with a serum potassium concentration greater than 5.0 mmol/L or serum creatinine levels greater than 2.5 mg/dL. There was no difference in the occurrence of hyperkalemia between the study and control populations.

Based on the results of this study, one would consider the early use of eplerenone to be an integral part of a life-saving regimen for patients with acute MI and reduced left ventricular function with clinical signs of heart failure. Caution should be used when treating patients with moderate to severe chronic kidney disease and baseline hyperkalemia. ■

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Coronary Artery Disease

Randomized Trials, Registries, and Revascularization

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Long-Term Outcomes of Coronary Artery Bypass Grafting Versus Stent Implantation

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This large study from the New York State Registry analyzed 3-year outcomes in patients with multivessel disease who underwent coronary artery bypass grafting (CABG, n = 37,212) or percutaneous coronary intervention (PCI) with stenting (n = 22,102), between January 1997 and December 2000.[1] Patients with left main coronary artery disease, prior revascularization, or myocardial infarction within 24 hours of revascularization were excluded. The CABG group were older, slightly less likely to be female, more likely to be white, and less likely to be Hispanic. There was also a higher prevalence of patients with left ventricular dysfunction and comorbidities including chronic obstructive pulmonary disease, diabetes, renal failure, peripheral vascular disease, carotid or cerebrovascular disease, aortoiliac disease, or prior stroke in this group.

Unsurprisingly, over a follow-up of approximately 3 years, rates of subsequent revascularization were much higher after stenting when compared to rates following coronary bypass surgery (7.8% versus 0.3% for subsequent CABG and 27.3% versus 4.6% for subsequent PCI). Unadjusted survival data demonstrated a higher mortality rate after CABG in patients with 2-vessel disease and no involvement of the proximal left anterior descending coronary artery (LAD). There was no significant difference in those with 2-vessel disease and proximal LAD involvement, a nonsignificant trend in favor of surgery in patients with 3-vessel disease without proximal LAD involvement, and a highly significant benefit for surgery in patients with 3-vessel disease and proximal LAD involvement. In most subgroups with 3-vessel disease, with or without proximal LAD involvement, the presence of an ejection fraction of less than 40% favored CABG.

Adjusted analyses, which take into account the sicker state of the surgical patients, demonstrated a survival advantage for CABG in virtually all anatomical subgroups. The adjusted hazard ratio for the long-term risk of death after CABG, relative to stent implantation, was 0.64 (95% confidence interval [CI], 0.56-0.74) for patients with 3-vessel disease and proximal LAD involvement and 0.76 (95% CI, 0.60-0.96) for patients with 2-vessel disease with involvement of the nonproximal LAD. In general, the benefits of surgery were enhanced in the subgroups with diabetes, particularly in patients with an ejection fraction of less than 40%.

The major conclusion from this study was that, for patients with 2 or more diseased coronary arteries, coronary bypass surgery is associated with higher adjusted rates of long-term survival than stenting. When one looks at the unadjusted data, it appears that bypass surgery is clearly associated with greater survival in comparison to stenting in all patients with 3-vessel disease, and in patients with 2-vessel disease associated with proximal LAD involvement and/or ejection fractions of less than 40%.

Commentary

This important study raises a number of issues in regard to the preferred method of coronary revascularization, and, as stated in the title of the accompanying editorial by Gersh and Frye, "things may not be as they seem."[2] Specifically, the results address the question of whether multivessel coronary artery disease should be treated by PCI or CABG. More broadly, the findings demonstrate several subtle but important principles with regard to the applicability of results of carefully controlled, randomized trials in clinical practice, as well as the complementary roles of randomized versus registry studies, in generating knowledge as it applies to clinical practice.

The last 3 decades have witnessed multiple randomized, controlled trials concerning indications for and preferred methods of coronary revascularization.[3] An initial series of trials focused on the indications for CABG versus medical therapy. Subsequent trials compared the results of PCI versus medical therapy and PCI versus CABG. These were followed by trials comparing devices, including stents with plain balloon angioplasty. One contemporary trial compared coronary revascularization (CABG or PCI) versus medical therapy in patients over the age of 75 years.[4] The most recently completed trials have compared outcomes after PCI (using stents with CABG), and ongoing trials are evaluating the role of drug-eluting stents in comparison with surgery. The relative merits of off-pump versus conventional CABG[5] and surgical revascularization with multiple arterial conduits versus a single arterial graft and supplementary venous conduits have been the subject of several smaller trials, but require much larger studies to resolve many of the unanswered issues.[6]

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In regard to the issues of PCI versus CABG, recent trials in patients with multivessel disease have not shown any difference in survival other than the subgroup of diabetes patients studied in the BARI Trial, where mortality was lower after CABG in comparison to following percutaneous transluminal coronary angioplasty.[7] An initial strategy of PCI would appear to cost the patient only an increased risk of recurrent angina and more frequent reintervention without any apparent penalty in terms of survival. Accordingly, and quite appropriately, the use of PCI has expanded. The principal findings of the New York State Registry data, however, appear quite different and the implications are both profound and somewhat disturbing. How can we reconcile these very different results and what are we to recommend to our patients?

Randomized trials are indispensable tools in determining best practice. Although data from large retrospective studies may be subjected to analysis using sophisticated statistical methods, subtle biases introduced by patient selection for interventional strategies cannot be entirely accounted for by multivariable analysis or propensity matching. Indeed, such selection bias is the consequence of clinical judgment, which is, in and of itself, the product of the subconscious integration of multiple factors including patient-specific comorbidities and past clinical experiences that result in a gut feeling about what is best to do for the individual patient. Only prospective randomization can eliminate this effect.

There remain, however, significant limitations to randomized trials. Entry into such trials demands that patients be considered suitable for both procedures, introducing an important entry bias at the level of the entire study group. For example, most patients entered into the trials of CABG versus PCI were at low risk as defined by strict clinical and angiographic inclusion and exclusion criteria. As a result, only a minority of all patients undergoing treatment are actually entered into such trials. In 2 trials, it was estimated that the patients enrolled represented only 5% to 12% of all patients undergoing revascularization in the participating institution.[5,8] Additionally, such trials are often underpowered to demonstrate significant differences in important clinical outcomes such as survival, hence the frequent reporting of composite endpoints.

Nonetheless, randomized trials have provided important answers to specific questions. Fortunately, their somewhat narrower or constrained focus has been complemented by a number of large registry studies. Some of these have been appendages of the primary trial (eg, the Coronary Artery Surgery Study [CASS] Registry and the Bypass Angioplasty Revascularization Investigation [BARI] Registry). The New York State registries of PCI and CABG are particularly valuable as they encompass all such procedures carried out in the state of New York, thereby addressing the limitations of both size and entry bias. Accordingly, they have been controversial as well as invaluable in determining outcomes in the real world, in addition to providing a resource for quality assurance and improvement initiatives. The New York State Registry data do suggest that the benefits of surgery are

greater than perhaps initially appreciated and that these benefits become manifest within a relatively short amount of time. Furthermore, the data imply that the benefits relate not only to durability, but also to survival.

How can we reconcile the apparent differences in findings of this study and those of the randomized studies? Do they contradict or complement one another? A critical concept in interpreting trials of management of coronary artery disease is *gradient of risk*. In general, lower risk patients have been studied in randomized trials. The problem lies in application of results obtained in these lower risk study groups to the higher risk real world. This is evident in the results of prior studies demonstrating that the major benefit of CABG over PCI or medical therapy is in "sicker" patients as characterized by the number of vessels diseased, involvement of the proximal LAD, left ventricular function, and perhaps diabetes.[3] The effect of the gradient of risk is also evident in studies from the Duke University database, which compared 5-year outcomes after CABG versus medical therapy and CABG versus PTCA.[9] The data showed that the greater the risk, as defined by the anatomic characterization of the severity of coronary disease, the greater the relative benefit of surgery over medical therapy or PTCA. On the other hand, in patients with less severe anatomic coronary disease, outcomes were similar with CABG or medical therapy or CABG versus PTCA. In fact, among patients in the lowest categories of risk, there was an adverse trend in regard to CABG.

This concept of the gradient of risk can also be used to understand the results of the BARI Trial. Among nondiabetics who were in a lower risk subgroup, survival with CABG and PCI was almost identical, as might have been expected from data in the Duke University database and from prior randomized, controlled trials.[3] In contrast, the diabetic population was at higher risk with a greater prevalence of 3-vessel disease, diffuse disease, left ventricular dysfunction, and proximal LAD involvement. These characteristics were present among a minority entered into the randomized trial, but in contrast were present in the majority of the diabetics. In this high-risk subgroup, one would have predicted from the Duke University database that CABG might be superior to PCI in regard to survival, and this was precisely the case in the BARI randomized trial. This is perhaps understandable because the target of PCI is the culprit lesion or lesions, whereas with CABG an effort is made to bypass all vessels with significant disease, including the culprit lesions as well as "future" culprits (Figure 1).[2] This could explain the benefits of CABG over PCI, at least over the intermediate term, in patients with more advanced coronary disease, particularly in the setting of left ventricular dysfunction.

The data from New York are also entirely consistent with the concept of the gradient of risk. The results demonstrated that the magnitude of the benefit is greater among those at higher risk: patients with 3-vessel disease, ejection fractions less than 40%, and diabetics. Does this mean that all patients in these subsets should be sent to surgery for coronary bypass? The question is a reasonable one but the answer is clearly no. Although a statistically significant difference in survival is a major factor to

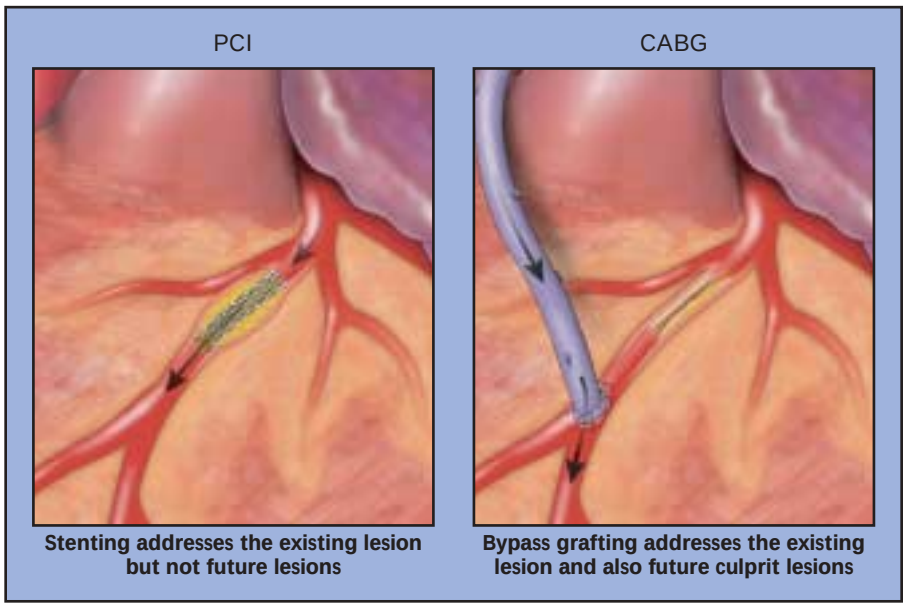

Figure 1. *Illustration of mechanisms whereby coronary artery bypass grafting (CABG) may be superior to percutaneous coronary intervention (PCI), at least in the intermediate term, in patients with multivessel disease. PCI is targeted at the "culprit" lesion or lesions (left), whereas CABG is directed at the epicardial vessel and the "future" culprits (right). Reproduced with permission from Gersh and Frye.*[2]

be taken into account in the selection of one procedure over another, other factors play an important role as well. These include periprocedural morbidity such as neurocognitive dysfunction and stroke,[10] a realistic perception of the magnitude of differences in outcomes between procedures on the part of both the physician and the patient, and the impact of comorbidities upon early and late outcomes.[2]

Other factors may play a role as well in making truly patient-centered decisions. Two individuals with identical anatomy may be treated differently for socioeconomic or personal reasons. A business executive with immediate access to advanced medical care, who is capable of making a major financial commitment, may choose PCI, whereas an individual with the same disease, who travels frequently to underdeveloped countries remote from advanced care may value durability more greatly and choose CABG. Clinical judgment and patient preference are part and parcel of the decision-making process.

The data from New York support this notion. The raw or unadjusted data make a strong although different point in regard to the perspective of the patient. Unadjusted survival curves from the New York State Registry do not demonstrate any substantial differences for patients with 2-vessel disease overall, whereas CABG was clearly superior in all subsets with 3-vessel disease. This is because patients were, in fact, being treated according to their position on this gradient of risk. Physicians in New York appear to have been practicing according to evidence-based principles in that the vast majority of patients with 2-vessel disease and no involvement of the proximal LAD were appropriately treated with PCI. Among those with 2-vessel disease and proximal LAD involvement, 42% underwent PCI and 58% underwent CABG.[1] In contrast, among patients with 3-vessel disease and nonproximal LAD disease, 70% went to CABG. If the proximal LAD was involved, 91% were treated with CABG. This might be a reflection of a high proportion with chronic total occlusions of the LAD and the presence of 3-vessel disease, but the published study does not provide this information.

Unadjusted survival curves from the New York State Registry do not demonstrate any substantial differences for patients with 2-vessel disease overall, whereas CABG was clearly superior in all subsets with 3-vessel disease.

This also explains the somewhat surprising observation that in this analysis of 59,314 patients, 63% of the revascularization procedures were CABG, which at first glance is in contrast to national and international data. A recent European study of 130 hospitals in 31 countries surveyed between 2001 and 2002 demonstrated that in patients with documented stenoses greater than 50% on coronary angiography, 58% underwent PCI, 21% CABG, and 21% medical therapy.[11] What was striking in this European study was the variability in the selection of therapy between hospitals and countries. The predominance of PCI in Europe and the United States as a whole might be a reflection of the large numbers of patients who undergo revascularization with single-vessel disease, whereas the New York State Registry analysis was confined to patients with multivessel disease.

A similar situation may have occurred in the BARI Registry and the BARI randomized trial.[12] The registry included patients who were clinically and angiographically eligible for the trial but refused randomization and were treated according to the preference of the patient or his or her physician. In the registry, as expected, lower risk patients were treated with PCI and those at higher risk underwent CABG. Outcomes in the registry, including those in diabetics, were similar between PCI and CABG. In other words, the trial demonstrated the superiority of one procedure over another in patients at higher risk (such as diabetics), but the combination of patient and physician preference in the registry diluted the magnitude of the benefit of 1 procedure over another. In the trial, it appeared that the process of randomization resulted in patients undergoing PCI, but in routine clinical practice, the majority would have been found to be more suitable for CABG. From a patient as opposed to a clinical trial perspective, it is entirely appropriate to select out lower risk patients for a percutaneous approach and to reserve CABG for a sicker subgroup. Dr. Michael O'Donnell in his book, *A Skeptic's Medical Dictionary*, stated that the definition of clinical experience is "making the same mistakes with increasing confidence over an increasing number of years," and that evidence-based medicine is defined as "making someone else's mistakes instead of your own."[13] In the case of these registry studies, however, it appears that the partnership between clinical judgment and evidence-based medicine has resulted in optimal therapeutic decisions for the individual patient.

Comparisons of outcomes of randomized control trials and registry studies are fascinating and teach us a good deal about the interpretation of trials and how to place them into perspective when extrapolated to the population at large. In a similar vein, risk-adjusted analyses, as is the case with randomized trials, tell us much about the

relative merits of one procedure over another. It is the synthesis of these results that is critical to making sense of data. Indeed, for trial results taken in isolation, "things may not be as they seem!"[2]

A final note should be made concerning the rapid advancement of technology and its impact on the applicability of trial data. It was Yogi Berra who stated that "the future ain't what it used to be,"[14] and from the perspective of coronary revascularization, the landscape is changing rapidly. Many of the studies involving PCI are criticized the moment they are reported on the grounds that the techniques are outdated (plain balloon angioplasty versus stents, and now bare metal versus drug-eluting stents). Of course, a similar argument can be made regarding the technique of CABG, be it on- or off-pump, with or without arterial grafts. Perhaps of even greater importance, however, is that many, if not all, of the published trials and registry studies are in many ways rendered obsolete by virtue of the ongoing revolution of secondary prevention. There is powerful evidence showing that the majority of events over a 5-year period after stenting are related to progressive disease in the nonstented vessels.[15] Moreover, as drug-eluting stents reduce the specter of restenosis, so will outcomes after percutaneous intervention be increasingly dependent upon the prevention of disease progression as well as risk factor modification. There is a rapidly expanding body of evidence to suggest that the aggressive control of risk factors, including hyperglycemia, will improve outcomes after PCI, CABG, and medical therapy alone. These are currently the subject of large, multicenter trials that should provide definitive answers in the near future. One can predict, however, that aggressive risk factor reduction will become an integral part of management regardless of whether revascularization or medical therapy is utilized.

Conclusions

As these ongoing trials provide us with new answers, so can we expect them to generate a whole new set of questions, which in many ways is a signature of progress. Clinical trials and registry studies generate evidence—the challenge is to be sure that it is disseminated into the practicing community, which must then exercise clinical judgment. These studies also demonstrate quite clearly the important role that can be played by the noninvasive cardiologist whose judgment is unencumbered by the biases inherent to the practice of procedural physicians (ie, interventional cardiologists or cardiac surgeons) who are understandably enthusiastic about the merits of their own modality. The New York State Registry supports the value of clinical judgment, and is a source of encouragement. Although we are all drawn to technology with the hope of improving outcomes for our patients, our clinical decision making (at least clinical practice outside clinical trials) must be driven by the data. For patients who undergo revascularization in the current era, the New York data remind us that CABG features prominently on the menu of options. ■

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