Risk of Stroke With Coronary Artery Bypass Graft Surgery Compared With Percutaneous Coronary Intervention

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Objectives
This study sought to determine whether coronary artery bypass graft (CABG) surgery is associated with an increased risk of stroke compared with percutaneous coronary intervention (PCI).

Background
Some, but not all, randomized trials have reported increased rates of stroke with CABG compared with PCI. However, all these studies were powered insufficiently to examine differences in the risk of stroke reliably.

Methods
We performed a meta-analysis of 19 trials in which 10,944 patients were randomized to CABG versus PCI. The primary end point was the 30-day rate of stroke. We also determined the rate of stroke at the midterm follow-up and investigated whether there was an interaction between revascularization type and the extent of coronary artery disease on the relative risk of stroke.

Results
The 30-day rate of stroke was 1.20% after CABG compared with 0.34% after PCI (odds ratio: 2.94, 95% confidence interval: 1.69 to 5.09, \( p < 0.0001 \)). Similar results were observed after a median follow-up of 12.1 months (1.83% vs. 0.99%, odds ratio: 1.67, 95% confidence interval: 1.09 to 2.56, \( p = 0.02 \)). The extent of coronary artery disease (single vessel vs. multivessel vs. left main) did not affect the relative increase in the risk of stroke observed with CABG compared with PCI at either 30 days (\( p = 0.57 \) for interaction) or midterm follow-up (\( p = 0.08 \) for interaction). Similar results were observed when the outcomes in 33,980 patients from 27 observational studies were analyzed.

Conclusions
Coronary revascularization by CABG compared with PCI is associated with an increased risk of stroke at 30 days and at the mid-term follow-up. (J Am Coll Cardiol 2012;60:798–805) © 2012 by the American College of Cardiology Foundation

Whether stroke is more frequent after coronary artery bypass graft (CABG) surgery compared with percutaneous coronary intervention (PCI) is controversial. Significant differences in the risk of stroke between CABG and PCI have not been found in most individual randomized controlled trials (RCT) (1,2), the 1 exception being the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial, in which a significantly higher risk of stroke was apparent for patients treated with CABG (3). However, all RCT to date were powered insufficiently to detect differences in stroke between CABG and PCI, possibly resulting in false positive or false negative findings. We therefore performed a meta-analysis to determine whether CABG is associated with similar or higher rates of stroke than PCI after coronary revascularization across the spectrum of coronary artery disease (CAD).

Methods

Patients and end points. RCT comparing CABG versus PCI in patients with single-vessel CAD, multivessel CAD, and unprotected left main CAD in which the rate of stroke at 30 days, midterm follow-up, or both were included. The primary end point was the 30-day rate of stroke with CABG versus PCI. The secondary end point was the risk of stroke at the midterm follow-up.
Data source and study selection. Relevant trials were identified through MEDLINE, Cochrane, and EMBASE database searches using the keywords coronary angioplasty, coronary artery bypass, single-vessel coronary artery disease, multivessel coronary artery disease, and left main coronary artery disease. Two investigators (T.P., L.A.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were resolved by consensus.

Statistical analysis. Data from RCT comprised the primary analysis set, whereas data from observational studies were considered secondary. The odds ratio (OR) and 95% confidence interval (CI) were used as the summary statistic. The pooled OR was calculated by using both fixed-effect (inverse variance-weighted) and random-effect (DerSimonian and Laird) models. Median follow-up and number needed to harm were calculated as previously described for meta-analysis (4,5). Potential interactions between revascularization method and the extent of CAD on the risk of stroke also were analyzed. Sensitivity analysis, between-study heterogeneity of effects, and publication bias were assessed as previously described (6,7). Statistical analyses were performed using Stata/SE software version 11.2 (StataCorp LP, College Station, Texas). Values of \( p < 0.05 \) were considered statistically significant.

Results

Of 2,191 potentially relevant articles initially screened, 19 RCT with 10,944 patients (including 5,448 assigned to CABG and 5,496 assigned to PCI) met the inclusion criteria and were included in the final meta-analysis (Fig. 1, Online Table 1). Patient characteristics appear in Table 1. Stroke definitions and the association between stroke and subsequent mortality are reported in Online Table 2.

Risk of stroke at 30-day follow-up. Fourteen trials with 8,744 randomized patients contributed to this analysis. As shown in Figure 2A and Table 2, patients treated with CABG had significantly higher rates of stroke than patients treated with PCI (1.20% vs. 0.34%, OR: 2.94, 95% CI: 1.69 to 5.09, \( p < 0.0001 \)). The number needed to harm was 155, with an excess of 7 strokes for every 1,000 patients treated with CABG rather than PCI. No significant interaction with the period in which the studies were performed was apparent (\( p = 0.25 \) for interaction) (Online Fig. 1). A gradient in the risk of stroke was observed in relation to the extent of CAD for patients treated with CABG, but not with PCI, although the interaction was not significant (\( p = 0.57 \) for interaction) (Fig. 3A), nor was there a relationship between the OR of stroke at the 30-day follow-up with CABG versus PCI in trials in which stents were used as opposed to balloon angioplasty only (\( p = 0.52 \) for interaction).

Risk of stroke at midterm follow-up. Twelve studies including a total of 7,052 patients contributed to this analysis. After a median follow-up of 12.1 months, patients treated with CABG had significantly higher rates of stroke than patients treated with PCI (1.84% vs. 0.99%, OR: 1.67, 95% CI: 1.09...
to 2.56, p = 0.02) (Fig. 2B, Table 2). A gradient in the risk of stroke was observed in relation to the extent of CAD only for patients treated with CABG, with nonsignificant interaction (p = 0.08 for interaction) (Fig. 3B).

**Risk of stroke in observational studies.** Similar findings were observed when we analyzed the results from 27 studies including 33,980 patients enrolled in observational studies (Online Table 3). As shown in Figure 4 and Table 2, patients treated with CABG had an increased risk of stroke compared with PCI both at 30 days and at a median follow-up of 14.2 months.

No significant heterogeneity was apparent across studies, and there was no apparent systematic bias as assessed by funnel plots and Peter's test (Table 2). No individual study unduly influenced the primary effect estimate for either the RCT or observational studies.

**Discussion**

The main results of the current study, drawn from 19 RCT in which 10,944 patients were enrolled, are as follows: (1) patients with CAD undergoing CABG have a significantly higher risk of stroke than those treated with PCI, both at 30 days and after a median follow-up of 12.1 months; (2) although stroke rates were higher in patients with more extensive CAD (especially after CABG), the relative increase in stroke with CABG compared with PCI was not significantly affected by the extent of disease; and (3) the risk
Figure 2  Risk of Stroke With CABG Surgery Versus PCI in Randomized Trials

(A) 30-day and (B) midterm (median follow-up of 12.1 months) odds ratio (OR) and 95% confidence interval (CI) of stroke in patients (pts) treated with CABG versus those treated with PCI. Results are reported in a logarithmic scale. ARTS = Arterial Revascularization Therapies Study; AWESOME = Angina With Extremely Serious Operative Mortality Evaluation; BARI = Bypass Angioplasty Revascularization Investigation; CARDIA = Coronary Artery Revascularisation in Diabetes; CI = confidence interval; EAST = Emory Angioplasty versus Surgery Trial; ERACI = Argentine Randomized Study; Coronary Angioplasty with Stenting vs. Coronary Bypass Surgery in Multivessel Disease; GABI = German Angioplasty Bypass Investigation; LE MANS = Study of Unprotected Left Main Stenting Versus Bypass Surgery; MASS = Medicine, Angioplasty, or Surgery Study; OR = odds ratio; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; RITA = Randomised Intervention Treatment of Angina; SIMA = Stenting vs. Internal Mammary Artery; SoS = Stent or Surgery; SYNTAX = Synergy between PCI with Taxus and cardiac surgery; other abbreviations as in Figure 1.
of stroke was substantially higher in observational studies than in RCT for patients treated with CABG (but not with PCI), and the relative reduction in stroke with PCI compared with CABG was even more pronounced in these so-called real-world studies, particularly at 30 days.

Debate over the optimal strategy of revascularization in patients with CAD has continued over several decades (1–3,6,7). Contrary to widespread belief, surprisingly few data on the relative risk of stroke between PCI and CABG are available (6), and a statistically significantly higher rate of stroke with CABG has been reported only from a single randomized study, the recent SYNTAX trial, in which patients with triple vessel and left main CAD were enrolled (3). Whether the findings of the SYNTAX trial are real and representative or denote the play of chance is uncertain.

The results from the observational studies confirm those from the RCT. The large number of patients included in this study and the satisfaction of all requirements for meta-analysis, in terms of low heterogeneity, absent publication bias, and sensitivity analysis, provide robust scientific validity to our findings, which can assist informed decision making by patients, their families, and physicians when deciding on the optimal strategy of revascularization in patients with severe CAD.

Two prior meta-analyses have analyzed the risk of stroke after CABG or PCI, with conflicting results (6,7). Compared with those studies, the present analysis is significantly larger, analyzed the relative rates of stroke both at 30 days and at the 1-year follow-up, and included patients with unprotected left main CAD. Also unique is our examination of the data for possible interactions between revascularization method and the extent of CAD and the inclusion of a separate meta-analysis of observational studies, which provides supportive insight into real-world outcomes with CABG versus PCI.

Some studies have reported that off-pump compared with on-pump CABG may reduce the risk of stroke significantly (8), but these findings have not been confirmed in other studies (9). In RCT included in our meta-analysis, off-pump surgery was almost exclusively used in patients with single-vessel CAD. For this reason, we could not determine whether there was an interaction between surgical technique and the risk of stroke with CABG. Careful pre-operative evaluation of patient risk factors, screening of the ascending aorta, assessment of carotid artery disease, implementation of no-touch techniques in high-risk patients, and aggressive and prompt treatment of post-operative atrial fibrillation remain mainstay strategies to reduce the risk of stroke in CABG-treated patients.

**Study limitations.** This report has some limitations that should be acknowledged. Follow-up was restricted to 1 year, and therefore whether the observed differences would remain constant, increase, or diminish with longer-term follow-up is unknown. Because this meta-analysis was based on aggregate data, we could not analyze the potential influence of classical risk factors for stroke such as diabetes and prior stroke. Few studies reported mortality rates subsequent to stroke occurrence, and therefore we could not investigate the relation between stroke and mortality. Definitions of stroke were not uniform across trials. Finally, observational studies are subject to confounding, and these results were not adjusted for differences in baseline characteristics. Nonetheless, the results in these real-world patients were consistent with those from the RCT, providing support that the observed differences in stroke between CABG and PCI are real.

### Table 2: Odds Ratio, Heterogeneity, and Publication Bias Across Randomized Controlled Trials and Observational Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Studies, 30 days, all</th>
<th>Patients</th>
<th>OR (95% CI)*</th>
<th>p Value Fixed Effects Random Effects OR (95% CI)*</th>
<th>p Value Random Effects OR (95% CI)*</th>
<th>Heterogeneity p Value</th>
<th>I² (%)</th>
<th>Peter’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs, 30 days, all</td>
<td>14</td>
<td>8,744</td>
<td>2.94 (1.69–5.09)</td>
<td>&lt;0.0001</td>
<td>2.94 (1.69–5.09)</td>
<td>&lt;0.0001</td>
<td>0.0% 0.97</td>
</tr>
<tr>
<td>RCTs, 30 days, MVCAD only†</td>
<td>8</td>
<td>6,192</td>
<td>2.62 (1.40–4.91)</td>
<td>0.003</td>
<td>2.62 (1.40–4.91)</td>
<td>0.003</td>
<td>0.0% 0.96</td>
</tr>
<tr>
<td>RCTs, 30 days, ULMCAD only</td>
<td>3</td>
<td>1,011</td>
<td>6.29 (1.11–35.77)</td>
<td>0.04</td>
<td>6.29 (1.11–35.77)</td>
<td>0.04</td>
<td>0.0% 0.95</td>
</tr>
<tr>
<td>RCTs, 30 days, SVCAD</td>
<td>3</td>
<td>530</td>
<td>1.76 (0.27–11.24)</td>
<td>0.55</td>
<td>1.76 (0.27–11.24)</td>
<td>0.55</td>
<td>0.0% 0.47</td>
</tr>
<tr>
<td>RCTs, 1 yr, all</td>
<td>12</td>
<td>7,052</td>
<td>1.67 (1.09–2.56)</td>
<td>0.02</td>
<td>1.69 (1.07–2.66)</td>
<td>0.02</td>
<td>4.8% 0.40</td>
</tr>
<tr>
<td>RCTs, 1 yr, SVCAD only</td>
<td>4</td>
<td>632</td>
<td>0.69 (0.16–3.00)</td>
<td>0.62</td>
<td>0.69 (0.16–3.00)</td>
<td>0.62</td>
<td>0.0% 0.58</td>
</tr>
<tr>
<td>RCTs, 1 yr, MVCAD only</td>
<td>4</td>
<td>3,798</td>
<td>1.79 (1.02–3.12)</td>
<td>0.04</td>
<td>1.79 (1.02–3.12)</td>
<td>0.04</td>
<td>0.0% 0.46</td>
</tr>
<tr>
<td>RCTs, 1 yr, ULMCAD only</td>
<td>4</td>
<td>1,611</td>
<td>6.58 (1.72–25.16)</td>
<td>0.006</td>
<td>6.58 (1.72–25.16)</td>
<td>0.006</td>
<td>0.0% 0.98</td>
</tr>
<tr>
<td>Observational studies, 30 days</td>
<td>27</td>
<td>33,980</td>
<td>6.38 (4.68–8.70)</td>
<td>&lt;0.0001</td>
<td>6.38 (4.68–8.70)</td>
<td>&lt;0.0001</td>
<td>0.0% 0.97</td>
</tr>
<tr>
<td>Observational studies, 1 yr</td>
<td>13</td>
<td>18,250</td>
<td>2.08 (1.63–2.66)</td>
<td>&lt;0.0001</td>
<td>2.12 (1.60–2.81)</td>
<td>&lt;0.0001</td>
<td>7.5% 0.37</td>
</tr>
</tbody>
</table>

*OR of coronary artery bypass grafting surgery versus percutaneous coronary intervention. †The RITA trial was not included in the stratification analysis because it enrolled a similar proportion of patients with MVCAD and SVCAD.

CI = confidence interval; HET = heterogeneity; MVCAD = multivessel coronary artery disease; OR = odds ratio; RCT = randomized controlled trial; SVCAD = single vessel coronary artery disease; ULMCAD = unprotected left main coronary artery disease; other abbreviation as in Table 1.
Figure 3 Risk of Stroke With CABG Versus PCI in Patients Stratified by the Extent of Coronary Disease

(A) 30-day and (B) midterm (median follow-up of 12.1 months) OR and 95% CI of stroke in pts treated with CABG versus those treated with PCI, stratified by multivessel coronary artery disease (MVCD), unprotected left main coronary artery disease (ULMCD), or single-vessel coronary artery disease (SVCD). Results are reported in a logarithmic scale. Abbreviations as in Figures 1 and 2.
Figure 4  Risk of Stroke With CABG Versus PCI in Observational Studies

(A) 30-day and (B) midterm (median follow-up of 14.2 months) OR and 95% CI of stroke in patients treated with CABG versus those treated with PCI. Results are reported in a logarithmic scale. Abbreviations as in Figures 1 and 2.
Conclusions

In this large contemporary meta-analysis of patients with CAD undergoing revascularization, CABG was associated with significantly higher rates of stroke compared with PCI at 30 days and 1 year, with no significant interaction apparent between the extent of CAD and revascularization method on the relative risk of stroke.

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REFERENCES


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APPENDIX

For supplemental tables and figures, please see the online version of this article.