

A double-blind, randomized, placebo-controlled multicenter clinical trial to evaluate the effects of the angiotensin II receptor blocker candesartan cilexetil on intimal hyperplasia after coronary stent implantation

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Background Preclinical data suggest beneficial effects of angiotensin II receptor blockers (ARBs) on neointima formation after vascular injury. Preliminary clinical data, however, revealed conflicting results. The AACHEN trial was a double-blind, randomized, placebo-controlled clinical multicenter trial to evaluate the effects of candesartan cilexetil on intimal hyperplasia after coronary stent implantation.

Methods A total of 120 patients (61 ± 9 years, 83% male) were randomized to receive either 32 mg candesartan cilexetil (active) or placebo starting 7 to 14 days before elective coronary stent implantation. A follow-up angiography including intravascular ultrasound assessment of the target lesion was performed 24 ± 2 weeks after stent implantation. The primary end point was defined as the difference in neointimal area between groups as assessed by intravascular ultrasound. Secondary end points included differences in angiographic parameters (ie, restenosis rate) and incidence of major cardiac events.

Results The mean stent length measured 15.0 ± 4.9 mm in the active and 14.6 ± 5.7 mm in the placebo group ($P = .81$). There was no significant difference in neointimal area between groups (2.1 ± 1.0 vs 2.1 ± 1.5 mm², $P = 1.00$), nor were there differences in angiographic end point parameters. Major cardiac event rates were not significantly different between treatment groups (8% vs 11%, $P = .75$).

Conclusions High-dose candesartan cilexetil therapy in patients with symptomatic coronary artery disease undergoing coronary stent implantation does not reduce clinical event rates, restenosis rates, or neointimal proliferation after elective stent implantation. (Am Heart J 2006;152:761.e1-761.e6.)

Neointimal proliferation leading to restenosis after coronary stent implantation remains the major clinical limitation of percutaneous coronary interventions. Most

systemic pharmacologic strategies to reduce neointimal proliferation, particularly using drugs that are routinely used in patients with coronary artery disease, have failed.¹

Recent preclinical studies revealed a pivotal role of the renin-angiotensin system in neointima formation after vascular injury (ie, angioplasty, stent implantation). Furthermore, experimental studies have consistently documented beneficial effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) on neointima formation after vascular injury.²

Clinical studies using ARBs to reduce neointimal proliferation revealed conflicting results. Whereas 2 open-label studies suggested beneficial effects of ARBs on neointimal proliferation,^{3,4} a smaller randomized open-label study did not show a reduction in neointimal proliferation for ARB-treated patients after coronary stent implantation.⁵

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To further elucidate and clarify the role of ARBs in the context of stent restenosis, the AACHEN trial, a double-blind, randomized, placebo-controlled clinical multicenter trial, was performed to evaluate the effects of candesartan cilexetil on intimal hyperplasia after coronary stent implantation as assessed by intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA).

Methods

Patient population and procedures

The AACHEN trial was a prospective, double-blind, randomized, placebo-controlled clinical multicenter trial to evaluate the effects of candesartan cilexetil on intimal hyperplasia after coronary stent implantation as assessed by QCA and IVUS.

A total of 11 centers participated in this trial (Appendix A). The study protocol was approved by the ethics committees of the participating centers. Study inclusion criteria were as follows: (1) males and females; (2) age ≥ 18 years; (3) angina pectoris and/or target vessel-related ischemia documented by noninvasive stress testing; (4) angiographically documented coronary stenosis ($>50\%$ diameter stenosis) in native vessels; (5) de novo lesions (type A/B according to American Heart Association (AHA)/American College of Cardiology (ACC) classification); (6) eligibility of the coronary stenosis for elective stent implantation; (7) suitability for emergency coronary bypass grafting; (8) suitability for therapy with an angiotensin II receptor antagonist; and (9) written informed consent. Exclusion criteria were as follows: (1) severe organic risk factors; (2) type 1 diabetes mellitus; (3) unstable angina pectoris (Braunwald class $\geq 1b$); (4) de novo coronary lesions type C (AHA/ACC classification); (5) acute myocardial infarction <4 weeks before randomization; (6) clinically relevant hypotension <100 mm Hg; (7) left ventricular ejection fraction of $<30\%$; (8) implantation of coil stents or self-expandable stents (wall stents); (9) lesion length >20 mm; (10) contraindication for candesartan cilexetil, or aspirin, or clopidogrel; (11) therapy with ACE inhibitors or angiotensin II receptor antagonist (after randomization); (12) increased risk for bleeding, thrombocytopenia, thrombocytopenia; (13) aggressive diuretic therapy; (14) pregnancy or the possibility to get pregnant; (15) breastfeeding; (16) drug/alcohol abuse; (17) reasons that make follow-up or control angiography unlikely or impossible; (18) known or expected poor compliance; and (19) participation in a clinical investigation within 30 days before trial enrolment.

Patients received 2 tablets per day including either 16 mg candesartan per tablet or placebo. When clinically necessary (ie, hypotension), medication could be reduced to 1 tablet per day (equivalent to 16 mg candesartan). Pretreatment with the study drug was performed 7 to 14 days before intervention. Only bare-metal stents (no coil design) were used.

A total of 3 follow-up investigations were scheduled (Table I): (1) telephone contact 4 weeks after procedure; (2) outpatient contact 12 weeks after procedure; and (3) readmission 6 ± 2 months after procedure including control angiography and IVUS. If patients did not undergo follow-up angiography, information regarding the occurrence of major cardiac events was obtained via telephone contact of the patient or the referring physician.

Table I. Schematic study plan including patient numbers and protocol-defined investigations

Visit	1	2	3	4	5
WK	-2	0	4 \pm 1	12 \pm 2	26 \pm 6
Patient sets					
Safety (n)	120	120	120	120	120
QCA (n)		120			94
IVUS (n)					77
Investigation					
Status	x	x		x	x
SAE	x	x	x	x	x
Compliance	x	x	x	x	x

SAE, Serious adverse event.

Primary end point was the difference in neointima area between groups as assessed by IVUS. Secondary end points included angiographic (differences in minimal lumen diameter, restenosis rate, late lumen loss) and clinical parameters (event-free survival, serious adverse event). Major cardiac events were defined as death, acute myocardial infarction, and recurrent target lesion revascularization.

Data quality assurance

An independent quality assurance unit audited the trial protocol, data recording, data transfer, and the final report to ensure compliance with good clinical practice. Baseline clinical demographics, in-hospital complications, and the occurrence of death, myocardial infarction, and late target vessel revascularization during follow-up were verified by independent hospital chart review and source documentation. The database was locked after all verified data entered the database. The code was broken after complete analysis.

Intravascular ultrasound imaging and analysis

The IVUS technique has been chosen as the primary end point imaging modality. IVUS provides direct and reliable visualization and quantification of in-stent neointimal dimensions leading to a significant reduction of sample sizes needed to demonstrate the effectiveness of strategies to reduce in-stent restenosis.⁶

Studies were performed using a single-element 30-MHz mechanically rotating transducer (SCIMED, Boston Scientific Corp, Natick, MA) and an automated pullback with a speed of 0.5 mm/s to obtain a complete and homogeneous image sequence.

Intravascular ultrasound imaging was started 2 minutes after intracoronary administration of 200 μ g nitroglycerin. The ultrasound catheter was carefully advanced beyond the target lesion and an imaging run was performed to the aorto-ostial junction. Image quality was adjusted to the relatively low echogenic in-stent neointima during catheter advancement to ensure optimal visualization. Studies were recorded during transducer pullback on high-resolution S-VHS tape for off-line analysis. Intravascular ultrasound analysis was performed in an IVUS core laboratory⁷ using the Tape Measure program (1.5.2, Indec Systems, Mountain View, CA) without access to any of the clinical data or treatment group.

Table II. Demographic and clinical baseline data (safety set)

	Candesartan group (n = 63)	Control group (n = 57)	P
Male, n (%)	52 (83)	47 (82)	.51
Age (y)	61 ± 9	61 ± 9	1.00
BMI (kg/m ²)	27.5 ± 3.5	28.5 ± 3.8	.14
Hypertension, n (%)	49 (78)	44 (77)	1.00
Current smoker, n (%)	22 (35)	15 (26)	.33
Diabetes mellitus, n (%)	12 (19)	16 (28)	.28
Hyperlipidemia, n (%)	53 (84)	42 (74)	.18
Statin intake, n (%)	34 (54)	26 (46)	.46
Previous CABG/PCI, n (%)	13 (21)	10 (18)	.82
Previous MI, n (%)	18 (29)	17 (30)	1.00
Lesion location			
LAD (%)	25 (40)	27 (47)	.46
LCX (%)	19 (30)	14 (25)	.54
RCA (%)	19 (30)	16 (28)	.84
Stent diameter (mm)	3.1 ± 0.3	3.1 ± 0.4	1.00
Stent length (mm)	15.0 ± 4.9	14.6 ± 5.7	.81

BMI, Body mass index; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

The off-line planar IVUS measurements were performed every 1 mm of the stented length and included (1) lumen cross-sectional area (CSA in mm²) and (2) stent CSAx (mm²). The intimal hyperplasia CSA was defined as the stent CSA minus lumen CSA. Mean areas over the total stent length were calculated.

Quantitative coronary angiography

All QCA analysis was performed in an angiographic core laboratory without access to any of the clinical data or treatment group. Quantitative coronary angiography analysis was performed off-line for all lesions with an automated edge-detection algorithm (CAAS II System, PieMedical, Maastricht, The Netherlands).⁸ The following measurements were obtained: reference diameter, minimal lumen diameter (MLD) within the lesion (mm), and percentage of diameter stenosis (DS) before intervention, postintervention, and at follow-up in multiple projections. The results from the worst view were analyzed. Immediate gain was calculated as the difference between MLD before and after procedure, late loss was calculated as the difference between MLD after procedure and that at follow-up, and net gain was calculated as the difference between MLD before procedure and that at follow-up.

The lesion length was measured as the distance from shoulder to shoulder in all available projections. The longest lesion length was recorded to avoid effects of foreshortening.

Procedural success was defined as a final diameter stenosis <50% without major in-hospital complications (death, bypass surgery, re-percutaneous transluminal coronary angioplasty, or Q-wave myocardial infarction). Recurrent restenosis at follow-up was defined as ≥50% DS.

Data analysis sets and statistics

Sample size calculation was primarily based on in-stent neointima volume data. Assuming an SD of 25mm³ on in-stent

Table III. Clinical, angiographic, and IVUS results

	Candesartan group (n = 63)	Placebo group (n = 57)	P
Major adverse cardiac events	5 (8%)	6 (11%)	.75
Death	0 (0%)	0 (0%)	1.00
Myocardial infarction	1 (2%)	2 (4%)	.60
Target lesion revascularization	5 (8%)	4 (7%)	.74
IVUS analysis	n = 36	n = 41	.13
Stent area (mm ²)	7.3 ± 2.3	7.4 ± 2.5	.86
Lumen area (mm ²)	5.2 ± 1.8	5.3 ± 2.2	.83
Neointimal area (mm ²)	2.1 ± 1.0	2.1 ± 1.5	1.00
QCA analysis	n = 52	n = 42	.27
RD (mm) preintervention	2.9 ± 0.5	2.9 ± 0.7	1.00
MLD (mm) preintervention	0.9 ± 0.4	1.0 ± 0.5	.28
DS (%) preintervention	67 ± 12	69 ± 11	.41
RD (mm) postintervention	2.9 ± 0.5	2.9 ± 0.6	1.00
MLD (mm) postintervention	2.3 ± 0.5	2.4 ± 0.5	.34
DS (%) postintervention	20 ± 19	14 ± 15	.10
RD (mm) at follow-up	2.8 ± 0.5	2.8 ± 0.6	1.00
MLD (mm) at follow-up	1.6 ± 0.5	1.8 ± 0.6	.08
DS (%) at follow-up	41 ± 19	34 ± 20	.09
Early gain (mm)	1.4 ± 0.5	1.5 ± 0.4	.30
Late lumen loss (mm)	0.7 ± 0.6	0.6 ± 0.5	.39
Net gain (mm)	0.7 ± 0.6	0.8 ± 0.6	.43
Loss index	0.5 ± 0.5	0.5 ± 0.4	1.00
Restenosis rate (%)	31	21	.35

RD, Reference diameter.

neointima volume, a 2-sided type I error α of 5% and a type II error β of 20%, and a 1:1 allocation ratio, 100 patients per group would have been needed to detect a difference in neointima volume of 10 mm³ between treatment groups. Allowing a 15% dropout, a total of 230 patients would have to be recruited for the trial. An interim analysis was scheduled after 50% of the patients (120 patients) had been analyzed (Bauer-Köhne approach). Primary end point data were expressed as neointima area as the initially planned number of patients was not recruited and the trial was discontinued.

Data analysis was based on the following sets (Table I): (1) safety set (all patients exposed to treatment), (2) angiography set (all patients exposed to treatment who underwent control angiography, and (3) full analysis set (all patients exposed to treatment who provided IVUS data).

Statistical evaluation was carried out using SAS for Windows, Version 8.2 (SAS Inc, Cary, NC). Descriptive statistics were performed for all primary and secondary efficacy parameters.

Categorical data were presented as frequencies and compared with the Pearson χ^2 test. Continuous data were presented as mean ± SD and compared with the Student *t* test or analysis of variance as adequate. *P* < .05 was considered statistically significant.

Results

One hundred-twenty patients recruited from 11 centers were included into this trial. A summary of baseline patient characteristics is provided in Table II.

Both treatment groups did not differ significantly regarding demographic, clinical, angiographic, or procedural variables.

Safety set results

There were no deaths in either treatment group. High-dose candesartan was well tolerated. A total of 9 patients (7.5%) had to reduce the candesartan dose to 16 mg/d (7 patients) or placebo (2 patients).

At baseline, systolic blood pressure was lower in the candesartan group as compared with the placebo group (133 ± 15 vs 139 ± 18 mm Hg, $P = .05$), whereas there was no difference in diastolic blood pressure (78 ± 8 vs 80 ± 8 mm Hg, $P = .18$) or heart rate (73 ± 10 vs 72 ± 9 mm Hg, $P = .57$). There were no significant differences in blood pressure or heart rate within groups over the study period.

A total of 11 patients experienced 12 major adverse cardiac events (3 myocardial infarctions, 3 coronary bypass operations, 6 percutaneous reinterventions). There were no differences in the prevalence of major cardiac events between study groups (Table III).

Intravascular ultrasound and QCA evaluation at follow-up

Complete IVUS data (full analysis set) were available in 77 (64%) of 120 patients, and complete quantitative angiography data were available in 94 (78%) of 120 patients (angiography set) (Table III). There was no difference in the primary end point analysis between treatment groups (2.1 ± 1.0 vs 2.1 ± 1.5 mm², 95% CI -0.56 to 0.59 , $P = 1.00$). Preprocedural, postprocedural, and follow-up angiography data did not differ significantly between study groups (Table III).

Discussion

Two recent clinical trials suggested a significant reduction of neointimal proliferation after coronary stent implantation using angiotensin II receptor blockers.^{3,4} The pathophysiologic concept of both clinical trials was based on numerous preclinical studies showing that the tissue renin-angiotensin system plays an important role in neointima formation.² Specifically, angiotensin II receptor expression is increased at the site of coronary angioplasty⁹ and induces vasoconstriction as well as vascular wall inflammatory responses.¹⁰ Furthermore, experimental studies have consistently demonstrated suppression of neointimal proliferation after balloon-mediated arterial injury using ARBs including candesartan cilexetil.¹¹⁻¹³ On the contrary, high-dose candesartan treatment did not reduce clinical event rates, restenosis rates, or neointimal proliferation after elective stent implantation in this first double-blind, randomized, placebo-controlled clinical multicenter trial.

There are potential reasons for this lack of effect and the observed discrepancy between recent studies and this trial.

First, inadequate dosing may have been responsible for local tissue levels too low for a biologic effect. In principal, this hypothesis is supported by the observation of a concentration-dependent reduction of neointimal proliferation in experimental and preclinical studies.^{11,14} Comparable doses in humans, however, are associated with toxicity and side effects. In this trial, however, most patients received 32 mg candesartan and only 7 patients received 16 mg of the drug per day. These are the highest systemic doses applied in this context. The only study that revealed positive results used a dose between 4 to 12 mg candesartan per day.⁴ Furthermore, based on preclinical data strongly supporting the need for pretreatment in renin-angiotensin system interventions,^{11,14-16} patients received candesartan pretreatment to increase local tissue levels before interventions. Pretreatment, however, was not performed in any other of the clinical trials before.

Second, the pathophysiologic concept may not be valid. Angiotensin II may not play a major role in neointimal proliferation and/or angiotensin II receptor antagonist therapy may principally not be sufficient to significantly suppress neointimal proliferation. Despite the fact that after vascular injury a number of biologically active mediators such as platelet-derived growth factor, fibroblast growth factor, insulin-like growth factor among others are also activated, the role of the tissue renin-angiotensin systems in neointima formation is well established in different experimental and preclinical models.² Furthermore, ARBs have been shown to reduce neointima proliferation in different experimental animal models.² It is noteworthy, however, that the only animal study evaluating the effects of ARBs on neointimal proliferation after stent implantation revealed negative results in the porcine coronary artery model.¹⁷

Third, the pathophysiologic concept is valid, but translation of preclinical data into the clinical scenario is difficult in the context of stent restenosis.¹⁸ There are, indeed, a number of examples of positive animal studies that failed to show efficacy in human beings. One explanation, clearly, is the inevitable difference between disease pathophysiology in animals and humans. In the specific context of restenosis, juvenile animal without an underlying atherosclerotic disease is used. Furthermore, even the double-injury rabbit model (cholesterol diet, endothelial denudation, and subsequent stent implantation) mimics only in part the restenosis process in humans.

Fourth, cofactors of restenosis (ie, diabetes mellitus, comedication) that potentially influence restenosis were not equally distributed. As depicted in Table II, however, prevalence of diabetes¹⁹ and use of statins²⁰ were equally distributed. In addition, use of glycoprotein IIb/IIIa inhibitors²¹ was not allowed per protocol, and

drug-eluting stents were commercially not available at the time the study was conducted.

Limitations

Important limitations of this trial have to be discussed. First, the calculated number of necessary patients for a trial comparing neointimal volume (230 patients) was not reached. Instead, after 120 patients, an analysis of end point parameters was performed in compliance with the study protocol. Therefore, the negative result of this study is based on an interim analysis. Despite this important limitation, this study was the largest clinical trial of this kind in this context. Moreover, in accordance with previous observations, there was a robust correlation between QCA measurements and IVUS calculations of in-stent neointimal formation.^{6,22} Second, the angiographic and IVUS follow-up rates (78%, 64%) were lower than estimated for the initial power calculation and also lower than in previously reported trials. In addition, the 6-month follow-up end point might have underestimated event rates as compared with an 8- or 9-month follow-up. Based on the mean difference (0.017 mm²) and confidence interval of the primary end point, however, a clinically relevant treatment effect >0.56 mm² can be excluded with 95% confidence, at least at the 6-month end point. Furthermore, a sample size recalculation based on the mean difference in neointimal area as observed in this trial would result in group sizes of >50,000 patients. Information regarding major adverse cardiac events within a 6-month period, however, was obtained in all patients. Third, this trial excluded patients with a significant local inflammatory response after stenting (ie, patients with acute coronary syndromes, type 1 diabetic patients). Potentially, different results might have been obtained in a higher-risk patient population.

Conclusions

In this first double-blind, randomized, placebo-controlled clinical multicenter trial, high-dose candesartan treatment did not reduce clinical event rates, restenosis rates, or neointimal proliferation after elective stent implantation. Despite the introduction of drug-eluting stents into clinical practice and the negative findings of this study, renin-angiotensin system interventions using ACE inhibitors and ARBs are a pivotal component in the treatment of patients with atherosclerosis and coronary artery disease.

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Appendix A

List of participating centers (principal investigator, number of patients included): Aachen (PW Radke, P Hanrath, 37), Jena (HR Figulla, 17), Hannover (H Drexler, D Fischer, 16), Krefeld (HG Klues, 16), Bochum (A Mügge, 13), München (S Silber, 9), Erlangen (W Daniel, 6), Dresden (A Schmeisser, 2), Bad Soden (N Reifart, 2), Karlsbad (W Motz, 1), Bad Krotzingen (H-J Büttner, 1).