Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk

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Aims Patients with stable coronary artery disease (CAD) are at increased risk. Estimation of individual risk is difficult. We developed a cardiovascular risk model based on the EUROPA study population and investigated whether benefit of long-term administration of the angiotensin-converting enzyme (ACE)-inhibitor perindopril was modified by risk level.

Methods and results A total of 12,218 patients with stable CAD were treated with 8 mg perindopril or placebo. Baseline patient characteristics were assessed for association with 1091 cardiovascular deaths or non-fatal myocardial infarction (MI). Risk factors were age over 65 years, male gender [hazard ratio (HR) 1.2], previous MI (HR 1.5), previous stroke and/or peripheral vascular disease (HR 1.7), diabetes, smoking, angina (all HR 1.5), and high serum cholesterol and systolic blood pressure. Treatment benefit by perindopril was consistent among high, intermediate, and low risk patients (HRs 0.88, 0.68, and 0.83, respectively). Risk reduction was thus not modified by absolute risk level.

Conclusion Risk factors such as age, male gender, smoking, total cholesterol, and blood pressure continue to play an important role once clinical sequelae of coronary heart disease have developed. Patients at moderate-to-high risk because of uncontrolled risk factors and those with other indications for ACE-inhibitors have the most to gain from ACE-inhibition.

KEYWORDS Coronary artery disease; Prognosis; Risk stratification; ACE inhibitors

Introduction

Patients with coronary artery disease (CAD) may be at considerable risk for recurrent cardiac events, and the goal of secondary prevention is to reduce that risk. In addition to lifestyle measures, therapeutic regimens including statins and antiplatelet agents are the well known and widely adopted cornerstones of such therapy.1 Also, angiotensin-converting enzyme (ACE)-inhibitors decrease the risk of new subsequent cardiovascular events in subjects at increased high risk, including patients with established ischaemic heart disease,2 and in patients with stable CAD.3 Nevertheless, such patients constitute a heterogeneous group and the absolute risk for recurrent cardiac events varies from individual to individual. Treatment decisions for a given patient should be based not only on the expected relative risk reduction, but also on the absolute risk reduction in the patient. Under the assumption of a constant relative risk reduction by baseline risk of disease, the absolute treatment benefit can be determined, i.e. the reduction in absolute risk for a given individual.4 Knowledge of the absolute risk in a patient with stable coronary artery would thus be extremely helpful. This is even more so since the recent publication of PEACE.5 This trial investigated the ACE-inhibitor trandolapril in patients with stable CAD, but, in contrast to comparable studies as HOPE (ramipril) and EUROPA (perindopril), reported only limited clinical benefit. The lack of a statistically significant reduction in cardiovascular clinical events in PEACE has been attributed to the relatively low risk of cardiovascular complications in their patient population.6 Therefore, the purpose of the present post hoc analysis study was two-fold. First, to develop a risk model from the EUROPA study to understand which baseline factors determine the risk of cardiovascular events in stable coronary disease and to produce a ‘risk score’ to be used in clinical practice. Secondly, to investigate whether the 20% risk reduction observed in the overall EUROPA population remained constant across different values of baseline risk.

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Methods

Patients

The design and principal results of the EUROPA study have been reported elsewhere. In short, the EUROPA study was a randomized, double-blind study designed to assess the effect of perindopril vs. placebo on the combined endpoint of cardiovascular death, myocardial infarction (MI), and resuscitated cardiac arrest in patients with stable coronary heart disease, but without overt heart failure or uncontrolled hypertension. Eligible patients included men and women 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 mmHg), uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg), use of ACE-inhibitors or angiotensin-2 receptor blockers in the last month, renal insufficiency (serum creatinine >150 μmol/L or 1.5 mg/dL), and serum potassium >5.5 mmol/L. The first patient was enrolled on 27 October 1997, and the trial was terminated on 20 March 2003.

Treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive perindopril 8 mg or matching placebo.

Statistical analysis

The endpoint of our study was the composite of cardiovascular mortality, non-fatal MI, and resuscitated cardiac arrest.

Univariable and multivariable Cox proportional hazard regression analyses were applied to study the relationship of prospectively defined and clinically plausible characteristics recorded at baseline, including demographic and clinical variables, medical history, laboratory tests, and medication with study endpoint. Information on candidate risk factors was complete in 98% of patients. Creatinine clearance was estimated using the Cockcroft and Gault formula. All variables entered the multivariable stage irrespective of the results of the univariable analyses. The final multivariable model was then constructed using a stepwise selection procedure until the removal of a variable caused a significant change between consecutive models. Interaction by treatment was investigated for each variable. Although higher values of both diastolic and systolic blood pressure were associated with increased risk, systolic blood pressure was entered in the final risk model. Obesity was defined as body mass index >30 kg/m². In all analyses, P-values less than 0.05 were considered significant (two-sided test). We report crude and multivariable adjusted hazard ratios (HRs) together with the corresponding 95% confidence intervals (CIs).

The performance of the multivariable models was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish patients with study endpoint from those without and is quantified by a measure of concordance, the c-statistic. For binary outcomes, this is identical to the area under the curve. In our analysis, the value of c-statistic amounted to 0.67. The proportional hazard assumption was verified by the introduction of a time-dependent co-variate, as well as by separate analyses distinguishing between early and late events. The calibration of the model was verified by plotting of expected vs. predicted events.

To develop a risk-scoring system, the log HRs from the multivariable analysis were converted back to an estimated risk score.
### Table 1: Baseline characteristics (mean values ± SD) of 12,218 patients with CAD and uni- and multivariate predictors of cardiovascular complications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate risk</th>
<th>Multivariate risk</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 9</td>
<td>1.08*</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>85</td>
<td>1.16</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>68 ± 10</td>
<td>1.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137 ± 16</td>
<td>1.01b</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.4 ± 1.1</td>
<td>1.17</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²</td>
<td>21</td>
<td>1.33</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12</td>
<td>1.75</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>15</td>
<td>1.37</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>85 ± 25</td>
<td>1.02</td>
</tr>
<tr>
<td>Symptomatic CADc (%)</td>
<td>25</td>
<td>1.97</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>27</td>
<td>1.06</td>
</tr>
<tr>
<td>Previous CV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or PVD (%)</td>
<td>9</td>
<td>2.04</td>
</tr>
<tr>
<td>MI (%)</td>
<td>65</td>
<td>1.48</td>
</tr>
<tr>
<td>Coronary revascularization (%)</td>
<td>55</td>
<td>0.67</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers (%)</td>
<td>32</td>
<td>1.37</td>
</tr>
<tr>
<td>Lipid-lowering drugs (%)</td>
<td>58</td>
<td>0.69</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>43</td>
<td>1.82</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>62</td>
<td>0.97</td>
</tr>
<tr>
<td>Perindopril (%)</td>
<td>50</td>
<td>0.80</td>
</tr>
</tbody>
</table>

PVD, peripheral vascular disease; BMI, body mass index. n.s., not significant; n.a., not applicable.

*Risk associated with the number of years above 65.

bRisk associated with increase in systolic blood pressure of 1 mmHg.

cAngina pectoris or previous heart failure.

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**Figure 1** Relationship of continuous baseline parameters and cardiovascular complications in 12,218 patients with stable CAD.
Therefore, the numbers needed to treat in the three risk strata are 410, 205, and 135, respectively.

Discussion

The findings of the present study highlight two important topical issues: the prognostic value of several well-known clinical risk factors in a population of patients with stable CAD and the effectiveness of the ACE-inhibitor perindopril across the whole spectrum of risk for subsequent fatal and non-fatal cardiovascular and cardiac disease in these patients.

Risk factors

Several predictors of risk in patients recovering from an acute coronary syndrome have been identified, including left ventricular (LV) dysfunction, the angiographic extent and severity of CAD, and the presence of spontaneous or stress-induced ischaemia as well as biomarkers of vascular inflammation. The current data confirm that the traditional cardiovascular risk factors such as age, gender, smoking, total cholesterol, and blood pressure continue to play an important role once clinical sequelae of coronary heart disease have developed.

The identification of these risk factors provides a useful tool for the assessment of long-term cardiac risk in a contemporary population of patients with stable coronary disease. Using simple, easy to obtain, and well-known clinical parameters, risk stratification in these patients proved to be very meaningful, as a surprisingly large risk gradient appeared to be present. Furthermore, although patients with stable coronary disease are often considered to have a relatively low risk for recurrent cardiac events, we found that ~30% of our patients had a 4-year risk between 10 and 15%, comparable to a 1-year risk exceeding 3%. This can hardly be considered low risk and stresses, the clinical utility of a risk stratification tool for such patients.

Assessment of LV function was not required to enter our trial. Nevertheless, information on LV function was collected in ~60% of the patients. LV function was found to be normal or near normal in the vast majority of these, with only 3% having an ejection fraction <40%. Furthermore, very few patients developed clinical heart failure in the 4-year course following randomization, which confirms that LV dysfunction was rare indeed. Still, the utility of the derived parameters is confined to the study population, i.e. patients with CAD with no clinical symptoms of heart failure and—mostly—without angina or with mild angina at the most.
The importance of co-morbidities in patients with CAD is well known, and the negative prognostic impact of diabetes, peripheral, and central vascular disease—probably reflective of more extensive atherosclerotic burden—was confirmed. Patients with end-stage renal disease have a poorer outcome after an MI or myocardial revascularization, whereas milder degrees of renal impairment have been shown to affect the prognosis of patients with chronic heart failure and acute coronary syndrome (ACS). Our findings extend these conclusions and show that even a mildly depressed renal function can negatively affect prognosis in otherwise stable patients. The negative impact of previous MI may be related to clinically unrecognized impaired LV function or more severe CAD, both of which are well-recognized risk factors. However, it remains to be seen whether assessment of LV function or angiographic extent and severity of CAD would provide incremental prognostic information in patients with stable CAD. A history of coronary revascularization was associated with a reduced risk for subsequent events in our analysis. This typical observation should be interpreted with some caution. Risk reduction by revascularization has been demonstrated in patients with severe coronary disease and impaired LV function, in patients with ischaemia after MI, and in some but not all studies of patients with ACSs. The effect of percutaneous coronary intervention on the prognosis in symptomatic patients with CAD was investigated in RITA-2: early intervention was associated with greater symptomatic improvement, but not with less events. Treatment with lipid-lowering drugs, mostly statins, was also associated with a lower risk, which is in agreement with previous randomized trials. However, the well-documented benefit of beta-blockers in patients after MI was not confirmed in the current study, to a certain extent by confounding by indication, but possibly also because of a lack of benefit of such therapy in the current patient population.

### Table 5 Distribution of patients, observed cardiovascular events, and calculated yearly risk

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of patients</th>
<th>Per cent</th>
<th>No. of events</th>
<th>Yearly event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>645</td>
<td>5</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4-6</td>
<td>3737</td>
<td>31</td>
<td>181</td>
<td>1-2</td>
</tr>
<tr>
<td>7-8</td>
<td>3401</td>
<td>28</td>
<td>254</td>
<td>2-3</td>
</tr>
<tr>
<td>9-10</td>
<td>2418</td>
<td>20</td>
<td>249</td>
<td>3-4</td>
</tr>
<tr>
<td>&gt;10</td>
<td>2017</td>
<td>16</td>
<td>388</td>
<td>&gt; 4</td>
</tr>
</tbody>
</table>

![Figure 3](https://example.com/f3.png)  
**Figure 3** Treatment effect (relative risk reduction) in patients categorized in tertiles according to 4.2 years risk of cardiovascular mortality and non-fatal MI.

Drugs (65 vs. 70%) was also similar between patients in both trials. In addition, levels of blood pressure (133 vs. 134 mmHg) and serum cholesterol (5.0 vs. 4.9 mmol/L) were also quite comparable. In our opinion, therefore, it is unlikely that the results of PEACE should be taken as evidence that the low risk of the patients in that trial was the main reason for the lack of efficacy of trandolapril.

It is uncertain whether the effect obtained with one drug given at a particular dose can be translated across to the whole class of such drugs. Dissimilarities between various ACE-inhibitors have been reported, e.g. differences in bioavailability, peak to through ratio, and effects on blood pressure. Subtle but perhaps clinically relevant differences between drugs of the same class, including statins and beta-blockers, have been reported. As it is unlikely that direct comparative trials of one drug to another one of the same class will be performed, any suggestion of differential efficacy of drugs within classes, however, will remain indirect by definition.

Notwithstanding the observed efficacy of perindopril in the lowest risk group in the EUROPA trial, it is clear that treatment decisions should not be based on the relative treatment efficacy, but on the true absolute treatment benefit. Of course, this absolute benefit will be lower in patients at relatively low risk, and it is a matter of debate, health economics, and health resources, as to what extent and at which level of risk additional treatment with a third- or fourth-line treatment regimen may be warranted in a given patient. Patients at moderate-to-high risk because of uncontrolled risk factors and those with other indications for ACE-inhibitors, namely, previous MI and/or impaired LV function, hypertension, and diabetes have the most to gain in absolute and health economic terms.

### Conflict of interest

### References


