EDITORIAL: APROTININ AND VEIN GRAFT OCCLUSION—THE CONTROVERSY CONTINUES

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Aprotinin therapy is now advocated by some enthusiasts to inhibit fibrinolysis and preserve platelet function in patients undergoing coronary artery bypass grafting (CABG). In these patients ischemia during harvesting and preparation of the saphenous vein already impairs endothelial cell anticoagulant function (Fig 1), the protease enzyme components of which are then inhibited by aprotinin.^{1,2} In every other branch of surgery, fibrinolysis is regarded as a vital physiologic process to maintain blood vessel patency in the face of surgically induced thrombin formation. Similarly, in patients with coronary artery disease, aspirin is prescribed to impair platelet adhesion.³ Can this paradox be rationalized? Should aprotinin be used in coronary surgery?

Trials of aprotinin during CABG operations have raised important issues regarding both heparin management and graft patency.⁴⁻⁶ In the United States, 3 consecutive randomized trials reported excess mortality and myocardial infarction when less than the full-dose aprotinin regimen was used in primary or reoperative coronary operations.⁷⁻⁹ In some patients, autopsy showed occlusion of the native coronary arteries in contrast to the vein grafts.⁷ Inasmuch as these trials were designed to confirm the blood-sparing effect, they were individually too small to determine the safety issues. Because of this, Smith and Muhlbaier¹⁰ pooled raw data for patients undergoing CABG from 6 trials and documented a 42% increase in observed CABG mortality in patients subjected to the half-dose regimen. The authors concluded that aprotinin was safe and effective only with the full-dose regimen. The effects on graft patency remained to be determined.

Studies of vein graft patency have produced conflict-

ing information depending on the dosage regimen and mode of investigation. Most investigators using early graft angiography or ultrafast computed tomography showed no difference between placebo and treatment groups.¹¹⁻¹⁴ In contrast, Van de Meyer and colleagues⁶ used graft angiography 1 year after the operation (non-randomized retrospective study) and showed distal anastomosis occlusion rates of 20.5% for aprotinin-treated patients versus 12.7% for those without aprotinin ($P = .09$). The proportions of patients with occluded grafts were 44.1% versus 26.3%, respectively ($P = .3$). Perioperative myocardial infarction occurred in 14.3% versus 7.0% ($P = .12$).

In an attempt to perform a definitive prospective randomized study of vein graft patency, Bayer commissioned a multicenter trial using graft angiography within a few days of surgery. The patients were recruited from 10 centers in the United States, 2 in Israel, and 1 in Denmark (designated "European centers"). During 1994 and 1995, 870 patients were randomized to either high-dose aprotinin (Hammersmith regimen) or placebo. The outcome of this study was eventually reported 2 years later at the Seventy-eighth Annual Meeting of The American Association for Thoracic Surgery (1998) in Boston.¹⁵ Only 703 patients (80%) had satisfactory graft angiograms. The studies showed thrombotic occlusion in 15.4% of aprotinin-treated patients versus 10.9% in the placebo group ($P = .03$). Given the significant increase in vein graft occlusion for aprotinin-treated patients, the whole population was subject to rigorous subanalysis. From this, Bayer reported "a significant treatment by site interaction for one of the non-US sites vs the US centers. When the analysis of graft closures was repeated for US centers only, there was no statistically significant difference in graft closure rates in patients who received Trasylol vs placebo."¹⁶

This conclusion from the Bayer advertising literature is open to discussion. Why were the differences in vein graft occlusion rates between US and non-US centers so dramatic (aprotinin: non-US 23%, US 9.4%; placebo: non-US 12.4%, US 9.5% (Table I)? Should aprotinin or the surgeons be blamed? Scrutiny of the data provides several explanations. The study protocol was changed at 1 Israeli site after blood for vein preparation was initially obtained from the central venous line into which the aprotinin had been administered. Remarkably, this

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Anticoagulant Function of the Endothelial Cell

Fig 1. The anticoagulant function of the endothelial cell acts to prevent intravascular thrombosis. During surgery, thrombin generation through activation of the coagulation cascade stimulates the endothelial cell (via thrombomodulin and heparan sulphate receptors) to release anticoagulants. The endothelium initiates activation of factor VII by tissue factor (the most potent initiator of coagulation known) and produces thrombomodulin, which is reduced by 30% during vein harvest. Binding of antithrombin III inactivates thrombin while tissue plasminogen activator (T.P.A.) triggers fibrinolysis and protein C inhibits coagulation. These enzymes are down-regulated by the nonspecific protease inhibitor aprotinin.

Table I. Comparison between US and non-US centers

				Patients with SVG angiographically investigated (n = 703)					
All study patients (n = 870)				Aprotinin		Placebo			
Site (No. of centers)	Total	Mean/ center	Range	Male (%)	Occlusion*/ total	Percent†	Occlusion*/ total	Percent†	P
US (10)	471	47	2-95	90	19/202	9.4	17/179	9.5	.72
Non-US (3)	399	133	105-168	85	37/161	23	20/161	12.4	.01

SVG, Saphenous vein graft.

*Calculated from provided occlusion rate and group size in Table IV.¹⁵

†By-patient occlusion rate.

produced a graft occlusion rate of 73% in the aprotinin group and an important indication of the risk of this agent in patients with coronary disease. After procedures at this center had been revised, graft occlusion rates with aprotinin decreased to 14% versus 3% for placebo for the remaining two thirds of the study. There were other important differences (Table I). First, the patients were selected, not consecutive, and the coronary surgery intervention rates in the United States ($>1000 \times 10^6$) greatly exceed those of European centers ($<500 \times 10^6$). Despite this, the US centers randomized on average only 47 patients over 2 years, of whom 90% were male. One center randomized only 2 patients.

Patients in US centers had larger and better-quality distal vessels. The US sites also had a higher proportion of patients receiving aspirin within 2 days of the operation, which could favor graft patency. Consequently, the US patient cohort was less likely to have graft occlusion with or without aprotinin. In contrast, European centers randomized an average of 133 patients per center, more women, more patients with vessels less than 1.5 mm in diameter, and more with distal disease. These variables were identified as predisposing to graft occlusion in aprotinin-treated patients, and certainly the difference in occlusion rates for women and those with less than satisfactory distal vessels was substantial

Table II. Observed “by-graft” occlusion rates and risk for designated high-risk variables

Variables	Occlusion rates (%)		P*	Adjusted risk ratio	90% CL
	Aprotinin	Placebo			
Female patients	20.7	4.2	.06	5.34	1.81-15.80
Distal vessel $\leq$ 1.5 mm	10.8	5.3	.06	1.92	1.15-3.20
Poor distal vessel	11.4	5.5	.08	1.90	1.09-3.32

CL, Confidence limits.

*To drug-by-covariate interaction.

(Table II). Vessel measurement is an inexact science and coronary angiography can underestimate native vessel size in the presence of a high-grade proximal stenosis or occluded vein graft. Some vessels said to be less than 1.5 mm may well have been larger.

Bayer’s interpretation that aprotinin does not promote vein graft occlusion in the United States is overly simplistic.¹⁶ Given the dramatic increase in interventional cardiology (since 1995) for patients with discrete lesions and good distal vessels, the vast majority of surgical candidates now have 1 or more coronary arteries with “high-risk” characteristics. Those randomized in the non-US centers now better represent the global CABG population and, from this study, are clearly at risk from aprotinin therapy during CABG.¹⁵ Although there was no significant difference in perioperative myocardial infarction rates, the incomplete revascularization resulting from early graft occlusion predisposes the patient to late myocardial infarction, recurrent angina, and reduced event-free survival. Occluded CABGs are a high price to pay for an average blood saving of 250 mL, particularly inasmuch as excessive pump prime volume, as well as blood loss, determines the postoperative hematocrit value in most straightforward operations. There are other ways to conserve blood, and the contrary view that hemodilution, temporary fibrinolysis, and platelet dysfunction convey benefit by promoting vein graft patency is more appealing.

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