Optimal Method of Coronary Revascularization in Patients Receiving Dialysis: Systematic Review

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Background and objectives: Patients receiving dialysis have a high burden of cardiovascular disease. Some receive coronary artery revascularization but the optimal method is controversial.

Design, setting, participants, & measurements: The authors reviewed any randomized controlled trial or cohort study of 10 or more patients receiving maintenance dialysis which compared coronary artery bypass graft (CABG) to percutaneous intervention (PCI) for revascularization of the coronary arteries. The primary outcomes were short-term (30 d or in-hospital) and long-term (at least 1 year) mortality.

Results: Seventeen studies were found. There were no randomized trials: all were retrospective cohort studies from years 1977 to 2002. There were some baseline differences between the groups receiving CABG compared with those receiving PCI, and most studies did not consider results adjusted for such characteristics. Given the variability among studies and their methodological limitations, few definitive conclusions about the optimal method of revascularization could be drawn. In an exploratory meta-analysis, short-term mortality was higher after CABG compared to PCI. A substantial number of patients died over a subsequent 1 to 5 yr, with no difference in mortality after CABG compared to PCI.

Conclusions: Although decisions about the optimal method of coronary artery revascularization in dialysis patients are undertaken routinely, it was surprising to see how few data has been published in this regard. Additional research will help inform physician and patient decisions about coronary artery revascularization.


Cardiovascular disease accounts for almost half of all deaths in patients with end-stage renal disease (1). More than two thirds of patients receiving dialysis have prevalent coronary artery disease, among whom three fourths are symptomatic and have multivessel disease (2). Coronary revascularization is often pursued in select patients who are sufficiently fit for the procedures or are symptomatic despite maximal medical therapy. The most appropriate method of revascularization is a matter of debate (3).

Percutaneous coronary intervention (PCI) is an increasingly attractive treatment option for patients with stable multivessel coronary artery disease. With advances in technology, the risk of complications has declined, and success has improved (4). New advances in coronary artery bypass graft (CABG) surgery have also reduced rates of operative morbidity and mortality (5).

In the general population, a recent trial suggested that survival and major cardiovascular events were no different in patients with atherosclerosis of the proximal left anterior descending artery randomized to receive either PCI or CABG surgery (4). However, the need for repeat revascularization was higher in patients receiving PCI (6). It has been highlighted that no quantitative review on this topic has been published regarding patients with kidney failure (7). Thus we undertook a systematic review to compile existing evidence on the following question: in patients receiving dialysis, what are the short and long-term risks of death for those undergoing CABG compared with those undergoing PCI? We also considered the effects of these procedures on cardiovascular outcomes of myocardial infarction and need for repeat revascularization.

Materials and Methods

This review was conducted and reported in accordance with published guidelines (8,9) using a prespecified protocol.

Study Eligibility

Randomized controlled trials and cohort studies of 10 or more patients receiving either chronic hemodialysis or peritoneal dialysis that compared CABG to PCI for revascularization of the coronary arteries.
were eligible for review. PCI included percutaneous transluminal coronary angioplasty and percutaneous transluminal coronary rotational angioplasty, including the use of stents. The primary outcomes were short-term (30 d, in-hospital) and long-term (at least 1 year) mortality. We also considered cardiac events, defined by the primary study authors as myocardial infarction or need for repeat revascularization. Studies published in any language were eligible for review (10). We excluded studies that described: (1) patients with non-dialysis dependent chronic kidney disease, as their comparative care differs substantially from patients on dialysis; (2) only a portion of the patients receiving dialysis, with no separate report of outcomes; (3) fewer than 10 patients; (4) patients who received combination surgery (i.e., valve and bypass surgery); and (5) patients with acute kidney injury in need of urgent dialysis.

Finding Relevant Studies
With the help of an experienced information specialist we searched MEDLINE, PreMedline, Experta Medica, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effectiveness, Cochrane Controlled Trials Register, BIOSIS Previews, the ISI Science Citation Index Expanded, Google Scholar, Elsevier's scientific search engine SCIRUS, clinicaltrials.gov, Cochrane Renal Group's Renal Trials Register, Cinii (Japan), and SCOPUS bibliographic databases, from the start date of each source to March 23, 2008. The search strategy was modified for each database and included the following terms as combinations of descriptors, subject headings and keywords: end-stage renal disease, hemodialysis, peritoneal dialysis, coronary artery bypass, and angioplasty.

The reference lists of all relevant articles and reviews were screened. Cross-reference searches were performed of Internet and citation tracking using SCOPUS and the ISI Science Citation Index, and using related articles featured in PubMed, OVID, Elsevier's SCIRUS and Google Scholar. Conference proceeding abstracts were reviewed. All citations were downloaded into Reference Manager, version 11.0 (Thomson ISI Research-Soft, Philadelphia, PA). Two reviewers independently screened each citation, and those considered potentially relevant were retrieved for full text review. Two reviewers independently evaluated the eligibility of each full-text article, with disagreements resolved by consensus. All non-English articles were reviewed with the help of translators.

Data Extraction
Two reviewers independently extracted data on all studies that met eligibility criteria: methods, setting, patient characteristics, renal and cardiac parameters, surgical methods, and outcomes. The methodological quality of each study was assessed using known validity criteria (11). Duplicate data were reviewed, and disagreements were resolved by consensus. Attempts were made to contact the primary author of each relevant article to check on the accuracy of data and to provide additional missing data.

Statistical Analysis. Reviewer agreement on study eligibility was quantified using the kappa (κ) statistic. Publication bias was assessed by funnel plot and Egger's test for funnel plot asymmetry (12). The number of events was estimated from Kaplan-Meier survival graphs when no other information was provided in the manuscript. This tends to overestimate the number of events (13) but would not influence the comparison (i.e., relative risk) between CABG and PCI. The I² statistic was used to quantify the magnitude of between-study heterogeneity. An I² value represents the percentage of total variation across studies that is due to true difference rather than chance, with values of 0% to 30%, 31% to 50%, and greater than 50% representing mild, moderate, and notable heterogeneity, respectively (14). Unadjusted and adjusted relative risks and associated variances were mathematically pooled by the random-effects method (15–17). This approach was based on generalized estimating equations, which accounted for the within-study and between-study variability (18). When zero events occurred in one arm of a study, a continuity correction factor of 0.5 was applied (19). A weighted average of the baseline characteristics of patients from the different studies was also done. Exploratory meta-regression analyses were performed to assess the impact of study-level factors on different results observed across the studies (i.e., between-study heterogeneity). We considered the association between outcomes and the following study-level factors: mean age, proportion of patients who were male, average duration of follow-up, midpoint year of recruitment, year of publication, whether recruitment occurred in a country where English was the official language, mean length of dialysis, mean ejection fraction, percent left main disease, percent single-vessel disease and multivessel disease, percent history of myocardial infarction, and population (percent hypertensive, current smokers, hyperlipidemic, diabetic). Statistical analyses were performed using SAS version 9.1 (SAS institute Inc., Cary, NC), SPSS version 14.0 (SPSS Inc., Chicago, IL), R version 2.0.1 (R Foundation for Statistical Computing, Vienna, Austria), and Review Manager Version 4.2 for Windows (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Description of Studies and Methods Used
The authors screened a total of 8176 citations, retrieved 139 full-text articles, and evaluated the eligibility of each full-text article (Figure 1). The chance-corrected agreement between the two independent reviewers who evaluated study eligibility was very good (κ = 0.79).

Seventeen studies from five different countries followed a total of 32,388 patients who received dialysis (Table 1). On average, patients received dialysis for 3.7 yr. In total, 15,175 patients underwent CABG, and 17,213 patients underwent PCI. With the exception of two studies, which each followed over 14,000 patients (20,21), each study followed between 25 and 452
Table 1. Baseline characteristics of included studies

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Country</th>
<th>Cohort Yr</th>
<th>No. of Patients on Dialysis</th>
<th>Mean (SD) Follow-Up, months</th>
<th>Outcomes reported</th>
<th>Mortality</th>
<th>Long-Term Cardiac events</th>
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<td></td>
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<td></td>
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<td>PCI</td>
<td>CABG</td>
<td>PCI</td>
<td>In-hospital</td>
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Dashes indicate data not reported in primary studies. CABG, coronary artery bypass graft; PCI, percutaneous intervention.

<sup>a</sup>Loss to follow up was reported to be <20%.

<sup>b</sup>Studies included a few patients with repeat revascularization.

<sup>c</sup>Studies included patients with emergent surgeries.

<sup>d</sup>Study did not include patients with repeat revascularization.

<sup>e</sup>Events of myocardial infarction could not be ascertained because patients were transferred to different dialysis centers, however mortality could be assessed.

<sup>f</sup>Study only followed patients with a successful revascularization procedure.

<sup>g</sup>Outcome assessed at different follow-up times for CABG and PCI groups. See follow-up column for exact time.

<sup>h</sup>Events were reported as part of a combined composite outcome.
patients. There were no published randomized controlled trials. All 17 studies examined data retrospectively using existing health records. Except for four studies (22–25), all were published in English. All 17 studies had a representative study sample and adequately defined both selection criteria and the presence of end-stage renal disease. All studies included patients on dialysis, although the modality of dialysis was not always reported. No study described the use of drug eluting stents. Five studies reported on coronary angiography being performed on patients before revascularization, although the indication for angiography was not reported (22,24,26–28). Three studies discussed the comparison of medical management with CABG and PCI; two of them reported that the medical group did not do better than the revascularization groups with regard to long-term survival (24,29). A valid comparison was not reported in the other study (22).

In some studies, long-term mortality and cardiac events were reported at differential lengths of follow-up between those who received CABG and PCI (25–28,30). However in the remaining studies all patients were followed to a defined time point (Table 1). Loss to follow-up was reported in three studies (21,27,31), and in another study, actual follow-up was done only for patients who had a successful revascularization (25). All four studies reported less than 20% loss to long-term follow-up (21,25,27,31), with the remaining studies not reporting any loss to follow up. Only one study (32) described the consecutive recruitment of patients.

**Patient Characteristics and Outcome Definitions**

The characteristics of patients before revascularization are shown in Table 2. Four studies included patients who underwent repeat revascularization, a larger proportion (22%) of patients in two studies (31,33), and a small proportion (11%) in the remaining two studies (25,32). Two of the studies included a small number of patients (13%) who had emergent surgeries (30,32). The weighted mean age of patients was 60 yr, and most relevant characteristics like hyperlipidemia, ejection fraction, hypertension, and diabetes mellitus were similar among those receiving CABG and PCI. Patients receiving CABG were less likely to have single-vessel coronary artery disease (6% versus 46%) and more likely to have multivessel coronary artery disease (85% versus 53%) and left main disease (14% versus 8%).

Short-term mortality was defined by intra- or postoperative deaths during the same hospital admission (20,21,25,26,30–32,34) or within 30 d after surgery (22,28,29,35), whereas long-term mortality was defined as any death that occurred during the follow-up period, which was at least 1 yr (29,31,34) to a maximum average of 8 yr (33). A cardiac event was defined as a composite outcome of myocardial infarction or need for repeat revascularization in nine studies (20,22,25–28,31,32,35). Eight studies also reported events of myocardial infarction on their own (20,25–27,30–32,35).

**Assessment of Publication Bias**

For outcomes of short and long-term mortality Egger’s test \( P \) ranged from 0.25 to 0.92. For cardiac outcomes, there were too few studies to allow for a proper visual assessment of funnel plot asymmetry; however, the largest study (20), which followed over 14,000 patients, was among the studies reporting the smallest benefit of CABG compared with PCI (Egger’s test \( P = 0.03 \)). Egger’s test was no longer statistically significant when this study was excluded from analysis \( (P = 0.53) \).

**Short-Term (30 D, In-Hospital) Mortality**

There was notable heterogeneity between the results of 13 studies (unadjusted results, \( \chi^2 = 32.4; \ P < 0.01; I^2 = 63\% \) (Figure 2a). Of the 11 studies that each enrolled fewer than 500 patients, a statistically higher risk of mortality after CABG compared with PCI was reported in two studies (25,26). In two larger database analyses, the risk of mortality was higher after CABG compared to PCI (20,21). The risk of short-term mortality with CABG compared to PCI adjusted for baseline characteristics was not reported in any study.

**Long-Term (at Least 1 Yr) Mortality**

There was moderate heterogeneity between the results of the 16 studies (unadjusted results, \( \chi^2 = 24.4; \ P = 0.06; I^2 = 38\% \) (Figure 2b). A substantial number of patients died in follow-up, and no difference in mortality between patients who received CABG compared with PCI was reported in 13 of the 16 studies. Four studies reported the risk of long-term mortality of CABG compared with PCI, adjusted for baseline characteristics (20,21,23,36). A lower risk of mortality after CABG compared with PCI was described in three studies (20,21,36), but not in the fourth study (23) (Figure 2d).

**Long-Term (at Least 1 Yr) Cardiac Events**

There was notable heterogeneity between the nine study results (\( \chi^2 = 15.5; \ P = 0.05; I^2 = 48.5\% \)). In no study was the competing event of death considered when examining cardiac events; for example, a composite outcome of long-term mortality and cardiac events was not described in any study. It remains possible that patients who died after CABG were not alive to develop long-term cardiac events, with the reported analyses overestimating any benefits attributable to CABG. Nonetheless, in all nine studies, the point estimate of the risk of cardiac events was lower after CABG compared to PCI, although in four studies the confidence interval overlapped with one (22,25,27,31).

**Meta-Analysis**

We conducted an exploratory meta-analysis. In the setting of notable heterogeneity as observed in this review, the pooled estimate may help identify a direction of plausible effect, but it is not a precise estimate of the true effect (14,37). The pooled absolute increase in short-term death with CABG compared with PCI was 5.2% (absolute rates 10.6% versus 5.4%). The unadjusted relative risk (RR) of short-term mortality was 1.91 (95% confidence interval [CI] 1.44 to 2.52; \( P < 0.001 \). Over the longer term, cumulative mortality was somewhat lower after CABG compared to PCI (51.6% versus 59.5%; absolute difference 6.9%, unadjusted RR 0.93, 95% CI 0.88 to 0.98; \( P = 0.01 \))
Table 2. Baseline characteristics of patients in included studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Agirbasli</th>
<th>Aoki</th>
<th>Baldovinos</th>
<th>Chertow</th>
<th>Fujimoto</th>
<th>Hara</th>
<th>Hemmelgarn</th>
<th>Heterog. 2012</th>
<th>Ivens</th>
<th>Koyanagi</th>
<th>Ohomoto</th>
<th>Rinehart</th>
<th>Simsir</th>
<th>Stczzech</th>
<th>Takeshita</th>
<th>Weighted average</th>
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The data are expressed as number (percent) unless otherwise indicated. Dashes indicate data not reported in primary studies. CABG, coronary artery bypass graft; PCI, percutaneous intervention.

*Study (20) followed 7,419 patients who underwent CABG and 6,887 who underwent PCI of whom 66% and 56% were male (included in calculations for the weighted average). Studies (20, 21) reported age categorically and majority (about 45%) of the patients were in the 45-65 yr group. Diabetes and hypertension were reported as pathogenesis of ESRD. Another study (34) reported baseline characteristics of all patients on dialysis regardless of the method of revascularization that they underwent. Mean age being 67.5 ± 0.32, percentage male 54.5%, and percent diabetics 57%.
Cardiovascular events were considerably lower after CABG compared to PCI (20.3% versus 32.4%; absolute difference 12.1%; RR 0.50, 95% CI 0.37 to 0.68; \(P < 0.01\)) (Figure 2c). When outcomes of myocardial infarction and need for revascularization were considered separately, all these events were consistently lower after CABG compared to PCI (myocardial infarction: RR 0.53, 95% CI 0.34 to 0.81; revascularization: RR 0.61, 95% CI 0.46 to 0.81).

**Figure 2.** Meta-analyses of short-term and long-term mortality, long-term cardiac events and adjusted long-term mortality for patients who underwent CABG and PCI.
dial infarction RR 0.62, 95% CI 0.51 to 0.75; P < 0.00001; revascularization RR 0.21, 95% CI 0.13 to 0.35; P < 0.00001) (data not shown). Given that two studies contributed over 30,000 of the 32,388 patients in this review (20,21), we excluded these studies and repeated the meta-analyses. Short-term mortality remained higher after CABG compared to PCI (RR 1.82, 95% CI 1.07 to 3.09; P = 0.02) (Figure 2a). The number of cardiac events remained lower after CABG than after PCI (RR 0.42, 95% CI 0.26 to 0.66; P < 0.01) (Figure 2c). However, long-term (1 to 8 yr) mortality no longer differed between the two groups (RR 1.01, 95% CI 0.87 to 1.18; P = 0.57) (Figure 2b).

Four of the included studies reported long-term mortality and cardiac events at different lengths of follow up for those who received CABG compared with those who received PCI (25,26,30,32). We repeated the meta-analysis, including only those studies that had the same length of follow-up for both groups. Long-term mortality remained somewhat lower after CABG than after PCI (RR 0.93; 95% CI 0.87 to 1.00; P = 0.04). However, the composite of cardiac events was lower after CABG compared to PCI (RR 0.58, 95% CI 0.42, 0.78; P = 0.0004) (data not shown).

Meta-Regression. There was no statistically significant association between any of the factors examined in meta-regression and short- or long-term mortality.

Discussion
The American College of Cardiology/American Heart Association guidelines recommend that CABG may be performed for select patients receiving dialysis, with increased but acceptable risks of perioperative morbidity and mortality (38). Although decisions regarding optimal modality of coronary artery revascularization in dialysis patients are undertaken routinely, it was surprising to see how few data have been published in this regard. There were no randomized trials on this topic, only retrospective observational studies. Given the variability among studies and their methodological limitations, few definitive conclusions about the optimal method of revascularization could be drawn.

Implications for Practice
In the general population, the incidence of short-term (30 d) mortality was 1% to 3% in those receiving PCI and 1% to 5% among those receiving CABG, according to one observational study and three other randomized controlled trials (36,39–41). However long-term mortality, myocardial infarction and the need for revascularization were lower after CABG compared to PCI (Table 3) (42). A similar result was described in a recent study comparing drug-eluting stents to coronary bypass grafting in patients with multivessel coronary disease (43). Unfortunately, in patients who receive dialysis, the long-term risk of mortality is substantial irrespective of the method of revascularization used (Table 3). If it is true that the absolute difference in long-term mortality is less than 8% for those receiving PCI compared with those receiving CABG as observed in this meta-analysis, this may suggest clinicians are making reasonable decisions about the method of revascularization for specific patients. Alternatively, it could be argued that neither method meaningfully improved long-term survival, as only three of the studies (22,24,29) compared the results of revascularization to treatment solely with medications. Indeed, the high rates of mortality associated with a large burden of comorbidity in such patients may mean that a single revascularization procedure is unlikely to have a large overall effect.

Approximately half of all patients receiving dialysis in this review had diabetes mellitus. Similar to the results of this exploratory meta-analysis for patients with renal failure, some studies of diabetic patients have identified a lower risk of long-term mortality after CABG compared to PCI (29% versus 39% an average of 3 yr after revascularization) (20,39). Nonetheless, when patients and their physicians are convinced of the potential long-term benefits of surgery, they must also accept the perioperative risks associated with this decision. It is intuitive that the perioperative mortality rate after CABG would be much higher in those receiving dialysis compared with the general population. For example, in-hospital mortality after CABG occurs in 11% of patients receiving dialysis, compared with 3% of other patients (44). Similar results are observed for outcomes of stroke (4.3% versus 1.7%), and need to return to the operating room as a result of bleeding (3.6% versus 2.9%) (44). Whether procedures like continuous dialysis or off-pump bypass can be used to reduce mortality in this patient population is a matter of ongoing investigation.

Important developments like the use of glycoprotein IIb/
IIIa antiplatelet agents, long-term use of the oral antiplatelet agent clopidogrel, and the development and more widespread application of stents have significantly reduced restenosis and need for revascularization after PCI (40), but not actual rates of mortality. Underutilization of these drugs in patients receiving dialysis should be considered. It is possible that calcific lesions in hemodialysis patients may be responsible for high restenosis rates after percutaneous transluminal coronary angioplasty, with stents not providing any meaningful benefit (28).

**Strengths and Limitations**

To identify relevant literature for this review, we performed a comprehensive search in accordance with published guidelines, using a prespecified protocol. Article identification, selection and data abstraction were all performed independently by two reviewers to minimize potential biases. The group of patients undergoing PCI in our review included those receiving percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary rotational angioplasty (32), or stent angioplasty (21,23,26).

When pooled results are considered, as in our exploratory meta-analysis, publication bias can always be a concern. Some patients analyzed in a large U.S. database (20,21) may have also been “double” counted in smaller individual center studies with more detailed data (27,28,31). This is another reason we repeated the analysis after excluding the studies that used large databases.

Meta-analyses are inherently limited by the quality of the primary studies. The exploratory pooled estimates of our review were derived from retrospective observational studies, using unadjusted parameters reported by the primary authors. There were often important baseline differences between individuals receiving CABG compared with those receiving PCI (Table 2), and only four studies considered long-term mortality adjusted for such characteristics (20,21,23,36). However, the adjusted pooled estimates for long-term mortality did not vary much from the unadjusted results. There are often indications why patients receive one type of therapy over the other. In some studies, it was unclear whether baseline coronary artery atherosclerosis was similar in those receiving CABG compared with those receiving PCI. Patients with single-vessel disease or those too ill to undergo CABG may be more likely to receive PCI; if patients in one of the groups had more unfavorable coronary anatomy, this could confound the results (25,31,32). Similarly, some studies also included patients who underwent emergent revascularization with either CABG or PCI (30,32). When considering the need for repeat revascularization outcome, the number of new coronary artery lesions could not be distinguished from old ones. In addition, surgery without cardiopulmonary bypass could have a significant effect on surgical results. These technological advances raise the question of whether studies conducted over a previous decade are relevant today or will remain relevant in the future. Nonetheless, in many studies, it did appear that repeat revascularization was lower with CABG compared with PCI (20,22,25–28,31,32,35), and CABG has long been the dominant revascularization strategy in select patients such as those with extensive multivessel disease (45).

**Conclusions and Future Research Directions**

Although there are strong recommendations for the management of cardiovascular disease in the general population, it is often difficult to make evidence-based decisions for the management of patients with concurrent renal disease. Certainly the potential long-term benefits of CABG may differ in those with end-stage renal disease compared with the general population, and the perioperative risk of death may be unacceptably high. Although conducting post hoc subgroup analyses of the existing randomized controlled trials (39–41,45) that compared CABG with PCI might prove helpful, it remains unfortunate that most existing trials did not include patients receiving dialysis (46). Rigorous randomized trials could be conducted in the future, with the recognition that a few thousand patients would need to be recruited for adequate statistical power if the true long-term relative risk of mortality with CABG compared with PCI is 0.9. An even larger number of patients would need to be recruited if the trial were to include a group treated strictly with medical management. Further complicating the execution of such trials are rapid technological advances, which could render the results obsolete if the type of PCI or technique of CABG used in the trial no longer represented the standard of care. Until such data become available for patients receiving dialysis, physicians can use currently available evidence, along with local expertise and knowledge of patient preferences to guide decisions about coronary artery revascularization. Because the long-term risk of mortality remains substantial irrespective of the method of revascularization, determining which intervention best offsets this risk remains a health priority.

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**Disclosures**

None.

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