Commentary

Debate: PCI or CABG for multivessel disease? Viewpoint: No clear winner in an unfair fight

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Abstract

The Arterial Revascularization Therapy Study (ARTS) and the Stent or Surgery (SoS) trial each randomized patients with multivessel disease to either stenting or bypass surgery. The ARTS showed no difference in mortality between the two strategies, other than in diabetic patients, who fared better with surgery. The SoS trial demonstrated increased mortality in the stent arm, a difference that was not attributable to diabetes. Both trials found that the rates of repeat revascularization were lower with surgery, although the rate with stenting was much lower than had been seen in previous trials of angioplasty. Use of antiplatelet therapy such as intravenous glycoprotein IIb/IIIa inhibitors, especially with their pronounced effects in diabetics and in those with multivessel disease, could potentially equalize the playing field or perhaps even tip the balance in favor of percutaneous intervention.

Keywords balloon angioplasty, coronary artery bypass surgery, diabetes, stents

Large, randomized trials of multivessel balloon angioplasty versus coronary artery bypass grafting (CABG) in aggregate show no difference in long-term mortality in patients randomized to either approach initially [1,2]. There is, however, an increased need for subsequent percutaneous or surgical target vessel revascularization (TVR) in patients who initially undergo balloon angioplasty. Additionally, in patients with diabetes mellitus, there appears to be a mortality benefit favoring an initial surgical approach for multivessel disease.

Compared with balloon angioplasty, stenting unequivocally reduces the need for TVR across a variety of lesion types [3–7]. However, there has never been evidence from randomized trials that stents decrease mortality, compared with balloon angioplasty. Indeed, existing data suggest that stents may increase mortality, in both acute myocardial infarction (MI) [8] and chronic stable angina [9]. The observed increase in mortality is likely to be related to the fact that stenting leads to more embolization than balloon angioplasty. This is manifest by increased periprocedural MI [10], through what has been termed a 'cheese grater' effect due to embolization of the plaque by the stent [11]. By contradistinction, CABG has been shown to decrease mortality in certain patient subgroups [12]. Data are particularly strong for patients with multivessel disease, left ventricular dysfunction, and left main coronary stenosis. However, compared with percutaneous coronary intervention (PCI), CABG carries a greater risk of death, MI, and stroke, as well as a risk of more subtle deficits in cognitive function [13]. For patients who have coronary anatomy suitable for either multivessel stenting or CABG, the question thus arises as to which is the better approach.

CABG = coronary artery bypass grafting; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target vessel revascularization.
ARTS = Arterial Revascularization Therapy Study; EPISTENT = Evaluation of IIb/IIIa Platelet Inhibitor for Stenting; SoS, Stent or Surgery; TARGET = Do Tirofiban and ReoPro Give Similar Efficacy Trial.

Stenting versus CABG for multivessel disease

The evidence

The ARTS and the SoS trial attempted to determine whether stenting would shift the balance in favor of multivessel PCI instead of CABG as the better approach [14].

The ARTS found that patients randomized to either stenting or CABG had similar rates of mortality after 1 year. TVR rates were lower with stenting than they had been in previous trials of balloon angioplasty; however, the CABG arm of the trial still had a significantly lower rate of TVR. The diabetic cohort did have a higher mortality in the stenting arm than in the CABG arm of the trial.

The SoS study found a lower mortality at 1 year in those undergoing CABG instead of PCI (0.8% versus 2.5%) [15]. As the prevalence of diabetes was quite low in the SoS trial, the increased mortality seen in the PCI patients cannot be attributed to this factor. While the results of SoS have in part been explained by some interventional cardiologists as 'surprisingly low surgical mortality' in the patients randomized to CABG, that level of mortality is not unreasonable with contemporary surgical technique. At the Cleveland Clinic, in a high-risk population, the perioperative mortality rate from CABG was 0.8% for the year 2000. There were a larger number of cancer deaths in the PCI arm than in the CABG arm in the SoS trial, and 'play of chance' is the most likely explanation for this finding. However, to dismiss outright the mortality difference observed in this randomized trial is scientifically unjustified.

The winner

Is CABG the treatment of choice for multivessel disease, particularly in the diabetic patient? Is the battle over? Well, not in our opinion. In both these trials, the fight was an unfair one from the start.

The PCI arms of both trials were sent to war without their armor. In contemporary PCI, the role of concomitant glycoprotein (GP) IIb/IIIa inhibition is firmly established. The Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) study demonstrated reduced mortality in patients receiving stents who were randomized to abciximab instead of placebo [16]. This mortality benefit of GP IIb/IIIa blockade is amplified in diabetic patients. In fact, in a pooled analysis of the abciximab in PCI trials, diabetic patients who were randomized to abciximab demonstrated mortality rates similar to that of non-diabetic patients receiving placebo [17]. Thus, abciximab administration essentially converted the risk of death for the diabetic to that of a non-diabetic. This mortality benefit is particularly marked in the subset of diabetics with multivessel disease [18]. If these findings are extrapolated to the ARTS diabetic substudy results, then the gap in mortality rates between PCI and CABG might vanish. Additionally, the EPISTENT trial showed that abciximab reduced clinical and angiographic restenosis in diabetic patients [19]. Importantly, restenosis may be linked to subsequent mortality in diabetics [20], and any benefit of abciximab in reducing TVR may consequently be linked to a survival advantage. GP IIb/IIIa blockade could thus have changed the results of the ARTS and the SoS trial dramatically both in terms of TVR and mortality, although this concept should be tested prospectively.

The Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET) found that abciximab was superior to tirofiban in reducing death, MI, or TVR after 30 days [21]. Thus, while all three commercially available intravenous GP IIb/IIIa inhibitors reduce periprocedural MI, it may be that abciximab in particular has an additional effect on TVR in diabetics with stents. However, further analysis of the TARGET study 6-month results for diabetics will be necessary to determine whether abciximab indeed had a specific effect.

Furthermore, the beneficial impact of long-term clopidogrel on patients with stents is currently being evaluated in the Clopidogrel for Reduction of Events During Observation trial. Prolonged dual antiplatelet therapy with aspirin plus the thienopyridine, clopidogrel, could further decrease both TVR (as had been shown with ticlopidine) and recurrent ischemic events [22,23]. Additionally, such a pharmacological approach may be applicable and beneficial after CABG [24]. Statin therapy and appropriate control of diabetes would be expected to improve outcome in PCI patients but, again, some degree of risk reduction would also be expected in the CABG patients. Drug-coated stents, currently being tested in clinical trials, could ultimately reduce restenosis rates to an unprecedented low level [25]. Off-pump surgery may diminish the cognitive decline noted with CABG.

Conclusion

Both PCI and CABG (as well as medical therapy) are improving. At present, a patient with multivessel disease may be considered for either PCI or CABG. When the disease is more extensive, when left ventricular dysfunction is more severe, or in the presence of diabetes, CABG may be the preferred mode of revascularization. However, PCI may be performed when there are more focal stenoses, although concomitant GP IIb/IIIa inhibition is essential. Given the clinical benefits and proven cost-effectiveness of GP IIb/IIIa inhibition [16], there is no longer justification for PCI without GP IIb/IIIa blockade, particularly in those patients with heightened risk features, such as multivessel disease or diabetes.

Competing interests

None declared.

References

1. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: **Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease.** *N Engl J Med* 1996, **335**:217-225.

2. King SB III, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS: **Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST).** *J Am Coll Cardiol* 2000, **35**:1116-1121.
3. Cohen DJ, Krumholz HM, Sukin CA, Ho KK, Siegrist RB, Cleman M, Heuser RR, Brinker JA, Moses JW, Savage MP: **In-hospital and one-year economic outcomes after coronary stenting or balloon angioplasty. Results from a randomized clinical trial. Stent Restenosis Study Investigators.** *Circulation* 1995, **92**: 2480-2487.
4. Leon MB, Popma JJ, Mintz GS, Pichard AD, Satler LF, Kent KM: **An overview of US coronary stent trials.** *Semin Intervention Cardiol* 1996, **1**:247-254.
5. Savage MP, Fischman DL, Rake R, Leon MB, Schatz RA, Penn I, Nobuyoshi M, Moses J, Hirshfeld J, Heuser R, Baim D, Cleman M, Brinker J, Gebhardt S, Goldberg S: **Efficacy of coronary stenting versus balloon angioplasty in small coronary arteries. Stent Restenosis Study (STRESS) Investigators.** *J Am Coll Cardiol* 1998, **31**:307-311.
6. Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA: **Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II).** *Lancet* 1998, **352**:673-681.
7. Cura FA, Bhatt DL, Lincoff AM, Kapadia SR, L'Allier PL, Ziada KM, Wolski KE, Moliterno DJ, Brener SJ, Ellis SG, Topol EJ: **Pronounced Benefit of Coronary Stenting and Adjunctive Platelet Glycoprotein IIb/IIIa Inhibition in Complex Atherosclerotic Lesions.** *Circulation* 2000, **102**:28-34.
8. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, Brodie BR, Madonna O, Eijgelshoven M, Lansky AJ, O'Neill WW, Morice MC: **Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group.** *N Engl J Med* 1999, **341**:1949-1956.
9. Kiemeneij F, Serruys PW, Macaya C, Rutsch W, Heyndrickx G, Albertsson P, Fajadet J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy JJ, Disco CM, Morel MA: **Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial.** *J Am Coll Cardiol* 2001, **37**: 1598-1603.
10. The EPISTENT Investigators: **Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting.** *Lancet* 1998, **352**:87-92.
11. Topol EJ, Yadav JS: **Recognition of the importance of embolization in atherosclerotic vascular disease.** *Circulation* 2000, **101**:570-580.
12. Chaitman BR, Fisher LD, Bourassa MG, Davis K, Rogers WJ, Maynard C, Tyras DH, Berger RL, Judkins MP, Ringqvist I, Mock MB, Killip T: **Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS).** *Am J Cardiol* 1981, **48**:765-777.
13. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: **Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery.** *N Engl J Med* 2001, **344**:395-402.
14. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA: **Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease.** *N Engl J Med* 2001, **344**:1117-1124.
15. Stables R: **SoS Results.** *Presented at the Annual Meeting of the American College of Cardiology, 2001*. Orlando, Florida.
16. Topol EJ, Mark DB, Lincoff AM, Cohen E, Burton J, Kleiman N, Talley D, Sapp S, Booth J, Cabot CF, Anderson KM, Califf RM: **Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting.** *Lancet* 1999, **354**:2019-2024.
17. Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ: **Abciximab reduces mortality in diabetics following percutaneous coronary intervention.** *J Am Coll Cardiol* 2000, **35**:922-928.
18. Bhatt DL, Lincoff AM, Tcheng JE, Califf RM, L'Allier PL, Marso SP, Wolski KE, Kereiakes DJ, Topol EJ: **The impact of abciximab on mortality after multivessel PCI: a striking effect in diabetics [abstract].** *J Am Coll Cardiol* 2000, **35**:91A.
19. Marso SP, Lincoff AM, Ellis SG, Bhatt DL, Tanguay JF, Kleiman NS, Hammoud T, Booth JE, Sapp SK, Topol EJ: **Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) diabetic substudy.** *Circulation* 1999, **100**:2477-2484.
20. Van Belle E, Ketelers R, Bauters C, Perie M, Abolmaali K, Richard F, Lablanche JM, McFadden EP, Bertrand ME: **Patency of percutaneous transluminal coronary angioplasty sites at 6-month angiographic follow-up: A key determinant of survival in diabetics after coronary balloon angioplasty.** *Circulation* 2001, **103**:1218-1224.
21. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Yakubov SJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L, for the TARGET Investigators: **Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary intervention.** *N Engl J Med* 2001, **344**:1888-1894.
22. Steinhubl SR, Ellis SG, Wolski K, Lincoff AM, Topol EJ: **Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events: data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) Trial.** *Circulation* 2001, **103**:1403-1409.
23. The CURE Investigators: **Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.** *N Engl J Med* 2001, **345**:494-502.
24. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ: **Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery.** *Circulation* 2001, **103**:363-368.
25. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW: **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.