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Reduced risk of myocardial infarct and revascularization following coronary artery bypass grafting compared with percutaneous coronary intervention in patients with chronic kidney disease

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Abstract

Coronary atherosclerotic disease is highly prevalent in chronic kidney disease (CKD). Although revascularization improves outcomes, procedural risks are increased in CKD and unbiased data comparing bypass surgery (CABG) and percutaneous intervention (PCI) in CKD are sparse. To compare outcomes of CABG and PCI in stage 3-5 CKD, we identified randomized trials

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Declaration of Helsinki
This research was conducted in accordance with the declaration of Helsinki. Informed consent was obtained for subjects at the time of enrollment in the original trials.

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comparing these procedures. Investigators were contacted to obtain individual, patient-level data. Ten of 27 trials meeting inclusion criteria provided data. These trials enrolled 3993 patients encompassing 526 patients with stage 3-5 CKD of which 137 were stage 3b-5 CKD. Among individuals with stage 3-5 CKD survival through 5-years was not different following CABG compared with PCI (hazard ratio 0.99, 95% confidence interval: 0.67, 1.46) or stage 3b-5 CKD (1.29: 0.68, 2.46). However, CKD modified the impact on survival free from myocardial infarction: it was not different between CABG and PCI for individuals with preserved kidney function (0.97: 0.80, 1.17), but was significantly lower following CABG in stage 3-5 CKD (0.49: 0.29, 0.82) and stage 3b-5 CKD (0.23: 0.09, 0.58). Repeat revascularization was reduced following CABG compared with PCI regardless of baseline kidney function. Results were limited by unavailability of data from several trials and paucity of enrolled patients with stage 4-5 CKD. Thus, our patient-level meta-analysis of individuals with CKD randomized to CABG versus PCI suggests that CABG significantly reduces the risk of subsequent myocardial infarction and revascularization without impacting survival in these patients.

Keywords

Coronary artery disease; Chronic kidney disease; Myocardial infarction; Coronary revascularization

Introduction

More than 10% of the adult U.S. population have chronic kidney disease (CKD)[1], which is associated with increased cardiovascular morbidity and mortality[2, 3]. Standard cardiovascular therapies have the potential to decrease morbidity and mortality, but utilization of established cardiovascular therapies including coronary angiography and revascularization procedures has remained lower in individuals with CKD than in patients with relatively preserved kidney function.[4, 5]

Although this selective underutilization of coronary revascularization in a population at high cardiovascular risk ("renalism"[5]) could represent inappropriate therapeutic nihilism, recent trials have failed to demonstrate efficacy of standard medical therapies in patients on dialysis[6, 7] while the majority of large cardiovascular trials have excluded individuals with CKD raising important questions about the efficacy or safety of other accepted cardiovascular therapies in this population. Indeed, patients with CKD experience higher perioperative mortality[8, 9] following coronary artery bypass grafting (CABG), are at higher risk of acute kidney injury following CABG surgery or percutaneous coronary intervention (PCI)[10, 11], and have generally much higher overall mortality[12, 13] compared with the subjects enrolled in landmark trials comparing CABG and PCI, in whom advanced kidney dysfunction was uncommon[8]. Therefore, a dedicated, CKD-specific comparison of the risks and benefits of PCI and CABG is needed to define the optimal role for each therapy in the setting of impaired kidney function.

Although several retrospective comparisons of PCI and CABG among individuals with CKD undergoing coronary revascularization for clinical indications have generally favored CABG[14-16], the potential for indication bias and residual confounding remains an important concern with non-randomized studies in this area. To provide highest-level evidence, we conducted a systematic review of the literature and, subsequently, a detailed, individual-level meta-analysis of patients with moderate to severe CKD from published randomized trials comparing CABG and PCI.

Results

Study Identification and Characteristics

Our pre-specified literature search identified 1111 citations (**Figure 1**). After title and abstract review, 75 citations were examined in detail; however, 48 were excluded because they failed to meet the specified inclusion criteria. A total of 27 eligible trials were identified for inclusion, but 17 had to be excluded for the following reasons: data no longer available (n=3)[17-19]; insufficient data to calculate eGFR (n=7)[20-26]unable to contact the investigators despite multiple attempts (n=3)[27-29]; investigators unable (n=2)[30, 31] or unwilling (n=2)[32, 33] to share data.

The remaining 10 trials comprised the analytical dataset and included the following trials: AMIST[34]; Bypass Angioplasty Revascularization Investigators Trial (BARI)[35]; Cisowski *et al.* [36]; Argentine Randomized Study: Coronary Angioplasty with Stenting *versus* Coronary Bypass Surgery in Multivessel Disease (ERACI II)[37]; German Angioplasty Bypass Surgery Investigation (GABI)[38]; Left Main Stenting (Le MANS)[39]; Leipzig[40]; Medicine, Angioplasty or Surgery Study (MASS 1)[41]; Medicine, Angioplasty or Surgery II Study (MASS 2)[42]; and Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (VA [AWESOME])[43].

All studies used central and concealed randomization and intention to treat analyses of outcomes. However, in 2 studies, outcomes assessors were not blinded to treatment assignment.[34, 36] Loss to follow-up was generally low, but exceeded 10% in 2 studies[34, 38] **(Table 1)**.

The majority of trials completed enrollment between 1991 and 2001 with exception of a single trial that completed enrollment in 2002[36] and the Le Mans trial, which enrolled subjects from 1997-2008[39]. As shown in Table 1, stents were utilized in all but 2 studies[38, 41], and off-pump bypass techniques were available for CABG patients in 5 studies[34, 36, 39-41]. Four studies required multi-vessel disease for inclusion[35, 37, 38, 42] while 4 excluded individuals with multi-vessel coronary disease[34, 36, 40, 41]. One study (AMIST)[34] did not collect data on at least one covariate leading to systematic missingness. Eligible studies for which we were unable to obtain data were qualitatively similar to included studies in terms of sample size, year enrolled, revascularization technique, inclusion criteria and the range of relative risks of study outcomes following PCI compared with CABG (Supplementary Tables 4 & 5).

Baseline Characteristics of Study Subjects

The study cohort included 3993 randomized subjects (CABG: 1994, PCI: 1999,) with 17,131 person-years (PY) of post-intervention follow-up time (post-CABG: 8528 PY, post-PCI: 8603 PY). There were 526 individuals with stage 3 or worse CKD with 1856 PY of follow-up (CABG: 892 PY, PCI: 964 PY), and 137 with stage 3b or worse CKD (20 with stage 4-5 CKD) with 402 PY of follow-up (CABG: 195 PY, PCI: 207 PY). There were 7 individuals with stage 5 CKD. Baseline characteristics of the enrolled patients and those with CKD are shown in **Tables 2 and 3**. Individuals with and without CKD were mostly similar, but those with CKD tended be older and a higher percentage of those with CKD were female.

Survival

All-cause mortality rates were similar following CABG or PCI, and were higher among individuals with CKD (CABG: 5.6/100 PY, PCI: 5.5/100 PY) compared to those with preserved kidney function (CABG: 2.1/100 PY, PCI: 2.3/100 PY).

In primary multiple imputation-based analysis adjusted for all covariates of interest, mortality did not differ between patients randomized to CABG *versus* PCI among individuals with relatively preserved kidney function (HR 0.90, 95% CI: 0.73, 1.11), those with stage 3-5 CKD (HR 0.99, 95% CI: 0.67, 1.46), those with stage 3a CKD (HR 0.79, 95% CI: 0.47, 1.33), or those with stage 3b-5 CKD (HR 1.29, 95% CI: 0.68, 2.46; **Figure 2A-C**). In the overall cohort, there was no significant evidence for effect modification by the presence of CKD ($P_{interaction}$=0.52). Among individuals with CKD there was no significant effect modification on survival according to the presence of proximal left anterior descending artery stenosis ($P_{interaction}$=0.88) or according to the presence or absence of multi-vessel disease ($P_{interaction}$=0.13). Results were similar in crude and adjusted analyses (Table 4). For the subgroup with stage 3-5 CKD, the I^2 statistic (0.0%) was consistent with minimal between-study heterogeneity.

Short-term results at 1 year were qualitatively similar to 5-year outcomes. Adjusted risks of mortality did not differ 1 year after CABG compared with PCI among individuals with preserved kidney function (HR 1.35, 95% CI: 0.95, 1.93), those with stage 3-5 CKD (HR 0.92, 95% CI: 0.54, 1.58), those with stage 3a CKD (HR 0.73, 95% CI: 0.35-1.54), or those with stage 3b-5 CKD (HR 1.28, 95% CI: 0.56, 2.95).

Myocardial Infarction

Among individuals with CKD, non-fatal MI rates were higher after PCI (5.1/100 PY) than CABG (2.7/ 100 PY, P=0.01) whereas the rates were similar after PCI (2.9/100 PY) and CABG (2.9/100 PY, P=0.95) amongst individuals with preserved kidney function. Among individuals with CKD 13.2% died within 30 days of an MI compared with 7.3% among those with preserved renal function.

In primary analysis models, the risk of non-fatal MI among individuals with preserved kidney function (HR 0.97, 95% CI: 0.80, 1.17) did not differ between the two treatments, whereas MI risk among patients was lower following CABG compared with PCI in those with stage 3-5 CKD (HR 0.49, 95% CI: 0.29, 0.82) and stage 3a CKD (HR 0.70, 95% CI: 0.36, 1.39), and was even lower among those with stage 3b-5 CKD (HR 0.23, 95% CI: 0.09, 0.58). A significant test of interaction in analyses of the full cohort was consistent with effect modification by the presence *versus* absence of stage 3-5 CKD ($P_{interaction}$=0.04).

Among individuals with CKD, CABG provided similar benefits between individuals with and without multi-vessel disease ($P_{interaction}$=0.13) and between those with *versus* without proximal LAD disease ($P_{interaction}$=0.32). Results were qualitatively similar in crude and adjusted analyses (Table 5). For the subgroup with stage 3-5 CKD, the I^2 statistic (0.0%) was consistent with minimal between-study heterogeneity.

Short-term results at 1 year were similar to 5-year outcomes. Adjusted risks of MI did not differ 1 year after CABG compared with PCI among individuals with preserved kidney function (HR 1.17, 95% CI: 0.92, 1.49), but were lower following CABG compared with PCI in those with stage 3-5 CKD (HR 0.44, 95% CI: 0.23, 0.81), those with stage 3b-5 CKD (HR 0.18, 95% CI: 0.05, 0.58), and were not significantly lower among those with stage 3a CKD (HR 0.59, 95% CI: 0.28-1.28).

Repeat Revascularization

Repeat revascularization was conducted more frequently after PCI than CABG (Figure 2) both among individuals with CKD (7.2 cases/100 PY *versus* 1.4 cases/100 PY, P<0.001) and those with preserved kidney function (13.7 cases/100 PY *versus* 1.7 cases/100 PY, P<0.001). Risk reduction associated with revascularization was similar for individuals with preserved kidney function (HR 0.14, 95% CI: 0.11, 0.17), those with stage 3-5 CKD (0.21, 95% CI: 0.11, 0.39), those with stage 3a CKD (HR 0.17, 95% CI: 0.08, 0.40) and those with stage 3b-5 CKD (HR 0.25, 95% CI: 0.09, 0.71). There was no evidence of effect modification by the presence of CKD, $P_{interaction}$=0.26). Tests of interaction with multi-vessel disease ($P_{interaction}$=0.93) or proximal LAD involvement ($P_{interaction}$=0.90) were also non-significant. Results were similar in crude and adjusted models (Table 6). For the subgroup with stage 3-5 CKD, the I^2 statistic (25.3%) was consistent with minimal between study heterogeneity.

Short-term results at 1 year were similar to 5-year outcomes. Adjusted risks of revascularization were lower 1 year after CABG compared with PCI among individuals with preserved kidney function (HR 0.08, 95% CI: 0.06, 0.11), as well as those with stage 3-5 CKD (HR 0.14, 95% CI: 0.06, 0.30), those with stage 3a CKD (HR 0.12, 95% CI: 0.04-0.33), or those with stage 3b-5 CKD (HR 0.17, 95% CI: 0.05, 0.61).

Sensitivity Analyses

Results of models with differing levels of covariate adjustment, excluding studies with systematic missingness, or using complete-case analysis rather than multiple imputation were qualitatively similar to our main findings (Supplementary Tables).

Acute Dialysis and Hospitalization—Information on dialysis was not available for GABI. In the remaining trials, there were 8 (0.5%) cases of dialysis requiring acute kidney injury (AKI) in the PCI group and 5 (0.3%) cases in the CABG group. Among individuals with stage 3-5 CKD there were 5 (2.4%) cases in the PCI group and 2 cases (1.1%) in the CABG group. The risk of dialysis-dependent AKI did not differ significantly with CABG compared to PCI overall (odds ratio [OR] 0.61, 95% CI 0.20, 1.88), those with preserved kidney function (OR 0.98, 95% CI: 0.20, 4.85), or those with stage 3-5 CKD (OR 0.41, 95% CI: 0.08, 2.15), or stage 3b CKD (OR 0.71, 95% CI: 0.10, 5.23).

Data on cardiovascular hospitalizations was available from 6 trials.[36, 38, 39, 41-43] CABG was generally associated with lower risks of hospitalization than PCI. At 5-years, the adjusted risk was lower after CABG than PCI among those with preserved kidney function (HR 0.30, 95% CI: 0.23, 0.39), those with stage 3-5 CKD (0.43, 95% CI: 0.27, 0.71), and those with stage 3a CKD (HR 0.32, 0.17, 0.60). CV hospitalization rates were lower but the change in risk was not significant with stage 3b-5 CKD (HR 0.77, 95% CI: 0.35, 1.72). There was no evidence of effect modification according to the presence of CKD ($P_{interaction}$=0.19). For the subgroup with stage 3-5 CKD, the I^2 statistic (1.0%) was consistent with minimal between study heterogeneity. Results during the first year were qualitatively similar to those at 5 years (data not shown).

Discussion

Although CKD is a common condition[1] with high risks of cardiovascular morbidity and mortality[3], high quality evidence to guide the use of PCI *versus* CABG in the setting of significant kidney impairment has been lacking. To better understand the risks and benefits of coronary revascularization in individuals with CKD, we analyzed individual, patient-level data from almost four thousand individuals enrolled in 10 trials in which patients were randomized to receiving CABG or PCI. To our knowledge, the 526 individuals with CKD that we identified represent the largest randomly assigned cohort comparing the risks of benefits of CABG and PCI in the setting of CKD.

We found that for individuals with stage 3-5 CKD in whom both CABG and PCI were clinically indicated and technically feasible, there were no significant differences in mortality with either approach to revascularization. However, despite the similarities in mortality, CABG strongly reduced both the risks of MI and the need for additional revascularization procedures without evidence for significant effect modification by the presence of single compared with multi-vessel disease. The present study provides important new evidence informing the decision faced by clinicians and their patients with CKD who require coronary intervention and have to decide between CABG and PCI.

While we are unaware of any published clinical trials specifically randomizing individuals with CKD to CABG versus PCI, several observational studies have suggested that CABG was associated with lower mortality than PCI in the setting of CKD[15, 44-46], and at least one suggested that the mortality benefit increased as eGFR declined[15]. In contrast, a study by Szczech[47] was consistent with our findings. This study may more closely resemble the randomized population we studied as it specifically excluded subjects belonging to anatomic subgroups with grossly unbalanced utilization of CABG and PCI (suggesting non-comparability of the indication for revascularization), and it did not find a survival benefit from CABG among individuals with serum creatinine ≥2.5 mg/dL.

In contrast with some observational studies, our findings are mostly consistent with a prior analysis by Ix *et al.* of 290 randomized participants with CKD from the Arterial Revascularization Therapies Study[48] in which CABG did not impact mortality (HR 0.93, 95% CI 0.54-1.60) compared with PCI, but led to a significant reduction in the need for repeat revascularization (HR 0.28, 95% CI: 0.14-0.54). Both results were confirmed by our analysis although the primary investigator of the Arterial Revascularization Therapies Study did not grant access to their data for our study. Our results differ, however, in that the former study did not demonstrate significant reductions in the risk of MI (HR 1.34, 95% CI: 0.55-3.23). However, the confidence intervals around this estimate were wide because of low the number of MI events (n=20). By contrast, we found a strong reduction in MI risk from CABG that also appeared to increase with decreasing kidney function. Therefore, owing to nearly double the number of participants, a larger number of events within the CKD population (103 deaths, 68 MIs, 65 repeat revascularizations), and a more clinically relevant duration of follow-up (5 *versus* 3 years), our analysis extends the findings by Ix et al. in several important ways. In particular, our cohort included subjects from multiple trials with a more generalizable set of inclusion criteria that more broadly represent the range of clinical indications for revascularization than the Arterial Revascularization Therapies Study[48], which included only subjects with multi-vessel disease and excluded subjects with overt congestive heart failure. Finally, the use of an individual patient data from multiple trials allowed us to adjust for multiple covariates simultaneously, which would not have been possible using traditional meta-analytic techniques.

Taken together, our study and the one by Ix *et al*[48] suggest that prior observational analyses showing large survival benefits may have overestimated the mortality benefits of CABG compared with PCI in the setting of CKD. In fact, observational studies have consistently demonstrated increasing risks of operative death as kidney function declines[49], and our estimates do not rule out worsened survival following CABG compared with PCI among subjects with the most advanced CKD—although confidence intervals around these estimates were very wide.

Indication bias or residual confounding *via* selective utilization of CABG in those individuals with the best underlying prognosis or with anatomic features most clearly favorable to surgical revascularization or, conversely, selective use of PCI in patients with very high operative risk, may have driven prior findings of a survival benefit with CABG compared with PCI in the setting of CKD. Although our findings do not support a conclusion that CABG reduces the hazard of mortality compared to PCI when both CABG and PCI are anatomically and clinically feasible, we did find that among CKD patients, CABG was associated with dramatically lower risks of MI and repeat revascularization during follow-up. Thus, CABG may be the preferable procedure that reduces overall morbidity despite not conferring a survival advantage.

Our study had certain limitations that require consideration. Unfortunately, despite including data from the largest number of trials and including the largest reported number of randomized patients with CKD (particularly those with ≥stage 3b disease), numerous trials either no longer had data available or failed to collect sufficient information to calculate eGFR. We were also unable to obtain data from several additional trials despite several attempts. The majority of trials were completed before IDMS-traceable creatinine assays were in wide use, and we did not have access to the assays used for creatinine testing. The lack of standardization or calibration may have led to some imprecision in estimation of GFR, although this should be balanced in the two treatment groups. In addition, for the BARI trial[35] we were unable to obtain the actual creatinine, and instead had to use a threshold value, as described above. Although we are confident with the specificity of this approach for the identification of CKD, some patients with moderate CKD may have been missed.

We were also unable to standardize outcomes or baseline variable definitions across trials. We cannot rule out the possibility that different assessments across trials could have impacted our findings. Lastly, most of the included trials were completed more than a decade ago. Whether results would differ in the context of contemporary medical therapy, newer revascularization techniques, or for subjects not meeting the entrance criteria of these trials cannot be answered by our analysis, and results should be extrapolated cautiously.

Finally, our study does not address the gaping hole in the evidence on how to best treat patients with severe kidney dysfunction who require revascularization including those with end-stage kidney disease requiring dialysis or kidney transplantation. Indeed, an important finding of our analysis is that among nearly 4000 patients included in a series of randomized trials that helped establish the standard of care for coronary artery disease only 137 had stage 3b or worse CKD, only 20 had stage 4-5 CKD, and none had ESRD. Assuming that trial practices have not changed, this finding raises serious questions about the extrapolation of standard of care practices to the care of those at the most advanced stages of CKD.

In conclusion, our study provides the highest-quality evidence to date regarding the morbidity and mortality benefits of CABG compared with PCI in the setting of CKD. While survival was similar following CABG and PCI, we found that CABG significantly reduced the risk of subsequent MI or revascularization procedures. In the absence of additional randomized data, our analysis should be reassuring to clinicians who can counsel individuals requiring coronary revascularization that benefits of CABG do not appear to be attenuated in the setting of moderate CKD and that surgical revascularization is more likely than PCI to prevent subsequent MI or revascularization without adversely impacting survival. Finally, the hypothesis generating findings indicating worse survival with CABG in the small subsample of patients with Stage 3b and 4-5 CKD should provide additional motivation for performing randomized studies specifically enrolling individuals with advanced CKD or ESRD in order to provide better answers on risks and benefits in these high risk patients.

Methods

Search Criteria and Identification of Eligible Trials

We searched MEDLINE, EMBASE and Cochrane databases (Ovid Technologies 1950-September 2010) for keywords related to coronary revascularization procedures including, "angioplasty, transluminal, percutaneous coronary, and coronary artery bypass". The search was limited to randomized controlled trials (not valid within EMBASE), humans, and English language publications. Following automated removal of duplicate citations, results of the computerized search were independently reviewed in duplicate by 2 investigators (DMC, NMS, or WCW) to identify unique, randomized trials comparing CABG and PCI. The reference lists of identified trials and relevant meta-analyses were subsequently reviewed for studies not identified electronically. Trials that randomly allocated patients to CABG or PCI were considered for inclusion without further restriction. The manuscript reporting the primary endpoint results was used to identify trials and investigators. Additional detail on the research plan and modifications to the study protocol are provided in the Supplementary Appendix. The PRISM individual patient meta-analysis statement was used as a guideline for structuring the manuscript.[50]

Data Extraction

The majority of identified studies had not published CKD-specific results. Investigators from each trial were therefore contacted and asked to prepare and share data on trial characteristics and individual, patient-level data including serum creatinine, baseline characteristics, interventions, and selected outcomes for enrolled subjects. Multiple attempts were made to contact study investigators before determining investigators' status as unreachable. Provided data sets were individually cleaned and compared against trial publications for consistency with baseline characteristics and main outcomes. Trial investigators were re-contacted and queried as needed to ensure fidelity, accuracy, and completeness of final data sets.

Kidney Function

Kidney function was determined using the estimated glomerular filtration rate (eGFR), which was calculated using the CKD-EPI equation[51] from baseline serum creatinine concentrations, age, sex, and race. The Bypass Angioplasty Revascularization Investigation (BARI) trial recorded only a dichotomized kidney dysfunction variable according to whether serum creatinine was >1.5 mg/dL but did not record the actual baseline values[35]. Therefore the theoretical maximum value of eGFR was calculated for BARI subjects using a creatinine of 1.6 mg/dL for individuals above this threshold and 0.1 mg/dL for individuals below this threshold. Given the primary analytic goal of assessing effects of CABG *versus* PCI in CKD patients, this approach was adopted in order to ensure a high specificity of the CKD definition for BARI subjects despite the possibility of misclassifying some BARI subjects with less significantly elevated creatinine as having preserved kidney function. Stages of CKD were defined as stage 3a (eGFR 45-59 mL/min/1.73m^2), stage 3b (eGFR 30-44 mL/min/1.73m^2), stage 4 (eGFR 15-29 mL/min/1.73m^2), or stage 5 CKD (eGFR <15mL/min/1.73m^2 or dialysis-dependent) according to the 2012 updates of the KDOQI guidelines[52].

Other Patient Characteristics

Baseline demographic and clinical characteristics were assessed according to trial-specific definitions. Covariates obtained were chosen on the basis of availability and well-established associations with outcomes and included assigned treatment, age, race, sex, history of diabetes, hypertension, hyperlipidemia, congestive heart failure, prior coronary revascularization, history of prior myocardial infarction (MI), presentation with MI, unstable angina, or elevated cardiac enzymes, ejection fraction, and coronary anatomy.

Endpoints

Given the advanced age of the population and inconsistent data capture beyond 5 years, we calculated follow-up time and examined time-to-event outcomes through 5 years for the following events: all-cause mortality, myocardial infarction (MI), and repeat coronary revascularization. MI and repeat coronary revascularization outcomes were assessed according to the definitions originally used in the individual trials. Subjects who did not experience the event of interest during the study period were censored at the date of last clinical visit or recorded activity with right censoring at 5-years.

Statistics and Analysis

Summary statistics are presented as counts (%) or mean ± standard deviation (SD) as appropriate. For the primary analyses, we used Cox proportional hazards regression models, stratified by trial, to model the hazard of each endpoint (all-cause mortality, MI, and repeat revascularization) as a function of treatment arm (PCI versus CABG), adjusting for age, diabetes, prior history of MI, proximal left anterior descending artery disease, ejection fraction <40%, prior revascularization, and multi-vessel disease. We fit models to the entire pooled dataset as well as within pre-defined subsets of clinical interest. Namely, subset analyses were conducted in subjects with: 1) preserved kidney function, 2) stage 3-5 CKD, 3) stage 3a CKD, 4) stage 3b-5 CKD, 5) CKD with multi-vessel disease, 6) CKD with single-vessel disease, 7) CKD with proximal left anterior descending [LAD] disease, or 8) CKD without proximal LAD disease. Kaplan-Meier estimates were used to graphically depict survival.

Multiple imputation was used to account for missing data. Multiple imputation is a statistical method used to address missing data by imputing values for missing observations from plausible distributions that preserve the interrelationships among the variables.[53, 54] Validity of the results relies on the assumption that data are missing at random (MAR), or that missingness is related to observed features only. Specifically, for primary analyses, we imputed data using predictive mean matching to impute each row independently. It is critical to include the outcome in the imputation model to reduce bias[55]; we therefore included an indicator for whether the observation was censored and also included the Nelson-Aalen estimator of cumulative hazard as a co-factor within the imputation models.[56] As a sensitivity analysis, we imputed under a linear multilevel model that accounts for a trial-specific underlying hazard of the event corresponding to the study's unique population. For this approach, computational limitations required the exclusion of trials (Angioplasty *versus* Minimally Invasive Surgery Trial, AMIST)[34] with systematic missingness on any variable (meaning that a variable is completely missing within a trial).

We conducted sensitivity analyses manipulating 3 analytic choices in all possible combinations to assess the effects on point estimates of covariate adjustment, inclusion of studies with systematic missingness, and method of handling missing data. Firstly, we conducted analyses adjusting for 1) all covariates of interest, as in primary analyses, 2) a “minimal” subset of only those covariates that were not systematically missing by trial, or 3) no covariates (unadjusted estimates). Secondly, we excluded either 1) none of the 10 eligible studies, as in primary analyses, or 2) all studies with systematic missingness on any variable. Thirdly, we handled missing data either 1) via multiple imputation, as in primary analyses, or 2) via complete-case analysis.

Heterogeneity of outcomes within the CKD group was analyzed by calculating the I-squared statistic. Published meta-analyses comparing CABG and PCI have not found evidence of publication bias.[8] Given our primary aim of comparing unpublished outcomes from the subset of those studies with available data on renal function and the attendant analysis of only a minority of published studies, testing for publication bias on the included studies was not repeated.

Baseline data and incidence rates and calculation of I-squared for measurement of heterogeneity were analyzed using STATA (version 13.0, STATA Corp, College Station, Texas). Multiple imputation and survival analyses were performed in R (Version 3.1.0, R Foundation for Statistical Computing, Vienna, Austria)[57-61]. All tests were two-sided, and we defined statistical significance using an alpha threshold of 0.05.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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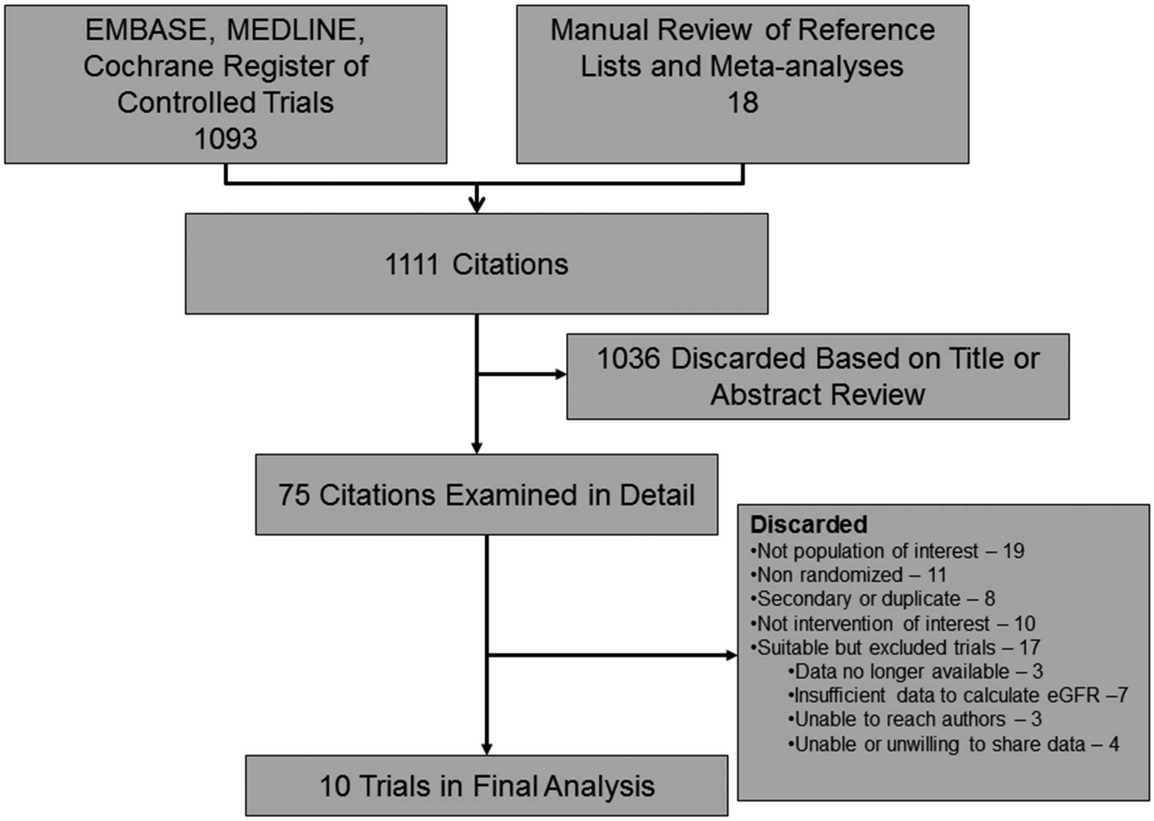

Figure 1.
Flow diagram of study selection

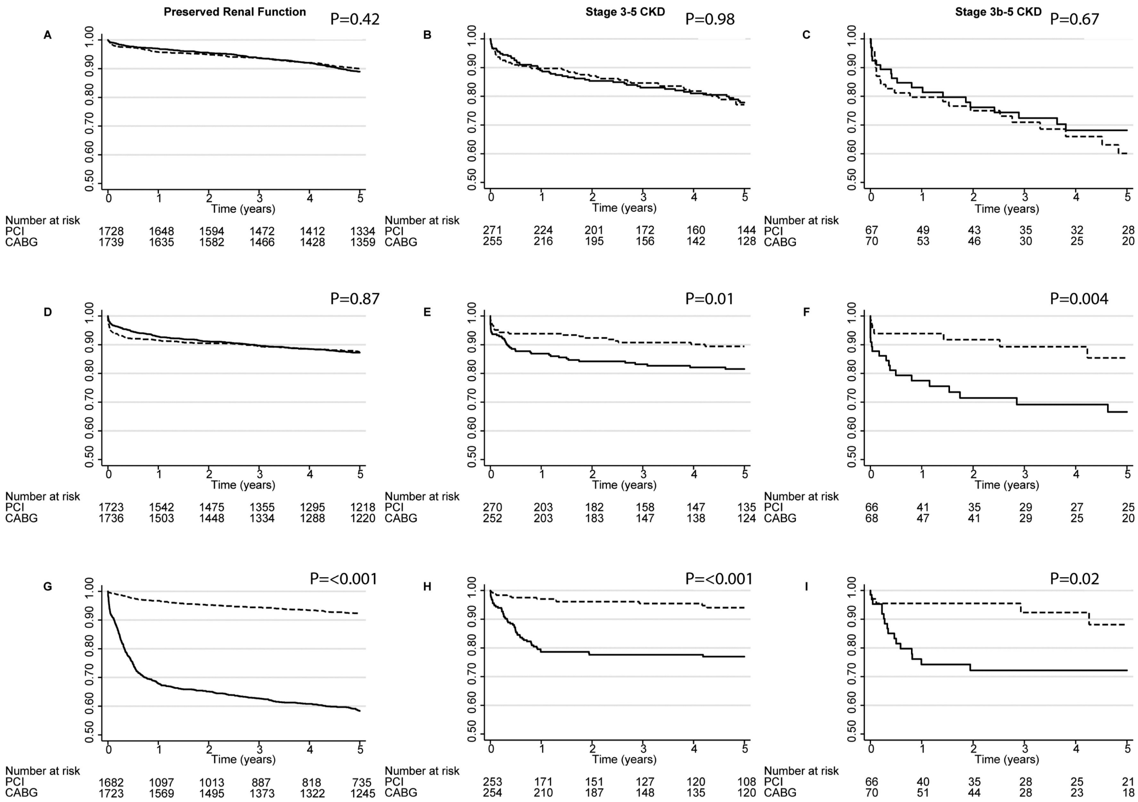

Figure 2.

Actuarial freedom from death, MI, or revascularization after CABG and PCI by clinical subset

Event-Free Survival after CABG and PCI calculated using the Kaplan-Meier method. (A-C) Overall survival. (D-F) Freedom from myocardial infarction. (G-I) Freedom from repeat revascularization. Unadjusted (Cox) P values stratified by trial are provided. CABG-dashed lines. PCI-solid lines.

Table 1

Trial characteristics

Characteristic	AMIST	BARI	Cisowski	ERACI II	GABI	Le MANS	Leipzig	MASS 1	MASS 2	VA
Central randomization	+	+	-	+	+	+	+	+	+	+
Concealed randomization	+	+	+	+	+	+	+	+	+	+
Blinded outcomes assessment	-	+	-	+	+	+	+	+	+	-
Intention to treat analysis	+	+	+	+	+	+	+	+	+	+
Stents used	+*	+	+*	+	-	+*	+*	-	+	+
Off-pump bypass	+*	-	+*	-	-	+	+*	-	-	NR
LIMA	+*	+	+*	+	+	+	+*	+*	+	+
Enrollment Period	1999-2001	1988-1991	2000-2002	1996-1998	1986-1991	1997-2008	1997-2001	1988-1991	1995-2000	1995-2000
Single vessel disease only	+	-	+	-	-	-	+*	+*	-	-
Multi-vessel disease only	-	+*	-	+*	+*	-	-	-	+*	-
Single or multi-vessel disease	-	-	-	-	-	+	-	-	-	+
Left main disease	-	-	-	+	-	+*	-	-	-	-

NR-not recorded. LIMA-left internal mammary artery.

*Required by protocol.

Table 2

Baseline characteristics of trial subjects

Characteristic N (%)	AMIST	BARI	Cisowski	ERACI II	GABI	Le MANS	Leipzig	MASS 1	MASS 2	VA
Year published	2004	1996	2002	2001	1994	2008	2005	1999	2002	2001
No. of subjects	89	1829	76	450	313	82	220	141	408	385
Age, years mean (SD)	57.7 (9.6)	61.0 (9.4)	53.4 (10.0)	60.7 (10.3)	58.9 (7.9)	61.0 (9.8)	62.0 (10.1)	56.5 (10.1)	59.7 (9.0)	67.4 (9.2)
Male	71 (79.8)	1340 (73.3)	63 (82.9)	357 (79.3)	248 (79.2)	56 (68.3)	164 (74.6)	104 (73.8)	283 (69.4)	381 (99.0)
White	87 (97.8)	1653 (90.4)	76 (100.0)	450 (100.0)	313 (100.0)	81 (98.8)	220 (100.0)	137 (97.2)	352 (86.3)	339 (88.1)
Stage 3-5 CKD	18 (20.2)	43 (2.4)	11 (14.5)	111 (24.7)	51 (16.3)	16 (19.5)	30 (13.6)	25 (17.7)	83 (20.3)	138 (35.8)
Stage 3b-5 CKD	4 (4.5)	23 (1.3)	4 (5.3)	14 (3.1)	11 (3.5)	5 (6.1)	4 (1.8)	4 (2.8)	18 (4.4)	50 (13.0)
Diabetes	--	353 (19.3)	6 (7.9)	78 (17.3)	39 (12.6)	14 (17.1)	63 (29.6)	30 (21.3)	115 (28.2)	125 (32.6)
Smoking	--	463 (25.3)	39 (51.3)	233 (51.8)	35 (11.8)	6 (9.0)	54 (25.4)	56 (39.8)	123 (30.2)	96 (34.0)
Hypertension	--	896 (49.0)	42 (55.3)	318 (70.7)	130 (41.8)	76 (92.7)	152 (71.4)	43 (30.5)	253 (62.0)	267 (69.5)
Hyperlipidemia	--	725 (44.0)	59 (77.6)	275 (61.1)	193 (62.7)	80 (97.6)	152 (71.4)	108 (76.6)	322 (78.9)	--
Prior revascularization	--	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.3)	0 (0.0)	0 (0.0.)	0 (0.0)	164 (42.7)
Prior MI	--	987 (54.5)	9 (11.8)	126 (28.0)	143 (46.3)	31 (37.8)	99 (46.5)	0 (0.0)	191 (46.8)	275 (72.0)
CHF	--	161 (8.9)	0 (0.0	16 (3.6)	151 (48.7)	1 (1.2)	--	0 (100.0)	2 (0.5)	294 (86.5)
Multi-vessel disease	0 (0.0)	1796 (98.4)	0 (0.0)	450 (100.0)	313 (100.0)	78 (95.1)	0 (0.0)	0 (0.0)	408 (100.0)	316 (82.1)
Left main disease	0 (0.0)	0 (0.0)	0 (0.0)	21 (4.7)	0 (0.0)	80 (97.6)	0 (0.0)	0 (0.0)	0 (0.0)	28 (7.5)
Proximal LAD disease	89 (100.0)	1081 (59.2)	76 (100.0)	230 (51.1)	90 (28.9)	28 (34.2)	220 (100.0)	141 (100.0)	381 (93.4)	221 (58.9)
No. diseased vessels	1 (0.0)	2.4 (0.5)	1 (0.0)	2.4 (0.5)	2.4 (0.5)	3.0 (1.0)	1.2 (0.4)	1 (0.0)	2.6 (0.5)	2.3 (0.8)
Ejection Fraction, %, mean (SD)	66.6 (10.6)	57.4 (11.0)	56.9 (4.9)	52.9 (5.6)	63.8 (10.6)	54.3 (8.6)	62.4(13.1)	69.2 (3.2)	67.3 (8.0)	46.0 (14.7)
Elevated cardiac biomarkers on admission	--	--	0 (0.0)	87 (19.3)	0 (0.0)	6 (7.3)	0 (0.0)	--	0 (0.0)	--
MI on admission	0 (0.0)	58 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.4)	0 (0.0)	0 (0.0)	191 (46.8)	134 (34.8)
Unstable angina on admission	18 (21.2)	1192 (65.2)	8 (10.5)	412 (91.6)	40 (13.5)	45 (54.9)	37 (16.8)	0 (0.0)	0 (0.0)	--

Table 1-Baseline characteristics. Data are presented as n (%) unless otherwise noted. CKD-chronic kidney disease, CHF-congestive heart failure, LAD-left anterior descending artery, MI-myocardial infarction, No-number, SD-standard deviation. Data on diabetes was not available for subjects in AMIST and was missing for 3 subjects in GABI, and 2 subjects in the VA study. Data on smoking was not available in AMIST, and was missing in 181 subjects from BARI, for 2 subject from GABI, 15 in LE MANS, 7 in Leipzig, and 103 subjects in the VA study. Hyperlipidemia was missing all AMIST subjects, 181 in BARI, 5 in GABI, 7 in Leipzig and all VA subjects. Data on baseline hypertension was unavailable in AMIST and was missing for 2 subjects from BARI, 2 in GABI, 7 in Leipzig and 1 in the VA study. Prior MI was unavailable for AMIST, and was missing in 18 subjects from BARI, 6 subjects from GABI, 7 in Leipzig, and 3 in the VA study. CHF was not available for AMIST participants and Leipzig and was missing in 10 subjects in BARI, 3 from GABI, and 45 subjects from the VA study. Prior revascularization was unavailable for AMIST and was missing 1 subject in the VA study. Multi-vessel disease was missing in 3 subjects from BARI. Left main disease was missing in 10 subjects from the VA study. Proximal LAD was missing in 3 subjects in BARI, 2 in GABI, and 10 in the VA study. Data on number of diseased vessels was missing in 7 subjects from GABI, 3 subjects from BARI, and 6 subjects from the VA study. Ejection fraction was missing in 55 subjects in AMIST, 475 in BARI 149

in GABI, 3 in Le MANS and 98 in the VA study. Cardiac biomarkers at baseline were not available for AMIST, BARI, VA, and MASS 1 studies. MI on admission was missing in 1 subject from Le MANS. Unstable angina at admission was missing in 4 subjects from AMIST, 17 from GABI, and all subjects in the VA study.

Table 3

Baseline characteristics of trial subjects with chronic kidney disease

Characteristic	AMIST (n=18)	BARI (n=43)	Cisowski (n=11)	ERACI II (n=111)	GABI (n=51)	Le MANS (n=16)	Leipzig (n=30)	MASS 1 (n=25)	MASS 2 (n=83)	VA (n=138)
Age, years mean (SD)	64.3 (8.9)	63.9.(8.8)	62.3 (10.0)	64.6 (9.4)	64.3 (7.0)	68.0 (8.3)	68.7 (7.2)	61.8 (9.4)	66.2 (6.5)	72.2 (6.6)
Male	11 (61.1)	31 (72.1)	7 (63.6)	44 (39.6)	26 (51.0)	7 (43.8)	16 (53.3)	8 (32.0)	3 (63.9)	136 (98.6)
White	18 (100.0)	33 (76.7)	11 (100.0)	111 (100.0)	51 (100.0)	16 (100.0)	30 (100.0)	25 (100.0)	76 (91.6)	122 (88.4)
Stage 3b-5 CKD	4 (22.2)	23 (53.5)	4 (36.4)	14 (12.6)	11 (21.6)	5 (31.3)	4 (13.3)	4 (16.0)	18 (21.7)	50 (36.2)
Stage 4-5 CKD,	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	4 (7.6)	1 (6.3)	0 (0.0)	0 (0.0)	4 (4.8)	10 (7.0)
eGFR mL/min/ 1.73m^2, mean (SD)	49.8 (8.1)	43.0 (6.7)	48.3 (8.1)	50.1 (6.6)	49.7 (11.4)	46.9 (8.4)	53.1 (6.5)	52.0 (6.7)	49.0 (10.4)	46.9 (10.6)
Diabetes	--	20 (46.5)	3 (27.3)	22 (19.8)	8 (15.7)	6 (37.5)	15 (5.7)	5 (20.0)	25 (30.1)	40 (29.0)
Smoking	--	7 (16.3)	3 (27.3)	50 (45.1)	3 (5.9)	1 (6.7)	4 (13.8)	7 (28.0)	14 (16.9)	20 (20.2)
Hypertension	--	33 (76.7)	8 (72.7)	91 (82.0)	32 (62.8)	16 (93.8)	28 (96.6)	7 (28.0)	58 (69.9)	113 (81.9)
Hyperlipidemia	--	18 (48.7)	5 (45.5)	72 (64.9)	36 (70.6)	16 (100.)	18 (62.1)	19 (76.0)	61 (73.5)	--
Prior revascularization	--	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	49 (35.5)
Prior MI	--	24 (57.1)	2 (18.2)	31 (27.9)	27 (54.0)	11 (68.8)	17 (58.6)	0 (0.0)	38 (45.8)	93 (68.4)
CHF	--	14 (32.6)	0 (0.0)	2 (1.8)	30 (58.8)	0 (0.0)	--	0 (0.0)	2 (2.4)	108 (88.5)
Multi-vessel disease	0 (0.0)	42 (97.7)	0 (100.0)	111 (100.0)	51 (100.0)	16 (100.0)	30 (0.0)	0 (0.0)	83 (100.0)	116 (84.1)
Left main disease	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.5)	0 (0.0)	16 (100.0)	0 (0.0)	0 (0.0)	0 (.0.0)	12 (8.9)
Proximal LAD disease	18 (100.0)	27 (62.8)	11 (100.0)	59 (53.2)	14 (27.5)	8 (50.0)	30 (100.0)	25 (100.0)	78 (94.0)	69 (51.1)
No. diseased vessels, mean (SD)	1 (0.0)	2.6 (0.5)	1 (0.0)	2.6 (0.5)	2.4 (0.5)	3.3 (0.8)	1.2 (0.4)	1 (0.0)	2.6 (0.5)	2.3 (0.8)
Ejection Fraction, %, mean (SD)	61.3 (14.1)	54.5 (12.5)	58.1 (5.9)	52.8 (5.3)	64.1 (11.1)	54.1 (5.0)	62.6 (13.5)	69.3 (3.2)	67.5 (9.2)	45.4(14.7)
Elevated cardiac biomarkers on admission	--	--	0 (0.0)	29 (26.1)	0 (0.0)	1 (6.3)	0 (0.0)	--	0 (0.0)	--
MI on admission	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	38 (45.8)	40 (29.0)
Unstable angina on admission	3 (16.7)	32 (74.4)	1 (9.1)	104 (93.7)	10 (20.0)	11 (68.8)	6 (20.0)	0 (0.0)	0 (0.0)	--

Table 1-Baseline characteristics. Data are presented as n (%) unless otherwise noted. eGFR estimates for BARI were calculated as described in the methods. CKD-chronic kidney disease, CHF-congestive heart failure, LAD-left anterior descending artery, MI-myocardial infarction, No-number, SD-standard deviation. Data on diabetes was not available for subjects in AMIST. Data on smoking was not available in AMIST, and was missing for 1 subject in LE MANS, and 39 subjects in the VA study. Hyperlipidemia was missing all AMIST subjects, 6 in BARI, 1 in Leipzig, and all VA subjects. Data on baseline hypertension was unavailable in AMIST and was missing for 1 subject from Leipzig. Prior revascularization was unavailable for AMIST. Prior MI was unavailable for AMIST, and was missing in 1 subject from BARI, 1 subject from GABI, 1 in Leipzig, and 2 in the VA study. CHF was not available for AMIST participants and was missing in 16 subjects from the VA study. Data on left main disease was missing in 3 VA subjects. Proximal LAD was missing in 3 subjects in the VA study. Data on number of diseased vessels was missing in 3 subjects from the VA study. Ejection fraction was missing in 10

subjects in AMIST, 23 in GABI, 1 in Le MANS and 33 in the VA study. Cardiac biomarkers at baseline were not available for AMIST, BARI, VA, and MASS 1 studies. Unstable angina at admission was missing in 1 subject from GABI, and all subjects in the VA study.

Table 4

Mortality risk with CABG compared to PCI

Group	Crude HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Overall (n=3993)	0.93	0.77, 1.12	0.43	0.92	0.76, 1.11	0.38
Preserved kidney Function (n=3467)	0.92	0.74, 1.13	0.42	0.90	0.73, 1.11	0.33
Stage 3-5 CKD (n=526)	1.01	0.68, 1.49	0.98	0.99	0.67, 1.46	0.96
Stage 3a CKD (n=389)	0.87	0.52, 1.45	0.60	0.79	0.47, 1.33	0.39
Stage 3b-5CKD (n=137)	1.15	0.62, 2.13	0.67	1.29	0.68, 2.46	0.43
CKD with multi-vessel disease* (n=419)	1.16	0.77, 1.75	0.49	1.10	0.73, 1.67	0.65
CKD with single-vessel disease* (n=107)	0.33	0.07, 1.61	0.17	0.32	0.06, 1.76	0.19
CKD proximal LAD disease* (n=342)	0.88	0.54, 1.43	0.61	0.94	0.57, 1.54	0.80
CKD without proximal LAD disease* (n=185)	1.31	0.67, 2.56	0.43	1.15	0.57, 2.27	0.71

All models were stratified by trial. Multivariable models adjusted for treatment, age, diabetes, prior myocardial infarction, proximal left anterior descending artery disease, ejection fraction <40%, prior revascularization, and multi-vessel.

*To avoid model overspecification, these subgroup models did not include terms for multi-vessel disease or proximal LAD disease, respectively. CKD-chronic kidney disease. LAD-left anterior descending artery.

Table 5

Risk of myocardial infarction with CABG compared to PCI

Group	Crude HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Overall (n=3981)	0.90	0.75, 1.07	0.23	0.88	0.73, 1.05	0.16
Preserved kidney Function (n=3459)	0.98	0.81, 1.19	0.87	0.97	0.80, 1.17	0.72
Stage 3-5 CKD (n=522)	0.49	0.30, 0.81	0.01	0.49	0.29, 0.82	0.01
Stage 3a CKD (n=388)	0.68	0.37, 1.27	0.24	0.71	0.36, 1.39	0.31
Stage 3b-5CKD (n=134)	0.27	0.11, 0.66	0.004	0.23	0.09, 0.58	0.002
CKD with multi-vessel disease* (n=416)	0.45	0.26, 0.79	0.01	0.43	0.24, 0.76	0.004
CKD with single vessel disease* (n=106)	0.71	0.20, 2.47	0.59	1.09	0.24, 4.86	0.91
CKD proximal LAD disease* (n=338)	0.39	0.19, 0.80	0.01	0.39	0.18, 0.82	0.01
CKD without proximal LAD disease* (n=183)	0.64	0.31, 1.33	0.23	0.74	0.34, 1.64	0.46

All models were stratified by trial. Multivariable models adjusted for treatment, age, diabetes, prior myocardial infarction, proximal left anterior descending artery disease, ejection fraction <40%, prior revascularization, and multi-vessel.

*To avoid model overspecification, these subgroup models did not include terms for multi-vessel disease or proximal LAD disease, respectively. CKD-chronic kidney disease. LAD-left anterior descending artery

Table 6

Risk of repeat revascularization for CABG compared to PCI

Group	Crude HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Overall (n=3912)	0.14	0.12, 0.17	<0.001	0.14	0.11, 0.17	<0.001
Preserved kidney Function (n=3405)	0.13	0.11, 0.16	<0.001	0.13	0.11, 0.16	<0.001
Stage 3-5 CKD (n=507)	0.21	0.11, 0.40	<0.001	0.21	0.11, 0.39	<0.001
Stage 3a CKD (n=371)	0.18	0.08, 0.41	<0.001	0.17	0.08, 0.40	<0.001
Stage 3b-5CKD (n=136)	0.30	0.11, 0.85	0.02	0.25	0.09, 0.71	0.01
CKD with multi-vessel disease* (n=400)	0.21	0.10, 0.46	<0.001	0.21	0.10, 0.46	<0.001
CKD with single vessel disease* (n=107)	0.20	0.07, 0.62	0.01	0.19	0.06, 0.61	0.01
CKD proximal LAD disease* (n=329)	0.19	0.09, 0.40	<0.001	0.18	0.09, 0.38	<0.001
CKD without proximal LAD disease* (n=176)	0.25	0.07, 0.87	0.03	0.25	0.07, 0.92	0.04

All models were stratified by trial. Multivariable models adjusted for treatment, age, diabetes, prior myocardial infarction, proximal left anterior descending artery disease, ejection fraction <40%, prior revascularization, and multi-vessel.

*To avoid model overspecification, these models did not include terms for multi-vessel disease or proximal LAD disease, respectively. CKD-chronic kidney disease. LAD