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FULL RESEARCH PAPER
Risk Prediction/Assessment & Stratification

Residual cardiovascular risk reduction guided by lifetime benefit estimation in patients with symptomatic atherosclerotic disease: effectiveness and cost-effectiveness

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Aims To determine the (cost)-effectiveness of blood pressure lowering, lipid-lowering, and antithrombotic therapy guided by predicted lifetime benefit compared to risk factor levels in patients with symptomatic atherosclerotic disease.

Methods and results For all patients with symptomatic atherosclerotic disease in the UCC-SMART cohort (1996–2018; $n = 7697$) two treatment strategies were compared. The lifetime benefit-guided strategy was based on individual estimation of gain in cardiovascular disease (CVD)-free life with the SMART-REACH model. In the risk factor-based strategy, all patients were treated the following: low-density lipoprotein cholesterol (LDL-c) < 1.8 mmol/L, systolic blood pressure <140 mmHg, and antithrombotic medication. Outcomes were evaluated for the total cohort using a microsimulation model. Effectiveness was evaluated as total gain in CVD-free life and events avoided, cost-effectiveness as incremental cost-effectivity ratio (ICER). In comparison to baseline treatment, treatment according to lifetime benefit would lead to an increase of 24 243 CVD-free life years [95% confidence interval (CI) 19 980–29 909] and would avoid 940 (95% CI 742–1140) events in the next 10 years. For risk-factor based treatment, this would be an increase of 18 564 CVD-free life years (95% CI 14 225–20 456) and decrease of 857 (95% CI 661–1057) events. The ICER of lifetime benefit-based treatment with a treatment threshold of ≥1 year additional CVD-free life per therapy was €15 092/QALY gained and of risk factor-based treatment €9933/QALY gained. In a direct comparison, lifetime benefit-based treatment compared to risk factor-based treatment results in 1871 additional QALYs for the price of €36 538/QALY gained.

Conclusion Residual risk reduction guided by lifetime benefit estimation results in more CVD-free life years and more CVD events avoided compared to the conventional risk factor-based strategy. Lifetime benefit-based treatment is an effective and potentially cost-effective strategy for reducing residual CVD risk in patients with clinical manifest vascular disease.

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Keywords Cardiovascular disease • Individualized medicine • Secondary prevention • Treatment effects • Cost-effectiveness

Introduction

According to current guidelines, all patients with symptomatic atherosclerotic disease are at very high 10-year risk of (recurrent) cardiovascular events.[1,2] Based on this very high-risk preventive treatment is advised for all patients, including lipid modifying therapy, blood pressure lowering, and antithrombotic therapy. However, even after such therapy is initiated, large variation remains in the residual risk of recurrent cardiovascular disease (CVD).[3] Identification of the patient who benefits most from further risk factor lowering may help to effectively reduce residual risk of CV events in patients with established CVD. It is unknown which is the most (cost)effective method of selecting the right combination of medications for each individual.

With the externally validated SMART risk score, the 10-year risk of CV events can be estimated in patients with clinical manifest vascular disease.[4] As age is one of the most important factors in CVD risk, treatment decisions solely based on 10-year risk can lead to more intensive treatment of the elderly. Due to their limited life expectancy, from both cardiovascular and non-cardiovascular causes, the actual treatment benefit may be overestimated in older patients. Although they may be presumed to have the highest 10-year risk for new CV events, this approach may not be the most (cost)effective method of selecting the right combination of medications. Younger patients on the other hand who may have a high lifetime risk may not be identified for intensive preventive treatment as their 10-year risks are low. To deal with these shortcomings, a more recent development is the possibility to predict CVD-free life expectancy rather than 10-year risk.[5,6] Combining CVD-free life expectancies with hazard ratios (HRs) from trials or meta-analyses opens the possibility of estimating the lifetime treatment benefit, defined as the gain in CVD-free life expectancy from preventive therapy.[7] The highest lifetime treatment benefit can be expected in younger patients (who have the largest life expectancy) with higher levels of vascular risk factors (who have the highest risk to reduce).[7] Intensive or expensive therapies like proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, intensive blood pressure lowering, dual anti-platelet therapy, or dual pathway inhibition (DPI) antithrombotic treatment have all proven to effectively reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic disease. These new treatment options are, however, costly or induce a bleeding risk which makes identification of patients that benefit most a key issue in clinical practice.[8,9] The aim of this study was to evaluate the effectiveness and cost-effectiveness of blood pressure lowering, lipid-lowering, and antithrombotic therapy guided by predicted lifetime benefit compared to treatment based on risk factor threshold levels in terms of total gain in CVD-free lifetime and CV events avoided in patients with symptomatic atherosclerotic disease.

Methods

Population

Patients with symptomatic atherosclerotic disease were included from the Utrecht Cardiovascular Cohort—Secondary Manifestations of ARTerial disease (UCC-SMART). UCC-SMART is a single-centre ongoing prospective cohort study at the University Medical Center Utrecht, The Netherlands.[10] Patients where included in the period 1996–2018 with coronary artery disease, cerebrovascular disease, peripheral artery disease, and/or abdominal aortic aneurysm. Patients between the age of 45 and 80 years ($n = 7697$) were included in the present analyses as the SMART-REACH model is validated for this range.[5] Detailed information about the used definitions, data collection, follow-up procedures, and endpoint verification from UCC-SMART can be found in the Supplementary material online, *Methods*. The study was approved by the local medical ethics committee and written informed consent was obtained from all patients.

Estimating individual lifetime treatment benefit

First, the CVD-free life expectancy was estimated for all UCC-SMART study participants using the externally validated SMART-REACH model.[5] This competing risk adjusted model uses the following predictors: sex, current smoking, diabetes mellitus, systolic blood pressure (SBP), total cholesterol, creatinine, number of locations of cardiovascular disease (coronary, cerebral and/or peripheral arterial disease), a history of atrial fibrillation, and a history of congestive heart failure, more information about the SMART-REACH model can be found in the Supplementary material online. The lifetime treatment benefit is defined as the difference in CVD-free life expectancy with and without medication and can be calculated by incorporating HRs from meta-analyses or trial data in the competing risk models.

Second, to model treatment effect, the SMART-REACH model's predictions are combined with hazard ratios from randomized trials and meta-analyses. For lipid-lowering therapies, a decrease in low-density lipoprotein (LDL) levels is modelled. Meta-analyses have shown an HR of 0.78 [95% confidence interval (CI) 0.76–0.80] for major vascular events per 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-c).[9,11] Moderate-intensity lipid lowering was defined as the use of a low or moderate-intensity statin and was modelled as if simvastatin 40 mg was used, lowering LDL by an average 37%.[12] High-intensity lipid lowering was defined as the use of either a high-dose statin or the addition of ezetimibe to moderate-intensity lipid lowering. To estimate the treatment effect of high-intensity lipid lowering, an additional LDL reduction of 24% was assumed, equal to the average LDL-reduction achieved by addition of ezetimibe to a moderate dose statin.[11,13] The expected decrease in LDL-c of PCSK9 inhibitors was assumed to be 59%.[14,15]

As the number of classes of antihypertensive drugs are large and the goal of the current analysis was not to compare those classes or a specific strategy combining those, the effect of blood pressure was evaluated through lowering SBP to 130 or 140 mmHg. The effect of 10 mmHg reduction corresponded to an HR of 0.80 (95% CI 0.77–0.83).[16] It was assumed that blood pressure was lowered exactly towards the intended

target. The effect of blood pressure lowering was truncated at 130 mmHg, assuming no effect from further reduction.

The effect of antithrombotic therapy was directly added to the hazard function for cardiovascular events. For aspirin, an HR of 0.81 (95% CI 0.75–0.87) was used.[17] Addition of a low-dose direct oral anticoagulant (DOAC) to aspirin (i.e. dual pathway inhibition; DPI) was assumed to have an HR of 0.76 (95% CI 0.66–0.86) compared to aspirin alone.[8] Patients with a vitamin K antagonist or a higher-dose DOAC at baseline were assumed to have the risk reduction in CVD events associated with aspirin.

It was assumed that all treatment effects of the different classes were independent of each other[18] and did not affect the risk of non-CVD mortality. No lifestyle interventions, such as smoking cessation, were evaluated as those should be performed regardless of pharmaceutical interventions. The effect of diabetes-specific medication was not evaluated in this study.

Lifetime benefit-based treatment decision-algorithm

Clinical decision-making was simulated in this study by following a stepwise decision-algorithm that was run for every individual patient in the study dataset (*Figure 1*). This decision-algorithm follows an iterative process, estimating therapy benefit in terms of gain in CVD-free life expectancy using the SMART-REACH model. With each iteration, the effect of the first next treatment option in the categories blood pressure lowering, lipid-lowering, and antithrombotic therapy is estimated. Out of those three treatment options, the treatment with the highest benefit in terms of extra CVD-free life years gained is compared with the treatment threshold. If the predicted effect of treatment exceeded the threshold, that single therapy was added to the patient's regimen and the algorithm was reiterated with the remaining options. Once there are no remaining treatment options that exceed the treatment threshold, the simulation ends and the total predicted extra CVD-free life years for that specific patient is summed up. For the main analyses, a treatment threshold of 12 months per therapy was evaluated. Treatment thresholds of 6 and 24 months per therapy were evaluated as secondary analyses. In clinical practice, this minimally desired benefit varies from patient to patient and should be part of a shared decision making process, based on preferences of patient and the treating physician.

For example, for a treatment-naïve subject, the next options would be moderate-intensity lipid lowering, SBP lowering <140 mmHg, and aspirin. For someone already on high-intensity lipid lowering, the benefit of a PCSK9 inhibitor on top of the high-intensity lipid lowering will be

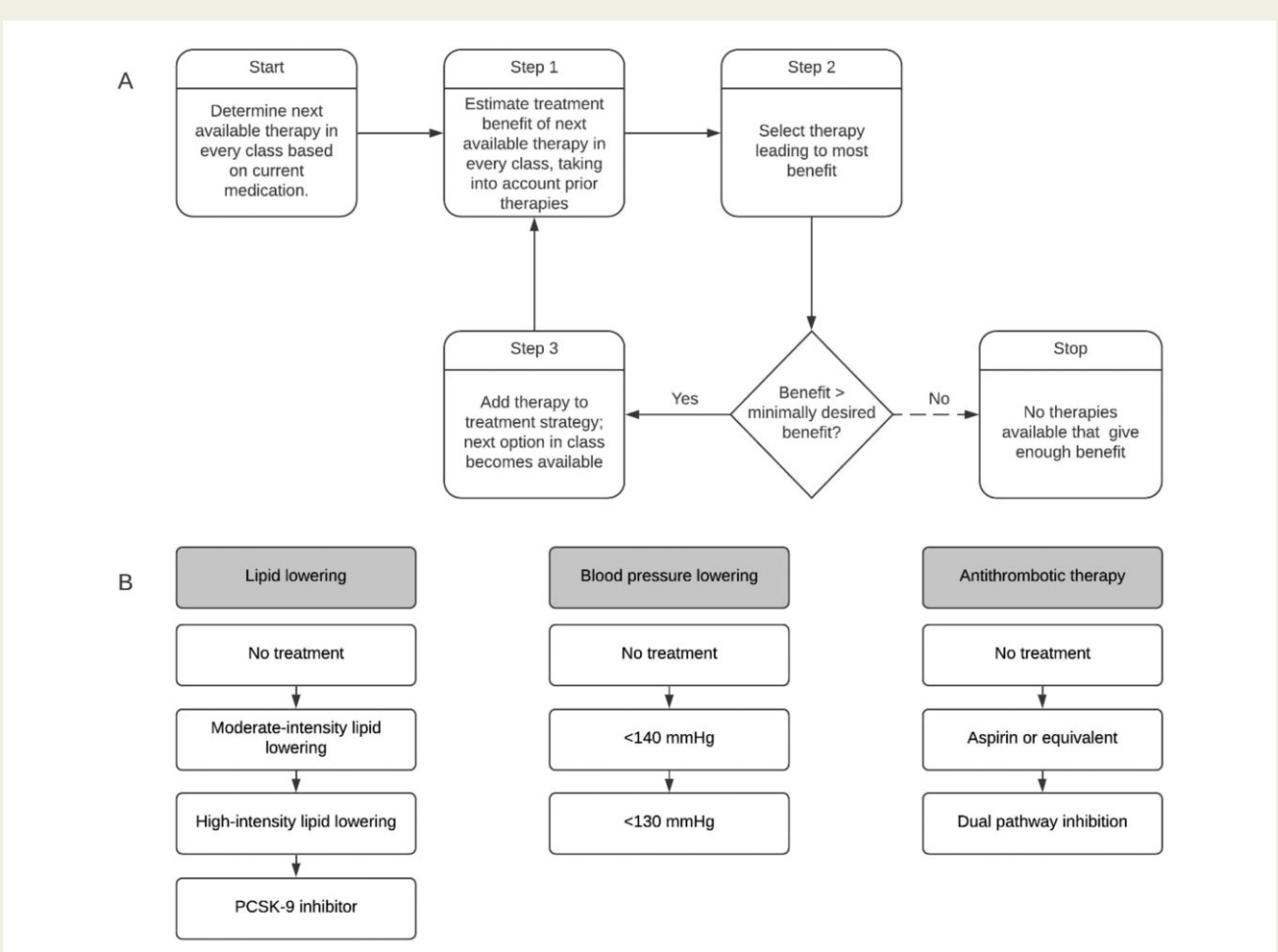

Figure 1 Stepwise decision algorithm of lifetime benefit-based treatment. (*A*) Schematic overview over lifetime benefit-based treatment selection. (*B*) The possible treatment options in the three different classes. PCSK9, proprotein convertase subtilisin/kexin type 9.

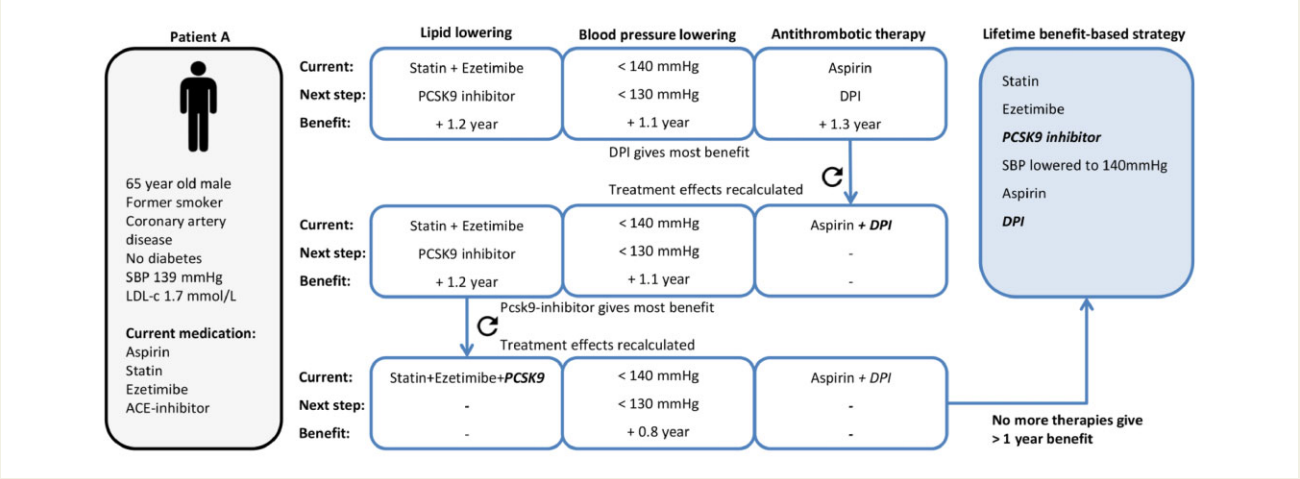

Figure 2 Patient example of lifetime benefit-based treatment strategy. This patient was already treated according to the current guidelines at baseline. On top of the current medication, cardiovascular prevention could be intensified by adding a PCSK9 inhibitor, dual pathway inhibition, or by lowering blood pressure below 130 mmHg. Dual pathway inhibition and a PCSK9 inhibitor led to most benefit and were added to the lifetime benefit-based strategy. DPI, dual pathway inhibition; LDL, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SBP, systolic blood pressure.

assessed. Next, the therapy benefit was estimated for the next available option in each category (Step 1). The most effective of these three options was selected (Step 2) and if the therapy benefit was larger than the minimally desired benefit, the therapy was added to the individual treatment strategy (Step 3). Then, the first step was repeated, taking into account the therapeutic effect of the selected therapy. In the category of the selected therapy, the therapy benefit of the next available therapy is evaluated. This continues until there are no more therapies that lead to more benefit than the minimally desired benefit (*stop*). Two patient examples are shown in *Figure 2*and Supplementary material online, *Figure S1*.

Risk factor-based decision algorithm

The risk factor-based decision algorithm simply consisted of treating all patients according to recommendations for very high-risk patients in the current ESC cardiovascular prevention, including the medication that was prescribed at baseline.[1] For lipid lowering, this meant lowering the LDL-c of all patients to ≤1.8 mmol/L. This was modelled using a stepwise approach: first, all patients with an LDL-c >1.8 mmol/L got assigned moderate-intensity lipid lowering. If the expected post-treatment LDL-c was >1.8 mmol/L, high-intensity lipid-lowering was started. If the expected post-treatment LDL-c was still >1.8 mmol/L, a PCSK9 inhibitor was initiated. Systolic blood pressure was lowered to 140 mmHg for all patients. All patients were treated with aspirin, none were treated with DPI as this is not (yet) recommended in the guidelines. A patient example of a risk factor-based treatment strategy is shown in Supplementary material online, *Figure S1*.

Microsimulation model

To evaluate outcomes of the different treatment strategies, a microsimulation model was developed to predict quality-adjusted life years (QALYs), costs, and clinical outcomes. The model was run three times for all patients in the UCC-SMART cohort, one time with the medication at baseline, one time with risk-based treatment, and one with lifetime benefit based treatment. A detailed description of the model and model assumptions can be found in the Supplementary material online, *Methods*.

Each year patients had a probability of acute events or death (Supplementary material online, *Figure S1*). The probabilities of events and death were based on patient characteristics and were modified by treatment effects for the risk factor-based and lifetime benefit-based treatment strategies. All chronic health states were associated with utility, after experiencing an acute event patients would transfer to the chronic health state associated with this event. A chronic 0.0015 reduction in utility was applied per drug used. All costs were discounted with 4%, utilities were discounted with 1.5% as is usual practice in the Netherlands. Costs were calculated from a healthcare perspective. Costs were estimated for acute events, chronic health states, and medication based on literature (Supplementary material online, *Table S2*), recent sources were selected if they were applicable to the Dutch healthcare and included all relevant costs.

Outcomes

Primary effectiveness outcomes were the total gain in CVD-free life-years and cardiovascular events avoided in comparison to treating all patients with the medication as prescribed at baseline. Primary cost-effectiveness outcomes were the difference in QALYs and costs in comparison to baseline treatment. Number of therapies was defined as the sum of different lipid lowering, antihypertensive and antithrombotic drugs, and included medication already prescribed at baseline. Confidence intervals and *P*-values were based on probabilistic sensitivity analyses.

Scenario analyses

Probabilistic scenario analyses were performed to assess robustness of the results, repeating the prior microsimulation model 1000 times for every strategy. In these analyses, drug and event costs, chronic health state utilities, annual event rates, and HRs of all therapies were randomly chosen from beta or gamma distributions. Additionally, several scenario analyses were performed for several model assumptions.

Statistical analysis

Because complete case analysis may lead to loss of statistical power and possible bias,[19] values of the following variables were imputed by single regression imputation: smoking status ($n = 32$, 0.4%), creatinin ($n = 31$, 0.3%), CRP ($n = 250$, 3.2%), SBP ($n = 18$, 0.2%), LDL ($n = 80$, 1.0%), or total cholesterol ($n = 34$, 0.4%). Patients were followed-up until death, lost to follow-up ($n = 561$, 6.1%) or until March 2018. All analyses were performed with R-statistic programming (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the included patients are presented in *Table 1*. The mean age of the patients was 62.0 ± 8.5 years and 75% was male. At inclusion, 69% of the patients was using a statin and 13% ezetimibe or a high-intensity statin. At baseline, 15% of the population had an LDL ≤1.8 mmol/L, 56% a SBP of ≤140 mmHg, and 84% was treated with aspirin or an equivalent drug.

Effectiveness

In comparison to baseline treatment, treatment according to lifetime benefit with a treatment threshold of 12 months would lead to an increase of 24 243 CVD-free life years (95% CI 19 980–29 909), risk factor-based treatment to an increase of 18 564 CVD-free life years (95% CI 14 225–20 456). In the next 10 years, predicted lifetime benefit-based treatment could avoid 940 (95% CI 742–1140) major adverse cardiovascular events and risk factor-based treatment could avoid 857 (95% CI 661–1057) events (*Table 2*).

At baseline, the mean number of preventive therapies was 2.3 ± 1.3. Using a lifetime benefit-based strategy this increased to 4.8 ± 1.8, based on risk factor levels this increased to 4.5 ± 1.5. PCSK9 inhibitors were assigned to 20% of the patients according to the lifetime benefit-based strategy and to 18% of the patients in the risk factor-based strategy, low-dose DOACs were started in 72% of the UCC-SMART population in the lifetime benefit-based treatment strategy. The distribution of the different treatments when using lifetime benefit-based treatment and risk factor-based treatment are presented in *Table 3*.

In younger patients (<60 years), lifetime benefit-based treatment with a treatment threshold of 12 months led to treatment with median 5.4 ± 1.7 therapies and risk factor-based to 4.3 ± 1.4 therapies in comparison to 2.4 ± 1.4 at baseline. In patients >75 year, lifetime benefit-based treatment led to a median of 3.4 ± 1.8 therapies and risk factor-based treatment to 4.8 ± 1.7 therapies, in comparison to 1.8 ± 1.2 at baseline (*Figure 3A*). The mean age of a PCSK9 inhibitor user was 57 ± 7 years when treating lifetime benefit-based and 62 ± 9 years old when treating risk factor-based. Treating according to lifetime benefit would lead to a decreased incidence of CVD in patients up to 75 years old, but a higher incidence in patients older than 75 years (*Figure 3B*).

When using a treatment threshold of 6 months gain in CVD-free life expectancy rather than 12 months, more events could be avoided and more CVD-free life years could be won (*Table 3*). However, this would be at the cost of increased medication use. In a treatment strategy with a threshold of 24 months per therapy, fewer medications would be started, but this would result in fewer events avoided and less CVD-free life won.

Table 1 Patient characteristics of the study population at baseline

	UCC-SMART ($n = 7697$)
Male sex	5774 (75%)
Age (years)	62 ± 8
Current smoker	2215 (29%)
Former smoker	3809 (49%)
Body mass index (kg/m^2)	26.9 ± 4.0
Systolic blood pressure (mmHg)	140 ± 20
Diabetes mellitus	1386 (18%)
Coronary artery disease	4835 (63%)
Peripheral artery disease	1356 (18%)
Cerebrovascular disease	2222 (29%)
Abdominal arterial aneurysm	687 (9%)
Number of disease locations	
One	6484 (84%)
Two	1050 (14%)
Three	163 (2%)
Total cholesterol (mmol/L)	4.7 (3.9–5.6)
HDL-cholesterol (mmol/L)	1.2 (1.0–1.4)
LDL-cholesterol (mmol/L)	2.7 (2.1–3.5)
Triglycerides (mmol/L)	1.4 (1.0–2.0)
Estimated GFR (mL/min/1.73 m^2)	76 ± 17
CRP (mg/dL)	2.1 (1.0–4.4)
Medication use	
Any statin	5323 (69%)
High-intensity statin	733 (10%)
Ezetimibe	304 (4%)
Diuretics	1740 (23%)
ACE inhibitors	2517 (33%)
Beta-blockers	4260 (55%)
Calcium channel blockers	1693 (22%)
Aspirin or equivalent	5999 (78%)
Oral anticoagulants	862 (11%)

All data are expressed as *n* (%), mean ± standard deviation, or median (IQR).
GFR, glomerular filtration rate [calculated with Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) formula].

Cost-effectiveness

Lifetime benefit-based treatment with a treatment threshold of 12 months led to 9664 additional QALYs, risk factor-based treatment led to 7793 additional QALYs compared to treatment as at baseline. The additional costs for the lifetime benefit-based strategy were €145.8 million and for risk factor-based treatment €77.4 million. The incremental cost-effectivity ratio (ICER) of lifetime benefit-based treatment was €15 092/QALY gained and of risk factor-based treatment €9933/QALY gained (*Table 4*). A lifetime benefit-based treatment approach was 90% likely to be cost-effective under the Dutch threshold of €20 000/QALY gained compared to treatment as at baseline (Supplementary material online, *Figure S3*). For a risk factor-

Table 2 Effectiveness of predicted lifetime benefit-based treatment and risk-factor based treatment

	Predicted lifetime benefit based			Risk-factor based
N = 7697	≥6 months	≥12 months	≥24 months	
Total gain in CVD-free lifetime (years)	35 972	24 243	8806	18 564
Event reduction next 10 years (*n*)	1329	940	324	857
Lifetime event reduction (*n*)	2597	2042	1056	1584
Mean number of preventive therapies (*n*)	6.3	4.4	3.0	4.1

The effectiveness of predicted lifetime benefit-based treatment and risk factor-based treatment. Treatment threshold is the minimal number of months gain in CVD life expectancy before a therapy was started, so the threshold of at least 12 months shows the treatment strategy including all preventive treatments leading to at least 1 year gain in CVD-free life expectancy as estimated with the SMART-REACH model. Gain in lifetime and event reduction are all in comparison to treating all patients with their baseline medication. Number of preventive therapies is the sum of the number of lipid lowering, blood pressure lowering, or antithrombotic drugs.
CVD, cardiovascular disease.

Table 3 Proportion of patients treated with every therapy according to their baseline prescriptions and after lifetime benefit- or risk factor-based treatment intensification

		Treatment intensification based on	
Therapy	**Treatment at baseline**	**Lifetime benefit (>12 months)**	**Risk factor**
Moderate-intensity lipid lowering	69%	93%	99%
High-intensity lipid lowering	13%	23%	52%
PCSK9 inhibitors	0%	20%	18%
SBP target <140 mmHg	43%	77%	88%
SBP target <130 mmHg	0%	8%	0%
Aspirin or equivalent	78%	92%	100%
DPI	0%	72%	0%

Proportion of patients of the UCC-SMART cohort that has a certain therapy assigned at study inclusion or after benefit- or risk factor-based treatment intensification.
DPI, dual pathway inhibition; PCSK9, proprotein convertase subtilisin/kexin type 9; SBP, systolic blood pressure.

based treatment approach, this was >99%. The results when using a treatment threshold of 6 or 24 months are in *Table 4*. When directly comparing lifetime benefit-based treatment to risk factor-based treatment, the ICER was €36 538/QALY gained, which was 20% probable to be cost-effective under the threshold of €20 000/QALY. A direct comparison for other commonly used cost-effectiveness thresholds is shown in Supplementary material online, *Table S3*. When discounting both costs and utilities with 3% as is usual in several other countries, the ICER for lifetime benefit-based treatment was €24 432/QALY gained. Excluding DPI led to an ICER of €19 529 for lifetime benefit-based treatment. When doubling the chronic disutility per drug used to 0.003 to account for side effects, the ICER increased to €16 281/QALY gained. The results of all scenario analyses are shown in Supplementary material online, *Figure S4* and *Table S4*.

Discussion

Results from this study show that lifetime benefit-based treatment is an effective for reducing residual CVD risk in patients with clinical manifest vascular disease. In direct comparison to risk factor-based treatment, treating lifetime benefit-based can avoid more cardiovascular events and can lead to more CVD-free life years with a similar amount of started preventive therapies, although at a higher price. Depending on the willingness-to-pay threshold, lifetime benefit-based treatment is potentially cost-effective.

Residual risk reduction based on predicted lifetime benefit leads to more intensive treatment of younger patients compared to the conventional risk factor-based strategy. As cardiovascular events are prevented at a younger age, a larger gain of CVD-free life expectancy can be obtained. However, this comes with the cost of longer treatment durations as preventive treatment is usually initiated lifelong, with increased costs and potential side effects. On the other hand, lifetime benefit based treatment may reduce overtreatment of older patients. Even though absolute risk reduction from preventive therapy can be substantial in older patients, the actual increase in life expectancy can be limited due to the high remaining risk of both CVD and non-CVD mortality. On top of that, this group has the highest rates of adverse events and interactions with other medications due to the high rates of polypharmacy, even further reducing the net-benefit this group has from preventive treatment.[20]

In the current study, only intensification of preventive treatment was evaluated. Overtreatment in older patients may be prevented even further by evaluating whether currently prescribed medication still leads to sufficient benefit. It should be noted that only

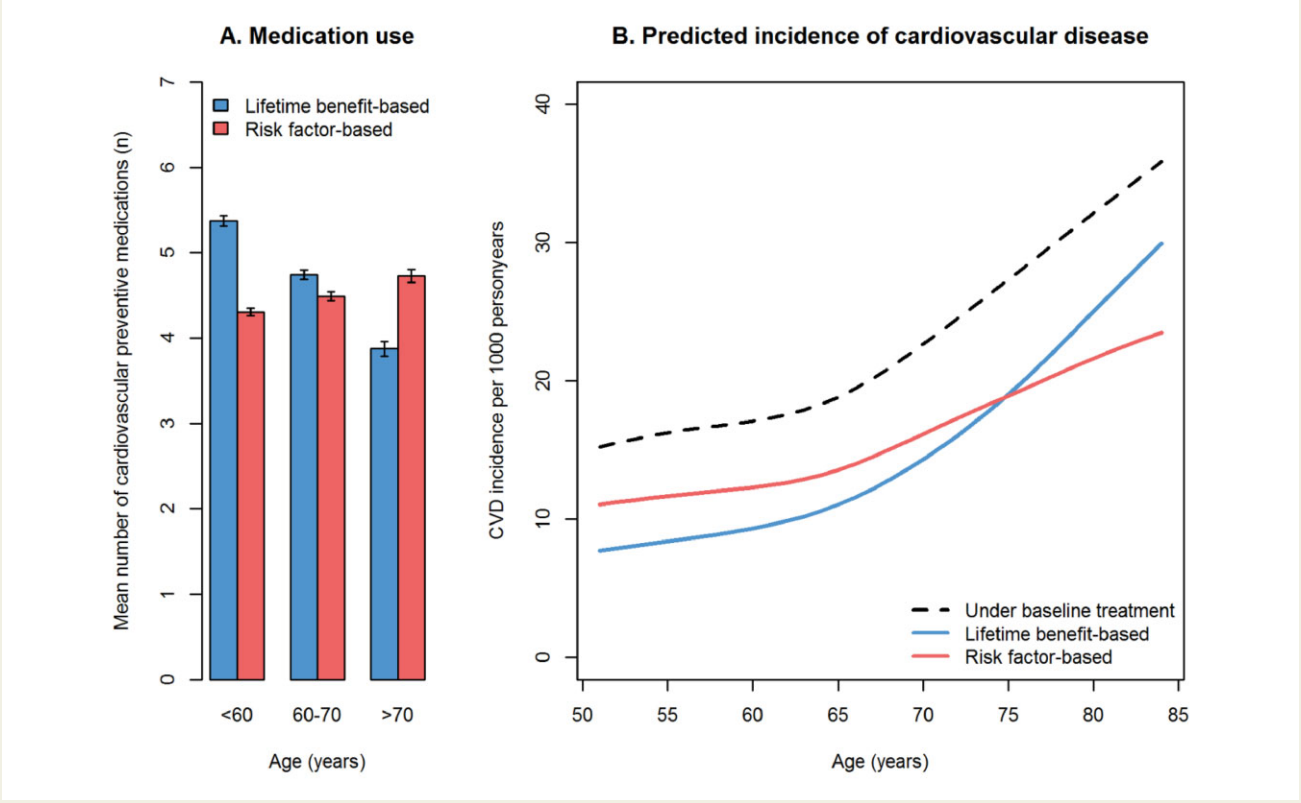

Figure 3 Medication use and predicted incidence of cardiovascular disease when treating lifetime benefit-based or risk factor-based per age group. Medication use and predicted incidence of cardiovascular disease when treating lifetime benefit-based (threshold >12 months) or risk factor-based per age group. (*A*) Medication use includes baseline use of medication and is the sum of the number of treatments for lipid lowering, blood pressure lowering and antithrombotic therapy. (*B*) Predicted incidence was calculated by combining the treatment effects per strategy with the observed incidence (dashed line).

pharmaceutical interventions were evaluated in the current study, as lifestyle improvements should be performed regardless of pharmaceutical interventions. Especially smoking cessation, of which the absolute risk reduction and gain in CVD-free life expectancy are often much greater than from any of the pharmaceutical interventions mentioned in the current study, should be recommended in clinical practice prior to considering pharmaceutical treatment intensification.

In this study, a minimally desired benefit of 12 months gain in CVD-free life expectancy was primarily used in order to make an analysis on a population scale. However, in clinical practice, it is unlikely that one threshold for treatment benefit can be used in all patients. Secondary analyses showed that the use of a smaller threshold like 6 months more events can be avoided, but at the cost of more intensive treatment. There is much variation in how much benefit patients and physicians consider enough in order to start or intensify risk factor treatment.[21] Deciding whether the expected therapy benefit is enough should be the result of shared decision-making between patient and healthcare professional. As the benefit in terms of gain in CVD-free life-expectancy is an intuitive measure, it is very suitable to be used in shared decision-making and should be used alongside the expected treatment duration and side effects.

A previous study found that lifetime benefit-based treatment is more cost-effective than a 10-year risk-based approach for PCSK9 inhibitors for patients with symptomatic atherosclerotic disease.[22] To our knowledge, there are no other studies assessing the effectiveness or cost-effectiveness of treatment decisions based on lifetime benefit or directly comparing an individual risk factor-based and lifetime benefit-based approach in the secondary prevention of cardiovascular disease. Results from the current study show that residual CV risk reduction based on lifetime benefit is an effective alternative to risk factor-based treatment as advocated in guidelines for patients with established atherosclerotic vascular disease.[1]

Both the lifetime benefit-based and risk factor-based strategies are cost-effective strategies in comparison to current practice. In direct comparison, it depends on the treatment threshold for lifetime benefit based treatment and the willingness-to-pay threshold used which strategy is most likely cost-effective. In the Netherlands, willingness-to-pay thresholds range from €20 000 to €80 000 per QALY gained.[23,24] Under the most conservative threshold of 20 000€/QALY, often used in The Netherlands when evaluating prevention programmes, only the 24-month threshold was cost-effective. However, at a willingness-to-pay threshold of 50 000€/QALY lifetime, benefit-based strategies are likely to be cost-effective regardless of the individual treatment threshold used.

Table 4: Cost-effectiveness of lifetime benefit-based and risk factor-based treatment

N = 7697	Baseline treatment	Predicted lifetime benefit based			Risk-factor based
		≥6 months	≥12 months	≥24 months	
Total costs (mln €)	442.1	818.2	587.9	472.0	519.4
CVD event costs	182.4	107.7	130.4	161.4	138.5
Chronic care costs	246.8	296.4	278.1	259.8	273.1
Therapeutic costs	12.8	414.1	179.4	50.8	107.8
Total QALYs (×1000)	74.4	90.0	84.0	78.7	82.2
Total life years (×1000)	149.2	176.0	164.9	155.8	161.9
Total events (MACE)	9633	7061	7591	8602	8049
ICER vs. current practice (€/QALY)		25 327	15 092	8217	9933
ICER vs. risk-factor based (€/QALY)		38 340	36 585	13 775	
Prob. of cost-effectiveness (<20 000 €/QALY)		0.16	0.90	>0.99	>0.99

Cost-effectiveness results of the different strategies. All results are on cohort level on a lifetime perspective. Treatment threshold is the minimal number of months gain in CVD life expectancy before a therapy was started, so the threshold of at least 12 months shows the treatment strategy including all preventive treatments leading to at least 1 year gain in CVD-free life expectancy as estimated with the SMART-REACH model. ICER is in comparison to baseline treatment. Probability of cost-effectiveness is defined as the probability that the treatment strategy costs <€20 000 per QALY.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In the current ESC guidelines, all patients with symptomatic atherosclerotic disease are in the very high-risk category.[1] As a consequence, treatment targets for SBP and LDL are equal for all patients with cardiovascular disease and all patients are advised to use an antiplatelet drug. In a recent ESC position paper, it is suggested that lifetime benefit can facilitate communication concerning treatment decisions and, after additional validation of the methodology, may play a more central role in future treatment recommendations in guidelines.[25] By prediction of treatment effects, cardiovascular prevention can be more precisely tailored to the individual patient, which can be more or less intensive than treatment advised in current guidelines.

A strength of this study is the use of a large, real-world cohort with patients with different types of symptomatic cardiovascular disease. Cardiovascular event- and (total) mortality rates could be accurately modelled in the cost-effectiveness analysis due to the extensive follow-up in the UCC-SMART cohort. Treatment selection was done using the externally validated SMART-REACH model. This model is competing-risk adjusted and left truncation allows the model to perform accurate predictions beyond the scope of the observed follow-up time, making it very suitable for evaluating the long-term effectiveness of interventions.[7] Also, extensive sensitivity analyses were performed to confirm the robustness and validity of the assumptions of the cost-effectiveness analysis, including probabilistic analyses and one-way scenario analyses. Finally, 'lifetime benefit-based treatment' as used in this study can be applied directly in clinical practice. Both the SMART-REACH model and (soon) the tool that was used for the individual treatment selection are available in an online calculator (www.u-prevent.com).

Limitations of the study should also be considered. Treatment effects were assumed to be constant for lifetime duration. Especially for more novel treatments like PCSK9 inhibitors and low-dose DOACs, this required extrapolation beyond the maximum follow-up of the relevant RCTs. Long-term results of treatment with those agents are not yet available, long-term efficacy and safety should be validated in future studies with longer follow-up durations. For PCSK9 inhibitors, the actual effect of long-term LDL-c reduction may be even larger than modelled, since the causal effect of LDL-c lowering on cardiovascular outcomes is cumulative and increases over time.[26,27] For DPI, such evidence unfortunately does not exist yet. Treatment algorithms like the one shown in the current study should be continuously adapted to growing knowledge and potentially changing priorities. Moreover, the effectivity of long-term treatment in individuals developing additional co-morbidities may be altered. As these long-term effects are often not captured in trials due to the limited follow-up duration, treatment effects from trials may become less applicable to the target population as time passes. Another limitation is that two variables of the SMART-REACH model, presence of atrial fibrillation and congestive heart failure, were not recorded at baseline in the UCC-SMART study. However, repeating the analysis on a simulated population resembling the UCC-SMART population including age- and sex-corrected prevalence rates of atrial fibrillation and congestive heart failure showed similar results as the main analysis.

In conclusion, residual CV risk reduction guided by lifetime benefit estimation is an effective and potentially cost-effective strategy which can lead to more CVD-free life years and event reduction compared to treating according to risk factor threshold based treatment in patients with established vascular disease. Treatment benefit expressed as gain in extra CVD-free life is an intuitive measure to be used in the shared decision making process, which can help to tailor preventive treatment to the individual patient.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability

Data used for the current study are available upon reasonable request and after approval by the UCC-SMART studygroup.

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