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Intracoronary Enalaprilat to Reduce Microvascular Damage During Percutaneous Coronary Intervention (ProMicro) Study

Fabio Mangiacapra, MD, PhD, Aaron J. Peace, MD, PhD, Luigi Di Serafino, MD, PhD, Stylianos A. Pyxaras, MD, Jozef Bartunek, MD, PhD, Eric Wyffels, MD, Guy R. Heyndrickx, MD, PhD, William Wijns, MD, PhD, Bernard De Bruyne, MD, PhD, Emanuele Barbato, MD, PhD

Aalst, Belgium

Objectives This study investigated the influence of intracoronary enalaprilat on coronary microvascular function and peri-procedural outcome measures in patients with stable angina undergoing percutaneous coronary intervention (PCI).

Background Intracoronary angiotensin-converting enzyme inhibitors have been shown to relieve myocardial ischemia in stable patients and to improve epicardial flow in patients with ST-segment elevation myocardial infarction. Yet, it is still unclear whether these effects are mediated by a modulation of the coronary microcirculation.

Methods We randomly assigned 40 patients to receive either an intracoronary bolus of enalaprilat (50 μg) or placebo before elective PCI. The index of microvascular resistance was measured at baseline, 10 minutes after study drug administration, and after PCI. High-sensitivity cardiac troponin T was measured as a marker of myocardial injury.

Results Infusion of enalaprilat resulted in a significant reduction in index of microvascular resistance (27 $\pm$ 11 at baseline vs. 19 $\pm$ 9 after drug vs. 15 $\pm$ 8 after PCI), whereas a significant post-procedural increase in index of microvascular resistance levels was observed in the placebo group (24 $\pm$ 15 at baseline vs. 24 $\pm$ 15 after drug vs. 33 $\pm$ 19 after PCI). Index of microvascular resistance levels after PCI were significantly lower in the enalaprilat group ($p < 0.001$). Patients pre-treated with enalaprilat also showed lower peak values (mean: 21.7 ng/ml, range: 8.2 to 34.8 ng/ml vs. mean: 32.3 ng/ml, range: 12.6 to 65.2 ng/ml, $p = 0.048$) and peri-procedural increases of high-sensitivity cardiac troponin T (mean: 9.9 ng/ml, range: 2.7 to 19.0 ng/ml vs. mean: 26.6 ng/ml, range: 6.3 to 60.5 ng/ml, $p = 0.025$).

Conclusions Intracoronary enalaprilat improves coronary microvascular function and protects myocardium from procedure-related injury in patients with coronary artery disease undergoing PCI. Larger studies are warranted to investigate whether these effects of enalaprilat could result into a significant clinical benefit. (J Am Coll Cardiol 2013;61:615–21) © 2013 by the American College of Cardiology Foundation

Angiotensin-converting enzyme (ACE) inhibitors improve clinical outcomes in patients with coronary artery disease (1–4). Beyond the long-term protective effect of the oral treatment, intracoronary administration of ACE inhibitors may be beneficial in patients undergoing percutaneous coronary intervention (PCI). Pretreatment with intracoronary enalaprilat of patients with stable coronary artery disease relieved myocardial ischemia during PCI, as assessed by intracoronary electrocardiogram and chest pain score (5). Moreover, in patients undergoing primary PCI for ST-segment elevation myocardial infarction, enalaprilat injection in the infarct-related artery reduces the adhesion of inflammatory cells and improves epicardial flow (6). Possible mechanisms underlying these protective effects include an improvement of the endothelium-dependent epicardial coronary vasodilation mediated by an increase in endogenous bradykinin activity (7). In addition, preliminary findings from experimental models suggest that enalaprilat also may lead to an improvement of coronary blood flow and coronary flow reserve (CFR) (8). Yet, it is still unclear whether this latter effect is exerted mainly at the level of the coronary microcirculation.

From the Cardiovascular Center Aalst OLV Clinic, Aalst, Belgium. Dr. Wijns has relationships with Ablynx, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Therabel, Abbott Vascular, Biotronik, Boston Scientific, Cordis J&J, Edwards, Medtronic, Orbus Neich, St. Jude, and Terumo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

CFR = coronary flow reserve

FFR = fractional flow reserve

hs-cTnT = high-sensitivity cardiac troponin T

IMR = index of microvascular resistance

PCI = percutaneous coronary intervention

PMI = periprocedural myocardial infarction

In the present study, we investigated whether enalaprilat improves coronary microvascular function, as assessed with the index of microvascular resistance (IMR), and we assess its relative impact on peri-procedural outcomes in patients undergoing elective PCI.

Methods

This was a prospective, randomized, double-blind, controlled study carried out at the Cardiovascular Center Aalst OLV Clinic, Aalst, Belgium, between February and September 2011.

Patient population. We enrolled 40 patients with stable coronary disease referred for elective PCI of an isolated, functionally significant (fractional flow reserve [FFR]: <0.80) lesion located in the proximal two-thirds of a major coronary artery. Patients were excluded in the presence of the following conditions: treatment with oral ACE inhibitors in the previous 15 days, previous myocardial infarction, left ventricle ejection fraction less than 50%, left ventricle wall-motion abnormalities, left ventricular hypertrophy, in-stent restenosis, bifurcation with side branch of more than 2 mm, ostial lesion, and contraindications to adenosine. The study protocol was approved by the institutional ethics committee, and patients gave informed consent for participation and data collection.

Adjunctive medications. All patients were administered a loading dose of 600 mg clopidogrel and 500 mg aspirin the day before the procedure. During catheterization, all patients received a weight-adjusted intravenous heparin bolus (100 IU/kg) to maintain an activated clotting time of between 250 and 300s.

Study protocol. Patients were assigned randomly to receive either an intracoronary bolus of enalaprilat or placebo before PCI. Assignment to 1 of the 2 treatments was determined by a computer-based randomization system, and randomization assignment for each patient was kept in a sealed envelope. Enalaprilat 50 μg in 5 ml NaCl 0.9% was administrated to the study patients (9); 5 ml NaCl 0.9% was administrated to the placebo patients. Both the patient and the catheterization laboratory team (operator and scrub nurse) were blinded to the assigned treatment. An independent study nurse not involved in the procedure was responsible of opening the sealed envelope and preparing the solution of enalaprilat (active drug) or placebo (pure saline) to be administered according to treatment allocation. Enalaprilat or placebo was infused in the target coronary artery through the guiding catheter over a 2-min period, followed by a 10-ml 0.9% NaCl solution flush. The dosage of enalaprilat was chosen on the basis of previous studies (9). Coronary physiological indexes (CFR, IMR, and FFR) were measured in each patient at baseline (before study drug administration), 10 min after study drug administration, and after PCI, as previously described (10–18). Briefly, an intracoronary pressure and temperature sensor-tipped guidewire (PressureWire Certus, RADI, St. Jude Medical, Uppsala, Sweden) was used to measure distal coronary pressure and to derive thermodilution curves. Thermodilution curves were obtained (in triplicate) from a hand-held, 3-ml rapid (<0.25 s) injection of room temperature saline at baseline and during maximal hyperemia, which was achieved by infusion of 140 μg/kg per minute of adenosine via the femoral vein. Mean transit time (T_{mn}) at baseline and during maximal hyperemia was derived from thermodilution curves. Simultaneous recordings of mean aortic pressure (guiding catheter, P_a) and mean distal coronary pressure (distal pressure sensor, P_d) also were obtained at baseline and during maximal hyperemia. The CFR was calculated from the ratio of hyperemic to baseline T_{mn}. The IMR was calculated using the following equation: $IMR = P_a \times T_{mn}\,[(P_d - P_w) / (P_a - P_w)]$, where P_w is the coronary wedge pressure. P_w was measured as the distal coronary pressure (from the distal pressure and temperature sensor) during complete balloon occlusion of the vessel obtained during PCI. The FFR was calculated from the ratio of distal to proximal pressures at maximal hyperemia. The PCI procedures were performed by standard technique. In all cases, balloon pre-dilatation was performed before stent implantation.

Peri-procedural myocardial necrosis. High-sensitivity cardiac troponin T (hs-cTnT) (Roche Diagnostics, Mannheim, Germany) was determined in blood samples taken before and 8 and 24 h after intervention. Peri-procedural myocardial infarction (PMI) was defined as a post-procedural increase in hs-cTnT more than 3 times the 99th percentile of the upper reference limit (i.e., 14 ng/ml) for patients with baseline negative myocardial necrosis markers, consistent with the joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation task force consensus statement on the redefinition of myocardial infarction for clinical trials on coronary intervention (19). In patients with increased baseline levels of hs-cTnT, a subsequent increase of more than 50% of the baseline value fulfilled the criteria for PMI (20).

Statistical analysis. At the time the ProMicro (EnalaPrilat to Reduce MICROvascular Damage During Percutaneous Coronary Intervention) (ProMicro) trial was conceived, no studies were available specifically reporting on the impact of enalaprilat on microvascular function. However, we based our sample size calculation on our previous studies showing that a strategy of direct stenting resulted in a significant impact on microvascular function with a 45% reduction in IMR after PCI compared with conventional balloon angioplasty followed by stent implantation (as performed in the present study) (21,22). Assuming a 33% reduction in IMR