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ORIGINAL RESEARCH

Time-Dependent Cardiovascular Treatment Benefit Model for Lipid-Lowering Therapies

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BACKGROUND: With the availability of new lipid-lowering therapy options, there is a need to compare the expected clinical benefit of different treatment strategies in different patient populations and over various time frames. We aimed to develop a time-dependent model from published randomized controlled trials summarizing the relationship between low-density lipoprotein cholesterol lowering and cardiovascular risk reduction and to apply the model to investigate the effect of treatment scenarios over time.

METHODS AND RESULTS: A cardiovascular treatment benefit model was specified with parameters as time since treatment initiation, magnitude of low-density lipoprotein cholesterol reduction, and additional patient characteristics. The model was estimated from randomized controlled trial data from 22 trials for statins and nonstatins. In 15 trials, the new time-dependent model had better predictions than cholesterol treatment trialists' estimations for a composite of coronary heart disease death, nonfatal myocardial infarction, and ischemic stroke. In explored scenarios, absolute risk reduction ≥2% with intensive treatment with high-intensity statin, ezetimibe, and high-dose proprotein convertase subtilisin/kexin type 9 inhibitor compared with high- or moderate-intensity statin alone were achieved in higher-risk populations with 2 to 5 years of treatment, and lower-risk populations with 9 to 11 years of treatment.

CONCLUSIONS: The time-dependent model accurately predicted treatment benefit seen from randomized controlled trials with a given lipid-lowering therapy by incorporating patient profile, timing, duration, and treatment type. The model can facilitate decision making and scenario analyses with a given lipid-lowering therapy strategy in various patient populations and time frames by providing an improved assessment of treatment benefit over time.

Key Words: atherosclerotic cardiovascular disease ■ ezetimibe ■ low-density lipoprotein cholesterol ■ PCSK9 inhibitor ■ statin

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The 2018 American Heart Association/American College of Cardiology guidelines recommend reduction of low-density lipoprotein cholesterol (LDL-C) with high-intensity or maximally tolerated statin therapy in patients with clinical atherosclerotic cardiovascular disease (ASCVD). Similarly, nonstatin therapy with ezetimibe or a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor is now recommended for patients with ASCVD with high-risk features and an LDL-C ≥70 mg/dL on maximally tolerated statin therapy.[1] Despite these guidelines and a wealth of trial evidence, real-world data suggest the utilization and optimal dosing of lipid-lowering therapy (LLT) are far from ideal, even among high-risk patients.[2–4] This may partially stem from the fact that the major clinical trials were typically only run for a finite duration; therefore, there is limited evidence demonstrating the clinical benefit derived from sustained lower LDL-C over time. Moreover, there exist relevant scenarios that have not been investigated previously by randomized controlled trials (RCTs), such as intensive treatment with LLTs in a primary prevention population with diabetes mellitus or other high-risk primary prevention populations. Models derived from past trial evidence can be a useful tool for

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CLINICAL PERSPECTIVE

What Is New?

- A time-dependent model for estimating the clinical benefit with lipid-lowering therapies was estimated from 22 published randomized controlled trials.
- The time-dependent aspect provides an improved assessment of the clinical benefit as compared with estimates utilizing a uniform relative risk reduction per 1 mmol/L reduction in low-density lipoprotein cholesterol.
- The model can be applied to investigate population- and patient-level scenarios representing different at-risk clinical profiles, treatment strategies, and treatment durations.

What Are the Clinical Implications?

- The clinical benefit of lipid-lowering therapy depends on a patient's baseline risk representing existing clinical characteristics, baseline low-density lipoprotein cholesterol level, expected magnitude of low-density lipoprotein cholesterol reduction with treatment, and duration of treatment.
- Although the baseline risk and low-density lipoprotein cholesterol levels represent characteristics before treatment and vary by patients, our model combines these with potential treatment choices and treatment duration to yield the magnitude of expected clinical benefit.
- By facilitating a patient-specific assessment, our model could help patient–physician shared decisions on choice and duration of treatment and help communicate to patients the clinical value of continued therapy and consistent low-density lipoprotein cholesterol reduction over time.

Nonstandard Abbreviations and Acronyms

ARR	absolute risk reduction
ASCVD	atherosclerotic cardiovascular disease
CTT	Cholesterol Treatment Trialists
HIS	high-intensity statin
hsCRP	high-sensitivity C-reactive protein
KM	Kaplan–Meier
LLT	lipid-lowering therapy
MIS	moderate-intensity statin
NNT	number needed to treat
PCSK9	proprotein convertase subtilisin/kexin type 9

evaluating these scenarios as it is not realistic to anticipate RCTs in all populations and treatment strategies of clinical interest.

To facilitate a generalizable assessment of the impact of LDL-C reduction on risk reduction for cardiovascular events, we developed a model from data representing past RCTs of LLTs, including statin trials and more recent nonstatin trials. A key area of focus in our investigation was to accurately model the time-dependent clinical benefit that has been observed in many trials of LLTs. We evaluated the validity of the model by comparing its predictions with trial-reported outcomes and applied the model to investigate the effects of treatment strategies not directly explored in past trials. Specifically, we explored implications of sustained LDL-C reduction over extended (5–15 years) time frames in both primary and secondary prevention populations via different treatment strategies. When taken together with a baseline risk estimate representing the risk before treatment, the final model can be used to estimate the patient- and population-level absolute risk reductions (ARRs) via both statin and nonstatin LLT-based strategies over varying treatment time frames.

METHODS

All supporting data are available within the article. Relevant program codes that support the findings of this study are available from the corresponding author upon reasonable request. Model development used published data from randomized trials of LLTs (statins, ezetimibe, PCSK9 inhibitors, and anacetrapib) involving at least 1000 individuals with end points specified as major cardiovascular events or mortality to match the strategy used by prior meta-analyses and contemporary guidelines.[1,5–7] An initial search of the literature was conducted using references from the American Heart Association/American College of Cardiology guidelines,[1] the Cholesterol Treatment Trialists' (CTT) meta-analysis,[5] and the Silverman et al[6] meta-analysis. These sources were chosen as a pragmatic starting point as they used relatively rigorous criteria in RCT selection along the lines of our study. This was augmented with a PubMed search that included keywords relating to this study (search strategy is provided in Data S1).

The resulting articles were manually reviewed and evaluated according to the inclusion criteria. The following exclusion criteria were then applied: open-label design, reported data not suitable for model estimation, trials involving special populations, and trials with bococizumab (trial stopped early owing to development of antidrug antibodies). A full CONSORT (Consolidated Standards of Reporting Trials) diagram showing the

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application of these criteria is given in Figure S1, and the list of excluded trials is provided in Table S1.[8–23] In addition to the selected RCTs, data from the Mendelian randomization meta-analysis from Ference et al[24] were used as a single study, which informed the model over an extended period of 40 years as compared with the Kaplan–Meier (KM) curves from the RCTs used for estimation.

Model Specification and Estimation

We define the concept of instantaneous relative risk reduction, $\alpha(t)$ as the percent reduction in events with treatment at a moment in time, t. For LLTs, we specify α to depend on time since treatment initiation (t), the magnitude of LDL-C reduction (ΔL), and additional patient characteristics ($\boldsymbol{X}$), and postulate that a universal and generic $\alpha(t, \Delta L, \boldsymbol{X}|\boldsymbol{\beta})$ function can be estimated from the control and treatment arms of RCTs, where $\boldsymbol{\beta}$ denotes model parameters. To facilitate this estimation, we digitized the reported KM curves for a composite end point in selected RCTs and estimated the event rates over time for relevant individual end points within the composite (eg, nonfatal myocardial infarction [MI]) from additional data reported in summary tables in the trials. Once event rates for individual end points were estimated in this manner, we confirmed that we were able to use them to replicate composite event rate curves via a simulation of first events. The LDL-C reduction was trial-reported at median follow-up or taken from another reported summary measure (Table 1).[25–46] All authors had full access to the data in the study and take responsibility for its integrity and the data analysis. This study was exempt from obtaining institutional review board approval and informed patient consent because it constitutes research of published data.

The model parameters, $\boldsymbol{\beta}$, were estimated by defining a cost function, F, as the sum of squares of the error between the model-predicted cumulative event rates over time with treatment [see Data S1 regarding estimation of event rates with treatment from $\alpha(t, \Delta L, \boldsymbol{X}|\boldsymbol{\beta})$], and those reported from the trials. The function F was minimized via the Broyden-Fletcher-Goldfarb-Shannon optimization algorithm in Python, which returned the set of estimated model parameters, $\boldsymbol{\beta}$.[47] We introduced the model covariates, $\boldsymbol{X}$, individually and retained those that improved the concordance between model prediction and actual RCT data. The full mathematical specification and functional form of $\alpha(t, \Delta L, \boldsymbol{X}|\boldsymbol{\beta})$, the rationale, and additional details are provided in Data S1.

Model Performance and Scenario Analyses

We descriptively summarized the model-predicted and trial-reported hazard ratios (HRs) for individual cardiovascular end points including nonfatal MI, ischemic stroke, coronary heart disease (CHD) death, unstable angina requiring hospitalization, and coronary revascularization. We also summarized the model-predicted and trial-reported HRs for the 3-part composite end point representing nonfatal MI, ischemic stroke, and CHD death and used the mean absolute difference of this HR averaged across all trials as a measure of overall model performance. In addition, we summarized these measures based on the 3-part composite using estimates from CTT instead of the current model. A recursive holdout validation was conducted by withholding each trial from estimation, one at a time, and re-estimating model parameters. These parameters were used to predict the end points representing the same 3-part composite of the withheld trial in the validation analysis.

The final model was applied to investigate additional scenarios representing different at-risk populations, treatment strategies, and treatment durations. The populations in these scenarios represented the following risk profiles: recent acute coronary syndrome (ACS), stable ASCVD, diabetes mellitus primary prevention, and primary prevention. The background risk and other characteristics for these populations were based on data from the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), TNT (Treating to New Targets), ASCEND (A Study of Cardiovascular Events in Diabetes), and HOPE (Heart Outcomes Prevention Evaluation) trials, respectively.[36,43,46,48] For each one of these populations, we simulated event rates over periods of 5 to 15 years via treatment with the application of the estimated model, with statins alone, and add-on therapies of ezetimibe and high-dose PCSK9 inhibitor (assumed to be alirocumab 150 mg) as compared with high-intensity statin (HIS).

RESULTS

Twenty-two RCTs met the selection criteria (Table 1). The selected trials included primary and secondary prevention populations, follow-ups ranging from 0.3 to 6.7 years, and treatments including statins, ezetimibe, PCSK9 inhibitors, and anacetrapib. The following covariates were retained in the final model as indicator variables: individual end point types (nonfatal MI, ischemic stroke, CHD death, unstable angina requiring hospitalization, and coronary revascularization), LLT type (PCSK9 inhibitor versus statin or ezetimibe), and high baseline hsCRP (high-sensitivity C-reactive protein) level. Retaining the last variable in the final model resulted in a substantially improved fit for the JUPITER (Justification

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Table 1. Trials Meeting the Selection Criteria and Included in Model Estimation

Trial	Year Published	Population	N	Treatment	Comparator	Follow-Up (y)	LDL-C Reduction (mmol/L)	Measure of LDL-C Reduction	Primary End point
WOSCOPS	1995	Hypercholesterolemia and no history of MI	6595	Pravastatin 40 mg	Placebo	4.9	0.83	Mean difference at median follow-up	Nonfatal MI or CHD death
CARE	1996	MI with average cholesterol levels	4159	Pravastatin 40 mg	Placebo	5	0.98	Mean difference at median follow-up	Fatal coronary event or nonfatal MI
LIPID	1998	History of MI or UA requiring hospitalization with a broad range of initial cholesterol levels	9014	Pravastatin 40 mg	Placebo	6.1	0.97	Mean difference over first 5 y of follow-up	CHD death
MIRACL	2001	ACS within last 1–4 d	3086	Atorvastatin 80 mg	Placebo	0.3	1.63	Mean difference over follow-up	Death, nonfatal acute MI, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency hospitalization
HPS	2002	At-risk for CHD death	20 536	Simvastatin 40 mg	Placebo	5	1.00	Mean difference over follow-up	Fatal or nonfatal vascular events
LIPS	2002	Angina/silent ischemia following first PCI	1677	Fluvastatin 80 mg	Placebo	3.9	0.79	Mean difference at median follow-up	Cardiac death, nonfatal MI, reintervention procedure
PROSPER	2002	Elderly at-risk for cardiovascular disease and stroke	5804	Pravastatin 40 mg	Placebo	3.2	1.02	Mean difference at 2-y follow-up	Coronary death, nonfatal MI, fatal or nonfatal stroke
ASCOT LLA	2003	Hypertensive not deemed dyslipidemic	10 305	Atorvastatin 10 mg	Placebo	3.3	1.00	Mean difference at median follow-up	Nonfatal MI, CHD death
A to Z	2004	Recent ACS	4497	Simvastatin 40/80 mg	Placebo+ Simvastatin 20 mg	2	0.36	Median difference over 4–24 mo follow-up	Cardiovascular death, nonfatal MI, readmission for ACS, stroke
PROVE-IT	2004	ACS within last 10 d	4162	Atorvastatin 80 mg	Pravastatin 40 mg	2	0.85	Median difference at follow-up	All cause death, MI, UA requiring hospitalization, revascularization (at least 30 d after randomization), stroke
CARDS	2004	Diabetes mellitus without ASCVD	2838	Atorvastatin 10 mg	Placebo	3.9	1.20	Mean difference over follow-up	Acute coronary heart disease events, coronary revascularization, stroke
TNT	2005	Stable CHD	10 001	Atorvastatin 80 mg	Atorvastatin 10 mg	4.9	0.62	Mean difference over follow-up	CHD death, nonfatal non-procedure-related MI, stroke, resuscitation after cardiac arrest
IDEAL	2005	History of acute MI	8888	Atorvastatin 80 mg	Simvastatin 20 mg	4.8	0.59	Mean difference over follow-up	Coronary death, nonfatal acute MI, cardiac arrest with resuscitation

(*Continued*)

Table 1. Continued

Trial	Year Published	Population	N	Treatment	Comparator	Follow-Up (y)	LDL-C Reduction (mmol/L)	Measure of LDL-C Reduction	Primary End point
ASPEN	2006	Type 2 Diabetes mellitus	2410	Atorvastatin 10 mg	Placebo	4	0.88	Mean difference at median follow-up	Cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac arrest, worsening or UA requiring hospitalization
SPARCL	2006	Patients with stroke or TIA within 1-6 mo without CHD	4731	Atorvastatin 80 mg	Placebo	4.9	1.44	Mean difference over follow-up	Nonfatal or fatal stroke
JUPITER	2008	Patients with high-sensitivity C-reactive protein levels without hyperlipidemia	17 802	Rosuvastatin 20 mg	Placebo	1.9	1.40	Median difference at 24 mo follow-up	MI, stroke, arterial revascularization, UA requiring hospitalization, cardiovascular death
SEARCH	2010	History of MI	12 064	Simvastatin 80 mg	Simvastatin 20 mg	6.7	0.39	Mean difference at median follow-up	Coronary death, MI, stroke, arterial revascularization
IMPROVE-IT	2015	ACS within the last 10 d	18 144	Simvastatin 40 mg+Ezetimibe	Simvastatin Monotherapy	6	0.41	Mean time-weighted average difference	Cardiovascular death, nonfatal MI, UA requiring hospitalization, coronary revascularization, nonfatal stroke
HOPE	2016	No cardiovascular disease and intermediate risk	12 705	Rosuvastatin 10 mg	Placebo	5.6	0.76	Mean difference at median follow-up	Cardiovascular death, nonfatal MI, nonfatal stroke
FOURIER	2017	ASCVD on statins	27 564	Evolocumab	Placebo	2.2	1.45	Least-squares mean at 48 wk	Cardiovascular death, MI, stroke, UA requiring hospitalization, coronary revascularization
REVEAL	2017	ASCVD on intensive atorvastatin	30 449	Anacetrapib	Placebo	4.1	0.68	Mean difference at trial midpoint	Coronary death, MI, coronary revascularization
ODYSSEY OUTCOMES	2018	ACS 1–12 mo prior	18 924	Alirocumab 75/150 mg	Placebo	2.8	1.05	Mean difference at median follow-up	CHD Death, nonfatal MI, fatal or nonfatal ischemic stroke, UA requiring hospitalizatio

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for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial[40] (absolute deviation for nonfatal MI improved from 23.7%–8.6%). Differences in model predictions with and without inclusion of baseline hsCRP are illustrated in Figure S2. Parameters for the final estimated model and confidence intervals are summarized in Table S2.

A trial-specific HR prediction was made from the estimated model for each individual end point based on the trial-specific assumptions on the follow-up and the magnitude of LDL-C lowering. Figure 1[25–46] depicts a comparison of model-estimated and trial-reported HRs and their confidence intervals for the end points of nonfatal MI, ischemic stroke, and CHD death (other end points are illustrated in Figure S3[25–46]). As an example, the reported HR for nonfatal MI from the TNT trial[36] was 0.78 (0.66, 0.93). The model-estimated HR for this end point based on TNT-specific LDL-C reduction and follow-up was 0.79 (0.75, 0.83). In general, the model confidence intervals were narrower than the trial-reported confidence intervals because the prediction was based on information from all 22 RCTs. The

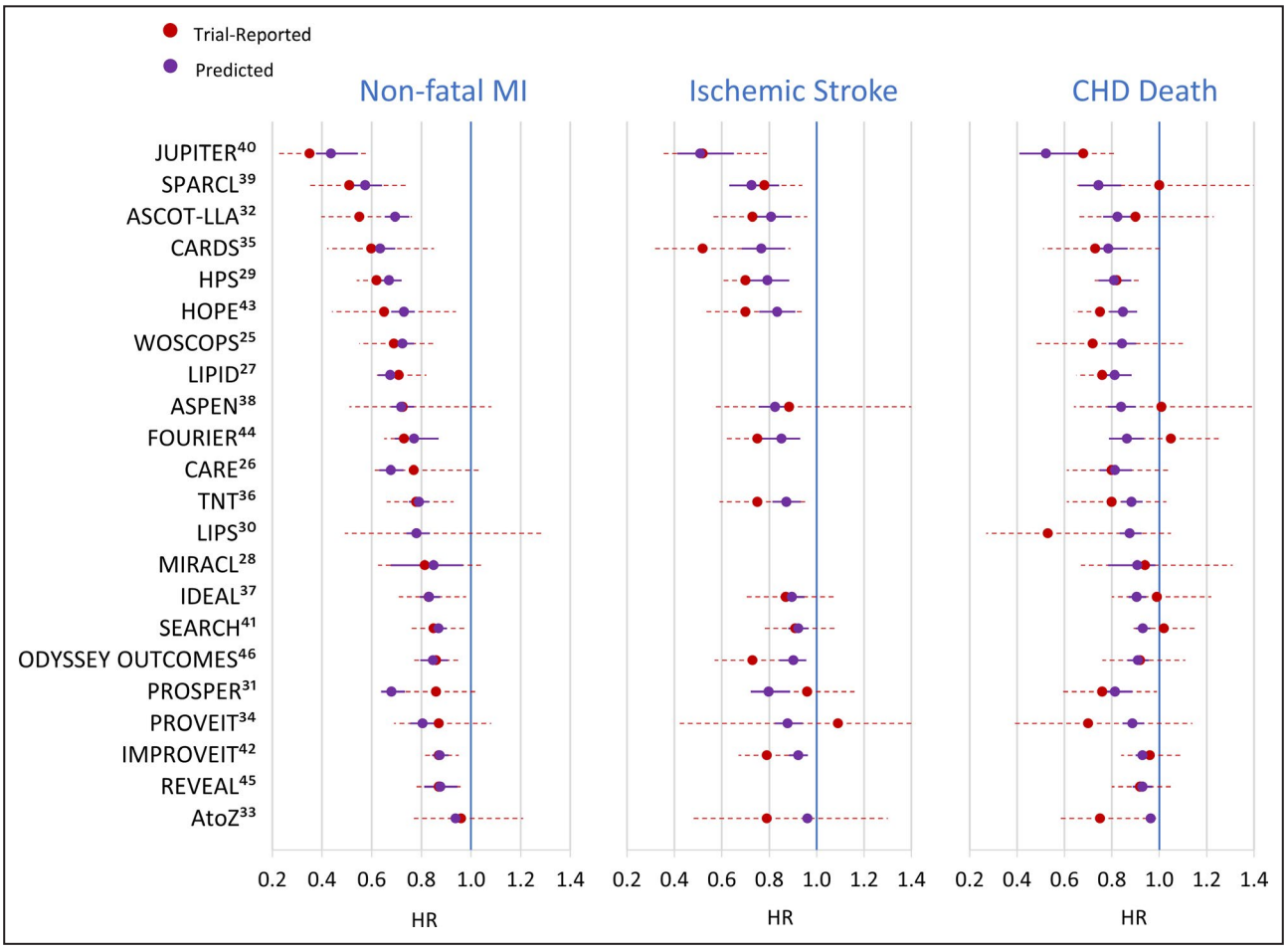


Figure 1. Model-predicted versus trial-reported hazard ratios by event type.
Trials included were: A to Z, Aggrastat to Zocor[33]; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm[32]; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus[38]; CARDS, Collaborative Atorvastatin Diabetes Study[35]; CARE, Cholesterol and Recurrent Events[26]; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk[44]; HOPE, Heart Outcomes Prevention Evaluation[43]; HPS, Heart Protection Study[29]; IDEAL, Incremental Disease in End Points Through Aggressive Lipid Lowering[37]; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial[42]; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin[40]; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease[27]; LIPS, Lescol Intervention Prevention Study[30]; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering[28]; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab[46]; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk[31]; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy[34]; REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification[45]; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine[41]; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels[39]; TNT, Treating to New Targets[36]; and WOSCOPS, West of Scotland Coronary Prevention Study.[25] CHD indicates coronary heart disease; HR, hazard ratio; and MI, myocardial infarction.

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model was also used to make trial-based event rate predictions over time for a composite end point in each RCT. Figure 2[25–46] shows the concordance between reported and predicted KM curves over trial-specific follow-up times. Model risk reduction predictions for a significantly longer period were also in agreement with long-term data at 40 years from the Ference et al Mendelian randomization analysis,[24] as shown in Figure S4.

Model Prediction Versus CTT

Figure 3 summarizes the trial-reported HRs, and point-estimate HR predictions from the model and CTT for a 3-part composite of nonfatal MI, ischemic stroke, and CHD death (with CTT estimation using 27%, 21%, and 20% reduction per 1 mmol/L LDL-C for each individual end point, respectively).[5] Out of 22 RCTs, 15 had closer predictions for this end point with the time-dependent model, as compared with 7 RCTs with CTT estimates. The most substantial improvements for this composite were for the JUPITER and MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trials,[28] where the absolute differences relative to the trial-reported HR were reduced by 0.21 and 0.19, respectively. There were also notable improvements with the ODYSSEY OUTCOMES'[46] prediction as the absolute deviation improved by 0.10.

Recursive One-Trial Holdout Validation

The model-predicted and trial-reported HRs with the holdout validation analysis are depicted in Figure 4 for the 3-part composite representing nonfatal MI, ischemic stroke, and CHD death. There was a slight decrease in the model performance in the recursive 1-trial holdout validation analysis as measured by mean absolute difference of 6.4% versus 4.7% (4.65% as per 2-decimal) with the final model. For all trials except JUPITER and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels),[39] the mean absolute difference was 5.3% versus 4.7% (4.74% as per 2-decimal); however, for JUPITER and SPARCL, the absolute difference increased from 4.0% to 22.0% and from 4.0% to 14.0%, respectively.

Scenario Analyses

Table 2 summarizes the event rates, ARR, and number needed to treat (NNT) for different treatment intensification strategies and duration for relevant subgroups and a composite of nonfatal MI, ischemic stroke, and CHD death. ARRs increased and NNTs declined with increased treatment intensification, treatment duration, and population risk level. The most notable reductions in risk were seen in a recent ACS population whose baseline LDL-C was >100 mg/dL (mean of 125.8 mg/dL), where the ARR increased from 9.0% to 23.0% from 5 to 15 years with the most intensive treatment of HIS, ezetimibe, and high-dose PCSK9 inhibitor (alirocumab 150 mg).

Utilizing a commonly accepted threshold of the NNT ≤50 (ARR ≥2%; denoting a good clinical value of treatment[49]) indicated that this threshold would be met with intensive treatment of HIS, ezetimibe, and high-dose PCSK9 inhibitor in the standard recent ACS population with ≥2.0 years of treatment (comparison with HIS); in the stable ASCVD population with ≥4.7 years (comparison with HIS); in the diabetes mellitus primary prevention population with ≥8.3 years (comparison with moderate-intensity statin [MIS]); and in the primary prevention population with ≥11.0 years (comparison with MIS). These estimates reflected the LDL-C levels (mean of 87.4–127.9 mg/dL) of the populations enrolled in trials that were used for the evaluation of scenarios. An ARR ≥2% was achieved in the recent ACS population representing a higher baseline LDL-C with only 1.2 years using this treatment strategy as compared with HIS alone.

DISCUSSION

Evaluation of the implications of sustained LDL-C lowering on cardiovascular outcomes is important for appropriate clinician–patient shared decision making. It is apparent given the evidence from lipid-lowering trials that the relative risk reduction gradually improves over time for cardiovascular events with sustained LDL-C lowering. Our study used the cumulative body of evidence from RCTs in a systematic manner to develop a model summarizing this link together with other key factors such as the magnitude of LDL-C lowering and impact on specific cardiovascular end points. We demonstrate the application of the estimated model for investigating scenarios representing different at-risk populations, LLT strategies, and treatment durations.

A key feature of the presented model is the time-dependent aspect, which results in a substantially improved agreement with past RCT data as compared with a scenario where a uniform estimate of relative risk reduction per 1 mmol/L reduction in LDL-C is used. For a 3-part composite of nonfatal MI, ischemic stroke, and CHD death, the current model had better prediction for 15 out of 22 trials as compared with CTT estimates. When a validation analysis was conducted by withholding trials one at a time, predictions were still in relatively good agreement with those from the final model and resulted in better predictions for 14 out of 22 trials as compared with CTT estimates. Trials with a relatively large

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Figure 2. Model-predicted versus trial-reported composite event rates over time.
Time is reported in years on the *x* axis. Trial-reported composite event rates have been adjusted to only account for the following cardiovascular events where applicable: nonfatal myocardial infarction, coronary heart disease death, ischemic stroke, unstable angina requiring hospitalization, and coronary revascularization. Therefore, event rates may be different from those reported in the trial. Not all trial composites contain all 5 events included in the model. The trial-reported composite may either be the primary end point or another reported composite end point. Trials included were: A to Z, Aggrastat to Zocor[33]; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm[32]; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus[38]; CARDS, Collaborative Atorvastatin Diabetes Study[35]; CARE, Cholesterol and Recurrent Events[26]; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk[44]; HOPE, Heart Outcomes Prevention Evaluation[43]; HPS, Heart Protection Study[29]; IDEAL, Incremental Disease in End Points Through Aggressive Lipid Lowering[37]; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial[42]; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin[40]; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease[27]; LIPS, Lescol Intervention Prevention Study[30]; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering[28]; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab[46]; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk[31]; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy[34]; REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification[45]; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine[41]; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels[39]; TNT, Treating to New Targets[36]; and WOSCOPS, West of Scotland Coronary Prevention Study.[25]

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decrease in performance with the holdout validation analyses were JUPITER[40] and SPARCL,[39] which likely reflects the fact they involved somewhat special populations with a high baseline hsCRP (JUPITER) or ischemic cerebrovascular disease without CHD (SPARCL). However, all other trials performed relatively well in the holdout validation analysis with the mean absolute deviation increasing by only 0.6% as compared with the final model. A qualitative trial by trial comparison of an observed and model-predicted composite end point over time also indicated a good agreement (Figure 2). This lends support to the robustness of the model in terms of replicating data across trials representing significant heterogeneity in terms of design, time periods, populations, treatments, end points, and follow-up duration. When the model was applied to a longer time frame, the risk reduction prediction was also in agreement with long-term evidence from the Ference et al[24] Mendelian randomization analysis.

The presented model shows the ability to capture treatment benefit accurately with both statin and nonstatin treatments. As opposed to some earlier investigations, our model indicated that LLT type (PCSK9 inhibitor versus other LLTs) is a significant predictor of treatment benefit in the short term. Incorporating this feature was essential for successfully replicating the risk reduction over time for the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)[44] and ODYSSEY OUTCOMES[46] trials. In PCSK9 inhibitor trials, patients were already receiving statin as background therapy (with 69%–89% receiving HIS), often for several years, which may have contributed to differences observed. It is important, however, to note that the model indicated that the difference in benefit between different LLTs dissipates over time, with all becoming equal when assessed over a longer time period and approaching the risk reduction indicated

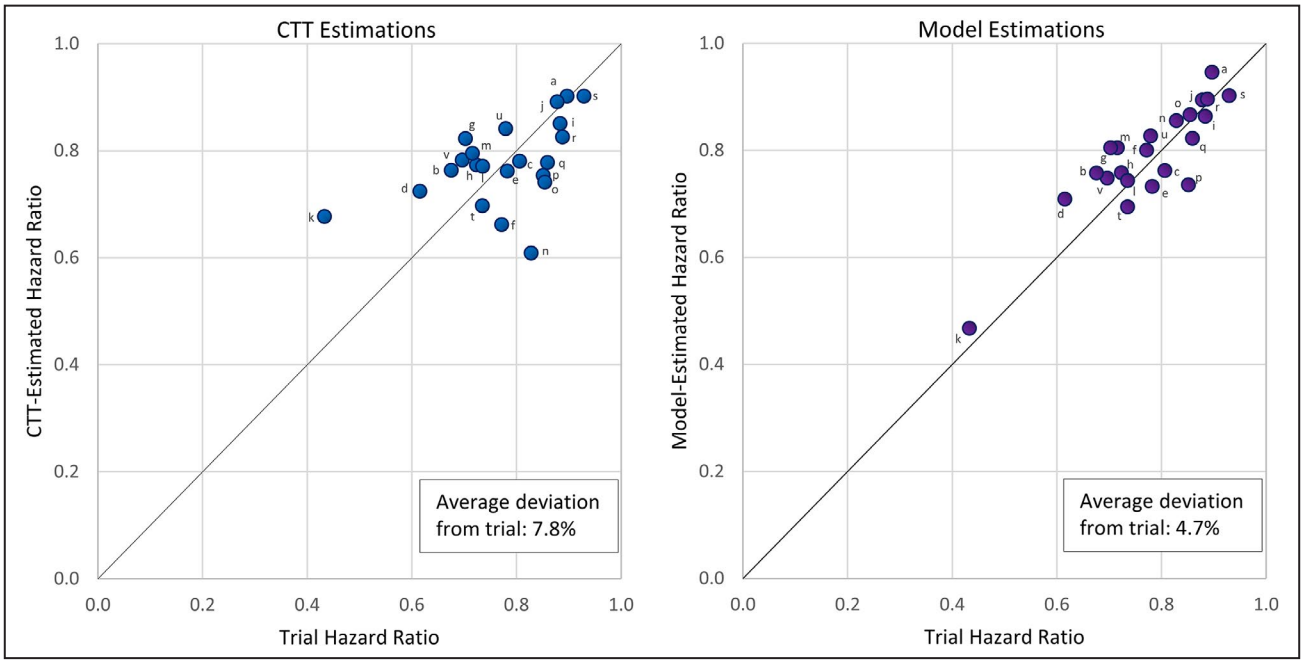


Figure 3. Estimated and trial-reported hazard ratios: Comparison of model versus cholesterol treatment trialists (CTT) estimates for the composite end point of nonfatal myocardial infarction, coronary heart disease death, and ischemic stroke. CTT estimated hazard ratios utilize a 27% risk reduction per 1 mmol/L for the nonfatal myocardial infarction end point, 20% per mmol/L for the coronary heart disease death end point, and 21% per mmol/L for the ischemic stroke end point.[5] Letters a to v denote the following trials: a, A to Z, Aggrastat to Zocor[33]; b, ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm[32]; c, ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus[38]; d, CARDS, Collaborative Atorvastatin Diabetes Study[35]; e, CARE, Cholesterol and Recurrent Events[26]; f, FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk[44]; g, HOPE, Heart Outcomes Prevention Evaluation[43]; h, HPS, Heart Protection Study[29]; i, IDEAL, Incremental Disease in End Points Through Aggressive Lipid Lowering[37]; j, IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial[42]; k, JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin[40]; l, LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease[27]; m, LIPS, Lescol Intervention Prevention Study[30]; n, MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering[28]; o, ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab[46]; HPS, Heart Protection Study[29]; p, PROSPER, Prospective Study of Pravastatin in the Elderly at Risk[31]; q, PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy[34]; r, REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification[45]; s, SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine[41]; t, SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels[39]; u, TNT, Treating to New Targets[36]; and v, WOSCOPS, West of Scotland Coronary Prevention Study.[25]

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in Mendelian randomization analyses. This is supported by genetic data that show over a 50-year period, the impacts of genetic variants mimicking drug targets (3-hydroxy3-methyl-glutaryl-coenzyme A reductase, Niemann-Pick C1-like 1, and PCSK9) have similar differences in risk when standardized by LDL-C difference.[24]

To highlight a population-level application of the model, we present an evaluation of scenarios representing various population risk profiles ranging from recent ACS to primary prevention (Table 2). The ARRs increased with the intensity of LLT and treatment duration, with the magnitude of increase dependent on the population risk level. The 2% ARR threshold, indicating a good clinical value of treatment, was met even sooner in a recent ACS population with a baseline LDL-C >100 mg/dL (mean LDL-C of 125.8 mg/dL) than a recent ACS population with a baseline LDL-C >70 mg/dL (mean LDL-C of 92.0 mg/dL). The summary conclusions support the proposed paradigm of intensive LDL-C lowering beginning earlier in life as a prevention strategy, especially in those with a higher baseline LDL-C.[50]

To highlight a patient-level application of the model, potentially in clinical practice, we present an example of an estimated treatment benefit in a 65-year-old male patient, a nonsmoker who has diabetes mellitus and CHD and no peripheral or cerebrovascular disease, with systolic blood pressure of 135 mm Hg and an LDL-C of 4 mmol/L (154.7 mg/dL). According to the SMART (Secondary Manifestations of Arterial Disease) risk calculator,[51,52] the 10-year risk of experiencing a major cardiovascular event (composite of MI, stroke, and cardiovascular death) is 22.0%. If this patient were to receive MIS only, the risk at 1 year would decrease from 2.5% to 1.8%, at 5 years from 11.7% to 8.0%, at 10 years from 22.0% to 14.9%, and at 15 years from 31.2% to 20.9%. If this patient were to receive an intensive treatment of HIS, ezetimibe, and high-dose PCSK9 inhibitor, the risk at 1 year would decrease from 2.5% to 1.4%, at 5 years from 11.7% to 5.2%, at 10 years from 22.0% to 9.0%, and at 15 years from 31.2% to 12.3%. As the SMART risk calculator provides 10-year risk, we used a constant hazard assumption to facilitate this calculation. However, the current model has flexibility to provide estimates of risk reduction based on any risk pattern over time and does not necessarily require a constant hazard assumption.

As is apparent from the preceding case example, the expected clinical benefit of LLT depends on a patient's baseline risk representing existing clinical characteristics, baseline LDL-C level, expected magnitude of LDL-C reduction with treatment, and duration of treatment. Although the baseline risk and LDL-C levels represent characteristics before treatment and vary by patients, the absolute risk reduction further combines these characteristics with potential treatment choices and treatment duration to yield the magnitude of expected clinical benefit. Our model facilitates this patient-specific assessment and could help patient–physician shared decisions on choice and duration of treatment and help communicate to patients the clinical value of continuing therapy and achieving consistent LDL-C reduction over time.

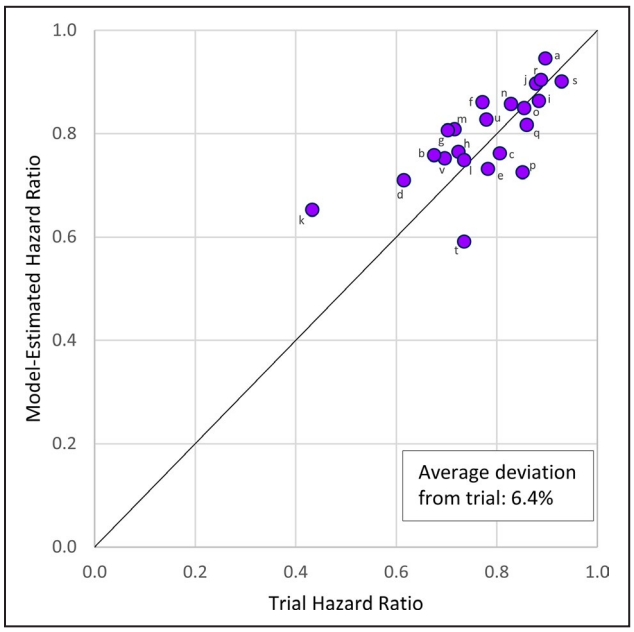


Figure 4. Recursive one-trial holdout validation: estimated and trial-reported hazard ratios.
Letters a to v denote the following trials: a, A to Z, Aggrastat to Zocor[33]; b, ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm[32]; c, ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus[38]; d, CARDS, Collaborative Atorvastatin Diabetes Study[35]; e, CARE, Cholesterol and Recurrent Events[26]; f, FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk[44]; g, HOPE, Heart Outcomes Prevention Evaluation[43]; h, HPS, Heart Protection Study[29]; i, IDEAL, Incremental Disease in End Points Through Aggressive Lipid Lowering[37]; j, IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial[42]; k, JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin[40]; l, LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease[27]; m, LIPS, Lescol Intervention Prevention Study[30]; n, MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering[28]; o, ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab[46]; p, PROSPER, Prospective Study of Pravastatin in the Elderly at Risk[31]; q, PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy[34]; r, REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification[45]; s, SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine[41]; t, SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels[39]; u, TNT, Treating to New Targets[36]; and v, WOSCOPS, West of Scotland Coronary Prevention Study.[25]

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Table 2. Estimated Event Rates, Absolute Risk Reduction, and Number Needed to Treat for the Composite End point of Nonfatal Myocardial Infarction, Coronary Heart Disease Death, and Ischemic Stroke for Alternate Treatment Strategies, Populations, and Treatment Durations

Population	Recent ACS			Recent ACS			Stable ASCVD			DM Primary Prevention			Primary Prevention		
Trial	ODYSSEY OUTCOMES			ODYSSEY OUTCOMES, Baseline LDL-C> 100 mg/dL			TNT			ASCEND			HOPE		
Baseline LDL-C (mg/dL)	92.0			125.8			98.0			87.4			127.9		
Duration (y)	5	10	15	5	10	15	5	10	15	5	10	15	5	10	15
	Event rates			Event rates			Event rates			Event rates			Event rates		
No treatment, %	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3.0	8.2	15.3
MIS, %	NA	NA	NA	NA	NA	NA	9.2	17.5	25.0	3.6	7.8	12.5	2.0	5.4	9.8
HIS, %	16.1	27.1	36.6	21.8	36.5	48.5	7.7	14.4	20.5	3.3	7.2	11.3	1.9	5.0	9.2
HIS+EZE, %	13.7	22.7	30.5	17.9	29.7	39.4	6.8	12.4	17.6	2.9	6.3	10.0	1.7	4.5	8.2
HIS+ALI 150, %	11.1	17.2	22.5	13.4	21.0	27.3	5.8	10.0	13.7	2.6	5.4	8.2	1.5	3.8	6.7
HIS+EZE+ALI 150, %	10.7	16.3	21.2	12.8	19.6	25.4	5.6	9.5	13.0	2.5	5.1	7.8	1.5	3.6	6.4
	ARR (reference MIS)			ARR (reference MIS)			ARR (reference MIS)			ARR (reference MIS)			ARR (reference MIS)		
HIS+EZE, %	NA	NA	NA	NA	NA	NA	2.4	5.0	7.4	0.6	1.5	2.5	0.3	0.9	1.6
HIS+ALI 150, %	NA	NA	NA	NA	NA	NA	3.4	7.5	11.2	0.9	2.5	4.3	0.4	1.6	3.0
HIS+EZE+ALI 150, %	NA	NA	NA	NA	NA	NA	3.7	8.0	11.9	1.0	2.8	4.7	0.5	1.7	3.3
	ARR (reference HIS)			ARR (reference HIS)			ARR (reference HIS)			ARR (reference HIS)			ARR (reference HIS)		
HIS+EZE, %	2.4	4.4	6.1	4.0	6.8	9.0	0.9	2.0	2.9	0.3	0.8	1.3	0.2	0.6	1.0
HIS+ALI 150, %	5.0	9.9	14.1	8.5	15.6	21.2	1.9	4.4	6.7	0.6	1.8	3.1	0.3	1.2	2.5
HIS+EZE+ALI 150, %	5.4	10.8	15.4	9.0	16.9	23.0	2.1	4.9	7.4	0.8	2.1	3.5	0.4	1.4	2.8
	NNT (reference MIS)			NNT (reference MIS)			NNT (reference MIS)			NNT (reference MIS)			NNT (reference MIS)		
HIS+EZE	NA	NA	NA	NA	NA	NA	41	20	14	162	67	40	374	114	63
HIS+ALI 150	NA	NA	NA	NA	NA	NA	29	13	9	108	40	23	226	64	33
HIS+EZE+ALI 150	NA	NA	NA	NA	NA	NA	27	13	8	95	36	21	194	58	30
	NNT (reference HIS)			NNT (reference HIS)			NNT (reference HIS)			NNT (reference HIS)			NNT (reference HIS)		
HIS+EZE	42	23	16	25	15	11	107	51	35	300	123	75	629	181	99
HIS+ALI 150	20	10	7	12	6	5	52	23	15	157	56	32	299	81	40
HIS+EZE+ALI 150	18	9	7	11	6	4	47	20	13	131	48	29	246	72	36

End points considered for all populations: nonfatal myocardial infarction, ischemic stroke, and coronary heart disease death. Event rates may differ from trial-reported values. See Data S1 for details. ACS indicates acute coronary syndromes; ACSVD, atherosclerotic cardiovascular disease; ALI 150, alirocumab 150 mg; ARR, absolute risk reduction; ASCEND, A Study of Cardiovascular Event in Diabetes[48]; DM, diabetes mellitus; EZE, ezetimibe; HIS, high-intensity statin; HOPE, Heart Outcomes Prevention Evaluation[43]; LDL-C, low-density lipoprotein cholesterol; MIS, moderate-to-low intensity statin; NNT, number needed to treat; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab[46]; and TNT, Treating to New Targets.[36]

The presented model has other potential applications, including its use to simulate treatment benefit over time with time-varying LDL-C caused by situations that are driven by trial design, real-world aspects (eg treatment adherence, intolerance, discontinuation, and switching) or other scenarios, such as exploring legacy effects of treatment. When taken together with a baseline risk model representing risk before treatment, our model offers a tool that can be used to estimate ARRs and NNTs for a range of treatment scenarios with varying population risk profiles, LLT types, doses, and treatment durations. To facilitate estimation of risk reduction with the presented model, an easy-to-use version, potentially via an online or an Excel-based application, can be developed with minimal inputs. We provide a prototype of this application as shown in Figure S5. Tools of this nature can help identify patients with the potential to have the highest clinical benefit with treatment, which is particularly relevant for add-on therapies to statins.

Limitations

We limited the selection of studies informing the model to large randomized trials with statins, ezetimibe, PCSK9 inhibitors, and anacetrapib. A few large studies, such as SSSS (Scandinavian Simvastatin Survival Study)[20] and the MEGA (Management of Elevated

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Cholesterol in the Primary Prevention Group of Adult Japanese) study[11] were excluded because the reported data were not amenable for use in the model and open-label design. Excluded trials can represent specific biases. We included high baseline hsCRP in the final model; however, this parameter was informed by evidence from a single trial, JUPITER. Trials with a relatively large deterioration in performance with the holdout validation analyses were JUPITER and SPARCL. As such, caution is warranted in the application of this model in those with high baseline hsCRP or ischemic cerebrovascular disease without CHD. Other clinical factors that may influence the treatment benefit can be those that are not reported in the trials we considered. As such, caution is needed in the application of the model in patients with specific clinical conditions not represented in trials used in model development. The development of the model was based on trial-level and not patient-level data. Specific biases can confound the results based on modeling from aggregate data.[53] In the development of the model, we used the LDL-C reduction as reported in RCTs. Where possible, we used the LDL-C reduction at median follow-up; otherwise, we used a main reported summary measure, such as the least-square mean or the time-weighted average reduction. Therefore, the LDL-C reduction used in the model development could be different from that used in the CTT meta-analysis, which was based on LDL-C difference at 1-year follow-up.[5]

CONCLUSIONS

The time-dependent model accurately predicted treatment benefit seen from RCTs with a given LLT strategy by incorporating patient profile, timing, duration, and type of treatment. The model can facilitate decision making and scenario analyses with a given LLT strategy in various patient populations and time frames by providing an improved assessment of treatment benefit over time.

ARTICLE INFORMATION

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Supplementary Materials

Data S1
Tables S1–S2
Figures S1–S5
References 3, 5, 8–48, 54

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SUPPLEMENTAL MATERIAL

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Data S1. Supplemental Methods.

PubMed Search Strategy

Estimation of Event Rate Curves for Individual Events within a Composite

Breaking Broader Events into Endpoints of Interest

Full Mathematical Specification of the Model

Estimation of Model Parameters

Clinical Benefit Calculator Prototype

Additional Details Regarding Scenario Analysis with ASCEND

Table S1. List of excluded trials and reason for exclusion

Table S2. Parameters retained in the model

Figure S1. Selection criteria of trials considered in model development

Figure S2. Estimated and trial-reported hazard ratios: comparison of final model and model without use of parameter for high baseline high-sensitivity C-reactive protein

Figure S3. Model-predicted vs. trial-reported hazard ratios for unstable angina requiring hospitalization and coronary revascularization

Figure S4. Estimated instantaneous relative risk reduction, α, over time for non-fatal MI by lipid-lowering therapy type and 1 mmol/L reduction in LDL-C

Figure S5. Prototype of clinical benefit calculator

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Data S1. Supplemental Methods

PubMed Search Strategy

363 results:

"lipid regulating agents"[Pharmacological Action] AND "randomized controlled trial"[Publication Type] AND "cholesterol"[MeSH Terms] AND "LDL"[All Fields] AND “cardiovascular”[All Fields] AND ("anacetrapib"[All Fields] OR "ezetimibe"[All Fields] OR "PCSK9"[All Fields] OR "statin"[All Fields]) AND ("1995"[PDAT] : "2019"[PDAT])

Estimation of Event Rate Curves for Individual Events within a Composite

The following approach was adopted for the estimation of event rates for an endpoint of interest, $E_i(t)$, from the composite event rate curve, $E_T(t)$, and additional data reported in the publication. We first invoke the identity that instantaneous hazard rates for parts of the composite are additive:

$$\lambda_T(t) = \lambda_1(t) + \cdots + \lambda_N(t)$$

Integrating both sides and invoking the identity $\int_0^t \lambda(\tau)d\tau = -\ln(1 - E(t))$ we get:

$$\ln\big(1 - E_T(t)\big) = \ln\big(1 - E_1(t)\big) + \cdots + \ln\big(1 - E_N(t)\big)$$

For a specific time T (e.g. median follow-up or total trial duration) this becomes:

$$\ln\big(1 - E_T(T)\big) = \ln\big(1 - E_1(T)\big) + \cdots + \ln\big(1 - E_N(T)\big)$$

We can define a ratio P_i as:

$$P_i = \frac{\ln\big(1 - E_i(T)\big)}{\ln\big(1 - E_T(T)\big)}$$

The value P_i can be estimated from additional data reported in publications and then utilized to estimate the event rate curves for an endpoint of interest, $E_i(t)$, from the composite event rate curve, $E_T(t)$, as follows:

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$$E_i(t) = 1 - \exp\left(P_i \ln\left(1 - E_T(t)\right)\right)$$

If applicable, P_is were renormalized to ensure the estimated $E_i(t)$s of interest were equal to the data reported in the publication (e.g. the nonfatal myocardial infarction [MI] endpoint in ODYSSEY OUTCOMES[46]) at the follow-up time. If a trial had coronary revascularization as a part of its composite endpoint, these individual event rates were re-estimated to reflect elective revascularizations not as a part of other cardiovascular (CV) events. Once event rates for the individual endpoints of interest, $E_i(t)$, were estimated in this manner, we confirmed that we were able to replicate reported composite curves, $E_T(t)$, via a simulation of first events from estimated $E_i(t)$.

As an example, in the IMPROVE-IT trial,[42] the event rate for nonfatal MI in the simvastatin monotherapy arm was 14.4%, which translates to $\ln\left(1 - E_i(T)\right) = -0.155$. The concurrent estimates for $\ln\left(1 - E_i(T)\right)$ for CV death, nonfatal stroke, coronary revascularization, and unstable angina [UA] requiring hospitalization were –0.070, –0.043, –0.267, and –0.019, respectively. Using these numbers and an estimate of $\ln\left(1 - E_T(T)\right) = 0.426$, coronary revascularization was re-estimated as –0.138. Thus, P_i for the nonfatal MI endpoint was estimated as 0.155/0.426 = 0.365, and the event rates were estimated as $E_i(t) = 1 - \exp\left(0.365 \ln\left(1 - E_T(t)\right)\right)$, where $E_T(t)$ is composite event rate curve reported in IMPROVE-IT.

Breaking Broader Events into Endpoints of Interest

A trial may not report the exact event of interest. For example, in some trials the risks for coronary heart disease (CHD) death and ischemic stroke are not reported as a separate event, but instead they are part of a broader CV event or stroke event. It was essential in model development to convert these into a consistent set of endpoints such as CHD death and ischemic stroke. To facilitate this, we estimated the ratio of rates P for a specific event type A (e.g. CHD death or ischemic stroke) to a broader event type B (e.g. death from other causes or any stroke) as $P = \ln(1 - E_A)/\ln(1 - E_B)$ by utilizing the data from Cholesterol Treatment Trialists' (CTT) 2010 meta-analysis.[5]

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	Estimated Ratio of Rates (P)	
	Placebo	**Treated**
CHD Death / Cardiac Death	0.544	0.554
CHD Death / CV Death	0.460	0.415
CHD Death / Any Death	0.259	0.236
Nonfatal Ischemic Stroke / Any Stroke	0.624	0.666

As an example, in the JUPITER trial[40], the number of patients experiencing any stroke in the rosuvastatin and placebo arms was 33 and 64, respectively. Using the table above, we re-estimated these numbers as nonfatal ischemic stroke in the rosuvastatin and placebo arms as 21 and 43, respectively.

Full Mathematical Specification of the Model

We define the concept of an instantaneous relative risk reduction (α), which represents percent reduction in events with treatment at a particular moment in time, t, (e.g. at 3 years) over a small incremental follow-up, dt. If $dE(t)$ and $dE_c(t)$ denote the incremental number of events in treatment and control populations, respectively, at time t, then $\alpha(t) = (dE_c(t) - dE(t))/dE_c(t)$. We similarly define an instantaneous risk (λ) as percent of population experiencing an event over a small incremental follow-up of dt. Thus $\lambda(t) = (dE(t)/S(t))/dt$, where $S(t) = 1 - E(t)$ represents the size of population at risk of events at time t (normalization by dt is required for consistency in mathematical framing), and the idea behind $\lambda(t)$ is identical to that of an instantaneous hazard rate.[54] It follows from these definitions that $\lambda(t) = \lambda_c(t)\ (1 - \alpha(t))$. As a generalization for the setting of lipid-lowering therapies (LLTs), we specify the instantaneous relative risk reduction, α, to depend on time since initiation of LLT (t), the magnitude of low-density lipoprotein cholesterol (LDL-C) reduction in mmol/L (ΔL), and additional patient characteristics ($\boldsymbol{X}$). The full functional form for α was specified as:

$$\alpha(t, \Delta L, \boldsymbol{X}) = 1 - \big(1 - \theta(t, \Delta L, \boldsymbol{X})\big)^{\Delta L}$$

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This functional form for α exhibits the correct limiting behavior with regards to the magnitude of reduction in LDL-C, ΔL (with θ between 0 and 1), meaning that as when $\Delta L = 0$, then $\alpha = 0$, and as ΔL increases, α increases, approaching a limiting value of 1. The parameter θ can be interpreted as the instantaneous risk reduction per 1 mmol/L reduction in LDL-C. As an example, if $\theta = 0.25$, and $\Delta L = 0.5$, then $\alpha = 0.13$. In other words, if the instantaneous risk reduction per 1 mmol/L reduction in LDL-C is estimated as 25%, then with an LDL-C reduction of 0.5 mmol/L, the instantaneous risk reduction would be estimated as 13%. The overall functional form for θ has to be chosen such that it lies between 0 and 1. We postulate the parameter θ can be partitioned into multiplicative parts θ_1 and θ_2 (with both θ_1 and θ_2 bound between 0 and 1), as follows:

$$\theta(t, \Delta L, \boldsymbol{X}) = \theta_1(\boldsymbol{X})\, \theta_2(t, \Delta L, \boldsymbol{X})$$

Where $\theta_1(\boldsymbol{X})$ captures the saturation effect with long duration of treatment and $\theta_2(t, \Delta L, \boldsymbol{X})$ captures the transient effect leading to the saturation effect. The parameter $\theta_1(\boldsymbol{X})$ can be modelled via a generic logistic transformation as:

$$\theta_1(\boldsymbol{X}) = \frac{1}{1 + \exp\left(-\boldsymbol{X\beta}\right)}$$

Where $\boldsymbol{X\beta}$ represents the linear combination $\beta_0 + \beta_1 X_1 + \cdots + \beta_N X_N$. The parameter $\theta_2(t, \Delta L, \boldsymbol{X})$ capturing the time-dependent part can be modelled via a blend of exponential terms:

$$\theta_2(t, \Delta L, \boldsymbol{X}) = \pi\left(1 - \exp(-t \exp\left(\boldsymbol{X\gamma}\right))\right) + (1 - \pi)(1 - \exp(-t\phi))$$

Where the second term represents a generic growth (or decay) model with a saturation value of 1, and the first term enables modeling of a change in the steepness of initial growth. The parameter π is bound between 0 and 1. To enforce this condition, a logistic transformation was again used such that $\pi = 1/\big(1 + \exp(\omega)\big)$, where ω is a global parameter that is free of constraints, and ϕ is an additional global parameter. The term $\boldsymbol{X\gamma}$ represents the linear combination $\gamma_0 + \gamma_1 X_1 + \cdots + \gamma_M X_M$. Thus, the final formulation of $\alpha(t, \Delta L, \boldsymbol{X})$ is:

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$$\alpha(t, \Delta L, \boldsymbol{X}) = 1 - \left(1 - \frac{(1 - \exp(-t\exp(\boldsymbol{X\gamma}))) + \exp(\omega)(1 - \exp(-t\phi))}{(1 + \exp(\omega))(1 + \exp(-\boldsymbol{X\beta}))}\right)^{\Delta L}$$

Estimation of Model Parameters

A cost function F was defined as the sum of squares of the error between actual event rate curves with treatment from randomized controlled trials (RCTs) and the model-predicted event rate curves for individual endpoints, averaged over the trial duration. The cost function F was minimized via the Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm in Python, which returned a set of estimated model parameters, $\boldsymbol{\beta}$.[47] The estimated parameters with confidence intervals (CIs) for the $\alpha(t, \Delta L, \boldsymbol{X})$ function are summarized in Table S2. When these confidence intervals were considered, five trials had better predictions with the model, and one had better prediction with the CTT estimation for a 3-part composite of nonfatal MI, ischemic stroke, and CHD death.

The covariates considered were individual endpoint types (indicator variables for non-fatal MI, ischemic stroke, CHD death, UA hospitalization, and coronary revascularization), LLT type (indicator variables for statin, ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor, and anacetrapib), established atherosclerotic cardiovascular disease (ASCVD) status, diabetes status, trial mean age, baseline LDL-C level, trial proportion female, high baseline high-sensitivity C-reactive protein (hsCRP) levels (variable relevant only for the JUPITER trial[40]), and established ischemic cerebrovascular disease (variable relevant only for the SPARCL trial[39]).

For each covariate of interest, we tried both $\boldsymbol{X\beta}$ and $\boldsymbol{X\gamma}$ terms and retained the covariate in the term that maximized model performance. For example, LLT types distinguishing PCSK9 inhibitors were retained in the $\boldsymbol{X\gamma}$ term. The CIs for retained model parameters and model-predicted hazard ratios were generated via the bootstrap method where hazard ratios were probabilistically sampled 1000 times from reported CIs in selected RCTs. Note the CIs for some parameter estimates overlap zero. In light of the mathematical framing, zero values for several model parameters such as β_0, γ_0, γ_2, ω, and ϕ convey a non-zero effect on the model.

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Hence, the estimates of these parameters are valid even if the CIs overlap zero. For other parameters, retaining them in the model was critical regardless of whether or not the CIs overlapped zero in order to ensure the overall model performed as described in the methods section (we confirmed dropping any of the variables in Table S2 deteriorated the overall model performance). This approach is consistent with the principles of model development when the aim is to maximize the overall model performance. Figure S4 provides the summary behavior of instantaneous risk reduction function, α, over time via the estimated model parameters for the non-fatal MI endpoint by LLT types, and 1 mmol/L reduction in LDL-C.

We have included the data point corresponding to the evidence from Mendelian randomization analysis from Ference et al.[24] in this Figure, which illustrates that the behavior of α with long duration of treatment is in excellent agreement with the Mendelian randomization data. Finally, the cumulative event rates curves over time (corresponding to the Kaplan-Meier curves) can be estimated from $\alpha(t, \Delta L, \boldsymbol{X})$ and the control population risk $\lambda_c(t)$ as:

$$E(t) = 1 - \exp\left(- \int_0^t \left(1 - \alpha(\tau, \Delta L, \boldsymbol{X})\right)\, \lambda_c(\tau)\, d\tau \right)$$

A simple way of modeling the control population risk, $\lambda_c(t)$, is via a constant hazard model, in which case it can be estimated as $-\ln(1 - E(t))/t$. As an example, if the 2-year risk is 10%, then $\lambda = -\ln(1 - 0.1)/2 = 0.05268$. In the case that a constant hazard model does not adequately describe the risk over time (i.e. the risk changes over time), a function of type $\lambda_c(t) = A + B\exp(-Ct)$ can be used, and is the one we have utilized in modeling the control population risk in RCTs. This function covers a range of behaviors, such as initial elevation of risk (e.g. in trials including recent acute coronary syndrome [ACS] population) that gradually declines over time to a more constant risk (e.g. representing a stable CHD risk profile). It also has the flexibility to model a constant risk over time (i.e. $B = 0$) to capture a stable risk profile.

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Clinical Benefit Calculator Prototype

A treatment benefit calculator based on the estimated model can be developed and implemented via an online tool or Microsoft Excel to provide an easy-to-use interface. An example of a prototype is provided in Figure S5**.** The calculator can rely on five inputs from the user: (1) time frame for which the treatment benefit estimate is desired; (2) estimated risk before treatment; (3) estimated reduction in LDL-C via LLT (this can be estimated from published evidence on LDL-C lowering efficacy from a given LLT); (4) LLT type; and (5) high hsCRP status. The outputs of the calculator include an estimate of risk over time with and without treatment, absolute risk reduction, and number needed to treat.

Additional Details Regarding Scenario Analysis with ASCEND

Complete information regarding baseline LDL-C levels and background LLT were not available for the ASCEND trial.[48] It was reported that 75% of patients in the ASCEND trial were receiving a statin at baseline. We estimated the statin potency for these 75% by utilizing published data on the relative proportion of diabetes without ASCVD patients receiving statins in the UK on low, moderate, and high-intensity statins.[3] We then estimated the overall mean LDL-C for the ASCEND population by utilizing data on achieved LDL-C by these groups (low, moderate, and high-intensity statins, and no statin) from published data.[3]

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Table S1. List of excluded trials and reason for exclusion

Trial	Year	Treatment	Comparator	Reason for Exclusion
ALLHAT-LLT	2002	Pravastatin 40 mg	Placebo	Open label
ALLIANCE	2004	Atorvastatin	Placebo	Open label
GISSI-P	2000	Pravastatin 20 mg	Placebo	Open label
MEGA	2006	Pravastatin 10-20 mg	Placebo	Open label; data reported as rates instead of KM curves
AFCAPS	1998	Lovastatin 20-40 mg	Placebo	Data not available to enable breakdown of KM curves by events
AURORA	2009	Rosuvastatin 10 mg	Placebo	Population with end stage renal disease
ALERT	2003	Fluvastatin 40 mg	Placebo	Population with end stage renal disease
4D	2005	Atorvastatin 20 mg	Placebo	Population with end stage renal disease
SHARP	2011	Simvastatin 20 mg + ezetimibe	Placebo	High proportion of patients with end stage renal disease
CORONA	2007	Rosuvastatin 10 mg	Placebo	Population with heart failure
SEAS	2008	Simvastatin 40 mg + ezetimibe	Placebo	Population with aortic stenosis
SPIRE	2017	Bococizumab	Placebo	Trial discontinued due to antidrug antibodies
SSSS	1994	Simvastatin	Placebo	Technical issues with digitization of KM curves
POST-CABG	1997	Lovastatin 40-80 mg	Lovastatin 2.5-5 mg	Two-by-two factorial design not conducive for model estimation
GISSI-HF	2008	Rosuvastatin 10 mg	Placebo	Technical issues with digitization of KM curves
GREACE	2002	Atorvastatin 10-80 mg	Usual Care	Data reported as rates instead of KM curves

KM, Kaplan-Meier; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[8]; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events[9]; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio[10]; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese[11]; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study[12]; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis[13]; ALERT, Assessment of Lescol in Renal Transplantation[14]; 4D, Die Deutsche Diabetes Dialyse Studie[15]; SHARP, Study of Heart and Renal Protection[16]; CORONA, Controlled Rosuvastatin in Multinational Trial in Heart Failure[17]; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis[18];

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SPIRE, Studies of PCSK9 Inhibition and the Reduction of Vascular Events[19]; SSSS, Scandinavian Simvastatin Survival Study[20]; POST-CABG, Post-Coronary Artery Bypass Graft[21]; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac[22]; GREACE, GREek Atorvastatin and Coronary-heart-disease Evaluation.[23]

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Table S2. Parameters retained in the model

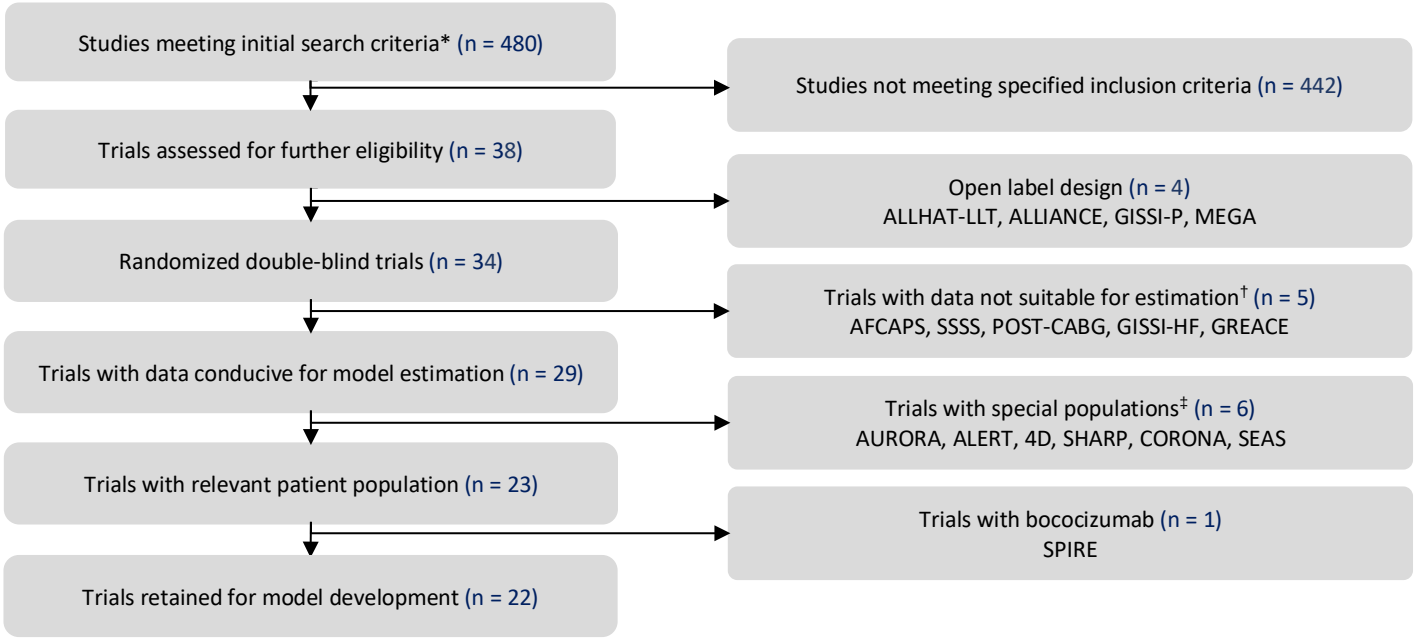
Parameter	Description	Value (95% CI)
$\boldsymbol{\beta_0}$	Intercept term for $\boldsymbol{X\beta}$ (MI)	0.521 (0.163, 0.833)
$\boldsymbol{\beta_1}$	UA requiring hospitalization	-0.731 (-2.035, 0.730)
$\boldsymbol{\beta_2}$	CHD Death	-1.084 (-1.761, -0.478)
$\boldsymbol{\beta_3}$	Ischemic Stroke	-0.986 (-1.821, -0.254)
$\boldsymbol{\beta_4}$	Coronary Revascularization	-0.269 (-0.908, 0.411)
$\boldsymbol{\beta_5}$	High hsCRP levels	1.687 (0.722, 3.781)
$\boldsymbol{\gamma_0}$	Intercept term for $\boldsymbol{X\gamma}$ (statin)	0.136 (-1.436, 0.893)
$\boldsymbol{\gamma_1}$	PCSK9 inhibitor	-1.871 (-3.616, -0.745)
$\boldsymbol{\gamma_2}$	Impact of ΔL on earlier risk reduction (early separation of event rate curves)	1.197 (-0.523, 2.638)
$\boldsymbol{\omega}$	Global parameter	-0.038 (-0.633, 0.367)
$\boldsymbol{\phi}$	Global parameter	0.031 (0.016, 0.153)

Values listed represent the median based on a sensitivity analysis rather than the point estimated model parameters. PCSK9 inhibitor parameter for PCSK9 inhibitors and anacetrapib therapy.

CHD, coronary heart disease; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; UA, unstable angina.

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Figure S1. Selection criteria of trials considered in model development

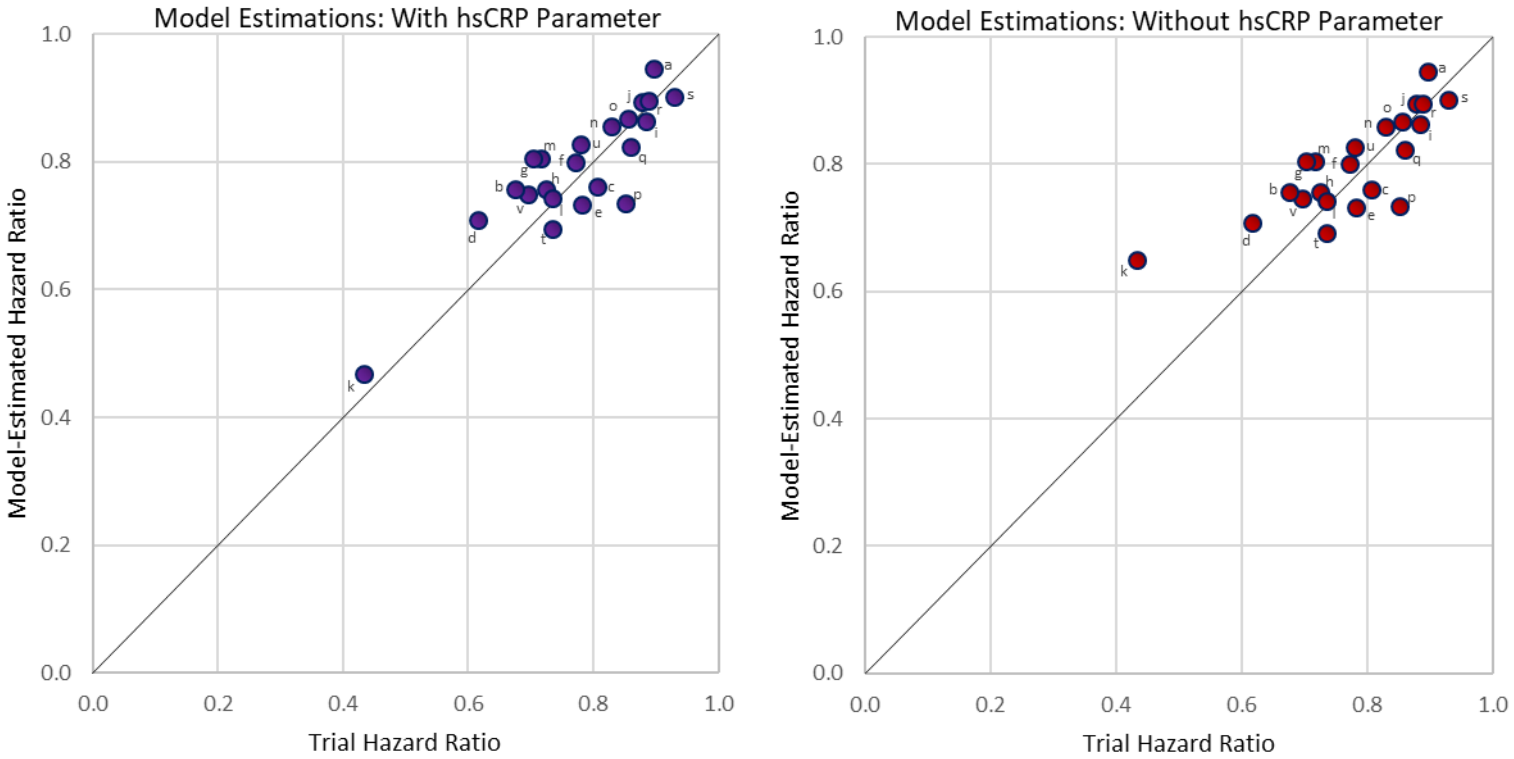


PCSK9; proprotein convertase subtilisin/kexin type 9

*Studies with lipid-lowering therapy (statins, ezetimibe, PCSK9 inhibitors, and anacetrapib), at least 1000 patients, an endpoint of cardiovascular events or mortality. †Data reported as rates and not as Kaplan-Meier curves over time, not possible to digitize published Kaplan-Meier curves, and factorial design resulting in limitations in appropriate data abstraction. ‡Populations with end stage renal disease, heart failure, or aortic stenosis.

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Figure S2. Estimated and trial-reported hazard ratios: comparison of final model and model without use of parameter for high baseline high-sensitivity C-reactive protein

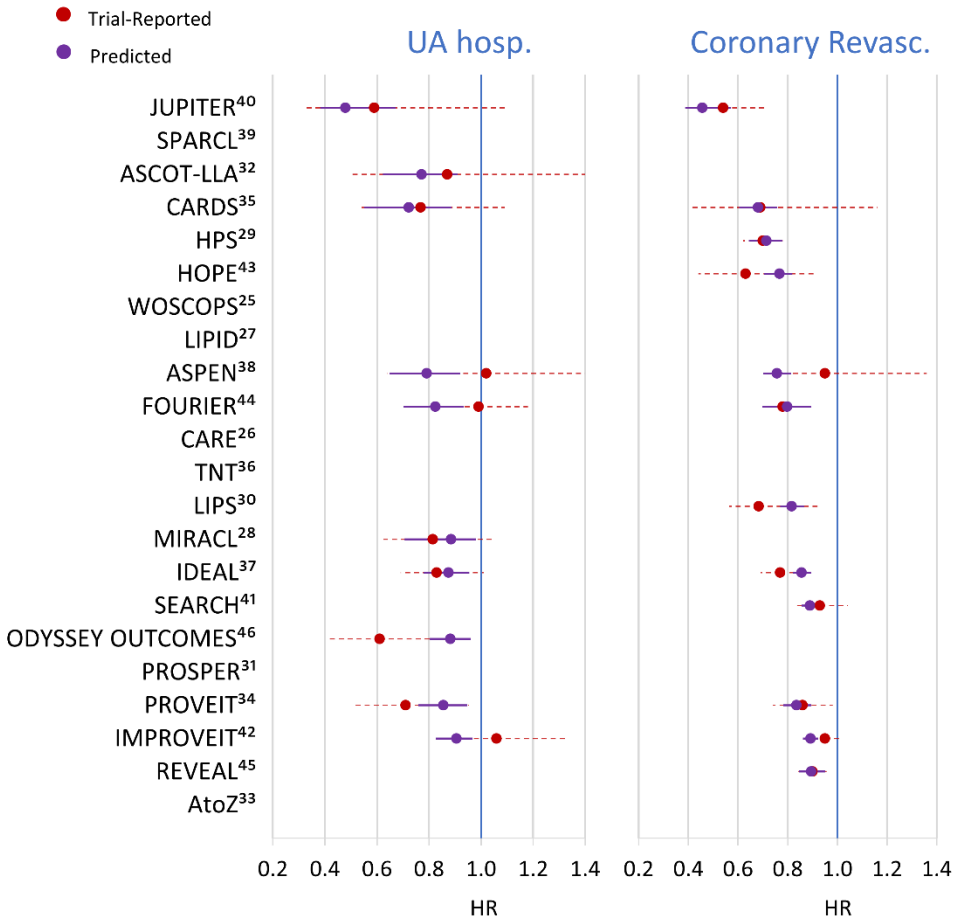


Hazard ratios were calculated for a composite of non-fatal myocardial infarction, ischemic stroke, and coronary heart disease death. Letters a to v denote the following trials: a, A to Z; b, ASCOT-LLA; c, ASPEN; d, CARDS; e, CARE; f, FOURIER; g, HOPE; h, HPS; i, IDEAL; j, IMPROVE-IT; k, JUPITER; l, LIPID; m, LIPS; n, MIRACL; o, ODYSSEY OUTCOMES; p, PROSPER; q, PROVE-IT; r, REVEAL; s, SEARCH; t, SPARCL; u, TNT; v, WOSCOPS.

hsCRP, high-sensitivity C-reactive protein

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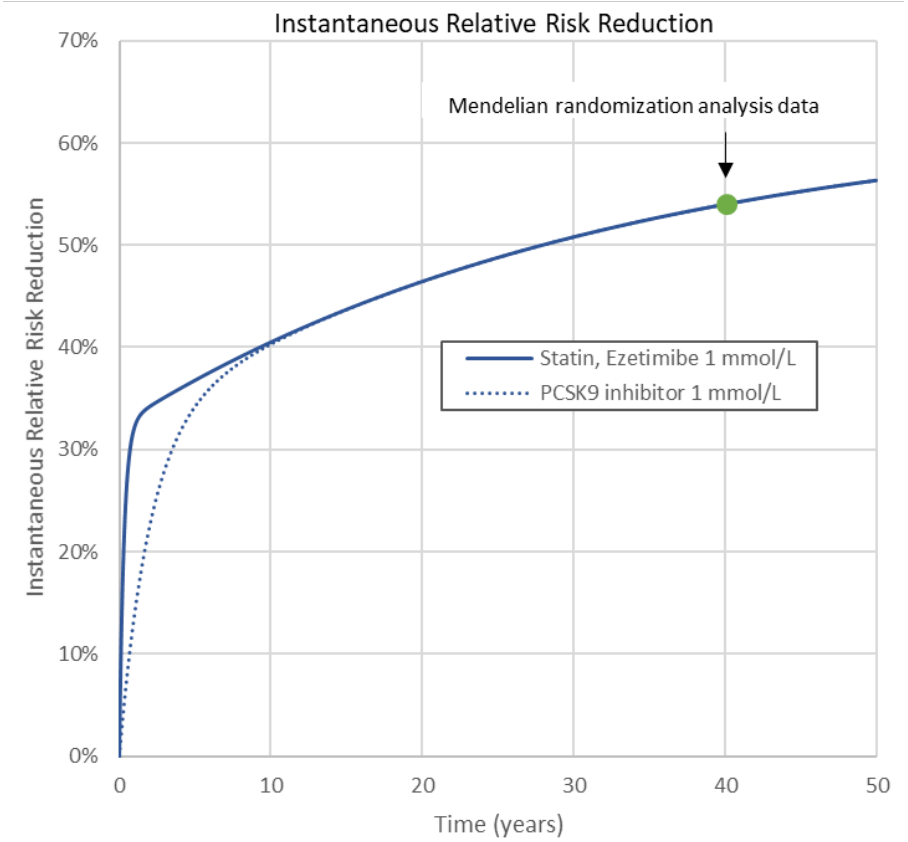
Figure S3. Model-predicted vs. trial-reported hazard ratios for unstable angina requiring hospitalization and coronary revascularization



Coronary revasc., coronary revascularization; HR, hazard ratio; UA hosp., unstable angina requiring hospitalization

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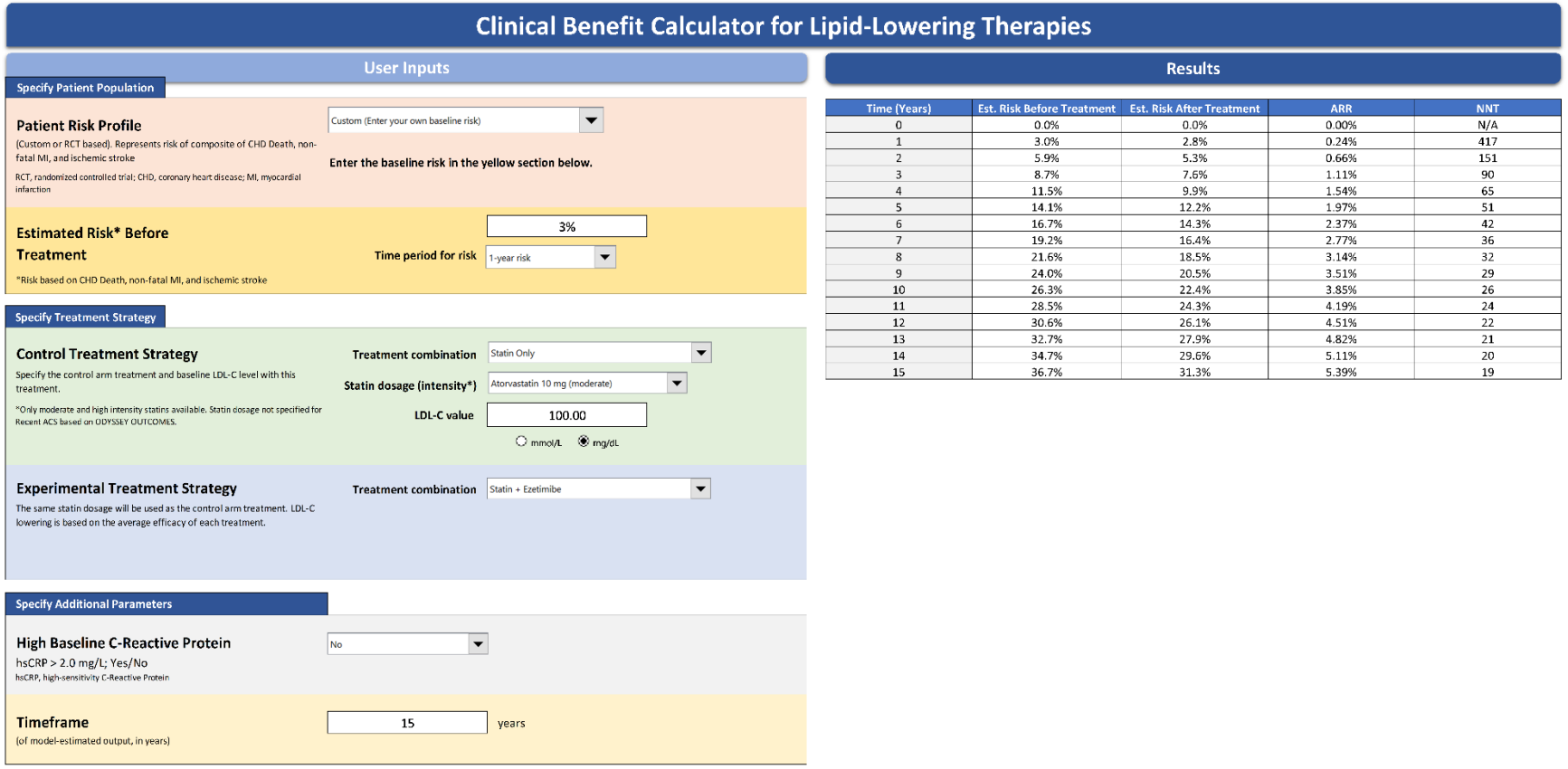
Figure S4. Estimated instantaneous relative risk reduction, α, over time for non-fatal MI by lipid-lowering therapy type and 1 mmol/L reduction in LDL-C



Instantaneous relative risk reduction is the relative risk reduction at a specific moment in time. Dotted line indicates estimates for PCSK9 inhibitors and anacetrapib..
LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

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Figure S5. Prototype of clinical benefit calculator



Time (Years)	Est. Risk Before Treatment	Est. Risk After Treatment	ARR	NNT
0	0.0%	0.0%	0.00%	N/A
1	3.0%	2.8%	0.24%	417
2	5.9%	5.3%	0.66%	151
3	8.7%	7.6%	1.11%	90
4	11.5%	9.9%	1.54%	65
5	14.1%	12.2%	1.97%	51
6	16.7%	14.3%	2.37%	42
7	19.2%	16.4%	2.77%	36
8	21.6%	18.5%	3.14%	32
9	24.0%	20.5%	3.51%	29
10	26.3%	22.4%	3.85%	26
11	28.5%	24.3%	4.19%	24
12	30.6%	26.1%	4.51%	22
13	32.7%	27.9%	4.82%	21
14	34.7%	29.6%	5.11%	20
15	36.7%	31.3%	5.39%	19

ACS, acute coronary syndromes; ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction

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