Cost-effectiveness analysis of alternative statin prescribing strategies for the secondary prevention of cardiovascular disease at a South African public sector tertiary hospital

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DECLARATION

I, Reneé de Waal, 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

Strokes and ischaemic heart disease are among the top ten causes of death in South Africa. Given that burden of disease, it is important to establish whether interventions aimed at preventing cardiovascular disease are not only effective, but cost effective too. Cost-effectiveness analyses compare interventions in terms of both their costs and consequences and are a useful tool for policymakers.

Statins reduce the risk of cardiovascular events such as myocardial infarctions and strokes, by lowering low density lipoprotein cholesterol (LDL-C) concentrations. Several studies, mostly conducted in Europe or North America, have demonstrated that statins are cost effective, particularly when used to reduce the risk of further cardiovascular events in patients who already have cardiovascular disease (secondary prevention). Despite their widespread use, there are no published cost-effectiveness analyses of statins for the secondary prevention of cardiovascular disease in South Africa. There are also only limited local efficacy data from clinical trials and no costing data of cardiovascular events from a public healthcare sector perspective.

There is some debate regarding the optimal statin dose. Some guidelines recommend increasing statin doses until target LDL-C concentrations are achieved, while others recommend prescribing statins at a fixed high dose without monitoring LDL-C. Monitoring LDL-C is relatively expensive compared to the cost of statins, but there is limited evidence that it might improve adherence.

I compared the costs (from a provider perspective) and outcomes (life years), of increasing statin doses based on regular measurement of LDL-C concentrations, to achieve a target LDL-C concentration of <1.8 mmol/L; prescribing atorvastatin 80 mg without LDL-C monitoring; and the status quo, simvastatin 20 mg without LDL-C monitoring. I constructed a Markov model with annual cycles; a five-year timeline; starting age of 60 years; and the following health states: ≤1 year after first cardiovascular event, ≤1 year after subsequent cardiovascular event, >1 year after any

cardiovascular event, and dead. I estimated transition probabilities using published literature. I estimated the costs of hospitalisation for myocardial infarctions, strokes, unstable angina pectoris and coronary revascularisation procedures using health services utilisation and expenditure data from a sample of patients at a public sector hospital. I discounted costs and outcomes at 3% per year; and explored alternative scenarios and timelines in sensitivity analyses.

Atorvastatin 80 mg without LDL-C monitoring, was both the cheapest and most effective option over a five-year period. It remained the most effective option over a lifetime period, but with an incremental cost-effectiveness ratio (ICER) of $146.94 per life year gained relative to the status quo. Treat to target was as effective as atorvastatin 80 mg if I assumed adherence rates of 80% and 60% respectively, but with an ICER of $54 930.96. Treat to target would dominate atorvastin 80 mg only if the frequency of LDL-C monitoring was reduced from 3-monthly to 6-monthly until targets were reached, and the cost of LDL-C monitoring decreased by $9.25 (84%).

Fixed-dose statin treatment without cholesterol monitoring is the most cost-effective option for providing statins for the secondary prevention of cardiovascular disease. The costs of regular LDL-C monitoring currently make a treat to target strategy unaffordable in our setting. These results might be used to help guide policy regarding secondary prevention of cardiovascular disease in South Africa.

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Contents

Background

Cardiovascular disease comprises several disorders of the heart and blood vessels, including heart attacks, angina and strokes. In South Africa, cardiovascular disease prevalence is increasing, and strokes and ischaemic heart disease are among the top ten causes of death.[1,2] The recent South African National Health and Nutritional Examination Survey (SANHANES) that included 25 532 individuals of all ages found the prevalence of self-reported heart disease was 6.1% (95% confidence interval (CI) 3.9 to 9.3) in those aged 55–64, and 4.4% (95% CI 2.6 to 7.1) in those aged 65 years or older. The prevalence of self-reported stroke was 6.1% (95% CI 4.0 to 9.3) in those aged 55–64, and 9.1% (95% CI 5.2 to 15.5) in those aged 65 years or older.[3]

High serum concentrations of low density lipoprotein cholesterol (LDL-C) increase the risk of cardiovascular disease.[4,5] Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are a class of drugs that lower LDL-C concentrations by inhibiting cholesterol synthesis in the liver.[6]

Reducing the risk of further events in patients who already have cardiovascular disease is known as secondary prevention. Owing to cost considerations, simvastatin is the statin that is currently recommended for secondary prevention of cardiovascular disease for most patients in South Africa.[7,8] Atorvastatin is recommended when high statin doses are needed, as high dose simvastatin has a higher risk of causing muscle pain or weakness; and for co-administration with protease inhibitors (a class of antiretroviral drugs) in HIV patients, because of its lower potential for drug interactions.[5]

Efficacy of statins in the secondary prevention of cardiovascular disease

Clinical trials that compared statins with placebo demonstrated a significant benefit in terms of both the surrogate endpoint of reduction of LDL-C and cardiovascular events.[9-15] More recent trials have focused on comparisons between different statins or different doses and have usually used

composite clinical endpoints comprising mortality, and cardiovascular events such as heart attacks and strokes.[16-19]

The Cholesterol Treatment Trialists' (CTT) collaboration conducted a meta-analysis of clinical trials using individual patient data.[20] Based on five trials comparing high versus low dose statins for secondary prevention, they found higher doses were associated with an average further reduction in risk of major cardiovascular event (non-fatal myocardial infarction, coronary heart disease related death, stroke or coronary revascularisation procedure) of 28% (95% confidence interval 19 to 34) per 1 mmol/L reduction in LDL cholesterol. They conclude that the greater the reduction in LDL-C (i.e. the higher the statin dose), the greater the clinical benefit.

Cost-effectiveness of statins in the secondary prevention of cardiovascular disease

Several studies have demonstrated that statin therapy is cost effective relative to placebo in patients with cardiovascular disease, assuming various willingness-to-pay thresholds.[21-28] In line with recent clinical trials, recent economic evaluations have compared the costs and benefits of different statins or different doses. [29-36]

To our knowledge, no cost-effectiveness analyses of statins for secondary prevention of cardiovascular disease have been conducted in South Africa.

Statin prescribing strategies

The current European Society of Cardiology (ECS)/European Atherosclerosis Society (EAS) guidelines recommend starting statin treatment at a relatively low dose, monitoring LDL-C concentration regularly, and increasing statin dose if necessary to achieve LDL-C concentrations of below 1.8 mmol/L for secondary prevention.[37] Current South African Heart Association/Lipid and Atherosclerosis Society of Southern Africa guidelines recommend treating to achieve the ECS/EAS target, with measurement of LDL-C (along with high density lipoprotein cholesterol and triglyceride

concentrations) at baseline, at four to eight weeks after treatment initiation or statin dose increase, and then six-monthly once stable.[5]

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and the National Institute for Health and Care Excellence (NICE) in the United Kingdom guidelines recommend atorvastatin 80 mg for secondary prevention unless patients have contra-indications to this drug or dose and measurement of LDL-C at baseline, then at 4-12 weeks (ACC/AHA guidelines) or three months (NICE guidelines), and then only as indicated clinically.[38,39]

Local guidelines

The current South African hospital and primary health care essential medicine list and standard treatment guidelines recommend use of a statin that reduces LDL-C by at least 25% for secondary prevention, and list simvastatin 10 mg as an example.[7,8]

In Western Cape primary health care clinics, simvastatin 10 mg is available for secondary prevention, and simvastatin 20 mg is available for primary prevention for those with a ten-year risk of cardiovascular disease that is greater than 20%.[40] In Western Cape hospitals, simvastatin 40 mg is available for prescription by physicians only, while doses greater than 40 mg may be prescribed at specialist lipid clinics only. Atorvastatin is available at lipid and antiretroviral clinics only.[41]

Current local practice (status quo)

Of 575 patients admitted to Groote Schuur Hospital for a cardiovascular event in 2012, 544 were discharged (the rest died during admission or absconded). Within the 544 patients who were eligible for secondary prevention, 385 (71%) had a statin prescribed within one month of admission. The most frequently prescribed statin was simvastatin 20 mg (91%), followed by simvastatin 10 mg (8%). Atorvastatin was prescribed in 1%. Sixty-six patients (12%) had cholesterol concentrations measured within one year of admission (excluding those done within one month of admission which are likely

to be screening for dyslipidaemia rather than monitoring response to treatment). Only 19% of those cholesterol concentrations were measured at outpatient clinics – the rest were done in wards or in the emergency department, so are most likely related to subsequent admissions for cardiovascular events, rather than monitoring. This analysis is restricted to Groote Schuur Hospital, and is limited by the fact that patients might have had cholesterol concentrations measured or statins prescribed at other facilities. However, it seems reasonable to assume that the vast majority of Groote Schuur Hospital patients eligible for secondary prevention received simvastatin 20 mg with very little cholesterol monitoring.

Rationale

Given the burden of cardiovascular disease in South Africa, it is important to establish whether interventions aimed at preventing cardiovascular disease are not only effective, but cost effective too. There is a paucity of data from our setting regarding the cost-effectiveness of statins in the secondary prevention of heart disease. The use of a Markov model allowed us to predict cost-effectiveness of various statin delivery strategies using assumptions based on data from a variety of sources. Those estimates might be used to guide policy regarding secondary prevention of cardiovascular disease in South Africa.

Aims

In this economic evaluation we aimed to establish whether implementing frequent LDL-C monitoring and statin dose titration or using fixed doses of statins without LDL-C monitoring are cost effective options for providing statins for the secondary prevention of cardiovascular disease at Groote Schuur Hospital.

Objectives

The objectives of the study were to compare the costs and clinical consequences (in terms of life years gained) of:

- simvastatin 20 mg without monitoring LDL-C concentrations;
- atorvastatin 80 mg without monitoring LDL-C concentrations; and
- increasing statin doses (from simvastatin 20 mg to simvastatin 40 mg then atorvastatin 80 mg) if necessary to achieve a target LDL-C concentration of <1.8 mmol/L.

Methods

Study design

We conducted a cost-effectiveness analysis. We compared the three statin prescribing strategies using incremental cost effectiveness ratios, and eliminated strategies that showed higher costs and lower effectiveness than an alternative strategy though absolute dominance.

Perspective

The analysis assessed the costs and consequences of the three statin prescribing strategies from a provider perspective. South Africa has a large private health sector, but over 80% of the population relies on the public sector for healthcare service provision.[42] This analysis will focus on the public health sector, in particular that serving the Western Cape population.

Interventions

Status quo: simvastatin 20 mg without LDL-C monitoring

The status quo comprised simvastatin 20 mg with a baseline lipogram only (to exclude patients with familial hypercholesterolaemia, who should not be treated according to the guidelines for secondary prevention patients), and no LDL-C monitoring on treatment.

LDL-C monitoring and statin dose titration

In this scenario statin dose depended on LDL-C concentration. Patients had a baseline lipogram, and follow-up measurement of LDL-C every three months until they achieved treatment targets, and then every six months.

Atorvastatin 80 mg without LDL-C monitoring

In this scenario all patients received atorvastatin 80 mg. They had a baseline lipogram, no LDL-C monitoring on treatment.

Analysis

We used a Markov model for the analysis as they are well suited for assessing chronic conditions where events might recur.[43] We developed a Markov model using TreeAge Pro software.[44] The model had annual cycles and the following disease states: alive less than one year after first cardiovascular event; alive within one year of a subsequent heart attack; alive within one year of a subsequent stroke; alive within one year of a subsequent episode of unstable angina pectoris; alive within one year after a subsequent coronary revascularisation procedure; alive for more than one year after a cardiovascular event; and dead. We ran the model over a five-year timeline. We expressed costs in United States dollars and outcomes in life years gained. We discounted costs and outcomes at a rate of 3%. Because of the uncertainty of our baseline assumptions and to explore the generalisability of our results to other settings, we conducted threshold, one-way and multivariate sensitivity analyses.

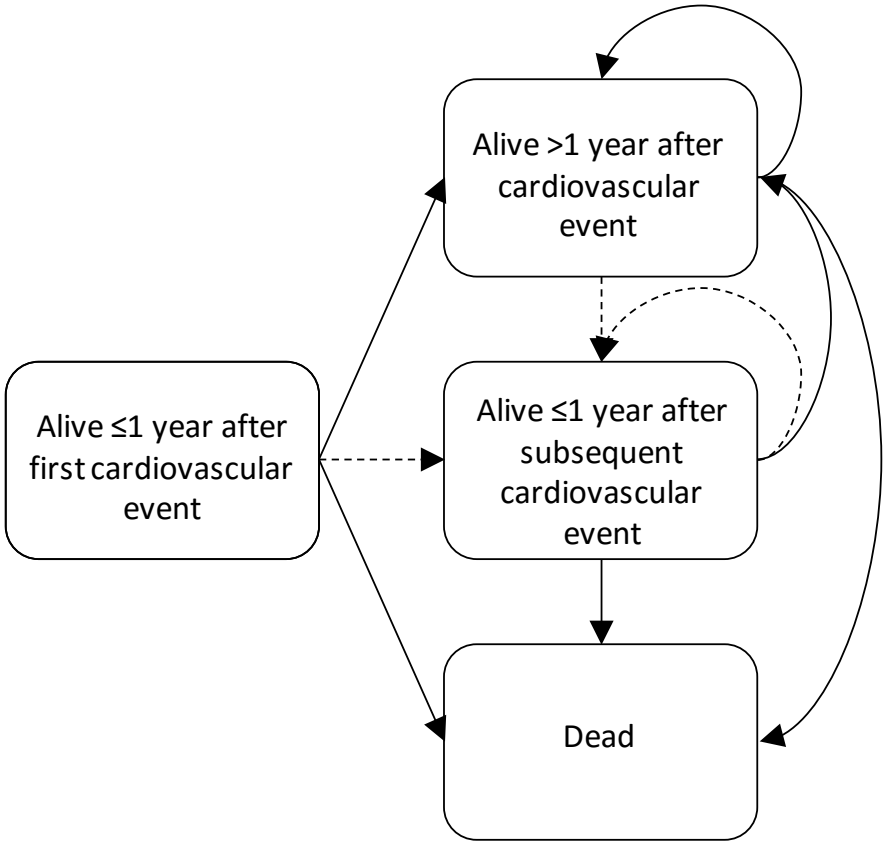

Figure 1. Simplified Markov model states and transitions.
Dashed lines indicate the occurrence of a cardiovascular event. Cardiovascular events comprise myocardial infarction, unstable angina pectoris, stroke, or coronary revascularisation procedure.

Transition probabilities

Most published cost-effectiveness analyses of statins used efficacy data from clinical trials. However, no published clinical trial has directly compared the three proposed interventions. For that reason, we used an indirect approach to estimate efficacy: using the expected decrease in LDL-C concentration for each statin dose to estimate the effects of the statins on reducing the risks of cardiovascular events and death. This approach has been used in several previous statin cost-effectiveness analyses.[29,30,35,45]

We estimated the effect of each statin dose on LDL-C using a network meta-analysis by Naci et al.[46] We then used the relevant reduction in LDL-C to estimate the associated risk reduction of cardiovascular events and death using the meta-analyses conducted by the Cholesterol Treatment

Trialists' collaboration.[20] We estimated the annual risks of cardiovascular events and cardiovascular death using the incidence rates seen in patients in the placebo arms of published clinical trials in secondary prevention populations.[9,12,13] We used published South African mortality statistics to estimate non-cardiovascular mortality rates.[47] We estimated the one-year outcomes after heart attacks, strokes, unstable angina pectoris and coronary revascularisation procedures using published data from various sources.[17,33,48-51]

Costs

We estimated the mean costs of treating cardiovascular events at Groote Schuur Hospital using an ingredients approach for diagnostic tests, drugs and surgical procedures and allocation using the patient day equivalent approach for hospital overhead costs.

We identified a sample of patients admitted to Groote Schuur Hospital between 01 January 2012 and 31 December 2013 using ICD10 codes for heart attack (I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8), stroke (I60.0, I60.1, I60.2, I60.3, I60.4, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.8, I61.9, I62.0, I62.9, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64), and unstable angina pectoris (I20.0). We also identified patients who had cardiac revascularisation procedures such as coronary artery bypass grafts or percutaneous transluminal coronary angioplasty. We included all adult patients (at least 18 years old) with relevant diagnoses or procedures who were admitted for at least one night. We included all relevant admission periods, so some patients had more than one eligible admission.

We used all admissions to estimate mean utilisation of health services according to admission diagnosis, but used 2012 prices to estimate mean costs. We identified all the laboratory tests, and diagnostic and surgical procedures done, and the drugs and blood products given during each eligible admission period. We restricted the tests, products and procedures to those related to treating the cardiovascular event. We obtained the prices paid for laboratory tests, drugs and blood

products from hospital expenditure records. We used Uniform Patient Fee Schedule prices for diagnostic procedures, such as x-rays, CT scans and ECGs, and surgical procedures.[52] Those fees are the prices to be paid by private patients at public sector facilities, and include staff, consumable and overhead costs for the procedures.

We calculated overall hospital overhead costs such as utilities (water, electricity, sewerage), catering, housekeeping, security, hospital management and administrative staff salaries, doctor salaries, and general maintenance using routine hospital accounting data. We used the approach suggested by Barron and Monitcelli to calculate a patient day equivalent: we added all of the inpatient days, half of the day cases and one third of the outpatient visits for the hospital over the time period.[53] We divided the total costs by the patient day equivalent to estimate a mean cost per patient day equivalent for the hospital. We calculated mean lengths of stay according to admission diagnosis using the patient sample. We multiplied the cost per patient day equivalent by the mean lengths of stay to calculate mean hospital overhead costs for each type of cardiovascular event.

We used a similar method to allocate ward costs, which comprised consumables, nurses' salaries, and certain 'ward stock' drug costs which are allocated by ward, rather than to specific patients.

Ethical considerations

We conducted the study in accordance with the Declaration of Helsinki 2008 and the South African Department of Health Good Clinical Practice guidelines.[54,55]

We used only anonymous patient identifiers (hospital numbers) to link patient data from various sources such as hospital, laboratory and pharmacy records. We stored data securely on a password-protected laptop. We did not perform any interventions on patients for the purpose of this analysis and we did not seek any information directly from patients. We therefore did not seek informed consent from patients.

The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee approved the study (reference number: 146/2014, Appendix 1) and the Groote Schuur Hospital superintendent granted permission for data collection at Groote Schuur Hospital.

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Part B: Literature review

Contents

Introduction

In order to allocate scarce resources, healthcare policy makers must know both the efficacy and cost-effectiveness of strategies to prevent or treat diseases. Cost-effectiveness analyses compare interventions in terms of both their costs and consequences and assess their cost-effectiveness, relative to willingness-to-pay thresholds. However, they can't assess affordability, so must be interpreted in terms of the overall impact of the interventions on finite budgets. They are a useful tool for policy-makers though, and are becoming increasingly expected, if not demanded, steps in drug approval processes in many countries. South Africa published guidelines for voluntary pharmacoeconomic evaluations in 2013.[1]

Statins are a class of drug that reduce the risk of cardiovascular events such as myocardial infarctions (heart attacks) and strokes by lowering blood cholesterol concentrations. They have proven efficacy, and many studies (mostly conducted in Europe or North America), have shown them to be a cost effective intervention, particularly for the secondary prevention of cardiovascular events (that is the prevention of further events in patients with existing cardiovascular disease).

This literature review summarises the prevalence of cardiovascular disease in South Africa, describes previously published cost effectiveness analyses of statins, particularly with respect to the methods used, and also discusses relevant data that were used to inform my cost-effectiveness analysis of three strategies for prescribing statins for the secondary prevention of cardiovascular disease from a South African public sector perspective.

Objectives

The objectives of this literature review were:

1. To describe the current epidemiology of cardiovascular disease in South Africa;

2. To describe the current available evidence for the benefits of atorvastatin and simvastatin in the secondary prevention of cardiovascular disease;
3. To describe the current available evidence regarding the cost-effectiveness of statins in the secondary prevention of cardiovascular disease;
4. To summarise important methodological considerations for the conduct of a cost-effectiveness analysis;
5. To summarise relevant efficacy data to inform my cost effectiveness analysis; and
6. To summarise relevant costing data to inform my cost effectiveness analysis.

Cardiovascular disease in South Africa

Data regarding the incidence of cardiovascular diseases in South Africa are limited. Several surveys have estimated the prevalence of heart disease (including previous myocardial infarctions) and previous strokes using patient self-report. The South African National Health and Nutrition Examination Survey (SANHANES) was a cross-sectional survey that was representative of the whole South African population, and took place in 2012.[2] Overall 25 532 people participated in the survey, which comprised an interview, physical examination and measurement of certain disease biomarkers (such as cholesterol concentration). The prevalence of self-reported heart disease was 6.1% (95% confidence interval (CI) 3.9 to 9.3) in those aged 55–64, and 4.4% (95% CI 2.6 to 7.1) in those aged 65 years or older. The prevalence of self-reported stroke was 6.1% (95% CI 4.0 to 9.3) in those aged 55–64, and 9.1% (95% CI 5.2 to 15.5) in those aged 65 years or older. Phaswana-Mufuya et al conducted a national cross-sectional survey among people aged 50 years or older in 2008.[3] In their sample of 3 840 people they found a lower prevalence of self-reported stroke (4.0%), and a prevalence of self-reported angina of 5.2%. Carrillo-Larco et al reported the prevalence of high cardiovascular risk in ten countries, including a sample of 691 people from an urban area in Cape Town, who were surveyed in 2008.[4] In the Cape Town sample the self-reported prevalence of heart disease or previous heart attack was 1.5% (95% CI 0.4 to 5.5) in men younger than 50 years; 4.9%

(95% CI 3.0 to 8.6) in women younger than 60 years; 7.2% (95% CI 3.9 to 12.7) in men 50 years or older; and 12.9% (95% CI 7.9 to 20.3) in women 60 years or older. The self-reported prevalence of previous stroke was 1.0% (95% CI 0.2 to 6.0) in men younger than 50 years; 5.0% (95% CI 2.8 to 8.6) in women younger than 60 years; 7.3% (95% CI 4.3 to 12.1) in men 50 years or older; and 1.8% (95% CI 0.5 to 6.4) in women 60 years or older.

The Global Burden of Disease 2013 study listed stroke as the sixth largest cause of life lost in South Africa (after HIV/AIDS, lower respiratory tract infections, tuberculosis, diarrhoea, and violence); and ischaemic heart disease as the eighth largest (after road accidents).[5]

Statins for the secondary prevention of cardiovascular disease: efficacy

Background: statin drugs

High serum low density lipoprotein cholesterol (LDL-C) concentrations increase the risk of cardiovascular disease. Statins (HMG CoA reductase inhibitors) reduce LDL-C concentrations by inhibiting cholesterol synthesis in the liver.[6] Several trials have demonstrated that statins have a significant benefit over placebo or no treatment, in terms of reducing LDL-C concentrations, and reducing the risk of clinical outcomes such as death, stroke or myocardial infarctions. The benefits of statins have been shown both in patients with raised LDL-C concentrations and those with normal LDL-C concentrations.[7-9]

Patients who have already experienced a cardiovascular event are at increased risk for subsequent events, so local and international guidelines agree that they should receive statins (unless they have contraindications). Some guidelines recommend prescribing a relatively low dose statin at first, with regular LDL-C monitoring, and then increasing the dose if necessary to achieve a target LDL-C concentration.[10,11] Others suggest prescribing a relatively high dose statin, at a fixed dose.[12,13]

Based on current local and international guidelines and local practice, my cost effectiveness analysis compared simvastatin 20 mg (the status quo), atorvastatin 80 mg, and increasing statin doses (from simvastatin 20 mg to simvastatin 40 mg, then atorvastatin 80 mg) based on regular measurement of LDL-C concentrations, to achieve a target LDL-C concentration of <1.8 mmol/L.

Search strategy: efficacy of atorvastatin and simvastatin for the secondary prevention of cardiovascular disease

I conducted a Pubmed search using the following search terms: 'statins', 'efficacy', and 'cardiovascular', restricted to randomised controlled trials.

The full search details were:

(("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statins"[All Fields]) AND efficacy[All Fields] AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields])) AND (Randomized Controlled Trial[ptyp] OR Clinical Trial[ptyp])

Inclusion criteria

- Types of studies: randomised controlled trials.
- Population: adults with a history of cardiovascular disease (eligible for statins for secondary prevention of cardiovascular disease).
- Interventions: atorvastatin or simvastatin (fixed doses or treat to target strategy).
- Comparators: placebo, atorvastatin, simvastatin, treat to target strategy (involving any statins or doses) or placebo.

- Outcomes: change in LDL-C or incidence of cardiovascular events.
- Language: full article available in English.

Results

The search identified 404 potential studies. Additional searches including various combinations of the terms above as well as 'simvastatin', 'atorvastatin', 'secondary prevention', 'low density lipoprotein', and 'target' identified one additional placebo-controlled trial. Eleven studies met the eligibility criteria.

Description of eligible studies

No trial simultaneously compared atorvastatin 80 mg, simvastatin 20 mg and a treat to target LDL-C concentration strategy. No trial compared a fixed dose of either atorvastatin or simvastatin with a treat to target strategy.

Five studies compared either simvastatin or atorvastatin with placebo or usual care. Three studies compared higher doses of either drug with lower doses of the same drug.

The Scandinavian Simvastatin Survival Study (4S) compared simvastatin to placebo in 4 444 patients with angina pectoris or myocardial infarction.[7] Simvastatin dose was increased if necessary to achieve a target LDL-C concentration of <3.0 mmol/L and median follow up was 5.4 years. They reported a relative risk of death of 0.7 (95% confidence interval 0.58 to 0.85). The A to Z trial compared simvastatin 40 mg, increased to 80 mg after one month, with placebo for four months, followed by simvastatin 20 mg in 4 497 patients who had an acute coronary syndrome event.[14] They reported a hazard ratio for cardiovascular death, non-fatal myocardial infarction, acute coronary syndrome or stroke of 0.84 (95% confidence interval 0.76 to 1.04) after two years of follow up. The SEARCH trial compared simvastatin 80 mg and simvastatin 20 mg in 12 064 patients who had a myocardial infarction.[15] They reported a relative risk of coronary death, MI, stroke of

revascularisation procedure of 0.94 (95% confidence interval 0.88 to 1.01) after a median of 6.7 years of follow up.

The Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study compared atorvastatin 80 mg to placebo in 3 086 patients with unstable angina pectoris or non-Q-wave myocardial infarction.[15] The study duration was 16 weeks. They reported a relative risk of death, non-fatal MI, resuscitated cardiac arrest or recurrent myocardial ishaemia of 0.84 (95% confidence interval 0.70 to 1.00). The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study compared atorvastatin 80 mg to placebo in 4 731 patients with a stroke or transient ischaemic attack.[16] Median duration of follow up was 4.9 years. The hazard ratio for stroke was 0.80 (95% confidence interval 0.69 to 0.92). The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study compared atorvastatin to usual care in 1 600 patients with coronary heart disease.[17] Atorvastatin dose was increased from 10 mg to a maximum of 80 mg if necessary to achieve a target LDL-C concentration of <2.6 mmol/L and 86% of the usual care patients received no cholesterol-lowering drugs. Mean duration of follow up was three years. The relative risk for death or coronary event was 0.49 (95% confidence interval 0.27 to 0.73). The Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE) compared atorvastatin with usual care in 2 442 patients with coronary heart disease.[18] Atorvastatin dose was increased from 10 mg to a maximum of 80 mg if necessary to achieve a target LDL-C concentration of <2.1 mmol/L. The drugs received (if any) by the usual care group were not described. Median duration of follow up was 54.3 months. The hazard ratio for cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularisation procedure or unstable angina was 0.83 (95% confidence interval 0.71 to 0.97). The Treating to New Targets (TNT) study compared atorvastatin 80 mg to atorvastatin 20 mg in 10 001 patients with coronary heart disease. Median duration of follow up was 4.9 years. The hazard ratio for coronary death, non-fatal MI, resuscitated cardiac arrest or stroke was 0.78 (95% confidence interval 0.69 to 0.89).

Three studies directly compared atorvastatin and simvastatin (the study settings and primary efficacy results are summarised in Table 1). Marz et al and Olsson et al compared atorvastatin and simvastatin in patients with existing coronary heart disease in terms of their ability to reduce LDL-C to below 2.6 mmol/L.[19,20] In both arms drug doses were increased (if necessary) based on LDL-C measurements. In both studies atorvastatin resulted in a greater proportion of patients reaching target LDL-C concentrations. Pedersen et al compared fixed doses of atorvastatin 80 mg and simvastatin 20 mg in patients who had a previous myocardial infarction.[21] Fewer patients had a major cardiovascular event in the atorvastatin arm, but the difference did not reach statistical significance.

Table 1. Atorvastatin versus simvastatin for the secondary prevention of cardiovascular disease

Study	n	Setting	Intervention	Duration	Primary outcome
Marz et al[19]	3 748	Germany	Atorvastatin 10–40 mg versus simvastatin 10–40 mg	14 weeks	67% of atorvastatin patients and 53% of simvastatin patients reached the target of LDL-C <2.6 mmol/L (p<0.001)
Olsson et al[20]	1 087	Denmark, Finland, Iceland, Norway, Sweden	Atorvastatin 20–40 mg versus simvastatin 20–40 mg	52 weeks	61% of atorvastatin patients and 42% of simvastatin patients reached the target of LDL-C <2.6 mmol/L (p<0.001)
Pedersen et al[21]	8 888	Northern Europe	Atorvastatin 80 mg versus simvastatin 20 mg	Median 4.8 years	Hazard ratio for coronary death, non-fatal MI or resuscitated cardiac arrest of 0.89 (95% CI 0.78 to 1.01)

The benefits of statin therapy relative to no treatment have been clearly demonstrated. Higher doses of atorvastatin relative to lower doses further reduce cardiovascular risk. Those findings led to several international guidelines recommending either high dose statins (at a fixed dose), or treating to a lower target LDL-C concentration than those described in the studies above. The current European Society of Cardiology (ECS)/European Atherosclerosis Society (EAS) guidelines and South African Heart Association/Lipid and Atherosclerosis Society of Southern Africa guidelines recommend titration of statin dose to achieve LDL-C concentrations of below 1.8 mmol/L for

secondary prevention.[10,11] Recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and National Institute for Health and Care Excellence (NICE) in the United Kingdom guidelines recommend atorvastatin 80 mg for secondary prevention unless patients have contra-indications to this drug or dose, or they are at an increased risk of statin side effects or drug interactions.[12,13] They state that there is no randomised controlled trial evidence to support treatment to target LDL-C concentrations, and instead recommend different statin doses for patients at different levels of risk of cardiovascular disease.

Local statin efficacy data

Most of the statin randomised controlled trials described above were conducted in Europe and/or North America. There were 81 South African participants in the A to Z trial, and 523 in the Treating to New Targets trial.[14,22] A PubMed search identified three randomised controlled trials that assessed statins exclusively in South African patients, but all those trials involved the treatment of familial hypercholesterolaemia (a genetic disorder that causes severe elevations in LDL-C) only.[23-25] Those studies are therefore not relevant to this analysis.

Statins for the secondary prevention of cardiovascular disease: cost-effectiveness

Background: assessing cost-effectiveness of interventions

Cost-effectiveness analyses compare health interventions in terms of both their costs and outcomes.[26] Cost-effectiveness analyses express outcomes in natural units, such as cases prevented or life years gained. Cost-utility analyses express outcomes in generic units, such as life years or quality adjusted life years (QALYs). Determining whether or not an intervention is cost effective depends on willingness-to-pay thresholds relevant to the particular setting. In cost effectiveness and cost utility analyses, determining cost-effectiveness involves the calculation of an incremental cost-

effectiveness ratio (ICER): the ratio of the difference in costs and the difference in outcomes between two interventions.[27] The ICER is compared to a threshold at which the payer is assumed to be willing to pay the additional costs in order to gain the additional outcomes.[28] The intervention is deemed cost-effective if it falls below the willingness-to-pay threshold.

Like most countries, South Africa doesn't have an explicitly stated threshold. The World Health Organization CHOICE (CHOosing Interventions that are Cost-Effective) guidelines suggest that an intervention that costs less than a country's GDP per capita per life year gained is highly cost-effective.[29] While interventions that cost below that threshold (per outcome gained) may be considered cost-effective, that does not necessarily mean that the interventions are affordable, given the finite health care budget in the public sector. The budget impact of choosing one intervention over another depends on the prevalence of the condition to be treated. There might also be ethical considerations in terms of resource allocation. That being said, cost-effectiveness analyses can be useful aids to policy-makers. The South African National Department of Health published guidelines for voluntary pharmacoeconomic submissions in 2013.[1]

Search strategy: cost effectiveness of statin therapy for the secondary prevention of cardiovascular disease

To address the objectives:

- to describe the current available evidence regarding the cost-effectiveness of statins in the secondary prevention of cardiovascular disease; and
- to summarise important methodological considerations for the conduct of a cost-effectiveness analysis;

I conducted a PubMed search using the following search terms: 'statins', 'cost effectiveness', and 'secondary prevention'.

The full search details were:

("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statins"[All Fields]) AND ("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]) AND ("secondary prevention"[MeSH Terms] OR ("secondary"[All Fields] AND "prevention"[All Fields]) OR "secondary prevention"[All Fields])

Inclusion criteria

- Types of studies: cost effectiveness or cost utility analyses.
- Population: adults with a history of cardiovascular disease (eligible for statins for secondary prevention of cardiovascular disease).
- Interventions: statin therapy (all statins at all doses).
- Comparators: placebo or alternative statin or dose.
- Outcomes: life years, QALYs or events averted.
- Language: full article available in English.

The inclusion criteria were quite broad to explore the methods used and not only the interventions assessed.

Eligible studies

The search identified 178 articles. I excluded 144 based on review of titles or abstracts. Twenty-five studies met the inclusion criteria. A further seven were potentially eligible but I was unable to access the full text articles. A further two eligible studies were identified through the reference lists of other studies.[30,31]

Most of the studies were conducted in North America or Europe. One was conducted in Hong Kong,[32] one in India,[33] and one in Brazil.[34] The interventions were compared within secondary prevention patients populations: mostly based on large statin randomised controlled trials, but some based on risks derived from meta-analyses or cohort studies.

Interventions and results

Eighteen studies compared the costs and outcomes of statins versus placebo or no statin (their interventions and results are summarised in Table 2). The other nine compared higher dose statins with lower dose statins (summarised in Table 3). None of the studies compared a fixed statin dose with a treat to target LDL-C concentration strategy.

It is difficult to compare the studies directly as many different strategies were compared, and many different outcomes were reported. Although most studies reported ICERs, they were reported in different currencies, and assessed in different settings, so accepted willingness to pay thresholds varied. In general, authors reported that statins could be considered cost-effective when compared to reported ICERs for other cardiovascular interventions, or accepted willingness to pay thresholds. In turn, authors generally reported that higher dose statins were cost-effective relative to lower dose statins. Where subgroup analyses were performed, ICERs tended to be lower for groups at the highest risk of cardiovascular events.

Table 2. Cost-effectiveness of statins in secondary prevention of cardiovascular disease: statins compared to placebo

Study	Setting	Intervention	Time frame	Incremental cost effectiveness ratio	Assumed WTP threshold
Jonsson et al[30]	Sweden	Simvastatin 20–40 mg versus placebo	5.4 years	£5 502 per life year	Not stated
Ashraf et al[35]	United States	Pravastatin 40 mg versus placebo	10 years	$7 124–12 665 per life year gained	Not stated
Johannesson et al[31]	Sweden	Simvastatin 10–40 mg versus placebo	5 years	$5 400 (men) and $10 500 (women) per life year	Not stated
Riviere et al[36]	Canada	Simvastatin 10–40 mg versus placebo	15 years	$6 108–29 888 per life year gained (depending on assumptions regarding duration of statin effects)	Not stated
Muls et al[37]	Belgium	Pravastatin 40 mg versus placebo	10 years	$13 274–24 359 per life year gained (depending on cardiovascular risk factors)	$20 000
Grover et al[38]	Canada	Simvastatin 10–40 mg versus placebo	5.4 years	$4 419–13 404 in men and $4 927–21 719 in women (depending on cardiovascular risk factors)	Not stated
Pickin et al[39]	United Kingdom	Simvastatin 10–40 mg versus placebo	Lifetime	£5 100–12 500 (depending on cardiovascular risk)	Not stated
Tsevat et al[40]	United States	Pravastatin 40 mg versus placebo	Lifetime	$16 000–32 000 per QALY (depending on model)	Not stated
Chau et al[32]	Hong Kong	Pravastatin 40 mg versus placebo	5 years	HK$207 151 per QALY	Not stated
Van Hout et al[41]	Netherlands	Statin versus placebo	5 years	€6 695–9 970 per life year gained	€18 000
Schwartz et al[42]	United States	Atorvastatin 80 mg versus placebo	16 weeks	$4 086 per event avoided	Not stated
Chaplin et al[43]	Netherlands	Fluvastatin 40 mg versus placebo	10 years	€9 312 per QALY; €8 954 per life year	€20 000
Olsson et al[44]	Sweden	Atorvastatin 80 mg versus placebo	16 weeks	€1643.64 per event avoided	Not stated
Scuffham et al[45]	United Kingdom	Fluvastatin 80 mg versus placebo	10 years	£3207 per QALY	£30 000
Fidan et al[46]	England and Wales	Statin versus no statin	10 years	£4 246 per life year gained	£30 000
Kongnakorn et al[47]	United States	Atorvastatin 80 mg versus placebo	Lifetime	$13 916 per QALY	Not stated
Bennet et al[48]	Ireland	Statin versus no statin	10 years	€4 340–6 982 per life year gained	Not stated
Sanmukhani et al[33]	India	Simvastatin 40 mg versus placebo Pravastatin 40 mg versus placebo	5.4 years	₹690 000 to prevent 1 major coronary event and ₹1 690 000 to prevent 1 CHD death ₹2 000 000 to prevent 1 event	Not stated

QALY: Quality Adjusted Life Year; WTP: willingness-to-pay

Table 3. Cost-effectiveness of statins in secondary prevention of cardiovascular disease: high dose statins compared to low dose statins

Study	Setting	Intervention	Time frame	Incremental cost	Assumed WTP threshold
Huse et al[49]	United States	Atorvastatin 10 mg versus simvastatin 10 mg Atorvastatin 10 mg versus pravastatin 20 mg Atorvastatin 10 mg versus lovastatin 20 mg Atorvastatin 10 mg versus fluvastatin 20 mg	Lifetime	Atorvastatin dominates Atorvastatin dominates Atorvastatin dominates $6 169–10 639 (men) & $6 122–22 512 (women) per life year gained, depending on cardiovascular risk	Not stated
Russel et al[50]	Canada	Atorvastatin 10 mg versus simvastatin 10 mg Atorvastatin 10 mg versus pravastatin 20 mg Atorvastatin 10 mg versus lovastatin 20 mg Atorvastatin 10 mg versus fluvastatin 20 mg	Lifetime	Atorvastatin dominates Atorvastatin dominates Atorvastatin dominates CDN$9 655–18 736 (men) & CDN$12 333–45 383 (women) per life year gained, depending on cardiovascular risk	Not stated
Lindgren et al[51]	Denmark Finland Norway Sweden	Atovastatin 80 mg versus simvastatin 20–40 mg	Lifetime	€31 179 per QALY €41 381 per QALY €23 261 per QALY €28 847 per QALY	€50 000 €50 000 €50 000 €50 000
Mark et al[52]	United States	Atorvastatin 80 mg versus 10 mg	5 years	$8 964 to prevent one coronary artery disease death, non-fatal MI, resuscitation from cardiac arrest or stroke	60% probability of cost-effectiveness at WTP threshold of $15 000
Wagner et al[53]	Canada	Atorvastatin 80 mg versus 10 mg	Lifetime	Canadian$ 11 969 per QALY (95% CI 5 469 to 40 531)	Canadian$50 000
Taylor et al[54]	United Kingdom Spain Germany	Atorvastatin 80 mg versus 10 mg	Lifetime	€9 500 per QALY €21 000 per QALY €15 000 per QALY	€29 400 €30 000 €50 000
Ara et al[55]	United Kingdom	Atorvastatin 80 mg versus simvastatin 40 mg Rosuvastatin 40 mg versus simvastatin 40 mg	Lifetime	£17 469 per QALY £12 484 per QALY	£20 000
Fragoulakis et al[56]	Greece	Rosuvastatin 40 mg versus atorvastatin 40 mg, simvastatin 40 mg and pravastatin 40 mg	20 years	Rosuvastatin dominated other treatments	Not stated
Ribeiro et al[34]	Brazil	Low dose (simvastatin 10 mg) versus no statin Intermediate dose (atorvastatin 10 mg, simvastatin 40 mg) versus low dose High dose (atorvastatin 20–80 mg, rosuvastatin 20 mg) versus intermediate dose	Lifetime	Int$2 827 per QALY Int$3 526 per QALY Int$40 418 per QALY	Int$11 770

QALY: Quality Adjusted Life Year; WTP: willingness-to-pay

Methodology of eligible studies

Statin efficacy estimates

Nine studies were based directly on the efficacy results of clinical trials, and were conducted over the time frame of the relevant study (Table 4). Some studies extrapolated costs and clinical outcomes beyond the time period of the clinical trials (Table 5). Both those types of analyses were restricted to direct comparisons of the statins and doses that were used in clinical trials.

Table 4. Cost-effectiveness analyses of statins in secondary prevention of cardiovascular disease: efficacy estimates based directly on clinical trial results

Study	Source of efficacy estimate
Jonsson et al[30]	Scandinavian Simvastatin Survival Study (4S)[7]
Johannesson et al[31]	4S study[7]
Grover et al[38]	4S study[7]
Chau et al[32]	Cholesterol and Recurrent Events (CARE) study[9]
Van Hout et al[41]	CARE,[9] 4S[7] & Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)[8] studies
Schwartz et al	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study[57]
Olsson et al[44]	MIRACL study[57]
Mark et al[52]	Treating to New Targets (TNT) study[22]
Sanmukhani et al[33]	CARE,[9] 4S[7] and LIPID[8] studies

Table 5. Cost-effectiveness analyses of statins in secondary prevention of cardiovascular disease: long term benefits extrapolated from clinical trials

Study	Source of efficacy estimate
Ashraf et al[35]	Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC) I & II studies[58,59] Framingham Heart Study[60]
Riviere et al[36]	Scandinavian Simvastatin Survival Study (4S)[7]
Muls et al[37]	PLAC I & II studies[58,59] and Framingham Heart Study[60]
Pickin et al[39]	4S[7] and UK actuary data
Tsevat et al[40]	Cholesterol and Recurrent Events (CARE) study[9]
Chaplin et al[43]	Lescol Intervention Prevention Study (LIPS)[61]
Scuffham et al[45]	LIPS[61]
Lindgren et al[51]	Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) study[21]
Wagner et al[53]	Treating to New Targets (TNT) study[22]
Taylor et al[54]	TNT study[22]
Kongnakorn et al[47]	Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[16] Saskatchewan health data

Several other cost effectiveness analyses compared statin effects indirectly, using data regarding the relative effects of statins on LDL-C and risk of cardiovascular events, to compare statins or doses not directly tested within a clinical trial (Table 6). Huse et al used United States Food and Drug Administration labelling as a source for the effects of various statins on LDL-C concentrations.[49] They used those reductions to estimate the relative risk of cardiovascular events based on risk tables derived in the Framingham Heart Study.[60] Russel et al used a similar method in their analysis: they also used Framingham Heart Study risk tables, but used the results of an eight-week clinical trial as a source of data for the reduction in LDL-C by various statins.[50,60,62] Fidan et al and Bennet et al used the relative reduction in mortality rates from published clinical trials and meta-analyses to estimate the number of deaths prevented by statin treatment in general in the secondary prevention population.[46,48] They did not list the specific data sources in the article, but referred readers to a website.[63] Ara et al used data from 28 clinical trials (combined using a mixed treatment comparison model) to estimate the effects of various statin doses on LDL-C cholesterol.[55] They then used a published meta-analysis as a source for the relative risk reduction of cardiovascular events associated with each 1 mmol/L decrease in LDL-C concentration.[64] Fragoulakis used a published meta-analysis as a data source for the effect of various statins on LDL-C, and estimated the risks of cardiovascular events using a risk table calibrated to the Greek population.[56,65,66] Ribeiro et al used a published meta-analysis of the relative risk reduction of cardiovascular effects of various statins and doses, grouped by their expected effect on LDL-C.[34,67] The data sources for the studies that compared statins effects indirectly are summarised in Table 5.

Table 6. Cost-effectiveness of statins in secondary prevention of cardiovascular disease: outcomes extrapolated indirectly from changes in low density lipoprotein cholesterol concentrations

Study	Source of relative risks of cardiovascular events and efficacy estimates
Huse et al[49]	FDA labelling and Framingham Heart Study[60]
Russel et al[50]	Clinical trial[62] and Framingham Heart Study[60]
Fidan et al[46]	IMPACT model[63]
Bennet et al[48]	IMPACT model[63]
Ara et al[55]	Mixed treatment comparison of 28 clinical trials. Meta-analysis of efficacy studies.[64]
Fragoulakis et al[56]	Meta-analysis of statin effects.[65] HellenicSCORE.[66]
Ribeiro et al[34]	Meta-analysis of statin effects.[67] Statins grouped by expected effect on LDL-C

Outcomes

Most of the published economic evaluations are cost effectiveness analyses, expressing outcomes in natural units such as life years gained or cardiovascular events prevented (Tables 1 and 2). Several studies are cost utility analyses, and express outcomes in quality-adjusted life years. None of the studies captured quality of life data prospectively. Instead they used quality of life weighting factors from other published studies to estimate QALYs.

Study perspective and costing data

The vast majority of the economic evaluations are from the provider perspective, and estimated direct medical costs only, although one captured data regarding productivity losses too.[51] All trials included the costs of the statin medication, usually derived from national formularies or reimbursement costs. Many excluded other concomitant medication, on the assumption that such costs would be similar between the intervention groups. Some included out-patient visits and laboratory costs related to statin use, while others didn't mention those intervention costs. Most calculated the costs of treating cardiovascular events such as myocardial infarctions or strokes using diagnosis related groups (DRGs) reimbursement costs. DRGs are based on healthcare resource utilisation and are used to calculate costs for treating illness according to many different patient types. DRGs are used in prospective payment systems such as Medicare in the United States. Other studies used costs from published studies conducted in similar settings. Sanmukhani et al included intervention costs only, and didn't include the costs of treating events.[33] Most of the published economic evaluations discounted costs and outcomes at rates of 3–5%.

Analysis

Most of the analyses used Markov modelling, usually over a five-year and/or lifetime timeframe, with annual cycles. Most calculated cost-effectiveness ratios that the authors compared to accepted

willingness-to-pay thresholds in order to make decisions regarding the cost-effectiveness of the interventions assessed.

Methodology of cost-effectiveness analyses

My review of relevant cost-effectiveness literature identified several important considerations for my analysis. Firstly, to my knowledge there are no published studies that have assessed health-related quality of life among patients with chronic cardiovascular disease in South Africa. For that reason, a cost-effectiveness analysis, calculating outcomes in terms of life years, was more appropriate than a cost-utility analysis. Secondly, there are several published cost-effectiveness analyses that based their efficacy estimates on indirect comparisons of statins, and conducted their analyses using Markov models. My analysis used this indirect approach as there are no published randomised controlled trials that directly compared the interventions assessed. Thirdly, as none of the analyses were conducted in South Africa, and I was unable to find suitable costing data (see below), I had to estimate the costs of treating cardiovascular events for my analysis. Finally, the literature search highlighted the importance of conducting sensitivity analyses in cost-effectiveness analyses.

Markov models

Markov models are used to calculate the costs and consequences of a particular intervention over time, and are thus particularly valuable when assessing chronic conditions such as prevention of myocardial infarction or strokes.[68] Markov models assume patients are always in one of several finite, discrete, health states, for a fixed length of time – the Markov cycle. Over time, patients can move from one state to another: transition probabilities describe the chance of transition from one state to another at the end of each Markov cycle.

Of particular relevance for this analysis, Markov models allow for the synthesis of data regarding costs and outcomes from various different sources.[69] They also allow one to extrapolate costs and outcomes beyond those observed in (relatively) short clinical trials, and as well as to link intermediate outcomes (such as reduction in LDL-C) to final outcomes (such as death).

Costing

The costs that are included in a cost-effectiveness analysis depend on the perspective of the analysis. My analysis was conducted from the provider perspective, so I included the costs of cardiovascular event-related hospital admissions, as well as the costs of the interventions, only. In general, costs are calculated by estimating the quantity of resources consumed, and multiplying that by the costs of the resources.[26] Microcosting, where utilisation of each resource is estimated individually, is considered more accurate than gross costing, which involves estimating overall costs per day across all patients. Tan et al (Netherlands) found microcosting to be more accurate than gross costing when estimating hospital admission costs for appendicectomy, normal delivery, stroke, and myocardial infarction.[70] Heerey et al (Ireland) found microcosting to be more accurate than using estimates based on Diagnostic Related Groups when estimating hospital admission costs for myocardial infarction, cardiac failure and HIV.[71] Both studies used patient utilisation data and unit costs to estimate costs of diagnostic tests, procedures and drugs, and used mean costs per patient day to estimate hotel costs (Tan et al) and nursing and medical salaries (Heerey et al). Barron and Monitcelli suggest estimating the mean cost per patient day by dividing the total hospital expenditure by the patient day equivalent, which is calculated by adding all inpatient days, half of day cases, and one third of outpatient visits.[72] I used patient utilisation data to estimate the costs of drugs, diagnostic tests, and surgical procedures and used a patient day equivalent approach for staff salaries and hospital overhead and hotel costs.

Uncertainty and sensitivity analyses

Briggs identifies four main sources of uncertainty in economic evaluations: data sources and sampling; extrapolation of data (for example using an intermediate outcome to estimate effects on mortality or morbidity); methods used (for example choice of discount rate); and generalisability of results to other settings.[73] He suggests assessing the effects on results of varying important efficacy and cost estimates through one-way, multiway and threshold analysis, as well as using 'extreme scenario' analyses. All of those are relevant to my analysis.

Data sources to inform cost-effectiveness analysis: efficacy

To my knowledge there are no randomised controlled trials that directly compare fixed statin doses with treating to a target cholesterol concentration. The effects of treating to target were assessed in several studies described above, but to my knowledge no trials have assessed the effects of treating to the new (lower) targets described in recent guidelines. For those reasons I used an indirect approach to assess the relative efficacy of the proposed strategies for my cost effectiveness analysis, similar to the approaches used by Ara et al, Huse et al and Russel et al (described above).[49,50,55]

To find relevant data regarding the effects of statins on LDL-C and risk of cardiovascular disease, I conducted a PubMed search using the terms 'statins' and 'low density lipoprotein cholesterol', restricted to meta-analyses.

The full search details were:

(("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statin"[All Fields]) AND ("cholesterol, ldl"[MeSH Terms] OR ("cholesterol"[All Fields] AND "ldl"[All Fields]) OR "ldl cholesterol"[All Fields] OR ("low"[All Fields]

AND "density"[All Fields] AND "lipoprotein"[All Fields] AND "cholesterol"[All Fields]) OR "low density lipoprotein cholesterol"[All Fields])) AND Meta-Analysis[ptyp]

The search identified 211 articles. Many of the studies were unsuitable for the purposes of my analysis as they assessed the effects of one particular statin only, or were conducted within a certain patient sub-population (for example patients with diabetes or renal disease). Others assessed statins overall, rather than by specific doses, or listed cardiovascular risk reduction by statins overall, rather than in the secondary prevention population. Some were completed before some of the major clinical trials had been published. Two were assessed as most relevant for my analysis.

Naci et al conducted a systematic review of randomised controlled trials that compared statins with placebo, or with other statins, in terms of their effect on LDL-C concentrations.[74] They included 181 trials, and used a network meta-analysis to directly or indirectly compare the effects on LDL-C of all the statins and doses studied. They estimated that atorvastin doses greater than 40 mg resulted in a mean decrease in LDL-C of 1.57 mmol/L (95% credible interval 1.31 to 2.07); doses of simvastatin 11–20 mg resulted in a mean decrease in LDL-C of 1.07 (95% credible interval 0.7 to 1.56); and doses of simvastatin 21–40 mg resulted in a mean decrease in LDL-C of -1.42 (95% credible interval 1.03 to 1.91).

The Cholesterol Treatment Trialists' (CTT) collaboration conducted a meta-analysis of statin randomised controlled trials using individual patient data.[75] Studies were eligible for inclusion if they enrolled at least 1 000 patients, and had at least two years' duration of treatment. They estimated that in patients with previous coronary heart disease, the rate ratio of cardiovascular events per 1 mmol/L reduction in LDL-C was 0.79 (95% confidence interval 0.76 to 0.82).

Data sources to inform cost-effectiveness analysis: costs of treating cardiovascular events in South Africa

I conducted a series of PubMEd searches to identify potential costing data sources for my analysis. Using the terms 'cost', 'myocardial infarction', and 'South Africa' identified 14 potential articles; and 'cost', 'stroke', and 'South Africa' resulted in 65 potential articles. Similar searches using the terms 'unstable angina pectoris' and 'revascularisation procedure' identified no articles. Three studies reported hospitalisation costs for myocardial infarction or stroke, but all were based on medical aid schemes' data or diagnosis related groups. No studies reported costs from a public health care sector perspective.

Moodley et al used a large private medical aid database to estimate mean hospitalisation costs for various events in patients receiving statins in 2003-2004.[76] They reported mean costs of R13 513 ($1 797) for myocardial infarction, R94 237 ($12 535) for stroke, R51 317 ($6 826) for ischaemic heart disease, and R54 919 ($7 305) for percutaneous transluminal coronary angioplasty. Bergh et al (published in 2013) used medical aid claim data to estimate the median hospitalisation costs of strokes and myocardial infarctions to use in a cost effectiveness analysis of dabigatran.[77] They reported a median cost of R10 156 to 39 353 ($1 045 to 4 091), depending on assumed disability after the stroke, and R78 869 ($8 199) for myocardial infarction). Torborg et al used a private medical aid scheme's costs according to diagnosis related groups in their cost effectiveness analysis of post-operative troponin monitoring.[78] The hospitalisation costs for a myocardial infarction ranged from R27 684.26 to 59 145.94 ($2 553 to 5 454).

Summary

Statins reduce the risk of cardiovascular events such as angina, heart attacks and strokes, by lowering low density lipoprotein cholesterol (LDL-C) concentrations. Several studies, mostly

conducted in Europe or North America, have demonstrated the cost-effectiveness of statins in the secondary prevention of cardiovascular disease. Some guidelines recommend increasing statin doses until target LDL-C concentrations are achieved, while others recommend prescribing a fixed statin dose without monitoring LDL-C.

Identification of areas for further research

Despite their widespread use, there are no published cost-effectiveness analyses of statins for the secondary prevention of cardiovascular disease in South Africa. There are also only limited efficacy data from clinical trials and no costing data of cardiovascular events from a public healthcare sector perspective.

Given the burden of cardiovascular disease in South Africa, it is important to establish whether interventions aimed at preventing cardiovascular disease are not only effective, but cost effective too. I estimated the costs of hospitalisation for myocardial infarctions, strokes, unstable angina pectoris and coronary revascularisation procedures using a sample of patients from a public sector hospital; and compared the costs and outcomes of prescribing statins at fixed doses versus treating to target LDL-C using efficacy estimates from published meta-analyses. The results might be used to help guide policy regarding secondary prevention of cardiovascular disease in South Africa.

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Part C: Manuscript

This manuscript was prepared according to the instructions for authors for the journal Cost Effectiveness and Resource Allocation (Appendices 2 and 3). The format deviates from the instructions in that the figure is inserted within the text, and co-authors are listed in a footnote on the title page, as per the MPH guidelines for mini dissertation.

Word count: 3 468 (excluding tables, figure and references)

Abstract: 350

Cost-effectiveness analysis of alternative statin prescribing strategies for the secondary prevention of cardiovascular disease at a South African public sector tertiary hospital

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Key words: statins, HMG-CoA reductase inhibitors, cost effectiveness, secondary prevention, cardiovascular disease

Abstract

Background

Statins reduce the risk of cardiovascular events such as angina, heart attacks and strokes, by lowering low density lipoprotein cholesterol (LDL-C) concentrations. Some guidelines recommend increasing statin doses until target LDL-C concentrations are achieved (treat to target: TTT), while others recommend prescribing a fixed statin dose without monitoring LDL-C. Monitoring LDL-C is relatively expensive compared to the cost of statins, but there is limited evidence that it might improve adherence. We explored the cost-effectiveness of three statin prescribing strategies for the secondary prevention of cardiovascular events at a South African public sector tertiary hospital.

Methods

We compared the costs and outcomes (life years), from a provider perspective, of TTT, or prescribing atorvastatin 80 mg without LDL-C monitoring, with the status quo, simvastatin 20 mg without LDL-C monitoring. We constructed a Markov model with annual cycles; a five-year timeline; starting age of 60 years; and the following health states: ≤1 year after first cardiovascular event, ≤1 year after subsequent cardiovascular event, >1 year after any cardiovascular event, and dead. We estimated cardiovascular event and intervention costs using hospital expenditure and utilisation records. We estimated transition probabilities using published literature. We discounted costs and outcomes at 3% per year. We explored alternative scenarios and timelines in sensitivity analyses.

Results

Atorvastatin 80 mg without LDL-C monitoring was both the cheapest and most effective option over a five-year period. It remained the most effective option over a lifetime period, but with an incremental cost-effectiveness ratio (ICER) of $146.94 per life year gained relative to the status quo. TTT was as effective as atorvastatin 80 mg if we assumed adherence rates of 80% and 60%

respectively, but with an ICER of $54930.96. TTT would dominate atorvastin 80 mg only if the frequency of LDL-C monitoring was reduced from 3-monthly to 6-monthly until targets were reached, and the cost of LDL-C monitoring decreased by $9.25 (84%).

Conclusions

Fixed-dose statin treatment without cholesterol monitoring is the most cost-effective option for providing statins for the secondary prevention of cardiovascular disease. The costs of regular LDL-C monitoring currently make a treat to target strategy unaffordable in our setting.

Background

The prevalence of cardiovascular disease is increasing in South Africa.[1] High serum concentrations of low density lipoprotein cholesterol (LDL-C) increase the risk of cardiovascular disease.[2, 3] Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are a class of drugs that lower LDL-C concentrations by inhibiting cholesterol synthesis in the liver, and have been shown to reduce the risk of cardiovascular events such as angina, heart attacks and strokes.[4] Several different strategies for prescribing statins have been proposed. This analysis focuses on strategies proposed for the secondary prevention of cardiovascular disease; that is the prevention of further cardiovascular events in those patients who have already experienced a cardiovascular event.

According to some South African and European guidelines, patients with existing atherosclerotic cardiovascular disease should start statin treatment at a dose based on their baseline LDL-C concentrations.[3, 5] LDL-C should be monitored regularly, and statin dose should be increased if necessary to achieve an LDL-C concentration <1.8 mmol/L. In contrast, guidelines from the United States and United Kingdom recommend a fixed high dose statin, namely atorvastatin 80 mg, for secondary prevention and measurement of LDL-C at baseline, at around three months after treatment initiation, and then only as indicated clinically.[6, 7]

Statin drug costs are decreasing over time, but monitoring LDL-C concentrations remains relatively expensive. In addition, there is evidence that in practice clinicians rarely increase statin doses as recommended, even in settings where frequent LDL-C monitoring is standard practice.[8-11] This raises the question of whether statins could or should be prescribed at a fixed dose without LDL-C monitoring. Some authors argue that measuring LDL-C concentration is essential to ensure patients' adherence to statin therapy, but there is little evidence to support this.[12]

Current practice at Groote Schuur Hospital, a public sector tertiary hospital in Cape Town, South Africa is to prescribe a fixed dose of simvastatin 20 mg, with LDL-C measured at baseline only (along

with a full screening lipogram to exclude familial hypercholesterolaemia), with no further LDL-C monitoring. This analysis explores the cost-effectiveness of prescribing statins according to LDL-C concentrations, or prescribing a high dose statin without LDL-C monitoring, relative to the status quo.

Methods

Study design

We conducted a cost-effectiveness analysis from a public sector provider perspective. We compared the costs and outcomes (in terms of life years) of simvastin 20 mg, atorvastatin 80 mg (both without cholesterol monitoring) and adjusting statin doses based on cholesterol concentration for the secondary prevention of cardiovascular events using a Markov model. We estimated cardiovascular event costs using an ingredients approach as well as allocation of costs according to inpatient days. We estimated transition probabilities using published literature. Strategies were compared using an incremental cost-effectiveness ratio and those showing higher costs and lower effectiveness than an alternative were eliminated through absolute dominance. All costs were expressed in 2012 prices, converted to United States (US) dollars using an average 2012 exchange rate of $0,12227/R1.[13] We discounted costs and outcomes at 3% per year.

Population

The study population comprises patients requiring secondary prevention of cardiovascular events at Groote Schuur Hospital.

Interventions

The status quo comprises simvastatin 20 mg daily, regardless of cholesterol concentration, with a baseline lipogram, but no further cholesterol monitoring. The atorvastatin arm comprises atorvastatin 80 mg daily, also with a baseline lipogram but no further cholesterol monitoring (a ‘fire-

and-forget' approach). In the treat-to-target arm, patients have a baseline lipogram and LDL-C monitoring and dose changes based on the following assumptions. A literature search revealed no published data regarding the baseline LDL-C concentrations of the population served by Groote Schuur Hospital. But in a cohort of 2 182 patients at Chris Hani Baragwanath Hospital in Johannesburg, baseline LDL-C concentrations were between 2.4–3.0 mmol/L depending on ethnicity.[14] So for the purposes of this analysis we assumed that everyone would start at simvastatin 20 mg (10–20 mg is recommended for those baseline concentrations).[3] A local guideline recommends measuring LDL-C concentrations every 8±4 weeks, and increasing statin dose if the target concentration is not reached.[3] While several local (and international) studies have shown that only around 10–50% of patients achieve target concentrations at those low doses, in practice, patients tend to stay on their starting dose, rather than having their doses increased.[8-11, 15] We assumed a best-case scenario, where concentrations not at target resulted in a dose increase according to recommendations. We conservatively assumed that 50% of patients had their dose increased to simvastatin 40 mg after 3 months of treatment, then 50% of those patients had a further dose increase, to atorvastatin 80 mg, at 6 months. The proportion of patients at the various doses then remained unchanged for subsequent model cycles (i.e. 50% on simvastatin 20 mg; 25% on simvastatin 40 mg; and 25% on atorvastatin 80 mg). We explored alternative prescribing scenarios in sensitivity analyses.

Costs of cardiovascular events

We estimated the costs of treating myocardial infarction, unstable angina, coronary revascularisation procedures and strokes using a sample of patients from Groote Schuur Hospital. We included all adult (>18 years) patients with relevant ICD10 codes or procedures (coronary artery bypass grafts or percutaneous transluminal coronary angioplasty), who were admitted between 01 January 2012 and 31 December 2013, and spent at least one night in a hospital ward. Some patients were admitted more than once during the period. During the two-year sampling period, 1 604

patients were admitted with relevant ICD10 diagnoses or procedures. We excluded five who were <18 years old; 31 with missing age data; and 14 with missing ward stay or cost centre data. Patient and admission numbers and characteristics are shown in Table 1.

Table 1: Characteristics according to diagnosis of 1 554 patients during 1 797 admissions to a South African public sector tertiary hospital

	Myocardial infarction	Unstable angina	Coronary revascularisation	Stroke
Patients				
n	434	586	182	519
Age, years (median (IQR))	59 (50–67)	57 (49–64)	58 (52–64)	51 (40–64)
Male (n (%))	282 (65)	362 (62)	131 (72)	233 (45)
Admissions				
n	446	630	183	538
Length of stay, days (mean (95% CI))	4.2 (3.8 to 4.6)	4.9 (4.4 to 5.4)	12.3 (10.7 to 13.9)	13.1 (12.2 to 13.9)

CI: confidence interval; IQR: interquartile range

We used all sample patients to estimate health services utilisation using hospital expenditure records, and calculated costs using 2012 prices or hospital expenditure. We estimated the mean costs of laboratory tests, drugs, blood products and diagnostic and surgical procedures per inpatient day, then multiplied those costs by the mean length of stay to estimate the mean cost of admission for each of the cardiovascular events. We obtained the prices of drugs, laboratory investigations, and blood products from hospital expenditure records. We estimated the costs of diagnostic investigations (such as xrays, CT scans and ECGs) and surgical procedures using the Uniform Patient Fee Schedule, which lists fees to be paid by private patients at public sector facilities.[16]

We calculated overall hospital overhead costs such as utilities (water, electricity, sewerage), catering, housekeeping, security, hospital management and administrative staff salaries, doctor salaries, and general maintenance using routine hospital accounting data. We assumed that all patients, regardless of diagnosis, consumed roughly the same amount of overhead resources. Following the standard approach in this setting, we calculated a patient day equivalent for Groote Schuur Hospital by adding all the inpatient days, half of the day cases and one third of the outpatient

120 visits over the time period, and divided the total cost by the patient day equivalent, to estimate the
121 cost per patient day equivalent. [17] We used a similar method to allocate ward costs, which
122 comprised consumables, nurses' salaries, and certain 'ward stock' drug costs which are allocated by
123 ward, rather than to specific patients. Mean hospitalisation costs for each cardiovascular event are
124 shown in Table 2.

125 Based on published estimates we assumed that 50% of stroke-related deaths and 30% of coronary
126 heart disease-related deaths occurred in hospital.[18-26] We included the costs of in-hospital
127 deaths, but not those deaths that occurred out of hospital. We also did not include costs of deaths
128 due to other causes.

129 We used Microsoft Excel and Stata 13.0 for data management and cost calculations.[27]

Table 2. Mean hospitalisation costs according to diagnosis at a South African public sector tertiary hospital in 2012 United States dollars

Cost category	Myocardial infarction		Unstable angina		Coronary revascularisation procedures		Stroke	
	Inpatient day	Admission	Inpatient day	Admission	Inpatient day	Admission	Inpatient day	Admission
Hospital	158.22	659.78	158.22	773.70	158.22	1950.86	158.22	2069.53
Ward	231.71	966.23	226.03	1105.28	251.54	3101.53	279.81	3659.93
Surgical procedures	218.02	909.14	275.35	1346.47	302.35	3727.92	27.68	362.10
Diagnostic procedures	46.38	193.42	39.78	194.51	28.73	354.24	108.19	1415.18
Laboratory investigations	30.94	129.00	26.65	130.34	24.98	307.99	10.29	134.64
Drugs	9.47	39.46	3.76	18.38	1.49	18.42	5.26	68.85
Blood products	12.98	54.14	16.43	80.36	61.69	760.62	2.87	37.49
Total	**707.72**	**2951.17**	**746.22**	**3649.03**	**829.00**	**10221.59**	**592.33**	**7747.72**

130

Intervention costs

The costs associated with providing statins according to the status quo include: the annual cost of simvastatin 20 mg; one lipogram at baseline only (first year); and two outpatient visits per year. The costs associated with providing statins according to the 'fire and forget' strategy include: the annual cost of atorvastatin 80 mg; one lipogram at baseline only (first year); and two outpatient visits per year. The costs associated with providing statins according to the 'treat to target' strategy include: annual drug costs (according to the proportion of patients expected to be receiving each statin dose), regular LDL-C monitoring, and clinic visits. Treat to target guidelines recommend 3 monthly monitoring until patients are at target, followed by 6 monthly monitoring. As described above, we assumed that 50% of patients would reach their target LDL-C concentration by 3 months, and a further 25% by 6 months. This results in a mean of 2.75 clinic visits and LDL-C measurements in the first year, and two per year thereafter. We calculated clinic overhead and consumable costs using Groote Schuur Hospital expenditure and utilisation data as described above for hospitalisation costs. The unit costs of the drugs, outpatient visits, and laboratory monitoring are shown in Table 3.

Table 3. Costs of providing statins for secondary prevention of cardiovascular events at a South African public sector tertiary hospital in 2012 United States dollars

Outpatient visit	
Cardiac or general medicine clinic	105.48
Annual drug costs	
Simvastatin 20 mg	8.27
Simvastatin 40 mg	16.23
Atorvastatin 80 mg	79.53
Laboratory costs	
Lipogram	24.22
LDL-cholesterol	10.96

Markov model

We constructed a Markov model with the following health states: alive in the first year of treatment; alive in subsequent years of treatment; alive within one year of myocardial infarction; alive within one year of unstable angina pectoris; alive within one year of stroke; alive within one year of

149 coronary revacularisation procedure; and death (Figure 1). We used a five-year timeline with a
150 starting age of 60 years, and cycles of one year. We used TreeAge Pro 2015 software for the cost-
151 effectiveness analysis.[28]

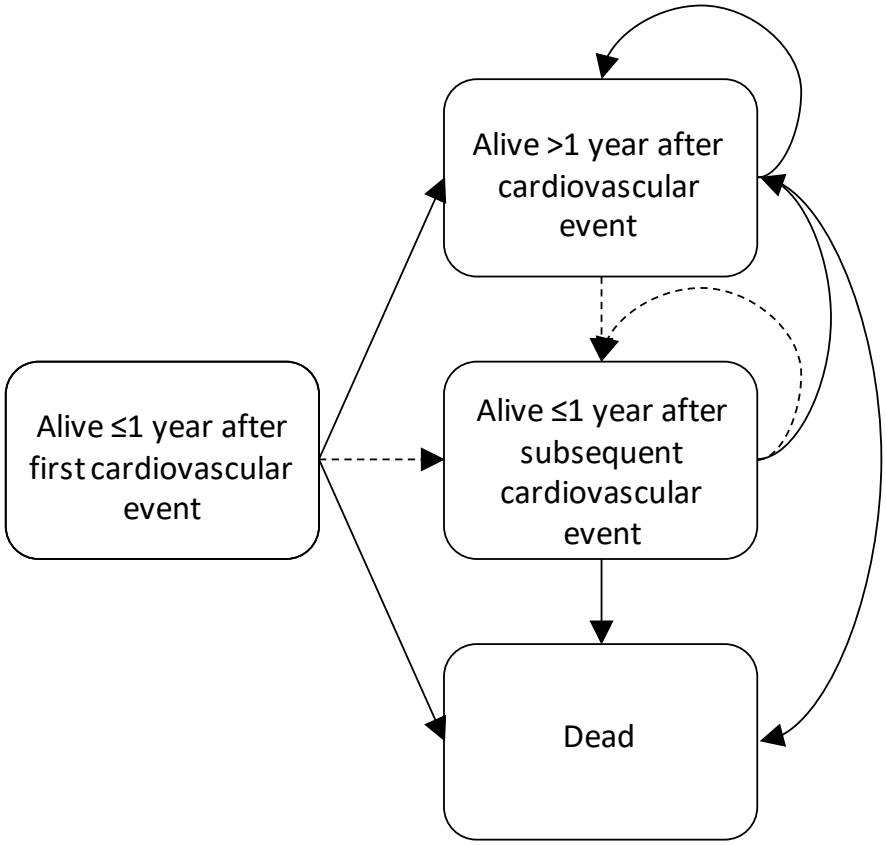

Figure 1. Simplified Markov model states and transitions.
Dashed lines indicate the occurrence of a cardiovascular event. Cardiovascular events comprise myocardial infarction, unstable angina pectoris, stroke, or coronary revascularisation procedure.

152 ## Transition probabilities

153 We estimated the effects of statin treatment by multiplying the risk reduction of major
154 cardiovascular events associated with each statin dose by the expected annual incidence of those
155 events in patients who are not on statins. Data regarding the incidence of those events in South
156 Africa are extremely limited. International cohort studies generally recruit patients who are already
157 on statins. For those reasons we estimated the annual incidences (in those not on statins) of
158 myocardial infarction, unstable angina pectoris, stroke, and coronary revascularisation procedures,
159 as well as cardiovascular mortality, from the placebo groups of three large international clinical trials

of statins in patients with existing cardiovascular disease, with follow up periods of around five years (Table 4). We estimated age-specific mortality from other causes by subtracting cardiovascular and cerebrovascular deaths from overall deaths using published South African mortality tables.[29] Naci et al conducted a network meta-analysis of 181 randomised controlled trials to estimate the average effect on LDL-C concentrations of various statins at various doses.[30] The Cholesterol Treatment Trialists' Collaboration conducted a meta-analysis of 26 randomised controlled trials to estimate the average risk reduction per 1 mmol/L reduction in LDL-C overall and for various patient subgroups.[4] They estimated a risk reduction of 0.79 for major cardiovascular events in those patients with existing cardiovascular disease. We used those two meta-analyses to estimate the risk reduction associated with the three statin doses in our analysis (Table 5).

Table 4. Annual transition probabilities in patients with existing cardiovascular disease

Event	Transition probability	Reference
Myocardial infarction	0.016	[31-33]
Unstable angina pectoris	0.038	[32, 33]
Stroke	0.007	[31-33]
Coronary revascularisation procedure	0.030	[31-33]
Cardiovascular death	0.017	[31, 33]
Cerebrovascular death	0.011	[31, 33]
Death – other causes	Varies by age	[29]

Table 5. Risk reduction of cardiovascular events by statins

Statin	Effect on LDL-C[30]	RR[1] per 1 mmol/L decrease[4]	Rate ratio
Simvastatin 20 mg	-1.07	0.79	0.7753
Simvastatin 40 mg	-1.42	0.79	0.7018
Atorvastatin 80 mg	-1.57	0.79	0.6703

1. Rate ratio

We used estimated transition probabilities for one-year outcomes after cardiovascular events from various sources (Table 6). The outcomes are for those already on statin treatment, and for the purposes of our analysis are the same for all treatment groups. As for the incidence of events, South African data regarding outcomes after events are extremely limited. Wagner et al listed outcomes after events from the Treating to New Targets clinical trial, which compared atorvastatin 10 and 80 mg.[34] Data from this trial are appropriate for our analysis as the trial population comprised

patients with existing cardiovascular disease, and all trial patients received statin treatment.[35] In addition, 523 (of 10 001) participants were South African. The authors report that probabilities of outcomes after events were similar across treatment groups, so we did not adjust the probabilities according to intervention group. Schamroth et al reported outcomes after myocardial infarction and unstable angina pectoris from 615 South African patients in the ACCESS (Acute Coronary Events – a Multinational Survey of Current Management Strategies) registry.[36] We estimated stroke mortality using two South African public-sector studies.[37, 38] We estimated mortality after revascularisation procedures using rates reported by Jones et al from the United Kingdom.[39]

Table 6. Transition probabilities: one-year outcomes after events

Outcomes after events	One-year rates	References
Myocardial infarction		
Myocardial infarction	0.0489	[34, 35]
Unstable angina pectoris	0.0890	[36]
Stroke	0.0147	[34, 35]
Revascularisation procedure	0.3961	[34, 35]
All-cause mortality	0.0670	[36]
Unstable angina pectoris		
Myocardial infarction	0.0109	[36]
Unstable angina pectoris	0.0890	[36]
Stroke	0.0109	[36]
Revascularisation procedure	0.5000	[36]
All-cause mortality	0.0500	[36]
Stroke		
Myocardial infarction	0.0191	[34, 35]
Stroke	0.0813	[34, 35]
Revascularisation procedure	0.0335	[34, 35]
All-cause mortality	0.2500	[37, 38]
Revascularisation procedure		
Myocardial infarction	0.0270	[34, 35]
Stroke	0.0105	[34, 35]
Revascularisation procedure	0.1349	[34, 35]
All-cause mortality	0.0539	[39]

Sensitivity analysis

The main sources of uncertainty in this analysis relate to the assumptions made regarding statin dose increases in the treat-to-target intervention arm and the generalisability of the results. We conducted threshold and multivariate sensitivity analyses to assess the robustness of the cost-

effectiveness estimates and to explore alternative scenarios. The base case assumes 100% adherence for all interventions. It has been proposed that the treat to target strategy results in better adherence than fixed doses of statins. The sensitivity analyses also explored different proportions of adherence for the alternative secondary prevention strategies.

Results

Costs, outcomes and cost-effectiveness

The costs, outcomes, and incremental cost effectiveness ratios (ICERs) of the three interventions are shown in Table 7. The three interventions were similar in terms of life years gained. Atorvastatin 80 mg was the most effective and the cheapest strategy, so dominated both the status quo, and the treat to target strategy.

Table 7. Costs, outcomes and cost-effectiveness ratios of three strategies for prescribing statins for the secondary prevention of cardiovascular disease at a South African public sector tertiary hospital

	Cost	Life years	ICER
Simvastatin 20 mg	$3924.19	4.32	Dominated
Treat to target	$4044.80	4.33	Dominated
Atorvastatin 80 mg	$3877.44	4.34	

ICER: incremental cost effectiveness ratio

Sensitivity analyses

The results did not change significantly when we changed the discount rate from 0 to 6%, or when we estimated event costs using the upper and lower limits of the 95% confidence intervals of the length of stay estimates. Atorvastatin 80 mg was still the most effective strategy when we extended the model to a lifetime timeline. It still dominated treat to target, but had an ICER of $146.94 relative to the status quo. In a lifetime timeline atorvastatin would dominate simvastatin 20 mg at a reduction in annual drug cost of $3.66 (a 5% reduction in 2012 prices). Assuming 80% adherence for the treat to target strategy and 60% for the others resulted in equivalent outcomes for treat to target and atorvastatin 80 mg, but treat to target was much more expensive. Changing the

proportions of patients on various statin doses in the treat to target intervention did not significantly change the results: treat to target was dominated by atorvastatin 80 mg even if we assumed that all patients were on atorvastatin 80 mg or all patients were on simvastatin 20 mg. If we assumed all patients were on atorvastatin 80 mg, and treat to target was associated with 80% adherence and atorvastin 80 mg (without LDL-C monitoring) was associated with 60% adherence, treat to target resulted in slightly better outcomes than atorvastatin (4.33 life years versus 4.31), with an ICER of $11 641.67. Treat to target was dominated by atorvastatin 80 mg even if the costs of measuring LDL-C were assumed to be zero. This is because the relatively high costs of the extra clinic visits needed in the treat to target strategy aren't offset by the costs saved by the reduction in cardiovascular events. The only scenario where treat to target was both more effective and cheaper than atorvastatin was if clinic visits were reduced to two in the first year (which is less than that recommended in some current guidelines), and the price of measuring LDL-C concentration decreased to $1.71 (an 84% reduction in the 2012 price).

Table 8. Sensitivity analyses: costs, outcomes and cost-effectiveness ratios of three strategies for prescribing statins for the secondary prevention of cardiovascular disease

		Cost	Life years	ICER
Discount rate 0%	Simvastatin 20 mg	$4164.15	4.56	dominated
	Treat to target	$4286.19	4.57	dominated
	Atorvastatin 80 mg	$4113.77	4.59	
Discount rate 6%	Simvastatin 20 mg	$3710.21	4.10	dominated
	Treat to target	$3829.54	4.11	dominated
	Atorvastatin 80 mg	$3666.73	4.12	
Length of stay: Lower limit of 95% CI	Simvastatin 20 mg	$3588.99	4.32	dominated
	Treat to target	$3725.57	4.33	dominated
	Atorvastatin 80 mg	$3583.33	4.34	
Length of stay: Upper limit of 95% CI	Simvastatin 20 mg	$4402.35	4.32	dominated
	Treat to target	$4366.95	4.33	dominated
	Atorvastatin 80 mg	$4536.86	4.34	
Lifetime timeline	Simvastatin 20 mg	$10888.26	11.37	
	Treat to target	$11128.53	11.49	dominated
	Atorvastatin 80 mg	$10930.94	11.66	$146.94
Adherence 60%	Simvastatin 20 mg	$3922.43	4.30	dominated
60%	Atorvastatin 80 mg	$3928.43	4.31	
80%	Treat to target	$4118.98	4.31	$54930.96

CI: confidence interval; ICER: incremental cost effectiveness ratio

Discussion

Our analysis of three statin prescribing strategies for the secondary prevention of cardiovascular disease demonstrated that atorvastatin 80 mg without LDL-C monitoring, was both the cheapest and most effective option in our setting over a five-year period. It remained the most effective option over a lifetime period, but with an ICER of $146.94 relative to the status quo (simvastatin 20 mg without LDL-C monitoring). Treating to a target LDL-C concentration would be more effective and cheaper than atorvastin 80 mg only if the number of clinic visits for each intervention were the same, and the cost of LDL-C monitoring decreased by $9.25 (84%).

The relatively low rates of cardiovascular events in the population we used in this analysis (in the absence of data from South Africa) resulted in only small differences between the three interventions that we compared in terms of outcomes. But the relatively high costs of cholesterol monitoring and clinic visits resulted in large differences in terms of costs. The fact that atorvastatin 80 mg dominated simvastatin 20 mg over five years, but had a relatively small ICER over a lifetime is probably due to the fact that death from cardiovascular disease becomes a relatively smaller proportion of overall deaths as the rate of death from other causes rises with age. This essentially means that in our model statins become relatively less effective at preventing death over time.

South African pharmacoeconomic guidelines do not specify a cost-effectiveness threshold below which interventions can be considered to be cost-effective.[40] World Health Organization CHOICE suggests that interventions can be considered very cost-effective at ICERs less than a country's per capita gross domestic product (GDP), and cost-effective at ICERs less than three times GDP.[41] South Africa's 2012 GDP per capita was US$7 590,03.[42] Therefore atorvastatin 80 mg could be considered very cost-effective even over a lifetime time period. However, treat to target could not be considered cost-effective, even if we assumed that adherence was improved by regular monitoring of LDL-C cholesterol concentrations.

Some authors have suggested that regular cholesterol monitoring is essential to ensure adherence to statin therapy. Wei et al used a United Kingdom record linkage database analysis to show that patients requiring statins for secondary prevention who were treated using a treat to target approach were 1.87 (95% confidence interval 1.58 to 2.22) times more likely to be at least 80% adherent than those treated according to a fire and forget approach.[12] To our knowledge this retrospective observational study is the only published attempt to address the question. It remains a potential area for further research, but the cost of frequent cholesterol monitoring currently makes a treat to target strategy unaffordable in most resource-limited settings.

While several previous studies have shown statins to be cost-effective at various doses, to our knowledge only one study (a systematic review and meta-analysis) has compared different monitoring strategies, but the comparison was essentially between frequency of monitoring within a treat to target strategy. Perera et al found annual lipid monitoring to be cost effective relative to three-yearly monitoring, assuming that abnormal concentrations resulted in starting statins or increasing statin dose in all cases.[43]

Our study has several strengths, most notably the fact that to our knowledge this is the first thorough costing of cardiovascular events in the public healthcare sector in South Africa. However, there are several limitations. We had to use indirect comparisons for statin efficacy, as there are no clinical trials that directly compared the three interventions of interest. This indirect approach to estimate relative efficacy has been used before,[44-46] but obviously a direct comparison would be ideal. We did not compare other possible interventions (atorvastatin 40 mg for example) as we based the interventions on recommendations in current international guidelines. However, our indirect comparison approach means that our model is flexible enough to be used to make multiple further comparisons in the future. We were not able to estimate the costs of treating potential statin side effects, so those costs were not included in our model. We also did not account for potential differences in tolerability between high dose atorvastatin and simvastatin. As high dose atorvastatin

might be associated with relatively more patients stopping treatment because of side effects, we might have overestimated the effectiveness of atorvastatin. We assumed that adherence was constant over time, but in practice there would likely be attrition over time in all groups. Our analysis is based on a tertiary hospital population, which limits the generalisability of our results. The vast majority of patients who require secondary prevention are actually treated at a primary health care level, where treatment costs (specifically clinic visit costs) are likely to be cheaper. However, those costs are the same for all interventions, so the cost-effectiveness rankings are unlikely to be different in different settings, although the lifetime costs and ICERs would change.

Conclusions

Our study shows that statin treatment without cholesterol monitoring is currently the most cost-effective option in our setting.

List of abbreviations

CI: confidence interval

ICER: incremental cost effectiveness ratio

IQR: interquartile range

LDL-C: low density lipoprotein cholesterol

TTT: treat to target

Declarations

Ethics approval and consent to participate

The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee approved the study (reference number: 146/2014).

We did not obtain consent from patients as we did not perform any interventions on patients for the purpose of this analysis and we did not seek any information directly from patients. We used only anonymous patient identifiers in the analysis.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from Groote Schuur Hospital, but restrictions apply to these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with the permission of Groote Schuur Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KS and NL proposed the study. RdW, SC, KS and NL designed the study. RdW conducted the analysis. SC provided technical expertise and advice regarding analysis. RdW wrote the manuscript.

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Appendix 1

UCT Human Research Ethics Committee approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

19 March 2014

HREC REF: 146/2014

A/Prof S Cleary
Health Economics Unit
Public Health & Family Medicine
Falmouth Building

Dear A/Prof Cleary

PROJECT TITLE: COST-EFFECTIVELY ANALYSIS OF ALTERNATIVE STATIN PRESCRIBING STRATEGIES FOR THE SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN THE WESTERN CAPE (Masters - Renee de Waal)

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 until the 30th March 2015

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)

We acknowledge that the student, Renee de Waal is also involved in this study.

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

Please quote the HREC reference no 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.

Appendix 2

Cost Effectiveness and Research Allocation: guidelines for research articles

Cost Effectiveness and Resource Allocation

Research article

Criteria

Research articles describe country-level or international primary research on the costs, effectiveness, or cost-effectiveness of (single or combined) interventions.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
  - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
  - or for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
  - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- Background: the context and purpose of the study
- Methods: how the study was performed and statistical tests used
- Results: the main findings
- Conclusions: brief summary and potential implications
- Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant),

you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated during and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state not applicable in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each author's competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

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Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

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All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission.

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely.

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Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link (e.g. for blogs) they should be included in the reference.

Example reference style:
Article within a journal
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Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI
Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement
Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

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Online document
Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database
Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

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ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

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Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Figures, tables additional files

See General formatting guidelines for information on how to format figures, tables and additional files.

Appendix 3

Cost Effectiveness and Research Allocation: general formatting guidelines

Cost Effectiveness and Resource Allocation

Preparing your manuscript

This section provides general style and formatting information only. Formatting guidelines for specific article types can be found below.

Preparing main manuscript text

Quick points:

- Use double line spacing
- Include line and page numbering
- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF
- Do not use page breaks in your manuscript

File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
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Please note: editable files are required for processing in production. If your manuscript contains any non-editable files (such as PDFs) you will be required to re-submit an editable file if your manuscript is accepted.

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TeX templates
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For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should consider:

• Visiting the English language tutorial which covers the common mistakes when writing in English.
• Asking a colleague who is a native English speaker to review your manuscript for clarity.
• Using a professional language editing service where editors will improve the English to ensure that your meaning is clear and identify problems that require your review. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts.

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For all journals, BioMed Central strongly encourages all datasets on which the conclusions of the manuscript rely to be either deposited in publicly available repositories (where available and appropriate) or presented in the main paper or additional supporting files, in machine-readable format (such as spread sheets rather than PDFs) whenever possible. Please see the list of recommended repositories in our editorial policies.

For some journals, deposition of the data on which the conclusions of the manuscript rely is an absolute requirement. Please check the Instructions for Authors for the relevant journal and article type for journal specific policies.

For all manuscripts, information about data availability should be detailed in an ‘Availability of data and materials’ section. For more information on the content of this section, please see the Declarations section of the relevant journal’s Instruction for Authors. For more information on BioMed Centrals policies on data availability, please see our [editorial policies].

Formatting the 'Availability of data and materials' section of your manuscript

The following format for the 'Availability of data and materials section of your manuscript should be used:

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For databases, this section should state the web/ftp address at which the database is available and any restrictions to its use by non-academics.

For software, this section should include:

- Project name: e.g. My bioinformatics project
- Project home page: e.g. http://sourceforge.net/projects/mged
- Archived version: DOI or unique identifier of archived software or code in repository (e.g. enodo)
- Operating system(s): e.g. Platform independent
- Programming language: e.g. Java
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Information on available repositories for other types of scientific data, including clinical data, can be found in our editorial policies.

References

See our editorial policies for author guidance on good citation practice.

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission. For further information including example references please read our reference preparation guidelines.

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Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited.

Unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE.

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Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They

should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

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Example reference style:Article within a journal
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Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI
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Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book
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Dataset with persistent identifier

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- Figures should be provided as separate files, not embedded in the main manuscript file.
- Each figure of a manuscript should be submitted as a single file that fits on a single page in portrait format.
- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
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- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.
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Figure file types

We accept the following file formats for figures:

- EPS (suitable for diagrams and/or images)
- PDF (suitable for diagrams and/or images)
- Microsoft Word (suitable for diagrams and/or images, figures must be a single page)
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Part E: Policy brief

Statins for the secondary prevention of cardiovascular disease: cost-effectiveness of prescribing strategies in the South African public healthcare sector

Policy brief
August 2016

Statins are an important public health intervention as they reduce the risk of cardiovascular events such as angina, heart attacks and strokes. But statin prescribing guidelines vary, even within South Africa. We explored the cost-effectiveness of three statin prescribing strategies for the secondary prevention of cardiovascular events at a South African public sector tertiary hospital. This policy brief outlines our methods and key findings.

Introduction

Cardiovascular disease prevalence is increasing in South Africa.[1] It is important to reduce the risk of cardiovascular events such as angina, heart attacks, and strokes in order to limit morbidity and mortality. From a public healthcare provider perspective, reducing cardiovascular risk also reduces the significant costs associated with hospitalisations for cardiovascular events.

Patients who have already experienced a cardiovascular event are at increased risk of a further event, so local and international guidelines agree that they should all receive statins (unless contraindicated). However, guidelines disagree on the best way to prescribe statins: some recommend monitoring low density lipoprotein cholesterol (LDL-C) regularly and increasing statin doses until target LDL-C concentrations are achieved, while others recommend prescribing a fixed statin dose without monitoring LDL-C.[2-5]

Statin drug costs are decreasing over time, but monitoring LDL-C concentrations remains relatively expensive. Some authors argue that measuring LDL-C concentration is essential to ensure patients' adherence to statin therapy, but there is little evidence to support this.

Research question

Our analysis compared the costs, from a provider perspective, and life years gained of:

- simvastatin 20 mg, with a lipogram (to exclude familial hypercholesterolaemia) at baseline only, with no further LDL-C monitoring (current practice);
- atorvastatin 80 mg, also with a baseline lipogram but no further monitoring; and
- starting simvastatin 20 mg then measuring LDL-C 3-monthly and increasing statin dose until target concentrations are reached, then measuring LDL-C 6-monthly (treat to target),

at Groote Schuur Hospital, Cape Town, South Africa.

Key messages

- High LDL-C concentrations increase the risk of cardiovascular disease
- Statins lower LDL-C and reduce the risk of cardiovascular disease
- Prescribing statins at a fixed high dose is more effective, and relatively less expensive, than treating to a target LDL-C concentration

Markov model

Markov models are used to estimate the costs and outcomes of interventions over time, and are particularly valuable when assessing chronic conditions such as cardiovascular disease. Markov models assume patients are always in one of several discrete health states, for a fixed length of time – the Markov cycle. At the end of each Markov cycle patients can move from one state to another. The probabilities of moving from one state to another (or staying in the same state for the next Markov cycle) are known as transition probabilities.

We constructed a Markov model with annual cycles; a five-year timeline; starting age of 60 years; and the following health states: ≤1 year after first cardiovascular event, ≤1 year after subsequent cardiovascular event, >1 year after any cardiovascular event, and dead (Figure 1).

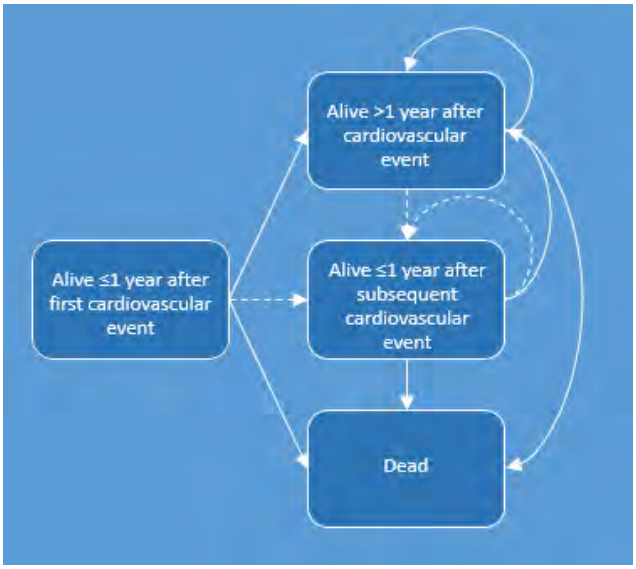

Figure 1. Markov model states and transitions. Dashed lines indicate the occurrence of a cardiovascular event.

Transition probabilities

No trial has directly compared the three proposed interventions, so we estimated the effects of statin treatment by multiplying the risk reduction of major cardiovascular events associated with each statin dose by the expected annual incidence of those events in patients who are not on statins. We estimated the annual incidences of cardiovascular events and cardiovascular mortality from published literature, as we could find no data specific to the South African population.[6-8] We estimated risk reduction for each statin dose using two meta-analyses: one which estimated the average effect on LDL-C concentrations of various statin doses; and one which estimated the average risk reduction per 1 mmol/L reduction in LDL-C.[9,10]

Definitions and terms

Cardiovascular event: myocardial infarction, unstable angina pectoris, coronary revascularisation procedure (coronary artery bypass grafts or percutaneous transluminal coronary angioplasty) or stroke.

Secondary prevention: the prevention of further cardiovascular events in those patients who have already experienced a cardiovascular event.

LDL-C: a type of cholesterol that causes plaque deposits in arteries, which can lead to cardiovascular events.

Statin: (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) a class of drugs that reduce serum LDL-C concentrations by inhibiting cholesterol synthesis in the liver.

Lipogram: a laboratory blood test that measures total cholesterol, LDL-C, high density lipoprotein cholesterol and triglycerides. It is used to screen for diseases where 'standard' statin prescribing strategies might not be suitable.

Incremental cost effectiveness ratio: the additional cost per life year gained by one intervention compared to another.

Figure 2 illustrates the effects of statin treatment that we used to calculate the transition probabilities for cardiovascular events in our model.

We used estimated transition probabilities for one-year outcomes after cardiovascular events from several published studies.[11-16] We estimated age-specific mortality from other causes using published South African mortality tables.[17]

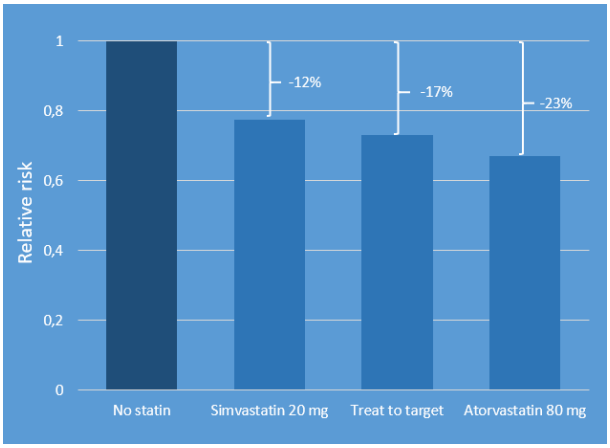

Figure 2. Effects of statin treatment on the risk of cardiovascular events in patients who have already had a cardiovascular event.

Costs

Cardiovascular events

We used hospital expenditure records for 1 554 patients admitted for cardiovascular events during 2012 and 2013 to estimate mean utilisation of laboratory tests, diagnostic and surgical procedures, drugs and blood products. We obtained the prices of drugs, laboratory investigations, and blood products from hospital expenditure records. We estimated the costs of diagnostic investigations (such as xrays, CT scans and ECGs) and surgical procedures using the Uniform Patient Fee Schedule, which lists fees to be paid by private patients at public sector facilities.[18] We calculated overall hospital overhead costs such as utilities (water, electricity, sewerage), catering, housekeeping, security, staff salaries, and general maintenance using routine hospital accounting data. We calculated a patient day equivalent by adding all the inpatient days, half of the day cases and one third of the outpatient visits over the time period, and divided the total cost by the patient day equivalent, to estimate hospitalisation cost per patient day equivalent.[19] We multiplied those costs by the mean length of stay to calculate overall admission costs (Figure 3). All costs were expressed in 2012 prices, converted to United States (US) dollars using an average 2012 exchange rate of $0,12227/R1.[20]

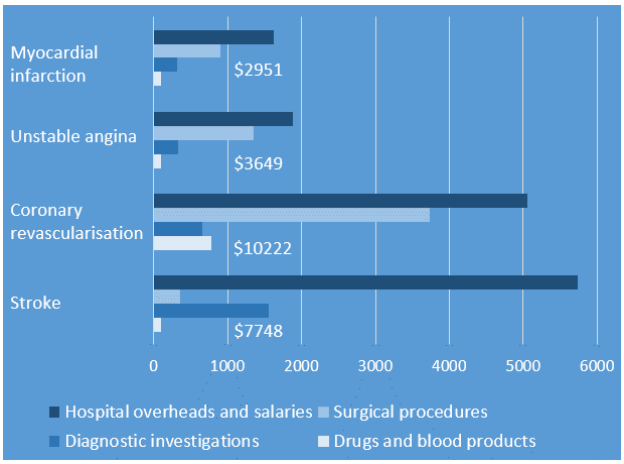

Figure 3. Mean hospitalisation costs according to cardiovascular event in 2012 United States dollars

Intervention costs

Intervention costs comprise drug costs, outpatient visits (calculated using hospital data as described for hospitalisation costs above), and the costs of measuring LDL-C. Each intervention also included a baseline lipogram. In the treat to target intervention we assumed that all patients would start at simvastatin 20 mg; 50% of patients would have a dose increase to simvastatin 40 mg at three months; and a further 25% would have a dose increase to atorvastatin 80 mg at six months. Figure 4 illustrates statin treatment costs.

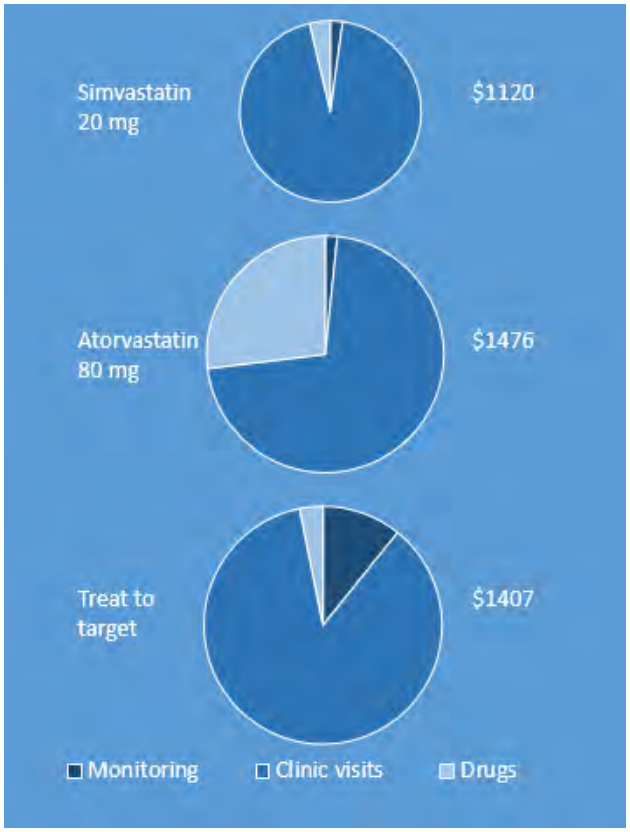

Figure 4. Mean costs of statin treatment for a five year period in 2012 United States dollars.

Results

Atorvastatin 80 mg without LDL-C monitoring, was both the cheapest and most effective option over a five-year period. The interventions resulted in similar outcomes of 4.32, 4.33 and 4.34 life years, with costs of $3 924.19, $4 044.80 and $3 877.44 respectively for simvastatin 20 mg, treat to target and atorvastatin. Atorvastatin 80 mg was also the most effective option when we ran the analysis over a lifetime period, but had an incremental cost-effectiveness ratio of $146.94 per life year gained relative to the simvastatin 20 mg. It would be more effective and cheaper than simvastatin 20 mg over a lifetime period if its price decreased by 5%.

Treat to target was as effective as atorvastin 80 mg if we assumed adherence rates of 80% and 60% respectively, but with an ICER of $54 930.96. Changing the proportions of patients on various statin doses in the treat to target intervention did not significantly change the results: treat to target was more expensive and less effective than atorvastatin 80 mg even if we assumed that all patients had their doses increased to atorvastatin 80 mg or all patients remained on simvastatin 20 mg.

Policy implications

World Health Organization CHOICE suggests that interventions can be considered cost-effective at ICERs less than three times a country's per capita gross domestic product (GDP).[21] South Africa's 2012 GDP per capita was US$7590.[22] Therefore atorvastatin 80 mg could be considered very cost-effective even over a lifetime period. However treat to target could not be considered cost-effective, even if we assumed that adherence was improved by regular monitoring of LDL-C cholesterol concentrations.

Our analysis is based on a tertiary hospital population, but outpatient costs are the same for all interventions, so intervention rankings are unlikely to be different in different settings, although the overall costs and ICERs would change.

In addition to being the most cost-effective option, prescribing statins without regular monitoring could have other potential benefits for the health system. Patients could attend clinics less frequently, and doctor or nurse consultation time saved by not monitoring could be used for other health promotion activities such as educating patients regarding diet or screening for other cardiovascular risk factors.

Conclusions

Fixed-dose statin treatment without cholesterol monitoring is the most cost-effective option for providing statins for the secondary prevention of cardiovascular disease. The costs of regular LDL-C monitoring currently make a treat to target strategy unaffordable in our setting.

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