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FULL RESEARCH PAPER

The potential benefit of statin prescription based on prediction of treatment responsiveness in older individuals: an application to the PROSPER randomized controlled trial

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Aims Clinical guidelines often recommend treating individuals based on their cardiovascular risk. We revisit this paradigm and quantify the efficacy of three treatment strategies: (i) *overall* prescription, i.e. treatment to all individuals sharing the eligibility criteria of a trial; (ii) *risk-stratified* prescription, i.e. treatment only to those at an elevated outcome risk; and (iii) prescription based on predicted *treatment responsiveness*.

Methods and results We reanalysed the PROSPER randomized controlled trial, which included individuals aged 70–82 years with a history of, or risk factors for, vascular diseases. We conducted the derivation and internal–external validation of a model predicting treatment responsiveness. We compared with placebo ($n = 2913$): (i) pravastatin ($n = 2891$); (ii) pravastatin in the presence of previous vascular diseases and placebo in the absence thereof ($n = 2925$); and (iii) pravastatin in the presence of a favourable prediction of treatment response and placebo in the absence thereof ($n = 2890$). We found an absolute difference in primary outcome events composed of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke, per 10 000 person-years equal to: −78 events (95% CI, −144 to −12) when prescribing pravastatin to all participants; −66 events (95% CI, −114 to −18) when treating only individuals with an elevated vascular risk; and −103 events (95% CI, −162 to −44) when restricting pravastatin to individuals with a favourable prediction of treatment response.

Conclusion Pravastatin prescription based on predicted responsiveness may have an encouraging potential for cardiovascular prevention. Further external validation of our results and clinical experiments are needed.

Trial registration ISRCTN40976937.

Lay summary This study investigates whether an algorithm to predict how much old age individuals would benefit from a statin treatment could be useful to guide clinicians in their prescription decision-making; the key findings are as follows:

- About one out of seven individuals included in the study has no predicted benefit of pravastatin.
- Compared with prescribing pravastatin to all old age individuals at risk of cardiovascular diseases, withholding pravastatin in those with no predicted benefit seems to lead to a better prevention of cardiovascular events.

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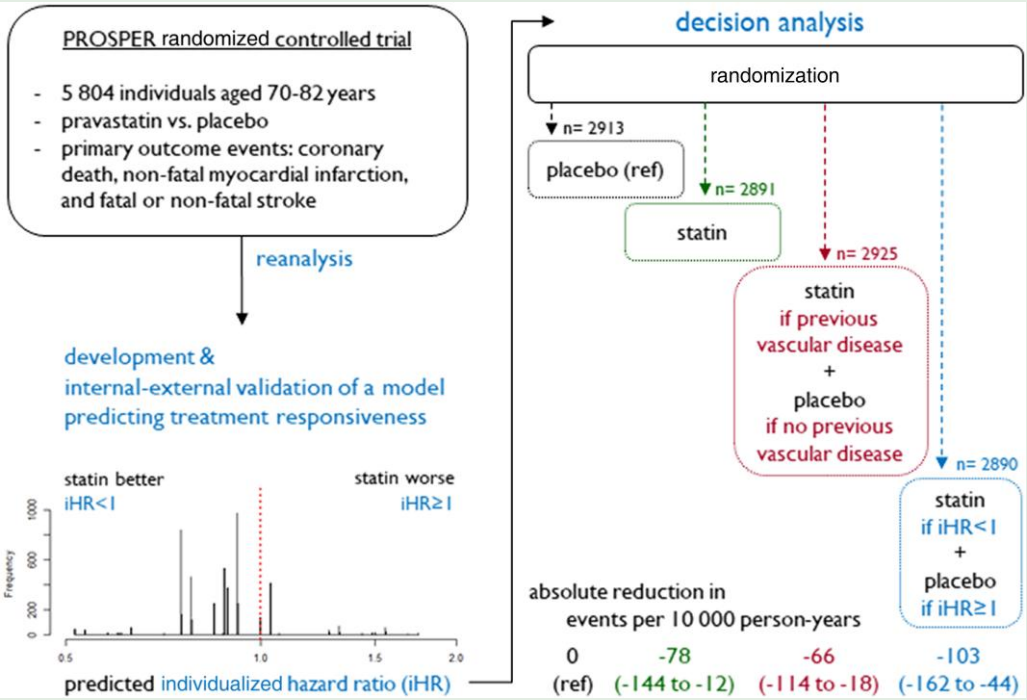
Graphical Abstract



Keywords Individualized treatment effect • Prediction • Cardiovascular prevention • Statin

Introduction

In the early 1990s, the concept of 'evidence-based medicine' (EBM) set a new foundation for treatment decision-making based on results preferably drawn on systematic studies of randomized controlled trials (RCTs).[1] Refinements of this paradigm rapidly emerged over the years, as some started questioning the applicability of the overall results of RCTs to patient treatment in clinical practice: while the RCT provides the best available evidence of the *average* effects of treatments, patients with different characteristics and risk profiles might display heterogeneous responses to treatments.[2–4] For instance, lowering cholesterol with statins decreases the risk of cardiovascular outcomes *on average*; yet, a person at low risk of cardiovascular disease may not benefit from this preventive treatment as much as a patient with a known history of cardiovascular disease and multiple chronic comorbidities.

In response to this issue, major contributions of the last decade have sharpened the initial concept of *overall* EBM to *risk-stratified* EBM[5–9]; the results of RCTs becoming tailored to the patient risk profile and showing, for instance, that patients at a high risk of poor outcome are likely to have a more beneficial treatment response than patients at a low risk.[10] However, a limitation of such a risk stratification may reside in the patient risk being explained in fact by different compositions of factors; for instance, a same high level of cardiovascular risk can be due to uncontrolled hypertension for one patient, and to advanced-stage diabetes for another. If those factors modify the treatment effect in different magnitudes and directions, e.g. suppose a treatment is highly effective in people with hypertension but ineffective in people with diabetes, the advantage of applying risk-stratified EBM to treatment decision-making becomes uncertain: on the one hand, treating only patients at high risk may lead to prescribing treatments to some for whom it is ineffective (i.e. overtreatment); on the other hand, leaving patients at low risk untreated may lead to neglecting an effective treatment for those who could benefit from it (i.e. undertreatment).

Instead of making a treatment decision based on the risk level, one may want to consider anticipated clinical responsiveness to treatment (i.e. benefit-to-harm balance) as the main criterion. The strength of such an approach may be two-fold, both by encouraging treatment prescription when benefits are expected and by suggesting no prescription, or deprescription, when harms or no benefits are predicted. For instance, while the benefit of widely prescribed statins might be expected in the majority of individuals, it is also crucial to anticipate treatment intolerance,[11] or side effects, such as the increase of diabetes risk.[12] In the population of older individuals, statin prescription strategy for cardiovascular prevention may not be straightforward, given the limitations of cardiovascular risk scoring systems [e.g. Systematic Coronary Risk Estimation (SCORE) applicable only to individuals aged ≤ 70 years], and little evidence of statin benefit in individuals aged > 75 years without history of vascular disease (see ESC/EAS guidelines 2019 for the management of dyslipidaemias).[13] Recent examples in cardiovascular diseases showed how the development and validation of clinical prediction models could help clinicians identify patients who may, or may not, benefit from pharmacological treatment, by predicting the responsiveness to drug therapies.[14–16] In this article, we intend to further demonstrate the importance of moving the paradigm on risk stratification towards predicted *treatment responsiveness*. As an application, we reanalyse the data of the PROSPER study: a major randomized controlled trial showing evidence of the overall protective effect of pravastatin treatment amongst older individuals at risk of vascular disease.[17] For the clinician, the issue of the prediction of individualized treatment responsiveness can be formulated as the shift in patient prognosis due to pravastatin prescription (i.e. the contrast in cardiovascular risk if the patient were to be prescribed pravastatin vs. if the patient were not to be prescribed

pravastatin). Such a prediction can be obtained by modelling the prognosis of individuals sharing similar characteristics (in terms of sex, lifestyle, and medical history) and who have been exposed to either pravastatin or placebo, respectively.

In this reanalysis, we aim to quantify the effect sizes of three different treatment strategies: (i) an *overall* strategy, i.e. prescribing pravastatin to all old individuals sharing the characteristics of those recruited in the experiment; (ii) a *risk-stratified* strategy, i.e. prescribing pravastatin only to those who have suffered a previous vascular event (secondary or tertiary prevention); and (iii) an individualized *treatment responsiveness* strategy, i.e. prescribing pravastatin only to those for whom a favourable outcome is predicted under statin treatment.

Methods

Data and participants

The PROSPER trial was a multicentre, randomized placebo-controlled trial evaluating the effect of pravastatin on major vascular events in older individuals with pre-existing vascular disease or increased risk (e.g. smokers, hypertension, or diabetes people).[17] The trial included 5804 individuals aged 70–82 years from Scotland, Ireland, and The Netherlands between 1997 and 1999.[17] Additional information about the PROSPER trial can be found elsewhere (e.g. see original report and protocol).[17,18]

The PROSPER trial complied with the Declaration of Helsinki; written informed consents were obtained.[17] The ethics committees of all centres approved the original study. Data sharing agreements can be made upon reasonable request to the investigators of the trial.

Outcomes

The primary outcome was defined as a composite outcome of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke.[17] In this reanalysis, we included the following as secondary outcomes: all-cause mortality, non-cardiovascular death, cardiovascular death, fatal stroke, and coronary heart disease death. A detailed definition of these outcomes can be found in the original protocol of the trial.[18]

Statistical analysis

To guide the treatment prescription, we derived a model predicting the responsiveness to pravastatin and assessed its performance. For a given person, the endpoint to be predicted was not the occurrence of the primary outcome *per se*, but the *responsiveness* to pravastatin—also referred to as 'individualized treatment effect'[19,20]—that is, the contrast in potential primary outcome under two scenarios: the probability of event if they were to receive pravastatin vs. the probability of event if they were to receive placebo.

We took advantage of the multicentre nature of the PROSPER trial to perform 'internal–external cross-validation' (IECV), which is a recent, attractive method for both deriving generalizable prediction models and assessing how well they would likely perform in practice, using large, clustered data.[21–25] Briefly, when performing IECV in data including K centres, one out of the K centres is left out to assess the validity of a prediction model derived on the remaining $K-1$ centres. This procedure is repeated by rotating the hold-out centres, thus allowing one to assess the generalizability of a prediction model K times, across K centres, where practice, measurement, and case-mix are likely to differ and affect the predictive performance. Throughout IECV, we fit a prediction model using Cox proportional hazard regression, including as explanatory variables the treatment status (i.e. pravastatin/placebo) and the following baseline covariates: age, sex, smoking status, baseline cholesterol and triglyceride levels, prior comorbidities, treatments (others than statins), and cognitive function [mini-mental state examination (MMSE)]. Based on clinical knowledge and the numerous existing prediction models of cardiovascular risk,[26] these variables were assumed to be likely predictors of the primary outcome. We included two-way interaction terms between the treatment status and these baseline covariates, which were also considered as highly credible potential effect modifiers. We applied penalization by least absolute shrinkage and selection operator (lasso) to reduce the risk of over-fitting predicted individualized treatment response.[20,27–30] We used IECV to identify the combination of interaction terms leading to the prediction model with the best performance at validation in the hold-out clusters (see Supplementary material online, Appendix *S1A* and *S1B*).

We defined the performance as the potential clinical impact of the prediction model, that is, the reduction in primary outcome associated with the treatment rule guided by the predicted treatment responsiveness. The prediction model using Cox regression returned for each person a predicted hazard under pravastatin and a predicted hazard under placebo, the ratio of the two corresponding to an individualized hazard ratio (iHR). We constructed a treatment rule based on this predicted responsiveness,[31] which defined individuals to be prescribed pravastatin as those with $iHR < 1$ (so-called 'treatment-favourable' individuals likely to benefit from pravastatin), and individuals to be prescribed no pravastatin (placebo) as those with $iHR \geq 1$ ('treatment-unfavourable' individuals unlikely to benefit from pravastatin). We computed the reduction in primary outcome associated with this treatment rule (see Supplementary material online, Appendix *S1B*). The greater this reduction, the greater the clinical benefit of the treatment decision strategy based on the prediction model. Thus, we identified throughout IECV the 'best' candidate prediction model with interaction terms that led to optimizing the clinical benefit of treatment decision at validation.

In a final step, we fit the 'best' candidate model to the full sample to make use of all data available at hand, applying a lasso penalization to the estimation of the model coefficients. We used this final model to identify 'treatment-favourable' and 'treatment-unfavourable' individuals in the full sample. We assessed the effect of the optimal treatment rule based on these predicted 'treatment-favourable'/'treatment-unfavourable' profiles on the primary outcome.[31] We estimated in the full sample the effect sizes of three decision strategies allocating treatment to (1) *all*, (2) those at high *risk*, and (3) those with predicted favourable *treatment responsiveness*. Group 1 included all individuals randomly allocated to pravastatin treatment (i.e. initial treatment arm); Group 2 included individuals with history of vascular disease randomly allocated to pravastatin treatment and individuals without history of vascular disease randomly allocated to placebo; and Group 3 included 'treatment-favourable' individuals randomly allocated to pravastatin treatment and 'treatment-unfavourable' individuals randomly allocated to placebo. An estimation of the effect sizes associated to each of the three groups was performed as an intention-to-treat analysis following randomization (see Supplementary material online, Appendix *S1C*). We defined a common reference as the group of all individuals not allocated to pravastatin (i.e. initial placebo arm). We estimated the effect sizes on an absolute scale [hazard difference (HD)] using Aalen additive hazard model, and on a relative scale [hazard ratio (HR)] using Cox proportional hazard model with Firth penalization.[32] We computed confidence intervals by bootstrapping (1000 iterations).

Overall, our analysis followed the Predictive Approach to Treatment Heterogeneity (PATH) statement[7,9] in limiting the set of variables to be included in the prediction model to highly credible effect modifiers, performing no one-variable-at-a-time selection, adopting penalized regression, and defining a clinically meaningful performance measure instead of conventional metrics of discrimination and calibration of predicted risk.

No imputation method was performed, given the very low rate of missing data regarding the aforementioned variables (1.2%). All statistical analyses were performed in R, version 3.6.2 (further details on statistical packages, estimation, and regression techniques are in Supplementary material online, Appendix *S1*).

Role of the funding source

The funding sources had no roles in the study design and in the collection, analysis, and interpretation of data nor in the writing of the manuscript and in the decision to submit it for publication.

Results

The primary outcome occurred in 473/2913 (16.2%) and 408/2891 (14.1%) individuals randomly allocated to treatment with placebo and pravastatin, respectively: HR = 0.85 (95% CI 0.74–0.97), which was the effect size of the *overall* treatment strategy reported in the original analysis of the PROSPER trial. On an absolute scale, this corresponded to a hazard difference of −78 events (95% CI, −144 to −12) per 10 000 person-years.

When applying a *risk-stratified* strategy initiating pravastatin treatment only in old individuals with a history of vascular disease and leaving

Table 1 Coefficients and baseline cumulative hazard functions of the model predicting the rate of primary outcome under two hypothetical scenarios: if pravastatin were prescribed and if pravastatin were not prescribed

Baseline characteristics	Coefficient	
	If pravastatin prescribed	If pravastatin not prescribed
Pravastatin	.	−0.0811
Age (years)	0.0392	0.0392
Male sex	0.3011	0.3011–0.1641
Smoker	0.1754	0.1754 + 0.1175
Lipid levels:		
HDL-cholesterol	−0.0177	−0.0177
Triglycerides	0.0068	0.0068
Comorbidities:		
History of hypertension	0.0641	0.0641
History of diabetes	0.3779	0.3779
History of vascular disease	0.0774	0.0774–0.0360
History of myocardial infarction	0.4373	0.4373
History of CABG	−0.0257	−0.0257
History of PTCA	0.0000	0.0000
History of angina	0.2122	0.2122
History of claudication	0.4708	0.4708
History of PVD surgery	−0.3184	−0.3184
Treatments:		
ACE inhibitors	0.0365	0.0365 + 0.0022
Beta-blockers	0.0981	0.0981
Calcium channel blockers	0.2017	0.2017
Other anti-hypertensives	0.5368	0.5368–0.3773
Aspirin	0.1489	0.1489
Anti-coagulants	0.1840	0.1840
Anti-arrhythmic	0.3936	0.3936
Non-insulin diabetes	−0.1994	−0.1994 + 0.5246
MMSE	−0.0546	−0.0546
Baseline cumulative hazard function	$\text{Ln}[H_0(\text{time})] = -5.1746 + 1.1076\ \text{Ln}(\text{time})$	

For each individual, the individualized hazard ratio (iHR) is predicted as follows: iHR = exp(−0.0811 + −0.1641*male sex + 0.1175*smoker + −0.0360*history of vascular disease + 0.0022*ACE inhibitors + −0.3773*other antihypertensive drugs + 0.5246*non-insulin diabetes)
Under each scenario, the hazard is predicted by calculating the product of the baseline cumulative hazard function H0(time) (in years) and the exponential of the linear predictor [i.e. linear predictor = sum (coefficients*predictor values)].

those without history of vascular disease untreated, we observed an absolute difference of −66 events (95% CI, −114 to −18) per 10 000 person-years. This corresponded to a 12% relative reduction of the primary outcome: HR = 0.88 (95% CI: 0.80 to 0.97).

We assessed the performance of a prescription strategy based on the prediction of an individualized treatment responsiveness. We reported the estimated coefficients of the prediction model, which was likely the best at distinguishing individuals who would have the primary outcome decreased under pravastatin (i.e. 'treatment-favourable') from those who would not (i.e. 'treatment-unfavourable') based on six treatment effect modifiers (see *Table 1*). We found that following the individualized *treatment responsiveness* strategy, prescribing pravastatin only to those who were predicted to be 'treatment-favourable' and leaving untreated those predicted to be 'treatment-unfavourable', yielded an absolute difference of −103 events (95% CI: −162 to −44) per 10 000 person-years, that is, a 19% relative reduction [HR = 0.81 (95% CI: 0.71 to 0.91)], which seemed to outperform the *overall* and *risk-stratified* treatment strategies (*Figure 1*). In a formal comparison, the individualized *treatment responsiveness* strategy led to an absolute difference of −23 events (95% CI: −47 to 1) per 10 000 person-years compared with the *overall* strategy [5% relative reduction of the primary outcome, HR = 0.95 (95% CI: 0.90 to 1.00)] and to an absolute difference of −37 events (95% CI: −76 to 2) per 10 000 person-years compared with the *risk-stratified* strategy [8% relative reduction, HR = 0.92 (95% CI: 0.85 to 1.00)]. To prevent possible optimism in the estimated effect sizes, we performed a bootstrap-correction procedure taking into account the uncertainty of all sequences of the analysis (see Supplementary material online, Appendix *S1D*). The results were similar, indicating no optimism (see Supplementary material online, Appendix *S2B*).

As depicted in *Figure 2*, the prediction model predicted pravastatin to provide benefit in a majority of old age people (86.1%); the rest (13.9%) predicted to have no benefit. We reported in *Table 2* the baseline characteristics of the 'treatment-favourable' and 'treatment-unfavourable' individuals. The group of 'treatment-favourable' individuals included on average more male, non-smoking individuals with history of hypertension, vascular disease, myocardial infarction, and angina. In addition, they were likely to be non-diabetic.

Conventional subgroup analyses based on treatment responsiveness indicated a clear protective effect of pravastatin on the primary outcome within individuals who were predicted to be 'treatment-favourable' [HD = −122 events (95% CI: −193 to −51) per 10 000 person-years; HR = 0.78 (95% CI: 0.68 to 0.90)]. Conversely, within individuals predicted to be 'treatment-unfavourable', there was an increase of the primary outcome under pravastatin compared with placebo [HD = 187 events (95% CI: 2 to 372) per 10 000 person-years; HR = 1.43 (95% CI: 1.01 to 2.05)]. We explicitly emphasize caution in interpreting this subgroup analysis made on 13.9% of the sample, which may be the result of chance finding. The results are reported for the sake of transparency only. The subgroup analyses for the secondary outcomes are summarized in *Table 3*.

We explored whether the 'treatment-favourable' and 'treatment-unfavourable' profiles were merely associated with adherence and non-adherence behaviours rather than the clinical responsiveness to pravastatin; we found no significant association (see Supplementary material online, Appendix *S2C*).

We also investigated whether the 'treatment-favourable' and 'treatment-unfavourable' profiles were associated with the change to baseline LDL-cholesterol (at 3, 6, 12, 24, and 36 months) under treatment with pravastatin; we found a very minor further reduction of LDL-cholesterol levels in 'treatment-favourable' individuals compared with 'treatment-unfavourable' individuals (see Supplementary material online, Appendix *S2C*).

Discussion

Using a newly derived and validated prediction model for estimating treatment responsiveness, we have identified a large subgroup of old age individuals who are likely to benefit from pravastatin, and on the other hand, a minority of old age individuals likely to have no benefit from this treatment. Our main results indicate that prescribing pravastatin only to old people who were predicted to have a favourable response under pravastatin may be a more effective strategy for reducing cardiovascular outcomes than prescribing pravastatin only to those at high risk (as those who suffered a previous clinical event), or to prescribing pravastatin to all older people.

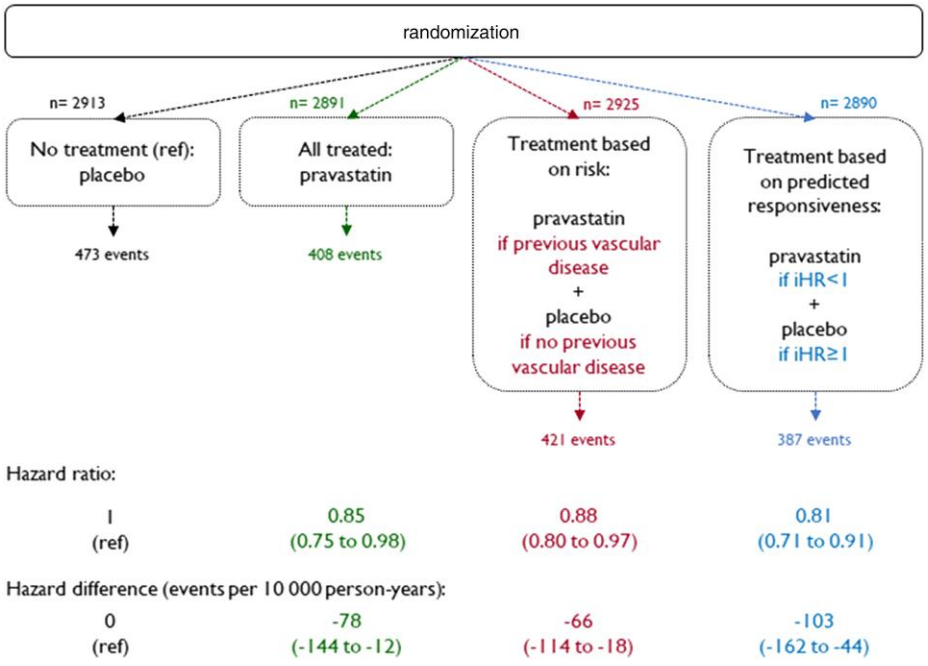


Figure 1 Effect sizes of three evidence-based decision strategies for prescribing pravastatin compared with placebo treatment: (i) prescription to all; (ii) prescription only for those at risk defined by a history of vascular disease; and (iii) prescription only to those expected to have a favourable treatment response defined by a predicted individualized hazard ratio (iHR) < 1. Hazard differences and hazard ratios (with 95% confidence intervals) are reported for the primary outcome: coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke.

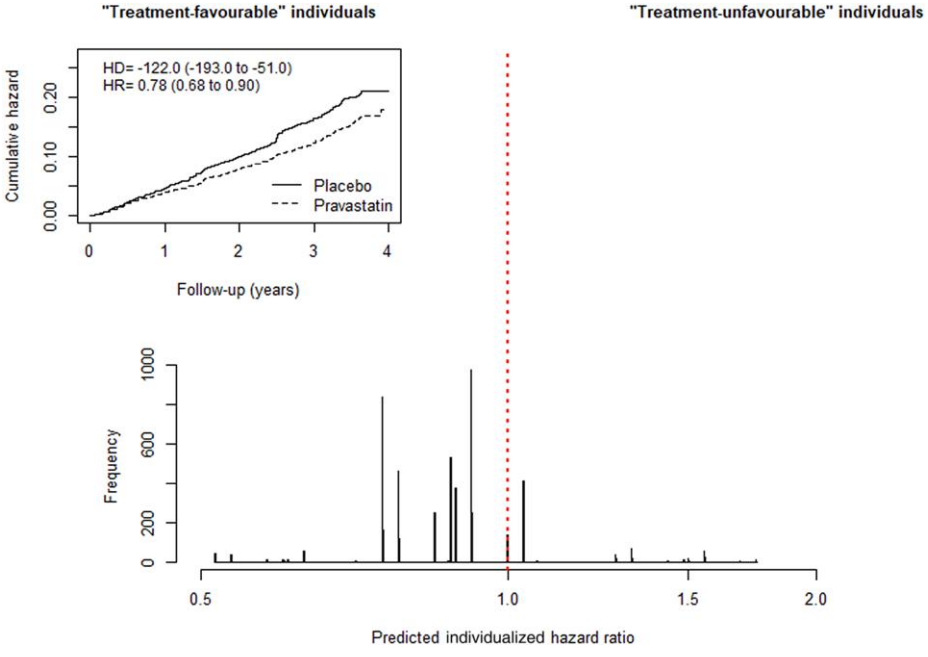


Figure 2 Hazard differences (HD) and hazard ratios (HR) of pravastatin to placebo for the primary outcome, according to predicted responsiveness (upper panels). Hazard differences are expressed in events per 10 000 person-years. Individuals with a predicted individualized hazard ratio (iHR) < 1 were labelled 'treatment-favourable' (86.1%); those with a predicted iHR ≥ 1 were labelled 'treatment-unfavourable' (13.9%). Lower panel represents the distribution of predicted individualized treatment responses to pravastatin of all randomized individuals (iHR).

Table 2 Characteristics across individuals predicted to benefit from pravastatin (i.e. 'treatment-favourable' individuals with iHR < 1) and individuals predicted to have no benefit from pravastatin (i.e. 'treatment-unfavourable' individuals with iHR ≥ 1). Means (standard deviations) and counts (percentages) are reported for continuous and categorical variables, respectively. *P*-values are not reported, as the non-random model-based subgrouping inherently eliminates the null hypothesis

Baseline characteristics	'Treatment-favourable' *n* = 4935 (86.1%)	'Treatment-unfavourable' *n* = 800 (13.9%)
Age (years)	75.40 (3.37)	74.91 (3.17)
Male sex	2581 (52.3)	189 (23.6)
Smoker	1042 (21.1)	495 (61.9)
Lipid levels:		
LDL-cholesterol	3.81 (0.79)	3.73 (0.83)
HDL-cholesterol	1.27 (0.34)	1.31 (0.39)
Total cholesterol	5.69 (0.91)	5.67 (0.90)
Triglycerides	1.54 (0.71)	1.59 (0.67)
Comorbidities:		
History of hypertension	3225 (65.3)	329 (41.1)
History of diabetes	262 (5.3)	355 (44.4)
History of vascular disease	2402 (48.7)	128 (16.0)
History of myocardial infarction	715 (14.5)	50 (6.2)
History of CABG	142 (2.9)	9 (1.1)
History of PTCA	92 (1.9)	7 (0.9)
History of angina	1465 (29.7)	74 (9.2)
History of claudication	355 (7.2)	25 (3.1)
History of PVD surgery	109 (2.2)	11 (1.4)
Treatments:		
ACE inhibitors	821 (16.6)	117 (14.6)
Angiotensin II receptor blockers	96 (1.9)	17 (2.1)
Beta-blockers	1374 (27.8)	111 (13.9)
Calcium channel blockers	1321 (26.8)	124 (15.5)
Other anti-hypertensives	222 (4.5)	11 (1.4)
Nitrates	1018 (20.6)	61 (7.6)
Aspirin	1914 (38.8)	160 (20.0)
Anti-coagulants	103 (2.1)	10 (1.2)
Anti-arrhythmics	135 (2.7)	19 (2.4)
Non-insulin diabetes	8 (0.2)	348 (43.5)
Insulin diabetes	43 (0.9)	8 (1.0)
MMSE	28.04 (1.53)	27.93 (1.63)

The overall results of RCTs, including the PROSPER trial,[17] have shown that treating old people with statins irrespective of their risk of vascular disease provides benefit—both from utilitarian and deontological perspectives. Although statins may provide protection in the majority of old individuals, our reanalysis of the PROSPER trial shows that pravastatin prescription lacks a favourable outcome in about one out of seven individuals. While it may be acceptable to overtreat a small portion of individuals of the general population given the low-risk safety profile and important benefits of statins, concerns are different in *old age*. Polypharmacy in elderly individuals is known to be a major health issue that deserves attention and action; we believe it would be unethical to continue a treatment that could be safely withheld in some individuals. To help clinicians identify old age individuals who are likely to benefit from pravastatin, we report a model predicting the responsiveness to pravastatin on vascular events. Estimating the effect sizes of different treatment decision strategies based on risk assessment or prediction models is pivotal to informing clinicians; yet, it is never or rarely done. Thus, we do *not* recommend interpreting the subgroup analysis reported in *Figure 2* alone; rather, our main analysis aims to infer the overall effect of prescription strategies (*Figure 1*). In this study, we have assessed the potential clinical efficacy of the prescription strategy guided by our prediction model, using novel methods.[31] Unlike conventional subgroup results—which are still recommended for they provide a rough guidance to clinicians[7,9]—we quantified the overall benefit-to-harm balance of treating some individuals while leaving others untreated following different prescription decision rules. This allowed us to infer the overall effect of decision rules, even though they may misclassify individuals who should be treated or not treated. For instance, it is likely that our prediction was not perfect, and that some individuals labelled 'favourable' were in fact 'unfavourable' and vice versa; the impact of such possible misclassification was accounted for in the estimate of the overall effect of the prescription strategy. Although the benefit of initiating treatment with pravastatin in older people without a previous history of vascular disease is still under debate,[13] our results indicate that disregarding such a

Table 3 Subgroup analyses of the primary and secondary outcomes within individuals predicted to benefit from pravastatin (i.e. 'treatment-favourable' individuals with iHR < 1) and individuals predicted to have no benefit from pravastatin (i.e. 'treatment-unfavourable' individuals with iHR ≥ 1). Hazard differences (with 95% confidence intervals) and hazard ratios (with 95% confidence intervals corrected by Firth penalization) are reported, along with *P*-values for additive and multiplicative interaction tests, respectively

Outcome	'Treatment-favourable' Hazard difference[a]	'Treatment-unfavourable' Hazard difference[a]	Interaction test *P*-value Additive scale
Primary outcome	−122.0 (−193.0 to −51.0)	187.0 (2.2 to 372.0)	0.002
All-cause mortality	−38.6 (−93.3 to 16.1)	226.0 (65.1 to 387.0)	0.002
Non-cardiovascular death	3.3 (−35.4 to 41.9)	135.0 (9.6 to 260.0)	0.052
Cardiovascular death	−41.9 (−80.5 to −3.3)	90.9 (−10.0 to 192.0)	0.014
Fatal stroke	3.6 (−9.2 to 16.4)	44.1 (−4.1 to 92.3)	0.109
CHD death	−38.9 (−72.2 to −5.6)	21.6 (−62.5 to 106.0)	0.161
	Hazard ratio	**Hazard ratio**	**Multiplicative scale**
Primary outcome	0.78 (0.68 to 0.90)	1.43 (1.01 to 2.05)	0.002
All-cause mortality	0.88 (0.74 to 1.05)	1.73 (1.18 to 2.58)	0.002
Non-cardiovascular death	1.02 (0.80 to 1.31)	1.72 (1.05 to 2.86)	0.066
Cardiovascular death	0.76 (0.59 to 0.98)	1.74 (0.95 to 3.30)	0.011
Fatal stroke	1.23 (0.58 to 2.63)	3.40 (0.91 to 18.17)	0.198
CHD death	0.71 (0.53 to 0.95)	1.20 (0.59 to 2.49)	0.155

[a]Hazard differences are expressed in events per 10 000 person-years.

preventive treatment may result in a loss of overall benefit of pravastatin therapy. Following the suggestion of a reviewer, we performed an additional analysis based on the recent SCORE2-OP developed and validated by de Vries et al. (2021).[33] Although the SCORE2-OP is valid to predict the 10-year risk of cardiovascular events in elderly individuals, we found that it did not perform well in indicating who would benefit from pravastatin and who would not benefit from this treatment (see Supplementary material online, Appendix *S2D*). These additional results are not at odds with de Vries et al.[33] who found no interaction between the effect of pravastatin and the SCORE2-OP (see their Supplementary Material).

While some have warned against the confusion between non-response and non-adherence to treatment,[34] our reanalysis shows that non-adherence is not associated with treatment responsiveness as predicted by our model. Neither the adherence to nor the reduction in LDL-cholesterol under pravastatin treatment is strongly associated with the predicted responsiveness. Both explain only little of the benefit amongst those who are predicted to have a favourable response to pravastatin. These results are not at odds with the findings that monitoring vascular risk in old age based on cholesterol may not suffice.[35,36] In a recent meta-analysis, the Cholesterol Treatment Trialists' Collaboration (2019) observed with increasing age a trend towards smaller proportional risk reductions in major coronary events from LDL lowering.[37] Further, from a prediction perspective, previous literature showed that LDL-cholesterol level was a poor risk indicator of cardiovascular death in old age (e.g. see Weverling-Rijnsburger et al. 2003).[38] The diverse, individual protective effect of pravastatin on clinical outcomes may be better predicted by considering other characteristics of the individual profile (e.g. diabetes and hypertension), which our prediction model may help to identify.

The use of prediction models has been advocated to guide clinical decision-making when treatments may display heterogeneous effects across different individual profiles.[7,9] Ideally, decision-making should be multi-dimensional and take into account multiple endpoints, such as risk for mortality, risk for non-fatal outcomes, risk for side effects, limited resources, and financial constraints. In this reanalysis, we defined the benefit/harm according to only the cardiovascular events used as primary outcomes in the PROSPER trial; this is a limitation of our study. As the identification of benefit, harm or null effect directly depends on model-based predictions; a key challenge to such an approach is a careful modelling of treatment effect heterogeneity by including relevant interaction terms between predictors and treatment variable.[27,28] When interactions are not properly handled, the predicted benefit/harm may be a mere result of over-fitting: in such a case, a seemingly neat distinction between individuals with and without a favourable response to treatment may in fact be over-optimistic.[27,28] To prevent spurious finding, we adopted a stringent penalization of our prediction model, assessed its generalizability multiple times using internal–external cross-validation, corrected our validation results for potential small sample bias, and performed a final bootstrap-correction procedure of the whole analysis. Limiting the set of effect modifiers to prevent over-optimistic results may have led to omitting possible, not yet identified, important variables and/or interactions.

The clinical prediction model we present could optimize the benefit and minimize the harm of pravastatin treatment by helping clinicians to 'choose wisely' and distinguish those individuals expected to benefit from the treatment from those expected to have no benefit or suffer harm. A key limitation is that the usefulness of our prediction model in daily clinical practice is still to be proven. External validation using other data than the PROSPER study needs to be conducted to establish the generalizability of our model. Further studies are needed, such as a randomized controlled trial comparing strategies of prescribing or deprescribing statins with or without the use of our prediction model. Moreover, because pravastatin was the sole treatment randomized in the PROSPER study, inference about the effect of other treatments (targeting other risk factors than LDL-cholesterol) could not be made; thus, our results cannot inform on what treatments could be prescribed to individuals in whom pravastatin should be withheld. Another limitation of our study is our inability to provide explanation on the mechanism behind the more pronounced responsiveness to pravastatin treatment in some individuals compared with others. Our model is meant to be predictive—and not aetiological—therefore, the coefficients reported are

to be used only to predict the treatment responsiveness, since the variables included in the model were found to be indicators (or predictors) of the response to pravastatin; they must *not* be interpreted as causes of the treatment responsiveness. Our prediction rule answers the question 'who are those individuals favoured by pravastatin treatment?' but not 'why do they respond to pravastatin better than other individuals?' Finally, it is worth clarifying that the prediction of *individualized* treatment responsiveness is obtained by modelling the treatment effect in groups of individuals sharing similar measurable characteristics; strictly speaking, this differs from the *individual* treatment responsiveness, which is inaccessible since a single individual (defined by an infinite set of characteristics) is unique and can be exposed only to either pravastatin or placebo, but never both at the same time.

Supplementary material

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

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Author contributions

T.L.N. is the guarantor of this manuscript. T.L.N. is responsible for the conception and design of the work, analysis and interpretation of data for the work, and wrote first draft of the manuscript. S.T. is responsible for the acquisition and interpretation of data for the work, verification of the underlying data, and critical revision of the first draft for important intellectual content. J.B.B. is responsible for the interpretation of data for the work and critical revision of the first draft for important intellectual content. J.H. is responsible for the analysis and interpretation of data for the work and critical revision of the first draft for important intellectual content. T.P.A.D. is responsible for the analysis and interpretation of data for the work and critical revision of the first draft for important intellectual content. J.W.J. is responsible for the acquisition and interpretation of data for the work, verification of the underlying data, and critical revision of the first draft for important intellectual content. R.G.J.W. is responsible for the conception and design of the work, interpretation of data for the work, and first draft of the manuscript.

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Data availability

Data sharing agreements can be made upon reasonable request to the investigators of the trial. Requests must be sent to S. Trompet (S.Trompet@lumc.nl), who will provide access to data. Access to data (de-identified participant data, and data dictionary) will require the investigator support, after approval of a proposal, with a signed data access agreement. Access to data will start after agreement signature until the end date mentioned in the agreement form.

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