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

Jaap W. Deckers1*, Dick M. Goedhart2, Eric Boersma1, Andrew Briggs3, Michel Bertrand4, Roberto Ferrari5, Willem J. Remme6, Kim Fox7, and Maarten L. Simoons1 on behalf of the EUROPA Investigators

1Department of Cardiology, Thoraxcenter, Erasmus University Medical Center Rotterdam, Room Ba 350, Dr Molewaterplein 40, 3015GD Rotterdam, The Netherlands; 2Cardialysis, Rotterdam, The Netherlands; 3University of Glasgow, Glasgow, UK; 4Lille Heart Institute, Lille, France; 5Azienda Ospedalier and University di Ferrara, Ferrara, Italy; 6Sticas Cardiovascular Research Foundation, Rotterdam, The Netherlands; and 7Royal Brompton and National Heart Hospital, London, UK

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.

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. 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, and in patients with stable CAD.

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. 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. 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.

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.
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.

Results

We studied 12,218 men and women followed for a median of 4.1 years (interquartile range 4.0–4.5 years) corresponding to about 50,000 patient years of information. During that time, 1,091 patients died from a cardiovascular cause, sustained a non-fatal MI, or were resuscitated from cardiac arrest.

The clinical characteristics of the patients and the prevalence of the major prognostic parameters are presented in Table 1. In addition, the relative risks of these baseline variables with subsequent events in univariable and in multivariable analysis are given. Figure 1 shows the relationship among age, systolic blood pressure, cholesterol level, creatinine clearance, and cardiovascular events by plotting deciles of the (univariable) risk factors against the annual incidence rate of the primary endpoint.

Most parameters significant in univariable analysis remained significantly associated with outcome in multivariable analysis. Not surprisingly, in the randomized comparison of patients with and without an ACE-inhibitor, treatment with perindopril was protective (HR 0.80, 95% CI 0.71–0.91). In the non-randomized comparison of patients with and without a beta-blocker, the use of beta-blockers was not found to be a significant predictor of prognosis. However, patients on beta-blockers more often had clinical features previously as well as currently associated with poorer prognosis, including elderly age (61 vs. 59 years), previous MI (67 vs. 61%), angina pectoris (27 vs. 19%), and hypertension (32 vs. 19%, all P = 0.05). Cholesterol-lowering drugs, although significantly associated with outcome, were not considered in the final model, because the clinical indication for these drugs is not at issue. Still, the cholesterol level at baseline, with or without cholesterol-lowering therapy, contributed significantly to outcome and was retained in the final model.

The cardiovascular risk-scoring system derived from the multivariable equation is presented in Tables 2 and 3. Predicted vs. observed events are presented in Figure 2. On the basis of the modelled risk score, the population was divided in tertiles, each consisting of about 4000 subjects. The main characteristics of these three groups, including the distribution of the most important risk predictors per tertile, are given in Table 4. The average risk of the whole study population was 2.5% per year. The risk in the highest tertile amounted to 15% during follow-up in the placebo group, three times higher than the average risk of the lowest tertile. The risk in the lowest tertile was on average ~1% per year. The range of risk encompassed with the use of the score was quite large and varied from a risk of fatal cardiovascular disease and no-fatal MI from <1%, in 5% of the study population, to over 3% per year in almost 40% of the patients (Table 5).

Treatment benefit associated with perindopril in the three modelled risk strata is given in Figure 3. The HRs associated with the ACE-inhibitor in the patients from the highest to lowest risk tertile were 0.88, 0.68, and 0.83, respectively. Test for heterogeneity of treatment effect was negative (P = 0.15), indicating that relative treatment benefit was not modified by the risk level. Thus, under the assumption of a consistent treatment effect of 20% across the whole risk spectrum, absolute treatment benefit in the three risk strata amounted to ~1, 2, and 3%, respectively.
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></th>
<th>Multivariate risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 9</td>
<td></td>
<td>1.08a</td>
<td>1.06–1.09</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>85</td>
<td></td>
<td>1.16</td>
<td>0.97–1.39</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>68 ± 10</td>
<td></td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137 ± 16</td>
<td></td>
<td>1.01b</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.4 ± 1.1</td>
<td></td>
<td>1.17</td>
<td>1.11–1.23</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²</td>
<td>21</td>
<td></td>
<td>1.33</td>
<td>1.16–1.53</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12</td>
<td></td>
<td>1.75</td>
<td>1.50–2.04</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>15</td>
<td></td>
<td>1.37</td>
<td>1.17–1.59</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>85 ± 25</td>
<td></td>
<td>1.02</td>
<td>1.01–1.02</td>
</tr>
<tr>
<td>Symptomatic CADc (%)</td>
<td>25</td>
<td></td>
<td>1.67</td>
<td>1.47–1.89</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>27</td>
<td></td>
<td>1.06</td>
<td>0.93–1.21</td>
</tr>
<tr>
<td>Previous CV disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or PVD (%)</td>
<td>9</td>
<td></td>
<td>2.04</td>
<td>1.74–2.39</td>
</tr>
<tr>
<td>MI (%)</td>
<td>65</td>
<td></td>
<td>1.48</td>
<td>1.30–1.70</td>
</tr>
<tr>
<td>Coronary revascularization (%)</td>
<td>55</td>
<td></td>
<td>0.67</td>
<td>0.59–0.75</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers (%)</td>
<td>32</td>
<td></td>
<td>1.37</td>
<td>1.21–1.54</td>
</tr>
<tr>
<td>Lipid-lowering drugs (%)</td>
<td>58</td>
<td></td>
<td>0.69</td>
<td>0.61–0.78</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>43</td>
<td></td>
<td>1.82</td>
<td>1.61–2.05</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>62</td>
<td></td>
<td>0.97</td>
<td>0.86–1.1</td>
</tr>
<tr>
<td>Perindopril</td>
<td>50</td>
<td></td>
<td>0.80</td>
<td>0.71–0.91</td>
</tr>
</tbody>
</table>

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

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 sequellae 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.

**Treatment effect**

The second important finding of this analysis relates to the effect of treatment in various strata of risk as defined as objectively as possible by the risk model. Our analysis demonstrates that treatment benefit was not modified by the level of risk, in other words, the treatment effect associated with the use of perindopril was the same in patients at high (>3%), medium (between 1 and 3%), and in those at relatively low (1%) level of risk per year. Of note, the risk in our lowest risk tertile was lower than the average risk observed in PEACE. In this low risk tertile, rates of previous revascularization were 75% compared to 72% in PEACE, whereas the use of aspirin (94 vs. 90%) and lipid-lowering 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 is it 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:** J.W.D., M.B., R.F., W.J.R., K.F., and M.L.S. have received consulting fees from Servier.

**References**


