Sudden death remains a dreaded consequence of coronary artery disease, and efforts to predict its incidence and to prevent its occurrence remain a major concern. A number of the challenges in management are highlighted in the article by Veenhuyzen et al in the present issue of Circulation. In their study, mortality and modes of death were assessed in 5410 patients with ischemic left ventricular dysfunction (SOLVD) study. There were 1870 patients who had had prior coronary artery bypass grafting (CABG) and 3540 who had not had prior CABG. The SOLVD trial database is a good source for these data, both because it is large and because the cause of death (ie, whether cardiac and whether sudden or not) was established.

The key findings of Veenhuyzen et al are that CABG was associated with a 25% reduction in the risk of death (from 24.3% to 18.4%) and a 46% reduction in the risk of sudden death (from 7.5% to 4.1%). These findings are independent of ejection fraction, severity of heart failure symptoms, age, and other clinical variables. In a stratified analysis by severity of left ventricular dysfunction, there was some evidence for interaction, but similar results were noted overall. Prior CABG was not associated with an alteration in the risk of death from progressive heart failure. The results were applied to a group of patients with left ventricular dysfunction from the Coronary Artery Surgery Study Registry who had not undergone surgery, offering a predicted annual rate of death of 8.2% and sudden death of 2.4%. This was similar to the rates of death and sudden death in the CABG Patch trial (7.9% and 2.3%). Veenhuyzen and colleagues conclude that in the setting of ischemic left ventricular dysfunction, CABG is associated with a significant independent reduction in mortality. The authors go on to conclude that these results might explain the lack of benefit from defibrillator therapy found in the CABG Patch trial.

The first issue to consider is the role of revascularization in patients with severe left ventricular dysfunction. The study by Veenhuyzen et al used a somewhat unusual design involving patients in the SOLVD registry, all of whom had to survive to enter the registry. If CABG was performed in these patients, it occurred before entering the registry. Thus, patients who died after CABG but before entering the registry cannot be included. If the timing of CABG is the beginning point of observation, then no beginning point is possible in the patients who were not treated with CABG. The starting point can be only sometime after the CABG—that is, time of entry into the SOLVD registry.

Furthermore, the study by Veenhuyzen et al was not a randomized comparison. Although attempts were made to correct for baseline differences in left ventricular function and severity of heart failure, unmeasured or poorly measured variables may account for differences in outcome. Thus, nonrandomized comparisons of therapy must always be considered somewhat limited. In fact, the one and only advantage that randomization has over observational study designs is that randomization eliminates selection bias. Selection bias occurs because patients or their health care providers may use criteria that cannot be accounted for to select one form of therapy. For instance, it is difficult to measure frailty, which may be a factor selecting against CABG surgery and may be a risk factor for mortality. Technically, this would mean that frailty confounds the ability to determine if surgery reduces mortality. This does not mean that nonrandomized studies are without value, but the limitations of such studies should be recognized.

That revascularization can save lives in patients with ischemia and abnormal left ventricular function has been known since the early 1980s, with the publication of the landmark Coronary Artery Surgery Study (CASS) and Veterans Administration (VA) cooperative studies. These were randomized trials comparing medical therapy with coronary surgery. In both studies, improved survival was seen in patients who had abnormal left ventricular function and severe coronary artery disease and who were treated with surgery. These studies, however, did not include patients with severe left ventricular dysfunction. Moreover, both medical therapy and coronary surgery have improved dramatically since that time. Although it seems unlikely that the CASS or VA studies will be repeated, there currently is interest in developing a randomized trial to compare medical therapy with CABG in patients with ischemia and severe left ventricular dysfunction. In the absence of such a trial, the only sources of information are either observational databases, such as that in the article by Veenhuyzen et al, or the generalization of the results of randomized trials to groups of patients who were not included in these trials.
The next issue relates to whether the low event rates seen in patients treated with CABG in the SOLVD and CABG Patch trials explain the failure of implantable cardioverter-defibrillator (ICD) placement to save lives in the CABG Patch trial. There certainly are convincing data from randomized trials indicating that in nonsurgical patients with left ventricular dysfunction, ICD placement decreases mortality when compared with anti-arrhythmic drug therapy. Why was CABG Patch different? There are 3 possibilities: (1) It is an attractive thought that CABG surgery might have decreased mortality in patients at high risk if the surgery prevented ischemia and thereby prevented sudden death, perhaps obviating the need for an ICD. (2) A second possibility, however, is that patients who underwent CABG had been selected and were at lower risk than were patients who did not undergo CABG, and that in these lower-risk patients, ICD therapy may have been ineffective. (3) A third possibility is that there may not have been sufficient power in CABG Patch to reveal the effectiveness of ICD placement, given the low event rate.

These 3 possibilities would require different management strategies. (1) If CABG were found to prevent ischemia, thereby preventing sudden death in patients with severely abnormal left ventricular function, then a greater effort should be made among patients with coronary artery disease and severe left ventricular dysfunction to find those patients with ischemic potential and offer them revascularization. This issue could be resolved if a trial of CABG versus medical therapy in patients with severe left ventricular dysfunction were initiated. (2) If the patients with severe left ventricular dysfunction who found their way to surgery were at lower risk and the ICD was ineffective, then CABG therapy should be considered, but perhaps not with the enthusiasm of the first scenario. (3) Finally, if these patients were lower-risk patients in whom ICD placement was found to be effective, but there was not sufficient power in the CABG Patch trial to demonstrate its effectiveness, then the potential cost-effectiveness of ICD placement in CABG patients with severe left ventricular dysfunction at varying levels of ICD effectiveness could be considered. If ICD placement still seemed to be potentially cost-effective, then another trial of ICD coupled with revascularization would be warranted. However, this issue may burn a little less brightly now than it did in the recent past because ICD placement now is little more complicated than the placement of a pacemaker, and there is no procedural advantage to coupling the ICD placement with CABG surgery. It must be noted that ICD placement remains expensive.

The epidemiological issues involved in disentangling the relationship between CABG and ICD placement in preventing sudden death after coronary surgery are indeed complex. The trials needed to sort this issue out perfectly may never be carried out. In the absence of perfect data, decisions need to be made. The study by Veenhuyzen et al1 highlights these issues and suggests, probably correctly, that revascularization is the appropriate therapy for patients with abnormal left ventricular function and residual ischemia. ICD placement makes most sense for patients who are at risk but who lack the ischemic potential that would send them to revascularization.

References
Revascularization Versus Implantable Cardioverter-Defibrillators to Prevent Sudden Death in Patients With Severe Left Ventricular Dysfunction

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