ORIGINAL RESEARCH

Cost-Effectiveness of Intensifying Lipid-Lowering Therapy With Statins Based on Individual Absolute Benefit in Coronary Artery Disease Patients

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Background—A validated prediction model estimates the absolute benefit of intensive versus standard lipid-lowering therapy (LLT) with statins on next major cardiovascular events for individual patients with coronary artery disease. We aimed to assess whether targeting intensive LLT therapy to coronary artery disease patients with the highest predicted absolute benefit is cost-effective compared to treating all with standard or all with intensive LLT.

Methods and Results—A lifetime Markov model was constructed for coronary artery disease patients (n=10 000) with mean age 61 years. Number of major cardiovascular events, (non) vascular death, costs, and quality-adjusted life years (QALYs) were estimated for the following strategies: (1) standard LLT for all (reference strategy); (2) intensive LLT for those with 5-year absolute major cardiovascular events risk reduction (ARR) ≥3%, ≥2.3%, or ≥1.5% (corresponding to ≥20%, ≥15%, or ≥10% 5-year major cardiovascular events risk); and (3) intensive LLT for all. With intensive LLT for those with ≥3% 5-year ARR (13% of patients), 380 QALYs were gained for €2423/QALY. Using a threshold of ≥2.3% ARR (26% of patients), 630 QALYs were gained for €5653/QALY. Using a threshold of ≥1.5% ARR (56% of patients), 1020 QALYs were gained for €10 960/QALY. By treating all intensively, 1410 QALYs were gained (0.14 QALY per patient) for €17 223/QALY. With benefit-based treatment, 0.16 to 0.17 QALY was gained per treated patient.

Conclusions—Intensive LLT with statins for all coronary artery disease patients results in the highest overall QALY gain against acceptable costs. However, the number of QALYs gained with intensive LLT by statins in individual patients can be increased with selective benefit-based treatment.

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In patients with coronary artery disease (CAD), intensive lipid-lowering therapy (LLT) with statins renders a 15% relative risk reduction in vascular events compared to standard LLT.[1] Therefore, the American College of Cardiology/American Heart Association (ACC/AHA) clinical guideline recommends intensive lipid lowering in patients with CAD unless characteristics like older age, history of statin intolerance, or serious comorbidities diminish safety of intensive LLT.[2] Nevertheless, high-dose statin treatment rates are low, especially in women.[3,4] This might be attributed to a dose-related higher incidence of adverse effects like myopathy, new-onset diabetes mellitus, and elevation of liver transaminits.[5,6] Selection of the appropriate statin and dosage is ideally made by weighing individual expected benefit against the potential for adverse effects. Given that CAD patients differ widely in history of and risk factors for vascular disease, there is a potential range in absolute benefit from intensification of LLT. Previously, we derived a prediction model in the Treating to New Targets (TNT) trial population that estimates 5-year absolute treatment effect of intensive versus standard LLT with statins on recurrent vascular events for an individual patient, which was validated in the Incremental Decrease in End point through Aggressive Lipid-lowering (IDEAL) trial

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population.[7–9] With this model, we are able to estimate the individual 5-year absolute risk reduction (ARR) for vascular events based on simple patient characteristics.[7,10] Considering the intention for lifelong treatment and potential adverse effects, it may be worthwhile to target intensification of LTT to those patients who benefit most.

Before implementing a benefit-based treatment strategy in clinical practice, an estimation of expected costs and health outcomes is required. Previous studies have shown that treating all patients with stable CAD with intensive LLT is a cost-effective strategy.[11–15] The costs and effects of treating patients with the highest predicted absolute benefit intensively and those with smaller benefit with standard therapy are unknown. Thus, is targeting intensive LLT with statins to CAD patients with the highest predicted absolute benefit cost-effective compared to standard or intensive LLT for all?

Box 1. Computational formula for 5-year absolute treatment effect of intensive versus standard LLT in patients with stable coronary artery disease.

Predicted 5-year treatment effect of intensive lipid-lowering therapy=(1−0.85)×5-year vascular risk with standard lipid-lowering therapy
5-year vascular risk with standard LLT (%)=(1−0.914 exp[A+1.5106])×100%, where A=−0.0478×age in years+0.000515×(age in years)^2+0.315 [if male]+0.410 [if history of myocardial infarction]+0.226 [if history of CABG]+0.469 [if history of congestive heart failure]+0.617 [if history of cerebrovascular disease]+0.432 [if diabetic]+0.538 [if current smoker]+0.00419×total cholesterol in mg/dL−0.0130×HDL-cholesterol in mg/dL−0.0605×eGFR in mL/min per 1.73 m^2+0.000419×(eGFR in mL/min per 1.73 m^2)^2+0.00371×systolic blood pressure in mm Hg+0.00254×systolic blood pressure in mm Hg [if on antihypertensive treatment]

CABG indicates coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LLT, lipid-lowering therapy.

Methods

Prediction Model for Vascular Events

The derivation of the prediction model in the TNT trial and validation in the IDEAL trial is explained in detail previously.[7] These studies were approved by the local or regional institutional review committee at each participating center, and all subjects gave informed consent. The prediction model for the combined outcome of myocardial infarction (MI), stroke, fatal coronary heart disease, and resuscitated cardiac arrest (RCA) contains the patient characteristics age, sex, history of MI, history of a coronary artery bypass graft (CABG), history of congestive heart failure (CHF), history of cerebrovascular disease, diabetes mellitus, current smoking, total cholesterol, high-density lipoprotein (HDL)-cholesterol, estimated glomerular filtration rate, systolic blood pressure (SBP), and treatment allocation (intensive vs standard LLT). Individual patients' 5-year risk and ARR with intensive LLT with statins for the combined outcome of vascular events is estimated with this model (Box 1).[7] Those at highest risk for vascular events will also have the highest ARR with intensive LLT. The prediction model can be applied in clinical practice by choosing a treatment threshold, which is the minimal predicted ARR from which a physician is willing to treat a patient intensively. Patients with a predicted ARR above this threshold will receive intensive LLT and those below the threshold standard LLT. This subjective treatment threshold includes what one considers a clinically relevant treatment effect and whether there are any treatment harms.

Markov Model Design

A Markov model was developed to predict major cardiovascular events (MACE), (non) vascular death, costs, and quality-adjusted life years (QALYs) for benefit-based treatment for different treatment thresholds and treating all patients with intensive LLT (Figure 1). The Markov model had 4 health states: "stable coronary artery disease"; "1 recurrent MACE"; "2 recurrent MACE"; and "death" (based on the model by Wagner et al[14]). All patients started in the health state "stable coronary artery disease" and could transit to another health state or stay in their respective health state each year as shown by the solid lines in Figure 1. If patients experienced a single MACE in a year, namely, an MI, a stroke, an RCA, a revascularization procedure (percutaneous coronary intervention [PCI] or CABG), or chronic heart failure, they transited to the health state "1 recurrent MACE." If patients experienced 2 of these events in 1 year, they transited to the health state "2 recurrent MACE." If patients died of any cause, they transited to the "death" health state. The model was run until all hypothetical patients had died, that is, for a lifetime horizon.

Model Variables

Transition risks

This economic evaluation was performed from a health care perspective, which means that only medical, and not societal, costs and effects were evaluated. Annual event risks were derived from the TNT trial (Table 1 shows them for standard LLT for all).[8] They increased with age according to the TNT/IDEAL prediction model (Box 1).[7] For selective benefit-based treatment, those with an ARR above the intensive treatment threshold had higher event probabilities than those with a predicted ARR beneath this threshold. Box 2 shows a detailed example of estimation of event risk and intensive LLT treatment effect for benefit-based

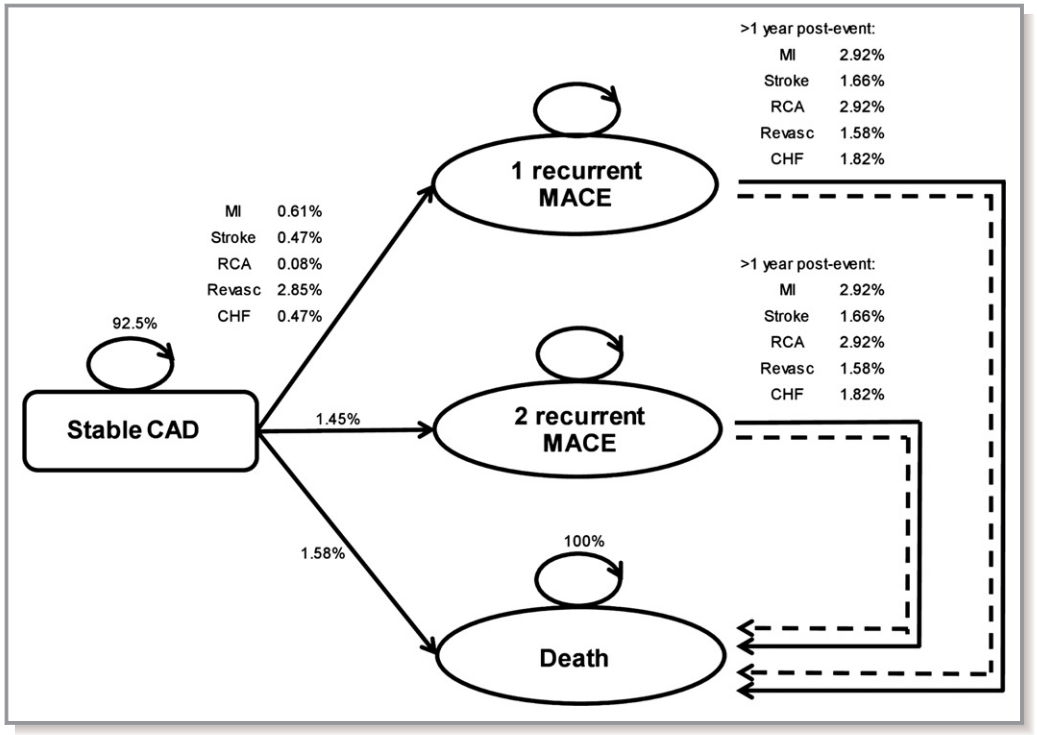

Figure 1. Diagrammatic representation of the Markov model with health states (boxes) and possible transitions (arrows). All patients start in the stable CAD health state (n=10 000). Solid arrows show the possible transitions after each year. Shaded arrows show the transition possible within each cycle. For example, if a patient experiences a myocardial infarction and dies *within* a year from this event, he will transfer from the health state "stable coronary artery disease" to "death" within one cycle. Transition probabilities are presented for a mean age of 61 years. Cardiovascular event and mortality probabilities increased with age. CAD indicates coronary artery disease; CHF, congestive heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; RCA, resuscitated cardiac arrest; Revasc, revascularization.

treatment. Case-fatality rates for MI and stroke were age dependent and obtained from Dutch nation-wide registries for in- and outside hospital deaths.[16–18] The probability of death for patients with stable CAD or patients in the different postevent health states was estimated by multiplying the age-adjusted probability of death not attributed to an MI or stroke in the general population by a disease-specific mortality multiplier (Table 1).[18–21]

Treatment effect

Intensive lipid lowering was defined as either daily high-dose statin therapy (simvastatin 80 mg, atorvastatin 80 mg, or rosuvastatin ≥20 mg) or the combination of ezetimibe 10 mg with usual- or high-dose statins (simvastatin ≥40 mg, atorvastatin ≥40 mg, or rosuvastatin ≥10 mg).[22] Standard LLT included simvastatin 20 to 40 mg, atorvastatin 10 to 20 mg, or rosuvastatin 5 mg each day. The relative treatment effect of intensive versus standard LLT for an MI, stroke, RCA, and revascularization procedure was obtained from a meta-analysis (Table 1).[1] The relative treatment effect of intensive LLT on CHF was based on the TNT trial.[8]

Health outcomes

The amount of life years and QALYs per patient were estimated for the different treatment strategies. QALYs were calculated by summing up the multiplication of the time a person spends in a certain health state by the utility associated with that particular condition (Table 2). A utility is a quality-of-life weight varying between 1.0 (perfect health) and 0.0 (death). For example, living 50 years in perfect health results in 50×1.0=50 QALYs and living 50 years with a utility of 0.70 results in 50×0.70=35 QALYs. Utilities were derived from published data and measured with multiattribute health status classification systems, mostly EQ-5D questionnaires.[23,24] Patients who experienced a single revascularization procedure were assumed to have the same quality of life as patients with stable CAD.

Costs

The mean costs of the cheapest generic preparations of intensive lipid-lowering and standard lipid-lowering drugs in The Netherlands were taken as base-case scenario (Table 2).[25] The frequency by which different statin

Table 1. Annual Event Risks, Mortality Multipliers, and Hazard Ratios for Intensive Versus Standard LLT

	Base Case	Lower Bound	Upper Bound	Source	Reference
Mean annual event risk if all receive standard LLT (%)					
Single recurrent MACE				RCT	8
MI	0.61	0.46	0.76		
Stroke	0.47	0.35	0.59		
Resuscitated cardiac arrest	0.08	0.06	1.00		
Revascularization	2.85	2.14	3.56		
Chronic heart failure	0.47	0.35	0.59		
Double recurrent MACE				RCT	8
MI, followed by:					
MI	0.06	0.05	0.08		
Stroke	0.02	0.02	0.03		
Revascularization	0.49	0.37	0.61		
Chronic heart failure	0.05	0.04	0.06		
Stroke, followed by:					
MI	0.01	0.008	0.01		
Stroke	0.05	0.04	0.06		
Revascularization	0.02	0.02	0.03		
Chronic heart failure	0.003	0.002	0.004		
Revascularization, followed by:					
MI	0.10	0.08	0.13		
Stroke	0.04	0.03	0.05		
Revascularization	0.47	0.35	0.59		
Chronic heart failure	0.05	0.04	0.06		
Chronic heart failure, followed by:					
MI	0.03	0.02	0.04		
Stroke	0.01	0.008	0.03		
Revascularization	0.05	0.04	0.06		
Mortality multipliers					
Coronary artery disease	2.0	1.4	2.6	Observational study	20
MI	3.7	2.7	4.7	Observational study	20
Stroke	2.1	1.5	2.8	Observational study	19
Resuscitated cardiac arrest	3.7	2.7	4.7	Observational study	20
Revascularization	2.0	1.4	2.6	Observational study	20
Chronic heart failure	2.3	1.4	3.2	Observational study	21
HR intensive vs standard LLT					
MI infarction, stroke, RCA	0.85	0.82	0.89	Meta-analysis	1
Revascularization	0.81	0.76	0.85	Meta-analysis	1
Chronic heart failure	0.74	0.59	0.94	RCT	8

HRs, hazard ratios; LLT, lipid-lowering therapy; MACE, major adverse cardiovascular event; MI, myocardial infarction; RCA, resuscitated cardiac arrest; RCT, randomized, controlled trial.

preparations and ezetimibe were used was obtained from the United Kingdom General Practice Research Database.[26] Event costs and lifetime health care costs associated with vascular events were derived from observational studies in The Netherlands and from Dutch nation-wide registries.[27–31] Mean costs for a revascularization procedure were estimated

Box 2. Calculation example for estimating event risk and the relative treatment effects of benefit-based intensive LLT (various thresholds) versus standard LLT for all.

Calculation example benefit-based treatment with a threshold ≥1.5% 5-year ARR for the outcome myocardial infarction, stroke, fatal CAD, and RCA, in the TNT/IDEAL population:

1. Risk if all patients are treated with standard LLT=5-year risk in trial arm on standard LLT (n=9455)=12.6%
2. Risk in patients on standard LLT for whom the prediction model recommends standard LLT=5-year risk in trial arm on standard LLT & predicted ARR ≤1.5% (n=4200)=7.4%
3. Risk in patients on standard LLT for whom the prediction model recommends intensive LLT=5-year risk in trial arm on standard LLT & predicted ARR ≥1.5% (n=5255)=16.7%
4. Risk in patients in (3) if they would have been treated with intensive LLT=risk in (3) multiplied by the hazard ratio=16.7%×0.85=14.2%
5. Overall risk if patients are treated according to the prediction model=(14.2%×5255+7.4%×4200)/9455=11.2%
6. Overall relative treatment effect of benefit-based intensive LLT versus standard LLT for all=risk in (5) divided by risk in (1)=11.2%/12.6%=0.89

ARR indicates absolute risk reduction; CAD, coronary artery disease; LLT, ipid-lowering therapy; RCA, resuscitated cardiac arrest; TNT, Treating to New Targets; IDEAL, Incremental Decrease in End point through Aggressive Lipid-lowering.

as the weighted sum of costs for a PCI and a CABG.[17] Lifetime costs for stroke and chronic heart failure made in the hospital, nursing home, and at the general practitioner were included.[27] Pharmacist's and laboratory tests costs for all patients were modeled, and the cost of 1 extra doctor's visit for prescription of intensive LLT was included.[32] Costs in euros were updated to 2014 with the Dutch consumer price indices.[18]

Analysis

The Markov model was run with a lifetime horizon for a cohort of 10 000 patients based on the TNT/IDEAL trial populations for the treatment strategies standard LLT for all, intensive LLT for all, and intensive LLT for those with ≥3%, ≥2.3%, and ≥1.5% 5-year ARR (corresponding to ≥20%, ≥15%, and ≥10% 5-year MACE risk). Patients had a mean age of 61 years, and 81% were male.[7] The medical history contained an MI in 78% of patients, a PCI in 40%, a CABG in 34%, and cerebrovascular disease in 6% of patients. Current smoking was present in 17%, past smoking in 61%, and diabetes mellitus in 14% of patients. Patients had a mean SBP of 134 and mean total and HDL-cholesterol levels of 4.8 and 1.2 mmol/L, respectively. Predicted 5-year MACE risk with standard LLT was ≤10% in 44% of patients, 10% to 20% in 43% of patients, and ≥20% in 13% of patients.[7]

Mean costs, life years, and QALYs per patient were estimated for each treatment strategy. Incremental costs and QALYs were estimated for benefit-based intensive LLT and intensive LLT for all compared to standard LLT for all. To calculate the incremental cost-effectiveness ratio (ICER), we divided incremental costs by incremental QALYs. Discount rates of 4.0% for costs and 1.5% for health outcomes were applied.[33]

Scenario analyses were done with varying drug costs, event probabilities, event costs, relative treatment effects of intensive versus standard LLT, discount rates, mortality multipliers, and utilities, fluctuating 1 parameter at a time (see Tables 1 and 2 for lower and upper bound). Furthermore, 2 alternative scenarios were modeled under the assumption that benefit-based treatment leads to higher treatment compliance (2.5% or 5% greater relative treatment effect). An additional scenario was considered that took statin-related muscle complaints into account, assuming a dose reduction from intensive to standard LLT if myopathy occurred. There was a 2% higher risk of myopathy with intensive LLT (11%) compared to standard LLT (9%).[34,35]

In probabilistic sensitivity analyses, the Markov model was run 1000 times (Monte Carlo simulations). For every simulation, event probabilities and utilities were randomly chosen from beta distributions, mortality multipliers, and costs from gamma distributions, and the relative treatment effects of intensive versus standard LLT from lognormal distributions. All model assumptions were varied at the same time. The ICERs derived from these simulations are presented in a scatter plot (1000 dots, 1 for each simulation). Cost-effectiveness acceptability curves show the probability that (benefit-based) intensive LLT is cost-effective compared to standard LLT for all, for various thresholds of euros willing to pay per QALY gained.

Results

Total costs and QALYs for the different treatment strategies on a population level are shown in Figure 2. Compared to standard therapy for all CAD patients (n=10 000), lifetime benefit-based intensive LLT with statins resulted in a gain of 380 QALYs for €2423/QALY using a threshold of ≥3% 5-year ARR (13% of patients). Using a threshold of ≥2.3% ARR (26% of patients), 680 QALYs were gained for €5653/QALY. Using a threshold of ≥1.5% ARR (56% of patients), 1020 QALYs were gained for €10 960/QALY. By treating all with intensive LLT, 1410 QALYs were gained (0.14 QALY per patient) for €17 223/QALY.

With benefit-based intensive LLT for patients with a ≥3% predicted 5-year ARR, 411 life years were gained. Using a threshold of ≥2.3% ARR, 699 life years were gained. Using a threshold of ≥1.5% ARR, 1150 life years were gained. Intensive LLT for all resulted in a gain of 1614 life years, which was an increase in life expectancy of approximately 2 months per patient (0.16 life year) compared to standard therapy for all. Lifetime drug costs were low, ranging from €1749 per patient if

Table 2. Costs and Utilities

	Base Case	Lower Bound	Upper Bound	Source	Reference
Costs					
Drug (annual costs for 1 patient)					
Intensive LLT	€357	€178	€535	Official tariff	25
Standard LLT	€9	€5	€14	Official tariff	25
Event					
MI	€5037	€3778	€6296	Observational study	29
Stroke	€19 030	€14 273	€23 788	Dutch registries	27
RCA	€28 636	€21 477	€35 795	Observational study	30
Revascularization	€6944	€5009	€8349	Observational study	27, 28, 31
Postevent care (annual)					
Stroke	€9827	€7370	€12 284	Dutch registries	27
Chronic heart failure	€6569	€4927	€8211	Dutch registries	27
Other costs (annual)					
Doctor's visit	€109	€69	€157	Official tariff	32
Pharmacy	€26	€11	€52	Official tariff	32
Laboratory	€25	€17	€37	Official tariff	32
Utilities				Observational study	23, 24
Stable CAD	0.78	0.58	0.97		
MI	0.65	0.49	0.81		
Stroke	0.64	0.48	0.80		
RCA	0.68	0.51	0.85		
Chronic heart failure	0.63	0.47	0.79		
2 recurrent MACE	0.62	0.47	0.78		

CAD indicates coronary artery disease; LLT, lipid-lowering therapy; MACE, major adverse cardiovascular event; MI, myocardial infarction; RCA, resuscitated cardiac arrest.

all would be treated with standard LLT to €5413 if all would be treated intensively. Lifetime event and postevent costs ranged from €9791 per patient if all would be treated with standard LLT to €8555 if all would be treated intensively.

The estimated number of different vascular events in 10 years for the different treatment strategies is shown in Figure 3. The 10-year absolute reduction in total MACE (MI, revascularization, chronic heart failure, RCA, and stroke) was 1.6%, 2.8%, and 5.1% if those with ≥3%, ≥2.3%, or ≥1.5% estimated 5-year ARR would be given intensive LLT and 7.8% if all would receive intensive LLT.

Individual Benefit

The mean amount of QALYs gained per treated patient was 0.17 for a ≥3% predicted 5-year ARR threshold, 0.17 for a ≥2.3% threshold, and 0.16 for a ≥1.5% threshold. Thus, benefit-based treatment resulted in an increase of individual benefit per treated patient compared to intensive LLT for all. Similarly, the 10-year absolute reduction in total MACE in these patients with intensive LLT was 8.8% for a threshold of ≥3% 5-year ARR, 9.1% for ≥2.3%, and 9.2% for ≥1.5% ARR.

Scenario Analyses

Results were sensitive to assumptions about the relative treatment effect of intensive versus standard LLT and drug costs (Figure 4). Under the assumption that benefit-based intensive LLT leads to higher treatment compliance, the ICER decreased to €2561/QALY and €609/QALY for a 2.5% and 5% higher treatment effect using a treatment threshold of ≥2.3% ARR. When statin-associated myopathy was taken into account, ICERs did not change substantially.

Sensitivity Analyses

Results of the probabilistic sensitivity analyses are shown in Figure 5. For a willingness to pay of €20 000 per additional QALY, the probability that benefit-based intensive LLT is cost-effective compared to standard LLT for all is 98% for a

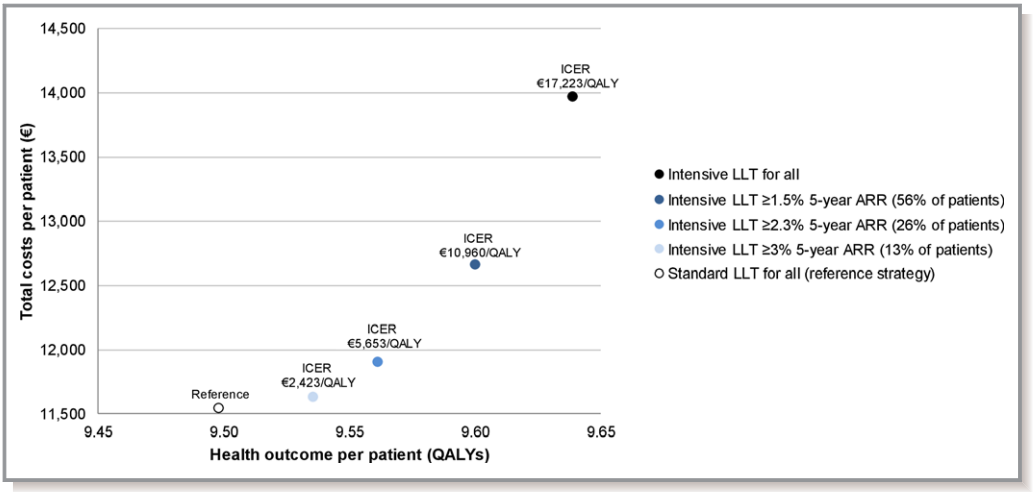

Figure 2. Total costs and health outcome in QALYs per patient for the different treatment strategies. ARR indicates absolute risk reduction in 5 years; ICER, incremental cost-effectiveness ratio, with standard LLT for all as the reference strategy; LLT, lipid-lowering therapy; QALYs, quality-adjusted life years.

threshold of ≥3% 5-year ARR, 97% for ≥2.3%, and 83% for ≥1.5% ARR. The probability that intensive LLT is cost-effective is 61%. For a willingness to pay of €50 000 per additional QALY, these probabilities increase to 99% to 100% for all 3 ARR thresholds. The chance that intensive LLT for all is cost-effective compared to standard LLT for all is 97% for a willingness to pay of €50 000 euros per QALY.

Benefit-Based Intensive LLT Versus Treating All Intensively

Compared to intensive LLT for all (n=10 000 patients), benefit-based intensification of statin therapy saved €23 371 for a loss of 1034 QALYs (ICER €22 604/QALY) using a threshold of ≥3.0% ARR, saved €20 708 for a loss of 778 QALYs (ICER €26 630/QALY) using a threshold of ≥2.3% ARR, and saved €13 101 for a loss of 390 QALYs (ICER €33 614/QALY) using a threshold of ≥1.5% ARR.

Discussion

A previously published model predicts the 5-year absolute benefit of intensive versus standard LLT with statins for individual CAD patients.[7] The present study assesses lifetime costs and health outcomes of benefit-based

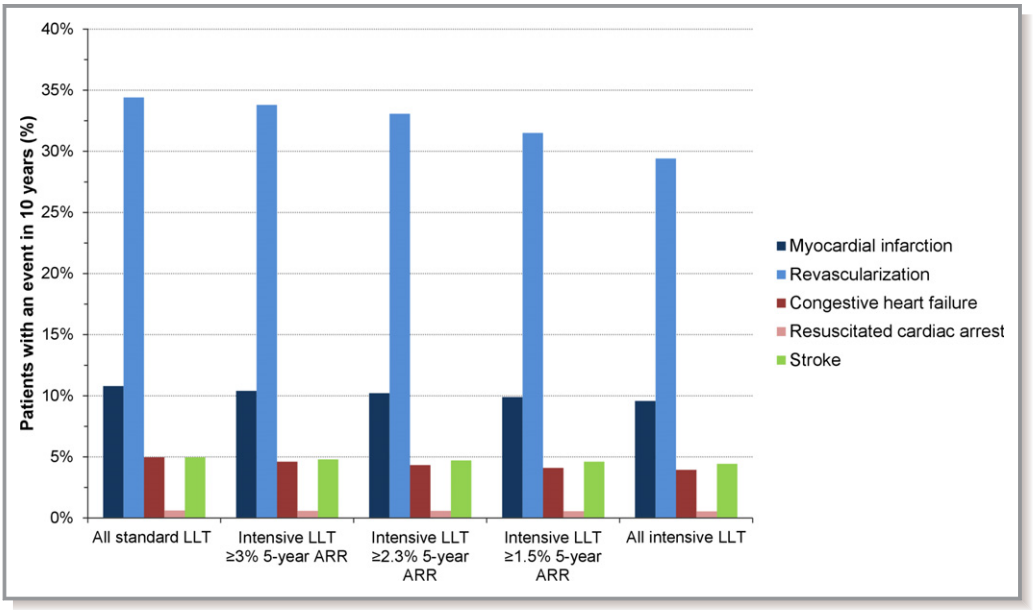

Figure 3. Occurrence of MACE in 10 years for the different treatment strategies. ARR indicates absolute risk reduction; LLT, lipid-lowering therapy; MACE, major adverse cardiovascular event.

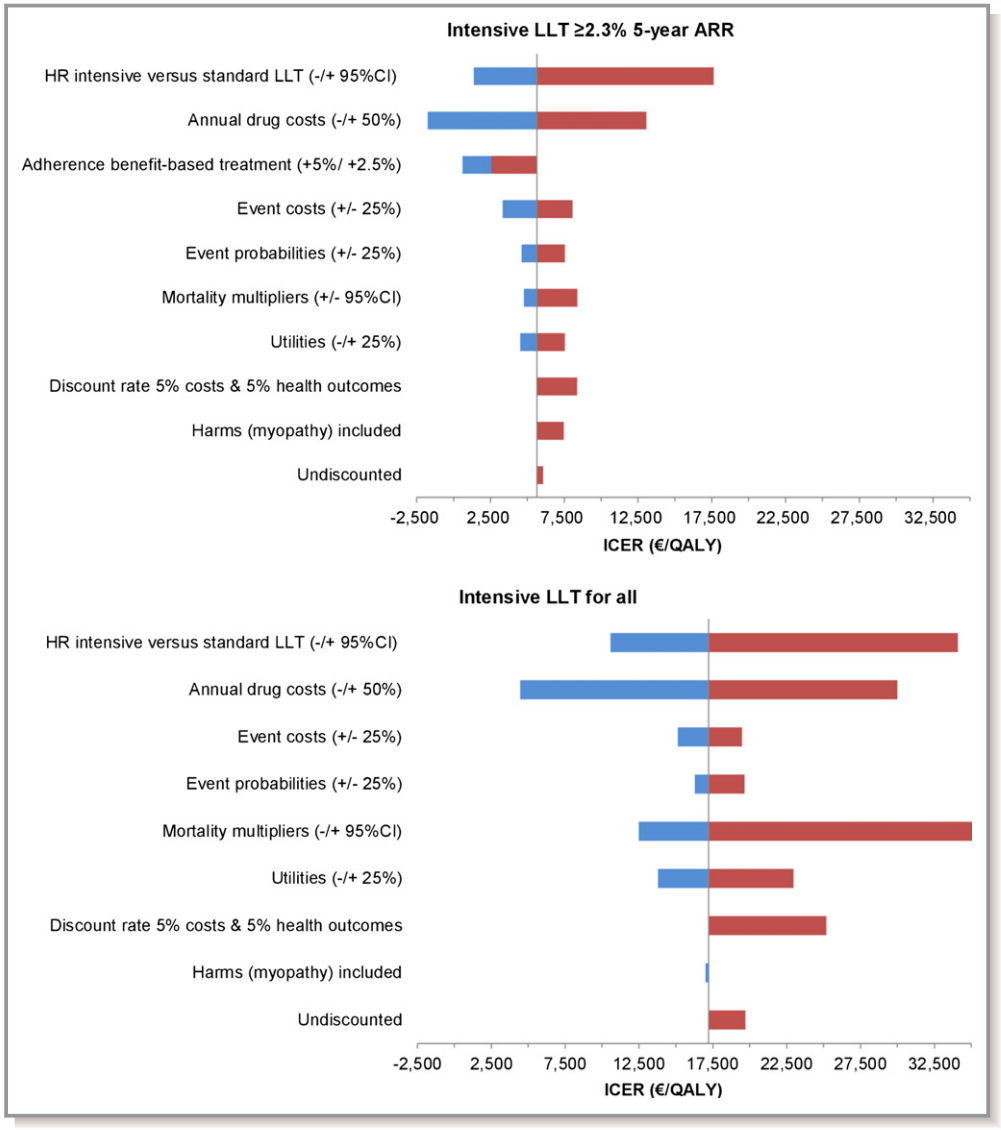

Figure 4. Scenario analyses assessing the influence of the different model assumptions on the estimated ICER for benefit-based treatment (upper chart) and intensive LLT for all (lower chart) versus standard LLT for all, varying 1 assumption at a time. ARR indicates absolute risk reduction; €/QALY, euro per quality-adjusted life year; ICER, incremental cost-effectiveness ratio; LLT, lipid-lowering therapy.

intensive LLT with statins compared to standard LLT for all in 10 000 CAD patients. The expected costs per additional QALY for benefit-based intensive LLT range from €2423 ($2744) to €10 960 ($12 412), depending on the treatment threshold chosen. Intensive LLT for all resulted in the highest QALY gain (1410 QALYs [0.14 QALY per patient]), for €17 223 ($19 504) per extra QALY. Yet, selective benefit-based treatment increases the QALY gain in those treated with intensive LLT to 0.16 per patient for a treatment threshold ≥1.5% 5-year ARR and 0.17 for a threshold ≥2.3% ARR. Results are sensitive to the assumed relative treatment effect of intensive versus standard LLT and the costs of these drugs.

Cost-Effectiveness of Benefit-Based Intensification of LLT in CAD Patients

The present cost-effectiveness study shows that benefit-based intensive LLT is cost-effective compared to standard LLT for all, attributed to the capacity of our prediction model to select the right patients who benefit most from intensive LLT. The total costs per extra QALY were lower for benefit-based intensive LLT than for intensive LLT for all, with an optimal ratio for a threshold ≥3% ARR. However, intensive LLT therapy for all results in the highest QALY gain against reasonable treatment costs. The AHA/ACC and the National Institute for Health and Care Excellence clinical guidelines

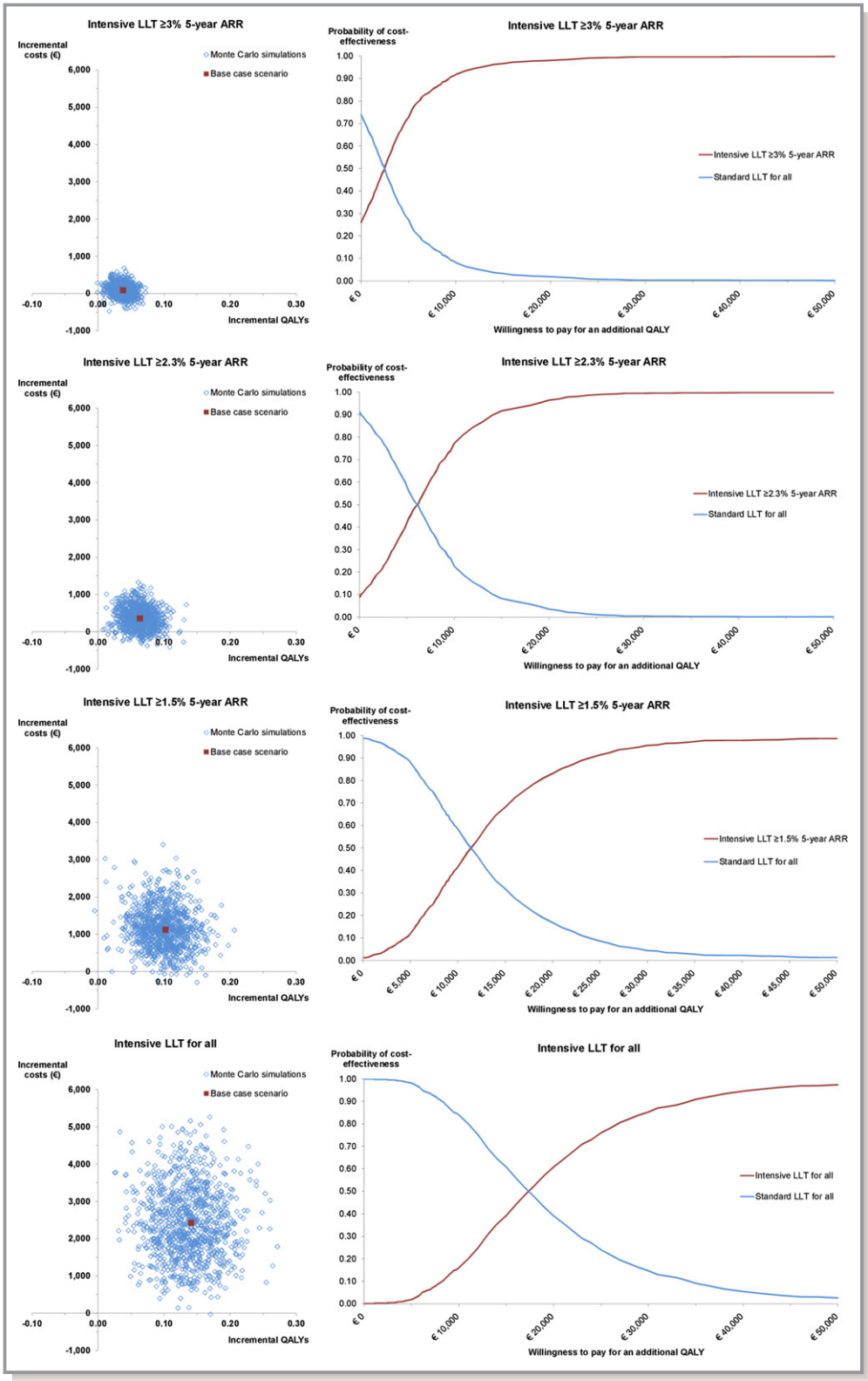

Figure 5. Sensitivity analyses: incremental cost-effectiveness planes and cost-effectiveness acceptability curves for benefit-based intensive LLT with various treatment thresholds versus standard LLT for all. *Left:* The *y*-axis shows incremental costs and the *x*-axis incremental QALYs for benefit-based treatment versus standard LLT for all. One dot is a single iteration. *Right:* The curves show the probability that benefit-based intensive treatment is cost-effective compared to standard LLT for all. ARR indicates absolute risk reduction; LLT, lipid-lowering therapy; QALYs, quality-adjusted life years.

recommend intensive LLT for patients with CAD in general.[2,36] Interestingly, LLT is only intensified in 25% of CAD patients in daily practice.[3,4,37] This may be because physicians tend to treat solely patients who they believe to be at high risk for recurrent vascular events with intensive LLT. For example, men, patients with high low-density lipoprotein-cholesterol (LDL-c) levels, and those with an ST-elevation MI are more often treated with a high-dose statin.[3,4] This is understandable because those at high risk for recurrent MACE benefit the most from intensive LLT in absolute terms. The present study shows that, on average, the life years and quality of life to be gained with intensive LLT are modest. Given that our prediction model accurately predicts absolute risk and treatment effect of intensive versus standard LLT for an individual patient taking multiple characteristics into account, those who benefit most can be identified. For individuals with moderate benefit, the expected beneficial and negative treatment effects can be weighed before making a treatment decision. Even though these health-economic results point toward intensive LLT for all, initiation and intensification of LLT is preferably done in close consultation with the patient taking into account potential drug interactions or adverse effects, an individual patient's life expectancy, and his or her preferences.

Optimization of the Health Gain Obtained by LLT in Individual Patients With CAD

An estimated mean of 2 months (≈1.7 months in perfect health) is gained with intensive therapy for all. These results are in line with a simulation study in CAD patients from 8 European countries, which showed that, by optimizing cardiovascular prevention in individuals (smoking cessation, diet and exercise, and better management of SBP and/or LDL-c), a mean of ≈0.25 QALYs (3 months in perfect health) could be gained.[38] The moderate health benefit to be obtained with intensive LLT may be attributable to the higher risk of nonvascular death in this secondary prevention setting, which is not decreased by LLT. Furthermore, the mean age at onset of CAD and initiation of intensive LLT is >60 years, which could limit life prolongation with these drugs despite a reduction in MACE in 10 years. Our study shows that targeting intensive LLT to those who benefit the most in terms of a 5-year vascular risk reduction increases the gain in life years and QALYs in individual patients. Benefit-based treatment may be even more appealing in the future now that the expensive LDL-c lowering monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) have been introduced to the market. Identification of CAD patients who benefit most from PCSK9 inhibitors is needed to keep the monetary costs down, and the presented model could be used for that purpose in CAD patients.

Whereas atherosclerosis is a chronic, and progressive disease, it would be interesting to assess the cost-effectiveness of benefit-based treatment in younger individuals with an unfavorable risk profile. Because of their lower age, the short-term benefit from intensive LLT may be moderate. However, without adequately regulated lipid levels, their lifetime risk for recurrent vascular disease could be high.[39] Therefore, intervening at an early stage could be beneficial in these patients. Starting lifelong treatment at a young age implies a long duration of treatment. The benefit in younger patients should be weighed against the inconvenience of taking a pill every day and the cost and health impairment by adverse effects (eg, higher risk of myopathy or new-onset diabetes mellitus).

Scenarios That Might Impact the Cost-Effectiveness of Benefit-Based LLT

There are some scenarios that might alter our main results. If the relative treatment effect of intensive versus standard LLT in a specific setting is smaller than assumed in the current model, it will be more attractive to treat according to predicted ARR from an economic perspective. For example, adherence to statin therapy is often lower in daily life than in the setting of a randomized trial, which might result in lower overall treatment effect of intensive LLT. If the difference in country-specific costs of intensive versus standard LLT is greater, this could result in a more-beneficial cost-effectiveness ratio of benefit-based intensive LLT. In a scenario analysis with mean event costs for the United States and Europe (assuming similar drug costs), the ICERs of both benefit-based treatment and intensive treatment for all slightly decreased compared to the Dutch situation.[40] Intensive LLT increased risk of new-onset diabetes mellitus in TNT/IDEAL with 20% in prediabetics, but did not confer a higher risk of diabetes mellitus in normoglycemic patients when compared to standard LLT.[41] Benefit-based treatment was slightly more attractive than treating all patients with intensive LLT when we included a higher risk of new-onset diabetes mellitus with intensive LLT in the model.

Strengths and Limitations

A strength of this study is the comprehensive Markov model, which is representative for current clinical practice. The validity of this model is confirmed by a comparable estimation of costs and health outcomes in previous studies assessing the cost-effectiveness of intensive LLT for all versus standard LLT for all.[11–15] Also, we based our assumptions on recent peer-reviewed literature and adjusted event probabilities and risk of death for the age and cardiovascular history of patients. Furthermore, we performed various scenario analyses, including one in which we took statin-induced myopathy

into account. A limitation of our study is that second events more than 1 year apart from the first event were not modeled. Alternatively, we adjusted the risk of death for the medical history of a patient and included lifelong costs for patients who had a stroke or chronic heart failure. Generalizability of event probabilities in the TNT trial to contemporary CAD patients in clinical practice could be doubted, attributable to trial inclusion and exclusion criteria (limited age range, LDL-c levels) and improvement of cardiovascular care and secondary prevention for CAD patients in recent years. Yet, it is reassuring that trial event probabilities resembled event probabilities in CAD patients from an ongoing observational cohort study in The Netherlands.[42] Ninety-four percent of patients in the TNT trial population were white. Because of overall higher event rates in black patients, intensive lipid-lowering therapy for all may be more cost-effective in black than in white patients.[43–45] Because of overall lower event rates in Asian patients, the cost-effectiveness of intensive versus standard LLT is presumably less beneficial in Asian than in white patients.[43–45] The distribution in individual ARRs of intensification of LLT in black and Asian patients with CAD is unknown. The prediction model should be validated in these groups before the cost-effectiveness of benefit-based intensive LLT in nonwhites can be assessed.

Estimation of the absolute treatment effect of intensive versus standard LLT with statins in individuals patients with CAD enables us to select those who benefit most from aggressive LLT. We conclude that intensive LLT with statins for all CAD patients results in a higher QALY gain than benefit-based intensive LLT against reasonable costs. Benefit-based intensive LLT is a less-favorable strategy from a health-economic perspective. However, the number of life years and QALYs to be gained with intensive LLT in individual patients is modest and can be increased with selective benefit-based treatment.

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Disclosures

None.

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