascular Disease*. Online. Available from www.hearstats.com. Accessed 2nd Nov 2011.

Billups SJ, Malone DC, and Carter BL. 2000. The relationship between drug therapy noncompliance and patient characteristics, health-related quality of life, and healthcare costs. *Pharmacotherapy* 20; 941-949.

Blackburn DF, Dobson RT, Blackburn JL, et al. 2005. Cardiovascular morbidity associated with nonadherence to statin therapy. *Pharmacotherapy* 25(8); 1035-1043.

Bland JM & DG Altman. 1997. Statistics notes: Cronbach's alpha. *BM* 314; 572.

BMA. 2011. *Quality and Outcomes Framework guidance for GMS contract 2011/12 - Delivering investment in general practice*. Online. Available from: www.nhsemployers.org. Accessed 9th July 2011.

Boden WE, O'Rourke RA, Teo KK, et al. 2007. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. *N Eng J Med* 356; 1503-1516.

Bowskill R, Clatworthy J, Parham R, et al. 2007. Patients' perceptions of information received about medication prescribed for bipolar disorder: Implications for informed choice. *Journal of Affective Disorders* 100(1–3); 253–257.

Braker C, Pistrang N and R Elliott. 1994. *Research Methods in Clinical and Counselling Psychology*. Chichester, England: John Wiley & Sons Ltd.

Bramlage P, Messer C, Bitterlich N, et al. 2010. The effect of optimal medical therapy on 1-year mortality after acute myocardial infarction. *Heart* 96; 604–609.

Brown MT & JK Bussell. 2011. Medication Adherence: WHO Cares? *Mayo Clinic Proc* 86(4); 304-314.

Bryson CL, Au DH, Young B, et al. 2007. A refill adherence algorithm for multiple short intervals to estimate refill compliance (ReComp). *Med Care* 45; 497–504.

Bunch TJ, Muhlestein JB, Bair TL, et al. 2005. Effect of beta-blocker therapy on mortality rates and future myocardial infarction rates in patients with coronary artery disease but no history of myocardial infarction or congestive heart failure. *American Journal of Cardiology* 95(1); 827-831.

Burwen DR, Galusha DH, Lewis JM, et al. 2003. National and state trends in quality of care for acute myocardial infarction between 1994-1995 and 1998-1999: the medicare health care quality improvement program. *Arch Intern Med* 163; 1430–1439.

Butler JA, Peveler RC, Roderick P, et al. 2004. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation* 77(5); 786–789.

CAPRIE Steering Committee. 1996. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 348(9038); 1329-1339.

Capewell S, Unal B, Critchley JA, et al. 2006. Over 20,000 avoidable coronary deaths in England and Wales in 2000: the failure to give effective treatments to many eligible patients. *Heart* 92; 521–523.

Carter S, David T and R Levenson. 2005. *A Question of Choice—Compliance in Medicine Taking: A Preliminary Review*. 3rd Edition. London, England: Medicines Partnership.

Chandrasekharan DP & DP Taggart. 2011. Informed consent for interventions in stable coronary artery disease: problems, etiologies, and solutions. *European Journal of Cardio-thoracic Surgery* 39(6); 912-917.

Chodick G, Shalev V, Gerber Y, et al. 2008. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. *Clin Ther* 30; 2167–2179.

Choudhry NK, Setoguchi S, Levin R, et al. 2008. Trends in adherence to secondary prevention medications in elderly postmyocardial infarction patients. *Pharmacoepidemiol Drug Saf* 17; 1189–1196.

Choudhry NK, Avorn J, Glynn RJ, et al. 2011. Full Coverage for Preventive Medications after Myocardial Infarction. *N Engl J Med* 365; 2088-2097.

Claxton AJ, Cramer J and C Pierce. 2001. A Systematic Review of the Associations Between Dose Regimens and Medication Compliance. *Clinical Therapeutics* 23(8); 1296 – 1310.

Clyne W, Blenkinsopp A and R Seal. 2008. *A Guide to Medication Review*. The National Prescribing Centre.

Cook CL, Wade WE, Martin BC, et al. 2005. Concordance Among Three Self-Reported Measures of Medication Adherence and Pharmacy Refill Records. *Journal of the American Pharmacists Association* 45(2); 151 – 159.

Corsonello A, Pedone C, Lattanzio F, et al. 2009. Regimen complexity and medication nonadherence in elderly patients. *Therapeutics and Clinical Risk Management* 5; 209–216.

Cramer JA and R Rosenheck. 1998. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv* 49; 196 – 201.

Daniels T, Goodacre L, Sutton C, et al. 2011. Accurate Assessment of Adherence Self-Report and Clinician Report vs Electronic Monitoring of Nebulizers. *Chest* 140; 425-432.

Dargie HJ. 2001. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 357(9266); 1385-1390.

Davidson D & W Freudenburg. 1996. Gender and environmental risk concerns: a review and analysis of available research. *Environ Behav* 28; 302-339.

Deeks A, Lombard C and H Teed. 2009. The effects of gender and age on health related behaviors. *BMC Public Health* 9; 213

DeWilde S, Carey IM, Richards N, et al. 2008. Trends in secondary prevention of ischaemic heart disease in the UK 1994–2005: use of individual and combination treatment. *Heart* 94; 83–88.

DiMatteo MR. 2004. Variations in Patients' Adherence to Medical Recommendations: A Quantitative Review of 50 Years of Research. *Med Care* 42(3); 200-209

Doggrell S. 2010. Adherence to medicines in the older-aged with chronic conditions: does an intervention concerning adherence by an allied health professional help? *Drugs and Aging* 27(3); 239-254.

DoH – Great Britain. Department of Health. 2008. *"Pharmacy in England. Building on strengths - delivering the future"*. (Cm 7341). TSO: London.

DoH – Great Britrain. Department of Health. 2000. *National Service Framework – Coronary Heart Disease*. Online. Available from: www.dh.gov.uk. Accessed 23rd Nov 2011.

DoH – Great Britain. Department of Health. 2012. *NHS charges to increase from April 2012*. Online. Available from: www.dh.gov.uk. Accessed 15th April 2012.

Dolder CR, Lacro JP, Warren KA, et al. 2004. Brief evaluation of medication influences and beliefs: development and testing of a brief scale for medication adherence. *J Clin Psychopharmacol* 24(4):404-409.

Dulman SV, Sluijs E, Dijk LV, et al. 2007. Patient Adherence to Medical Treatment: a review of reviews. Online. *BMC Health Services Research* 7;55.

Ediger JP, Walker JR, Graff L, et al. 2007. Predictors of Medication Adherence in Inflammatory Bowel Disease. *The American Journal of Gastroenterology* 102(7); 1417-1426.

Elwyn G, Edwards A and N Britten. 2003. 'Doing prescribing': how doctors can be more effective. *BMJ* 327; 864–867.

Erickson SR, Coombs JH, Kirking DM, et al. 2001. Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *Ann Pharmacother* 35; 997-1003.

Ferrari R. 2009. A step further with ivabradine: SIGNIfY (Study assessInG the morbidity–mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease). *European Heart Journal Supplements* 11 (Supplement D); D19–D27.

Fidan D, Unal B, Critchley J, et al. 2007. Economic analysis of treatments reducing coronary heart disease mortality in England and Wales, 2000–2010. *QJM* 100;277–289.

Field AP. 2009. *Discovering statistics using SPSS*: (and sex and drugs and rock 'n' roll). 3rd Edition. London: Sage.

Flather MD, Yusuf S, Kober L, et al. 2000. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 355(9215); 1575-1581.

Fox K, Alonso Garcia MA, Ardissino D, et al. 2006 Guidelines on the management of stable angina pectoris: executive summary. The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *European Heart Journal* 27; 1341 – 1381.

Fox KM & EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. 2003. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 362(9386); 782-788.

Freemantle N, Cleland J, Young P, et al. 1999. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 318(7200); 1730-1737.

Fulton MM & ER Allen. 2005. Polypharmacy in the elderly: a literature review. *J Am Acad Nurse Pract* 17; 123–132.

Galesic M & M Bosnjak. 2009 .Effects of questionnaire length on participation and indicators of response quality in a web survey. *Public Opinion Quarterly* 73(2); 349–360.

Gao X & DP Nau. 2000. Congruence of three self-report measures of medication adherence among HIV patients. *Ann Pharmacother* 34; 1117-22.

Garber MC, Nau DP, Erickson SR, et al. 2004. The concordance of self-report with other measures of medication adherence: a summary of the literature. *Med Care* 42(7); 649-652.

Gehi AK, Ali S, Na B, et al. 2007. Self-reported Medication Adherence and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arch Intern Med* 167(16); 1798-1803.

George CF, Peveler RC, Heiliger S, et al. 2000. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *Br J Clin Pharmacol* 50; 166-171.

George J, Kong DC, Thoman R, et al. 2005. Factors associated with medication nonadherence in patients with COPD. *Chest* 128(5); 3198–3204.

Gibbons RJ, Abrams J, Chatterjee K, et al. 2003. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 107(1); 149-158.

Golomb BA, McGraw JJ, Evans MA, et al. 2007. Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. *Drug Safety* 30(8); 669-675.

Granger BB, Ekman I, Granger CB, et al. 2009. Adherence to medication according to sex and age in the CHARM programme. *European Journal of Heart Failure* 11; 1092–1098.

Gray HH, Dawkins KD, Morgan JM, et al. 2008. *Lecture Notes: Cardiology*. 5th Edition. Oxford: Blackwell Publishing.

Hahn SR, Park J, Skinner EP, et al. 2008. Development of the ASK-20 Adherence Barrier Survey. *Current Medical Research and Opinion* 24(7); 2127 – 2138.

Hamilton GA. 2003. Measuring adherence in a hypertension clinical trial. *Eur J Cardiovasc Nurs* 2(3); 219-228.

Hansen RA, Kim MM, Song L, et al. 2009. Comparison of Methods to Assess Medication Adherence and Classify Nonadherence. *Ann Pharmacother* 43; 413-422.

Hawkshead J & MA Krousel-Wood. 2007. Techniques for measuring medication adherence in hypertensive patients in outpatient settings: advantages and limitations. *Dis Manag Health Out* 15(2); 109-118.

Haynes RB, Ackloo E, Sahota N, et al. 2008. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* Apr 16;(2):CD000011.

Ho PM, Bryson CL and JS Rumsfeld. 2009. Medication Adherence: Its Importance in Cardiovascular Outcomes. *Circulation* 119; 3028 – 3035.

Ho PM, Magid DJ, Shetterly SM, et al. 2008. Medication non-adherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J* 155; 772–779.

Holland R, Desborough J, Goodyer L, et al. 2007. Does Pharmacist-led medication review help to reduce hospital admissions and deaths in older people? – A systematic review and meta-analysis. *BJCP* 65(3); 303 – 316.

Hope CJ, Wu J, Tu W, et al. 2004. Barriers to adherence in elderly heart failure patients. *Drug Inf J* 38(4); 331-341.

Horne R & J Weinman. 1999. Patients' beliefs about prescribed medicines and their role in adherence to treatments in chronic physical illness. *J Psychosom Res* 47; 555–567.

Horne R & J Weinman. 2002. Self-regulation and self-management in asthma: Exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychol Health* 17; 17-32.

Horne R, Hankins M and R Jenkins R. 2001. The Satisfaction with Information about Medicines Scale (SIMS): A new measurement tool for audit and research. *Qual Health Care* 10; 135-140.

Horne R, Weinman J and M Hankins. 1999. The Beliefs about Medicines Questionnaire: The Development and Evaluation of A New Method For Assessing The Cognitive Representation Of Medication. *Psychology and Health* 14; 1-24.

Horne R, Weinman J, Barber N, et al. 2005. *Concordance, adherence and compliance in medicine taking*. National Co-ordinating Centre for NHS Service Delivery and Organisation NCCSDO. Online. Available from: http://www.sdo.nihr.ac.uk/files/project/76-final-report.pdf. Accessed 11th Dec 2011.

Horne R. 2001. Non-adherence to medication: Causes and implications for care. In: Gard P (ed). *A behavioural approach to pharmacy practice*. Oxford: Blackwell, pp. 111-130.

Horne R. 2003. Treatment Perceptions and self-regulation. In: Cameron L & H Leventhal (eds). *The self-regulation of health and illness behaviour*. London: Routledge.

Horwitz RI, Viscoli CM, Berkman L, et al. 1990. Treatment adherence and risk of death after a myocardial infarction. *Lancet*. 336(8714); 542-545.

Howitt D & D Cramer. 2011. *Introduction to Research Methods in Psychology*. 3rd Edition. Harlow: Prentice Hall.

Information Centre. 2011. *Prescriptions Dispensed in the Community: England, Statistics for 2000 to 2010*. Online. Available from: www.ic.nhs.uk. Accessed 23rd April 2012.

Insull W, 1997. The problem of compliance to cholesterol altering therapy. *Journal of Internal Medicine* 241; 317–325.

Inui TS, Carter WB and RE Pecoraro. 1981. Screening for noncompliance among patients with hypertension: is self-report the best available measure? *Med Care* 19; 1061- 1064.

Jackevicius CA, Li P and JV Tu. 2008. Prevalence, predictors, and outcomes of primary nonadherence after myocardial infarction. *Circulation* 117; 1028-1036.

Jamieson S. 2004. Likert scales: how to (ab)use them. *Medical Education* 38; 1217–1218.

Johnson MJ & S Rogers. 2006. Development of the Purposeful Action Medication-Taking Questionnaire. *Western Journal of Nursing Research* 28(3); 335-351.

Joint Formulary Committee. 2011. *British National Formulary*. 62nd edition. London: British Medical Association and Royal Pharmaceutical Society.

Jolly K, Lip GY, Taylor RS, et al. 2005. Recruitment of ethnic minority patients to a cardiac rehabilitation trial: The Birmingham Rehabilitation Uptake Maximisation (BRUM) study. *BMC Medical Research Methodology* 5:18.

Karaeren H, Yokuşoğlu M, Uzun S, et al. 2009. The effect of the content of the knowledge on adherence to medication in hypertensive patients. *Anadolu Kardiyol Derg* 9(3); 183-188.

Khanderia U, Townsend KA, Erickson SR, et al. 2008. Medication Adherence Following Coronary Artery Bypass Graft Surgery: Assessment of Beliefs and Attitudes. *Ann Pharmacother* 42:192-199.

Khatib R & C Keenan. 2011. The Development of a Sublingual Glyceryl Trinitrate (GTN) Advice Card in Collaboration with Coronary Heart Disease (CHD) Patients. *International Journal of Pharmacy Practice* 19(Suppl 2); 39.

Khatib R, Waterman E, Acomb C, et al. 2011. Assessment of Medicines Adherence by Primary and Secondary Care Pharmacists in Yorkshire and Humber – a survey. *Clinical Pharmacist* Suppl 2; S42-S43.

Kripalani S, Risser J, Gatti ME, et al. 2009. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value in Health* 12; 118-123.

Kripalani S, Yao X and B Haynes. 2007. Interventions to Enhance Medication Adherence in Chronic Medical Conditions – a systemic review. *Arch Intern Med* 167; 540-550.

Krousel-Wood M, Islam T, Webber LS, et al. 2009. New Medication Adherence Scale Versus Pharmacy Fill Rates in Seniors With Hypertension. *The American Journal of Managed Care* 15(1); 59 – 66.

Krumholz HM, Radford MJ, Ellerbeck EF, et. al. 1995. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries. Patterns of use and outcomes. *Circulation* 92; 2841–2847.

Kumar P & M Kumar. 2009. Clinical Medicine. 7th Edition. London: Elsevier Limited

Landis JR & GG Koch. 1977. The measurement of observer agreement for categorical data. *Biometrics* 33, 159-174.

Latif A, Pollock K, and Boardman HF. 2011. The contribution of the Medicines Use Review (MUR) consultation to counseling practice in community pharmacies. *Patient Education and Counseling* 83(3); 336-344.

Lavsa SM, Holzworth A and NT Ansani. 2011. Selection of a Validated Scale for Measuring Medication Adherence. *J Am Pharm Assoc* 51(1); 90-94.

Lau DT, Briesacher B, Mercaldo ND, et al. 2008. Older Patients' Perceptions of Medication Importance and Worth: An Exploratory Study. *Drugs Aging* 25(12); 1061–1075.

Lee JK, Grace KA and AJ Taylor. 2006. Effect of a Pharmacy Care Program on Medication Adherence and Persistence, Blood Pressure, and Low-Density Lipoprotein Cholesterol - A Randomized Controlled Trial. *JAMA* 296(21); 2563-2571.

Lexchin J & P Grootendorst. 2004. Effects of prescription drug user fees on drug and health services use and on health status in vulnerable populations: a systematic review of the evidence. *Int J Health Serv* 34; 101-122.

Lim WY, Ma S, Heng D, et al. 2007. Gender, ethnicity, health behaviour & self-rated health in Singapore. *BMC Public Health* 7**;** 184.

Llewellyn CD, Miners AH, Lee CA, et al. 2003. The illness perceptions and treatment beliefs of individuals with severe haemophilia and their role in adherence to home treatment. *Psychology and Health* 18(2); 185-200.

Lloyd-Jones DM, Larson MG, Beiser A, et al. 1999. Life-time risk of developing coronary artery disease. *Lancet* 353; 89 – 92.

Lowry KP, Dudley TK, Oddone EZ, et al. 2005. Intentional and unintentional nonadherence to antihypertensive medication. *Ann Pharmacother* 39; 1198 –1203.

LTHT – Leeds Teaching Hospitals NHS Trust. 2011. Leeds Teaching Hospitals NHS Trust. Online. Available from: www.leedsteachinghospitals.com. Accessed 20th Dec 2011.

Machin D, Campbell MJ and SJ Walters. 2007. *Medical Statistics – A textbook for the health sciences*. 4th Edition. Chichester: Wiley.

Mahler C, Hermann K, Horne R, et al. 2010. Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany. *Journal of Evaluation in Clinical Practice* 16; 574–579.

Majumdar SR, Gurwitz JH and SB Soumerai. 1999. Under treatment of hyperlipidemia in the secondary prevention of coronary artery disease. *J Gen Intern Med* 14; 711–717.

Marston L. 2010. *Introductory Statistics for Health and Nursing Using SPSS*. London: Sage Publications Ltd.

Matthews B & L Ross. 2010. *Research Methods – a practical guide for social sciences*. Edinburgh: Pearson Education Limited.

McBurney DH & TL White. 2007. *Research Methods*. 7th Edition. United Kingdom: Thomson/Wadsworth.

McHorney CA, Victor Spain C, Alexander CM, et al. 2009. Validity of the Adherence Estimator in the Prediction of 9-Month Persistence With Medications Prescribed for Chronic Diseases: A Prospective Analysis of Data From Pharmacy Claims. *Clin Ther* 31; 2584–2607.

McHorney CA. 2009. The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. *Curr Med Res Opin* 25(1); 215-238.

MHRA - The Medicines and Healthcare products Regulatory Agency. 2012. *Good Manufacturing Practice*. Online. Available from: www.mhra.gov.uk. Accessed 15th April 2012.

MHRA - The Medicines and Healthcare products Regulatory Agency. *Advice on Good Manufacturing Practice and Regulations Governing Manufacturing of Medicines*. [email]. (Personal communication 20th April 2012).

Mikhail GW. 2005. Coronary heart disease in women. *BMJ* 331; 467–468.

Modi AC, Lim CS, Yu N, et al. 2006. A multi-method assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros* 5(3); 177 – 185.

Morisky DE, Ang A, Krousel-Wood M, et al. 2008. Predictive Validity of a Medication Adherence Measure for Hypertension Control. *Journal of Clinical Hypertension* 10(5); 348-354.

Morisky DE, Green LW and DM Levine. 1986. Concurrent and predictive validity of a self-reported measurement of medication adherence and long-term predictive validity of blood pressure control. *Med Care* 24; 67-74.

Morisky DE. 2009. *8-item Morisky Score*. [email]. (Personal communication 26 May 2009)

Morisky DE. 2011. *Results of the 8-item Morisky Score*. [email]. (Personal communication 11th July 2011)

Nabel EG & E Braunwald. 2012. A Tale of Coronary Artery Disease and Myocardial Infarction. *N Engl J Med* 366;54-63.

NCMMSP (National Collaborative Medicines Management Services Programme). 2002. *Room for review: guide to medication review, the agenda for patients, practitioners and managers*. London: Medicines Partnership.

Neubeck L, Redfern J, Fernandez R, et. al. 2009. Telehealth interventions for the secondary prevention of coronary heart disease: a systematic review. *Eur J Cardiovasc Prev Rehabil* Advance online publication. doi:10.1097/HJR.0b013e32832a4e7a. Online. Available from: http://journals.lww.com/ejcpr/pages/articleviewer.aspx?year=9000&issue=00000&article=99916&type=abstract. Accessed 9th July 2011.

Newby LK, Allen LaPointe NM, Chen AY, et al. 2006. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. 113; 203-212.

NICE. 2006. *Statins for the prevention of cardiovascular events*. Technology appraisal 94. Online. Available from: http://www.nice.org.uk/TA094. Accessed 23rd Nov 2011.

NICE. 2007. MI: secondary prevention - Secondary prevention in primary and secondary care for patients following a myocardial infarction. Clinical Guideline 48. Online. Available from: http://guidance.nice.org.uk/CG48. Accessed 23rd Nov 2011.

NICE. 2009. *Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence*. Clinical Guideline 76. Online. Available from http://www.nice.org.uk/Guidance/CG76. Accessed 23rd March 2011.

NICE. 2011. *Management of stable angina*. Clinical Guideline 126. Online. Available from: http://www.nice.org.uk/guidance/CG126. Accessed 23rd Nov 2011.

Norman G. 2010. Likert scales, levels of measurement and the ''laws'' of statistics. *Advances in Health Sciences Education* 15:625–632.

ONS - Office of National Statistics. 2011. *Population Estimates by Ethnic Group 2002 – 2009*. Online. Available from www.ons.gov.uk. Accessed 15th April 2012.

Osterberg L & T Blaschke. 2005. Adherence to Medication. *N Engl J Med* 353; 487-497.

Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al. 2004. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *J Acquir Immune Defic Syndr* 36(5); 1100-1102.

Ozkan O, Odabasi J, and U Ozcan. 2008. Expected treatment benefits of percutaneous transluminal coronary angioplasty: the patient's perspective. *Int J Cardiovasc Imaging* 24; 567-575.

Prado-Aguilar CA, Martínez YV, Segovia-Bernal Y, et al. 2009. Performance of two questionnaires to measure treatment adherence in patients with Type-2 Diabetes. *BMC Public Health* 9:38.

PSNC - Pharmaceutical Services Negotiating Committee. 2011. *Changes to the pharmacy contract 2011/12*. Online. Available from: www.psnc.org.uk. Accessed 21st April 2012.

Rand CS & RA Wise. 1994. Measuring adherence to asthma medication regimens. *Am J Resp Crit Care Med* 149; S69-76.

Rasmussen JN, Chong A and DA Alter. 2007. Relationship between adherence to evidence based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA*. 297: 177-186.

Rathore SS, Mehta RH, Wang Y, et al. 2003. Effects of age on the quality of care provided to older patients with acute myocardial infarction. *Am J Med* 114; 307–315. Recommendations: Results from the Medical Outcomes Study. *Journal of Behavioral Medicine* 15(5); 447-468.

Raynor DK, Blenkinsopp A, Knapp P, et al. 2007. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. *Health Technol Assess* 11(5); 1–160.

Rolley JX, Davidson PM, Dennison CR, et al. 2008. Medication Adherence – Self Report Instruments. Implications for Practice and Research. *J Card Nursing* 23(6); 497-505.

Rolnick S, Bruzek R, Pawloski P, et al. 2011. PS2-33: Patient Characteristics Associated with Medication Adherence. *Clinical Medicine & Research* 9(3-4) 158

Ross S, Walker A and MJ MacLeod. 2004. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. *Journal of Human Hypertension* 18; 607 – 613.

Roter DL, Hall JA, Merisca R, et al. 1998. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Medical Care* 36(8); 1138-1161.

Rudd P, Ramesh J, Bryant-Kosling C, et al. 1993. Gaps in cardiovascular medication taking: the tip of the iceberg. *J Gen Intern Med* 8(12); 659-666.

Sainsbury P, Zamvar D, Hall AS, et al. 2005. The elevation of biomarkers of myocardial injury in patients undergoing Percutaneous Coronary Intervention (PCI). Protocol Version 4. The OPERA Study Protocol. Cardiovascular Research Unit, Leeds Teaching Hospitals NHS Trust.

Sainz I, Amaya J, and M Garcia. 2004. Erectile dysfunction in heart disease patients. *International Journal of Impotence Research* 16; S13–S17.

Sakthong P, Chabunthom R and R Charoenvisuthiwongs. 2009. Psychometric Properties of the Thai Version of the 8-item Morisky Medication Adherence Scale in Patients with Type 2 Diabetes. *Ann Pharmacother* 43; 950-957.

Samani NJ, Burton P, Mangino M, et al. 2005. A Genomewide Linkage Study of 1,933 Families Affected by Premature Coronary Artery Disease: The British Heart Foundation (BHF) Family Heart Study. *Am J Hum Genet* 77; 1011–1020

Schafheutle EI. 2009. The impact of prescription charges on asthma patients is uneven and unpredictable: evidence from qualitative interviews. *Prim Care Respir J* 18(4); 266-272.

Schafheutle EI, Hassell K, and Noyce PR. 2004. Coping with prescription charges in the UK. *Int J Pharm Pract* 12; 239-246.

SEPHO (South East Public Health Observatory). 2011. *Cardiovascular disease network health profile – West Yorkshire*. Online. Available from: www.sepho.org.uk. Accessed 11th April 2012.

Shalansky SJ & AR Levy. 2002. Effect of Number of Medications on Cardiovascular Therapy Adherence. *Ann Pharmacother* 36; 1532-1539.

Shalansky SJ, Levy AR and AP Ignaszewski. 2004. Self-reported Morisky score for identifying nonadherence with cardiovascular medications. *Ann Pharmacother* 38:1363–1368.

Sherbourne CD, Hays RD, Ordway L, et al. 1992. Antecedents of Adherence to Medical Recommendations: Results from the Medical Outcomes Study. Journal of Behavioral Medicine 15(5); 447-468.

Shi L, Liu J, Fonseca V, et al. 2010. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health Qual Life Outcomes* 8:99.

Shi L, Liu J, Koleva Y, et al. 2010a. Concordance of Adherence Measurement Using Self-Reported Adherence Questionnaires and Medication Monitoring Devices. *Pharmacoeconomics* 28(12); 1097-1107.

Silcock J & C Standage. 2007. Exploring patient adherence to cardiovascular medicines. *British Journal of Cardiac Nursing* 2(5); 223 – 228.

Simoni JM, Kurth AE, Pearson CR, et al. 2006. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behav* 10; 227-245.

Smith FJ. 2010. *Conducting Your Pharmacy Practice Research Project*. 2nd Edition. London: Pharmaceutical Press.

Steiner JF & AV Prochazka. 1997. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 50; 105-116.

Sung JC, Nichol MB, Venturini F, et al. 1998. Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. *American Journal of Managed Care*, 4; 1421–1430.

Svarstad BL, Chewning BA, Sleath BL, et al. 1999. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient Educ Couns* 37(2); 113-124.

Teo KK, Mitchell LB, Pogue J et al. 2004. Effect of ramipril in reducing sudden deaths and nonfatal cardiac arrests in high-risk individuals without heart failure or left ventricular dysfunction. *Circulation* 110(11); 1413-1417.

The Health and Social Care Information Centre. 2010. Hospital Prescribing, England: 2010. Online. Available from www.ic.nhs.uk. Accessed 2nd Nov 2011.

The Health and Social Care Information Centre. 2011. Number of prescription items dispensed in England rises by nearly 70 per cent in a decade, report shows. Available from: www.ic.nhs.uk. Accessed 2nd Nov 2011.

Trueman P, Lowson K, Blighe A, et al. 2010. *Evaluation of the scale, causes and costs of waste medicines: final report*. York: University of York.

UKCRN - United Kingdom Clinical Research Network. 2012. EMMACE-3. Online. Available from: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=9102. Accessed 22nd April 2012.

Unal B, Critchley J and S Capewell. 2004. Explaining the decline in coronary heart disease mortality in England and Wales, 1981–2000. *Circulation* 109; 1101- 1107.

Unni EJ & Farris KB. 2011. Unintentional non-adherence and belief in medicines in older adults. *Patient Education and Counseling* 83(2); 265-268.

Voils CI, Hoyle RH, Thorpe CT, et al. 2011. VARIANCE AND DISSENT - Improving the measurement of self-reported medication nonadherence. *Journal of Clinical Epidemiology* 64; 250-254.

Walliman N. 2011. Research methods: the basics. London: Routledge.

Wetzels G, Nelemans P, van Wijk B, et al. 2006. Determinants of poor adherence in hypertensive patients: Development and validation of the ‘‘Maastricht Utrecht Adherence in Hypertension (MUAH)-questionnaire’’. Patient Education and Counselling 64; 151–158.

WHO. 2003. *Adherence to Long-term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf. Accessed 17th Feb 2011.

Wu JY, Leung WY, Chang S, et al. 2006. Effectiveness of telephone counselling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomised controlled trial. *BMJ*, doi:10.1136/bmj.38905.447118.2F (published 17 August 2006). Online. Available from: http://www.bmj.com/cgi/reprint/333/7567/522. Accessed 9th July 2011.

Zeller A, Ramseier E, Teagtmeyer A, et al. 2008. Patients' Self-Reported Adherence to Cardiovascular Medication Using Electronic Monitors as Comparators. *Hypertension Research* 31; 2037–2043.

Zeller A, Schroeder K and TJ Peters. 2008a. An adherence self-report questionnaire facilitated the differentiation between nonadherence and nonresponse to antihypertensive treatment. *Journal of Clinical Epidemiology* 61; 282 – 288.

Zimmerman FH, Fass AE, Katz DR, et al. 2009. Nitroglycerin Prescription and Potency in Patients Participating in Exercise-Based Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation & Prevention* 29(6); 376 – 379.

7 Appendices

Appendix 1 – Summary of Some of the Self-report Adherence Assessment Tools

Appendix 2 – The Heart Medicines Survey

Appendix 3 – Protocol for the RANI-1 study

Appendix 4 – Consent form

Appendix 5 – Covering letter

Appendix 6 – Patient information leaflet

Appendix 7 – GP letter

Appendix 8 – NHS R&D and REC application forms

Appendix 9 – Letters of approval

Appendix 10 – Thank you letter

Appendix 11 – The RANI-1 *Microsoft Access®* Database

Appendix 12 – Level 1 Medicines Review

Appendix 13 – Leaflets Designed for Participants in RANI-1 Study

Appendix 14 – Agreements with Authors of Adherence Assessment Tools

Appendix 15 – Statistical Tools and Principles Used

Appendix 16 – Detailed Results and Additional Statistical Tests