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Carvedilol for Prevention of Restenosis After Directional Coronary Atherectomy

Final Results of the European Carvedilol Atherectomy Restenosis (EUROCARE) Trial

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Background—In addition to its known properties as a competitive, nonselective β and α-1 receptor blocker, carvedilol directly inhibits vascular myocyte migration and proliferation and exerts antioxidant effects that are considerably greater than those of vitamin E or probucol. This provides the basis for an evaluation of carvedilol for the prevention of coronary restenosis.

Methods and Results—In a prospective, double-blind, randomized, placebo-controlled trial, 25 mg of carvedilol was given twice daily, starting 24 hours before scheduled directional coronary atherectomy and continuing for 5 months after a successful procedure. The primary end point was the minimal luminal diameter as determined during follow-up angiography 26 ± 2 weeks after the procedure. Of 406 randomized patients, 377 underwent attempted atherectomy, and in 324 (88.9%), a $\leq$50% diameter stenosis was achieved without the use of a stent. Evaluable follow-up angiography was available in 292 eligible patients (90%). No differences in minimal luminal diameter (1.99 ± 0.73 mm versus 2.00 ± 0.74 mm), angiographic restenosis rate (23.4% versus 23.9%), target lesion revascularization (16.2 versus 14.5), or event-free survival (79.2% versus 79.7%) between the placebo and carvedilol groups were observed at 7 months.

Conclusions—The maximum recommended daily dose of the antioxidant and β-blocker carvedilol failed to reduce restenosis after successful atherectomy. These findings are in contrast to those of the Multivitamins and Probucol Trial, which raises doubts regarding the validity of the interpretation that restenosis reduction by probucol was via antioxidant effects. The relationship between antioxidant agents and restenosis remains to be elucidated. **(*Circulation*. 2000;101:1512-1518.)**

Key Words: restenosis ■ prevention ■ atherectomy ■ carvedilol ■ angiography ■ β-blocker ■ antioxidants

Pharmacological approaches to a reduction in restenosis after coronary interventions using agents to prevent vascular smooth muscle cell proliferation have been largely ineffective.[1–3] Two trials using antioxidants, one with vitamin E[4] and the other using vitamin E and probucol,[5] reported a reduction in restenosis after balloon angioplasty. This reduction initially had no mechanistic explanation,[5] but a later study suggested an inhibition of vessel remodelling as the possible mode of action.[6]

Carvedilol is a nonselective β-adrenergic receptor antagonist with vasodilating properties that are mediated by α-1 receptor inhibition.[7] It is approved for the treatment of angina pectoris, hypertension, and heart failure. It is also a direct inhibitor of myofibroblast migration in the vascular media and adventitia.[8,9] Significant inhibition of rat carotid intimal hyperplasia after injury, even with acute carvedilol dosing,[10] and of human pulmonary artery vascular smooth muscle cells in culture[8,9] has been reported. Furthermore, carvedilol and its

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A list of all EUROCARE investigators is given in the Appendix.

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metabolites exhibit antioxidant properties that are some 30 to 80 times more potent than vitamin E or probucol.[11–13]

In the EUROCARE trial, this generalized potential for carvedilol to inhibit restenosis was evaluated in patients undergoing successful directional coronary atherectomy (DCA). This procedure was chosen because in 1994, DCA was known to be more effective than balloon angioplasty, but it was limited by a greater tendency toward restenosis.[14–16] Thus, a positive outcome would enhance the clinical usefulness of DCA and could be generalized to other interventions. Equally important, the trial hypothesis could be meaningfully tested using a smaller sample size than would be required in a population undergoing balloon angioplasty.[17]

Methods

Primary and Secondary End Points

The primary end point of EUROCARE was the MLD at angiographic follow-up 26±2 weeks after successful DCA (this was defined by the core laboratory; see below). Secondary end points included MACE[18] at 7 months, angiographic indices of absolute and relative loss in MLD, loss index, restenosis rate, and adverse events.

Study Population

Patients with stable or unstable angina pectoris (except Braunwald Class 3 unstable angina) who were scheduled to undergo elective DCA of a single native primary coronary stenosis were eligible for inclusion. Major exclusion criteria were contraindications to carvedilol (eg, bradycardia <50 bpm, second or third degree atrioventricular block, obstructive airway disease, insulin-dependent diabetes, etc) or to a discontinuation of existing β-blocker therapy, ineligibility for DCA (eg, unprotected left main stem disease and/or vessel size <3 mm), and planned stent implantation. Patients were also excluded if they had a documented myocardial infarction (see Definitions) within the preceding 5 days or intolerance to acetylsalicylic acid (aspirin).

Study Design

The trial was a multicenter, randomized (block size of four), double-blind, parallel-group design. Patients were assigned to fixed oral doses of carvedilol (25 mg BID) or placebo and, before enrolment, were tapered off all previous antihypertensive, vasoactive, and antianginal medication other than nitrates. Treatment started a minimum of 24 hours before the scheduled DCA and was continued for a 5-month period after successful DCA (see Definitions). One month before scheduled follow-up angiography, the study medication was tapered off over a 1-week period (12.5 mg of carvedilol BID or placebo). During the course of the trial, antihypertensive and antianginal therapy could be initiated at the discretion of the investigators. Concomitant therapy with β-blockers, α-blockers, anti-arrhythmics, antioxidants (eg, high-dose vitamin E or C or probucol), antiproliferative agents (eg, cytostatics), drugs that influence the pharmacodynamics or kinetics of carvedilol (ie, psychopharmaceuticals and nonsteroidal anti-inflammatory agents, excluding aspirin and laxatives), or anticoagulants (except heparin during the procedure) was not allowed during the trial.

Compliance was assessed by capsule counts. Trial medication was discontinued in patients who did not have a successful DCA and in those who experienced a MACE (except non–Q wave myocardial infarction) or other serious adverse event. The study was conducted in accordance with the Declaration of Helsinki and the Committee for Proprietary Medicinal Products/Good Clinical Practice Guidelines. The protocol was approved by the ethics committees of all participating centers, and all patients gave written informed consent before inclusion.

DCA Procedure

After sheath introduction, 10 000 IU/L heparin was given; further bolus doses were given as needed to keep an activated coagulation time >350 s. Intravenous doses of 250 mg of acetylsalicylic acid were also administered in patients not already taking 75 to 500 mg daily. DCA was recommended to be guided by on-line quantitative coronary angiography and, where possible, IVUS, with adjunctive balloon angioplasty to achieve optimal results (see Definitions).

Angiographic Procedures and Quantitative Coronary Angiography at the Core Laboratory

Angiographic procedures and core laboratory evaluations were strictly standardized, as has been described in previous trials.[2,3,14,16] After intracoronary nitrate bolus injection, the target stenosis was filmed in a minimum of 2 projections before and after the procedure; these projections were repeated identically at follow-up. The Cardiovascular Angiographic Analysis System II (Pie Medical) was used for the angiographic analysis at the core laboratory, using a well-described methodology.[2,3,14,16]

Clinical Assessments

Patients returned for clinical follow-up visits at 1, 5, 6, and 7 months. Shortly before reangiography, a symptom-limited exercise tolerance test was performed. To monitor the safety of trial medication, serial recordings of creatinine, alkaline phosphatase, γ-galactosyl transferase, glutamic pyruvic transaminase, and glutamic-oxaloacetic transaminase were assessed at each visit. Cardiac enzymes were determined when clinically indicated and according to local practice. Adverse events were recorded continuously, whether or not they were considered drug-related.

Definitions

Successful DCA was defined off-line by the core laboratory as ≤50% diameter stenosis; optimal DCA indicated ≤20% diameter stenosis in every angiographic view, without the use of a stent or the occurrence of a MACE, which was defined as cardiac death, myocardial infarction, coronary artery bypass graft surgery, or reintervention at the site of the original DCA (target lesion revascularization).[18] Myocardial infarction was defined as development of new pathological Q waves and/or an increase of more than twice the upper limit of normal of levels of creatine kinase, with concomitant elevation of the MB fraction. Compliance with trial medication was defined as consumption of >80% of trial medication in the first month and >75% of medication thereafter.

Statistical Methods

Sample size calculation was based on a postulated difference in MLD at follow-up between the placebo and carvedilol groups of 0.20±0.62 mm (mean MLD: control group, 1.76 mm[14] and carvedilol group, 1.96 mm), which is equivalent to a 30% reduction in restenosis rate. A sample size of 152 patients per group would be required to detect such a difference with a power of 0.80 and a 2-sided α of 0.05. To allow for nonevaluable patients, we decided to recruit 400 total patients.

As specified in the protocol, the analysis was based on the intention-to-treat principle; this then included all patients who took ≥1 tablet of study medication, underwent successful DCA, and had an analyzable follow-up angiogram. Safety evaluation included all randomized patients who took ≥1 dose of study medication. Student's t test was used for intergroup comparisons of continuous measurements, and the χ^2 test was used for categorical variables. Frequency distribution curves are used to display MLD measurements before and after DCA and at follow-up, and Kaplan-Meier survival curves illustrate freedom from MACE.

Results

Procedural Results

From December 1994 to February 1997, 406 patients were randomized to receive ≥1 dose of trial medication (206 took

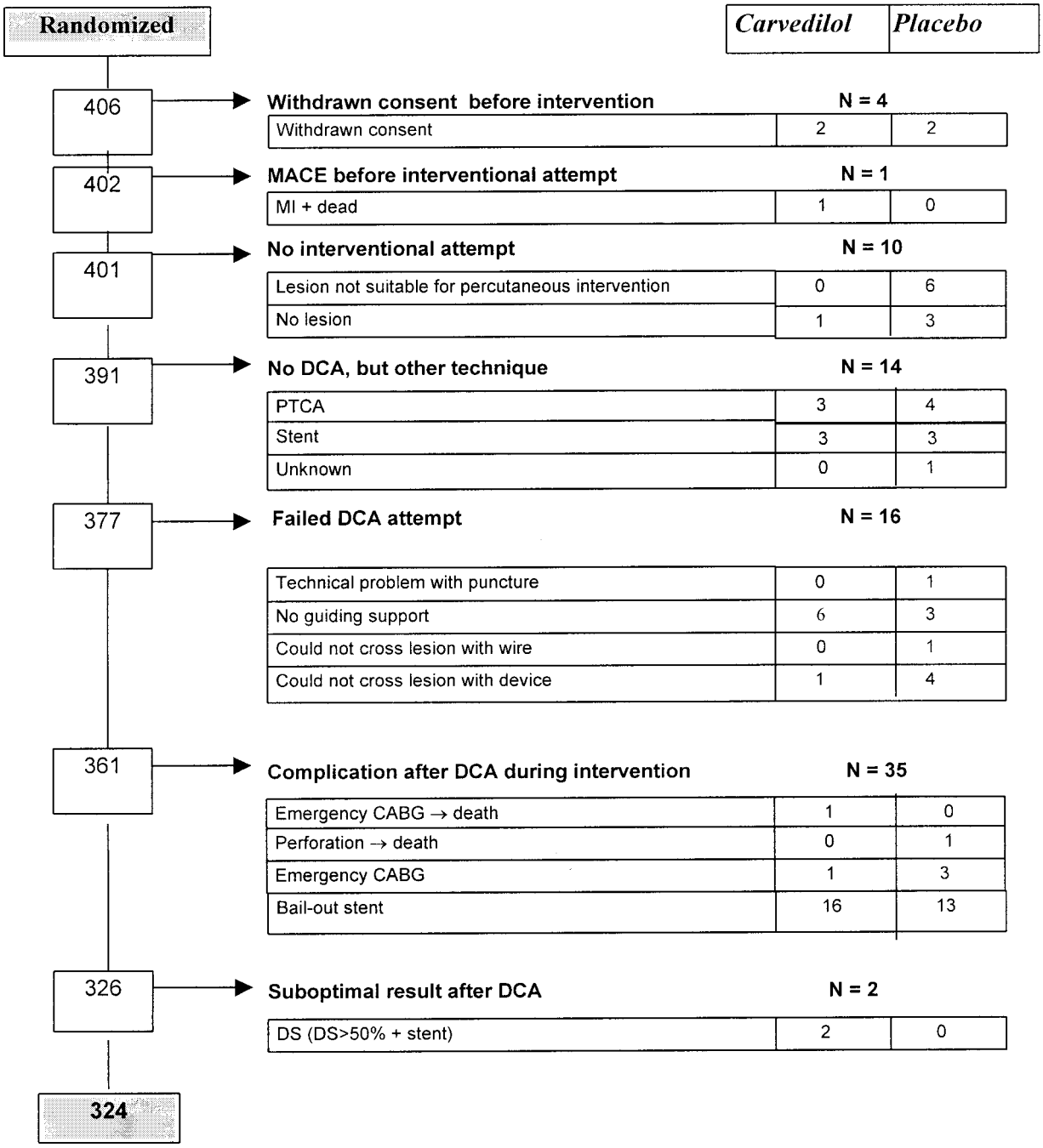

Figure 1. Flow chart showing derivation of the intention-to-treat population. MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and DS, diameter stenosis.

carvedilol and 200 took placebo). Among these, 377 underwent attempted DCA (Figure 1). One patient died after coronary perforation, and 5 were referred for emergency coronary artery bypass grafting. One of these 5 patients died perioperatively. Successful bailout stenting was performed in 29 patients.

Of the 324 patients with successful DCA (Table 1), 292 (90%) had an evaluable follow-up angiogram; these 292 patients made up the trial population. Quantitative angiographic baseline and procedural parameters are shown in Tables 2 and 3. Predilatation was performed in 6% of patients. A 7-French device was used in 84% of cases. A median of 13 cuts were done (interquartile range, 9 to 30), and a maximum of 4.8 atm of balloon pressure (range, 1 to 8 atm) was applied. Postdilatation was performed in 66% of cases using a mean balloon size of 3.65 ± 0.50 mm at a maximal pressure of 8.2 ± 3.19 mm and a balloon-to-artery ratio of 1.08 ± 0.15 mm. An optimal result was reported by the investigator in 68% of cases and by the core laboratory (determined by $\leq$20% diameter stenosis) in 26% of cases.

In the intention-to-treat population, 132 patients in the carvedilol group (78%) and 127 in the placebo group (81.9%) were compliant.

TABLE 1. Demographics and Baseline Characteristics

	Carvedilol (n=169)	Placebo (n=155)	All
Male sex	147 (87)	137 (88.4)	284 (87.7)
Age, y	57.9±10.0	58.6±9.7	58.2±9.8
Smoking			
Never smoked	42 (24.9)	51 (32.9)	93 (28.7)
Previous smoker	95 (56.2)	72 (46.5)	167 (51.5)
Current smoker	32 (18.9)	32 (20.6)	64 (19.8)
Diabetes mellitus	17 (10.1)	14 (9)	31 (9.6)
Hypercholesterolemia	36 (21.3)	22 (14.2)	58 (17.9)
Other hyperlipidemia	32 (18.9)	30 (19.4)	62 (19.1)
Hypertension	50 (29.6)	43 (27.7)	93 (28.7)
Previous MI	84 (49.7)	56 (36.1)	140 (43.2)
Previous PTCA	0 (0.0)	1 (0.6)	1 (0.3)
Previous CABG	0 (0.0)	4 (2.6)	4 (1.2)
Peripheral vascular disease	5 (3.0)	9 (5.8)	14 (4.3)
Medication			
Calcium antagonists	40 (23.7)	50 (32.3)	90 (27.8)
ACE inhibitors	38 (22.5)	34 (21.9)	72 (22.2)
β-Blockers	105 (62.1)	97 (62.6)	202 (62.3)
Nitrates	128 (75.7)	107 (69)	235 (72.5)

Values are n (%) or mean±SD. MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and ACE, angiotensin-converting enzyme.

Late Outcomes

No differences in the minimal luminal diameter (MLD), angiographic restenosis rate (Table 3 and Figure 2), or the occurrence of major adverse cardiac events (MACE) between the placebo and carvedilol groups were observed during a follow-up of ≤7 months (Table 4 and Figure 3).

Other Adverse Events

No difference in the incidence of adverse events was observed between the groups (carvedilol, 50%; placebo, 47.5%), although a higher incidence of hypotension (7.3% versus 1%) and bradycardia (6.3% versus 0%) existed in the carvedilol group.

TABLE 2. Baseline Angiographic Characteristics

	Carvedilol (n=169)	Placebo (n=155)
AHA/ACC lesion type		
A	12 (7.1)	11 (7.1)
B1	63 (37.5)	65 (41.9)
B2	93 (55.4)	79 (51.0)
C	0 (0.0)	0 (0.0)
No. of diseased vessels		
1	140 (83.8)	125 (81.2)
2	21 (12.6)	16 (10.4)
3	6 (3.6)	13 (8.4)
Calcification	47 (27.8)	31 (20.0)
Thrombus	5 (3.0)	3 (2.0)
Lesion length, mm	8.39±2.57	8.71±3.04
Vessel size, mm	3.36±0.56	3.49±0.61

Values are n (%) or mean±SD. AHA indicates American Heart Association, and ACC, American College of Cardiology.

TABLE 3. Acute and Follow-Up Angiographic Indices

	Carvedilol (n=154)	Placebo (n=138)
Reference diameter, mm		
Preoperative	3.38±0.57	3.48±0.59
Postoperative	3.56±0.51	3.61±0.56
Follow-up	3.25±0.59	3.20±0.61
MLD, mm		
Preoperative	1.19±0.34	1.26±0.44
Postoperative	2.77±0.49	2.85±0.50
Follow-up*	1.99±0.73	2.00±0.74
Diameter stenosis, %		
Preoperative	64.33±9.78	63.56±11.27
Postoperative	22.19±7.71	20.86±7.94
Follow-up†	39.13±17.93	37.54±18.35
Acute gain, mm	1.58±0.51	1.59±0.50
Late loss, mm	0.77±0.70	0.85±0.70
Relative loss, mm	0.23±0.21	0.25±0.21
Loss index	0.51±0.49	0.55±0.48
Restenosis rate, %	23.4	23.9

Values are mean±SD, unless otherwise indicated.
*P=0.92; †P=0.46.

Discussion

Despite the extensive in vitro and in vivo evidence for a potential benefit of carvedilol (through the inhibition of myofibroblast migration in the media and adventitia and of free radical–mediated vascular inflammation and remodelling, as well as its direct antiproliferative effects[7–13]), the maximum recommended daily dosage failed to reduce restenosis after successful DCA. Because carvedilol and its metabolites have considerably greater antioxidant effects than vitamin E or probucol,[11–13] each of which have been reported to reduce restenosis after balloon angioplasty,[4,5] the purported antioxidant mechanism of probucol for the observed selective

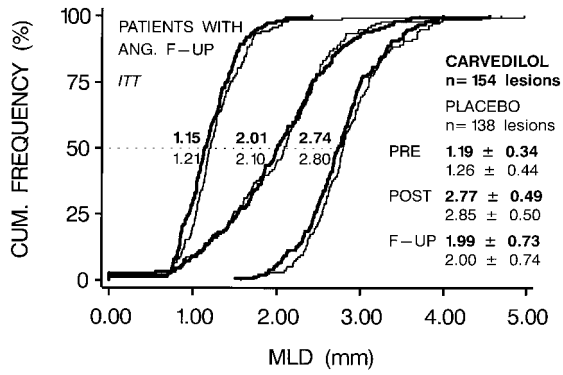

Figure 2. Cumulative frequency curves of MLD before (PRE) and after (POST) successful DCA and at follow-up (F-UP). Mean values (±SD) are on the right, and median values are next to the curves. CUM indicates cumulative; ITT, intention-to-treat; and ANG, angiographic.

TABLE 4. MACE in Each Group at 7-Month Follow-Up

	Carvedilol (n=169)	Placebo (n=155)
Death	0 (0.0)	2 (1.3)
MI	5 (3.0)	5 (3.2)
Q wave MI	1 (0.6)	0 (0.0)
Non-Q Wave MI	4 (2.4)	5 (3.2)
CABG	3 (1.8)	3 (1.9)
Re-PTCA (TLR)	26 (15.4)	24 (15.5)
No MACE	135 (79.9)*	121 (78.1)*

Values are n (%). MI indicates myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; and TLR, target lesion revascularization.

*P=0.64 by Wilcoxon rank sums text at 240 days.

benefit in the Multivitamins and Probucol Trial in Prevention of Restenosis Post Percutaneous Coronary Angiography seems putative.[6] On the basis of the neutral outcome of this trial, we think that in the probucol trial, either another mechanism was responsible for the observed reduction in renarrowing or the outcome was serendipitous. In addition, it must be concluded that the role of systemic antioxidants for the prevention of restenosis is debatable and must be further elucidated.

The question arises as to why no effect was observed in this multicenter clinical trial of an agent that has greater antioxidant effects than probucol[11–13] in addition to its other listed effects.[7–10] First, although it may be claimed that the rat model is not an ideal in vivo platform for a clinical trial, this trial hypothesis was based on the combined evidence from many other studies,[7–13] as well as the acceptability of this drug for clinical use.

Adequacy of Dose and Pretreatment Period

Carvedilol reaches peak plasma levels 2 hours after an oral dose of 25 mg, and steady-state plasma levels are achieved after 5 half-lives of ≈7 hours each,[7] which is a 35-hour period. In this trial, for practical purposes, patients were pretreated for a minimum of 24 hours, undergoing DCA within 2 hours after taking the third dose of trial medication. Thus, although a steady-state plasma level of carvedilol may not yet have been reached in all patients, DCA was usually performed to coincide with peak plasma levels, and carvedilol accumulates rapidly in the lipid environment, including cell membranes and the lipid moiety of lipoproteins.[7,19] In a trial that used a dose regimen similar to that of this trial, 84% suppression of neointimal hyperplasia was observed in the rat carotid artery balloon angioplasty model, with pretreatment for only 2 hours before and 14 days after balloon angioplasty.[10] Additionally, protection by carvedilol from oxygen free-radical–induced damage has been demonstrated at concentrations that are consistent with the plasma levels of the drug attained in patients on a dose of 25 to 50 mg a day (ie, 100 to 300 nmol/L).[13] Furthermore, clinical studies have recently demonstrated that carvedilol creates a marked reduction in low-density lipoprotein oxidation in hypertensive patients[19] and helps stop the development of nitrate tolerance, which is associated with superoxide anion production.[20] Thus, it can be assumed that the pretreatment and dose regimen should have been sufficient to reproduce, in humans, the experimental effects observed in vitro and in animals.

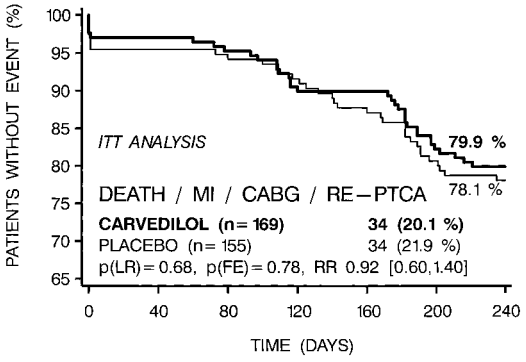

Figure 3. Kaplan-Meier estimates of freedom from death, myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (Re-PTCA). LR indicates log ranking; F(E), Fischer exercise test; and RR, relative risk.

It is also important to note that the trial medication was safe; no differences between groups existed in the incidence of adverse events, except hypotension and bradycardia. This led to discontinuation of carvedilol in only 3.9% of patients, which is not untoward given that carvedilol is a vasodilating β-blocker.

Appropriateness of DCA-Treated Patients for This Trial

At the time this trial was planned, it was known that DCA achieved greater acute results but was limited by a greater tendency toward renarrowing when compared with conventional balloon angioplasty.[14–16] Stenting was in the early phase of clinical evaluation: the Belgian Netherlands Stent Study (BENESTENT) and Stent Restneosis Study (STRESS) had not yet been completed; thus, stenting was only performed as a bailout procedure, which indicated a failed DCA. The mean luminal loss observed after DCA by the core laboratory was 0.81 mm,[14,16] which is >2 times the average after balloon angioplasty.[2,3,14,16] Before intravascular ultrasound (IVUS) studies, which changed our perception of restenosis,[21–23] we assumed this renarrowing was due to neointimal hyperplasia.[24] For this reason, the investigation of an agent with antioxidant, antichemotactic, and direct antiproliferative effects seemed ideally suited to an atherectomy-treated patient population. IVUS studies have since demonstrated that vessel remodelling may account for >50% of the luminal renarrowing response after DCA,[21,22] which reduces the target for antiproliferative drugs. However, if the report by Côté et al[6] on probucol is correct, the antioxidant effects of carvedilol should have the potential to inhibit vascular remodelling as well as inflammation such that a general reduction of the response to injury could have been reasonably expected.[7–13,19,20]

Because the pretreatment and dose regimen used seems adequate, it can only be speculated that the many alternative pathway cascades that lead to vascular remodelling and neointimal hyperplasia have the capacity to overcome spe-

cific inhibitory agents to achieve what is essentially an effective natural wound healing response.[23]

Comparison of Atherectomy Results With Other Trials

Although the present study is not a trial asserting the specific value of atherectomy (because DCA is now used in <2% of patients undergoing percutaneous therapies), it is appropriate to compare the short- and long-term results with those of other trials. Procedural success was obtained in 88.9% of cases, as compared with 92% in the Balloon versus Optimal Atherectomy Trial (BOAT).[25] The MLD after the procedure was 2.81 mm in this trial and 2.82 mm in BOAT; in the subgroup of patients with "optimal atherectomy," the MLD after the procedure was 3.09 mm in this trial compared with 3.16 mm in the Optimal Atherectomy Restenosis Study (OARS).[26] The late loss (0.81 mm) in EUROCARE was substantially less than that in both BOAT (0.96 mm) and OARS (1.18 mm), so the restenosis rate in EUROCARE is also lower (23.6%) than that in BOAT (31.4%) and OARS (28.9%). The incidence of target lesion revascularization in EUROCARE (17.1%) was slightly lower than that in BOAT (21.1%) and similar to that in OARS (17.8%). Thus, the level of intervention by DCA that was performed in this trial was representative of the concurrent best clinical practice, and an adequate platform was created for testing an anti-restenosis strategy.

Limitations

Because this was an atherectomy study, it would have been ideal to have IVUS guidance; however, in 1994, IVUS was not yet widely used and, given the lack of difference in outcome between the groups, it would not have changed the outcome of the trial. Also, the antioxidant activity of carvedilol was not measured in this trial because the previously accumulated specific studies of antioxidant effects[7–10,20,21] were considered sufficient evidence to assume a greater clinical effect in this regard than vitamin E or probucol.

Conclusions

Carvedilol was safe and well tolerated by patients undergoing DCA, both during the procedure and in the follow-up period. Despite extensive evidence depicting its potent antioxidant, antichemotactic, and antiproliferative effects, the maximum recommended daily dosage failed to demonstrate any reduction in restenosis as measured by quantitative angiographic and clinical parameters. These results question the validity of the explanation that the reported reduction in restenosis by probucol in the Multivitamins and Probucol Trial was via antioxidant mechanisms. The relationship between antioxidant agents and restenosis remains to be elucidated.

Appendix

Participating Investigators, Listed in Order of Recruitment

Prof Höfling and Dr Engelmann, Klinikum Grosshadern, München, Germany; Prof Puel and Dr Marco, Hôpital Purpan, Toulouse, France; Prof Glogar and Dr Hassan, Allgemeines Krankenhaus der Stadt, Vienna, Austria; Prof Kiel and Dr Alexander, Christian Albrechts Universitätsklinik, Kiel, Germany; Prof Serruys, Dr de Feyter, and Dr Foley, Thoraxcentre Academic Hospital Dijkzigt, Rotterdam, The Netherlands; Prof Seabra-Gomes, Hospital de la Santa Cruz, Linda-a-Velha, Portugal; Dr Macaya and Dr Goicolea, Hospital Clínico San Carlos, Madrid, Spain; Dr Coste, CHRU Bordeaux, Talence, France; Prof Rutsch, Paraskevaides, University Hospital Charité, Berlin, Germany; Prof Katus and Dr. Brachmann, University Hospital, Heidelberg, Germany; Dr Bonnier, Catharina Ziekenhuis, Eindhoven, The Netherlands; Dr Wijns and Dr Heyndrickx, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; Dr Betriu, Hospital Clínico I Provincial, Barcelona, Spain; Dr Anivarro, Hospital Universario Vall d'Hebron, Barcelona, Spain; Dr Hertzfeld, Karolinska Hospital, Stockholm, Sweden; Prof Schroeder and Dr Chenu, Hôpital Universitaire de Mont-Godinne, Yvoir, Belgium; Dr Haude, Universität Essen, Germany; Prof de Scheerder, UZ St Raphael–Gasthuisberg, Leuven, Belgium; Dr Waas, University Hospital Giessen, Belgium; Prof Providencia, Hospitals da Universidade de Coimbra, Portugal; and Dr Horstkotte, Universitätsklinikum Benjamin Franklin, Berlin, Germany.

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