Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis

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ABSTRACT

Objective To assess the cost-effectiveness of low dose statins for primary prevention of vascular disease, incorporating current prices, non-adherence (reduced clinical efficacy while maintaining healthcare costs), and the results of the recently published JUPITER trial.

Design Cost-effectiveness analysis using a Markov model. Sensitivity analyses and Monte Carlo simulation evaluated the robustness of the results.

Setting Primary care in The Netherlands.

Participants Hypothetical populations of men and women aged 45 to 75 years without a history of vascular disease at different levels of risk for vascular disease (myocardial infarction and stroke) over 10 years.

Interventions Low dose statin treatment daily versus no treatment for 10 years.

Main outcome measures Number of fatal and nonfatal vascular events prevented, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios over 10 years.

Results Over a 10-year period, statin treatment cost €35 000 (£30 000, $49 000) per QALY gained for men aged 55 years with a 10-year vascular risk of 10%. The incremental cost-effectiveness ratio improved as risk for vascular disease increased. The cost per QALY ranged from approximately €5000 to €125 000 when the 10-year vascular risk for men aged 55 years was varied from 25% to 5%. The incremental cost-effectiveness ratio slightly decreased with age after the level of vascular risk was specified. Results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.

Conclusions In daily practice, statin treatment seemed not to be cost-effective for primary prevention in populations at low risk of vascular disease, despite low costs of generic drug pills. Adherence to statin treatment needs to be improved to enhance the cost-effectiveness of the use of statins for primary prevention.

INTRODUCTION

Cardiovascular disease is the leading cause of death and disability in more developed countries and contributes substantially to healthcare spending.[12] Several clinical trials and meta-analyses have shown the beneficial effects of statins in reducing mortality and cardiovascular morbidity in a range of different populations and risk groups.[3 4] Four recent systematic reviews focused on the efficacy of statins in primary prevention populations at high risk, and concluded that statin treatment was associated with a significant reduction in the risk of major vascular events, but it had no benefit on all cause mortality.[5-8]

In view of the large treatment effects on major vascular events, a considerable number of people in high risk primary prevention populations could probably benefit from long term statin use. Recently, the introduction of generic statins has led to sharp price reductions. Consequently, statin use today could come at a reasonable price in lower risk primary prevention populations. However, a substantial gap exists between expected and actual benefits, which can be attributed to poor adherence to statin therapy.[9 10] Furthermore, treating all people in high risk, low risk, and very low risk primary prevention populations would mean treating a very large number of people and could have important implications for public health costs and use of healthcare resources. Moreover, healthy people might not wish to receive medical therapy, and such considerations should be taken into account when deciding on the use of statins.[11] Decision analysis is an appropriate way to gain insight in the balance of benefits, risks, and costs of statin treatment in different subgroups.[12]

To help inform clinical and policy decisions about primary prevention of vascular disease, we did a cost-effectiveness analysis that examined the use of statins in men and women of different ages with various underlying levels of vascular disease risk. This analysis extends the results of previous cost-effectiveness analyses[13-18] by examining the effect of non-adherence, examining a greater number of subgroups, and including generic statin prices and updated estimates of statin effectiveness. This analysis incorporates the results from the recently published JUPITER trial (Justification for the Use of Statins in Prevention: an

Intervention Trial Evaluating Rosuvastatin), which is probably the last large placebo controlled primary prevention trial with statins.[19]

METHODS

Model structure

A Markov model was used to evaluate the costs and effects associated with low dose statin treatment and no treatment.[20] The model was designed to simulate cohorts of apparently healthy men or women aged 45, 55, 65, or 75 years with various levels of risk of vascular disease (myocardial infarction and stroke) within 10 years (10-year vascular risk). The model comprises six health states: healthy, post-myocardial infarction, post-major stroke, post-minor stroke, post-myopathy, and death (figure 1). All people entered the model in the healthy state. From there, age and sex specific probabilities of fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, or dying of another cause determined which people made transitions to other health states, in each annual cycle. People who experienced adverse effects from statin therapy (myopathy and rhabdomyolysis) stopped taking their statins permanently; thereafter their procession through the model was similar to that of healthy people who did not use statins. We did not consider angina pectoris or transient ischaemic attacks as separate health states in our model because insufficient data about the effects of statins on these outcomes were available. Additionally, these outcomes are transient health states that may be considered an integral part of survival with vascular disease without specific long term consequences.

Model variables

Probabilities of transition to the next health state, effectiveness of statin treatment, utilities, and costs for a 55 year old person are shown in table 1. Webtable 1 shows these data for people aged 45, 65, and 75 years old. Annual baseline incidence rates of initial vascular

Fig 1 | General structure of the Markov model. People enter the model while taking statins or not and can progress from healthy to one of the other health states (shaded boxes), including death, in each cycle. Those who have statin related adverse effects (myopathy and rhabdomyolysis) stop taking statins. MI=myocardial infarction

events (fatal and nonfatal myocardial infarction and stroke) by age group and sex were obtained from a record linkage study of nationwide registers and included hospitalised patients of all ages and deaths out of hospital.[1 21 22] We calculated age specific incidence rates with linear interpolation between age groups. We used these rates in our model rather than fixed annual rates, because incidence rates increase with age. Similarly, we derived age and sex specific case fatality rates for myocardial infarction and stroke.[22 23] The risks of adverse effects associated with statins (myopathy and rhabdomyolysis) were drawn from a systematic review of cohort studies supported by data from randomised controlled trials.[24] The case fatality of rhabdomyolysis was estimated at 10%.[24] We derived age and sex specific annual probabilities of dying from Dutch life tables.[25] These data were used to take into account the ageing of the cohort in the model.

Because we were interested in primary prevention, we did not simulate or examine the details of a patient's course after a first, nonfatal vascular event. Instead, we assigned survivors of a first vascular event an increased risk of death based on the average long term experience (for example, increased event rate) of patients after a first vascular event.[26-29] We assumed that all patients received optimal secondary prevention and we applied a two-fold increased risk for death to the general mortality rates from the Dutch life tables to generate the estimated post event mortality rates. We assumed that risk of permanent severe disability after stroke is 33%.[30]

Treatment efficacy

Treatment efficacy was modelled by application of risk ratios from a recent meta-analysis of ten randomised controlled trials of statins for primary prevention to the incidence rates of myocardial infarction and stroke.[7] We assumed similar treatment efficacy in men and women at different ages since risk ratios did not differ significantly between the sexes, and between elderly and young people, but we varied these estimates widely in the sensitivity analysis to reflect data that suggested that statins have lower relative risk reductions at older ages.[7] For the base case analysis, we assumed a real world non-adherence scenario. We derived real world adherence rates from the literature (60% adherence after year 1, 45% after year 2, 40% after year 3, and thereafter remaining stable).[31-33] On the basis of statin trial data that indicated that adherence to statin therapy was 90% after one year, 85% after two years, and 80% after three years of trial follow-up (i.e. a 'full' adherence scenario),[7] we calculated reduced adherence rates of 33% (1-0.6/0.9) in year 1, 21% (1-0.45/[0.85/0.90*0.60]) in year 2 and 6% (1-0.40/[0.80/0.85*0.45]) in year 3. Real world non-adherence was modelled by decreasing statin efficacy and statin pill costs, but leaving the costs of doctors' visits at 50% and laboratory test monitoring at 100%.
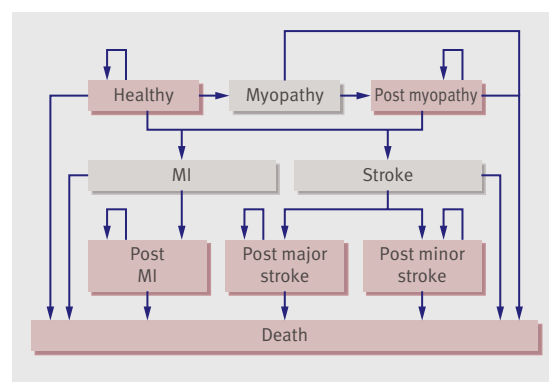
Table 1 | Incidence, case fatality, and overall mortality rates for a person aged 55 years and effectiveness of statin treatment, utilities, and costs (95% CI)

Parameters	Men	Women	Distribution	Data source	Reference
Incidence (per 100 000 person-years)*					
Myocardial infarction	426 (413 to 440)	101 (95 to 108)	Beta	Cohort study	21
Stroke	189 (177 to 202)	116 (106 to 126)	Beta	Cohort study	1, 22
Myopathy	12 (1 to 33)	12 (1 to 33)	Beta	Meta-analysis	24
Rhabdomyolysis	3.4 (1.6 to 6.0)	3.4 (1.6 to 6.0)	Beta	Meta-analysis	24
One-year case fatality rate*					
Myocardial infarction	0.28 (0.26 to 0.29)	0.27 (0.25 to 0.30)	Beta	Cohort study	23
Stroke	0.18 (0.16 to 0.21)	0.18 (0.14 to 0.21)	Beta	Cohort study	22
Rhabdomyolysis	0.10 (0.08 to 0.12)	0.10 (0.08 to 0.12)	Beta	Cohort study	24
Overall one-year mortality rate* (per 100 000 person-years)	658 (607 to 709)	407 (366 to 448)	-	Actual rates	25
Treatment effectiveness of statins (risk ratios)					
Major coronary events	0.71 (0.61 to 0.82)	0.71 (0.61 to 0.82)	Lognormal	Meta-analysis	7
Stroke	0.81 (0.71 to 0.93)	0.81 (0.71 to 0.93)	Lognormal	Meta-analysis	7
Real-world adherence, first year	0.60 (0.50 to 0.70)	0.60 (0.50 to 0.70)	Beta	Cohort study	31-33
Utilities					
Post-myocardial infarction	0.88 (0.8 to 0.95)	0.88 (0.8 to 0.95)	Triangular	Interview	34
Post-major stroke	0.5 (0 to 0.75)	0.5 (0 to 0.75)	Triangular	Review	35
Post-minor stroke	0.75 (0.63 to 0.90)	0.75 (0.63 to 0.90)	Triangular	Review	35
Act of taking statin medication	0.999 (0.995 to 1.0)	0.999 (0.995 to 1.0)	Beta	Estimate	17, 36, 37
Annual cost data (€)					
Statin treatment					
Simvastatin 40 mg (generic)	9 (4 to 15)	9 (4 to 15)	Gamma	Official tariff	38
Doctors' visit costs	99 (64 to 142)	99 (64 to 142)	Gamma	Official tariff	39
Pharmacists' fee	25 (10 to 49)	25 (10 to 49)	Gamma	Official tariff	39
Laboratory costs	24 (16 to 35)	24 (16 to 35)	Gamma	Official tariff	39
Post-myocardial infarction					
During first year	17 342 (17 087 to 17 603)	17 342 (17 087 to 17 603)	Gamma	Cost study	38
During subsequent years	1054 (992 to 1118)	1054 (992 to 1118)	Gamma	Cost study	39
Post-major stroke					
During first year	36 173 (35 801 to 36 546)	36 173 (35 801 to 36 546)	Gamma	Cost study	40
During subsequent years	21 122 (20 839 to 21 408)	21 122 (20 839 to 21 408)	Gamma	Cost study	40
Post-minor stroke					
During first year	6343 (6187 to 6500)	6343 (6187 to 6500)	Gamma	Cost study	40
During subsequent years	1085 (1021 to 1150)	1085 (1021 to 1150)	Gamma	Cost study	40
Death	2698 (2597 to 2801)	2698 (2597 to 2801)	Gamma	Expert opinion	40

*Risk of events and mortality rates increase with advancing age, except for rhabdomyolysis.

Health outcomes

We determined the expected number of each of the vascular disease events (myocardial infarction and stroke) along with differences in quality-adjusted life-years (QALYs). QALYs were calculated by multiplying the time a person remained in a certain health state by the utility associated with that particular health state and subsequent summing up over all health states. Utility weights for the health states after myocardial infarction (0.88), major stroke (0.5), and minor stroke (0.75) were derived from data published in the literature.[34][35] Most studies used time trade-off techniques to generate utility weights. We included a small disutility from taking a statin pill every day (0.001) in the model.[17][36][37]

Costs

We conducted our economic analysis from the perspective of the healthcare payer. Costs of treatment were divided into those incurred by the drug, laboratory tests, doctors' visits, and pharmacists' fees. For our base case scenario, we estimated the annual costs of statin pills at €9 euros (£7.65, $12.60; conversion rate €1=£0.85, $1.40) for 40 mg generic simvastatin.[38] Since statin pill costs vary greatly between countries (see webtable 2), we varied the drug costs over wide ranges in scenario analyses. Annual costs of laboratory tests were estimated at €24, cost of doctors' visits at €99, and of pharmacists' prescription fees at €25 based on four visits a year.[39]

Costs associated with morbidity after vascular events were divided into costs for the first year and annual costs for subsequent years. Morbidity associated estimates of cost were derived from Dutch costs studies, and if these data were not available, we applied European costs estimates.[40-42] The associated costs of managing adverse events were expected to be

Table 2 | Men: quality-adjusted life expectancy and costs of statins compared with no statins on cohorts of Dutch men at different ages over a 10-year period

| Age (years) | 10-year vascular risk* | | | QALYs | | | Costs (€) | | | ICER (€ per QALY) |
	No statins	Statins	Absolute risk reduction	Statins	No statins	Incremental QALYs	Statins	No statins	Incremental costs (€)	
45										
	1.0%	0.9%	0.1%	9.162	9.166	-0.005	1192	236	956	NA
	2.5%	2.1%	0.4%	9.143	9.144	-0.001	1409	494	916	NA
	5.0%	4.3%	0.7%	9.111	9.107	0.004	1774	925	848	195 372
	7.5%	6.5%	1.0%	9.079	9.069	0.010	2141	1360	781	78 136
	10.0%	8.6%	1.4%	9.047	9.032	0.016	2511	1796	715	45 669
	15.0%	13.0%	2.0%	8.981	8.954	0.027	3262	2678	584	21 651
55										
	2.5%	2.1%	0.4%	8.937	8.938	0.000	1501	603	898	NA
	5.0%	4.3%	0.7%	8.900	8.893	0.007	1856	1024	832	125 544
	7.5%	6.5%	1.0%	8.862	8.849	0.013	2215	1448	767	57 442
	10.0%	8.6%	1.4%	8.824	8.804	0.020	2577	1875	702	34 995
	15.0%	13.0%	2.0%	8.746	8.712	0.033	3311	2737	574	17 158
	20.0%	17.4%	2.6%	8.666	8.619	0.047	4059	3611	448	9572
	25.0%	21.8%	3.2%	8.584	8.523	0.060	4823	4499	324	5395
65										
	5.0%	4.3%	0.7%	8.277	8.266	0.010	2052	1265	787	75 237
	7.5%	6.5%	1.0%	8.228	8.210	0.019	2374	1644	729	38 613
	10.0%	8.7%	1.3%	8.180	8.152	0.027	2698	2026	672	24 607
	15.0%	13.0%	2.0%	8.080	8.036	0.044	3357	2799	558	12 652
	20.0%	17.5%	2.5%	7.978	7.917	0.061	4030	3585	445	7323
	25.0%	21.9%	3.1%	7.873	7.795	0.077	4719	4384	334	4319
75										
	5.0%	4.3%	0.7%	6.928	6.912	0.016	2382	1696	686	42 439
	7.5%	6.5%	1.0%	6.865	6.838	0.027	2604	1961	643	23 846
	10.0%	8.7%	1.3%	6.802	6.764	0.038	2829	2230	600	15 901
	15.0%	13.1%	1.9%	6.673	6.614	0.059	3288	2774	514	8695
	20.0%	17.5%	2.5%	6.540	6.460	0.080	3758	3328	429	5343
	25.0%	21.9%	3.1%	6.403	6.301	0.101	4241	3895	346	3410
	30.0%	26.4%	3.6%	6.260	6.138	0.122	4739	4475	264	2156

ICER=incremental cost-effectiveness ratio, NA=not applicable.
*The 10-year vascular disease risk was estimated from the expected number of first vascular events (fatal and nonfatal myocardial infarction or stroke) over the first 10 years divided by the total number of simulated people.

small and were not modelled. All cost estimates were updated to 2008 with the Dutch consumer price indices (http://statline.cbs.nl), and calculated in euros (table 1).

Analysis

We examined the effect of different levels of 10-year risk of vascular disease (1%, 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, and 30%) separately for men and women of different ages. For the analysis, clinical courses of 100 000 hypothetical persons for both strategies were evaluated and a time horizon of 10 years was used. Discounting was done at a rate of 4% for costs and 1.5% for health outcomes following Dutch guidelines.[43] One way sensitivity analyses were done for statin pill costs, adverse effects, lower effectiveness of statins for people older than 65 years,[7] non-adherence, disutility from taking a daily pill, varying baseline utility by age to account

for declining quality of life over time,[44] and discount rate. Our base case scenario considered men aged 55 years with a 10-year risk for vascular disease of 10%. We also explored the impact of alternative time horizons (20-year and lifetime). For these analyses, we assumed that both groups (initial statin users and non-users) adopted statin treatment after 10 years.

Parameter uncertainty was dealt with by probabilistic sensitivity analysis using Monte Carlo simulation with 1000 iterations for each evaluation. For each iteration, a value of each input variable was selected randomly from its distribution given in table 1. Results from the probabilistic sensitivity analysis were presented as a scatter plot of incremental cost-effectiveness ratios and as a cost-effectiveness acceptability curve. The latter curve shows the probability that statin therapy is cost-effective for a range of cost-effectiveness thresholds.

Table 3 | Women: quality-adjusted life expectancy and costs of statins compared with no statins on cohorts of Dutch women at different ages over a 10-year period

Age (years)	10-year vascular risk*			QALYs			Costs (€)			ICER (€ per QALY)
	No statins	Statins	Absolute risk reduction	Statins	No statins	Incremental QALYs	Statins	No statins	Incremental costs (€)	
45										
	1.0%	0.9%	0.1%	9.178	9.183	-0.005	1225	271	954	NA
	2.5%	2.2%	0.3%	9.157	9.158	-0.001	1507	600	907	NA
	5.0%	4.4%	0.6%	9.120	9.116	0.005	1982	1152	829	177 029
	7.5%	6.6%	0.9%	9.084	9.073	0.011	2460	1709	752	71 474
	10.0%	8.8%	1.2%	9.046	9.030	0.016	2943	2269	675	41 275
55										
	2.5%	2.2%	0.3%	9.045	9.046	-0.001	1488	582	906	NA
	5.0%	4.4%	0.6%	9.008	9.003	0.005	1891	1053	838	16 7080
	7.5%	6.5%	1.0%	8.971	8.960	0.011	2298	1527	770	70 207
	10.0%	8.7%	1.3%	8.934	8.917	0.017	2708	2005	703	41 544
	15.0%	13.1%	1.9%	8.857	8.829	0.029	3541	2972	569	19 772
	20.0%	17.6%	2.4%	8.779	8.739	0.041	4392	3955	437	10 758
	25.0%	22.0%	3.0%	8.699	8.646	0.052	5263	4957	306	5846
65										
	5.0%	4.4%	0.6%	8.719	8.711	0.008	1892	1061	831	99 857
	7.5%	6.5%	1.0%	8.673	8.657	0.016	2236	1462	773	48 837
	10.0%	8.7%	1.3%	8.626	8.603	0.023	2583	1867	716	30 673
	15.0%	13.2%	1.8%	8.531	8.493	0.038	3287	2686	601	15 703
	20.0%	17.6%	2.4%	8.434	8.380	0.053	4008	3520	488	9177
	25.0%	22.1%	2.9%	8.333	8.265	0.068	4746	4369	376	5531
75										
	5.0%	4.4%	0.6%	7.906	7.893	0.013	2080	1299	781	58 110
	7.5%	6.6%	0.9%	7.846	7.823	0.023	2328	1591	737	31 712
	10.0%	8.8%	1.2%	7.785	7.752	0.033	2578	1886	692	20 981
	15.0%	13.2%	1.8%	7.661	7.608	0.052	2484	604	11 513	
	20.0%	17.6%	2.4%	7.533	7.461	0.072	3611	3094	517	7190
	25.0%	22.1%	2.9%	7.401	7.310	0.091	4147	3717	430	4719
	30.0%	26.6%	3.4%	7.265	7.155	0.110	4700	4355	344	3122

ICER=incremental cost-effectiveness ratio, NA=not applicable.

* The 10-year vascular disease risk was estimated from the expected number of first vascular events (fatal and nonfatal myocardial infarction or stroke) over the first 10 years divided by the total number of simulated people.

RESULTS

Table 2 and table 3 show the costs per QALY estimates for the use of statin treatment in primary prevention by vascular risk levels, age, and sex. Statin treatment in men aged 55 years with a 10-year vascular risk of 10% resulted in a mean QALY gain (from 8.80 to 8.82) over 10 years. The statin treatment strategy was associated with additional mean costs of €702 per person (€1875 for no treatment versus €2577 for statin treatment strategy). The cost difference was attributable to statin treatment costs (€932 per person), which were partly compensated for by fewer vascular events in the statin treatment strategy. Statin treatment for 10 years resulted in an incremental cost-effectiveness ratio of €35 000 per QALY gained compared with no treatment.

Statin treatment in men aged 65 with a 10-year vascular risk of 10% resulted in a larger QALY gain (from 8.15 to 8.18) over ten years. Statin treatment was associated with additional €672 costs per person, resulting in an incremental cost-effectiveness ratio of €24 600 per QALY gained.

In general, the incremental cost-effectiveness ratios improved as risk for vascular disease increased. The incremental cost-effectiveness ratios slightly decreased with age after the level of vascular risk was specified. The predicted health benefits were somewhat lower in women, which resulted in slightly higher incremental cost-effectiveness ratios.

Sensitivity analyses

One way sensitivity analyses showed that the results of the model were most sensitive to assumptions on the costs of statin treatment, statin effectiveness, non-adherence, and disutility from taking a statin pill every day (table 4). Statin pill costs (€9 a year in the base case) had an important effect on the incremental cost-effectiveness ratio. If costs of the statin pills were as high as €100 a year, the cost per QALY gained would increase from €35 000 to almost €55 000. If statins were
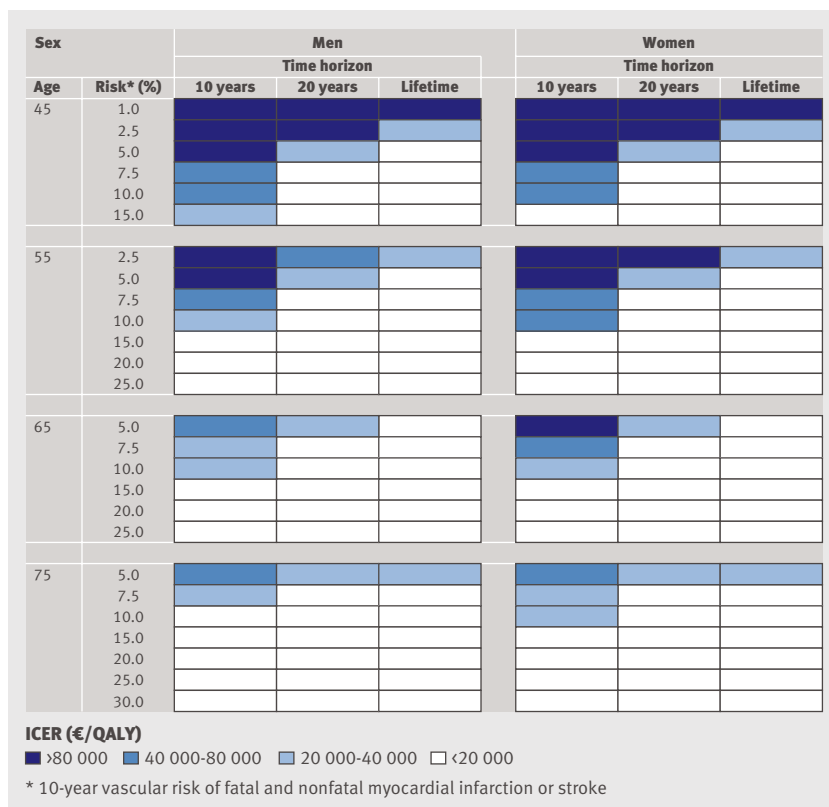
as seen in the trials ("full" adherence scenario) were reached, the cost per QALY gained with statins would decrease to €26 000. Assuming no disutility from taking a statin pill every day improved the incremental cost-effectiveness ratio substantially, the cost per QALY gained would decrease to €26 000. The impact of the time horizon on the results was also subjected to sensitivity analysis. Extending the time horizon of the model to 20 years or lifetime decreased the costs per QALY relative to base case levels, particularly for people at younger ages (fig 2).

Figure 3 shows the results of the probabilistic sensitivity analysis for 55 year old men with a 10-year vascular risk of 10%. Hence, at a threshold of €20 000 per QALY, the probability that statin treatment is cost-effective is 16%. There is a 97% chance that statin treatment is cost-effective at a threshold of €80 000/QALY.

DISCUSSION
This study showed that the cost-effectiveness of statin treatment for primary prevention in daily practice ranged from €5 000 to €125 000 when the 10-year vascular risk for middle aged men was varied from 25% to 5%. Results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.

In the past few decades, many studies have been published on the cost-effectiveness of statin treatment for primary prevention of vascular disease.[13-18] Previous studies showed that the cost-effectiveness of statin treatment depends on the absolute level of vascular disease risk in the population treated and the age and sex of the population under consideration. Such studies introduced labelling of risk of vascular disease or

Sex		Men			Women		
		Time horizon			**Time horizon**		
Age	Risk* (%)	10 years	20 years	Lifetime	10 years	20 years	Lifetime
45	1.0						
	2.5						
	5.0						
	7.5						
	10.0						
	15.0						
55	2.5						
	5.0						
	7.5						
	10.0						
	15.0						
	20.0						
	25.0						
65	5.0						
	7.5						
	10.0						
	15.0						
	20.0						
	25.0						
75	5.0						
	7.5						
	10.0						
	15.0						
	20.0						
	25.0						
	30.0						

ICER (€/QALY)
■ >80 000   ■ 40 000-80 000   ■ 20 000-40 000   □ <20 000

* 10-year vascular risk of fatal and nonfatal myocardial infarction or stroke

Fig 2 | Sensitivity analysis: cost-effectiveness results for different time horizons of the model.

less effective in elderly people, the incremental cost-effectiveness ratio would also become less favourable. Improvement in adherence would enhance the cost-effectiveness of statin treatment. If adherence levels

Table 4 | One-way sensitivity analyses examining incremental cost-effectiveness ratio of 10 years statin treatment in men aged 55 years and 65 years with a 10-year risk of vascular disease of 10%

Assumption	55 year old men			65 year old men		
	QALYs	Costs (€)	ICER (€ per QALY)	QALYs	Costs (€)	ICER (€ per QALY)
Base-case scenario	0.020	702	34 995	0.027	672	24 607
Statin pill costs (base case, €9 per year)						
€100	0.020	1096	54 595	0.027	1042	38 151
€300	0.020	1958	97 545	0.027	1852	67 832
Risk for myopathy (base case, 12 per 100 000 persons per year)						
20	0.020	702	35 115	0.027	672	24 665
100	0.019	702	36 320	0.027	671	25 238
Statin effectiveness varies by age (base case, fixed effectiveness by age)						
If less effective for people aged >65 years*	NA	NA	NA	0.016	710	43 914
Adherence (base case, real world adherence)						
Full adherence	0.032	831	25 848	0.044	804	18 315
Disutility from taking a pill every day, in days traded away assuming a 10-year course of treatment (base case, 5 days)						
No disutility	0.027	702	26 394	0.033	672	20 098
Baseline utility (base case, 1 for all ages)						
If baseline utility decreases by age	0.017	702	41 071	0.023	672	28 875
Discount rate (base case, costs 4%, health outcomes 1.5%)						
4% for both costs and health outcomes	0.017	702	41 764	0.023	672	29 174
3% for both costs and health outcomes	0.018	732	40 557	0.025	699	28 375

ICER=incremental cost-effectiveness ratio, NA=not applicable.
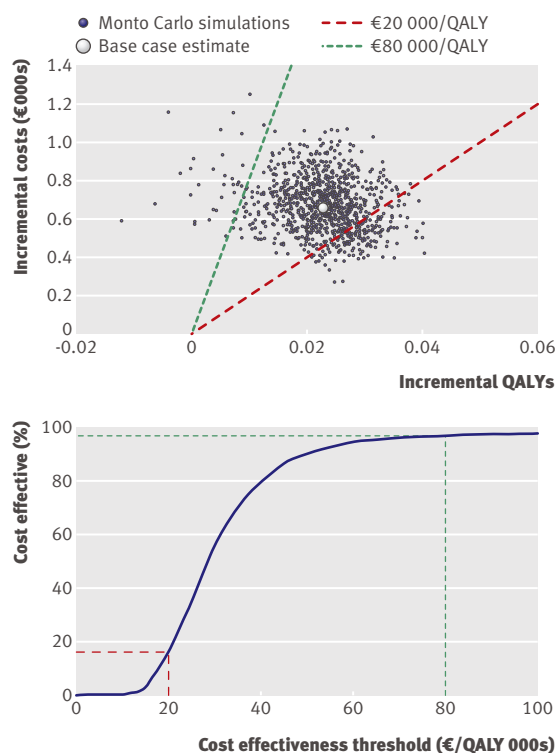*Risk ratio for myocardial infarction 0.86 (95% CI 0.67 to 1.0) and for stroke 0.79 (0.53 to 1.18).[7]

Fig 3 | Probabilistic sensitivity analysis and cost-effectiveness acceptability curve. Top: results of probabilistic sensitivity analysis for base case of 55 year old men (10-year vascular risk of 10%). Each dot represents 1 iteration of the model. Y axis represents incremental costs of statins compared with no therapy. X axis represents incremental QALYs with statins compared with no therapy. Diagonal lines represent a cost per QALY gained of €20 000 and of €80 000. Below: Y axis represents probability that the cost per QALY gained is less than or equal to values on X axis. ICER=incremental cost-effectiveness ratio

mortality as "low", "medium" or "high". In view of the natural increase in vascular risk owing to age, it is difficult to label a certain level of risk as low, average, or high. For example, a 10-year vascular risk of 15% is a very high risk for men aged 45 years, whereas it is an average risk in people aged 65 years. We propose that a reference to absolute risk levels should always be made when labelling risks as low, medium, or high.

Strengths of the study

Although the prices of statins have fallen, our model produced cost-effectiveness results similar to those of earlier analyses. This finding may seem counterintuitive, because the price of statins does affect the cost-effectiveness results. However, other factors are involved when targeting statins to primary prevention populations. We took into account the effect of incomplete adherence to statin therapy, attributed a disutility to the act of taking medication daily, and shortened the time frame of the model to 10 years. These factors offset the cost saving effect of generic statin prices. None of the previous studies accounted for all these factors simultaneously. Consequently, our study provides a

more complete overview of the cost-effectiveness of the use of statins for the primary prevention of vascular disease in daily practice. Clinicians who wish to use these results need to assess the risk of vascular disease in all middle aged and older adults and in younger adults with additional risk factors, using one of the validated risk prediction models (SCORE or Framingham). Depending on a country's willingness to pay for a QALY, clinicians should prescribe statins to all people in risk groups with relatively attractive levels of cost-effectiveness, irrespective of the level of any of the individual risk factors.

Limitations

Our model has some limitations. First, the base case analysis was run for 10 years instead of the complete lifetime. The sensitivity analysis showed that if the modelling was undertaken over a person's lifetime this would lead to more favourable cost-effectiveness results, especially for younger people. However, we believe that if treatment is started in relatively healthy young individuals it will be very difficult to continue this treatment over the person's lifetime. Moreover, we judged a 10-year period to be long enough to capture the major health and economic consequences of taking statins in the primary prevention of vascular events. Second, our results are based on a model that did not incorporate the details of a patient's course after a first, nonfatal vascular event. Instead, we assigned them an increased risk for death, increased costs, and a disutility associated with their health state. This simplified approach was adopted because modelling secondary events did not have a large influence on our results, and it prevented the model from becoming too complex. Third, we assumed that statin treatment confers a continuous benefit beyond the trial follow-up period. This assumption is common in cost-effectiveness models and may be reasonable since treatment is still ongoing at the end of trial follow-up. Fourth, we used Dutch estimates for drug costs. The low statin pill costs in the Netherlands are not achievable in most countries in the foreseeable future. Higher costs of statin pills would strengthen our conclusion that statins have a limited role in primary prevention in view of the current low adherence rates. Fifth, we conducted our economic analysis from the healthcare payer's perspective (implying that only direct medical costs are included). If indirect costs representing the loss of productivity were included, statin treatment would be expected to become more cost-effective.[45]

Implications

In conclusion, this study showed that even at current low costs for generic statin pills, statin treatment seemed not to be cost-effective for low risk primary prevention populations (10-year vascular disease risk <5%) in the Netherlands, when non-adherence was taken into account. Adherence to statin therapy needs to be improved to enhance the cost-effectiveness of the use of statins for primary prevention.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

Statins reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease.

Overall risk of vascular disease events, rather than single risk factors, determines the absolute benefits of statin therapy.

Adherence to statin treatment in daily practice is suboptimal and may impair cost-effectiveness.

WHAT THIS STUDY ADDS?

Statin treatment seemed not to be cost-effective for low risk primary prevention populations, despite low costs of generic drugs

Adherence to statins needs to be improved to enhance cost-effectiveness.

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