Effect of Nifedipine and Cerivastatin on Coronary Endothelial Function in Patients With Coronary Artery Disease

The ENCORE I Study (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function)

The ENCORE Investigators*

Background—Endothelial dysfunction is an important feature of atherosclerosis. Inhibition of the HMG-CoA pathway and of calcium channels improves endothelial function experimentally and in the forearm circulation. Thus, we investigated the effects of a statin and/or a calcium antagonist on coronary endothelial function in patients with coronary artery disease (CAD).

Methods and Results—In 343 patients undergoing percutaneous coronary intervention in 29 centers, acetylcholine (10^{-6} to 10^{-4} mol/L) was infused in a coronary segment without angiographically significant CAD. Changes in coronary diameter were measured by quantitative angiography. Endothelium-independent responses were assessed by intracoronary adenosine (1.2 mg/mL) and nitroglycerin (250 μg). Thereafter, patients were randomized in a double-blind manner to placebo, cerivastatin 0.4 mg/d, nifedipine 30 to 60 mg/d, or their combination. Studies were repeated at 6 months. In the most constricted segment, nifedipine but not cerivastatin reduced vasoconstriction to acetylcholine (18.8% versus placebo 10.0%; \( P<0.05 \)). Patients not taking ACE inhibitors showed a smaller improvement in the placebo group (6.0%), but nifedipine still had an effect (17.0%; \( P<0.05 \) versus placebo). Analysis of all evaluable coronary segments revealed an 11% reduction of acetylcholine-induced vasoconstriction in patients receiving nifedipine and cerivastatin (\( P<0.05 \) versus placebo). Cerivastatin lowered LDL cholesterol by 35% (\( P<0.001 \)).

Conclusions—The ENCORE I trial demonstrates that multicenter studies on coronary endothelial function are feasible. After 6 months’ treatment, nifedipine improved coronary endothelial function in the most constricted segment. The combination of nifedipine and cerivastatin tended to improve endothelial function; however, this only reached significance in an analysis of all coronary segments. (Circulation. 2003;107:422-428.)

Key Words: coronary disease ■ endothelium ■ acetylcholine ■ angiography ■ drugs

In coronary artery disease (CAD), atherosclerosis exhibits functional and structural changes.1,2 Functional changes precede lesion formation, and they become more pronounced as the disease progresses.3–5 The endothelial injury theory assumes that an alteration in the release of endothelial factors (ie, nitric oxide [NO] and endothelin) mediates abnormal coronary vasomotion, increased adherence of monocytes and platelets, and smooth muscle migration and proliferation.2,3 Endothelial dysfunction occurs as a “response to injury” in oxidized LDL,2,6 hypertension,2–9 diabetes,10,11 and oxygen-derived free radicals.12

Treatments able to reverse coronary endothelial dysfunction might have great advantages. Inhibition of HMG-CoA reductase not only reduces cholesterol but leads to prenylation and geranylation of proteins involved in the regulation of NO and other endothelial mediators.13 Calcium channel blockers may reduce oxidative stress and improve NO release.14,15 We therefore investigated the effects of a statin and/or a calcium antagonist on coronary endothelial function over a 6-month period in patients with CAD.16

Methods

Patients

The ENCORE I (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function) study was a randomized, double-blind study comparing nifedipine GITS (Gastro-Intestinal Therapeutic System) 30 mg/d increased to 60 mg/d, cerivastatin 0.4 mg/d, and their combination with placebo on coronary endothelial vasomotor function in patients undergoing percutaneous coronary intervention. Inclusion criteria were age >18 years, LDL cholesterol <180 mg/dL (4.7 mmol/L), and a left coronary artery segment with ≤40% stenosis (index artery). Main exclusion criteria were Q-wave myocardial infarction within 2 weeks, stroke, peripheral revascularization or major surgery within 3 months, unstable angina unless stabilized by intervention, unstable diabetes, symptomatic hypertension or uncontrolled hypertension, left ventricular ejection fraction <40%, creatinine twice upper limit of normal (ULN), creatine phosphokinase (CPK) 3 times ULN, amylase 1.5 times ULN,
transaminases twice ULN, history of liver or gastrointestinal diseases, and lipid-lowering or calcium channel blocker treatment for >2 months. If ACE inhibitors had been used for more than 2 months, their use was continued during the study; otherwise, use of ACE inhibitors was not allowed. All participating sites had approval for the study from an internal review board or ethics committee, and all patients provided written informed consent.

Study Design
Before intervention, cardiovascular drugs were withheld for 24 hours (short-acting nitrates were withheld for 3 hours). After percutaneous coronary intervention, an infusion catheter was positioned in a proximal segment of the left anterior descending coronary artery or right circumflex artery. Acetylcholine (Miochol, Ciba Vision) and adenosine (Krenosin/Adrekar, Sanofi-Winthrop) were infused at 2 mL/min for 3 minutes in the following order: acetylcholine 0.36, 3.6, and 18 μg/mL; isotonic saline; adenosine 1.2 mg/mL; and finally, 250 μg of nitroglycerin by injection. At baseline and after each infusion, heart rate and blood pressure were recorded, and angiography was performed with nonionic contrast medium, which was primarily injected manually. Patients with at least 1 segment of an artery without vasodilation to acetylcholine (by visual inspection) were eligible. Patients were seen at week 2, 4, 12, and 26 for clinical assessments. Chemistry and hematology were analyzed centrally (University Hospital of Freiburg, Germany).

At follow-up, patients underwent catheterization after withdrawal of study medication for 2 days and other cardiovascular drugs for 24 hours. The x-ray tube and catheter were set at identical positions as at baseline, and the protocol was repeated.

Assessment of Coronary Artery Diameters
Angiograms were analyzed centrally in a blinded fashion (Medical School, Hannover, Germany). Two to 7 (mean 3) segments of the index artery distal to the infusion catheter were measured by the CMS edge-detection algorithm (MEDIS). Each segment was referenced to a specific anatomic landmark for identification at the follow-up angiogram. Coronary responses were expressed as the percentage change from baseline in mean lumen diameter. Target segment for the main comparison was the one with the most pronounced vasodistraction at any acetylcholine dose at baseline.

Statistical Analysis
The primary end point was the effect of treatment compared with placebo on acetylcholine-induced coronary vascular response at the highest dose of acetylcholine applied both at baseline and at follow-up. A sample size of 60 evaluable patients per treatment group was estimated to have a 90% power to detect a mean difference of 12 percentage points with a 2-tailed t test with a 0.05 significance level, assuming a within-group SD of 20%. A hierarchical stepwise testing procedure was used, with the 0.05 significance level kept at each step because steps 2 and 3 were of a confirmatory nature and only to be tested if the previous step showed significant difference. Step 1 tested the difference between the combination treatment and placebo; step 2 simultaneously tested the difference between each of the single treatments and placebo; and step 3 tested the differences between any of the active treatments. Steps 2 and 3 kept the 5% significance level with Bonferroni correction. The analyses were done by ANCOVA, with treatment and centers as fixed effects and the baseline measurement as covariate. The between-center effect was insignificant in all statistical analyses.

Exploratory analyses were performed on (1) the change in mean coronary lumen diameter of the index segment in patients not undergoing ACE inhibitor therapy and (2) the change in mean coronary lumen diameter of all evaluable segments. Statistical analyses were performed with SAS, version 6.12. Data are presented as mean±SD unless otherwise indicated.

Results

Patient Characteristics
Of 368 patients who gave informed consent, 343 were randomized (85, 84, 85, and 89 to placebo, nifedipine, cerivastatin, and combination, respectively), and 334 (82, 83, 81, and 88) received treatment (Table 1). A total of 243 patients were evaluable for intention-to-treat analysis and 233 for per-protocol analysis. Reasons for nonevaliability are given in Table 2. A total of 211 of the 243 patients evaluable had a history of smoking, equally distributed in the 4 groups. Two thirds had quit smoking before study entry. Most patients were taking aspirin (217 of 243) and an ADP antagonist (217 were taking ticlopidine, and 62 were taking clopidogrel, usually for several weeks after the baseline study only). Recorded vitamin use was very rare. Of the nifedipine-treated patients, 84% to 90% were taking 60 mg/d.

Blood pressure averaged 130.9±19.0/76.3±9.9 mm Hg and heart rate 66±11 bpm at baseline. Sixty patients (24%) had blood pressure >140/90 mm Hg, and 41% had a history of hypertension. Neither blood pressure nor heart rate changed in the 4 treatment groups.

Plasma Cholesterol Levels
At baseline, total plasma cholesterol averaged 204±34 mg/dL, LDL cholesterol averaged 133±33 mg/dL, and HDL cholesterol averaged 39±13 mg/dL (Figure 1).

Acetylcholine Test at Baseline
At baseline, acetylcholine caused dose-dependent constriction of the index segment. Among the 334 patients with readable angiograms, 3 doses could be infused in 310 patients (92.8%), whereas in 16 patients (4.8%) and 6 patients (1.8%), marked vasoconstriction (diameter <0.2 mm) occurred at the second or first dose, respectively. In 42 patients (14.4%), complete coronary occlusion occurred at either dose.

Transient ECG changes were noted in 11 patients (3.3%) and chest pain in 3 (0.9%). In 2 patients, diffuse vasoconstriction with hemodynamic consequences required resuscitation, in both cases without sequelae.

Acetylcholine Test at 6-Month Follow-Up
At 6 months, the test could be repeated in 250 patients (75% of patients). In 240 patients (96%), all doses could be infused, whereas in 5 (2%) and 4 (2%) patients, marked vasoconstriction occurred at the second or first dose, respectively. In patients evaluable per protocol, the change from baseline of mean luminal diameter at the highest comparable dose of acetylcholine averaged 10.0±3.0% with placebo, 18.8±3.0% (P=0.04) with nifedipine, 11.1±3.0% (P=NS) with cerivastatin, and 12.9±3.3% (P=NS) with combination treatment (Figure 2). Complete coronary occlusion (diameter <0.2 mm) occurred at any of the 3 doses of acetylcholine in 6.5% of patients with placebo (versus 8.1% at baseline), 0% with nifedipine (versus 10.5% at baseline), 6.6% with cerivastatin (versus 14.8% at baseline), and 5.7% with combination treatment (unchanged from baseline).

Exploratory analyses revealed a potential effect of ACE inhibitors. Among patients in the placebo group, the percent
change in response to acetylcholine from baseline to follow-up averaged 21.2 ± 11.0% in those taking ACE inhibitors (n = 15) and 6.0 ± 3.6% in those not taking ACE inhibitors (n = 47; P = 0.11). Overall, after exclusion of 49 patients taking ACE inhibitors, the percent difference was 6.0 ± 3.6%, 17.0 ± 3.6% (P = 0.0278), 11.6 ± 3.6% (P = NS), and 11.2 ± 3.9% (P = NS) in the placebo, nifedipine, cerivastatin, and combination groups, respectively (Figure 3).

TABLE 1. Baseline Characteristics (Patients Evaluable per Protocol)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 62)</th>
<th>Nifedipine (n = 57)</th>
<th>Cerivastatin (n = 61)</th>
<th>Combination (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.9 ± 10.8</td>
<td>58.3 ± 11.0</td>
<td>57.5 ± 9.0</td>
<td>59.1 ± 9.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>59 (90.3)</td>
<td>47 (82.5)</td>
<td>49 (80.3)</td>
<td>45 (84.9)</td>
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<tr>
<td>Body weight, kg</td>
<td>78.1 ± 9.9</td>
<td>79.7 ± 12.2</td>
<td>81.0 ± 15.4</td>
<td>79.7 ± 12.7</td>
</tr>
<tr>
<td>Race, % white</td>
<td>100.0</td>
<td>100.0</td>
<td>95.1</td>
<td>98.1</td>
</tr>
<tr>
<td>Smoker, present or past, n (%)</td>
<td>47 (75.8)</td>
<td>37 (64.9)</td>
<td>41 (67.2)</td>
<td>40 (75.5)</td>
</tr>
<tr>
<td>Diagnostic findings, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Vessel disease</td>
<td>33 (53.2)</td>
<td>35 (61.4)</td>
<td>39 (63.9)</td>
<td>38 (71.7)</td>
</tr>
<tr>
<td>2-Vessel disease</td>
<td>24 (38.7)</td>
<td>12 (21.1)</td>
<td>17 (27.9)</td>
<td>11 (20.8)</td>
</tr>
<tr>
<td>3-Vessel disease</td>
<td>5 (8.1)</td>
<td>10 (17.5)</td>
<td>5 (8.2)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Intervention, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PTCA only</td>
<td>7 (11.3)</td>
<td>14 (24.6)</td>
<td>14 (23.0)</td>
<td>9 (17.0)</td>
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<td>Direct stenting</td>
<td>13 (21.0)</td>
<td>10 (17.5)</td>
<td>8 (13.1)</td>
<td>8 (15.1)</td>
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<tr>
<td>PTCA + stent</td>
<td>42 (67.7)</td>
<td>33 (57.9)</td>
<td>39 (63.9)</td>
<td>36 (67.9)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>25 (40.3)</td>
<td>19 (33.3)</td>
<td>26 (42.6)</td>
<td>26 (49.1)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>128 (18)</td>
<td>133 (17)</td>
<td>132 (21)</td>
<td>131 (20)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>76 (9)</td>
<td>76 (11)</td>
<td>77 (10)</td>
<td>76 (9)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68 (10)</td>
<td>66 (9)</td>
<td>66 (13)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Concurrent treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE or ARBs</td>
<td>15 (24.2)</td>
<td>11 (19.3)</td>
<td>10 (16.4)</td>
<td>13 (24.5)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>40 (64.5)</td>
<td>38 (66.7)</td>
<td>41 (67.2)</td>
<td>35 (66.0)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6 (9.7)</td>
<td>8 (14.0)</td>
<td>6 (9.8)</td>
<td>5 (9.4)</td>
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<tr>
<td>Nitrates and vasodilators</td>
<td>20 (32.3)</td>
<td>21 (36.8)</td>
<td>22 (36.1)</td>
<td>14 (26.4)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ACEI, ACE inhibitors; and ARBs, angiotensin II receptor blockers.

TABLE 2. Reasons for Premature Withdrawal and Nonevaluability

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 85)</th>
<th>Nifedipine (n = 84)</th>
<th>Cerivastatin (n = 85)</th>
<th>Combination (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>85 (100)</td>
<td>84 (100)</td>
<td>85 (100)</td>
<td>89 (100)</td>
</tr>
<tr>
<td>Never on study drug</td>
<td>3 (3.5)</td>
<td>1 (1.2)</td>
<td>4 (4.7)</td>
<td>1 (1.1)</td>
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<tr>
<td>Premature withdrawals</td>
<td>18 (21.2)</td>
<td>23 (27.4)</td>
<td>17 (20.0)</td>
<td>30 (33.7)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>7 (8.2)</td>
<td>11 (13.1)</td>
<td>6 (7.1)</td>
<td>16 (18.0)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.2)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>4 (4.7)</td>
<td>5 (6.0)</td>
<td>3 (3.5)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>5 (5.9)</td>
<td>6 (7.2)</td>
<td>6 (7.1)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Excluded from efficacy evaluation</td>
<td>1 (1.2)</td>
<td>...</td>
<td>1 (1.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>63 (74.1)</td>
<td>63 (75)</td>
<td>63 (74.1)</td>
<td>54 (60.7)</td>
</tr>
<tr>
<td>Excluded from per-protocol evaluation</td>
<td>...</td>
<td>3 (3.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td>62 (72.9)</td>
<td>57 (67.9)</td>
<td>61 (71.8)</td>
<td>53 (59.6)</td>
</tr>
</tbody>
</table>

Values are n (%).
Exploratory analysis of all coronary segments (≈3 segments/patient) showed changes in response of 5.8±1.6%, 9.6±1.8% (P=NS), 9.1±1.8% (P=NS), and 10.4±1.8% (P<0.05) with placebo, nifedipine, cerivastatin, and combination treatment, respectively (Figure 4). No difference in endothelium-independent vasodilation to adenosine or nitroglycerin was noted over time or between groups.

Drug-Related Side Effects
Peripheral edema occurred in 22 patients (12.9%) taking nifedipine compared with 2 patients (2.4%) taking placebo, which caused premature withdrawal of 7 patients taking nifedipine. Liver enzymes and CPK were measured regularly. Changes >3 times ULN occurred for CPK in 14 patients (4.2%), for serum glutamic-oxaloacetic transaminase in 7 (2.1%), and for serum glutamate pyruvate transaminase in 13 patients (3.9%). Of those, 7, 4, and 10 patients, respectively, were treated with cerivastatin. Two patients taking cerivastatin had CPK >10 times ULN; both normalized despite continued treatment. Two patients taking cerivastatin were withdrawn because of elevated liver enzymes. Muscle pain led to withdrawal of 1 patient taking cerivastatin and 1 taking nifedipine.

Discussion
ENCORE I is the largest clinical trial investigating endothelial dysfunction in CAD with the acetylcholine test: in 29 centers, 334 patients were enrolled and 250 completed the 6-month follow-up protocol. Nifedipine improved...
coronary endothelial function in the most constricted coronary segment. Although cerivastatin achieved the National Cholesterol Education Program/European Society of Cardiology LDL cholesterol targets in the majority of patients, it did not alter endothelial function in the most constricted segment. The combination of nifedipine and cerivastatin tended to improve endothelial function if all analyzed coronary segments were considered.

Withdrawal rates were comparable to those in similar studies and were similar among treatment arms. The reasons for withdrawal were adverse events; withdrawal of consent, mainly for the second angiography; and protocol violations. Although intracoronary acetycholine led to constriction of epicardial coronary arteries, it was well tolerated in the vast majority of patients. Only 3 of 250 patients tested either once or twice experienced chest pain and 11 patients showed ECG changes. Two patients experienced severe vasospasm that required resuscitation, both without sequelae. This is in line with other, smaller reports.

Cerivastatin was used because of its effects on endothelial NO synthase (eNOS) expression. Furthermore, statins may mobilize stem cells and improve endothelialization of diseased coronary segments. LDL cholesterol was reduced by one third with monotherapy or combination therapy, without major side effects. However, cerivastatin was withdrawn from the market in August 2001 because of possible cases of rhabdomyolysis with fatal outcome. Therefore, muscle enzymes were analyzed carefully. Only 2 patients experienced a transient 10-fold rise in CPK, and 2 patients were withdrawn because of elevated liver enzymes. No patient received cerivastatin with a fibrate, a combination known to be associated with a higher incidence of side effects. ENCORE is likely the last placebo-controlled trial with a statin in patients with CAD. At the time of planning, this was thought to be ethically justifiable, because dietary measures were recommended, the study period was short, and LDL was required to be below 180 mg/dL.

Cerivastatin led to no significant change in the primary end point after 6 months. This is in contrast to results from experimental studies and trials in the forearm circulation but in line with the CARAT (Coronary Artery Risk Assessment and Treatment) study on the coronary effects of simvastatin. Several factors may account for this outcome. First, in contrast to the forearm circulation, coronary arteries develop pronounced atherosclerosis. Second, in large trials, the clinical event curves in the statin groups separate from placebo only after 12 to 18 months, which suggests that longer treatment periods are required to change coronary function. Third, the results of the recent MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial are only applicable to patients with acute coronary syndromes, who usually show increased CRP, which is known to depress endothelial function. Patients in the present study had stable coronary disease without high-sensitivity C-reactive protein elevation (data not shown). Fourth, study medication was stopped 2 days before follow-up measurements, which may have blunted the effects of cerivastatin, because at least in mice, statin withdrawal transiently increases Rho activity and suppresses eNOS expression.

In contrast, nifedipine improved coronary endothelial function. This is in line with experimental studies in hyperlipidemia and hypertension and clinical studies in the forearm circulation in hypertension and hyperlipidemia. Although a true improvement of endothelial function, probably due to its antioxidative properties and effects on eNOS expression and activity, is likely, a reduced vasoconstrictor response of vascular smooth muscle cells after long-term treatment with nifedipine cannot be excluded (S. Taddei, lecture, 2001). Along with the results of PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial), in which amlodipine reduced recurrent ischemic events, and the ongoing ACTION trial (A Coronary Disease Trial Investigating Outcome with Nifedipine GIS) on clinical outcomes, the ENCORE II study, which was designed to detect the effects of nifedipine on coronary morphology, may help us understand the role of calcium antagonists in CAD.

In ENCORE I, as in CARAT, an improvement of endothelial function was seen in the placebo group. This could be related to regression to the mean, a phenomenon observed in many trials and particularly likely in analysis of the most constricted segment, selected in the present study as a well-defined end point. In an exploratory analysis of all evaluable coronary segments (on average, 3 per patient), the combination of nifedipine and cerivastatin significantly improved the response, which may be a more relevant outcome because CAD is generalized. Another explanation might be a general improvement in patient management associated with clinical trials. Furthermore, concomitant medications might play a role. An exploratory analysis excluding patients taking ACE inhibitors revealed notable effects of these drugs on endothelial function. However, this analysis was in line with the main results.

In summary, the ENCORE I study showed that endothelial dysfunction as assessed by acetylcholine is quite pronounced in a large patient population with stable CAD. Current cardiovascular management, particularly ACE inhibitors, had marked effects on coronary endothelial dysfunction. After 6 months of treatment, nifedipine improved endothelial function in the most constricted segment, whereas the combination of the calcium antagonist and cerivastatin had a modest effect when several coronary segments were considered. Long-term trials are required to assess the true effects of statins on endothelial dysfunction in patients with stable CAD.

Appendix

ENCORE Investigators

I. Azancot, Paris, France; M. Balbi, Genova, Italy; J.J.R.M. Bonnier, Eindhoven, Netherlands; W. Desmet, Leuven, Belgium; K.-W. Diederich, Leipzig, Germany; H. Drexel, Feldkirch, Austria; J. Dubois-Rande, Créteil, France; R. Erbel, Essen, Germany; V. da Gama Ribeiro, Vila nova de Gaia, Portugal; H. Glogar, Vienna, Austria; P. Hanrath, Aachen, Germany; O.M. Hess, Bern, Switzerland; G. Heyer, Salzburg, Austria; P.G. Hugenholtz, Netherlands; A. Lafont, Paris, France; T.F. Lüscher, Zürich,
Core and Central Laboratories

Angiography
Wolf Rafflenbeul, Cardiology, Medical School, Hanover, Germany.

Clinical Chemistry
Winfried März, Markus Nauck, Clinical Chemistry, University Hospital, Freiburg, Germany.

Study Planning and Conduct
InterCorNet, Foundation for Cardiovascular Research, Zurich, Switzerland; Clinical Project Coordination: Eva Mühldorfer and Gilbert Wagener, Bayer, Leverkusen, Germany; Statistical Analysis: C. Dierig, Bayer, Leverkusen, Germany and Jörg Muntwyler, InterCorNet, Foundation for Cardiovascular Research, Zurich, Switzerland.

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