Achievement of Secondary Prevention Goals 6 to 9 months after Acute Coronary Syndrome – a Retrospective, Cross-Sectional Analysis

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DECLARATION

I, Bradley Paul Griffiths, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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ABSTRACT

Study Rationale

Good evidence exists to support the use of secondary prevention medications (aspirin, HMG-CoA reductase inhibitors [statins], beta-blockers and angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) and smoking cessation in patients after acute coronary syndromes. At present, little is known about adherence to medication and smoking behaviour after discharge in South Africa. This information is essential to optimising both in-patient care and post-discharge planning of these patients.

Methods

We conducted a cross sectional analysis of all patients discharged from the Groote Schuur Hospital Coronary Care Unit with a diagnosis of acute coronary syndrome between 15 November 2011 and 15 April 2012. A follow up telephone call was performed 6 to 9 months after discharge, and a standardized questionnaire completed detailing current medication use, reasons for non-adherence, and smoking status at time of the interview.

Results

Prescribing of secondary prevention medications at discharge was found to be high (aspirin 94.5%, statins 95.7%, beta blockers 85.4%, ACEIs/ARBs 85.9%), and 70.7% of patients were discharged on a combination of all 4 drugs. At 6 to 9 month follow-up, the proportion of patients using these medications had reduced by 8.9% for aspirin, 10.1% for statins, 6.2% for beta-blockers and 17.9% for ACEIs/ARBs. Only 47.2% remained on all 4 drugs, a reduction of 23.5%. Of the 56% of patients who were smokers on admission to hospital, 31% had stopped smoking at the time of interview.

Conclusions

Despite high rates of pre-discharge prescription of recommended therapy following admissions for acute coronary syndromes, we observed a significant decline in adherence rates 6 to 9 months post discharge and a poor rate of

smoking cessation. An exploration of possible reasons for these findings suggests that efforts to educate patients about the importance of long-term adherence need to be improved. Furthermore, more effective interventions are needed to improve smoking cessation than in-hospital reminders about the hazards of smoking.

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ABBREVIATIONS

ACC – American College of Cardiology
ACS – Acute coronary syndrome
ACEI – Angiotensin converting enzyme inhibitor
AHA – American Heart Association
AIDS – Acquired immunodeficiency syndrome
ARB – Angiotensin receptor blockers
ARV - Antiretroviral
BB – Beta-blocker
CCU – Coronary care unit
CPACS – Clinical Pathways for Acute Coronary Syndromes in China
ESC – European Society of Cardiology
GRACE – Global Registry of Acute Coronary Events
GSH – Groote Schuur Hospital
HIV – Human immunodeficiency virus
HMG-CoA - 3-hydroxy-3-methylglutaryl coenzyme A
IHD – Ischaemic heart disease
LL – Lipid lowering medication
MAINTAIN – Medication Applied and Sustained Over Time
MEMS – Medication event monitoring systems
MI – Myocardial infarction
MMAS – Morisky Medication Adherence Scale
NCD – Non-communicable disease
NICE – National Institute for Health and Clinical Excellence
NSTEMI – Non-ST-elevation myocardial infarction
OASIS – Organisation to Assess Strategies in Acute Ischaemic Syndromes
PCI – Percutaneous coronary intervention
PURE – Prospective Rural Epidemiological
SRQ – Self-reported questionnaire
STEMI – ST-elevation myocardial infarction
UA(P) – Unstable angina (pectoris)
UCT – University of Cape Town

USA – United States of America

WHO – World Health Organisation

PART A: PROTOCOL

Title: Achievement of secondary prevention goals 6 to 9 months after acute coronary syndrome – a retrospective, cross-sectional analysis

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Problem

The use of evidence-based medicines (aspirin, statin, ACE-inhibitor, beta-blocker), and cessation of smoking after acute coronary syndrome (ACS) is known to reduce adverse outcomes[1-5], yet attainment of these goals in patients after discharge is often disappointing[6-9]. The reasons for this are complex and vary according to the population studied[10-11].

Justification

Preventable adverse outcomes after ACS, particularly repeat admissions to hospital and reduction in functional capacity, lead to increased strain on already overburdened healthcare and social welfare systems. The simple interventions of medication adherence and smoking cessation can lead to a reduction of this burden.

Objective

To assess the self-reported adherence of patients discharged from the Groote Schuur Hospital Coronary Care Unit (GSH CCU) with a diagnosis of ACS to prescribed discharge medication, as well as self-reported smoking status, at 6 to 9 months post-discharge.

Secondary objectives

To identify factors that may be responsible for poor attainment of these goals.

Methodology

Study design: Cross-sectional, analytical study, with retrospective subject identification.

Subject selection: Medical record analysis to include all patients discharged alive from the GSH CCU 6 to 9 months previously with a diagnosis of ACS. This time frame may need to be extended to enroll more patients if numbers are insufficient for statistical significance.

Measurement: Data collection will take place in the form of a standardized questionnaire populated by retrospective data collected from the medical record, specifically:

- Demographics
- ACS diagnosis (UA/NSTEMI/STEMI) and in-hospital management
- Comorbidities
- Factors which will be compared in telephonic interview pertaining to secondary prevention goals:
    - Admission medication
    - Admission smoking status

Further data collection in the form of a telephonic interview will then be performed to ascertain achievement of secondary prevention goals, specifically:

- Medication use
- Reason(s) for non-compliance (if relevant)
- Smoking status

The specific wording of the questions is attached (Appendix 1). These will be piloted on similar subjects who fall outside the research time frame, and minor changes may be made prior to formal data collection. A sample data capture sheet is attached (Appendix 2).

Ethics

A full explanation of the nature of the study will be given to the subject at the beginning of the telephonic interview. This will leave no confusion as to the role of the interviewer as data-capturer rather than health service provider. Each subject will then be given the opportunity to give verbal informed consent, or withdraw from the interview if they so wish.

If behavior hazardous to health is picked up in the interview (ongoing smoking, medication non-adherence), the subject will be encouraged to alter this behavior at the end of the interview.

Anonymity will be maintained by writing the name of the subject only on the hand written data capture sheet. Subject identification in electronic capture will be by way of a coding system. Hand written data capture sheets will be accessible only to the Principal Investigator.

Analysis

Data analysis will be performed in conjunction with Dr Maia Lesosky from the Department of Internal Medicine, looking specifically at medication adherence and smoking.

Reporting and Implementation

The results of the study will be presented to the Department of Cardiology in the appropriate forum. Publication will be attempted in a reputable journal.

Funding

Costs directly related to the study, such as telephone calls, will be covered by a R5000 grant from the Department of Internal Medicine. Spending will be documented and any excess funds returned to the department.

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PART B: STRUCTURED LITERATURE REVIEW

Objectives

The objectives of this literature review are:

- To provide an overview of the burden of ischemic heart disease (IHD) in South Africa (SA) and its contribution to morbidity and mortality
- To provide an overview of the importance of secondary prevention medication after recent acute coronary syndrome (ACS)
- To provide an overview of the importance of smoking cessation in patients with a recent ACS
- To provide an overview of what is known about patient and non-patient factors that influence adherence to medication
- To identify the different methods available to measure medication adherence rates and how best to use them in a research setting
- To identify the different methods available to measure smoking cessation rates and how best to use them in a research setting
- To explore what is known about medication adherence in patients after ACS in SA
- To explore what is known about smoking cessation rates in patients after ACS in SA

Literature Search Strategy

PubMed and Google Scholar were searched using a combination of the following terms: ‘acute coronary syndrome’, ‘ischaemic heart disease’, ‘coronary artery disease’, ‘burden of disease’, ‘South Africa’, ‘Sub-Saharan Africa’, ‘secondary prevention’, ‘medication’, ‘adherence’, ‘smoking’ and ‘cessation’. Studies referenced from the articles found in the initial search were also reviewed for relevance and inclusion in the literature review. Articles were accessed through the UCT Medical Library *ezproxy* service.

Inclusion and Exclusion Criteria

Preference was given to English articles published in peer-reviewed journals providing the most recent, comprehensive, and up to date data on the listed objectives. Specific emphasis was placed on data from South Africa, or countries with similar income profiles where data from South Africa was not available. Where available, meta-analyses combining the largest evidence base were used.

Studies not in English and not published in peer-reviewed journals were not considered for inclusion in this literature review.

Summary of the Literature

Burden of Disease

In the first national burden of disease study in 2000, IHD was found to be the single leading cause of death in the Western Cape (12%), followed by stroke (8.8%) and HIV/AIDS (8.4%), and deaths from non-communicable diseases (NCDs) accounted for a larger proportion of deaths in the Western Cape (58%) when compared to the rest of South Africa (38%)[1]. In a subsequent study, mortality from IHD in Cape Town was found to be very similar to HIV/AIDS (76 vs. 83 deaths per 100 000 population, respectively), and IHD featured as the leading cause of death from NCDs[2]. We are awaiting the full data from the second national burden of disease study, but initial estimates show a downward trend in mortality from HIV/AIDS due to the extensive antiretroviral (ARV) rollout[3]. With this in mind we can expect an even higher contribution of non-communicable diseases to overall mortality.

Two studies looking at the prevalence of IHD in Sub-Saharan Africa both came to the conclusion that good epidemiological evidence is lacking, and current evidence suggests the prevalence of IHD to be low compared to cerebrovascular disease and other causes of heart disease[4,5]. Despite this, it is accepted that with the epidemiologic transition from developing to developed countries we can expect a higher incidence of NCDs, particularly IHD and cerebrovascular disease, in future. This is mainly attributed to high-fat diet, tobacco smoking and sedentary lifestyles[6]. It is predicted that NCD's will become the leading cause of death in Africa by 2030[7], and this view is

supported by World Health Organisation (WHO) predictions that the highest rate of increase of NCDs in the next decade will be in Africa[8].

It is thus evident from the literature that IHD is a considerable health burden in the Western Cape Province of South Africa, and we can expect the burden of disease in other provinces of South Africa and other African countries to increase as these areas become more developed and mortality from HIV infection is reduced.

Importance of Secondary Prevention Medication after Acute Coronary Syndrome:

Acetylsalicylic acid (aspirin) as antiplatelet therapy is proven to confer a survival benefit in patients with ACS[9]. Treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) not only lowers lipid levels, but also has beneficial effects on platelet adhesion, thrombosis, endothelial function, inflammation, and plaque stability, providing mortality and morbidity reduction after ACS beyond what is expected for the degree of lipid reduction alone[10]. Beta-blockers (BB) act by competitively blocking the effects of catecholamines on cell membrane beta-receptors, and have been proven to reduce mortality in patients with ACS with compensated heart failure and left ventricular dysfunction[11], and those undergoing percutaneous coronary intervention (PCI)[12]. Angiotensin converting enzyme inhibitors (ACEIs) have been shown to reduce 30-day mortality after ACS[13] and confer long-term reduction in vascular events in patients with atherosclerosis[14].

In a trial of 1358 patients with acute coronary syndromes discharged consecutively from a single institution, the use of combination therapy with aspirin, statins, BBs and ACEIs or angiotensin receptor blockers (ARBs) was independently and strongly associated with a 72% to 87% reduction in 6-month mortality[15]. Another trial of 1521 patients discharged after ACS on aspirin, beta-blockers and statins showed a reduction in 1-year survival from 97.7% to 88.5% in those discontinuing all medication after 1 month[16]. Three other trials have also demonstrated a relationship between discontinuation of evidence based combination therapy after ACS and increased mortality[17-19].

This and other evidence has led the European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA)

guidelines to recommend that aspirin, statin and BB therapy should be initiated and continued indefinitely after acute coronary syndrome, and ACEI or ARB therapy should be considered in all patients unless contraindicated[20-22]. Thienopyridine therapy for 12 months is also recommended in these guidelines but was not yet available for all patients at our institution at the time of the study.

Importance of Smoking Cessation after Acute Coronary Syndrome:

Cigarette smoking is a well-established risk factor for the development of cardiovascular disease[23]. Smoking cessation in patients with established coronary artery disease has been studied to determine if this is of benefit in the secondary prevention of ischaemic coronary events and death.

Two studies from Israel looked at the effect of smoking cessation and long-term mortality in patients with IHD. The first looked at 3122 patients with established coronary artery disease and found a significant increase in sudden cardiac death (8.1% vs. 4.6%) and all cause mortality (24.9% vs. 14.9%) in ongoing smokers when compared to non-smokers. Quitting smoking reduced this risk to that comparable with non-smokers over an 8-year period[24]. The second, a population-based cohort study, followed 1521 patients after first MI and found that smoking cessation after the acute event led to a significant mortality reduction over a 13 year period compared to ongoing smoking (HR 0.63; 95% CI 0.48 – 0.82). On multivariable adjustment they also found the intensity of smoking to be directly linked to mortality, with a reduction of 5 cigarettes per day in those who continued to smoke leading to an 18% (95% CI 9% to 25%) decline in mortality risk over the same period[25].

Two studies have looked at the short- to medium-term effect of smoking cessation after ACS. A study of 18 809 patients from 41 countries enrolled in the Organization to Assess Strategies in Acute Ischaemic Syndromes (OASIS) 5 trial found that quitting smoking after an episode of unstable angina or non-ST elevation myocardial infarction (NSTEMI) resulted in a significantly reduced risk of subsequent myocardial infarction within 6 months compared to ongoing smokers (OR 0.57; 95% CI 0.36 – 0.89)[26]. Another study of 1206 patients enrolled in in-patient cardiac rehabilitation programs after ACS at 2 sites in Germany found a dose-response relationship between smoking after ACS and occurrence of secondary cardiovascular event (death due to cardiovascular

disease, non-fatal MI, ischaemic cerebrovascular event or coronary revascularization procedure) within 1 year[27].
A systematic review looking specifically at the mortality risk reduction associated with smoking cessation in patients with coronary artery disease (unstable angina [UA], previous MI or chronic stable angina) found an overall risk reduction of 36% when compared to ongoing smoking in the 20 studies assessed. This appeared relatively consistent between the studies, regardless of the type of index cardiac event or years in which the study was conducted[28].
It is thus clear from current evidence that smoking cessation after ACS confers a significant survival benefit and reduces the incidence of repeat coronary events.

Factors that Influence Adherence to Medication:

The reasons for poor medication adherence are often multifactorial. The World Health Organization (WHO) has categorized potential reasons for medication non-adherence into 5 broad groups, including patient, condition, therapy, socioeconomic and health system-related factors[29].
Patient factors include younger age, nonwhite race, and depression. Conditions that are asymptomatic or chronic in nature that require long-term therapy, and therapy-related factors including regimen complexity and medication side effects, are shown to have a higher rate of non-adherence. Lower education level and low health literacy are socioeconomic factors that also correlate with poor adherence[30].
Healthcare system factors also have a significant role to play in medication adherence in chronic illness. Problems identified include patients not being able to list their medication at hospital discharge[31], discrepancies between pre-hospital, discharge, and post-hospital medication regimens[32], and care providers not asking directly about medication taking at scheduled visits[33].
The vast majority of publications in South Africa looking at adherence to medication is in the setting of tuberculosis and antiretroviral medication for HIV infection. A study looking at general medication adherence in the context of the South African primary health care system found that socioeconomic factors, specifically low income and competing demands for time, and psychological

factors, such as social support and health literacy, are important factors that play significant roles in adherence to medication in our setting[34].

Measuring Medication Adherence:

Adherence to a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. The methods available for measuring adherence can be broken down into direct and indirect[35]. Examples of direct measurements are directly observed therapy, measurement of a drug or its metabolite in body fluid, or measurement of a biological marker added to the drug formulation. Although more robust than indirect methods, these direct methods are expensive, time-consuming and still susceptible to distortion by the patient, for example by hiding pills in the mouth and discarding later. Indirect methods of measurement of adherence include self-report (interview, questionnaire or medication diary), assessment of clinical response, pill counts, ascertaining pharmacy refill rates and electronic medication monitors. Each method has advantages and disadvantages (Table 1), and no method is considered the gold standard[36].

A systematic review of the literature looking at the suitability of measures of self-reported medication adherence found 58 different self-reported measures of adherence and concluded that there is a need for a single measure in the routine continual monitoring of adherence[37]. Self-reported questionnaires (SRQs) were found to have moderate to high concordance with electronic measures in 12 of 16 comparisons (75%) in one review, and this was found to be superior to interview-based self-reports[38]. A recent meta-analysis found moderate correlation between SRQs and electronic medication event monitoring systems (MEMS)[39]. The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines have identified that while other measures of adherence are appropriate for clinical trials of new drugs, self-report is an appropriate tool for clinical practice[40].

Measuring Smoking Cessation Rates:

Cotinine is the major metabolite of nicotine and can be measured in various biological specimens including plasma, saliva and urine. As a biomarker it is highly sensitive and specific for tobacco use in the absence of nicotine

replacement therapy, and is recommended as the best biomarker to confirm reported smoking cessation[41]. A systematic review of 67 studies looking at the relationship between self-reported smoking and cotinine-assessed smoking status found that self-report tended to underestimate smoking rates, and this was probably due to social desirability bias. However there was considerable variability between the population group studied and the medium in which the biological sample was measured[42].

We could find two studies looking specifically at the accuracy of self-reported smoking status in patients with coronary artery disease. A study from Scotland compared the validity of self-reported smoking status in 665 patients with ACS at the time of admission with members of the general public. On univariate analysis, the percentage of “smoking deceivers” (self-reported non-smokers but serum cotinine levels more than 12ng/ml) in the ACS and general public group were similar (11% vs. 12%), but following adjustment for age, sex and exposure to environmental tobacco smoke, ACS patients were more likely to misclassify themselves (OR 14.06, 95% CI 2.12-93.01, p=0.006). The probability of misclassification was found to fall significantly with increasing age in the ACS group[43]. A study from a single tertiary centre in Sweden assessed smoking biomarkers in 260 self-reported previous smokers who had previously been admitted with an ischaemic event and were following up at a routine nurse-run secondary prevention clinic. They found a good correlation between self-reported smoking status and biochemical validation, with only 17 patients (6.5%) testing positive for exhaled carbon monoxide or serum cotinine when claiming to be non-smokers[44].

It is thus evident from the literature that the ideal method of assessing smoking status in medical research is with biochemical validation with cotinine measurement. However, this method comes with a time and cost burden that makes it difficult to use in large population-based studies, or studies with limited funding. Self-report generally underestimates smoking rates, however in patients with coronary artery disease at least one study suggests that this under-reporting may be reasonably low.

Adherence to Secondary Prevention Medication after Acute Coronary Syndrome in South Africa:

There were no published studies looking specifically at the adherence to secondary prevention medication after ACS in South Africa. The best data available to us comes from the Prospective Rural Epidemiological (PURE) study, where use of secondary prevention medication in patients with any given history of coronary artery disease (myocardial infarction [MI], coronary artery bypass grafting or PCI) was assessed in countries grouped according to stage of economic development. South Africa was grouped with 6 other upper middle-income countries as per the World Bank Country Classifications[45]. In this group, usage of secondary prevention medications in patients with coronary artery disease was low: 27.1% for antiplatelet agents, 31% for BB, 30.9% for ACEI/ARB and 21.1% for statins. These figures were even lower when Africa as a whole was compared to other countries (antiplatelet agents 3.4%, BB 1.9%, ACEI/ARB 6.8%, statins 1.4%)[46].

Usage of secondary prevention medication after ACS has been assessed in studies from countries other than South Africa. A long-term follow up study of 31 750 patients from discharged from a single centre in the USA after having undergone a cardiac procedure for ACS showed usage rates of 56% for aspirin, 32.8% for BB, 18.3% for ACEI/ARB and 31.5% for lipid lowering medication (LL) over a 7 year period[47]. A study of from France using a pharmacy database to assess medication adherence of 11604 patients at 30 months after acute coronary syndrome found adherence rates of 81.7% for aspirin, 68% for BB, 77.3% for ACEI/ARB and 76% for statins[48].

We found 5 studies looking specifically at the adherence rates to secondary prevention medication after ACS in the 3 to 12 month period after discharge from hospital[49-53]. Eagle et al researchers completed a telephonic questionnaire at 6 months of 13 830 patients from the Global Registry of Acute Coronary Events (GRACE) database. They found adherence rates of 92.7% for aspirin, 87.7% for BB, 80.2% for ACEI/ARB and 87.3% for lipid lowering agents (LL) [49]. Yufang et al performed a telephonic interview at 6 months after ACS in 2521 patients recruited into the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. They found adherence rates of 95.1% for aspirin, more than 100% for BB (due to BB being added in the period between discharge and interview), 89.4% for ACEI/ARB and 81.8% for LL[50]. Melloni et al followed up 1077 patients from the Medication Applied and Sustained Over

Time (MAINTAIN) database with a telephonic questionnaire at 3 months. They found adherence rates of 93.4% for aspirin, 89.9% for BB, 83.1% for ACEI/ARB and 88.8% for LL[51]. A small trial from a single centre in the USA performed telephonic interviews of 208 patients 6 to 12 months after ACS and found adherence rates of 92.2% for aspirin, 88.6% for BB, 93% for ACEI/ARB and 91.7% for LL[52]. Results of these 4 studies[49-52] can be found in Table 2. Rates of prescribing of secondary prevention medication at discharge in these studies vary significantly and must be interpreted in the context of the time during which the patients were treated for ACS. There has been significant advancement in evidence for secondary prevention therapy after ACS in the last 2 decades, and this is reflected in the gradual increase in prescribing rates of these medications in more recent years.

A recent study from Malaysia had 190 patients at routine 6 month follow up appointments after ACS complete a standardized questionnaire assessing adherence with the Morisky Medication Adherence Scale (MMAS). They found only 18.4% of patients reporting a high level of adherence to secondary prevention medication, while 51.1% reported medium adherence, and 30.5% low adherence[53].

We found another 2 studies looking at usage of medication in the 3 to 6 month period after ACS, but not giving prescribing rates at discharge, therefore not allowing us to assess adherence rates[54,55]. A multi-centre study from the USA assessed 1135 patients using a pharmacy database 3 months after ACS, and found the percentage of patients filling out at least one prescription for medication to be 63.9% for BB, 51.8% for ACEI/ARB and 62.6% for statins. There was no record of aspirin use[54]. A very big study from Finland looked at the filling of prescriptions after ACS for 53 353 patients using a countrywide pharmacy database found that in the time period of 1 to 90 days after discharge, 85% of patients filled prescriptions for BB, and 72% for LL. This dropped to 75% for BB and 66% for LL at 91-180 days[55].

It is thus evident from the literature that prescribing rates at discharge of secondary prevention medication vary depending on the area or centre in which the study took place and the time frame in which data was collected. Adherence rates for each medication varies between 80.2% and 100% in the studied

populations. Data from South Africa looking at adherence rates after ACS is lacking.

Smoking Cessation Rates after Acute Coronary Syndrome in South Africa:
There are no published studies looking specifically at smoking cessation rates after ACS in South Africa. Evidence from the PURE study shows a clear link between smoking cessation after coronary heart disease or stroke event, and country income category, with cessation rates highest in upper income countries, and decreasing along with income category of the country. The smoking cessation rate in upper-middle-income countries, into which group South Africa is included, was found to be 54.6%[56]. Published smoking cessation rates after ACS vary between 33% and 69.9%[26,57-60]. In each of these studies there is significant variability in cessation rates according to age, gender, income category and other factors. It is clear from 2 of the studies that the majority of smoking relapses occur within the first month after the event[26,59].

Need for Further Research:
There were no published studies looking specifically at the use of secondary prevention medication and smoking cessation rates after acute coronary syndrome in South Africa. We have identified this as an important gap in our knowledge and structured our study to address this need.

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Tables and Figures:

Table 1: Methods of Measuring Adherence*

Test	Advantages	Disadvantages
Direct Methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect Methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g. pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; required return visits and downloading data from medication vials
Measurement of physiologic markers (e.g heart rate in patients taking beta-blockers)	Often easy to perfrom	Marker may be absent for other reasons (e.g. increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

* Reproduced from: Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005 Aug 4;353(5):487-97

Table 2: Comparison of Discharge Prescribing and Adherence rates Between 4 Studies

Study	Eagle et al *			Yufang et al †			Melloni et al ‡			Sud et al §		
	DC	FU	AR	DC	FU	AR	DC	FU	AR	DC	FU	AR
Aspirin	90.1	82.9	92	92.7	88.2	95.1	93.4	87.2	93.4	94.7	87.3	92.2
BB	56	49.1	87.7	70	71.8	100	91.2	82	89.9	90.3	80	88.6
ACEI/ARB	17.2	13.8	80.2	75.6	67.6	89.4	69.2	57.5	83.1	71	66	93
LL	45.7	39.9	87.3	80.4	65.8	81.8	89.9	79.8	88.8	83.3	76.4	91.7

All numbers are percentages, DC = Medication use at discharge, FU = Medication use at follow up, AR = Adherence rate

* Eagle et al. Adherence to Evidence-Based Therapies after Discharge for Acute Coronary Syndrome: An Ongoing Prospective, Observational Study. Am J Med. 2004;117:73-81

† Yufang Bi et al. Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: Results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. Am Heart J 2009;157(3):509-516

‡ Melloni C et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. Am J Cardiol. 2009 Jul 15;104(2):175-81

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PART C: MANUSCRIPT

Achievement of Secondary Prevention Goals 6 to 9 months after Acute Coronary Syndrome – a Retrospective, Cross-Sectional Analysis

Bradley Griffiths, MBChB, Maia Lesosky, PhD, Mpiko Ntsekhe, MD PhD

Abstract

Background. Good evidence exists to support the use of secondary prevention medications (aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) and smoking cessation in patients after acute coronary syndromes (ACSs). Little is currently known about adherence to medication and smoking behaviour after discharge in South Africa.

Methods. We conducted a cross-sectional analysis of all patients with a diagnosis of ACS discharged from the Coronary Care Unit at Groote Schuur Hospital, Cape Town, between 15 November 2011 and 15 April 2012. Patients were telephoned 6 - 9 months after discharge and completed a standardised questionnaire detailing current medication use, reasons for non-adherence, and smoking status.

Results. Prescribing of secondary prevention medications at discharge was high (aspirin 94.5%, statins 95.7%, beta-blockers 85.4%, ACEIs/ARBs 85.9%), and 70.7% of patients were discharged on a combination of all four drugs. At 6 - 9-month follow-up, the proportion using these medications had dropped by 8.9% for aspirin, 10.1% for statins, 6.2% for beta-blockers and 17.9% for ACEIs/ARBs. Only 47.2% remained on all four drugs, a reduction of 23.5%. Of the 56.0% of patients who were smokers, 31.4% had stopped smoking.

Conclusions. A significant decline in adherence to recommended therapy 6 - 9 months after discharge and a poor rate of smoking cessation suggest that efforts to educate patients about the importance of long-term adherence need to be improved. Furthermore, more effective interventions than in-hospital reminders about the hazards of smoking are needed to improve smoking cessation.

Introduction

The incidence of ischaemic heart disease (IHD) is on the rise in Africa. Recent projections suggest that by 2030 non-communicable diseases (NCDs) will become a leading cause of death on the continent, surpassing HIV/AIDS.[1] In the South African National Burden of Disease Study in 2000,[2] IHD was found to be the largest single cause of death in the Western Cape Province (12%), followed by stroke (8.8%) and HIV/AIDS (8.4%), and non-communicable diseases accounted for a larger proportion of deaths in the Western Cape (58%) than in the rest of South Africa (SA) (38%). In a subsequent study,[3] mortality from IHD in Cape Town was found to be very similar to HIV/AIDS (76 v. 83 deaths per 100 000 population, respectively), and IHD featured as the leading cause of death from non-communicable diseases. The Second National Burden of Disease Study is nearing completion and will give us more current data on mortality trends. The epidemiological transition of cardiovascular disease described by Yusuf *et al*.[4] suggests that with progression from under-development to industrialisation we can expect an increasing burden of degenerative disease, particularly IHD and stroke.

The use of evidence-based optimal medical therapy (dual antiplatelet therapy, statins, beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) after acute coronary syndrome (ACS) is known to reduce 6-month mortality by up to 87%.[5] Patients who continue to smoke after an ACS have a significantly increased risk of a future acute myocardial infarction (MI) compared with those who quit.[6] Furthermore, smoking in the presence of established IHD is associated with a significantly increased risk of death, including sudden cardiac death. Over an 8-year period, smoking cessation reduces this risk to levels comparable to that for people who have never smoked.[7] Despite this, medication adherence and smoking cessation in patients after discharge is often disappointing.[6-9] Results from the Prospective Urban Rural Epidemiology (PURE) study suggest that in SA, and in countries with similar income profiles, use of these medicines in patients with coronary heart disease at a median follow-up period of 4 years varies between 21.1% and 31%, compared with 46.5% and 70.9% for upper-income countries.

These figures are even lower when Africa as a whole is compared with other areas.[10] The reasons for medication discontinuation are diverse, and include high cost of obtaining medicine, high pill burden and lower level of education.[11] To date there are no published SA data on the medium- to long-term (>6 months) use of secondary prevention medication and smoking cessation among patients discharged from hospital after an ACS. We designed this cross-sectional study to assess the continued use of four selected drug classes and rates of smoking cessation at a follow-up period of 6 - 9 months post discharge after an ACS.

Methods

Study design

Cross-sectional analysis with retrospective subject identification.

Study population

Groote Schuur Hospital is an 893-bed state-funded tertiary hospital in Cape Town, SA. It has a 6-bed coronary care unit (CCU) and a cardiac catheterisation laboratory. Patients who are admitted to the CCU either present directly to the emergency unit or are referred from secondary-level institutions. Those who survive their acute cardiac insult are discharged home on optimal medical therapy and advised about smoking cessation. Clopidogrel, the only $P2Y_{12}$ receptor antagonist available in our setting and now widely available, was only offered to those patients who underwent percutaneous coronary intervention during the study period, owing to funder-induced prescribing limitations at the time. Apart from a limited discussion about the hazards of smoking and its adverse effects on coronary artery disease, no specific smoking cessation guidance is offered. Long-term care and follow-up take place at the community health centre closest to the patient's home. Medication is supplied free of charge to patients who are pensioners, unemployed, or earn less than R36 000 per annum, which includes the vast majority of patients admitted to the unit.

We retrospectively enrolled all patients discharged alive from the CCU with a final diagnosis of unstable angina pectoris, non-ST elevation MI or ST-elevation MI during the 5-month period between 15 November 2011 and 15 April 2012. In

each case the consultant cardiologist in charge of the patient's care made the diagnosis.

Approval to conduct the study was obtained from the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town.

Data collection

A medical record review was performed and a standardised data capture form completed for each eligible patient. Information gathered included demographic characteristics, income group, comorbid conditions, medication use on admission, smoking status, ACS diagnosis, ACS in-hospital treatment, length of stay and discharge medication.

The principal author performed follow-up via a telephone call with the patient or primary caregiver at a time period between 6 and 9 months after discharge. A Xhosa-speaking interpreter performed three of the interviews under the guidance of the principal author, and a single patient was contacted by email. Verbal informed consent for enrolment into the study was obtained at this time from the patient or caregiver, and it was made clear that the telephone call was for study purposes only.

Patients were encouraged to fetch their current medications and actively list them over the telephone. Where a medication of interest was not listed, the patient was asked why this was the case. They were then asked a standardised smoking question: 'Do you smoke every day, only some days, or never?' Any reported smoking classified the patient as an ongoing smoker.

Interviews were conducted primarily in English, Afrikaans or Xhosa only being used if the patient was unable to communicate in English or requested otherwise, and the interviewer did not identify himself as a doctor unless specifically asked. Where behaviour hazardous to health was identified during the interview, such as ongoing smoking or non-adherence to medication, this was addressed prior to completing the interview.

Statistical analysis

Means and standard deviations were calculated for the full data and various data subsets. Comparisons of differences between groups were calculated using Fisher's exact test or the Wilcoxon sum rank test (for categorical and

continuous variables), as appropriate. A significance level of $p<0.05$ was used. All statistical analysis was done using R 3.0.

Results

Patient characteristics

A total of 164 patients with a diagnosis of ACS were discharged alive from the CCU and were therefore eligible for enrolment into the study. Their mean age was 58.6 years, and 97 (59.1%) were male. The baseline demographic variables, type of ACS and inpatient treatment strategy are summarised in Table 1.

Of the 164 patients enrolled in the study, 125 (76.2%) completed follow-up interviews. Two patients (1.6%) fell outside the planned follow-up range of 6 - 9 months (9.5 and 10.75 months), but were included for the sake of completeness and the low likelihood of two individuals making a difference to the results. Of the remaining patients, 19 (11.6%) had died, 19 (11.6%) were not contactable, and 1 (0.6%) declined participation (Fig. 1). The patients who died or were lost to follow-up were more likely to have received medical treatment only (p=0.01), were less likely to have undergone coronary angiography (p=0.01), and were significantly older (p<0.01).

The overall rate of revascularization was 42% which is low when compared to similar studies. This is in part due to resource limitation and is in keeping with current hospital ACS management protocols.

Medication use at discharge and at 6 - 9 months' follow-up

Of the 164 patients enrolled in the study, 155 (94.5%) were discharged on aspirin. Of the patients followed up (N=125), 85.6% (n=107) remained on this medication, a reduction of 8.9% (p=0.01). Factors associated with ongoing aspirin use, by univariate analysis, were a prior diagnosis of IHD (p=0.01) and undergoing coronary angiography (p<0.01). Reasons given for aspirin non-adherence were dyspepsia (n=3), iron deficiency anaemia (n=1), introduction of warfarin therapy (n=1), and not realising the importance of continued use (n=7).

Statins were prescribed to 157 patients (95.7%) at discharge. At follow-up 85.6% (107/125) remained on this medication, a reduction of 10.1% (p<0.01). The only factor associated with continued use was a diagnosis of

hypercholesterolaemia (p=0.02). Reasons given for discontinuation of statins were nausea (n=2), and not realising the importance of continued use (n=7).
Beta-blockers were prescribed for 140 patients (85.4%) at discharge. At follow-up, 79.2% (99/125) remained on this medication, a reduction of 6.2% (p<0.01). Factors associated with adherence were hypercholesterolaemia (p<0.01), a prior diagnosis of IHD (p<0.01), and female gender (p=0.02). Reasons given for discontinuation were doctor-initiated cessation due to a reduced heart rate (n=2), and not realising the importance of continued use (n=11).
ACEIs/ARBs were prescribed for 141 patients (85.9%) at discharge. At follow-up, 68.0% (85/125) were still using this medication, the largest reduction in use for any of the four drug classes at 17.9% (p<0.01). Ongoing use was associated with a prior diagnosis of IHD (p=0.04). Reasons given for discontinuation were angio-oedema (n=1), cough (n=4), doctor-initiated cessation due to low blood pressure (n=4), and not realising the importance of continued use (n=12).
The number of patients discharged on a combination of all four drug classes was 116 (70.7%). Of the 125 patients followed up, only 47.2% (n=59) remained on all four drugs, a reduction of 23.5% (p<0.01). A total of 5 patients (4.0%) had stopped all medications, as they did not realise the importance of ongoing use.
Results are summarised in Table 2a. There was no significant difference in adherence rates found when recalculated to include only paired patients (Table 2b).

Smoking on admission and at 6 - 9 months' follow-up

Of the 125 patients who were followed up, 70 (56.0%) had been active smokers on admission to hospital, and 22 of these had had stopped smoking by the time of the interview, representing a smoking cessation rate of 31.4%. One patient had taken up smoking for the first time after discharge. The only factor independently associated with an increased rate of smoking cessation, by univariate analysis, was a longer length of hospital stay (p<0.01). We could find no relationship between smoking cessation rate and age, gender, income category, comorbid conditions, admission diagnosis or treatment received.

Discussion

There was good early initiation of secondary prevention medication after ACS in our cohort of patients. It has been shown that patients who do not start medication shortly after the acute event are unlikely to ever have medication added, and a focused effort to start treatment in the immediate post-infarction period is likely to provide long-term benefit.[12] When we compare these findings with those of the Clinical Pathways for Acute Coronary Syndromes in China (CPACS)[8] and the Global Registry of Acute Coronary Events (GRACE)[9] studies, our prescribing rates for the four selected drugs at discharge after ACS are higher for all drug classes (Table 3 and Fig. 2). Since both the above studies used the same method of follow-up as we did, namely telephone calls and active listing of medications, they provide a reasonable comparison. The CPACS investigators felt that there was a significant gap between evidence and practice in medication prescribing after ACS, which was not found in our study. It should be noted that the low rates of prescribing of secondary prevention medication found in the GRACE study may in part be because the data were collected from 1999 to 2003, when less emphasis was placed on these medications. Our finding of a high early initiation rate of all four recommended drugs is important and demonstrates that adherence to best-practice guidelines in our setting is feasible.

We found a significant increase in the rate of non-adherence to the selected medications in our group of patients beyond 6 months. Medication cessation for appropriate reasons, such as ACEI-induced angio-oedema or beta-blocker-induced symptomatic bradycardia, is unavoidable and expected for a minority of patients. What is more concerning is that patients stopped medication because they did not realise the importance of ongoing use, which was found to be a reason for non-adherence for each of the four drug classes, and for the 5 patients who stopped all four drugs completely. Rates of discontinuation of medication were higher for most of the drug classes when compared with the CPACS and GRACE studies (Table 3 and Fig. 2), the exceptions being lipid-lowering agents when compared with CPACS (a 10.1% drop-off in adherence v. 14.6%) and beta-blockers when compared with GRACE (6.2% v. 6.9%). It is not clear from our data why the rates of non-adherence are higher. There is not a clear link to a language barrier, as all but 3 of the patients could speak English

or Afrikaans, both of which are spoken in the CCU by doctors and nursing staff. There was also no demonstrable link between income category and adherence, and SA and China are both rated as upper middle-income countries by the World Bank Country Classification, so adherence rates based purely on income would be expected to be similar. It is possible that level of education and insight into disease could play a role, but these were not included in our questionnaire. No patient mentioned a shortage of medication at a local clinic as a reason for discontinuation. The frequent reporting of non-adherence to medication due to not understanding the importance of ongoing use implies that good communication with the patient during the index hospital admission, with a focus on education about the disease and future treatment, is essential. Enhanced communication between treating doctor and patient, as well as involving ancillary health care providers such as nursing staff and pharmacists, have both been shown to improve adherence, both during admission and through community-based cardiac rehabilitation programmes. Innovative measures such as the use of short message service (SMS) reminder technology for mobile phones, which has been demonstrated to improve adherence to antiretroviral medication in SA and to other chronic medications elsewhere, should be looked at to improve adherence in our setting.

More of our patients continued to smoke after an ACS than has been found in similar studies. Evidence from the PURE study shows a clear link between smoking cessation after a coronary heart disease or stroke event and country income category, with cessation rates highest in upper-income countries, and decreasing with declining income category of the country.[13] The smoking cessation rate in upper middle-income countries such as SA was found to be 54.6%,[13] which is still higher than the 31% rate in our group. We did not ask patients whether they had tried to stop smoking, or indeed whether they wanted to try to stop, so the rate of failed attempts at smoking cessation is unknown. The Western Cape is known to have the highest smoking rate of all the SA provinces, at 44.7% of men and 27% of women.[14] A recent Cochrane review found that intensive behavioural interventions in hospitalised patients, followed by at least a month of outpatient supportive contact, was effective at significantly improving smoking cessation rates, and it should be considered as an option in this group of patients. The addition of nicotine replacement therapy

in gum or patch form further improves smoking cessation. At present there is not sufficient evidence to prove that bupropion or varenicline in addition to intensive counselling in hospitalised patients increases cessation rates over intensive counselling alone.[15] The smoking cessation rates in our cohort suggest that adoption of these and other evidence-based methods of influencing smoking behaviour should be made an urgent priority.

Study limitations

Our study has a number of limitations. We measured adherence by self-report, with no electronic or pill count data to back up our findings. Although this method of active listing of medications over the telephone tends to overestimate adherence, it has been used successfully in similar studies[8,9,11] and is highly specific. While measurement of smoking by self-report can lead to an overestimation of smoking cessation, this method has been shown to correlate well with cotinine testing in most studies. Other limitations include enrolling patients from only a single urban tertiary centre, having a relatively small sample size, and borderline significance of univariate analyses. Not knowing the medication adherence and smoking cessation rates of those patients who died is another limitation, as this information may have improved insight into mortality in this group of patients. These factors raise the concern that our findings may not be representative of the population as a whole, or indeed to secondary level hospitals in our area. In order to avoid selection bias at enrolment, we included every patient with ACS discharged alive from the CCU over the selected 5-month period, and did not limit inclusion to those patients who were followed up at our institution. SA is a diverse country with broad variations in culture, income and access to healthcare, and a similar multicentre, prospective study in future could enable us to better understand the challenges with regard to medication adherence and smoking cessation after ACS.

Conclusion

This study has provided valuable insight into prescribing practices, medium-term adherence patterns after ACS, and smoking cessation rates beyond 6 months, areas for which there are currently no published data in our setting.

Three findings were of particular importance: (*i*) we found that our prescribing of secondary prevention medication at discharge is high (70.7% for the four-drug combination); (*ii*) we noted that a reasonably large proportion of our patients are discontinuing medication within a 6 - 9-month period (23.5% for the four-drug combination); and (*iii*) we demonstrated that a large proportion (68.6%) of patients who were active smokers on admission to hospital continued to smoke, giving a cessation rate of 31.4%. Given the importance of smoking cessation in improving short- and long-term outcomes, more focused strategies to improve this adverse behaviour, particularly in this high risk population, are required.

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Tables and Figures

Table 1. Demographic characteristics of patients enrolled, completing interviews and lost to follow up.

Variable	Enrolled Total N = 164	Completed Interview Total N=125	Lost to Follow Up Total N=39	P-values
Age (years), mean (±SD)	58.6 (11.2)	57.0 (10.9)	63.8 (11.0)	<0.01
Male, *n* (%)	97 (59.1)	71 (56.8)	26 (66.7)	0.35
Income Category, *n* (%)				0.08
Unemployed/Pensioner	47 (28.6)	31 (24.8)	16 (41.0)	
Income < R36000 per annum	85 (51.8)	66 (52.8)	19 (48.7)	
Income R36000 to R72000 per annum	14 (8.5)	14 (11.2)	-	
Income >R72000 per annum	13 (7.9)	9 (7.2)	4 (10.3)	
Private Medical Aid/Foreigner	4 (2.4)	4 (3.2)	-	
Unknown	1 (0.6)	1 (0.8)	-	
Medical History, *n* (%)				
Hypertension	99 (60.3)	71 (56.8)	28 (71.8)	0.09
Diabetes Mellitus	51 (31.0)	36 (28.8)	15 (38.5)	0.23
Hypercholesterolaemia	73 (44.5)	57 (45.6)	16 (41.0)	0.85
IHD	83 (50.6)	61 (48.8)	22 (56.4)	0.36
Current smoker, *n* (%)	90 (54.8)	70 (56.0)	20 (51.3)	0.09
Diagnosis, *n* (%)				0.48
ST-elevation MI	59 (35.9)	44 (35.2)	15 (38.5)	
Non ST-elevation MI	77 (46.9)	57 (45.6)	20 (51.3)	
Unstable angina pectoris	28 (17.0)	24 (19.2)	4 (10.3)	
Treatment, *n* (%)				0.01
Medical only	95 (57.9)	65 (52.0)	30 (76.9)	
PCI	59 (35.9)	50 (40.0)	9 (23.1)	
Coronary artery bypass graft	10 (6.09)	10 (8.0)	-	
Angiogram (including PCI), *n* (%)	112 (68.2)	92 (73.6)	20 (51.3)	0.01
Length of Stay (days) - mean (±SD)	3.018 (1.9)	2.98 (2.0)	3.13 (1.7)	0.43

SD = standard deviation; IHD = ischaemic heart disease (previous myocardial infarction or unstable angina pectoris); MI = myocardial infarction; PCI = percutaneous coronary intervention.

Figure 1. Flow diagram demonstrating follow up of enrolled patients.

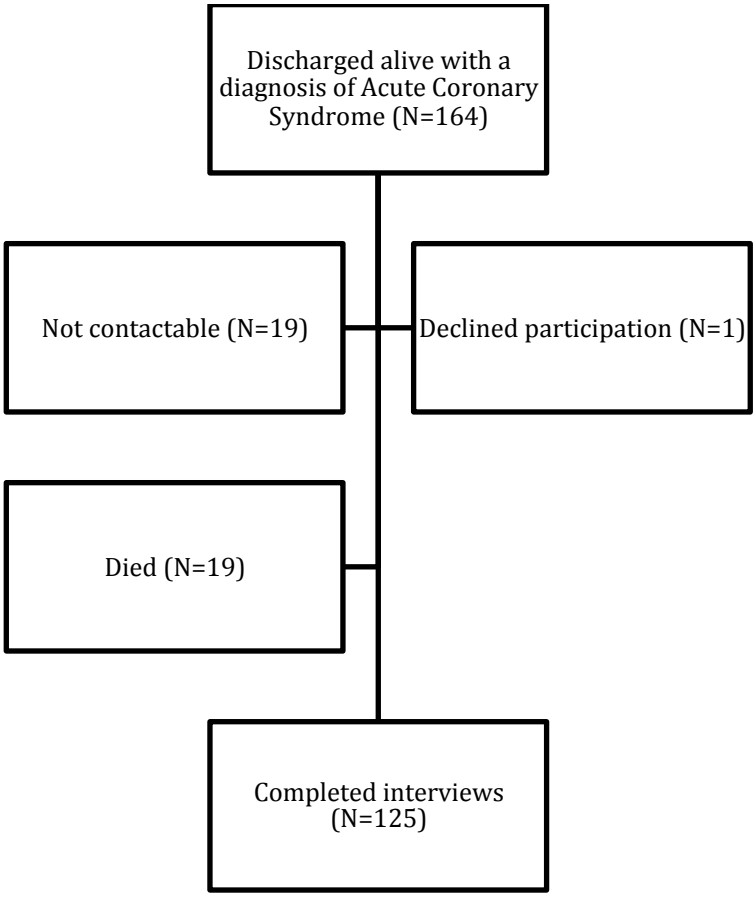


Table 2a. Medication use at discharge and follow up.

	Discharge, N=164, *n* (%)	**Follow up, N=125, *n* (%)**	**Reduction in Use (%)**	**P-value**
Aspirin	155 (94.5)	107 (85.6)	8.9	<0.01
Statin	157 (95.7)	107 (85.6)	10.1	<0.01
Beta-blocker	140 (85.4)	99 (79.2)	6.2	<0.01
ACEI/ARB	141 (85.9)	85 (68.0)	17.9	<0.01
4-drug combination	116 (70.7)	59 (47.2)	23.5	<0.01

ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker

Table 2b. Medication use at discharge and follow up for paired patients

	Discharge, N=125, *n* (%)	**Follow up, N=125, *n* (%)**	**Reduction in Use (%)**	**P-value**
Aspirin	118 (94.4)	107 (85.6)	8.8	<0.01
Statin	118 (94.4)	107 (85.6)	8.8	<0.01
Beta-blocker	109 (87.2)	99 (79.2)	8	<0.01
ACEI/ARB	107 (85.6)	85 (68.0)	17.6	<0.01
4-drug combination	92 (73.6)	59 (47.2)	26.4	<0.01

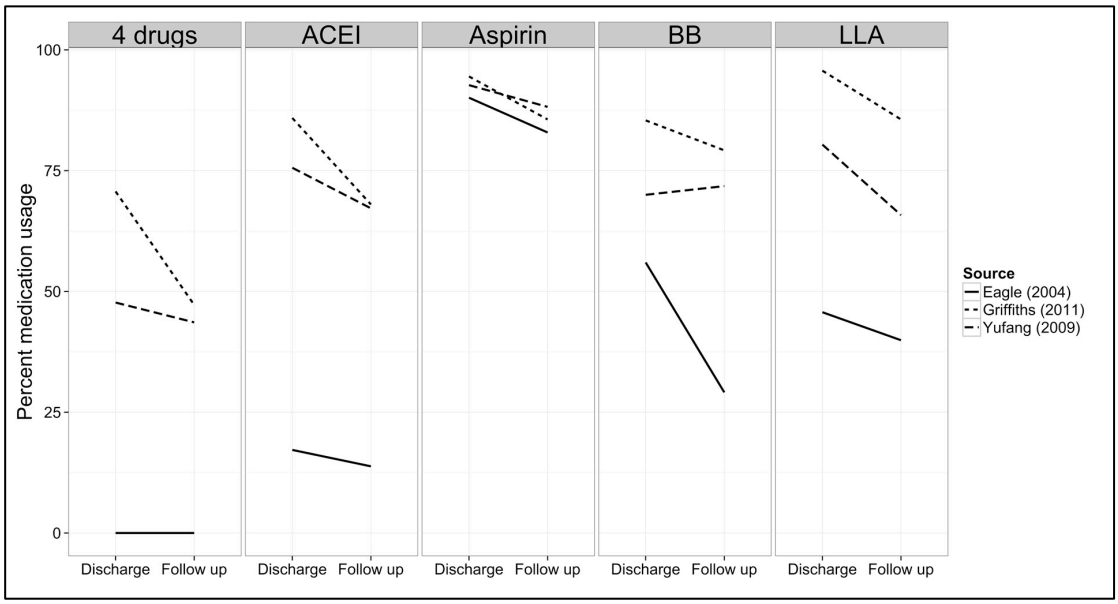
ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker

Table 3. Comparison between medication use at discharge and follow up in the present study and two similar studies.

	Griffiths *et al* (South Africa)			Yufang *et al*[8] (CPACS China)			Eagle *et al*[9] (GRACE multi-country)		
	DC (N=164), *n* (%)	**FU (N=125), *n* (%)**	**Diff., %**	**DC (N=2901), *n* (%)**	**FU (N=2521), *n* (%)**	**Diff., %**	**DC (N=13830), *n* (%)**	**FU (N=13830), *n* (%)**	**Diff., %**
Aspirin	155 (94.5)	107 (85.6)	-8.9	2687 (92.7)	2211 (88.2)	-4.5	12463 (90.1)	11465 (82.9)	-7.2
Lipid-Lowering Agent	157 (95.7)	107 (85.6)	-10.1	2332 (80.4)	1654 (65.8)	-14.6	6320 (45.7)	5522 (39.9)	-6.1
Beta Blocker	140 (85.4)	99 (79.2)	-6.2	2031 (70.0)	1798 (71.8)	+1.8	7738 (56.0)	6796 (49.1)	-6.9
ACEI/ARB	141 (85.9)	85 (68.0)	-17.9	2194 (75.6)	1694 (67.2)	-8.4	2379 (17.2)	1906 (13.8)	-3.4
4 Drug Combo	116 (70.7)	59 (47.2)	-23.5	1384 (47.7)	1088 (43.6)	-4.1	NA	NA	NA

DC = medication prescribed at discharge; FU = medication use reported at follow-up; Diff. = difference between DC and FU; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker; CPACS = Clinical Pathways for Acute Coronary Syndromes in China study; GRACE = Global Registry of Acute Coronary Events study; NA = not applicable

Figure 2: Graphic representation of the comparison between medication use at discharge and follow up in the present study and two similar studies.



ACEI = Angiotensin converting enzyme inhibitor; BB = Beta-blocker; LLA = Lipid lowering agent

PART D: APPENDICES

Appendix 1: Interview Structure

1. **Introduction:**

   "Bradley Griffiths from Groote Schuur Hospital Cardiac Clinic" – *will not introduce myself as a doctor as this may influence honesty of responses to questions. Not an ethical problem as makes no difference to subject if interviewer is a doctor or not.*

2. **Explanation of study:**

   "Phoning to collect information from patients who have previously been admitted to the ICU with a heart attack in order to improve the service to future patients. Participation is voluntary and anonymous, and will not influence any further treatment at Groote Schuur or elsewhere. This is a study and is not aimed at providing a health service at the present time"

3. **Opportunity for subject to ask questions, raise concerns or decline participation**

4. **Study question 1:**

   "With regard to smoking, do you smoke cigarettes every day, some days or never?"- *any answer other than "never" will classify subject as a smoker.*

5. **Study question 2:**

   "Please could you list the medication you are taking at present" – *subject will be encouraged to fetch actual medication and read out list*
   If medication listed above is different to discharge medication, a follow up question will be asked. This will need to be individualized according to the medication listed. Dose adjustments will be documented but ignored as far as interview structure is concerned. For example:
   "What do you think is the main reason for you not taking your prescribed medication?"
   or
   "Do you know why you no longer take Atenolol?"

6. **Opportunity for interviewer to give advice if behavior hazardous to health is picked up** – *if subject is a smoker, will be advised that this is hazardous to health; if subject is not adherent to medication, will be advised that this is hazardous to health. Specific advice with regard to how to renew script if this is a problem will be given.*

Appendix 2: Data Capture Sheet

NAME & HOSP NO.		
DOB & SEX		
RESIDENTIAL AREA		
PHONE NUMBERS		
DOA & DOD		
DIAGNOSIS (ACS)		
TREATMENT		
COMORBIDITIES		
ADMISSION MEDS		
ADMISSION SMOKING		
DISCHARGE MEDS		
CURRENT MEDS		
REASON(S) FOR NON-COMPLIANCE		
CURRENT SMOKING		
ENGLISH		
RIP		
NOT CONTACTABLE		
REFUSED		
DATA CAPTURER		
DATE AND TIME		

Appendix 3: Human Research Ethics Committee Approval Letter

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

31 July 2012

HREC REF: 373/2012

Dr B Griffiths
c/o Dr M Ntsekhe
Internal Medicine
J46
OMB

Dear Dr Griffiths

PROJECT TITLE: ACHIEVEMENT OF SECONDARY PREVENTION GOALS 6 TO 9 MONTHS AFTER ACUTE MYOCARDIAL INFARCTION - A RETROSPECTIVE, CROSS-SECTIONAL ANALYSIS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th August 2013

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

s.thomas

Appendix 4: South African Medical Journal (SAMJ) Instructions for Authors

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Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

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Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

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RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters will be considered for publication as shorter ***Research articles***.

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Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minumum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be

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REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

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Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

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Appendix 5: PDF of manuscript accepted for publication under the heading "Self-reported use of evidence-based medicine and smoking cessation 6-9 months after acute coronary syndrome: A single centre perspective"

Self-reported use of evidence-based medicine and smoking cessation 6 - 9 months after acute coronary syndrome: A single-centre perspective

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Background. Good evidence exists to support the use of secondary prevention medications (aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) and smoking cessation in patients after acute coronary syndromes (ACSs). Little is currently known about adherence to medication and smoking behaviour after discharge in South Africa.
Methods. We conducted a cross-sectional analysis of all patients with a diagnosis of ACS discharged from the Coronary Care Unit at Groote Schuur Hospital, Cape Town, between 15 November 2011 and 15 April 2012. Patients were telephoned 6 - 9 months after discharge and completed a standardised questionnaire detailing current medication use, reasons for non-adherence and smoking status.
Results. Prescribing of secondary prevention medications at discharge was high (aspirin 94.5%, statins 95.7%, beta-blockers 85.4%, ACEIs/ARBs 85.9%), and 70.7% of patients were discharged on a combination of all four drugs. At 6 - 9-month follow-up, the proportion using these medications had dropped by 8.9% for aspirin, 10.1% for statins, 6.2% for beta-blockers and 17.9% for ACEIs/ARBs. Only 47.2% remained on all four drugs, a reduction of 23.5%. Of the 56.0% of patients who were smokers, 31.4% had stopped smoking.
Conclusions. A significant decline in adherence to recommended therapy 6 - 9 months after discharge and a poor rate of smoking cessation suggest that efforts to educate patients about the importance of long-term adherence need to be improved. Furthermore, more effective interventions than in-hospital reminders about the hazards of smoking are needed to improve smoking cessation.

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The incidence of ischaemic heart disease (IHD) is on the rise in Africa. Recent projections suggest that by 2030 IHD will become a leading cause of death on the continent, surpassing HIV/AIDS.[1] In the South African National Burden of Disease Study in 2000,[2] IHD was found to be the largest single cause of death in the Western Cape Province (12%), followed by stroke (8.8%) and HIV/AIDS (8.4%), and non-communicable diseases accounted for a larger proportion of deaths in the Western Cape (58%) than in the rest of South Africa (SA) (38%). In a subsequent study,[3] mortality from IHD in Cape Town was found to be very similar to HIV/AIDS (76 v. 83 deaths/100 000 population, respectively), and IHD featured as the leading cause of death from non-communicable diseases. The Second National Burden of Disease Study is nearing completion and will give us more current data on mortality trends. The epidemiological transition of cardiovascular disease described by Yusuf *et al.*[4] suggests that with progression from under-development to industrialisation we can expect an increasing burden of degenerative disease, particularly IHD and stroke.

The use of evidence-based optimal medical therapy (dual antiplatelet therapy, statins, beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) after acute coronary syndrome (ACS) is known to reduce 6-month mortality by up to 87%.[5] Patients who continue to smoke after an ACS have a significantly increased risk of a future acute myocardial infarction (MI) compared with those who quit.[6] Furthermore, smoking in the presence of established IHD is associated with a significantly increased risk of death, including sudden cardiac death. Over an 8-year period, smoking cessation reduces this risk to levels comparable to that for people who have never smoked.[7] Despite this, medication adherence and smoking cessation in patients after discharge are often disappointing.[6-9] Results from the Prospective Urban Rural Epidemiology (PURE) study[10] suggest that in SA, and in countries with similar income profiles, use of these medicines in patients with coronary heart disease at a median follow-up period of 4 years varies between 21.1% and 31%, compared with 46.5% and 70.9% for upper-income countries. These figures are even lower when Africa as a whole is compared with other areas.[10] The reasons for discontinuation of medication are diverse, and include the high cost of obtaining medicine, high pill burden and lower level of education.[11]

To date there are no published SA data on the medium- to long-term (>6 months) use of secondary prevention medication and smoking cessation among patients discharged from hospital after an ACS. We designed this cross-sectional study to assess the continued use of four selected drug classes and rates of smoking cessation at a follow-up period of 6 - 9 months post discharge after an ACS.

Methods

Study design

Cross-sectional analysis with retrospective subject identification.

Study population

Groote Schuur Hospital is an 893-bed state-funded tertiary hospital in Cape Town, SA. It has a 6-bed coronary care unit (CCU) and a cardiac catheterisation laboratory. Patients who are admitted to the CCU either present directly to the emergency unit or are referred from secondary-level institutions. Those who survive their acute cardiac insult are discharged home on optimal medical therapy and advised about smoking cessation. Clopidogrel, the only $P2Y_{12}$ receptor antagonist available in our setting and now widely available, was only offered to those patients who underwent percutaneous coronary intervention during the study period, owing to funder-induced prescribing limitations at the time. Apart from a limited discussion about the hazards of smoking and its adverse effects on coronary artery disease, no specific smoking cessation guidance is offered. Long-term care and follow-up take place at the community health centre closest to the patient's home. Medication is supplied free of charge to patients who are pensioners, unemployed, or earn less than R36 000 per annum, which includes the vast majority of patients admitted to our unit.

We retrospectively enrolled all patients discharged alive from the CCU with a final diagnosis of unstable angina pectoris, non-ST elevation MI or ST-elevation MI during the 5-month period between 15 November 2011 and 15 April 2012. In each case the consultant cardiologist in charge of the patient's care made the diagnosis.

Approval to conduct the study was obtained from the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town.

Data collection

A medical record review was performed and a standardised data capture form completed for each eligible patient. Information gathered included demographic characteristics, income group, comorbid conditions, medication use on admission, smoking status, ACS diagnosis, ACS in-hospital treatment, length of stay and discharge medication.

The principal author performed follow-up via a telephone call with the patient or primary caregiver at a time period between 6 and 9 months after discharge. A Xhosa-speaking interpreter performed three of the interviews under the guidance of the principal author, and a single patient was contacted by email. Verbal informed consent for enrolment into the study was obtained at this time from the patient or caregiver, and it was made clear that the telephone call was for study purposes only.

Patients were encouraged to fetch their current medications and actively list them over the telephone. Where a medication of interest was not listed, the patient was asked why this was the case. They were then asked a standardised smoking question: 'Do you smoke every day, only some days, or never?' Any reported smoking classified the patient as an ongoing smoker.

Interviews were conducted primarily in English, Afrikaans or Xhosa only being used if the patient was unable to communicate in English or requested otherwise, and the interviewer did not identify himself as a doctor unless specifically asked. Where behaviour hazardous to health was identified during the interview, such as ongoing smoking or non-adherence to medication, this was addressed prior to completing the interview.

Statistical analysis

Means and standard deviations were calculated for the full data and various data subsets. Comparisons of differences between groups were calculated using Fisher's exact test or the Wilcoxon rank-sum test (for categorical and continuous variables), as appropriate. A significance level of $p<0.05$ was used. All statistical analysis was done using R 3.0.

Results

Patient characteristics

A total of 164 patients with a diagnosis of ACS were discharged alive from the CCU and were therefore eligible for enrolment into the study. Their mean age was 58.6 years, and 97 (59.1%) were male. The baseline demographic variables, type of ACS and inpatient treatment strategy are summarised in Table 1.

Of the 164 patients enrolled in the study, 125 (76.2%) completed follow-up interviews. Two patients (1.6%) fell outside the planned follow-up range of 6 - 9 months (9.5 and 10.75 months), but were included for the sake of completeness and the low likelihood of two individuals making a difference to the results. Of the remaining patients, 19 (11.6%) had died, 19 (11.6%) were not contactable, and one (0.6%) declined participation (Fig. 1). The patients who died or were lost to follow-up were more likely to have received medical treatment only ($p=0.01$) and were significantly older ($p<0.0001$).

Medication use at discharge and at 6 - 9 months' follow-up

Of the 164 patients enrolled in the study, 155 (94.5%) were discharged on aspirin. Of the patients followed up ($n=125$), 85.6% ($n=107$) remained on this medication, a reduction of 8.9% ($p=0.01$). Factors associated with ongoing aspirin use, by univariate analysis, were a previous diagnosis of IHD ($p=0.01$) and having undergone coronary angiography ($p=0.0002$). Reasons given for aspirin non-adherence were dyspepsia, iron deficiency anaemia, introduction of warfarin therapy, and not realising the importance of continued use.

Statins were prescribed to 157 patients (95.7%) at discharge. At follow-up 85.6% (107/125) remained on this medication, a reduction of 10.1% ($p=0.0008$). The only factor associated with continued use was a diagnosis of hypercholesterolaemia ($p=0.02$). Reasons given for discontinuation of statins were nausea, and not realising the importance of continued use.

Beta-blockers were prescribed for 140 patients (85.4%) at discharge. At follow-up 79.2% (99/125) remained on this medication, a reduction of 6.2% ($p<0.0001$). Factors associated with adherence were hypercholesterolaemia ($p=0.005$), a previous diagnosis of IHD ($p=0.005$), and female gender ($p=0.02$). Reasons given for discontinuation were doctor-initiated cessation due to a reduced heart rate, and not realising the importance of continued use.

ACEIs/ARBs were prescribed for 141 patients (85.9%) at discharge. At follow-up, 68.0% (85/125) were still using this medication, the largest reduction in use for any of the four drug classes at 17.9% ($p<0.0001$). Ongoing use was associated with a previous diagnosis of IHD ($p=0.04$). Reasons given for discontinuation were angio-oedema, cough, doctor-initiated cessation due to low blood pressure, and not realising the importance of continued use.

The number of patients discharged on a combination of all four drug classes was 116 (70.7%). Of the 125 patients followed up, only 47.2% ($n=59$) remained on all four drugs, a reduction of 23.5% ($p=0.001$). A total of five patients (4.0%) had stopped all medications because they did not realise the importance of ongoing use. Results are summarised in Table 2.

Smoking on admission and at 6 - 9 months' follow-up

Of the 125 patients who were followed up, 70 (56.0%) had been active smokers on admission to hospital, and 22 of these had had stopped smoking by the time of the interview, representing a smoking cessation rate of 31.4%. One patient had taken up

Table 1. Demographic characteristics of patients enrolled, completing interviews and lost to follow-up

Variable	Enrolled (*N*=164)	Completed interview (*N*=125)	Lost to follow-up (*N*=39)
Age (yrs), mean (±SD)	58.6 (±11.2)	57.0 (±10.9)	63.8 (±11.0)
Male, *n* (%)	97 (59.1)	71 (56.8)	26 (66.7)
Income category, *n* (%)			
Unemployed/pensioner	47 (28.6)	31 (24.8)	16 (41.0)
Income <R36 000 p.a.	85 (51.8)	66 (52.8)	19 (48.7)
Income <R72 000 p.a.	14 (8.5)	14 (11.2)	-
Income >R72 000 p.a.	13 (7.9)	9 (7.2)	4 (10.3)
Private medical aid/foreigner	4 (2.4)	4 (3.2)	-
Unknown	1 (0.6)	1 (0.8)	-
Medical history, *n* (%)			
Hypertension	99 (60.3)	71 (56.8)	28 (71.8)
Diabetes mellitus	51 (31.0)	36 (28.8)	15 (38.5)
Hypercholesterolaemia	73 (44.5)	57 (45.6)	16 (41.0)
IHD	83 (50.6)	61 (48.8)	22 (56.4)
Current smoker, *n* (%)	90 (54.8)	70 (56.0)	20 (51.3)
Diagnosis, *n* (%)			
ST-elevation MI	59 (35.9)	44 (35.2)	15 (38.5)
Non ST-elevation MI	77 (46.9)	57 (45.6)	20 (51.3)
Unstable angina pectoris	28 (17.0)	24 (19.2)	4 (10.3)
Treatment, *n* (%)			
Medical only	95 (57.9)	65 (52.0)	30 (76.9)
PCI	59 (35.9)	50 (40.0)	9 (23.1)
Coronary artery bypass graft	10 (6.09)	10 (8.0)	-
Angiogram (including PCI), *n* (%)	112 (68.2)	92 (73.6)	20 (51.3)
Length of stay (d), mean (±SD)	3.018 (±1.9)	2.98 (±2.0)	3.13 (±1.7)

SD = standard deviation; p.a. = per annum; IHD = ischaemic heart disease (previous myocardial infarction or unstable angina pectoris); MI = myocardial infarction; PCI = percutaneous coronary intervention.

smoking for the first time after discharge. The only factor independently associated with an increased rate of smoking cessation, by univariate analysis, was a longer length of hospital stay (p=0.006). We could find no relationship between smoking cessation rate and age, gender, income category, comorbid conditions, admission diagnosis or treatment received.

Discussion

There was good early initiation of secondary prevention medication after ACS in our cohort of patients. It has been shown that patients who do not start medication shortly after the acute event are unlikely to ever have medication added, and a focused effort to start treatment in the immediate post-infarction period is likely to provide long-term benefit.[12] When we compare these findings with those of the Clinical Pathways for Acute Coronary Syndromes in China (CPACS)[8] and the Global Registry of Acute Coronary Events (GRACE)[9] studies, our prescribing rates for the four selected drugs at discharge after ACS are higher for all drug classes (Table 3 and Fig. 2). Since both the above studies used the same method of follow-up as we did, namely telephone calls and active listing of medications, they provide a reasonable comparison. The CPACS investigators felt that there was a significant gap between evidence and practice in medication prescribing after ACS, which was not found in our study. It should be noted that the low rates of prescribing of secondary prevention medication found in the GRACE study may in part be because the data were collected from 1999 to 2003, when less emphasis was placed on these medications. Our finding of a high early initiation rate of all four recommended drugs is important and demonstrates that adherence to best-practice guidelines in our setting is feasible.

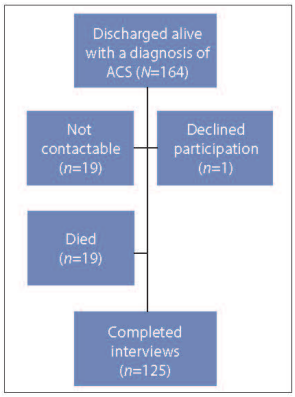

Fig. 1. Flow diagram demonstrating follow-up of enrolled patients. (ACS = acute coronary syndrome.)

Table 2. Medication use at discharge and follow-up

	Discharge (*N*=164), *n* (%)	Follow-up (*N*=125), *n* (%)	Reduction in use (%)	*p*-value
Aspirin	155 (94.5)	107 (85.6)	8.9	0.01
Statin	157 (95.7)	107 (85.6)	10.1	0.0008
Beta-blocker	140 (85.4)	99 (79.2)	6.2	<0.0001
ACEI/ARB	141 (85.9)	85 (68.0)	17.9	<0.0001
Four-drug comb.	116 (70.7)	59 (47.2)	23.5	0.001

ACEI/ARB = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Table 3. Comparison between medication use at discharge and follow-up in the present study and two similar studies

	Griffiths *et al.* (SA, present study)			Bi *et al.*[8] (CPACS China)			Eagle *et al.*[9] (GRACE multi-country)		
	DC (*N*=164) *n* (%)	FU (*N*=125) *n* (%)	Diff., %	DC (*N*=2 901) *n* (%)	FU (*N*=2 521) *n* (%)	Diff., %	DC (*N*=13 830) *n* (%)	FU (*N*=13 830) *n* (%)	Diff., %
Aspirin	155 (94.5)	107 (85.6)	-8.9	2 687 (92.7)	2 211 (88.2)	-4.5	12 463 (90.1)	11 465 (82.9)	-7.2
Lipid-lowering agent	157 (95.7)	107 (85.6)	-10.1	2 332 (80.4)	1 654 (65.8)	-14.6	6 320 (45.7)	5 522 (39.9)	-6.1
Beta-blocker	140 (85.4)	99 (79.2)	-6.2	2 031 (70.0)	1 798 (71.8)	+1.8	7 738 (56.0)	6 796 (49.1)	-6.9
ACEI/ARB	141 (85.9)	85 (68.0)	-17.9	2 194 (75.6)	1 694 (67.2)	-8.4	2 379 (17.2)	1 906 (13.8)	-3.4
Four-drug comb.	116 (70.7)	59 (47.2)	-23.5	1 384 (47.7)	1 088 (43.6)	-4.1	NA	NA	NA

SA = South Africa; DC = medication prescribed at discharge; FU = medication use reported at follow-up; Diff. = difference between DC and FU; ACEI/ARB = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CPACS = Clinical Pathways for Acute Coronary Syndromes in China study; GRACE = Global Registry of Acute Coronary Events study; NA = not applicable.

We found a significant increase in the rate of non-adherence to the selected medications in our group of patients beyond 6 months. Medication cessation for appropriate reasons, such as ACEI-induced angio-oedema or beta-blocker-induced symptomatic bradycardia, is unavoidable and expected for a minority of patients. What is more concerning is that patients stopped medication because they did not realise the importance of ongoing use, which was found to be a reason for non-adherence for each of the four drug classes, and for the five patients who stopped all four drugs completely. Rates of discontinuation of medication were higher for most of the drug classes when compared with the CPACS and GRACE studies (Table 3 and Fig. 2), the exceptions being lipid-lowering agents when compared with CPACS (a 10.1% drop-off in adherence v. 14.6%) and beta-blockers when compared with GRACE (6.2% v. 6.9%). It is not clear from our data why the rates of non-adherence are higher. There is no clear link to a language barrier, as all but three of the patients could speak English or Afrikaans, both of which are spoken in the CCU by doctors and nursing staff. There was also no demonstrable link between

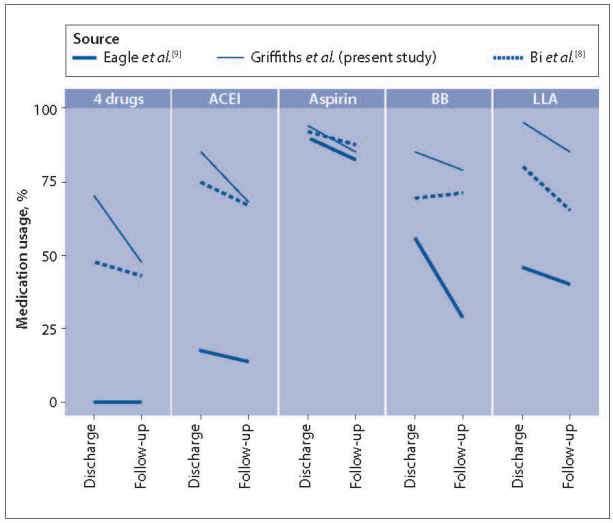

Fig. 2. Graphic representation of the comparison between medication use at discharge and follow-up in the present study and two similar studies. (ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; LLA = lipid-lowering agent.)

income category and adherence, and SA and China are both rated as upper middle-income countries by the World Bank Country Classification, so adherence rates based purely on income would be expected to be similar. It is possible that level of education and insight into disease could play a role, but these were not included in our questionnaire. No patient mentioned a shortage of medication at a local clinic as a reason for discontinuation. The frequent reporting of non-adherence to medication as a result of not understanding the importance of ongoing use implies that good communication with the patient during the index hospital admission, with a focus on education about the disease and future treatment, is essential. Enhanced communication between treating doctor and patient, as well as involving ancillary healthcare providers such as nursing staff and pharmacists, have both been shown to improve adherence, both during admission and through community-based cardiac rehabilitation programmes. Innovative measures such as the use of short message service (SMS) reminder technology for mobile phones, which has been demonstrated to improve adherence to antiretroviral medication in SA and to other chronic medications elsewhere, should be looked at to improve adherence in our setting.

More of our patients continued to smoke after an ACS than has been found in similar studies. Evidence from the PURE study shows a clear link between smoking cessation after a coronary heart disease or stroke event and country income category, with cessation rates highest in upper-income countries, and decreasing with declining income category of the country.[13] The smoking cessation rate in upper middle-income countries such as SA was found to be 54.6%,[13] which is still higher than the 31% rate in our group. We did not ask patients whether they had tried to stop smoking, or indeed whether they wanted to try to stop, so the rate of failed attempts at smoking cessation is unknown. The Western Cape is known to have the highest smoking rate of all the SA provinces, at 44.7% of men and 27% of women.[14] A recent Cochrane review found that intensive behavioural interventions in hospitalised patients, followed by at least a month of outpatient supportive contact, was effective at significantly improving smoking cessation rates, and it should be considered as an option in this group of patients. The addition of nicotine replacement therapy in gum or patch form further improves smoking cessation. At present there is not sufficient evidence to prove that bupropion or varenicline in addition to intensive counselling in hospitalised patients increases cessation rates over intensive counselling alone.[15] The smoking cessation rates in our cohort suggest that adoption of these and other evidence-based methods of influencing smoking behaviour should be made an urgent priority.

Study limitations

Our study has a number of limitations. We measured adherence by self-report, with no electronic or pill count data to back up our findings. Although this method of active listing of medications over the telephone tends to overestimate adherence, it has been used successfully in similar studies[8,9,11] and is highly specific. While measurement of smoking by self-report can lead to an overestimation of smoking cessation, this method has been shown to correlate well with cotinine testing in most studies. Other limitations include enrolling patients from only a single urban tertiary centre, having a relatively small sample size, and borderline significance of univariate analyses. Not knowing the medication adherence and smoking cessation rates of those patients who died is another limitation, as this information may have improved insight into mortality in this group of patients. These factors raise the concern that our findings may not be representative of the population as a whole. In order to avoid selection bias at enrolment, we included every patient with ACS discharged alive from the CCU over the selected 5-month period, and did not limit inclusion to those patients who were followed up at our institution. SA is a diverse country with broad variations in culture, income and access to healthcare, and a similar multicentre, prospective study in future could improve our understanding of the challenges posed by medication adherence and smoking cessation after ACS.

Conclusion

This study has provided valuable insight into prescribing practices, medium-term adherence patterns after ACS, and smoking cessation rates beyond 6 months, areas for which there are currently no published data in our setting. Three findings were of particular importance: (*i*) we found that our prescribing of secondary prevention medication at discharge is high (70.7% for the four-drug combination); (*ii*) we noted that a fairly large proportion of our patients are discontinuing medication within a 6 - 9-month period (23.5% for the four-drug combination); and (*iii*) we demonstrated that a large proportion (68.6%) of patients who were active smokers on admission to hospital continued to smoke, giving a cessation rate of 31.4%. Given the importance of smoking cessation in improving short- and long-term outcomes, more focused strategies to improve this adverse behaviour, particularly in this high risk population, are required.

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