Indications for CABG in the DES Era

There continues to be a significant role for surgery in the current management of coronary artery disease.

BY MICHAEL MACK, MD

The introduction of drug-eluting stents (DESs) into interventional cardiology has further catalyzed the trend to perform coronary revascularization more frequently by a percutaneous approach and less frequently by a surgical one. Currently, 70% to 75% of all coronary revascularization is performed by a percutaneous approach.[1] The widely publicized COURAGE trial has also brought a renewed emphasis on the role of optimal medical therapy in the management of coronary artery disease (CAD).[2] Because all three therapies have progressively improved the care of patients with coronary disease, it is easy for comparative trials of the various approaches to become quickly outdated and irrelevant to current practice. Therefore, given the choice of three excellent options for the management of patients with CAD, how does a clinician decide the best current treatment for a particular patient? Factors that help us make decisions as to what treatment is best for an individual patient include data from randomized controlled trials (RCTs), observational, population-based databases, society practice guidelines, and perhaps most of all, our own clinical experiences. However, one has to first acknowledge that there are biases in all of these sources that affect our clinical decision making. First, each practitioner, whether interventionist, surgeon, noninvasive cardiologist, or internist, has a predilection to select the treatment for which he or she is the practitioner. This is only natural and to expect anything different is not realistic. All else being equal, interventionists are going to choose percutaneous coronary intervention (PCI), surgeons will choose coronary artery bypass grafting (CABG), and noninterventionists will tend toward medical management. Second, all evidence upon which we base our patient care decisions is also subject to bias.[3] Randomized controlled trials, the highest order in the hierarchy of evidence-based medicine, are subject to the biases introduced by trial design. Information on outcomes gleaned from large, population-based observational databases is, of course, subject to treatment bias. To objectively decide on the best therapeutic option for the individual patient, each practitioner needs, as best they can, to acknowledge the biases upon which decision making is based and divorce themselves as much as possible from those influences.

> ". . . there is strong evidence from large, observational databases [of] a survival advantage of CABG vis-à-vis PCI in patients with multivessel coronary artery disease."

If one were to ask an interventional cardiologist what are the current indications for CABG, the response might be "only for those patients who can't technically have a stent placed." If one were to ask a cardiac surgeon the same question, the response in all likelihood would be "CABG is indicated in all patients with multivessel disease, especially when the left anterior descending (LAD) coronary artery is involved and in diabetics or in patients with decreased left ventricular function." The noninterventionist response would be "no intervention should be considered without first a trial of optimal or guideline-based medical therapy

TABLE 1. LARGE OBSERVATIONAL DATABASES OF CABG VERSUS PCI		
Registry	**No. of Patients**	**CABG/PCI Hazard Ratio**
CARE[1]	4,336	0.76
New York State (2008)[4] Three-vessel disease Two-vessel disease	17,400	 0.8 0.71
New York State (1999)[6]	59,576	Not reported
New York State (2005)[7] Three-vessel disease Two-vessel disease	59,314	 0.64 0.76
Duke[8]	18,481	Not reported
Northern New England[9]	14,493	0.86
Alberta, Canada[10]	9,890	0.81
Scotland[11]	11,661	0.48

unless the patient is at high risk on noninvasive testing." It should always be remembered that, from the patient's perspective, less invasive is better than more invasive. If a procedure is warranted, providing the outcome of a less-invasive procedure is equivalent to a more-invasive procedure, the less-invasive procedure (PCI vs CABG) is preferred by patients. However, if that less-invasive procedure is associated with decreased long-term survival, which has been suggested in the New York State Database, the procedures cannot be considered equivalent, and a balance between outcomes and invasiveness needs to be considered.[4]

RANDOMIZED CONTROLLED TRIALS

The multiple comparative randomized trials between PCI and CABG have all shown no difference in mortality or myocardial infarction (MI).[3] The only difference has been a decreased need for repeat revascularization with coronary bypass surgery. With the introduction of DESs and the promise of decreased restenosis compared with bare-metal stents, the inexorable shift toward percutaneous intervention has continued.

A recent systematic review of the comparative effectiveness of PCI and CABG was performed.[5] Twenty-three RCTs compared 5,019 patients randomly assigned to PCI and 4,944 patients randomly assigned to CABG. The difference in survival between the two procedures was <1% over 10 years of follow-up. Unlike the mortality benefit for CABG in patients with diabetes seen in the BARI trial, the six other trials that have examined this patient subgroup did not find a procedural difference for CABG. Anginal relief was greater after CABG than after PCI, and repeat revascularization was more common after PCI than after CABG. Risk difference for repeat revascularization with PCI was 24% greater at 1 year and 33% greater at 5 years (P<.001). The absolute rates of repeat revascularization were 40.1% after PCI with stents and 9.8% after CABG at 5 years.

OBSERVATIONAL DATABASES

Although observational databases lack the scientific rigor of randomized trials and are subject to many biases, they do have a significant value in the real-world use of coronary revascularization techniques. Even though there is clearly a treatment bias in observational databases, it can be somewhat mitigated by risk adjustment. Five major clinical registries have shown a very different story than comparative RCTs. Those registries are two analyses of the New York State Database in 1999 and 2005, the Duke Medical Center Database, the Northern New England Database, the Alberta Canada Registry, and the Scotland Registry. They have all shown a mortality benefit favoring CABG in the long term (Table 1).[6-11] The most recent analysis of the New York State Database examined patients with multivessel disease who received either DESs or CABG in a 15-month period starting in late 2003 and ending in 2004.[4] In comparison with treatment with a DES, CABG was associated with a lower 18-month rate of death or MI, both in patients with three-vessel disease and two-vessel disease. Among patients with three-vessel disease who underwent CABG as compared to those who received a stent, the adjusted hazard ratio for death was 0.80 (95% CI, 0.65-0.97), and the adjusted survival rate was 94% versus 92.7% (P=.03). This benefit was also seen among patients with two-vessel disease who underwent CABG compared to those who received a stent, with the adjusted hazard ratio for death being 0.71 (95% CI, 0.57-0.89). The conclusion of this analysis was that for patients with multivessel disease, CABG continues to be associated with a lower mortality rate than treatment with DESs and is also associated with lower rates of death, or MI and repeat

TABLE 2. PATIENTS WITH A SURVIVAL BENEFIT OF CABG VERSUS PCI IN VARIOUS OBSERVATIONAL STUDIES

- Two-vessel disease
- Three-vessel disease
- Multivessel disease including the proximal left anterior descending artery
- Diabetics
- Decreased ejection fraction

revascularization (Table 2).

A recently performed "all-comer" study of coronary revascularization in eight community hospitals, the CARE study, tracked outcomes at 18 months in 4,336 patients, with 71.2% of the patients receiving PCI and 28.8% undergoing CABG.[1] Seventy-three percent of the stents placed were DESs, and 47.8% of the CABG procedures were performed off-pump. The major adverse cardiac event rate at 18 months was 14.4% in the CABG group compared to 23.2% in the PCI group, mainly due to an increase in repeat revascularization in the PCI arm despite the high use of DESs. Overall mortality and incidence of MI were the same. Analysis of the patients undergoing CABG and PCI revealed that 60% of the CABG patients had three-vessel disease and 30% had two-vessel disease. Forty-eight percent of the PCI patients had single-vessel disease and 32% had two-vessel disease.

The discrepancy in findings between RCTs and observational databases is not surprising. Although RCTs constitute the highest degree of evidence-based medicine, the concern of the "generalizability" of the results to the population at large is an issue (Table 3). In all RCTs of CABG versus PCI, only 4% to 6% of screened patients were entered into a randomized trial.[3] Therefore, one has to make the leap of faith that the results in this small percentage (4%–6%) will be externally valid or the same in the population at large. It is this logic that led to the widespread off-label use of DESs after superb results were demonstrated in the regulatory approval-designed randomized trials. With broader application in patients with more extensive disease and diverse coronary anatomy and pathology, the outcomes have not been as optimal.[1] Influential factors in RCT design that lead to selectivity include inclusion/exclusion criteria, selection of endpoints, composite endpoints, homogeneity of the patient population studied, the size and length of the trial, and the purpose of the trial.

ROLE FOR CABG

How does one synthesize all this information and apply it to an individual patient? Table 4 lists some patient-specific factors that may mitigate toward choosing CABG versus PCI. Despite a plethora of technological innovations to address chronic total occlusions and bifurcation disease, the results of PCI in those conditions are still not satisfactory. Strong consideration should be given to CABG in those instances.

TABLE 3. WHY RCTs OF CABG VERSUS PCI ARE NOT THE FINAL ANSWER

- Low percentage of enrolled/screened patients (4%–6%)
- May not be generalizable to the population at large
- Inclusion of only patients treatable by both modalities
- Short-term follow-up favors PCI
- Powered for composite endpoints not mortality

TABLE 4. SPECIFICS OF CORONARY DISEASE THAT ARE PROBLEMATIC FOR PCI IN WHICH CABG SHOULD BE CONSIDERED

- Chronic total occlusions
- Left main disease (especially bifurcation)
- Bifurcation disease
- Ostial lesions of the left anterior descending and circumflex coronary arteries
- Long lesions
- Small vessels
- Early in-stent restenosis
- Clopidogrel resistance
- Inability to take antiplatelet therapy due to concomitant medical conditions
- Anticipated surgical procedure in the near future
- Patient unreliability to take antiplatelet therapy

The necessity for adjuvant antiplatelet therapy after DES placement is a continuing daily issue in patient care. Frequently, when concern exists due to patient compliance issues, concomitant medical conditions, or anticipated need for surgical or endoscopic procedures in the foreseeable future, a bare-metal stent is selected. Because stent thrombosis still occurs with bare-metal stents upon cessation of antiplatelet medication, perhaps a more reasonable alternative is CABG in these patients.

Another issue is the treatment of left main CAD. Although this vessel being relatively large and quite accessible presents an attractive target for DES treatment, and safe-

ty has been demonstrated in single-center registries, there is not enough information yet available to change practice.[12] There are insufficient data on the selectivity of patients treated in these registries to justify abandoning CABG. It will only be a few more months before the results of the randomized trial of DES versus CABG in left main disease (the SYNTAX trial) are available.[13,14] Continuing surgical treatment of left main disease is appropriate until we can scrutinize these trial results.

> "The 'all-comer' trial design of SYNTAX may to some degree mitigate the selectivity and generalizability shortcomings of RCTs."

SUMMARY

Although the past decade has seen a diminishing role for CABG in the management of CAD, there will still continue to be a significant place for surgery in the therapeutic armamentarium for the foreseeable future. Even though it is "maximally invasive," there is strong evidence from large, observational databases that there is a survival advantage of CABG vis-à-vis PCI in patients with multivessel CAD.[4,5] However, it behooves us as surgeons to decrease the morbidity rate associated with CABG and to increase the use of arterial grafts to maximize this benefit. Evidence from the New York State Database demonstrates a decrease in procedural mortality and morbidity with off-pump compared with on-pump CABG, albeit with an increased need for repeat revascularization in the long term.[15] In addition, if we as surgeons continue to place mainly saphenous vein grafts, which in a recent large study have been demonstrated to have a graft failure rate of 29% at 1 year, then we are probably not accomplishing anything surgically that could not be done with stents.[16] A therapeutic alternative, which has recently received renewed interest, is the "hybrid procedure" in which a left internal mammary artery is placed to the LAD coronary artery through a limited access incision and stents are placed in the remaining vessels. The increased availability of hybrid operating rooms with catheterization lab quality imaging has obviated some of the logistical issues associated with the earlier thrusts into this therapeutic option in the late 1990s.

The recently completed SYNTAX Trial (the results of which will be available later this year) and the FREEDOM Trial (which is more than 50% enrolled) will further help us delineate the relative roles of CABG and PCI in left main, three-vessel disease and multivessel disease in diabetics, respectively. The "all-comer" trial design of SYNTAX may to some degree mitigate the selectivity and generalizability shortcomings of RCTs.[13] Although neither will be "final answers," they are likely to help us make more intelligent patient management decisions. As the field progresses, our patients are best served by objectively assessing all the data, presenting it to patients in an unbiased manner, factoring in patient preferences, and helping them make as an informed decision as possible. ■

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1. Mack MJ, Prince SL, Herbert M, et al. Current 18-month clinical outcomes of percutaneous coronary intervention in coronary artery bypass grafting: the CARE (Coronary Artery REvascularzation) Study. Ann Thorac Surg. 2008. In press.
2. Boden WE, O'Rourke, Teo KK, et al. COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Eng J Med. 2007;356:1503-1516.
3. Mack MJ. Clinical trials versus registries in coronary revascularization: which are more relevant? Curr Opin Cardiol. 2007;22:524-528.
4. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary artery bypass grafting in multivessel coronary disease. N Engl J Med. 2008;358:331-341.
5. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med. 2007;147:703-716.
6. Hannan EL, Racz MJ, McCallister BD, et al. A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. J Am Coll Cardiol. 1999;33:63-72.
7. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary artery bypass grafting versus stent implantation. N Engl J Med. 2005;352:2174-2183.
8. Smith PK, Califf RM, Tuttle RH, et al. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. Ann Thorac Surg. 2006;82:1420-1428.
9. Malenka DJ, Leavitt BJ, Hearne MJ, et al. Northern New England Cardiovascular Disease Study Group. Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. Circulation. 2005;112:1371-1376.
10. Dzavik V, Ghali WA, Norris C, et al. Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Am Heart J. 2001;142:119-126.
11. Pell JP, Walsh D, Norrie J, et al. Outcomes following coronary artery bypass grafting and percutaneous transluminal coronary angioplasty in the stent era: a prospective study of all 9,890 consecutive patients operated on in Scotland over a two-year period. Heart. 2001;85:662-666.
12. Taggart DP, Kaul S, Boden WE, et al. Revascularization for unprotected left main stem coronary artery stenosis stenting or surgery. J Am Coll Cardiol. 2008;51:885-892.
13. Ong AT, Serruys PW, Mohr FW, et al. The synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J. 2006;151:1194-1204.
14. Kappetein AP, Dawkins KD, Mohr FW, et al. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease: insights from the SYNTAX run-in phase. Eur J Cardio Thorac Surg. 2006;29:486-491.
15. Hannan EL, Wu C, Smith CR, et al. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. Circulation. 2007;116:1145-1152.
16. Alexander JH, Hafley G, Harrington RA, et al, Prevent IV Investigators. A randomized trial assessing the safety and efficacy of edifoligide, an e2f transcription decoy, to prevent vein graft failure following coronary artery bypass graft surgery: PREVENT IV. JAMA. 2005;294:2446-2454.