

Myocardial Revascularization for Patients With Diabetes: Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention?

Serenella Castelvechio, MD, Lorenzo Menicanti, MD, Andrea Garatti, MD, PhD, Roberto Tramarin, MD, Marianna Volpe, MD, and Alessandro Parolari, MD, PhD

Departments of Cardiac Surgery and Cardiac Rehabilitation, and Unit of Cardiac Surgery and Translational Research, IRCCS Policlinico San Donato, Milan; and Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy

Patients affected by diabetes usually have extensive coronary artery disease. Coronary revascularization has a prominent role in the treatment of coronary artery disease in the expanding diabetic population. However, diabetic patients undergoing coronary artery bypass grafting or percutaneous coronary intervention experience worse outcomes than nondiabetic patients. Several studies comparing coronary artery bypass grafting vs percutaneous coronary intervention in subgroups of diabetic

patients demonstrated a survival advantage and fewer repeat revascularization procedures with an initial surgical strategy. This review summarizes the current state of evidence comparing the effectiveness and safety of coronary artery bypass grafting and percutaneous coronary intervention in diabetic patients.

(Ann Thorac Surg 2016;■:■-■)

© 2016 by The Society of Thoracic Surgeons

The prevalence of diabetes mellitus (DM) is growing rapidly. Approximately 8% of adults in developed countries have DM [1], and diabetic patients represent at least one-fourth of all patients referred for myocardial revascularization [2]. However, diabetic patients are at increased risk for adverse cardiovascular events such as myocardial infarction (MI), chronic heart failure, and stroke [3]. Compared with patients without DM, patients with DM show a more diffused and severe coronary artery disease (CAD) due to specific characteristics of the atherosclerosis, which, in turn, expose them to a higher risk when they are referred for revascularization independently of the selected strategy [4].

Percutaneous coronary interventions (PCI) are limited by a higher rate of repeat revascularization, primarily due to target-vessel restenosis [5], and a worse clinical outcome in diabetic patients compared with nondiabetic patients. Similarly, coronary artery bypass grafting (CABG) carries a greater morbidity, increased length of stay, and longer recovery times in diabetic patients than in nondiabetic patients [6]. However, both strategies have been improved during the last decade. In particular, the introduction of stents, bare-metal stents (BMS) before and drug-eluting stents (DES) later, has dramatically changed the landscape for PCI, with a significant reduction in the rate of restenosis even in diabetic patients [7–10]. On the other side, a more widespread use of arterial conduits has improved the outcome after CABG [11]. As a matter of

fact, these continuing refinements have left open a long-standing debate on which strategy should be preferred for diabetic patients.

This review summarizes the current state of evidence comparing the effectiveness and safety of CABG and PCI in diabetic patients, starting from the earliest studies to current literature.

Methods

Literature Search

To review current knowledge on the results of PCI and CABG in diabetic patients, we systematically searched PubMed free terms to identify peer-reviewed articles related to the results of myocardial revascularization in diabetics. The free search string text was as follows: “(diabetes or diabetics) and (cabg or coronary bypass or coronary artery bypass) and (pci or ptca or percutaneous coronary intervention or percutaneous coronary angioplasty or balloon angioplasty).” This was the primary search. An additional search (secondary search) added the term “meta-analysis” to the primary search. Candidate articles were published in PubMed between January 1, 1997, and September 30, 2015.

Search Results

Our search revealed 1,425 articles for the primary search and 45 for the secondary search. The titles of the primary search and the abstracts of the secondary search were reviewed in duplicate by independent reviewers. To be included, each paper had to report data on outcomes of myocardial revascularization procedures performed with

Address correspondence to Dr Parolari, Unit of Cardiac Surgery and Translational Research, IRCCS Policlinico San Donato, Via Morandi 30, 20097 San Donato Milanese, Milan, Italy; email: alessandro.parolari@unimi.it

PCI or CABG. Two reviewers had to agree to select an abstract for inclusion in our review, and 3 reviewers had to agree to exclude a paper. Further research was initiated when general information was considered useful to the reader, and tangential electronic explorations of related articles and hand searches of bibliographies and of related journals were also performed. Finally, our literature search led to the 56 references quoted in the present review.

From Evolution to Revolution in PCI and the Challenge of an Historical Competition

Historically, the BARI (Bypass Angioplasty Revascularization Investigation) trial [12] was the first to report that patients with DM (a subgroup not specified a priori) had substantially better 5-year survival after CABG than after PCI in the era of balloon angioplasty (BA). This first result was not universally accepted because further comparisons from large clinical registries [13, 14] and randomized trials [15–17] were inconsistent, with some data confirming and others not supporting the BARI findings in diabetic patients.

Subsequently, an extended post hoc analysis of patients with treated DM randomly assigned to an initial treatment strategy of CABG or PCI in the BARI trial was performed [18]. At 7 years, there was a statistically significant survival advantage for patients treated surgically compared with BA (76.4% vs 55.7%, respectively; $p = 0.0011$). The BA group had a significantly higher rate of subsequent revascularization than the CABG group (59.7% vs 13.1%, $p < 0.001$). The final results at the 10-year follow-up confirmed the long-term survival benefit of CABG in respect to BA (CABG, 57.8%; BA, 45.5%; $p = 0.025$) in treated diabetic patients [19].

A collaborative analysis of individual data from 10 randomized controlled trials (RCTs) of elective myocardial revascularization summarized the major findings, confirming the survival advantage for CABG over PCI in diabetic patients with multivessel CAD [20]. Data for 7,812 patients were retrieved, among whom 1,233 were diabetic (CABG, $n = 615$; PCI, $n = 618$). The 5-year mortality was 20.0% with PCI and 12.3% with CABG (odds ratio, 0.70; 95% confidence interval [CI], 0.56 to 0.87) in diabetic patients, whereas no difference was found for nondiabetic patients (odds ratio, 0.98; 95% CI, 0.86 to 1.12). The interaction between diabetic status and type of revascularization was significant ($p = 0.014$). Six of the trials (the earliest) [15–17, 19, 21] included in this analysis were done before the introduction of coronary stents, and the remaining four studies (the latest) [22–25] were after the introduction of BMS. None of the 10 trials included in this study used DES.

The pooling of individual patient data from RCTs to assess treatment might be considered more appropriate compared with the more common technique of meta-analysis of published aggregate data. However, this methodologic approach shares the underlying limitations of the participating trials, which were not designed to

randomize diabetic patients and, overall, are almost never fully representative of the entire real population.

The AWESOME trial (Angina With Extremely Serious Operative Mortality Evaluation Trial) randomized 454 high-risk patients to CABG or PCI using BMS. The patients had at least one risk factor, including prior CABG, MI within 7 days, left ventricular ejection fraction below 0.35, age older than 70 years, or requiring stabilization with an intraaortic balloon [26]. Survival among the 144 diabetic patients (32%) was not significantly different ($p = 0.27$) throughout a 5-year follow-up period between CABG-treated and PCI-treated patients (stents were used in 54%), but there was less recurrent unstable angina and the need for repeat revascularization with CABG. The 3-year freedom from unstable angina or the need for repeated revascularization was 59% vs 38% in the CABG and PCI groups, respectively ($p = 0.001$).

Moreover, in diabetic patients with triple-vessel disease from the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial (CABG, $n = 143$; PCI, $n = 153$), the major adverse cardiac and cerebrovascular event rate at 5 years was twice as high as with PCI using paclitaxel-eluting stents compared with CABG (hazard ratio, 2.30, 95% CI, 1.50 to 3.55; $p < 0.001$). Interestingly, a higher incidence of the composite safety end point of death/stroke/MI, all-cause death, MI, and repeat revascularization was also observed after PCI vs CABG, whereas stroke rates were similar in the two treatment arms [27].

The CARDia (Coronary Artery Revascularization in Diabetes) trial was the first prospective RCT specifically designed to evaluate the safety and efficacy of PCI using BMS (31%) or DES (69%) compared with CABG in patients with diabetes and multivessel CAD [28]. The 1-year results of the trial did not demonstrate the noninferiority of PCI vs CABG for revascularization of patients with DM. At 1 year, the combined incidence of death, MI, or stroke was 10.5% in the CABG arm and 13.0% in the PCI arm (hazard ratio, 1.25; 95% CI, 0.75 to 2.09), and repeat revascularization was 2.0% vs 11.8%, respectively ($p < 0.001$), reflecting the higher use of DES.

The VA CARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes) trial, before being stopped for slow recruitment after enrolling only 25% of the intended sample size, randomized 198 patients with diabetes and severe CAD to CABG or PCI with DES and monitored them for at least 2 years. The primary outcome measure was a composite of nonfatal MI or death; however, due to premature termination, no statistically significant differences could be documented in the composite end point, although a trend toward better results in CABG arm was evident [29].

In the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, 1,900 diabetic patients with multivessel CAD were randomly allocated to PCI with DES or CABG. The primary outcome was the composite of death, nonfatal MI, or stroke. The 5-year results showed that this occurs less frequently in patients undergoing CABG (18.7% vs 26.6% in diabetic patients receiving DES, $p < 0.005$). The benefit of CABG was

mainly driven by lower 5-years rates of MI (6.0% vs 13.9%, $p < 0.001$) and by reduced rates of death from any cause (10.9% vs 16.3%, $p = 0.049$); conversely, stroke was lower in patients allocated to PCI (2.4% vs 5.2%, $p = 0.03$) [30]. The FREEDOM study also showed that CABG in diabetic patients is associated with improved health status at follow-up [31] and with reduced costs for health maintenance organizations at long-term [32].

Concurrently, several meta-analyses have been published in the more recent years on this topic. Table 1 and Figure 1 summarize the results from meta-analyses assessing only prospective randomized studies and with DES use in the PCI arm [33–37]. These meta-analyses confirm that, overall, CABG in diabetic patients confers improved survival rates, lower repeat revascularization, and a trend toward lower nonfatal MI rates as well with respect to PCI performed with DES at midterm follow-up, at the expense of a possible increase in the risk of stroke.

One of these studies, however, raises the issue of the role of newer-generation DES [37]. The authors suggest that by indirect comparisons and data pooling from different studies (currently, there is no direct study that has assessed the role of CABG vs second-generation DES), the survival of diabetic patients might be similar for CABG and for patients undergoing PCI with a zotarolimus DES or everolimus DES [37].

Besides the well-known limits of indirect comparisons that combine trial-level data and do not account at all for between-trial differences, other important issues greatly reducing the possible findings of this study are that even after data pooling, the risk of low statistical power of this analysis cannot be excluded at all. The relative risk of death at follow-up, although statistically nonsignificant, still favors CABG and is of the same extent and magnitude with comparison of CABG vs first-generation DES, especially for the zotarolimus DES.

The hypothesis that second-generation DESs outperform first-generation DESs and give comparable results in mortality as CABG in diabetic patients with multivessel disease still needs to be tested in appropriate multicenter prospective randomized trials because current evidence is not enough to sustain such an hypothesis. In fact, a recently published study reporting the results of the New York state registries suggests that the everolimus-eluting stent has similar results in late death compared with CABG and has lower stroke rates at the expense of the more frequent need of repeat revascularization. Of note, patients receiving everolimus-eluting stents showed reduced survival and a higher MI rate at long-term follow-up when the revascularization that was achieved with stents was not complete [38]. Interestingly, this occurred in more than 80% of patients receiving a stent, and the authors correctly conclude, "If complete revascularization is not achievable for any reason with PCI, patients should be considered for CABG" [38].

Improving Outcomes in Diabetic Patients Undergoing PCI

Restenosis is the driving force behind the increased need for repeat revascularization in diabetic patients after PCI.

Beside optimal glycemic control [39] aimed at decreasing hyperglycemia or intimal hyperplasia, or both, the introduction of the DES has further changed the landscape for PCI, with significant reductions in angiographic restenosis rates and need for repeat revascularization procedures. A large collaborative network meta-analysis compared DES with BMS in 3,852 diabetic patients retrieved from 35 trials [40]. Mortality appeared significantly higher ($p = 0.02$) with DES than with BMS when the duration of dual antiplatelet therapy was less than 6 months (8 trials); in contrast, no difference in death and the combined end point of death or MI was found when dual antiplatelet therapy duration was 6 months or longer (27 trials). Whatever the duration of dual antiplatelet therapy, the need for repeat target-vessel revascularization was considerably less with DES than with BMS, with an odds ratio of 0.29 for the sirolimus-eluting stent and 0.38 for the paclitaxel-eluting stent, which was similar to the restenosis reduction observed in nondiabetic patients.

Improving Outcomes in Diabetic Patients Undergoing CABG

Different surgical techniques have been investigated in diabetic patients. The use of multiple arterial conduits, including bilateral internal thoracic artery (BITA) grafts, appears to improve the long-term results of CABG [11]. However, there is no direct randomized evidence in this regard. Locker and colleagues [41] retrospectively reviewed 802 consecutive diabetic patients undergoing PCI and stenting or CABG with BITAs. They found similar 30-day and 6-year mortality in both groups. However, recurrence of angina, repeated revascularizations, and cardiovascular event-free survival at follow-up were significantly better in patients receiving CABG. Interestingly, survival in the subgroup of patients with left main or 3-vessel CAD was significantly better in CABG patients. Moshkovitz and coworkers [42] reported 542 consecutive diabetic patients with multivessel CAD undergoing BITA grafting or PCI with Cypher stents (Cordis, Miami Lakes, FL). The authors found that assignment to the PCI group was associated with decreased adjusted survival and increased risk of target vessel reinterventions. Interestingly, the adjusted risk of major adverse cardiovascular events increased with the number of DES-treated vessels.

The Cleveland Clinic recently reported the results of 11,922 patients with diabetes who underwent primary isolated CABG from 1972 to 2011, documenting a survival advantage at a median follow-up of 7.8 years for patients receiving bilateral mammary grafting and complete myocardial revascularization. This occurred, however, at the expense of a higher rate of deep sternal wound infections (DSWI) that did not sensibly affect overall survival because of its rare occurrence [43]. DSWI, an infrequent yet potentially devastating complication after CABG, is associated with increased cost of care, prolonged hospitalization, and increased morbidity and death. That BITA harvesting is a significant risk factor for DSWI is well known, and this fact has probably limited the widespread use of BITA among the community of

Table 1. Overview of the Results of Meta-Analyses of Randomized Studies Comparing Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention With Drug-Eluting Stents in Diabetic Patients

First Author	Year	Journal	Trials, No.	Pooled Patients (CABG/PCI), No.	Primary End Point	Measure of Outcome (95% CI) CABG vs PCI With DES	Secondary End Points	Measure of Outcome (95% CI) CABG vs PCI	Subanalysis	Subanalysis of Main Results
Lee [33]	2010	Am J Cardiol	5	757/786	MACE at 18 months	RR = 0.59 (0.46–0.74) <i>p</i> value <0.001	Death at 18 months MI at 18 months Repeat revascularization at 18 months Cerebrovascular events at 18 months	RR = 0.76 (0.53–1.09) <i>p</i> value = 0.12 RR = 0.81 (0.47–1.42) <i>p</i> value = 0.47 RR = 0.22 (0.14–0.35) <i>p</i> value <0.001 RR = 2.52 (1.13–5.62) <i>p</i> value <0.001		
Hakeem [34]	2013	J Am Heart Assoc	4	1,513/1,539	MACE at ≥4 years	RR = 0.75 (0.65–0.86) <i>p</i> value <0.0001	Death at 4 years Cardiovascular death at 4 years MI at 4 years Stroke at 4 years Repeat revascularization at 4 years	RR = 0.66 (0.48–0.92) <i>p</i> value = 0.01 RR = 0.64 (0.48–0.85) <i>p</i> value = 0.002 RR = 0.69 (0.38–1.27) <i>p</i> value = 0.23 RR = 1.69 (1.11–2.56) <i>p</i> value = 0.01 RR = 0.54 (0.29–1) <i>p</i> value = 0.05	CABG vs DES	CABG has advantage in the primary end-point (MACE) over DES after 5 years of follow-up Advantage of CABG over PCI in reducing MACE is a function of time DES, has an advantage over CABG in terms of stroke

(Continued)

Table 1. Continued

First Author	Year	Journal	Trials, No.	Pooled Patients (CABG/PCI), No.	Primary End Point	Measure of Outcome (95% CI) CABG vs PCI With DES	Secondary End Points	Measure of Outcome (95% CI) CABG vs PCI	Subanalysis	Subanalysis of Main Results
Verma [35]	2013	Lancet Diabetes Endocrinol	8	1,576/1,555	Death at ≥ 5 years	RR = 0.67 (0.52–0.86) p value = 0.002	Death at 1 year Nonfatal MI at 1 year Nonfatal stroke at 1 year Repeat revascularization at 1 year Nonfatal MI at ≥ 5 years Nonfatal stroke at ≥ 5 years Repeat revascularization at ≥ 5 years	RR = 1.01 (0.72–1.41) p value = 0.98 RR = 0.90 (0.46–1.77) p value = 0.77 RR = 2.41 (1.22–4.76) p value = 0.01 RR = 0.38 (0.23–0.65) p value = 0.0003 RR = 0.67 (0.36–1.26) p value = 0.22 RR = 1.84 (1.22–2.78) p value = 0.004 RR = 0.49 (0.33–0.71) p value = 0.0002	CABG vs BMS CABG vs DES	CABG has similar advantage in terms of mortality over BMS and DES DES, but not BMS, has an advantage over CABG in terms of stroke CABG has advantage in terms of repeat revascularization over BMS and DES that is greater over BMS

(Continued)

Table 1. Continued

First Author	Year	Journal	Trials, No.	Pooled Patients (CABG/PCI), No.	Primary End Point	Measure of Outcome (95% CI) CABG vs PCI With DES	Secondary End Points	Measure of Outcome (95% CI) CABG vs PCI	Subanalysis	Subanalysis of Main Results
Fanari [36]	2014	Interact Cardiovasc Thorac Surg	3	1,416/1,438	Composite outcome death/MI/stroke at 1 year	RR = 1.12 (0.88–1.43) <i>p</i> value = 0.33	Death at 1 year MI at 1 year Stroke at 1 year Repeat revascularization at 1 year Death at 5 years MI at 5 years Stroke at 5 years Composite outcome death/MI/stroke at 5 years	RR = 1.03 (0.72–1.47) <i>p</i> value = 0.85 RR = 0.79 (0.47–1.33) <i>p</i> value = 0.37 RR = 2.5 (1.23–5.26) <i>p</i> value = 0.0012 RR = 0.40 (0.25–0.64) <i>p</i> value < 0.0001 RR = 0.74 (0.60–0.90) <i>p</i> value = 0.003 RR = 0.50 (0.38–0.65) <i>p</i> value < 0.0001 RR = 1.69 (1.12–2.56) <i>p</i> value = 0.013 RR = 0.68 (0.57–0.82) <i>p</i> value = 0.0002		

(Continued)

Table 1. Continued

First Author	Year	Journal	Trials, No.	Pooled Patients (CABG/PCI), No.	Primary End Point	Measure of Outcome (95% CI) CABG vs PCI With DES	Secondary End Points	Measure of Outcome (95% CI) CABG vs PCI	Subanalysis	Subanalysis of Main Results
Bangalore [37]	2014	Circ Cardiovasc Interv	68	NA	Death		MI			
					CABG vs PES	RR = 0.64 (0.45–0.87)	CABG vs PES	RR = 0.70 (0.41–1.32)		
					CABG vs SES	RR = 0.70 (0.51–0.94)	CABG vs SES	RR = 0.82 (0.49–1.51)		
					CABG vs ZES-E	RR = 0.76 (0.43–1.21)	CABG vs ZES-E	RR = 0.65 (0.28–1.59)		
					CABG vs ZES-R	RR = 0.69 (0.11–3.23)	CABG vs ZES-R	RR = 0.86 (0.20–4.17)		
					CABG vs CoCr EES	RR = 0.90 (0.54–1.49)	CABG vs CoCr EES	RR = 1.39 (0.63–3.7)		
							Repeat revascularization			
							CABG vs PES	RR = 0.55 (0.36–0.84)		
							CABG vs SES	RR = 0.68 (0.45–1.05)		
							CABG vs ZES-E	RR = 0.43 (0.24–0.77)		
							CABG vs ZES-R	RR = 0.42 (0.17–0.99)		
							CABG vs CoCr EES	RR = 0.76 (0.44–1.35)		
							Stroke			
							CABG vs PES	RR = 1.85 (0.52–5.88)		
							CABG vs SES	RR = 1.59 (0.51–4.76)		

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CI = confidence interval; CoCr EES = cobalt-chromium everolimus-eluting stent; DES = drug-eluting stent; MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention; NA = not available; PES = paclitaxel-eluting stent; RR = relative risk; SES = sirolimus-eluting stent; ZES-E = zotarolimus-eluting stent Endeavor (Medtronic, Minneapolis, MN); ZES-R = zotarolimus-eluting stent Resolute (Medtronic, Minneapolis, MN).

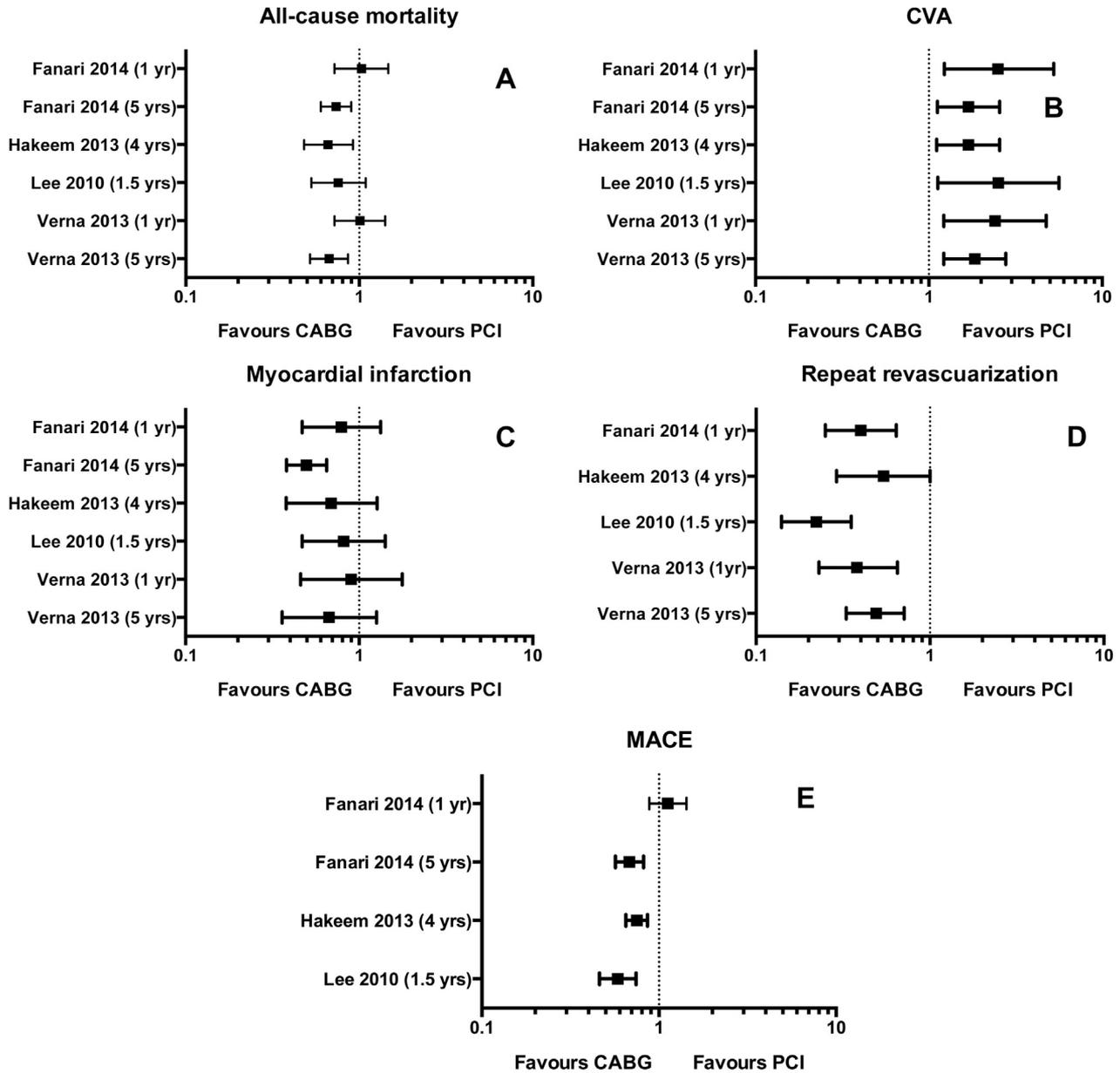


Fig 1. Forest plots for the major outcomes in recent meta-analysis comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in diabetic patients: (A) all-cause mortality, (B) cerebrovascular accident, (C) myocardial infarction, (D) repeated revascularization, and (E) major adverse cardiovascular events (MACE). The solid squares indicate the mean difference, the dashed vertical line indicates no effect, and the horizontal lines represent the 95% confidence interval.

cardiac surgeons. Indeed, the reported incidence of DSWI ranges from 1.3% to 4.7% in patients with BITA grafting [44], but its incidence can be as high as 10% in diabetic patients undergoing BITA grafting [45].

Skeletonized use of BITAs has been associated with mediastinitis ranging from 0.4% to 2.6% in the whole context of CABG and from 0.5% to 3.3% in diabetic patients [46]. The beneficial effect of BITA skeletonization with respect to reduced rates of mediastinitis can be attributed to the statistically significant increased sternal perfusion with skeletonized BITAs compared with

pedicled BITAs. This was shown clearly in a randomized, double-blind within-patient comparison study that randomized patients to receive 1 skeletonized and 1 pedicled ITA graft [47].

To our knowledge, no randomized studies are reported comparing multiple arterial grafting with BITAs and radial artery with PCI and stenting in diabetic patients. However, Habib and colleagues [48] recently reported their single-center experience in more than 8,000 patients who underwent CABG (single ITA or multiple arterial) or PCI (with BMS or DES), comparing 9-year survival and

freedom from repeated revascularization. Diabetes was present in nearly 35% of the population, although a subgroup analysis in diabetic patients was not performed. After adjusting for baseline differences, the authors found that multiarterial surgical revascularization, compared with BMS-PCI or DES-PCI, resulted in enhanced survival and reintervention-free survival.

Recommendations

In 2012, the task forces of the most important scientific American societies and associations, including American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and The Society of Thoracic Surgeons, issued updated guidelines for revascularization. These guidelines assessed the appropriateness of revascularization procedures irrespective of whether this was accomplished by PCI or CABG, reserving only for some selected subgroups of presentations the assessment of the appropriateness of PCI and CABG indication individually [49]. Only in the revised version of the same guidelines dated 2015, is the issue of diabetes assessed separately for the first time, with the indication that CABG seems to be associated with a reduced risk of death with respect to PCI in most patients with DM and complex multivessel disease; at the same time, the class of this recommendation has improved from IIa to I, further supporting this indication [50].

In 2014 a joint European Society of Cardiology/European Association of Cardiothoracic Surgery task force released an update on guidelines for myocardial revascularization [51]. Interventional cardiologists, surgeons and cardiac clinicians have recognized that in patients with stable multivessel CAD and with acceptable surgical risk, CABG is recommended over PCI (class of recommendation: I; Level of Evidence: A), leaving a very limited role for PCI that is allowed only in these patients presenting with a SYNTAX score of 22 or less (class of recommendation: IIb; Level of Evidence: B); however, a SYNTAX score of 22 or less is quite unusual in case of multivessel disease and diabetes, because diabetic patients are well known to suffer from the most aggressive form of coronary atherosclerosis. In these relatively limited cases, the use of DES is recommended to reduce restenosis and repeat target vessel revascularization (class of recommendation: I; Level of Evidence: A).

Practically, in the more recent guidelines both from Europe and the United States, there has been a clear paradigm shift in the treatment of patients with diabetes in favor of CABG. This has been due to the bulk of data coming from the FREEDOM study and from recent meta-analyses that have been published on this topic. However, there is still reluctance in daily practice, especially from the average interventional cardiologist's point of view, in accepting CABG as the most reasonable, effective, and efficient option in most diabetic patients needing

coronary revascularization. This also strongly underscores the need of further objective data from appropriately designed trials to support the evidence that is constantly emerging in favor of CABG.

Criticism, Perplexities, and Future Expectations

The revascularization strategy for diabetic patients favors CABG because it currently constitutes the most reasonable option for most diabetic patients. However, with the exception of the FREEDOM trial, the mentioned RCTs comparing CABG and PCI reported outcomes only for subgroups of diabetic patients.

Besides the well-recognized weaknesses of RCTs (eg, small numbers of patients, small percentage of patients in respect to the eligible population, highly selected and atypical populations that might not be fully representative of patients encountered in the ordinary clinical practice, and short duration of follow-up), subgroup analyses need to be interpreted with caution, because of the lack of statistical power making specific information from subgroup analyses of an observational nature, the evidence from these studies parallels the evidence coming from the FREEDOM trial.

The diabetic patient is one of the most complex patients to face, showing a more complex anatomic pattern of CAD (eg, more completely occluded segments, smaller luminal diameters in segments adjacent to obstructive coronary lesions, a larger amount of lipid-rich plaques, less coronary collaterals, etc) [52–54] and higher comorbidity. What we also know, at the moment, is that insulin-treated patients undergoing PCI or CABG have worse long-term results, as expected, and this occurs irrespective of the initial treatment chosen [55]. In the meantime, the clinician's judgment remains an important tool in the final decision making, although more recent data are clearly favoring a surgical approach rather than stenting of whatever type. In view of the above considerations, it is expected that future trials will take into account the recently introduced Clinical SYNTAX Score [56], incorporating anatomic and clinical characteristics that could help to better stratify diabetic patients and optimize the strategy to treat these patients.

Conclusions

Coronary revascularization has an important role in the treatment of CAD in the expanding population of diabetic patients. Multiple studies comparing CABG surgery vs PCI (from BA to BMS and, most recently, DES) in diabetic patients have demonstrated a clear survival advantage that increases with longer follow-up, fewer repeat revascularization procedures, and lower MI rates with an initial surgical strategy.

References

1. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 1998;21:518–24.

2. Rydén L, Standl E, Bartnik M, et al, Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;28:88–136.
3. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes* 1974;23:105–11.
4. Lüscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. *Circulation* 2003;108:1655–61.
5. Smith SC Jr, Faxon D, Cascio W, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease Writing Group VI: revascularization in diabetic patients. *Circulation* 2002;105:e165–9.
6. Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. *J Am Coll Cardiol* 2002;40:418–23.
7. Moses JW, Leon MB, Popma JJ, et al, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–23.
8. Holmes DR Jr, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004;109:634–40.
9. Stone GW, Ellis SG, Cox DA, et al, TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004;109:1942–7.
10. Jiménez-Quevedo P, Sabaté M, Angiolillo DJ, et al, DIABETES Investigators. Long-term clinical benefit of sirolimus-eluting stent implantation in diabetic patients with de novo coronary stenoses: long-term results of the DIABETES trial. *Eur Heart J* 2007;28:1946–52.
11. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularization on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001;358:870–5.
12. The BARI Investigators. Influence of diabetes on five-year mortality and morbidity in a randomized trial comparing PTCA and CABG in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1997;96:1761–9.
13. Barsness GW, Peterson ED, Ohman EM, et al. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. *Circulation* 1997;96:2551–6.
14. Niles NW, McGrath PD, Malenka D, et al, Northern New England Cardiovascular Disease Study Group. Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study. *J Am Coll Cardiol* 2001;37:1008–15.
15. King SB, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS. Eight-year mortality in the Emory Angioplasty Versus Surgery Trial (EAST). *J Am Coll Cardiol* 2000;35:1116–21.
16. Henderson RA, Pocock SJ, Sharp SJ, et al, Randomized Intervention Treatment of Angina (RITA-1) trial participants. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. *Lancet* 1998;352:1419–25.
17. Kurbaan AS, Bowker TJ, Ilesley CD, Sigwart U, Rickards AF. Difference in the mortality of the CABRI diabetic and nondiabetic populations and its relation to coronary artery disease and the revascularization mode. *Am J Cardiol* 2001;87:947–50.
18. The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000;35:1122–9.
19. The BARI Investigators. The final ten-years follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 2007;49:1600–6.
20. 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;373:1190–7.
21. Kaebler J, Koester R, Billmann W, et al. 13-year follow-up of the German angioplasty bypass surgery investigation. *Eur Heart J* 2005;26:2148–53.
22. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease. The final analysis of the Arterial Revascularization Therapies (ARTS) randomized trial. *J Am Coll Cardiol* 2005;46:575–81.
23. Rodriguez AE, Baldi J, Fernández Pereira C, et al, ERACI II Investigators. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 2005;46:582–8.
24. Hueb W, Lopes NH, Gersh BJ, et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2007;115:1082–9.
25. Booth J, Clayton T, Pepper J, et al, SoS Investigators. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 2008;118:381–8.
26. Sedlis SP, Morrison DA, Lorin JD, et al. Percutaneous coronary intervention versus coronary bypass graft surgery for diabetic patients with unstable angina and risk factors for adverse outcomes with bypass: outcome of diabetic patients in the AWESOME randomized trial and registry. *J Am Coll Cardiol* 2002;40:1555–66.
27. Head SJ, Davierwala PM, Serruys PW, et al. Coronary artery bypass grafting vs percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 2014;21(35):2821–30.
28. 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;55:432–40.
29. Kamalesh M, Sharp TG, Tang XC, et al, VA CARDS Investigators. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol* 2013;61:808–16.
30. Farkouh ME, Domanski M, Sleeper LA, et al, FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375–84.
31. Abdallah MS, Wang K, Magnuson EA, et al, FREEDOM Trial Investigators. Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 2013;310:1581–90.
32. Magnuson EA, Farkouh ME, Fuster V, et al, FREEDOM Trial Investigators. Cost-effectiveness of percutaneous coronary intervention with drug eluting stents versus bypass surgery for patients with diabetes mellitus and multivessel coronary artery disease: results from the FREEDOM trial. *Circulation* 2013;127:820–31.
33. Lee MS, Yang T, Dhoot J, Iqbal Z, Liao H. Meta-analysis of studies comparing coronary artery bypass grafting with drug-eluting stenting in patients with diabetes mellitus and

- multivessel coronary artery disease. *Am J Cardiol* 2010;1;105:1540-4.
34. Hakeem A, Garg N, Bhatti S, Rajpurohit N, Ahmed Z, Uretsky BF. Effectiveness of percutaneous coronary intervention with drug-eluting stents compared with bypass surgery in diabetics with multivessel coronary disease: comprehensive systematic review and meta-analysis of randomized clinical data. *J Am Heart Assoc* 2013;7;2:e000354.
 35. Verma S, Farkouh ME, Yanagawa B, et al. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomized controlled trials. *Lancet Diabetes Endocrinol* 2013;1:317-28.
 36. Fanari Z, Weiss SA, Zhang W, Sonnad SS, Weintraub WS. Meta-analysis of three randomized controlled trials comparing coronary artery bypass grafting with percutaneous coronary intervention using drug-eluting stenting in patients with diabetes. *Interact Cardiovasc Thorac Surg* 2014;19:1002-7.
 37. Bangalore S, Toklu B, Feit F. Outcomes with coronary artery bypass graft surgery versus percutaneous coronary intervention for patients with diabetes mellitus: can newer generation drug-eluting stents bridge the gap? *Circ Cardiovasc Interv* 2014;7:518-25.
 38. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus eluting stents versus coronary artery bypass graft surgery for patients with diabetes mellitus and multivessel disease. *Circ Cardiovasc Interv* 2015;8:e002626.
 39. Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol* 2004;43:8-14.
 40. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 2008;337:a1331.
 41. Locker C, Mohr R, Lev-Ran O, et al. Comparison of bilateral thoracic artery grafting with percutaneous coronary interventions in diabetic patients. *Ann Thorac Surg* 2004;78:471-5.
 42. Moshkovitz Y, Mohr R, Medalion B, et al. Drug-eluting stents compared with bilateral internal thoracic artery grafts for diabetic patients. *Ann Thorac Surg* 2012;94:1455-62.
 43. Raza S, Sabik JF 3rd, Masabni K, Ainkaran P, Lytle BW, Blackstone EH. Surgical revascularization techniques that minimize surgical risk and maximize late survival after coronary artery bypass grafting in patients with diabetes mellitus. *J Thorac Cardiovasc Surg* 2014;148:1257-64.
 44. Ioannidis JP, Galanos O, Katritsis D, et al. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. *J Am Coll Cardiol* 2001;37:521-8.
 45. Tavalacci MP, Merle V, Josset V, et al. Mediastinitis after coronary artery bypass graft surgery: influence of the mammary grafting for diabetic patients. *J Hosp Infect* 2003;55:21-5.
 46. Pevni D, Mohr R, Lev-Run O, et al. Influence of bilateral skeletonized harvesting on occurrence of deep sternal wound infection in 1,000 consecutive patients undergoing bilateral internal thoracic artery grafting. *Ann Surg* 2003;237:277-80.
 47. Boodhwani M, Lam BK, Nathan HJ, et al. Skeletonized internal thoracic artery harvest reduces pain and dysesthesia and improves sternal perfusion after coronary artery bypass surgery: a randomized, double-blind, within-patient comparison. *Circulation* 2006;114:766-73.
 48. Habib RH, Dimitrova KR, Badour SA, et al. CABG versus PCI: greater benefit in long-term outcomes with multiple arterial bypass grafting. *J Am Coll Cardiol* 2015;66:1417-27.
 49. Fihn SD, Gardin JM, Abrams J, et al. American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: 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. *Circulation* 2012;126:3097-137.
 50. Fihn SD, Blankenship JC, Alexander KP, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg* 2015;149:e5-23.
 51. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg* 2014;46:517-92.
 52. Ledru F, Ducimetière P, Battaglia S, et al. New diagnostic criteria for diabetes and coronary artery disease: insights from an angiographic study. *J Am Coll Cardiol* 2001;37:1543-50.
 53. Moreno PR, Murcia AM, Palacios IF, et al. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation* 2000;102:2180-4.
 54. Abaci A, Oğuzhan A, Kahraman S, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999;99:2239-42.
 55. Dangas GD, Farkouh ME, Sleeper LA, et al, FREEDOM Investigators. Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: results from the FREEDOM trial. *J Am Coll Cardiol* 2014;23(64):1189-97.
 56. Garg S, Sarno G, Garcia-Garcia HM, et al, ARTS-II Investigators. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 2010;3:317-26.