Review

Coronary Artery Bypass Graft Surgery vs Percutaneous Interventions in Coronary Revascularization
A Systematic Review

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IMPORTANCE Ischemic heart disease is the leading cause of death globally. Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) are the revascularization options for ischemic heart disease. However, the choice of the most appropriate revascularization modality is controversial in some patient subgroups.

OBJECTIVE To summarize the current evidence comparing the effectiveness of CABG surgery and PCI in patients with unprotected left main disease (ULMD, in which there is >50% left main coronary stenosis without protective bypass grafts), multivessel coronary artery disease (CAD), diabetes, or left ventricular dysfunction (LVD).

EVIDENCE REVIEW A search of OvidSP MEDLINE, EMBASE, and Cochrane databases between January 2007 and June 2013, limited to randomized clinical trials (RCTs) and meta-analysis of trials and/or observational studies comparing CABG surgery with PCI was performed. Bibliographies of relevant studies were also searched. Mortality and major adverse cardiac and cerebrovascular events (MACCE, defined as all-cause mortality, myocardial infarction, stroke, and repeat revascularization) were reported wherever possible.

FINDINGS Thirteen RCTs and 5 meta-analyses were included. CABG surgery should be recommended in patients with ULMD, multivessel CAD, or LVD, if the severity of coronary disease is deemed to be complex (SYNTAX >22) due to lower cardiac events associated with CABG surgery. In cases in which coronary disease is less complex (SYNTAX ≤22) and/or the patient is a higher surgical risk, PCI should be considered. For patients with diabetes and multivessel CAD, CABG surgery should be recommended as standard therapy irrespective of the severity of coronary anatomy, given improved long-term survival and lower cardiac events (5-year MACCE, 18.7% for CABG surgery vs 26.6% for PCI; P = .005). Overall, the incidence of repeat revascularization is higher after PCI, whereas stroke is higher after CABG surgery. Current literature emphasizes the importance of a heart-team approach that should consider coronary anatomy, patient characteristics, and local expertise in revascularization options. Literature pertaining to revascularization options in LVD is scarce predominantly due to LVD being an exclusion factor in most studies.

CONCLUSIONS AND RELEVANCE Both CABG surgery and PCI are reasonable options for patients with advanced CAD. Patients with diabetes generally have better outcomes with CABG surgery than PCI. In cases of ULMD, multivessel CAD, or LVD, CABG surgery should be favored in patients with complex coronary lesions and anatomy and PCI in less complicated coronary disease or deemed a high surgical risk. A heart-team approach should evaluate coronary disease complexity, patient comorbidities, patient preferences, and local expertise.

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Coronary artery disease (CAD) is the leading cause of death globally.[1,2] Coronary artery bypass graft (CABG) surgery was first performed in the 1960s by Kolesov and Favaloro and quickly became the principal modality for invasive treatment of CAD.[3] A decade later, Gruntzig introduced the less invasive alternative, percutaneous coronary intervention (PCI).[4] These 2 modalities remain the main invasive therapeutic options for coronary revascularization.

During the past 4 decades, both technologies have undergone major advances. In CABG surgery, the use of the internal mammary artery along with improvements in cardiopulmonary bypass, vigilant myocardial protection, off-pump techniques, and optimal postoperative pharmacotherapy resulted in excellent outcomes.[5-7] Percutaneous intervention also evolved from balloon angioplasty to bare-metal stent (BMS) technology and then drug-eluting stent (DES) technology, addressing the issue of in-stent restenosis and stent thrombosis. Drug-eluting stent technology has progressed tremendously and is in its third generation of devices, with advances in the stent platform, the polymer coating, and the antiproliferative agent that is eluted (**Table 1**).[6,8] Advances in adjunctive pharmacotherapy, including dual antiplatelet therapy after PCI, have also helped achieve excellent outcomes.[4]

BMS *bare-metal stent*

CABG *coronary artery bypass graft*

CAD *coronary artery disease*

DES *drug-eluting stent*

LVD *left ventricular dysfunction*

LVEF *left ventricular ejection fraction*

MACCE *major adverse cardiac and cerebrovascular events (defined as all-cause mortality, myocardial infarction, stroke, or repeat revascularization)*

PCI *percutaneous coronary intervention*

RCTs *randomized clinical trials*

ULMD *unprotected left main disease*

Given these advances, multiple randomized clinical trials (RCTs) have attempted to determine which modality is superior. Major controversies of revascularization options involve patients with unprotected left main disease (ULMD), multivessel CAD, diabetes mellitus, and left ventricular dysfunction (LVD). The goal of our study was to systematically review major studies and current guideline statements and provide evidence-based summary recommendations in these 4 areas for stable ischemic heart disease.

Methods

We searched OvidSP MEDLINE, EMBASE, and Cochrane (the Evidence-Based Medicine Reviews, Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews) databases using subject and text terms for *coronary artery bypass grafting*, *balloon angioplasty*, *stenting*, and *percutaneous coronary intervention*. We limited our search to published RCTs between January 2007 and the present to reflect contemporary practices comparing PCI with CABG surgery in patients with stable ischemic CAD. Studies that only included single-vessel disease were excluded. We also searched for meta-analyses in the above databases and manually retrieved the most current meta-analysis that included RCTs, observational studies, or both for the 4 major topics. We also reviewed reference lists of identified studies.

Duplicate references were identified and removed using EndNote X5 Library (Thomson Reuters) program. Statistical software was not required because no numerical syntheses were performed. The reported *P* values were derived from the individual studies. $P < .05$ was considered significant in all studies, unless otherwise specified.

Search Results

The systematic search of RCTs yielded 380 studies after removal of duplicates, with 13 being included in the review (**Figure**). In most cases of multiple publications, only the most recent publications of RCTs were included except for the SYNTAX (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) study[9] in which both 1-year and 5-year results were reported. We also included 5 meta-analyses representing the most recent in the topic areas. A systematic review of PCI vs CABG surgery found in the Cochrane database was excluded because it was last updated in 2004.[10] The search strategy for the RCTs and meta-analyses is current as of June 20, 2013 (see eAppendix in the Supplement).

Assessing the Quality of the RCTs

Each RCT was graded for quality of study design and reporting using the JADAD score (range, 0 [weakest] to 5 [strongest])[11] (**Table 2**).[9,12-23] Most scored a 3, the highest possible score without double-blinding, which is not feasible in these invasive intervention studies.

Patients With Significant ULMD

Epidemiology

Significant ULMD is defined as left main artery luminal narrowing of more than 50% without patent bypass grafts to its branches. Unprotected left main disease occurs in 5% to 7% of patients undergoing coronary angiography and the 3-year mortality without revascularization is 50%.[24,25]

Results for CABG Surgery vs PCI

Initial attempts to treat ULMD with balloon angioplasty alone were abandoned due to high rates of elastic recoil and vessel dissection.[26] The use of BMS in these patients resulted in persistently high repeat revascularization mostly due to restenosis. The marked reduction of restenosis rates associated with DES has reignited interest in percutaneous techniques for ULMD (**Table 3**).[9,14,18,19,22]

The Study of Unprotected Left Main Stenting vs Bypass Surgery (LE MANS)[14] was an early, small (n = 105) RCT between CABG surgery and PCI in patients with ULMD (mostly distal left main). At 1 year, compared with CABG surgery, the PCI cohort had a statistically significant increase in left ventricular function (3.3% change PCI vs 0.5% change CABG surgery, $P = .047$). Freedom from the composite end points of cardiac death, myocardial infarction (MI), stroke, reintervention, or stent thrombosis was similar beyond 1 year (mean [SD] follow-up, 28 [9.9] months). The major limitations of this study included the small size and the low rate (72%) of internal mammary artery use in the CABG surgery cohort.[14]

The Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) study[18] is one of the largest (n = 600) published RCT comparing DES with CABG surgery, with more than 60% of patients having bifurcated lesions. Percutaneous coronary intervention was found to be noninferior to CABG sur-

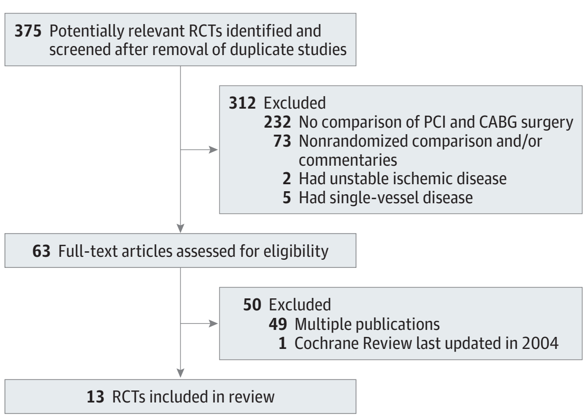
Table 1. Contemporary First-, Second-, and Third-Generation Stents Used for Percutaneous Coronary Interventions

Type of Drug[a]	Name	Drug Effect	Drug Release	Comments
First-Generation Stents[b]				
Sirolimus	Cypher	Inhibits vascular smooth muscle cell proliferation	80% in 4 weeks	First-generation stent with strut thickness of 140 μm; less deliverable. No longer manufactured.
Paclitaxel	Taxus Express	Inhibits vascular smooth muscle cell proliferation	10% during first 10 days	Strut thickness of 132 μm
Paclitaxel	Taxus Liberte	Inhibits vascular smooth muscle cell proliferation	10% during first 10 days	Strut thickness of 97 μm; more deliverable compared with Taxus Express
Second-Generation Stents[b]				
Zotaralimus	Endeavor	Inhibits vascular smooth muscle cell proliferation (synthetic analog of sirolimus)	100% in 4 weeks	
Zotaralimus	Resolute	Inhibits vascular smooth muscle cell proliferation	80% in 4 weeks	Slower drug release compared with Endeavor; less late lumen loss (0.27 mm vs 0.61 mm for Endeavor)
Everolimus	Xience-V	Antiproliferative and immunosuppressive	80% in 4 weeks	
Everolimus	Promus	Antiproliferative and immunosuppressive	80% in 4 weeks	
Everolimus	Promus Element	Antiproliferative and immunosuppressive	80% in 4 weeks	Stent material is more radio-opaque and visible
Third-Generation Stents[b]				
Biolimus	BioMatrix	Inhibits vascular smooth muscle cell proliferation (semisynthetic analog of sirolimus; similar in potency but more lipophilic)	45% in 4 weeks	Bioabsorbable polymer

[a] Based on Roberts[6] and Iqbal et al.[8]

[b] Categorization by generation is based on drug type, with first generation being stents with either sirolimus or paclitaxel, which were the first to be evaluated and approved. Second-generation drug-eluting stents are characterized by newer drugs, as well as improvements in stent platform and polymer type, which aim to improve effectiveness and safety. Third-generation stents have bioabsorbable polymers/stent struts, or are polymer free, with the objective to further improve the safety profile of these stents.

Figure. Flow Diagram of the RCTs Included in the Review Comparing CABG Surgery With PCI



CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; RCTs, randomized clinical trials. A formal search was also conducted for current meta-analysis involving randomized studies, observational studies, or both. The most current meta-analysis for each topic was selected. Five meta-analyses resulted from our search (1 for left main disease, 1 for multivessel disease, 1 for diabetes, and 2 for left ventricular dysfunction). Altogether, the left main section included 6 studies, multivessel disease included 6 studies, diabetes included 6 studies, and left ventricular dysfunction included 2 studies.

gery at 1 year for a composite of all-cause death, MI, stroke, or ischemia-driven target vessel revascularization (6.7% for CABG surgery vs 8.7% for PCI, *P* = .01 for noninferiority). Given the low overall event rates, study investigators cautioned that these findings were hypothesis generating. No differences were found in the individual components of the composite end points at 1 year; however, at 2 years, ischemia-driven revascularization was higher in the PCI group (9.0% vs 4.2%, *P* = .02). Similarly, an RCT by Boudriot et al,[19] with patients mostly with distal left main disease, showed that PCI was inferior to CABG surgery with respect to 1-year composite outcome of cardiac-cause death, MI, or repeat reintervention (13.9% for CABG surgery vs 19.0% for PCI, *P* = .19); this was driven mainly by high rates of repeat revascularization.

The SYNTAX trial[15] was an international, 85-center, "all comers" trial for patients with either left main disease or 3-vessel disease. Participants deemed suitable for both interventions (CABG surgery or paclitaxel-eluting stents) by a heart team (surgeon and interventional cardiologist) were eligible for randomization; the remainder were entered into a registry. A total of 1800 patients were enrolled with mean age of 65 years, an EuroSCORE of 3.8, and a SYNTAX score of 28.8. The EuroSCORE provides an estimate of surgical in-hospital mortality. The SYNTAX score is an assessment of overall coronary lesion complexity, with higher scores representing more complex coronary disease (a low scores is defined as ≤22, an intermediate score as 23-32, and a high score as ≥33). The primary study hypothesis was that major adverse cardiac and cerebrovascular events (MACCE, defined as all-cause mortality, myocardial infarction, stroke, or repeat revascularization) at 1 year were noninferior with PCI compared with CABG surgery. Because MACCE were significantly higher following PCI compared with CABG surgery (17.8% vs 12.4%, *P* = .002), the SYNTAX investigators cautioned that any additional early and late SYNTAX comparisons (some of which will be covered elsewhere in this review) should be considered hypothesis generating.

Of 705 patients with ULMD (a prespecified subgroup),[9] most had distal left main lesions. The primary end point of 1-year MACCE in patients with ULMD was similar between CABG surgery and PCI (13.7% and 15.8%, respectively; *P* = .44). Stroke incidence was higher with CABG surgery (2.7% for CABG surgery vs 0.3% for PCI, *P* = .009); reintervention rates were higher with PCI (6.5% for CABG surgery vs 11.8% for PCI, *P* = .02). One-year MACCE rates were increased in CABG surgery in patients with isolated left main or left main and 1-vessel disease; PCI was inferior to CABG surgery in patients with left main and 2- or 3-vessel disease. A MACCE predictor for the PCI cohort was SYNTAX score, whereas for CABG surgery, it was the EuroSCORE. This suggests that lesion complexity defined by the SYNTAX score is an essential consideration for stenting, whereas patient comorbidity as reflected in EuroSCORE is an essential consideration for CABG surgery.

The recently reported 5-year results for the ULMD cohort showed no difference in MACCE between the CABG surgery and PCI groups with low and intermediate SYNTAX scores; results were significantly worse in PCI for high scores (for SYNTAX ≥33, MACCE was 29.7% vs 46.5%, respectively; *P* = .003).[22]

A 2013 meta-analysis[27] of the current RCTs and 11 observational studies involving 5628 patients undergoing treatment of ULMD (mostly distal lesions) with CABG surgery or DES reinforced these findings. Beyond 1 year, there was no significant difference in the risk of all-cause mortality; however, stroke was lower while repeat revascularization and MACCE were higher in PCI.

Current Guidelines

The European 2010 guidelines[28] recommend CABG surgery (class I, level A) for any ULMD (isolated or with concomitant 2- or 3-vessel disease) in patients with stable CAD. Percutaneous coronary intervention is designated as class IIa, level B (conflicting but evidence in favor of PCI) for isolated ULMD with ostial or trunk lesion, and class IIb, level B (conflicting and evidence less established) for distal or bifurcated ULMD, or ULMD with 2- or 3-vessel disease, and class III, level B (not useful/possibly harmful) for SYNTAX score of 33 or more. The 2011 American College of Cardiology Foundations/American Heart Association guidelines[29] have similar recommendations of CABG surgery for any ULMD lesions (class I, level B) in stable patients to improve survival. Percutaneous coronary intervention is reasonable (class IIa, level B) in patients with low-risk left main lesions (ostial/trunk), a SYNTAX score of 22 or less, and patients with high risk of surgery defined as Society of Thoracic Surgery risk score of 5% or more. In patients with more comorbidities (moderate surgical risk with Society of Thoracic Surgery risk score of >2%) and low to intermediate severity of lesion anatomy (SYNTAX score <33), PCI may be a reasonable option (class IIb, level B).

Percutaneous coronary intervention is also reasonable (class IIa, levels B and C) in patients with acute coronary syndromes (unstable angina/non–ST-segment elevation MI or acute ST-segment elevation MI), in which the left main is deemed the culprit lesion (and distal coronary flow is less than Thrombolysis In Myocardial Infarction [TIMI] grade 3 in the case of an ST-segment elevation MI) and where the patient is not a candidate for CABG surgery or PCI can be performed more rapidly and safely.

Summary Findings and Recommendations

Current evidence (mostly hypothesis generating) suggests that 1- to 5-year mortality is similar following CABG surgery or PCI in patients with ULMD; although repeat revascularization rates are higher after PCI and stroke rates are higher after CABG surgery.

The currently underway Evaluation of Xience Prime vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) study[30] is a pivotal multicentered RCT (n = 2600), which randomizes patients with either ULMD or in association with additional coronary disease and SYNTAX scores of less than 33 to PCI (Xience DES) or CABG surgery. The primary end point is a composite of death, MI, or stroke with a mean follow-up of 2 years.

Our systematic results are consistent with current guidelines. We recommend that CABG surgery remain as the standard of care

Table 2. Quality of RCTs Using the JADAD Score

Source	Study Design	JADAD Score[a]
BARI Investigators,[12] 2007 (BARI)	Multicenter RCT of CABG surgery vs balloon angioplasty in patients with multivessel CAD	3
Booth et al,[13] 2008 (SOS)	Multicenter RCT of CABG surgery vs PCI (any commercially available stent) in patients with multivessel CAD	3
Buszman et al,[14] 2008 (LE MANS)	RCT of CABG surgery vs PCI of patients with >50% narrowing of left main with or without multivessel disease. Bare-metal stents were used for left main diameter of ≥3.8 mm and drug-eluting stents if <3.8 mm.	2
Serruys et al,[15] 2009 (SYNTAX - 1 year)	Multicenter RCT of CABG surgery vs PCI (TAXUS Express [paclitaxel-eluting stents]) in patients with 3-vessel or left main (alone or with 1-, 2-, or 3-vessel) disease	3
Morice et al,[9] 2010 (SYNTAX - 1 year, left main cohort)	Multicenter RCT of CABG surgery vs PCI (TAXUS Express [paclitaxel-eluting stents]) in patients with 3-vessel or left main (alone or with 1-, 2-, or 3-vessel) disease	3
Hueb et al,[16] 2010 (MASS II)	Single-center RCT of CABG surgery vs PCI (any catheter based therapeutic strategies including stents, lasers, directional atherectomy and balloon angioplasty) vs medical therapy of patients with multivessel CAD	2
Kapur et al,[17] 2010 (CARDIa)	Multicenter RCT of CABG surgery vs PCI (trial began with bare-metal stents followed by Cypher [sirolimus-eluting stents] when it became available) of patients with diabetes and multivessel CAD or complex single-vessel disease	3
Park et al,[18] 2011 (PRECOMBAT)	Multicenter RCT in Korea of CABG surgery vs PCI (Cypher [sirolimus-eluting stents]) in patients with >50% stenosis of left main artery	3
Boudriot et al,[19] 2011	Multicenter RCT of CABG surgery vs PCI (sirolimus-eluting stents) of patients with >50% narrowing of left main with or without multivessel CAD	3
Farkouh et al,[20] 2012 (FREEDOM)	Multicenter RCT of CABG surgery vs PCI (sirolimus-eluting stents and paclitaxel-eluting stents) of patients with diabetes and multivessel CAD	3
Kamalesh et al,[21] 2013 (Veterans Affairs study)	Multicenter RCT of CABG surgery vs PCI (operator's discretion of drug-eluting stents) of veterans with diabetes and multivessel CAD or proximal left anterior descending disease	3
Mohr et al,[22] 2013 (SYNTAX - 5 years)	Multicenter RCT of CABG surgery vs PCI (TAXUS Express [paclitaxel-eluting stents]) in patients with 3-vessel or left main (alone or with 1-, 2-, or 3-vessel) disease	3
Kappetein et al,[23] 2013 (SYNTAX - 5 years, diabetic cohort)	Multicenter RCT of CABG surgery vs PCI (TAXUS Express [paclitaxel-eluting stents]) in patients with 3-vessel or left main (alone or with 1-, 2-, or 3-vessel) disease	3

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; PCI, percutaneous coronary intervention; RCTs, randomized clinical trials.

[a] The JADAD scaling system is composed of 5 questions, with a score ranging from 0 (weakest) to 5 (strongest).[11]

Table 3. RCTs Comparing CABG Surgery With PCI in Patients With Significant ULMD

Source	Patient Profile	Follow-up Time, y	Groups	Mortality, No. (%)	*P* Value[a]	Repeat Revascularization, No. (%)	*P* Value[a]	MACCE, No. (%)	*P* Value[a]
Buszman et al,[14] 2008 (LE MANS)	>50% narrowing of unprotected left main, with or without multivessel CAD	1	CABG surgery (n = 53)	4 (7.5)	.37	5 (9.4)	.01	13 (24.5)[c]	.29
			DES/BMS (n = 52)[b]	1 (1.9)		15 (28.8)		16 (30.8)	
Park et al,[18] 2011 (PRECOMBAT)	>50% stenosis of left main; stable or unstable angina or NSTEMI or asymptomatic	2	CABG surgery (n = 300)	10 (3.4)	.45	12 (4.2)	.02	24 (8.1)	.12
			Sirolimus (n = 300)	7 (2.4)		26 (9.0)		36 (12.2)	
Boudriot et al,[19] 2011	≥50% of the unprotected left main, with or without multivessel CAD	1	CABG surgery (n = 101)	5 (5.0)	<.01	6 (5.9)	.35	14 (13.9)[d]	.19
			Sirolimus (n = 100)	2 (2.0)		14 (14.0)		19 (19.0)	
Morice et al,[9] 2010 (SYNTAX - 1 year, left main cohort)[e]	Left main >50% alone or with 1-, 2-, or 3-vessel disease	1	CABG surgery (n = 348)	(4.4)[f]	.88	(6.5)[f]	.02	46 (13.7)	.44
			Paclitaxel (n = 357)	(4.2)[f]		(11.8)[f]		56 (15.8)	
								CABG vs paclitaxel	
Mohr et al,[22] 2013 (SYNTAX - 5 years, left main cohort)[e]	Left main >50% alone or with 1-, 2-, or 3-vessel disease	5	CABG surgery (n = 345) vs paclitaxel (n = 356)	NR	NR	NR	NR	(31.0)[f] vs (36.9)[f] (O)	.12 (O)
								(31.5)[f] vs (30.4)[f] (L)	.74 (L)
								(32.3)[f] vs (32.7)[f] (I)	.88 (I)
								(29.7)[f] vs (46.5)[f] (H)	<.01 (H)

Abbreviations: BMS, bare-metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; H, high SYNTAX score; I, intermediate SYNTAX score; L, low SYNTAX score; MACCE, major adverse cardiac and cerebrovascular events (defined as all-cause mortality, myocardial infarction, stroke, or repeat revascularization); NR, not reported; NSTEMI, non–ST-segment elevation myocardial infarction; O, overall SYNTAX score; PCI, percutaneous coronary intervention; RCTs, randomized clinical trials; ULMD, unprotected left main disease (significant ULMD defined as left main artery luminal narrowing >50% without patent bypass grafts to its branches).

[a] *P* value testing for differences between CABG surgery and PCI.

[b] Bare-metal stents were used for left main diameter of more than 3.8 mm and DES for left main diameter of less than 3.8 mm.

[c] MACCE also included in-stent thrombosis; death in MACCE was cardiac related.

[d] Stroke not part of composite end point. Death is cardiac death.

[e] For SYNTAX studies, the primary end point of MACCE was reported by stratified SYNTAX score (overall; low, 0-22; intermediate, 23-32; and high, ≥33). The results from the left main cohort at 1 and 5 years are reported.

[f] Only percentage was reported.

for ULMD in all stable patients (class I, level B). When the patient is deemed high risk for surgery, PCI is an alternative particularly if ostial or trunk lesions in the left main exist (class IIa, level B). Percutaneous coronary intervention should be avoided in patients with advanced and diffuse CAD (ie, SYNTAX score ≥33 or double/triple vessel disease) (class III, level B). In addition, patients should receive care from a multidisciplinary team consisting of at least 1 noninvasive cardiologist, an interventional cardiologist, and a cardiac surgeon. Inclusion of physicians from different specialties is conducive to selection of the optimal choice of therapy for an individual patient that accounts for a patient's medical condition and preferences, expertise of the health care organization, and an application of the current evidence (class I, level C).[31]

Patients With Significant Multivessel CAD

Epidemiology

Significant multivessel CAD is defined as more than 70% stenosis in at least 2 major epicardial coronary arteries. According to the CASS registry, almost 50% of patients undergoing coronary angiography have significant 2- or 3-vessel disease.[32,33] Moreover, patients with multivessel CAD have poorer survival rates compared with counterparts with no or single-vessel disease.[33]

Results for CABG Surgery vs PCI

Bypass Angioplasty Revascularization Investigation (BARI)[12] was an early, 18-center, North American, randomized study comparing CABG surgery and balloon angioplasty in 1829 patients with multivessel CAD. At 10 years, overall survival was similar (73.5% for CABG surgery vs 71.0% for PCI, *P* = .18); however, angioplasty led to higher subsequent revascularization rates (20.3% for CABG surgery vs 76.8% for PCI, *P* < .001) (**Table 4**).[12,13,15,16,22]

The Medicine, Angioplasty, or Surgery Study (MASS II)[16] randomized 611 patients with ischemia and multivessel CAD to medical management, CABG surgery, or PCI. Compared with CABG surgery, the 10-year adjusted event-free survival (defined as all-cause mortality, MI, or repeat revascularization due to angina) was lower with medical management (hazard ratio [HR], 2.29; 95% CI, 1.69-3.10; *P* < .001) and PCI (HR, 1.46; 95% CI, 1.06-2.02; *P* = .02). The Stent or Surgery trial (SoS),[13] another large, 53-center RCT (n = 988), reported a survival advantage for patients with multivessel CAD undergoing CABG surgery compared with stenting at 6 years (HR, 1.66; 95% CI, 1.08-2.55; *P* = .02).

The previously mentioned SYNTAX trial[15] enrolled patients with ULMD, 3-vessel disease, or both, with the majority of the patients enrolled (61%) having 3-vessel disease. Although the primary end point of 1-year MACCE in the entire 1800-patient study did not meet noninferiority, the composite safety end point (all-cause mortality or MI or stroke), and the individual end points of all-cause mortality

Table 4. RCTs Comparing CABG Surgery With PCI in Patients With Significant Multivessel CAD

Source	Patient Profile	Time, y	Groups	Mortality, No. (%)	*P* Value[a]	Repeat Revascularization, No. (%)	*P* Value[a]	MACCE, No. (%)	*P* Value[a]
BARI Investigators,[12] 2007 (BARI)	Symptomatic/ischemic multivessel CAD	10	CABG surgery (n = 914)	(26.5)[b]	.18	(20.3)[b]	<.01	NR	NR
			Balloon (n = 915)	(29.0)[b]		(76.8)[b]			
Booth et al,[13] 2008 (SoS)	Multivessel CAD	6	CABG surgery (n = 500)	34 (6.8)	.02	NR	NR	NR	NR
			PCI (n = 488)[c]	53 (10.9)					
Hueb et al,[16] 2010 (MASS II)	Proximal multivessel CAD >70% stenosis	10	CABG surgery (n = 203)	51 (25.1)	.09[e]	15 (7.4)[f]	<.01	(33.0)[b,g]	<.01
			PCI (n = 205)[d]	49 (23.9)		85 (41.5)		(42.4)[b]	
			Medical (n = 203)	63 (31.0)		80 (39.4)		(59.1)[b]	
								CABG vs paclitaxel	
Serruys et al,[15] 2009 (SYNTAX - 1 year)[h]	Main study results (3-vessel or left main [alone or with 1-, 2-, or 3-vessel] disease)	1	CABG surgery (n = 897) vs paclitaxel (n = 903)	30 (3.5) vs 39 (4.4)	.37	50 (5.9) vs 120 (13.5)	<.01	105 (12.4) vs 159 (17.8) (O)	<.01 (O)
								(14.7)[b] vs (13.6)[b] (L)	.71 (L)
								(12.0)[b] vs (16.7)[b] (I)	.10 (I)
								(10.9)[b] vs (23.4)[b] (H)	<.01 (H)
Mohr et al,[22] 2013 (SYNTAX - 5 years)[h]	Main study results (3-vessel or left main [alone or with 1-, 2-, or 3-vessel] disease)	5	CABG surgery (n = 897) vs paclitaxel (n = 903)	(11.4)[b]	.10	(13.7)[b]	<.01	(26.9)[b] vs (37.3)[b] (O)	<.01 (O)
								74/275 (28.6) vs 94 /299 (32.1) (L)	.43 (L)
				(13.9)[b]		(25.9)[b]		72/300 (25.8) vs 110 /310 (36.0) (I)	<.01 (I)
								80/315 (26.8) vs 126 /290 (44.0) (H)	<.01 (H)
Mohr et al,[22] 2013 (SYNTAX - 5 years)[h]	3-Vessel cohort	5	CABG surgery (n = 545) vs paclitaxel (n = 543)	NR	NR	NR	<.01	(24.2)[b] vs (37.5)[b] (O)	<.01 (O)
								(26.8)[b] vs (33.3)[b] (L)	.21 (L)
								(22.6)[b] vs (37.9)[b] (I)	<.01 (I)
								(24.1)[b] vs (41.9)[b] (H)	<.01 (H)

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease (significant multivessel CAD defined as >70% stenosis in ≥2 major epicardial coronary arteries); DES, drug-eluting stent; H, high SYNTAX score; I, intermediate SYNTAX score; L, low SYNTAX score; MACCE, major adverse cardiac and cerebrovascular events (defined as all-cause mortality, myocardial infarction, stroke, or repeat revascularization); NR, not reported; O, overall SYNTAX score; PCI, percutaenous coronary intervention; RCTs, randomized clinical trials.

[a] *P* value testing for differences between CABG surgery and PCI, unless otherwise specified.

[b] Only percentage was reported.

[c] Choice of any commercially available stents permitted.

[d] Strategies included stents, lasers, directional atherectomy, and balloon angioplasty.

[e] *P* value testing for difference between medical management, PCI, and CABG surgery.

[f] Represent additional revascularization since last follow-up at 5 years.

[g] Does not include stroke.

[h] For SYNTAX, the primary end point of MACCE was reported by stratified SYNTAX score (overall; low, 0-22; intermediate, 23-32; and high, ≥33). The main SYNTAX study results are reported herein for 1 and 5 years along with the 3-vessel cohort results at 5 years.

and MI were similar. Repeat revascularization was lower with CABG surgery (5.9% for CABG surgery vs 13.5% for PCI, *P* < .001), and stroke was higher (2.2% for CABG surgery vs 0.6% for PCI, *P* = .003). Similar results were reported for the 3-vessel subgroup (n = 1095) with respect to MACCE (11.5% for CABG surgery vs 19.2% for PCI, *P* < .001) and repeat revascularization (5.5%for CABG surgery vs 14.6% for PCI, *P* < .001) at 1 year.

In the recently reported 5-year outcomes of the entire study,[22] patients undergoing CABG surgery experienced fewer MACCE (26.9% for CABG surgery vs 37.3% for PCI, *P* < .001) and the safety end point of all-cause mortality or stroke or MI (16.7% for CABG surgery vs 20.8% for PCI, *P* = .03). Although all-cause mortality was similar (11.4% for CABG surgery vs 13.9% for PCI, *P* = .10), cardiac death was significantly lower following CABG surgery (5.3% for CABG surgery vs 9.0% for PCI, *P* = .003), as was MI (3.8% for CABG surgery vs 9.7% for PCI, *P* < .001) and repeat revascularization (13.7% for CABG surgery vs 25.9% for PCI, *P* < .001). There was no difference in the cumulative incidence of stroke at 5 years.

In the subset of patients with isolated 3-vessel disease, the incidence of 5-year MACCE was higher in the PCI group (24.2% for CABG surgery vs 37.5% for PCI, *P* < .001). There were no differences in the incidence of 5-year MACCE for the low SYNTAX scores (≤22); however, PCI was inferior for intermediate scores (22.6% for CABG surgery vs 37.9% for PCI, *P* < .001) and high scores (24.1% for CABG surgery vs 41.9% for PCI, *P* < .001).[22]

In addition, a 2012 meta-analysis[34] (n = 15 193) of CABG surgery vs PCI in 3-vessel disease including SYNTAX results at 3 years reported higher all-cause mortality in PCI compared with CABG surgery (HR, 1.38; 95% CI, 1.20-1.59; *P* < .001).

Current Guidelines

Current European guidelines recommend CABG surgery (class I, level A) for 3-vessel disease (simple or complex) or 2-vessel disease involving the proximal left anterior descending. Moreover, there is conflicting but evidence in favor of PCI (class IIa, level B) for 2-vessel disease involving the proximal left anterior descending and 3-vessel disease if the SYNTAX score is 22 or less and harmful/no benefit for 3-vessel disease with SYTNAX score of more than 22 (class III, level A). In these circumstances, the US guidelines are similar, although weaker for PCI (class IIb, level B). In patients with 2-vessel disease not involving the proximal left anterior descending, the European guidelines suggest PCI as an option (class I, level C) and less favorable for CABG surgery (class IIb, level C); whereas the US guidelines state CABG surgery would be reasonable in the presence of extensive ischemia (class IIa, level B) and PCI is of uncertain benefit (class IIb, level B).[28,29]

Summary Findings and Recommendations

The current studies indicate that although the number of diseased vessels is important, anatomical complexity may be more important in determining optimal treatment for patients with multivessel CAD, with PCI being reasonable for lower SYNTAX scores and CABG surgery for higher scores. We recommend the following for patients with stable multivessel CAD: (1) A heart-team approach, which should weigh the SYNTAX score along with patient comorbidities to decide between PCI and CABG surgery (class I, level C); (2) For 3-vessel disease and a SYNTAX score of more than 22, CABG surgery should be the preferred modality of treatment (class I, level A); (3) For 3-vessel disease and a SYNTAX score of 22 or less, PCI with DES can be offered with equivalent outcomes (class IIa, level B); and (4) For 2-vessel disease involving the proximal left anterior descending, both PCI and CABG surgery are reasonable options. Where the proximal left anterior descending lesion is uncomplicated, PCI can be recommended; but for more complex lesions, CABG surgery should be considered (class IIa, level A). For SYNTAX scores of more than 22, CABG surgery provides better long-term outcomes than PCI, barring excessive preoperative risk factors.

Patients With Diabetes Mellitus and Significant Multivessel CAD

Epidemiology

A total of 220 million people worldwide currently have diabetes mellitus, with an expected increase to 360 million by 2030.[35] Patients with diabetes are 2 to 4 times more likely to develop coronary disease and myocardial ischemia often diffuse with multivessel CAD.[36]

Results for CABG Surgery vs PCI

Most RCTs comparing CABG surgery to PCI studied the effect of diabetes as an a priori subgroup analysis. The Coronary Artery Revascularization in Diabetes (CARDia) study[17] was the first RCT with patients with only diabetes (n = 510; 24 centers) with multivessel CAD or complex single-vessel disease randomized to PCI or CABG surgery. At 1 year, the composite of all-cause mortality, nonfatal MI, or stroke was nonsignificantly lower in CABG surgery. When repeat revascularization was included (ie, MACCE), the difference was significant (11.3% for CABG surgery vs 19.3% for PCI, $P = .016$). Although the study was underpowered, it did not show that PCI was noninferior to CABG surgery in this diabetic cohort (**Table 5**).[12,17,20,21,23]

The previously mentioned BARI study[12] showed that 10-year survival of the treated diabetic cohort (n = 353) was better with CABG surgery (57.8% for CABG surgery vs 45.5% for PCI, $P = .025$). The 5-year SYNTAX trial results of the diabetic subgroup (n = 452)[23] showed that the composite end point of MACCE was significantly lower in CABG surgery compared with PCI (29.0% vs 46.5%, respectively; $P < .001$). These findings were qualitatively similar across the terciles of anatomical complexity and were driven largely by repeat revascularization (14.6% for CABG surgery vs 35.3% for PCI, $P < .001$). Five-year all-cause mortality was 12.9% in the CABG surgery group and 19.5% in the PCI group ($P = .065$).

The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial,[20] published in 2012, is the largest multicenter RCT (n = 1900; mean age, 63 years; 29% female, with majority with 3-vessel disease) to investigate whether contemporary practice of CABG surgery or DES is preferred in patients with diabetes and multivessel CAD. The 5-year composite end point of all-cause mortality, MI, or stroke was lower in the CABG surgery group (18.7% for CABG surgery vs 26.6% for PCI, $P = .005$). This was also true for MACCE at 1 year (11.8% for CABG surgery vs 16.8% for PCI, $P = .004$). These findings for the primary end point and MACCE were present independent of the SYNTAX score. Individual outcomes including 5-year mortality (10.9% vs 16.3%, $P = .049$) and nonfatal MI (6.0% vs 13.9%, $P < .001$) favored CABG surgery in the patients with diabetes. Nonfatal stroke was lower in the PCI group (5.2% vs 2.4%, $P = .03$).

An RCT published in 2013 of patients with diabetes and severe coronary disease randomized to either CABG surgery (n = 97) or DES (n = 101) showed that all-cause mortality at 2 years was 5% in the CABG surgery group vs 21% in the PCI group, despite being severely underpowered due to slow recruitment.[21]

In addition, a 2012 meta-analysis of patients with diabetes and multivessel CAD[37] analyzed 9 RCTs comparing PCI (n = 1047) with CABG surgery (n = 1054) revealed a higher frequency of 1-year MACCE (risk difference [RD], 12%; $P < .001$) and 5-year mortality (RD, 7%; $P < .001$) after PCI compared with CABG surgery; however, frequency of stroke was higher in the CABG surgery group (RD, −2%; $P = .004$).

Current Guidelines

The 2011 American College of Cardiology Foundations/American Heart Association and European 2010 guidelines recognize the importance of diabetes status when deciding on revascularization strategy. The US guidelines state that it is reasonable to choose CABG surgery using the left internal mammary artery over PCI in patients with diabetes and multivessel CAD (class IIa, level B); whereas the European guidelines state that CABG surgery should be considered in patients with diabetes and stable multivessel CAD when the extent of the disease justifies a surgical approach, especially in patients with multivessel CAD with an acceptable risk profile (class IIa, level B). Furthermore, when stents are used, they recommend using DES to reduce restenosis (class I, level A).[28,29]

Table 5. RCTs Comparing CABG Surgery With PCI in Patients With Diabetes and Significant Multivessel CAD

Source	Patient Profile	Time, y	Groups[a]	Mortality, No. (%)	*P* Value	Repeat Revascularization, No. (%)	*P* Value	MACCE, No. (%)	*P* Value
BARI Investigators,[12] 2007 (BARI)	Symptomatic/ischemic multivessel CAD (diabetic cohort)	10	CABG surgery (n = 180)[b]	(42.2)[c]	.03	(18.3)[c]	NR	NR	NR
			Balloon (n = 173)[b]	(54.5)[c]		(79.7)[c]			
Kapur et al,[17] 2010 (CARDIa)	Diabetes and either multivessel CAD or complex single-vessel disease	1	CABG surgery (n = 248)	8 (3.2)	.97	5 (2.0)	<.01	28 (11.3)	.02
			BMS/sirolimus (n = 254)[d]	8 (3.2)		30 (11.8)		49 (19.3)	
Farkouh et al,[20] 2012 (FREEDOM)	Diabetes and multivessel CAD	5	CABG surgery (n = 947)	83 (10.9)	.05	42 (4.8)	<.01[e]	106 (11.8)	<.01[e]
			Paclitaxel or sirolimus (n = 953)	114 (16.3)		117 (12.6)		157 (16.8)	
Kappetein et al,[23] 2013 (SYNTAX)	Diabetes with left main and/or 3-vessel disease	5	CABG (n = 221)	26 (12.9)	.07	28 (14.6)	<.01	59 (29.0)	<.01
			Paclitaxel (n = 231)	44 (19.5)		75 (35.3)		105 (46.5)	
Kamalesh et al,[21] 2013 (Veterans Affairs study)	Diabetes and multivessel CAD or isolated proximal left anterior descending disease	2	CABG (n = 97)	(5)[c]	NR	(19.5)[c]	NR	NR	NR
			DES (n = 101)[f]	(21)[c]		(18.9)[c]			

Abbreviations: BMS, bare-metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease (significant multivessel CAD defined as >70% stenosis in ≥2 major epicardial coronary arteries); DES, drug-eluting stent; MACCE, major adverse cardiac and cerebrovascular events (defined as all-cause mortality, myocardial infarction, stroke, or repeat revascularization); NR, not reported; PCI, percutaneous coronary intervention; RCTs, randomized clinical trials.

[a] Comparison pertaining to the diabetic cohort reported.

[b] Subset of patients with treated diabetes.

[c] Only percentage was reported.

[d] Initially started with BMS and switched to sirolimus-eluting stents when they became available.

[e] These outcomes are defined at 1 year in the FREEDOM trial.

[f] Choice of any US Food and Drug Administration–approved DES.

Summary Findings and Recommendations

Based on the major trials, in particular the FREEDOM study,[20] and in conjunction with the overall 5-year SYNTAX results, we agree that CABG surgery should be recommended in patients with diabetes and multivessel CAD, because it has been shown to have better survival and lower major adverse cardiac events. Based on the strong current evidence, we further recommend that both guidelines be urgently updated to a class I, level A indication.

Patients With CAD and LVD

Epidemiology

Heart failure and LVD are associated with poor quality of life and a 5-year mortality of 40% to 50%.[38-40] Coronary artery disease is the most common cause of LVD and the cause of heart failure in almost two-thirds of patients.[41] Revascularization, in such patients, has generally been predicated on the results of viability testing that discriminates viable but dysfunctional or "hibernating" myocardium from left ventricular scar.[42,43]

Results for CABG Surgery vs PCI

There are limited data directly comparing CABG surgery and PCI in patients with LVD, because this is often an exclusion criterion. A 2012 meta-analysis[44] identified 19 studies involving patients with LVD who were treated with PCI (n = 4766; mean left ventricular ejection fraction [LVEF], 30%). In-hospital and 24-month cumulative mortality were 1.8% and 15.6%, respectively. Five studies compared PCI and CABG surgery showed late survival was similar in both cohorts (relative risk, 0.98; 95% CI, 0.8-1.2; *P* = .83). Separately, the same group summarized the surgical results (26 studies; n = 4119; mean LVEF, 25%) reporting operative mortality and cumulative 5-year mortality of 5.4% and 26.6%, respectively.[45] A caveat is that the reviewed studies may not accurately reflect contemporary peri-operative outcomes as predicted by well-validated risk calculators.[46]

More recently, the Surgical Treatment for Ischemic Heart Failure (STICH) trial[40] raised doubts regarding the benefit of surgical revascularization in LVD. Patients with coronary disease were randomized to medical therapy with or without CABG surgery (n = 1212; LVEF≤35%). At 5 years, all-cause mortality was similar in both groups (36% for CABG surgery vs 41% for medical therapy, *P* = .12); however, cardiac death was lower with CABG surgery (28% vs 33%, *P* = .05). The composite end point of all-cause mortality or hospitalization was also lower for CABG surgery (65% for CABG surgery vs 73% for medical therapy; HR, 0.81; 95% CI, 0.71-0.93; *P* = .003).

Current Guidelines

The current American Heart Association guidelines state that revascularization in patients with CAD and LVD is based on numerous clinical variables, including coronary anatomy, other comorbidities, severity of LVD, patient preference, and a multidisciplinary team approach. Specifically, CABG surgery is reasonable (class IIa, level B) in patients with moderate LVD (LVEF, 35%-50%) and may be considered (class IIb, level B) for patients with severe LVD (LVEF<35%) without significant left main disease. There is insufficient data to make a recommendation regarding the role of PCI in patients with LVD. The European guidelines state for patients having LVEF of 35% or less with anginal or heart failure symptoms, CABG surgery is beneficial in the presence of left main or multivessel CAD (class I, level B). There is conflicting and less well-established evidence for PCI, if anatomy is suitable (class IIb, level C).[28,29]

Summary Findings and Recommendations

There is a lack of strong evidence regarding revascularization treatment options in patients with moderate to severe LVD secondary to coronary ischemia. We recommend the following for patients with CAD and LVD: (1) Given the lack of strong evidence of superiority for PCI or CABG surgery, especially for long-term outcomes, we recommend a heart-team approach including heart failure specialists, interventional cardiologists, and cardiac surgeons (class I, level C); (2) For less severe coronary anatomy (SYNTAX score <22) and patients with high surgical risk, PCI may be considered (class IIb, level C). For patients with moderate to severe coronary anatomy and disease, surgery should be recommended (class I, level B); (3) Candidacy and likelihood of ventricular assist backup should be considered (class I, level C); and (4) More studies are required in this area.

Limitations

These recommendations must be interpreted in the context of a number of limitations that merit discussion. First, the subgroup results from the SYNTAX trial are hypothesis generating, as acknowledged by the investigators, given that the primary hypothesis for noninferiority was not met. Second, our systematic search was limited to between January 2007 and June 2013. Although this may have excluded early seminal studies in coronary surgery and PCI, we thought the chosen period would best reflect contemporary practice. Third, the paucity of high-quality evidence comparing PCI to CABG surgery for patients with LVD was limited; this section was largely based on meta-analyses involving observational studies. In addition, the majority of the studies reported results using first- or second-generation DES platforms. Stent technology is rapidly evolving and is currently in its third generation. With ongoing advances, such as the emergence of bioabsorbable stent platforms, newer, less inflammatory polymer coatings, and indeed stents that do not require polymer coating at all, these recommendations will need to be revisited.

Conclusions

Both CABG surgery and PCI are reasonable options for patients with advanced CAD. Current evidence dictates that despite advances in stent technology, patients with diabetes are better served with CABG surgery than PCI. In cases of left main disease, multivessel CAD, or patients with LVD, CABG surgery should be favored in patients with complex coronary lesions and anatomy and PCI in less complicated coronary disease or deemed a high surgical risk. The severity of coronary disease should be quantified using methods like the SYNTAX score and a surgical risk with Society of Thoracic Surgery risk score or Euroscore. A heart-team approach should evaluate coronary disease complexity, patient comorbidities, patient preferences, and local expertise. As technology and innovation continue to emerge, ongoing and future trials will further refine these decisions. Revascularization modalities continue to advance; in particular, given the rapid ongoing evolution of stent technology, it is important to update these revascularization recommendations as contemporary studies are completed.

ARTICLE INFORMATION

Author Contributions: Drs Deb and Fremes had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Deb, Wiljesundera, Ko, Fremes.

Acquisition of data: Deb, Tsubota, Hill.

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Drafting of the manuscript: Deb, Fremes.

Critical revision of the manuscript for important intellectual content: Deb, Wiljesundera, Ko, Tsubota, Hill, Fremes.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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