

Authors: E. AGABITI-ROSEI - G. AMBROSIO - L. BADIMON - JP. BASSAND - A. BAYÉS DE LUNA - M.E. BERTRAND - E. CHAZOV - S. CHIERCHIA - J. CLELAND - D. CLEMENT - D. COKKINOS - N. DANCHIN - R. DIETZ - P. DOMINIAC - I. EDES - E. ERDMANN - R. FERREIRA - H.R.FIGULLA - W. FLAMENG - I. GRAHAM - G. JACKSON - W. JANUSZEWICZ - J.C. KASKI - P. KEARNEY - W. KLEIN - F. KOLBEL - M. KOMAJDA - W. KÜBLER - J.L.LOPEZ-SENDON HENTSCHHEL - G. MANCIA - W.J. MCKENNA - T. MEINERTZ - J.MLCZOCH - D. MULCAHY - E. O'BRIEN - A. OTO - J. PAPP - W.J. PAULUS - J. POLONIA - I. PRÉDA - L.A. PROVIDENCIA - J. REID - W.J. REMME - W. RUZYLLO - Z. SADOWSKI - P. SERRUYS - P. SLEIGHT - J. SOLER-SOLER - J. SOMERVILLE - P.G. STEG - H.A.J. STRUIJKER BOUDIER - B. SWYNGHEDAUW - L. TAVAZZI - M. TENDERA - P. TOUTOUZAS - A. VAHANIAN - J.L. VANOVERSCHELDE - J. WIDIMSKY - M. YACOB

### ACE inhibition after coronary artery bypass surgery: the IMAGINE trial

The IMAGINE (Ischemia Management with Acupril post by-pass graft via Inhibition of the Converting Enzyme) trial has recently been published.<sup>1</sup> This study was conducted in the immediate post operative period in patients who had undergone coronary artery bypass surgery.

This work was along the lines of the QUO VADIS trial,<sup>2,3</sup> published in 2001, in which 149 patients were randomized before coronary artery bypass surgery to receive either quinapril (an ACE inhibitor) or a placebo. At the end of 1 year of follow-up, there was a significant ( $P=0.04$ ) reduction of ischemic events in the group treated by the ACE inhibitor.

The main objective of the IMAGINE<sup>1</sup> trial was to determine whether the early initiation of an ACE inhibitor (quinapril with gradually increasing dose up to 40 Mg) could reduce the risk of ischemic events after coronary artery bypass grafting (CABG).

Patients were screened for eligibility and randomized in hospitals at 57 sites in Canada, the Netherlands, Belgium, or France within 7 days after CABG, except for patients in France, where randomization could occur within 10 days after CABG. They were older than 18 years, were in a stable condition after the surgery, and had LVEF  $\geq 40\%$ , determined within 6 months before surgery.

The exclusion criteria were intolerance or contraindication to ACE inhibitor, insulin-dependent diabetes mellitus, or type II diabetes with microalbuminuria, clinical need for an ACE inhibitor or an angiotensin receptor blocker, current need for post-CABG urgent intervention or valve replacement; creatinine level  $>2.26$  mg/dL (200  $\mu\text{mol/L}$ ), severe hypertension (SBP  $>160$  mm Hg or DBP  $>90$  mm Hg) or a significant perioperative myocardial infarction (MI), (defined as CK Mb  $>100$  U/L (or  $>75$   $\mu\text{g/L}$ ), troponin I  $>20$   $\mu\text{g/L}$ , or troponin T  $>15$   $\mu\text{g/L}$ ; or new Q waves or LBBB with corresponding wall-motion abnormality.

The original primary end point (PEP) consisted of time to first occurrence of any of the composite of cardiovascular (CV) death or resuscitated cardiac arrest, nonfatal MI, coronary revascularization, unstable angina that required hospitalization, and documented angina that did not require hospitalization. However, at the beginning of 2003, and owing to a lower than expected event rate, the steering committee concluded that the required number of end points would likely not be reached, and decided to add stroke and congestive heart failure requiring hospitalization to the PEP. The sample size was increased to 2500 patients.

From December 1999 to 2005, 2 553 patients were randomized and received either quinapril (N=1280), or a placebo (N=1273). The median follow-up was 2.95 years. Only 5 patients were lost to follow-up (1 in the quinapril group and 4 in the placebo group). The study population was homogeneous in the two groups with 13% of women, 10% of diabetics, and 21% of subjects with prior revascularization. The randomization was carried out on average 4 days ( $\pm 2$  days) after the intervention. There were 2% with minimally invasive interventions, and 19% with off-pump surgery. On average, 3.2 grafts were implanted per patient and more than 4 in 39% of the cases. More than 2 arterial grafts were implanted in 39% of the patients. Other medical treatments were identical in the two groups: more than 90% received aspirin or antiplatelet drugs, 80% a lipid lowering drug, 70%  $\beta$ -blockers, and in 7 to 9% of the cases, an oral anticoagulant treatment.

At the end of the 2 year-period, there was no significant difference between the two groups concerning the PEP (HR: 1,15 [95 % CI: 0,90-1,42]  $P=0.224$ ). It was the same for each type of event considered separately (Table).

Table. Results.

Outcome	Quinapril	Placebo	HR (95% CI)	P
Primary end point	13.7%	12.2%	1.15 (0.92-1.42)	0.212
Total death	2.0%	2.0%	1.00 (0.59-1.69)	0.997
CV death	1.4%	1.2%	1.2 (0.6-2.38)	0.604
Nonfatal MI	1.3%	1.6%	0.76 (0.40-1.46)	0.414
Stroke	1.2%	1.1%	1.07 (0.52-2.21)	0.860
Hospitalization for HF	1.2%	1.1%	1.09 (0.53-2.26)	0.818

The percentage of patients presenting hypotension and cough was higher in the quinapril group compared with the placebo group (respectively 12.1% versus 5.5%,  $P<0.0001$  and 20.9% versus 10.9%,  $P<0.0001$ ).

The IMAGINE trial<sup>1</sup> was designed because ACE inhibitors reduce activation of the renin-angiotensin system and improve endothelial function, two situations which are markedly modified in the early phase after coronary artery bypass surgery. Thus, IMAGINE<sup>1</sup> was expected to show a benefit of quinapril when given immediately after operation.

Actually, IMAGINE<sup>1</sup> failed to show a benefit of quinapril in these particular patients. Even more, within the first 3 months the rate of CV death, nonfatal MI and stroke was higher (but not significantly) in the quinapril group when compared to placebo during the first 3 months. These findings are surprising, because IMAGINE<sup>1</sup> was well designed with adequate study population and sample size. One can raise the point of a class effect since, it is the second time that quinapril failed to be efficient in patients after revascularization. The QUIET<sup>4</sup> study conducted in 1750 patients undergoing balloon angioplasty or atherectomy was a negative trial with no reduction of cardiac death, nonfatal MI, or the composite of death, MI, cardiac arrest, revascularization or hospitalization for unstable angina. However, the sample size of that study was too small.

Other studies conducted with different ACE inhibitors before or after CABG have shown a benefit. In the HOPE<sup>5</sup> study 2399 patients with history of CABG ( $>4$  years) had an 11% reduction of PEP. In the EUROPA<sup>6</sup> trial and among the 3587 patients with a history of CABG ( $>6$  months) there was a reduction in PEP of 17%. In PEACE<sup>7</sup> there was a nonsignificant modest reduction (4.7%). On the other hand, the APRES<sup>8</sup> study, conducted in only 159 patients after CABG and with ramipril, showed a large relative risk reduction (58%).

**Thus, it is clear that the results of IMAGINE<sup>1</sup> should not modify the interpretation of the previous studies, which showed a strong benefit in terms of secondary prevention in patients with a history of myocardial revascularization treated with ramipril or perindopril.**

**M. BERTRAND – Lille, France**

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