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Chapter 6

Risk stratification and treatment effect of statins in secondary cardiovascular prevention in old age: additive value of NT-proBNP

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ABSTRACT

Aims

To assess predictive values for recurrent cardiovascular disease, of models with age and sex, traditional cardiovascular risk markers, and SMART risk score, with and without N-terminal pro-B-type natriuretic peptide (NT-proBNP). To assess treatment effect of pravastatin across low and high risk groups identified by these models.

Methods and Results

Post-hoc analysis in participants (n=2348, age 70-82 years) with a history of cardiovascular disease within the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized placebo-controlled study. Primary endpoint was recurrent cardiovascular event (myocardial infarction and/or stroke) or cardiovascular mortality. The models with age and sex, traditional risk markers and SMART risk score had comparable predictive values (area under the curve (AUC) 0.58, 0.61 and 0.59, respectively). Addition of NT-proBNP to these models improved AUCs with 0.07 (p_{diff}=0.003), 0.05 (p_{diff}=0.009) and 0.06 (p_{diff} <0.001), respectively, and net reclassification improvements were 41% (p<0.001), 39% (p<0.001) and 25% (p=0.002), respectively. For the model with age, sex and NT-proBNP, the hazard ratio for the primary endpoint with pravastatin treatment compared to placebo was 0.67 (95%CI 0.48-0.96) for participants in the high third of predicted risk and 0.94 (0.65-1.36) in the low third, number needed to treat 16 (8.7-121) and 116 (17-∞), respectively.

Conclusion

In secondary cardiovascular prevention in old age predictive value of traditional risk markers and SMART risk score is poor. Addition of NT-proBNP improves prediction of recurrent cardiovascular disease and mortality. A minimal model including age, sex and NT-proBNP predicts as good as complex risk models including NT-proBNP.

INTRODUCTION

Persons with known cardiovascular disease are at high risk of recurrent events, and guidelines worldwide advise statins for secondary prevention,[1-3] even in old age.[4] Yet, prescription of secondary preventive treatment decreases with age.[5,6] This might be caused by dilemmas regarding starting, continuing, or safely stopping preventive treatment, as physicians have to weigh postponed benefit versus current harm and priorities of care in old age. As many more patients are surviving their initial cardiovascular event, prediction of recurrent events becomes increasingly important. Ideally, the risk markers or risk models used, not only predict recurrence risk, but predict treatment effect as well. In secondary prevention in old age, traditional cardiovascular risk markers loose predictive value[7,8] and most risk scores are either too complex or only apply to restricted subgroups of hospitalized patients.[9,10] To date, for the general older population, no risk scores for prediction of recurrence risk and/or treatment effect exist. Recently the SMART risk score was developed to predict recurrent cardiovascular events in a younger cohort of patients with a history of cardiovascular disease (mean age 60 years),[11] but this risk score has not been validated in older age.

A new promising predictor of cardiovascular risk in old age is N-terminal pro-brain natriuretic peptide (NT-proBNP),[8,12-15] a polypeptide released in reaction to myocardial wall stress or ischemia. Addition of NT-proBNP to a model with the traditional cardiovascular risk markers or SMART risk score might improve predictive performance, especially in older patients.

Therefore, we first validated the SMART risk score in 1157 old subjects (mean age 75 years, placebo group) with a history of cardiovascular disease participating in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).[16] We compared the predictive value for recurrent cardiovascular events and mortality of the SMART risk score, with a model with traditional cardiovascular risk markers and with a minimal model including only age and sex. Second, we investigated whether addition of NT-proBNP to these prediction models could improve prediction. Third, we studied whether treatment effect of pravastatin was different across groups with low and high risk, calculated with the different models.

METHODS

Study design

Data in this study were obtained from the PROSPER study, a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older persons. Details of the design and outcome of PROSPER have

been published elsewhere.[16-18] Between December 1997 and May 1999, a total of 5804 individuals were screened and enrolled in Scotland, Ireland and the Netherlands. Men and women aged 70-82 years were recruited. A total of 2565 participants had a history of cardiovascular disease (including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and vascular surgery), and were included in the present study.

Individuals with congestive heart failure (New York Heart Association functional class III and IV) or poor cognitive function (Mini-Mental State Examination score <24 points) were excluded from PROSPER.[18] Participants were randomized into a group who received 40 mg pravastatin a day and a control group receiving placebo and were followed 3.2 years on average. Throughout the study, all study personnel was unaware of the allocated study medication status of the participants. The institutional ethics review boards of all centres approved the protocol and all participants gave written informed consent. The protocol adhered to the principles of the Declaration of Helsinki.

Traditional cardiovascular risk markers and SMART risk score variables

During the pre-randomization visits, baseline participant characteristics were collected,[17] including a detailed medical history with date(s) of last cardiovascular events, smoking status and current medication use. Participants weight, height and blood pressure were measured and fasting venous blood samples were taken including biobank samples. A history of diabetes was defined as a known diabetes mellitus or fasting blood glucose >7 mmol/L. Baseline serum creatinine levels were measured at central laboratories. Estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease equation[19]:

$$eGFR=186 \times \text{serum creatinine level } (mg/dl)^{(-1.154)} \times age^{(-0.203)} \times 0.742 \text{ [if female]}$$

Data of eGFR was missing for 5 included participants. High sensitivity C-reactive protein (hsCRP) levels were measured on stored K_2EDTA (at -80ºC) baseline samples.[20] Data of hsCRP was missing for 41 included participants due to technical problems. All laboratory analyses were conducted by technicians blind to the identity of samples and outcomes. Time since last cardiovascular event was calculated from the recorded date(s) of last cardiovascular event.

NT-proBNP measurements

Blood samples were taken at 6 months after baseline in EDTA tubes.[18] The venous blood samples were stored in the biobank. From biobank samples NT-proBNP was determined using electrochemiluminescence immunoassay on a Roche Modulator E170. NT-proBNP measurements were missing for 167 participants due to technical problems.

Outcomes

For the present study the primary outcome of the trial was used: the combination of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke.[18] The PROSPER Endpoints Committee assessed all endpoints. The Endpoints Committee was blinded for study medication, and for plasma levels of NT-proBNP.

Statistical analysis

From the 2565 participants with a history of cardiovascular disease, participants with coronary events or who died in the first 6 months of the study (n=50) and participants with missing NT-proBNP values at 6 months (n=167) were excluded. Baseline summary characteristics are reported as median with interquartile range (IQR) for continuous variables and as numbers with percentage (%) for categorical variables for all participants (n=2348) and for participants on placebo and those on pravastatin separately. Follow-up for the outcomes was calculated from 6 months onward up to a maximum of 2.5 years.

Calibration of the SMART risk score

For calculation of the SMART risk score the SMART formula[11] was used (Supplement 1). Calibration of the SMART risk score for the PROSPER trial population was investigated by comparing the predicted versus observed cardiovascular disease risks. Participants taking placebo were divided into five categories of 2.5-year predicted risk, <10%, 10 to <20%, 20 to <30%, 30 to <40%, and ≥40%. Within each category, predicted risk was compared to actual observed Kaplan-Meier cardiovascular disease free survival at 2.5 year follow-up (Supplement 2). In addition, the fitted regression coefficient (beta) was assessed in a Cox proportional hazard model fit, using only the linear prognostic score (A) as variable.[21] The continuous predictive SMART prognostic risk score was multiplied with the calculated regression coefficient to recalibrate the SMART risk score for the PROSPER population, as the calibrated regression coefficient significantly differed from 1 (0.466, p<0.001).

Risk prediction with three models in the placebo group

The 2.5-year cardiovascular disease risk (%) was predicted for all participants using a Cox proportional hazards models (complete case analysis) fit based on 1) age and sex (minimal model); 2) age, sex, smoking, systolic blood pressure, high density lipoprotein and total cholesterol, history of diabetes, history of hypertension, history of myocardial infarction, history of stroke/transient ischaemic attack and history of surgery for peripheral artery disease (all as assessed at baseline; traditional model); and 3) recalibrated SMART risk score (SMART model). Using the continuous predicted risks from the three

models, area under the curves (AUCs) and receiver operating characteristic (ROC) curves with p-values (level of significance 5%) and 95% confidence intervals for difference were calculated.

Additional value of NT-proBNP in the placebo group

NT-proBNP was non-normally distributed and therefore log transformed. Cox proportional hazards models for the occurrence of the primary endpoint were fitted based on three additional models including 1) minimal model plus NT-proBNP; 2) traditional model plus NT-proBNP; and 3) SMART model plus NT-proBNP. AUCs and ROC curves were calculated and compared to the reference models without NT-proBNP (STATA 12.1). Cross validation method was used for comparison of optimism-corrected estimates.[22]

Net Reclassification Improvement

We calculated the category-less Net Reclassification Improvement (NRI) for the primary endpoint with logistic regression, comparing the models including NT-proBNP to the reference models without NT-proBNP.[23,24]

Treatment effect comparing placebo and treatment group

Predicted risk for the primary endpoint was calculated for all participants using the regression coefficients from the models developed in the placebo group. The treatment effect of pravastatin according to the thirds of predicted risk for the primary endpoint of the three models including NT-proBNP was assessed in three ways. First, the presence of multiplicative interaction was tested by adding the interaction term 'treatment x thirds of predicted risk' in the Cox model. Second, per third of predicted risk, the absolute numbers of events in the pravastatin group and the placebo groups were calculated and the absolute risk reduction (ARR) by pravastatin was calculated using the life-table method. Differences in ARR between the thirds of predicted risk, were tested using a *z*-test. Numbers needed to treat (NNT) were calculated over 2.5 years based on the difference in cumulative proportion surviving in the pravastatin and placebo groups. Finally, the hazard ratio (HR) for the occurrence of cardiovascular events in the pravastatin group versus placebo group was calculated using the Cox proportional hazard model per third of predicted risk.

RESULTS

Table 1 presents the baseline characteristics for the participants. Of the 2348 participants 57% (n=1334) were men, 73% (n=1713) had a history of cardiac disease, 25% (n=594)

had a history of cerebrovascular disease and 17% (n=408) had a history of peripheral disease. The median NT-proBNP level was 176 ng/L (IQR 96-359).

Table 1 Baseline characteristics of the participants stratified for non-treatment and treatment group

	Total group n=2348	Placebo n=1157	Pravastatin n=1191
Age (years)	75 (73-78)	75 (73-78)	75 (73-78)
Male Sex	1334 (57)	658 (57)	676 (57)
Current smoker	427 (18)	214 (19)	213 (18)
Systolic blood pressure (mm Hg)	152 (138-168)	151 (136-168)	153 (138-168)
High-density lipoprotein cholesterol (mmol/L)	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
Total cholesterol (mmol/L)	5.6 (5.0-6.3)	5.6 (5.0-6.2)	5.6 (5.0-6.3)
History of diabetes mellitus	200 (9)	99 (9)	101 (9)
History of coronary artery disease[a]	1713 (73)	831 (72)	882 (74)
History of myocardial infarction	701 (30)	365 (32)	336 (28)
History of cerebrovascular disease[b]	594 (25)	299 (26)	295 (25)
History of peripheral artery disease[c]	408 (17)	204 (18)	204 (17)
History of surgery for peripheral artery disease	113 (5)	53 (5)	60 (5)
Time since first diagnose	6.0 (3.0-11.0)	6.0 (3.0-11.3)	7.0 (3.0-11.0)
Creatinine clearance[d]	52 (43-63)	52 (43-63)	52 (43-63)
High-sensitivity C-reactive protein (mg/L)[e]	3.1 (1.6-6.3)	3.1 (1.7-6.1)	3.2 (1.6-6.5)
N-terminal pro-brain natriuretic peptide (ng/L)[f]	176 (96-359)	174 (96-354)	177 (95-367)

Data are presented as median with interquartile range (IQR) for continuous variables and as numbers with percentage (%) for categorical variables.
[a] History of angina, myocardial infarction, coronary artery bypass surgery or percutaneous transluminal coronary angioplasty.
[b] History of transient ischemic attack or stroke.
[c] History of claudication or surgery for peripheral disease.
[d] Calculated with the Cockroft-Gault formula , missing n=5.
[e] Missing n=41.
[f] Measured at 6 months after study entrance.

Traditional cardiovascular risk markers and SMART risk score

During the maximum follow-up of 2.5 years, 16% (n=187) of participants in the placebo group (n=1157) developed a cardiovascular event or died of cardiovascular disease (primary endpoint). We calculated AUCs and created ROC curves for the minimal model, the traditional model and the SMART model, with the primary endpoint at 2.5-year (Figure 1). The three models had similar AUCs: 0.58 (95% CI 0.54-0.63) for the minimal model; 0.61 (95%CI 0.57-0.66) for the traditional model; and 0.59 (95% CI 0.54-0.63) for the SMART model (Table 2).
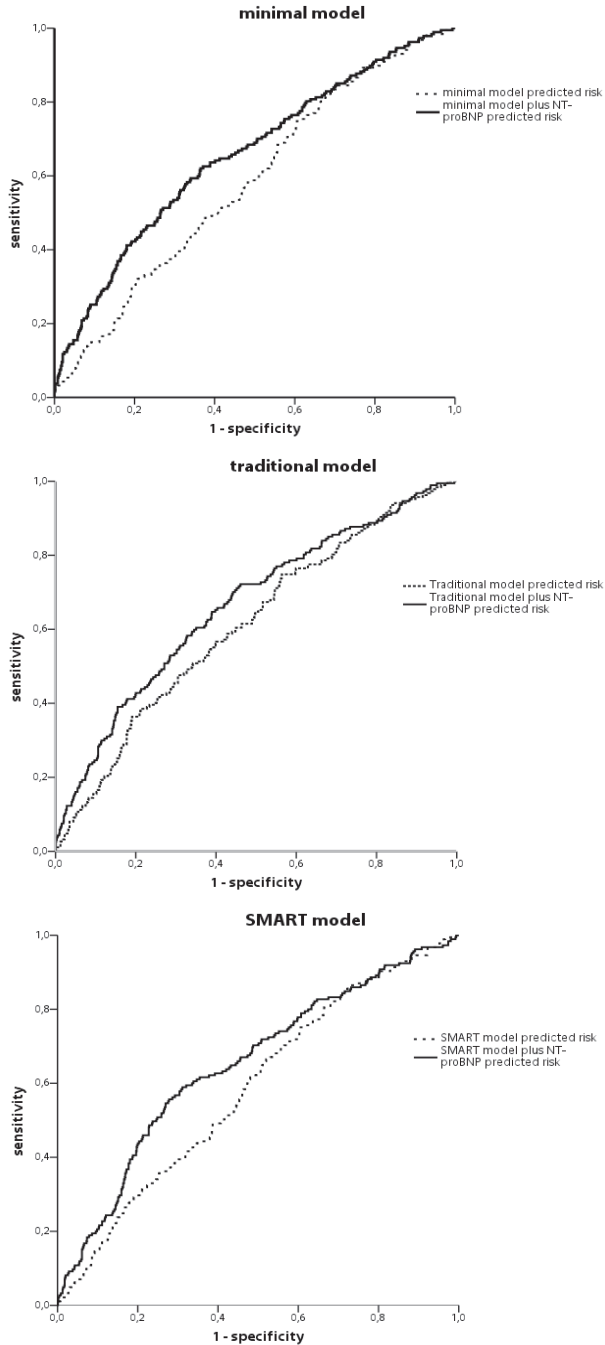
Figure 1. Receiver operating characteristic curves for three models without NT-proBNP (dotted lines) and with NT-proBNP (black lines) for cardiovascular events and cardiovascular mortality. Model with age and sex (top, minimal model) model with traditional risk markers (middle, traditional model) and model with SMART risk score (bottom, SMART model) (p Δ 0.003, 0.003 and< 0.001, respectively)

Addition of NT-proBNP

Figure 1 shows that the addition of NT-proBNP improved the AUC of all three models similarly. Addition of NT-proBNP to the minimal model increased the AUC from 0.58 to 0.65 (95% CI 0.6-0.70), Δ 0.07, p for difference (p_{diff}) =0.003. The increase in AUC was similar for both the traditional and the SMART model (Δ 0.05, p_{diff}=0.009 and Δ 0.06, p_{diff}<0.001, respectively) (Table 2).

The minimal model with addition of NT-proBNP performed similarly to the traditional model with addition of NT-proBNP (p_{diff}=0.26) as well as to the SMART model plus NT-proBNP (p_{diff} =0.87).

Cross validation of the minimal model led to an AUC of 0.56 (95%CI 0.52-0.61) and for the minimal model with addition of NT-proBNP to an AUC of 0.64 (95%CI 0.60-0.69). The difference between these two cross validated AUCs was 0.08 (p=0.0016). Cross validation of the other models showed similar results (data not shown).

Table 2. Absolute number of events in tertiles of predicted risk of the different models, with area under the curve (AUC), delta AUC with addition of NT-proBNP, and category free net reclassification improvement (NRI) for the primary endpoint

Risk models	Absolute numbers of events in tertiles of risk			AUC (95%CI)	ΔAUC	p Δ	NRI (%)	p value
	Low	Medium	High					
Minimal model	43 (11.2)	68 (17.8)	76 (19.4)	0.58 (0.54-0.63)				
Minimal model plus NT-proBNP	58 (14.8)	56 (14.4)	73 (19.4)	0.66 (0.61-0.70)	0.07	0.0026	41	<0.001
Traditional model	42 (11.0)	56 (14.6)	89 (22.7)	0.61 (0.57-0.65)				
Traditional model plus NT-proBNP	35 (9.0)	54 (13.7)	98 (26.1)	0.66 (0.62-0.70)	0.05	0.0091	39	<0.001
SMART model	60 (15.8)	60 (16.0)	65 (16.9)	0.59 (0.54-0.63)				
SMART model plus NT-proBNP	53 (14.4)	65 (16.0)	67 (18.3)	0.65 (0.61-0.70)	0.06	0.0006	25	0.002

Primary endpoint: 2.5-year risk for cardiovascular morbidity and mortality in the placebo group.
Minimal model including age and sex.
Traditional model including age, sex, smoking, systolic blood pressure, high density lipoprotein and total cholesterol, history of diabetes, history of hypertension, history of myocardial infarction, history of cerebrovascular disease and history of surgery for peripheral artery disease.
SMART model including age in years, age in years², sex, sex, smoking, systolic blood pressure, histories of diabetes, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm and peripheral artery disease, years since first diagnosis of vascular disease, estimated glomerular filtration rate and high sensitive C-reactive protein.

NRI

The category-less NRI with addition of NT-proBNP to the minimal model was 41% (p<0.001, 57% of participants reclassified up, minus 43% reclassified down in the group that experienced the endpoint, plus 63% reclassified down, minus 37% reclassified up in the group that did not experience the endpoint). The category-less NRI with addition of NT-proBNP to the traditional model was 39% (p<0.001). Addition of NT-proBNP to the SMART model had an NRI of 25% (p=0.002) (Table 2).

Treatment effect

Overall, in the 2348 participants with a history of cardiovascular disease within the PROSPER study population, the ARR by pravastatin treatment was 3.6% for 2.5 year. After, the 2.5-year HR for the development of the primary endpoint was 0.77 (95% CI 0.62-0.95) in the pravastatin group compared to the placebo group.

We divided participants according to thirds of predicted risk. Multiplicative interaction between treatment and thirds of predicted risks of all models was not significant (all p>0.1). Table 3 shows the treatment effect (2.5-year) of pravastatin according to thirds of predicted risk of cardiovascular disease and mortality for three risk models, all with NT-proBNP, including number of events (primary endpoint), ARR and HR. The ARR in primary endpoint with 2.5-year pravastatin treatment in the low predicted risk group of the minimal model plus NT-proBNP was 0.86% (95% CI -4.1-5.9) and in the high predicted risk group 6.2% (95% CI 0.8-11.5), difference=5.3% (95% CI 2.0-12.6, p diff=0.07). (Figure 2) In this model, participants with the highest predicted risk (highest third) and pravastatin treatment had a HR of 0.67 (95% CI 0.48-0.96) for the development of the primary endpoint compared to those on placebo. The NNT during 2.5 years with pravastatin was 16 (95% CI 8.7-121). HR for participants in the lowest third of predicted risk was 0.94 (95% CI 0.65-1.36), with a NNT of 116 (95% CI 17-∞).

DISCUSSION

This study shows that the predictive value of traditional cardiovascular risk markers and the (recalibrated) SMART risk score is poor in older people with a history of cardiovascular disease, and comparable to prediction with a model including only age and sex. Addition of NT-proBNP improved prediction of recurrent cardiovascular disease and mortality. We observed that a model with age, sex and NT-proBNP predicts as good as more complex risk models including NT-proBNP. Moreover in high risk individuals as identified by age, sex plus NT-proBNP level, NNT for 2.5-year pravastatin treatment was 16, whereas, in patients with a low predicted risk in this model, NNT was 116. As many

Table 3. Treatment effect after 2.5-year of treatment with pravastatin according to tertiles of predicted risk of cardiovascular disease and mortality for three risk models including NT-proBNP

	Events in pravastatin group	Events in placebo group	ARR (95%CI)	HR (95% CI)
Minimal model plus NT-proBNP				
Low	54 (13.9)	58 (14.8)	0.86 (-4.14-5.86)	0.94 (0.65-1.36)
Medium	41 (10.3)	56 (14.4)	4.2 (-0.48-8.86)	0.70 (0.47-1.05)
High	55 (13.5)	73 (19.4)	6.2 (0.83-11.54)	0.67 (0.48-0.96)
Traditional model plus NT-proBNP				
Low	26 (6,6)	35 (9.0)	2.5 (-1.28-6.33)	0.73 (0.44-1.20)
Medium	45 (11.6)	54 (13.7)	2.0 (-2.73-6.77)	0.83 (0.56-1.24)
High	79 (19.4)	98 (26.1)	7.2 (1.18-13.29)	0.71 (0.53-0.95)
SMART model plus NT-proBNP				
Low	45 (11.3)	53 (14.4)	3.0 (-1.86-7.78)	0.78 (0.52-1.15)
Medium	42 (11.6)	65 (16.0)	4.5 (-0.43-9.45)	0.72 (0.49-1.06)
High	60 (14.9)	67 (18.3)	4.0 (-1.45-9.43)	0.78 (0.55-1.11)

Minimal model including age and sex.
Traditional model including age, sex, smoking, systolic blood pressure, high density lipoprotein and total cholesterol, history of diabetes, history of hypertension, history of myocardial infarction, history of cerebrovascular disease and history of surgery for peripheral artery disease.
SMART model including age in years, age in years^2, sex, sex, smoking, systolic blood pressure, histories of diabetes, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm and peripheral artery disease, years since first diagnosis of vascular disease, estimated glomerular filtration rate and high sensitive C-reactive protein.

more patients are surviving their initial cardiovascular event, prediction and prevention of recurrent events becomes increasingly important and according to our study NT-proBNP is a promising risk predictor in old age.

Comparison with the literature

The combination of prediction of recurrent events and treatment effect has seldom been examined in secondary cardiovascular prevention. Our findings contrast with the findings in the CORONA and Heart Protection Study in patients with chronic heart failure, where the benefit of rosuvastatin was higher in the low NT-proBNP group. However, this relationship might have been modified by other patient characteristics in this specific population of ischemic heart failure patients.[25]

Previously, Sattar et al. have investigated within the entire PROSPER study population whether hsCRP could predict treatment effect and they observed that hsCRP did not predict response to statin therapy.[20] In contrast, Drewes et al. found a positive relation of homocysteine levels with treatment effect.[26] However, physicians are perhaps
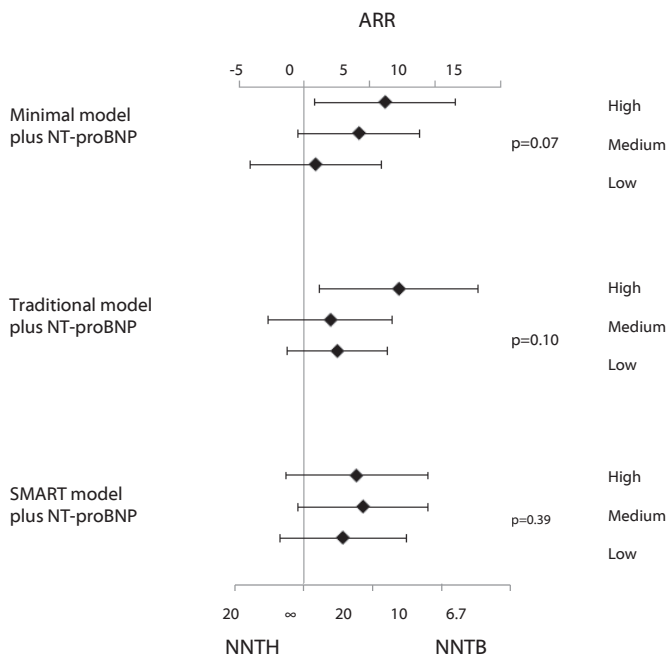
Figure 2. Absolute risk reduction (ARR) and number needed to treat to benefit (NNTB) and number needed to harm (NNTH) with pravastatin for 2.5 years, according to tertiles of predicted risk, p-value of difference between lowest and highest predicted risk group for NNTB, estimated using z-test

more inclined to determine serological biomarkers that have a direct association with cardiac strain such as NT-proBNP.

With regard to prediction of recurrent events, the predictive value of NT-proBNP has been described in primary as well as in secondary prevention,[12] even in very old age[8,13,15] and in persons with[27] and without clinical heart failure.[28] In the literature, addition of NT-proBNP to traditional cardiovascular risk markers results in an improvement of the AUC ranging from 0.01-0,1.[8,12,29] The HOPE study findings[29] showed that of all biomarkers added to traditional risk markers in secondary prevention, NT-proBNP was the strongest (increase in AUC 0.05 as compared to traditional risk markers, p<0.001). This is consistent with the present study in a secondary prevention population. The SMART risk score, which includes hsCRP, was not superior to the model including age and sex. This might be explained by the decreasing predictive value of hsCRP with age,[30,31] as our study population was older by around 15 years on average, than the population in which the original SMART risk score was developed. Also, even if the true risks are the same in both populations, shrinkage can be expected when a prediction model is validated in a different population.

Implications for clinical practice and future research

In our cohort of older persons the SMART risk score had to be recalibrated as it overestimated actual risk for recurrent cardiovascular disease and cardiovascular mortality, especially in persons assigned to the high risk category. Physicians should be aware of the derivation cohort characteristics, before applying new risk scores to their patients.

Our result suggest than in secondary cardiovascular prevention in old age, measuring NT-proBNP helps physicians and patients better estimate recurrence risk. A more complex model including traditional cardiovascular risk markers including the history of cardiovascular disease, or the SMART risk score, is not required as predictive value was the same in a model with age and sex only. However this requires further validation and then evaluation of clinical impact, especially regarding treatment effect, before it can be implemented. Nevertheless, the wide availability of NT pro-BNP assays in routine laboratories means clinical translation is ultimately possible, although current assays remain expensive.

Strengths and limitations

To analyse NT-proBNP levels in the well-defined secondary prevention population within the PROSPER study population, and to calculate treatment effect accordingly, was a tempting opportunity, since placebo controlled RCT's concerning treatment effect of statins are ethically impossible to perform in the present era.

PROSPER is a randomised controlled trial, therefore, the participants were selected using more strict criteria than in a cohort study, like the SMART study. The observed risks could have been influenced. NT-proBNP was measured at 6 months, not at baseline due to limited plasma availability in latter. Therefore, follow-up was calculated form 6 months onward. Pravastatin treatment had no effect on NT-proBNP levels in the first 6 months, which is in line with previous studies.[32] Since NT-proBNP was measured at 6 months from baseline, we had to exclude participants that already died or experienced a cardiac event in the first 6 months of the study. As these participants are likely to be high risk individuals in the models, exclusion may have led to an underestimation of the true magnitude of predictive value of the models. Finally, the relatively low AUCs might be considered as a limitation. However, an AUC between 0.65 and 0.70 is common in studies in older populations.[8,33]

Conclusions

Due to increased survival following an acute cardiovascular event, prediction of recurrent events is becoming increasingly important and according to our study NT-proBNP is a promising risk predictor. Addition of NT-proBNP to (traditional) risk models improves prediction in old age and a minimal model with age, sex and NT-proBNP is as good as complex risk models including NT-proBNP.

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APPENDIX

Supplement 1

SMART formula:

2.5-year cardiovascular disease risk (%) = (1- $0.9488765^{exp[A + 2.099]}$) x 100%

Where A is the prognostic risk score:

A = -0.0850 x age in years + 0.00105 x (age in years)^2 + 0.156 [if male] + 0.262 [if current smoker] + 0.00429 x systolic blood pressure in mmHg + 0.223 [if diabetic] + 0.140 [if history of coronary artery disease] + 0.406 [if history of cerebrovascular disease] + 0.558 [if abdominal aortic aneurysm] + 0.283 [if peripheral artery disease] + 0.0229 x years since first diagnosis of vascular disease - 0.426 x HDL-cholesterol in mmol/L + 0.0959 x total cholesterol in mmol/L - 0.0532 x eGFR in mL/min/1.73m^2 + 0.000306 x (eGFR in mL/min/1.73m^2)^2 + 0.139 x log(hsCRP in mg/L)

Supplement 2
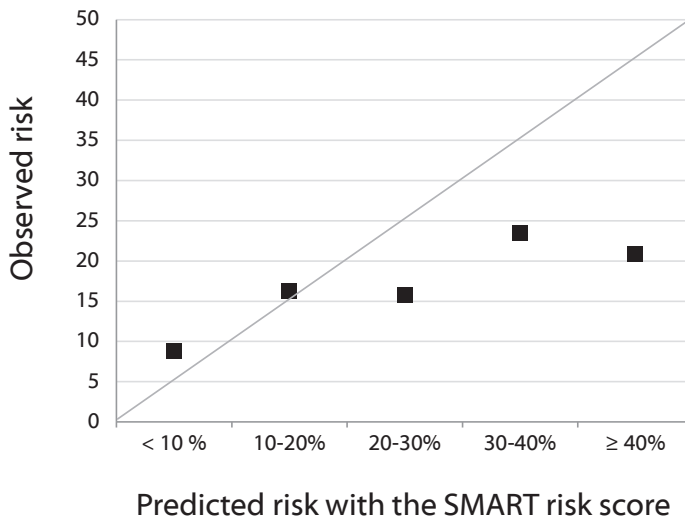
Figure 1. Calibration plot of 2.5-year predicted risk with the SMART risk score versus observed risk of cardiovascular events and cardiovascular mortality in PROSPER study participants