

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Bypass Surgery Versus Stenting for the Treatment of Multivessel Disease in Patients With Unstable Angina Compared With Stable Angina

P.J. de Feyter, P.W. Serruys, F. Unger, R. Beyar, V. de Valk, S. Milo, R. Simon, D. Regensburger, P.A. Crean, E. McGovern, P. van den Heuvel, C. van Cauwelaert, I. Penn, G.F.O. Tyers and W. Lindeboom

Circulation 2002;105;2367-2372; originally published online May 6, 2002;

DOI: 10.1161/01.CIR.0000016643.34907.17

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2002 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online
ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/105/20/2367>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21202-2436. Phone 410-5280-4050. Fax: 410-528-8550. Email:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/static/html/reprints.html>

Bypass Surgery Versus Stenting for the Treatment of Multivessel Disease in Patients With Unstable Angina Compared With Stable Angina

P.J. de Feyter, MD; P.W. Serruys, MD; F. Unger, MD; R. Beyar, MD; V. de Valk, MSc; S. Milo, MD; R. Simon, MD; D. Regensburger, MD; P.A. Crean, MD; E. McGovern, MD; P. van den Heuvel, MD; C. van Cauwelaert, MD; I. Penn, MD; G.F.O. Tyers, MD; W. Lindeboom, MSc

Background—Earlier reports have shown that the outcome of balloon angioplasty or bypass surgery in unstable angina is less favorable than in stable angina. Recent improvements in percutaneous treatment (stent implantation) and bypass surgery (arterial grafts) warrant reevaluation of the relative merits of either technique in treatment of unstable angina.

Methods and Results—Seven hundred fifty-five patients with stable angina were randomly assigned to coronary stenting (374) or bypass surgery (381), and 450 patients with unstable angina were randomly assigned to coronary stenting (226) or bypass surgery (224). All patients had multivessel disease considered to be equally treatable by either technique. Freedom from major adverse events, including death, myocardial infarction, and cerebrovascular events, at 1 year was not different in unstable patients (91.2% versus 88.9%) and stable patients (90.4% versus 92.6%) treated, respectively, with coronary stenting or bypass surgery. Freedom from repeat revascularization at 1 year was similar in unstable and stable angina treated with stenting (79.2% versus 78.9%) or bypass surgery (96.3% versus 96%) but was significantly higher in both unstable and stable patients treated with stenting (16.8% versus 16.9%) compared with bypass surgery (3.6% versus 3.5%). Neither the difference in costs between stented or bypassed stable or unstable angina (\$2594 versus \$3627) nor the cost-effectiveness was significantly different at 1 year.

Conclusions—There was no difference in rates of death, myocardial infarction, and cerebrovascular event at 1 year in patients with unstable angina and multivessel disease treated with either stented angioplasty or bypass surgery compared with patients with stable angina. The rate of repeat revascularization of both unstable and stable angina was significantly higher in patients with stents. (*Circulation*. 2002;105:2367-2372.)

Key Words: angioplasty ■ revascularization ■ stents ■ surgery

There is uncertainty as to the appropriate intervention, bypass surgery or percutaneous intervention, required for the treatment of unstable angina. Coronary artery bypass surgery is highly effective in relieving ischemic symptoms, but earlier studies reported a higher perioperative mortality rate in unstable patients, particularly when performed early after myocardial infarction (MI).¹⁻⁴ Late survival and sustained symptom relief is excellent after surgery for unstable angina.⁵

Recent improvements in bypass surgery, notably the use of arterial grafts, have made the procedure safer and more effective, although the presence of instability at the time of surgery is still a predictor of increased perioperative risk.⁶⁻¹⁰

Balloon angioplasty for unstable angina was less successful and associated with a higher complication rate and late

restenosis rate compared with balloon angioplasty for stable angina.¹¹⁻¹⁵ The adjunctive treatment with platelet glycoprotein IIb/IIIa inhibitors has significantly reduced the 30-day major complication rate,¹⁶⁻¹⁹ and the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPI-STENT) trial demonstrated that stent implantation combined with platelet glycoprotein IIb/IIIa inhibitors for treatment of predominantly single-vessel disease (90%) achieved similar results in unstable patients compared with stable patients.²⁰

Recent randomized trials comparing surgery and percutaneous intervention for the treatment of multivessel disease have shown that both treatments were associated with similar death and MI rates, but they have not specifically addressed the outcome in unstable patients compared with stable patients.²¹⁻²⁴

Received December 17, 2001; revision received March 14, 2002; accepted March 14, 2002.

From the University Hospital Rotterdam, Dijkzigt, Thoraxcenter, Rotterdam, the Netherlands (P.J.d.F., P.W.S.); Klinik für Herzchirurgie, Landeskliniken, Salzburg, Austria (F.U.); Rambam Medical Centre, Haifa, Israel (R.B., S.M.); Cardialysis B.V., Rotterdam, the Netherlands (V.d.V., W.L.); Christian Albrechts Universität, Kiel, Germany (R.S.); Klinik für Kardiologie, Kiel, Germany (D.R.); St James's Hospital, Dublin, Ireland (P.A.C., E.M.); Academic Hospital Middelheim, Antwerp, Belgium (P.v.d.H., C.v.C.); and Vancouver Hospital and Health Science Centre, Vancouver, Canada (I.P., G.F.O.T.).

Correspondence to P.J. de Feyter, MD, University Hospital Rotterdam, Thoraxcenter Bd 410, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail defeyter@card.azr.nl

© 2002 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000016643.34907.17

TABLE 1. Baseline Characteristics

	Stented Angioplasty		CABG	
	Stable (n=374)	Unstable (n=226)	Stable (n=381)	Unstable (n=224)
Male sex, %	75	80	77	75
Age, y (range)	61±10 (35–83)	61±10 (30–78)	62±10 (32–81)	61±10 (34–82)
Body mass index	28±4	27±4	28±4	27±4
Previous conditions, %				
Q-wave MI	27	24	24	26
Non-Q-wave MI	16	22	15	22
Diabetes mellitus	19	19	17	15
Hypertension	42	49	46	43
Hypercholesterolemia	62	52	60	54
Family history	42	36	42	42
Smoking	70	74	74	71
Stable angina/silent ischemia CCS classification, %				
1	8	...	8	...
2	42	...	42	...
3	35	...	37	...
4	6	...	6	...
Silent ischemia	10	...	8	...
Unstable Braunwald, %				
IB/IIb/IIb	...	16/34/23	...	16/37/27
IC/IIc/IIc	...	7/17/5	...	3/13/5
Ejection fraction, %	61±12	62±13	62±13	59±14
Number vessel diseased, %				
2	69	67	65	64
3	31	33	35	36
Vessel territory, %				
RCA	73	74	72	74
LAD	88	93	88	90
CX	69	67	73	73

There were no statistically significant differences between the 4 groups.

In this prespecified subanalysis of the Arterial Revascularization Therapies Study (ARTS) trial, the clinical outcomes, costs, and cost-effectiveness of treatment of patients with multivessel disease and unstable angina were compared with those of patients with stable angina who were randomized to either percutaneous coronary intervention (PCI) with stent implantation or coronary artery bypass grafting (CABG) using arterial grafts.

Methods

Patients

ARTS is a randomized trial comparing PCI versus CABG. Patients with multivessel disease and a left ventricular ejection of at least 30% were included if they were deemed equally treatable with either technique by consensus of cardiac surgeon and interventional cardiologist. After providing written informed consent, the patients were randomized to either CABG or PCI. Patients with left main stem stenosis, prior CABG or PCI, transmural MI within the previous week, history of prior cerebrovascular accident (CVA), concomitant severe hepatic or renal disease, need for other major surgery, intolerance or contraindication to acetyl salicylic acid or ticlopidine,

or presence of leucopenia, neutropenia, or thrombocytopenia were excluded. Recruitment took place between April 1997 and June 1998. The clinical outcomes, costs, and cost-effectiveness are being determined at 30 days and 1, 3, and 5 years. Details and results of the main trial are provided elsewhere.²⁵

Classification and Revascularization of Patients

Patients were classified as having stable angina (Canadian Cardiovascular Society class 1 through 4),²⁶ silent ischemia, or unstable angina (Braunwald classification I B, C through III B, C).²⁷ They must have had at least 2 de novo coronary lesions located in different vessels. At least 1 stent per patient had to be implanted, but the total number of stents was not restricted. For the purpose of this study, the Cordis Palmaz Crown stent and the Crossflex stent were used for stent implantation. Whenever feasible, the internal mammary artery had to be used for revascularization of the left anterior descending coronary artery or the diagonal branches.

End Points

The primary end point was defined as the absence of any of the following major adverse cardiac and cerebrovascular events (MACCE) within 12 months after randomization: death, CVA, documented nonfatal MI, or repeat revascularization by PCI or

TABLE 2. Procedural Details of PCI and CABG

	Stented Angioplasty		CABG	
	Stable (n=374)	Unstable (n=226)	Stable (n=381)	Unstable (n=224)
Total no. stenotic lesions (>50% diameter)	2.76±1.0	2.93±1.1	2.75±1.0	2.9±1.0
Actually treated or bypassed, n	2.59±1.1	2.76±1.2	2.66±1.0	2.64±1.0
Arterial conduit, n	1.1±0.54	1.11±0.6
Conduit to LAD, %	95	94
Lesions stented, n	2.36±0.95	2.38±0.92
Balloon angioplasty, n	0.23±0.6	0.38±0.8

LAD indicates left anterior descending coronary artery.

CABG. All deaths, cardiac and noncardiac, were reported. Cerebrovascular events were classified into 3 categories: stroke, transient ischemic attacks, and reversible ischemic neurological deficits. All MIs were counted as events, whether occurring spontaneously or as a periprocedural complication during PCI or CABG.

The Minnesota Code for pathological Q waves was used.²⁸ The serum levels of creatine kinase (CK) and CK muscular brain (CK-MB) were sampled at 6, 12, and 18 hours after intervention, and their ratios were calculated. Within the first 7 days after intervention, a definite diagnosis of MI was made if new Q waves were documented together with 1 sampled ratio of CK-MB >10% or 1 plasma level of CK-MB 5 times the upper limit of normal.²⁹ After 7 days, either Q-wave or enzymatic elevation were sufficient as criteria for MI.

A core laboratory analyzed relevant electrocardiograms, and the diagnosis of MI was made after adjudication by a clinical event committee. Repeat revascularization was performed if patients had recurrent angina. The choice between (repeat) PCI and (repeat) CABG was left to the discretion of the investigator.

Costs and cost-effectiveness of both techniques were compared at 1 year. Costs were limited to the direct medical costs per patient, calculated as the product of each patient's use of resources and the corresponding unit cost. The cost-effectiveness was calculated using MACCE event-free survival as the measure of effectiveness. The incremental cost-effectiveness ratio is defined as the additional costs per additional year of MACCE-free survival.

Statistical Analysis

Continuous variables were expressed as mean±SD and were compared using the unpaired Student's *t* test. The Fisher's exact test was

used for categorical variables. The Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables were expressed as counts and percentages and were compared in terms of relative risks (for CABG compared with PCI) with 95% CI.³⁰ All analyses were based on the intention-to-treat principle, and statistical tests were 2-tailed. Event-free survival distribution was estimated

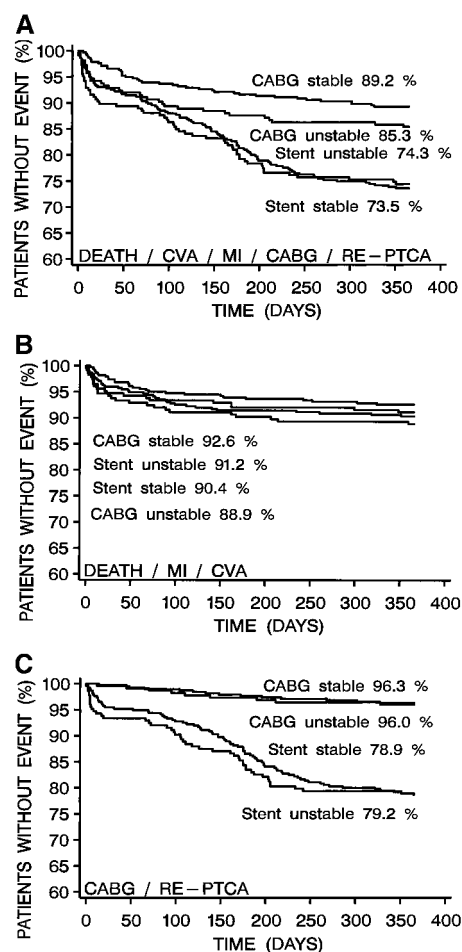


TABLE 3. Frequency of Major Cardiac Events Per Patient at 1 Year in Descending Order of Severity

	Stented Angioplasty, %		CABG, %	
	Stable (n=374)	Unstable (n=226)	Stable (n=381)	Unstable (n=224)
Death	2.4	2.7	3.2	2.2
CVA	2.1	0.4	1.3	3.1
MI	5.1	5.8	2.9	5.8
Q-wave MI	4.3	5.3	2.9	4.9
Non-Q-wave MI	0.8	0.4	0	0.9
CABG*	3.7	6.2	0.3	0.9
Repeat PCI*	13.1	10.6	3.2	2.7
No MACCE†	73.5	74.3	89.2	85.3

*All bypass patients vs stented patients, *P*<0.01.

†Stable and unstable angina bypass surgery vs stable and unstable stented angioplasty, *P*<0.0001.

A, Actuarial survival. Kaplan-Meier estimates of survival without CVA, MI, repeat CABG, or repeat PTCA. B, Survival without repeat CABG or repeat PTCA. C, Survival without death, MI, or CVA among stable and unstable patients undergoing stenting or CABG. There was a statistically significant difference between stented patients (either stable or unstable) and CABG patients (either stable or unstable) except for in rate of survival with MI or CVA.

TABLE 4. Costs and Cost-Effectiveness at 1 Year (Measured in US Dollars)

	Stable		Unstable	
	CABG	Stent	CABG	Stent
Initial procedure	6504	5054	6823	5192
Initial hospitalization	3829	1173	4371	1605
Total procedure	10 333	6227	11 194	6797
Follow-up event diagnostic test	486	1433	488	1558
Rehospitalization	1537	1738	2395	1952
Total follow-up	2023	3171	2883	3510
Medication	604	970	705	849
Total direct medical cost	12 960	10 368	14 783	11 156
Difference in cost	2592		3627*	
Difference in effectiveness percent	15.7		11.0	
Incremental cost-effectiveness ratio†	16.530 (8.270–31.563)		32.983 (13.389–122.316)	

*Difference not significant.

†95% CI.

according to the Kaplan-Meier method, and the overall incidence of MACCE was tested using the log-rank test.

Cost are expressed in United States dollars and calculated by multiplying resource use, documented by the investigators, with unit cost from the Netherlands. Incremental cost-effectiveness ratios were expressed with 95% CIs.³¹

Results

A total of 1205 stable and unstable patients were randomly assigned to stent implantation (total, 600 patients; stable, 374; unstable, 226) or bypass surgery (total, 605 patients; stable, 381; unstable, 224). The baseline characteristics (demographic and angiographic) were not different among the 4 groups of patients (Table 1). Most patients had 1 or more risk factors, and two thirds of patients presently or formerly smoked. Only 8% to 10% had silent ischemia, and these patients were classified as having stable angina. Most of the patients had a significant obstruction of the left anterior descending coronary artery.

Patients with unstable angina had a similar number of stenotic lesions as those with stable angina (Table 2). The number of treated stenoses was also not significantly different among the 4 groups. As per protocol, the left anterior descending artery was bypassed with the use of an arterial conduit in almost all cases.

Clinical Outcomes

Absence of MACCE at 1 year in stented unstable patients was not statistically different compared with stable patients and surgically treated unstable and stable patients (Table 3 and Figure, A). However, the patients, unstable or stable, who underwent CABG had a significantly higher absence of MACCE at 1 year compared with those who were stented. This was mainly attributable to the higher frequency of revascularizations in the stented group (Figure, C), whereas there were no significant differences between the rates of death, MI, or CVA (Figure, B).

Absence of MACCE at 1 year was not statistically different in stented unstable patients classified according to Braunwald

classification (class I, 73%; class II, 74%; and class III, 77%) or in bypass patients (class I, 88%; class II, 87%; class III, 81%).

At 1 year, 77%, 83%, 90%, and 89%, respectively, of the stented patients with stable or unstable angina or bypassed patients with stable or unstable angina were angina free. A total of 18% of the stable and 21% of the unstable stented patients were angina and medication free, compared with 42% of the stable and 34% of the unstable bypassed patients ($P<0.003$).

Cost

At the end of 1 year, the average total costs per patient with stable angina were \$12 960 for CABG versus \$10 368 for stenting (a difference of \$2592) compared with \$14 783 versus \$11 156 (a difference of \$3627) in patients with unstable angina (Table 4). This difference in cost was largely attributable to the higher costs of both the initial and follow-up hospitalization.

There was no significant difference in MACCE event-free survival between the 2 treatments, which was 11% for unstable angina and 15.7% for stable angina (Table 4). The incremental cost-effectiveness ratio in favor of stenting compared with bypass surgery was \$16 530 for patients with stable angina compared with \$32 983 for patients with unstable angina.

Discussion

At the time of the conception of the ARTS trial, there were no studies available about the relative merits of modern surgical or percutaneous revascularization techniques with regard to the outcome of treatment of multivessel disease in unstable patients with angina compared with stable patients. The ARTS trial offered the opportunity to investigate whether there are differences in outcome between unstable and stable patients undergoing either bypass surgery with arterial grafts or percutaneous intervention with stent implantation.

This subanalysis demonstrated that there were no significant differences in early and 1-year major adverse events between patients with unstable and stable angina undergoing

either treatment modality. However, the need for repeat revascularization was significantly higher for both stable and unstable patients undergoing stent implantation, whereas there was no difference in repeat revascularization rate between unstable and stable patients.

Earlier trials²¹ comparing balloon angioplasty without stent implantation with CABG demonstrated that the difference of freedom of MACCE between angioplasty and surgery was $\approx 30\%$, which was almost entirely attributable to the greater need for repeat revascularization in the angioplasty group. This 30% difference has now been reduced by half, to 11% for unstable patients and 16% for stable patients, with the use of stenting. Additional improvements in stent technology, such as drug-eluting stents, may additionally reduce this difference in event-free survival between PCI and CABG.³²

The efficacy of new treatments must be weighed against their costs. The respective difference in costs at 1 year was less for stenting both in unstable patients (\$3627) and stable patients (\$2592). This implies that if an approach of bypass surgery rather than stenting was pursued, the cost of each additional patient who survives event free would be \$32 983 for unstable patients compared with \$16 530 for stable patients.

Limitations

The patients randomized in this study may not be representative of all patients with multivessel disease undergoing revascularization procedures because of the prespecified inclusion and exclusion criteria and the requirement for a consensus between cardiologist and surgeon on equal treatability. This is further exemplified by the fact that only a small portion of the total number of screened patients with multivessel disease were actually enrolled in the study. In addition, patients with significant left main disease and patients with refractory unstable angina were excluded from this study.

This study is a subanalysis, albeit prespecified, and hence suffers from inherent limitations, such as the lack of sufficient power because of the limited number of patients in the subgroups to provide definite answers.

Conclusions

There is no difference in the rate of major adverse events in unstable patients with multivessel disease treated with either stented angioplasty or bypass surgery using arterial grafts compared with stable patients. In addition, the need for repeat revascularization in unstable patients undergoing stenting or bypass surgery was similar compared with stable patients. However, the overall need for repeat revascularization was significantly higher in stented patients compared with bypass surgery patients. The cost and cost-effectiveness in patients with unstable angina was not different from stable angina, although overall stenting was a cost-effective alternative to surgery.

Acknowledgment

The authors are indebted to Dr Brian Firth for his careful review of the manuscript.

References

- McCormick JR, Schick EC Jr, McCabe CH, et al. Determinants of operative mortality and long-term survival in patients with unstable angina: the CASS experience. *J Thorac Cardiovasc Surg.* 1985;89:683–688.
- Kouchoukos NT, Murphy S, Philpott T, et al. Coronary artery bypass grafting for postinfarction angina pectoris. *Circulation.* 1989;79:168–172.
- Gardner TJ, Stuart RS, Greene PS, et al. The risk of coronary bypass surgery for patients with postinfarction angina. *Circulation.* 1989;79:179–180.
- Fremes SE, Goldman BS, Weisel RD, et al. Recent preoperative myocardial infarction increases the risk of surgery for unstable angina. *J Card Surg.* 1991;6:2–12.
- Rahimtoola SH, Nunley D, Grunkemeier G, et al. Ten-year survival after coronary bypass surgery for unstable angina. *N Engl J Med.* 1983;308:676–681.
- Tu JV, Sykora K, Naylor CD. Assessing the outcomes of coronary artery bypass graft surgery: how many risk factors are enough? Steering Committee of the Cardiac Care Network of Ontario. *J Am Coll Cardiol.* 1997;30:1317–1323.
- Jones RH, Hannan EL, Hammermeister KE, et al. Identification of preoperative variables needed for risk adjustment of short-term mortality after coronary artery bypass graft surgery: the Working Group Panel on the Cooperative CABG Database Project. *J Am Coll Cardiol.* 1996;28:1478–1487.
- Magovern JA, Sakert T, Magovern GJ, et al. A model that predicts morbidity and mortality after coronary artery bypass graft surgery. *J Am Coll Cardiol.* 1996;28:1147–1153.
- Bjessmo S, Ivert T, Flink H, et al. Early and late mortality after surgery for unstable angina in relation to Braunwald class. *Am Heart J.* 2001;141:9–14.
- Sergeant P, Blackstone E, Meyns B. Early and late outcome after CABG in patients with evolving myocardial infarction. *Eur J Cardiothorac Surg.* 1997;11:848–856.
- de Feyter PJ, van den Brand M, Laarman GJ, et al. Acute coronary artery occlusion during and after percutaneous transluminal coronary angioplasty: frequency, prediction, clinical course, management, and follow-up. *Circulation.* 1991;83:927–936.
- Rupprecht HJ, Brennecke R, Kottmeyer M, et al. Short- and long-term outcome after PTCA in patients with stable and unstable angina. *Eur Heart J.* 1990;11:964–973.
- Foley JB, Chisholm RJ, Common AA, et al. Aggressive clinical pattern of angina at restenosis following coronary angioplasty in unstable angina. *Am Heart J.* 1992;124:1174–1180.
- Bauters C, Lablanche JM, McFadden EP, et al. Repeat percutaneous coronary angioplasty: clinical and angiographic follow-up in patients with stable or unstable angina pectoris. *Eur Heart J.* 1993;14:235–239.
- Serruys PW, Herrman JP, Simon R, et al. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty: Helvetica Investigators. *N Engl J Med.* 1995;333:757–763.
- Lincoff AM, Califf RM, Anderson KM, et al. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization: EPIC Investigators. Evaluation of 7E3 in Preventing Ischemic Complications. *J Am Coll Cardiol.* 1997;30:149–156.
- Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet.* 1997;349:1429–1435.
- Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization: the EPILOG Investigators. *N Engl J Med.* 1997;336:1689–1696.
- Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty: the RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *Circulation.* 1997;96:1445–1453.
- Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade: the EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet.* 1998;352:87–92.
- Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet.* 1995;346:1184–1189.

22. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol*. 2000;35:1122–1129.
23. Henderson RA, Pocock SJ, Sharp SJ, et al. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. *Lancet*. 1998;352:1419–1425.
24. King SB 3rd, Kosinski AS, Guyton RA, et al. Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol*. 2000;35:1116–1121.
25. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117–1124.
26. Campeau L. Grading of angina pectoris (letter). *Circulation*. 1976;54: 522–523.
27. Braunwald E. Unstable angina: a classification. *Circulation*. 1989;80: 410–414.
28. Edlavitch SA, Crow R, Burke GL, et al. Secular trends in Q wave and non-Q wave acute myocardial infarction: the Minnesota Heart Survey. *Circulation*. 1991;83:492–503.
29. Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. *J Am Coll Cardiol*. 1998;31:241–251.
30. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics*. 1985;41:55–68.
31. Cox DR. Fieller's theorem and a generalization. *Biometrika*. 1967;54: 567–572.
32. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound Study. *Circulation*. 2001;103:192–195.