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Prediction of absolute risk reduction of cardiovascular events with perindopril for individual patients with stable coronary artery disease — Results from EUROPA

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ABSTRACT

Background: Angiotensin-converting-enzyme inhibition reduces the risk of cardiovascular events at a group level. Presumably, the absolute effect of treatment varies between individuals. We sought to develop multivariable prediction scores to estimate individual treatment effect of perindopril in patients with stable coronary artery disease (sCAD).

Methods: In EUROPA trial participants, we estimated the individual patient 5-year absolute risk reduction (ARR) of major adverse cardiovascular events(MACE) by perindopril. Predictions were based on a new Coxproportional-hazards model with clinical characteristics and an external risk score in combination with the observed relative risk reduction. Second, a genetic profile modifying the relative efficacy of perindopril was added. The individual patient ARR was defined as the difference in MACE risk with and without treatment. The group level impact of selectively treating patients with the largest predicted treatment effect was evaluated using net benefit analysis.

Results: The risk score combining clinical and genetic characteristics estimated the 5-year absolute treatment effect to be absent or adverse in 27% of patients. On the other hand, the risk score estimated a small 5-year ARR of $\leq$2% ($NNT_5 \geq 50$) in 20% of patients, a modest ARR of 2–4% (NNT_5 25–50) in 26%, and a large ARR of $\geq$4% ($NNT_5 \leq 25$) in 28%. The external risk score yielded similar predictions. Selective prediction-based treatment resulted in higher net benefit compared to treat everyone at any treatment threshold.

Conclusion: A prediction score combining clinical characteristics and genetic information can quantify the ARR of MACE by perindopril for individual patients with sCAD and may be used to guide treatment decisions.

Trial registration number: ISRCTN37166280

1. Introduction

Activation of the renin–angiotensin system (RAS) has an important role in the development of cardiovascular disease [1]. The beneficial effects of blocking RAS by angiotensin-converting-enzyme inhibitors (ACE-i) were first demonstrated in patients with heart failure [2,3]. Further studies showed the efficacy of ACE-i in a wider range of clinical conditions and these agents are currently recommended for the treatment of patients with hypertension, recent myocardial infarction and stable coronary artery disease (sCAD) [4]. One of the landmark trials in patients with sCAD is the EUROPA trial, evaluating the effect of perindopril on the occurrence of new major adverse cardiovascular events (MACE) in sCAD patients without heart failure. The trial found an average relative reduction in MACE of 20% [5]. The average 4-year absolute treatment effect of perindopril was 2%, translating to an average 4-year number-needed-to-treat (NNT_4) of 50 patients to prevent one event [5]. In search of patients who are most likely to benefit, stratified analyses based on clinical characteristics and levels of baseline risk revealed similar relative risk reductions across all subgroups [6,7]. However, genetic variations in pharmacodynamic pathways affected by ACE-i were

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shown to influence the efficacy of perindopril [8]. Three polymorphisms located in the angiotensin-II type 1 receptor and bradykinin type 1 receptor genes were associated with a larger, smaller or even adverse effect of perindopril. To quantify the effect of treatment for individual patients, relative risk reductions need to be interpreted in combination with absolute event risks [9–12]. In general, patients with higher baseline risk tend to benefit more from treatment in terms of absolute risk reduction [13,14]. Baseline risk is determined by the combined action of multiple risk factors such as age, cholesterol and blood pressure [15]. In the present study we sought to develop prediction scores based on a combination of multiple patient-specific clinical and genetic characteristics to estimate the absolute risk reduction of MACE with perindopril for individual patients with sCAD. In clinical practice, these scores can be used to quantify treatment benefit at an individual patient level and to guide treatment decisions.

2. Methods

The design, rationale and outcomes of the EUROPA trial and the PERindopril GENetic association study (PERGENE) substudy have been described elsewhere [16,17]. Briefly, the EUROPA trial was a randomized, double blind study evaluating the effect of perindopril 8 mg once daily versus placebo on major cardiovascular adverse events (MACE) comprising cardiovascular death, myocardial infarction (MI), and resuscitated cardiac arrest in 12,218 patients with sCAD. Eligible patients were men and women of 18 years or older, with evidence of coronary heart disease documented by previous MI (>3 months before screening), percutaneous or surgical coronary revascularization (>6 months before screening), angiographic evidence of at least 70% narrowing of at least one major coronary artery, or a history of typical chest pain in male patients with an abnormal stress test. Exclusion criteria included clinically evident heart failure, planned revascularization procedure, hypotension (sitting systolic blood pressure <110 mm Hg), uncontrolled hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg), use of ACE-i or angiotension-2 receptor blockers in the last month, renal insufficiency (serum creatinine >150 μmol/L), and serum potassium >5.5 mmol/L. PERGENE is a substudy of the EUROPA trial designed to investigate whether common genetic variation is related to risk of future events and modifies the treatment effect of perindopril [8]. Blood samples were received from 10060 patients and 8726 patients had complete genotype data on rs275651, rs5182 and rs12050217, the three single nucleotide polymorphisms (SNPs) identified to modify the effect of perindopril [8,18]. A genetic profile was constructed by counting the number of unfavorable alleles and grouping them into 3 categories: ≤1 unfavorable allele (reference), 2 unfavorable alleles and ≥3 unfavorable alleles. Approval for the trial was obtained from the institutional ethics committee of each center and all participants provided written informed consent.

2.1. Model derivation

The individual patient absolute treatment effect on MACE was estimated with clinical models and with models combining clinical and genetic characteristics. First, we fitted a new Cox proportional hazards model (i.e. EUROPA score) based on a set of clinical characteristics together with a treatment variable (placebo vs. active treatment) [7]. The prespecified predictors were: sex, age, systolic blood pressure, cholesterol, body-mass index (BMI), diabetes, smoking, estimated glomerular filtration rate (eGFR; by CKD-EPI equation [19]), symptomatic CAD, family history of CAD, prior stroke or transient ischemic attack, prior MI, prior coronary revascularization and prior peripheral arterial disease and treatment status. Restricted cubic splines were used to assess the linearity assumption for continuous predictors. If the association between a continuous predictor and the outcome was not linear, the predictor was transformed to improve model fit [20,21]. As a result, age, BMI and eGFR were included both as linear and squared terms. We used the Lasso method (i.e. penalized partial maximum likelihood with a restriction on the sum of the absolute coefficients of standardized predictors) to select the model and shrink the model coefficients to minimize over-optimism [22,23]. The interaction between treatment and baseline risk was evaluated but not significant [24]. The model was fitted for the prediction of 4.3-year (median follow-up) risks and extrapolated to yield 5-year estimates. The individual patient absolute risk reduction (ARR) was defined as the difference between estimated on-treatment and off-treatment risk.

Second, we evaluated the combination of clinical and genetic characteristics to predict absolute treatment effect for individual patients. Hereto, we expanded the EUROPA model with a genetic profile (3-level categorical variable) and the interaction between perindopril treatment and this profile (i.e. EUROPA-GEN score). Again, the Lasso method was used to select the model and shrink the coefficients. The clinical model was fitted in the full EUROPA cohort, whereas the model with additional genetic variables was fitted in the PERGENE subsample. All models were evaluated in the PERGENE subsample to ensure comparability of results.

Supplementary analyses encompassed the use of an externally developed risk algorithm, the SMART risk score, together with the relative treatment effect observed in the trial [25]. The baseline risk of the SMART risk score was recalibrated to the 5-year disease incidence of the target population. Data on HDL cholesterol, high sensitivity C-reactive protein and history of abdominal aortic aneurysm were not available and were set to zero. In addition, the genetic profile and the treatment interaction of perindopril with this profile were added to this model. The Lasso method was used to select and shrink the newly added variables.

Data was missing in 10.1% of participants for the variable 'years since first vascular event' and in <1% for all other variables. Missing data were reduced by single imputation methods using predictive mean matching [26].

2.2. Model performance

Discrimination of the risk scores was assessed by calculation of Harrell's c-statistic [21]. Calibration of predicted risk was assessed by plotting observed 4.3-year event free survival against the average predicted 4.3-year event free survival within deciles and was formally checked by the Gronnesby and Borgan test [27,28]. Since the actual interest was the accuracy of predicted ARR rather than risk, we also assessed whether predicted ARR was in agreement with observed ARR by comparing observed survival within quintiles of patients with similar estimated ARR from the placebo and intervention group. Optimally, the observed survival difference between these paired quintiles should be similar to the estimated ARR.

2.3. Distribution of absolute treatment effect and net benefit

The distributions of predicted individual 5-year ARR of MACE were displayed in histograms. Next, we evaluated the incremental value of applying therapeutic prediction models in clinical practice using the net benefit method [29]. The calculation of net benefit is based on the weighing of positive and negative effects of treatment. The severity of treatment disadvantages is expressed relative to the outcome by a threshold NNT. For example, a 5-year threshold NNT of 50 implies that the disadvantages of treating 50 patients for 5 years are considered to be well balanced by the benefit obtained by preventing one outcome. Net benefit is calculated as the observed ARR in patients for whom the treatment recommended by the prediction algorithm is congruent with randomized allocation minus the disadvantages of treatment. The latter is defined as the proportion of patients treated weighted by the inverse of the threshold NNT (net benefit = ARR − proportion of patients treated * [1/threshold NNT]). Net benefit can be interpreted as the excess number of events prevented per 100 patients on top of the minimally required number of events prevented to offset treatment disadvantages. We considered the following treatment strategies; (i) treat no one, (ii) treat everyone or (iii) prediction-based treatment (i.e. selective treatment of patients whose predicted treatment effect exceeds the specified threshold NNT). Lastly, we showed the impact of using a prediction-based treatment strategy in clinical practice. Statistical analyses were conducted in R, version 2.15.2 (R Development Core Team, Vienna, Austria) with Harrell's Regression Modelling Strategies package and Goeman's 'penalized' package.

3. Results

Baseline characteristics of the PERGENE participants (n = 8726) are shown in Table 1 and are similar to those of the whole EUROPA population. During a median follow-up of 4.3 years 794 major cardiovascular events occurred. The hazard ratio of the overall treatment effect for MACE was 0.80 (95% CI 0.71–0.91) favoring treatment with perindopril.

3.1. Model derivation & performance

3.1.1. Clinical model

The EUROPA models are presented in Box 1. All predictors in the EUROPA model were retained. Detailed statistics are presented in Supplement Table 1. Discrimination was moderate with a c-statistic of 0.67 [95% CI 0.65–0.69]. The EUROPA model showed good risk calibration (*p*-value 0.34) (Supplement Fig. 1). The ARR calibration plot showed an acceptable agreement between predicted and observed ARR (Fig. 1). The externally developed SMART model is shown in Supplement Box 1.

3.1.2. Clinical model combined with genetic profile

During model selection all clinical, genetic and interaction variables were retained in the EUROPA-GEN score (Box 1). Detailed statistics are available in Supplement Table 1. Discrimination was moderate with a c-statistic of 0.68 [95% CI 0.66–0.70]. The EUROPA-GEN models showed good visual calibration (although contradicted by a *p*-value of 0.01 by the formal test statistics) (Supplement Fig. 1). Notably, the ARR calibration plot of the expanded model showed a wider range of predicted and observed treatment effects. The agreement between predicted and observed absolute treatment effect was generally close (Fig. 1). The

Table 1
Baseline characteristics of 8726 EUROPA participants with available genetic profile and stratified according to predicted 5-year absolute risk reduction (ARR) by the EUROPA-GEN score.

	Total population (n = 8726)	<2% ARR (n = 4077)	≥2% ARR (n = 4649)
Clinical characteristics			
Age (years)	59.8 (9.3)	58.8 (8.9)	60.7 (9.5)
Gender, % female	14.5	17.3	12.0
Hypertension, %	28.5	27.2	29.7
Diabetes, %	12.7	8.9	16.1
Current smoking, %	14.7	12.8	16.5
Duration of vascular disease, years	4.3 (4.7)	3.9 (4.3)	4.6 (4.9)
Body mass index (kg/m^2)	27.5 (3.5)	27.3 (3.2)	27.6 (3.7)
Symptomatic CAD[†], %	25.4	19.8	30.4
Family history of CAD, %	27.2	27.2	27.2
Prior myocardial infarction, %	65.4	59.9	70.1
Prior revascularization, %	54.6	59.7	50.1
Prior stroke or TIA, %	3.5	2.6	4.4
Prior PVD, %	7.4	5.1	9.4
Total cholesterol (mmol/L)	5.4 (1.0)	5.3 (1.0)	5.5 (1.1)
eGFR (mL/min/1.73 m^2)	75 (64–87)	77(66–89)	73 (62–86)
Randomized treatment, %	49.7	50.4	49.1
Systolic blood pressure (mm Hg)	137(15)	136 (15)	138 (15)
Diastolic blood pressure (mm Hg)	82 (8)	82 (8)	82 (8)
Genetic profile			
≤1 unfavorable allele, %	41.1	2.7	74.7
2 unfavorable alleles, %	32.4	40.5	25.3
≥3 unfavorable alleles, %	26.5	56.8	0

Summary statistics for continuous variables are presented as mean (standard deviation) or as median (interquartile range). Categorial variables are presented as precentages. ARR: absolute risk reduction. eGFR: estimated glomerular filtration rate estimated by CKD-EPI equation, LDL: low density lipoprotein, HDL: high density lipoprotein, TIA: transient ischemic attack, PVD: peripheral vascular disease.
[†] Agina pectoris or previous heart failure.

Box 1
The EUROPA risk scores

Individual patient off−treatment risk : "treatment" = 0 (NO)
Individual patient on−treatment risk : "treatment" = 1 (YES).

A) EUROPA score

$$\textbf{5-year MACE risk}\ (\%) = \left(1 - 0.91^{\exp(A\ +\ 6.415)}\right) \times 100\%$$

A = age * −0.1324 + age^2 * 0.0013 + female sex * −0.4643 + SBP * 0.0041 + total cholesterol * 0.1499 + eGFR eGFR * −0.0339 + eGFR^2 * 0.0002 + BMI * −0.2590 + BMI^2 * 0.0049 + diabetes * 0.4481 + current smoking * 0.3876 + family history of CAD * 0.1662 + prior MI * 0.3671 + prior TIA or stroke * 0.4446 + prior PVD * 0.5092 + prior coronary revascularization * −0.2235 + symptomatic CAD * 0.3981 + treatment * −0.2167

B) EUROPA-GEN score

$$\textbf{5-year MACE risk}\ (\%) = \left(1 - 0.91^{\exp(A\ +\ 7.390)}\right) \times 100\%$$

A = age * −0.1351 + age^2 * 0.0013 + female sex * −0.5474 + SBP * 0.0040 + total cholesterol * 0.1237 + eGFR eGFR * −0.0358 + eGFR^2 * 0.0002 + BMI * −0.2958 + BMI^2 * 0.0056 + diabetes * 0.4673 + current smoking * 0.4449 + family history of CAD * 0.0791 + prior MI * 0.4055 + prior TIA or stroke * 0.4433 + prior PVD * 0.5340 + prior coronary revascularization * −0.1582 + symptomatic CAD * 0.4080 + genetic profile 1 * −0.2062 + genetic profile 2 * −0.5112 + treatment * −0.5466 + treatment & 2 unfavorable alleles * 0.3207 + treatment & ≥3 unfavorable alleles * 0.7498

SMART-GEN model is shown in Supplement Box 1 and detailed model statistics are presented in Supplement Table 1.

3.2. Distribution of treatment effect of perindopril

The EUROPA score predicted a small 5-year ARR ≤2% (NNT$_5$ ≥ 50) in 60.1% of patients. The predicted 5-year ARR was between 2 and 4% (NNT$_5$ 25–50) in 33.5% of patients and ≥4% (NNT$_5$ ≤ 25) in 6.4% of patients (Fig. 2). The SMART score identified similar proportions of patients in these categories of absolute treatment effect (Supplement Fig. 2).

The EUROPA-GEN score predicted an absent or adverse treatment effect in 26.5% of patients (Fig. 2). These adverse responders were characterized by an unfavorable genetic profile (i.e. ≥3 unfavorable alleles) and were at higher cardiovascular risk when treated with perindopril compared with placebo. Alternatively, the EUROPA-GEN score predicted a large 5-year ARR of ≥4% (NNT$_5$ ≤ 25) in 27.7% of patients. The SMART-GEN score identified similar proportions per category (Supplement Fig. 2). Table 1 displays the characteristics of patients stratified according to predicted treatment effect, showing higher risk factor levels and a skewed genetic profile in patients with a larger ARR.

3.3. Net benefit and clinical consequences of individualized prediction of treatment effect of perindopril

Across the entire range of 5-year treatment threshold NNTs, the clinical EUROPA score was not associated with higher net benefit at a population level compared to treating everyone or no one (Fig. 3). Hence, this model does not succeed in accurately directing treatment to sCAD patients who can anticipate the largest benefit from perindopril. On the other hand, the EUROPA-GEN score showed higher net benefit compared to treating everyone or no one across a wide range of treatment thresholds (Fig. 3). Even if the treatment threshold is infinite, suggesting one is prepared to treat a vast number of patients (e.g. >250) for 5 years to prevent a single event, prediction-based treatment is superior. This could be expected since prediction-based treatment limits prescription to the 73.5% of sCAD patients with an estimated positive effect, while withholding treatment for the 26.5% of patients with an estimated adverse or null effect (Table 2). Results were similar for the SMART risk scores with and without genetic characteristics (Supplement Fig. 3). When restricting treatment to patients with larger predicted treatment effects, the average 5-year NNT among treated patients could be reduced from 42 to 12 depending on the choice of treatment threshold (Table 2).

4. Discussion

In the present study we demonstrated that therapeutic prediction models based on clinical and genetic characteristics were able to quantify the ARR of major cardiovascular events by perindopril for individual patients with sCAD. Of all participants, 27% had an absent or adverse treatment effect whereas 28% had a large estimated 5-year ARR of ≥4% (NNT$_5$ ≤ 25). Selective treatment of patients based on a prediction score can result in a more optimal trade-off between the number of events prevented and number of patients treated.

Guidelines recommend ACE-i in patients with sCAD, especially if there are co-existing conditions such as hypertension, reduced left ventricular ejection fraction or chronic kidney disease [30,31]. These recommendations are based on the overall results of large randomized clinical trials showing reductions in cardiovascular events and mortality [5,32,33]. Even if the relative risk reduction is constant, the absolute risk reduction with treatment varies and is likely to increase with baseline event risk. However, in the present study the relative efficacy of perindopril was influenced by the patients' genetic profile and patients with similar baseline risks had different risk reductions. Consequently, the clinical scores with just a single treatment variable (i.e. active vs.

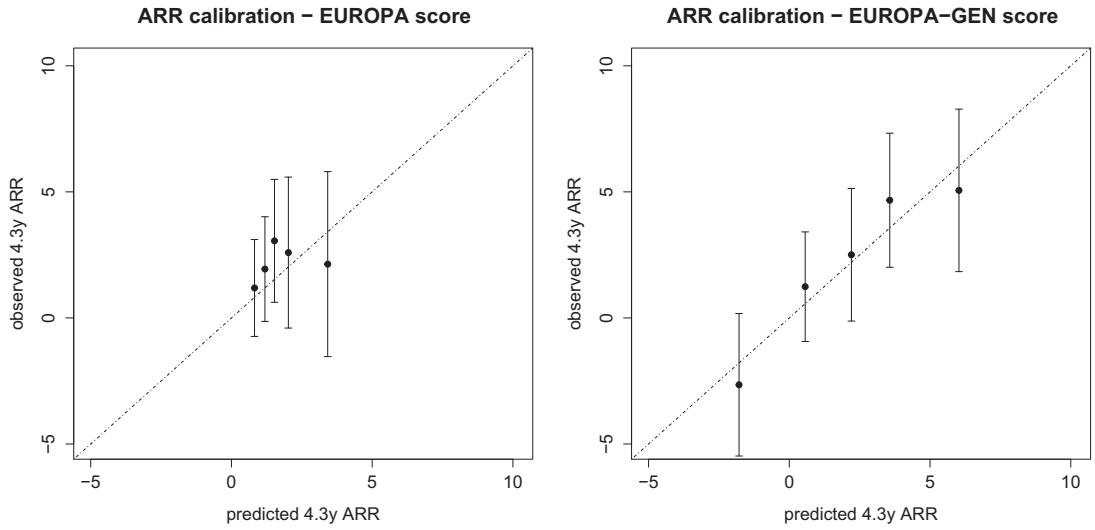

Fig. 1. Calibration plots of predicted versus observed 4.3 year absolute risk reduction (ARR) of major cardiovascular events (MACE) in quintiles for different prediction scores.

placebo) were unable to accurately pinpoint the expected individual patient treatment benefit as was illustrated by the weak relation between predicted and observed ARR. Conversely, the prediction scores with both clinical and genetic variables combined the patient's baseline risk with an efficacy measure (i.e. hazard ratio) that was applicable to the patient's specific genetic profile and yielded accurate estimates of individual treatment effect. The patient-specific ARR can be translated to an individualized NNT (iNNT), which refers to the number of patients with the same characteristics as the patient under care that require treatment for a specific time to prevent one event (Box 3)[11].

The effect of implementing an individualized treatment strategy in clinical practice was evaluated at a group level [29]. Selective drug prescription, based on an individualized treatment prediction algorithm, can direct treatment to those patients who might expect the largest benefit and least harm of treatment. The choice of an appropriate treatment threshold is difficult as the threshold comprises adverse effects of the drug, the inconvenience of daily taking a drug and monetary costs. Notably, the frequency of adverse effects is difficult to estimate based on trial results as only patients who tolerated perindopril were randomized after a run-in period. For randomized patients, the difference in adherence to allocated therapy was 3.4% in the EUROPA [5]. Hence, treating for example 100 patients in clinical practice will result in at least 3 patients experiencing an adverse effect prompting them to discontinue the drug. Secondly, disadvantages include the inconveniences of 100 patients who need to take perindopril daily for 5 years (i.e. 500 person-years of treatment). Thirdly, there are economic costs of perindopril prescription. At a 5-year threshold NNT of 100, we consider all the negative effects of treating 100 patients together to be balanced by the prevention of, for example, one MACE. We acknowledge that this summary of positive and negative effects is incomplete and subject to interpretation. Therefore, we specified a range of treatment thresholds, defined as the number of patients one would be willing to treat to prevent one adverse cardiovascular outcome, to allow clinicians and patients to make their own appraisal of treatment risks and benefits. Further, the treatment threshold may change over time as for example drug costs decrease. A prediction-based treatment strategy using the EUROPA-GEN or SMART-GEN treatment score yielded the highest net benefit at any treatment threshold considered. Hence, implementing these scores in clinical practice can improve the balance between number of patients treated and number of adverse cardiovascular outcomes prevented, irrespective of the treatment threshold.

Strengths of the present study include the large number of available events to derive treatment scores, the use of both clinical and genetic data and the use of existing and newly developed prediction scores.

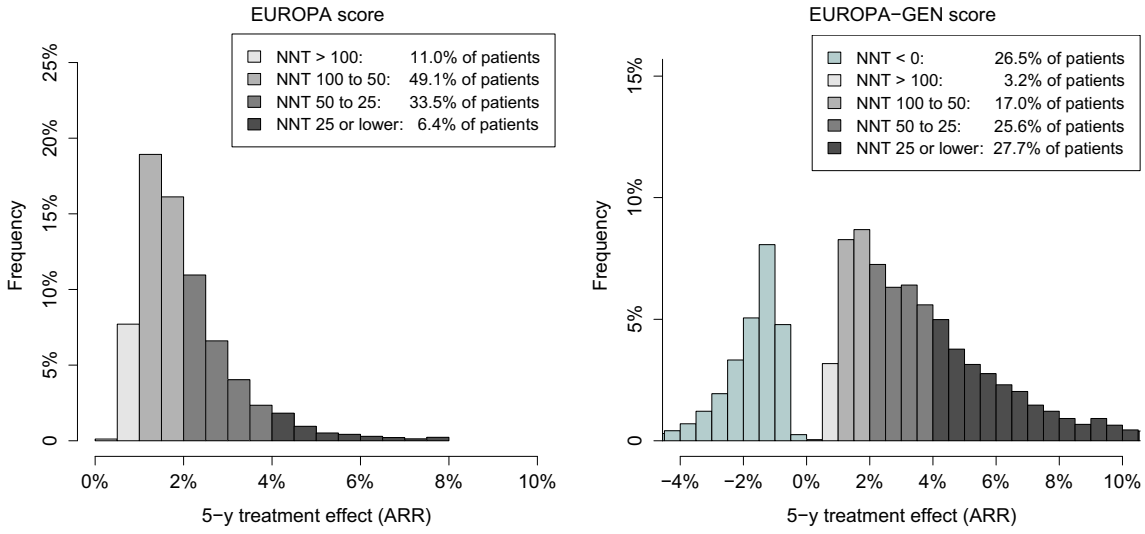

Fig. 2. Distribution of 5-year absolute risk reduction (ARR) of major cardiovascular events with perindopril treatment for individual patients with stable CAD.

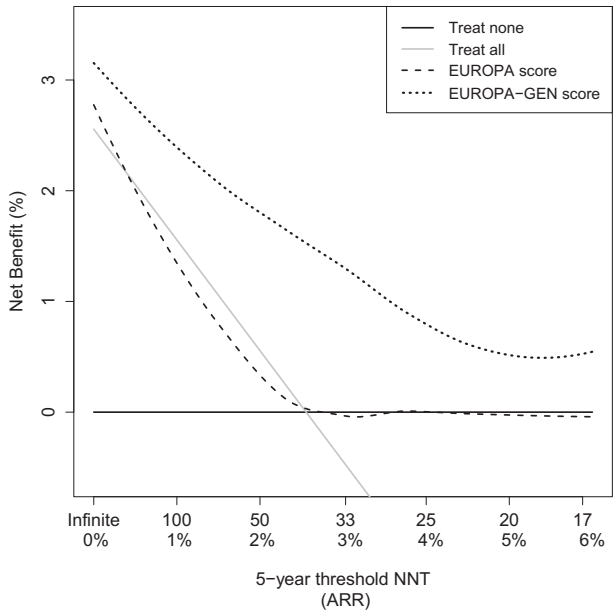

Fig. 3. Net benefit curves of different treatment strategies for major cardiovascular events (MACE). Net benefit is calculated as the observed ARR of MACE (%) in patients whose randomized allocation is similar to recommendations from the treatment score minus the disadvantages of treatment. The disadvantages of treatment are expressed as the proportion of patients receiving treatment weighted by the threshold NNT. First, a (range of) threshold NNT should be determined and next the strategy associated with the highest net benefit for this (range of) threshold can be extracted from the graph. The threshold NNT may vary among clinicians and patients. The treat all line originates at the average ARR observed in the trial, since the negative effects of treatment are assumed to be zero at an infinite threshold NNT_5. Treat none is associated with zero net benefit.

Box 3
Predicted 5-year absolute risk reduction of MACE when treated with perindopril for two different patient profiles.

Patient A

A asymptomatic 60-year old non-smoking male patient without diabetes, an SBP of 130 mm Hg, a BMI of 25 kg/m^2, no family history of CAD, no prior MI, no prior stroke, no prior PVD, a CABG procedure 2 years ago, a TC of 6 mmol/L, an eGFR of 60 ml/min and 2 unfavorable alleles.
➔ 5-year ARR with perindopril is 1.1% (individual $NNT_5 = 88$)

Patient B

A symptomatic 60-year old smoking male patient with diabetes, an SBP of 150 mm Hg, a BMI of 30 kg/m^2, no family history of CAD, no prior MI, no prior stroke, no prior PVD, no prior revascularization, a TC of 6 mmol/L, an eGFR of 60 ml/min and ≤ 1 unfavorable allele.
➔ 5-year ARR with perindopril is 11.6% (individual $NNT_5 = 9$)

Further, the present study is the first to provide a treatment score to calculate an individualized estimate of the effect of perindopril. These estimates may help physicians to engage patients in shared-decision making by facilitating an appraisal of risks and benefits of treatment at an individual patient level. In addition, we evaluated the group level effects of implementing a prediction score in clinical practice, which is relevant to guideline makers. Potential limitations of our study also merit consideration. One of the main concerns of developing a new prediction score is that a score is likely to perform optimistically if tested in the sample from which it was derived [20]. To reduce optimism, we used penalized model estimation based on cross-validation and used a limited number of prespecified predictors. The effect-size of treatment interactions by genetic profile could not be based on external data, although the magnitude and directions of the interactions have been reproduced in ex-vivo experiments and in the PROGRESS trial [8,34]. In addition, the risk of chance findings was greatly reduced by only evaluating SNPs in 12 candidate genes that are part of biological pathways affected by ACE-i. This is different from genome wide association studies without a specific biological hypothesis. Other potential limitations include the generalizability of findings. As with the average trial result, the treatment prediction scores apply to patients who would be eligible for inclusion in the EUROPA trial. Since the number of female participants was relatively small, the models should be used with caution in female patients. Further, current predictions apply to a 5-year time period. In addition, the individualized effect estimates were not accompanied by uncertainty margins. In the setting op medical decision making, the interpretation of such margins can be difficult since the point estimate is the most likely value for an individual patient [35]. Further, the use of a prediction score to select patients for treatment is more time consuming than treating everyone. However, the widespread use of electronic patient records in clinical practice may facilitate the use of prediction rules by automatically feeding information to risk calculators (Supplement Fig. 4). Nevertheless, genetic information regarding the SNPs that modify treatment effect is not routinely assessed in clinical practice. Given the promising results and potential clinical implications, external validation of treatment prediction algorithms including genetic information should be pursued.

In conclusion, treatment effect prediction scores based on clinical and genetic characteristics can quantify the ARR of major cardiovascular events for individual patients with sCAD. The use of a therapeutic prediction score in clinical practice can improve the balance between the number of patients treated and the number of events prevented compared with one-size-fits-all approaches such as treating no one or everyone.

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The EUROPA study was funded by Servier, Paris. The current study was designed, conducted, interpreted, and reported independently of the original sponsor.

Table 2
Consequences for clinical practice based on EUROPA-GEN score.

5-year threshold NNT	Tx-strategy	Tx-rate*	5-year average ARR†	5-year average NNT†
–	Treat all	100%	2.4%	42
250	Prediction-based Tx	73%	3.9%	25
100	Prediction-based Tx	70%	4.1%	25
50	Prediction-based Tx	53%	4.9%	20
25	Prediction-based Tx	28%	6.7%	15
17	Prediction-based Tx	13%	8.7%	12

Tx: Treatment. *Percentage of total population treated with perindopril. †Predicted average reduction in absolute risk of MI, resuscitated cardiac arrest and vascular death in selection of patients actively treated with perindopril.

Conflicts of interest

W.R., M.B., R.F., K.F. and M.S. have received honoraria and research grants from Servier for the EUROPA-trial.

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All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.12.046.

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