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Isolated Disease of the Proximal Left Anterior Descending Artery

Comparing the Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Surgery

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Objectives This study sought to systematically compare the effectiveness of percutaneous coronary intervention and coronary artery bypass surgery in patients with single-vessel disease of the proximal left anterior descending (LAD) coronary artery.

Background It is uncertain whether percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) surgery provides better clinical outcomes among patients with single-vessel disease of the proximal LAD.

Methods We searched relevant databases (MEDLINE, EMBASE, and Cochrane from 1966 to 2006) to identify randomized controlled trials that compared outcomes for patients with single-vessel proximal LAD assigned to either PCI or CABG.

Results We identified 9 randomized controlled trials that enrolled a total of 1,210 patients (633 received PCI and 577 received CABG). There were no differences in survival at 30 days, 1 year, or 5 years, nor were there differences in the rates of procedural strokes or myocardial infarctions, whereas the rate of repeat revascularization was significantly less after CABG than after PCI (at 1 year: 7.3% vs. 19.5%; at 5 years: 7.3% vs. 33.5%). Angina relief was significantly greater after CABG than after PCI (at 1 year: 95.5% vs. 84.6%; at 5 years: 84.2% vs. 75.6%). Patients undergoing CABG spent 3.2 more days in the hospital than those receiving PCI (95% confidence interval: 2.3 to 4.1 days, $p < 0.0001$), required more transfusions, and were more likely to have arrhythmias immediately post-procedure.

Conclusions In patients with single-vessel, proximal LAD disease, survival was similar in CABG-assigned and PCI-assigned patients; CABG was significantly more effective in relieving angina and led to fewer repeat revascularizations. (J Am Coll Cardiol Intv 2008;1:483–91) © 2008 by the American College of Cardiology Foundation

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Percutaneous coronary interventions (PCI) (with or without stents) and coronary artery bypass graft (CABG) surgery are the alternative approaches to revascularization for patients with isolated stenosis of the proximal left anterior descending (LAD) (1,2). Some studies have reported fewer repeat revascularization procedures and more freedom from angina among patients with isolated LAD stenosis who have received CABG rather than PCI (3,4). However, procedural morbidity such as stroke is reported to be higher among CABG recipients (5). Some investigators argue that advances in CABG procedures, such as the use of minimally invasive direct coronary artery bypass (MIDCAB) (which was developed initially to treat proximal LAD stenosis), may decrease procedural morbidity with similar graft patency rates compared with traditional CABG (6). However, others suggest that the technical challenge of MIDCAB may lead to poor or improper anastomosis, acute graft failure, and need for full sternotomy (5,7). In light of these conflicting views, there is no clear consensus as to the best coronary revascularization procedure for patients with single-vessel proximal LAD lesions.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CI = confidence interval

LAD = left anterior descending

MIDCAB = minimally invasive direct coronary artery bypass

PCI = percutaneous coronary interventions

RCT = randomized controlled trial

See page 492

Prior systematic reviews of trials comparing CABG and PCI have not specifically reported outcomes for patients with single-vessel disease of the proximal LAD (8–13). Additionally, since the publication of these reviews, new trial data from patients with proximal LAD disease have become available (5,14–19). We therefore reviewed current data on outcomes after random assignment to PCI or CABG among patients with single-vessel disease of the proximal LAD.

Methods

Search strategy. We identified randomized controlled trials (RCTs) that compared outcomes for patients with single-vessel proximal LAD disease assigned to either PCI or CABG. We performed individualized searches of relevant databases (MEDLINE, EMBASE, and Cochrane from 1966 to 2006) with terms such as *angioplasty*, *coronary*, and *coronary artery bypass surgery* (complete search strategies are available elsewhere [12]). We also manually searched reference lists of included articles and the bibliographies of expert advisors. We did not limit searches to the English language.

Study selection. We searched for RCTs that compared PCI and CABG in patients with angiographically proven single-vessel disease of the proximal LAD. Trials were included without limitation to subject population, year, or type of surgical or percutaneous intervention. We excluded RCTs comparing only 2 or more PCI technologies or 2 or more CABG technologies. The trials included a variety of PCI technologies (i.e., balloon angioplasty, with or without stents) and a variety of surgical procedures (i.e., traditional on-pump and off-pump bypass procedures, and minimally invasive procedures).

Data extraction. We abstracted the following data from the included trials: study design; setting; population characteristics; detailed information about the PCI and CABG interventions performed; numbers of patients screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. The outcomes of interest included both procedural outcomes (e.g., procedural stroke, length of stay) and long-term outcomes (e.g., survival, angina relief, repeat revascularization, quality of life). Two authors independently reviewed the title, abstract, and full text of each included study. We resolved abstraction conflicts by re-review and discussion.

Quality assessment of individual studies. We used predefined criteria to assess the quality of included trials as good, fair, or poor (20–22). These quality criteria included the method of randomization, the use of intention-to-treat analysis, the report of dropout rates, and the extent to which valid outcomes were described.

Data synthesis. We computed summary risk differences and summary odds ratios for each outcome of interest using random effects models. Because the results were consistent between these methods, we present summary risk differences because several of the outcomes of interest (e.g., procedural mortality) were rare events and the risk difference is a more stable outcome metric than odds ratios under these circumstances (23,24).

We assessed heterogeneity for summary effects by calculating the chi-square and I^2 statistics (25) and considered I^2 statistics in excess of 50% to indicate heterogeneity. We sought evidence of publication bias by evaluating the association between the sample size of a study and the likelihood of that study reporting statistically significant outcomes by visual inspection of funnel plots. We also performed sensitivity analyses by evaluating the effects of individual studies on reported summary effects by removing each study individually.

Results

Our searches for RCTs comparing the efficacy of PCI and CABG yielded 1,695 potentially relevant articles, of which 204 articles merited full-text review. A total of 17 articles reporting on 9 RCTs met our inclusion criteria (Fig. 1).

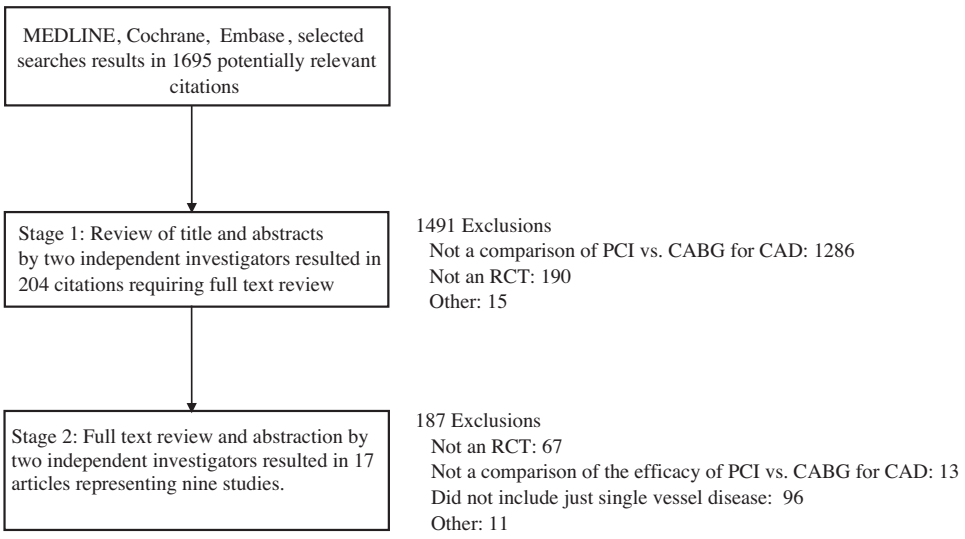

Figure 1. Search Results

The number of citations retrieved from the literature searches and the rationale for inclusion and exclusion for each citation. CABG = coronary artery bypass graft; CAD = coronary artery disease; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

Description of the RCTs. The 9 RCTs of patients with single-vessel disease of the proximal LAD artery enrolled 1,210 patients (633 received PCI and 577 received CABG) (Table 1). Seven of the 9 trials were single-center studies, and most were conducted in Europe. The early studies (patient entry 1987 to 1993) used balloon angioplasty as the PCI technique (1,3,4,26), and the recent studies (1994 to 2002) used stents as the PCI technique (5,14–19,27–32). The early studies used traditional CABG, whereas the more recent studies used MIDCAB and off-pump techniques (5,15–18). Although there were some differences in the inclusion criteria of the RCTs, all 9 trials limited entry to patients with single-vessel disease of the proximal LAD.

The mean age of trial participants ranged from 53 to 63 years. Roughly 20% had diabetes, and more than half had hypertension and/or hyperlipidemia (Table 2). The proportion of women included in the trials ranged from 17% to 36%. The prevalence of heart failure was low, and left ventricular function was generally well preserved.

Quality of the randomized controlled trials. The quality of most trials was high, and 7 trials received a grade of good because they clearly explained their randomization methods, their dropout rates were low, and they performed intention-to-treat analyses. Because it was not clear that there was concealment of allocation or intention-to-treat and some data were obtained via a retrospective review of charts, the Seoul-Kim (18) trial received a fair grade. We assigned a grade of poor to the Seoul-Hong (17) trial because, in addition to the fact that it was a small trial with very short follow-up (6 months), it may not have been truly randomized, as evidenced by the imbalance between the number of patients assigned to PCI (119) and to CABG (70). Neither the investigators nor the journal editor responded to requests for clarification of the method of randomization. We performed sensitivity analyses by removing the Seoul-Hong trial from our main outcome analysis, without any substantial change in our results. The Seoul-Hong trial is the only included trial that compared PCI using drug-eluting stents (17).

Short-term/procedural outcomes. SURVIVAL. We defined short-term/procedural complications as those occurring within the first 30 days of the revascularization procedure. Procedural survival was above 99% for both procedures (Table 3). When data from all trials were combined, the absolute difference in procedural survival did not differ significantly between procedures (risk difference: 0.3%, 95% confidence interval [CI]: −0.9% to +1.4%) (Fig. 2). We performed separate analyses for the patients who received MIDCAB and those that received traditional CABG, and found no differences in procedural survival between PCI and CABG—regardless of the specific surgical technique performed. Similarly, we found no difference in comparative procedural survival between MIDCAB or off-pump trials compared with PCI at 1 month. There was no substantial evidence for statistical heterogeneity or publication bias.

OTHER OUTCOMES. Procedural strokes were also relatively rare: about 0.5% for both procedures. There was no difference in the absolute rate of procedural stroke (reported by 6 trials) between PCI and CABG (absolute risk difference: 0.2%, 95% CI: −1.2% to +1.6%).

In all 5 studies that reported length of stay (Table 4), patients undergoing CABG consistently spent more time in the hospital (range: 4.5 to 10.1 days) than those receiving

Table 1. General Description of the Randomized Controlled Trials

Trial (Associated References)	Region(s)	Number of Sites	Years of Enrollment	Number of Subjects Randomized/ Receiving Assigned Therapy		PCI Intervention	Surgical Intervention
				PCI	Surgery		
AMIST (14)	UK	6	1999–2001	50/48	50/46	Stents available, not required	LIMA to LAD
Groningen (15,27–29)	Holland	1	1997–1999	51/51	51/48	BMS	LIMA using small left anterior thoracotomy, beating heart with mechanical stabilizer
Lausanne (3,4)	Europe	1	1989–1993	68/68	66/59	Balloon angioplasty	Median sternotomy, LIMA, hypothermia
Leipzig (5,30,31)	Europe	1	1997–2001	110/110	110/110	BMS	MIDCAB: limited left anterolateral thoracotomy, LIMA with mechanical stabilizers, beating heart
MASS (1,26)	South America	1	1988–1991	72/NS	70/NS	Balloon angioplasty	LIMA, mild hypothermia, extracorporeal circulation
Poland (16,32)	Europe	1	2000–2001	50/50	50/50	BMS	MIDCAB: LIMA under mechanical stabilization on beating heart through anterior thoracotomy
Seoul-Hong (17)	Asia	1	2003	119/NS	70/NS	DES	Off-pump LIMA with mechanical stabilization on beating heart, anterolateral thoracotomy
Seoul-Kim (18)	Asia	1	2000–2001	50/49	50/49	BMS	MIDCAB: LIMA with mechanical stabilization on beating heart through mini-sternotomy
SIMA (19)	Europe	6	1994–1998	63/62	60/54	BMS	MIDCAB, cardioplegia and hypothermia

BMS = bare-metal stent; CABG = coronary artery bypass graft; DES = drug-eluting stent; LAD = left anterior descending artery; LIMA = left internal mammary artery; MIDCAB = minimally invasive direct coronary artery bypass; NS = not specified; PCI = percutaneous coronary intervention.

PCI (range: 2.3 to 6.1 days) (absolute difference = 3.2 days, 95% CI: 2.3 to 4.1 days, $p < 0.0001$).

The summary rate of procedural myocardial infarction was reported by all studies and did not differ significantly between PCI and CABG: absolute risk difference = −0.8%; 95% CI: −2.6% to +0.9%. It is important to note that the definition of myocardial infarction varied among studies, and post-procedure serial monitoring of electrocardiograms and serum biomarker levels was not routine, so that ascertainment of procedural myocardial infarctions may not have been uniform or complete.

The AMIST (Angioplasty versus Minimally Invasive Surgery Trial) (14) and SIMA (Stenting versus Internal Mammary Artery) (19) trials reported differences in rates of procedural arrhythmias, and both found an increased risk of events with CABG than with PCI. None of the patients in the PCI arms of either trial experienced any arrhythmias, whereas 19% of CABG recipients experienced atrial fibrillation and approximately 2% had a ventricular arrhythmia.

In the 3 studies that reported procedural bleeding, more CABG-assigned patients required transfusions than did PCI-assigned patients (Table 5); however, the total number of patients requiring transfusion was small, and the difference in procedural bleeding was not significant.

Long-term outcomes. SURVIVAL. Overall survival among CABG-assigned patients was 97.9% at 1 year and 92.8% at 5 years. Overall survival among PCI-assigned patients was 99.7% at 1 year and 90.6% at 5 years. The combined data from all trials showed no statistically significant difference in overall survival in either the first or fifth year post-procedure for PCI and CABG. There was no substantial evidence for statistical heterogeneity or publication bias.

Survival did not differ between PCI and CABG for either balloon angioplasty or stents. At 1 year, survival in studies using balloon angioplasty was 1% greater for CABG recipients (95% CI: −5% to +2%), but the difference was not statistically significant. In trials that used stents, the risk difference (0.1% favoring PCI) also was not statistically significant (95% CI: −4% to +4%).

In addition to reporting overall mortality, 3 studies reported cardiovascular mortality at 5 years (the MASS [Medicine, Angioplasty or Surgery Study] [1], Leipzig [5],

Table 2. Subject Baseline Demographics and Clinical Characteristics

Trial	Intervention	Age (Mean)	Women, %	Diabetes, %	HTN, %	Hyperlipidemia, %	Unstable Angina, %	LVEF (Mean)
AMIST (14)	PCI	Median 54.5	14	NR	NR	NR	18	NR
	CABG	Median 58.8	30	NR	NR	NR	20	NR
Groningen (15)	PCI	61.0	25	18	NR	45	NR	NR
	CABG	60.0	22	8	NR	41	NR	NR
Lausanne (3)	PCI	57.0	20	12	46	50	12	NR
	CABG	54.0	20	12	41	52	8	NR
Leipzig (5)	PCI	62.5	28	34	72	70	NR	63
	CABG	61.6	23	25	71	73	NR	63
MASS-I (1)	PCI	54.0	19	15	34	NR	NR	77
	CABG	58.0	17	18	30	NR	NR	74
Poland (16)	PCI	53.3	16	8	52	78	10	NR
	CABG	54.1	18	6	56	76	8	NR
Seoul-Hong (17)	PCI	60.5	36	37	50	55	50	53
	CABG	61.4	36	49	56	51	43	52
Seoul-Kim (18)	PCI	61	40	20	55	60	65	51
	CABG	63	30	15	55	70	55	49
SIMA (19)	PCI	59.0	24	11	44	60	48	67
	CABG	60.0	17	13	47	53	48	67

HTN = hypertension; LVEF = left ventricular ejection fraction; NR = not reported; other abbreviations as in Table 1.

Lausanne [3]), but none reported significant differences between the procedures.

OTHER OUTCOMES. Angina relief was significantly greater 1 year after CABG (absolute rate: 95.5%) than 1 year after PCI (absolute rate: 84.6%) in the 4 trials that reported this outcome (risk difference = 7.9%, 95% CI: 1.9% to 14.0%, p = 0.01). Similarly, angina relief remained significantly greater 5 years after CABG (absolute rate: 84.2%) than 5

Table 3. Procedural Outcomes

				Other Short-Term Complications*		
Trial	Intervention	Procedural All-Cause Mortality, %*	Procedural Nonfatal MI, %*	Stroke, %	PCI Reintervention, %	Surgical Reintervention, %
AMIST (14)	PCI	0	0	NR	NR	NR
	CABG	0	0	NR	NR	2.0
Groningen (15)	PCI	0	9.8	2.0	NR	0.0
	CABG	3.9	2.0	0.0	NR	2.0
Lausanne (3)	PCI	0	2.9	NR	NR	NR
	CABG	0	1.5	NR	NR	NR
Leipzig (5)	PCI	0	1.8	0.0	1.8	NR
	CABG	1.8	3.6	0.9	NR	2.7
MASS-I (1)	PCI	0	2.8	0.0	NR	NR
	CABG	0	1.4	0.0	NR	NR
Poland (16)	PCI	0	2.0	NR	6.0	NR
	CABG	0	0	NR	0.0	NR
Seoul-Hong (17)	PCI	1.7	3.3	0.0	1.7	NR
	CABG	1.4	2.9	1.4	1.4	NR
Seoul-Kim (18)	PCI	0	4	NR	2.0	2.0
	CABG	0	2	NR	2.0	0.0
SIMA (19)	PCI	1.6	4.8	1.6	NR	NR
	CABG	0	3.3	NR	NR	NR

*Percentage based on the number of subjects randomized at the start of the study.
MI = myocardial infarction; other abbreviations as in Tables 1 and 2.

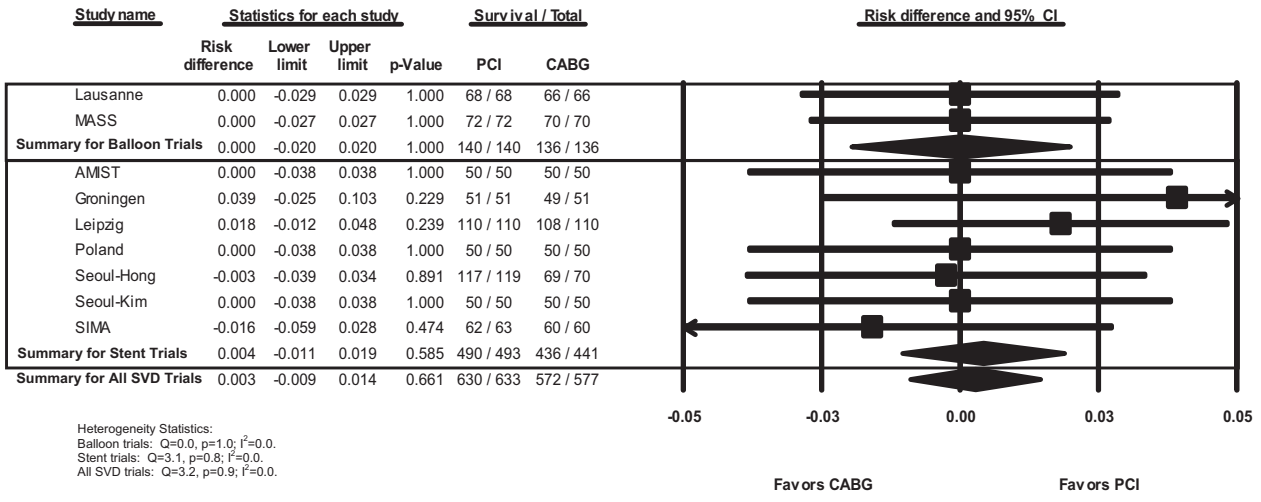

Figure 2. Procedural Survival in Balloon Angioplasty or Stent Trials Versus CABG

A comparison of absolute differences in procedural survival in the PCI and CABG groups in each of the trials. SVD = single-vessel disease; other abbreviations as in Figure 1.

years after PCI (absolute rate: 75.6%) in the 2 trials that reported this outcome (risk difference = 8.8%, 95% CI: 1.8% to 15.8%).

The rate of repeat revascularization was significantly greater after PCI (19.5%) than after CABG (4%) in the 2 trials that reported this at 1 year (risk difference = 14.4%, 95% CI: −6.1% to 22.6%, p = 0.001,). The 3 trials that reported revascularization rates at 5 years also reported reduced revascularization after CABG (summary rates 33.5% for PCI vs. 7.3% for CABG; p < 0.0001, risk difference = 26.7%, 95% CI: 20.1% to 33.3%) (Fig. 3).

Data on quality of life were collected by only 2 trials with a maximum follow-up of 15 months (Table 6). The measures chosen included the SF-36, Seattle Angina Questionnaire, and the EuroQol. No significant differences were reported between PCI and CABG recipients.

Table 4. Length of Hospital Stays

Trial	Intervention	Length of Stay (Mean Number of Days ± SD)	p Value
AMIST (14)	PCI	Median = 2	NR
	CABG	Median = 6	
Groningen (15)	PCI	3	NR
	CABG	7	
Seoul-Hong (17)	PCI	5.8 ± 2.1	0.001
	CABG	8.9 ± 2.6	
Seoul-Kim (18)	PCI	6.1 ± 3.2	0.0008
	CABG	10.1 ± 3.1	
Poland (16)	PCI	2.3 ± 0.3	<0.001
	CABG	4.5 ± 1.3	

Abbreviations as in Tables 1 and 2.

Discussion

This meta-analysis of randomized controlled trials comparing PCI and CABG in patients with single-vessel disease of the proximal LAD who were eligible for both procedures had 3 key findings. First, there was no difference in survival at any time point between PCI and CABG recipients. Second, within the first 30 days of the procedure, there was no difference in the rates of stroke or myocardial infarction, but CABG patients were more likely to require transfusions, have arrhythmias, and require longer hospital stays. Third, there was a much lower rate of repeat revascularization and higher rate angina relief in patients undergoing CABG than PCI.

The finding of equivalent survival between CABG and PCI in patients with isolated LAD disease parallels other

Table 5. Blood Transfusion Rates Reported

Trial	Intervention	Number of Patients Requiring Blood Transfusion (%)	p Value
AMIST (14)	PCI	0/49 (0)	NR
	CABG	1/49 (2)	
Seoul-Kim (18)	PCI	0/50 (0)	0.5
	CABG	1/50 (2)	
SIMA (19)	PCI	2/121 (3)	0.01
	CABG	5/121 (9)	

Abbreviations as in Tables 1 and 2.

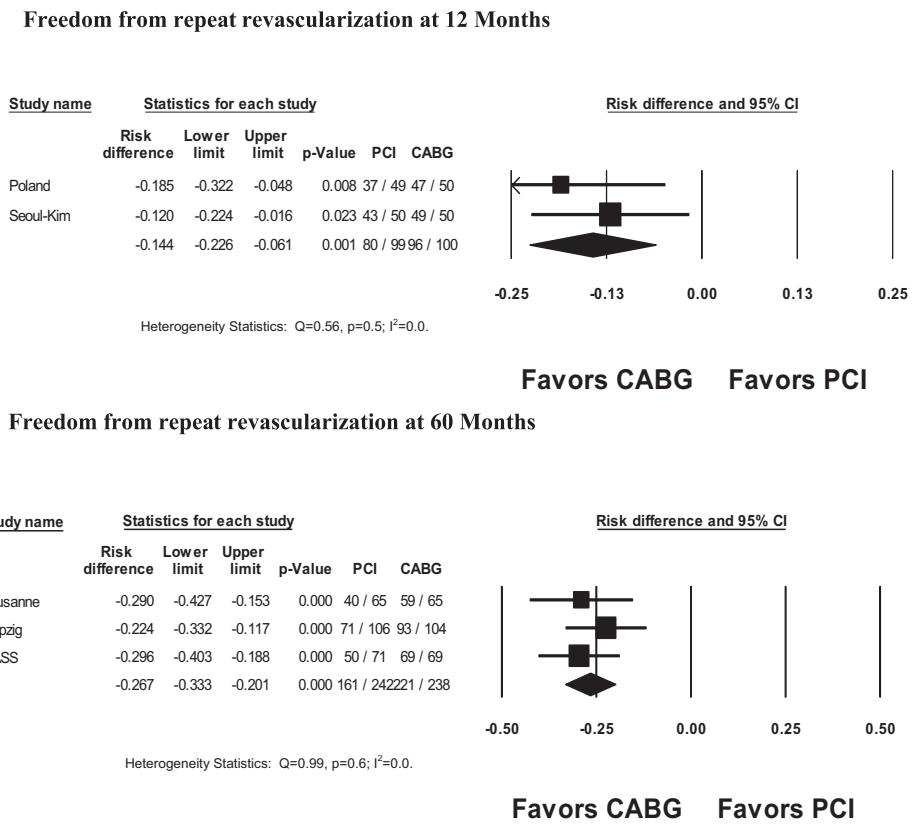

Figure 3. Freedom From Repeat Revascularization at 12 and 60 Months

A comparison of absolute differences in repeat revascularizations in the PCI and CABG groups in each of the trials. Abbreviations as in Figure 1.

Table 6. Quality of Life Information

Trial	Instrument	Measure	Time Point	PCI	CABG	Intervention Favored
AMIST (14)	SAQ	Physical limitation	6 months	76.3	78.6	NS
		Quality of life	6 months	68.1	68	NS
		Physical limitation	Year 1	80.4	81	NS
		Quality of life	Year 1	72.6	71.5	NS
	SF-36	Physical Component Summary Score	6 months	37.4	38.0	NS
		Mental Component Summary Score	6 months	51.1	52.4	NS
		Physical Component Summary Score	Year 1	37.7	39.4	NS
		Mental Component Summary Score	Year 1	51.4	55.0	CABG†
	Euroqol	Utility	6 months	0.78	0.80	NS
		Health status	6 months	74.3	79.7	NS
		Utility	Year 1	0.77	0.82	NS
		Health status	Year 1	74.6	81.7	NS
SIMA (19)	SF-36		9–15 months*			
	SAQ	Physical limitation	9–15 months	86	91	NS
		Quality of life	9–15 months	79	76	NS

*No summary scores were provided; however, the scores on each section are available in the text. There was no statistically significant difference between PCI and CABG scores in any domain. †$p < 0.05$.
SAQ = Seattle Angina Questionnaire; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; other abbreviations as in Table 1.

recent analyses of patients with other types of coronary artery disease receiving either revascularization procedure (33). Two major clinical registries have reported long-term survival for patients with single-vessel disease (34,35). These registries clearly suggest that most patients with single-vessel disease received PCI, and most patients with more extensive disease received CABG. In the Duke University Medical Center registry overall, 2,924 patients were treated by angioplasty and 3,890 patients underwent bypass surgery (34). The adjusted 5-year survival in patients with single-vessel, proximal LAD stenosis of 95% was 0.89 when treated with CABG and 0.88 when treated with PCI. In the New York registry overall, 29,930 patients underwent angioplasty and 29,646 patients underwent bypass surgery, of which 9,998 patients had single-vessel LAD angioplasty and 2,070 patients had single-vessel LAD bypass (35). The adjusted 3-year survival for patients with proximal LAD disease was 96.6% for CABG versus 95.2% for PCI ($p = 0.01$). Interestingly, we found no evidence that newer PCI technologies such as the use of bare-metal stents conferred a survival benefit over CABG. Similarly, advances in surgical techniques such as the use MIDCAB or off pump did not result in greater survival benefit than PCI. However, because there has been only 1 small trial of PCI versus CABG used drug-eluting stents (17), further clinical trials are needed to address the comparative efficacy of PCI and CABG for patients with isolated LAD lesions. Recent safety concerns about drug-coated stents emphasize the need for extended follow-up and trials large enough to detect clinically meaningful differences in outcomes. Furthermore, although longer follow-up will be required to measure the impact of saphenous vein bypass graft disease on comparative outcomes, the procedural risk of CABG in large registries has also declined progressively over time, indicating that both CABG and PCI methods continue to evolve.

Prior reviews of patients with a broad spectrum of coronary artery disease (not just patients with single-vessel disease) have shown that the rate of procedural stroke was higher after CABG (1.2%) than after PCI (0.6%) (12,13). Our finding that the rate of procedural stroke was equivalent for PCI and CABG likely reflects the limited nature of both coronary and cerebrovascular disease in this review.

The finding that CABG was associated with improved angina relief and decreased need for revascularization supports the finding of prior systematic reviews (12,13). It is uncertain whether the greater angina relief seen was attributable to more complete initial revascularization with surgery or because of restenosis after PCI.

Our analysis had several key limitations. First, given the small number of studies available for review, our analysis may be underpowered to detect differences in clinical outcomes and adverse events. Second, the generalizability of our results reflects the inclusion criteria of the RCTs. Namely, the trials generally excluded patients over the age of 75 years, with acute myocardial infarction, or severe left ventricular systolic dysfunction, and the proportion of women included in the trials ranged from 17% to 36%; thus, our conclusions about the comparative efficacy of PCI and CABG is limited for these patients. In addition, many studies excluded technically difficult lesions for PCI such as LAD bifurcation lesions, again limiting generalizability. Also, the included trials did not report specific outcomes by key subgroups (e.g., by race/ethnicity, by comorbidities), limiting our ability to evaluate the comparative efficacy of PCI and CABG by these critical subgroups. Although both the exact location and severity of a proximal LAD stenosis relate to prognosis, few of these trials strictly defined proximal LAD by these criteria prospectively.

The combined comparative evidence on PCI and CABG for isolated LAD disease suggests that because there is no significant difference in mortality, other factors such as patient preference or hospital or provider experience as well as anatomic variables (LAD diameter, lesion length, side branch involvement, ostial disease, calcification, and so on) should weigh heavily in the treatment decision. Future studies should evaluate the extent to which the comparative efficacy of PCI and CABG might be affected by other key patient characteristics such as age, gender, and comorbidities to provide more patient-specific data to inform the treatment decisions of patients and their clinicians.

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