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Original Studies

Intracoronary Stenting Without Coumadin: One Month Results of a French Multicenter Study

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In order to simplify post-coronary stenting treatment and to obtain a lower rate of complications, especially in bailout situations, seven French institutions treated 246 stented patients with 0.25 g/day of ticlopidine, 0.1 g/day of IV aspirin, and 2 days of heparin followed by low-molecular-weight heparin for 1 month. Fifty percent of patients had a planned stenting procedure, and 50% had an unplanned procedure, including 29 (11.8%) in bailout situations. Subacute occlusion occurred in three (1.2%) patients (one death, two non-Q-wave infarctions). During the 1 month follow-up period, another death was reported (non-stent-related), two elective coronary artery bypass grafts were performed, and three additional patients presented with non-Q-wave myocardial infarctions. Nine (3.7%) patients had a groin complication that required blood transfusion or surgical repair. These results suggest that while waiting for the technological advancements of stents, postprocedural treatment that includes a low dosage of ticlopidine, aspirin, and low-molecular-weight heparin is a very effective alternative to conventional poststenting therapy.

Key words: coronary stenting, subacute occlusion, ticlopidine

INTRODUCTION

The treatment of coronary artery disease has undergone enormous changes in the last 20 years. Percutaneous transluminal coronary angioplasty (PTCA), developed by the creative genius of Andreas Gruentzig, catapulted diagnostic cardiology into the age of interventional cardiology. However, soon after the introduction of PTCA it was clear that acute occlusion and late restenosis were the main drawbacks of this procedure. Despite advances in interventional cardiology, such as lasers, atherectomy, and stenting, these limitations were not significantly reduced. In 1964, Dotter [1,2] recognized during his early experience with angioplasty the fragility of the arterial wall. He therefore introduced into his own practice the concept of a mechanical prosthesis designed to maintain the intravascular lumen [3]. The research that followed resulted in the over 20 types of vascular stents currently available on the market [4]. Implantation of a coronary stent is well accepted today in cases of flow-obstructing dissection caused by PTCA [5]. Recent randomized studies have shown a reduction of the restenosis rate after de novo coronary stenting as compared to classical PTCA [6,7]. However, a relatively high rate of thrombotic occlusion remains the major obstacle to general acceptance and widespread usage of intravascular coronary stents [8].

In an earlier study [9] that was designed to reduce the rate of subacute occlusion poststenting, low-molecular-weight heparin (LMWH) was used instead of coumadin. In spite of this therapeutic change, subacute occlusion occurred in 10.3% of patients, during days 5–8, suggesting to us that a thrombotic mechanism independent of the switch from heparin to coumadin was the cause. The purpose of this study was to evaluate a new medication protocol using aggressive antiplatelet therapy (ticlopidine and aspirin), in conjunction with heparin and LMWH, in order to prevent subacute thrombotic occlusions.

METHODS

Population

From December 1992 to December 1993, 246 consecutive patients were included in a prospective, nonran-

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domized, multicenter study. Seven participating centers evaluated the 1 month results of a new medication protocol following coronary stenting procedures. Advanced age, unstable angina, low ejection fraction or previous myocardial infarction, coronary artery bypass graft (CABG), or PTCA were not considered exclusion criteria. All patients implanted with stents in the seven centers were included in this study. The only patients excluded from coronary stenting, and therefore from this study, were those with contraindications to aggressive anticoagulation treatment, such as uncontrolled hypertension, peptic ulcer, etc. All patients included in this study presented with angina or with inducible ischemia and were treated with an angioplasty of a vessel of 3 mm or larger. However, two patients with smaller vessels were stented in emergency. Informed consent was obtained from all patients.

Measurements of Coronary Arteries

This study reports the results of seven centers without the use of a core lab, as this presents a major limitation. However, all the centers involved were equipped with on-line QCA, which enabled the physicians to measure the arteries, to select the appropriate size of the balloon, to measure the balloon to artery ratio, and to assess residual stenoses. However, since the equipment used varied from center to center, and since the measurements were performed by the operators themselves, no absolute value of artery diameter, stenosis diameter, or poststent residual stenosis can be accurately reported.

Definition

Successful stenting was defined by correct placement of the prosthesis, in combination with TIMI 3 flow with residual stenosis of less than 10%, with no visible emboli and with no branch occlusion. We defined nonocclusive dissections as type A, B, C, and D1 of the NHLBI classification and bailout situations as clinical and ECG ischemia associated with dissections type D2, E, and F.

Major complications during the 1 month follow-up period included death, myocardial infarction (new Q waves or CPK elevation over twice 150 UI/l), CABG, or chest pain due to subacute occlusion of the stented vessel. Bleeding complications necessitating blood transfusion or surgery were also reported. This study included both planned stenting procedures (restenosis, vein grafts, and de novo lesions), as well as unplanned procedures (large dissections, elastic recoil, and bailout (TIMI 0 or TIMI 1 grade flow). Subacute occlusion was defined as symptomatic occlusion of the stented vessel occurring during the first month.

PTCA and Stenting Procedure

All centers used the classical PTCA technique. All patients received intravenous sedation and a bolus of 10,000 IU of IV heparin prior to the procedure. PTCA was performed via the femoral approach using a 6–8F guiding catheter. Prophylactic antibiotic therapy was given intravenously. Intracoronary vasodilators (molsidomine, nitroglycerin) were administered. The lesion was always predilated using an appropriately sized balloon. Stenting was carried out with a balloon that was carefully chosen according to the size of the artery (balloon to artery ratio of 1:1–1:1.2). After checking for correct placement, the stent was deployed. In all cases, a balloon pressure of 10 atm and above was applied to the stented segment either during stent deployment or with a postdilatation balloon. All centers insisted upon residual stenoses of 10% or less, often performing postdilatation of the stent, either using higher pressure inflations or using larger sized balloons. The arterial sheath was removed 4–24 hours postprocedure, with an ACT below three times normal at baseline level, and compression was carried out either manually or mechanically. As in routine PTCA, all patients received preprocedural aspirin (250 mg/day per os), which was reduced to 100 mg after the stent procedure for 1 month. Ticlopidine therapy (0.25 g/day per os for a duration of 1 month) was commenced immediately following the stent procedure. After withdrawal of the sheath, continuous intravenous heparin was administered for 48 hours followed by LMWH (Fraxiparine) 0.1 ml/10 kg twice a day subcutaneously for 1 month. Blood analysis included anti-Xa activity at the peak of activity, at day 3 and once a week thereafter, as well as blood count, fibrinogen, and liver enzymes once a week. A compression bandage was applied for two days while the patient was confined to bed. Gradual mobility was recommended beginning on day 3. Residual anti-Xa activity was checked once, at day 3 or 4 (just before the fourth injection of LMWH).

Data Collection

A detailed case report form was completed for each patient. The centers reported (1) patient information (including indication for PTCA); (2) procedural information (including reason for stenting, immediate results, residual stenosis measured by QCA or calipers, and assessment of the TIMI flow), (3) follow-up information (including clinical data, ECG recording, and biological measurements).

All major and minor complications were precisely detailed. A control angiogram was performed in all patients who were suspected to have a suboptimal result for clinical or ECG reasons. Since this multicenter study was conducted without a core lab and since the angiographic systems differed in the seven centers, we chose to use balloon diameter as a reference instead of measured arterial diameter. The results are expressed as mean value $\pm$ 1 standard deviation.

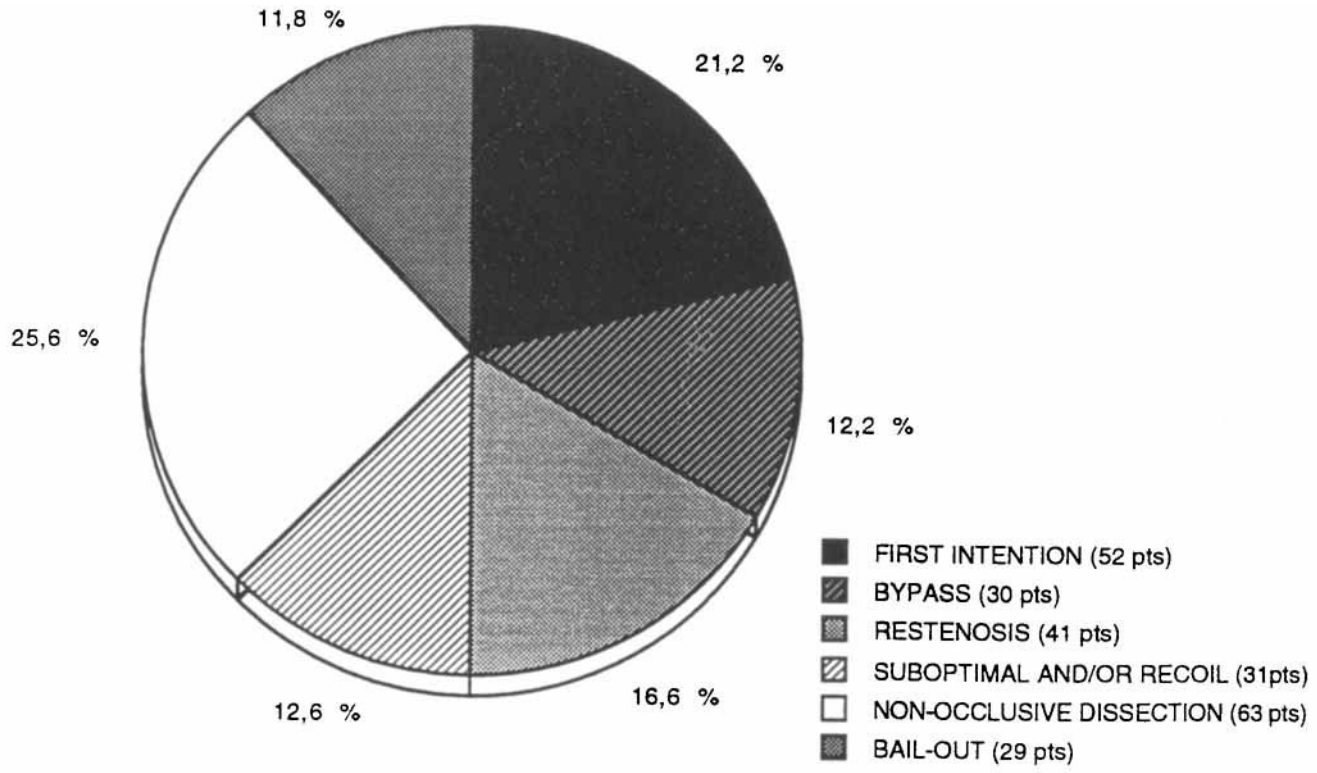

Fig. 1. Reasons for stenting.

RESULTS

Population

Out of a total of 5,083 patients treated with PTCA in the seven centers during the reference period, 246 (4.24%) patients underwent successful stenting procedures. There were 222 males and 24 females. The mean age was 59.7 ± 9.2 years (19–81), and 39 patients (15.8%) were over 70.

PTCA indications were stable angina in 65 patients (26.4%), unstable angina in 89 patients (36.1%), post-PTCA restenosis in 27 patients (11.0%), and post-CABG angina in 27 patients (11.0%). In addition, 38 patients (15.4%) showed ischemia following fibrinolized MI.

Reasons for stent implantation included 123 (50%) planned and 123 (50%) unplanned procedures (Fig. 1). In the group of patients undergoing planned stenting procedures, 82 patients (33.3% of total patients) had a de novo lesion in a native vessel or in a vein graft, and 41 patients (16.6%) were stented for restenosis. In the group of patients undergoing unplanned stenting procedures, 31 (16.6%) patients had suboptimal results and/or recoil, 63 patients (25.6%) had a nonocclusive dissection, and 29 patients (12.3%) were implanted in bailout situations.

Lesion characteristics and stent types. Of the 249 vessels stented, 79 (31.7%) were in the left anterior descending coronary artery (LAD), 83 (33.3%) in the right coronary artery (RCA), 44 (17.7%) in the circumflex coronary artery, 38 (15.3%) in a vein graft, and 5 (2.0%) in a protected left main (Table I). The mean balloon diameter used for optimal stent expansion was 3.5 ± 0.3 mm (2.5–5 mm). Fifty (20.0%) of the stented vessels were 3 mm or less (Table II). Two hundred and seventy-four stents were implanted, including 257 Palmaz-Schatz, 12 Roubin, 4 Wiktor, and 1 Strecker. Two hundred and twenty-two (90.2%) patients had a single stent, 20 patients (8.1%) had two stents, and 4 (1.6%) had three stents. The majority (83.9%) of stents were implanted in a native vessel (Table III).

Follow-Up

Death. During the 1 month follow-up period, there were two deaths (0.8%). The first was in a 63-year-old male who had a stent implanted in a dominant 4 mm RCA (single vessel disease) for a suboptimal result without visible dissection. Twenty-two days postprocedure he suddenly died following a 5 minute period of chest pain. Although no autopsy was performed, we attributed this death to the stent.

The second death occurred in an 80-year-old female with cardiac insufficiency and low cardiac output (ejection fraction = 22%). Successful PTCA and stenting were performed but did not result in an improved clinical

TABLE I. Reason for Stenting

	Indication			
	Planned	Suboptimal result	Bailout	Total
LAD	30	41	8	79
RCA	45	28	10	83
LCX	15	21	8	44
SVG	32	5	0	37
LM	2	1	3	6
Total	124	96	29	249

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery, RCA = right coronary artery; LM = left main coronary artery; SVG = saphenous vein graft.

TABLE II. Size and Location of Stents

	Stent diameter (mm)						
	25	3	35	4	45	5	Total
LAD	0	25	50	4	2	0	81
RCA	1	10	50	28	1	0	90
LCX	1	15	30	4	1	0	51
SVG	0	4	25	14	0	1	44
LM	0	0	5	3	0	0	8
Total	2	54	160	53	4	1	274

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; LM = left main coronary artery; SVG = saphenous vein graft.

TABLE III. Number of Stents by Artery

	Number of stents			
	1	2	3	Total
LAD	73	3	0	79
RCA	76	4	2	90
LCX	37	5	1	50
SVG	33	4	1	44
LM	3	1	0	5
LAD/LM	0	1	0	2
LAD/LCX	0	1	0	2
LAD/RCA	0	1	0	2
Total	222	20	4	274

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; LM = left main coronary artery; SVG = saphenous vein graft.

status. Further deterioration occurred at day 5. The stent was found patent angiographically. The patient died within 24 hours of terminal cardiac insufficiency. No autopsy was performed.

CABG. In one center that systematically recatheterizes all cases prior to hospital discharge, doctors chose to send two (0.8%) asymptomatic patients to bypass surgery despite a patent stent because of suboptimal results due to incomplete coverage of the dissection by the stent. There were no other patients sent to surgery.

Subacute occlusions and myocardial infarctions. In total there were three (1.2%) subacute occlusions. Besides the previously mentioned death, which was probably due to a stent thrombosis, there were two other reported cases of subacute occlusion. One occurred in a 79-year-old patient who received a Palmaz-Schatz stent for acute occlusion complicating a 3 mm LAD angioplasty. Ticlopidine had to be stopped on day 3 due to a hematuria and the stent occluded on day 5. The other was in a 64-year-old patient who presented with a symptomatic restenosis of a 3.5 mm circumflex. The angioplasty procedure was complicated by a nonocclusive dissection, which required three Palmaz-Schatz stents. Subacute occlusion occurred at day 23, even though the medication protocol was strictly followed. Both these patients had emergency revascularization by PTCA with excellent angiographic results. We observed five non-Q-wave infarctions. Two of these were due to previously described subacute stent occlusion. Two cases were both post PTCA occlusions in which successful revascularization and stenting were achieved. However, the duration of ischemia between the onset of acute occlusion and the reopening of the artery caused significant CPK elevation. The last case was an isolated CPK elevation post saphenous vein graft (SVG) stenting, probably due to an embolization.

Minor complications. Twenty-seven (10.9%) hematomas or false aneurysms were reported, and nine (3.7%) required intervention (blood transfusion in four patients and surgical repair in five patients). In one (0.4%) patient ticlopidine induced an asymptomatic leucopenia, which occurred on day 15. This was reversible by suppression of the drug. Minor bleeding complications included one hematemesis and one bloody diarrhea, neither of which required therapeutic modification.

During the 1 month study period, clinical success (no death, no repeat PTCA, no myocardial infarction, and no surgery) was obtained in 237 patients (96.3%). The average length of the hospital stay for this group was 10 ± 5.5 days. The average duration of the stay postprocedure was 7.4 ± 4.2 days. Eighteen (7.3%) patients were discharged on day 3.

DISCUSSION

The Study

This multicenter study reports poststenting antiplatelet therapy combining low doses of ticlopidine and aspirin associated with low-molecular-weight heparin for 1 month. Since the exclusion criteria were extremely limited, the patient population was representative of routine interventional practice in France. All seven centers included in the study had significant previous experience with coronary stenting, thus explaining the absence of learning curve complications. Even though 50% of the

cases in the study were unplanned stenting procedures, the complication rates were acceptable (1.2% of subacute occlusions and 3.7% of severe groin complications).

Subacute Occlusion

The Benestent and Stress studies show a significant reduction of the restenosis rate in de novo coronary stenting as compared to PTCA. The major limitations of coronary stenting that have been reported in the literature [10–13] are the rate of subacute occlusion and the rate of bleeding complication. Predictors of subacute occlusion have been reported to be multiple stents, bailout implantation, stent diameter $\leq$3.25 mm, and impaired LVF [14,15]. Monitoring of prothrombin fragments 1 + 2 [16] seems to show promising results but remains a complicated and infrequently used measurement.

A previous study [9] carried out by the same group of investigators replaced coumadin with LMWH. This protocol failed to reduce the subacute complication rate. However, since the peak in subacute occlusion remained during day 5–8, we were able to eliminate the heparin/coumadin switch as the mechanism of stent occlusion. This allowed us to consider an aggressive antiplatelet therapy. Palmaz et al. [17] were the first to describe the major role of platelet aggregation in stenting despite heparin therapy and to insist upon antiplatelet treatment. Recently Barragan et al. reported a low stenting subacute occlusion rate using 500 mg of ticlopidine and subcutaneous heparin [18]. Therefore, it was tentatively assumed that a wide antiplatelet treatment, capable of inhibiting interaction between newly formed endothelial cells and recently released platelets, with a maximal effect 5–6 days after stenting, was required.

Acetyl salicylic acid (ASA) at a dosage as low as 100 mg daily efficiently inhibits thromboxane A_2 formation in platelets, thus lowering their adhesion, release, and aggregation [19]. Conversely, higher ASA dosage may inhibit cyclooxygenase action and prostacyclin formation in endothelial cells [20]. Prostacyclin probably has an important protective in vivo effect against unwanted platelet-to-cell adhesion.

Ticlopidine has no inhibitory effect on thromboxane formation but is a potent inhibitor of ADP-induced platelet aggregation [21]; the maximal effect is obtained after 3–6 days of treatment. Side effects are not uncommon at the recommended dosage of 500 mg daily. Gastrointestinal symptoms (20–40% among patients given ticlopidine only), cutaneous rashes (15%), and severe leukopenia (1–8%) are regularly mentioned. Conversely, two studies [22,23] reported a lower incidence of side effects with a daily dose of 200–300 mg of ticlopidine. The frequency and severity of hemorragic complications are also dose dependent and are enhanced by other anticoagulant agents.

These pharmacological and practical facts led us to combine a daily regimen of 250 mg of ticlopidine with 100 mg of ASA, started on the day of stent implantation. Heparin therapy, however, was still required to prevent both fibrin formation and the stimulating effect of thrombin on inflammatory and proliferative cells at the site of implantation. In accordance with our previous experience, it was decided to maintain a conventional intravenous heparin infusion for 48 hours, and then start LMWH therapy by the subcutaneous route, which is more convenient for the patient. Further investigations are currently in progress to reduce heparin treatment duration or to find alternatives to this treatment (heparin coated prosthetic material, the use of other specific thrombin inhibitors) [24].

The very low subacute occlusion rate (1.2%) seems to clinically confirm our theoretical hypothesis. Subacute occlusion remains low even in the subgroup of bailout patients (3.4%), as compared to what has been reported in the literature [8,25,26]. Even though the rate of bleeding complication in this study is lower than that reported in poststenting conventional treatments, it does remain higher than that reported for conventional PTCA. Ticlopidine therapy had rare side effects (only one case [0.4%] of leukopenia), most likely due to the short duration of treatment (1 month) and the low dosage (0.25 g). Poststenting treatment is very easy to manage using this medication protocol. At the beginning of the study, we did not know when occlusions would occur and what the rate would be. Therefore, we remained extremely cautious, and we kept all patients in hospital for at least 1 week, which is the duration of hospital stay for conventional treatment with coumadin. During the course of the study, hospital stay was reduced as the investigators became more confident in the reduced rate of subacute occlusions.

Limitation of the Study

A major limitation of this study is that it is nonrandomized. It was started as a pilot study with the intent of confirming the basic concept. Another limitation of this study is the lack of a central core lab.

CONCLUSIONS

Several studies are currently being conducted with the intention of reducing poststenting bleeding complications. These include stenting with 6F guiding catheters, ultrasound guided stent deployment [27], and, most importantly, stent design research, and in particular, research on stent coatings [28]. While waiting for the results of these important advancements, this medication protocol combining two antiplatelet at low doses with LMWH allowed us to implant intracoronary stents in

routine situations with an extremely acceptable rate of subacute occlusion. The results of this pilot study should be validated in a randomized trial. This low complication rate, in conjunction with the reports of reduced restenosis rates by stenting, should allow interventional cardiologists to expand their stenting indications.

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