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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

Prevention of Cardiac Events in Coronary Artery Disease with Perindopril
The EUROPA Study

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The angiotensin-converting enzyme (ACE) inhibitors reduce mortality and morbidity in patients with left ventricular (LV) dysfunction and myocardial infarction (MI), and in those at high risk for cardiovascular events. However, their long-term effect on a broad spectrum of patients with coronary artery disease (CAD), including those deemed low risk, has not been established. The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) Study was designed to assess the effects of the ACE inhibitor, perindopril, on the reduction of cardiac events in patients with proven stable CAD and no evidence of heart failure or LV dysfunction. This issue of *Cardiology Scientific Update* reviews the recently presented results of EUROPA and their clinical applications.

Cardiovascular (CV) diseases, of which CAD is the most common form, are the major causes of mortality in middle-aged and older patients in most developed countries, as well as in many developing countries.[1] Over the past decades, preventive measures and pharmacological treatment – principally the use of antiplatelet agents and statins[2-4] – have improved the prognosis for these patients. However, the risk of adverse events in patients with CAD remains high.[5] ACE inhibitors have an established role in secondary prevention in patients with congestive heart failure (CHF) with LV dysfunction and post-MI.[6-8] In recent years, it has become increasingly evident that the renin-angiotensin system (RAS) plays a major role in atherosclerotic progression[9,10] and that ACE inhibitors can exert multiple potentially anti-atherosclerotic effects, including plaque stabilization, fibrinolysis, reduced neointimal formation, and improved endothelial function.[9,11-13] Indeed, secondary analyses of several landmark trials of ACE inhibitors in CHF and MI have also demonstrated that ACE inhibitors reduce the risk of hospitalization for unstable angina and the recurrence of myocardial ischemia/infarction, suggesting that they exert anti-ischemic effects in these patients.[14,15]

Subsequently, the Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that ACE inhibition reduces cardiac events in patients deemed at high risk for CV events (ie, those with diabetes, stroke, peripheral artery disease, hypertension, and a history of CAD).[16] The examination of the baseline characteristics of the study population in HOPE indicates that it was a high-risk population, as intended by the design of the trial. It was, therefore, unclear whether the benefit of ACE inhibition could also be extended to a broad spectrum of patients with documented CAD, including those who were deemed at a lower risk for CV events. Accordingly, two large-scale studies, namely the EUROPA and the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial, were specifically designed to study the long-term effects of ACE inhibition on a broad spectrum of patients with CAD.[17-19] The recently presented and published results of the EUROPA trial are presented in this review.

EUROPA: Study design

Details of the rationale, design, and baseline demographics of EUROPA have been published previously.[17] In brief, EUROPA was a multicentre European trial that involved 424 centres in 24 countries. The study population included men and women aged ≥18 years without clinical evidence of CHF and with evidence of CAD documented by:

- previous MI at least 3 months prior to the selection visit

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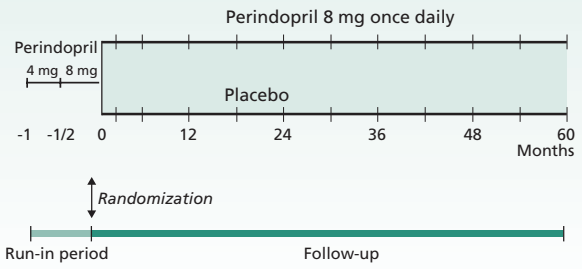
Figure 1: EUROPA study design



• coronary revascularization at least 6 months prior to the selection visit

• angiographic evidence of ≥70% narrowing of ≥1 major coronary artery

• males with chest pain and a positive exercise test or regional wall motion abnormalities during stress echocardiography or nuclear scintigraphy or with transient perfusion defects during perfusion imaging.

Key exclusion criteria included planned revascularization, systolic blood pressure (SBP) <110 mg Hg or >180 mm Hg, diastolic blood pressure (DBP) >110 mm Hg, use of ACE inhibitors or angiotensin receptor blockers (ARBs) within 1 month, serum creatinine >150 µmol/L and potassium >5.5 mmol/L.

The study protocol is summarized in Figure 1. The study consisted of:

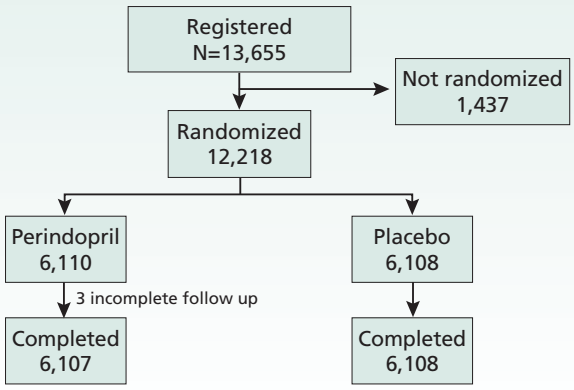
• a first run-in period of 2 weeks during which patients received perindopril 4 mg/day in addition to their usual medication,

• a second run-in period of 2 weeks during which patients received perindopril 8 mg/day, provided that the 4 mg/day of perindopril was well-tolerated in the first run-in period.

For patients >70 years, perindopril was administered as 2 mg daily in the first week of screening, 4 mg daily in the second week, and 8 mg in the last 2 weeks. At the end of the run-in period, a double-blind treatment period of at least 36 months began, during which patients received either perindopril 8 mg/day or placebo. Patients continued in the study until the last patient completed the 3-year follow-up period.

The primary study endpoint was combined CV mortality, nonfatal MI, and resuscitated cardiac arrests. The secondary endpoints included a composite of all-cause mortality, nonfatal MI, hospitalization for unstable angina, and resuscitated cardiac arrests, and individually, admission for CHF, revascularization, and stroke. It should be pointed out that the original primary endpoint was a composite of total mortality, nonfatal MI, unstable angina, and resuscitated arrests.[17] The modified primary endpoint was therefore a reflection of changing clinical practice and a broadened definition of MI based on raised markers of myocardial necrosis as recommended by the European Society of Cardiology and the American College of Cardiology.[20]

Figure 2: Patient follow-up



EUROPA: Results

The main results of EUROPA were recently presented and published.[21] Patient recruitment is shown in Figure 2. Follow-up was completed in April 2003, with a mean duration of follow-up of 4.2 years. A total of 12,218 patients were randomized from 424 European centres. Selected baseline characteristics are shown in Table 1. Of note, a high proportion of patients were on anti-platelet and lipid-lowering agents at randomization; 81% of the patients did not experience angina.

Results of the primary endpoint are shown in Figure 3. The annualized event rate was only 2.4%, suggesting that patients in the EUROPA study were not a very high-risk patient population. Compared to placebo, the proportion of combined CV death,

Table 1: Selected baseline patient characteristics

	Perindopril (n=6110)	Placebo (n=6108)
Age (mean±SD) (years)	60±9	60±9
Female	14.5%	14.7%
CAD history: MI	64.9%	64.7%
PCI	29.0%	29.5%
CABG	29.3%	29.4%
CAD based on:		
Positive stress test (men)	22.6%	23.3%
Angiography (stenosis >70%)	60.4%	60.5%
Hypertension	27.0%	27.2%
Previous stroke or TIA	3.4%	3.3%
Diabetes	11.8%	12.8%
Hypercholesterolemia	63.3%	63.3%
Use of anti-platelet drugs	91.9%	92.7%
Lipid-lowering drugs	57.8%	57.3%
ß-blockers	62.0%	61.3%
Calcium channel blockers	31.7%	31.0%
Systolic blood pressure (mm Hg)	137±16	137±15

PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; TIA = transient ischemic attack; MI= myocardial infarction; CAD = coronary artery disease

Figure 3: EUROPA – Primary endpoint

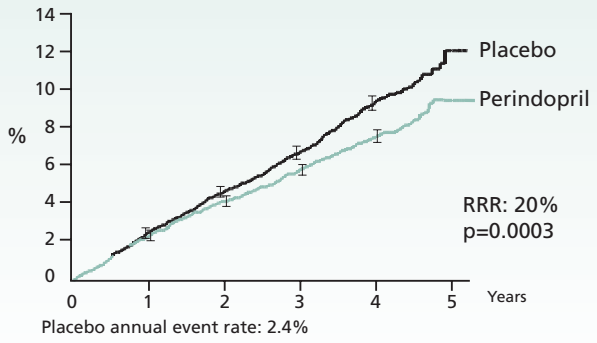
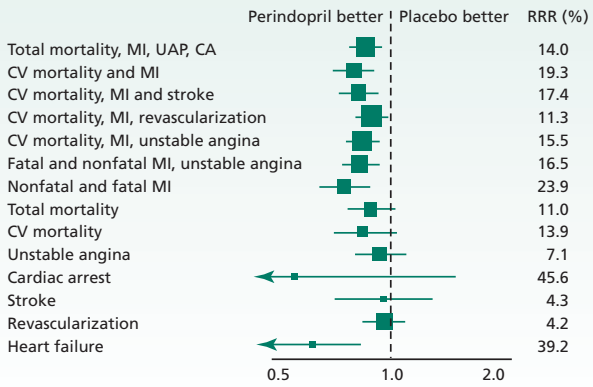


Figure 4: EUROPA – Secondary endpoint



non-fatal MI, and resuscitated cardiac arrest was reduced by 10%, 11%, and 14% in the first, second, and third year, respectively post-randomization. The differences reached significance by the third year. The relative risk reduction over 4.2 years of follow-up was 20%. The beneficial effects of perindopril on primary outcome were consistent in every prespecified subgroup, regardless of age, gender, history of MI, previous revascularization, hypertension, and diabetes, and the use of lipid-lowering agents and ß-blockers. Perindopril reduced SBP and DBP by 5 mm Hg and 2 mm Hg, respectively.

Results of the key secondary endpoints are shown in Figure 4. Perindopril reduced all secondary endpoints; however, the reduction was not significant for every endpoint because the event rate was low in some endpoints. Of interest is the significant reduction in combined all-cause mortality, MI, unstable angina, and cardiac arrest, which was the original primary endpoint. Both fatal and nonfatal MI, as well as CHF requiring hospitalization, were also significantly reduced. The study medication was well-tolerated. At the end of the study, withdrawal for any reason occurred in 23% and 21% of patients in the perindopril and placebo group, respectively. Withdrawal due to cough was slightly more frequent in the perindopril versus the placebo group (2.7% versus 0.5%, respectively). On the other hand, use of antiplatelet agents, lipid-lowering therapy, and ß-blockers increased to 91%, 69%, and 63%, respectively, at the conclusion of the study.

Clinical implications of the EUROPA study

The reported benefit on the primary outcome translates into an absolute benefit of treating 50 patients for a period of 4 years to prevent 1 major CV event. These favourable results are significant, given the relatively low annualized primary outcome event rate of only 2.4%. Furthermore, the reduction in MI provides further evidence of an anti-ischemic effect of ACE inhibition, as first suggested by earlier landmark trials of MI and CHF.[14-16] Indeed, extensive experimental and clinical data that have accumulated on perindopril all implicate either direct or indirect anti-atherosclerotic properties. These effects include:

- decrease in neointimal proliferation[13]
- up-regulation of endothelial nitric oxide synthase[22]
- increase in plasma bradykinin[23]
- attenuation or prevention of experimental atherosclerosis[24-26]
- enhanced fibrinolysis[27,28]
- improved vessel structure and endothelial function[29,30]
- sustained blood pressure lowering in patients with essential hypertension[31]
- favourable safety profile, even in patients with stroke.[32,33]

Finally, the significant reduction in hospitalization for CHF in patients without a previous history of this diagnosis is consistent with observations from previous studies of ACE inhibitors.[8,14,16,33]

EUROPA extends the observations of the HOPE study, in which CV events were reduced in patients deemed at high risk for CV events.[16] However, as shown in Table 2, important differences existed between the two study populations. By definition, all patients in EUROPA had CAD, whereas in HOPE, a significant proportion were included based on a history of stroke, peripheral vascular disease, or diabetes (with at least one additional CAD risk factor). All of these risk factors were more frequent in the HOPE population. On the other hand, because HOPE was carried out much earlier than EUROPA, lower percentages of patients were treated with antiplatelet and lipid-lowering drugs and ß-blockers. These observations imply that patients in HOPE represented a higher risk study population. Indeed, over 4.5 years of follow-up, HOPE reported a placebo CV mortality rate of 8%, an MI rate of 3%, and an all-cause mortality rate of 12%. The corresponding event rate over 4.2 years in EUROPA was 4%, 2%, and 7%, respectively, almost half that in the HOPE study. Yet, the relative risk reductions in combined events, slightly above 20%, appeared comparable. These data, therefore, strongly indicate that patients with CAD – who are not necessarily deemed to be at high risk and who are on optimal therapy for secondary prevention – would likely benefit from ACE inhibitor therapy to a similar degree as those who are deemed to be at higher risk and on less optimal therapy. Finally, the contribution of the observed reduction in blood pressure

Table 2: Demographics of EUROPA and HOPE

	EUROPA (n=11236)[17]	HOPE (n=9297)[16]
Mean age (years)	60	66
Female	15%	27%
Evidence of CAD	100%	81%
Previous MI	65%	53%
Peripheral vascular disease	7%	43%
Stroke or TIA	3%	12%
Diabetes	12%	38%
Hypertension	27%	46%
Use of anti-platelet drugs	92%	76%
Lipid-lowering drugs	58%	29%
ß-blockers	62%	39%
Mean systolic blood pressure (mm Hg)	137	139

by 5/2 mm Hg with perindopril is unclear. However, given the fact that these patients were normotensive at entry, the reduction in CV events was probably greater than what could be explained by blood pressure lowering alone.

Summary

In summary, the results of the EUROPA study extend the indications for ACE inhibitor therapy beyond those of LV dysfunction and MI, and to patients deemed at high risk for CV events. Therefore, unless contraindicated, an ACE inhibitor such as perindopril should be considered in all patients with documented CAD.

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