Original Investigation

# Coronary Artery Bypass Grafting vs Percutaneous Coronary Intervention and Long-term Mortality and Morbidity in Multivessel Disease

## Meta-analysis of Randomized Clinical Trials of the Arterial Grafting and Stenting Era

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**IMPORTANCE** Recent trials of percutaneous coronary intervention (PCI) vs coronary artery bypass grafting (CABG) for multivessel disease were not designed to detect a difference in mortality and therefore were underpowered for this outcome. Consequently, the comparative effects of these 2 revascularization methods on long-term mortality are still unclear. In the absence of solid evidence for mortality difference, PCI is oftentimes preferred over CABG in these patients, given its less invasive nature.

**OBJECTIVES** To determine the comparative effects of CABG vs PCI on long-term mortality and morbidity by performing a meta-analysis of all randomized clinical trials of the current era that compared the 2 treatment techniques in patients with multivessel disease.

**DATA SOURCES** A systematic literature search was conducted for all randomized clinical trials directly comparing CABG with PCI.

**STUDY SELECTION** To reflect current practice, we included randomized trials with 1 or more arterial grafts used in at least 90%, and 1 or more stents used in at least 70% of the cases that reported outcomes in patients with multivessel disease.

**DATA EXTRACTION** Numbers of events at the longest possible follow-up and sample sizes were extracted.

**DATA SYNTHESIS** A total of 6 randomized trials enrolling a total of 6055 patients were included, with a weighted average follow-up of 4.1 years. There was a significant reduction in total mortality with CABG compared with PCI ($I^2$ = 0%; risk ratio [RR], 0.73 [95% CI, 0.62-0.86]) ($P$ < .001). There were also significant reductions in myocardial infarction ($I^2$ = 8.02%; RR, 0.58 [95% CI, 0.48-0.72]) ($P$ < .001) and repeat revascularization ($I^2$ = 75.6%; RR, 0.29 [95% CI, 0.21-0.41]) ($P$ < .001) with CABG. There was a trend toward excess strokes with CABG ($I^2$ = 24.9%; RR, 1.36 [95% CI, 0.99-1.86]), but this was not statistically significant ($P$ = .06). For reduction in total mortality, there was no heterogeneity between trials that were limited to and not limited to patients with diabetes or whether stents were drug eluting or not. Owing to lack of individual patient-level data, additional subgroup analyses could not be performed.

**CONCLUSIONS AND RELEVANCE** In patients with multivessel coronary disease, compared with PCI, CABG leads to an unequivocal reduction in long-term mortality and myocardial infarctions and to reductions in repeat revascularizations, regardless of whether patients are diabetic or not. These findings have implications for management of such patients.

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Despite advances in medical, surgical, and percutaneous therapies, coronary artery disease (CAD) remains a leading cause of death in the Western world as well as many in developing countries. One of every 6 deaths in the United States is caused by CAD. Approximately every 25 seconds, an American will have a coronary event, and approximately every minute, someone will die of one.[1]

The optimal treatment approach for patients with multivessel coronary disease remains unclear despite a myriad of randomized clinical trials performed in the last several decades. Several contemporary trials comparing coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) have reported similar mortality rates with the 2 treatment techniques.[2-11] These trials have also reported similar myocardial infarction (MI) rates with the 2 treatment approaches,[4,6-11] although a longer-term follow-up of one of these trials suggested a reduction in MIs with CABG.[12] Given no clear superiority of surgical treatment with regard to mortality and MIs, and given an increase in early strokes with CABG,[9] PCI is often preferred in patients with multivessel CAD. Accordingly, between 2001 and 2006, the number of PCIs performed annually for multivessel disease increased by 56%, and the total number of CABG surgeries decreased by 24% and continued to decline at a rate of approximately 5% per year subsequently.[13]

Despite the large number of clinical trials comparing CABG with PCI for multivessel disease, all of these trials were underpowered to detect a difference in all-cause mortality, the most important outcome of cardiovascular trials.[2,6,7,9-11] Similarly, these trials were also underpowered to detect differences in MI, a major cause of morbidity in these patients. Consequently, the current practice regarding treatment of multivessel coronary disease is not evidence based for hard end points. Therefore, our aim was to overcome the power limitation of the existing data sets by performing a meta-analysis all randomized trials directly comparing CABG with PCI in the current era of high arterial graft and stent use and examine the comparative effects of these procedures on long-term mortality and morbidity in patients with multivessel disease.

## Methods

### Literature Search

A systematic search was made of MEDLINE using PubMed through December 2012 to retrieve all published "randomized controlled trials" comparing CABG and PCI in multivessel coronary disease. The search term was *[(bypass or by-pass) and (PCI or stent) and (multi-vessel or multivessel or three-vessel or three vessel or two vessel or two-vessel)]*. The search was limited to "randomized controlled trials," and there was no time limit used in the search criteria. Supplementary searches were made using Scopus (covering MEDLINE, Embase, and several other databases from a variety of disciplines) and Cochrane Central Register of Controlled Trials using similar search terms.

### Study Selection

All of the 102 publications retrieved from the PubMed-MEDLINE search were reviewed carefully for exclusion criteria. Studies were excluded if they (1) were not randomized, (2) did not have a dedicated CABG and PCI arm, (3) did not report mortality, (4) did not report outcomes in patients with multivessel disease, (5) had an average follow-up duration shorter than 1 year, (6) did not use at least 1 arterial graft in at least 90% of the patients receiving CABG, and (7) did not use stents in at least 70% of the patients in the PCI arm. The last 2 exclusion criteria were chosen to assure that the included clinical trials reflected the current clinical practice.

### Data Extraction

Data from studies meeting the selection criteria were extracted and verified independently by 2 of us (I.S. and M.H.A.). Information on inclusion criteria, duration of follow-up, procedural characteristics, and baseline patient characteristics were collected. Subsequently, number of events and total sample size for the outcomes of interest according to treatment arms at the longest possible follow-up were extracted for each trial. If the actual numbers of events were not stated, Kaplan-Meier estimates were used.

### Statistical Analysis

Statistical heterogeneity was tested by the Cochran *Q* statistic and was reported as $I^2$. To obtain meta-analytic risk ratios (RRs) and 95% CIs, fixed effects models using number of events and total sample size were used, unless there was heterogeneity among the included trials. In cases of heterogeneity (defined as $I^2 > 40\%$), random effects models were used. Sensitivity analyses were performed according to whether trials were limited or not limited to diabetics, whether bare-metal or drug-eluting stents were used, and by using the one-study-out method. To address the issue of publication bias, the Begg-Rank correlation method was used.[14] The reported *P* values with this method are 2-tailed, with continuity correction. Additionally, funnel plots were generated to further examine publication bias. Comprehensive Meta Analysis software, version 2.2.064 (Biostat Inc) was used for all analyses.The PRISMA checklist for this meta-analysis can be found in the eTable in the Supplement.

## Results

### Search Results

The results of the literature search are shown in **Figure 1**. Of the 102 results, 6 clinical trials without the exclusion criteria enrolling a total of 6055 patients (3023 CABG, 3032 PCI) were included in the meta-analysis. Supplementary searches of Scopus and Cochrane Central Register of Controlled Trials did not reveal any additional relevant data.

### Study and Patient Characteristics

The characteristics of the included trials are listed in **Table 1**. The duration of longest follow-up varied between 1 and 6 years, with a weighted average of 4.1 years. The CARDia[7] and



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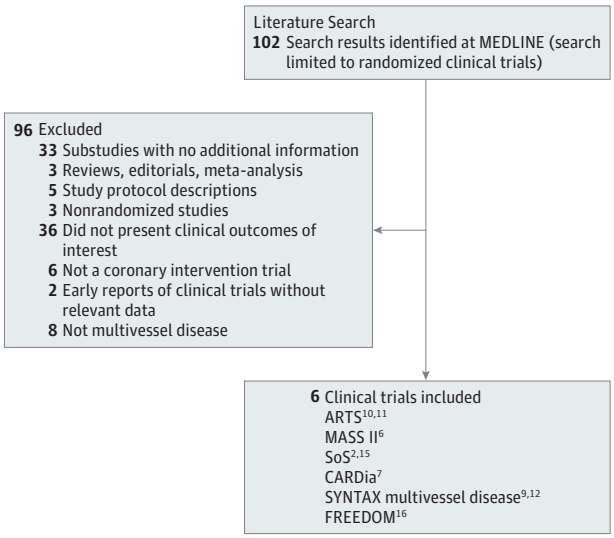
FREEDOM[16] trials were limited to patients with diabetes, and the remaining 4 trials enrolled mostly nondiabetic patients (77% nondiabetic). The SYNTAX[9] and FREEDOM[16] trials used only drug-eluting stents; ARTS,[11] MASS II,[6] and SoS[2] used only bare-metal stents; and CARDia[7] used both. Use of off-pump CABG was 0% to 31% in the included trials. Baseline patient characteristics are listed in **Table 2** and **Table 3**. These were similar in the CABG and PCI arms of the individual studies, as expected in large randomized trials. Left ventricular systolic function was preserved in most patients. Patients had either 2-vessel or 3-vessel coronary disease in all trials except the SYNTAX trial multivessel group,[9] where all patients had 3-vessel disease.

No evidence of publication bias was detected when this issue was examined by the Begg-Rank correlation method. The test statistic for the Begg approach, the Kendall τ, was nonsignificant for reporting of mortality and MI ($P > .80$ for both mortality and MI). Funnel plots examining publication bias are presented in **Figure 2**.

Figure 1. Flowchart of Trials Included in the Meta-analysis




For study acronym expansions, see the cited references.

## Quantitative Data Synthesis

The comparative effect of CABG vs PCI on total mortality is shown in **Figure 3**. There was a significant 27% reduction in total mortality with CABG compared with PCI ($I^2$ = 0%; RR, 0.73 [95% CI, 0.62-0.86]) ($P < .001$). There were numerically fewer myocardial infarctions in all of the included trials (**Figure 4**). On meta-analysis there was a significant 42% reduction in MI with CABG compared with PCI ($I^2$ = 8.02%; RR, 0.58 [95% CI, 0.48-0.72]) ($P < .001$). There was a trend toward excess strokes with CABG ($I^2$ = 24.9%; RR, 1.36 [95% CI, 0.99-1.86]), but this was not statistically significant ($P = .06$) (**Figure 5**). Repeat revascularizations ($I^2$ = 75.6%; RR, 0.29 [95% CI, 0.21-0.41]) ($P < .001$) and major adverse cardiac and cerebrovascular events (MACCE) ($I^2$ = 33.0%; RR, 0.61 [95% CI, 0.54-0.68]) ($P < .001$) were significantly reduced with CABG compared with PCI (**Figure 6** and **Figure 7**).

The number needed to treat was calculated using the obtained meta-analytic RRs and observed cumulative event rates in the PCI arms of the trials. Accordingly, CABG had to be preferred over PCI in 37 patients to save 1 life and in 26 patients to prevent 1 MI for the weighted average duration of follow-up of 4.1 years. The number needed to treat was 7 for repeat revascularizations and 10 for MACCE. The number needed to harm was 105 to cause 1 excess stroke with CABG.

Table 1. Characteristics of Randomized Trials of CABG vs PCI in Patients With Multivessel Disease Included in The Meta-analysis

| Study (Publication Year of Longest Follow-up) | Patients, Total No. | Patients Assigned to Each Arm, No. | | Follow-up, Median, y | Outcomes of Interest Assessed | ≥1 Arterial Graft Used in CABG, % | ≥1 Stent Used in PCI, % | Off-Pump CABG Rate, % | Type of Stent Used |
|---|---|---|---|---|---|---|---|---|---|
| | | CABG | PCI | | | | | | |
| ARTS,[10,11] (2005) | 1174 | 584 | 590 | 5 | Death, MI, stroke, repeat revascularization, MACCE[a] | 93 | 99 | 0 | BMS |
| MASS II[6] (2007)[b] | 408 | 203 | 205 | 5 | Death, MI, stroke, repeat revascularization | >92 | 72 | 0 | BMS |
| SoS[2,15] (2008) | 988 | 500 | 488 | 6 | Death, repeat revascularization (at second year only) | 93 | >78 | 3 | BMS |
| CARDia[7] (2010) | 490 | 242 | 248 | 1 | Death, MI, stroke, repeat revascularization, MACCE[a] | 94 | 100 | 31 | 69% DES (sirolimus); 31% BMS |
| SYNTAX multivessel[9,12] (2011)[c] | 1,095 | 547 | 548 | 3 | Death, MI, Stroke, Repeat revascularization, MACCE | 97.3 | 100 | 15 | 100% Paclitaxel DES |
| FREEDOM[16] (2012) | 1900 | 947 | 953 | 3.8 | Death, MI, stroke, repeat revascularization (at first year only), MACCE[a] (at first year only) | 94.4 | >94 | 18.5 | Any DES (51% sirolimus; 43% paclitaxel |

Abbreviations: CABG, coronary artery bypass grafting; BMS, bare-metal stent; DES, drug-eluting stent; MACCE, major adverse coronary and cerebrovascular events; PCI, percutaneous coronary intervention.

[a] MACCE is the combined end point of death, non-fatal MI, non-fatal stroke and repeat revascularization.

[b] MASS II trial had 3 arms (medical therapy vs CABG vs PCI). Only the CABG and PCI arms were included in this meta-analysis.

[c] Number assigned to each arm were calculated assuming equal 1:1 distribution. Data for trial characteristics are from the whole SYNTAX population.



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## Sensitivity Analysis

The magnitude of risk reduction in mortality was similar in trials limited to patients with diabetes and those not limited to patients with diabetes ($P$ = .80 for heterogeneity) (**Table 4**). There was also no evidence of heterogeneity according to type of stent used (heterogeneity $P$ = .56 for bare-metal vs drug-

**Table 2. Characteristics of Patients Enrolled in Randomized Trials of CABG vs PCI in Patients With Multivessel Disease Included in the Meta-analysis[a]**

| | Mean Age, y | | Male | | Diabetes | | Hypertension | | Hyperlipidemia | | Mean or Median EF, % | | Smoker | | Previous MI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Source | CABG | PCI | CABG | PCI | CABG | PCI | CABG | PCI | CABG | PCI | CABG | PCI | CABG | PCI | CABG | PCI |
| ARTS[10,11] | 61 | 61 | 76 | 77 | 16 | 19 | 45 | 45 | 58 | 58 | 60 | 61 | 26 | 28 | 42 | 44 |
| MASS II[6] | 60 | 60 | 72 | 67 | 29 | 23 | 63 | 61 | NA | NA | 67 | 67 | 32[a] | 27[a] | 41 | 52 |
| SoS[2,15] | 62 | 61 | 78 | 80 | 15 | 14 | 47 | 43 | 50 | 53 | 57 | 57 | 14 | 16 | 47 | 44 |
| CARDia[7] | 64 | 64 | 71 | 78 | 100 | 100 | 77 | 81 | 93 | 82 | 60 | 59 | 23 | 25 | NA | NA |
| SYNTAX[b] multivessel[9,12] | 65 | 65 | 79 | 76 | 35 | 36 | 64 | 69 | 77 | 79 | NA | NA | 22 | 19 | 34 | 32 |
| FREEDOM[16] | 63 | 63 | 70 | 73 | 100 | 100 | 85[c] | | 84[c] | | 67 | 66 | 17 | 15 | 25 | 26 |

Abbreviations: CABG, coronary artery bypass grafting; EF, ejection fraction; NA, not available; PCI, percutaneous coronary intervention.

[a] Unless otherwise noted, data are reported as percentage of participants.

[b] Data for patient characteristics are from the whole SYNTAX population.

[c] Rates for the whole FREEDOM cohort.

**Table 3. Disease Types in Patients Enrolled in Randomized Trials of CABG vs PCI in Patients With Multivessel Disease Included in the Meta-analysis[a]**

| | 2-Vessel Disease | | 3-Vessel Disease | | Unstable Angina | | Stable Angina | |
|---|---|---|---|---|---|---|---|---|
| Source | CABG | PCI | CABG | PCI | CABG | PCI | CABG | PCI |
| ARTS[10,11] | 67 | 68 | 33 | 30 | 35 | 37 | NA | NA |
| MASS II[6] | 42 | 42 | 58 | 58 | 0 | 0 | 100 | 100 |
| SoS[2,15] | 52 | 62 | 47 | 38 | NA | NA | NA | NA |
| CARDia[7] | 35 | 28 | 60 | 65 | ''Mostly stable coronary artery disease'' | | | |
| SYNTAX[b] multivessel[9,12] | 0 | 0 | 100 | 100 | 28 | 29 | 57 | 57 |
| FREEDOM[16] | 16 | 18 | 84 | 82 | 31[c] | | 69[c] | |

Abbreviations: CABG, coronary artery bypass grafting; NA, not available; PCI, percutaneous coronary intervention.

[a] All data are reported as percentage of participants.

[b] Data for patient characteristics are from the whole SYNTAX population.

[c] Of the whole FREEDOM cohort, 31% had acute coronary syndrome, and 69% had stable coronary artery disease.

**Table 4. Sensitivity Analyses for the Outcome of Mortality**

| Characteristic | $I^2$, % | Model | RR (95% CI) | $P$ Value | Comparison of 2 Groups for Heterogeneity |
|---|---|---|---|---|---|
| **Diabetes Status** | | | | | |
| Trials limited to patients with diabetes (CARDia,[7] FREEDOM[16]) (n = 2390) | 0 | Fixed effects | 0.75 (0.58-0.97) | .03 | 0.80 |
| Trials not limited to patients with diabetes (ARTS,[10,11] MASS II,[6] SoS,[2,15] SYNTAX multivessel[9,12]) (n = 3665) | 13.3 | Fixed effects | 0.72 (0.58-0.89) | .003 | |
| **Type of Stent Used** | | | | | |
| Trials using only drug-eluting stents (SYNTAX multivessel,[9,12] FREEDOM[16]) (n = 2995) | 0 | Fixed effects | 0.69 (0.55-0.87) | .001 | 0.56 |
| Trials using only bare-metal stents (ARTS,[10,11] MASS II,[6] SoS[2,15]) (n = 2570) | 19.9 | Fixed effects | 0.77 (0.59-0.99) | .04 | |
| **Excluded Study in 1-Study-Out Model** | | | | | |
| ARTS[10,11] | 0 | Fixed effects | 0.69 (0.57-0.83) | <.001 | NA |
| MASS II[6] | 0 | Fixed effects | 0.74 (0.62-0.88) | <.001 | NA |
| SoS[2,15] | 0 | Fixed effects | 0.75 (0.63-0.90) | .002 | NA |
| CARDia[7] | 0 | Fixed effects | 0.72 (0.61-0.86) | <.001 | NA |
| SYNTAX multivessel[9,12] | 0 | Fixed effects | 0.76 (0.63-0.91) | .003 | NA |
| FREEDOM[16] | 0 | Fixed effects | 0.73 (0.59-0.91) | .004 | NA |

Abbreviation: NA, not applicable



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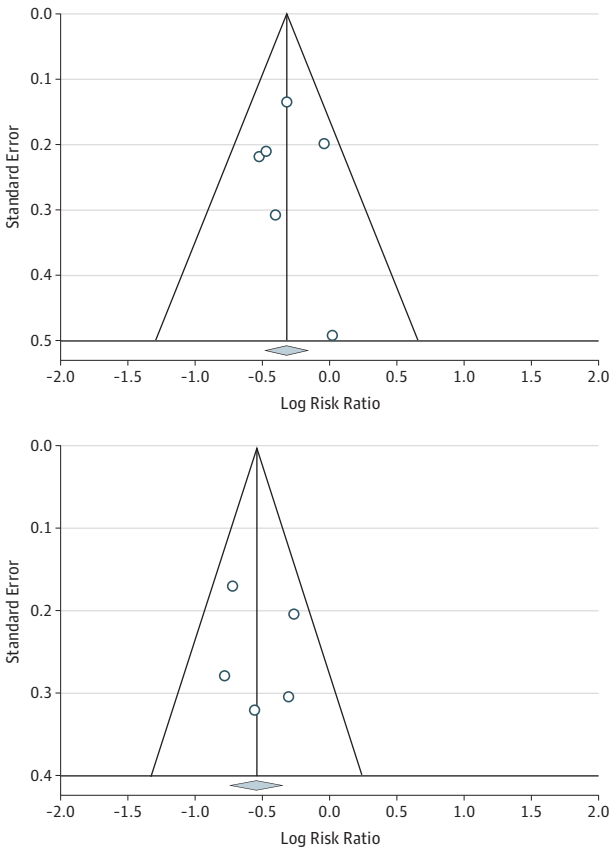
eluting stents). The findings of the meta-analysis remained stable with the one-study-out method ruling out the possibility of a single clinical trial dominating the results of the meta-analysis. There was also no statistically significant heterogeneity for risk reduction in MI according to whether trials were limited to patients with diabetes or the type of stent used (heterogeneity $P > .10$ for both). For the outcome of stroke, there was again no heterogeneity in results according to diabetes status or the type of stent used (heterogeneity $P > .10$ for both). For repeat revascularizations, there was significant heterogeneity according to the type of stent used ($P = .002$), with greater risk reduction in this outcome with CABG if bare-metal stents were used (RR, 0.27 [95% CI, 0.22-0.34] with bare-metal stents vs RR, 0.45 [95% CI, 0.36-0.56] with drug-eluting stents). There was no significant heterogeneity according to diabetes status for repeat revascularizations ($P > .10$).

One well-known clinical trial from South America did not meet the study inclusion criteria because the frequency of the use of arterial grafts in the CABG arm and the frequency of stent use in the PCI arm of this trial were too low.[17] A sensitivity analysis adding this trial did not change the statistically significant reduction in mortality with CABG compared with PCI.

Figure 2. Funnel Plots Examining Publication Bias for Mortality (A) and Myocardial Infarction (B)




Log risk ratios less than 0 favor coronary artery bypass grafting; those greater than 0 favor percutaneous coronary intervention. These funnel plots represent a measure of study size on the vertical axis as a function of effect size on the horizontal axis. Large studies appear toward the top of the graph, and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. In the absence of publication bias, as is demonstrated in these funnel plots, the studies, represented by pale dotted circles, are distributed symmetrically about the combined effect size. The dashed diamond appearing below the x-axis represents the summary effect.

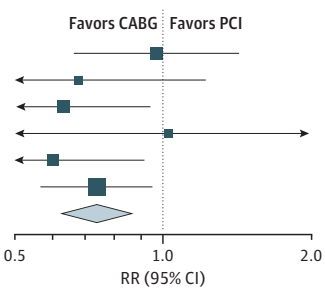
## Discussion

This meta-analysis of the contemporary era shows that in patients with multivessel CAD, CABG reduces long-term mortality by 27% compared with PCI, regardless of whether the study population is limited to patients with diabetes or not. Regarding major morbidity, a 42% risk reduction in MI was observed in patients randomized to CABG. There was a trend for excess strokes with CABG, probably related to an increase in periprocedural strokes. However, the absolute risk increase in stroke was small compared with the absolute risk reduction in mortality and MI, as demonstrated by the numbers needed to treat.

Although CAD is a leading cause of death worldwide, the optimal treatment strategy for this disease remains to be well defined. There have been important advances in nonsurgical therapies, including drug-eluting stents, newer anticoagulant-antiplatelet drug regimens, and aggressive lipid-lowering treatment, all of which have led to improved outcomes in nonsurgically treated patients with multivessel CAD. Additionally, improvements in surgical techniques including nearly universal arterial graft use and better postoperative care have ren-

Figure 3. Mortality According to Treatment Arm

| | Statistics for Each Study | | | | Death/Total | |
|---|---|---|---|---|---|---|
| Source | RR (95% CI) | | *Z* Value | *P* Value | CABG | PCI |
| ARTS[10,11] | 0.97 | (0.66-1.43) | -0.16 | .87 | 46/584 | 48/590 |
| MASS II[6] | 0.67 | (0.37-1.23) | -1.29 | .20 | 16/203 | 24/205 |
| SoS[2,15] | 0.63 | (0.41-0.95) | -2.23 | .03 | 34/500 | 53/488 |
| CARDia[7] | 1.02 | (0.39-2.69) | 0.05 | .96 | 8/242 | 8/248 |
| SYNTAX multivessel[9,12] | 0.60 | (0.39-0.92) | -2.36 | .02 | 31/547 | 52/548 |
| FREEDOM[16] | 0.73 | (0.56-0.95) | -2.31 | .02 | 86/947 | 118/953 |
| **Meta-analysis** | **0.73** | **(0.62-0.86)** | **-3.69** | **<.001** | **221/3023** | **303/3032** |




Total number of patients, 6055 ($I^2$ = 0% for the fixed effects model). CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; RR, risk ratio; for expansion of all study name acronyms, see the cited references.



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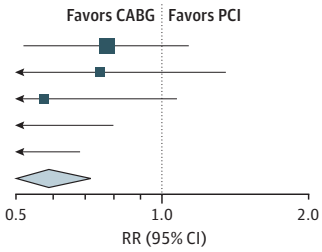
dered obsolete much of the surgical outcomes data from the clinical trials published before the turn of the century.[18-21] As PCI methods continue to evolve and surgical outcomes improve, it has become increasingly difficult to answer the ultimate question: "What is the best revascularization method for the patient with multivessel CAD?"

The more recent stent era trials comparing CABG with PCI have been underpowered for mortality and major morbidity,

**Figure 4. Myocardial Infarctions (MIs) According to Treatment Arm**

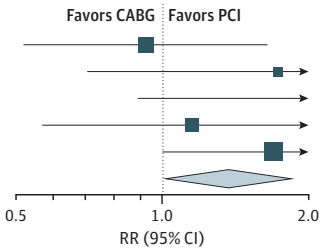
| Source | Statistics for Each Study RR (95% CI) | Z Value | P Value | MI/Total CABG | PCI |
|---|---|---|---|---|---|
| ARTS[10,11] | 0.77 (0.52-1.15) | -1.26 | 0.21 | 39/584 | 51/590 |
| MASS II[6] | 0.75 (0.41-1.35) | -0.96 | 0.34 | 17/203 | 23/205 |
| CARDia[7] | 0.57 (0.31-1.08) | -1.73 | 0.08 | 14/242 | 25/248 |
| SYNTAX multivessel[9,12] | 0.46 (0.27-0.80) | -2.77 | 0.01 | 18/547 | 39/548 |
| FREEDOM[16] | 0.49 (0.35-0.68) | -4.23 | <.001 | 48/947 | 99/953 |
| **Meta-analysis** | **0.58 (0.48-0.72)** | **-5.17** | **<.001** | **136/2523** | **237/2544** |




Total number of patients, 5067 ($I^2$ = 8.02% for the fixed effects model). CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; RR, risk ratio; for expansion of all study name acronyms, see the cited references.

**Figure 5. Strokes According to Treatment Arm**

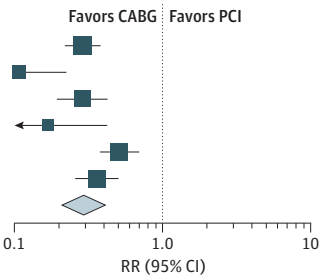
| Source | Statistics for Each Study RR (95% CI) | Z Value | P Value | Stroke/Total CABG | PCI |
|---|---|---|---|---|---|
| ARTS[10,11] | 0.92 (0.52-1.65) | -0.27 | 0.79 | 21/584 | 23/590 |
| MASS II[6] | 1.73 (0.70-4.31) | 1.18 | 0.24 | 12/203 | 7/205 |
| CARDia[7] | 7.17 (0.89-57.87) | 1.85 | 0.06 | 7/242 | 1/248 |
| SYNTAX multivessel[9,12] | 1.14 (0.56-2.32) | 0.38 | 0.71 | 16/547 | 14/548 |
| FREEDOM[16] | 1.69 (1.01-2.85) | 1.98 | 0.05 | 37/947 | 22/953 |
| **Meta-analysis** | **1.36 (0.99-1.86)** | **1.91** | **0.06** | **93/2523** | **67/2544** |




Total number of patients, 5067 ($I^2$ = 24.9% for the fixed effects model). CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; RR, risk ratio; for expansion of all study name acronyms, see the cited references.

**Figure 6. Repeat Revascularizations According to Treatment Arm**

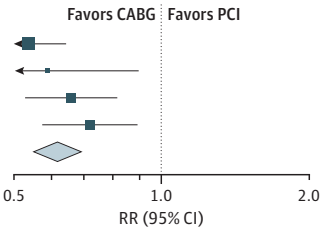
| Source | Statistics for Each Study RR (95% CI) | Z Value | P Value | Repeat Revascularization/Total CABG | PCI |
|---|---|---|---|---|---|
| ARTS[10,11] | 0.29 (0.22-0.39) | -8.45 | <.001 | 53/584 | 182/590 |
| MASS II[6] | 0.11 (0.05-0.23) | -5.80 | <.001 | 7/203 | 66/205 |
| SoS[2,15] | 0.29 (0.20-0.43) | -6.26 | <.001 | 30/500 | 101/488 |
| CARDia[7] | 0.17 (0.07-0.43) | -3.72 | <.001 | 5/242 | 30/248 |
| SYNTAX multivessel[9,12] | 0.52 (0.38-0.70) | -4.23 | <.001 | 55/547 | 106/548 |
| FREEDOM[16] | 0.37 (0.26-0.51) | -5.83 | <.001 | 43/947 | 118/953 |
| **Meta-analysis** | **0.29 (0.21-0.41)** | **-7.00** | **<.001** | **193/3023** | **603/3032** |




Total number of patients, 6055 ($I^2$ = 75.6% for the random effects model). CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; RR, risk ratio; for expansion of all study name acronyms, see the cited references.

**Figure 7. Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) According to Treatment Arm**

| Source | Statistics for Each Study RR (95% CI) | Z Value | P Value | MACCE/Total CABG | PCI |
|---|---|---|---|---|---|
| ARTS[10,11] | 0.53 (0.45-0.64) | -6.95 | <.001 | 132/584 | 250/590 |
| CARDia[7] | 0.59 (0.38-0.90) | -2.44 | .01 | 28/242 | 49/248 |
| SYNTAX multivessel[9,12] | 0.65 (0.53-0.81) | -3.83 | <.001 | 103/547 | 158/548 |
| FREEDOM[16] | 0.71 (0.57-0.89) | -2.95 | <.001 | 112/947 | 158/953 |
| **Meta-analysis** | **0.61 (0.54-0.68)** | **-8.55** | **<.001** | **375/2320** | **615/2339** |




Total number of patients, 4659 ($I^2$ = 33.0% for the fixed effects model). CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; RR, risk ratio; for expansion of all study name acronyms, see the cited references.



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making the results difficult to interpret. This is partially because, unlike in previous eras, in the present era, the annual mortality of these patients is very low, under 2% to 3% in most studies. Consequently, the composite primary end point of MACCE was introduced to overcome the power limitation of these studies, and CABG almost always led to lower MACCE rates.[7,9,11] However, MACCE is driven mainly by the soft end point of repeat revascularizations, which can be acceptable for many physicians and patients wishing to avoid cardiac surgery. This is especially important in the absence of evidence for significant improvement in mortality or major morbidity such as MI with CABG.[3-5,7-10] For example, in the seminal first report of one of the landmark trials comparing CABG with PCI, mortality and MI rates were similar, while the stroke rate was higher in the CABG arm.[9] As a result of this and other previous trials, as well as very large observational data sets reporting no mortality or morbidity benefit with CABG,[22] practice patterns shifted toward stenting.[13] To overcome the limitations of the underpowered studies, we performed this meta-analysis pooling data from multiple studies including a total of more than 6000 patients. Our analysis demonstrates that both long-term mortality and MIs are reduced significantly with CABG compared with PCI, regardless of whether drug-eluting or bare-metal stents are used. The validity of our findings are supported by a recent propensity-matched analysis of over 100 000 patients reporting superior survival and lower MI rates with multivessel CABG compared with multivessel PCI.[23] It is notable that the results of the clinical trials included in this meta-analysis were homogeneous for all of the outcomes studied (ie, $I^2$<40%) except for the outcome of repeat revascularization. For this outcome, the effect size was relatively smaller for the SYNTAX[9] and FREEDOM[16] trials (RR, >0.35 in both), where there was universal use of drug-eluting stents that reduce in-stent restenosis, compared with the other trials, which used bare-metal stents (RRs <0.30).

It has been long debated whether the presence of diabetes should dictate the revascularization method in patients with multivessel CAD. Traditionally, surgery has been preferred over PCI for this population. Evidence for this is largely based on the BARI study[19] and comes from the plain balloon era. While the BARI study did not show an overall mortality benefit between the 2 revascularization methods, a post hoc subgroup analysis of diabetic patients showed a long-term mortality of 34.5% for balloon angioplasty and 19.4% for surgery ($P$ = .03). Very recently, the results of the FREEDOM study[16] enrolling only diabetic patients confirmed the mortality and morbidity benefit of CABG over PCI in this population. Therefore, it may be argued that the benefit of CABG over PCI is limited to patients with diabetes and that the mortality benefit of CABG seen in our meta-analysis is driven by diabetic patients. In this regard, among the trials included in our meta-analysis, 2 of them were limited to patients with diabetes alone, and 4 of the trials included primarily nondiabetic patients. On further analysis, there was no heterogeneity in reduction of mortality and MIs among the trials limited to and not limited to diabetic patients. The effect size for mortality reduction was very similar in trials enrolling only diabetic patients (25%) and the trials enrolling primarily nondiabetic patients (28%). While the FREEDOM trial is a landmark study that will consolidate the approach to revascularization in patients with diabetes and multivessel CAD, the vast majority of patients with multivessel disease are nondiabetic.[24] Our results strongly suggest that CABG should be the revascularization method in patients with multivessel CAD, regardless of their diabetic status. However, it should be remembered that the included trials enrolled patients mostly with stable or unstable angina and excluded patients with acute MI. Therefore, our findings do not apply to the type of patients who were systematically excluded from these trials.

Our results must be interpreted in light of several limitations. This was necessarily a trial-level meta-analysis because we did not have access to individual patient-level data. Therefore, we were not able to perform subgroup analysis to see whether the superiority of CABG over PCI for mortality reduction was limited to certain subgroups (eg, those with intermediate to high SYNTAX scores or those with 3-vessel disease). Also, it may be argued that newer generation drug-eluting stents that are now commonly used during PCI such as the everolimus- or the zotarolimus-eluting stents were not tested in the trials included in this meta-analysis. In this context, it should be noted that the newer generation drug-eluting stents did not improve mortality compared with the sirolimus- or paclitaxel-eluting stents[25,26] or the bare-metal stents[27] in randomized controlled trials. Another argument could be that CABG may still not be the best approach for the management of patients with multivessel disease because our meta-analysis compared CABG only to PCI and not to medical therapy, and CABG may not be superior to medical therapy alone. In this context, there are 2 major contemporary randomized trials comparing CABG with medical therapy.[6,28] The MASS II trial,[6] which was also included in our meta-analysis, is one of these trials. This trial, primarily enrolling nondiabetic patients, had 3 arms, namely, CABG, PCI, and medical therapy arms. In MASS II, the 5-year mortality was 12.8% with CABG and 16.2% with medical therapy, although the difference was not statistically significant. Risk of acute MI was significantly reduced with CABG compared with medical therapy (RR, 0.41 [95% CI, 0.18-0.94]). The BARI 2D trial[28] including patients with diabetes is the other relevant trial. In BARI 2D, within the CABG stratum, MIs were significantly less frequent in CABG plus intensive medical therapy vs intensive medical therapy alone groups (10.0% vs 17.6%) ($P$ = .003), and the composite end point of death or MI (21.1% vs 29.2%) ($P$ = .01) was also less frequent. These data, along with other data showing equivalence of stenting with medical therapy in stable multivessel coronary disease, suggests that CABG is not only superior to PCI but also to medical therapy for at least prevention of MI. Nevertheless, an appropriately sized randomized trial examining the effect of CABG vs medical therapy on total mortality in patients with preserved ejection fraction does not exist for the current era.

## Conclusions

In patients with multivessel coronary disease, CABG does not only lead to a dramatic reduction in repeat revascularization and MACCE but also leads to a 27% reduction in long-



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term all-cause mortality and a 42% reduction in MIs compared with PCI. The benefits were not only observed in trials of diabetic patients but also in trials where the great majority of patients were nondiabetic. Use of bare-metal or drug-eluting stents did not alter the mortality benefit. Given these meaningful benefits, CABG should be the preferred revascularization method for most patients with multivessel coronary artery disease.

## ARTICLE INFORMATION

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*Study concept and design:* Sipahi, Akay, Dagdelen, Alhan.
*Acquisition of data:* Sipahi, Akay.
*Analysis and interpretation of data:* Sipahi, Blitz, Alhan.
*Drafting of the manuscript:* Sipahi, Akay.
*Critical revision of the manuscript for important intellectual content:* Sipahi, Dagdelen, Blitz, Alhan.
*Statistical analysis:* Sipahi.
*Administrative, technical, or material support:* Sipahi.
*Study supervision:* Sipahi, Dagdelen, Alhan.

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