

## REVIEW ARTICLE

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## Coronary-Artery Bypass Grafting

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CORONARY-ARTERY BYPASS GRAFTING (CABG) IS A PROCEDURE IN WHICH autologous arteries or veins are used as grafts to bypass coronary arteries that are partially or completely obstructed by atherosclerotic plaque. CABG is among the most commonly performed major surgical procedures, with approximately 400,000 operations performed annually in the United States. During the past decade, however, there has been nearly a 30% decline in CABG procedures in the United States, despite an aging population and growing evidence to support the effectiveness and safety of the operation.<sup>1-6</sup> This decline has been accompanied by a corresponding increase in percutaneous coronary revascularization procedures.

## THE CABG PROCEDURE

CABG is typically performed through a median (midline) sternotomy. No muscles are divided, and at the conclusion of the procedure, the sternum is repaired by means of wire fixation. This incision provides optimal exposure. Major complications, such as sternal wound infection, occur in approximately 0.4% of patients.<sup>7</sup>

To allow for the precision necessary to perform successful CABG surgery, the heart is typically arrested. This is achieved by occluding the ascending aorta and then perfusing the heart with cold, high-potassium cardioplegia solution. Arrest requires the use of a cardiopulmonary-bypass machine, which provides both perfusion pressure and oxygenation, to support the circulation during the 1-to-2-hour period of ischemic cardiac arrest.

The most commonly used bypass conduits are the left internal thoracic artery and the greater saphenous vein. The use of a left-internal-thoracic-artery graft to the left anterior descending coronary artery is considered a major quality indicator in CABG and is associated with higher long-term patency rates than are saphenous-vein grafts; also, the associated clinical outcomes are better than those of patients with no left-internal-thoracic-artery graft.<sup>1,7-10</sup> Saphenous-vein grafts are typically obtained from the patient's thigh through small incisions under endoscopic guidance.<sup>11</sup> Grafts from other arteries, such as the radial artery, the right internal thoracic artery, and the gastroepiploic artery, have been investigated and generally have been shown to have better patency than saphenous-vein grafts but are not routinely used.<sup>12-15</sup>

To ensure that the CABG procedure is tailored to the patient's coronary anatomy, the surgeon will review the coronary angiogram before the operation and may have access to the angiographic images in the operating room. Coronary arteries with clinically significant proximal stenoses and patent distal vessels are considered potentially suitable for grafting.

During the operation, each epicardial coronary artery containing a proximal stenosis is evaluated by direct external inspection and palpation for a suitable distal target site. An incision is then made in the coronary artery distal to the

stenosis, and the bypass graft is hand-sewn (anastomosed) end-to-side to the incision. The sewing of the distal anastomosis is aided by optical magnification and constitutes the most technically difficult portion of the operation. The proximal anastomosis for each graft is completed by sewing the graft end-to-side to an aortotomy in the proximal ascending aorta, except for in situ arterial grafts (e.g., a left-internal-thoracic-artery graft) in which the native arterial inflow is preserved (Fig. 1).

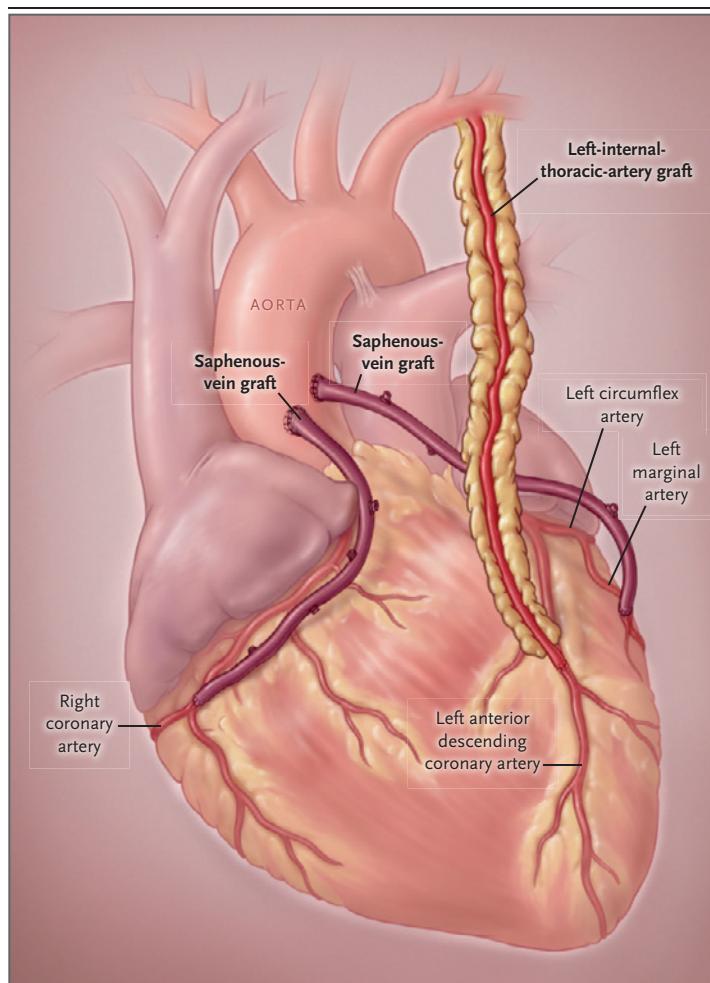
The typical CABG procedure takes 3 to 4 hours. Patients usually remain in the hospital for 5 to 7 days after the procedure and require 6 to 12 weeks after discharge to recover completely.<sup>16</sup>

#### EVIDENCE FROM TRIALS AND OBSERVATIONAL STUDIES

##### CABG VERSUS MEDICAL THERAPY

For patients with severe multivessel coronary artery disease, CABG was shown to provide a survival benefit over medical therapy alone in the following three pivotal randomized, controlled trials from the 1970s and 1980s: the Veterans Administration Cooperative Study, the European Coronary Surgery Study, and the Coronary Artery Surgery Study.<sup>17-19</sup> A 1994 meta-analysis that included data on 2649 patients from these and several smaller trials showed that, as compared with medical therapy, CABG resulted in lower mortality at 5 years (10% vs. 16%,  $P < 0.001$ ), 7 years (16% vs. 22%,  $P < 0.001$ ), and 10 years (26% vs. 31%,  $P = 0.03$ ).<sup>20</sup> The relative survival benefit of CABG over medical therapy is consistent across subgroups; however, the absolute survival benefit is greater for patients at greater risk, including those with more extensive coronary artery disease and those with left ventricular dysfunction. Because of the early surgical risk associated with CABG, its survival advantage over medical therapy does not become evident until 1 to 2 years after surgery and then tends to increase with longer follow-up.<sup>17-19,21</sup>

The major clinical trials comparing CABG with medical therapy were limited because they involved few older patients (only 7% were more than 60 years of age) and few women. In addition, because there have been no large trials addressing this comparison in the past two decades, CABG has not been compared with contemporary medical management, including



**Figure 1. Coronary-Artery Bypass Grafting.**

Shown are a left-internal-thoracic-artery graft to the left anterior descending coronary artery and saphenous-vein grafts to the left marginal and right coronary arteries.

consistent use of antiplatelet therapy and lipid-lowering statin drugs.

##### CABG VERSUS PERCUTANEOUS CORONARY INTERVENTION

A 2009 meta-analysis of 10 trials conducted before 2006, including data on 7812 patients with various types of multivessel coronary disease, showed that CABG and percutaneous coronary intervention (PCI) resulted in similar overall mortality at 5.9 years of follow-up (15% and 16%, respectively;  $P = 0.12$ ).<sup>22</sup> Patients who had undergone CABG, as compared with those who had undergone PCI, were more likely to have a stroke but were less likely to undergo a repeat

revascularization procedure. This meta-analysis was limited because early trials did not include large numbers of patients in whom CABG is known to improve survival, including those with three-vessel disease or proximal left anterior descending coronary artery disease, diabetes, or left ventricular dysfunction.

Observational studies and more recent trials have updated the previous work by including higher-risk patients and reflecting changes in practice.<sup>23-31</sup> These studies included large numbers of patients with complex coronary artery disease who were treated with contemporary medical therapy and first-generation drug-eluting stents. An important trial was the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) study, which randomly assigned 1800 patients with either three-vessel or left main coronary artery disease to CABG or PCI.<sup>32</sup> Evaluation of each participant included determination of the SYNTAX score (a measure of the extent and complexity of coronary artery disease) and the anticipated complexity of PCI.<sup>33</sup> SYNTAX scores are used to classify the complexity of coronary artery disease as low ( $\leq 22$ ), intermediate (23 to 32), or high ( $\geq 33$ ).<sup>34</sup> At 5 years, patients assigned to CABG, as compared with those assigned to PCI, had a lower rate of the composite end point of death, myocardial infarction, stroke, or repeat revascularization (26.9% vs. 37.3%,  $P < 0.001$ ), a lower rate of myocardial infarction (3.8% vs. 9.7%,  $P < 0.001$ ), a similar rate of death (11.4% vs. 13.9%,  $P = 0.10$ ), a similar rate of stroke (3.7% vs. 2.4%,  $P = 0.09$ ), and a lower rate of death from cardiac causes (5.3% vs. 9.0%,  $P = 0.003$ ).<sup>27</sup>

#### *Three-Vessel Disease*

Overall, patients with three-vessel disease in the SYNTAX trial had a survival benefit with CABG as compared with PCI (rate of death, 9.2% vs. 14.6%;  $P = 0.006$ ).<sup>35</sup> In patients with the least complex three-vessel disease (SYNTAX score  $\leq 22$ ), PCI was noninferior to CABG. In patients with more complex disease (SYNTAX score  $\geq 23$ ), CABG was superior to PCI. The survival benefit of CABG over PCI for patients with multivessel coronary artery disease has been confirmed in other studies and appears to be consistent when PCI is performed with second-generation drug-eluting stents.<sup>23-26,28,31,36-38</sup> The American College of Cardiology Foundation–American Heart As-

sociation (ACCF-AHA) guidelines for the treatment of stable ischemic heart disease now give CABG a class I recommendation for patients with multivessel coronary artery disease.<sup>1</sup>

#### *Left Main Coronary Artery Disease*

In the SYNTAX study, the outcomes with PCI as compared with CABG were noninferior for patients with left main coronary artery disease. The outcomes of the two procedures were indistinguishable in patients with isolated left main coronary artery disease or left main coronary artery disease and single-vessel coronary artery disease (SYNTAX score  $< 33$ ). These findings have been supported by more recent randomized trials and observational studies.<sup>27,39</sup> However, in patients with left main and two- or three-vessel coronary artery disease (SYNTAX score  $\geq 33$ ), there was a significant reduction in the rate of the composite end point of death, myocardial infarction, stroke, or repeat revascularization with CABG as compared with PCI (29.7% vs. 46.5%,  $P = 0.003$ ).<sup>27</sup> These findings have resulted in new guidelines recommending PCI in patients with uncomplicated left main coronary artery disease and a suitable anatomy for PCI, particularly if they are at increased surgical risk with CABG.<sup>1,40-43</sup>

## COMPLICATING FACTORS

### **DIABETES MELLITUS**

Patients with multivessel coronary artery disease and diabetes have an increased cardiovascular risk as compared with those without diabetes, and they have a survival benefit from CABG as compared with PCI. In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, patients with diabetes and multivessel coronary artery disease were randomly assigned to CABG or PCI.<sup>44</sup> At 5 years, those assigned to CABG had lower rates of the primary composite outcome of death, myocardial infarction, or stroke (18.7% vs. 26.6%,  $P = 0.005$ ) and of overall mortality (10.9% vs. 16.3%,  $P = 0.05$ ) but a higher rate of stroke (5.2% vs. 2.4%,  $P = 0.03$ ) as compared with patients assigned to PCI.<sup>36</sup> These findings of superior survival after CABG in patients with diabetes are supported by the results of the Bypass Angioplasty Revascularization Investigation (BARI) and

BARI in Type 2 Diabetes (BARI-2D) trials and from the diabetes subgroups in the SYNTAX trial and the Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial.<sup>31,45-47</sup> On the basis of these data, the ACCF-AHA guidelines for the treatment of patients with stable ischemic heart disease now give CABG a class I comparative recommendation, favoring CABG over PCI for patients with multivessel coronary artery disease and diabetes.<sup>1</sup>

#### LEFT VENTRICULAR DYSFUNCTION AND MITRAL-VALVE DISEASE

Patients with left ventricular dysfunction or mitral-valve disease also have increased cardiovascular risk and a survival benefit from CABG.<sup>48</sup> Subgroup analyses of early clinical trials suggest a particular benefit of CABG over medical therapy in patients with left ventricular dysfunction.<sup>19</sup> The Surgical Treatment for Ischemic Heart Failure (STICH) trial compared CABG with medical therapy in a group of high-risk patients with multivessel coronary artery disease, severe left ventricular dysfunction, and heart failure.<sup>49</sup> CABG did not significantly reduce all-cause mortality (the primary outcome) as compared with medical therapy (36% vs. 41%,  $P=0.12$ ). However, there were significant reductions in important secondary outcomes with CABG, including cardiovascular mortality (28% vs. 33%,  $P=0.05$ ) and death or hospitalization for cardiovascular conditions (58% vs. 68%,  $P<0.001$ ).<sup>21</sup> An as-treated analysis that accounted for treatment crossovers showed a significant advantage of CABG over medical therapy with respect to all-cause mortality (33% vs. 44%,  $P<0.001$ ).<sup>21</sup> Recently, long-term follow-up of the STICH population was reported.<sup>50</sup> After almost 10 years of follow-up, patients assigned to CABG, as compared with patients assigned to medical therapy, had lower rates of death from any cause (58.9% vs. 66.1%,  $P=0.02$ ), of death from cardiovascular causes (40.5% vs. 49.3%,  $P=0.006$ ), and of death from any cause or hospitalization for cardiovascular causes (76.6% vs. 87.0%,  $P<0.001$ ).

Patients with multivessel coronary artery disease and concomitant ischemic mitral regurgitation represent a particularly high-risk group in which, according to observational studies, med-

ical therapy or PCI is associated with poor outcomes and CABG with comparatively better outcomes.<sup>51</sup> Although longer-term follow-up and additional studies are needed, preliminary randomized data suggest that in appropriately selected patients, surgical coronary revascularization alone might be sufficient to reduce moderate mitral regurgitation and reverse ventricular remodeling, as compared with CABG and mitral-valve repair.<sup>52,53</sup>

#### ACUTE CORONARY SYNDROMES AND ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

The evidence in favor of CABG is almost entirely based on studies of patients with stable ischemic heart disease. Nevertheless, the recommendations for CABG are commonly extended to include patients with acute coronary syndromes, including unstable angina and stable non-ST-segment elevation myocardial infarction. In practice, more than 60% of CABG procedures are performed during an acute care hospitalization and 29% follow a recent myocardial infarction.<sup>54</sup>

The best initial treatment for patients with acute ST-segment elevation myocardial infarction is reperfusion therapy with either PCI or fibrinolytic therapy. As compared with CABG, PCI restores coronary blood flow more rapidly, preserves myocardium, and improves outcomes. In this patient population, CABG is reserved for those who have a coronary anatomy that is not amenable to PCI or who have mechanical complications, such as ventricular septal defect, myocardial rupture, or papillary-muscle rupture with acute, severe mitral regurgitation.

#### PATIENT CARE

##### INDICATIONS AND EVALUATION FOR CABG

CABG is very effective in providing durable relief of angina, but in contemporary practice, it is performed primarily to improve the survival of patients with coronary artery disease.<sup>1,55,56</sup> Appropriate selection of patients for CABG is critical to ensure good outcomes. The evaluation of patients for CABG relies on a systematic assessment of the characteristics and coronary anatomy known to be associated with a survival benefit from CABG as compared with medical therapy or PCI (Table 1). Central factors to be considered in determining whether CABG is indicated are the extent of coronary artery disease, whether

**Table 1. Indications for Coronary-Artery Bypass Grafting (CABG).\*****Indications for CABG that are associated with a survival benefit over medical therapy with or without PCI**

## Acute STEMI

Coronary anatomy not amenable to PCI

Mechanical complications (e.g., ventricular septal defect, rupture of the free wall of the ventricle, or papillary-muscle rupture with severe mitral regurgitation)

## Coronary artery disease other than acute STEMI

Left main coronary artery disease ( $\geq 50\%$  stenosis) and high complexity for PCI (SYNTAX score  $\geq 33$ )Three-vessel coronary artery disease ( $\geq 70\%$  stenosis) and intermediate or high complexity for PCI (SYNTAX score  $\geq 23$ )Two-vessel coronary artery disease ( $\geq 70\%$  stenosis) involving the LAD artery and intermediate or high complexity for PCI (SYNTAX score  $\geq 23$ )**Factors increasing the survival benefit of CABG**Left ventricular dysfunction (ejection fraction  $\leq 45\%$ )

Diabetes mellitus

Ischemic mitral regurgitation

PCI failure with or without acute myocardial infarction

**Indications for CABG when PCI is noninferior to CABG and when PCI or CABG is preferred over medical therapy**Left main coronary artery disease ( $\geq 50\%$  stenosis) and low-to-intermediate complexity for PCI (SYNTAX score  $\leq 32$ )Three-vessel coronary artery disease ( $\geq 70\%$  stenosis) and low complexity for PCI (SYNTAX score  $\leq 22$ )Two-vessel coronary artery disease ( $\geq 70\%$  stenosis) involving the LAD artery and low complexity for PCI (SYNTAX score  $\leq 22$ )**Factors increasing the benefit of PCI over CABG**

Elevated risk of death with CABG

Elevated risk of stroke

Extreme frailty

Prior CABG

Acute STEMI at presentation

**Other indications for CABG**Clinically significant coronary artery disease ( $\geq 70\%$  stenosis) in  $\geq 1$  vessel and refractory angina despite medical therapy and PCIClinically significant coronary artery disease ( $\geq 70\%$  stenosis) in  $\geq 1$  vessel in survivors of sudden cardiac arrest presumed to be related to ischemic ventricular arrhythmiaClinically significant coronary artery disease ( $\geq 50\%$  stenosis) in  $\geq 1$  vessel in patients undergoing cardiac surgery for other indications (e.g., valve replacement or aortic surgery)

\* The SYNTAX scoring system, developed as part of the Synergy between PCI with Taxus and Cardiac Surgery study, classifies the extent and complexity of coronary artery disease, with a score of 22 or lower indicating low complexity, a score of 23 to 32 indicating intermediate complexity, and a score of 33 or higher indicating high complexity. CABG denotes coronary-artery bypass grafting, LAD left anterior descending, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

the disease is acute or stable, the status with respect to coexisting conditions (diabetes and peripheral or cerebrovascular disease), and the presence or absence of left ventricular systolic dysfunction.

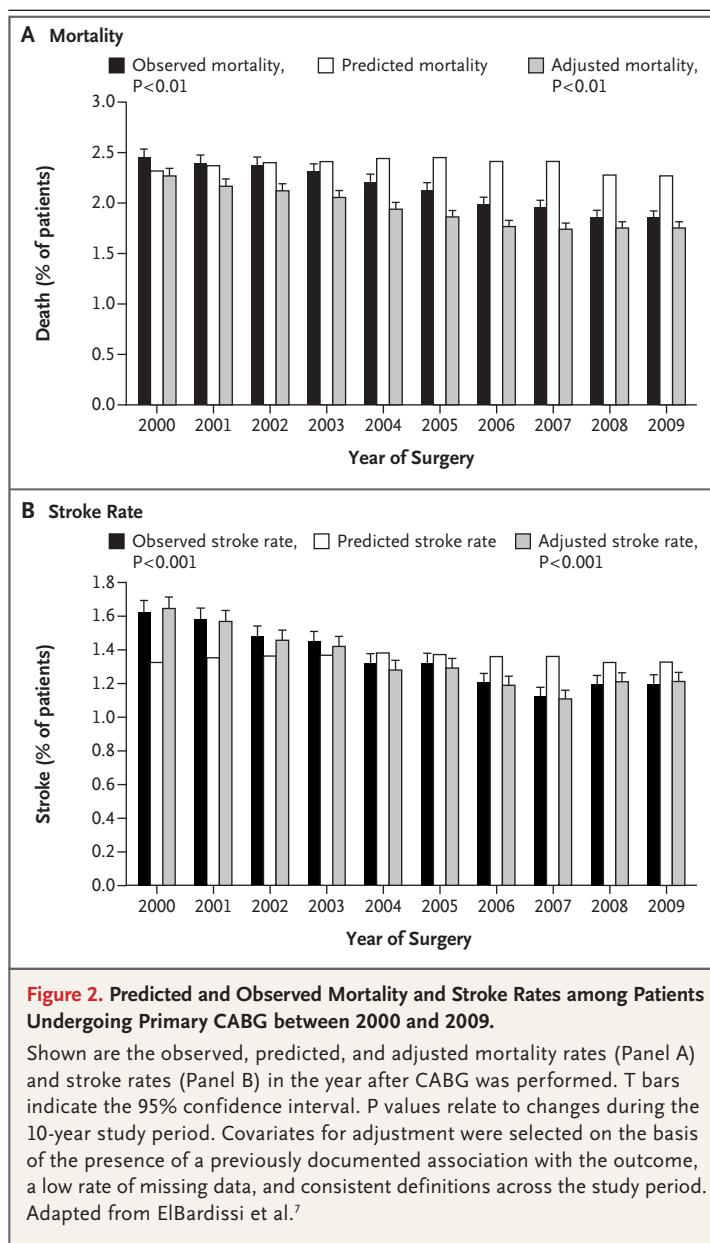
Patients with single-vessel or two-vessel coronary artery disease that does not involve the proximal left anterior descending coronary artery have no survival benefit from CABG and should

generally receive medical therapy with or without PCI. Overall, patients with three-vessel disease, complex two-vessel disease, or complex left main coronary artery disease have a benefit from CABG over medical therapy with or without PCI and should typically be considered for CABG. The presence of left ventricular dysfunction or diabetes increases the benefit of CABG over medical therapy with or without PCI.

Beyond these well-established factors are a number of less well understood variables that are sometimes considered in the selection of patients for CABG. These include myocardial viability, the extent of myocardial ischemia, and the proportion of myocardium that is considered to be at risk.<sup>57,58</sup> In addition, fractional flow reserve (FFR), an invasive technique that measures the pressure difference across a coronary stenosis, has been investigated in patients undergoing PCI.<sup>59,60</sup> The usefulness of FFR in selecting patients with multivessel coronary artery disease for CABG or in identifying bypass graft targets in patients undergoing CABG has not been studied.<sup>61-63</sup> Patient characteristics that increase the risk associated with CABG, potentially offsetting the benefit, include advanced cerebrovascular disease and a risk of stroke, prior cardiac surgery, and less well defined factors such as frailty and immobility.<sup>64-66</sup> Comprehensive information on the indications for CABG, based on evidence and expert opinion, can be found in the ACCF-AHA guidelines for CABG,<sup>1</sup> the ACCF-AHA guidelines for the treatment of stable ischemic heart disease,<sup>40</sup> and the joint report on appropriate criteria for coronary revascularization.<sup>67</sup>

#### THE HEART TEAM AND SHARED DECISION MAKING

In an effort to aid in the patient selection and referral process, current guidelines recommend a multidisciplinary heart team to facilitate shared decision making regarding revascularization strategies for patients with ischemic heart disease.<sup>1,40</sup> There is increasing evidence that treatment decisions for patients with complex coronary artery disease are best made through a process of shared decision making that includes the patient, the patient's family, an interventional cardiologist, a cardiac surgeon, and ideally, the patient's general cardiologist or primary care physician.<sup>4,68</sup> Physicians who have known the patient over time should play a substantial role in making decisions about coronary angiography as well as in discussing the most appropriate revascularization strategy once the patient's coronary anatomy is known. This approach is appealing because the risk-benefit assessment depends on evidence that is best known by specialists but is made on behalf of patients who are best known by their primary care physicians. Leaving the choice of revascularization strategy to the cardiologist performing coronary angiography



may lead to more PCI procedures and fewer appropriate referrals for CABG.<sup>3,69-73</sup>

#### MORBIDITY AND MORTALITY

CABG has predictable short-term morbidity and mortality.<sup>74-77</sup> Advances in CABG and quality-improvement initiatives, made possible by nearly universal participation of CABG centers in the Society of Thoracic Surgeons National Adult Cardiac Surgery Database, have led to important reductions in observed mortality over the past decade (Fig. 2A), despite virtually no change in

predicted risk.<sup>7,8,78</sup> Although the surgeon has a central role in the outcome of CABG, the efficacy and safety of the procedure also depend greatly on the efforts of other members of the multidisciplinary management team and on established perioperative and postoperative processes of care.<sup>1,40</sup> The risks of CABG are highest during and shortly after surgery; these short-term risks must be weighed against the known long-term benefits of the operation.

#### STROKE AND NEUROCOGNITIVE DYSFUNCTION

Stroke remains the most serious complication of CABG, occurring in 1 to 2% of patients in the perioperative period.<sup>79</sup> Notable risk factors for stroke include a history of neurologic events, advanced age, peripheral or cerebrovascular disease, and diabetes.<sup>80,81</sup> Aortic atherosclerosis is also a major risk factor for stroke after CABG because of the necessary manipulation or clamping of the ascending thoracic aorta.<sup>82</sup> The use of a single aortic cross-clamp and epiaortic ultrasonography during CABG have been associated with a reduction in the risk of stroke over the past decade (Fig. 2B).

Neurocognitive dysfunction has also been attributed to CABG and particularly to the use of cardiopulmonary bypass.<sup>80</sup> However, these associations were observed in uncontrolled longitudinal studies. Randomized trials comparing CABG performed with and without cardiopulmonary bypass and comparing CABG with PCI have not confirmed these findings.<sup>83-85</sup> The current view is that neurocognitive dysfunction after CABG is due to a combination of short-term effects of major surgery and the long-term effects of advanced age, depression, and a common predisposition to coronary artery disease and neurocognitive dysfunction.<sup>86,87</sup>

#### SECONDARY PREVENTION AFTER CABG

Many patients, and some physicians, have the misconception that CABG cures coronary artery disease. In fact, CABG does not prevent the progression of native coronary artery disease, and internal-thoracic-artery and saphenous-vein grafts can fail. However, both disease progression and vein-graft failure can be ameliorated by aggressive secondary prevention with medical therapy. There is a growing understanding of factors associated with vein-graft failure.<sup>88</sup> The majority of

vein grafts that fail do so with little immediate clinical consequence to the patient.<sup>10,89</sup>

According to a recent AHA scientific statement on appropriate secondary prevention after CABG, patients should receive lifelong antiplatelet therapy.<sup>1,90</sup> Low-dose aspirin (81 mg daily) may be preferable to full-dose aspirin (325 mg daily) because of the lower risk of bleeding.<sup>1,90</sup> There are limited data from randomized trials on the use of aspirin and a P2Y<sub>12</sub>-receptor inhibitor, such as clopidogrel or ticagrelor, in patients who have undergone CABG. If a patient was receiving a P2Y<sub>12</sub>-receptor inhibitor before surgery, it should be continued after surgery for the original indication. A 12-month course of a P2Y<sub>12</sub>-receptor inhibitor after CABG may promote vein-graft patency and is used in more than 25% of patients.<sup>90-96</sup> Beta-blockers should be used in patients with a recent myocardial infarction, left ventricular systolic dysfunction, or nonrevascularized coronary artery disease.<sup>78,90</sup> All patients, regardless of lipid values, should receive lifelong high-intensity statin therapy.<sup>90,97</sup> Angiotensin-converting-enzyme inhibitors should be used in patients with diabetes or left ventricular dysfunction.<sup>40</sup> Aldosterone antagonists should be considered in patients with left ventricular systolic dysfunction.<sup>90</sup> To ensure long-term adherence to treatment, the best time to start preventive strategies is before hospital discharge. Patients should also participate in a short-term cardiac rehabilitation program, which accelerates recovery and facilitates positive lifestyle changes, including regular aerobic exercise, a diet low in saturated fats and carbohydrates, and smoking cessation.<sup>1,40,90</sup>

#### FUTURE DIRECTIONS

Attempts have been made to achieve the benefits of CABG with the use of less invasive methods. Approaches that avoid median sternotomy have been developed; however, they require specialized training and may not allow for complete revascularization. In addition, CABG can be performed without cardiopulmonary bypass; however, greater surgical skill is required to perform surgery on the beating heart, and complete revascularization is more difficult to achieve. To date, off-pump surgery has shown no consistent advantage over on-pump surgery.<sup>83,98-101</sup> A recent

development is hybrid surgical and percutaneous revascularization. In this approach, patients undergo minimally invasive grafting with the use of a left-internal-thoracic-artery graft to the left anterior descending coronary artery and also undergo PCI of lesions in the left circumflex artery, the right coronary artery, or both.<sup>102,103</sup> Whether hybrid coronary revascularization provides the benefits of CABG with lower morbidity requires additional investigation.

## CONCLUSIONS

CABG offers significant improvement in survival and quality of life for appropriately selected patients with multivessel coronary artery disease. Those with more advanced coronary artery dis-

ease, left ventricular dysfunction, or diabetes are particularly likely to benefit from CABG. Primary care physicians, internists, and cardiologists play a key role in the patient selection and referral process. Although ongoing research may incrementally improve the CABG procedure, the largest improvements in outcomes are likely to be realized by appropriately selecting patients to undergo CABG.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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