Coronary bypass for diabetic heart patients

Masoor Kamalesh1 & Thomas Sharp*1

Practice Points

- Two-thirds of diabetic patients will eventually die from cardiovascular causes, making revascularization an important strategy at some point in the course of most patients with diabetes.
- In its early stages, coronary artery disease can be successfully managed by intensive medical therapies without adversely impacting intermediate term mortality.
- Coronary anatomy is a crucial element in the choice between surgical revascularization strategies and either percutaneous coronary intervention (PCI) or intensive medical management.
- Larger territories of ischemia, particularly in the anterior wall of the heart and multivessel coronary disease favor surgery over medical management.
- Patients with three-vessel coronary artery disease who receive surgical revascularization experience lower mortality and myocardial infarction rates over 2–5 years than patients treated medically or with PCI.
- The survival benefit of surgery may be delayed for 1–4 years, depending upon the underlying surgical risk of the patient and the severity of the coronary artery disease.
- Stroke risk after bypass surgery is variable in diabetics, but may offset survival advantages in some groups of patients.

SUMMARY  A literature search for clinical trials evaluating the role of bypass surgery for revascularization of diabetics with significant coronary artery disease that reported results in that past 4 years was undertaken. Six clinical trials were identified that recently reported intermediate to long-term outcomes of coronary bypass in diabetic patients. Three studies were conducted exclusively in diabetics, while three represent subset analyses of larger trials. Two meta-analyses of the clinical trial data and several large database studies have been reported in the past few years as well. We will review the major findings of these studies and the implication of their findings for clinical practice. We will also identify areas where persistent uncertainty remains.
The high prevalence of coronary artery disease among diabetics and the fact that approximately two-thirds of patients with diabetes will eventually succumb to cardiovascular disease means that coronary revascularization is an extremely important component of management strategies for diabetes [1,2,101]. It has been estimated that the risk of dying from a myocardial infarction (MI) among diabetics is similar to the risk that a nondiabetic with a previous heart attack faces [5]. Thus, medical management of cardiovascular risk factors in a diabetic patient should always follow guidelines for secondary prevention regardless of whether coronary disease has been proven.

Several recent trials have specifically addressed the role of revascularization for patients with diabetes. BARI 2D examined the role of revascularization versus intensive medical management alone in diabetic patients with moderate coronary artery disease and stable symptoms. Three randomized trials have addressed the choice of either surgery or percutaneous coronary intervention (PCI) for diabetic patients with more extensive coronary artery disease: CARDia, FREEDOM and VA CARDS. Two other trials have recently reported long-term results for diabetic subsets. SYNTAX reported 5-year results between PCI and surgery for diabetics with left main or three-vessel disease. MASS II reported 10-year results for their diabetic subpopulation treated with intensive medical management, PCI or surgery. Additionally, there is recent information regarding the optimal choice of revascularization for diabetics from several large database analyses. The ASCERT study examined patients from the Society of Thoracic Surgeons (STS) surgical database and compared the results of surgery to those from the American College of Cardiology (ACC) PCI registry. An analysis of PCI versus surgery in a large sample from Medicare databases and two meta-analyses of major trials have also recently been published. We will review the results of these investigations and the implications they have for management decisions in diabetic patients with coronary disease.

It is important to realize in reviewing these studies that the coronary anatomy was known for each of these patients and was a critical element in directing therapy. The topic of when to proceed to coronary angiography in diabetic patients is a complex one that cannot be adequately addressed in this review. Important information, however, was added in BARI 2D where an analysis of long-term mortality outcomes showed that the symptom status of a patient (angina, angina equivalent symptoms or no symptoms) at baseline did not predict mortality risk [4]. Since silent ischemia is fairly prevalent among diabetics, it is tempting to assume that screening for ischemia might guide decisions regarding when to perform angiography. However, several large trials [5,6] have shown no benefit to large-scale screening of asymptomatic diabetics. Taken together these two factors suggest that waiting for symptoms to appear or widespread use of stress testing are not useful strategies to guide decisions regarding when to proceed with angiography, and accurate risk models may be more important as clinical decision tools.

**Surgery versus medical management for stable coronary disease**

There are no contemporary studies exclusively comparing surgical revascularization to optimal medical management for the treatment of stable coronary artery disease in diabetic patients. Thus, there are no definitive data from which to derive recommendations. However, two recent analyses of subsets of larger trials have examined this issue and shed some light on the potential for benefit from surgery compared with medical management alone.

BARI 2D randomized over 2000 patients with stable coronary artery disease and treated diabetes to either intensive medical therapy alone or intensive medical therapy plus revascularization [7]. Medical management was further randomized between insulin-sensitizing and insulin-providing regimens. The revascularization arm of the trial was stratified by a prespecified intention to treat with either PCI or coronary artery bypass surgery (CABG). Overall, 67.7% of patients were assigned to a PCI strategy. The primary end point after 5 years of follow up was all-cause mortality. A composite end point of all-cause mortality plus nonfatal MI plus nonfatal stroke (cerebrovascular accident [CVA]) was also assessed. In the PCI stratum, there was no improvement in either all-cause mortality or the composite end point for revascularization compared with medical management, and the trends actually favored medical management. This result in diabetic patients is consistent with that of the COURAGE trial in which an unselected population with stable coronary artery disease was randomized between PCI and medical management [8].
Selection of patients for surgical revascularization in BARI 2D was driven by complexity of disease such as triple vessel involvement, a proximal left anterior descending (LAD) stenosis or a chronic total occlusion of a major epicardial vessel [9]. In the surgical stratum of BARI 2D, there was a small absolute improvement in survival (2.8%) with revascularization, but this was not statistically significant. There were also small absolute improvements in the risk of MI and stroke, so that the composite did show a statistically significant improvement favoring revascularization. 77.6% of patients in the revascularization arm were free of major adverse events at 5 years compared with 69.5% of those in the optimal medical treatment arm (p = 0.01). In a further analysis, the magnitude of benefit from surgical revascularization correlated with both the clinical Framingham risk score and an angiographic risk score [10]. Optimal risk stratification, however, required a composite of both clinical and angiographic risk.

In addition to the reduction in cardiovascular events, a substudy of BARI 2D showed significant improvement in quality-of-life measures related to angina in the revascularization arm. Freedom from angina was also better for PCI compared with medical management, but this was only statistically significant during the first year of follow up [4].

The results of medical treatment in BARI 2D as an initial strategy must also be understood in the context of a very liberal use of subsequent revascularization on clinical grounds. During follow up, 38% of patients randomized to medical therapy underwent revascularization. This compares to the 20.6% of patients randomized to prompt revascularization that underwent repeat revascularization by 5 years [4]. Overall, surgical revascularization in the type of patients treated in BARI 2D resulted in sustained symptom relief, a modest reduction in mortality and significant reduction in cardiovascular event rates over a 5-year period.

The MASS II trial was a single-center study in Brazil that randomized 611 patients with multivessel coronary artery disease and stable symptoms to either medical treatment, surgery or percutaneous treatment [11]. Diabetic patients (232) accounted for 38% of the study population. A long-term follow up of the diabetic subset of patients in this trial recently demonstrated improved survival over 10 years for surgical treatment compared with medical management (72.5 vs 62.5%, p = 0.015). There was also improvement in survival in the PCI arm compared with medical treatment, but the difference was smaller and not statistically different (6.2% absolute difference, p = 0.35).

### Percutaneous intervention versus surgery for stable angina

Three randomized trials have now been completed that have assessed the impact of revascularization using PCI versus CABG among diabetics with complex coronary artery disease. CARDia was a European trial that compared surgery to PCI in 490 diabetics with coronary artery disease [12,102]. A combination of bare metal and sirolimus-eluting (69%) stents were used in the PCI group. At 1 year (10.5 vs 13.0%, p = 0.393) and 5 years (20.5 vs 26.6%, p = 0.11) there were trends favoring surgery, but no statistically significant differences in the composite outcome of death, MI and CVA between surgery and PCI. However, the study remained underpowered for its primary outcome.

The FREEDOM study randomized 1900 diabetic patients in North American (n = 770) and international (n = 1130) sites to either PCI with drug-eluting stents or bypass surgery [13]. Both the primary composite end point and the all-cause mortality end point showed statistically significant differences at 5 years favoring surgery. The composite of death, MI and CVA was 26.6% in the PCI group, compared with 18.7% in the surgery group (p = 0.005). All-cause mortality was 16.3% for PCI versus 10.9% for CABG (p = 0.049). Advantages in death and MI were offset somewhat by a higher risk of stroke for patients having bypass surgery.

VA CARDS was a randomized multicenter trial conducted in VA hospitals comparing PCI with drug-eluting stents to surgery for diabetic patients with at least significant LAD involvement [14]. The trial was stopped because of slow recruitment after enrolling 198 patients, and was therefore underpowered for its composite end point. Analysis of the data that was obtained, however, demonstrated a significant difference in all-cause mortality at 2 years favoring surgery (5.0 vs 21.0%, p = 0.02).

The SYNTAX investigators have published a 5-year follow up of diabetics treated in their study. A total of 452 (25%) diabetics were
included in the 1800 patients randomized in the SYNTAX trial. The overall SYNTAX trial failed to show noninferiority for PCI vs surgery [15]. In the diabetic subset, the composite MACCE end point (death MI, stroke and repeat revascularization) was significantly lower for surgery than PCI (29 vs 46.5%, p < 0.001). All-cause mortality favored surgery (12.9 vs 19.5%, p = 0.065) but did not reach statistical significance.

A meta-analysis of the three randomized trials comparing PCI to surgery in diabetes and the diabetic subset of the SYNTAX trial was recently reported in Journal of the American Heart Association [16]. Overall mortality was reduced from 14% in the PCI arms to 9.7% in the surgical arms at a mean follow up of 4 years in the four trials. The composite outcome of death, MI or stroke was reduced from 22.5 to 16.8% (risk ratio [RR] 1.34, 1.16–1.54 CI, p < 0.0001). An additional meta-analysis of eight randomized trials with published results in diabetic patients had a similar conclusion with a hazard ratio for long-term mortality of 0.67 (CI: 0.52–0.86) for surgery compared with PCI with either drug-eluting or bare metal stents [17].

Randomized trials have been criticized because their limited enrollment may not reflect ‘real world’ experiences with the treatments being studied. Most of the major clinical trials have had multiple exclusion criteria that potentially limit enrollment (see Tables 1–3). One notable feature of the reported randomized trials is a low to moderate average predicted surgical risk and low observed surgical mortality. Thus, the results of these trials apply primarily to patients at low to moderate risk of surgical complications. Large database studies suffer from selection bias at the decision to treat stage, but do reflect the outcomes of procedures as they are actually applied to large population groups. Several large database analyses have recently been published that support the overall finding that surgery offers better survival for an unselected population of diabetics with multivessel coronary artery disease undergoing revascularization procedures. The ASCERT study compared the results of PCI in the American College of Cardiology (ACC) database to the results of surgery from the STS database [18]. These large datasets included over 160,000 risk-matched patients. A survival advantage was shown for surgery in multiple subsets of patients, including those with diabetes. A similar survival advantage was found in a recent analysis of a large Medicare database [19]. A total of 105,156 propensity matched Medicare recipients undergoing either PCI or surgery were compared for all-cause mortality over 5 years following the procedure. In the overall population CABG was associated with a lower mortality (hazard ratio [HR]: 0.92, CI: 0.90–0.95, p < 0.001). The effect was greater in the subset of patients with diabetes (HR: 0.88, p < 0.002).

Role of coronary anatomy

When surgical revascularization was originally compared with medical management for stable coronary artery disease, the greatest impact on survival was found when certain anatomic subsets were evaluated. The presence of left main stenosis or three-vessel coronary disease led to much larger differences in survival than when other anatomic subsets were assessed [20]. In a large database analysis from the Duke Clinical Research Institute, the minimum anatomic involvement where a survival advantage could be demonstrated for surgery compared with medical management was with proximal LAD coronary artery stenosis [21]. The differences in outcomes between the three randomized trials comparing PCI to surgery in diabetics may, to some degree be related to the anatomic entry criteria of the trials (Table 4). CARDia, for example, allowed patients with single-vessel non-LAD coronary disease into the trial if a complex bifurcation lesion was present [12]. While complex bifurcation lesions impact PCI procedure success rates, they are not known to impact survival for surgical revascularization versus medical management. The bulk of patients in FREEDOM had three-vessel disease. However, the trial did accept some patients with two-vessel disease that did not involve the LAD [13]. This again is not a subset of patients for whom there is a clear survival advantage for revascularization over medical therapy. In subsets of patients with a small or absent survival advantage for revascularization over medical management, one would expect outcomes similar to the PCI strata of BARI 2D. The utility of comparing revascularization strategies in these subgroups is dubious. Inclusion of patients with no expected survival advantage for revascularization increases random variability in outcomes and thus the chance of type II errors in trials that have included them. One of the unique entry criteria for VA CARDS was the requirement that the anterior wall be affected by a significant coronary stenosis. In VA CARDS about 14% of patients had single-vessel LAD.
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Disease and mortality after PCI was as high in this subgroup of patients as in those with three-vessel disease. Thus, the greater difference in mortality seen in VA CARDS may be related to its emphasis on patients with the greatest survival effect from revascularization.

While there is a general consensus that patients with significant left main stenosis fare better with revascularization as opposed to intensive medical management, the optimal choice of revascularization techniques for this group remains an unanswered question. Only the SYNTAX trial included patients with left main stenosis. In the overall trial, patients with low to moderate complexity left main stenosis actually had better outcomes with PCI than surgery, although the differences did not reach statistical significance [22]. The left main subgroup of the diabetic subset of SYNTAX was small and was not independently analyzed. It remains possible that low-to-moderate-complexity left main lesions may best be treated with PCI, but this will not be resolved until additional trials are completed.

**Surgical techniques**

No randomized trials have addressed the issue of the optimal surgical revascularization techniques in diabetics. However, there is some intriguing data from selected case series suggesting that specific surgical techniques may impact long-term outcomes after bypass surgery. Given the importance of the LAD, the role of internal mammary artery (IMA) grafting is generally assumed. Multiple arterial grafts are, however, still somewhat controversial. Data from multiple retrospective series suggest that bilateral IMA grafts may increase the risk of mediastinitis, particularly in patients with diabetes. This has resulted in reluctance on the part of many surgeons to employ more than one IMA graft in a diabetic patient. However, a recent analysis of diabetic patients undergoing bilateral IMA grafting at Emory showed a survival advantage for bilateral IMA grafts compared with single IMA grafts [23]. While diabetic patients were at higher risk for mediastinitis in general, the incremental risk associated with bilateral IMA grafts as opposed to single IMA grafts was only 0.2%. A propensity matched series from the Florida Medical Center in Fort Lauderdale (FL, USA) also showed a survival advantage for bilateral IMA grafting as opposed to single IMA grafting in diabetics. The median survival for a single IMA graft was 9.8 years compared with...

<table>
<thead>
<tr>
<th>Trial</th>
<th>Candidate</th>
<th>Age</th>
<th>Urgent</th>
<th>Creatinine</th>
<th>HgbA1c</th>
<th>Class III HF</th>
<th>Class IV HF</th>
<th>Hepatic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI 2D</td>
<td>Y</td>
<td>&gt;21 years</td>
<td>N</td>
<td>&lt;2 mg/dl</td>
<td>&lt;13.0%</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>Y</td>
<td>&gt;18 years</td>
<td>&lt;80 years</td>
<td>&lt;2.5 µM/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDia</td>
<td>Y</td>
<td>&gt;18 years</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FREEDOM</td>
<td>Y</td>
<td>&gt;18 years</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA CARDS</td>
<td>Y</td>
<td>&gt;18 years</td>
<td>If compensated</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Exclusion criteria of the major trials.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Past PCI</th>
<th>Past surgery</th>
<th>Congenital HD</th>
<th>Dialysis</th>
<th>Recent MI</th>
<th>Valve</th>
<th>Other surgery</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI 2D</td>
<td>&gt;12 months</td>
<td>&gt;12 months</td>
<td>N</td>
<td></td>
<td>Enzymes &lt;2× ULN</td>
<td></td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>SYNTAX</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>&gt;6 months</td>
<td>Q wave &gt;6 weeks</td>
<td>N</td>
<td>Controlled</td>
<td></td>
</tr>
<tr>
<td>CARDia</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>&gt;6 months</td>
<td>CK MB &lt;2× ULN</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>FREEDOM</td>
<td>Stent</td>
<td>&gt;6 months</td>
<td>No if instent restenosis</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA CARDS</td>
<td>&gt;12 months</td>
<td>&gt;12 months</td>
<td>N</td>
<td>No for evolving STEMI</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HD: Heart disease; MI: Myocardial infarction; N: No; PCI: Percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; ULN: Upper limit of normal.
In this series the rates of mediastinitis between the two groups were not significantly different, but there was a trend for a higher rate of mediastinitis in the bilateral IMA group (3.1 vs 1.7%, p = 0.179). The concern over increased risk of mediastinitis with the use of bilateral IMA grafts may be mitigated to some degree by the use of a skeletonized IMA harvest technique. Individual case series have reported varying success with this technique. A meta-analysis of 22 studies involving 4817 patients comparing skeletonized IMA harvest to pedicled harvest was reported in 2012 [25]. The odds ratios for deep sternal wound infection favored the skeletonized harvest technique (odds ratio [OR]: 0.443, 0.323–0.608 CI, p < 0.001). Importantly, the risk reduction related to the use of a skeletonized IMA graft was particularly significant for the diabetic subgroup. Another recent meta-analysis involving 126,235 patients with diabetes concluded that the use of a skeletonized harvest technique could reduce the risk of mediastinitis among diabetic patients undergoing bilateral IMA harvest [26].

Taken together, these recent analyses suggest that greater adoption of the skeletonized IMA harvest technique could enable diabetic patients to benefit from multiple IMA grafts more often.

Despite harvest techniques that help to mitigate the risk of bilateral IMA grafts, a small increased risk may persist, particularly for diabetic patients with other significant risk factors for mediastinitis. These patients might never be considered as reasonable candidates for bilateral IMA grafting. In such patients, radial artery grafting may be an alternative to bilateral IMA grafts. There is some observational data suggesting that this approach confers an element of survival benefit over a single IMA graft alone. An encouraging report from the cardiac surgical group in Toledo (OH, USA) recently showed a late survival advantage for a radial artery graft (RA) in addition to an IMA graft among diabetics undergoing bypass grafting [27]. In a retrospective review of 2281 diabetic patients undergoing bypass surgery, a radial artery graft was used as a second-line conduit in 41%, as opposed to only saphenous vein (SV). All patients received at least one IMA graft. Late mortality was significantly lower among patients receiving an IMA/RA combination compared with IMA/SV (HR = 0.78, 0.65–0.95 CI, p = 0.012). This finding was similar to that of the group at Beth Israel Hospital in New York
In a cohort of 1843 diabetic patients followed for up to 15 years, the radial artery as a second graft after an IMA produced better survival than saphenous vein (HR: 0.683, 0.507–0.920 CI, \( p = 0.0122 \)).

Neurologic outcomes

Neurologic deficits have generally been reported more frequently following bypass surgery than after PCI and are reported more frequently in diabetics than in nondiabetics. An increased risk of stroke after bypass surgery compared to PCI was seen in FREEDOM at both 2 years and 5 years of follow up \([13]\). Interestingly, not only was the procedure-related risk higher, but the increment in stroke risk between years 2 and 5 was greater in the surgical arm than in the PCI. The subset analysis of diabetic subjects in SYNTAX also demonstrated greater stroke risk for surgery than PCI at both 3 and 5 years after revascularization \([15, 29]\). Like FREEDOM, the stroke risk between years 3 and 5 was greater for surgery than for PCI. This increased late stroke risk has not been explained. CARDia also demonstrated a higher stroke risk for surgery in early follow up, but in contrast to FREEDOM and SYNTAX the gap became narrower over time \([12, 102]\). VA CARDS had a low risk of stroke overall in both arms of the study and no differences were found at 2 years of follow up \([14]\). In the surgical stratum of BARI 2D, the 5 year stroke risk after CABG was 1.9% which was actually lower than the 2.6% incidence of stroke in the intensive medical management arm \([7]\). The meta-analysis of the three randomized trials and the SYNTAX substudy found the risk of stroke to be higher for CABG than PCI (3.8 vs 2.3%, \( p = 0.01 \)) \([16]\). A compendium of reported stroke rates is given in Table 5. The finding of greater stroke risk for surgery than PCI in multiple studies requires caution when assessing patients for revascularization who also have significant risk of cerebrovascular events and suggests that this may be a potential area for improvement in surgical treatment.

As with mediastinitis, there are some encouraging results from case series that suggest surgical techniques can be altered to reduce the risk of stroke. A recent study from Ruhr University Bochum in Germany found a reduction in the risk of stroke from 5.4 to 1.7% with the use of off-pump grafting (OR: 0.31, 0.12–0.77 CI, \( p = 0.012 \)) \([30]\). Presumably, this results from a decrease in the manipulation of the ascending aorta associated with this technique. In this series, off-pump surgery was also associated with a reduction in all-cause mortality after bypass grafting in diabetics (0.3 vs 4.2%, \( p = 0.021 \)). While several large randomized trials have failed to show any advantage of off-pump surgery in the general population of bypass patients, selected use of this technique in centers with specialized expertise might be helpful for specific high-risk subsets of patients.

Delay to benefit after surgery

The risk of complications related to major surgery leads to higher early risk with bypass surgery than with either medical therapy or PCI. Data from multiple studies show that a net benefit does not accrue for 1–3 years following the procedure. While a small net benefit was observed at 1 year in the meta-analysis by Hakeem et al., the difference did not become statistically significant for more than 4 years \([16]\). This delay to benefit must be taken into account before recommending bypass surgery, particularly in elderly patients with significant noncardiac disease burdens. In any situation the impact of other comorbid conditions on long-term prognosis should be carefully assessed prior to undertaking coronary bypass surgery. It is also important to realize that surgical risk models such as the EuroScore or STS score have shown lower predicted operative mortality for patients enrolled in major trials than the average.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Angiographic inclusion</th>
<th>50–70% with ischemia</th>
<th>Critical stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolated LAD</td>
<td>No LAD</td>
<td>2 vessel</td>
</tr>
<tr>
<td>BARI 2D</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>CARDia</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>VA CARDS</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

LAD: Left anterior descending; N: No; Y: Yes.
mortality derived from large databases of cardiac surgery. Patients with higher than average risk may have a longer delay to net benefit than has been observed in these trials.

**Unanswered questions**

The optimal timing of surgical intervention for diabetic patients with significant coronary artery disease has not yet been precisely determined. While it is clear that patients with more advanced disease will benefit both in symptom reduction and improved survival with multivessel coronary bypass compared with either PCI or intensive medical management, there is still considerable uncertainty about the timing of surgical treatment with patients with one or two-vessel coronary disease and a significant territory of myocardium at jeopardy. Both COURAGE and BARI 2D suggested that such patients might be initially managed medically without compromising overall survival and that PCI could improve symptoms when refractory angina was present, but this impact faded after a relatively short time period. However, both studies employed a liberal use of delayed revascularization in the initial medical treatment arm and the criteria leading to these late ‘crossovers’ were not defined.

Coronary anatomy remains a critical element in risk stratification for diabetic patients with coronary artery disease. Since neither the severity of symptoms nor the presence of silent ischemia have been helpful in determining which diabetic patients are at highest risk for mortality from cardiovascular disease, better risk models are needed to help differentiate when to proceed to coronary artery catheterization to define anatomy. In BARI 2D, both Framingham risk scores and angiographic risk scores predicted higher 5-year event rates [10]. The highest discriminating power of these risk scores, however, required both risk scores to be known. Thus, the clinical risk established by the Framingham score cannot substitute for risk established by angiographic evaluation. While it seems that a high clinical risk score in a diabetic patient, even one who is asymptomatic, should prompt coronary angiography, the conundrum of when to proceed to coronary angiography in patients at moderate clinical risk remains.

Since trials comparing surgery to PCI or medical management have enrolled patients at relatively low risk for surgical complications, the issue of what level of surgical risk offsets the clinical benefits of surgical revascularization has not been examined. Patients at high risk for cardiovascular events as evidenced by high angiographic and clinical risk who are also at high risk for surgical morbidity and/or mortality are poorly studied and the best approach for these patients is still not known. Moreover, balancing surgical risk against PCI risk is still a difficult task. Many cardiologists employ the SYNTAX score for decision-making regarding the utility of PCI. The SYNTAX score correlates well with procedure failures after PCI, but has no impact on the outcomes of bypass surgery. Among diabetic patients, neither FREE-DOM nor VA CARDS found any discriminating power of the SYNTAX score for the choice between surgery and PCI. Thus it is not a good model to project net benefit from surgery. The SYNTAX II score has been developed to try to balance surgical risk against the predicted PCI risk derived from the SYNTAX score [31]. SYNTAX II, however, contains only limited surgical risk factors and is derived from a population of

<table>
<thead>
<tr>
<th>Table 5. Reported incidence of cerebrovascular accident after coronary artery bypass surgery in diabetics in major trials.</th>
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<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>BARI 2D†</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>SYNTAX†</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CARDia</td>
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<tr>
<td></td>
</tr>
<tr>
<td>FREEDOM</td>
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<td></td>
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<tr>
<td>VA CARDS</td>
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†Subset analysis.
CABG: Coronary artery bypass surgery; PCI: Percutaneous coronary intervention.

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patients with generally low surgical risk and either three-vessel or left main disease. Importantly, diabetes does not factor into the SYNTAX II score, despite multiple studies that show a difference in outcomes between surgery and PCI for diabetics. The limitations of SYNTAX II make it a poor choice of models to differentiate the relative benefits of surgery vs PCI in diabetics with significant coronary artery disease.

The increased risk of stroke seen in diabetics with bypass surgery is a critical factor in decisions regarding surgery versus medical management. Many elderly patients may be less concerned about a fatal heart attack than they are with a debilitating stroke, raising the question of treatment goals directed at quality of life as opposed to strictly quantity of life. The ability to accurately predict stroke risk would be invaluable before recommending bypass surgery. In addition, the severity of strokes that occur with various risk factors should become part of the decision-making process. The major clinical trials have generally given equal weight to all elements of composite outcomes so that all events deemed to represent a stroke are the equivalent of death. This means that a transient neurologic event that resolves completely after a few days or weeks has the same impact on the outcome measure as mortality. This is also true for a small non-ST segment elevation MI (NSTEMI) that leaves little residual clinical effects. Accurate weighting of composite outcome elements is important if individualized assessment of treatment options is to be achieved.

### Conclusion

Secondary prevention strategies are important for all diabetic patients regardless of whether they are known to have coronary artery disease. Aggressive risk factor modification can delay the onset of severe complications from coronary artery disease. However, the natural history of coronary artery disease in the presence of diabetes means that coronary revascularization is highly likely to occur over the lifetime of these patients. Routine screening for ischemia has not been helpful and coronary anatomy plays a critical role in the risk stratification of these patients so that a high index of suspicion must be maintained with a low threshold to proceed with coronary angiography.

Once significant coronary artery disease has been established, coronary bypass surgery offers better symptom control than medical management alone and can improve mortality over 5–10 years among patients with significant multivessel disease. Bypass surgery is likely to be beneficial for patients with high-grade single-vessel LAD disease and two-vessel disease that includes the LAD, provided that the projected surgical risk is low. MI rates also appear to be lower over time with surgical revascularization, but a higher stroke risk may offset some of the advantages of surgery particularly in elderly patients or those with known cerebrovascular disease.

### Future perspective

#### Timing of intervention

The finding in BARI 2D that initial aggressive medical management can be successful in avoiding cardiac mortality at least for a period of time suggests that this should be the primary initial strategy for the majority of diabetic patients with stable coronary artery disease. However, better risk models are needed to predict when progression of disease warrants consideration of repeat catheterization and revascularization. Importantly, the decision to randomize in BARI 2D came only after coronary anatomy was known and approximately 30% of patients were excluded from randomization because of a perceived need for immediate revascularization. Algorithms predicting when initial or repeat cardiac catheterization is indicated are lacking. The duration and severity of diabetes appear to be important factors in predicting severe coronary artery disease, as do the duration of other significant cardiovascular risk factors.

#### Anatomic gray areas

The most compelling evidence for a survival advantage for surgical revascularization compared with either aggressive medical management or PCI comes from patients who have all three systems of coronary arteries significantly narrowed. The majority of patients in SYNTAX, FREEDOM and VA CARDS had three-vessel disease. However, VA CARDS and FREEDOM included modest populations of patients with either single or two-vessel disease and in BARI 2D only 48% of the patients in the CABG stratum had three-vessel disease. Thus, there is a reasonable possibility that bypass surgery may be the best option for reducing long-term cardiovascular risk for patients with single or double-vessel coronary artery disease when the LAD coronary artery is involved and projected surgical risk is low. Further study of these anatomic subsets is warranted and should include all three treatment options.
options: aggressive medical management, surgery and percutaneous treatments.

- **Weighing surgical risk against the risk of PCI**
  Current models lack adequate discrimination of surgical risk factors compared with angiographic predictors associated with PCI risk. Adequate comparison of surgical versus PCI risk will require assessment of higher risk patients than are generally found in large clinical trials. The dichotomy between outcomes of mortality and MI favoring surgery on one hand and stroke risk favoring PCI on the other means that variable weighting of these components of composite outcomes for large clinical studies is needed as well.

- **Improvements in surgical techniques**
  Selected clinical series suggest a role for improvements in surgical techniques that could potentially impact the outcomes for diabetics undergoing surgical revascularization. There is a potential for multiple arterial conduits to impact long term survival in a favorable manner. However the optimum use of either a second internal mammary artery or a radial artery has not yet been adequately determined. Likewise, techniques that minimize surgical manipulation of the ascending aorta during revascularization seem to have a favorable impact on the risk of stroke, but this needs to be confirmed by well-designed studies.

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**References**

Papers of special note have been highlighted as:
- of interest
- of considerable interest


- The BARI 2D trial: a large randomized multicenter trial comparing immediate revascularization with either percutaneous coronary intervention (PCI) or surgery to aggressive medical management in diabetes associated with stable coronary artery disease


- The COURAGE trial: a large randomized trial of medical management versus PCI for patients with stable coronary artery disease. Not limited to patients with diabetes.


- A subset analysis of the MASS II randomized clinical trial. This reports a 10-year follow up of diabetic patients treated with medicine, angioplasty or surgery.


- The early results of CARDia, a randomized trial between surgery and PCI for diabetic patients with coronary artery disease.

Coronary bypass for diabetic heart patients  REVIEW

- The FREEDOM trial: a large international trial of diabetic patients randomized to either surgery or PCI with drug-eluting stents.

- A meta-analysis of eight randomized trials that reported outcomes for diabetic subsets treated with either PCI or surgery. It includes subsets from several older trials that used bare metal stents.

- The VA CARDS trial: a randomized trial conducted in the US Department of Veterans Affairs for diabetic patients with coronary artery disease treated with either bypass surgery or PCI with drug-eluting stents.

- This is a diabetic subset analysis of the SYNTAX trial. Diabetic patients with either left main or three-vessel coronary artery disease were randomized between surgery and PCI.

- A meta-analysis of the three randomized trials (CARDia, FREEDOM and VA CARDS) and the diabetic subset of SYNTAX.

- A meta-analysis of randomised controlled trials (CARDia, FREEDOM and VA CARDS) and the diabetic subset of SYNTAX.


- Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 381(9867), 639–650 (2013).

**Websites**


- Kapur A, Baumbach A, Beatt, K et al. Five year follow up of the CARDia Trial. www.escardio.org/congresses/esc-2012/congress-reports/Pages/710-5-CARDia.aspx