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All-Cause Mortality and Progression to End-Stage Kidney Disease Following Percutaneous Revascularization or Surgical Coronary Revascularization in Patients with CKD

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Introduction: Relative impacts of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) on mortality and end-stage kidney disease (ESKD) in chronic kidney disease (CKD) are uncertain.

Methods: Data from Massachusetts residents with CKD undergoing CABG or PCI from 2003 to 2012 were linked to the United States Renal Data System. Associations with death, ESKD, and combined death and ESKD were analyzed in propensity score–matched multivariable survival models.

Results: We identified 6805 CABG and 17,494 PCI patients. Among 3775 matched-pairs, multi-vessel disease was present in 97%, and stage 4 CKD was present in 11.9% of CABG and 12.2% of PCI patients. One-year mortality (CABG 7.7%, PCI 11.0%) was more frequent than ESKD (CABG 1.4%, PCI 1.7%). Overall survival was improved and ESKD risk decreased with CABG compared to PCI, but effects differed in the presence of left main disease and prior myocardial infarction (MI). Survival was worse following PCI than following CABG among patients with left main disease and without MI (hazard ratio = 3.7, 95% confidence interval = 1.3–10.5). ESKD risk was higher with PCI for individuals with left main disease and prior infarction (hazard ratio = 8.1, 95% confidence interval = 1.7–39.2).

Conclusion: Risks following CABG and PCI were modified by left main disease and prior MI. In individuals with CKD, survival was greater after CABG than after PCI in patients with left main disease but without MI, whereas ESKD risk was lower with CABG in those with left main and MI. Absolute risks of ESKD were markedly lower than for mortality, suggesting prioritizing mortality over ESKD in clinical decision making.

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Atherosclerotic heart disease is a major cause of morbidity and mortality in individuals with chronic kidney disease (CKD).[1,2] Although percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are widely used and have the potential to improve survival and to reduce the incidence of myocardial infarction or cardiovascular death, the relative merits of PCI compared with CABG in the setting of CKD remains uncertain in the absence of randomized data specific to this population. Extrapolation from trials conducted in the general population may not be appropriate given important differences in coronary plaque distribution and morphology, the underlying physiology of cardiovascular disease, and the risk of peri-procedural complications such as contrast nephropathy in the setting of CKD compared with preserved kidney function.[3–5] Furthermore, consistent with the overall pattern of exclusion of individuals with CKD from cardiovascular trials,[6] the number of patients with CKD included in randomized trials comparing CABG and PCI is small. A recent meta-analysis of 10 trials identified only 526 included subjects with stage 3 CKD or higher, and many fewer (only 137) with stage 3b CKD or higher.[7] Furthermore, although the risk of acute kidney injury following CABG and PCI is well described,[5,8] the

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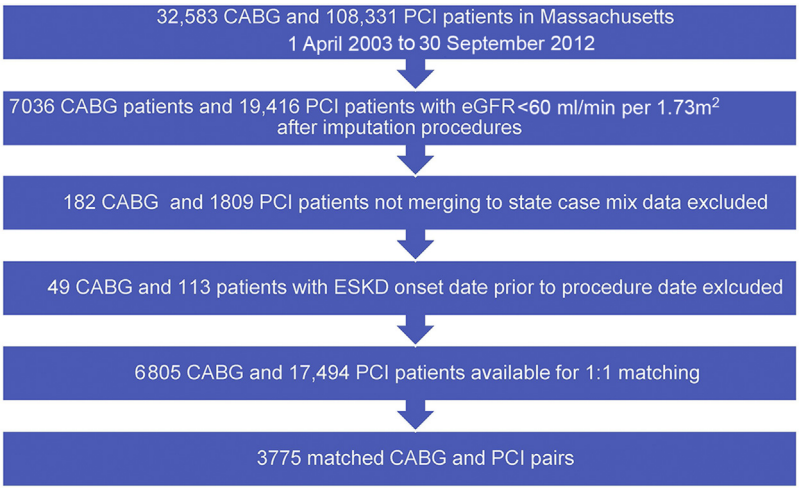

Figure 1. Study flow chart for sample imputed data set. CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PCI, percutaneous coronary intervention.

risks of progression to end-stage kidney disease (ESKD) following CABG and PCI are not.

As avoiding dialysis-dependent ESKD and its profound effects on quality of life are of primary importance for many patients, the paucity of information on this outcome represents an important knowledge gap. Conversely, although retrospective data have been used to analyze the comparative efficacy of CABG and PCI on overall survival, these analyses have typically lacked detail on coronary anatomy and other clinical factors likely to drive clinical decision making regarding the choice between CABG and PCI. To better define the relative risks of both all-cause mortality and ESKD following CABG compared with PCI in the setting of CKD, we used data from the Massachusetts statewide cardiac catheterization and cardiac surgery databases linked to the United States Renal Data System (USRDS).

MATERIALS AND METHODS

Study Population

Study flow is shown in Figure 1. We used data on Massachusetts residents undergoing PCI or isolated CABG (CABG without concurrent valve surgery) between 1 April 1, 2003 and 30 September, 2012 from all non-federal hospitals in Massachusetts performing coronary revascularization. Only individuals with non−dialysis-dependent stage 3 CKD or higher were included in this analysis. During the study period, prospective collection of procedural and outcomes data and reporting to the Massachusetts Data Analysis Center were legally mandated. Staff were trained in the use of the National Cardiovascular Data Registry (NCDR) and Society for Thoracic Surgeons (STS) data collection instruments, which were used for collection of data on PCI and CABG procedures, respectively. Audits of designated fields were used to verify accuracy of key parameters. Procedural characteristics and comorbidities were derived from the relevant field codes in the NCDR and STS instrument. The study was approved by the Partners Healthcare and Harvard Medical School Institutional Review Boards with a waiver of informed consent. Only the first procedure was used for each patient during the study period.

Definition of CKD and Comorbid Conditions

For CABG patients, we defined CKD on the basis of the pre-procedure serum creatinine recorded on the STS instrument. The procedure for identifying PCI patients differed based on the year and data instrument used to capture information. For patients undergoing PCI from October 2009 onward, the pre-procedure creatinine was used to calculate estimated glomerular filtration rate (eGFR). Between January 2005 and September 2009, the pre-procedure creatinine was utilized where available. If the pre-procedure creatinine was missing, the "renal failure−previous history" variable (defined as pre-procedure creatinine >2.0 mg/dl) was used to identify the presence of CKD. Individuals undergoing PCI prior to January 2005 were identified on the basis a variable confirming documented history of kidney failure diagnosed and treated with medication or a low protein diet by a physician. For these subjects with "renal failure−previous history" (2005−2009) or history of diagnosed kidney failure (2003−2004), serum creatinine was imputed to be 2.1 mg/dl, the minimum value above the threshold, in order to subsequently calculate the theoretical maximum potential eGFR. For both the CABG and PCI cohorts, patients identified as being on dialysis using the dialysis field in the STS or NCDR instrument, respectively, were excluded. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[9]

Chronic kidney disease was classified as stage 4 to 5 (eGFR < 30 ml/min per 1.73 m^2), stage 3b (eGFR 30 to <45 ml/min per 1.73 m^2), or stage 3a (eGFR 45 to <60 ml/min per 1.73 m^2).

Comorbid conditions were extracted from the MASS-DAC (Massachusetts Data Analysis Center) data using the data recorded at the time of hospitalization in the PCI and CABG instruments.

Linkage to the USRDS

We determined progression to and date of onset of ESKD by cross-matching CABG and PCI patients with CKD in the Massachusetts Data to the USRDS[10] using full name, date of birth, and last known alive date. Social security numbers were not used for linking to the USRDS because of Massachusetts Departments of Health data privacy regulations that precluded sharing these data outside the state. Individuals with ESKD defined by receipt of either outpatient dialysis or kidney transplantation prior to the procedure were excluded from further analysis.

Outcomes

Outcomes of interest included all-cause mortality and ESKD, with the date of ESKD defined by the date of the first kidney transplantation or dialysis treatment as recorded in the USRDS. We did not distinguish between transplantations performed pre-emptively from those done after the onset of symptoms. In-hospital mortality (for PCI) and 30-day mortality (for CABG) are reported directly to Mass-DAC. Linkage to the Massachusetts Registry of Vital Records and Statistics allows confirmation of both short-term and post-discharge mortality for the initial hospitalization as well as for long-term mortality. The Social Security Death Index is used where necessary for additional clarification. End-stage kidney disease was defined on the basis of the linked USRDS renal data. To quantify the balanced risks of these 2 key outcomes, we also examinedacombined endpoint of ESKD and all-cause mortality. Other outcomes included repeat revascularization, which is reported directly to the MASS-DAC, and myocardial infarction. Infarction occurring during the index hospitalization is identified directly from MASS-DAC data on the basis of mandatory reporting of in-hospital complications. Postdischarge events were identified from hospital administrative data and defined as the presence of an *International Classification of Diseases,* 9th Revision (ICD-9) principal diagnosis of 410.x1.

Statistical Analysis

Baseline data are reported as mean ± SD, median (interquartile range [IQR]), or n (%), according to the distribution. We used a full conditional specification model to impute 5 completed data sets for missing data. Where necessary, eGFR was calculated using imputed race or age.

The imputed data were next used to calculate a propensity score for PCI versus CABG. Subjects were matched 1:1 on the propensity score using a greedy algorithm a caliper of 0.6 SDs[11] of the estimated propensity score logits using a logistic model of treatment that included all of the baseline factors in Table 1. We did not include discharge medication use (Supplementary Table S1) in the propensity score model, as these variables are on the causal pathway and should not be adjusted for when assessing the comparative effectiveness of the 2 procedures. Specifically: (i) decisions to use discharge medications may be a consequence of procedural choice, with postdischarge use of optimal medical therapy more likely in patients with postprocedural care dictated by cardiologists compared with surgeons; (ii) postdischarge medical therapy may be influenced by complications of or guidelines regarding the index procedure: for example, aspirin and anti-platelet are mandatory in individuals receiving stents and may be contraindicated by post-surgical bleeding; conversely, anti-hypertensive choice may be influenced by post-CABG arrhythmias and hypotension; and (iii) discharge medications were not available at the time of the index procedure and may be frequently started days or weeks after the index procedure, with an anticipated differential start time in PCI and CABG patients as well as differential availability in those with in-hospital death. Inclusion in the propensity score would therefore be inappropriate.

Standardized differences (reported as percentages) were calculated before and after matching to assess covariate balance. Differences ≤10% were considered negligible.[12] Baseline, postmatch characteristics, and standardized differences are presented for 1 of 5 imputed data sets for illustrative purposes.

The cumulative incidence of each outcome during follow-up was estimated; for ESKD and secondary outcomes, death was considered a competing event. The hazard ratio (HR) for ESKD or the combined outcome of death or ESKD were calculated using Cox proportional hazards. Competing risks models were used to assess the risk of ESKD according to the methods of Fine and Gray[13,14] to handle competing risk. All analyses used the 5 multiply imputed data sets, and estimates were combined according to standard (Rubin) rules.[15] Because of imbalance in the distribution of left main disease and myocardial infarction (MI) following propensity score matching, outcomes were determined individually for each of the 4 strata of left main and MI. We tested for interactions of

Table 1. Baseline characteristics of the study population

Variable	Overall CABG (n = 6805)	Overall PCI (n = 17,494)	Standardized difference	Matched CABG (n = 3775)	Matched PCI (n = 3775)	Standardized[a] difference (%)
Demographics						
Age, yr	72.9	73.9	−0.11	73.0	72.9	0.0
Male sex	4483 (65.9)	9962 (56.9)	18.4	2419 (64.1)	2385 (63.2)	1.9
White race	6205 (91.3)	15,786 (90.3)	3.1	3414 (90.5)	3415 (90.7)	−0.4
Government insurance	4737 (69.6)	11,803 (67.5)	4.6	2609 (69.1)	2576 (68.2)	1.9
Private insurance	1971 (29.1)	5435 (31.2)	−4.6	1110 (29.5)	1150 (30.5)	−2.1
Other insurance	91 (1.3)	238 (1.4)	−0.2	50 (1.3)	49 (1.3)	0.3
Medical history						
CKD stage						
Stage 4	732 (10.8)	2616 (15.0)	−12.6	449 (11.9)	460 (12.2)	−1.0
Stage 3b	1964 (28.9)	5269 (30.2)	−2.8	1095 (29.0)	1057 (28.1)	2.1
Stage 3a	4109 (60.4)	9587 (54.9)	11.2	2231 (59.1)	2250 (59.7)	−1.3
Ejection fraction						
<30%	636 (9.3)	993 (5.7)	14.0	352 (9.3)	331 (8.8)	1.9
30–45%	1927 (28.3)	2738 (15.7)	30.9	1018 (27.0)	952 (25.2)	4.0
>45%	4005 (58.9)	6328 (36.2)	46.6	2190 (58.0)	2273 (60.2)	−4.5
Not measured	237 (3.5)	7435 (42.5)	−104.7	215 (5.7)	219 (5.8)	−0.5
NYHA classification						
NYHA 1	67 (0.0)	175 (1.0)	−10.0	41 (1.1)	42 (1.1)	−0.3
NYHA 2	350 (5.1)	676 (3.9)	6.2	186 (4.9)	172 (4.6)	1.7
NYHA 3	758 (11.1)	1433 (8.2)	10.0	411 (10.9)	392 (10.4)	1.6
NYHA 4	730 (10.7)	1979 (11.3)	−1.9	382 (10.1)	368 (9.7)	1.2
Acute coronary syndrome	3783 (55.6)	12,847 (73.4)	−37.9	2238 (59.3)	2162 (57.3)	4.1
Arrhythmia	1003 (14.7)	1294 (8.3)	20.4	421 (11.2)	330 (10.0)	3.7
Coronary disease	1961 (28.8)	4033 (23.1)	13.2	1038 (27.5)	1002 (26.5)	2.1
Cerebrovascular disease	1441 (21.2)	2857 (16.3)	12.4	755 (20.0)	751 (19.9)	0.3
Diabetes	3257 (47.9)	6915 (39.5)	16.9	1801 (47.7)	1748 (46.3)	2.8
Hyperlipidemia	5997 (88.1)	14,439 (82.5)	15.8	3332 (88.3)	3325 (88.1)	0.5
Hypertension	6213 (91.3)	15,253 (87.2)	13.3	3424 (90.7)	3448 (91.3)	−2.2
Peripheral vascular disease	1688 (24.8)	3430 (19.6)	12.5	879 (23.3)	880 (23.3)	−0.1
Prior myocardial infarction	3916 (57.5)	5075 (29.0)	60.1	1939 (51.4)	1738 (46.0)	10.7
Prior CABG	139 (2.0)	2901 (16.6)	−51.7	135 (3.6)	204 (5.4)	−8.8
Prior PCI	838 (12.3)	2883 (16.5)	−11.9	544 (14.4)	582 (15.4)	−2.8
Cancer	182 (2.7)	557 (3.2)	−3.0	101 (2.7)	92 (2.4)	1.5
Current smoker	832 (12.2)	2108 (12.1)	0.5	452 (12.0)	432 (11.4)	1.6
Chronic lung disease	1225 (18.0)	3121 (17.8)	0.4	711 (18.8)	700 (18.5)	0.7
Aspirin use	5472 (80.4)	16,980 (97.1)	−54.6	3512 (93.0)	3567 (94.5)	−6.0
Procedural and angiographic characteristics						
Elective	2184 (32.1)	4268 (24.4)	17.2	1266 (33.5)	1368 (36.2)	−5.7
Emergency or salvage	201 (3.0)	4180 (23.9)	−64.5	163 (4.3)	162 (4.3)	0.1
Procedure						
Urgent procedure	4420 (65.0)	9046 (51.7)	27.1	2346 (62.1)	2245 (59.5)	5.5
Done in a teaching hospital	5753 (84.5)	13,626 (77.9)	17.1	3129 (82.9)	3135 (83.0)	−0.4
Shock	85 (1.2)	766 (4.4)	−19.0	61 (1.6)	64 (1.7)	−0.6
Left main disease	2756 (40.5)	1288 (7.5)	83.7	629 (16.7)	462 (12.5)	11.8
Multi-vessel disease	6690 (98.3)	12,002 (70.4)	83.3	3662 (97.0)	3575 (97.1)	−0.4
Left main and MI stratum						
Left main disease (+), prior MI (+)	1604 (23.6)	673 (3.9)	59.5	264 (7.0)	281 (7.6)	−2.4
Left main disease (+), prior MI (−)	1152 (16.9)	615 (3.6)	45.1	365 (9.7)	181 (4.9)	18.4
Left main disease (−), prior MI (+)	2312 (34.0)	4264 (24.9)	20.0	1675 (44.4)	1410 (38.2)	12.6
Left main disease (−), prior MI (−)	1737 (25.5)	11,579 (67.6)	−93.0	1471 (39.0)	1821 (49.3)	−20.9

Data are n (%) unless otherwise indicated. Data are shown for 1 of 5 imputed data sets. NYHA class, acute coronary syndrome, coronary artery disease, hyperlipidemia, insurance, race, smoking, and estimated glomerular filtration rate were missing in <1% of the overall data of the matched data set. History of arrhythmia was missing in 12.7%, multi-vessel disease in 2.4%, and left main in 2.2% of matched pairs. Matched data are shown for illustrative purposes from 1 of the 5 imputed data sets. CABG, coronary artery bypass surgery; CKD, chronic kidney disease; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
[a]For categorical variables, standardized differences were compared for each level of a categorical variable between the 2 treatment groups.

treatment with these strata in regression models using absence of left main and absence of prior MI as the reference category. Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), with $P < 0.05$ considered significant. No multiplicity adjustment was applied.

RESULTS

Cohort and Baseline Characteristics

We identified a total of 32,583 CABG patients and 108,331 PCI patients between 1 April 2003 and 30 September 2012 (Figure 1). After excluding patients with a history of dialysis, imputing missing values (including missing race) to define the final values for GFR, there were 7036 CABG patients and 19,416 PCI patients with GFR values <60 ml/min per 1.73 m^2 at the time of the procedure. Linkage to the USRDS and exclusion of individuals not linking to the state case-mix data or with ESKD onset date prior to the index cardiovascular procedure yielded 6805 CABG and 17,494 PCI patients. Following 1:1 matching, there were a maximum of 3775 pairs available, although the exact number varied slightly across the 5 imputed data sets (n = 3768−3775). Median follow-up time for the matched pairs was 1985 day (IQR = 1153−2617) with a maximum follow-up time of 3471 days. The distribution of propensity scores was qualitatively similar across the sets with an area under the receiver operating characteristic curve of 0.934 in each set (Supplementary Figure S1).

As shown in Table 1, in the overall population, age was advanced (CABG 73 years, PCI 74 years); the majority of individuals were male (CABG 66%, PCI 57%); and the majority had stage 3a (CABG 60%, PCI 55%) or 3b (CABG 29%, PCI 30%) CKD rather than stage 4 to 5 CKD (CABG 11%, PCI 15%). Among PCI procedures, 3616 (96%) involved use of 1 or more stents. The majority of procedures (2504 of 3775 [66%]) included the use of a drug-eluting stent.

There were considerable differences between the CABG and PCI patients, with CABG patients more likely to be male and to have a history of arrhythmia, MI, cerebrovascular disease, or diabetes. Conversely, CABG patients were less likely than PCI patients to have acute coronary syndrome, prior PCI, or prior CABG. In addition, CABG patients were more likely to have left main disease or multi-vessel disease and less likely to have an emergency or salvage procedure. Following matching (Table 1), differences between the CABG and PCI patients were markedly reduced. However, small residual differences remained for left main disease (left main−CABG 17%, PCI 13%, standardized difference 11.8; and MI−CABG 51%, PCI 46%, standardized difference 10.7). The distribution of eGFR was similar in the PCI and CABG groups (Supplementary Table S2), with a distribution of CKD stages among the matched pairs that was no different from the distribution in overall population: stage 3a (CABG 59%, PCI 60%), stage 3b (CABG 29%, PCI 28%), and stages 4 and 5 CKD (CABG 12%, PCI 12%).

Binary Outcomes

In crude analyses (Supplementary Table S3), the 30-day mortality (overall: CABG 3%, PCI 5%; matched: CABG 3%, PCI 3%) and 1-year all-cause mortality (overall: CABG 8%, PCI 13%; matched: CABG 8%, PCI 11.0%) tended to be higher in the overall population than in the matched patients. In contrast, ESKD incidence at 1 year was not different from the overall population (overall: CABG 2%, PCI 2%; matched: CABG 1%, PCI 2%).

Further analyses of the matched population were stratified according to the presence of left main disease and MI given the inability to match successfully on these characteristics. There were between 2262 and 2297 deaths across the imputed data sets (CABG 1049−1059, PCI 1210−1238) with median onset of 864 days (IQR = 272−1617). The range of ESKD cases was 312 to 320 (CABG 172−175, PCI 137−146), with median time to ESKD of 669 days (IQR = 143−1362). In crude analyses (Table 2), there was no significant evidence of effect modification between patients admitted with left main disease and MI for either 30-day or 1-year mortality with PCI compared to CABG. However, in individuals with left main disease without prior MI, 1-year mortality was numerically higher with PCI (27%) compared with CABG (8%, $P = 0.10$). One-year mortality was also numerically higher with PCI (12.0%) compared to CABG (8% $P = 0.14$) among patients without left main disease and with prior MI. Rates of ESKD were low at 1-year but appeared to be higher among patients with left main disease treated with PCI compared to those treated with CABG (odds ratio [OR] = 6.7, 95% confidence interval [CI] = 1.0−45.5).

Survival Models

For the primary outcome model, there was evidence of significant effect modification by left main disease and MI status (Table 3). PCI was associated with a higher risk of all-cause death in those with left main disease without MI (hazard ratio [HR] = 3.7, 95% CI = 1.3−10.5, $P = 0.02$). However, the interaction was quantitative rather than qualitative, and risk of death was higher with PCI in each of the 4 subgroups. Results for the combined outcome of death and ESKD were essentially similar to those for death alone, with higher risk of the combined outcome with PCI compared with CABG in all subgroups, and a quantitative interaction demonstrating a magnified risk for patients with left main disease without MI (HR = 3.3, 95% CI = 1.4−8.1, $P = 0.01$). For both outcomes, differences in survival appeared early and were maintained throughout follow-up (Figures 2 and 3 and Supplementary Figure S2). In contrast, there was evidence of qualitative effect modification for the ESKD outcome. Risk of

Table 2. All-cause death and ESKD at 30 days and 1 year according to procedure type, left main disease, and history of myocardial infarction

	30-Day mortality				1-Year mortality			
Group	CABG (n = 3747)	PCI (n = 3747)	OR (95% CI)	*P* interaction	CABG (N = 3747)	PCI (N = 3747)	OR (95% CI)	*P* interaction
All	95 (2.5)	115 (3.1)	—	—	251 (7.7)	360 (11.0)	—	—
Left main disease (+), prior MI (+)	19 (7.2)	21 (7.1)	0.9 (0.3–3.1)	0.84	43 (19.6)	59 (22.4)	1.4 (0.4–4.2)	0.56
Left main disease (+), prior MI (–)	<11 (<3.0)	15 (8.2)	3.6 (0.6–22.8)	0.17	25 (7.9)	45 (27.4)	6.0 (1.6–22.4)	0.01
Left main disease (–), prior MI (+)	48 (2.9)	49 (3.4)	1.3 (0.6–2.8)	0.43	120 (8.4)	148 (12.0)	1.5 (0.9–2.7)	0.14
Left main disease (–), prior MI (–)	21 (1.4)	30 (1.6)	1.3 (0.7–2.5)	0.43	63 (4.9)	(6.7)	1.5 (0.9–2.6)	0.14
	1-Year ESKD				1-Year ESKD and mortality			
	CABG (N = 3261)	PCI (N = 3261)	OR (95% CI)	*P* interaction	CABG (N = 3261)	PCI (N = 3261)	OR (95% CI)	*P* interaction
All	47 (1.4)	55 (1.7)	—	—	292 (9.0)	405 (12.4)	—	—
Left main disease (+), prior MI (+)[a]	<11 (<4.8)	<11 (<4.1)	6.7 (1.0–45.5)	0.05	44 (20.1)	63 (24.0)	1.5 (0.5–4.4)	0.48
Left main disease (+), prior MI (–)[a]	<11 (3.3)	<11 (6.3)	a	a	25 (7.9)	45 (27.4)	5.5 (1.4–21.1)	0.02
Left main disease (–), prior MI (+)	31 (2.2)	24 (1.9)	0.8 (0.4–1.8)	0.59	147 (10.3)	170 (13.8)	1.4 (0.8–2.3)	0.18
Left main disease (–), prior MI (–)	14 (1.1)	22 (1.4)	1.3 (0.5–3.6)	0.56	76 (5.9)	127 (7.9)	1.5 (0.9–2.5)	0.13

Binary outcome data and odds ratios for comparison of PCI versus CABG. ORs are for PCI versus CABG within the strata. *P* values are for the interaction of PCI with the category with a reference category of left main disease (–), MI (–). Data privacy concerns prevent reporting cell sizes ≥11.
CABG, coronary artery bypass grafting; CI, confidence interval; ESKD, end-stage kidney disease; LM, left main disease; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; Ref, reference.
[a]Because of small cell sizes for this outcome, LM (+) cells were combined for estimating applicable ORs.

ESKD was not lower with PCI for patients without left main disease (with or without MI) and those with left main disease without MI. Although the overall incidence of ESKD was low, for individuals without prior MI, it was higher with PCI compared with CABG during early follow-up and modestly lower with longer duration of follow-up (Figure 4). In contrast, the risk of ESKD was greater with PCI compared to CABG among individuals with concomitant left main disease and MI (HR = 8.1; 95% CI = 1.7−39.2, $P = 0.01$), although the confidence intervals around this estimate were wide. This differential effect on ESKD risk was not obviously attributable to differential effects on acute kidney injury, as risk of acute kidney injury was lower with PCI than with CABG (Supplementary Table S4).

Given the small sample size overall and in cells of several imputations, we were unable to estimate stage 4 CKD−specific effects. Similar issues affected estimates of stage 3 CKD−specific associations of PCI with risk of ESKD, although data from available imputations were consistent with attenuated but directionally similar effect estimates in stage 3 CKD patients and the overall population. Associations with mortality were qualitatively similar overall and within the subgroup with stage 3 CKD (data not shown).

DISCUSSION

In this study, we analyzed demographic, procedural, and clinical data from patients undergoing CABG and PCI in Massachusetts between 2003 and 2012, to compare the effects of surgical with percutaneous intervention on overall survival and progression to ESKD in the setting of CKD. Although point estimates were consistent with better survival following CABG compared with PCI across the board, the effects differed markedly according to the presence of significant left main disease and history of prior MI, with robust and independent survival benefits observed for CABG compared to PCI in individuals with left main disease but without a prior MI. Conversely, the benefits of surgical revascularization were not significant in adjusted models and were less robust in individuals with neither left main disease nor MI or with both conditions. In contrast to all-cause mortality, the overall incidence of ESKD (<2% at 1 year) was several-fold lower than the incidence of mortality. Risk of

Table 3. Survival analyses for all-cause mortality, ESKD, and combined death and ESKD

		Left main disease absent		Left main disease present	
History of MI	Outcome	HR (95% CI)	*P* value	HR (95% CI)	*P* value
No history of prior MI	Mortality	1.2 (0.9–1.7)	0.19	3.7 (1.3–10.5)	0.02
	ESKD	0.8 (0.4–1.5)	0.40	0.6 (0.1–4.0)	0.56
Death or ESKD	1.2 (0.9–1.6)	0.16	3.3 (1.4–8.1)	0.01	
Positive history of prior MI	Mortality	1.6 (1.3–2.0)	<0.001	1.5 (0.6–3.4)	0.33
	ESKD	0.7 (0.4–1.4)	0.31	8.1 (1.7–39.2)	0.01
Death or ESKD	1.4 (1.2–1.8)	0.002	1.6 (0.7–3.5)	0.22	

Binary outcome data and hazard ratios for comparison of PCI versus HRs are for PCI versus CABG within the strata. *P* value is for the interaction of PCI with the category with a reference category of left main disease (–), MI (–).
CABG, coronary artery bypass grafting, CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

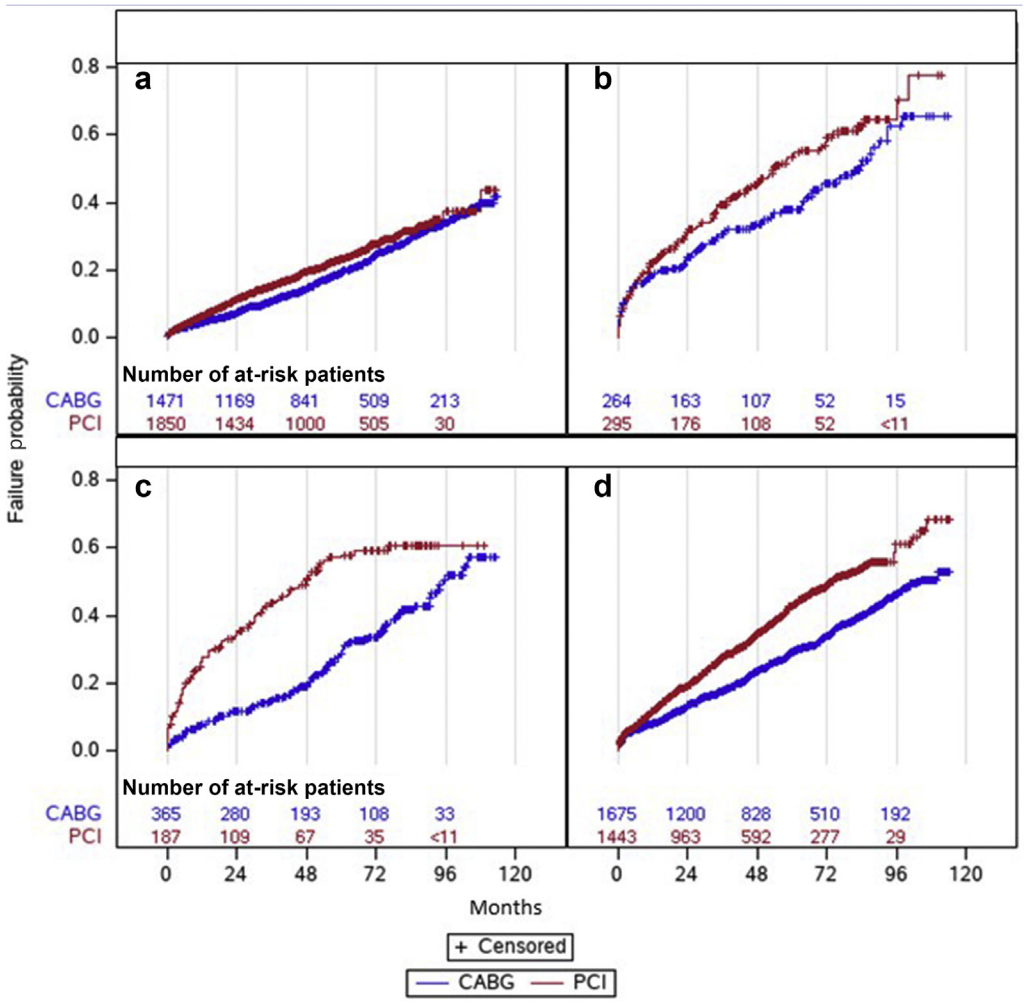

Figure 2. All-cause mortality according to treatment presence of left main disease and prior myocardial infarction (MI). (a) Left main negative, prior MI negative. (b) Left main positive, prior MI positive. (c) Left main positive, prior MI negative. (d) Left main negative, prior MI positive. Data are shown for a single imputed set. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

ESKD was not different with PCI compared with CABG, except in individuals with both left main disease and a prior MI, in whom long-term ESKD risk was higher with CABG. However, the confidence intervals around the latter estimate were broad.

Our findings contrast with some reports comparing CABG and PCI in the setting of CKD, which suggested that survival is dramatically better with CABG than PCI.[16–18] However, these studies generally lacked detailed access to angiographic or clinical data, limiting ability to fully adjust for angiographic and clinical risk. In contrast, a study of individuals undergoing CABG or PCI between 1993 and 1995 suggested that there was no survival benefit to CABG when creatinine was ≥2.5 mg/dl.[19] Conversely, several studies have had more nuanced findings in which the relative benefits of various therapies were dependent on baseline risk strata. Although not explicitly compared to each other, CABG appeared to be superior to PCI in CKD patients admitted with acute coronary syndromes but not in lower-risk patients in a recent analysis of Medicare data, although the underlying data were insufficiently granular to adjust for angiographic risk.[20] Similarly, in a meta-analysis of randomized trials comparing CABG and PCI including few patients with left main disease, no difference in survival was apparent.[7] These latter results are consistent with data from studies performed in the general population that have suggested no or only minimal survival advantages to CABG compared with PCI or medical therapies, except when left main disease is present or when there is multi-vessel disease with reduced ejection fraction.[21–23]

Our analysis is consistent with these data in demonstrating that early analyses suggesting a universal benefit to CABG compared with PCI were insufficiently nuanced and may have missed marked differences in the benefits according to baseline anatomic and clinical risk. They confirm, in a cohort not restricted to elderly individuals or those with Medicare coverage and in individuals undergoing

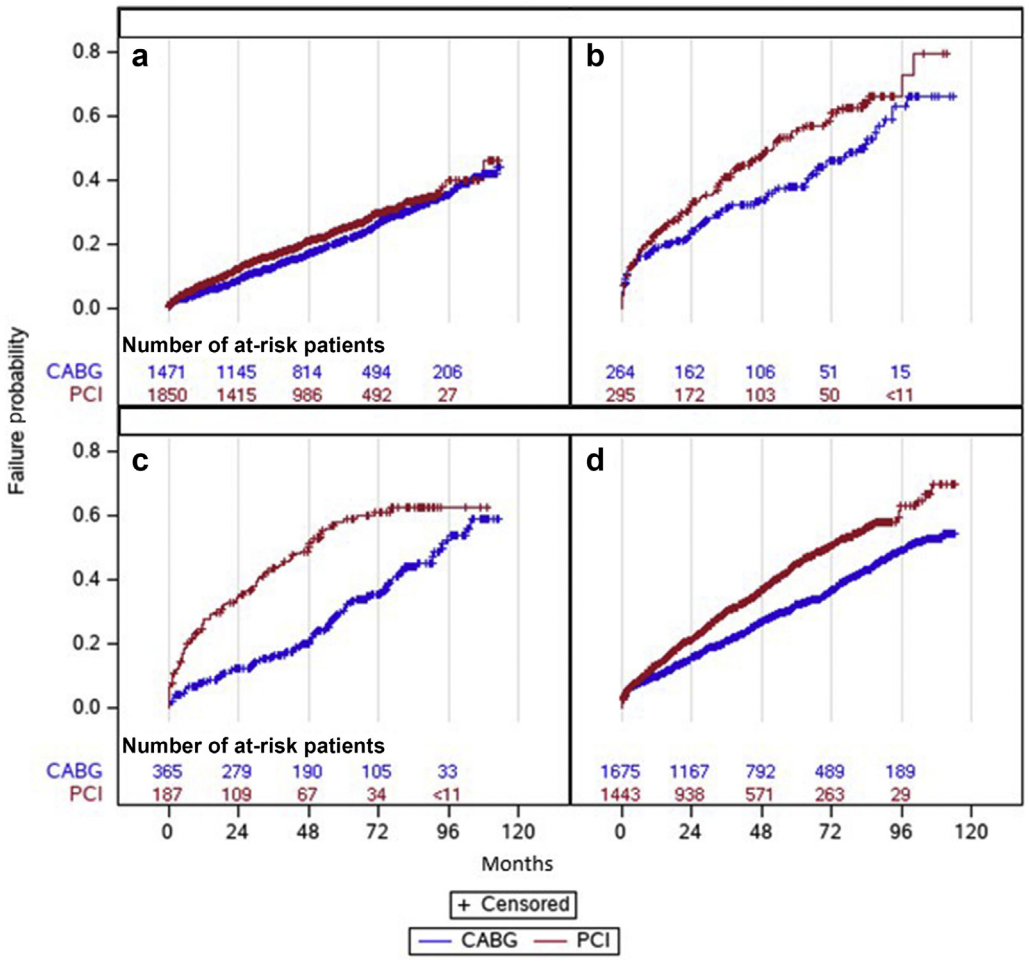

Figure 3. All-cause mortality or end-stage kidney disease (ESKD) according to treatment presence of left main disease and prior myocardial infarction (MI). (a) Left main negative, prior MI negative. (b) Left main positive, prior MI positive. (c) Left main positive, prior MI negative. (d) Left main negative, prior MI positive. Data are shown for a single imputed set. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

revascularization with contemporary technologies, that the survival benefits of CABG compared with PCI in the setting of CKD are, as in the general population, largely dependent upon the background anatomic and clinical risk—with the greatest benefits in patients with left main disease. Our analysis extends upon prior research by demonstrating these findings within a data set allowing for direct eGFR calculation (rather than identification of CKD upon the basis of diagnostic codes), with availability of angiographic and anatomic characteristics and standardized, prospective collection of procedural, comorbidity, and demographic data. In addition, our analysis is among the first to compare the impact of both revascularization procedures on progression to ESKD.

Although risks of AKI following PCI and CABG are well recognized, relatively few studies have assessed associations with CKD progression. We previously analyzed postprocedural risk of ESKD using Medicare data. In that study of elderly patients, we found that the risk of ESKD was higher in the first few months after CABG compared with PCI, but that overall risks thereafter were similar with a minimal difference of only 1.4% in ESKD incidence at 3 years.[17] In a more recent analysis, the risk of ESKD with CABG and PCI were not compared directly. However, point estimates and confidence intervals suggested a higher risk of EKSD with CABG compared to PCI in individuals undergoing revascularization following an admission with acute coronary syndrome.[20]

Our data are consistent with these prior studies in demonstrating that the incidence of ESKD (ESKD incidence at 1 year: CABG 1.4%, PCI 1.7%) after coronary revascularization is markedly lower than the incidence of death (CABG 7.7%, PCI 11.0%). We similarly found that in the overall population, there were lower adjusted risks of ESKD with PCI compared to CABG. We did identify effect modification such that the risk of ESKD was increased with PCI in individuals with concomitant left main disease and a history of prior MI.

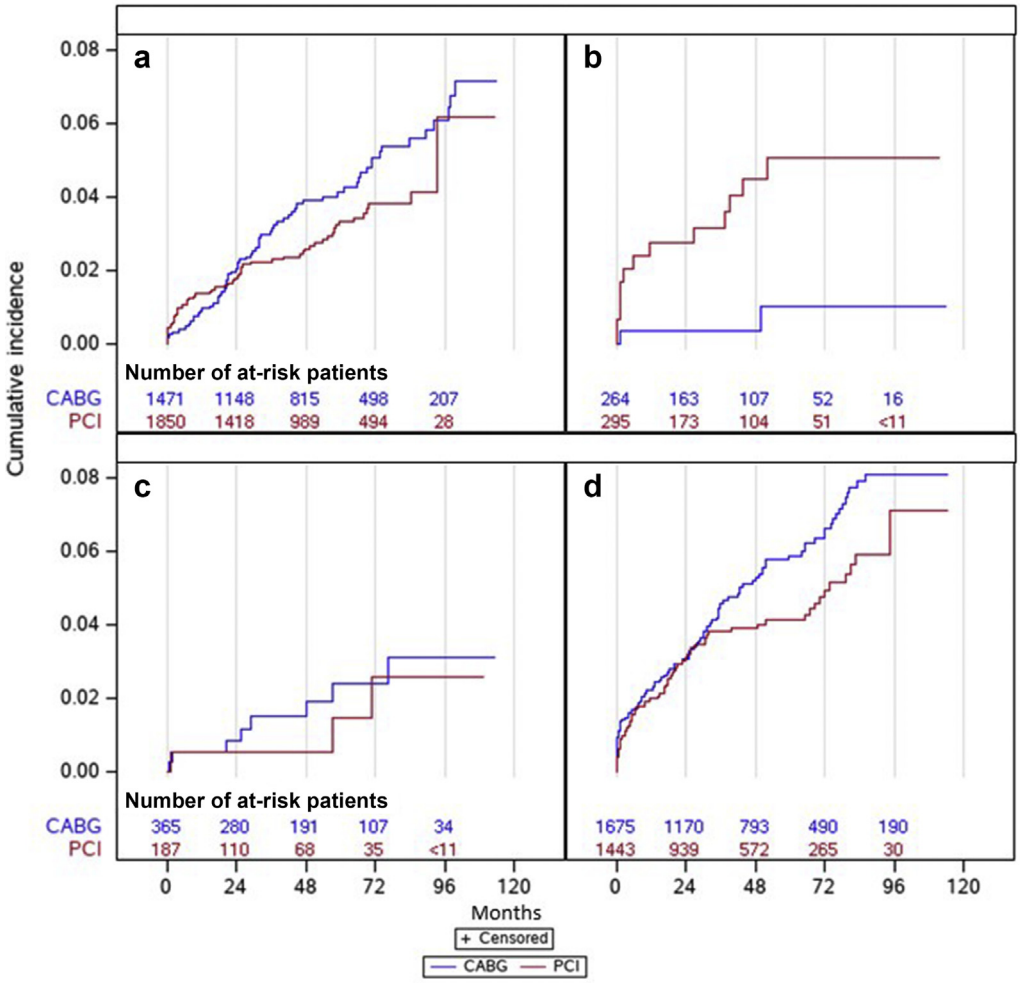

Figure 4. Cumulative incidence of end-stage kidney disease (ESKD) according to treatment presence of left main disease and prior myocardial infarction (MI). (a) Left main negative, prior MI negative. (b) Left main positive, prior MI positive. (c) Left main positive, prior MI negative. (d) Left main negative, prior MI positive. Data are shown for a single imputed set. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

The nature of the divergent effects on ESKD risk in this group are uncertain, and these results should be interpreted cautiously given the wide confidence intervals around the estimate. Although 1 possibility is that individuals with this combination of risk factors have complex anatomy leading to complicated percutaneous procedures with outsized exposure to cholesterol embolism and high contrast loads and resultant kidney injury, we did not detect an increase in acute kidney injury. Alternatively, initial PCI has been shown to provide less robust relief of angina in this setting of left main disease than CABG,[24] and any initial benefits in terms of acute kidney injury may be offset by a greater need for additional, downstream revascularization procedures. Despite a good balance of observable baseline characteristics in our matched cohort, the possibility of indication bias and residual confounding must be acknowledged. Furthermore, the absolute number of cases of ESKD in this subgroup was small, and confidence intervals around effect estimates were wide. Additional study of this issue is clearly warranted.

What are the clinical implications of our findings? First, our analysis suggests that there is no universally preferable revascularization procedure for individuals with moderate to advanced CKD, and that standards used in the general population apply to individuals with CKD. Use of PCI appears to be a reasonable strategy when background cardiovascular risk is low and high-risk anatomy is absent. Conversely, high-risk anatomic features, particularly left main disease, magnify the potential survival benefits of CABG compared with PCI, and suggest that surgical revascularization is preferable when left main disease is present, particularly if risks are otherwise low—for example, in individuals without prior MI. Second, although the risk of ESKD is of the utmost importance to many patients, our data contribute additional

evidence that absolute rates of ESKD are low and that the choice between PCI and CABG is unlikely to have a substantial impact on the long-term risks of progression to ESKD, with the possible exception of patients in whom left main disease is present in the absence of prior MI. Any increase in the *relative* ESKD risk in this setting is likely to translate into marginal differences in *absolute* ESKD risk, and, except for patients with very strong preferences for avoiding ESKD, it would be reasonable to frame decisions primarily in terms of the impact on all-cause mortality. Whether the results would differ according to severity of CKD is an important question. Unfortunately, the sample size was insufficient, particularly after stratification by left main and MI status for reliable estimation of CKD stage 4–specific effects, particularly for ESKD. Given the high rate of cardiovascular death in individuals with advanced CKD and inevitability of ESKD in those with very advanced pre-procedural CKD stages, it is possible that potential mortality benefits of CABG should still dominate. However, well-powered analyses specific to individuals with advanced CKD are clearly needed for definitive conclusions.

Strengths of our analysis include the estimation of eGFR rather than the use of diagnostic codes to define CKD; the availability of data on coronary anatomy; the prospective capture of procedural details and clinical history using standardized information; and the capture of data on patients across a spectrum of ages. In addition, our ability to link outcomes to the United States Renal Disease System allowed for definitive identification of incident ESKD.

Our results should also be interpreted within the context of the study design. In particular, angiographic and coronary anatomic risk factors such as lesion location, lesion complexity, and touchdown sites that may play important roles in the likelihood of procedural success[25] were not available. In general, we could match only for those clinical and procedural characteristics collected in the databases, and confirmation in randomized trials not susceptible to confounding would be of great interest. Specifically, data on albumin excretion and cause of CKD would have allowed finer discrimination of ESKD risk but were not available. In addition, our cohorts were assembled using data from a single northeastern state in the United States on procedures performed from 2003 to 2012. Our findings should be generalized cautiously to other settings, given the potential for temporal or regional differences in practice patterns. Despite a large overall sample size, the number of clinical endpoints, particularly ESKD events, in some of the strata was low, which limited the precision of some effect estimates. Type 2 error is possible, particularly for several subgroups that were small and thus inadequately powered to detect meaningful differences. Confirmation of our findings, particularly negative findings in a larger cohort, is desirable.

In addition, our analysis cannot distinguish between the direct impact of procedural choice and downstream impacts of procedural choice on use of medical therapies. However, mortality benefits with CABG were observed despite rates of guideline-based cardiovascular therapies, with the exception of β-blockers, that were equivalent or higher with PCI compared to CABG. Finally, use of propensity score matching facilitated simultaneous adjustment for a large number of covariates and is a semi-parametric approach that does not require specification of the relationship between confounding variables and outcomes. However, we were unable to propensity score match nearly half of CABG patients to corresponding PCI patients because of lack of baseline comparability as measured by the propensity score. Our analysis informs only on outcomes of coronary revascularization in individuals who are likely to be considered in standard clinical practice for both CABG and PCI. We considered a complete case approach with full-covariate adjustment, but we believe that such an approach would not have adequately accounted for confounding and indication bias inherent to use of CABG or PCI in individuals at the extremes of the propensity score distribution.

In conclusion, we found that associations of CABG and PCI with all-cause mortality and progression to ESKD were modified by the presence of left main disease and prior MI. Improvement in survival with CABG compared with PCI was greatest in individuals with left main disease but without prior MI, whereas risk of ESKD was less with CABG when left main and prior MI were both present. Moreover, absolute risks of ESKD were several-fold lower than those for mortality, suggesting that if patient preferences are equally weighted between these outcomes, mortality effects should be prioritized in decision making.

DISCLOSURE

DMC has received funding from Medtronic, Gilead, Janssen, and Novo Nordisk and has received personal fees for consulting or service on trial related committees from PLC medical, Merck, Amgen, Janssen, Novo Nordisk, Gilead, GlaxoSmithKline, and Astra Zeneca. All the other authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

DMC, SLN, RW, and KZ contributed to the conception and design, or acquisition of data, analysis, and interpretation of data, DMC drafted the manuscript. All authors contributed important intellectual content during manuscript drafting and revision, and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Medication use according to index procedure

Table S2. Distribution of eGFR in the matched pairs

Table S3. Unadjusted and adjusted all-cause mortality and end stage kidney disease at 30 days and 1 year in the matched and unmatched data

Table S4. Risk of in-hospital acute kidney injury according to procedure type, left main disease, and prior myocardial infarction

Figure S1. Distribution of propensity scores by revascularization procedure in matched sets, across imputed datasets.

Figure S2. Overall cumulative incidence of mortality, mortality and ESKD combined, or ESKD alone. Data are shown for a single imputation.

REFERENCES

1. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295.
2. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
3. Himmelfarb J, Stenvinkel P, Ikizler TA, et al. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int*. 2002;62:1524–1538.
4. Shroff GR, Herzog CA. Coronary revascularization in patients with CKD stage 5D: pragmatic considerations. *J Am Soc Nephrol*. 2016;27:3521–3529.
5. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation*. 1997;95:878–884.
6. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int*. 2006;70:2021–2030.
7. Charytan DM, Desai M, Mathur M, et al. Reduced risk of myocardial infarct and revascularization following coronary artery bypass grafting compared with percutaneous coronary intervention in patients with chronic kidney disease. *Kidney Int*. 2016;90:411–421.
8. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393–1399.
9. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
10. U.S. Renal Data System. 2014 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.
11. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Statistician*. 1985;39:33–38.
12. Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: structures, distances, and algorithms. *J Comput Graph Stat*. 1993;2:405–420.
13. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1141–1154.
14. Fine J, Gray RJ. A proportional hazards model for the subdistribiton of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
15. Carpenter JR, Kenward MG. Chapter 2.2. *Multiple Imputation and Its Application*. Chichester, UK: John Wiley & Sons Ltd; 2013.
16. Ashrith G, Lee VV, Elayda MA, et al. Short- and long-term outcomes of coronary artery bypass grafting or drug-eluting stent implantation for multivessel coronary artery disease in patients with chronic kidney disease. *Am J Cardiol*. 2010;106:348–353.
17. Charytan DM, Li S, Liu J, et al. Risks of death and end-stage renal disease after surgical compared with percutaneous coronary revascularization in elderly patients with chronic kidney disease. *Circulation*. 2012;126:S164–S169.
18. Reddan DN, Szczech LA, Tuttle RH, et al. Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. *J Am Soc Nephrol*. 2003;14:2373–2380.
19. Szczech LA, Reddan DN, Owen WF, et al. Differential survival after coronary revascularization procedures among patients with renal insufficiency. *Kidney Int*. 2001;60:292–299.
20. Charytan DM, Natwick T, Solid CA, et al. Comparative effectiveness of medical therapy, percutaneous revascularization, and surgical coronary revascularization in cardiovascular risk subgroups of patients with CKD: a retrospective cohort study of Medicare beneficiaries. *Am J Kidney Dis*. 2019;74:463–473.
21. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med*. 2007;147:703–716.
22. Lee CW, Ahn JM, Cavalcante R, et al. Coronary artery bypass surgery versus drug-eluting stent implantation for left main or multivessel coronary artery disease: a meta-analysis of individual patient data. *JACC Cardiovasc Interv*. 2016;9:2481–2489.

23. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563–570.

24. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.

25. Kim YH, Park DW, Kim WJ, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. *JACC Cardiovasc Interv*. 2010;3:612–623.