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Effects of perindopril on long-term clinical outcome of patients with coronary artery disease and preserved left ventricular function

Michel E. Bertrand [a,*], Willem J. Remme [b], Kim M. Fox [c], Roberto Ferrari [d], Maarten L. Simoons [e]
On behalf of the EUROPA investigators

[a] *Lille Heart Institute, Lille, France*
[b] *Sticares Cardiovascular Research Foundation, Rotterdam, The Netherlands*
[c] *Royal Brompton and National Heart Hospital, London, United Kingdom*
[d] *Azienda Ospedalier and University di Ferrara, Ferrara, Italy*
[e] *Erasmus University, Rotterdam, The Netherlands*

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Abstract

Background: The EUROPA trial has demonstrated that an ACE inhibitor perindopril, was able to significantly decrease the risk of major cardiac events in patients with stable coronary heart disease without apparent heart failure.
Aim: To assess the long-term clinical outcome of patients with stable coronary heart disease and preserved left ventricular function (left ventricular ejection fraction (LVEF $\geq$ 40%).
Methods: A retrospective evaluation of LVEF was performed in the EUROPA study population. Among the 12,218 patients of EUROPA, we identified 7096 (58%) patients who had LVEF measurement before randomization. The measurements were obtained mainly by echocardiography in 5214 cases (73%) or by angiography in 1470 cases (21%). Two groups of patients were studied: 6878 (97 %) patients with LVEF $\geq$ 40% (3429 received 8 mg of perindopril and 3449 received a placebo) and 218 patients (3%) with a LVEF < 40% (111 received perindopril and 107 a placebo).
Results: The baseline characteristics of patients with documented LVEF were similar to the whole EUROPA population in terms of demographics, medical history, physical examination (heart rate, blood pressure), and medications at screening. The mean LVEF of this population was 57.0 ± 10.4%.

In patients (n = 6878) with preserved LV function (LVEF $\geq$ 40%), there was a significant relative risk reduction of 16% of the primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction and resuscitated cardiac arrest) in the group treated with perindopril (8.3%) in comparison to the group treated with placebo (9.8%): Hazard ratio (HR) = 0.84 [95% CI: 0.72–0.99] p = 0.033). Similar results were obtained for the first secondary endpoint (total mortality, non-fatal myocardial infarction, hospital admission for unstable angina and cardiac arrest with successful resuscitation): HR = 0.85 [95% CI: 0.76–0.96] p = 0.008, for cardiovascular mortality and non-fatal MI: HR = 0.84 [95% CI: 0.72–0.99] p = 0.036.

Similar benefits were observed in patients with an LVEF $\geq$ 40% and a history of previous myocardial infarction and in patients with an LVEF < 40%.
Conclusions: LVEF was documented in 58% of the EUROPA study population and only 3% had an impaired LV function, confirming that EUROPA patients did not have asymptomatic LV dysfunction. Results in patients with preserved LV function are consistent with those of the whole EUROPA study population and perindopril 8 mg is beneficial in the broad spectrum of patients with stable coronary artery disease without evidence of heart failure.

Keywords: ACE inhibition; Cardiovascular disease prevention; Secondary prevention; Coronary artery disease; Left ventricular dysfunction

* Corresponding author. Hopital Cardiologique, Boulevard du Prof. Leclercq, 59037 Lille, France. Tel.: +33 320 92 13 34; fax: +33 320 0065 09.
E-mail address: mbertrand@cardiolille.net (M.E. Bertrand).

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1. Introduction

Angiotensin converting enzyme (ACE) inhibitors represent one of the major advances in modern cardiovascular medicine. These agents are very effective in the treatment of hypertension and heart failure. During the last years, the indications for ACE inhibitors use have widened to include different groups of patients with coronary artery disease.

Many randomised, multicentre, clinical trials have established the role of ACE inhibitors after myocardial infarction: AIRE [1], SAVE [2],TRACE [3],SMILE [4],CCS-1 [5], ISIS-4 [6],GISSI-3 [7]: From these studies ACE inhibitors appear to be an important addition to the treatment of acute MI and the only contra-indications are hypotension, known hypersensitivity and pregnancy.

In some of these trials, the recurrence of major ischemic events was significantly reduced. In particular, in AIRE [1], SOLVD [8] and SAVE [2] a significant reduction of re-infarction was observed. A meta-analysis of 12,763 patients [9] enrolled in SAVE [2], AIRE [1], TRACE [10], SOLVD [8] showed that the risk of re-infarction was decreased by 21% ($p=0.0001$).

Importantly, patients in these studies had left ventricular dysfunction and/or heart failure.

More recently, several studies [11–14] were designed to evaluate the preventive effects of ACE inhibition on cardiovascular and/or ischemic events in patients with cardiac or cardiovascular disease not selected for cardiac dysfunction or heart failure.

The EUROPA [13] study was a large (12,218 patients) clinical, prospective, double-blinded randomised controlled trial in patients with established coronary artery disease without clinical symptoms of heart failure. EUROPA [13] demonstrated that treatment with perindopril 8 mg reduced significantly ($p=0.0003$) from 9.9% to 8% (relative risk reduction (20%) the primary endpoint (cardiovascular death, non-fatal myocardial infarction and cardiac arrest with successful resuscitation). Patients with clinical heart failure were excluded but, taking into account that EUROPA [13] study population included a large cohort of patients with a prior history of myocardial infarction, the question was raised whether the positive results might not be related to the previously established effect occurring in patients with impaired left ventricular function.

Therefore, we analyzed the EUROPA [13] results in patients with documented left ventricular ejection fraction (LVEF) and we present the results observed in a cohort of 7096 patients (58% of the EUROPA [13] study population) with assessment of left ventricular function before entry in the trial.

2. Methods

The EUROPA trial [13] enrolled 12,218 men and women >18 years of age, with objective evidence of coronary artery disease and without clinical heart failure.

Table 1
Study population

Characteristics	Patients with LVEF measurements	Patients without LVEF measurements	All EUROPA patients
N	*N*=7096	*N*=5122	*N*=12,218
Mean (SD),age (years)	59.4±9.4	60.8±9.2	60.1±9.3
Female sex	986 (13.9%)	767 (15%)	1779 (14.6%)
History			
MI	4384 (68.1%)	3076 (60.1%)	7910 (64.7%)
PCI	2083 (29.4%)	1490 (29.1%)	3573 (29.2%)
CABG	2059 (29%)	1528 (29.8%)	3587 (29.4%)
Previous stroke or TIA	248 (3.5%)	161 (3.1%)	409 (3.3%)
Peripheral vessel disease	541 (7.6%)	342 (6.7%)	883 (7.2%)
Hypertension	2206 (31.1%)	1106 (21.6%)	3312 (27.4%)
Diabetes mellitus	954 (13.4%)	548 (10.7%)	1502 (12.3%)
Hypercholesreolmemia	4429 (62.4%)	3308 (64.6%)	7737 (63.3%)
Medications			
Platelet inhibitors	6544 (92.2%)	4713 (92%)	11277 (92.3%)
Lipid-lowering drugs	3854 (54.3%)	2977 (58.1%)	7025 (57.5%)
β-blockers	4709 (66.4%)	2941 (57.4%)	7579 (61.7%)
Ca-channel blockers	2272 (32.0%)	1683 (32.9ù)	3836 (31.4%)
Nitrates	3465 (48.8%)	1955 (38.2%)	5254 (43%)
Diuretics	602 (8.5%)	341 (6.7%)	1124 (9.2%)
Mean (SD) heart rate (beats/min)	68.1±9.9	68.3±10.4	68.2±10.1
Mean (SD) systolic blood pressure (mmHg)	137±14.9	137.8±16.1	137.1±15.5
Mean (SD) diastolic blood pressure (mm Hg)	82.1±7.8	81.2±8.7	81.7±8.2

Comparison with the whole EUROPA study.
MI = myocardial infarction, PCI = percutaneous coronary intervention, TIA = transient ischemic attack, CABG = coronary bypass surgery, SD = standard deviation.