Pharmacoeconomic evaluation of testing for angiotensin-converting enzyme genotype before starting β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitor therapy in men

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This study aimed to assess the potential cost-effectiveness of screening men for their angiotensin-converting enzyme (ACE)-genotype before starting statin therapy. We used a combination of decision-analytic and Markov modelling techniques to evaluate the long-term incremental clinical and economic effects associated with genetic testing of men with hypercholesterolemia before starting treatment with statins. The study was performed from a health care payer perspective. We used data from the Rotterdam study, a prospective population-based cohort study in the Netherlands, which was started in 1990 and included 7983 subjects aged 55 years and older. Men treated with cholesterol-lowering drugs at baseline or with a baseline total cholesterol ⩾ 6.5 mmol/l were included. The ratio of difference in lifelong costs between the screening strategy and the no screening strategy to difference in life expectancy between these strategies was calculated. We also performed a cost-utility analysis. The base case was a 55-year-old man with hypercholesterolemia who was initially untreated. Several univariate sensitivity analyses were performed. All costs were discounted with an annual rate of 5%. Screening men for their ACE-genotype was the dominant strategy for the base case analysis, because the screening strategy saved money (€851), but life expectancy was not changed. Screening was the dominant strategy for all age-groups in our cohort. Even in 80-year-old subjects, with the shortest life-expectancy, it was cheaper to screen than to give lifelong treatment to men with a DD genotype without success. Even if all DD subjects were treated with other (non-statin) cholesterol-lowering drugs, screening remained the cost-effective strategy. The results of the cost-utility analysis were similar. Discounting the effects with 5% per year also had no major impact on the conclusions. If other studies confirm that men with the DD genotype do not benefit from treatment with statins, screening for ACE genotype in men most likely will be a cost-effective strategy before initiating statin therapy.
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Introduction

The clinical benefits of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been well established in at least six large clinical trials [1–6], which have shown an average risk reduction of coronary events of approximately 30%. However, these effects are the average effects for all patients in these trials. Recent pharmacogenetic findings suggest that patients may differ substantially in their response to statins. Genetic polymorphisms of cholesteryl ester transfer protein, hepatic lipase, apolipoprotein E, and the angiotensin-converting enzyme-insertion deletion (ACE I/D) polymorphism may influence the effectiveness of statins [7]. Statins are widely used drugs, and the amount of people taking these drugs is still rising. According to the cholesterol guidelines issued by the US National Institutes of Health in 2001, approximately 36 million people in the USA are candidates for statin treatment. In 2002, global sales of statins reached US$21.7 billion as doctors wrote

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more than 118 million statin prescriptions according to IMS Health [8].

The Rotterdam Study is a prospective follow-up study in an elderly population, which has already resulted in numerous international publications. Although the study is community based, the results are probably generalizable to the Dutch population [9]. In a recent prospective study of the Rotterdam Study cohort ($n = 3624$), we found a difference in the effectiveness of statins in men with regard to the gene coding for ACE. The confidence intervals for the relative risks found in this study were large, which is due to small sample sizes for the groups that were treated for $\geqslant 2$ years with statin therapy in each genotype group. Men with the DD genotype (27%) who used statins for $\geqslant 2$ years had a relative risk (RR) of coronary heart disease of 1.34 [95% confidence interval (CI) 0.44–4.09] compared to men who did not use statins, while men with the ID genotype (51%) had a RR of 0.87 (95% CI 0.43–1.76) and men with the II genotype (22%) had a RR of 0.23 (95% CI 0.04–1.28). Therefore, in males, the interaction between ACE I/D polymorphism and statins was significantly increased. The synergy index (SI) for all coronary events was 7.41 (95% CI 1.17–46.8). The SI is calculated as the ratio of the RR in subjects with the DD genotype and the RR in subjects with the II genotype [10]. An $SI = 1$ means that the RR in the two subgroups are the same and that there is no interaction on the multiplicative scale; an $SI = 7.41$ means that the joint effect of ACE II genotype and statins is larger than their expected effect.

Because statin treatment did not lower the risk of coronary disease in men with the DD genotype, statin therapy may not be warranted for these patients. Before investing resources to confirm these findings in a large clinical trial, it is important to assess not only the potential effectiveness of a screening strategy, but also its cost-effectiveness.

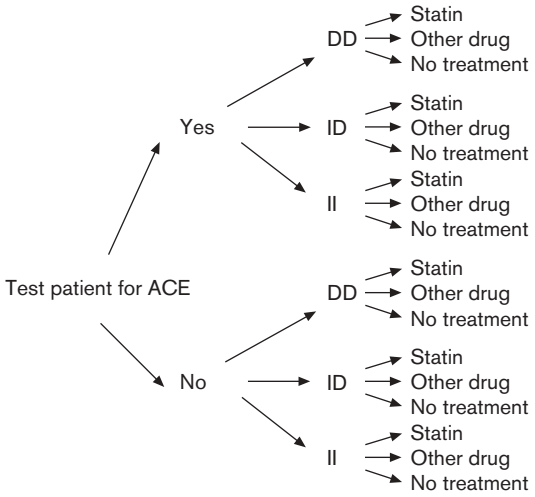
Thus, the objective of this study was to assess the potential cost-effectiveness of determining the ACE-genotype in men before starting statin therapy.

Methods

Study design

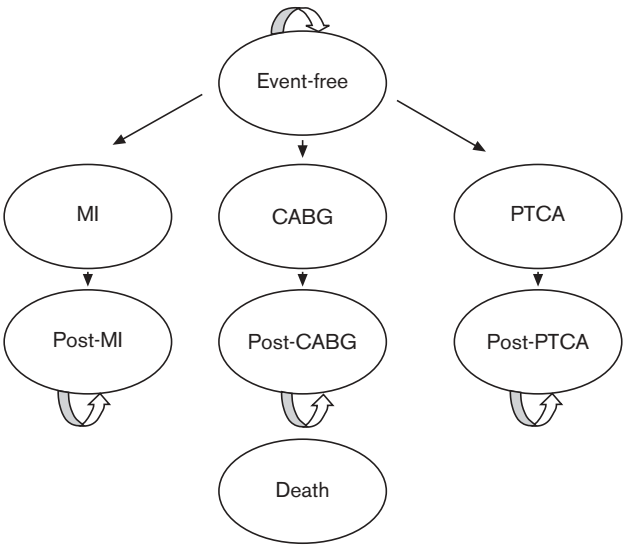
We used a combination of decision-analytic and Markov modelling techniques to evaluate the long-term incremental clinical and economic outcomes associated with genetic testing of men with hypercholesterolemia before starting treatment with statins. A decision model allocated patients to distinct cohorts based on their genotype and subsequent treatment for hypercholesterolemia (Fig. 1). We then used a Markov model to simulate disease progression and calculate long-term costs, and treatment effectiveness for each cohort (Fig. 2). A Markov model was chosen because of its ability to model disease events involving continuous risk over time [11]. The outcomes of interest were non-fatal myocardial infarction, coronary artery bypass graft

Fig. 1



Decision tree representing the decision to perform an angiotensin-converting enzyme (ACE) genotype genetic test.

Fig. 2



The Markov model. Health states are depicted by ovals; arrows represent allowed transitions. All health states can be followed by death. All patients start off event-free and can either remain in that state, or go on to have a myocardial infarction (MI), a coronary artery bypass graft (CABG), a percutanuous transluminar coronary artery (PTCA) or die. Subjects with a myocardial infarction can go on to post-myocardial infarction or die. Subjects that are in the post-myocardial infarction state can remain in that state or die.

(CABG), percutanuous transluminar coronary angioplasty (PTCA) and coronary mortality. Each year, patients could remain free of cardiovascular events, have a fatal or non-fatal coronary event, or die of other causes. After experiencing a non-fatal coronary event, patients could go into the post-event state or die. After the post-event state, patients could remain in that state, or die.

The base case in our analyses was a hypothetical cohort of 55-year-old men with hypercholesterolemia who were initially untreated. This cohort was followed until all patients in this hypothetical cohort died.

We conducted this analysis from a health care payer perspective in which only direct medical costs were taken into account. The ratio of costs of screening (*Cs*) minus costs of not screening (*Cns*) to the difference in life expectancy between screening (*Es*) and no screening (*Ens*) was calculated:

$$\text{Incremental cost-effectiveness ratio} =$$

$$(Cs - Cns)/(Es - Ens)$$

All analyses were performed using the decision-analysis program DATA (Treeage Software, Williamstown, Massachusetts, USA).

Data

Rotterdam study

The Rotterdam Study started in 1990 as a population-based prospective follow-up study. All 10 275 residents of the suburb Ommoord in Rotterdam, aged 55 years or over, were invited to participate, of whom 7983 (78%) subjects provided their written informed consent. The baseline measurements took place until 1993 [9]. We performed a cohort study of patients in the Rotterdam Study to assess whether the effectiveness of statins in the prevention of coronary heart disease and mortality was influenced by ACE genotype in an elderly population [12], and we also assessed the yearly mortality rate and the rates of myocardial infarction, CABG, PTCA and coronary mortality in our hypercholesterolemic cohort. Every individual who had a baseline serum cholesterol $\geqslant 6.5$ mmol/l or who used cholesterol-lowering drugs at baseline was included in this cohort study. The end of the follow-up was set at 31 December 1999. During follow-up, we considered the occurrence of myocardial infarction, coronary mortality, CABG and PTCA. Use of statin therapy was assessed on the basis of pharmacy records. These records include the name of the drug, the Anatomical Therapeutic Chemical code of the drug [13], the day of dispensing, the dosage form, the numbers of units dispensed and the prescribed daily dose. On the basis of these data, we calculated the cumulative exposure to statins in the study population in the period preceding the outcome of interest. We did not distinguish between individual statins because of the small numbers, but also because the daily treatment costs were comparable between the different statins, and because there is no evidence of differential statin–ACE gene interactions. A total of 3624 subjects were included in the analyses.

Effectiveness of drug treatment

Compared to untreated subjects, the adjusted relative risk of all coronary events was 0.81 (95% CI 0.55–1.19) for subjects treated with statins for $\geqslant 2$ years. This risk reduction was comparable with the risk reductions found in clinical trials. The relative risk of developing a coronary event in men using statins for $\geqslant 2$ years compared to men who did not use statins was 1.34 [95% CI 0.44–4.09] among those with the DD genotype, while a non-significantly reduced risk was found in men with the ID genotype (RR = 0.87; 95% CI 0.43–1.76) and in subjects with the II genotype (RR = 0.23; 95% CI 0.04–1.28). Therefore, in men, the interaction between ACE I/D polymorphism and statins was significantly increased (synergy index for all coronary events of 7.41; 95% CI 1.17–46.8). A more detailed description of the results of the effectiveness study is provided elsewhere [12]. We assumed that subjects with the DD genotype had no beneficial effect from statin therapy (RR = 1) for this cost-effectiveness study. If subjects with the DD genotype experienced a beneficial effect of statin therapy, screening for the DD genotype would not be reasonable. Therefore, this study evaluated the potential cost-effectiveness of screening for the ACE DD genotype.

The mean effects of the use of other cholesterol-lowering drugs (fibrates, nicotinic acid derivates and bile acid sequestrants) on cardiovascular disease were estimated from several published clinical trials. We used a relative risk reduction of 15% for fatal and non-fatal events [14–16].

Risk of events

The yearly mortality rate in our cohort in the Rotterdam Study was 0.021. This risk was adjusted for age in our model using the data from Dutch life tables (CBS Dutch Central Bureau of Statistics, http://www.cbs.nl), assuming a constant excess risk of mortality associated with hypercholesterolemia in all age groups. The yearly risk on developing non-fatal myocardial infarction, PTCA, CABG and coronary mortality were calculated from our data for subjects with II, ID and DD genotypes separately (Table 1).

The risks of dying after a myocardial infarction [17,18], CABG [19,20] or PTCA [21,22] were derived from several large Dutch follow-up studies. These risks were calculated for a period of 1 year after the event and per

Table 1 Parameters used in disease simulation model

Variable	Base case (range)	Reference
Genotype prevalence		
II	0.22	Rotterdam Study
ID	0.51	
DD	0.27	
% Treated with statins after screening		
II	100	Assumption
ID	100	
DD	0	
% Treated with non-statin after screening		
II	0	Assumption
ID	0	
DD	0–100	
Risk of MI (per 1000 person years)		
II	9.51	Rotterdam Study
ID	11.25	
DD	8.68	
Risk of CABG (per 1000 person years)		
II	3.96	Rotterdam Study
ID	4.54	
DD	4.08	
Risk of PTCA (per 1000 person years)		
II	0.79	Rotterdam Study
ID	2.37	
DD	3.57	
Risk of fatal CHD (per 1000 person years)		
II	4.36	Rotterdam Study
ID	6.05	
DD	7.66	
Mortality rate (per 1000 person years)	21	Rotterdam Study
Mortality rate first year after non-fatal MI (per 1000 person years)	53.64	15, 16
Mortality rate post-MI (per 1000 person years)	15.41	15, 16
Mortality rate first year after PTCA (per 1000 person years)	19.11	19, 20
Mortality rate post-PTCA (per 1000 person years)	12.32	19, 20
Mortality rate first year after CABG (per 1000 person years)	19.72	17, 18
Mortality rate post-CABG (per 1000 person years)	12.92	17, 18
Efficacy of statin for prevention of MI, CABG, PTCA, fatal CHD (relative risk)		
II	0.23	Rotterdam Study
ID	0.87	
DD	1 (0.44–4.09)	
Discount rate	5%	34

MI, Myocardial infarction; CABG, coronary artery bypass graft; percutanuous transluminar coronary angioplasty.

year for the period after this first year. These risks were adjusted for age based on data from Dutch life tables (CBS Dutch Central Bureau of Statistics).

In the no-screening strategy, we assumed that all men with hypercholesterolemia would be treated with statins. In the screening strategy, we assumed that men with the DD genotype would not be treated with statins. We performed several analyses in which these men were treated with other cholesterol-lowering drugs. The values of all parameters in the model are shown in Table 1.

Costs

Total costs with and without screening were obtained by considering the costs for screening and one additional general practitioner office visit, costs of medication and by multiplying the various events (as considered in the model) with unit costs per event (Table 2). The unit costs per event were restricted to direct medical costs, estimated on the basis of different studies in the Netherlands [23], an economic evaluation of the 4S study [24,25] and data from the REGRESS study [26], as described by van Hout *et al*. [27]. The costs of drug treatment were calculated as the mean costs of treatment for 1 year with statins and the mean costs of treatment for 1 year with non-statin cholesterol-lowering drugs in the Netherlands (Dutch reference prices: Pharmaco-therapeutic Kompas 2002). All costs were expressed in 2002 Euros. All costs were discounted at an annual rate of 5%.

Health-related quality of life

Because subjects using statins do not report many side-effects, we assumed that the quality of life for subjects using statins was not negatively affected [4,5].

Several studies have described the utility after myocardial infarction. For utility after non-fatal myocardial infarction, we used a utility of 0.9 [28]. Because we lacked data about quality of life after CABG and

Table 2 Costs of drug therapy and medical care after event (in 2002 euros)

	Costs (€)	Range for sensitivity analysis (euro)	Reference
Statin (cost/year)	345	317–536	Pharmacotherapeutic Kompas 2002
Other cholesterol-lowering drugs	355	112–555	Pharmacotherapeutic Kompas 2002
Cost of general practitioner visit	22		
Screen for ACE-genotype	7	4–10	Personal communication[a]
Costs of MI	7302		25
Costs of CABG	16353		25
Costs of PTCA	7102		25
Coronary heart death	1094		25

[a]A. A. Kroon, Department of Internal Medicine, University Hospital Maastricht, The Netherlands, personal communication, May 2002. ACE, angiotensin-converting enzyme; MI, Myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutanuous transluminar coronary angioplasty.

PTCA, we used a utility of 0.9 for all subjects that experienced such an event.

Sensitivity analysis

To examine the effects of the model's assumptions, probabilities, costs and utilities on results, we varied these parameters over the ranges given in the sensitivity analyses in Tables 1 and 2.

Results

We calculated the cost-effectiveness of screening for the ACE I/D polymorphism for 55-year-old men (Table 3). Our results suggest that, potentially, screening is a dominant strategy. The screening strategy saved €851 compared to the no screening strategy, and life expectancy (15.8 years) was not influenced by screening. If the effectiveness of statins in the DD group is varied within the confidence interval, 0.26 life years are lost in the screening strategy and €679 are saved for RR = 0.44, while 0.67 life years are gained in the screening strategy and €1376 are saved for RR = 4.09 (Table 3 and Fig. 3). Indeed, screening was the dominant strategy for all age-groups in our cohort (Table 3 and Fig. 3). Even in 80-year-old subjects, with the shortest life-expectancy (4.90 years), screening saved €333.

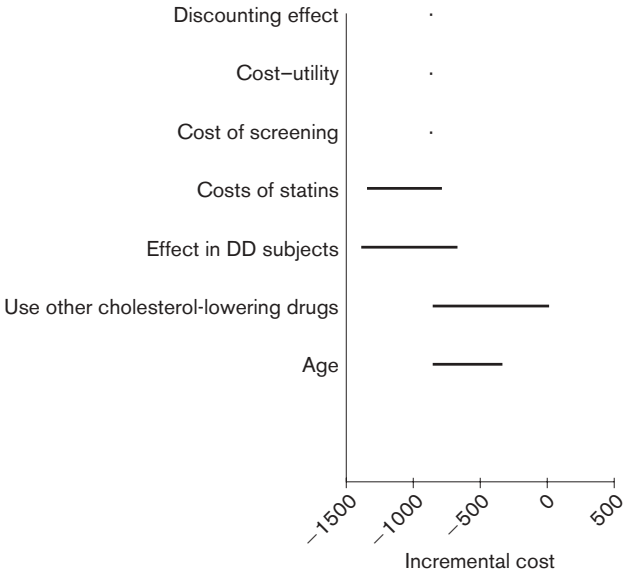
When a subject is not treated with a statin, other cholesterol-lowering drugs might be prescribed. When we modelled 50% of the DD men being treated with other cholesterol-lowering drugs, €419 and 0.03 life years were saved, and screening was still the dominant strategy. When all DD men are treated with non-

Table 3 Cost-effectiveness of screening for ACE DD genotype

	Screen		Not screen		Incremental		
	Effect (lyrs)	Cost (€)	Effect (lyrs)	Cost (€)	Effect (lyrs)	Cost (€)	C/E
Sensitivity analysis effect in DD-subjects							
0.44	15.75	3727.42	16.01	4406.86	−0.26	−679.44	−2661.99
4.09	15.75	3727.42	15.08	5103.38	0.67	−1375.76	D
Influence of age on cost-effectiveness (years)							
55	15.75	3727.42	15.75	4578.24	0	−850.81	D
65	10.97	2991.21	10.97	3652.13	0	−690.92	D
80	4.90	1665.05	4.90	1998.48	0	−333.42	D
Influence of use of other cholesterol-lowering drugs (%)							
0	15.75	3727.42	15.75	4578.24	0	−850.81	D
50	15.79	4158.80	15.75	4578.24	0.03	−419.44	D
100	15.82	4590.18	15.75	4578.24	0.06	+11.94	193.43
Cost-utility analysis							
	15.56	3727.42	15.56	4578.24	0	−850.81	D
Sensitivity analysis discounting of effect by 5%							
	9.67	3724.04	9.67	4578.24	0	−850.81	D
Sensitivity analysis cost of statins							
317	15.75	3527.23	15.75	4306.40	0	−797.17	D
345	15.75	3727.42	15.75	4578.24	0	−850.81	D
536	15.75	5086.04	15.75	6423.09	0	−1337.05	D
Sensitivity analysis cost of screening							
25.6	15.75	3724.42	15.75	4578.24	0	−853.81	D
28.6	15.75	3727.42	15.75	4578.24	0	−850.81	D
31.6	15.75	3730.42	15.75	4578.24	0	−847.81	D

D, Dominant strategy.

Fig. 3



Incremental costs for different parameters.

statins, the costs per life year saved were €193 (Table 3).

The cost-utility analysis showed that patients in either group had a quality adjusted life-expectancy of 15.56 years (QALYs) (Table 3).

Discounting the effects by 5% per year reduced the remaining number of life years to 9.67. Costs did not change in this analysis (Table 3).

The greatest variation in cost savings was associated with the cost of statin therapy. Varying costs of treatment between €317 and €536 produced an incremental cost saving in the range €779–1337. Varying the cost of a genetic test only marginally influenced cost savings. Even if the test would cost €200, testing would still be the dominant strategy.

Discussion

Our analyses suggest that testing for the ACE genotype in men could result in considerable cost savings. The screening strategy was dominant in most scenarios, and remained cost-effective when all subjects with a DD genotype were treated with non-statin cholesterol-lowering drugs. This is only true when subjects with the DD genotype do not experience a beneficial effect from statin therapy.

The prevalence of the ACE DD genotype was based on the prevalence in our hypercholesterolemic cohort in the Rotterdam Study. This is comparable with the prevalence found in other studies [29].

The main uncertainty in our study was the validity of the interaction between statin therapy and the ACE genotype. When men with the DD genotype experience beneficial effects, screening for the DD genotype would not be reasonable. Therefore, this study evaluated the potential cost-effectiveness of screening for the ACE DD genotype. Concerning the influence of the ACE genotype on effectiveness of statins, next to our own study, contradictory results have been published. Our findings were in accordance with the interaction found in the REGRESS trial [30] in which the beneficial effect of pravastatin on angiographically defined coronary atherosclerosis was apparently blunted in men with the DD genotype. However, our results were not in agreement with the results of the LCAS study [31] and the CARE trial [32]. In both of these studies, no effect of the ACE genotype was found on the reduction of coronary endpoints. These studies included both men and women. Larger studies examining clinical endpoints are needed to confirm our findings.

Another limitation of this study is that our model assumes that men only experience one coronary event. This simplification might lead to lower costs than would be expected in the real world. Furthermore, we made the assumption that statin therapy did not have an effect on the mortality rate after experiencing a coronary event, and we did not include stroke as an outcome. However, these assumptions would likely have little impact on our results because the primary benefit of screening was to avoid drug costs in patients who had no benefit from statin therapy.

The study was performed from a third-party payer perspective because we lacked valid data on indirect (non-)medical costs. The expected cost of the screening strategy was driven predominantly by the costs of statin therapy. The cost of testing was only a one-time cost. Thus, varying this cost widely in our model did not influence the cost-effectiveness of the screening versus the no screening strategy. Statins are expected to become much cheaper in the near future because patent protection will no longer be available for lovastatin, pravastatin and simvastatin. This will influence the cost-effectiveness, but even if the price were reduced by more than 50% (to €150 per year), screening would still save €357.

Although money is saved when men are not unnecessarily treated with statins, it is also important that these men are not unnecessarily exposed to the possible side-effects of these drugs. While statins are relatively safe drugs and severe side-effects (such as rhabdomyolysis)

are sporadically reported [33], inclusion of these events in our models would only increase cost-savings and life expectancy for the screening strategy.

In another recent study, the cost-effectiveness of screening for C-reactive protein before the start of statin treatment was US$48 100 per QALY for 56-year-old men. This is far less cost-effective than testing for the ACE genotype. The main difference between these two studies comprises the base population. Our population was a hypercholesterolemic cohort, whereas the population in the other study was normocholesterolemic [34]. Furthermore, the cost of a C-reactive protein test was US$100, which is significantly more than a single genetic test (€7).

The cost-effectiveness of statin treatment for the Dutch situation was calculated by van Hout and Simoons [27]. When cost-effectiveness ratios up to €18 000 per life year gained are acceptable, statin treatment should be considered in subjects with known cardiovascular disease and in a limited group of subjects who are at high risk of developing cardiovascular disease [27]. The results of our study show that screening for the ACE genotype before the start of statin therapy saves money. We calculated that when all hypercholesterolemic males aged 55–80 years in the Netherlands who start using statins (approximately 14 000 men) [35] were screened for the ACE DD genotype before the start of lifelong statin treatment, approximately €9 million would be saved (in the next 15 years). If patients with the DD-genotype had been excluded from therapy with statins in the study of van Hout and Simoons [27], the total costs per life year gained would have been reduced and, because fewer patients would have been eligible for treatment with statins, more money would have been made available to provide statins to patients with a lower risk of cardiovascular disease.

Studying the economic impact of patient's genotypes raises ethical questions. Possibly patients with certain genotypes run a higher risk of developing certain (severe) diseases. In this case, the ACE D allele behaves as a marker of atherosclerotic cardiovascular complications [36]. A knowledge of this genotype might lead to other consequences (e.g. problems with health insurance) for the patient, and possibly also for his family. Thus, this might be one reason why patients do not want to be screened for their ACE genotype. These ethical issues might be partially solved when proper legislation for the use of this genetical information becomes available.

If other studies also demonstrate that there is no effective treatment with statins in men with the DD genotype, then our study suggests that genetic testing before the start of statin therapy is likely to be cost-effective. In the future, if other genotypes turn out to be predictors for the effectiveness of statins, disease simulation models such as this one could be used to quantify the economic consequences of these tests.

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