Circulation
Volume 93, Issue 3, 1 February 1996; Pages 412-422
https://doi.org/10.1161/01.CIR.93.3.412

ARTICLE

Heparin-Coated Palmaz-Schatz Stents in Human Coronary Arteries

Early Outcome of the Benestent-II Pilot Study

Patrick W. Serruys, Håkan Emanuelsson, Wim van der Giessen, Anthony C. Lunn, Ferdinand Kiemeney, Carlos Macaya, Wolfgang Rutsch, Guy Heyndrickx, Harry Suryapranata, Victor Legrand, Jean Jacques Goy, Pierre Materne, Hans Bonnier, Marie-Claude Morice, Jean Fajadet, Jorge Belardi, Antonio Colombo, Eulogio Garcia, Peter Ruygrok, Peter de Jaegere, Marie-Angèle Morel, and on behalf of the Benestent-II Study Group

Abstract: *Background* The purpose of the Benestent-II Pilot Study was to evaluate the safety of delaying and eliminating anticoagulant therapy in patients receiving a heparin-coated stent in conjunction with antiplatelet drugs.*Methods and Results* The study consisted of three initial phases (I, II, III) during which resumption of heparin therapy after sheath removal was progressively deferred by 6, 12, and 36 hours. In phase IV, coumadin and heparin were replaced by 250 mg ticlopidine and 100 mg aspirin. Of the 207 patients with stable angina pectoris and a de novo lesion in whom heparin-coated stent implantation was attempted, implantation was successful in 202 patients (98%). Stent thrombosis did not occur during all four phases, and the overall clinical success rate at discharge was 99%. Bleeding complications requiring blood transfusion or surgery fell from 7.9% in phase I to 5.9%, 4%, and 0% in the three following phases. Hospital stay was 7.4, 6.1, 7.2, and 3.1 days for the consecutive phases. The restenosis rate for the combined four phases was 13% (15% in phase I, 20% in phase II, 11% in phase III, and 6% in phase IV). The overall rate of reintervention for the four phases was 8.9%. At 6 months, 84%, 75%, 94%, and 92% of the patients of phases I to IV, respectively, were event free. For the four phases, the event-free rate was 86%, which compares favorably with the rate observed in the Benestent-I study (80%; relative risk, 0.68 [0.45 to 1.04]).*Conclusions* The implantation of stents coated with polyamine and end-point–attached heparin in stable patients with one significant de novo coronary lesion is well tolerated, is associated with no (sub)acute stent thrombosis, and results in a favorable event-free survival after 6 months.

Key Words: heparin ■ stents ■ anticoagulants ■ angina ■ coating

Despite advances in the clinical use of coronary stents, there still are limitations to general applicability of the technique. Thrombogenicity necessitating multidrug anticoagulation

therapy poses the most important problem.[1] [2]

The Benestent-I trial, a multicenter randomized study comparing the safety and efficacy of primary Palmaz-Schatz stent implantation with PTCA in patients with stable angina pectoris and a single de novo lesion in a native coronary artery demonstrated that event-free survival was higher at 6 months' follow-up in patients who received a stent compared with patients treated with PTCA (80% versus 70%).[3] This was largely due to a reduction in repeat revascularization in patients treated with a stent, associated with a significantly lower RR in this group (22% versus 32%).

However, the incidence of bleeding complications (13.5%, bleeding episodes or peripheral vascular complications at the puncture site) and subacute coronary thrombosis (3.5%) reflects the difficult balance between the thrombogenicity of the stent and the need for an intensive anticoagulation regimen.[4] In addition, the hospital stay was considerably longer (8.3 days) in the stent group because of the need to monitor anticoagulation. Thus, the positive effects in terms of event-free survival were partly negated by a prolonged hospital stay and bleeding complications. To further improve the clinical results of coronary stenting, attention was directed to coating the stent with material that would minimize the risk of abrupt stent closure and thereby allow a reduction in anticoagulant therapy. With this objective in mind, a heparin-coated stent has been developed.[5] [6] [7] [8]

Covalent binding of heparin onto solid surfaces by end-point attachment has become technically possible, allowing heparin to interact freely with plasma components and enzymes, thereby expressing its biological activities and resulting in a highly biocompatible surface. The compatibility of this bioactive surface with circulating blood is achieved by at least three mechanisms: inhibition of the activation of coagulation, potentiation of the inhibition of the activated coagulation enzymes, and prevention of platelet adhesion to the surface.

Data from animal studies indicate that Palmaz-Schatz stents with this heparin coating are associated with a significant reduction in acute thrombus formation. In stented rabbit iliac arteries a reduction in angiographically detected thrombus was observed at 4 and 24 hours.[5] [6] In a baboon extracorporeal arteriovenous shunt (N. Chronos, MD, private communication, 1995) and in an in vitro circulation loop with bovine blood, indium-labeled platelet attachment to the same stents was reduced by 95% or more by the heparin coating compared with uncoated stents.

In a porcine coronary model, heparin-coated and uncoated Palmaz-Schatz stents were implanted in the LAD. In pigs that received a coated stent, no thrombotic events were recorded compared with a 30% to 40% occlusion rate with uncoated stents.[8] These data formed the basis of the present study investigating this heparin-coated version of the Palmaz-Schatz stent in clinical practice.

Methods

Objectives

The primary objective of the present study was to determine the safety of elective implantation of a heparin-coated Palmaz-Schatz stent in patients with a single de novo lesion in a native coronary artery in a patient population comparable with that enrolled in the Benestent-I study. For this purpose, the incidence of acute and subacute thrombotic stent occlusion and the incidence, location, and severity of bleeding complications during hospital stay and within 30 days after stent implantation were determined.

The secondary objectives were the determination of the efficacy of heparin-coated stent implantation (symptom and event-free survival at 6 months—freedom from death, MI, repeat intervention, or CABG) and the evaluation of the changes in stenosis geometry immediately after stent implantation and at 6 months by quantitative coronary angiography.

Definitions

(Sub)acute thrombotic stent occlusion was defined as either the angiographic documentation of a complete occlusion (TIMI flow 0 or 1) or the angiographic documentation of a flow-limiting thrombus (TIMI flow 1 or 2). Intracoronary thrombus was defined as the presence of a filling defect within the lumen, surrounded by contrast material seen in multiple projections in the absence of calcium within the filling defect, or the persistence of contrast material within the lumen or a visible embolization of intraluminal material downstream. Acute occlusion was defined as occurring in the interventional suite when the guiding catheter was still in place; subacute occlusion was defined as occurring after removal of the guiding catheter and outside the interventional suite.

Bleeding complications included any clinical (ie, direct) or biological (ie, indirect) evidence of bleeding. Bleeding was classified as major if it was overt and produced a fall in hemoglobin of at least 5 g/dL or 3.1 mmol/L, if it led to transfusion of 2 or more units of whole blood or packed cells, if it was retroperitoneal, or if it occurred into a major prosthetic joint space. Bleeding was classified as minor if it was overt but did not meet the criteria of major bleeding. Hematuria was classified as follows: macroscopic (ie, clinically evident), microscopic (more than four erythrocytes per high-power field in the urine sediment obtained from fresh, concentrated, clean voided urine specimen), or absent (absence of red cells or presence of less than four erythrocytes per high-power field). Intracranial hemorrhage: All cerebrovascular accidents occurring in patients receiving anticoagulant drug therapy were considered as intracranial hemorrhage unless CT scan of the brain unequivocally demonstrated an ischemic stroke.

False aneurysms and arteriovenous fistula necessitating transfusion and/or surgical treatment were reported as adverse events and bleeding complications.

The occurrence of all cardiac and noncardiac clinical events over an observational period of 7 months (death, MI, repeat intervention—percutaneous reintervention or CABG) was assessed. Death was defined as all deaths, regardless of cause. MI was diagnosed if there were new pathological Q waves according to the Minnesota Code[9] or if there was an increase in serum creatine kinase to more than twice the normal value, together with a pathological increase in myocardial isoenzymes. Bypass surgery was defined to include emergency or elective bypass surgery involving the previously treated segment. Emergency bypass surgery was defined as involving an immediate transfer from the interventional suite to the operating room during the initial phase of treatment. Repeat interventions were those involving the target lesion that followed the initial procedure. Revascularization (surgical or percutaneous) involving other coronary arteries did not constitute an end point.

Study Design

After stent implantation, heparin was reinstituted in a stepwise fashion. The study consisted of four phases in which a total of 203 patients were treated with a single stent (51, 51, 51, and 50 patients in each of the four phases). One attempt to implant a stent failed and resulted in the death of the patient; the remaining 202 patients successfully received a heparin-coated stent. Heparin infusion was started 6, 12, and 36 hours after sheath removal in the first three phases, respectively. In phase IV, no heparin or coumadin was given, but patients were treated with aspirin (>100 mg/d) and ticlopidine (250 mg/d).

The decision to proceed with the study from one phase to the next was based on a predetermined incidence of (sub)acute thrombotic stent occlusion. If three or more incidents of subacute stent thrombosis occurred in any phase (based on a 3.5% angiographically demonstrated subacute thrombosis rate in Benestent-I), the study had to be terminated.

Selection of Patients

Patients scheduled to undergo angioplasty because of stable angina due to a single de novo lesion in a coronary artery were eligible if they had no contraindication to anticoagulation or antiplatelet therapy and if they were suitable candidates for CABG. The target lesion was required to be less than 15 mm long and located in a vessel ≥3.0 mm supplying normally functioning myocardium. Patients having an ostial lesion or a lesion at a bifurcation or in a previously grafted vessel were excluded as well as patients in whom an intracoronary thrombus was suspected.

The study was carried out according to the Declaration of Helsinki. Written or witnessed oral informed consent according to the local practice was obtained for every patient.

Stent Coating

Palmaz-Schatz PS 153 coronary stents, 15 mm long with a central articulation, were coated with a modified version of the Carmeda Bioactive Surface (Carmeda AB).[10] The stainless steel stent was coated with base layers of polyethylene imine and dextran sulfate (Fig 1). Aldehyde-terminated heparin (porcine mucosal origin) was covalently bonded to the polyethylene imine surface layer.[11] After coating, the stents were washed in borate buffer and deionized water to remove unbound heparin. The efficacy of this coating is based on the continuous and repeated interaction between the active site of the immobilized heparin and circulating antithrombin III. The coated stents were mounted on 3.0-, 3.5-, and 4.0-mm polyethylene balloon delivery catheters with integral sheath (Johnson & Johnson Interventional Systems Co) and sterilized with ethylene oxide gas. The coating was optimized to provide a high level of antithrombin-III binding-site bioavailability, as measured by antithrombin-binding assay and expressed as picomoles (antithrombin III binding activity) per stent.

Medical Regimen

Beginning the day before the procedure, all patients received 250 to 500 mg of aspirin daily. This medication was continued for 6 months. Diltiazem 120 mg BID was continued until hospital discharge. In the first three phases, coumadin was given from the day of stent implantation for a period of 3 months. Heparin was administered as a bolus dose of 10 000 IU at the start of the procedure and reinstituted as a continuous infusion 6 hours (phase I), 12 hours (phase II), and 36 hours (phase III) after removal of the arterial sheath. Sheath removal took place when the activated partial thromboplastin time had fallen to below twice the normal value (normal range, 30 to 40 seconds). Heparinization was gradually decreased when the international normalized ratio was within the therapeutic range (2.5 to 3.5) for at least 36 hours. In phase IV, patients received ticlopidine (250 mg/d) for 1 month starting the day before the procedure. In this phase coumadin was not given and heparin 10 000 IU was administered only during the procedure. No heparin was administered after removal of the sheath. An additional outpatient visit at day 15 was planned for the patients recruited in phase IV to detect any abnormality in white blood cell count or liver enzyme elevation induced by ticlopidine. None was documented at 15 or 30 days in the 50 patients of phase IV.

Clinical and Angiographic Follow-up

Patients were seen at the outpatient clinic at 1, 3, and 6 months for an interview, physical examination, exercise testing, and ECG. One of the major drawbacks of studies on the prevention of coronary restenosis is that at follow-up the angiographic knowledge of coronary anatomy may influence the physician's therapeutic decision and artificially increase (or decrease) the number of repeat interventions. To circumvent this possible source of bias, a second intervention was considered an end point only when it was substantiated on the basis of anginal symptoms or objective evidence of ischemia. For that purpose, exercise testing was performed before the 6-month repeat catheterization. The objective signs of ischemia as well as the exercise protocols followed in the different participating centers were left to the discretion and judgment of the respective exercise testing laboratories.

Three angiograms were obtained for each patient—one immediately before the intervention, one immediately after, and one at follow-up. If a revascularization procedure involving the treated segment had been performed before the 6-month repeat angiography, the last angiogram obtained before this intervention was used as the follow-up angiogram irrespective of the timing of repeat intervention. If the time to follow-up angiography was less than 3 months and no repeat intervention was performed, the patient was asked to undergo another angiogram at 6 months. In the absence of a 6-month repeat angiogram, the last angiogram obtained within the previous 3 months, if available, was used provided that no end point had occurred.

All angiograms were analyzed by the Cardiovascular Angiography Analysis System and sent to the core laboratory (Cardialysis, Rotterdam, the Netherlands). To standardize the method of data acquisition and to ensure exact reproducibility of postintervention and follow-up angiograms, methodology was standardized as described previously.[12]

The quantitative analysis was applied to two different segment lengths of the treated coronary artery: the vessel analysis was applied to the segment located between two sizeable side branches that were used as landmarks to determine the length of the segment to be analyzed. If a lesion overlapped a side branch, the next side branch was taken as a landmark. The stent analysis was applied to the part of the vessel (stenotic and nonstenotic) actually stented. This dual type of analysis was deemed necessary because most of the vessels taper, and frequently after stenting the MLD is found to be outside the stented area. In each analyzed segment, a mean diameter, an MLD, and a reference interpolated diameter were determined. The stent/artery ratio was defined as the ratio between the mean diameter of the stent (stent analysis) and the RD (vessel analysis) predilatation. It quantifies correct stent deployment more appropriately than the measurement of the DS within the stent.

Statistical Analysis

The main clinical analysis consisted of the determination of the primary clinical end points in the time period between stent implantation and 30 days after the implantation; this analysis included all patients except those in whom no stent implantation had taken place.

The secondary clinical end point was evaluated by performing a total count of all clinical events (nonmutually exclusive) and by ranking these clinical events according to the highest category on a scale ranging from (1) death, (2) MI, (3) emergency CABG, (4) elective CABG, and (5) repeat PTCA.

The main angiographic analysis consisted of the determination of the MLD at follow-up of all patients in whom a stent had been implanted and whose angiogram was suitable for quantitative coronary angiography.

Discrete variables were expressed as counts and percentages. The χ^2 test with Yates' correction was used to compare proportions. Comparison of proportions was expressed as relative risks (for stenting compared with the historical series of Benestent-I), with 95% CIs calculated by the formula of Greenland and Robins.[13] Continuous variables were expressed as mean±SD and compared by the unpaired Student's *t* test. All statistical tests were two-tailed. A value of $P<.05$ was considered statistically significant.

Results

Study Population

Between February and November 1994, 207 patients were included in the Benestent-II Pilot Study. Phases I through IV enrolled 51, 55, 51, and 50 patients, respectively.

In phases I, III, and IV all the implantation procedures were successful. In one phase II patient, the ostium of a right coronary artery was dissected, mandating acute surgery. This patient died postoperatively from intractable arrhythmias and is included in the report. Four other patients from phase II were excluded from further analysis as they did not receive a stent. In 3 patients, the Stent Delivery System could not cross the lesion; they underwent an uneventful balloon angioplasty and were asymptomatic at follow-up. In 2 other patients there was a problem with removal of the Stent Delivery System sheath. One of these patients could not be stented, was dilated, and had an uneventful long-term outcome, and in the other a "bare" heparin-coated stent was implanted by removing the protective sheath prior to crossing of the lesion. This latter patient has been included in the evaluable population. Baseline clinical characteristics and lesion characteristics are displayed in Tables 1 and 2, respectively. For comparison, data on stented patients participating in the Benestent-I study are included in the tables (Tables 1 and 2).

Procedural Data

During the course of the study, on-line quantitative coronary angiography became increasingly used, in 53%, 63%, 59%, and 68% of cases analyzed during the four phases, respectively. In 12%, 8%, 20%, and 8% (phases I to IV) of the enrolled patients, intravascular ultrasound was used to guide the stent procedure. Dilatation after stenting to optimize final results was applied in 82%, 86%, 84%, and 92% of the patients in the four phases, respectively. Inflation pressure inferior to 12 atm was used in 57%, 29%, 33%, and 18%, whereas pressures greater than 12 atm were applied in 43%, 71%, 67%, and 82%, respectively. In all groups, a mean of 2.8 devices (stent included) were used to achieve an acceptable final result. Maximal balloon diameter (nominal size) increased from 3.56±0.40 mm to 3.55±0.36, 3.62±0.43, and 3.62±0.42 mm in the four respective phases. For comparison, in Benestent-I the mean maximal balloon diameter was 3.40±0.40 mm, which is significantly different from the overall balloon diameter used in Benestent-I (3.59±0.40 mm, $P<.0001$).

Acute Angiographic Results

In Table 3, data on preprocedural and postprocedural RD, MLD, and DS are given. When compared with Benestent-I (RD of 3.00 mm), a trend toward selecting patients with a larger RD was seen (3.17, 3.05, 3.22, and 3.19 mm in phases I to IV, respectively) as well as an increase in MLD after stenting (2.51 mm in Benestent-I versus 2.77, 2.76, 2.78, and 2.77 mm in the four consecutive phases of the present study). In phases I to IV a preprocedural RD of <3.0 mm was encountered in 40% of the 203 patients, an RD<2.75 mm in 15%, and an RD<2.5 mm in 3%. In

Fig 2 cumulative frequency curves of MLD and DS are represented for Benestent-I and the four pooled phases of Benestent-II. As mentioned in “Methods,” the stent/vessel size ratio (0%±9%, mean±SD) describes the appropriateness of stent deployment more adequately than the DS measured within the stent (18%±6%, mean±SD), which is presumably related to the small unscaffolded vessel area located at the site of the stent articulation.

Clinical Outcome in Hospital and at 30 Days

Stent thrombosis, clinically or angiographically demonstrated, did not occur in the hospital or during the first 30 days (primary objective). In phase II, 1 patient described above died after a failed attempt to deploy a stent. A cardiac enzyme rise (CPK: 349 IU [normal upper limit=190 IU]) was detected in 1 phase I patient as the result of a transient occlusion of a side branch. An additional stent had to be implanted in 7 patients (two coated and five noncoated stents) to cover a distal or proximal dissection. All the remaining patients were free of cardiac events during hospitalization and at 30 days. Bleeding complications requiring therapy fell from 7.9% in phase I to 5.9%, 4.0%, and 0% in the following three phases of the pilot study. Fig 3 details the type of bleeding complications encountered in the four phases of the pilot study as well as during the course of Benestent-I. Hospital stay was 7.4, 6.1, and 7.2 days in the first three phases when anticoagulation and heparin were still used and was reduced to 3.1 days once the anticoagulation regimen was replaced by an antiplatelet regimen.

6-Month Follow-up

Clinical Events At the 6-month follow-up visit, 3 patients had died. In phase I, 1 patient (No. 17) anticoagulated with antivitamin K (coumadin) died at 75 days from intracranial bleeding documented by a CT scan; another asymptomatic patient (No. 35) no longer anticoagulated with coumadin died at 6 months from intracranial bleeding also documented by CT scan while waiting for his repeat catheterization. In phase III, a symptomatic patient (No. 30) scheduled for a catheterization at 4 months died suddenly at home. In phase III, 1 patient (No. 23) still on anticoagulant treatment presented with a reversible ischemic neurological deficit diagnosed as an intracranial bleed by CT scan. Fortunately, he recovered without sequelae.

At follow-up, 2 patients were readmitted with persisting signs of acute ischemia. One patient in phase I (No. 4) sustained an acute anterior MI at 4 months with a CPK rise of 537 IU and later developed a Q-wave MI; the patient was acutely treated with a thrombolytic agent and urgently catheterized; coronary angiography revealed a patent stent with an intrastent defect suspected to be a thrombus. One patient in phase IV (No. 38) presented at 2 months with signs of acute anterior infarction; thrombolytics were administered and the maximal rise in CPK was 271 IU (normal upper limit=110 IU); no Q wave developed, and catheterization did not disclose any angiographic abnormality within the stent or in the stented vessel.

Finally, at the time of the 6-month angiographic follow-up, an iatrogenic dissection of the left main stem occurred with subsequent occlusion of the vessel. The dissection was successfully stented and the patient was referred for emergency surgery. In the postoperative phase, elevation of the creatine kinase enzyme to 2700 IU was observed, but no Q wave developed on a 12-lead ECG.

At the 6-month follow-up, 21 reinterventions for revascularization (19 percutaneous, 2 surgical) were performed. Table 4 summarizes clinical events ranked in the following order: death, intracranial hemorrhage or cerebrovascular accident, Q-wave and non–Q-wave MI, urgent CABG, elective CABG, and repeat PTCA.

Quantitative Angiography at Follow-up and Exercise Testing At the 6-month follow-up, repeat catheterization and quantitative angiography were obtained in 192 patients, 97% of the eligible population. Two additional patients had their repeat angiography at 9 and 12 months, outside the time window (6 months±4 weeks) allotted by the protocol for the angiographic follow-up; their angiographic results were therefore not included in the results although both had a DS<50% with an MLD of 2.75 and 2.51 mm, respectively. The actual angiographic follow-up is thus 98% of the eligible cases. The results of the angiographic follow-up are tabulated in Table 3; the overall RR for the pooled patients of the four phases is 13%, which is statistically lower (relative risk, 0.65 [0.42 to 1.02]) than the RR of 20% observed in the stent group of the Benestent-I trial, which has similar inclusion criteria.

Although the preprocedural MLD, the acute gain, and the MLD after stenting were almost identical in each phase, important variations of the RRs between the four phases were observed with a recurrence of 15% in phase I, 20% in phase II, 11% in phase III, and 6% in phase IV. Accordingly, similar variations from phase to phase in loss, net gain, and loss index are shown in Table 3.

Prior to the repeat catheterization, 172 of 192 eligible patients (90%) performed an exercise test. This exercise test was required by the protocol to justify prospectively any intervention that might otherwise have been driven primarily by the angiographic findings. Only 2 patients (with a DS of 52% and 55%, respectively) among the 21 patients who underwent either a surgical (n=3) or a percutaneous (n=18) reintervention for revascularization might possibly have been redilated unnecessarily.

Conversely, “treatment denial” can be suspected in 3 patients who had a positive exercise test and a DS>50% and did not undergo a reintervention.

The overall rate of percutaneous reintervention on the target lesion for the four phases was 8.9% (n=18 patients).

At 6 months, 84%, 75%, 94%, and 92% of the patients of phases I to IV were event free. When pooled, 86% of the patients were event free, which compares favorably with the event-free survival (80%) of the patients enrolled in the stent group (n=259) of the Benestent-I trial (relative risk, 0.68 [0.45 to 1.04]) (Table 4, Fig 4).

Discussion

Principles of Heparin Surface Modification

The principles of heparin coating have been previously described[7] and are briefly summarized here. Contact of blood with a foreign surface results in a multiplicity of phenomena including competitive deposition of protein and other blood components and activation of the clotting cascade and complement system.[14] [15] These events can lead to formation of thrombus on the stent surface. To minimize thrombus, the surface of the Palmaz-Schatz stent is made microscopically smooth and is passivated by electropolishing. Nevertheless, stent thrombosis remains a potential problem, particularly in smaller vessels and in situations such as acute MI or total vessel occlusion. A number of materials have therefore been evaluated in vitro and in vivo as potential thromboresistant stent coatings. These include hydrogels, polyurethanes, and other materials developed specifically as thromboresistant surfaces. The end-point–attached heparin surface proved to be significantly superior in these models and was consequently used for the Benestent-II study reported here.

It has been shown that heparin-like molecules with anticoagulant activity are synthesized on the luminal surface of endothelial cells.[16] [17] Indeed, the endothelium plays an important part in the inactivation of thrombin and possibly other coagulation factors. Not unexpectedly, therefore, heparin has been one of the most extensively explored substances for absorption or binding to the surface of biomaterials. Heparin-coated surfaces have been evaluated in various types of devices where thromboresistance might be of particular clinical value, eg, arteriovenous shunts, catheters, arterial filters, oxygenators, cardiopulmonary bypass circuits, and vascular endoprostheses.[18] [19] [20] [21] [22]

The principal anticoagulant mechanism of heparin is its interaction with antithrombin-III, accelerating the inactivation of thrombin and other coagulation factors. It has been shown that the active site of heparin contains a specific carbohydrate sequence.[23] [24] [25] When the heparin molecule is modified by the process of surface coating, it is essential that the active sequence responsible for anticoagulation remains unaltered. The simplest solution for binding heparin to a surface is adsorbing a heparin solution to the biomaterial surface.[26] A problem with this type of coating is the lack of control of the rate of release; the heparin molecule contains a large number of negatively charged groups and may therefore be ionically or electrostatically bound to surfaces with positive charges.[27] [28] [29] Another principle is to incorporate heparin molecules into a polymer, either to make heparin a permanent component of the polymer (“surface-grafted” heparin)[30] or to provide a controlled release of heparin upon introduction into the bloodstream.[31] [32] Since heparin is a highly charged and hydrophillic polymer, the binding has to be prepared by pretreatment of the surface to be coated with reactive groups (“functionalizing”). In the early development of heparin coatings, a reduction of heparin activity was frequently observed when the molecules were covalently attached to the surface, probably due to alteration of the active carbohydrate sequence during the linking process.[33] It was found that this problem was circumvented if heparin was coupled by end-point attachment.[34] [35] The first step in this procedure is partial degradation of heparin with nitrous acid, creating reactive terminal aldehyde groups. In 1983 it was shown by Larm et al[33] that heparin fragments could be immobilized by end-point attachment on materials coated with polyethylenemine. The aldehyde group was subsequently coupled to the aminated surface by reductive amination. By this method, the active carbohydrate sequence of the heparin molecule could be preserved functionally intact throughout the coupling reaction.

In addition to being compatible with the plasma coagulation system, a thromboresistant surface should not promote adhesion and activation of platelets and leukocytes. Because heparin has been reported to induce platelet activation,[35] this consequence might be expected with surface-immobilized heparin as well. However, it has been shown that in comparison with uncoated material, the surface with end-point–attached heparin on a high-molecular-weight polyamine stabilized with glutaraldehyde is highly compatible with platelets as well as granulocytes and macrophages.[9] [36]

The principle of perpendicularly oriented, end-attached, covalently bound, and immobilized heparin molecules on a polymer surface (Carmeda Bioactive Surface, Carmeda AB) was considered to be the best technique for coating of coronary stents. A new “CH5” coating, a special form of the Carmeda Bioactive Surface, was developed, allowing higher heparin activity on the stent surface.

In vitro and in vivo studies of thromboresistance of the heparin-coated stent, as summarized at the beginning of this article, formed the basis for implantation in humans in this Benestent-II pilot study.

Rationale for the Trial Design

The primary goal of this registry was to demonstrate the feasibility and the safety of implantation of a heparin-coated stent. The design and the objectives of this trial reflect the state of the art in stenting in 1993. At that time, the Benestent-I trial was close to completion and it was already recognized that the rate of subacute occlusion (3.5%) was not negligible, that the incidence of bleeding complications (13.9%) was substantial, and that the length of in-hospital stay (8.3 days) was not acceptable.

It was evident that these three major drawbacks of the treatment had to be eliminated to render this new modality of angioplasty widely applicable. A thromboresistant, or at least a less-thrombogenic stent, was conceptually an appealing solution to the above-mentioned limitations. On the other hand, around the same period a pharmacological regimen after stenting different from the conventional approach was introduced by French practitioners[37] : the use of intravenous heparin and oral antivitamin K was progressively replaced by subcutaneous low-molecular-weight heparin and administration of ticlopidine. Subsequently, registries demonstrated a favorable impact of this regimen on subacute thrombosis and bleeding.[38] Around the same period, Colombo and his colleagues[39] also reported their experience with ultrasound-guided stent deployment without anticoagulation; they attributed subacute thrombotic occlusion of the stent to inappropriate and incomplete deployment, emphasizing the need for almost perfect normalization of the intrastent rheology to prevent subacute occlusion.[4] Ticlopidine was nevertheless also incorporated in their treatment after stenting. It is therefore understandable that the investigators in the Benestent-II Pilot Study agreed to test the new heparin-coated stent provided the anticoagulant was replaced by an antiplatelet drug such as ticlopidine. The dosage of ticlopidine (250 mg/d) and the timing of administration (within 12 hours of the procedure) selected for this trial are based on the favorable clinical experience of the French registry and are at variance with the recommendations of the pharmaceutical industry, which, on the basis of their pharmacokinetic studies, would advise a BID administration (500 mg/d) preceding the stent procedure by 72 hours.[40]

In addition to this safety issue, concerns also were expressed about potential inflammatory reactions that might be induced by the polymeric coating of the stent, although animal experiments had been most reassuring on that point.[7] For all these reasons, the trial was cautiously phased with a stepwise postponement of the heparin infusion and replacement of the anticoagulation by antiplatelet regimen combining ticlopidine and aspirin to prevent subacute occlusion while reducing the bleeding complications and the length of the in-hospital stay. In designing the pilot study as well as the randomized trial (currently underway), we have adopted a very practical and pragmatic approach: a presumably thromboresistant stent is used in conjunction with two antiplatelet drugs. Our goal was clearly not to demonstrate the intrinsic value of the thromboresistance of the heparin-coated stent but rather to evaluate from a cost-effectiveness point of view a combined therapy of device and drugs by comparison with a strategy of conventional balloon angioplasty.

A specific demonstration of the thromboresistant properties of the heparin-coated stent might require either a large double-blind randomized trial or the evaluation of the coated stent versus an uncoated version in a very thrombogenic environment such as unstable angina, impending infarction, or even evolving MI, so that the beneficial thromboresistant properties of the heparin-coated stent may become manifest. These latter trials are currently in the planning stage.

Have the Thromboresistant Properties of the Heparin-Coated Stent Been Demonstrated?

We have to emphasize that the favorable short- and long-term outcome observed in the pilot study is multifactorial: careful selection of the patient with vessel size slightly larger than in the Benestent trial, better techniques of implantation partially guided by either on-line quantitative angiography or intravascular ultrasound resulting in a large postprocedure MLD, and use of two antiplatelet drugs of which the synergic action is presumably beneficial.[41 42]

We are therefore not entitled to make any scientific statement on the specific merits of this thromboresistant stent. Currently our knowledge on the thromboresistant properties of this stent mainly originates from in vitro, ex vivo, and animal experiments, and it can only be assumed that these thromboresistant properties are “operational” in our patients. Although it is tempting to compare the overall results of the four phases of the Benestent-II pilot with the outcome of the stent group in Benestent-I, we must bear in mind that this type of comparison is a post hoc analysis, partially invalidated by small differences in baseline characteristics and in procedural treatment. In particular it must be pointed out that the vessel sizes of the selected patients in the Benestent-II pilot were slightly but statistically larger than in Benestent-I; we have previously demonstrated that larger vessel size in itself is an independent determinant of reduction in loss in MLD at follow-up.[43]

Obviously, a significantly higher procedural gain due to better techniques of deployment resulted in a larger postprocedural MLD, which is known to be a major determinant of the MLD at follow-up. Identification of the major determinants of the MLD at follow-up have been derived from multivariate analysis performed on the stent population of the Benestent-I trial.[44] If the current vessel size (VS=3.16 mm) recorded in the pilot study and the MLD postprocedure (2.77 mm) as well as the nature of the treated vessel (LAD 56%) are incorporated in the multivariate analysis derived from Benestent-I (MLD at follow-up=−0.26+0.47×MLD post+0.35×VS (pre)−0.11×LAD), then it appears that the predicted MLD at follow-up (2.08 mm) is in fact identical to the MLD at follow-up observed in the pilot study of Benestent-II (2.08 mm).

In other words, presently there is no compelling evidence indicating that the heparin coating is actively affecting the neointimal hyperplasia within the stent. However, it should be pointed out that the low RR and loss index observed in this series at least indicate that the polymeric coating used in the clinical trial does not induce an excess of intimal hyperplasia, a reaction frequently observed in animal experiments with a variety of biodegradable or nonbiodegradable polymers previously tested.[45]

Conversely, the variation in RR from phase to phase does not necessarily have to be interpreted in biological terms. From a purely statistical point of view, these variations may be simply explained in probabilistic terms: sequential statistical analyses of RRs in four cohorts of 50 patients are compatible with a range of RRs varying between 8.3% and 17.8% (95% CIs) in the case of an overall RR of 13%. Interestingly, however, the RR of phase IV (6%) falls outside the 95% CIs.

Benestent-II Pilot Study as a Preamble to the Benestent-II Trial

The ultimate goal of the substantive Benestent-II trial will be to investigate the efficacy and cost-effectiveness of a strategy of elective stenting versus a treatment with conventional balloon angioplasty; the use of a heparin-coated stent in combination with two antiplatelet drugs as adjunctive therapy represents a pragmatic approach that has apparently eliminated the risk of subacute occlusion and bleeding complications as well as the need for a prolonged stay in the hospital; thus, the heparin-coated stent should be viewed as a safety net for the interventional cardiologist. In other words, the pilot study must be viewed strictly as a preamble to the

randomized Benestent-II trial, the goal of which will be mainly economic: the cost-effectiveness assessment of stenting versus balloon angioplasty.

Conclusions

The postponement of heparin treatment to 6, 12, and 36 hours after sheath removal has not resulted in (sub)acute occlusions in these patients treated with antivitamin K (coumadin). A trend toward less bleeding and fewer peripheral vascular complications was observed. Heparin-coated stents are well tolerated. No thrombogenic, allergic, toxic, or immunologic side effects were observed.

The absence of (sub)acute occlusion as well as the virtual disappearance of bleeding and peripheral vascular complications in phase IV (ticlopidine and aspirin only) confirm the feasibility of conducting a randomized trial testing the clinical value of this new stent coating, as well as the innocuous nature of the new posttreatment regimen.

The very low rate of restenosis observed in phase IV seems promising and needs confirmation in a larger randomized approach.

Appendix

The following institutions and investigators participated in the Benestent-II Pilot Study. The number of patients enrolled at each center is given in parentheses.

Erasmus University, Thoraxcenter, Rotterdam, the Netherlands (16): P.W. Serruys, P. de Jaegere, P. Ruygrok; Sahlgrenska Hospital, Goteborg, Sweden (14): H. Emanuelsson, P. Albertsson; University Hospital San Carlos, Madrid, Spain (13): C. Macaya, F. Alfonso, J. Goicolea, R. Hernandez, A. Iniguez; Rudolph Virchow, Berlin, Germany (12): W. Rutsch; OLVZ, Aalst, Belgium (11): G. Heyndrickx, B. de Bruyne, W. Wijns; Ziekenhuis De Weezenlanden, Zwolle, the Netherlands (10): H. Suryapranata, J. Hoorntje; Sart Tilman, Liège, Belgium (10): V. Legrand; CHUV, Lausanne, Switzerland (9): J. Goy, E. Eeckhout; La Citadelle, Liège, Belgium (9): P. Materne, J. Boland; Catharina Ziekenhuis, Eindhoven, the Netherlands (9): H. Bonnier, J. Koolen; CCN, Paris, France (8): M.C. Morice; Clinique Pasteur, Toulouse, France (8): J. Marco, J. Fajadet, P. Brunell; Instituto Cardiovascular, Buenos Aires, Argentina (7): J. Berlardi, R. Piraino; Centro Cuore Columbus, Milan, Italy (7): A. Colombo; Gregorio Marañon, Madrid, Spain (7): E. Garcia, J. Delcan; Ospedale Maggiore, Trieste, Italy (6): S. Klugmann, E. Della Grazia, A. Salvi; St. James, Dublin, Ireland (6): P. Crean; Middelheim, Antwerp, Belgium (6): P. van den Heuvel, F. van den Brande; St. Luc, Brussels, Belgium (5): C. Hanet; RBNHBLI, London, United Kingdom (5): U. Sigwart; Christian-Albrecht University, Kiel, Germany (5): R. Simon, M. Lins; OLVG, Amsterdam, the Netherlands (4): F. Kiemeneij, G.J. Laarman; CHUR, Nancy, France (4): N. Danchin; St. Antonius, Nieuwegein, the Netherlands (4): G. Mast, T. Plokker; Hopital Kantonal, Geneva, Switzerland (3): P. Urban; Academic Hospital, Groningen, the Netherlands (3): P. den Heijer; Instituto Dante Pazzanese, Sao Paulo, Brazil (3): E. Sousa; Ziekenhuis De Klokkenberg, Breda, the Netherlands (3): H. te Riele; Polyclinique Volney, Rennes, France (2): C. Bourdonnec; AMC, Amsterdam, the Netherlands (1): K. Koch, J. Piek; Franz-Volhard Klinik, Berlin, Germany (1): D. Gulba; Hopital Cochin, Paris, France (1): C. Spaulding; University Essen, Essen, Germany (1): M. Haude.

Steering Committee: Patrick W. Serruys (Chairman), Håkan Emanuelsson, Stan Rowe. *Critical Event Committee:* Pim de Feyter, Paul van den Heuvel. Coordinating Center, Cardialysis BV, Rotterdam, the Netherlands: Aida Azar, Gerrit-Anne van Es, Linda Goderie, Marie-Angèle Morel.

Angiographic Core Laboratory, Cardialysis BV, Rotterdam, the Netherlands: Diny Amo, Marcel van den Brand, David Foley, Ina Hoekman. *Safety Committee:* Jan Tijssen, Freek Verheugt.

Selected Abbreviations and Acronyms

CABG	=	coronary artery bypass graft surgery
CI	=	confidence interval
CPK	=	creatine phosphokinase
CT	=	computed tomographic
DS	=	diameter stenosis
LAD	=	left anterior descending coronary artery
MI	=	myocardial infarction
MLD	=	mean luminal diameter
PTCA	=	percutaneous transluminal coronary angioplasty
RD	=	reference diameter
RR	=	restenosis rate
TIMI	=	Thrombolysis in Myocardial Infarction

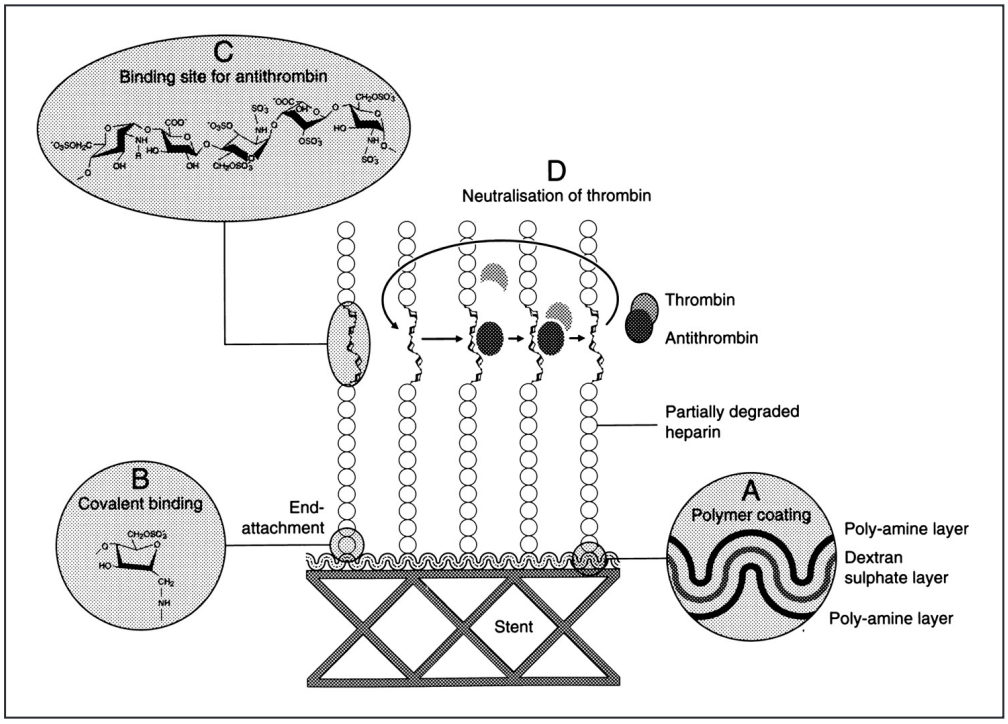

Figure 1. Schematic illustrations of the prominent features of a heparin-coated stent. A, The stent is coated with a polymer made of multiple layers of polyamine and dextran sulphate; B, depolymerized molecules of heparin are covalently bound to this polymer and the nature of the covalent binding is described; C, pentasaccharide constituting the binding site for antithrombin of each heparin molecule is depicted; and D, continuous neutralization cycle of thrombin is illustrated.

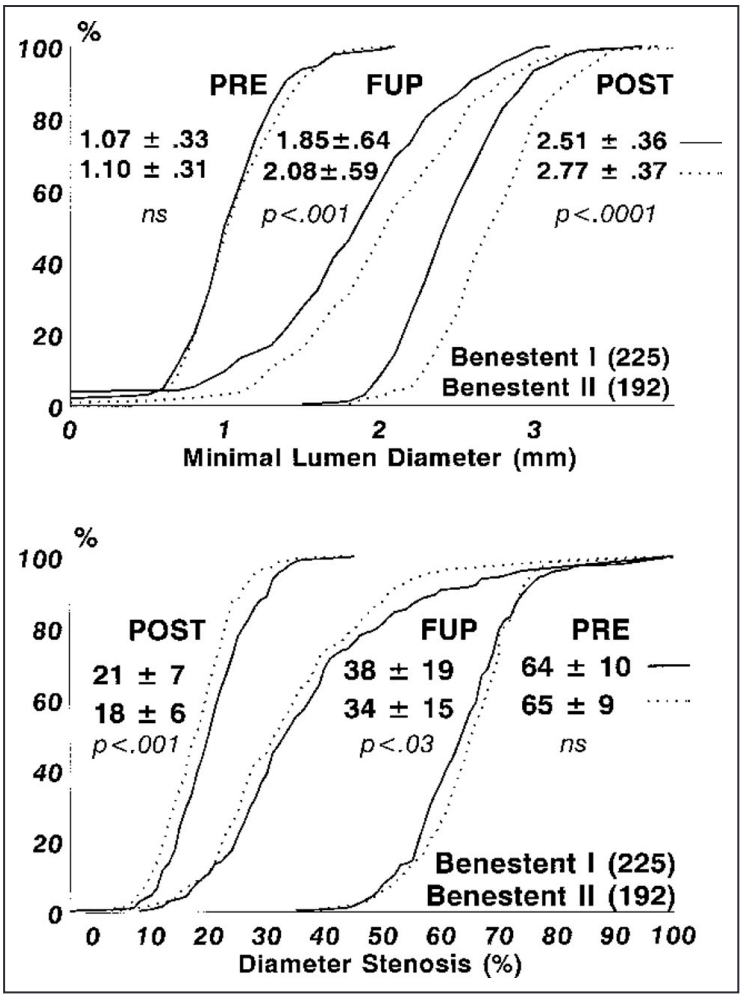

Figure 2. Cumulative distribution curve for MLD (top) and DS (bottom) before and after stenting and at 6-month follow-up. —— indicates Benestent-I; – – –, Benestent-II.

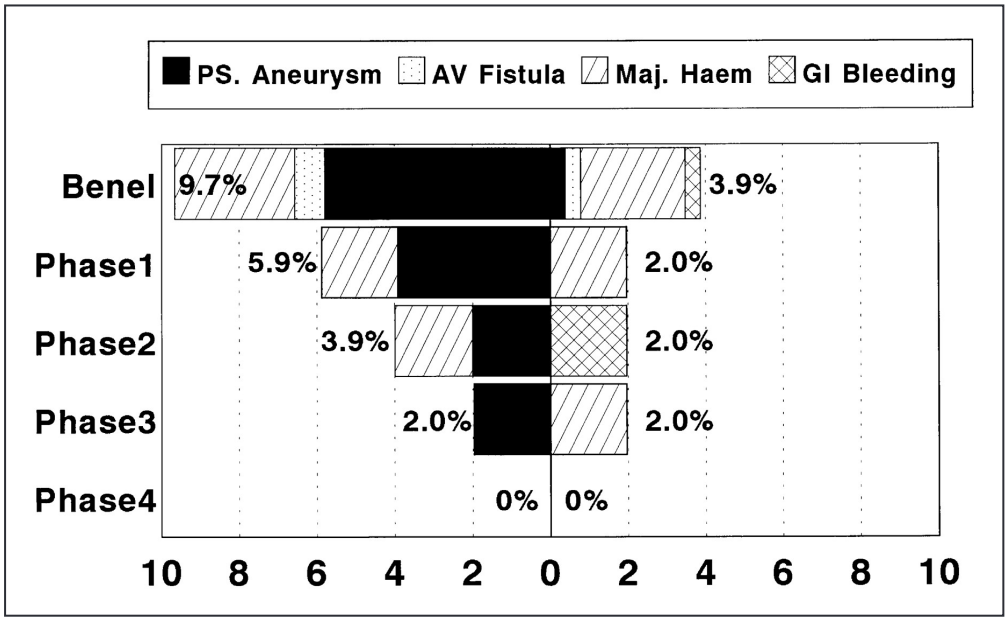

Figure 3. Frequency and types of bleeding complications necessitating therapy encountered during the four phases of the pilot study and the Benestent-I study. The left side shows the incidence of bleeding complications necessitating vascular surgery and the right side shows the incidence of bleeding complications necessitating blood transfusion. PS indicates pseudo; AV, arteriovenous; Maj, major; haem, hematoma; and GI, gastrointestinal.

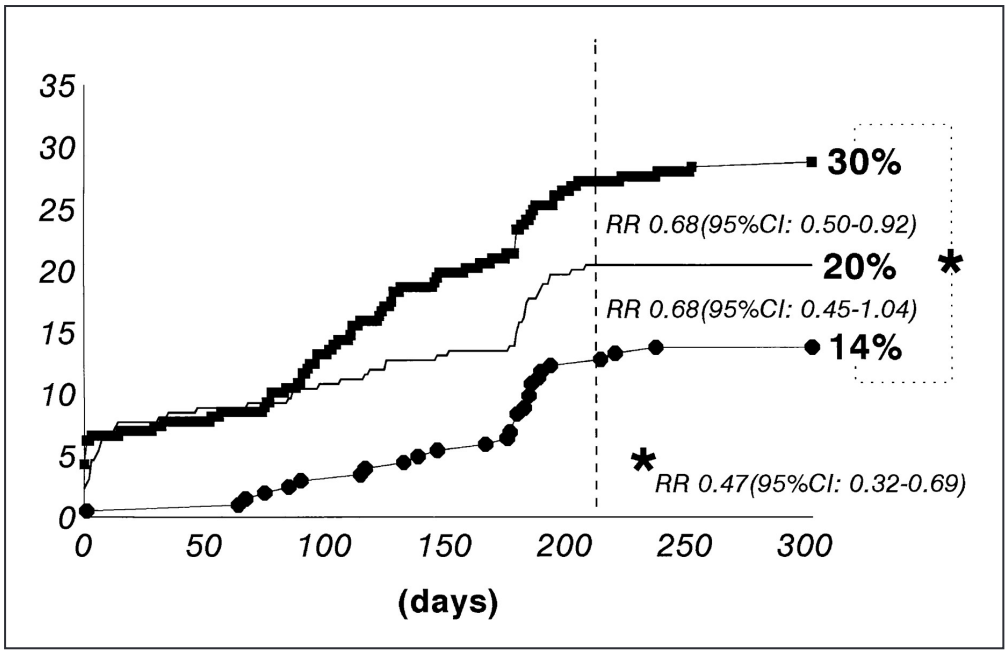

Figure 4. Cumulative distribution curves for clinical events up to 210 days in the Benestent-I trial balloon angioplasty (▪) and stent groups (——) as well as in the patients in the Benestent-II pilot trial (•). RR indicates relative risk.

Table 1. Baseline Demographic Characteristics (Table view)

	Benestent-I (n=225)	*P*	Benestent-II (n=203)	Phase I (n=51)	Phase II (n=51)	Phase III (n=51)	Phase IV (n=50)
Male, %	80	NS	84	88	76	82	88
Age, y	57 ±9	NS	58±10	60±10	60±9	58 ±9	54±11
CCS I, %	4	<.01	9	4	11	9	11
CCS II, %	35	<.01	44	52	44	36	43
CCS III, %	54	<.01	40	37	42	51	30
CCS IV, %	7		6	2	2	4	14
Mixed, %	34	NS	31	24	36	31	34
MI, %	20	NS	23	10	25	35	20
CABG, %	0	<.01	3	6	2	4	2
PTCA, %	2	<.05	6	8	10	6	2
Diabetes, %	7	NS	8	8	12	6	8
Hypertension, %	31	NS	29	24	39	24	28
Cholesterol, %	35	NS	36	35	41	31	36
Smoker							
Previous	46	NS	37	39	33	25	50
Current	24	NS	29	22	29	37	26

CCS indicates Canadian Cardiovascular Society.
The χ^2 test with Yates' correction was used to compare proportions.

Table 2. Lesion Characteristics (Table view)

	Benestent-I (n=225), %	*P*	Benestent-II (n=203), %	Phase I (n=51), %	Phase II (n=51), %	Phase III (n=51), %	Phase IV (n=50), %
Concentric[1]	50		23	28	22	41	20
Eccentric	43		71	64	74	53	74

	Benestent-I (n=225), %	*P*	Benestent-II (n=203), %	Phase I (n=51), %	Phase II (n=51), %	Phase III (n=51), %	Phase IV (n=50), %
Tandem	1	.05	3	4	4	0	2
Multiple irregularities	6	.05	3	4	0	4	4
Calcified	11	NS	9	8	6	10	12
LAD	63	NS	57	51	55	61	60
LCx	13	NS	11	8	16	12	10
RCA	23	<.05	32	41	29	27	30
TIMI 0	<1	<.001	1	0	2	0	0
TIMI I	<1	<.001	2	2	0	2	2
TIMI II	1	<.001	9	10	12	6	8
TIMI III	98	<.001	89	88	86	92	90

[1] According to the classification system of Ambrose et al.[46]
LCx indicates left circumflex coronary artery; RCA, right coronary artery.
The χ^2 test with Yates' correction was used to compare proportions.

Table 3. Acute and Long-term Angiographic Results (Table view)

	Benestent-I (n=225)			Benestent-II (n=203)			Phase I (n=47)	
	Pre	Post	Follow-up	Pre	Post	Follow-up	Pre	Post
RD, mm	3.00±0.44	3.17±0.42	2.97 ±0.48	3.16±0.41[2]	3.38±0.37[2]	3.14±0.46[2]	3.17 ±0.42	3.41±0.3
MLD, mm	1.07±0.33	2.51 ±0.36	1.85±0.64	1.10±0.31[5]	2.77±0.37[2]	2.08 ±0.59[2]	1.11±0.25	2.77±0.3
DS, %	64 ±10	21±7	38±19	65±9[5]	18±6[2]	34±15[3]	65 ±8	19±6
Stent/artery ratio, %[1]		1 ±10			0±9			0±10
RR, %			20			13[4]		
Gain, mm			1.44±0.42			1.67 ±0.38[2]		
Loss, mm			0.66 ±0.58			0.68±0.50[5]		
Net gain, mm			0.78±0.66			0.97±0.59[2]		
Loss index			0.46±1.39			0.41 ±1.18[5]		

Reference values are the interpolated diameters of normal vessels; Gain, the MLD after the procedure minus the value obtained before the procedure; Loss, the MLD after the procedure minus the follow-up value; Net gain, the MLD at follow-up minus the value obtained before the procedure; and Loss index, the late loss divided by the acute gain.

[1] Ratio between the mean diameter of the stent (stent analysis) and the reference diameter (vessel analysis) predilatation×1/100.

[2] *P*<.001 with respect to the equivalent measurement of lesions analyzed in Benestent-I (per protocol analysis[44]).

[3] *P*<.02 with respect to the equivalent measurement of lesions analyzed in Benestent-I (per protocol analysis[44]).

[4] *P*=.08 with respect to the equivalent measurement of lesions analyzed in Benestent-I (per protocol analysis[44]).

[5] *P*=NS.

Table 4. Frequency of Major Adverse Clinical Events at 1 and 7 Months in Descending Order of Severity (Table view)

	Benestent-I (n=257), %	Relative Risk, 95% CI	Benestent-II (n=203), %	Phase I (n=51), %	Phase II (n=51), %	Phase III (n=51), %	Phase IV (n=50), %
Death							
At 30 d	0	…	1 (0.5)	0	1 (2.0)	0	0
At 7 mo	2 (0.8)	2.53 (0.47-13.7)	4 (2.0)	2 (4.0)	0	1 (2.0)	0
All events	2 (0.8)	2.53 (0.47-13.7)	4 (2.0)	2 (4.0)	2 (2.0)	1 (2.0)	0
Cerebrovascular accident							
At 30 d	0	…	0	0	0	0	0
At 7 mo	0	…	1 (0.5)	0	0	1 (2.0)	0
All events	0	…	3 (1.5)	2 (4.0)	0	1 (2.0)	0
Q-wave MI							
At 30 d	5 (1.9)	…	0	0	0	0	0
At 7 mo	7 (2.7)	0.18 (0.02-1.46)	1 (0.5)	1 (2.0)	0	0	0
All events	7 (2.7)	0.18 (0.02-1.46)	1 (0.5)	1 (2.0)	0	0	0
Non–Q-wave MI							
At 30 d	4 (1.5)	…	0	0	0	0	0
At 7 mo	4 (1.5)	0.63 (0.12-3.42)	2 (1.0)	1 (2.0)	0	0	1 (0.5)
All events	4 (1.5)	0.63 (0.12-3.42)	2 (1.0)	1 (2.0)	0	0	1 (0.5)
Urgent CABG							
At 30 d	5 (1.9)	…	0	0	0	0	0
At 7 mo	5 (1.9)	…	0	0	0	0	0
All events	6 (2.3)	0.21 (0.03-1.74)	1 (0.5)	0	1	0	0
Elective CABG							
At 30 d	3 (1.2)	…	0	0	0	0	0
At 7 mo	8 (3.1)	0.32 (0.07-1.47)	2 (1.0)	0	2 (4.0)	0	0
All events	10 (3.9)	0.38 (0.11-1.36)	3 (1.5)	1	2 (4.0)	0	0
Repeat PTCA							
At 30 d	1 (0.4)	…	0	0	0	0	0
At 7 mo	26 (10.0)	0.85 (0.48-1.50)	18 (8.9)	4 (7.8)	10 (20.0)	1 (2.0)	3 (6.0)
All events	35 (13.5)	0.65 (0.38-1.11)	18 (8.9)	4 (9.8)	10 (20.0)	1 (2.0)	3 (6.0)
Any event							
At 30 d	18 (6.9)	0.07 (0.01-0.52)	1 (0.5)	0	1 (2.0)	0	0
At 7 mo	52 (20.1)	0.68 (0.45-1.04)	28 (13.9)	8 (15.7)	13 (25.5)	3 (5.9)	4 (8.0)

"All events" refers to the total count of events at 7 months (ie, if a patient required repeat angioplasty and later CABG, the total count at 7 months would reflect both events, not just the first that occurred).

Table 3B. Continued (Table view)

Phase II (n=50)			Phase III (n=48)			Phase IV (n=47)		
Pre	Post	Follow-up	Pre	Post	Follow-up	Pre	Post	Follow-up
3.05±0.36	3.33±0.34	2.96 ±0.38	3.22±0.46	3.42±0.36	3.21±0.47	3.19 ±0.41	3.38±0.46	3.18±0.56
1.09±0.34	2.76 ±0.35	1.82±0.59	1.13±0.29	2.78±0.35	2.24 ±0.59	1.09±0.35	2.77±0.42	2.15±0.62
64±10	17 ±7	39±17	65±7	18±6	31±12	66±11	18 ±6	32±15
	−1±8			0±8			1±11	
		20			11			6
		1.67±0.33			1.67±0.29			1.68±0.49
		0.94±0.51			0.55±0.44			0.58±0.51
		0.73±0.58			1.11±0.52			1.07±0.67
		0.56±1.52			0.33±1.55			0.34 ±1.32

I

Article Information

Received November 28, 1995; revision received December 13, 1995; accepted December 13, 1995; published online February 1, 1996.

Correspondence

Correspondence to Prof P.W. Serruys, MD, PhD, Thoraxcenter, Department of Interventional Cardiology, Erasmus University, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands.

Affiliations

From the Thoraxcenter, Department of Interventional Cardiology, Erasmus University, Rotterdam, Netherlands. .

References

1. Serruys PW, Beatt KJ, Van der Giessen WJ. Stenting of coronary arteries: are we the sorcerer's apprentice? *Eur Heart J.* 1989;*10*:774-782. Crossref. PubMed.
2. Serruys PW, Strauss BH, Van Beusekom HMM, van der Giessen WJ. Stenting of coronary arteries: has a modern Pandora's box been opened? *J Am Coll Cardiol.* 1991;*17*:143B-154B. PubMed.
3. Serruys PW, De Jaegere P, Kiemenij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy J, van den Heuvel P, Delcan J, Morel M. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med.* 1994;*331*:489-495. Crossref. PubMed.
4. Serruys PW, Di Mario C. Who was thrombogenic: the stent or the doctor? *Circulation.* 1995;*91*:1891-1893. Crossref. PubMed.
5. Bailey SR, Paige S, Lunn AC, Palmaz J. Heparin coating of endovascular stents decreases subacute thrombosis in a rabbit model. *Circulation*. 1992;86(suppl I):I-186. Abstract.

6. Stratienko AA, Zhu D, Lambert CR, Palmaz J, Schatz RA, Santamore WP. Improved thromboresistance of heparin-coated Palmaz-Schatz coronary stents in an animal model. *Circulation*. 1993;88(Pt 2):I-596. Abstract.
7. Emanuelsson H, Van der Giessen WJ, Serruys PW. Benestent II: back to the future. *J Interven Cardiol.* 1994;*7*:587-592. Crossref. PubMed.
8. Hårdhammer PA, Van Beusekom H, Emanuelsson HV, Hofma SH, Albertsson PA, Verdouw PD, Boersma E, Serruys PW, Van der Giessen WJ. Reduction of thrombotic events using heparin-coated Palmaz-Schatz stents in normal porcine coronary arteries. *Circulation.* 1996;*93*:423-430. Crossref. PubMed.
9. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsars R. The electrocardiogram in population studies: a classification system. *Circulation.* 1960;*21*:1160-1175. Crossref. PubMed.
10. Hoffman AS, Schmer G, Harris C, Kraft WG. Covalent bonding of biomolecules to radiografted hydrogels on inert polymer surfaces. *Trans Am Soc Artif Intern Organs.* 1972;*18*:10-16. Crossref. PubMed.
11. Larm O, Larsson R, Olsson P. Surface-immobilized heparin. In: Lane DA, Lindahl U, eds. *Heparin: Chemical and Biological Properties, Clinical Applications*. London, UK: Edward Arnold Press; 1989;99:597-608.
12. Serruys PW, Foley DP, De Feyter PJ, eds. *Quantitative Coronary Angiography in Clinical Practice*. Dordrecht, the Netherlands: Kluwer Academic; 1994.
13. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics.* 1985;*41*:55-68. Crossref. PubMed.
14. Hastings GW, ed. *Cardiovascular Biomaterials*. London, UK: Springer-Verlag; 1992.
15. Eloy R, Belleville J. Biomaterial-blood interaction. In: Williams D, ed. *Concise Encyclopedia of Medical and Dental Materials*. Elmsford, NY: Pergamon Press; 1990:74-85.
16. Marcum JA, Rosenberg RD. Heparin-like molecules with anticoagulant activity are synthesized by cultured endothelial cells. *Biochem Biophys Res Commun.* 1985;*126*:365-372. Crossref. PubMed.
17. Awbrey B, Hoak JC, Owen WG. Binding of human thrombin to cultured human endothelial cells. *J Biol Chem.* 1979;*254*:4092-4095. Crossref. PubMed.
18. Lelah MD, Lambracht LK, Cooper SL. A canine ex vivo series shunt experiment for evaluating thrombus deposition on polymer surfaces. *J Biomed Mater Res.* 1984;*18*:475-496. Crossref. PubMed.
19. Von Segesser LK, Turina M. Cardiopulmonary bypass without systemic heparinization. *J Thorac Cardiovasc Surg.* 1989;*98*:386-396. Crossref. PubMed.
20. Palanzo DA, Kurusz M, Butler BD. Surface tension effects of heparin coating on arterial line filters. *Perfusion.* 1990;*5*:277-284. Crossref. PubMed.
21. Taylor KM, Von Segesser LK, Weiss BM, Gallino A, Leskosek B, Redha F, Von Felten A, Turina M. Superior hemodynamics in left heart bypass without systemic heparinization. *Eur J Cardiothorac Surg.* 1990;*4*:384-389. Crossref. PubMed.
22. Hsu L-C. Principles of heparin-coating techniques. *Perfusion.* 1991;*6*:209-219. Crossref.
23. Lindahl U, Bäckström G, Höök M, Thunberg L, Linker A. Structure of the antithrombin-binding site in heparin. *Proc Natl Acad Sci U S A.* 1979;*76*:3198-3202. Crossref. PubMed.
24. Thunberg L, Bäckström G, Lindahl U. Further characterization of the antithrombin-binding sequence in heparin. *Carbohydr Res.* 1982;*100*:393-410. Crossref. PubMed.
25. Pratt CW, Church FC. Antithrombin: structure and function. *Semin Hematol.* 1991;*28*:3-9. PubMed.
26. Breckwoldt WL, Belkin M, Gould K, Allen M, Connoly RJ, Termin P. Modification of the thrombogenicity of a self-expanding vascular stent. *J Invest Surg.* 1991;*4*:269-278. Crossref. PubMed.
27. Grode GA, Anderson SJ, Grotta HM, Falb RDD. Nonthrombogenic material via a simple coating process. *Trans Am Soc Artif Intern Organs.* 1969;*15*:1-5. PubMed.

28. Tanzawa H, Mori Y, Harumiyua N, Miyama H, Hori M. Preparation and evaluation of a new antithrombogenic heparinized hydrophyllic polymer for use in cardiovascular systems. *Trans Am Soc Artif Intern Organs.* 1973;*19*:1888-1894.
29. Jozefowicz M, Jozefowicz J. Heparin-containing and heparin-like polymers. In: Chiellini E, Giusti P, eds. *Polymers in Medicine*. New York, NY: Plenum Press; 1983.
30. Labarre D, Boffa MC, Jozefowicz M. Properties of heparin-poly(metyl methacrylate)copolymer. *J Biomed Mater Res.* 1977;*11*:283-295. Crossref. PubMed.
31. Miyama H, Harumiya N, Mori Y, Tanzawa H. A new antithrombogenic heparinized polymer. *J Biomed Res.* 1977;*11*:251-265. Crossref.
32. Heyman PW, Cho CS, McRea JC, Olsen DB, Kim SW. Heparinized polyurethanes: in vitro and in vivo studies. *J Biomed Mater Res.* 1985;*19*:419-436. Crossref. PubMed.
33. Larm O, Larsson R, Olsson P. A new non-thrombogenic surface prepared by selective covalent binding of heparin via a modified reducing terminal residue. *Biomater Med Devices Artif Organs.* 1983;*11*:161-173. Crossref. PubMed.
34. Hoffman J, Larm O, Scholander E. A new method for covalent coupling of heparin and other glycosaminoglycans to substances containing primary amino groups. *Carbohydr Res.* 1983;*117*:328-331. Crossref. PubMed.
35. Salzman EW, Rosenberg RDS, Smith MH, Lindon JH, Favrean L. Effect of heparin and heparin fragments on platelet aggregation. *J Clin Invest.* 1980;*65*:64-73. Crossref. PubMed.
36. Larsson R, Larm O, Olsson P. The search for thromboresistance using immobilized heparin. *Ann N Y Acad Sci.* 1987;*516*:102-115. Crossref. PubMed.
37. Barragan P, Sainsous J, Silvestri M, Bouvier JL, Comet B, Siméoni JB, Charmasson C, Bremondy M. Ticlopidin and subcutaneous heparin as an alternative regimen following coronary stenting. *Cathet Cardiovasc Diagn.* 1994;*31*:133-138. Crossref. PubMed.
38. Morice MC, Zemour G, Benveniste E, Biron Y, Bourdonnec C, Faivre R, Fajadet J, Gaspard P, Glatt B, Joly P, Labrunie P, Lienhart Y, Marco J, Petiteau PY, Royer T, Valeix B. Intracoronary stenting without coumadin: one month results of a French multicenter study. *Cathet Cardiovasc Diagn.* 1995;*35*:1-7. Crossref. PubMed.
39. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM. Intravascular stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation.* 1995;*91*:1676-1688. Crossref. PubMed.
40. Hass WK, Easton JD. *Ticlopidine, Platelets and Vascular Disease*. New York, NY: Springer-Verlag; 1993.
41. Gawaz M, Neumann F, Ott I, May A, Schömig A. Platelet activation and coronary stent implantation: effect of antithrombotic therapy. *Circulation*. In press.
42. Gregorini L, Marco J, Fajadet J, Brunnel P, Cassagneau B, Bossi I. Ticlopidine attenuates post-angioplasty thrombin generation. *Circulation*. 1995;92(suppl I):I-608. Abstract.
43. Foley DP, Melkert R, Serruys PW. Influence of coronary vessel size on renarrowing process and late angiographic outcome after successful balloon angioplasty. *Circulation.* 1994;*90*:1239-1251. Crossref. PubMed.
44. Palmaz-Schatz balloon-expandable stent and delivery system: PMA 900043 Panel Package: Circulatory System Devices Panel: May 3, 1994: Division of Cardiovascular, Respiratory and Neurological Devices: US Food and Drug Administration.
45. Lincoff AM, Van der Giessen WJ, Schwarz RS, Van Beusekom HMM, Serruys PW, Holmes DR, Ellis SG, Topol EJ. Biodegradable and biostable polymers may both cause vigorous inflammatory responses when implanted in the porcine coronary artery. *J Am Coll Cardiol*. 1993;21(suppl A):179A. Abstract.

46. 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. Crossref. PubMed.