Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus

The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study

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Background—In this study, we aimed to translate the average relative effect of statin therapy from trial data to the individual patient with type 2 diabetes mellitus by developing and validating a model to predict individualized absolute risk reductions (ARR) of cardiovascular events.

Methods and Results—Data of 2725 patients with type 2 diabetes mellitus from the Lipid Lowering Arm of the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) study (atorvastatin 10 mg versus placebo) were used for model derivation. The model was based on 8 clinical predictors including treatment allocation (statin/placebo). Ten-year individualized ARR on major cardiovascular events by statin therapy were calculated for each patient by subtracting the estimated on-treatment risk from the estimated off-treatment risk. Predicted 10-year ARR by statin therapy was <2% for 13% of the patients. About 30% had an ARR of >4% (median ARR, 3.2%; interquartile range, 2.5%–4.3%; 95% confidence interval for 3.2% ARR, –1.4% to 6.8%). Addition of treatment interactions did not improve model performance. Therefore, the wide distribution in ARR was a consequence of the underlying distribution in cardiovascular risk enrolled in these trials. External validation of the model was performed in data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT; pravastatin 40 mg versus usual care) and Collaborative Atorvastatin Diabetes Study (CARDS; atorvastatin 10 mg versus placebo) of 3878 and 2838 patients with type 2 diabetes mellitus, respectively. Model calibration was adequate in both external data sets, discrimination was moderate (ALLHAT-LLT: c-statistics, 0.64 [95% confidence interval, 0.61–0.67] and CARDS: 0.68 [95% confidence interval, 0.64–0.72]).

Conclusions—ARRs of major cardiovascular events by statin therapy can be accurately estimated for individual patients with type 2 diabetes mellitus using a model based on routinely available patient characteristics. There is a wide distribution in ARR that may complement informed decision making.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00327418 (CARDS) and NCT00000542 (ALLHAT). (Circ Cardiovasc Qual Outcomes. 2016;9:213-221. DOI: 10.1161/CIRCOUTCOMES.115.001980.)

Key Words: cardiovascular diseases ■ decision making, shared ■ diabetes mellitus ■ precision medicine ■ statins, HMG-CoA ■ treatment outcome

Statin therapy is effective in preventing major cardiovascular events in patients with type 2 diabetes mellitus with an average relative risk reduction that is similar to the effect of statins in patients without type 2 diabetes mellitus.1 Based on this, guidelines recommend statin therapy for most patients with type 2 diabetes mellitus.2,3 In clinical practice, decision...
WHAT IS KNOWN

• Moderate-intensity statin therapy shows a significant relative reduction in risk of cardiovascular events in patients with type 2 diabetes mellitus.

• Individualized absolute effects from statin therapy, instead of average relative effects, are more informative for patients and clinicians and may contribute to shared decision-making as part of personalized cardiovascular medicine.

WHAT THE STUDY ADDS

• There is a wide distribution in 10-year absolute treatment effects of moderate-intensity statin therapy in patients with type 2 diabetes mellitus, ranging from low to high absolute risk reductions.

• The net benefit of applying a prediction model for selective treatment of patients with type 2 diabetes mellitus with a statin is higher than a strategy in which all patients are treated, especially for 10-year numbers willing to treat of ≤50.

• Individualized predicted absolute risk reductions can therefore be used for informed clinical decision-making for statin therapy in patients with type 2 diabetes mellitus.

making goes beyond relative effects from randomized trials and general recommendations from guidelines. Trial results are average effects on a group level and the effect in absolute risk terms for the individual patient depends on a patient’s specific characteristics. The absolute risk reduction (ARR) that can be expected for a patient provides information to discuss the individual benefit for statin therapy. Moreover, informed decisions about additional interventions to reduce the risk of cardiovascular events, such as potent statin therapy, or novel lipid-lowering therapies with biologicals, depend on the expected remaining risk of cardiovascular events when a patient is on moderate-intensity statin therapy. By translating trial results and guideline recommendations to an expected benefit for the individual patient, individualized treatment effects may contribute to shared decision-making as part of personalized cardiovascular medicine.4

Subgroup analyses, a traditional approach to individualize treatment effects, have not displayed any significant heterogeneity in the relative effect of statins in patients with type 2 diabetes mellitus between most subgroups examined.1 However disadvantages of subgroup analysis should be acknowledged, including that only 1 characteristic is studied at a time, whereas treatment effects are likely to be determined by a combination of patient characteristics.5-7 Estimated treatment effects based on several patient characteristics, as well as the expected remaining risk when a patient is treated with a statin, might be more informative than average effects and recommendations from guidelines for both patients and clinicians. Therefore, we aimed to develop and validate a multivariable prediction model for ARR of major cardiovascular events by statin therapy for individual patients with type 2 diabetes mellitus.

Methods

Analyses were performed in data from 9441 patients with type 2 diabetes mellitus from 3 randomized trials: the Lipid Lowering Arm of the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT-LLA), the Collaborative Atorvastatin Diabetes Study (CARDS; ClinicalTrials.gov Identifier: NCT00327418), and the Lipid-Lowering Trial subgroup from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT; ClinicalTrials.gov Identifier: NCT00000542).8-13 In short, ASCOT-LLA included patients aged 40 to 79 years in the United Kingdom and Scandinavia with hypertension and ≥3 cardiovascular risk factors, without previous coronary heart disease.14 The effect of 10-mg atorvastatin was compared with placebo among a subgroup of patients with type 2 diabetes mellitus with total cholesterol levels ≤6.5 mmol/L (ALLHAT-LLT included patients in North America aged ≥50 years with hypertension and at least 1 additional risk factor. Pravastatin 40 mg was compared with usual care in patients with triglycerides lower than 4.0 mmol/L and low-density lipoprotein-cholesterol between 3.1 and 4.9 mmol/L (2.6–3.3 mmol/L if they had a history of cardiovascular events).12 Twenty-eight patients (0.7%) were excluded because follow-up time was missing. In CARDS, patients aged 40 to 75 years with type 2 diabetes mellitus, low-density lipoprotein-cholesterol ≤4.14 mmol/L, triglycerides ≤0.78 mmol/L, and no history of cardiovascular disease but with at least 1 additional risk factor were recruited in the UK and the Republic of Ireland and randomized to atorvastatin 10 mg or placebo.5 The effect of statin therapy in ALLHAT was relatively low and nonsignificant (hazard ratio for major cardiovascular events in patients with type 2 diabetes mellitus, 0.85; 95% confidence interval [CI], 0.71–1.02), which was probably partly because of a relatively high crossover to statin treatment in the nonblinded usual care arm (17% by 4 years). Nevertheless, pravastatin 40 mg and atorvastatin 10 mg result in similar reductions in event rates and are both considered moderate-intensity statins.11 Therefore in this study, we refer to moderate-intensity statin therapy rather than atorvastatin or pravastatin.

To enable external validation of the developed model, we decided to perform model development in 1 data set and to reserve the other 2 for model validation. For model derivation, the ASCOT data were used because the cardiovascular risk of the ASCOT population is in between the ALLHAT and CARDS populations (yearly event rate 1.9% in ASCOT, 2.6% in ALLHAT, and 1.6% in CARDS) and ASCOT is a relatively heterogeneous population because of their inclusion criteria (eg, patients with and without vascular disease and geographically diverse). We therefore expected a model fitted in ASCOT to result in the most generalizable model. Because trials generally are selected populations, a sensitivity analysis was performed by testing the performance of the presented model in an observational population. For this, data from the observational Dutch Second Manifestations of Arterial Disease (SMART) cohort15 were used of 1758 patients with type 2 diabetes mellitus (Table I in the Data Supplement) with and without a history of vascular disease that were enrolled between 1996 and 2013 and followed up every 6 months in which 303 major cardiovascular events observed during a median of 6.1-year follow-up (interquartile range [IQR], 3.1–9.4).

The applied criteria for diagnosis of type 2 diabetes mellitus in the study populations are shown in Table II in the Data Supplement. End points were adjudicated by investigators (ALLHAT) and independent, blinded End point Committees (ASCOT and CARDS 10% of the end points in ALLHAT). All trials obtained approval from institutional review boards and all participants provided written informed consent. Throughout the article, the data sets are referred to as ASCOT, ALLHAT, and CARDS.

Model Development

A Cox proportional hazards model was fitted including 8 prespecified predictors measured at baseline and on literature and whether predictors were measured in the 3 trials. These included the 5 most frequently used predictors in cardiovascular risk models17: age, sex, current smoking, systolic blood pressure, and a measure of blood lipids. Non–high-density lipoprotein cholesterol (total minus high-density lipoprotein cholesterol) was chosen as measure of dyslipidemia,
being easily calculated, having good predictive value for cardiovascular events, and being increasingly recommended in guidelines to be used in clinical practice. 18–20 The other 3 predictors were history of cardiovascular events, fasting plasma glucose level, and treatment allocation (statin or placebo). History of cardiovascular events was a self-reported or physicians’ record of overt clinically manifest disease including peripheral artery disease, coronary heart disease, or cerebrovascular disease. In ASCOT, this variable consisted of a history of vascular disease other than coronary heart disease because this was an exclusion criterion. CARDS included a few patients with nonsevere peripheral artery disease. Fasting plasma glucose was chosen because hemoglobin A1c (HbA1c) or details on diabetes mellitus duration were not available in ASCOT and ALLHAT. No additional predictor selection was performed because the predefined predictors were known predictive for cardiovascular disease. 21 The outcome of interest was a composite of nonfatal myocardial infarction, nonfatal ischemic or hemorrhagic stroke, and cardiovascular death, which was chosen because this is a clinically relevant outcome and is the most accepted outcome for prediction models in clinical guidelines. In ASCOT, 164 major cardiovascular events occurred during a median follow-up of 3.2 years, this was 454 in ALLHAT during 4.5 years, and 172 in CARDS during 4.0 years. To obtain reliable predictions, the baseline survival of the model was estimated at the median follow-up time in ASCOT and extrapolated to 10 years to result in predictions that are consistent with the 10-year time span that is generally applied in clinical guidelines. Linear extrapolation of the baseline hazard was performed, assuming a constant hazard and thus exponential survival over time, which is a reasonable assumption for cardiovascular disease. 22 Multivariable effect modification was tested by comparing a model with all interactions between treatment allocation and single predictors to the model without interactions with a likelihood ratio test. No single interactions with treatment effect were tested because previous literature has not displayed any significant heterogeneity in the relative treatment effect between most subgroups examined, suggesting that an interaction between statin treatment and single patient characteristics is unlikely. 1 Second, an interaction between baseline cardiovascular risk and treatment allocation was tested in all 3 data sets. Significance levels for likelihood ratio test and interaction terms were set at a P=0.05.

Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers because outliers may be unrealistic values and may be of such influence to the effect estimates that this limits generalizability of the model to patients outside the derivation data set. 21 Linearity of continuous predictors was assessed with restricted cubic splines and transformed if this improved model fit based on Akaike’s Information Criterion. 21 Proportional hazard assumptions were evaluated using scaled Schoenfeld residuals. Missing data were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming these values were missing at random because excluding patients with missing values may lead to bias and loss of statistical power and we did not consider a multiple imputation technique of additional value as we were interested in the predictor coefficients (rather than the uncertainty around the coefficients for which multiple imputation is recommended). 21 Moreover, 3 external populations were available based on which we were able to judge the external validity of the developed model. Analyses were conducted with R statistical software V.3.1.0 and V.3.0.1 (www.R-project.org). This article was written in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines (www.tripod-statement.org). 21

ARR Calculation
Estimated 10-year risks with and without treatment were calculated for each patient. ARR by statin therapy was calculated by subtracting a patient’s predicted risk on treatment, from the predicted risk on placebo/usual care (ARR=-risk off treatment–risk on treatment). Distributions of estimated risk and ARR were shown in histograms. Based on the estimated ARR, a 10-year individualized number needed to treat (tNNT) was calculated (tNNT=1/ARR×100), indicating how many patients with similar characteristics would have to be treated to prevent 1 cardiovascular event. 24

External Validation and Net Benefit
The agreement between quintiles of predicted and observed event-free survival (calibration) was shown in calibration plots and formally tested with the Gronnesby and Borgan goodness-of-fit test. 23 Discrimination was expressed by c-statistics. Because individualized treatment effects may support the process of shared decision making, we aimed to evaluate the net benefit of using such a prediction model for treatment decisions on a population level. A net benefit analysis, as suggested by Vickers et al. 26 was performed for several levels of 10-year numbers willing to treat (NWT in the pooled validation sets (ALLHAT and CARDS). A 10-year NWT is defined as the amount of patients with type 2 diabetes mellitus that one is willing to treat with a statin for 10 years to prevent 1 major cardiovascular event. The NWT thereby defines the threshold (1/NWT×100=threshold ARR) above which the expected benefit from treatment with a statin is considered to outweigh disadvantages of treatment, such as side effects and costs. The NWT is thus subjective and conditional on disadvantages of 10-year treatment. The prediction-guided treatment strategy was compared with treating no one and treating everyone (Methods in the Data Supplement)

Results
Baseline Characteristics
Baseline characteristics of the study populations are shown in Table 1. Baseline low-density lipoprotein-cholesterol varied with an average of 3.0 mmol/L in CARDS, 3.3 mmol/L in ASCOT, and 3.8 mmol/L in ALLHAT as defined by the inclusion criteria of the trials. The percentage of women was relatively low in ASCOT (23%) and CARDS (32%) compared with ALLHAT (52%), and the average blood pressure was higher in ASCOT than in ALLHAT and CARDS. In contrast to ASCOT and CARDS, the ALLHAT population was ethnically heterogeneous and included the highest proportion of patients with a history of cardiovascular events.

Prediction of ARR by Statin Therapy in Individual Patients
The fitted model and its coefficients and hazard ratios are presented in Figure 1 and Table III in the Data Supplement. The addition of treatment interactions with all predictors did not improve model fit (likelihood ratio test, P=0.76). The relative effect of statin therapy was independent of a patient’s baseline cardiovascular risk in all 3 data sets with P values for the interaction term of 0.89, 0.94, and 0.39 in ASCOT, ALLHAT, and CARDS respectively. The predicted and observed event-free survival showed adequate agreement, as presented in the calibration plots in Figure 2 and supported by nonsignificant Gronnesby and Borgan tests (P=0.33 and 0.42 in ALLHAT and CARDS, respectively). Discrimination was moderate with c-statistics of 0.64 (95% CI, 0.61–0.67) in ALLHAT and 0.68 (95% CI, 0.64–0.72) in CARDS. A sensitivity analysis of the validity of the prediction model in observational data from patients with type 2 diabetes mellitus showed similar performance, with a c-statistic of 0.65 (95% CI, 0.61–0.68), and reasonable calibration (Figure I in the Data Supplement and a Gronnesby and Borgan P=0.37), with a tendency toward overestimation of risk in the higher risk patients and underestimation in lower risk patients (expected/observed ratio 0.74;
Figure I in the Data Supplement). Some nonproportionality was observed for the coefficients of sex and fasting glucose ($P=0.03$ and $P=0.02$, respectively), although visual exploration of the residual plots showed reasonable proportionality for both predictors (Figure II in the Data Supplement). Nevertheless, the coefficients for these predictors should be interpreted as the weighted average effect over follow-up. For the other coefficients and the overall model, the proportionality assumption was met.

The median estimated 10-year risk of major cardiovascular events without a statin was 17% (IQR, 13%–23%) in ASCOT, 21% (IQR, 16%–30%) in ALLHAT, and 15% (IQR, 11%–19%) in CARDS (Figure 3). As a consequence of the distribution in cardiovascular risk, the predicted 10-year ARR also varied widely with a median of 3.2% (IQR, 2.5%–4.3%) or a median 10-year iNNT of 31 (IQR, 23%–41%). The 95% CI for an individualized ARR of 3.2% was −1.4% to 6.7% and estimations were most precise for low ARRs (eg, ARR of 1.0%; 95% CI, −0.5% to 2.1%) compared with high ARRs (ARR of 5.0%; 95% CI, −2.2% to 10.7%). ARR by statin therapy was <2% for 13% of the patients with type 2 diabetes mellitus (Figure 3), translating to a 10-year iNNT that

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASCOT</th>
<th>ALLHAT</th>
<th>CARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2725</td>
<td>Missing</td>
<td>n=3906</td>
<td>Missing</td>
</tr>
<tr>
<td>Age (y)</td>
<td>64 (8)</td>
<td>66 (7)</td>
<td>62 (8)</td>
</tr>
<tr>
<td>Female</td>
<td>621 (23)</td>
<td>2035 (52)</td>
<td>909 (32)</td>
</tr>
<tr>
<td>Non-white ethnicity</td>
<td>247 (9)</td>
<td>1824 (47)</td>
<td>162 (6)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>600 (22)</td>
<td>501 (13)</td>
<td>631 (22)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165 (17)</td>
<td>147 (15)</td>
<td>144 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>93 (10)</td>
<td>84 (10)</td>
<td>83 (8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30 (5)</td>
<td>31 (6)</td>
<td>29 (4)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.4 (0.8)</td>
<td>5.8 (0.7)</td>
<td>38 (1)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.3 (0.7)</td>
<td>3.8 (0.6)</td>
<td>44 (1)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>38 (1)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.6 (1.2–2.3)</td>
<td>1.7 (1.2–2.4)</td>
<td>42 (1)</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/L)</td>
<td>4.1 (0.8)</td>
<td>4.6 (0.7)</td>
<td>38 (1)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.5 (2.7)</td>
<td>9.3 (3.7)</td>
<td>818 (21)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>98 (17)</td>
<td>866 (32)</td>
<td>86 (25)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>393 (14)</td>
<td>1171 (30)</td>
<td>97 (3)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>2290 (84)</td>
<td>3606 (92)</td>
<td>1896 (67)</td>
</tr>
</tbody>
</table>

All data are displayed as mean (SD), median (interquartile range) or n (%). Because of inclusion criteria, in ALLHAT, lipid levels are on average lower in patients with a history of CHD (mean LDL-cholesterol, 3.6 mmol/L or without CHD (mean LDL-cholesterol, 3.8 mmol/L). ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo Scandinavian Cardiac Outcomes Trial; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

### Figure 1. Calculation of statin treatment effect on major cardiovascular events for the individual patient with type 2 diabetes mellitus. HDL indicates high-density lipoprotein.
Net Benefit
A translation of the model to clinical practice is shown in Table 2 and the net benefit curve in Figure 4 for a range of 10-year NWT. The treat none line in Figure 4 represents the net benefit of treating no one which is zero for all NWT. For 10-year NWT of <100, the net benefit of using individual predictions for decision making is slightly higher compared with a strategy in which all patients are treated.

Discussion
In this analysis of the ASCOT, ALLHAT, and CARDS data, the ARRs of major cardiovascular events by moderate-intensity statin treatment were predicted in individual patients with type 2 diabetes mellitus. Among these trial participants there is a wide range (from 1% to 8%) in predicted treatment effect. Of all patients with type 2 diabetes mellitus, 13% had <2% 10-year ARR (individualized 10-year NNT >50) and about one third of the patients had a 10-year ARR of >4% (10-year iNNT <25). This distribution in individual ARR is a consequence of the distribution in their baseline absolute cardiovascular risk. Depending on the NWT, prediction-guided clinical decision-making results in slightly higher net benefit compared with treating all patients with type 2 diabetes mellitus. The present findings are consistent with a similar analysis for statin therapy in the primary prevention in patients without diabetes mellitus, in which also a wide variation was found in predicted ARR from statin therapy and the prediction model was associated with a higher net benefit than treating all patients for 10-year NWTs of ≤50. This study shows that these conclusions are also applicable to patients with type 2 diabetes mellitus.

Our findings confirm standard expectations that the relative effect of statin therapy is not affected by a patient's baseline risk in 3 separate type 2 diabetes mellitus populations despite different risk profiles. This finding of a constant relative effect of statin across risk groups is important because it supports a risk-based approach to select patients with type 2 diabetes mellitus for statin therapy, resulting in highest benefit by treating higher risk patients.

Current clinical guidelines recommend statin therapy for the majority of the patients with type 2 diabetes mellitus. The American Diabetes Association and the American College of Cardiology/American Heart Association guidelines, for example, recommend statin therapy for all patients with type 2 diabetes mellitus aged >40 years. The recent National Institute for Health and Care Excellence guidelines introduce risk estimation in patients with type 2 diabetes mellitus and recommend treatment above a 10-year risk threshold of 10%. The appropriate selection strategy for statin use is currently controversial following the publication of the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol. Clearly, clinicians are reluctant to treat all patients regardless of individual characteristics or risk profiles. Individualized estimates of statin treatment effect may be complementary to current guidelines in several ways. First, because adherence to statin therapy is known to be poor, a targeted approach with appropriate informing of the individual patient may improve adherence. Previous studies have shown that communicating individual risk to the patient resulted in marginally better...
control of modifiable risk factors. The potential additional value of communicating predicted treatment effects is just an hypothesis which could be evaluated in a future study. Additionally, because recommendations in guidelines are changing toward a more aggressive lipid-lowering treatment strategy for patients with diabetes mellitus, information about the remaining 10-year risk of cardiovascular events if a patient is treated with a moderate-intensity statin (Figure III in the Data Supplement) can be used to discuss the need for further low-density lipoprotein lowering. Based on the presented model incorporated in electronic patient records or by the use of an online calculator, the estimated effect of statin therapy, as well as the on-treatment remaining risk of the individual patient, can easily be calculated and presented to the patient.

If patient selection for statin therapy would be based on the presented prediction model, this is likely to result in higher net benefit than a strategy in which all patients are treated.

Figure 3. Distribution of estimated absolute 10-y risk of major cardiovascular events and treatment effects of statin therapy. A. Distribution of estimated absolute risks and individualized treatment effects of statin therapy in Anglo Scandinavian Cardiac Outcomes Trial (ASCOT), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and Collaborative Atorvastatin Diabetes Study (CARDS). B. Individualized treatment effects in all 9441 patients with type 2 diabetes mellitus.
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development of prediction-based strategies with application to diabetes mellitus. The treatment threshold indicates net benefit gain in cardiovascular events. Also it should be noted that existing prediction models are not applicable to patients with a history of cardiovascular disease (ASCVD) model, the Joint British Societies 3 (JBS3) calculator, or the British cardiovascular disease risk score (Qrisk) models,17,44,45 are not applicable to patients with a history of cardiovascular events, whereas our study aimed to cover a broad population including patients with a history of cardiovascular disease. Also it should be noted that existing prediction models for patients with type 2 diabetes mellitus are known to perform generally moderate, even after recalibration.6 Moreover, it was recently shown that ARRs estimated with models that are internally developed in trial data result in limited bias compared with predictions based on external risk scores, given that the number of events per predictor does not exceed 10.6 Also the fact that the newly developed model performs well in 2 external validation sets in which the patients differ considerably in baseline characteristics (Table 1) as well as in an observational cohort of patients with type 2 diabetes mellitus (Figure 1 in the Data Supplement) is reassuring for the generalizability of this model to a broad range of patients with type 2 diabetes mellitus.

Finally, as with all risk models, risk predictions include a variable degree of uncertainty. Highest accuracy was seen for the lower ARRs, for which individualized weighing of benefit and disadvantages of treatment is most relevant. The single imputation methods used in this study might have resulted in some overstatement of this precision. Nevertheless, the estimates made are the best available for each individual and the

Table 2. Inferences and Consequences for Clinical Practice

<table>
<thead>
<tr>
<th>Treatment Threshold (in % ARR)</th>
<th>% of Patients Withheld From Treatment*</th>
<th>Mean Tx-Effect (ARR)†, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>&lt;1</td>
<td>3.5</td>
</tr>
<tr>
<td>75</td>
<td>1.3</td>
<td>3.6</td>
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<tr>
<td>50</td>
<td>2</td>
<td>3.8</td>
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<tr>
<td>33</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>&lt;25</td>
<td>&gt;4</td>
<td>5.4</td>
</tr>
</tbody>
</table>

ARR indicates estimated individualized absolute risk reduction; NWT, number willing to treat; and Tx, treatment.

*Percentage of patients that would not be treated with a statin given the 10-year NWT.

†Predicted mean reduction in absolute risk of major cardiovascular events in those patients treated with statin.

Figure 4. Net benefit decision curve for statin therapy in patients with type 2 diabetes mellitus. The treatment threshold indicates the percent of absolute risk reduction.

Importantly, in patients at relatively high risk of cardiovascular events, the net benefit of a prediction-based treatment strategy will be comparable to a strategy in which all patients are treated because high-risk patients are likely to exceed the treatment threshold and therefore will be treated in both scenarios. Therefore, the additional value of a prediction-based strategy lies in selective treatment of patients in the lower risk groups (not exceeding the treatment threshold). Because of inclusion criteria, all patients in this study populations had at least 1 additional risk factor. In daily clinical practice, however, the risk factor distribution is known to be more favorable (eg, lower levels for blood pressure and lipids and less patients with a history of cardiovascular disease compared with the present study populations). Therefore, the net benefit of the prediction model is likely to be even higher in daily clinical practice in which the prevalence of lower risk patients is higher than in the present study populations.

Some limitations of randomized trials are not overcome with the method presented in this study. First, the choice of predictors was limited by the variables available in the 3 trials. For example, we aimed to include a diabetes mellitus specific predictor. Although other measures of diabetes mellitus regulation, such as Hba1c or diabetes mellitus duration, would have been preferred, fasting glucose is known to be strongly correlated to Hba1c and is predictive for cardiovascular disease.41-43 Second, we did not make a comparison with currently existing risk scores. Reasons for this included the fact that risk scores for patients with diabetes mellitus that are currently adopted in clinical guidelines, such as the North American Atherosclerotic Cardiovascular Disease (ASCVD) model, the Joint British Societies 3 (JBS3) calculator, or the British cardiovascular disease risk score (Qrisk) models,17,44,45 are not applicable to patients with a history of cardiovascular events, whereas our study aimed to cover a broad population including patients with a history of cardiovascular disease. Also it should be noted that existing prediction models for patients with type 2 diabetes mellitus are known to perform generally moderate, even after recalibration.6 Moreover, it was recently shown that ARRs estimated with models that are internally developed in trial data result in limited bias compared with predictions based on existing external risk scores, given that the number of events per predictor does not exceed 10.6 Also the fact that the newly developed model performs well in 2 external validation sets in which the patients differ considerably in baseline characteristics (Table 1) as well as in an observational cohort of patients with type 2 diabetes mellitus (Figure 1 in the Data Supplement) is reassuring for the generalizability of this model to a broad range of patients with type 2 diabetes mellitus.

Finally, as with all risk models, risk predictions include a variable degree of uncertainty. Highest accuracy was seen for the lower ARRs, for which individualized weighing of benefit and disadvantages of treatment is most relevant. The single imputation methods used in this study might have resulted in some overstatement of this precision. Nevertheless, the estimates made are the best available for each individual and the

![Figure 4](http://circoutcomes.ahajournals.org/)
uncertainty around that prediction therefore is of less clinical relevance because the point estimate is the most reliable prediction for clinical decision making.

In conclusion, the absolute reduction of cardiovascular risk by moderate-intensity statin therapy and the remaining risk when on statin therapy can be predicted for individual patients with type 2 diabetes mellitus using a prediction model based on trial data. There is a wide range in ARR which is a consequence of the distribution in baseline cardiovascular risk. The approach presented in this article may be of additional value in personalizing cardiovascular medicine in patients with type 2 diabetes mellitus.

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References


Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study
on behalf of the CARDS, ALLHAT, and ASCOT Investigators

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Supplemental Methods Net benefit decision curve

The net benefit decision curve, suggested by Vickers et al., provides the net benefit on group level for several decision-making strategies and for a range of 10-year treatment thresholds. The treatment threshold is the ARR above which the effect of treatment is considered to outweigh disadvantages of treatment, such as side effects and medicalization. For this consideration, a 10-year number willing to treat (NWT) can be defined, expressing the amount of patients that one is willing to treat for 10 years, to prevent one major cardiovascular event. The net benefit on a group level can be increased compared to a strategy in which all patients are treated, by selecting patients that exceed this threshold and not treating those patients for whom burdens of taking medicine exceed the potential individual benefit. Although for statin therapy in patients with type 2 diabetes the 10-year NWT is likely to be high, the NWT may change between guideline makers, health care providers and patients. Therefore the net benefit of ARR-guided treatment decisions was evaluated for several ARR thresholds (thus for several NWTs).

The net benefit represents the balance between benefit and disadvantages of treatment for a specific treatment threshold. The net benefit is calculated as the benefit of treating the subgroup of patients that exceed a predicted ARR treatment threshold, expressed as the decrease in event rate, minus the disadvantages of treatment, expressed as the treatment rate multiplied by the treatment threshold (net benefit = decrease in event rate – treatment rate × treatment threshold, table 2). Since the appropriate threshold may vary between different patients and clinicians, the net benefit was calculated for several treatment thresholds ranging from a 10-year ARR treatment threshold of 0% to 5% (10-year NWT between infinite and 20).

For example, say the 10-year NWT is 50. This means that one is willing to treat 50 patients for 10 years to prevent one major cardiovascular event. The treatment threshold of a 10-year NWT of 50 is 2% (1/50). If this treatment threshold would be applied to all 9,441 study participants, this would result in 87% of the patients being treated with an average ARR on group level of 3.8% (Supplemental table 3). As can be seen from the net benefit curve (figure 3), if a treatment threshold of 2% would be applied on a group level, this would result in similar to slightly higher net benefit than treating all patients.
**Supplemental Table 1. Baseline characteristics of the observational SMART population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SMART (n = 1,758)</th>
<th>missings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>537 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Non-white ethnicity (%)</td>
<td>0 (0)</td>
<td>NA¥</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>436 (25)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>146 (21)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83 (12)</td>
<td>17 (1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29 (5)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.9 (1.4)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.8 (1.1)</td>
<td>164 (9)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.1 (0.3)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>1.7 (1.2-2.5)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/l)</td>
<td>3.7 (1.4)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>8.8 (3.0)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>93 (43)</td>
<td>8 (&lt;1)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>1207 (69)</td>
<td>72 (4)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>1344 (76)</td>
<td>0</td>
</tr>
</tbody>
</table>

*All data are displayed as mean (SD), median (interquartile range) or n (%)*  
¥ In SMART, no details on ethnicity were available, however most participants are of Caucasian ethnicity
**Supplemental Table 2. Diabetes diagnoses in ASCOT, ALLHAT and CARDS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Applied definition of diabetes mellitus type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCOT</strong></td>
<td>Self-reported history <em>and</em> receiving any treatment including dietary advice, oral hypoglycemic agents, or insulin. Participants were also considered to have type 2 diabetes if they had a fasting glucose &gt;6.0 mmol/L and a 2 hour value of ≥11.1 mmol/L after a 75 g oral glucose load at baseline.³</td>
</tr>
<tr>
<td><strong>ALLHAT</strong></td>
<td>Plasma glucose &gt;7.8 mmol/L (fasting) or &gt;11.1 mmol/L (nonfasting) or on oral hypoglycemic agents.⁴</td>
</tr>
<tr>
<td><strong>CARDS</strong></td>
<td>WHO criteria 1985: fasting glucose ≥7.8 mmol/L or ≥11.1 mmol/L 2 hours after a 75 g oral glucose load.⁵</td>
</tr>
<tr>
<td><strong>SMART cohort</strong></td>
<td>Self-reported history of type 2 diabetes, use of oral glucose-lowering therapy or insulin, or a fasting plasma glucose ≥7.0 mmol/L with the start of diabetes treatment (dietary advice, weight reduction, or medication) within 1 year from inclusion.</td>
</tr>
</tbody>
</table>
### Supplemental Table 3. Model coefficients and HRs

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>LRT</th>
<th>p-value</th>
<th>HR</th>
<th>lower.95</th>
<th>upper.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>0.0395</td>
<td>14.0</td>
<td>&lt;0.01</td>
<td>1.04</td>
<td>1.02</td>
<td>1.06</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.1902</td>
<td>1.1</td>
<td>0.30</td>
<td>0.83</td>
<td>0.57</td>
<td>1.19</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.2930</td>
<td>2.4</td>
<td>0.12</td>
<td>1.34</td>
<td>0.93</td>
<td>1.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>0.0017</td>
<td>0.1</td>
<td>0.71</td>
<td>1.002</td>
<td>0.993</td>
<td>1.011</td>
</tr>
<tr>
<td>Non-HDL cholesterol in mmol/l</td>
<td>0.2539</td>
<td>6.8</td>
<td>&lt;0.01</td>
<td>1.29</td>
<td>1.07</td>
<td>1.56</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>0.7655</td>
<td>16.8</td>
<td>&lt;0.01</td>
<td>2.15</td>
<td>1.52</td>
<td>3.04</td>
</tr>
<tr>
<td>Fasting glucose in mmol/l</td>
<td>0.0465</td>
<td>2.4</td>
<td>0.12</td>
<td>1.05</td>
<td>0.99</td>
<td>1.11</td>
</tr>
<tr>
<td>Treatment with statin (versus placebo)</td>
<td>-0.2216</td>
<td>2.0</td>
<td>0.16</td>
<td>0.80</td>
<td>0.59</td>
<td>1.09</td>
</tr>
</tbody>
</table>

*LRT: likelihood ratio test; HR: hazard ratio*
Supplemental Figure 1 External calibration in the observational SMART population of 1,758 patients with type 2 diabetes

Predicted and observed event-free survival for major cardiovascular events within quintiles of predicted risk and plotted at the median follow-up time in SMART, Gronnesby and Borgan p-value 0.37, c-statistic 0.65 (95% CI 0.61-0.68).
Supplemental Figure 2 Plotted Schoenfeld Residuals for the predictors sex and fasting glucose
Supplemental Figure 3 Patient example – calculation sheet

Absolute treatment effect of moderate-intensity statin therapy - Calculation Sheet

Estimating absolute treatment effects for individual patients with type 2 diabetes mellitus based on the results of randomized clinical trials - results from ASCOT-LLA, ALLHAT-LLT and CARDS

10-y risk of major cardiovascular events without treatment

(Will appear once all characteristics are completed)

Sex
Age 62 Years
Current Smoking Yes
History of cardiovascular disease No
Systolic blood pressure 140 mm Hg
Fasting glucose 7.8 mmol/l 4.9 mmol/l
Non-HDL cholesterol (total cholesterol - HDL cholesterol) 3%
10-year treatment effect*

iNNT_{10}^* = 33

* iNNT = individualized NNT
Moderate-intensity statin versus placebo/usual care

Note: only apply to patients that are similar to the type 2 diabetes mellitus patients in ASCOT-LLA, ALLHAT-LLT and CARDS.
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ASCOT Investigators (as published in Lancet 2005; 366: 895–906)


Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000542 (ALLHAT).

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