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Angiographic Features of Vein Grafts Versus Ungrafted Coronary Arteries in Patients With Unstable Angina and Previous Bypass Surgery

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Objectives. **The aim of the study was to compare the angiographic features of culprit coronary lesions located in grafts with those in native coronary arteries in patients with unstable angina and previous coronary artery bypass graft surgery (CABG).**

Background. **Deterioration of angina in patients with previous CABG is usually due to progression of atherosclerosis in coronary arteries or in vein grafts, but the relative importance of graft versus native coronary artery disease as well as the morphologic features of the culprit lesions in unstable angina have not been systematically assessed.**

Methods. **Disease progression and angiographic features of vein grafts and ungrafted and grafted coronary arteries were assessed in 95 consecutive patients admitted with unstable angina or non–Q wave myocardial infarction with CABG >6 months previously. All patients were receiving aspirin and heparin, and 46 had received streptokinase during the acute phase in a double-blind, placebo-controlled study. Coronary and vein angiography was performed within 8 days after admission (mean [±SD] 5 ± 2 days). The most recent angiogram served to assess disease progression by quantitative angiography.**

Results. **The culprit lesion was located in a vein graft in 51 patients, an ungrafted coronary artery in 17 and a grafted artery (proximal and distal to the site of graft insertion) in 9 and was of undetermined site in the remaining 18. The proportion of grafts accounting for acute disease increased to 85% with CABG ≥5 years. Total occlusion occurred in 25 vein grafts and 4 ungrafted coronary arteries (49% vs. 24%, $p = 0.02$). Intravessel thrombus was found in 18 culprit vein grafts but in only 2 ungrafted coronary arteries (37% vs. 12%, $p = 0.04$). Both intravessel thrombus and total occlusion were demonstrated in six culprit vein grafts but in none of the ungrafted coronary arteries (12% vs. 0%, p = NS). The prevalence of total occlusion and thrombus was not influenced by trial medication, streptokinase or placebo.**

Conclusions. **Unstable angina in patients with previous CABG is most often due to graft disease and is associated with more frequent thrombi that are more refractory to medical therapy.**

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Unstable angina and myocardial infarction (MI) are frequent complications after coronary artery bypass graft surgery (CABG). In active surgical centers, as many as 20% of patients admitted with these syndromes had had previous CABG (1). The prognosis in these patients is impaired compared with that of patients with unstable angina and non–Q wave MI and no antecedent operation (2,3). Explanations proposed have been different baseline characteristics, including more frequently impaired left ventricular function (2), less possibility for a revascularization procedure and different pathophysiologic mechanisms (3).

Unstable angina in patients with or without previous CABG shares a common pathogenesis of plaque rupture and intravessel thrombosis formation (4,5). Pathologic vein graft atherosclerosis differs from coronary artery atherosclerosis (6,7) and may be more thrombogenic (8). Although atherosclerotic progression in coronary arteries and vein grafts is universally demonstrated in patients with deterioration of symptoms after CABG, the angiographic features associated with unstable angina have not been systematically investigated. In the present study, the progression of atherosclerosis and the angiographic features of the culprit lesions located in grafts and native coronary arteries in patients with unstable angina with previous CABG were characterized by visual inspection and by quantitative angiography.

Methods

Patients. This randomized, double blind, placebo controlled trial included a consecutive series of 125 patients admitted to the coronary care unit between December 1991 and September 1993 for unstable angina or non–Q wave MI and who had undergone CABG at least 6 months previously

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
ECG = electrocardiographic
MI = myocardial infarction
TIMI = Thrombolysis in Myocardial Infarction

and were enrolled in a prospective trial of thrombolytic therapy (9). Bypass surgery had been performed an average of 96 ± 55 (mean ± SD) months before hospital admission: <5 years in 30 patients, between 5 and 10 years in 34 and >10 years in 31. *Unstable angina* was defined as 1) recent onset of angina (within the previous 2 months) at rest or with minimal exertion; 2) rapid and marked deterioration of chronic stable angina; 3) recurrent episodes of angina at rest, with the most recent episode of chest pain within the previous 24 h; or 4) a prolonged episode of chest pain at rest. *Non–Q wave MI* was considered unstable angina. Electrocardiographic (ECG) changes were not required for inclusion, but in their absence, the diagnosis of unstable angina needed to be confirmed by two independent cardiologists (P.T., F.S.).

The exclusion criteria were a treatable cause of unstable angina (severe anemia, arrhythmia, hypotension, hyperthyroidism, aortic stenosis, heart failure); CABG or coronary angioplasty within the previous 6 months; uncontrolled hypertension (systolic arterial pressure >200 mm Hg or diastolic arterial pressure >110 mm Hg); revascularization by arterial grafts only; acute Q wave MI, anticoagulation with warfarin within the previous 1 week; and contraindication to the use of aspirin, streptokinase or heparin.

After inclusion in the study, the patients were randomized in double-blind manner to streptokinase 1.5×10^6 U administered in 45 min or to placebo. All patients received concomitant intravenous heparin and oral aspirin. The initial dose of aspirin was 325 mg orally followed by 80 mg daily. Heparin was infused at a rate of 1,000 U/h with no initial bolus; the infusion rate was adjusted after 6 h to an activated partial thromboplastin time 1.5 to 2.5 times the control values. The infusion of heparin was maintained for 96 to 120 h.

Thirty (30%) of the 125 patients were subsequently excluded from the present angiographic study for the following reasons: 27 because of coronary artery/graft angiogram not performed during the hospital period for various medical reasons, including previously known anatomy or a relative contraindication to cardiac catheterization; and 3 because of a recent angioplasty. Thus, the study included 95 patients with unstable angina and previous CABG who underwent coronary artery/graft angiography. Angiography was performed before hospital discharge between 1 and 8 days (mean [±SD] 5 ± 2) after admission.

Angiographic analysis. Ventriculograms and selective coronary artery and graft arteriograms were acquired using standardized and angulated projections as previously described (10). Aortic root angiography was performed when the origin of an occluded graft could not be selectively catheterized and injected. To assess progression in native arteries or grafts among the patients, angiographic findings after unstable angina were compared with those from the most recent angiogram in the same patient; this angiogram had been performed preoperatively in 31 patients and postoperatively (89 ± 51 months) in 64 patients. Indications for postoperative angiography were symptoms in 36 patients and a research protocol in 28.

Quantitative assessment. Coronary artery and vein graft stenoses were quantitatively analyzed by an independent observer who had no knowledge of the patient's trial medication assignment. Stenosis ≥50% was considered "significant," and a lesion <50% was considered "nonsignificant." The extent of coronary artery disease was defined as one-, two- or three-vessel disease based on the presence of significant stenosis. The functional evaluation of vessel disease severity considered stenoses ≥50% in both the artery and graft or in the artery distal to the graft anastomosis in the absence of graft stenoses (11). The Cardiovascular Measurement System, developed by Reiber et al. (12) and extensively validated, was used to measure percent diameter reduction and minimal stenosis diameter. For each segment, measurements were carried out on end-diastolic frames showing maximal stenosis. Disease progression was defined as ≥20% diameter reduction of a preexisting stenosis or ≥50% reduction of a previously normal or nearly normal segment or new total occlusion in a native coronary artery or in graft.

Qualitative assessment. The morphology of all coronary artery stenoses ≥50% (total occlusion excluded) was assessed visually by two experienced observers (L.C., J.L.) who had no knowledge of the identity and clinical characteristics of the patients. All significant stenoses were assessed selectively, viewed in multiple orthogonal projections and classified as "complex" or "simple" (13–16). Stenoses were considered *complex* in the presence of overhanging edges, irregular borders or ulceration or thrombus. *Simple* lesions were those with smooth edges in the absence of complex features. Stenosis morphology could not be assessed when grafts or arteries were occluded. An *intravessel thrombus* was defined as a globular or linear filling defect located proximal, within or distal to a stenosis, surrounded by contrast medium on at least three sides and visible in multiple projections. *Thrombus grade* was assessed visually using the following grading system adapted from Thrombolysis in Myocardial Infarction (TIMI) IIIA study (17): grade 0 = no cineangiographic characteristics of thrombus present; grade 1 = possible thrombus present (reduced contrast density, haziness, irregular border); grade 2 = small thrombus present (definite thrombus with greatest dimensions <50% vessel diameter); grade 3 = moderate thrombus present (definite thrombus but with greatest linear dimension ≥50% but less than two-vessel diameters); grade 4 = larger thrombus present (as in grade 3 but with largest dimension greater than or equal to two-vessel diameters). Thrombus grades 2 to 4 were combined to determine the incidence of angiographically certain thrombus. Stenoses with ulceration were those contain-

Table 1. Clinical and Angiographic Characteristics of 95 Patients Assigned to Streptokinase or Placebo

	Streptokinase (n = 46)	Placebo (n = 49)	p Value
Age (yr)	63 ± 9	63 ± 10	0.9
Presentation at admission			
Unstable angina	41 (89)	44 (90)	0.9
Non-Q wave MI	4 (11)	5 (10)	
Postadmission angiography			
<1 day	1 (2)	1 (2)	0.7
≥1 to <5 days	24 (52)	24 (49)	
≥5 days	21 (46)	23 (49)	
Culprit vessel			
Graft	25 (54)	26 (53)	0.9
Artery	10 (22)	16 (33)	0.2
Undetermined	11 (24)	7 (14)	0.3
Distribution of culprit vessel			
LAD	7 (15)	12 (24)	0.6
LCx	16 (35)	14 (29)	
RCA	15 (33)	13 (27)	
Undetermined	8 (17)	10 (20)	

Data presented are mean value ± SD or number (%) of patients. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

ing a neck with contrast material dissecting under the plaque either proximally or distally or showing distinct extravasation of contrast material. Angiographic morphology was scored independently, and when discrepancies arose, a consensus decision was obtained with a third observer (P.G.).

Culprit lesions. *Culprit lesions* were defined by the following criteria: 1) the location of stenosis progression (in coronary artery or graft by comparison with the next most recent coronary angiogram) corresponding to ECG abnormalities; and 2) the location of stenosis progression corresponding to the new wall motion abnormalities. When multiple progression was observed in one graft–vessel system, the more severe, complex lesion was selected as the culprit lesion. Agreement had to be achieved by a treating cardiologist and a cardiovascular radiologist (L.C., P.T.) in determining the location of culprit lesions.

Statistical analysis. Descriptive statistics for the variables assessed in the study were computed, and differences were assessed by Yates corrected chi-square analysis or Student *t* test, as appropriate. Data are presented as mean value ± SD, unless otherwise specified. Significance was defined as $p < 0.05$.

Results

Patients. The study included 79 men and 16 women with a mean age of 63 ± 9 years (range 40 to 80). Forty-six patients (48%) received streptokinase and 49 (52%) placebo. Age, gender, clinical presentation (unstable angina or non–Q wave MI) at admission, timing of angiography performed after admission and angiographic findings were similar in both treatment groups (Table 1). One-, two- and three-vessel disease was angiographically documented, respectively, in 6 (6%), 27 (28%) and 62 (65%) patients. By functional evaluation, as defined earlier, 32 patients (34%) had no or one-vessel disease, and the remaining 63 (66%) had three-vessel disease.

Angiographic features of culprit vein grafts versus native coronary arteries. The culprit vessel could be determined in 77 patients (79%) (vein graft in 51 [66%], ungrafted native coronary artery in 17 [22%], grafted coronary artery in 9 [12%]; proximal to the site of graft insertion in 3, distal in 6). Sixty-two of the 77 patients with an identifiable culprit lesion had ischemic ST-T changes; 7 had nondiagnostic changes; and 8 had no changes. Of 18 patients whose culprit vessel could not be determined with certainty, 5 showed no disease progression of either coronary arteries or grafts, and 8 had no ECG changes at admission, suggesting less severe disease in these patients. The clinical, ECG and angiographic findings were discordant in seven patients. Two of these patients had neither progression nor ECG changes. The clinical characteristics according to this classification are shown in Table 2.

Angiographic findings in patients with culprit lesions in vein grafts and ungrafted native coronary arteries are shown in Table 3. Total occlusion occurred in 25 vein grafts (49%) and four ungrafted coronary arteries (24%, p = 0.02). Intravessel thrombus was found in 18 culprit vein grafts but in only 2 ungrafted coronary arteries (37% vs. 12%, p = 0.04). Both an intracoronary thrombus and a total occlusion were demonstrated in six culprit vein grafts but in none of the ungrafted

Table 2. Clinical Features in Patients With Culprit Lesion in Grafts, Native Coronary Arteries or Undetermined

	All Patients (n = 95)	CV Determined			CV Undetermined (n = 18)
		Graft (n = 51)	Ungrafted Arteries (n = 17)	Grafted Arteries (n = 9)	
Age (yr)	63 ± 9	61 ± 9	64 ± 10	63 ± 10	63 ± 9
Men	79 (83)	43 (84)	14 (82)	7 (78)	15 (83)
Family history	56 (59)	32 (63)	9 (53)	5 (56)	10 (56)
Smoking	35 (37)	18 (35)	7 (42)	4 (44)	6 (33)
Hypertension	36 (38)	19 (37)	6 (35)	4 (44)	7 (39)
Hyperlipidemia	54 (57)	28 (55)	10 (59)	5 (56)	11 (61)
Diabetes mellitus	24 (25)	16 (31)	3 (18)	2 (22)	3 (17)

Data presented are mean values ± SD or number (%) of patients. CV = culprit vessel.

Table 3. Angiographic Findings in Patients With Culprit Lesions in Vein Grafts and Ungrafted Coronary Arteries

	Graft (n = 51)	Artery (n = 17)	p Value
Extent of coronary disease			
One-vessel disease	4 (8)	1 (6)	0.7
Multivessel disease	47 (92)	16 (94)	
Functional vessel disease			
No or one-vessel disease	16 (31)	6 (35)	0.7
Multivessel disease	35 (69)	11 (65)	
Postadmission angiography (days)	5 ± 2	5 ± 2	0.8
% stenosis of culprit lesion	66 ± 14	68 ± 10	0.7
MLD of culprit lesion (mm)	1.34 ± 0.67	1.10 ± 0.4	0.01
Lesions/CV	1.2 ± 1.0	1.3 ± 0.9	0.9
CV occlusion	25 (49)	4 (24)	0.02
CV thrombus	18 (37)	2 (12)	0.04
Occlusion and thrombus	6 (12)	0	NS
Culprit complex lesion*	16 (62)	8 (62)	1.0
Possible thrombus	5 (19)	2 (13)	0.8
LVEF	62 ± 10	63 ± 12	0.8

*Totally occlusive lesions excluded for this analysis. Data presented are mean value ± SD or number (%) of patients. CV = culprit vessel; LVEF = left ventricular ejection fraction; MLD = minimal lumen diameter.

coronary arteries (12% vs. 0%, p = NS). The prevalence of complex lesions (totally occluded arteries were not analyzed) was similar in vein grafts and ungrafted coronary arteries (16 [62%] vs. 9 [62%]). Possible thrombus and ulceration were found in five (19%) and four (15%) of culprit lesions in vein grafts and in two (15%) and one (8%) ungrafted native coronary arteries (p = NS). There were no significant differences in clinical features, other angiographic characteristics and timing for coronary artery/graft angiography after onset of symptom between patients with culprit lesions in vein grafts and those with culprit lesions in ungrafted coronary arteries (Table 3). Administration of streptokinase or placebo did not modify the findings: The prevalence of new total occlusion was, respectively, 33% and 39%; for thrombus the prevalence was 17% and 24%, and that for a complex stenosis was 28% and 33% (Table 4).

Culprit vessel and age at operation. Of the 77 patients with identifiable culprit vessels, the age of vein grafts was <5 years

Table 4. Influence of Streptokinase on Morphologic Features of Culprit Lesions

	Streptokinase (n = 46)	Placebo (n = 49)	p Value
Occlusion	15 (33)	19 (39)	0.8
Vein grafts	13	16	
Native arteries	2	3	
Thrombus	8 (17)	12 (24)	0.8
Vein grafts	8	10	
Native arteries	0	2	
Occlusion and thrombus	23 (50)	31 (63)	0.3
Complex stenosis	13 (28)	16 (33)	0.6
Vein grafts	10	11	
Native arteries	3	5	

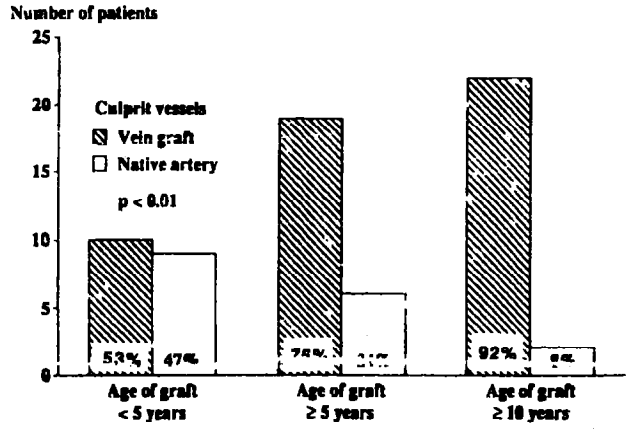

Figure 1. Age of graft at <5, ≥5 and ≥10 years after CABG showing relative contribution of graft versus native coronary artery disease as a cause of unstable angina. **Numbers within bars** = percent of patients.

in 19, between 5 and 10 years in 25 and >10 years in 24. Within the first 5 years, the vein graft was responsible for the unstable angina episode in 10 patients and the native artery in 9. Between 5 and 10 years, the culprit lesion was located in a graft in 19 patients and in a native artery in 6; after 10 years, the lesion was located in a graft in 22 of the 24 patients (p < 0.01) (Fig. 1). The unstable angina episode occurred within 5 years after operation in five of the nine patients with culprit lesion located in grafted arteries and between 5 to 10 years in the four other patients.

Disease progression in grafts and native coronary arteries. The angiogram obtained after the unstable angina episode was compared with the patient's most recent angiogram to assess disease progression in ungrafted native coronary arteries, grafted native arteries and grafts. This angiogram had been acquired postoperatively in 64 patients and preoperatively in 31. There were 101 patent and 24 occluded vein grafts and 13 patent and 4 occluded arterial grafts in the 64 patients with a postoperative angiogram. In patients with a preoperative angiogram only, 57 vein grafts and 14 arterial grafts had been placed. Disease progression was not significantly different on angiograms acquired after or before CABG and was observed, respectively, in 56 (55%) and 22 (42%) vein grafts, 20 (53%) and 9 (47%) ungrafted native arteries, and 13 (11%) and 6 (8%) grafted arteries distal to the site of graft insertion. However, disease progression in the grafted artery proximal to the site of vein insertion was more common in patients with angiography performed before than after CABG (33 [60%] vs. 11 [19%], p < 0.05). Disease progression distal to the site of an arterial graft implant was rare and was observed in only 1 of 27 implants. Eight of the 80 vein grafts with disease progression had diffuse graft disease (multifocus progression). Obstructive lesions (including total occlusion) were observed at the ostium of the graft in 23 (25%), in the graft body in 51 (56%) and at the site of vein insertion in 17 (19%).

Discussion

Deterioration of angina in patients with previous CABG is usually associated with progression of atherosclerosis in native arteries or vein grafts (18–20). However, the relative importance of stenosis progression in grafts versus coronary arteries as well as the morphologic features of the culprit lesions in unstable angina have not been previously assessed. The present study documents that vein graft failure by an occlusive atherosclerotic-like disease is responsible for unstable angina in 66% of patients, with proportions increasing as the grafts age. Coexistence of coronary artery disease progression is also frequently observed. Culprit lesions located in grafts are also more complex than in native coronary arteries.

Prevalence of intracoronary thrombi and total occlusion in culprit vein grafts versus ungrafted native coronary arteries. The important role of coronary thrombosis in unstable angina has been demonstrated by angiography, angioscopy, autopsy and effect of treatment (17,21–29). Intravascular thrombi have been described in 6% to 70% of patients undergoing catheterization during an unstable angina episode, with the highest incidence observed on angiograms obtained early during the acute phase. No data are available on the frequency of intravessel thrombus in vein grafts. In the present study, although angiography was performed relatively late after the acute episode, a thrombus could be demonstrated in 37% of the culprit graft lesions compared with 12% of the culprit ungrafted coronary arteries. The thrombus is usually completely occlusive in patients with Q wave MI and partially occlusive in patients with unstable angina or non–Q wave MI (30–33). In our study, occlusion was found in 24% of native coronary arteries but twice as frequently in grafts. Waters et al. (11) reported a smaller infarct size in patients undergoing CABG compared than control patients but the same frequency of total occlusion, suggesting that patients with previous CABG have additional myocardial protection or less viable myocardium perfused by the graft. The higher incidence of intravessel thrombi and total occlusion in grafts in our patients with unstable angina suggests in addition that once plaque complication occurs, it is more refractory to spontaneous and therapeutic thrombolysis. This conclusion is reinforced by the fact that angiography was performed relatively late during the acute phase, after a course of medical treatment.

Prevalence of complex lesions in ungrafted native arteries versus grafts. The prevalence of complex lesions, which represent plaque rupture or a partially occlusive thrombus, or both (33), was similar in culprit grafts and ungrafted native arteries, in accordance with a common pathophysiologic mechanism for grafts (6,5) and coronary arteries (33) in patients with unstable angina. However, vein graft atherosclerosis lesions may differ from native coronary artery atherosclerosis (6), in that they do not have a fibrous cap, resulting in direct exposure of foam cells and lipid debris to the bloodstream (6). Solymoss et al. (34), in a histopathologic study of vein grafts obtained at operation, described vein graft atherosclerosis as a major factor predisposing to thrombosis. Thus, although plaque rupture may be the common event leading to unstable angina in both vein grafts and native coronary arteries, the angiographic expression of this process is more complex in vein grafts than native coronary arteries.

Effect of thrombolytic and antithrombotic therapies. Previous angiographic trials of thrombolytic therapy in patients with unstable angina have described a modest angiographic improvement with thrombolysis but no clinical improvement (17,35). The TIMI IIIA study (17), for example, showed significantly more frequent substantial reduction of culprit lesion severity 18 to 48 h after administration of tissue-type plasminogen activator than after placebo, when an intracoronary thrombus was documented. That study excluded patients with previous CABG. In the current study involving only patients with previous CABG, the severity and complexity of culprit graft stenoses observed during the first week after treatment were similar regardless of whether the patients had received thrombolysis. This finding suggests that vein graft disease is either more active or less responsive to treatment. This refractoriness could contribute to the worse long-term prognosis of patients with unstable angina with previous CABG. Although the success of conventional intravenous thrombolysis in restoring coronary flow is relatively low, it is possible that higher doses and more prolonged infusions of thrombolytic agents could have resulted in more effective clot lysis, as has been suggested by some studies (36).

Disease progression and risk factors. The relative contribution of graft disease versus progression in native arteries to the development of unstable angina became greater the longer the postoperative period in those patients who developed unstable angina. The culprit lesion was located in the graft in 52% of patients with episodes of unstable angina that developed between 6 months and 5 years postoperatively, in 76% of those with episodes that developed between 5 and 10 years and in 92% after 10 years. This observation parallels the pathologic finding of increasing atherosclerosis as grafts age (37). Graft atherosclerosis is influenced by risk factors and plasma lipoprotein levels (38). Although a detailed analysis of the role of plasma lipids and other risk factors was beyond the scope of the present study, no association was found between coronary disease risk factors and disease progression. This result may reflect the entry criteria for this trial, with progression expected in nearly all patients, or a differential role of risk factors in disease progression and local factors in triggering unstable angina. The culprit lesion was more occlusive and thrombogenic in grafts than in native arteries but, in general, not more obstructive.

Limitations of the study. Although patients were entered consecutively in the trial and the data prospectively collected, the present study was not specifically designed as an angiographic study. Image acquisitions were not standardized with regard to nitroglycerin administration. The timing of angiography during the hospital period was also not standardized, with preceding periods of treatment varying between 1 to 8 days, precluding an exact description of the prevalence of thrombosis. However, thrombi were more frequent at any time

in culprit vein grafts than in native arteries; it should be stressed that identification of thrombus in grafts could be less reliable than in native arteries because of flow separation, steaming and vessel wall deposition of proteinaceous material. Nevertheless, in this study, only three lesions classified initially as thrombi grade ≥2 by an observer were finally classified as possible thrombus (grade 1) on consensus decision.

Clinical implications. Patients with previous CABG with unstable angina have a worse prognosis than those without previous CABG. Explanations proposed have been a higher risk profile in patients with previous CABG and more severe disease less amenable to a corrective intervention (2,3). The present study further suggests that graft disease is less responsive to conventional therapy in some instances. A greater thrombogenic substrate in grafts (34), decreased prostacyclin production (37) and different shear stress and rheologic properties influencing thrombus composition and washout of thrombogenic material (39) may explain this finding. The different pathophysiologic characteristics stress the need for more potent therapeutic regimens and more effective antithrombotic therapy in these patients, especially when grafts are older. These observations do not apply to internal mammary arteries, which are now routinely used because of their superior long-term patency. However, the vast majority of patients require one or more additional saphenous vein bypass grafts. Aspirin has been shown (40) to improve early vein graft patency but not long-term patency. Patients with unstable angina and previous CABG form a high risk population suitable for the evaluation of new therapies.

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