The importance of adequate anticoagulation to prevent early thrombosis after stenting of stenosed venous bypass grafts

Stent implantation in native coronary arteries may be complicated by acute thrombosis, despite the use of stringent anticoagulation. Thrombotic occlusion of stented venous grafts may occur less frequently, possibly because of the larger caliber of these grafts. We report our experience with 46 stents (Wallstent, Medinvent, Lausanne, Switzerland) implanted in 35 lesions of 24 consecutive patients (mean age 64 years, range 43 to 75). Two overlapping stents were implanted in seven patients, and three overlapping stents were positioned in two. After implantation, activated partial thromboplastin time was maintained at two to three times the control level by intravenous administration of heparin (160 to 550 mg daily) until thrombotest values were reduced 5% to 10% by acenocoumarol. Impending thrombotic occlusion was recognized in two suboptimally anticoagulated patients: patient A after implantation of four stents and patient B after anticoagulation therapy was discontinued because of acute upper gastrointestinal bleeding. Coronary artery bypass grafting was performed successfully in both patients. A third patient had a myocardial infarction on day 7 after stent implantation, in spite of adequate anticoagulation and optimal medical drug therapy. It is concluded that stringent anticoagulation therapy appears mandatory to maintain graft patency after stent implantation.

Jeroen J. J. Bucx, MD, Ivan de Scheerder, MD, Kevin Beatt, MD, Marcel van den Brand, MD, Harry Suryapranata, MD, PhD, Pim J. de Feyter, MD, PhD, and Patrick W. Serruys, MD, PhD.

Rotterdam, The Netherlands

Patients with venous bypass grafts are at risk of having atherosclerotic degeneration of the graft. Both short- and long-term results after balloon dilatation of this type of lesion, and notably angioplasty of completely occluded grafts, appear to be less favorable than results in native coronary arteries. In approximately 3% of patients the procedure may be complicated by peripheral embolization of the bypass atheroma, resulting in peripheral occlusion and myocardial infarction. The restenosis rate in dilated venous bypass grafts is higher than that in native vessels; particularly the proximal anastomosis is prone to restenosis (46%), the risk is intermediate in the shaft of the vein graft (35%) and lowest at the distal anastomosis (24%). It has been reported that only 46% of patients were symptom free 5 years after angioplasty of a saphenous vein graft compared with 79% after balloon dilatation of native vessels.

Recently it has been suggested that stent implantation at the dilatation site may improve both short- and long-term results. Evaluation of the use of these devices may be even more appealing in view of the increasing number of patients that have recurrent angina after venous bypass grafting. The aim of this analysis was to assess the need for anticoagulation therapy to prevent thrombotic complications after successful stent implantation in venous bypass grafts. Obviously the risk of complications inherent in anticoagulation therapy should compare favorably with the possible gain in safety, improved success rate, and better immediate hemodynamic results when these new interventions are applied in a high-risk patient population.

METHODS

Patients. The patient population consisted of 24 consecutive patients who had previously undergone venous sartorcoronary bypass surgery and had recurrent angina pectoris (Canadian Heart Association class III to IV). The...
coronary anatomy and the expected gain from surgery. In
correspondence of recent myocardial infarction. All patients were discussed
with the cardiothoracic surgeon and were considered not to
symptoms had to have been present for more than 7 days
and unresponsive to maximal drug treatment without signs
of any bleeding disorders. For this reason patients
with recent gastrointestinal bleeding, cerebrovascular ac-
cident, or other bleeding disorders did not undergo stent
implantation. This report focuses on elective procedures;
therefore two patients with evolving myocardial infarction
and two with stent implantation in an occluded bypass at
the time of the study will not be discussed. The mean age
of the 20 men and four women was 63.6 years (+ 9.4). Six
patients had hypertension and five had hypercholester-
olemia. Diabetes mellitus was diagnosed in seven patients;
the remaining five the lesion was stented and an-
gioplasty was subsequently performed in the stented artery
(“Swiss kiss”). Catheters were introduced either via sheaths
in the femoral artery by percutaneous puncture according
to the Seldinger technique (n = 22) or by direct dissection
of the brachial artery (n = 2). At the end of the procedure
the brachial vessels were surgically closed. Femoral sheaths
were left in place during the ensuing 24 hours; the next day
the sheaths were removed 2 hours after heparin was
discontinued; 1 hour later heparin was resumed.

**Drug protocol before, during, and after implantation.**
The protocol for drug treatment consisted of administra-
tion of oral dipyridamole (4 x 75 mg), sulfipyrazone
(4 x 200 mg), and salicylic acid (2 x 500 mg) on the day be-
fore implantation and 1 x 100 mg thereafter), as well as
ifedipine (3 x 20 mg), which was started before stent im-
plantation and continued for approximately 3 months
(Table II). Before balloon dilatation heparin, 10,000 IU,
and dextran, 500 mg/4 hr, were given intravenously.
Immediately after stent implantation 100,000 to 250,000 IU
of urokinase was administered intracoronarily, followed
by an additional 100,000 IU during the next 60 minutes.

**intravascular stent.** The self-expanding stent consisted
of 16 metal alloy filaments (outer diameter 0.08 mm) that
formed a geometrically stable tubular meshwork; the max-
imal outer diameter of the device that was attained after
implantation was determined on the one hand from the ra-
dial forces generated by the device and on the other hand
from the vascular elasticity of the vascular wall. In
the unconstrained state the maximal diameter ranged from 3.5
to 6 mm (mean 4.2 mm) with a length that varied from 15
to 30 mm (mean 22 mm). Before implantation the stent was
stretched and mounted on the tip of a 5F central-hole
catheter; subsequently the device was covered by a coaxial
balloon that was removed during the procedure. To ascer-
tain continuous outward compression of the vascular wall
after implantation, the unconstrained diameter of the stent
was chosen to exceed the measured reference diameter of
the stenosed area by approximately 0.5 mm.

The implantation procedure is described in detail
elsewhere. In seven patients the stent was implanted
without angioplasty, and in 27 the implantation was
preceded by balloon angioplasty. In five patients balloon
angioplasty was performed before and after stent implant-
ation; in the remaining five the lesion was stented and an-
gioplasty was subsequently performed in the stented artery
(“Swiss kiss”). Catheters were introduced either via sheaths
in the femoral artery by percutaneous puncture according
to the Seldinger technique (n = 22) or by direct dissection
of the brachial artery (n = 2). At the end of the procedure
the brachial vessels were surgically closed. Femoral sheaths
were left in place during the ensuing 24 hours; the next day
the sheaths were removed 2 hours after heparin was
discontinued; 1 hour later heparin was resumed.

**Baseline hemostatic parameters.** Twelve hours before

### Table I. Drug treatment before and 3 months after stent
implantation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Before implantation</th>
<th>3 mo after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>NTG</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Ca++ entry blockers</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Phenprocoumon/Acenocoumarin</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Aspirin</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Sulfipyrazone</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

NTG, Nitroglycerin.
implantation, baseline coagulation status and bleeding time were evaluated in all patients. Bleeding time was determined according to the method of Hemker et al. Thrombocytes were counted by means of an automated whole blood platelet analyzer (Serono-Baker Diagnostics, Allentown, Pa.). APTT was determined with activated cephaloplastin reagent (Actin, Merz and Dade AG, Düdingen, Switzerland); prothrombin time (PT) was obtained by the method of Quick with calibrated thromboplastin reagent. In addition, fibrinogen levels were determined in citrate plasma by means of thrombin solution (Thrombin, Hoffmann-La Roche & Co., Basel, Switzerland) according to the method of Claus; Factor V levels were measured in citrate plasma by means of human thromboplastin reagent (Thromborel S, Behringwerke AG, Marburg, West Germany).

Thrombotest, consisting of ox brain thromboplastin devoid of coagulation factors, was used to adjust the dosage of oral anticoagulation therapy; it is a modified PT assay that is sensitive to reduced levels of coagulation factors II, VII, and X and the presence of protein-induced by the absence of vitamin K or antagonists that result from anticoagulation therapy. In view of the lack of standardization of PT determinations, the primary standard (World Health Organization international thromboplastin) was recently calibrated against three secondary standards among which ox brain thromboplastin (Thrombotest), the international normalized ratio that was subsequently assigned to each preparation, facilitates comparison of results obtained by each method.

According to the TT, coagulation activity was expressed as a percentage of control activity. In the presence of anemia or polycythemia, the values were corrected according to the specifications of the assay. TT measurements may seemingly be lowered during concomitant heparin administration; in our patients this effect was not compensated for by neutralization of serum samples with protamine sulfate. Instead TT was determined daily until heparin was gradually discontinued when TT values were within the therapeutic range.

RESULTS

Stent implantation. The angiographic results after stent implantation were evaluated by means of quantitative angiography, with an automated edge-detection technique. Before balloon dilatation the mean luminal diameter of the stenosed bypass was 1.5 mm ± 0.9 (range 0.7 to 2.9). The mean estimated reference bypass diameter at the stenosis (interpolated technique) was 3.4 mm ± 1.1 (range 1.6 to 7.0), and the average diameter of the angioplasty balloon was 3.2 mm ± 0.6 (range 2 to 4.2). The unconstrained diameter of the stent that was implanted after balloon dilatation was 4.1 mm ± 0.7 (range 3.5 to 6.0). All procedures were successful and without complications. The procedure allowed easy delivery of the device without misplacement and reduced the diameter of the stenosis to <50%. There were no acute bypass occlusions. Immediately after angioplasty and stent implantation, the mean diameter of the lesion was 2.0 (± 0.6) and 2.8 (± 0.9) mm, respectively.

Baseline hemostatic parameters. Baseline coagulation parameters are summarized in Table III. Before stent implantation, TT, PT, and APTT were all outside the normal range, which was accounted for by the treatment with oral or intravenous anticoagulants in almost half of the patients (see Drug protocol before, during, and after implantation.) Fibrinogen levels were strikingly elevated as well. The changes in the coagulation parameters during and after stent implantation are shown in Fig. 1. Initially the mean APTT (closed circles, SEM as bars) increased to 120 seconds and thereafter stabilized around 80 seconds. As soon as the thrombotest values had decreased between 5% and 10% on days 2 to 3, heparin was gradually discontinued, resulting in normalization of the APTT. Note that two patients had early occlusion of the stented graft. In patient A the occlusion (day 2) coincided with suboptimal anticoagulation treatment; in patient B anticoagulants had to be discontinued on day 7 after implantation as a result of acute gastrointestinal bleeding (see below).

Complications (Table IV). Four patients had hematomas with a diameter exceeding 5 cm, resulting in anemia that had to be corrected by blood transfusions. One patient had a transient attack, but fortunately the clinical condition normalized without sequelae. As mentioned previously patient A, who initially had two stents implanted, had a recurrence of angina pectoris after 3 months; results of repeat angiography showed severe stenosis proximal to the

### Table II. Drug treatment protocol

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day before implant</th>
<th>Before PTCA</th>
<th>Before/After implant</th>
<th>1st day after implant</th>
<th>2nd day after implant</th>
<th>Long term</th>
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</thead>
<tbody>
<tr>
<td>Salicylic acid, 1000/100 mg daily</td>
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<tr>
<td>Dipyridamole, 300 mg daily</td>
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<td>Sulfinpyrazone, 800 mg daily</td>
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<td>Nifedipine, 60 mg daily</td>
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<td>Urokinase, 100,000 to 250,000 IU</td>
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<tr>
<td>Heparin &gt;1000 IU/kg/hr (guided by APTT)</td>
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<tr>
<td>Acenocoumarol</td>
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<tr>
<td>(guided by TT or Quick test)</td>
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</table>
Fig. 1. Mean activated partial thromboplastin time (APTT in seconds [●]) and thrombotest (TT in %) of patients before and after stent implantation (mean ± SEM). A and B indicate actual APTT and TT in two patients at time of acute thrombotic occlusion.

Table III. Baseline coagulation status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ± SEM</th>
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</thead>
<tbody>
<tr>
<td>Bleeding time (1-4 min)</td>
<td>2.1 ± 0.8</td>
</tr>
<tr>
<td>Thrombocytes (150-350* 10^9/L)</td>
<td>220 ± 45</td>
</tr>
<tr>
<td>APTT (22-45 sec)</td>
<td>45 ± 37</td>
</tr>
<tr>
<td>PT (14-19 sec)</td>
<td>22 ± 9</td>
</tr>
<tr>
<td>TT (65-150%)</td>
<td>51 ± 30</td>
</tr>
<tr>
<td>NT (65-110%)</td>
<td>78 ± 43</td>
</tr>
<tr>
<td>Fibrinogen (1.6-2.8 g/L)</td>
<td>3.4 ± 0.7</td>
</tr>
<tr>
<td>Factor V (0.5-1.5 E/ml)</td>
<td>1.3 ± 0.4</td>
</tr>
</tbody>
</table>

APTT, activated partial thromboplastin time; NT, normotest; PT, prothrombin time; TT, thrombotest.

implanted stents. This was corrected by balloon angioplasty followed by implantation of two additional stents. However, 3 days later the patient again had angina. Results of recatheterization showed that the peripheral native vessels supplied by the stented bypass graft showed thrombi that were not present on the angiogram before the second implantation. Subsequently it was decided to perform a reoperation, which was uneventful.

Patient B (Fig. 2) had upper gastrointestinal bleeding in spite of the absence of gastrointestinal complaints before the intervention. As a result of continuous vomiting with blood loss and melena, heparin and acenocoumarol were discontinued. Subsequently the patient had angina with ECG signs of myocardial ischemia (i.e., negative T waves) without elevation of creatine kinase levels. During recatheterization it appeared that this was related to impending occlusion of the bypass by a fresh thrombus located outside the stented segment. Subsequently, repeat coronary bypass surgery was performed without evidence of perioperative myocardial infarction.

A third patient had an uneventful implantation of one stent. However, on day 7 he had an acute myocardial infarction (maximal creatine kinase level, 706 U/L) without signs of congestive heart failure. Results of recatheterization showed total occlusion of the bypass within the stent, notwithstanding adequate anticoagulation therapy. In one patient continued blood loss from the sutured brachial artery necessitated surgical reexploration; a false aneurysm of the brachial artery was sutured and the vessel reconstructed by means of a venous flap. The subsequent clinical course was uneventful, and the patient was given anticoagulants and discharged. One patient had hematuria without anemia.

**DISCUSSION**

Short term follow up after stent implantation. Our results show that stent implantation after balloon angioplasty of stenosed venous bypass grafts is technically feasible and successful at an early stage, provided that the patients are carefully selected. To be a candidate for stent implantation, each patient was
screened for the presence of all possible contraindica-
tions for anticoagulation therapy. Therefore possi-
ble bleeding disorders, notably upper or lower gas-
trointestinal bleeding as a result of ulcers, gastritis,
esophageal varices, or Mallory-Weiss syndrome, had

to be ruled out. Other disorders that precluded stent
implantation were any recent bleeding, cerebral hem-
orrhage, severe liver or kidney dysfunction, throm-
bocyte dysfunction, thrombocytopenia, or hyperten-
sion (>180/110 mm Hg), and diabetic or hypertensive
retinopathy. For this reason complete hematologic
and coagulation status was obtained from all patients
before the intervention, and stool samples were
checked for the presence of microscopic blood loss.
Notwithstanding these precautions, one patient had
upper gastrointestinal bleeding, necessitating inter-
ruption of the anticoagulation therapy.

Another important determinant of the ultimate
success is the regional anatomy of the coronary
arteries that are supplied by the diseased venous by-
pass graft. In our previous experience with stenting
of coronary arteries, poor distal runoff, small diam-
eter of the stenosed vessel, and previous myocardial
infarction in the region supplied by the stenosed
artery, as well as haziness of the dilated lesion, were
contraindications for stent implantation. Our favor-
able results within the first day may be explained, at
least in part, by the diameter of the venous grafts,
which exceeded the luminal diameter of native cor-
onary vessels by a factor of 1.5 to 3.

In general the extensive anticoagulation therapy
was continued until 3 months after stent implan-
tation. The rationale for this approach is based on
observations in animal experiments; it has been
reported that stents that were implanted in pig fem-
oral arteries were completely covered by endothelium
within 1 to 3 weeks. Since histologic data in humans

![Fig. 2. Coronary angiogram (patient B) of venous bypass
graft connected to left anterior descending coronary artery,
immediately after successful stent implantation (a) and
during acute occlusion (b), showing impending occlusion of
bypass graft by fresh thrombus located outside stented
segment (arrow).](image)

are still lacking, we decided not to risk acute throm-
botic occlusion and therefore continued anticoagula-
tion therapy until 3 months after implantation. Stringent anticoagulation was accomplished by scru-
pulous and frequent monitoring of the coagulation
status of each patient for approximately 3 months. It
is conceivable that in some patients the burden of
frequent visits to the outpatient clinic and extensive
medication may compromise the quality of life to
such an extent that it would have been preferable to
perform bypass surgery despite the possibility of in-
creased risk of myocardial infarction or even death as
a result of the latter procedure. The possible advan-
tageous long-term effects of stent implantation on
the rate of restenosis should be well established to
gain acceptance as an alternative to bypass surgery.
Thus long-term follow-up including quantitative an-
giography of treated patients is necessary and is cur-
rently under investigation.

Hemostatic monitoring: Theoretic and practical con-
siderations. The adequacy of anticoagulation therapy
was controlled by assessing the TT (in percentages) and APTT levels (in seconds). The concept of the thrombotest was initially introduced by Owren. It is well known that coumarin derivatives, such as acenocoumarol or phenprocoumon, prevent incorporation of vitamin K in coagulation factors II, VII, IX, and X. Consequently inactive proteins induced by the absence of vitamin K (or antagonists) are formed. The resulting lengthening of coagulation time may be measured by means of the thrombotest; the test assesses the serum coagulation time in the presence of excess kefaline, thrombokinase, factors V and VIII, and calcium chloride. The assay is sensitive to the presence of coagulation factors II, VII, (IX), and X and is more or less equivalent to the PT as measured by the Quick test. Normal thrombotest values of 40 seconds or less have been reported in healthy control subjects; in our patients the preferable TT level ranged between 180 and 210 seconds, which is equivalent to a thrombotest value of 5% to 10% (international normalized ratio 2.5 to 5). According to the manufacturer, thrombotest values may be seemingly increased in the presence of heparin. Although this does not seem relevant in daily clinical practice, this effect may be compensated for by neutralization of the serum before the test. We preferred to gradually discontinue heparin administration and frequently monitored TT at the same time.

The effect of heparin administration was adjusted according to the APTT. The patient's pretreatment APTT' (30 to 35 seconds) was increased by a factor of 2 or 3. The white cell count appeared elevated after the procedure in almost every patient; this may have been caused by acenocoumarol, which may induce redistribution of white cells, notably neutrophils, as has been reported recently. However, in our patients the observed leukocytosis may be equally well accounted for by hematoma formation and subsequent resorption.

We conclude that stent implantation after percutaneous transluminal coronary angioplasty of stenosed venous bypass grafts may result in normalization of the regional hemodynamic profile. Unfortunately the drastic improvement in rheologic conditions, as evidenced by the virtual disappearance of poiseuille resistance and normalization of laminar flow, was inadequate to prevent thrombotic complications in three patients. Our observations therefore suggest that the primary cause of thrombotic occlusion must be ascribed to the thrombogenic nature of the stent itself or to its direct thrombogenic interaction with the diseased and atherosclerotic vessel wall. Likewise the observed thrombotic complications may have resulted from local thrombotic mechanisms that were triggered by the interaction of the self-expanding stent with the more compliant vessel wall. To prevent these acute thrombotic complications, we applied stringent anticoagulation therapy after successful implantation of the stent. The rationale for the drug treatment was to provide maximal antithrombotic effects by interference with the normal function of platelets and endothelial lining and by inhibition of coagulation factors.

As a result of stent implantation the intimal lining of the venous graft was damaged, which may have given rise to aggregation of platelets and formation of thrombin.

Therefore platelet aggregation was antagonized by aspirin and sulfinpyrazone, both of which inhibit production of thromboxane A₂; dipyridamole, on the other hand, was administered in an attempt to inhibit platelet deposition and aggregation to damaged vessels because of increased production of platelet c-AMP. Thrombin formation was prevented by administration of heparin and if present lysed by urokinase, thereby preventing acute occlusion.

Vasospasm, which may be triggered by release of vasoactive agents during angioplasty, was prevented by nifedipine and diltiazem. Dextran (Rheomacrodex) was infused, since this inert plasma volume expander is known to reduce platelet adhesiveness and platelet aggregation induced by injury to the vessel wall. In addition, it reduces factor VIII activity and increases clot lysability. It remains to be seen whether this extensive anticoagulation regimen is an absolute requirement for prevention of the complications of acute thrombosis. A less extensive protocol may appear equally effective for prevention of early thrombotic complications after stent implantation in venous bypass grafts. In addition, the number of patients with complications induced by the stringent anticoagulation regimen may be reduced.

The stents that were implanted in our patients were not coated. It has been reported that heparin or polymer-coated stents may be advantageous, since endothelial cell proliferation is enhanced by various anticoagulation and antiplatelet drugs, as was shown in cell cultures. Notably low-molecular-weight heparin seems to exert a favorable effect on endothelial cell growth. Future designs for stents should include polished endings for the wires that form the device; alternatively the device could be covered by a layer of endothelial cells or polymer or corticoid coating to prevent early thrombotic occlusion and endothelial proliferation for the longer term. More recently it has been suggested that the device be cov-
tered with heparin benzalkonium chloride complex (II-BAC), which is known to prevent thrombosis. Other designs such as biodegradable devices, may also prove useful and diminish the rate of restenosis.

To prevent some of the bleeding complications, anticoagulation therapy, notably acenocoumarin, may be considered 1 day before stent implantation. Likewise removal of the arterial sheaths immediately after the procedure rather than 12 hours later could reduce the number of severe hematomas.

Recently it was suggested that the effects of heparin administration be monitored by measurement of activated clotting time during and after percutaneous transluminal angioplasty. The same technique could be applied equally well in patients after stent implantation. Since the method is reliable, cheap, and easy to perform, it may be considered more frequently to adjust heparin administration and attain an optimal coagulation status. Introduction and application of these and other laboratory techniques without any doubt will reduce the rate of thrombotic occlusions resulting from inadequate heparin administration.

REFERENCES