References

1. Dotter CT. Transluminally-placed coilspring endarterial tube grafts: long term patency in canine popliteal artery. *Invest Radiol*. 1969;4:329-332.
2. Sigwart U, Puel J, Mirkovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med*. 1987;316:701-706.
3. Stack RE, Califf RM, Phillips HR, et al. Interventional cardiac catheterization at Duke Medical Center. *Am J Cardiol*. 1988;62(suppl F):3F-24F.
4. Zidar J, Lincoff A, Stack R. Biodegradable stents. In: Topol EJ, ed. *Textbook of Interventional Cardiology*. 2nd ed. Philadelphia: WB Saunders;1994:787-802.
5. Van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary artery. *Circulation*. 1996;94:1690-1697.
6. Lincoff AM, Furst JG, Ellis SG, et al. Sustained local delivery of dexamethasone by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. *J Am Coll Cardiol*. 1997;29:808-816.

Stenting Plus Abciximab vs tPA in Acute Myocardial Infarction

Reviewed by David P. Faxon, MD
University of Chicago Pritzker School of Medicine
[*Rev Cardiovasc Med.* 2001;2(2):107–108]

The increase in the use of primary angioplasty as compared with thrombolysis is based on a growing number of clinical trials that have shown improved short-term and long-term clinical benefit with the use of angioplasty.[1] The critics of these studies point to the relatively small number of patients who have been studied in primary angioplasty trials and to the fact that these trials are carried out in large centers and the procedures performed by highly experienced operators, which does not reflect the situation of the majority of centers where angioplasty is performed in the United States. Support of this concern comes from the National Registry of Myocardial Infarction (NMRI), with more than 27,000 patients, which shows that the majority of these patients underwent primary angioplasty more than 2 hours after presentation at the emergency department and that the success rates in these centers was significantly lower than those published in clinical trials.[2] In addition, the GUSTO IIb trial showed angioplasty to have only a minimal benefit over tPA.[3] GUSTO IIb, a multicenter trial in 57 centers, enrolling 1,138 patients, is the largest trial of primary angioplasty to date.

The enthusiasts for primary angioplasty point to the significant advances that have been made in the procedure with the current widespread use of coronary stents and glycoprotein IIb/IIIa agents. Stenting in most clinical trials has been shown to provide a better initial result and a decreased rate of restenosis. Glycoprotein IIb/IIIa agents, particularly abciximab, have been shown to reduce the incidence of acute complications and improve long-term outcomes in certain subgroups of patients, such as those with diabetes. In the RAPPORT trial, a study of abciximab in acute myocardial infarction and primary angioplasty, significant improvement in short-term outcomes was demonstrated.[4]

Coronary Stenting Plus Platelet Glycoprotein IIb/IIIa Blockade Compared with Tissue Plasminogen Activator in Acute Myocardial Infarction

Schömig A, Kastrati A, Dirschinger J, et al., for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators
N Engl J Med. 2000;342:385-391.

Schömig and colleagues compared coronary stenting plus abciximab to tissue plasminogen activator (tPA) in 140 patients with ST-segment elevation who presented within 12 hours of the onset of chest pain. The primary end point of this randomized, single-center study was myocardial salvage, as determined by technetium-99m sestamibi imaging done at baseline and at 1 week. The study demonstrated that patients receiving a stent and abciximab had greater salvage (57% vs 26%, $P = .001$) and smaller infarct size (14.3% vs 19.4% of the left ventricle, $P = .02$) than patients receiving tPA. In addition, 6-month outcomes were improved, with a lower incidence of death, reinfarction, and stroke in the stent plus abciximab group (8.5% vs 23.3%, $P = .02$). It should be noted that the study was small and that therefore individual end points, such as death, were not statistically different, although directionally consistent with the overall findings (3 deaths in the stent group vs 9 deaths in the tPA group).

This study differs from previous studies in that the primary end point was infarct size as determined by ^{99}mTc sestamibi rather than clinical events or mortality. Nevertheless, it adds further data to a growing body of information concerning the value of an interventional approach to the treatment of patients with acute myocardial infarction. The benefit of percutaneous coronary intervention (PCI) in this study is likely because of the high TIMI 3 flow rate achieved (95.8%), a rate higher than that seen in the GUSTO IIb trial. The value of abciximab is also inferred by the authors, who suggest that it reduced thrombotic occlusion and distal microembolization and that this may have further limited infarct size.

While this study supports the role of PCI over tPA, it was not specifically designed to compare balloon angioplasty with stenting or the use of abciximab with its omission in the setting of acute myocardial infarction. The larger multicenter, randomized trial CADILLAC addressed these issues specifically, but the results are not yet published.[5] Preliminary data suggest an extremely low overall mortality rate of 1.5% at 30 days in this study, without any significant difference between balloon alone, stenting alone, and the use of balloon or stenting with abciximab. If the final trial results confirm these preliminary results, then the routine use of stents and abciximab may need to be questioned. Improved outcomes, in both Schömig and colleagues' study and the CADILLAC trial, are more likely due to the rapid reperfusion that was achieved at these centers (within 60 minutes in the Schömig study) and the very high TIMI 3 perfusion rate (96% in Schömig, 98% in CADILLAC). The key message from this report and previous studies is that optimal reperfusion is the central element in obtaining maximum myocardial salvage and a low 6-month event rate, no matter how achieved.

References
1. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA*. 1997;278:2093-2098.
2. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000; 283:2941-2947.
3. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med*. 1997;336:1621-1628.
4. Brener SJ, Barr LA, Burchenal JEB, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation*. 1998;98:734-741.
5. Stone G. The CADILLAC Trial. Presented at: American Heart Association 72nd Scientific Sessions; November 7-10,1999, Atlanta, Georgia.

Angiogenesis

The Role of Nitric Oxide in Atherogenesis

Reviewed by Alan C. Yeung, MD
Stanford University Medical Center, Stanford, CA
[*Rev Cardiovasc* 2001;2(2):108]

Nitric oxide (NO) is known to be important in the control of vasomotor tone and as an inhibitor of atherogenesis. Not until recently, however, has the role NO plays in angiogenesis been defined. A number of angiogenic factors up-regulate the expression of endothelial NO synthase (eNOS) and stimulate the release of NO. Vascular endothelial growth factor (VEGF) stimulates the release of NO, and secretion is enhanced by NO's precursor, L-arginine.

NO seems to play a critical role in angiogenesis. Endothelial cells, when stimulated by VEGF or fibroblast growth factor (FGF), release NO and form 3-dimensional capillary-like structures. These effects are blocked by the NOS antagonist N-nitro-L-arginine methylester (L-NAME). An endogenous antagonist to NOS, called asymmetric dimethylarginine (ADMA), has been discovered recently and has been shown to compete with L-arginine for NOS. Hypercholesterolemia is associated with the elevation of ADMA. This paper explores the role of ADMA as an endogenous antiangiogenic factor.

The experiment was performed in normal (E+) and in apolipoprotein E–deficient hypercholesterolemic (E-) mice using a subcutaneous implantable disk angiogenesis system. Fibrovascular growth was assessed as an index of angiogenesis after 2 weeks. Basal and FGF-stimulated angiogenesis was impaired in E-mice, a finding associated with an elevation in plasma ADMA level. This inhibition was reversed by oral administration of L-arginine. Direct addition of ADMA to the disk also inhibited angiogenesis in a dose-dependent manner.

Angiogenesis Is Impaired by Hypercholesterolemia: Role of Asymmetric Dimethylarginine

Jang JJ, Ho H-KV, Kwan HH, et al.
Circulation. 2000;102:1414-1419.

This basic science report brings together several pieces of information that shed light on the pathogenesis of angiogenesis, showing that hypercholesterolemia inhibits angiogenesis and that ADMA plays a key role. This observation firmly ties together the NO pathway and the ability of the vascular system to regenerate itself at times of ischemia. Exactly how NO can lead to angiogenesis is still largely unknown. Whether angiogenesis supported by NO leads to collateral vessel formation or angiogenesis in the vasa vasorum is under active investigation.

Suggested Reading
1. Hood JD, Meninger CJ, Ziche M, et al. VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. *Am J Physiol*. 1998;274:H1054-H1058.
2. Boger RH, Bode-Boger SM, Szuba A, et al. Asymmetric dimethyarginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterolemia. *Circulation*. 1998;1842-1847.
3. Cooke JP, Singer AH, Tsao P, et al. Anti-atherogenic effects of L-arginine in the hypercholesterolemic rabbit. *J Clin Invest*. 1992;90:1168-1172.