Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease

Reneé de Waal, Chairperson PHC EML expert review committee

No conflicts of interest

Background

While the benefits of statins for the secondary prevention of cardiovascular events have been clearly demonstrated, there is some debate regarding the optimal statin dose. Several trials have compared high dose to low dose statins (summarised in Table 1). Most studies found better outcomes with higher doses, but the difference was not always statistically significant, and the higher dose statins were often associated with an increase in adverse events too.

The Cholesterol Treatment Trialists' (CTT) collaboration conducted a meta-analysis of clinical trials using individual patient data.[1] 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 low density lipoprotein cholesterol (LDL-C). They conclude that the greater the reduction in LDL-C (i.e. the higher the statin dose), the greater the clinical benefit.

Sniderman et al have criticised the CTT collaboration's meta-analysis, in particular their use of revascularisation procedures such as bypass grafting or stents (which they state are not as clear predictors of death as the other endpoints) in the composite endpoint, and the comparison between the extremes of dosing ranges.[2] They suggest that a comparison between moderate and high doses would be more realistic, and estimate that the added benefit of high doses in such a comparison would be very small, and that high doses would be more likely to cause adverse effects which might negatively affect adherence.

In contrast to the CCT collaboration's conclusion, Takagi et al found that the relationship between LDL-C reduction and cardiovascular risk is not linear.[3] They used a fractional polynomial regression model to show that there is very little further benefit after a reduction in LDL-C of 1 mmol/L.

Comparisons such as those proposed by Sniderman et al (between intermediate and high statin doses) have not been made directly in clinical trials. However, the relative effects on LDL-C of various statin doses can be extrapolated using the network meta-analysis conducted by Naci et al.[4] They found that reductions of around 1 mmol/L can be achieved using atorvastatin 10 mg and simvastatin 10–20 mg.

Table 1. High dose versus low dose statins for the secondary prevention of cardiovascular disease

Study	n	Setting	Intervention	Duration of follow up	Primary outcome
Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE)[5]	2 442	United States	Atorvastatin 10–80 mg (to achieve LDL-C <2.1 mmol/L) versus usual care	Median 54.3 months	Hazard ratio for cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularisation procedure or unstable angina of 0.83 (95% CI 0.71 to 0.97)
A to Z[6]	4 497	41 countries, including South Africa (81 patients)	Simvastin 40–80 mg versus placebo (4 months) then simvastatin 20 mg	721 days	Hazard ratio for cardiovascular death, non-fatal MI, acute coronary syndrome or stroke of 0.84 (95% CI 0.76 to 1.04)
Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE-IT-TIMI 22)[7]	4 162	Australia, Europe and North America	Atorvastatin 80 mg versus pravastatin 40 mg	Mean 24 months	16% reduction in the hazard of death, MI, unstable angina, revascularisation procedure or stroke (95% CI 5 to 26)
Treating to New Targets (TNT)[8]	10 001	Australia, Europe, North America and South Africa (523 patients)	Atorvastatin 80 mg versus 10 mg	Median 4.9 years	Hazard ratio for coronary death, non-fatal MI, resuscitated cardiac arrest or stroke of 0.78 (95% CI 0.69 to 0.89)
Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL)[9]	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)
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)[10]	12 064	United Kingdom	Simvastatin 80 mg versus 20 mg	Median 6.7 years	Relative risk of coronary death, MI, stroke of revascularisation procedure of 0.94 (95% CI 0.88 to 1.01)

This analysis aims to assess the cost effectiveness of high and intermediate dose statins for the secondary prevention of cardiovascular disease, relative to the status quo, which comprises simvastatin 10 mg. It is based on the CTT meta-analysis described above. If one based statin efficacy estimates on the Takagi et al meta-analysis, a cost minimisation analysis would be more appropriate, as the proposed interventions could then be considered to have similar efficacy.

Methods

Study design

I conducted a cost-effectiveness analysis from a public sector provider perspective. I compared the costs and outcomes (in terms of life years) of simvastin 10 mg (the status quo), simvastatin 20 mg, simvastatin 40 mg, atorvastatin 40 mg, and atorvastin 80 mg for the secondary prevention of cardiovascular events using a Markov model. I estimated cardiovascular event costs using an ingredients approach as well as allocation of costs according to inpatient days. I estimated transition probabilities using published literature. Doses 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 2017 Rands. I discounted costs and outcomes at 3% per year.

Costs of cardiovascular events

The event costs used in this analysis were derived from a costing exercise undertaken as part of another project using data from 2012. I adjusted cardiovascular event costs for inflation using the consumer price index.

I estimated the costs of treating myocardial infarction, unstable angina, coronary revascularisation procedures and strokes using a sample of patients from Groote Schuur Hospital. I 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. Patient and admission numbers and characteristics are shown in Table 2.

Table 2: Characteristics according to diagnosis of 1 554 patients during 1 797 admissions to Groote Schuur 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

I used all sample patients to estimate health services utilisation using hospital expenditure records, and calculated costs using 2012 prices or hospital expenditure. I 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. I obtained the prices of drugs, laboratory investigations, and blood products from hospital expenditure records. I 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.[11]

I 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. I assumed that all patients, regardless of diagnosis, consumed roughly the same amount of overhead resources. Following the standard approach in this setting, I 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 visits over the time period, and divided the total cost by the patient day equivalent, to estimate the cost per patient day equivalent. [12] I 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. Mean hospitalisation costs for each cardiovascular event are shown in Table 3.

Based on published estimates I assumed that 50% of stroke-related deaths and 30% of coronary heart disease-related deaths occurred in hospital.[13-21] I included the costs of in-hospital deaths, but not those deaths that occurred out of hospital. I also did not include costs of deaths due to other causes.

Table 3. Mean hospitalisation costs according to diagnosis at Groote Schuur Hospital in 2017 Rands

Cost category	Myocardial infarction		Unstable angina		Coronary revascularisation procedures		Stroke	
	Inpatient day	Admission	Inpatient day	Admission	Inpatient day	Admission	Inpatient day	Admission
Hospital overheads	1695.18	7068.88	1695.18	8289.41	1695.18	20901.51	1695.18	22172.89
Ward overheads	2482.53	10352.14	2421.67	11841.95	2695.04	33229.80	2997.90	39212.48
Surgical procedures	2335.86	9740.54	2950.12	14426.09	3239.33	39940.92	296.60	3879.49
Diagnostic procedures	496.95	2072.28	426.17	2083.97	307.81	3795.31	1159.19	15162.24
Laboratory investigations	331.44	1382.12	285.57	1396.42	267.62	3299.75	110.29	1442.58
Drugs	101.42	422.92	40.27	196.92	16.01	197.38	56.40	737.65
Blood products	139.10	580.03	176.06	860.95	660.93	8149.32	30.71	401.64
Total	**7582.47**	**31618.91**	**7995.03**	**39095.70**	**8881.91**	**109514.00**	**6346.25**	**83008.97**

Intervention costs

The costs associated with providing statins included in this analysis were: the annual drug cost; one lipogram at baseline only (first year); and two outpatient visits per year. I 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 baseline screening are shown in Table 4.

Table 4. Costs of providing statins for secondary prevention of cardiovascular events at Groote Schuur Hospital in 2017 Rands

Outpatient visit	
Cardiac or general medicine clinic	1130.07
Annual drug costs	
Simvastatin 10mg	72.48
Simvastatin 20 mg	94.12
Simvastatin 40 mg	188.24
Atorvastatin 40 mg	338.36
Atorvastatin 80 mg	676.71
Laboratory costs	
Lipogram	216.34

Markov model

For this analysis I used 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 coronary revacularisation procedure; and death (Figure 1). I used a five-year timeline with a starting age of 60 years, and cycles of one year.

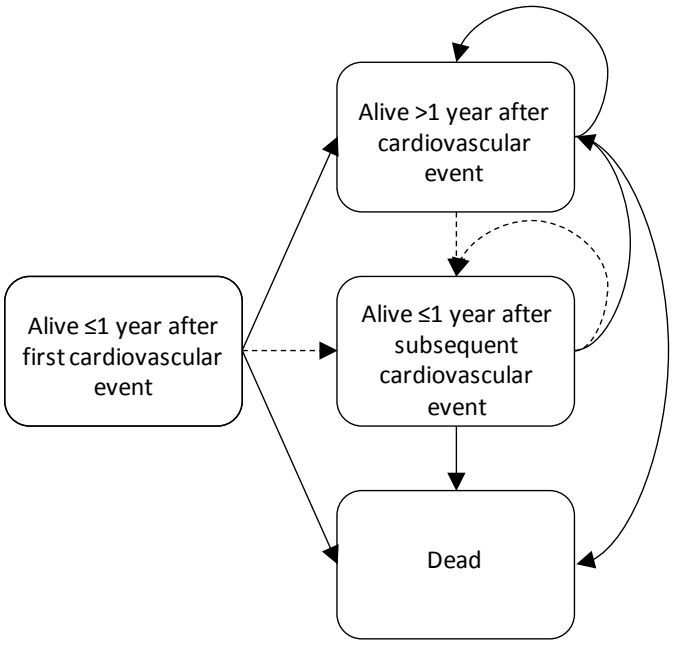

Figure 1. Simplified Markov model states and transitions.
Dashed lines indicate the occurrence of a cardiovascular event. Cardiovascular events comprise myocardial infarction, unstable angina pectoris, stroke, or coronary revascularisation procedure.

Transition probabilities

I 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. Data regarding the incidence of those events in South Africa are extremely limited. International cohort studies generally recruit patients who are already on statins. For those reasons I estimated the annual incidences (in those not on statins) of myocardial infarction, unstable angina pectoris, stroke, and coronary revascularisation procedures, 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 5). I estimated age-specific mortality from other causes by subtracting cardiovascular and cerebrovascular deaths from overall deaths using published South African mortality tables.[22] 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.[23] 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.[1] They estimated a risk reduction of 0.79 for major cardiovascular events in those patients with existing cardiovascular disease. I used those two meta-analyses to estimate the risk reduction associated with the three statin doses in our analysis (Table 6).

Table 5. Annual transition probabilities in patients with existing cardiovascular disease

Event	Transition probability	Reference
Myocardial infarction	0.016	24-26
Unstable angina pectoris	0.038	25,26
Stroke	0.007	24-26
Coronary revascularisation procedure	0.030	24-26
Cardiovascular death	0.017	24,26
Cerebrovascular death	0.011	24,26
Death – other causes	Varies by age	22

Table 6. Risk reduction of cardiovascular events by statins

Statin	Effect on LDL-C[23]	RR[1] per 1 mmol/L decrease[1]	Rate ratio
Simvastatin 10 mg	-0.95	0.79	0.8005
Simvastatin 20 mg	-1.07	0.79	0.7753
Simvastatin 40 mg	-1.42	0.79	0.7018
Atorvastatin 40 mg	-1.41	0.79	0.7039
Atorvastatin 80 mg	-1.57	0.79	0.6703

1. Rate ratio

I used estimated transition probabilities for one-year outcomes after cardiovascular events from various sources (Table 7). 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.[27] 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.[28] 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 I 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.[29] I estimated stroke mortality using two South African public-sector studies.[30,31] I estimated mortality after revascularisation procedures using rates reported by Jones et al from the United Kingdom.[32]

Table 7. Transition probabilities: one-year outcomes after events

Outcomes after events	One-year rates	References
Myocardial infarction		
Myocardial infarction	0.0489	27,28
Unstable angina pectoris	0.0890	29
Stroke	0.0147	27,28
Revascularisation procedure	0.3961	27,28
All-cause mortality	0.0670	29
Unstable angina pectoris		
Myocardial infarction	0.0109	29
Unstable angina pectoris	0.0890	29
Stroke	0.0109	29
Revascularisation procedure	0.5000	29
All-cause mortality	0.0500	29
Stroke		
Myocardial infarction	0.0191	27,28
Stroke	0.0813	27,28
Revascularisation procedure	0.0335	27,28
All-cause mortality	0.2500	30,31
Revascularisation procedure		
Myocardial infarction	0.0270	27,28
Stroke	0.0105	27,28
Revascularisation procedure	0.1349	27,28
All-cause mortality	0.0539	32

Sensitivity analysis

I conducted several 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. The sensitivity analyses also explored different proportions of adherence for the alternative statin doses.

Results

Costs, outcomes and cost-effectiveness

The costs, outcomes, and incremental cost effectiveness ratios (ICERs) of the five statin doses are shown in Table 8. The interventions were similar in terms of life years gained. Simvastatin 40 mg was more effective, and cheaper, than simvastatin 10 and 20 mg, and atorvastatin 40 mg. Atorvastatin 80 mg was slightly more effective than simvastatin 40 mg, but also cost more, with an ICER of R128 142.33 per life year gained.

Table 8. Costs. outcomes and cost-effectiveness ratios of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease

	Cost	Life years	ICER
Simvastatin 10mg	42829.40	4.31	Dominated
Simvastatin 20 mg	42024.12	4.32	Dominated
Atorvastatin 40 mg	40500.50	4.34	Dominated
Simvastatin 40 mg	39773.00	4.34	
Atorvastatin 80 mg	40737.80	4.34	128142.33

ICER: incremental cost effectiveness ratio

Sensitivity analyses

The results did not change significantly when changing the discount rate from 0 to 6%, or when estimating event costs using the upper and lower limits of the 95% confidence intervals of the statin efficacy estimates, and cardiovascular event hospital length of stay estimates (Table 9).

Table 9. Sensitivity analyses: model assumptions

Assumption	Intervention	Cost	Life years	ICER
Discount rate 0%	Simvastatin 10mg	45449.71	4.56	Dominated
	Simvastatin 20 mg	44596.37	4.56	Dominated
	Atorvastatin 40 mg	42978.87	4.58	Dominated
	Simvastatin 40 mg	42209.56	4.58	
	Atorvastatin 80 mg	43226.16	4.59	123766.39
Discount rate 6%	Simvastatin 10mg	40492.69	4.09	Dominated
	Simvastatin 20 mg	39730.35	4.10	Dominated
	Atorvastatin 40 mg	38290.61	4.11	Dominated
	Simvastatin 40 mg	37600.40	4.11	
	Atorvastatin 80 mg	38519.06	4.12	132663.28
Relative risk:	Simvastatin 10mg	42152.41	4.32	Dominated
Lower limit 95% CI	Simvastatin 20 mg	41255.80	4.32	Dominated
	Atorvastatin 40 mg	39467.18	4.34	Dominated
	Simvastatin 40 mg	38730.66	4.34	
	Atorvastatin 80 mg	39577.79	4.35	102151.71
Relative risk:	Simvastatin 10mg	43837.83	4.31	Dominated
Upper limit 95% CI	Simvastatin 20 mg	43167.60	4.31	Dominated
	Atorvastatin 40 mg	42034.50	4.32	Dominated
	Simvastatin 40 mg	41320.28	4.33	
	Atorvastatin 80 mg	42457.81	4.33	177764.88
Length of stay:	Simvastatin 10mg	39134.45	4.31	Dominated
Lower limit of	Simvastatin 20 mg	38432.83	4.32	Dominated
95% CI	Atorvastatin 40 mg	37207.05	4.34	Dominated
	Simvastatin 40 mg	36488.41	4.34	
	Atorvastatin 80 mg	37586.67	4.34	145868.23
Length of stay:	Simvastatin 10mg	46454.31	4.31	Dominated
Upper limit of	Simvastatin 20 mg	45547.36	4.32	Dominated
95% CI	Atorvastatin 40 mg	43731.56	4.34	Dominated
	Simvastatin 40 mg	42995.37	4.34	
	Atorvastatin 80 mg	43829.25	4.34	110754.04

CI: confidence interval; ICER: incremental cost effectiveness ratio

The relative rankings remained the same when I ran the model with a lifetime timeline, but the ICER for atorvastatin 80 mg decreased to R34 862.24 per life year (Table 10). The rankings also remained the same when I assumed the incidences of cardiovascular events were half those in the base case, or twice those in the base case. Simvastatin 40 mg was both the cheapest and most effective intervention when I assumed that higher doses cause poor adherence because of adverse drug reactions; simvastatin 20 mg was the cheapest and most effective in a more extreme example (Table 10).

Table 10. Sensitivity analyses: alternative scenarios

Assumption	Intervention	Cost	Life years	ICER
Lifetime timeline	Simvastatin 10mg	118361.06	11.30	Dominated
	Simvastatin 20 mg	116675.64	11.37	Dominated
	Atorvastatin 40 mg	113835.84	11.57	Dominated
	Simvastatin 40 mg	111928.31	11.57	
	Atorvastatin 80 mg	115024.98	11.66	34862.24
Event incidence	Simvastatin 10mg	45825.60	4.41	Dominated
50% of estimated	Simvastatin 20 mg	44913.10	4.41	Dominated
	Atorvastatin 40 mg	43104.70	4.42	Dominated
	Simvastatin 40 mg	42355.87	4.42	
	Atorvastatin 80 mg	43226.73	4.42	212224.17
Event incidence	Simvastatin 10mg	68203.51	4.14	Dominated
200% of estimated	Simvastatin 20 mg	66862.62	4.15	Dominated
	Atorvastatin 40 mg	63716.34	4.18	Dominated
	Simvastatin 40 mg	62964.07	4.18	
	Atorvastatin 80 mg	63117.49	4.19	11597.83
Adherence 75%	Simvastatin 10mg	44510.72	4.30	Dominated
75%	Simvastatin 20 mg	43916.87	4.30	Dominated
75%	Atorvastatin 40 mg	42807.33	4.32	Dominated
75%	Simvastatin 40 mg	42264.90	4.32	
75%	Atorvastatin 80 mg	43000.84	4.32	132274.32
Adherence 80%	Simvastatin 10mg	44176.48	4.30	Dominated
80%	Simvastatin 20 mg	43540.90	4.31	Dominated
60%	Atorvastatin 80 mg	44327.27	4.31	Dominated
70%	Atorvastatin 40 mg	43262.11	4.31	Dominated
70%	Simvastatin 40 mg	42756.43	4.31	
Adherence 40%	Atorvastatin 80 mg	46059.98	4.30	Dominated
80%	Simvastatin 10 mg	44176.48	4.30	Dominated
60%	Atorvastatin 40 mg	44165.16	4.31	Dominated
60%	Simvastatin 40 mg	43732.73	4.31	Dominated
80%	Simvastatin 20 mg	43540.90	4.31	

Discussion

This cost effectiveness analysis found that simvastatin 40 mg was cheaper, and more effective than the status quo (simvastatin 10 mg). Although atorvastatin 80 mg was slightly more effective, it was also more expensive, with an ICER of R128 142.33 per life year gained.

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 interventions compared in terms of outcomes.

This analysis has several limitations. I used indirect comparisons for statin efficacy, as there are no clinical trials that directly compared the statin doses of interest. This indirect approach to estimate relative efficacy has been used before,[33-35] but obviously a direct comparison would be ideal. I was not able to estimate the costs of treating potential statin side effects, so those costs were not included in the model. I assumed that adherence was constant over time, but in practice there would likely be attrition over time in all groups. This analysis is based on a tertiary hospital population, which limits the generalisability of the 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 costs and ICERs would change.

Conclusions

From a public sector provider perspective, simvastatin 40 mg is a cost-effective intervention for the secondary prevention of cardiovascular disease in our setting. A budget impact assessment should be done to further inform recommendations.

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