Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR study: a multicenter, randomized, double-blind placebo-controlled trial. Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group

Circulation 1992;86;100-110
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Does the New Angiotensin Converting Enzyme Inhibitor Cilazapril Prevent Restenosis After Percutaneous Transluminal Coronary Angioplasty?

Results of the MERCATOR Study: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial

The Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group

Background. **Cilazapril is a novel angiotensin converting enzyme inhibitor with antiproliferative effects in the rat model after balloon injury.**

Methods and Results. **We conducted a randomized, double-blind placebo-controlled trial to assess the effect of cilazapril in angiographic restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA). Patients received cilazapril 2.5 mg in the evening after successful PTCA and 5 mg b.i.d. for 6 months or matched placebo. In addition, all patients received aspirin for 6 months. Coronary angiograms before PTCA, after PTCA, and at 6-month follow-up were quantitatively analyzed. In 94% of 735 recruited patients, PTCA was successful and all inclusion and exclusion criteria were met. For the per-protocol analysis, quantitative angiography after PTCA and at follow-up was available in 595 patients who complied with the treatment regimen (309 control, 286 cilazapril). The mean difference in minimal coronary lumen diameter between post-PTCA and follow-up angiogram (primary end point) was -0.29 ± 0.49 mm in the control group and -0.27 ± 0.51 mm in the cilazapril group. Clinical events during 6-month follow-up, analyzed on an intention-to-treat basis, were ranked according to the most serious clinical event ranging from death (control, two; cilazapril, three), nonfatal myocardial infarction (control, eight; cilazapril, 5), coronary revascularization (control, 51; cilazapril, 53), or recurrent angina requiring medical therapy (control, 67; cilazapril, 68) to none of the above (control, 224; cilazapril, 212). There were no significant differences in ranking.**

Conclusions. **Long-term angiotensin converting enzyme inhibition with cilazapril in a dose of 5 mg b.i.d. does not prevent restenosis and does not favorably influence the overall clinical outcome after PTCA. (*Circulation* 1992;86:100–110)**

KEY WORDS • **clinical trials** • **cilazapril** • **angiotensin converting enzyme** • **percutaneous transluminal coronary angioplasty**

Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Andreas Gruentzig in 1977 as an alternative treatment for coronary artery bypass grafting (CABG) in patients with angina pectoris.[1] Increased experience and advances in technology have resulted in a high primary success rate (over 90%) and a low complication rate (death or nonfatal myocardial infarction, 4–5%).[2] However, the late restenosis rate (17–40%) still limits the long-term benefit of the procedure.[3–8]

The cause of restenosis is unclear, but factors such as platelet aggregation, formation of mural thrombi, intimal proliferation of smooth muscle cells, elastic recoil, and active vasoconstriction at the site of PTCA injury have all been implicated.[9–17] A decade of intensive clinical and pharmacological research has not succeeded in altering the restenosis rate.[18,19] Various treatments started shortly before or after PTCA and sometimes given for up to 6 months, such as intravenous administration of heparin, antiplatelet therapy (aspirin, dipyridamole, ticlopidine, prostacyclin, ciprostene, thromboxane A_2 receptor blocker), anticoagulants (coumadin), calcium channel blockers (nifedipine, diltiazem, verapamil), and other agents such as corticosteroids and colchicine, have failed to reduce the restenosis rate.[20,21] Fish oil and cholesterol-lowering agents have shown promise, although the published results are conflicting.[20,22]

Balloon angioplasty extensively damages the medial smooth muscle cells as well as the endothelial lining of

From the Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group.

Supported by F. Hoffmann–La Roche Ltd., Basel, Switzerland.

Address for correspondence: P.W. Serruys, MD, PhD, Catheterization Laboratory, Thoraxcenter, Postbox 1738, 3000 DR Rotterdam, The Netherlands.

Received December 20, 1991; revision accepted March 10, 1992.

the coronary vessel wall.[23] Recent data have shown that mitogens from platelets are not wholly responsible for initiating the proliferative response in balloon catheter–injured arteries, because smooth muscle cell proliferation occurred in the absence of platelets.[24] The smooth muscle cell proliferation was correlated with the severity of trauma inflicted by the denuding technique to the arterial wall, which would suggest a role for endogenous factors possibly released from damaged endothelial and smooth muscle cells.[12,25] The basic fibroblastic growth factor (bFGF) is one of the main factors, as it is released from disrupted cultured vascular cells and is a growth factor for smooth muscle cells in vitro and in vivo.[24,26] Platelet-derived growth factor (PDGF) may regulate the migration of smooth muscle cells from the media into the intima.[27,28] In this process, angiotensin II might act as a comitogen and stimulate increased proliferation of smooth muscle cells that have been activated to enter the cell cycle and have migrated to the subintima.[29] Based on the hypothesis that a local angiotensin system may regulate the vascular response to endothelial injury, Powell et al[30] examined the effects of various doses of the angiotensin converting enzyme (ACE) inhibitor cilazapril on neointimal proliferation in the rat carotid

See p 325

artery. Administration of a high dose resulted in an 80% reduction in neointima formation in this balloon-injured artery model.

The present multicenter, randomized, double-blind placebo-controlled trial was designed to test whether ACE inhibition can prevent late restenosis after PTCA in humans.

Methods

Study Population

All symptomatic and asymptomatic patients scheduled for PTCA with an angiographically proven, functionally significant narrowing in one or more major coronary arteries were considered for inclusion in 26 participating centers (see "Appendix"). A screening log was maintained in 17 participating centers. Between June 1989 and December 1989, 27% of patients screened in these centers were enrolled. Reasons for exclusion are listed in Table 1.

Treatment Allocation

The trial was carried out according to the Declaration of Helsinki (1963; revised in Venice, 1983). Informed consent was obtained in 735 recruited patients before the PTCA procedure. Patients were randomly assigned to cilazapril or placebo, but only 693 patients with successful PTCA (defined as a visually assessed diameter stenosis of <50% after PTCA) who met all inclusion and exclusion criteria as stated in the protocol continued the trial and formed the study population (Figure 1). Forty-two patients were excluded for the following reasons. 1) The PTCA procedure could not be performed (lesion not suitable). 2) The PTCA procedure was unsuccessful or unsatisfactory (either inability to reach or to cross the lesion or a diameter stenosis of >50% after PTCA, or abrupt occlusion not responding to intracoronary spasmolytic or thrombolytic therapy). 3) The PTCA procedure was complicated by myocardial

TABLE 1. Screening Results of 17 Log-Keeping Clinics

	n	%
Total number of screened patients	1,755	100
Number of recruited patients	478	27.2
Excluded from the trial	1,277	72.8
Reason for exclusion		
History of sustained essential hypertension	271	15.4
Previous and/or failed PTCA at the same site	268	15.3
Q wave MI <4 weeks before study entry	174	9.9
Follow-up coronary angiography unlikely	109	6.2
Logistic reasons	67	3.8
Significant concomitant disease	50	2.8
Older than 75 years	43	2.5
Dilatation of bypass graft	40	2.3
Primary perfusion therapy	39	2.2
No informed consent given	39	2.2
Current evidence or history of heart failure	28	1.6
Other reasons* (<1% each)	122	8.6

PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; MERCATOR, Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis; ACE, angiotensin converting enzyme.

*Participation in other trial; planned directional atherectomy procedure or stent implantation; left main disease; history of type II hypercholesterolemia; previous cerebrovascular accident; previous participation in MERCATOR; hypotension; contraindication to ACE inhibition/aspirin; women of childbearing potential; insulin-dependent diabetes; miscellaneous.

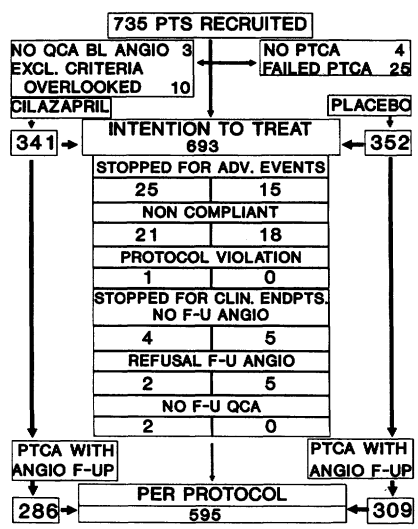

FIGURE 1. *Patient flowchart in MERCATOR (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis). Pts, patients; QCA, quantitative coronary angiography; BL, baseline; Excl, exclusion; PTCA, percutaneous transluminal coronary angioplasty; ADV, adverse; Clin endpts, clinical end points; F-UP, F-U, follow-up; ANGIO, angiogram.*

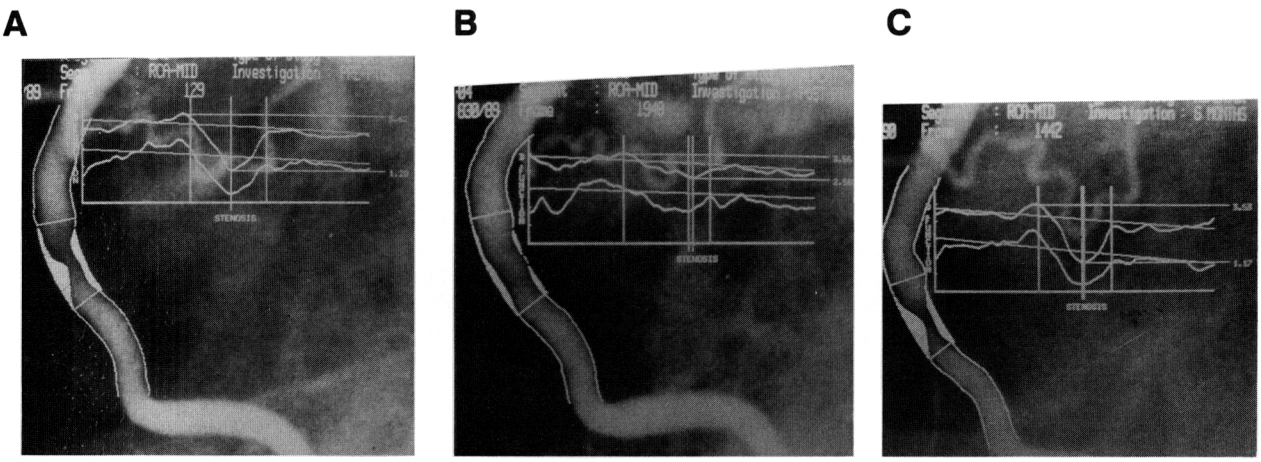

FIGURE 2. *Video images: Single frame of a narrowing in the right coronary artery before percutaneous transluminal coronary angioplasty (PTCA)* (panel A), *after PTCA* (panel B), *and at follow-up* (panel C). *Superimposed on the video image is the diameter function curve (upper curve) together with the interpolated reference curve. Minimal lumen diameter is 1.28 mm before PTCA, 2.58 mm after PTCA, and 1.17 mm at follow-up.*

infarction before the first drug intake (symptoms, ECG changes, and creatine kinase levels more than twice the upper limit of normal). Retroactively, patients were excluded from the study for the following reasons. 1) The baseline film could not be quantitatively analyzed. 2) The exclusion criterion was overlooked at the time of screening.

Trial medication was given for the first time in the evening after successful PTCA and consisted of either capsules of cilazapril (first evening, 2.5 mg; 5 mg b.i.d. thereafter) or matching placebo for 6 months. In addition, all patients received 75–125 mg aspirin b.i.d. before coronary PTCA until follow-up angiography.[31,32]

Follow-up Evaluation

Patients returned to the outpatient clinic after 1, 2, 4, and 6 months for an interview, a cardiac examination, ECG, laboratory tests, and a capsule count. Follow-up angiography was performed at the 6-month visit after the trial medication was discontinued. When symptoms recurred within 6 months, coronary angiography was carried out earlier. When no definite restenosis was present and the follow-up time was less than 3 months, the patient was asked to undergo another coronary angiogram at 6 months.

One to 4 days before follow-up angiography but after discontinuation of the trial medication, a symptom-limited exercise test was performed on a bicycle ergometer according to a standard protocol. The test was performed with the patient in a sitting position, starting with a work load of 20 W, which was increased by 20 W every minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or an ST depression of more than 1 mm occurred or the patient stopped because of fatigue. A 12-lead ECG was recorded during exercise and recovery. ST changes were measured 80 msec after the J point.

PTCA Procedure and Angiographic Analysis

At the beginning of the procedure, all patients received a bolus of 10,000 IU intravenous heparin. After 2 hours, an additional infusion of 5,000 IU/hr was given until the end of the procedure. Use of a calcium channel blocker for 48 hours after PTCA was permitted. Choice of balloon type, inflation duration, and pressure were left to the operator.

For the purpose of the study, three coronary angiograms were obtained in each patient—one just before PTCA, one immediately after PTCA, and one at follow-up. Angiograms were recorded in such a way that they were suitable for quantitative analysis by the Coronary Angiography Analysis System (CAAS). An example of an analysis is shown in Figure 2. To standardize the method of data acquisition and to ensure exact reproducibility of post-PTCA and follow-up angiograms, measures were taken as described earlier.[21,33] All angiographic analyses, including qualitative assessment of certain lesion characteristics,[34–36] were performed at a core laboratory, which was blinded to treatment allocation and did not have access to clinical data.

As visual assessment of coronary angiograms is hampered by a large interobserver and intraobserver variability,[33,37] all cineangiograms were quantitatively analyzed using the CAAS system, which has been validated and described in detail.[33,38] The absolute values of the stenosis diameter as well as the reference diameter are measured by the computer, using the known contrast–empty catheter diameter as a scaling device. To achieve maximal vasodilatation, intracoronary nitroglycerin or isosorbide dinitrate was given for each coronary artery involved before PTCA, after PTCA, and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for pincushion distortion introduced by the individual image intensifiers. Because the algorithm is not able to measure total occlusions and lesions with TIMI-1 perfusion, a value of 0 mm was used for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases, the post-PTCA reference diameter was used as the reference diameter before PTCA or at follow-up.

End Points

The primary end point of this study was the within-patient change in minimal lumen diameter as deter-

mined by quantitative angiography after PTCA and at follow-up. Post-PTCA values were obtained from the last post-PTCA angiogram made directly after removal of the guide wire. The initial procedure was considered finished when the guide catheter was removed. In the case that the clinical condition required repeat PTCA, the angiogram made before repeat PTCA was used to obtain follow-up values irrespective of the timing of repeat PTCA (hours, days, or weeks).

For each dilated segment, the minimal lumen diameter was taken as the mean value from multiple matched projections. Within-patient change was defined as the follow-up value minus the post-PTCA value. In the case that more than one segment was dilated (multivessel or multisite procedures), the mean change over all lesions dilated was taken as the end point. Secondary end points were restenosis rates, exercise test results, and clinical events. These were death (irrespective of cause), New York Heart Association class III–IV as a result of congestive heart failure, nonfatal myocardial infarction (symptoms, ECG changes, and creatine kinase enzymes above twice the upper limit of normal), coronary revascularization (CABG, repeat PTCA, stent implantation, or atherectomy at the same site or other site), and recurrent angina requiring initiation or increase in medical therapy, or none of the above. Only revascularizations that were done before the 6-month time window (6 months±3 weeks) were counted as a clinical event.

Statistical Methods and Analysis

As stated in the original protocol, the required sample size (200 evaluable patients per treatment group) was based on the assumption of a restenosis rate of 30% in the control group and of 15% (i.e., a 50% difference) in the cilazapril group (two-sided test with an α error of 0.05 and a power of 0.80). However, as more and more quantitative data became available, we realized that restenosis should be viewed as a continuous process. This is best measured by the mean overall change in absolute minimal luminal diameter instead of applying arbitrarily selected cutoff criteria of 50% diameter stenosis at follow-up or ≥0.72-mm change in minimal diameter between post-PTCA and follow-up. Consequently, the initial power calculations were changed during the trial in a protocol amendment with continuous data. With the assumption of a change of −0.40±0.50 mm in mean minimal lumen diameter between postangioplasty and follow-up angiogram in the control group and −0.25±0.50 mm (i.e., a 37.5% difference) in the active drug group (two-sided test with an α error of 0.05 and a power of 0.90), the minimal sample size was estimated to be 233 patients in each group. Thus, enough patients were recruited to detect a significant difference between the two treatment groups.

For statistical evaluation, intention-to-treat and per-protocol populations were defined. The intention-to-treat population comprised patients who fulfilled all inclusion and exclusion criteria and received at least one dose of test medication. The per-protocol population consisted of all compliant patients of the intention-to-treat population who had an analyzable follow-up angiogram. A patient was judged compliant if at least 80% of the test medication was taken and the test medication was not stopped more than 5 days before follow-up angiography.

To test the hypothesis that the mean change in minimal lumen diameter is equal in the two treatment groups, ANOVA was done with treatment and center as main factors and treatment times center as interaction term. As the change in minimal luminal diameter after PTCA follows a near-gaussian distribution, parametric tests were allowed to be used.[39] The treatment effect was defined as the difference in mean change in minimal lumen diameter between the two treatment groups. In addition, 95% confidence intervals of the treatment effect were obtained from the ANOVA.

Comparison of the clinical outcome was done for the intention-to-treat population. Each patient was assigned at the time of follow-up to the most serious applicable event on the scale described above. For comparison of the clinical outcome between the two treatment groups, standard nonparametric statistical methods were used.

Results

In total, 735 patients gave informed consent, and subsequently, 693 continued the trial and constituted the intention-to-treat population. Figure 1 shows the patient flowchart. Forty-two patients (23 patients randomly assigned to cilazapril and 19 patients to placebo) were not included in the trial for the following reasons. In four patients, no PTCA was performed because the lesion was no longer an indication for PTCA; in 25 patients, the outcome of the PTCA procedure was unsatisfactory (two patients with a post-PTCA diameter stenosis of >50% by visual assessment), unsuccessful (11 patients because of inability to cross the lesion), or complicated (four patients with emergency CABG, eight patients with sustained occlusion). Thirteen patients were excluded from the analysis (10 because a selection criterion was overlooked, three because no baseline quantitative analysis was possible). Of the remaining 693 patients, 352 were randomized to receive placebo and 341 were randomized to receive cilazapril.

Baseline Characteristics and Clinical Follow-up

Selected demographic and clinical characteristics of the two study groups are shown in Tables 2 and 3. In general, baseline characteristics were evenly distributed in the two groups except for patients with pain at rest and patients currently smoking, who were more frequently encountered in the control group.

Clinical follow-up was obtained for all 693 patients. During the course of the study, five patients died (control, two; cilazapril, three). The cause of death was cardiovascular in four cases and of other origin in one case. Nonfatal myocardial infarction was documented in 13 patients (control, eight; cilazapril, five); 17 patients underwent bypass surgery (control, eight; cilazapril, nine); repeat PTCA, atherectomy, or stent implantation was performed in 87 patients (control, 43; cilazapril, 44); and recurrent angina was observed in 135 patients (control, 67; cilazapril, 68). Finally, 224 (64%) in the control group and 212 (62%) in the treated group were event free at 6-month follow-up. Table 4 shows the number of events on a per-patient basis, with only the most serious event listed. Adjusted χ^2 test revealed no difference in ranking between the two groups.

During follow-up, 40 patients stopped their treatment because of adverse experiences (hypotension: control, one; cilazapril, nine; cough: control, none; cilazapril, four; rash: control, three; cilazapril, two; dizziness:

TABLE 2. Clinical Characteristics of the Intention-to-Treat Population

	Control patients (n=352)	Cilazapril patients (n=341)
Men (No.)	292 (83%)	282 (83%)
Age (years)	56±8 (32–74)	57±9 (35–74)
Ever smoked	269 (76%)	259 (76%)
Current smokers*	70 (20%)	49 (14%)
Non–insulin-dependent diabetes	20 (6%)	21 (6%)
One-vessel disease	228 (65%)	225 (66%)
Two-vessel disease	106 (30%)	99 (29%)
Three-vessel disease	18 (5%)	17 (5%)
Total cholesterol (mg/dl)	228±59	227±54
No angina present	30 (9%)	28 (8%)
Angina present	322 (91%)	313 (92%)
CCS class I	46 (13%)	53 (16%)
CCS class II	108 (31%)	103 (30%)
CCS class III	102 (29%)	100 (29%)
CCS class IV	66 (19%)	57 (17%)
Pain at rest*	133 (38%)	99 (29%)
Controlled by oral medication	92	64
Controlled by nitrates (i.v.)	28	15
Controlled by maximal medication	11	16
Continues at maximal medication	2	4
Duration of angina (days)	432±902	422±921
Previous MI	146 (41%)	142 (42%)
Previous CABG	6	7
Previous angioplasty	6	4
PTCA+CABG	1	1
No. of patients on		
Nitrates	246 (70%)	236 (69%)
Ca antagonists	228 (65%)	217 (64%)
β-Blockers	182 (52%)	180 (53%)
No medication	14 (4%)	19 (6%)
Monotherapy	89 (25%)	91 (27%)
Double therapy	180 (51%)	151 (44%)
Triple therapy	69 (20%)	80 (23%)

CCS, Canadian Cardiovascular Society angina classification; MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
Values are mean±SD. *$p<0.05$.

control, two; cilazapril, three; gastrointestinal problems: control, three; cilazapril, four; other reasons: control, five; cilazapril, four). Nine patients stopped treatment because they had a clinical event (death: control, two; cilazapril, three; CABG: control, one; cilazapril, one; nonfatal myocardial infarction: control, two; cilazapril, none), and one patient became a protocol violator. Thirty-nine patients did not fulfill compliance criteria (control, 18; cilazapril, 21); in nine patients, no angiogram suitable for quantitative analysis could be obtained due to either refusal (control, five; cilazapril, two) or to technical reasons (absence of matched views or poor quality of the follow-up film: control, none; cilazapril, two). Thus, the per-protocol population consisted of 309 control patients and 286 patients treated with cilazapril.

TABLE 3. Angiographic Characteristics of Per-Protocol Population

	Control patients (n=309, 367 lesions)	Cilazapril patients (n=286, 342 lesions)
Vessel dilated		
RCA	103 (28%)	101 (30%)
LAD	173 (47%)	153 (45%)
LCx	93 (25%)	88 (25%)
Number of sites dilated		
One	305 (82%)	283 (82%)
Two	51 (15%)	51 (15%)
Three	8 (2%)	7 (2%)
Four	3 (1%)	1 (1%)
Lesion type		
Concentric	188 (51%)	179 (52%)
Eccentric	135 (37%)	108 (31%)
Tandem	3 (1%)	18 (5%)
Multiple irregularities	31 (8%)	25 (7%)
Total occlusion	10 (3%)	12 (4%)
Calcified lesion	45 (12%)	46 (14%)
Side branch in stenosis	213 (58%)	197 (56%)
Lesion at bend point	34 (9%)	48 (13%)
Thrombus after PTCA	10 (3%)	14 (4%)
Dissection*		
No*	262 (72%)	235 (69%)
Type A	32 (9%)	39 (12%)
Type B	57 (16%)	49 (15%)
Type C	12 (3%)	13 (4%)
Type D	1	1
Type E	0	2
Largest size balloon (mm)	2.88±0.41	2.83±0.65
Maximal pressure (atm)	8.3±2.5	8.0±2.7
Total inflation (seconds)	245±226	247±214
Balloon artery ratio	1.14±0.20	1.12±0.18

RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; PTCA, percutaneous transluminal coronary angioplasty.
Values are mean±SD. *Modified from Reference 35.

Angiographic Efficacy Analysis

Table 5 summarizes the quantitative angiographic findings in the per-protocol population. On per-protocol basis, the loss at follow-up in minimal lumen diameter was −0.29±0.49 mm in the control group and

TABLE 4. Ranking per Patient Based on Most Serious Clinical Event During 6-Month Follow-up

	Control patients (n=352)	Cilazapril patients (n=341)
Death	2 (<1%)	3 (<1%)
NYHA III/IV	0	0
Nonfatal myocardial infarction	8 (2.3%)	5 (1.4%)
Coronary revascularization	51 (14.5)	53 (15.5)
Angina recurrence	67 (19.0%)	68 (19.9%)
No event	224 (63.6%)	212 (62.2%)

NYHA, New York Heart Association classification for congestive heart failure.

TABLE 5. Quantitative Analysis in the Per-Protocol Population

	Control patients (n=309)	Cilazapril patients (n=286)
Obstruction diameter (mm)		
Before angioplasty	0.98±0.35	1.05±0.35
After angioplasty	1.77±0.34	1.80±0.36
Follow-up	1.48±0.54	1.54±0.54
Reference diameter (mm)		
Before angioplasty	2.61±0.54	2.66±0.51
After angioplasty	2.67±0.48	2.72±0.49
Follow-up	2.68±0.56	2.74±0.52
Difference in obstruction diameter (mm)		
After preangioplasty	0.79±0.42	0.75±0.37
Follow-up postangioplasty	−0.29±0.49	−0.27±0.51
Percentage stenosis (%)		
Before angioplasty	61.4±13.4	60.1±12.3
After angioplasty	32.9±9.0	33.0±10.0
Follow-up	44.2±18.0	43.5±17.2
Difference in percentage stenosis (%)		
After preangioplasty	−28.5±15.3	−27.1±13.7
Follow-up postangioplasty	11.3±18.2	10.5±18.0

Values are mean±SD.

−0.27±0.51 mm in the cilazapril-treated group (treatment effect, 0.023 mm; 95% CI, −0.06–0.11 mm). Figures 3 and 4 represent a cumulative frequency curve of the minimal lumen diameter and of the change in minimal lumen diameter observed in both groups. Adjustment for current smoking and pain at rest did not affect the results. When participating clinics were analyzed separately, the results were consistent.

Table 6 summarizes the restenosis rates in the per-protocol population per lesion according to seven frequently used restenosis criteria.

Bicycle Ergometry

Of 693 patients, 564 (81%) underwent exercise testing at follow-up. Reasons for not performing the test were death in five patients (control, two; cilazapril, three), unstable angina in 58 patients (control, 30; cilazapril, 28), refusal in 18 patients (control, five; cilazapril, 13), adverse event in 23 patients (control, 11; cilazapril, 12), logistic reasons in six patients (control, four; cilazapril, two), and other reasons in 14 patients (control, five; cilazapril, nine). The exercise test was not performed according to protocol in five patients (control, four; cilazapril, one). Table 7 summarizes results of exercise testing in both groups. No difference in objective parameters was observed. Chest pain during exercise was reported in 74 patients (25%) receiving placebo and 42 patients (15%) receiving cilazapril (p=0.03). ST deviation (depression or elevation) of >0.1 mV associated with anginal symptoms was observed in 39 patients (13%) in the control group and 25 patients (9%) in the cilazapril group.

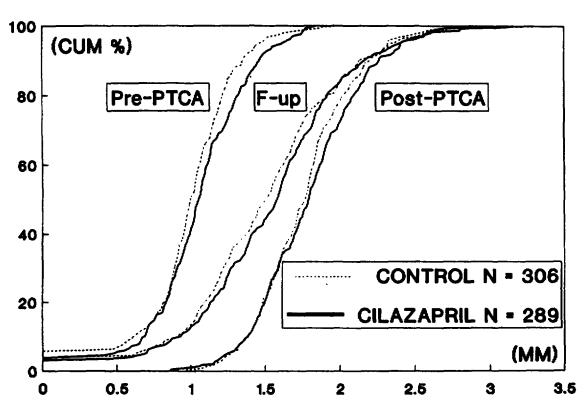

FIGURE 3. *Cumulative distribution curve (CUM %, cumulative percentage of patients) of the minimal lumen diameter before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at 6-month follow-up (F-up) in both treatment groups.*

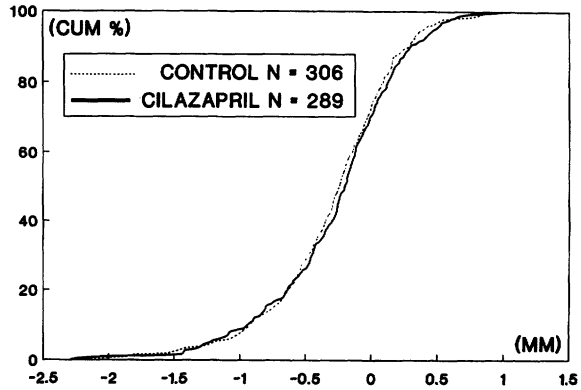

FIGURE 4. *Cumulative distribution curve of the change in minimal lumen diameter from before percutaneous transluminal coronary angioplasty (PTCA) to follow-up in both treatment groups. CUM %, cumulative percentage of patients.*

Discussion

Rationale for ACE Inhibition After PTCA

Over the past decade, it has been repeatedly demonstrated that treatment of chronic hypertensive rats with ACE inhibitors reduces the medial hypertrophy of muscular arteries.[40–42] Therefore, it has been postulated that the local renin–angiotensin system may participate in regulating the vascular response to arterial injury.

TABLE 6. Restenosis Rates per Lesion According to Frequently Used Definitions

	Control patients (n=309, 368 lesions)	Cilazapril patients (n=286, 342 lesions)
MLD (post-PTCA follow-up) ≥0.72	59 (16%)	56 (17%)
MLD (post-PTCA follow-up) ≥0.36	153 (42%)	129 (38%)
>30% DS increase in DS at follow-up	45 (12%)	42 (13%)
<50% DS after PTCA to >70% DS follow-up	25 (7%)	20 (6%)
DS follow-up <10% DS before PTCA	66 (18%)	55 (16%)
Loss of >50% of gain or >30% ↑ DS	144 (39%)	125 (37%)
<50% DS after PTCA to >50% DS follow-up	103 (28%)	96 (28%)

MLD, minimal lumen diameter; PTCA, percutaneous transluminal coronary angioplasty; DS, diameter stenosis.

TABLE 7. Exercise Test Results of 564 Patients

	Control patients (n=291)	Cilazapril patients (n=273)	p
Maximum work load (W)	146±39	151±44	NS
Exercise time (seconds)	446±124	454±127	NS
Systolic blood pressure at peak exercise (mm Hg)	196±27	192±28	NS
Heart rate at peak exercise (beats per minute)	142±22	142±21	NS
Double product (mm Hg · 100/beats per minute)	279±65	275±66	NS
ST deviation >1 mm	102 (36%)	99 (37%)	NS
Anginal symptoms during test	74 (25%)	42 (15%)	0.03
Combination of ST >1 mm and symptoms	39 (13%)	25 (9%)	NS

This hypothesis has prompted the investigation of the role of angiotensin II after injury. For this purpose, the effect of the long-acting ACE inhibitor cilazapril on the proliferative response to arterial injury was examined by Powell et al[30] in an animal model. This inhibitor was selected because at a dose of 10 mg/kg/day, it lowered blood pressure over a 24-hour period and reduced the medial hypertrophy of hypertensive rats. Using the same dose of cilazapril, neointima formation was decreased by 80% and lumen integrity was preserved in normotensive rats in which the left carotid artery was subjected to endothelial denudation and injury by balloon catheterization.[30]

More recently, several groups have studied the effects of angiotensin II on smooth muscle cell proliferation in vitro as well as the influence of ACE inhibition on smooth muscle cell proliferation. Angiotensin II induced expression of several growth factor genes, such as genes encoding PDGF, transforming growth factor-β (TGF-β), and thrombospondin (TS).[43–46] These results demonstrate that, in cultured cells, angiotensin II induces messenger ribonucleic acids to encode several important growth factor genes and thus induces cell proliferation. Cilazapril or its active metabolite did not have a direct effect by itself, but the antiproliferative effect was mediated through angiotensin II. Consequently, the inhibition of angiotensin II production may prevent the proliferative response that occurs after PTCA in humans.

Trial Design: Quantitative Angiography as Primary End Point

The primary goal of a restenosis prevention trial is the improvement in short-term and long-term clinical outcome of patients having undergone a PTCA procedure. It is assumed that the improvement in clinical outcome is related to an anatomical phenomenon, namely, the prevention of the recurrence of the stenosis in the treated vessel. However, in trials testing pharmacological compound with possible anti-ischemic or antianginal effects unrelated to the postinjury hyperplasia, the clinical outcome might be misleading and obscure the reason for the observed improvement. Quantification of luminal dimension changes over time may provide insight into the biological and mechanistic effects on the treatment after PTCA. The appearance (or reappearance) of angina as a sole criterion of restenosis underestimates the angiographic rate of restenosis. The poor value of recurrent anginal symptoms as a marker of restenosis is confirmed by the low predictive value of symptoms found in many studies.[18] Similarly, the usefulness of ergometry to detect restenosis after PTCA has been questioned since several studies have found that the presence of exercise test–induced angina or ST segment depression/elevation or both are not highly predictive for restenosis when the test is performed early or late after PTCA.[18] A drug tested for its ability to prevent restenosis may be shown to be beneficial after PTCA by reducing angina during exercise testing and yet have no effect on intimal hyperplasia after balloon-induced injury.

In the present study, fewer patients in the cilazapril-treated group experienced anginal pain during exercise testing. This symptomatic beneficial effect was not corroborated by an increase in work load or in double product or by ST changes. It must be emphasized that this difference in behavior between the two groups remains unexplained and had no bearing on the general outcome of the trial.

TABLE 8. Prognostic Value of Minimal Lumen Diameter at Follow-up in the Per-Protocol Population Divided Into Five Equal Groups

	Exercise test		Clinical outcome			
MLD follow-up (mm)	<1 mm ST changes and no chest pain	≥1 mm ST changes and chest pain	MI	Reintervention	Angina	None
<1.10	70 (75%)	24 (26%)	5 (4%)	49 (41%)	24 (20%)	41 (35%)
1.10–1.39	88 (88%)	12 (12%)	1 (1%)	18 (15%)	25 (21%)	74 (63%)
1.39–1.63	103 (90%)	11 (10%)	2 (2%)	10 (8%)	31 (26%)	77 (64%)
1.63–1.91	99 (93%)	8 (7%)	1 (1%)	7 (6%)	21 (15%)	89 (75%)
≥1.91	111 (98%)	2 (2%)	1 (1%)	7 (6%)	18 (15%)	94 (78%)
Total patients	471	57	10	91	119	375

MLD, minimal lumen diameter; MI, myocardial infarction.

In contradistinction, the prognostic value of the change in sequential coronary angiogram has been largely underestimated as a surrogate end point for clinical atherosclerotic events. In the second phase of the pharmacological investigation, the main emphasis should be put on the pathophysiological mechanism of prevention of restenosis in the postinjury model, and the improvement in clinical outcome should be viewed as a secondary benefit dependent on the anatomical status.

When the patient population of this trial is stratified according to the minimal lumen values at follow-up, it appears that the percentage of patients having reached one of the predefined clinical end points is as high as 65% in the worst category (minimal lumen diameter at follow-up <1.10 mm), whereas the percentage of event-free patients ranges from 63% to 78% in the other categories (Table 8). It must be emphasized that 41% of the patients in the worst anatomical category had reintervention versus only 6% in the best anatomical category irrespective of the initial dilatation site. Besides the prognostic value, the anatomical results also have a clear functional impact because only 2% of the patients had a positive exercise test in the best anatomical category versus 26% of the patients in the worst anatomical category.[47]

Lack of Effect on Angiographic Restenosis

The lack of angiographic effect in MERCATOR (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis) might have been dilution because of the loss to angiographic follow-up. If cilazapril had an important effect on restenosis, then clinical events such as sudden death, etc., would have predominated in the placebo group. Inasmuch as such events lead to loss to angiographic follow-up, angiographic restenosis might have been underestimated in the placebo group but not in the cilazapril group. Dilution would also occur if patients who are completely asymptomatic refuse repeat angiography. This kind of distortion (bias) of the effect assessment in an angiographic restenosis trial cannot be avoided as a matter of principle. Because there was no difference in clinical events leading to loss to angiographic follow-up and because the percentages of patients who had angiographic follow-up was relatively high (cilazapril, 94%; control, 94%), we do not believe that the lack of angiographic effect of cilazapril observed relates to loss to angiographic follow-up.

Several explanations (which are not mutually exclusive) may account for the apparent failure of cilazapril to decrease the rate of coronary restenosis.

Dose Relation

The dose selected for this trial was based on pharmacokinetic data in healthy volunteers, demonstrating that a single dose of 5 mg cilazapril reduced the plasma ACE activity to virtually unmeasurable levels.[48,49] Pharmacokinetic data from hypertensive patients demonstrate that after a single dose of 5 mg cilazapril, the plasma angiotensin II concentration starts to return to baseline in 8–10 hours, although a sustained blood pressure reduction is achieved. Therefore, the dosage of 5 mg b.i.d. was chosen.

After the trial was designed, it was shown that inhibition of neointima formation is a dose-dependent phenomenon and that the dose required for inhibition of neointimal formation appears to be somewhat higher than for lowering blood pressure.[46] In the rat model, this dose relation for the antiproliferative effect of cilazapril is different from the dose relation for the antihypertensive effect. Thus, a possible explanation for the lack of effect in MERCATOR is that the dose used was too low, as the dose used in the rat model was 70 times higher (10 mg/kg/day). The ongoing American/Canadian sister trial to MERCATOR, MARCATOR, which is similar in design but randomizes between 1, 5, and 10 mg of cilazapril b.i.d., will give us the unique opportunity to further investigate this relation in humans. If the antihypertensive effect in the 10 mg–b.i.d. subset of patients does not materially differ from that in the two other arms of the trial (1 and 5 mg b.i.d.), although a direct antiproliferative effect is observed, further investigation of the role of the renin–angiotensin system in tissue proliferation after vascular injury seems warranted.

Time Relation

As in animal experiments, no major difference in inhibition of neointimal proliferation was observed whether the drug was given 1 hour before or within 2 days after the wall injury. It was assumed that ACE inhibition by cilazapril could be started immediately after PTCA.[30]

In experimental studies, the strongest inhibition of neointima formation was obtained when treatment was started 6 days before injury. It could be that a period of drug impregnation before injury might be required to obtain an inhibitory effect, although a significant but slightly attenuated effect was observed when it was started 2 days after injury.

Species Relation

Powell et al[46] compared the effects of high doses of cilazapril (10 mg/kg/day) and captopril (100 mg/kg/day) on neointimal proliferation in the rat carotid artery model. Both agents were highly effective and, in addition, concomitant heparin therapy appeared to exert a synergistic antiproliferative effect. Similarly, in the atherosclerotic rabbit iliac model, cilazapril (5 mg/kg/day) reduced the incidence of restenosis after balloon injury.[50] In contrast, Lam et al[51] found no benefit of high-dose cilazapril (20 mg/kg b.i.d.) in the porcine carotid artery injury model. Churchill et al[52] and Huber et al[53] could not demonstrate significant benefit of captopril or enalapril in preventing restenosis in the swine model. Despite the fact that all species show an effect on blood pressure, the postinjury proliferation in baboons and pigs was not clearly affected by cilazapril at the doses used, whereas rats, guinea pigs, and rabbits did respond.[54] Rakugi et al[55] have shown that vascular injury results in the induction of ACE in proliferating cells in the neointima and supports the role of the local renin–angiotensin system in restenosis. Although quite attractive, the close parallel between the muscular response to experimental arterial injury and the development of restenosis in humans after therapeutic angioplasty remains a working hypothesis. The response of atherosclerotic human arteries may be modulated by cellular and molecular influences that are not exactly

similar to those acting in nondiseased nonhuman arteries.

Alternative Pathways of Angiotensin II Production

Other enzymes besides ACE are known for their ability to metabolize angiotensin I to angiotensin II (chymase, tonin, and cathepsin). It could well be that these alternative pathways resulted in sufficient levels of angiotensin II to activate or to stimulate the restenosis process. Because no actual measurement was done of angiotensin I or II, it is difficult to say whether these alternative pathways were active. However, we found a significant decrease in blood pressure immediately after the first drug intake in patients randomized to cilazapril compared with patients taking placebo. This effect was maintained during the entire 6-month follow-up period. Thus, clinically, there was an effect of cilazapril by reducing blood pressure, presumably by lowering the level of angiotensin II. The use of an angiotensin II receptor blocker might be worth exploring,[56] as in this case all angiotensin II, irrespective of the metabolic pathway that is used, is blocked.

Possible Mitogenic Effect of Angiotensin I

Another explanation for failure of cilazapril to reduce restenosis is that as a logical consequence of the use of ACE inhibitors, the concentration of angiotensin I is increased, which has been shown to be mitogenetic for arterial muscle cells.[45] This unavoidable side effect of ACE inhibitors may, perhaps only in some species, annihilate their favorable actions exerted through angiotensin II suppression.

Relevance of Mechanism of Action

The most recent theory on restenosis put forward by Lindner and Reidy[12] indicates that bFGF released after disruption and cell necrosis of the endothelium and media is the factor that initiates the proliferation and duplication of the smooth muscle cells. These subsequently activated smooth muscle cells tend to migrate in the subintima of the vessel, where they are attracted by the PDGF stemming from the aggregated platelets: It is in this location and stage that angiotensin II acts on them as a comitogen. This complex interaction may be the predominant biological scenario in certain species such as rat and rabbit but may be inoperative in other species such as the baboon and guinea pig.

Recently, Forrester et al[17] hypothesized that restenosis is a manifestation of the general wound-healing process expressed specifically in vascular tissue. They list five different groups of growth factors: PDGF, FGF, EGF (epidermal growth factor), IGF (insulin-like growth factor), and TGF (transforming growth factor), each with a specific role and with possibly many interactions. It is of course possible that angiotensin II has only a minor role in this complex process and that ACE inhibition did not result in less angiographic restenosis.

In contrast, Schwartz et al[57] hypothesize that mural thrombus is the most important factor in the restenosis process: It is seen in all treated animals after injury; after 3 days it is covered by endothelium, and later on, smooth muscle cells start to grow downward toward the media, suggesting that neointimal cells are probably not derived from arterial media at the immediate injury site.

Conclusions

Long-term ACE inhibition with cilazapril in a dose of 5 mg b.i.d. does not prevent restenosis and does not favorably influence the overall clinical outcome after PTCA in patients. The results of the MARCATOR trial must be awaited to see whether a higher dose of cilazapril has any effect on angiographic restenosis.

Appendix

Steering Committee, Writing Group, and Authors

Patrick W. Serruys, MD (chairman); Wolfgang Rutsch, MD; Nicolas Danchin, MD; William Wijns, MD; Hakan Emanuelsson, MD; François Chappuis, MD; and Walter R.M. Hermans, MD.

MERCATOR Study Group: Participating Clinics and Investigators

The following institutions and investigators participated in MERCATOR. The number of patients enrolled at each center is given in parentheses. Log-keeping centers are identified with an asterisk.

The London Chest Hospital, London (21)*: R. Balcon, MD, principal investigator; J. Timmins, MD; D.C. Springings, MD; S.J.D. Brecker, MD; and S.W. Davies, MD.

Hôpital TIMONE, Marseille, France (14)*: J.L. Bonnet, MD, principal investigator; and F. d'Houdain, MD.

University Hospital Leiden, Leiden, The Netherlands (41)*: B. Buis, MD, principal investigator; A.L.M. Bakx, MD; and M.I. Sedney, MD.

Ospidale Nuguarda CA'Granda, Milan, Italy (12)*: L. Campolo, MD, principal investigator; G.B. Danzi, MD; and A.M. de Biase, MD.

Hôpital Cantonal, Geneva, Switzerland (20): F. Chappuis, MD, principal investigator; W. Rutishauser, MD; P. Urban, MD; and B. Meier, MD.

CHU Brabois, Vandoeuvre, France (40)*: N. Danchin, MD, principal investigator; Y. Juillière, MD; and V. Voilquin-Thomas, MD.

University of Göteborg, Göteborg, Sweden (44)*: H. Emanuelsson, MD, principal investigator; P. Albertsson, MD; K. Selin, MD; and L. Ekström, MD.

Medizinische Klinik, München, FRG (32): R. von Essen, MD, principal investigator; H. Nebelsieck, MD; A. Uberreiter, MD; and K. Igerl, MD.

Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium (44)*: G.R. Heyndrickx, MD, principal investigator; P. Nellens, MD; B. de Bruyne, MD; and M. Goethals, MD.

Städtisches Krankenhaus Bogenhausen, München, FRG (23)*: T. Ischinger, MD, principal investigator; M. Fischer, MD; and K. Coppenrath, MD.

Albert-Ludwigs-Universität, Freiburg, FRG (18)*: H.J. Just, MD, principal investigator; H. Wollschläger, MD; H. Drexler, MD; and G. Elias, MD.

Medizinische Poliklinik, Zürich, Switzerland (20): H.P. Krayenbühl, MD, principal investigator; O. Hess, MD; F.W. Amann, MD; R. Schläpfer, MD; and M. Büchi, MD.

Universität Erlangen, Erlangen, Germany (28): B. Kunkel, MD, principal investigator; and T. Fürste, MD.

CHRU–Hôpital Cardiologique, Lille, France (40)*: J.M. Lablanche, MD, principal investigator; J.M. Joris, MD; T. Eeman, MD; and M. Henry, MD.

Kantonsspital Basel, Basel, Switzerland (24): M. Pfisterer, MD, principal investigator; F. Burkart, MD; W. Kiowski, MD; E. Straumann, MD; and R. Schäfers, MD.

Medizinische Hochschule, Hannover, FRG (24)*: W. Raffenbeul, MD, principal investigator; and D. Gulba, MD.

Hôpital Trousseau, Tours, France (12)*: P. Raynaud, MD, principal investigator; B. Desvaux, MD; and L. Quillet, MD.

Freeman Hospital, Newcastle-Upon-Tyne, England (12)*: D.S. Reid, FRCP, principal investigator; M. Been, MD; and T.K. Oliver, DCRR, CHSM.

Herzzentrum Hirslanden, Zürich, Switzerland (8): M. Rothlin, MD, principal investigator; R. Tartini, MD; U. Dürst, MD; and H.O. Hirzel, MD.

Universitäts Klinikum Virchow, Berlin (56): W. Rutsch, MD, and H. Schmutzler, MD, principal investigators; and J. Bott, MD.

Universitätsklinik, Kiel, FRG (32): R. Simon, MD, principal investigator; M. Höfig, MD; and G. Herrmann, MD.

UCL Clinique de Mont-Godinne, Yvoir, Belgium (24)*: E. Schroeder, MD, principal investigator; R. Krémer, MD; B. Marchandise, MD; and P. Chenu, MD.

Thoraxcenter, Rotterdam, The Netherlands (56)*: P.W. Serruys, MD, principal investigator; W.R.M. Hermans, MD; and B.J. Rensing, MD.

Walsgrave Hospital, Coventry, England (15)*: M. Fai Shiu, MD, principal investigator; J. Escaned, MD; and R. Ahmed, MD.

Medizinische Klinik I, Aachen, FRG (40): R. Uebis, MD, principal investigator; J. vom Dahl, MD; C. Stellbrink, MD; and S. Nase-Hüppmeier, MD.

St. Luc University Hospital, Brussels, Belgium (35)*: W. Wijns, MD, principal investigator; J.M. Detry, MD; J. Col, MD; J. Cosyns, MD; C. Hanet, MD; X. Michel, MD; and J. Renkin, MD.

Data Coordinating and Analysis

F. Hoffmann–La Roche Ltd., Basel, Switzerland; and SOCAR SA, Givrins, Switzerland.

Angiographic Core Laboratory

Cardialysis/Thoraxcenter, Rotterdam, The Netherlands: P.W. Serruys, MD; B.J. Rensing, MD; W.R.M. Hermans, MD; and J. Pameyer.

Angiographic Assessment Committee

P.W. Serruys, MD (chairman); W.R.M. Hermans, MD; R. Balcon, MD; R. Uebis, MD; J.M. LaBlanche, MD; and W. Rafflenbeul, MD.

Study Directors

T. Widmann, MD, F. Hoffmann-La Roche Ltd., Basel, Switzerland; and P.G. Hugenholtz, MD, Ferme Mont-de-Vaux, Echichens, Switzerland.

References

1. Gruentzig AR, Senning A, Siegenthalter WE: Nonoperative dilatation of coronary artery stenosis: Percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;301:61–68
2. Detre K, Holubkov R, Kelsey S, Cowley M, Kent K, Williams D, Myler R, Faxon D, Holmes D Jr, Bourassa M, Block P, Gosselin A, Bentivoglio L, Leatherman L, Dorros G, King S III, Galichia J, Al-Bassam M, Leon M, Robertson T, Passamani E, Co-Investigators of the NHLBI PTCA Registry: Percutaneous Transluminal Coronary Angioplasty in 1985–1986 and 1977–1981: The National Heart, Lung, Blood Institute Registry. *N Engl J Med* 1988;318: 265–270
3. Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS, King SB III, Gruentzig AR: Restenosis after successful angioplasty in patients with single-vessel disease. *Circulation* 1986;73:710–717
4. Kaltenbach M, Kober G, Scherer D, Vallbracht C: Recurrence rate after successful angioplasty. *Eur Heart J* 1985;6:276–281
5. de Feyter PJ, Suryapranata H, Serruys PW, Beatt K, van Domburg R, van den Brand M, Tijssen JJ, Azar A, Hugenholtz PG: Coronary angioplasty for unstable angina: Immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. *J Am Coll Cardiol* 1988;12:324–333
6. Serruys PW, Luijten HE, Beatt KJ, Geuskens R, de Feyter PJ, van den Brand M, Reiber JHC, Ten Katen HJ, van Es GA, Hugenholtz PG: Incidence of restenosis after successful coronary angioplasty: A time-related phenomenon: A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation* 1988;77:361–371
7. Vandormael MG, Deligonul U, Kern M, Harper M, Presant S, Gibson P, Galan K, Chaitman BR: Multilesion coronary angioplasty: Clinical and angiographic follow-up. *J Am Coll Cardiol* 1987;10:246–252
8. Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Yokoi H, Hamasaki N, Horiochi H, Ohishi H: Restenosis after successful percutaneous transluminal coronary angioplasty: Serial angiographic follow-up of 299 patients. *J Am Coll Cardiol* 1988;12: 616–623
9. Ross R: The pathogenesis of atherosclerosis: An update. *N Engl J Med* 1986;314:488–500
10. Steele PM, Chesebro JH, Stanson AW, Holmes DR Jr, Dewanjee MK, Badimon L, Fuster V: Balloon angioplasty: Natural history of the pathophysiological response to injury in the pig model. *Circ Res* 1985;57:105–112
11. Wilentz JR, Sanborn TA, Haudenschild CC, Valeri CR, Ryan TJ, Faxon DP: Platelet accumulation in experimental angioplasty: Time course and relation to vascular injury. *Circulation* 1987;75: 636–642
12. Lindner V, Reidy MA: Proliferation of smooth muscle cells after vascular injury is inhibited by an antibody against basic fibroblast growth factor. *Proc Natl Acad Sci U S A* 1991;88:3739–3743
13. Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH: Syndromes of accelerated atherosclerosis: Role of vascular injury and smooth muscle cell injury. *J Am Coll Cardiol* 1990;15: 1667–1687
14. Clowes AW: Pathologic intimal hyperplasia as a response to vascular injury and reconstruction, in Rutherford RB (ed): *Vascular Surgery.* Philadelphia, WB Saunders Co, 1989, pp 266–275
15. Liu MW, Roubin GS, King SB: Restenosis after coronary angioplasty: Potential biologic determinants and role of intimal hyperplasia. *Circulation* 1989;79:1374–1387
16. Schwartz SM, Campbell GR, Campbell JH: Replication of smooth muscle cells in vascular disease. *Circ Res* 1986;58:427–444
17. Forrester JS, Fishbein M, Helfant R, Fagin J: A paradigm for restenosis based on cell biology: Clues for the development of new preventive therapies. *J Am Coll Cardiol* 1991;17:758–769
18. Califf RM, Ohman EM, Frid DJ, Fortin DF, Mark DB, Hlatky MS, Herndon JE, Bengtson JR: Restenosis: The clinical issues, in Topol EJ (ed): *Textbook of Interventional Cardiology.* Philadelphia, WB Saunders Co, 1990, pp 63–394
19. Serruys PW, Rensing BJ, Luijten HE, Hermans WRM, Beatt KJ: Restenosis following coronary angioplasty, in Meier B (ed): *Interventional Cardiology.* Bern, Hogrefe and Huber Publishers, 1990, pp 79–115
20. Hermans WRM, Rensing BJ, Strauss BH, Serruys PW: Prevention of restenosis after percutaneous transluminal coronary angioplasty (PTCA): The search for a magic bullet. *Am Heart J* 1991;122: 171–187
21. Serruys PW, Rutsch W, Heyndrickx GR, Danchin N, Mast G, Wijns W, Rensing BJ, Vos J, Stibbe J, CARPORT Study Group: Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A_2 receptor blockade: A randomized, double blind, placebo-controlled trial. *Circulation* 1991;84: 1568–1580
22. Sahni R, Maniet AR, Voci G, Banka VS: Prevention of restenosis by lovastatin after successful angioplasty. *Am Heart J* 1991;121: 1600–1608
23. Fingerle J, Au YPT, Clowes AW, Reidy MA: Intimal lesion formation in rat carotid arteries after endothelial denudation in absence of medial injury. *Atherosclerosis* 1990;10:1082–1087
24. Fingerle J, Johnson R, Clowes AW, Majesky MW, Reidy MA: Role of platelets in smooth muscle cell proliferation and migration after vascular injury in rat carotid artery. *Proc Natl Acad Sci U S A* 1989;86:8412–8416
25. Lindner V, Lappi DA, Baird A, Majack RA, Reidy MA: Role of basic fibroblast growth factor in vascular lesion formation. *Circ Res* 1991;68:106–113
26. Jawien A, Lindner V, Bowen-Pope DF, Schwartz SM, Reidy MA, Clowes AW: Platelet derived growth factor (PDGF) stimulates arterial smooth muscle cell proliferation in vivo. (abstract) *FASEB J* 1990;4:342
27. Hammacher A, Hellman U, Johnsson A, Östman A, Gunnarsson K, Westermark B, Wasteson Å, Heldin CH: A major part of platelet-derived growth factor purified from human platelets is a heteromer of one A and one B chain. *J Biol Chem* 1988;263: 16493–16498

28. Majesky MW, Reidy MA, Bowen-Pope DF, Hart CE, Wilcox JN, Schwartz SM: PDGF ligand and receptor gene expression during repair ligand. *J Cell Biol* 1990;111:2149–2158
29. Daemen MJAP, Lombardi DM, Bosman FT, Schwartz SM: Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. *Circ Res* 1991;68:450–456
30. Powell JS, Clozel JP, Müller RKM, Kuhn H, Hefti F, Hosang M, Baumgartner HR: Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science* 1989;245:186–188
31. Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA, Henderson M, Bonan R, David PR: Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 1988;318: 1714–1719
32. Barnathan ES, Schwartz JS, Taylor L, Laskey WK, Kleveland JP, Kussmaul WG, Hirshfeld JW: Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation* 1987;76:125–134
33. Reiber JHC, Serruys PW: Quantitative coronary angiography, in Marcus ML, Schelbert HR, Skorton DJ, Wolf GL (eds): *Cardiac Imaging: A Companion to Braunwald's Heart Disease.* Philadelphia, WB Saunders Co, 1990, pp 211–280
34. Mabin TA, Holmes DR Jr, Smith HC, Vlietstra RE, Bove AA, Reeder GS, Chesebro JH, Bresnahan JF, Orszulak TA: Intracoronary thrombus: Role in coronary occlusion complicating percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1985; 5:198–202
35. Dorros G, Cowley MJ, Simpson J, Bentifoglio LG, Block PC, Bourassa M, Detre K, Gosselin AJ, Gruentzig AR, Kelsey SF, Kent KM, Mock MB, Mullins SM, Myler RK, Passamani ER, Stertzer SH, Williams DO: Percutaneous transluminal coronary angioplasty: Report of complications from the National Heart, Lung, and Blood Institute PTCA Registry. *Circulation* 1983;67: 723–730
36. Ambrose JA, Winters SL, Stern A, Eng A, Teichholz LE, Gorlin R, Fuster V: Angiographic morphology and the pathogenesis of unstable angina pectoris. *J Am Coll Cardiol* 1985;5:609–616
37. Flemming RM, Kirkeeide RL, Smalling RW, Gould KL, Stuart Y: Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography. *J Am Coll Cardiol* 1991;18:945–951
38. Reiber JHC, Serruys PW, Kooyman CJ, Wijns W, Slager CJ, Gerbrands M, Schuurbiers JCH, den Boer A, Hugenholtz PG: Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantification of coronary cineangiograms. *Circulation* 1985;71:280–288
39. Rensing BJ, Hermans WRM, Deckers JW, de Feyter PJ, Tijssen JGP, Serruys PW: Luminal narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution: A quantitative angiographic study in 1,445 successfully dilated lesions. *J Am Coll Cardiol* 1992;19:939–945
40. Owens GK, Schwartz SM: Vascular smooth muscle cell hypertrophy and hyperploidy in the Goldblatt hypertensive rat. *Circ Res* 1983;53:491–500
41. Owens GK, Reidy MA: Hyperplastic growth response of vascular smooth muscle cells following induction of acute hypertension in rats by aortic coarctation. *Circ Res* 1985;57:659–670
42. Owens GK: Influences of blood pressure on development of aortic medial smooth muscle hypertrophy in spontaneously hypertensive rats. *Hypertension* 1987;9:178–187
43. Scott-Burden T, Resink TJ, Hahn AWA, Bühler FR: Induction of thrombospondin expression in vascular smooth muscle cells by angiotensin II. *J Cardiovasc Pharmacol* 1990;16(suppl 7):17–20
44. Naftilan AJ, Pratt RE, Dazau VJ: Induction of platelet derived growth factor A chain and C-myc gene expressions by angiotensin II in culture rat vascular smooth muscle cells. *J Clin Invest* 1989; 83:1419–1424
45. Powell JS, Rouge M, Muller RK, Baumgartner HR: Cilazapril suppresses myointimal proliferation after vascular injury: Effects on growth factor induction and vascular smooth muscle cells. *Basic Res Cardiol* 1991;86(suppl I):65–74
46. Powell JS, Muller RKM, Rouge M, Kuhn H, Hefti F, Baumgartner HR: The proliferative response to vascular injury is suppressed by angiotensin-converting enzyme inhibition. *J Cardiovasc Pharmacol* 1990;16(suppl 4):S42–S49
47. Renkin J, Melin J, Robert A, Richelle F, Bachy JL, Col J, Detry JMR, Wijns W: Detection of restenosis after successful coronary angioplasty: Improved clinical decision making with use of a logistic model combining procedural and follow-up variables. *J Am Coll Cardiol* 1990;16:1333–1340
48. Burnier M, Mooser V, Nussberger J, Waeber B, Brunner HR: Correlation between plasma concentration of cilazapril and hemodynamic and hormonal effects in healthy man. *Br J Clin Pharmacol* 1989;27:189S–197S
49. Nussberger J, Brunner DB, Waeber B, Brunner HR: True versus immunoreactive angiotensin II in human plasma. *Hypertension* 1985;7(suppl I):1–17
50. Bilazarian SD, Currier JW, Haudenschild C, Heyman D, Powell J, Ryan TJ, Faxon DP: Angiotensin converting enzyme inhibition reduces restenosis in experimental angioplasty. (abstract) *J Am Coll Cardiol* 1991;17:268A
51. Lam JYT, Bourassa MG, Blaine L, Lachapelle C: Can cilazapril reduce the development of atherosclerotic changes in the balloon injured porcine carotid arteries? (abstract) *Circulation* 1990; 82(suppl III):III-429
52. Churchill DA, Siegel CO, Dougherety KG, Raizner A, Minor ST: Failure of enalapril to reduce coronary restenosis in a swine model. (abstract) *Circulation* 1991;84(suppl II):II-297
53. Huber KC, Schwartz RS, Edwards WD, Camrud AR, Murphy JG, Jorgenson M, Holmes DR: Restenosis and angiotensin-converting enzyme inhibition: Effects on neointimal proliferation in a porcine coronary injury model. (abstract) *Circulation* 1991;84(suppl II): II-298
54. Hanson SR, Powell JS, Dodson T, Lumsden A, Kelly AB, Anderson JS, Clowes AW, Harker LA: Effects of angiotensin-converting enzyme inhibition with cilazapril on intimal hyperplasia in injured arteries and vascular grafts in the baboon. *Hypertension* 1991; 18(suppl II):II-70–II-76
55. Rakugi H, Krieger J, Wang DS, Dzau VJ, Pratt RE: Induction of angiotensin converting enzyme in neointima after balloon injury. (abstract) *Circulation* 1991;84(suppl II):II-113
56. Christen Y, Waeber B, Nussberger J, Porchet M, Borland RM, Lee RJ, Shum L, Timmermans PBMWH, Brunner HR: Oral administration of DuP 753, a specific angiotensin II receptor antagonist, to normal male volunteers: Inhibition of pressor response to exogenous angiotensin I and II. *Circulation* 1991;83:1333–1342
57. Schwartz RS, Huber KC, Edwards WD, Camrud AR, Jorgenson M, Holmes DR: Coronary restenosis and the importance of mural thrombus: Results in a porcine coronary model. (abstract) *Circulation* 1991;84(suppl II):II-71