Strategies for Management of Stable Coronary Disease in Type 2 Diabetes Mellitus

Jeremy P. Berman, MD,[1] Sanjum S. Sethi, MD,[1] Michael E. Farkouh, MD, MSc[1,2]
[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Peter Munk Cardiac Centre and Heart and Stroke Richard Lewar Centre of Excellence, University of Toronto, Toronto, ON, Canada

In recent decades, there have been significant advances in both surgical and minimally invasive approaches to revascularization in ischemic heart disease. This article discusses the evidence from key clinical trials comparing the various management strategies in stable coronary artery disease, and culminates in a discussion of the recently published Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, which randomized patients with type 2 diabetes mellitus and multivessel coronary disease to coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with drug-eluting stents, and found, for the first time, a survival advantage with CABG relative to PCI.

[Rev Cardiovasc Med. *2013;14(suppl 1):S50-S58 doi: 10.3909/ricm13S1S0006]*

KEY WORDS

Coronary artery disease • Drug-eluting stents • Type 2 diabetes mellitus

In recent decades, several strategies for management of stable ischemic heart disease (SIHD) have evolved in parallel. Lifestyle modification, intensive medical management, and revascularization are the mainstays of therapy.[1] Two revascularization strategies, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), are the subject of much debate. Both strategies have seen significant advances since their inception. PCI has evolved from the era of balloon angioplasty, first used in 1977, to bare metal stenting in the 1990s, to the era of drug-eluting stents (DES) in the 21st century. CABG outcomes have also improved over time, led by the development of advanced

surgical techniques, particularly grafting of the left internal mammary artery to the left anterior descending artery and the use of newer anticoagulation drugs. The primary aim of contemporary clinical trials has been to elucidate the comparative benefits of these revascularization strategies with respect to mortality, myocardial infarction (MI), and other endpoints, such as stroke. In addition, appropriate stratification of subgroups in the population that will benefit most from these strategies is an equally important goal. A cohort of interest are patients with type 2 diabetes mellitus (DM) and coronary artery disease (CAD). This population often has severe cardiovascular disease, and has been shown to benefit the most from revascularization.[2,3] This is the foundation for the recently published Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial,[4] which randomized patients with DM and multivessel coronary disease to PCI with DES versus CABG. The Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) trial found that ranolazine reduced angina and sublingual nitroglycerin use compared with placebo in patients with DM and SIHD. This demonstrates that medical therapy is and should be part of the treatment algorithm in patient with DM and SIHD.[5]

In acute coronary syndrome, PCI reduces the incidence of death and MI compared with noninvasive strategies, including fibrinolysis, but similar benefits have not been shown in patients with stable CAD.

Revascularization Versus Medical Therapy Alone for Stable CAD

In acute coronary syndrome (ACS), PCI reduces the incidence of death and MI compared with noninvasive strategies, including fibrinolysis,[6-11] but similar benefits have not been shown in patients with stable CAD.[12-16] Before publication of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[17] coronary intervention had been studied in $<$ 3000 patients with stable coronary disease. In 2005, the results of a meta-analysis of 11 randomized studies comparing PCI with conservative treatment for stable CAD showed no reduction in mortality, nonfatal MI, or the need for subsequent revascularization, but did show improvement of angina symptoms.[18] However, many of the patients included in the meta-analysis were treated in the era of balloon angioplasty before widespread use of intracoronary stenting and modern medical therapies.

The COURAGE trial,[17] published in 2007, randomized 2287 patients with stable coronary disease to an initial strategy of PCI plus optimal medical therapy versus optimal medical therapy alone. The COURAGE trial included patients from 50 sites in the United States and Canada with SIHD and those with Canadian Cardiovascular Society (CCS) Class IV angina—subsequently stabilized medically—and stenosis in $\geq$ one proximal epicardial vessel of $\geq$ 70% (single-vessel disease in 30%-31%, two- or three-vessel disease in 69%-70% of patients). Exclusion criteria included patients with high-risk characteristics, including persistent CCS Class IV angina, markedly positive stress test result, an ejection fraction $<$ 30%, and coronary anatomy not suitable for PCI; 42% of patients were either asymptomatic or CCS Class I. The median follow-up was 4.6 years. The primary outcome measures, all-cause mortality and nonfatal MI, occurred in 211 patients in the PCI group versus 202 patients in the medical therapy alone group, with cumulative 4.6 year event rates of 19% versus 18.5% (P = .62). Over the course of this trial, there was significant crossover of patients from the optimal medical therapy arm to revascularization consistent with the progression of disease even when a truly optimal medical approach was applied. The results of the COURAGE trial showed that, as an initial strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular event when added to optimal medical therapy. Patients in the PCI group had significantly more freedom from angina during the majority of the follow-up period, but it should be noted that both groups had improvement in the rates of freedom from angina, which were typically realized in the first year of therapy but continued throughout the 5-year follow-up—74% of patients in the PCI group and 72% in the medical therapy alone group were free from angina at 5 years. Most of the 1149 patients in the PCI arm received bare metal stents, as DES were not approved for clinical use until the final 6 months of the trial. The authors of COURAGE point to the difference in atherosclerotic

The results of the COURAGE trial showed that, as an initial strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular event when added to optimal medical therapy.

plaque morphology between stable plaques (thick fibrous cap, small lipid core) and vulnerable plaques (thin fibrous cap, large lipid core), which precede ACS and cause less significant stenosis prior to rupture, as a possible explanation for the lack of robust mortality and cardiovascular event benefit in the stenting of stable CAD patients. Thus, treating a stenosis caused by a plaque that is unlikely to trigger an ACS, regardless of whether the stent used is bare metal or a DES, would not be expected to alter the rate of death or MI.

… treating a stenosis caused by a plaque that is unlikely to trigger an ACS, regardless of whether the stent used is bare metal or a DES, would not be expected to alter the rate of death or MI.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study,[19] published in 2009, was designed to determine the optimal treatment for patients with both DM and stable ischemic CAD. The primary aim of the BARI 2D trial was to test two hypotheses of treatment efficacy in patients with DM and documented stable CAD, in the setting of uniform glycemic control and intensive management of all other risk factors, including dyslipidemia, hypertension, smoking, and obesity: (1) Coronary Revascularization Hypothesis: a strategy of initial elective revascularization of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared with a strategy of aggressive medical therapy alone; and (2) Method of Glycemic Control Hypothesis: with a target hemoglobin A_{1c} level of $< 7.0\%$, a strategy of hyperglycemia management directed at insulin sensitization results in lower 5-year mortality compared with a strategy of insulin provision.

A total of 2368 patients from 49 sites in 6 nations were randomized to revascularization plus intensive medical therapy or intensive medical therapy alone. A priori, patients were selected to participate in the PCI stratum or the CABG stratum based on what the treating physician determined to be most clinically appropriate. Within each stratum, patients were randomly assigned to the predesignated revascularization procedure plus intensive medical therapy or intensive medical therapy alone. The average follow-up was 5.3 years. The primary outcomes were the rate of death and the rate of major adverse cardiovascular event (MACE), a composite of death, MI, and stroke.[19]

Rates of survival did not differ significantly between the revascularization group and the intensive medical therapy group (88.3% vs 87.8%; $P = .97$). Rates of freedom from MACE were also similar (77.2% vs 75.9%; $P = 0.70$). Likewise, there was no significant difference in mortality or MACE in patients undergoing PCI for revascularization versus medical therapy alone. However, in patients undergoing CABG for revascularization, the MACE rate was significantly lower in the revascularization group compared with the medical therapy alone group (22.4% vs 30.5%; $P = .01$; $P = .002$ for interaction with PCI cohort), a difference driven mostly by the lower rate of nonfatal MI.[19]

Of patients in the PCI stratum undergoing revascularization, approximately one-third received DES, but their use was not thought to impact results. Also noteworthy, 42% of patients initially randomized to medical therapy alone crossed over and underwent revascularization by the end of 5 years, similar to what was observed in the COURAGE trial. It is important to note that a majority of the cohort was maintained on a strategy of medical therapy alone for the term of follow-up. The use of newer antianginal agents such as ranolazine was not reported in this trial and was, perhaps, infrequent.

Patients prespecified for CABG, at the discretion of the investigator, as the intended method of revascularization had more extensive coronary disease, were more likely to have had a previous MI, and were less likely to have undergone previous coronary revascularization than those selected for the PCI stratum. BARI 2D was designed to compare revascularization versus medical therapy alone, not the comparative effectiveness of CABG versus PCI. The findings of BARI 2D suggested that a strategy of prompt revascularization may be indicated in diabetic patients with the most severe coronary disease, but left the question of comparative effectiveness of CABG versus PCI in these patients unanswered.

Intracoronary pressure wires to measure fractional flow reserve (FFR) have been used to characterize the functional significance of angiographic stenosis during cardiac catheterization procedures.[20] The Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary disease (FAME 2) trial[21] randomized patients with stable CAD to FFR-guided PCI or to best medical therapy alone. Like the COURAGE and BARI 2D trials,[17,19] FAME 2 made a direct comparison of PCI with best medical therapy alone. The primary outcome was a composite of death, MI, or urgent revascularization. The study was stopped early because of a benefit observed in favor of the FFR-guided PCI group. The rate of the primary endpoint was 4.3% versus 12.7% ($P < .001$)

for FFR-guided PCI versus medical therapy alone. The lower event rate in the PCI group was driven largely by a lower rate of urgent revascularization.

In summary, neither the FAME 2[21] nor the COURAGE[17] trial showed a reduction in the rate of MI or mortality from PCI with stenting of stable CAD. Although FFR provides a strategy for a more targeted approach to PCI, this may be at the expense of time, case complexity, and risk of complications, such as coronary artery perforation. An ongoing clinical trial, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA [http://www.clinicaltrials.gov/ct2/show/NCT01471522]) is powered to study the long-term effects of revascularization versus medical therapy alone on rates of mortality and MI in patients with stable CAD and documented myocardial ischemia measured by noninvasive testing. That study is currently underway, but results are not expected for several years. Whether antianginal therapy needs to be tailored to the specific metabolic abnormalities in the diabetic patient is open to debate as there is a dearth of clinical trial data to direct clinicians. From a theoretical basis, it may be reasonable to avoid drugs that cause insulin resistance such as that observed with selective β1-blockers (atenolol, propranolol, or metoprolol) versus an agent such as ranolazine that has been found to reduce HbA_{1c} levels in diabetic patients.[22] A recent evaluation of ranolazine in diabetic patients found it to have increasing antianginal efficacy as HbA_{1c} levels increased.[5]

Revascularization: PCI Versus CABG

The comparative effectiveness of revascularization with CABG versus PCI for patients with stable multivessel coronary disease has been the subject of much scrutiny over the past 2 decades. In a post hoc subgroup analysis of patients with DM, the landmark BARI study[3] signaled that CABG may provide a survival benefit over percutaneous transluminal coronary angioplasty (PTCA) in diabetic patients with multivessel disease. This cohort of patients, with both DM and SIHD, were the subject of the subsequent BARI 2D study, the underpowered Coronary Artery Revascularization in Diabetes (CARDia) trial,[23] and the recently published FREEDOM trial.[4,19] The following is a summary of these key trials and a discussion of the implications for the practicing physician.

The comparative effectiveness of revascularization with CABG versus PCI for patients with stable multivessel coronary disease has been the subject of much scrutiny…

For context, the trend over the past decade has been toward increased utilization of PCI relative to CABG. In Canada, from 1994 to 2005, rates of PCI increased from 85.6/100,000 persons-years to 186.7/100,000 ($P < .001$), whereas CABG rates stayed the same (75.6/100,000 to 70.8/100,000; $P = .43$).[24] Another study found that rates of stent implantation had increased in patients with a Class I indication for CABG in the era of DES.[25] This study included >265,000 patients from the National Cardiovascular Data Registry and documented that the rate of stent implantation had increased from 29.4% in the pre-DES era to 34.7% in the DES era in patients with a Class I indication for CABG.

The BARI study randomized 1829 patients with multivessel CAD to PTCA or CABG.[3] The hypothesis of the investigators was that, in patients suitable for both procedures, undergoing an initial strategy of PTCA would not lead to worse 5-year clinical outcomes. The study found that an initial strategy of PTCA did not lead to worse 5-year clinical outcomes in patients with multivessel disease, although there were more subsequent revascularizations. The 5-year survival rate in the CABG group and the PTCA group was 89.3% and 86.3%, respectively ($P = .19$). The rate of repeat revascularization was 8% and 54%, respectively. In contrast, in patients with DM receiving insulin or oral hypoglycemic medication, 5-year survival was significantly better after CABG compared with PTCA (80.6% vs 65.5%; $P = .003$). The influence of DM and this striking reduction in mortality in patients undergoing CABG rather than PTCA was described in more detail in a subgroup analysis by the BARI Investigators.[2] This finding led to a National Heart, Lung, and Blood Institute alert and revised American College of Cardiology Foundation/American Heart Association guidelines recommending CABG as the preferred method of revascularization in diabetic patients with multivessel coronary disease.[26]

The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial,[27] a recently published noninferiority study designed to compare PCI with DES to CABG in patients with left main or three-vessel CAD disease, confirmed CABG as the standard of care for revascularization in these patients. In SYNTAX, 1800 patients with three-vessel coronary disease or left main disease were randomly assigned to PCI

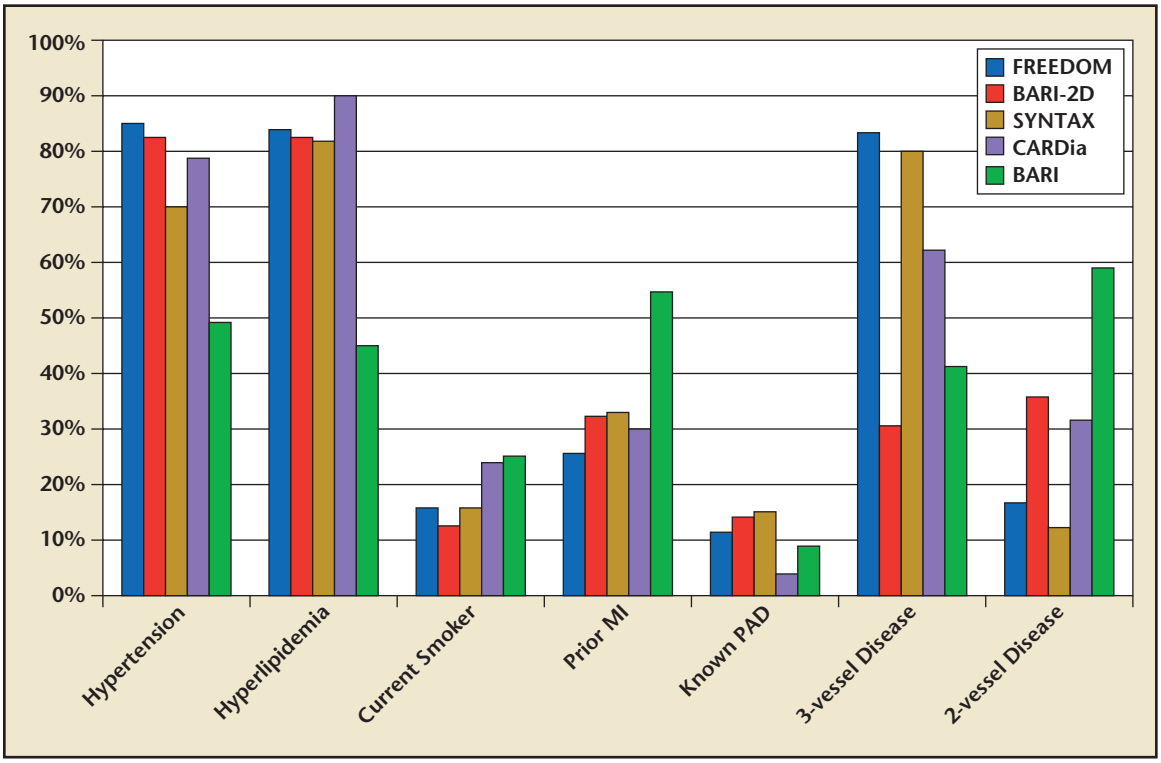

Figure 1. Comparison of baseline characteristics in contemporary trials. BARI, Bypass Angioplasty Revascularization Investigation; CARDia, Coronary Artery Revascularization in Diabetes; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; MI, myocardial infarction; PAD, peripheral artery disease; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. Reprinted with permission from Bansilal S et al.[29]

with DES or CABG. Rates of the primary outcome, major adverse cardiovascular or cerebrovascular events (MACCE), at 1 year, were significantly higher in the PCI group (17.8% vs 12.4%; $P = .002$), driven primarily by the need for repeat revascularization (13.5% vs 5.9%; $P < .001$). Thus, PCI with DES was not found to be noninferior to CABG in these patients, although the rates of death and MI were similar between the two groups. A subgroup analysis of the SYNTAX trial, focusing on the subset of patients with DM, showed further divergence of the event curves at 3-year follow-up.[28]

The CARDia trial,[23] although small (n = 510) and underpowered, was the first trial to randomize diabetic patients with multivessel or complex single-vessel CAD to CABG versus PCI; 69% of patients were treated with DES, which were used once they became available. The 1-year results failed to demonstrate a difference for PCI with respect to CABG, with MACCE rates of 13.0% and 10.5% for PCI and CABG, respectively ($P = .39$). The consensus was that a larger trial with longer follow-up was needed.

In this landscape, the FREEDOM trial[4] sought to discover the comparative effectiveness of CABG versus PCI with DES in patients with DM and multivessel CAD. A total of 1900 patients at 140 international centers were randomized to either PCI with DES or CABG. Minimum follow-up was 2 years and median follow-up was 3.8 years. The baseline clinical and angiographic characteristics of the patients in both the CABG and PCI groups were well matched. These baseline characteristics were remarkably similar to those of patients in other contemporary trials—BARI 2D, SYNTAX, CARDia, and BARI.[29] In the FREEDOM trial, a greater proportion (> 80%) of patients had three-vessel disease. The rates of hypertension and hyperlipidemia were almost twice those of the historic BARI trial (Figure 1).

COURAGE and BARI 2D used nurse practitioners or study coordinators to organize an intensive protocol-based approach to medical therapy. Although FREEDOM did not use such a rigorous approach, medication use was similar in all the contemporary trials (Figure 2). In the FREEDOM trial, intensive evidence-based medical therapies were mandated in both groups. Although the use of thienopyridines remained higher in the PCI group compared with the CABG group at 5 years, there was no significant difference in the rate of use of other evidence-based cardiovascular medications—including statins, β-blockers, angiotensin-converting enzyme

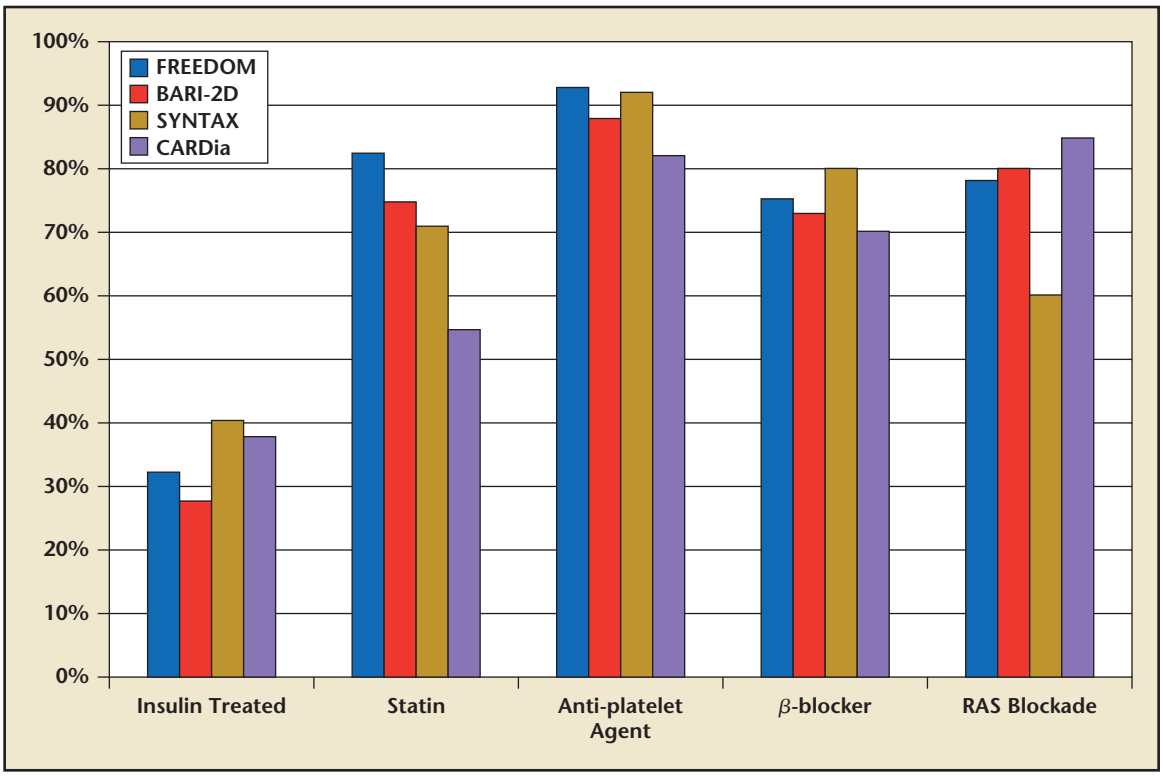

Figure 2. Comparison of evidence-based medication use across trials. BARI, Bypass Angioplasty Revascularization Investigation; CARDia, Coronary Artery Revascularization in Diabetes; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. Reprinted with permission from Bansilal S et al.[29]

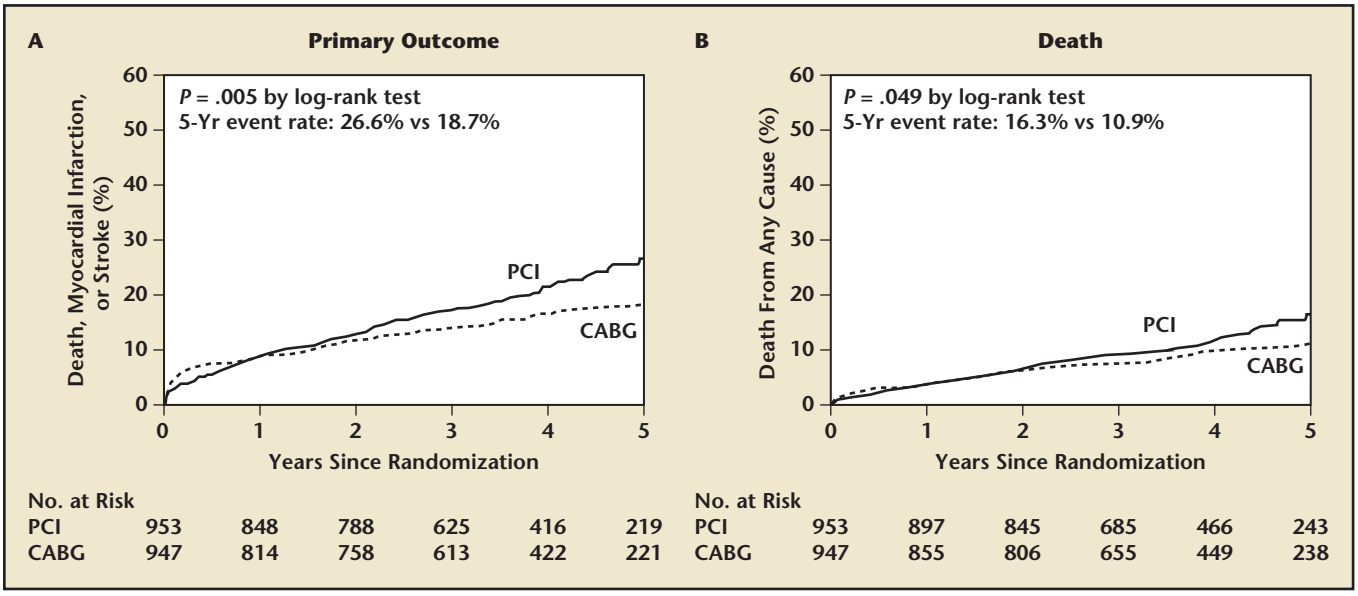

Figure 3. Kaplan-Meier estimates of the composite primary outcome and death in the FREEDOM trial. **(A)** Primary outcome. **(B)** Death. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Reprinted with permission from Farkouh ME et al.[4]

inhibitors, and angiotensin receptor blockers—between the two groups. Patients in both groups had a wide range of SYNTAX scores, an angiographic measure of complexity of CAD[30]; approximately 20% of patients in each group had a high SYNTAX score (≥ 33), indicating extensive disease. The primary outcome was a composite of all-cause mortality, nonfatal MI, and nonfatal stroke. The primary outcome occurred more frequently in the PCI group compared with the CABG group (5-year event rates 26.6% vs 18.7%; $P = .005$) (Figure 3).[4] This was driven by higher rates of MI (13.9% vs 6.0%; $P < .001$) and all-cause mortality (16.3% vs 10.9%; $P = .049$) for PCI versus CABG.

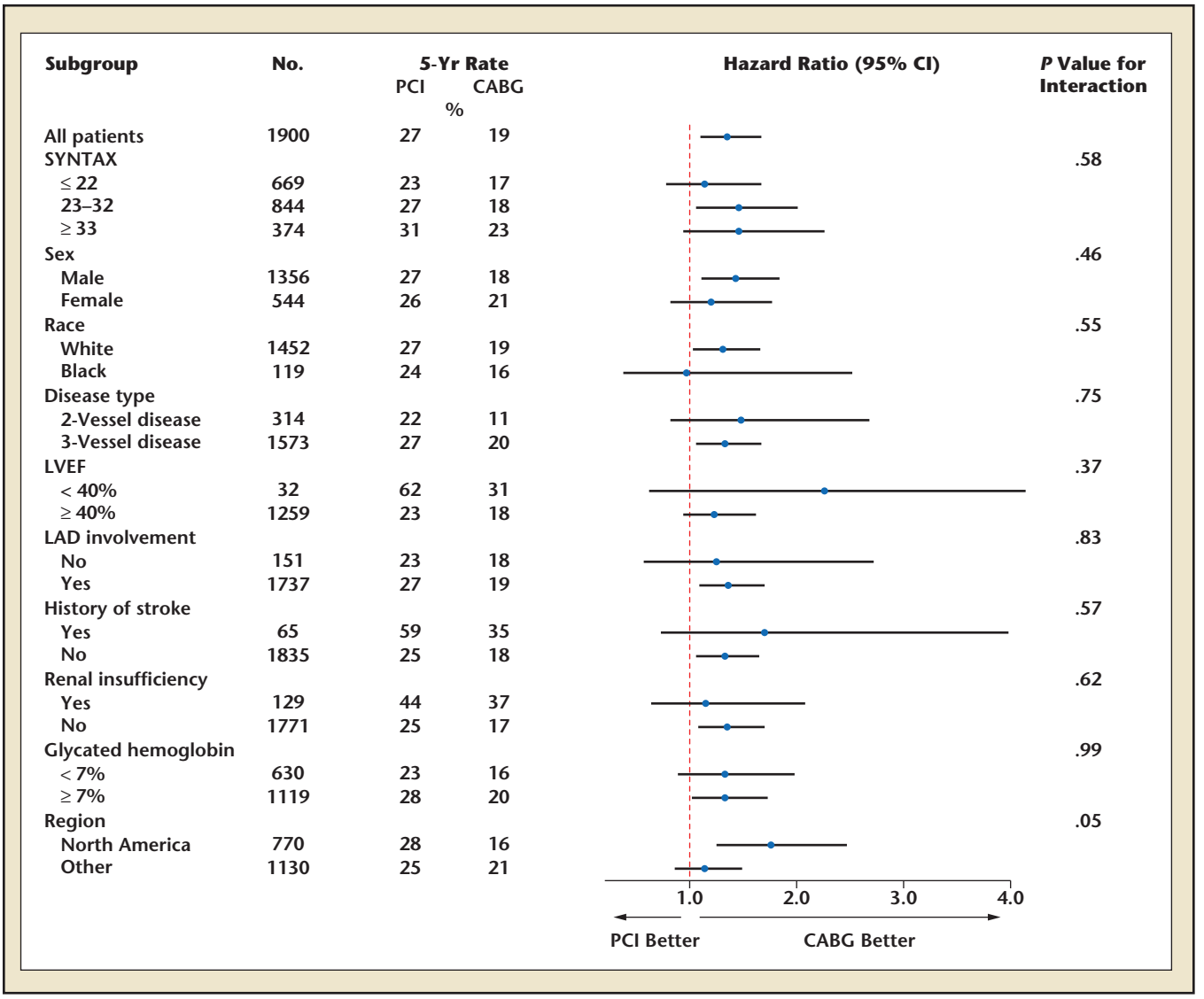

Figure 4. Primary composite outcome according to subgroup in the FREEDOM trial. CABG, coronary artery bypass graft; CI, confidence interval; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. Reprinted with permission from Farkouh ME et al.[4]

Strokes occurred more frequently in the CABG group (2.4% vs 5.2%; $P = .03$), and were largely periprocedural, occurring during the first 30 days after randomization. The prespecified subgroup analysis according to tertile of SYNTAX score revealed no significant subgroup interaction. The greater benefit of CABG versus PCI was consistent across all subgroups (Figure 4).

Since BARI was published in the mid-1990s, multiple studies have found an excess of MACCE with PCI compared with CABG in diabetics. A comprehensive meta-analysis, published in 2009, including 7812 patients from 10 randomized trials comparing CABG with balloon angioplasty (6 trials) or bare metal stenting (4 trials), found excess mortality with PCI compared with CABG in diabetic patients and patients ≥ age 65.[31] In contemporary trials, including CARDia and a subgroup analysis of SYNTAX, which used primarily PCI with DES compared with CABG in diabetics, the higher event rates after an initial strategy of PCI were driven primarily by higher rates of repeat revascularization. The FREEDOM trial results are different. In FREEDOM, the benefit from CABG is derived from a reduction in rates of MI and all-cause mortality. The excess risk of early postprocedural stroke observed with CABG as compared with PCI has been observed consistently in comparative trials, and was described in a recent meta-analysis.[32]

Because most PCIs are performed at the time of diagnostic coronary angiography, a discussion about the survival benefits of CABG should begin prior to cardiac catheterization, especially in patients with

DM. Ideally, this discussion would include family members and a multidisciplinary care team, and would allow time for the patient and physician to make an informed decision about the most appropriate revascularization strategy.

Conclusions

Much of the attention in interpretation of these trials has focused on identifying the appropriate revascularization modalities. Of equal importance, modern trials, including FREEDOM and BARI 2D, have demonstrated that patients with DM with SIHD remain at risk for subsequent adverse events despite optimal treatment. This residual risk demands further advances in medical treatment and revascularization strategies. Whether specific anti-ischemic therapies may have a unique role in patients with DM remains to be elucidated. ■

References

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44-e164.
2. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 1997;96:1761-1769.
3. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med*. 1996;335:217-225.
4. Farkouh ME, Domanski M, Sleeper LA, et al; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375-2384.
5. Kosiborod M, Arnold SV, Spertus JA, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina. Results from the TERISA randomized clinical trial [published online ahead of print]. *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.02.011.
6. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet*. 1999;354:708-715.
7. Cannon CP, Weintraub WS, Demopoulos LA, et al; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)—Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879-1887.
8. Fox KA, Poole-Wilson PA, Henderson RA, et al; Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet*. 2002;360:743-751.
9. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13-20.
10. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation*. 2004;110:588-636.
11. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005;293:2908-2917.
12. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Engl J Med*. 1992;326:10-16.
13. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet*. 1997;350:461-468.
14. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med*. 1999;341:70-76.
15. Henderson RA, Pocock SJ, Clayton TC, et al; Second Randomized Intervention Treatment of Angina (RITA-2) Trial Participants. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol*. 2003;42:1161-1170.
16. Hueb W, Soares PR, Gersh BJ, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol*. 2004;43:1743-1751.

MAIN POINTS

- In recent decades, there have been significant advances in both surgical and minimally invasive approaches to revascularization in stable ischemic heart disease (SIHD). The recently published Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial found, for the first time, a survival advantage with coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) in patients with type 2 diabetes mellitus (DM).
- The results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (which randomized patients with stable coronary disease to an initial strategy of PCI plus optimal medical therapy versus optimal medical therapy alone) showed that—as an initial strategy in patients with stable coronary artery disease—PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular event when added to optimal medical therapy.
- Because most PCIs are performed at the time of diagnostic coronary angiography, a discussion about the survival benefits of CABG should begin prior to cardiac catheterization, especially in patients with DM.
- Much of the attention in interpretation of these trials has focused on identifying the appropriate revascularization modalities. Of equal importance, modern trials, including FREEDOM and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D), have demonstrated that patients with DM with SIHD remain at risk for subsequent adverse events despite optimal treatment. This residual risk demands further advances in medical treatment and revascularization strategies. Whether specific anti-ischemic therapies may have a unique role in patients with DM remains to be elucidated.

17. Boden WE, O'Rourke RA, Teo KK, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
18. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation*. 2005;111:2906-2912.
19. Frye RL, August P, Brooks MM, et al; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503-2515.
20. De Bruyne B, Pijls NH, Paulus WJ, et al. Transstenotic coronary pressure gradient measurement in humans: in vitro and in vivo evaluation of a new pressure monitoring angioplasty guide wire. *J Am Coll Cardiol*. 1993;22:119-126.
21. De Bruyne B, Pijls NH, Kalesan B, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.
22. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA_{1c} in patients with chronic angina and diabetes. *Eur Heart J*. 2006;27:42-48.
23. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol*. 2010;55:432-440.
24. Hassan A, Newman A, Ko DT, et al. Increasing rates of angioplasty versus bypass surgery in Canada, 1994-2005. *Am Heart J*. 2010;160:958-965.
25. Frutkin AD, Lindsey JB, Mehta SK, et al; NCDR (National Cardiovascular Data Registry). Drug-eluting stents and the use of percutaneous coronary intervention among patients with class I indications for coronary artery bypass surgery undergoing index revascularization: analysis from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2009;2:614-621.
26. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e652-e735.
27. Serruys PW, Morice MC, Kappetein AP, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.
28. Groot MW, Head SJ, Bogers AJ, Kappetein AP. Coronary revascularization in diabetic patients. A focus on the 3-year SYNTAX trial outcomes. *Herz*. 2012;37:281-286.
29. Bansilal S, Farkouh ME, Hueb W, et al. The Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease (FREEDOM) trial: clinical and angiographic profile at study entry. *Am Heart J*. 2012;164:591-599.
30. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219-227.
31. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373:1190-1197.
32. Palmerini T, Biondi-Zoccai G, Reggiani LB, et al. Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol*. 2012;60:798-805.