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FASTTRACK CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Estimating individual lifetime benefit and bleeding risk of adding rivaroxaban to aspirin for patients with stable cardiovascular disease: results from the COMPASS trial

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Aims Adding rivaroxaban to aspirin in patients with stable atherosclerotic disease reduces the recurrence of cardiovascular disease (CVD) but increases the risk of major bleeding. The aim of this study was to estimate the individual lifetime treatment benefit and harm of adding low-dose rivaroxaban to aspirin in patients with stable cardiovascular disease.

Methods and results Patients with established CVD from the COMPASS trial ($n = 27\ 390$) and SMART prospective cohort study ($n = 8139$) were used. Using the pre-existing lifetime SMART-REACH model for recurrent CVD, and a newly developed Fine and Gray competing risk-adjusted lifetime model for major bleeding, individual treatment effects from adding low-dose rivaroxaban to aspirin in patients with stable CVD were estimated, expressed in terms of (i) life-years free of stroke or myocardial infarction (MI) gained; and (ii) life-years free from major bleeding lost. Calibration of the SMART-REACH model for prediction of recurrent CVD events in the COMPASS study was good. The major bleeding risk model as derived in the COMPASS trial showed good external calibration in the SMART cohort. Predicted individual gain in life expectancy free of stroke or MI from added low-dose rivaroxaban had a median of 16 months (range 1–48 months), while predicted individualized lifetime lost in terms of major bleeding had a median of 2 months (range 0–20 months).

Conclusion There is a wide distribution in lifetime gain and harm from adding low-dose rivaroxaban to aspirin in individual patients with stable CVD. Using these lifetime models, benefits and bleeding risk can be weighed for each individual patient, which could facilitate treatment decisions in clinical practice.

Keywords Life expectancy • Predictive model • Secondary prevention • Treatment effect • Antithrombotic therapy

Introduction

Patients with a history of cardiovascular disease (CVD) remain at elevated risk for recurrent vascular events despite preventive strategies, including lifestyle changes, lipid-lowering, blood pressure-lowering, and the use of antiplatelet therapy.[1–3] The 'Cardiovascular Outcomes for People Using Anticoagulation Strategies' (COMPASS) trial showed that adding rivaroxaban 2.5 mg twice daily to aspirin was

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superior to aspirin alone in prevention of major cardiovascular events (MACE) and all-cause mortality in a secondary prevention setting. Lowering of CVD risk by adding rivaroxaban to aspirin was achieved accompanied by a slight increase in bleeding risk.[4]

In clinical practice, clinicians face the challenge of translating average efficacy and safety results from clinical trials like COMPASS to individual patients.[5] Trial results are usually reported in terms of average relative risk reductions for the primary outcome, and relative risk increases of adverse events. However, due to different patient characteristics, the absolute individual treatment effect differs between individuals.[5] Likewise, the absolute risk of adverse events, e.g. major bleeding with anticoagulants, differs between individual patients. This means that one patient may have a large treatment benefit with a low risk of bleeding, while another might have little treatment benefit with a high risk of major bleeding. Predicting the individual lifetime treatment benefit and harm in COMPASS has the potential to identify those patients who will benefit most from adding rivaroxaban to aspirin, while having an acceptable risk of major bleeding.

The objective of the present study was to estimate the absolute individual lifetime treatment benefit and harm of low-dose rivaroxaban added to aspirin for individual patients with stable CVD in terms of: (i) life-years without myocardial infarction (MI) or stroke gained; and (ii) life-years free from major bleeding lost.

Methods

Study populations

The COMPASS trial (registration number: NCT01776424) was a double-blind, randomized, placebo-controlled clinical trial comparing aspirin alone with rivaroxaban 2.5 mg twice daily with aspirin or rivaroxaban 5 mg twice daily without aspirin for the prevention of MACE in 27 395 participants from 33 countries. In the current study, data from 27 390 patients with a history of stable atherosclerotic vascular disease were used. The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study of patients with established CVD or cardiovascular risk factors at the University Medical Center Utrecht. For the current study, data were used from 8139 patients with clinically manifest CVD enrolled between 1996 and 2017. Detailed descriptions of both studies have been published elsewhere.[6,7] Both studies complied with the Declaration of Helsinki, were approved by institutional review boards and all participants provided written informed consent.

All included study participants were people aged >18 years with clinically manifest vascular disease, defined as either coronary artery disease (CAD) or peripheral artery disease, and in the SMART cohort also as cerebrovascular disease or abdominal aortic aneurysm. A comprehensive overview of eligibility criteria for the original studies is provided in Supplementary material online, *Table S1a*.

Outcomes

Cardiovascular disease was defined as MI, stroke, or vascular mortality. Non-vascular mortality was defined as death without a cardiovascular cause. Major bleeding was defined according to the *International Society on Thrombosis and Haemostasis* (ISTH) criteria: fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in haemoglobin level of ≥20 g/L (>1.24 mmol/L), and/or leading to transfusion of ≥2 units of whole blood or red cells.[8] Endpoint definitions are described in Supplementary material online, *Table S1b*. Outcome assessment in COMPASS was blinded to randomization.

External validation of SMART-REACH model

The SMART-REACH prediction algorithm is a previously derived, externally validated competing risk-adjusted Fine and Gray model for lifetime predictions for MACE and non-cardiovascular death in patients with clinically manifest vascular disease (Supplementary material online, *Methods*).[9] After adjusting for differences in underlying event rates, external validation of this model in COMPASS was performed, using the c-statistic for discrimination and plots of predicted vs. observed 2-year risk for calibration (detailed descriptions of the used methodology provided in the Supplementary material online, *Methods*).

Development of a prediction model for major bleeding

In the COMPASS trial, we developed two complementary Fine and Gray competing risk-adjusted subdistribution-hazard functions for cause-specific estimates of the cumulative incidence with left truncation and right censoring[10]: for lifetime predictions of risk of major bleeding, and for competing mortality. These statistical methods have been previously described in detail.[9,11–14] In short, age was used as underlying time-function. Patients contribute data to the survival function from age of study entry to age of study exit (either time of event or censoring). This results in overlapping observations, allowing for lifetime predictions to be made across the range of baseline ages. Estimates derived from these models are limited by age distribution of study participants rather than follow-up time. As predictions can be unstable when the number of people and events of interest are limited in a specific age group, the age-range was limited to 45–90 years. Predictors were pre-specified, based on previous bleeding models,[15–17] and selected on availability in the studies and in clinical practice: age, gender, ethnicity, geographical region, current smoking, systolic blood pressure (SBP), number of CVD locations, diabetes mellitus, history of congestive heart failure, history of bleeding requiring transfusion, serum creatinine, and total cholesterol. Furthermore, a dummy variable for treatment with rivaroxaban-plus-aspirin or rivaroxaban alone was added to the model to adjust for treatment-related increases in bleeding risk. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. Whether the association of continuous predictors with the outcome variable is log-linear was assessed with restricted cubic splines; to improve the robustness of the model, transformation was applied when this improved model fit, based on Akaike's Information Criterion.[18] The proportional hazards assumptions were checked by visually assessing the correlations between scaled Schoenfeld residuals for the various predictors and age.

Lifetime predictions of event-free survival for individual patients

Life expectancy without recurrent cardiovascular events and without major bleeding was estimated using the SMART-REACH model and major bleeding risk model, respectively. Beginning at age at baseline for each individual participant, the risk of the event of interest (a_t) and the risk of the competing event (b_t) was estimated for each future life-year. Next, the probability of being healthy and alive at interval t (e_{t+1}) was calculated by multiplying the survival probability at the beginning of each life-year (e_t) by the event-free survival probability during that year ($1 - a_t - b_t$). This process is repeated until the maximum age of 90 years. These predictions together form an individual life table with 1-year intervals. Event-free life expectancy was defined as median estimated survival, the age where the predicted individual survival curve is 50%. Ten-year risk (or

other durations of interest) of the event of interest can be predicted by calculating the cumulative cause-specific event-risk truncated at 10 years after age at baseline.

Model validation

Internal validity of the major bleeding risk model was assessed with calibration plots of predicted vs. observed 2-year risk in the COMPASS trial; c-statistics were obtained using bootstrapping with 1000 bootstrap samples. External validity of the major bleeding risk model was tested in the SMART cohort at 10-year follow-up in patients without oral anticoagulants. Calibration plots were used to assess goodness-of-fit for bleeding-free survival, bleeding events, and non-bleeding mortality functions after recalibration based on the incidence rate of bleeding and non-bleeding mortality using the expected vs. observed ratio; discrimination was assessed using c-statistics.

Individual treatment effect predictions

The competing risk-adjusted Cox proportional hazard function for the prediction of the event of interest from the SMART-REACH and major bleeding risk model were combined with hazard ratios (HRs) from the COMPASS trial for the treatment arm aspirin-plus-rivaroxaban according to previously described methods.[9,12,19,20] These HRs were applied to the 1-year estimates of respectively the SMART-REACH model and the major bleeding model by adding the logarithm of the HR to the linear predictor of the model. Because these methods make use of life tables, any gain or loss in event-free survival will be adjusted for the competing risks because the time at risk for the competing event changes. For the CVD survival function, the HR for added rivaroxaban is 0.76.[4] For the major bleeding function, to account for the decrease in increased risk from the addition of rivaroxaban to aspirin after the 1st year, several HRs were used: 2.32 in the 1st year after commencement of the added rivaroxaban, 1.19 in the 2nd year, and 1.05 after more than 2 years.[21] Heterogeneity of treatment effect across baseline risk for disease was assessed by fitting a model including an interaction term between the linear predictor and treatment allocation for all models.[5]

The median CVD-free life expectancy with aspirin was estimated for each patient. Treatment benefit or harm for individual patients, the expected lifetime benefit or harm when adding rivaroxaban to aspirin when compared with aspirin only, was defined as the patient's predicted event-free life expectancy when using aspirin (baseline risk with standard of care) minus the patient's predicted event-free life expectancy when adding low-dose rivaroxaban to aspirin. Similarly, the 10-year absolute event-risk reduction and increase for individual persons were estimated by calculating the difference between the predicted 10-year event-risk with and without added rivaroxaban.

Missing data (<1% in both COMPASS and SMART) were imputed by single imputation using predictive mean matching (areglmpute-algorithm in R, Hmisc-package). All analyses were conducted with R statistical software V.3.4.1 (www.r-project.org, packages Hmisc, survival, cmprsk, rms, car, mstate).

To enable the use of the SMART-REACH lifetime model and the major bleeding risk model in clinical practice, we have developed a calculator that allows for the estimation of the potential gain in life expectancy free from CVD, or loss in life expectancy free from major bleeding due to adding rivaroxaban to the treatment strategy for individual patients, as well as the 10-year absolute changes in risk (Supplementary material online, or with the online calculator on www.U-Prevent.com).

Table 1 Baseline characteristics

	COMPASS study ($n = 27\,390$)	SMART cohort ($n = 8139$)
Male sex	21 371 (78%)	6002 (74%)
Age (years)	68 ± 8	60 ± 10
Current smoker	5867 (21%)	3847 (47%)
Race		
White	17 023 (62%)	NA
Black	262 (1%)	NA
Asian	4268 (16%)	NA
Other	5837 (21%)	NA
Systolic blood pressure (mmHg)	139 ± 18	139 ± 21
Body mass index (kg/m^2)	28.3 ± 4.7	26.9 ± 4.0
Laboratory values		
Total cholesterol (mmol/L)	4.2 ± 1.1	4.8 ± 1.2
Creatinine (μmol/L)	90 ± 25	92 ± 36
Estimated GFR (mL/min/1.73 m^2)	74 ± 18	77 ± 18
Medical history		
Coronary artery disease	24 824 (91%)	4939 (61%)
Peripheral artery disease	7470 (27%)	1455 (18%)
Cerebrovascular disease	1032 (4%)	2462 (30%)
Number of cardiovascular disease locations		
One	21 186 (77%)	6897 (85%)
Two	4800 (18%)	1081 (13%)
Three	1404 (5%)	161 (2%)
Atrial fibrillation	NA[a]	101 (1%)[b]
Congestive heart failure	5902 (22%)	NA[c]
Diabetes mellitus	10 340 (38%)	1415 (17%)
History of bleeding requiring transfusion	723 (2.6%)	NA

All data in *n* (%) or mean ± standard deviation.
GFR, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration formula); NA, not available.
[a]Patients requiring anticoagulation were excluded.
[b]Only atrial fibrillation at baseline; history of atrial fibrillation not available.
[c]Information not available.

Results

Baseline characteristics of the study populations are shown in *Table 1*. SMART participants were more often current smokers (47% vs. 21%), while in COMPASS more patients had diabetes mellitus (38% vs. 17%). In SMART, more patients were included with cerebrovascular disease (30% vs. 4%), and in COMPASS, more patients were included with CAD (91% vs. 61%).

In the COMPASS trial, a total of 1323 cardiovascular events, 499 non-cardiovascular deaths, and 497 major bleedings were observed during a median follow-up of 1.9 years [interquartile range (IQR) 1.3–2.5]. In the SMART cohort, 1568 cardiovascular events, 907 non-cardiovascular deaths, and 335 major bleedings occurred during a median follow-up of 7.6 years (IQR 3.9–11.7).

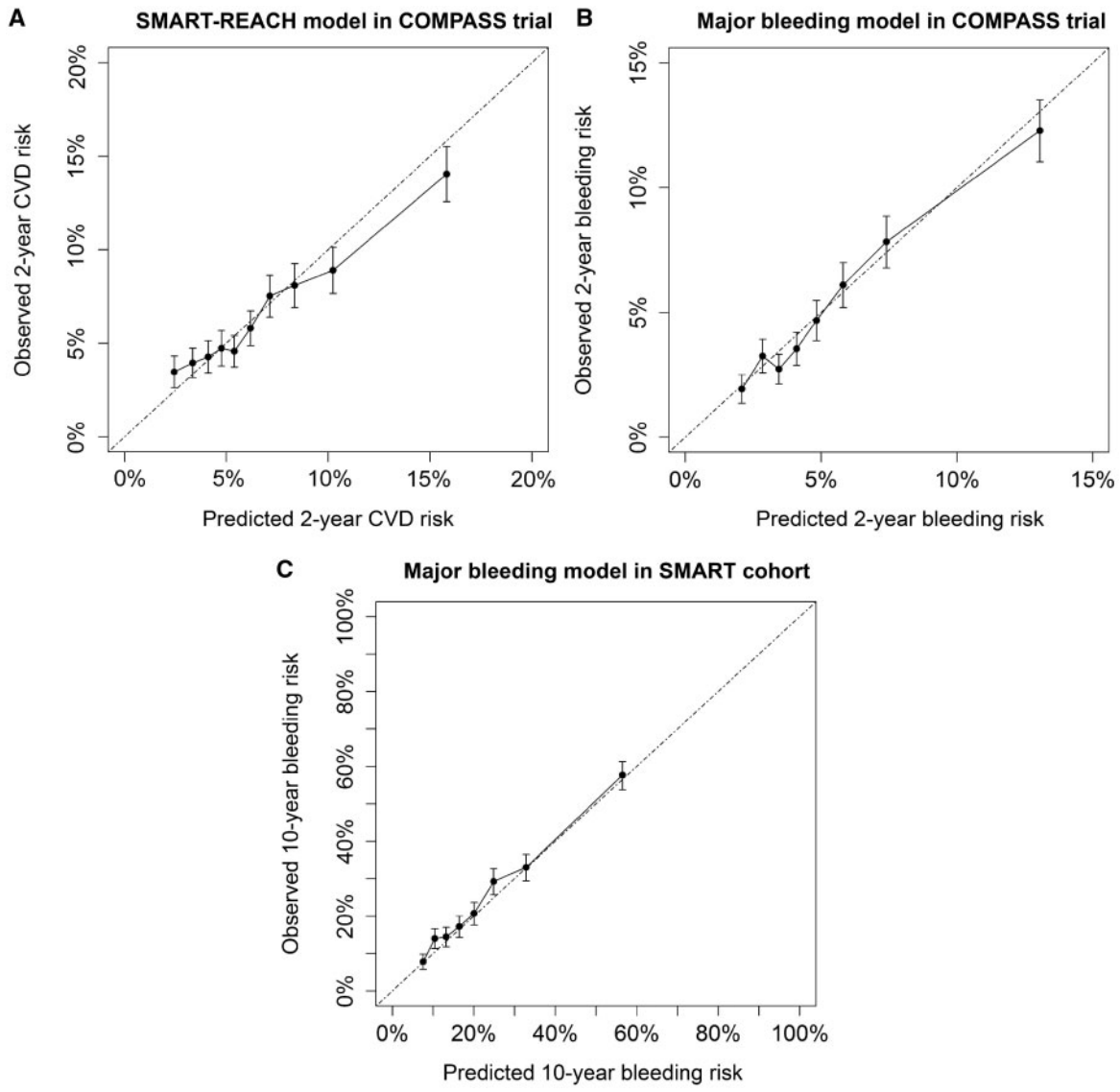


Figure 1 (*A*) Predicted vs. observed 2-year risk of CVD and all-cause mortality (SMART-REACH model) in the COMPASS trial. (*B*) Predicted vs. observed 2-year risk of major bleeding and all-cause mortality in the COMPASS trial. (*C*) Predicted vs. observed 10-year risk of major bleeding and all-cause mortality in the SMART cohort.

Validation of the SMART-REACH model in COMPASS

The recalibrated calibration plot of the predicted 2-year risk from the SMART-REACH model vs. the observed 2-year risk of CVD in the COMPASS study population is shown in *Figure 1A*. C-statistics were 0.62 [95% confidence interval (CI) 0.61–0.64] for recurrent vascular events and 0.66 (95% CI 0.63–0.68) for non-CVD mortality risk.

Development and validation of the major bleeding risk model

The coefficients and subdistribution HRs of the major bleeding and non-bleeding mortality models, age-specific baseline survivals, and calculation formulas of the models are presented in Supplementary material online, *Tables S2–S4*. No interaction terms with age were included in the functions as the proportional hazard assumptions were met. Quadratic terms for SBP, total cholesterol, and creatinine were included in the non-bleeding mortality model.

Figure 1B shows good agreement between the predicted 2-year risk for major bleeding and mortality and the observed 2-year risk in the development data set. Discrimination of the estimated 2-year bleeding risk was assessed, with a c-statistic of 0.69 (95% CI 0.66–0.71), and the c-statistic of the 2-year non-bleeding mortality risk was 0.71 (95% CI 0.69–0.73). *Figure 1C* shows good agreement between the predicted and observed 10-year risk for bleeding and non-bleeding mortality after recalibration to account for differences in

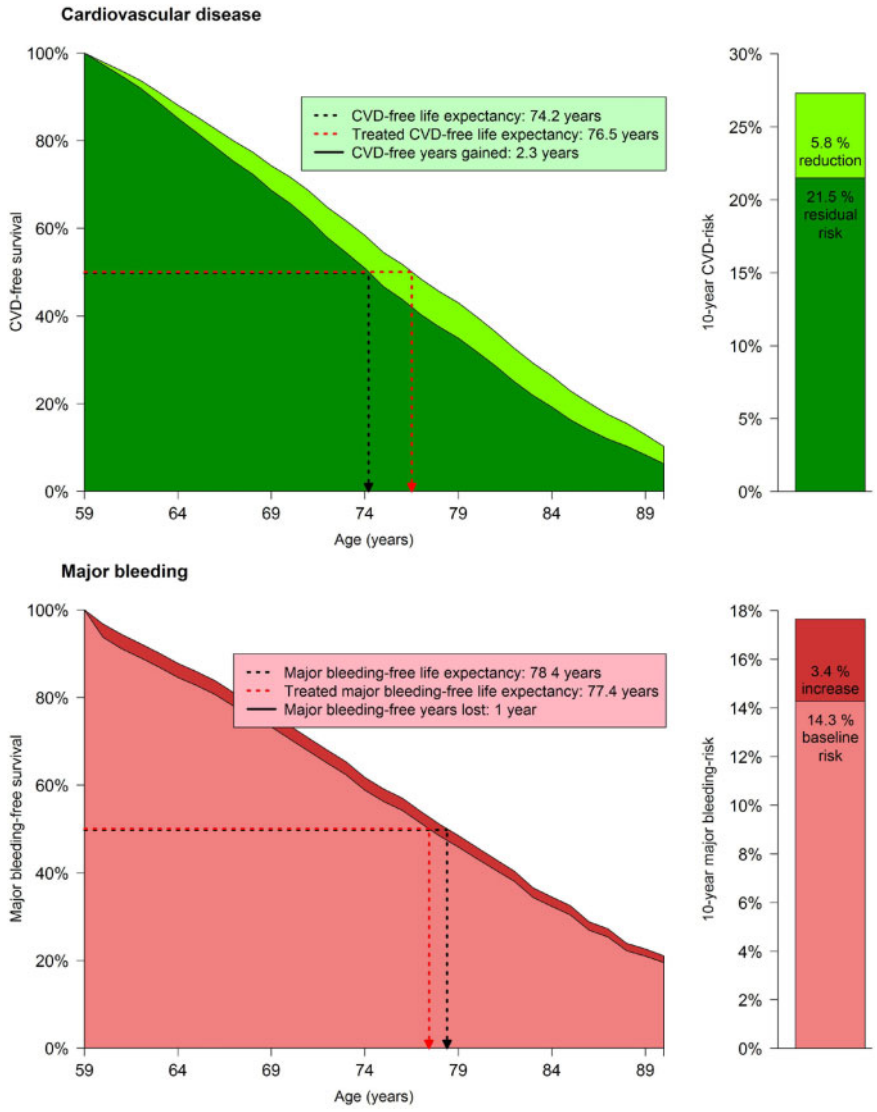


Figure 2 Patient example. A patient characteristics: a 59-year-old woman from Canada; not a current smoker; SBP 145 mmHg; total cholesterol 4.2 mmol/L; creatinine 90 μmol/L; history of coronary artery disease and peripheral artery disease; and does not have diabetes mellitus, atrial fibrillation, or congestive heart failure. The dark green survival curve is the current estimated survival without recurrent cardiovascular disease. The light green area reflects the increase in estimated survival when adding low-dose rivaroxaban to aspirin (treatment benefit). The dark red + light red areas of the lower survival curve represent the estimated survival without major bleeding. The light red area represents the estimated decrease in survival without major bleeding when adding rivaroxaban to aspirin (treatment harm). The bar charts show the absolute 10-year risk and 10-year risk increase or decrease, respectively, of adding rivaroxaban to aspirin.

baseline risk in the SMART study population. Discrimination for major bleeding-free survival was assessed, with a c-statistic of 0.69 (95% CI 0.67–0.70) in SMART.

Individual lifetime estimates and treatment effects

Figure 2 illustrates the use of the SMART-REACH and major bleeding risk model to estimate lifetime estimates of benefit and harm from rivaroxaban in a patient example.

The distribution of lifetime benefit in terms of months of lifetime gained without MACE and lifetime harm in terms of months lost without major bleeding with rivaroxaban added to aspirin in the combined study populations of the COMPASS and SMART studies is shown in *Figure 3*. The median lifetime benefit is 16 months (range 1–48 months) without MACE; the median lifetime harm is 2 months (range 0–20 months) without major bleeding. *Figure 4* shows the balance between the individual absolute benefit and harm from adding rivaroxaban to aspirin in 20 groups ordered by increasing net benefit (defined as individual lifetime benefit minus lifetime major bleeding risk). For most of the patients, lifetime benefit in terms of CVD-free life expectancy is higher than lifetime harm. Supplementary material online, *Table S5*

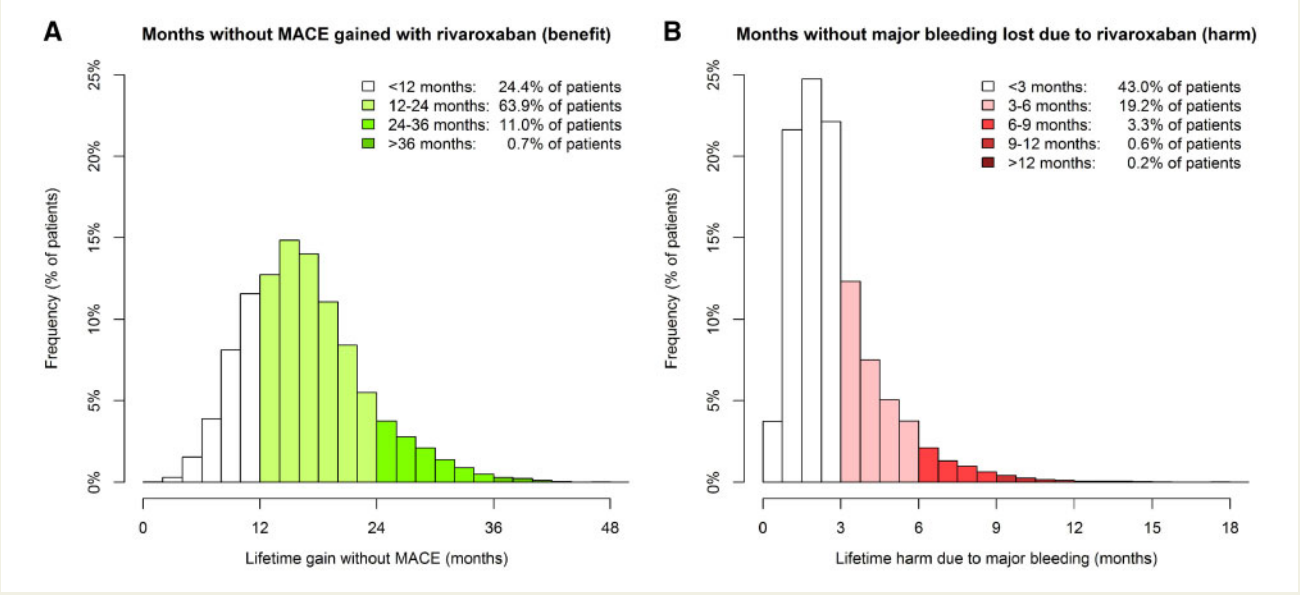


Figure 3 Distribution of (*A*) lifetime benefit (months gained without recurrent myocardial infarction or stroke); (*B*) lifetime harm (months lost without major bleeding).

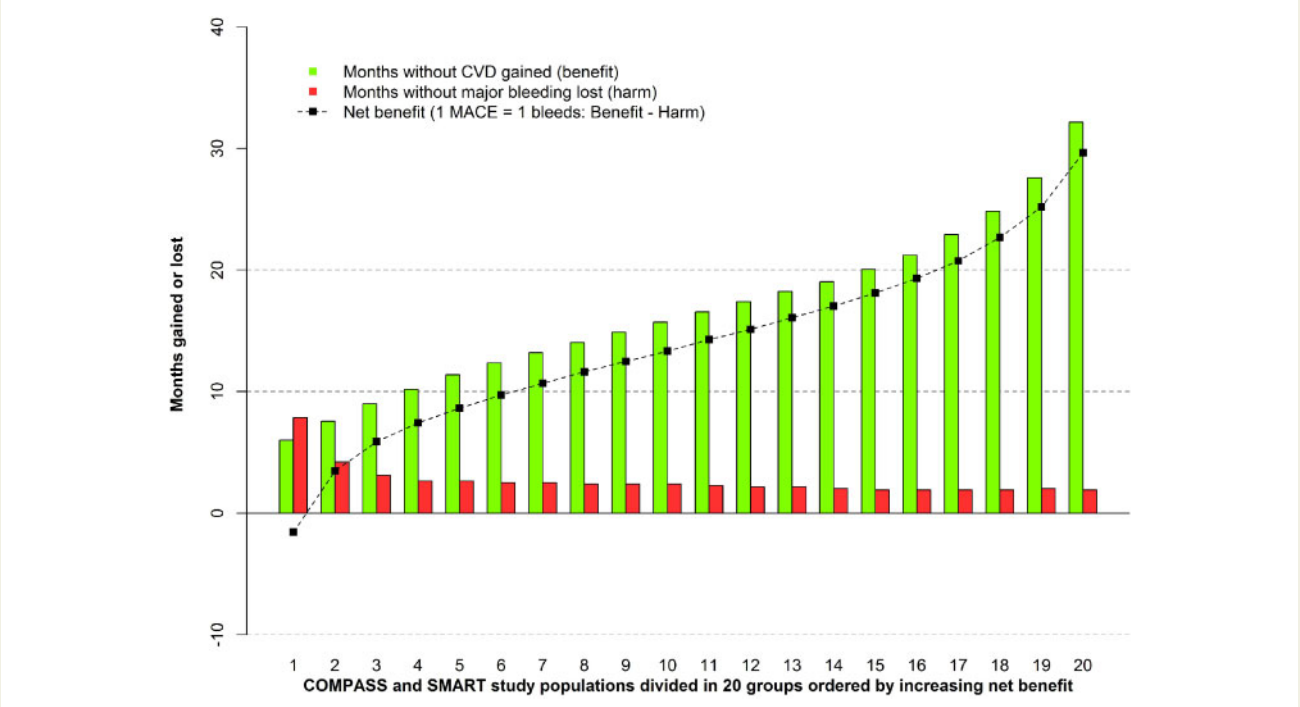
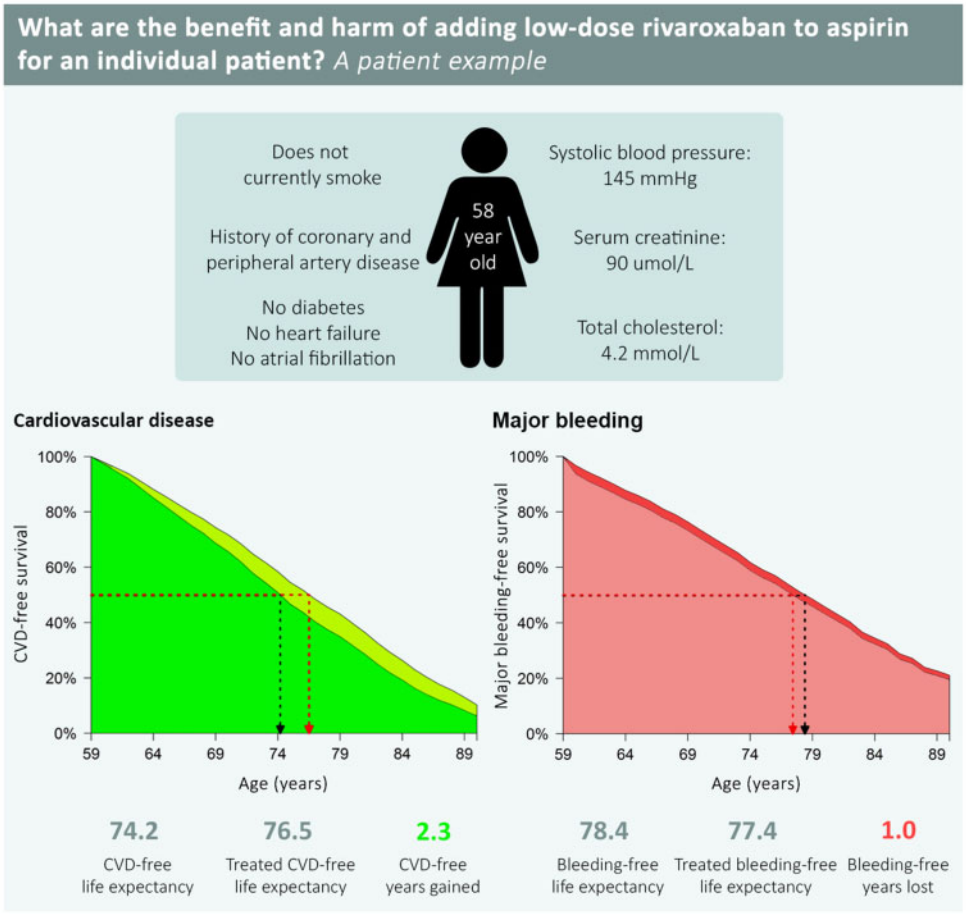


Figure 4 Individual lifetime benefit and associated lifetime harm from adding rivaroxaban to aspirin.

shows patient characteristics for quartiles of the study population based on the lifetime benefit in terms of CVD. Supplementary material online, *Figure S1* shows the distribution of 10-year risks and 10-year absolute risk reductions with rivaroxaban for MACE and major bleeding respectively.

Discussion

In the current study, it is shown that individual lifetime benefit and lifetime risk of major bleeding from adding low-dose rivaroxaban to aspirin can be predicted in patients with stable CVD (*Take home*



Take home figure An individual patient example of the lifetime models for predicting the treatment effects of adding low-dose rivaroxaban to aspirin.

figure). Lifetime benefit predictions were based on the externally validated SMART-REACH score, and major bleeding risk was based on the newly developed major bleeding risk score. These estimations can be made with simple, readily available patient characteristics. This enables the identification of patients who are likely to have long-term net benefit from rivaroxaban added to aspirin, in terms of additional CVD-free life expectancy, while having low risks of major bleeding.

An important clinical dilemma in the initiation of any antithrombotic is that the relative risk reduction of MACE is accompanied by a relative risk increase of bleeding. Because this study presents estimations for both lifetime treatment gain and treatment harm in terms of major bleeding, it aids in weighing the benefits vs. harms when discussing with an individual patient with stable CVD whether or not to add rivaroxaban to the treatment strategy. *Figure 4* shows that in the large majority of the COMPASS study population, lifetime benefit exceeds lifetime harm. However, there is a large inter-individual variation in what patients and physicians consider a meaningful lifetime benefit for preventive medication.[22] Preconceived notions of treatment benefits and possible adverse effects of preventive treatment also influence these expectations. Furthermore, what is deemed acceptable benefit and harm from treatment is interdependent, as patients who have a higher benefit, might accept a higher risk of harm. Therefore, the data from the present study form the basis of shared decision-making in clinical practice. Using individual lifetime estimates of treatment effects, a doctor and patient can discuss whether the estimated lifetime benefit, in terms of CVD-free life, of adding rivaroxaban to aspirin is worthwhile, by weighing the benefit against potential burden of taking an extra pill twice daily, costs, and the risk of potential side effects, including bleeding. What is considered a meaningful balance between benefit and potential harms and disadvantages of preventive therapy may differ between patients. By shared decision-making, patients are better informed and more involved in the process of making important decisions on life-long treatments which may lead in better treatment adherence as treatment decisions are tailored to their needs.

An advantage of the statistical methods of these models is that they can also be used to calculate 10-year risk estimations (as shown in *Figure 2*). As physicians are not yet widely familiar with the use of lifetime estimations, these absolute risk estimations might enable easier adoption of lifetime models, as they can be shown next to, and compared to, lifetime predictions in an online calculator. This can aid in a 'transitional phase' in going from traditional risk models to the adoption of lifetime risk models.

The lifetime scores presented in this study offer functionality superior to 'traditional' risk scores which estimate absolute risks of CVD or major bleeding during a limited period, usually 5–10 years. Lifetime treatment effects can be expressed in both months of CVD free lifetime gained or lifetime lost with treatment and are intuitive to understand for both patients and physicians, facilitating doctor–patient communication and thus aiding shared treatment decision-making. Lifetime prediction has the potential to shift the focus from treatment of patients with high absolute risks, often older patients, to treatment of patients with the largest possible lifetime treatment gain. This strategy might lead to initiation of preventive medication at a younger age and presumably taken lifelong.

An important strength of this study is that in developing the models, competing risks are taken into account. Often, traditional risk scores do not take competing (i.e. non-CVD or non-bleeding, respectively) mortality into account, which results in overestimation of risks in these patients in traditional risk models, and thus in overestimation of treatment effects. As treatment decisions are dependent on accurate predictions, this might have important implications for clinical practice. Secondly, due to the methodology using left-truncation, i.e. age as underlying time-function, estimations of these models are not limited by follow-up time in the derivation cohort. This means that despite limited follow-up time in the COMPASS trial, this study can be used for long-term estimations. Thirdly, the predictions in this model can be applied directly in clinical practice (Supplementary material online, *Calculator*; www.U-Prevent.com). Finally, this study uses large study populations from a clinical trial with diverse geographical backgrounds, and from an observational cohort.

Some limitations of the study should also be considered. Validation could only be performed for 2-year predictions in COMPASS due to limited follow-up time in the study. External validation of 10-year predictions in the SMART cohort, however, showed good calibration. Although remaining life expectancy, especially in younger patients, might be longer than 10 years, previous studies have shown that lifetime estimates based on the methods employed in this study appear to be reliable for predictions of up to at least 17 years, which is long enough for the purpose of making treatment decisions.[12] C-statistics for discrimination of both models are moderate (0.62–0.71), comparable to other risk models in patients with established CVD.[15,17,23–26] External validation of 10-year predictions in the SMART cohort, however, showed good calibration. As reliability of the predicted probabilities influence treatment decisions, calibration may be a clinically more relevant metric than discrimination for the purpose of clinical decision-making.[27]

Furthermore, the treatment effect estimations of rivaroxaban are based on studies with relatively short follow-up time, but projected for lifetime estimates. Although no data on long-term effects of rivaroxaban are yet available, for now there are no reasons to assume changes in efficacy or safety over time. Studies with long follow-up are needed. Furthermore, it should be acknowledged that non-compliance in the COMPASS trial may have affected the trial results. The estimated treatment effects in the current study approach the maximum attainable treatment effect with therapy. However, due to non-adherence in the trial, it is possible these predictions are underestimations of the true maximum attainable treatment effects with perfect therapy adherence.

Another limitation in that not all baseline predictors were available in both studies. For the SMART-REACH model, atrial fibrillation was not available in the COMPASS trial. For the major bleeding risk model, the history of heart failure, and history of bleeding requiring transfusion were not available in the SMART cohort. Assuming that none of the participants in these studies had a history of atrial fibrillation and congestive heart failure or bleeding requiring transfusion, respectively, might lead to underestimation of the predictive value of the model. Additionally, there was some underestimation of the predicted risk of CVD and mortality combined in the patients in the lowest decile of risk, and some overestimation in the highest decile of risk in the COMPASS study population. In clinical practice, however, this may not be of clinical relevance as this most likely does not result in misclassification or incorrect treatment decisions. Finally, the baseline risk for both cardiovascular and non-cardiovascular mortality was vastly different in the COMPASS trial compared to the study population in which the SMART-REACH model was derived due to differences in patient populations, for example the higher percentage of current smokers and patients with cerebrovascular disease at baseline in the SMART cohort. Additionally, this may be due to a healthy trial participant effect, as the SMART-REACH model was derived in cohorts, which better reflects real-life patients than a trial.[28,29] As the major bleeding risk model was derived in a trial, additional validation with recalibration for baseline risk in real-life situations or cohorts should be considered.

Conclusion

Lifetime treatment effects from adding rivaroxaban to aspirin in individual patients with stable CVD can be estimated using readily available patient characteristics. There is a wide distribution in lifetime gain and harm from adding rivaroxaban to aspirin in patients with stable CVD. Using this lifetime model, benefits and bleeding risk can be weighed for each individual patient, facilitating informed treatment decisions in clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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