High-Dose Statin Therapy in Patients with Stable Coronary Artery Disease:
Treating the Right Patients Based on Individualized Prediction of Treatment Effect

Running title: Dorresteijn et al.; High-dose statins in individual patients

Johannes A. N. Dorresteijn, MD, MSc, PhD1; S. Matthijs Boekholdt, MD, PhD2; Yolanda van der Graaf, MD, PhD3; John J. P. Kastelein, MD, PhD4; John C. LaRosa, MD5; Terje R. Pedersen, MD, PhD6; David A. DeMicco, DPharm7; Paul M Ridker, MD, MPH, FACC8; Nancy R. Cook, ScD8; Frank L. J. Visseren, MD, MSc, PhD1

1Dept of Vascular Medicine, University Medical Center Utrecht, Utrecht; 2Dept of Cardiology; 4Dept of Vascular Medicine, Academic Medical Center, Amsterdam, 3Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands; 5State University of New York, Health Science Center, Brooklyn, New York, NY; 6Center for Preventive Medicine, Oslo University Hospital, and University of Oslo, Oslo, Norway; 7Pfizer Inc, New York, New York, NY; 8Div of Preventive Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

Address for Correspondence:
Frank L.J. Visseren, MD, MSc, PhD
Department of Vascular Medicine
University Medical Center Utrecht
P.O. Box 85500
3508 GA Utrecht, The Netherlands
Tel: +31 (0)88 7555161
Fax: +31 (0)30 2523741
E-mail: F.L.J.Visseren@umcutrecht.nl

Journal Subject Codes: Treatment:[122] Secondary prevention
Abstract:

**Background**—Clinicians need to identify coronary artery disease patients for whom the benefits of high-dose versus usual-dose statin therapy outweigh potential harm. We therefore aimed to develop and validate a model for prediction of the incremental treatment effect of high-dose statins for individual patients in terms of reduction of 5-year absolute risk for myocardial infarction, stroke, coronary death or cardiac resuscitation.

**Methods and Results**—Based on data from the Treating to New Targets trial (TNT; n=10,001), a Cox proportional hazards model was developed comprising 13 easy-to-measure clinical predictors: age, sex, smoking, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, history of myocardial infarction, coronary artery bypass grafting, congestive heart failure or abdominal aortic aneurysm, glomerular filtration rate, and treatment status (i.e. atorvastatin 80mg or 10mg). External validation in the Incremental Decrease in End Points Through Aggressive Lipid Lowering trial (IDEAL; n=8,888) confirmed adequate goodness-of-fit and calibration, but moderate discrimination (C-statistic 0.63; 95%CI 0.62-0.65). Still, among participants of both trials combined, the model identified a group of 11.7% whose predicted 5-year number needed to treat (NNT) was 25 or lower and a group of 41.9% whose predicted NNT was 50 or higher. A decision curve shows that making treatment decisions on the basis of predictions using our model may improve net benefit.

**Conclusions**—Estimation of the incremental treatment effect of high-dose versus usual-dose statin therapy in individual coronary artery disease patients enables selection of high-risk patients that benefit most from more aggressive therapy.

**Clinical Trial Registration Information**—www.clinicaltrials.gov. Identifiers: NCT00327691 and NCT00159835.

**Key words**: statins, coronary disease, prevention, treatment effectiveness, prediction
Introduction

Lipid-lowering is the cornerstone of secondary prevention for vascular events in patients with coronary artery disease (CAD). Randomized clinical trials evaluating high-dose versus usual-dose statin therapy have shown that intensive lipid lowering results in additional reduction of vascular events.\textsuperscript{1-6} Despite this high quality evidence of superior effectiveness, high-dose statin therapy is not unequivocally recommended for all patients with stable CAD.\textsuperscript{7,8} This reluctance may be explained by concern about high-dose statins causing higher rates of side-effects such as myalgia, and transaminits.\textsuperscript{1-3} Moreover, intensive treatment is more costly and requires closer follow-up of patients, since high-dose versus usual-dose statin therapy is associated with a somewhat higher risk of developing diabetes mellitus.\textsuperscript{9} Therefore, clinicians need to identify patients who will benefit most from high-dose versus usual-dose statin therapy. Guidelines recommend titration of statin-dose, but only in patients whose low-density lipoprotein (LDL) cholesterol level is not at target.\textsuperscript{7,8} Although this approach seems sensible from a pharmacodynamic perspective, meta-analyses show that the effectiveness of statin therapy in terms of reduction of vascular events does not depend on pre-treatment LDL-cholesterol level.\textsuperscript{6} Instead, the absolute cardiovascular risk reduction achieved by high-dose statin therapy is only proportional to the absolute baseline risk. Previously, Deedwania et al have indicated that selecting patients with the metabolic syndrome or diabetes mellitus is a simple and effective method for identifying high-risk patients whom significantly benefit from high-dose statin therapy.\textsuperscript{10} Such risk stratification, however, may be further improved by taking into account additional patient characteristics.

In the present study we aimed to develop and validate a model, based on multiple clinical patient characteristics, for prediction of treatment effect (i.e. 5-year absolute risk reduction of
major cardiovascular events; MCVEs) of high-dose statin therapy versus usual-dose statin therapy in individual patients with stable CAD. For this purpose we use data from the Treating to New Targets (TNT) trial and the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial.\textsuperscript{1,2} Because such a predicted treatment effect may be used for guiding individual treatment decisions, we also compare the net benefit of a number of strategies to select high-risk patients with stable CAD to qualify for high-dose statin therapy, i.e.: (1) all patients, (2) no patients, (3) patients with the metabolic syndrome or diabetes mellitus, and (4) patients whose predicted treatment effect exceeds a certain threshold. Here we present our results.

Methods

The design, rationale, and outcomes of the TNT and IDEAL trials have been described in detail elsewhere.\textsuperscript{1,2,11,12} In brief, both trials evaluated the efficacy and safety of high-dose statin therapy (i.e. atorvastatin 80 mg) versus usual-dose statin therapy (i.e. atorvastatin 10 mg in TNT and simvastatin 20 or 40 mg in IDEAL) for the prevention of new vascular events in patients with stable CAD. The TNT trial enrolled 10,001 patients in the United States, Europe and Australia with a history of myocardial infarction, angina with objective evidence of atherosclerotic CAD or a history of coronary revascularization. After a median follow-up period of 4.9 years, the hazard ratio for the occurrence of MCVE (i.e. fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, fatal coronary heart disease or resuscitation after cardiac arrest) was 0.78 (95%CI 0.69-0.89) favoring atorvastatin 80 mg. The IDEAL trial enrolled 8,888 patients in Northern Europe with a history of myocardial infarction. After a median follow-up of 4.8 years, the hazard ratio for the occurrence of MCVE was 0.87 (95%CI 0.78-0.98) favoring atorvastatin 80mg.
Model derivation

Based on data from the TNT trial a Cox proportional hazards model was developed for prediction of 5-year treatment effect (i.e. absolute reduction of MCVE risk) of high-dose statin therapy versus usual-dose statin therapy in individual patients with stable CAD using previously described methods.\textsuperscript{13,14} Data from the IDEAL trial were reserved as a validation data set. MCVE was defined by the above described primary end point definition of the TNT-trial. Candidate predictors were based on the Framingham risk score for general cardiovascular disease,\textsuperscript{15} with the addition of a few readily available clinical characteristics of particular importance in secondary prevention. As a result, the following candidate predictors were considered: age, sex, current smoking, diabetes mellitus, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, a history of myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), congestive heart failure (CHF; New York Heart Association, NYHA, class I-IIa) or abdominal aortic aneurysm (AAA), glomerular filtration rate (GFR; estimated using the Modification of Diet in Renal Disease, MDRD, formula\textsuperscript{16}), and treatment status (i.e. atorvastatin 80 mg or usual-dose statin). In accordance with the Framingham risk score, an interaction-variable between systolic blood pressure and blood pressure treatment (yes/no) was considered. Finally, because separate Framingham risk scores exist for men and women, any sex-based interactions were evaluated to allow the effect of risk factors to differ between men and women. Interaction-terms with treatment were not evaluated because modification of relative treatment effect by clinical patient characteristics was not anticipated based on previous studies.\textsuperscript{6}

One or more covariate data were missing in 43 (0.4%) TNT trial participants and these were single imputed by weighted probability matching on the basis of multivariable regression
using covariate and outcome data, since complete case analysis leads to loss of statistical power and possibly to bias. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. If the association between a continuous predictor and the outcome was not linear, the predictor was transformed to improve model fit. As a result, a quadratic term was added for age and GFR to obtain optimal model fit.

First, sex-based interactions with p-values ≥0.05 were removed from the starting model. Next, the model was further simplified by stepwise backward selection on the basis of the Akaike’s Information Criterion (AIC). Although all candidate predictors are well-known risk factors for vascular events and, thus, little optimism was expected, the coefficients of the remaining predictors were penalized by uniform shrinkage. The percentage optimism and appropriate shrinkage factor were determined by bootstrap resampling. Models were fitted for prediction of 5-year MCVE risk. This duration of follow-up was achieved by 4,755 TNT participants (47.5%). The proportional hazard assumption was assessed by testing the correlations between scaled Schoenfeld residuals for the various predictors and time.

Model validation

One or more covariate data were missing in 248 (2.8%) IDEAL participants and these were single imputed using the same methods described above. Likewise, continuous variables were truncated at the 1st and 99th percentile. The discriminatory ability of the model (i.e. the extent to which the model can separate those with and without a MCVE) was expressed by the C-statistic. Model calibration, reflecting the precision of how close the predicted survival-probabilities are to the actual (observed) survival, was demonstrated by calibration plots. In addition, overall goodness-of-fit of both models was assessed in the validation cohort with the Gronnesby and Borgan test.
Risk stratification and net benefit

Data of the TNT and IDEAL trials were combined to determine the ability of the derived model to stratify risk and treatment effect. Predictions of 5-year MCVE risk while on usual-dose statin treatment were made for all trial participants and displayed in a histogram. Similarly, the distribution of predictions of 5-year effect of high-dose versus usual-dose statin treatment was presented in a histogram.

Moreover, we determined the incremental value of treatment decision-making on the basis of predicted treatment effect. Such incremental value is conditional on the estimated harm of unnecessary high-dose statin treatment (i.e. adverse events, inconvenience and costs) and can be expressed in terms of net benefit. By unnecessary treatment we mean high-dose statin treatment of patients who will not have a MCVE even on usual-dose statin treatment. When unnecessary treatment is assumed to be relatively harmless, there is no need for selection and, thus, no rationale for using a prediction model. However, when unnecessary treatment is considered detrimental, the treatment effect needs to be adjusted for treatment harm (i.e. net benefit). To enable adjustment of treatment effect for treatment harm, a quantitative estimate of the latter is needed. For this purpose, treatment harm can be quantified by estimating at which level of MCVE risk the benefits of high-dose statin treatment start to outweigh treatment harm (i.e. the cut-off value for determining high risk). For example, when \( \geq 15\% \) MCVE risk is thought to outweigh treatment harm, the threshold is 15%. This threshold reflects the relative weight of unnecessary treatment of low-risk patients versus correct treatment of high-risk patients and is incorporated in the net benefit calculation.

In this study, we compared the net benefit of selecting patients for high-dose statin therapy based on our prediction model versus the net benefit of treating all patients, no patients
or just the patients with the metabolic syndrome or diabetes mellitus with high-dose statin therapy. Metabolic syndrome was defined by the same criteria used by Deedwania et al as the presence of three or more of the following risk factors: body-mass index of $\geq 28$ kg/m$^2$, triglycerides $\geq 150$ mg/dL (1.7 mmol/L), HDL-cholesterol $\leq 40$ mg/dL (1.0 mmol/L) in men or $\leq 50$ mg/dL (1.3 mmol/L) in women, blood pressure $\geq 130/85$ mmHg, or fasting glucose $\geq 100$ mg/dL (5.6 mmol/L).$^{10}$ We did not evaluate the net benefit of selective administration of high-dose statin treatment to patients whose LDL-cholesterol is not on target ($<70$mg/dL or $<1.8$ mmol/L) during usual-dose statin therapy, like is currently recommended by guidelines.$^7,8$

Because the LDL-cholesterol was $<70$ mg/dL ($\sim 1.8$ mmol/L) in only 4% of trial patients, the net benefit of that strategy is approximately equal to the net benefit of high-dose statin treatment for all patients. Calculations were based on pooled data of control group patients (treated with usual-dose statin) of the TNT and the IDEAL trials. We refrained from making subjective assumptions about the appropriate decision-threshold level and present the net benefit for a range of thresholds in a decision curve.

Analyses were conducted with R statistical software version 2.11.1. (http://www.R-project.org) using add-on packages Design, Hmisc, Survival, Survcomp, stdca (http://www.decisioncurveanalysis.org).

**Results**

**Table 1** shows baseline characteristics of participants of the TNT and IDEAL trials. Patients had a median age of 62 years and were 81% men in both trials. Almost half of patients fulfilled the criteria of the metabolic syndrome. In TNT, baseline lipids were recorded during the run-in phase on atorvastatin 10 mg, whereas in IDEAL baseline lipids were measured with the majority of patients still using lipid-lowering medication (doses not exceeding the equivalent of...
simvastatin 20mg) that was prescribed prior to enrollment. Almost all participants received aspirin or anticoagulants and the majority was using antihypertensive medication. In TNT, 982 MCVEs occurred during 47,369 person-years follow-up (yearly event rate: 2.1%). In IDEAL 1,141 MCVEs occurred during 39,099 person-years follow-up (yearly event rate: 2.9%).

**Model derivation**

Interaction terms for sex-based differences and terms for history of AAA and history of PCI were removed from the starting model during backward selection. Next, coefficients were penalized by a uniform shrinkage factor of 0.965 and the proportional hazards assumption was confirmed. The 16 coefficients of the final model, accompanying likelihood ratio statistics, p-values and (unpenalized) hazard ratios with corresponding 95% confidence intervals are presented in Table 2. The computational formulas for 5-year treatment effect of high-dose versus usual-dose statin treatment are presented in Supplemental table 1. Moreover, a calculation sheet is available as Online-Only Supplement and an example of treatment effect prediction for an individual patient with this calculation sheet is demonstrated in Figure 1.

**Model validation**

The model C-statistic was 0.67 (95%CI 0.65-0.68) in its derivation sample (i.e. TNT), and 0.63 (95%CI 0.62-0.65) in the validation sample (i.e. IDEAL). The calibration plots of 5-year predicted versus observed event-free survival (i.e. 1-risk) in the derivation and validation sample (Figure 2A and B) show that model calibration was excellent. The p-values of the Gronnesby and Borgan tests were 0.65 in the derivation sample and 0.30 in the validation sample, thus confirming satisfactory goodness-of-fit.

**Risk stratification**

The median 5-year MCVE risk of patients on usual-dose statin therapy was 11% [interquartile...
range 8-15%. **Figure 3A** shows that 44% of patients had ≤10% predicted baseline MCVE risk, 43% had intermediate (10 to <20%) predicted MCVE risk, and 13% had ≥20% predicted 5-year MCVE risk. As a consequence, predicted treatment effect of high-dose versus usual-dose statin therapy also varied widely (**Figure 3B**). The median absolute reduction of 5-year MCVE risk was 2.2% [IQR 1.6-3.1%; 5-year number needed to treat, NNT 45]. However, 41.9% of patients had <2% predicted treatment effect (5-year NNT>50) and 46.4% of patients had 2 to 4% predicted treatment effect (5-year NNT between 25 and 50). A total of 11.7% of patients had >4% predicted reduction of absolute 5-year MCVE risk (5-year NNT <25).

The decision curve in **Figure 4** presents the net benefit of decision-making on the basis of model predictions at a range of thresholds of clinical relevance. The appropriate decision-threshold level is subjective and conditional on the estimated harm (i.e. adverse events, inconvenience and costs) of unnecessary high-dose statin treatment. A low threshold is appropriate when estimated harms are low and vice versa. For threshold levels between ~6% and ~23% 5-year MCVE-risk, prediction-based treatment is associated with higher net benefit than making the same decisions for all patients (i.e. atorvastatin 80 mg for all or usual-dose statin treatment for all).

In other words, **Figure 4** shows that if treatment of patients with <6% 5-year MCVE-risk with atorvastatin 80mg instead of usual-dose statin is acceptable, the strategy that leads to optimal net benefit is to simply prescribe atorvastatin 80 mg to all. The median treatment effect will then be 2.0% reduction of absolute MCVE risk (effective NNT=49; **Table 3**). If a threshold between ~6% and ~23% is considered appropriate, more selective prediction-based treatment can reduce the treatment rate and average NNT. For example, if treatment is reserved for patients with ≥15% 5-year MCVE risk, the treatment rate is only 26% of CAD patients and the effective
NNT decreases to 26 (Table 3). If a 5-year NNT of $\geq 21$ is still considered unacceptably high, our prediction model is not able to identify patients whose MCVE risk is high enough for the benefits of treatment to outweigh treatment harm. In that situation, maximum net benefit is achieved by treating all patients with usual-dose statins. Selective high-dose treatment of patients with the metabolic syndrome or diabetes mellitus is not associated with the highest net benefit at any decision-threshold level. If this was the strategy of choice, however, the treatment rate would be 49% and the average treatment effect 2.8% (NNT=36).

**Discussion**

The present study shows that prediction of the incremental treatment effect of high-dose versus usual-dose statin therapy in individual coronary artery disease patients by means of a multivariable prediction model enables selection of high-risk patients that benefit to a larger extent than other participants in the study. The prediction model presented in this paper is based on 13 clinical patient characteristics that are readily available in clinical practice without the need for additional diagnostic tests. Based on this prediction model we show that the 5-year MCVE risk varies widely and, thus, that the predicted treatment effect of high-dose statin therapy in terms of absolute reduction of 5-year MCVE risk has a wide range, even within the seemingly homogeneous group of patients with stable CAD who participated in the TNT and IDEAL trials. Predicted treatment effect was $\leq 2\%$ reduction of 5-year MCVE risk in 41.9% of those patients, meaning that their NNT is 50 or higher. In contrast, a group of 11.7% of patients having $\geq 4\%$ predicted treatment effect was identified, indicating that their NNT is $\leq 25$. In addition, we demonstrate that the discrimination and calibration of our prediction model remain adequate when applied in an external population. Our prediction model can therefore be used in...
clinical practice. Finally, we show that the incremental value of prediction-based treatment is conditional on the estimated harm that is associated with high-dose statin treatment. The estimated harm of treatment needs to be quantified in terms of a decision-threshold. If the threshold ranges between $-6\%$ and $-23\%$, selective treatment with high-dose statins of high-risk patients (i.e. whose predicted treatment effect is higher than average) results in higher net benefit than using the same statin dose (high or low) for everyone. Moreover, prediction-based treatment led to higher net benefit than selective treatment based on the presence of the metabolic syndrome or diabetes mellitus,\textsuperscript{10} meaning that the present risk score provides a superior estimate of absolute risk and treatment effect. Individual treatment-effect prediction can thus be used to reduce the treatment rate, reduce the effective NNT and increase the average treatment effect of patients who receive high-dose statins such as atorvastatin 80 mg.

This post-hoc analysis of the TNT and IDEAL trials addresses an ongoing discussion about appropriate indications for high-dose statin treatment in patients with stable CAD. Historically, results of randomized controlled trials are implemented in clinical practice by either applying the intervention to all patients (in the case of a positive trial result) or to no one (in the case of a negative result). The situation of high-dose statin treatment in patients with stable CAD, however, is different. TNT, IDEAL and a wealth of other studies have provided consistent high-quality evidence of superior effectiveness of high-dose statin over usual-dose statin therapy.\textsuperscript{6} Moreover, there are no indications that effectiveness is lacking in subgroups of CAD patients,\textsuperscript{6} except perhaps those with severe congestive heart failure (NYHA class II-IV),\textsuperscript{23,24} aortic stenosis\textsuperscript{25} or those undergoing hemodialysis.\textsuperscript{26} Still, clinicians are reluctant to use high-dose statin treatment and only do it in a selective subset of CAD-patients, most often those not reaching treatment targets with usual-dose statins. Reasons include a higher frequency of side
effects, although the magnitude of this association is not exactly known. Higher rates of
myopathy were observed during simvastatin 80mg compared with simvastatin 20mg in the
SEARCH trial, but it is often argued that this problem could be specific to simvastatin.3
Moreover, higher rates of myalgia, diarrhea, abdominal pain and nausea were observed during
atorvastatin 80mg in the IDEAL-trial, but this was an open-label trial which could have
influenced adverse event reporting.2 Still, higher rates of adverse reactions were also observed
during double-blind treatment with atorvastatin 80mg versus atorvastatin 10mg in the TNT-trial
(8.1% versus 5.8%, p<0.001), and this led to a higher discontinuation rate.1 In addition, high-
dose statins are associated with a 12% increased relative risk of new-onset diabetes mellitus.9 A
meta-analysis, however, demonstrates that this translates to only a small absolute risk increase:
the average 1-year number needed to harm was 498.9

Nevertheless, treatment guidelines endorse the clinicians’ reluctance and recommend
reserving high-dose statin treatment for patients whose LDL-cholesterol is not on target during
usual-dose statin treatment.7, 8 Yet, because cholesterol treatment is aimed at reducing MCVEs,
not just lowering cholesterol, this apparently obvious recommendation may not be entirely
logical. In fact, meta-analyses demonstrate that the relative treatment effect of statin therapy for
reducing MCVEs is not dependent on baseline LDL-cholesterol level.6 Importantly, in the
absence of such modification of relative treatment effect, absolute treatment effect of high-dose
statin therapy (i.e. reduction of absolute MCVE risk) is proportional to the patient’s absolute
MCVE risk. Of course, LDL-cholesterol level can be considered as one of the indicators of risk
in this respect. However, other patient characteristics or multiple characteristics combined may
be superior predictors of MCVE risk.

Barriers towards widespread implementation of prediction models in clinical practice
include the complexity of computing treatment effect for individual patients and the fact that it is
time-consuming. Simple decision-algorithms are, therefore, preferred, whereas 13 patient-
specific variables were required for treatment effect estimation using the model presented in this
paper. However, the patient characteristics that are required for estimation of treatment effect
with the present prediction model are easy to measure and usually already available in practice.
Furthermore, the calculation sheet presented in the **Supplemental material** facilitates treatment
effect estimation in the consulting room by simply entering these patient specific variables.
Apart from improvement of net benefit, individualized treatment effect prediction may have
important additional advantages. First, it can be used by the clinician to educate patients about
their individual prognosis and risk factors for recurrent events. This may improve patients’
understanding of the disease and the need for preventive treatment. Second, it enables patients to
be involved in treatment decision-making. The calculation sheet’s interactive bar graph
demonstrates potential treatment effect in an insightful manner. Since patients’ disagreement
with the need for treatment is one of the main reasons for non-adherence, the shared decision-
making may increase patient compliance. This is important, because the adherence-rate to self-
administered treatments is typically only 50%, thereby seriously compromising the effect of
preventive therapy. Experience with a similar health decision aid shows that implementation in
routine clinical practice is feasible, increases patients’ perception of shared decision-making, and
reduces patients’ anxiety.

Limitations of the present study include the fact that our prediction model is derived from
a trial population that was selected on the basis of strict eligibility criteria. Participants of the
TNT trial were, for example, ≤75 years, were not allowed to have a left ventricular ejection
fraction <30%, and did not have any survival-limiting diseases other than CAD. It is, therefore,
uncertain whether predictions of our model can be generalized to patients who do not fit the TNT trial eligibility profile. Furthermore, as atherosclerosis is a systemic progressive condition, many CAD patients have multiple manifestations of disease. Although concomitant cerebrovascular disease, aortic aneurysmal disease, and peripheral artery disease were allowed, the prevalence of these conditions in the TNT and IDEAL populations was low. For example, an AAA was present in only 101 TNT participants (1%). Although we know from previous research that having multiple disease manifestations is a strong risk factor for recurrent vascular events, the low prevalence of AAA in this population explains why its regression coefficient did not reach statistical significance and was removed from the model. Participants of the IDEAL trial were even more homogeneous, since all had a history of a definite myocardial infarction.12 This explains why the C-statistic of our prediction model was considerably lower in the IDEAL dataset than in the derivation set. In fact, the C-statistics that we found in this study may be considered low for a risk score in an asymptomatic population. Yet, the distribution of predicted treatment effect (Figure 3B) shows that the model can still discriminate patients whose expected gain from high-dose statin treatment is considerably higher than average. Furthermore, the decision curve (Figure 4) demonstrates that using model predictions for treatment assignment can improve net benefit at clinically relevant threshold levels. We recognize that the model’s discrimination could be further improved by including additional information on biomarkers, such as C-reactive protein (hs-CRP), or imaging, such as carotid intima-media thickness or coronary CT-angiography. Yet, because such information is not readily available for most patients, this would come at the expense of more limited applicability in clinical practice. Also, due to limited duration of follow-up in trials, models like these can only predict treatment effect for a certain duration of follow-up (in this case 5 years), while statins are usually prescribed
lifelong in practice. It may be argued that patients with low predicted 5-year treatment effect, still benefit from high-dose statins after a longer time period. Finally, although the treatment arms of the trial were pooled for derivation of the prediction model, this does not violate the randomized distribution of the study interventions. Therefore, we stress that treatment effect predictions on the basis of this model are not vulnerable to confounding bias.

**Conclusions**

The incremental treatment effect of high-dose statin therapy over usual-dose statin therapy in individual CAD-patients can be estimated by a prediction model, containing 13 easy-to-measure clinical predictors that are readily available in clinical practice. Predicted treatment effect can be used to guide treatment decisions in clinical practice and this may improve net benefit of therapy.

**Funding Sources:** This study was not supported by any funding. The TNT and IDEAL trials were funded by Pfizer. **Role of the sponsors:** The sponsors of the contributing trials provided the requested data, but they did not play any role in the statistical analysis.

**Conflict of Interest Disclosures:** Dr. Boekholdt reports receipt of consultancy fees from Pfizer. Dr Kastelein reports receipt of lecture honoraria from Merck Sharpe & Dohme, Roche, Novartis, ISIS, Genzyme, Pfizer, Kowa, and AstraZeneca. Dr LaRosa reports receipt of consultancy fees from Pfizer and Amgen; and travel expenses from Pfizer. Dr Pedersen reports receipt of research grant support and lecture fees from Pfizer. Dr DeMicco reports having stock/stock options with and being a full-time employee of Pfizer. Dr Ridker reports receipt of research grant funding from Novartis and AstraZeneca; serving as a consultant to ISIS, Vascular Biogenics, Merck Sharpe & Dohme, Abbott, and Boerringer-Ingelheim; board membership with Merck Sharpe & Dohme; receipt of a grant or pending grant to his institution from Amgen; and being listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to

16
AstraZeneca and Siemens. Dr. Visseren’s department receives grant support from the Netherlands Organisation for Health research and Development, and the Catharijne foundation Utrecht; and speaker fees from Merck. Dr. Dorrestijn, van der Graaf, and Cook reported no conflicts of interest.

References:


Table 1. Characteristics of TNT and IDEAL participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TNT (N=10,001)</th>
<th>IDEAL (N=8,888)</th>
<th>Total (N=18,889)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>62 [55 to 68]</td>
<td>62 [55 to 69]</td>
<td>62 [55 to 69]</td>
</tr>
<tr>
<td>Male sex</td>
<td>8,099 (81%)</td>
<td>7,187 (81%)</td>
<td>15,286 (81%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1,341 (13%)</td>
<td>1,838 (21%)</td>
<td>3,179 (17%)</td>
</tr>
<tr>
<td>Past smoking</td>
<td>6,322 (63%)</td>
<td>5,191 (58%)</td>
<td>11,513 (61%)</td>
</tr>
<tr>
<td>Systolic blood pressure [mmHg]</td>
<td>130 [120 to 140]</td>
<td>135 [120 to 150]</td>
<td>130 [120 to 145]</td>
</tr>
<tr>
<td>Diastolic blood pressure [mmHg]</td>
<td>80 [70 to 84]</td>
<td>80 [74 to 87]</td>
<td>80 [70 to 85]</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>27.9 [25.5 to 30.7]</td>
<td>26.9 [24.7 to 29.4]</td>
<td>27.4 [25.1 to 30.1]</td>
</tr>
</tbody>
</table>

**Medical History:**
- Myocardial infarction: 5,834 (58%) 8,879 (100%) 14,713 (78%)
- Cerebrovascular event: 517 (5%) 655 (7%) 1,172 (6%)
- Abdominal aortic aneurysm: 101 (1%) 76 (1%) 177 (1%)
- Percutaneous coronary intervention: 5,407 (54%) 2,052 (23%) 7,459 (40%)
- Coronary artery bypass grafting: 4,654 (47%) 1,769 (20%) 6,423 (34%)
- Congestive heart failure: 781 (8%) 537 (6%) 1,318 (7%)
- Diabetes mellitus: 1,501 (15%) 1,069 (12%) 2,570 (14%)
- Metabolic syndrome: 4,686 (47%) 3,948 (44%) 8,634 (46%)

**Laboratory assessment:**
- Total cholesterol [mg/dL]: 173 [158 to 190] 193 [170 to 220] 180 [162 to 201]
- HDL-cholesterol* [mg/dL]: 45 [39 to 53] 46 [39 to 54] 45 [39 to 53]
- Triglycerides [mg/dL]: 135 [101 to 183] 133 [97 to 177] 133 [98 to 181]
- eGFR† [mL/min/1.73m²]: 65.1 [58.1 to 72.2] 67.8 [59.6 to 76.4] 66.1 [58.5 to 74.1]

**Medication use:**
- Any antihypertensive medication: 7,916 (79%) 8,006 (90%) 15,922 (84%)
- Aspirin: 8,653 (87%) 7,033 (79%) 15,686 (83%)
- Statin [prior to enrolment]: 6,203 (62%) 6,713 (76%) 12,916 (68%)

Data are presented as median [interquartile range] or Number (percentage). * HDL = high density lipoprotein, †eGFR = glomerular filtration rate, estimated by the Modification of Diet in Renal Disease (MDRD) equation.
Table 2. Coefficients of the treatment effect prediction model.

<table>
<thead>
<tr>
<th></th>
<th>Model coefficient</th>
<th>LRT Statistics</th>
<th>P-value</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>in years</td>
<td>-0.0478</td>
<td>12.8*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age squared</td>
<td>in years</td>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>if male</td>
<td>0.3147</td>
<td>12.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td></td>
<td>0.4097</td>
<td>38.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of CABG †</td>
<td></td>
<td>0.2263</td>
<td>12.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td></td>
<td>0.4694</td>
<td>25.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td></td>
<td>0.6172</td>
<td>32.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>0.4318</td>
<td>30.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td>0.5379</td>
<td>38.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>per 10 mg/dL</td>
<td>0.0042</td>
<td>9.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-cholesterol ‡</td>
<td>per 10 mg/dL</td>
<td>-0.0130</td>
<td>15.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>eGFR §</td>
<td>mL/min/1.73m²</td>
<td>-0.0605</td>
<td>11.7*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>eGFR § squared</td>
<td>mL/min/1.73m²</td>
<td>0.0004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure [treated or not]</td>
<td>per 10 mmHg</td>
<td>0.0371</td>
<td>3.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Systolic blood pressure [if on treatment]</td>
<td>per 10 mmHg</td>
<td>0.0254</td>
<td>14.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High-dose statin</td>
<td>vs. usual dose statin</td>
<td>-0.2411</td>
<td>15.2</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* The risk model contains linear and squared terms for age and eGFR. Therefore, the chi-square and p-value of age and eGFR are computed for both terms together. Furthermore, hazard ratios were computed for the difference between the study population’s 75th and the 25th percentile of age (i.e. 69 versus 55 years) and eGFR (i.e. 72 versus 58 mL/min/1.73m²). † CABG — coronary artery bypass grafting. ‡ HDL — high-density lipoprotein. § eGFR — glomerular filtration rate, estimated by the Modification of Diet in Renal Disease (MDRD) equation. || LRT = Likelihood Ratio Test. ¶ Uniform shrinkage was applied to the coefficients but not the hazard ratios, because penalization increases external validity of the model overall, yet leads to underestimation of the importance of the individual risk factors.
Table 3. Inferences and consequences for clinical practice.

<table>
<thead>
<tr>
<th>Tx threshold (5-year MCVE risk)</th>
<th>Tx strategy associated with optimal NB</th>
<th>Tx rate†</th>
<th>Median Tx effect (ARR) ‡</th>
<th>5-year NNT to prevent 1 MCVE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6%</td>
<td>Treat all with high-dose statin</td>
<td>100%</td>
<td>2.0%</td>
<td>49</td>
</tr>
<tr>
<td>10%</td>
<td>Prediction-based Tx</td>
<td>56%</td>
<td>2.9%</td>
<td>34</td>
</tr>
<tr>
<td>15%</td>
<td>Prediction-based Tx</td>
<td>26%</td>
<td>3.9%</td>
<td>26</td>
</tr>
<tr>
<td>20%</td>
<td>Prediction-based Tx</td>
<td>13%</td>
<td>4.8%</td>
<td>21</td>
</tr>
<tr>
<td>&gt;23%</td>
<td>Treat all with usual-dose statin</td>
<td>0%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Tx = treatment, NB = net benefit. † Percentage treated with atorvastatin 80mg instead of usual dose statin. ‡ Median reduction of absolute risk (ARR) for major cardiovascular events (MCVE) achieved by atorvastatin 80mg versus usual dose statin in treated patients.
Figure Legends:

**Figure 1.** Example of high-dose statin treatment effect prediction for an individual patient with the calculation sheet available online. This 65-year old non-smoking male with a medical history of CABG following myocardial infarction who has on-target blood pressure while on medication, stage 3 kidney disease, and whose cholesterol is not on-target despite low-dose statin therapy, has 18% 5-year MCVE risk. High-dose statin treatment could reduce his MCVE risk by 4%, meaning that the number of similar patients that need to be treated during 5 years to prevent one MCVE (NNT) is 25. This patient, however, will still have 14% residual MCVE risk.

**Figure 2.** Calibration plots. Predicted and observed event free survival (i.e. 1-risk) within deciles of predicted survival at 5-years in the derivation sample (i.e. the TNT-cohort; panel A) and the validation sample (i.e. the IDEAL-cohort; panel B).

**Figure 3.** Distribution of predicted baseline MCVE risk and treatment effect of high-dose versus usual-dose statin that is derived thereof. A) Distribution of predicted baseline 5-year MCVE risk among all participants of the TNT and IDEAL trials (given usual-dose statin use). B) Deducted from A: distribution of predicted 5-year treatment effect of atorvastatin 80mg (5-year absolute risk reduction, ARR for MCVEs). NNT = number needed to treat.

**Figure 4.** Decision curve. Graphical representation of net benefit at a range of decision-thresholds. Net benefit is a measure by which the correct identification of high-risk patients is weighed against over diagnosis of non-disease. The relative weight of over diagnosis of non-disease (leading to unnecessary treatment) is dependent the severity of treatment harm (i.e.
adverse events, inconvenience and costs). These harms are reflected by the decision-threshold. For example, when treatment harm is thought to be equivalent to the treatment effect in patients having 15% MCVE risk, the decision-threshold is 15%. Tx = treatment. LDLc = low-density lipoprotein cholesterol. MS = Metabolic Syndrome. DM = Diabetes Mellitus.
Figure 1
Figure 2
Figure 3

A) 5-year MCVE risk on usual-dose statin

B) Treatment effect of high versus usual-dose statin (ARR for MCVE)
Figure 4
High-Dose Statin Therapy in Patients with Stable Coronary Artery Disease: Treating the Right Patients Based on Individualized Prediction of Treatment Effect
Johannes A. N. Dorresteijn, S. Matthijs Boekholdt, Yolanda van der Graaf, John J. P. Kastelein, John C. LaRosa, Terje R. Pedersen, David A. DeMicco, Paul M Ridker, Nancy R. Cook and Frank L. J. Visseren

Circulation. published online May 14, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2013/05/14/CIRCULATIONAHA.112.000712

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2013/05/14/CIRCULATIONAHA.112.000712.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

TO

High-dose statin therapy in patients with stable coronary artery disease: treating the right patients based on individualized prediction of treatment effect.


N.R. Cook, F.L.J. Visseren
Supplemental table 1

Computational formula for 5-year absolute treatment effect of high-dose versus usual-dose statin treatment in patients with stable coronary artery disease.

<table>
<thead>
<tr>
<th>Predicted 5-year treatment effect of high-dose statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>= (1 - 0.78) x 5-year MCVE risk on usual-dose statin</td>
</tr>
</tbody>
</table>

5-year MCVE risk on usual-dose statin (%) = \(1 - 0.914^{\exp[A + 1.5106]}\) x 100%, where

\[A = -0.0478 \times \text{age in years} + 0.000515 \times \text{(age in years)}^2 + 0.315 \times [\text{if male}] + 0.410 \times [\text{if history of myocardial infarction}] + 0.226 \times [\text{if history of CABG}] + 0.469 \times [\text{if history of congestive heart failure}] + 0.617 \times [\text{if history of cerebrovascular disease}] + 0.432 \times [\text{if diabetic}] + 0.538 \times [\text{if current smoker}] + 0.00419 \times \text{total cholesterol in mg/dL} - 0.0130 \times \text{HDL-cholesterol in mg/dL} - 0.0605 \times \text{eGFR in mL/min/1.73m^2} + 0.000419 \times (\text{eGFR in mL/min/1.73m^2})^2 + 0.00371 \times \text{systolic blood pressure in mmHg} + 0.00254 \times \text{systolic blood pressure in mmHg [if on antihypertensive treatment]}
