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ORIGINAL RESEARCH

Invasive Versus Medical Management in Patients With Chronic Kidney Disease and Non–ST-Segment–Elevation Myocardial Infarction

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BACKGROUND: The role of invasive management compared with medical management in patients with non–ST-segment–elevation myocardial infarction (NSTEMI) and advanced chronic kidney disease (CKD) is uncertain, given the increased risk of procedural complications in patients with CKD. We aimed to compare clinical outcomes of invasive management with medical management in patients with NSTEMI-CKD.

METHODS AND RESULTS: We identified NSTEMI and CKD stages 3, 4, 5, and end-stage renal disease admissions using *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes from the Nationwide Readmission Database 2016 to 2018. Patients were stratified into invasive and medical management. Primary outcome was mortality (in-hospital and 6 months after discharge). Secondary outcomes were in-hospital postprocedural complications (acute kidney injury requiring dialysis, major bleeding) and postdischarge 6-month safety and major adverse cardiovascular events. Out of 141 052 patients with NSTEMI-CKD, 85 875 (60.9%) were treated with invasive management, whereas 55 177 (39.1%) patients were managed medically. In propensity-score matched cohorts, invasive strategy was associated with lower in-hospital (CKD 3: odds ratio [OR], 0.47 [95% CI, 0.43–0.51]; $P<0.001$; CKD 4: OR, 0.79 [95% CI, 0.69–0.89]; $P<0.001$; CKD 5: OR, 0.72 [95% CI, 0.49–1.06]; $P=0.096$; end-stage renal disease: OR, 0.51 [95% CI, 0.46–0.56]; $P<0.001$) and 6-month mortality. Invasive management was associated with higher in-hospital postprocedural complications but no difference in postdischarge safety outcomes. Invasive management was associated with a lower hazard of major adverse cardiovascular events at 6 months in all CKD groups compared with medical management.

CONCLUSIONS: Invasive management was associated with lower mortality and major adverse cardiovascular events but minimal increased in-hospital complications in patients with NSTEMI-CKD compared with medical management, suggesting patients with NSTEMI-CKD should be offered invasive management.

Key Words: chronic kidney disease ■ invasive management ■ medical management ■ mortality ■ non–ST-segment–elevation myocardial infarction

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CLINICAL PERSPECTIVE

What Is New?

- In propensity-score matched analysis of the national database in patients with non–ST-segment–elevation myocardial infarction and chronic kidney disease (CKD), invasive management was associated with lower mortality, major adverse cardiovascular events, myocardial infarction, and revascularization at 6 months in CKD stages 3 to 5 and end-stage renal disease.
- Invasive management was associated with minimal increased risk of in-hospital acute kidney injury requiring dialysis and major bleeding, but no difference in safety outcomes at 6 months after discharge.
- Diagnostic angiography was not associated with a higher risk of postprocedure acute kidney injury requiring dialysis compared with medical management.

What Are the Clinical Implications?

- CKD is an independent predictor of morbidity and mortality. Current guidelines acknowledged the lack of evidence on invasive management's beneficial role and safety in patients with non–ST-segment–elevation myocardial infarction and CKD compared with medical management.
- Benefits versus risk balance favored invasive management and should be offered to all patients presenting with non–ST-segment–elevation myocardial infarction and CKD, and the risk of dialysis and major bleeding discussed before revascularization.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
CA	coronary angiography
CAR	coronary angiography with revascularization
CAWR	coronary angiography without revascularization
MACE	major adverse cardiovascular events
NRD	Nationwide Readmission Database

Chronic kidney disease (CKD) is an independent predictor of cardiovascular morbidity,[1] cardiovascular mortality,[2] and all-cause mortality.[3] Advanced CKD in patients with non–ST-segment–elevation myocardial infarction (NSTEMI) is associated with worse morbidity and mortality. This can be attributed to accelerated atherosclerosis/calcification and more severe comorbidities like hypertension and diabetes, other than CKD itself.[4] Patients with CKD are not routinely included in randomized clinical trials of invasive treatment of acute coronary syndrome, given the theoretical risk of accelerating the need for renal replacement therapy because of concern for contrast-induced nephropathy in patients undergoing coronary angiography (CA).[5] However, these patients have significantly higher rates of major bleeding and poorer outcomes regardless of CA.[6]

There is a reluctance to offer early invasive management to patients with NSTEMI-CKD in clinical practice, because there is an increased risk of contrast-induced nephropathy,[7,8] bleeding,[6,9] and mortality[6] compared with patients without CKD. Patients with CKD may benefit from an invasive approach despite the risk of adverse outcomes.[6,10] The American Heart Association/American College of Cardiology 2021 and European Society of Cardiology 2020 guidelines acknowledged the limited evidence on the beneficial role and safety of invasive management in patients with NSTEMI-CKD compared with medical management.[11,12]

Here, we performed a propensity-score matched analysis using the Nationwide Readmission Database (NRD) and examined the safety and efficacy of invasive approach in patients with NSTEMI and CKD stages 3, 4, 5, and end-stage renal disease (ESRD).

METHODS

Data Source

We extracted data from the NRD 2016 to 2018. The NRD is part of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality. The NRD contains data from ≈18 million discharges each year across 28 geographically dispersed states. This data set accounts for 60% of the total US resident population, 59% of all US hospitalizations, and includes all-payer data.[13] The present study was deemed exempt by the institutional review board because the database contained deidentified data sets with prior ethical committee approval. NRD is publicly available and can be procured from the Healthcare Cost and Utilization Project website.

Patient Selection

We identified 688 147 patients with NSTEMI, aged ≥18 years, using previously validated *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes (I21.4 and I22.2) in the primary diagnosis field only.[14] Out of all patients with NSTEMI, 141 052 patients with CKD stages 3, 4, 5, and ESRD were identified using *ICD-10-CM* codes (N18.3, N18.4, N18.5, and N18.6) in the secondary diagnosis

fields. We excluded patients who died during index hospitalization (n=7410) for postdischarge outcomes to avoid immortal bias. These codes and strategies were validated and used in the previous study.[14–17]

Baseline Variables

We used the variables provided in the NRD by the Healthcare Cost and Utilization Project to identify patients' baseline characteristics, including age, sex, primary expected payer, median household income category by patient zip code, admission day, and hospital information such as bed size, teaching status, and location.[18] We used *ICD-10-CM* codes given by the Elixhauser comorbidity index calculator provided by the Healthcare Cost and Utilization Project to report hypertension, diabetes, hyperlipidemia, peripheral vascular disease, chronic heart failure, chronic pulmonary disease, anemia, obesity, smoking, and coagulopathy. Other comorbidities, such as a history of stroke or transient ischemic attack, ischemic cardiomyopathy, carotid artery disease, prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), atrial fibrillation, and history of nonadherence to medications were identified using appropriate *ICD-10-CM* codes (Table S1).[14]

Intervention

The invasive approach included CA with or without PCI and/or CABG. Medical management was defined as patients who did not undergo CA, PCI, or CABG. We stratified the invasive management into CA with revascularization (CAR) and CA without revascularization (CAWR)/diagnostic angiography. We compared invasive and CAR strategies with medical management for all outcomes, whereas patients in the CAWR group were compared with medical management for in-hospital postprocedural acute kidney injury (AKI) requiring dialysis. CA, PCI, and CABG were identified using administrative *ICD-10-CM* procedure codes in the primary or secondary procedural fields (Table S1).[14]

Study Outcomes

The primary outcome was in-hospital and postdischarge 6-month mortality during readmission. Secondary outcomes were divided into in-hospital and 6-month postdischarge outcomes. In-hospital outcomes included AKI requiring dialysis, major bleeding, and stroke. Postdischarge outcomes included major adverse cardiovascular events (MACE), efficacy, safety, renal safety, myocardial infarction (MI), need for revascularization during readmission, and AKI within 6 months.

MACE are a composite of all-cause mortality, MI readmission, stroke readmission, or heart failure readmission. The safety outcome was a composite of AKI readmission, major bleeding readmission, vascular complication during readmission, and stroke readmission. Major bleeding was defined as bleeding requiring blood transfusion. NRD provides a procedure day variable that gives information on the day a procedure occurred during admission. We used procedure day for dialysis and blood transfusion to determine if dialysis and blood transfusion occurred after the invasive procedure. The efficacy outcome was the composite of all-cause mortality, MI readmission, and the need for revascularization during the readmission. The renal safety outcome was the composite of all-cause mortality or need for dialysis during readmissions. Postdischarge outcomes were identified by applying *ICD-10-CM* codes to the primary diagnosis field of readmission. We described the *ICD-10-CM* coding of each outcome in Table S2.

Statistical Analysis

Continuous and categorical variables were compared using descriptive statistics. We generated propensity-score matched cohorts for patients who underwent invasive versus medical management, CAR versus medical management, and CAWR versus medical management in CKD 3, 4, 5, and ESRD groups. Propensity scores were generated using 26 variables (patients' demographics, comorbidities, hospital characteristics, admission day, type of admission, primary payer, household income) through multivariable logistic regression. Patients with similar propensity scores in 2 groups were matched using a 1-to-1 scheme without replacement using a greedy method. Maximum propensity-score differences (caliper width) of 0.1 to 0.01 were permitted between matched pair observations in various models to keep standardized differences <10%.[19] Patients without matched observations were excluded. The appropriateness of all models was assessed by C statistic, which was above 0.75 for all the included models. The standardized difference was used to assess the balance of variables between 2 matched cohorts (Table 1) and depicted graphically (Figures S1 through S3). Kaplan-Meier curves were constructed for postdischarge mortality and MACE. Follow-up of events other than mortality was calculated by time of readmission subtracted by time of index admission plus length of stay. Follow-up event of mortality was calculated by time of readmission plus length of stay of readmission subtracted by time of index admission plus length of stay of index admission. Logistic regression and Cox proportional hazard regression were used to calculate odds ratio and hazard ratio for in-hospital and postdischarge outcomes, respectively. Missing values were not imputed. Two-sided P values <0.05 were taken to indicate statistical significance. We adhered to all methodological standards.[20]

Table 1. Baseline Characteristics of Invasive Versus Medical Management Across Different Stages of CKD After Propensity-Score Matching

	CKD 3			CKD 4			CKD 5			ESRD		
	Invasive	Medical management	SMD	Invasive	Medical management	SMD	Invasive	Medical management	SMD	Invasive	Medical management	SMD
	n=21 719	n=21 719		n=7326	n=7326		n=815	n=815		n=9004	n=9004	
Age, y	77.1±9.3	77.1±11.6	0.1	75.2±9.8	75.0±11.7	2.1	71.2±10.7	71.0±12.6	1.5	68.7±11.1	68.4±12.7	2.9
Sex			1.1			0			5			0.3
Men	12 533 (58%)	12 468 (57%)		4159 (57%)	4158 (57%)		486 (60%)	506 (62%)		5121 (57%)	5136 (57%)	
Women	9037 (42%)	8922 (41%)		3154 (43%)	3155 (43%)		329 (40%)	309 (38%)		3860 (43%)	3845 (43%)	
Comorbidities												
History of nonadherence to medications	1394 (6%)	1341 (6%)	1	408 (6%)	412 (6%)	0.2	60 (7%)	67 (8%)	3.2	709 (8%)	656 (7%)	2.3
Hypertension	20 454 (94%)	20 466 (94%)	0.3	7038 (96%)	7053 (96%)	1.1	793 (97%)	795 (98%)	1.5	8703 (97%)	8700 (97%)	0.2
Diabetes	12 282 (57%)	12 273 (57%)	0.1	4984 (68%)	5013 (68%)	0.8	594 (73%)	607 (75%)	3.5	6353 (71%)	6442 (72%)	2.2
Hyperlipidemia	15 272 (70%)	15 448 (71%)	1.8	5250 (72%)	5273 (72%)	0.7	571 (70%)	582 (71%)	2.9	5417 (60%)	5490 (61%)	1.7
History of stroke/TIA	2860 (13%)	2758 (13%)	1.4	885 (12%)	863 (12%)	0.9	98 (12%)	98 (12%)	0	1321 (15%)	1253 (14%)	2.2
Ischemic cardiomyopathy	18 282 (84%)	18 339 (84%)	0.7	6511 (89%)	6475 (88%)	1.3	713 (88%)	715 (88%)	0.6	7205 (80%)	7189 (80%)	0.5
Carotid artery disease	819 (4%)	850 (4%)	0.7	289 (4%)	310 (4%)	1.4	19 (2%)	21 (3%)	1.5	169 (2%)	180 (2%)	0.8
Peripheral vascular disease	5356 (25%)	5255 (24%)	1.1	1724 (24%)	1768 (24%)	1.4	167 (21%)	165 (20%)	0.6	2009 (22%)	1980 (22%)	0.8
Prior PCI	4433 (20%)	4376 (20%)	0.7	1559 (21%)	1571 (21%)	0.4	152 (19%)	158 (19%)	2	1832 (20%)	1754 (20%)	2.2
Prior CABG	5168 (24%)	4962 (23%)	2.4	1519 (21%)	1502 (21%)	0.6	137 (17%)	140 (17%)	1	1959 (22%)	1813 (20%)	4.3
Chronic heart failure	15 469 (71%)	15 182 (70%)	2.8	5619 (77%)	5607 (77%)	0.4	618 (76%)	622 (76%)	1.1	6483 (72%)	6459 (72%)	0.6
Atrial fibrillation	5033 (23%)	4968 (23%)	0.7	1520 (21%)	1500 (21%)	0.7	127 (16%)	120 (15%)	2.4	1733 (19%)	1739 (19%)	0.2
Chronic pulmonary disease	6609 (30%)	6552 (30%)	0.6	2126 (29%)	2132 (29%)	0.2	201 (25%)	204 (25%)	0.9	2331 (26%)	2268 (25%)	1.6
Anemia	1868 (9%)	1774 (8%)	1.6	764 (10%)	776 (11%)	0.5	103 (13%)	96 (12%)	2.6	536 (6%)	535 (6%)	0
Smoker	7109 (33%)	7140 (33%)	0.3	2292 (31%)	2302 (31%)	0.3	247 (30%)	265 (33%)	4.9	2317 (26%)	2372 (26%)	1.4
Obesity	3904 (18%)	3926 (18%)	0.3	1541 (21%)	1560 (21%)	0.6	176 (22%)	177 (22%)	0.3	1255 (14%)	1417 (16%)	4.7
Coagulopathy	1901 (9%)	1944 (9%)	0.7	708 (10%)	735 (10%)	1.2	80 (10%)	84 (10%)	1.6	1185 (13%)	1193 (13%)	0.3
Hospital characteristics												
Bed size			1.3			1.1			0.7			3.5
Small	3298 (15%)	3454 (16%)		899 (12%)	916 (13%)		83 (10%)	100 (12%)		1241 (14%)	1155 (13%)	
Medium	7176 (33%)	6652 (31%)		2334 (32%)	2242 (31%)		228 (28%)	198 (24%)		2831 (31%)	2784 (31%)	
Large	11 096 (51%)	11 464 (53%)		4080 (56%)	4155 (57%)		504 (62%)	517 (63%)		4909 (55%)	5042 (56%)	
Hospital teaching status			0.6			2.8			2.8			0.7

(*Continued*)

Table 1. Continued

	CKD 3			CKD 4			CKD 5			ESRD		
	Invasive	Medical management	SMD	Invasive	Medical management	SMD	Invasive	Medical management	SMD	Invasive	Medical management	SMD
Nonteaching	7468 (34%)	7403 (34%)		2258 (31%)	2162 (30%)		214 (26%)	224 (28%)		2737 (31%)	2710 (30%)	
Teaching	14 102 (65%)	14 167 (65%)		5055 (69%)	5151 (70%)		601 (74%)	591 (73%)		6244 (69%)	6271 (70%)	
Hospital location			0.1			0.3			3.8			0.3
Nonurban	10 197 (47%)	10 212 (47%)		3293 (45%)	3281 (45%)		316 (39%)	301 (37%)		3338 (37%)	3325 (37%)	
Urban	11 373 (52%)	11 358 (52%)		4020 (55%)	4032 (55%)		499 (61%)	514 (63%)		5643 (63%)	5656 (63%)	
Admission day			0.2			1.1			1.9			0.2
Weekdays	15 760 (73%)	15 745 (73%)		5379 (73%)	5344 (73%)		603 (74%)	596 (73%)		6713 (75%)	6719 (75%)	
Weekend	5810 (27%)	5825 (27%)		1934 (27%)	1969 (27%)		212 (26%)	219 (27%)		2268 (25%)	2262 (25%)	
Primary payer			0.7			0.5			2.9			0
Medicare	18 966 (87%)	18 633 (86%)		6250 (85%)	6170 (84%)		631 (77%)	623 (76%)		7648 (85%)	7592 (84%)	
Medicaid	669 (3%)	1251 (6%)		326 (4%)	462 (6%)		63 (8%)	95 (12%)		574 (6%)	696 (8%)	
Private insurance	1738 (8%)	1470 (7%)		653 (9%)	597 (8%)		106 (13%)	84 (10%)		709 (8%)	632 (7%)	
Median household income category by patient zip code			1.1			0.1			3.5			0
0–25th percentile	6095 (28%)	6157 (28%)		2120 (29%)	2197 (30%)		239 (29%)	242 (30%)		2959 (33%)	3065 (34%)	
26th–50th percentile	6277 (29%)	6063 (28%)		2119 (29%)	2028 (28%)		247 (30%)	234 (29%)		2421 (27%)	2306 (26%)	
51st–75th percentile	5425 (25%)	5403 (25%)		1785 (24%)	1726 (24%)		183 (23%)	169 (21%)		2122 (24%)	2037 (23%)	
76th–100th percentile	3773 (17%)	3947 (18%)		1289 (18%)	1362 (19%)		146 (18%)	170 (21%)		1479 (16%)	1573 (18%)	

CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; ESRD, end-stage renal disease; PCI, percutaneous coronary intervention; SMD, standardized mean difference; and TIA, transient ischemic attack.

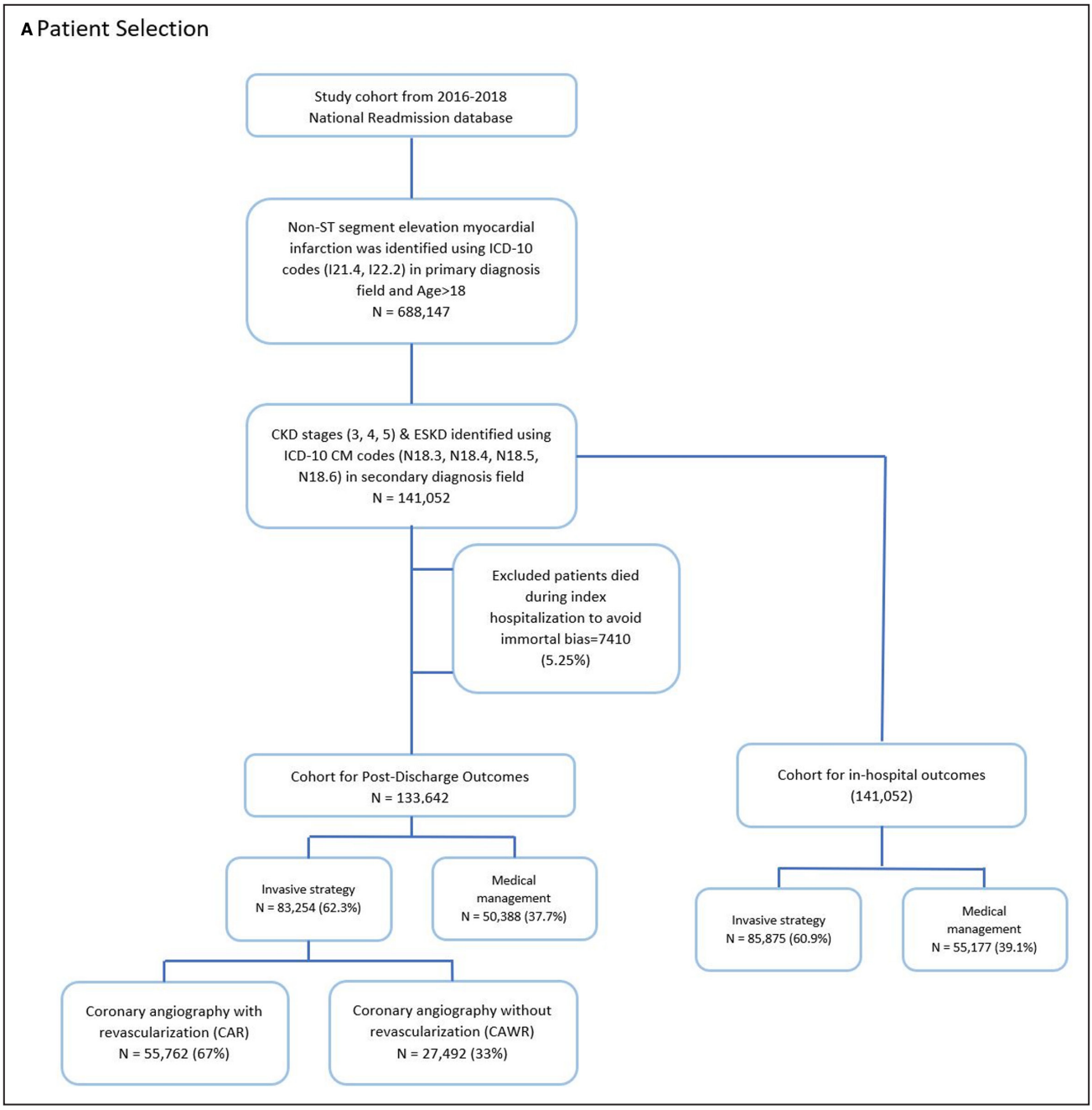

Figure 1. Patient selection and study design.
A, Patient selection flow diagram. **B**, Study design by chronic kidney disease groups for in-hospital outcomes. **C**, Study design by chronic kidney disease groups for postdischarge outcomes. CAR indicates coronary angiography with revascularization; CAWR, coronary angiography without revascularization; CKD, chronic kidney disease; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; *ICD-10*, *International Classification of Diseases, Tenth Revision*; and *ICD-10-CM*, *International Classification of Diseases, Tenth Revision, Clinical Modification*.

Unmeasured Bias Analysis and Sensitivity Analysis

To evaluate the robustness of our findings, we conducted a falsification end point and E-value analysis to determine the validity of the study.[21,22] The E-value identifies the minimum strength of association that unmeasured confounders may need to have with both treatment and outcome, conditional on measured covariates, to fully explain the observed association. This estimates what the relative risk may have to be for any unmeasured confounder to overcome the observed association of study intervention with study outcomes. In the falsification method, we selected an alternative

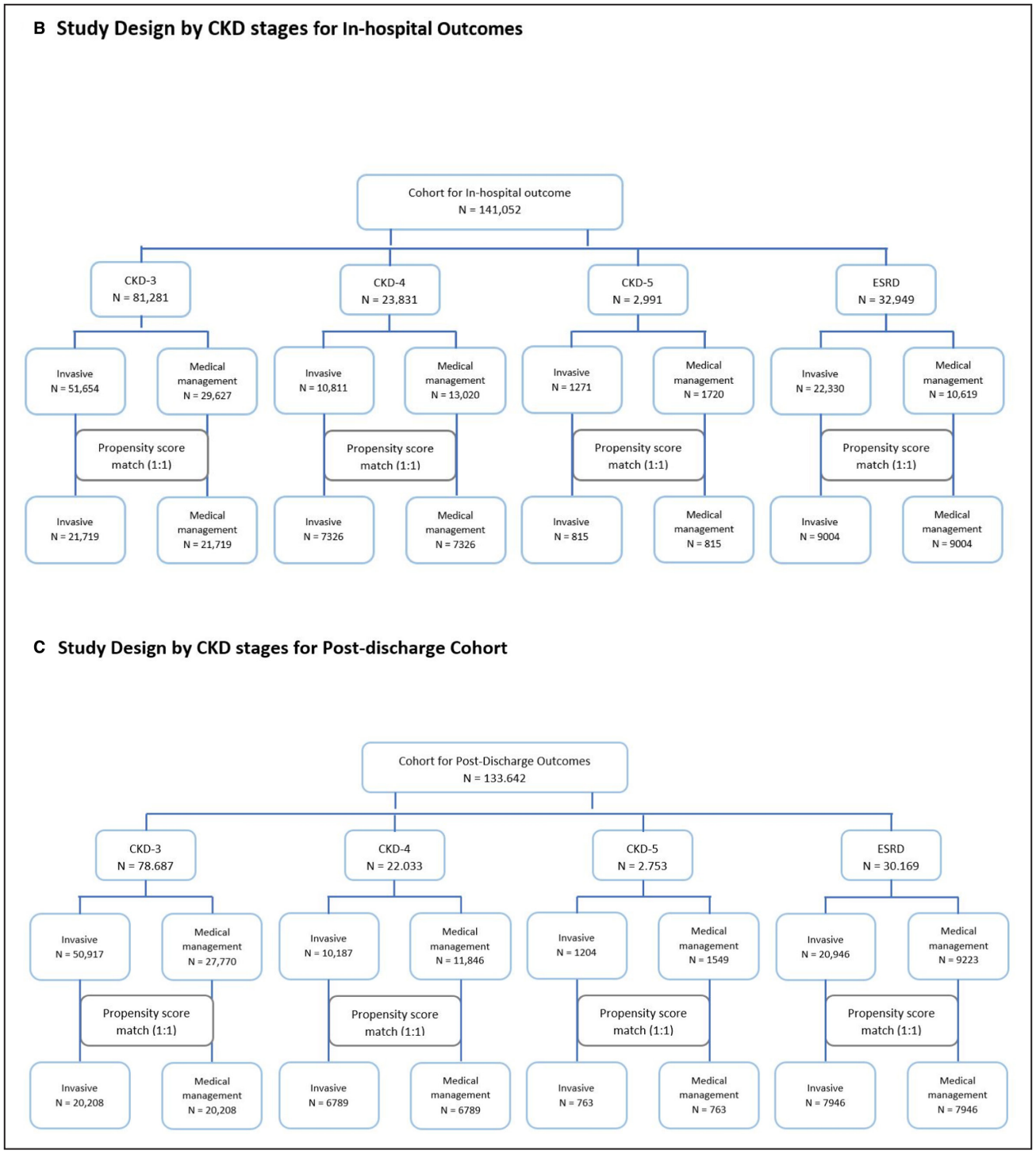

Figure 1. Continued

outcome that may not be expected to be causally affected by the treatment being studied.[23] Then, we assessed if study intervention affects alternative outcomes by a similar method we used to assess other study outcomes. If no treatment effect is seen for the alternative outcome, it supports but does not prove that there may be a causal treatment effect for the study outcomes. Thus, a successful falsification analysis can strengthen the causal claims between study intervention and outcome in the observational study. We chose a composite of gastrointestinal and urinary tract infection readmission as an alternative outcome and studied the effect of interventions. These methods were used in cardiovascular medicine previously.[24,25]

Table 2. In-Hospital Outcomes Between Invasive Strategy and Medical Management in Propensity Score-Matched Cohorts Across CKD Stages

Invasive vs medical management								
	CKD 3							
	Invasive (21 719)	Medical management (21 719)	OR	95% CI		*P* value	NNH	NNT
Mortality	821 (3.8%)	1677 (7.7%)	0.47	0.43	0.51	<0.001		26
AKI requiring dialysis	130 (0.6%)	94 (0.43%)	1.39	1.06	1.81	0.016	588	
Major bleeding, bleeding requiring blood transfusion	603 (2.8%)	544 (2.5%)	1.11	0.99	1.25	0.078	333	
Stroke	485 (2.2%)	474 (2.2%)	1.02	0.9	1.16	0.719		
E-value for mortality, point estimate, lower limit CI	2.75, 2.6							
	CKD 4							
	Invasive (7326)	Medical management (7326)	OR	95% CI		*P* value		
Mortality	459 (6.3%)	591 (8.1%)	0.79	0.69	0.89	<0.001		56
AKI requiring dialysis	149 (2.0%)	84 (1.2%)	1.87	1.43	2.45	<0.001	125	
Major bleeding, bleeding requiring blood transfusion	296 (4.0%)	215 (2.9%)	1.42	1.19	1.7	<0.001	91	
Stroke	134 (1.8%)	121 (1.7%)	1.11	0.86	1.42	0.42		
E-value for mortality, point estimate, lower limit CI	1.63, 1.39							
	CKD 5							
	Invasive (815)	Medical Management (815)	OR	95% CI		*P* value		
Mortality	47 (5.8%)	64 (7.9%)	0.72	0.49	1.06	0.096		48
AKI requiring dialysis	35 (4.3%)	30 (3.7%)	1.17	0.71	1.93	0.527		
Major bleeding, bleeding requiring blood transfusion	38 (4.7%)	18 (2.2%)	2.17	1.23	3.83	0.008	40	
Stroke	17 (2.1%)	14 (1.7%)	1.22	0.6	2.49	0.587		
E-value for mortality, point estimate, lower limit CI	1.82, 1.0							
	ESRD							
	Invasive (9004)	Medical management (9004)	OR	95% CI		*P* value		
Mortality	611 (6.8%)	1128 (12.5%)	0.51	0.46	0.56	<0.001		18
Major bleeding, bleeding requiring blood transfusion	297 (3.3%)	306 (3.4%)	0.97	0.82	1.14	0.709		

(*Continued*)

Table 2. Continued

	ESRD							
	Invasive (9004)	Medical management (9004)	OR	95% CI		*P* value		
Stroke	207 (2.3%)	224 (2.5%)	0.92	0.76	1.12	0.407		
E-value for mortality, point estimate, lower limit CI	2.56, 2.35							
Coronary angiography without revascularization vs medical management								
	CKD 3							
	CAWR (14 605)	Medical management (14 605)	OR	95% CI		*P* value		
AKI requiring dialysis	54 (0.37%)	69 (0.47%)	0.85	0.59	1.21	0.367		
	CKD 4							
	CAWR (3559)	Medical management (3559)	OR	95% CI	*P* value			
AKI requiring dialysis	48 (1.4%)	52 (1.5%)	0.95	0.64	1.41	0.791		
	CKD 5							
	CAWR (380)	Medical management (380)	OR	95% CI	*P* value			
AKI requiring dialysis	12 (3.2%)	18 (4.7%)	0.66	0.31	1.38	0.267		

AKI indicates acute kidney injury; CAWR, coronary angiography without revascularization; CKD, chronic kidney disease; ESRD, end-stage renal disease; NNT, number needed to treat; NNH, number needed to harm; and OR, odds ratio.

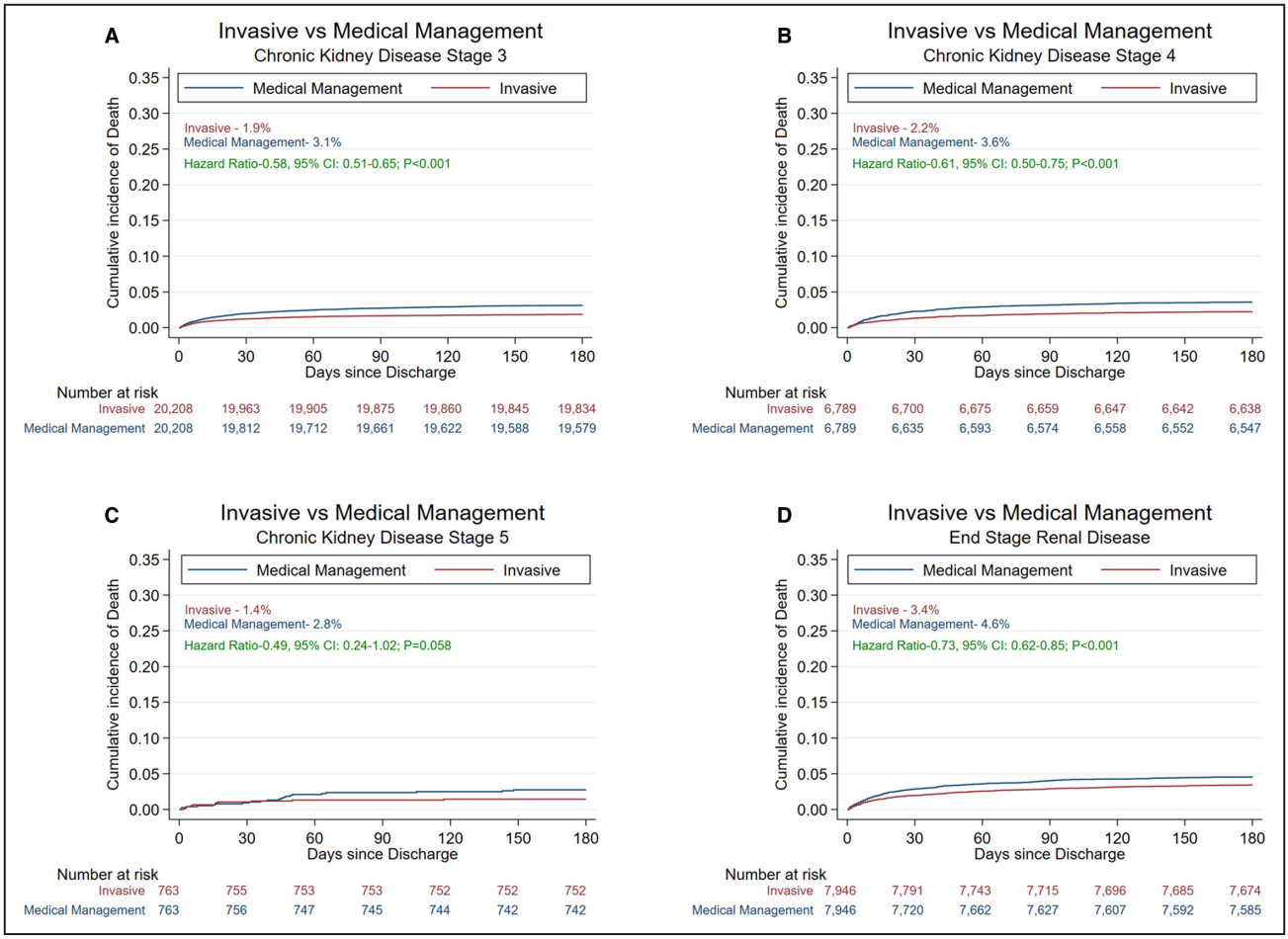

Figure 2. Kaplan-Meier graphs plotting readmission mortality in invasive vs medical management.
A, Chronic kidney disease 3. **B**, Chronic kidney disease 4. **C**, Chronic kidney disease 5. **D**, End-stage renal disease.

We performed sensitivity analysis by performing inverse probability of treatment weighting (IPTW) to evaluate postdischarge mortality.

All statistical analyses were performed on an unweighted sample using Stata version 16.1 (StataCorp, College Station, TX).

RESULTS

A total of 141 052 patients with NSTEMI with CKD 3, 4, 5, or ESRD were identified and included in the present analysis (Figure 1A). Of 141 052 patients, 85 875 (60.9%) were treated with invasive management, whereas 55 177 (39.1%) patients were managed medically. Out of 141 052 patients, 7410 (5.25%) patients died in the hospital and were excluded from postdischarge outcomes analysis to avoid immortal bias. Of 133 642 patients who were discharged alive, 83 254 (62.3%) patients were in invasive management, and 50 388 (37.7%) were in medical management groups during the index admission. Out of 141 052 patients with NSTEMI, 81 281 (57.9%) had CKD Stage 3, 23 831 (16.9%) had CKD Stage 4, 2991 (2.1%) had CKD Stage 5, and 32 949 (23.4%) had ESRD. In CKD 3, 4, 5, and ESRD, 64%, 45%, 42%, and 68% underwent invasive management, respectively. Figure 1B and 1C represent inclusion of patients with NSTEMI based on the CKD stage before and after propensity-score matching for in-hospital and postdischarge outcomes, respectively.

Baseline Characteristics of CKD 3, 4, 5. or ESRD (Invasive Management Versus Medical Management)

Table S3 showed baseline characteristics in the unmatched cohort by CKD stages. In the unmatched cohort of patients with NSTEMI-CKD, patients treated with medical management were older and had a higher percentage of women than invasive management in all advanced CKD groups. Medical management had a lower percentage of hypertension, diabetes, hyperlipidemia, ischemic cardiomyopathy, carotid artery disease, previous PCI, smoking history, obesity, and

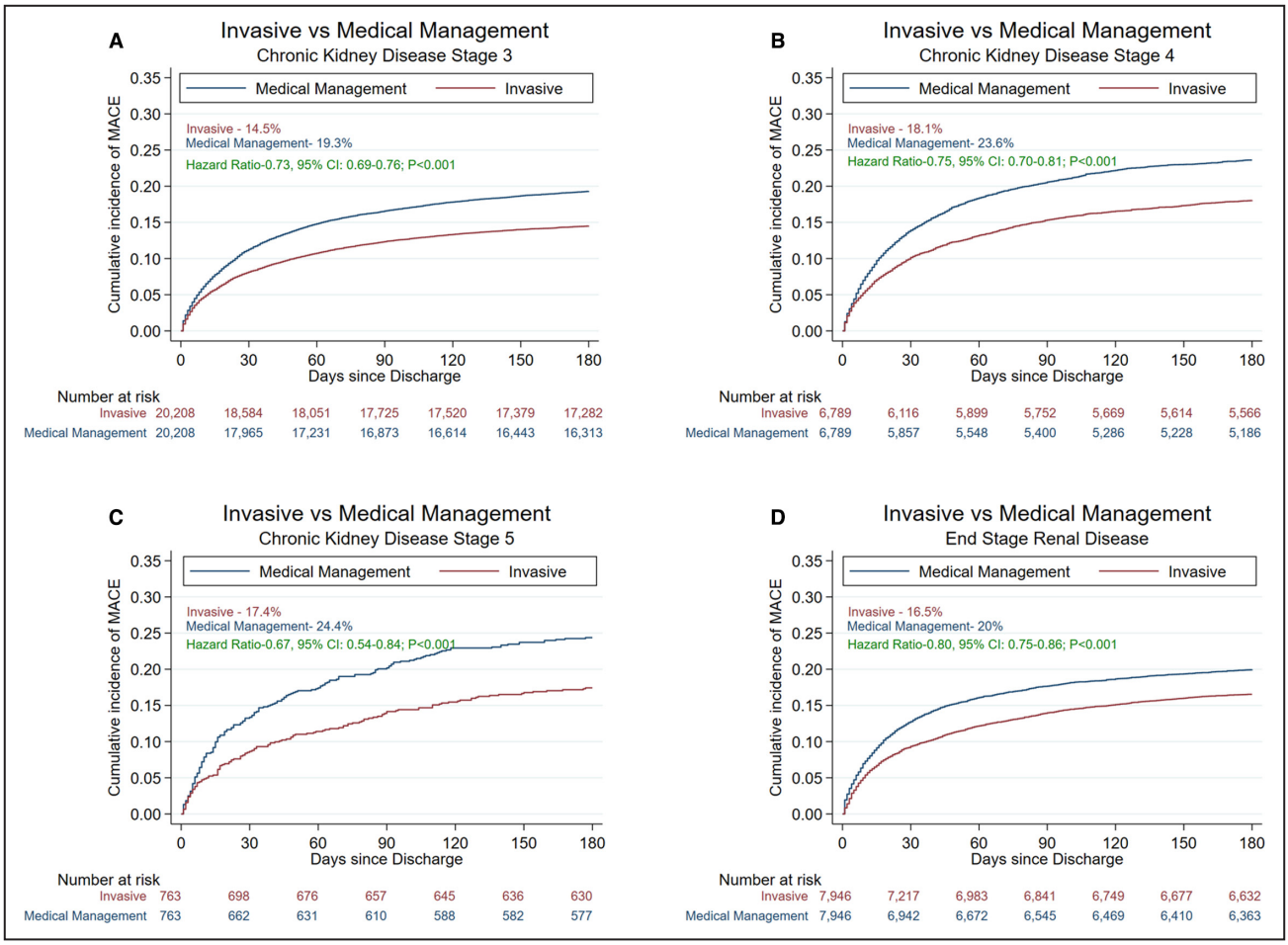

Figure 3. Kaplan-Meier graph plotting major adverse cardiovascular events (MACE) in invasive vs medical management. **A,** Chronic kidney disease Stage 3. **B**, Chronic kidney disease Stage 4. **C**, Chronic kidney disease Stage 5. **D**, End-stage renal disease. MACE are a composite of all-cause mortality, myocardial infarction readmission, stroke readmission, or heart failure readmission.

coagulopathy than patients treated with invasive management. However, medical management had a higher percentage of CABG history than patients treated with invasive management. Medical management had a lower percentage of patients in large-bed and teaching hospitals than invasive management. Medical management had a lower percentage of private insurance than invasive management. Table 1 reports the baseline characteristics of patients with NSTEMI-CKD undergoing invasive versus medical management, subgrouped based on the CKD stage in a propensity-score matched cohort. Both groups were well balanced based on the standardized mean difference between the 2 groups and presented graphically in Figure S1. Figure S2 depicts a balance of variables between CAR and medical management. Figure S3 depicts the balance of variables between CAWR and medical management. The matching of variables between all 3 strategies and medical management was well balanced. Figure S4 shows predictors of invasive management over medical management in all patients with CKD.

Invasive Versus Medical Management: In-Hospital Outcomes in the Propensity-Score Matched Cohort

In patients with NSTEMI-CKD, invasive management was associated with lower in-hospital mortality across all CKD stages compared with medical management. However, lower mortality in the invasive group compared with medical management in CKD 5 was not statistically significant. Invasive management was associated with a higher risk of postprocedure AKI requiring dialysis in CKD stages 3 and 4, and major bleeding in CKD stages 4 and 5. However, there was a similar risk of stroke between the 2 strategies. The number needed to harm (NNH) for AKI requiring dialysis was 588 in CKD 3 and 125 in CKD 4. The NNH for major bleeding was 333 in CKD 3, 91 in CKD 4, and 40 in CKD 5. The number needed to treat for in-hospital mortality was 26 in CKD 3, 56 in CKD 4, 48 in CKD 5, and 18 in ESRD (Table 2).

Table 3. Postdischarge Outcomes Between Invasive Strategy and Medical Management in Propensity-Score Matched Cohorts Across CKD Stages

	CKD 3		CKD 4		CKD 5		ESRD	
	Invasive	Medical management	Invasive	Medical management	Invasive	Medical management	Invasive	Medical management
	20 208	20 208	6789	6789	763	763	7946	7946
All-cause readmission mortality								
No. of patients with events	373	630	151	242	11	21	272	363
Cumulative event rate, %								
At 30 d	1.2	2	1.3	2.3	1.1	0.9	2	2.9
At 3 mo	1.6	2.7	1.9	3.2	1.3	2.4	2.9	4
At 6 mo	1.9	3.1	2.2	3.6	1.4	2.8	3.4	4.6
HR (95% CI; *P* value)	0.58 (0.51–0.65; <0.001)		0.61 (0.50–0.75; <0.001)		0.49 (0.24–1.02; 0.058)		0.73 (0.62–0.85; <0.001)	
IPTW method: HR (95% CI; *P* value)	0.56 (0.50–0.64; <0.001)		0.66 (0.54–0.81; <0.001)		0.32 (0.16–0.62; 0.001)		0.69 (0.60–0.79; <0.001)	
MACE: MI, stroke, HF, readmission mortality								
No. of patients with events	2931	3899	1225	1601	133	186	1312	1585
Cumulative event rate, %								
At 30 d	8.16	11.27	10.2	13.9	8.7	13.4	9.4	12.8
At 3 mo	12.37	16.56	15.3	20.6	14.2	20.2	14	17.7
At 6 mo	14.5	19.3	18.1	23.6	17.4	24.4	16.5	20
HR (95% CI; *P* value)	0.73 (0.69–0.76; <0.001)		0.75 (0.70–0.81; <0.001)		0.67 (0.54–0.84; <0.001)		0.80 (0.75–0.86; <0.001)	
Safety outcome: AKI, stroke, major bleeding, vascular complication								
No. of patients with events	656	664	303	284	30	33	185	162
Cumulative event rate, %								
At 30 d	1.8	1.8	2.6	2.1	2.5	2.5	1.4	1.2
At 3 mo	2.7	2.8	3.7	3.3	3.5	3.8	2.1	1.8
At 6 mo	3.3	3.3	4.5	4.2	3.9	4.3	2.3	2.1
HR (95% CI; *P* value)	0.99 (0.89–1.10; 0.822)		1.07 (0.91–1.26; 0.406)		0.91 (0.55–1.49, 0.698)		1.14 (0.93–1.41, 0.213)	
Efficacy outcome: MI, all-cause mortality, revascularization								
No. of patients with events	1647	2377	633	927	73	106	993	1257
Cumulative event rate, (%)								
At 30 d	4.5	7.2	5.1	8.4	3.8	7.9	6.6	10.6
At 3 mo	6.8	10.1	7.8	11.9	7.3	11.9	10.2	14
At 6 mo	8.2	11.8	9.3	13.7	9.6	13.9	12.5	15.8
HR (95% CI; *P* value)	0.68 (0.64–0.72; <0.001)		0.66 (0.60–0.73; <0.001)		0.66 (0.49–0.90, 0.007)		0.77 (0.71–0.83, <0.001)	
MI								
No. of patients with events	837	1337	300	537	39	58	471	684
Cumulative event rate, %								
At 30 d	2.2	4	2.3	4.7	2	4.7	3.1	6.1
At 3 mo	3.4	5.6	3.6	6.8	3.9	6.9	4.8	7.6
At 6 mo	4.2	6.6	4.4	7.9	5.1	7.6	5.9	8.6
HR (95% CI; *P* value)	0.61 (0.56–0.66; <0.001)		0.55 (0.47–0.63; <0.001)		0.63 (0.42–0.95; 0.026)		0.67 (0.59–0.75; <0.001)	
Revascularization								
No. of patients with events	967	1179	346	441	45	60	602	681
Cumulative event rate, %								
At 30 d	2.5	3.8	2.7	4.3	2.2	4.9	3.7	6
At 3 mo	3.9	5.1	4.2	5.7	4.5	6.8	5.9	7.7
At 6 mo	4.8	5.8	5.1	6.5	5.9	7.9	7.6	8.6
HR (95% CI; *P* value)	0.80 (0.73–0.87; <0.001)		0.77 (0.67–0.88; <0.001)		0.71 (0.48–1.04; 0.077)		0.86 (0.77–0.96; 0.006)	

(*Continued*)

Table 3. Continued

	CKD 3		CKD 4		CKD 5		ESRD	
	Invasive	Medical management	Invasive	Medical management	Invasive	Medical management	Invasive	Medical management
Renal safety outcome: death or new dialysis								
No. of patients with events	427	679	265	366	65	71		
Cumulative event rate, %								
At 30 d	1.4	2.1	2.3	3.2	5	4.2		
At 3 mo	1.9	2.9	3.3	4.7	7.6	7.3		
At 6 mo	2.1	3.4	3.9	5.4	8.5	9.3		
HR (95% CI; *P* value)	0.63 (0.55–0.71; <0.001)		0.72 (0.61–0.84, <0.001)		0.92 (0.66–1.28, 0.613)			
Acute kidney injury								
No. of patients with events	350	394	204	204	18	25		
Cumulative event rate, %								
At 30 d	0.97	1.11	1.8	1.5	1.4	2.1		
At 3 mo	1.5	1.7	2.5	2.4	2.1	3		
At 6 mo	1.73	1.95	3	3	2.4	3.3		
HR (95% CI; *P* value)	0.86 (0.74–0.99; 0.040)		0.98 (0.81–1.19; 0.816)		0.68 (0.37–1.25; 0.213)			
Falsified end point,* HR (95% CI; *P* value)	0.96 (0.79–1.18, 0.719)		0.94 (0.62–1.11, 0.482)		1.06 (0.53–2.88, 0.572)		1.15 (0.87–1.52, 0.317)	
E-value for mortality, point estimate, lower limit CI	2.27, 2.03		2.16, 1.74		2.65, 1.0		1.80, 1.48	

AKI indicates acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

*Falsified end point is the composite of gastrointestinal or urinary tract infection.

Invasive Versus Medical Management: Postdischarge 6-Month Outcomes in the Propensity-Score Matched Cohort

In patients with NSTEMI-CKD, invasive management was associated with lower all-cause readmission mortality rates than medical management (Figure 2). Invasive management was associated with reduced hazard of MACE (Figure 3), similar safety outcomes, and better efficacy outcomes compared with medical management at 6-month follow-up. Invasive management was also associated with a reduced hazard of MI readmission and revascularization during readmission at a 6-month follow-up. Invasive management compared with medical management was also associated with lower rates of renal safety outcomes in CKD 3 and CKD 4 at 6-month follow-up, which is driven by lower mortality rates. Invasive management was associated with similar rates of AKI readmission compared with medical management (Table 3).

Subgroup Analysis (CAWR Versus Medical Management, CAR Versus Medical Management)

Table 4 shows a comparison of CAR versus medical management for in-hospital outcomes. Similar to invasive versus medical management, CAR was associated with lower mortality (statistically significant in CKD 5), higher AKI requiring dialysis in CKD 3 and 4, and major bleeding across all CKD stages with higher NNH and lower number needed to treat for mortality. CAR was associated with lower readmission mortality, MACE, MI, need for revascularization, better efficacy outcome, similar safety outcome, and AKI compared with medical management at 6-month follow-up (Table 5). CAWR/diagnostic angiography was not associated with a higher risk of AKI requiring dialysis than medical management. Kaplan-Meier curves showing event rates for readmission mortality and MACE for all CKD groups are extrapolated in Figure 4 and Figure 5.

Unmeasured Confounders Analysis

The falsification end point remained similar between invasive and medical management, implying a balance of unmeasured confounder between the 2 groups if it exists. In the E-value analysis, the point estimate was higher for the mortality for invasive versus medical management, implying that if an unmeasured confounder exists, it requires higher relative risk with treatment and outcome, conditioned on 26 variables used in propensity-score matching, to explain the measured effect. This implies a low likelihood that current results will be altered because of unmeasured confounders. Moreover, postdischarge mortality was lower in

Table 4. In-Hospital Outcomes Between CAR and Medical Management in Propensity-Score Matched Cohorts Across CKD Stages

	CKD 3						
	CAR (17 507)	Medical management (17 507)	OR	95% CI		*P* value	NNH/ NNT
Mortality	711 (4.1%)	1293 (7.4%)	0.52	0.48	0.58	<0.001	30
AKI requiring dialysis	145 (0.8%)	78 (0.5%)	1.85	1.41	2.44	<0.001	333
Major bleeding, bleeding requiring blood transfusion	662 (3.8%)	441 (2.5%)	1.54	1.34	1.74	<0.001	77
Stroke	390 (2.2%)	383 (2.2%)	1.02	0.89	1.18	0.746	
	CKD 4						
	CAR (5514)	Medical management (5514)	OR	95% CI		*P* value	
Mortality	327 (5.9%)	410 (7.4%)	0.78	0.68	0.91	0.002	66
AKI requiring dialysis	146 (2.7%)	72 (1.3%)	2.1	1.55	2.73	<0.001	72
Major bleeding, bleeding requiring blood transfusion	297 (5.4%)	163 (3%)	1.87	1.54	2.27	<0.001	42
Stroke	125 (2.3%)	89 (1.6%)	1.05	0.64	1.86	0.567	
	CKD 5						
	CAR (617)	Medical management (617)	OR	95% CI		*P* value	
Mortality	25 (4.1%)	53 (8.6%)	0.45	0.28	0.73	0.001	22
AKI requiring dialysis	31 (5%)	23 (3.7%)	1.37	0.79	2.37	0.267	
Major bleeding, bleeding requiring blood transfusion	36 (5.8%)	14 (2.3%)	2.67	1.42	5.0	0.002	29
Stroke	12 (1.9%)	12 (1.9%)	1.0	0.45	2.24	1.00	
	ESRD						
	CAR (9004)	Medical management (9004)	OR	95% CI		*P* value	
Mortality	514 (6.6%)	976 (12.6%)	0.49	0.44	0.55	<0.001	17
Major bleeding, bleeding requiring blood transfusion	347 (4.5%)	263 (3.4%)	1.33	1.13	1.57	0.001	91
Stroke	220 (2.8%)	187 (2.4%)	1.18	0.77	1.44	0.648	

AKI indicates acute kidney injury; CAR, coronary angiography with revascularization; CKD, chronic kidney disease; ESRD, end-stage renal disease; NNH, number needed to harm; NNT, number needed to treat; and OR, odds ratio.

invasive strategy across all CKD stages using the inverse probability of treatment weighting method. With the inverse probability of treatment weighting method, the invasive strategy showed statistical significance for lowering mortality in CKD stage 5, likely overcoming type 2 error imposed by 1:1 matching (Tables 2, 3).

DISCUSSION

In this real-world analysis of patients with NSTEMI-CKD, we derived 3 important results: (1) invasive management was associated with lower in-hospital mortality, higher postprocedural AKI requiring dialysis, and major bleeding in advanced CKD stages, but with higher NNH for complications compared with lower number needed to treat for mortality; (2) invasive management was associated lower readmission-related mortality, MACE, MI, and need for revascularization compared with medical management after discharge at 6 months; (3) invasive management was associated with similar safety outcomes after discharge at 6 months (Figure 6). American Heart Association/American College of Cardiology 2021 and European Society of Cardiology 2020 guidelines provided IIa (B-NR) and I (C) recommendations for invasive management in NSTEMI with CKD, respectively. However, recommendations were supported by a lower level of evidence because of insufficient data on the beneficial role of the invasive approach over medical management, causing ambiguity on management strategy in patients with CKD.[11,12] Moreover, it is observed that patients with NSTEMI with CKD less frequently receive evidence-based treatments such as antithrombotic agents and

Table 5. Postdischarge Outcomes Between CAR and Medical Management in Propensity-Score Matched Cohorts Across CKD Stages

	CKD 3		CKD 4		CKD 5		ESRD	
	CAR	Medical management	CAR	Medical management	CAR	Medical management	CAR	Medical management
	16 508	16 508	5145	5145	583	583	6902	6902
All-cause mortality during readmission								
No. of patients with events	255	513	91	173	8	18	201	314
Cumulative event rate, %								
At 30 d	1	2	1.1	2.1	0.9	1.4	1.7	2.8
At 3 mo	1.4	2.7	1.6	2.9	1.2	2.6	2.5	4
At 6 mo	1.5	3.1	1.8	3.4	1.4	3.1	2.9	4.6
HR (95% CI; *P* value)	0.47 (0.41–0.55; <0.001)		0.51 (0.39–0.66; <0.001)		0.40 (0.17–0.92; 0.032)		0.61 (0.51–0.73; <0.001)	
MACE: MI, stroke, HF, all-cause mortality								
No. of patients with events	2229	3263	874	1229	91	141	1089	1416
Cumulative event rate, %								
At 30 d	7.4	11.6	9.6	14.1	7.9	13.6	8.4	13.1
At 3 mo	11.4	17.1	14.4	20.9	12.2	20.9	13.2	18.1
At 6 mo	13.5	19.8	17	23.9	15.6	24.2	15.8	20.5
HR (95% CI; *P* value)	0.65 (0.62–0.69; <0.001)		0.68 (0.63–0.75; <0.001)		0.58 (0.45–0.76; <0.001)		0.74 (0.68–0.80; <0.001)	
Safety outcome: AKI, stroke, major bleeding, vascular complication								
No. of patients with events	514	542	224	223	22	35	148	136
Cumulative event rate (%)								
At 30 d	1.8	1.8	2.5	2.3	2.1	3.4	1.4	1.2
At 3 mo	2.6	2.9	3.6	3.6	2.9	5.2	1.9	1.7
At 6 mo	3.1	3.3	4.4	4.3	3.8	6	2.1	2
HR (95% CI; *P* value)	0.95 (0.84–1.07, 0.385)		1.01 (0.84–1.21, 0.947)		0.62 (0.36–1.06, 0.078)		1.09 (0.86–1.38, 0.469)	
Efficacy outcome: MI, all-cause mortality, revascularization								
No. of patients with events	1159	2045	423	705	46	86	835	1123
Cumulative event rate, %								
At 30 d	3.5	7.6	4.2	8.2	2.7	8.4	5.7	10.7
At 3 mo	5.6	10.7	6.7	11.7	5.3	12.7	9.5	14.3
At 6 mo	7	12.4	8.2	13.7	7.9	14.8	12.1	16.3
HR (95% CI; *P* value)	0.55 (0.51–0.59, <0.001)		0.58 (0.51–0.65, <0.001)		0.51 (0.35–0.73, <0.001)		0.71 (0.65–0.78, <0.001)	
MI								
No. of patients with events	571	1162	201	421	23	42	398	628
Cumulative event rate, %								
At 30 d	1.6	4.2	1.8	4.8	1.4	4.5	2.4	6.3
At 3 mo	2.7	6	3	7	2.9	6.9	4.4	8
At 6 mo	3.5	7.1	3.9	8.2	3.9	7.2	5.8	9.1
HR (95% CI; *P* value)	0.47 (0.42–0.52; <0.001)		0.46 (0.39–0.54; <0.001)		0.49 (0.30–0.82; 0.007)		0.61 (0.54–0.69; <0.001)	
Revascularization								
No. of patients with events	752	1036	255	347	31	48	575	623
Cumulative event rate, %								
At 30 d	2	4.1	2.2	4.2	1.5	5	3.4	6.3
At 3 mo	3.4	5.5	3.8	5.6	3.3	7	6.1	8
At 6 mo	4.6	6.3	5	6.8	5.3	8.2	8.3	9.1
HR (95% CI; *P* value)	0.69 (0.63–0.76; <0.001)		0.71 (0.60–0.83; <0.001)		0.58 (0.37–0.91; 0.017)		0.88 (0.80–0.99, 0.033)	
Renal safety outcome: death or dialysis								
No. of patients with events	304	554	178	278	44	57		

(*Continued*)

Table 5. Continued

	CKD 3		CKD 4		CKD 5		ESRD	
	CAR	Medical management	CAR	Medical management	CAR	Medical management	CAR	Medical management
Cumulative event rate, %								
At 30 d	1.2	2.1	2	3.2	4.8	5		
At 3 mo	1.7	2.9	2.9	4.6	6.9	8.1		
At 6 mo	1.8	3.4	3.5	5.4	7.6	9.8		
HR (95% CI; *P* value)	0.55 (0.47–0.63, <0.001)		0.63 (0.53–0.77, <0.001)		0.77 (0.52–1.14, 0.184)			
AKI								
No. of patients with events	275	328	144	154	11	26		
Cumulative event rate, %								
At 30 d	1	1.1	1.7	1.5	0.9	2.9		
At 3 mo	1.4	1.7	2.3	2.4	1.2	4.1		
At 6 mo	1.7	2	2.8	3	1.9	4.5		
HR (95% CI; *P* value)	0.80 (0.68–0.94; 0.006)		0.90 (0.72–1.13; 0.360)		0.38 (0.19–0.77; 0.008)			
Falsified end point, HR (95% CI; *P* value)	1.0 (0.79–1.27, 0.997)		0.84 (0.56–1.30, 0.450)		0.71 (0.23–2.25, 0.564)		1.08 (0.57–1.71, 0.84)	
E-value for mortality, point estimate, lower limit CI	2.45, 2.26		2.3, 2.0		2.84, 1.96		2.04, 1.81	

AKI, acute kidney injury; CAR, coronary angiography with revascularization; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; HF, heart failure; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

early invasive management.[11] One of the reasons is the underrepresentation of CKD in randomized clinical trials undergoing CA because of the fear of the increased risk of contrast-induced nephropathy, AKI, renal replacement therapy, bleeding, and mortality compared with patients without CKD. Similarly, physicians' minds have a common perception on an early invasive approach associated with poorer renal safety outcomes and more vascular and bleeding complications than medical management in NSTEMI-CKD.

In recent years, meta-analyses have called into question the use of contrast as a cause of AKI, inviting clinicians to rethink the use of contrast for diagnostic or therapeutic purposes in patients with CKD, because the benefits of using contrast could outweigh the risks.[7,26,27] A review from Mehran et al[28] reframed the name from contrast-induced nephropathy to contrast-associated nephropathy. Bhatia et al reported that patients with NSTEMI with CKD stages 3, 4, 5, or ESRD had an increased risk of bleeding requiring transfusion than patients without CKD.[10] However, there is limited evidence for the association of invasive management with a higher bleeding risk than medical management in NSTEMI-CKD. We found that the invasive management was associated with an increased risk of in-hospital AKI requiring dialysis in CKD 3 and 4, major bleeding in CKD 3 to 5, but a similar risk of post-discharge safety end points such as AKI, bleeding, vascular complication, or stroke across all CKD stages compared with medical management. Moreover, the NNH for in-hospital AKI requiring dialysis and major bleeding was very high. Subsequently, there was no increased risk of AKI requiring dialysis in the subgroup of patients who underwent CAWR/diagnostic angiography. This might encourage physicians to subject patients more often to invasive management, following a discussion on the risk related to the procedure. Similar to these findings, Goulden et al[29] showed that contrast was not associated with increased risk of AKI or renal replacement therapy at 6 months using a regression discontinuity analysis in a quasiexperimental cohort study of 156 028 patients who underwent a computed tomography pulmonary embolism protocol. Alternatively, increased use of iso-osmotic or low-osmotic contrast in such patients may reduce the risk of AKI.

CKD is associated with an increased burden of atherosclerosis, and the burden progresses with CKD progression.[30] Because of the higher burden of atherosclerosis in CKD, invasive management might be more beneficial than patients without CKD in NSTEMI. A meta-analysis of 5 randomized clinical trials concluded that early invasive management reduced the risk of hospitalization and death. Although statistical significance was not achieved for death because of the low number of subjects, there was a trend in reducing the risk of death in patients with NSTEMI-CKD.[31] Furthermore, Bhatia et al showed that PCI was associated with lesser odds of in-hospital mortality in NSTEMI-CKD irrespective of CKD stages using the National Inpatient Sample.[10] The Swedish web-system for enhancement and development of evidence-based

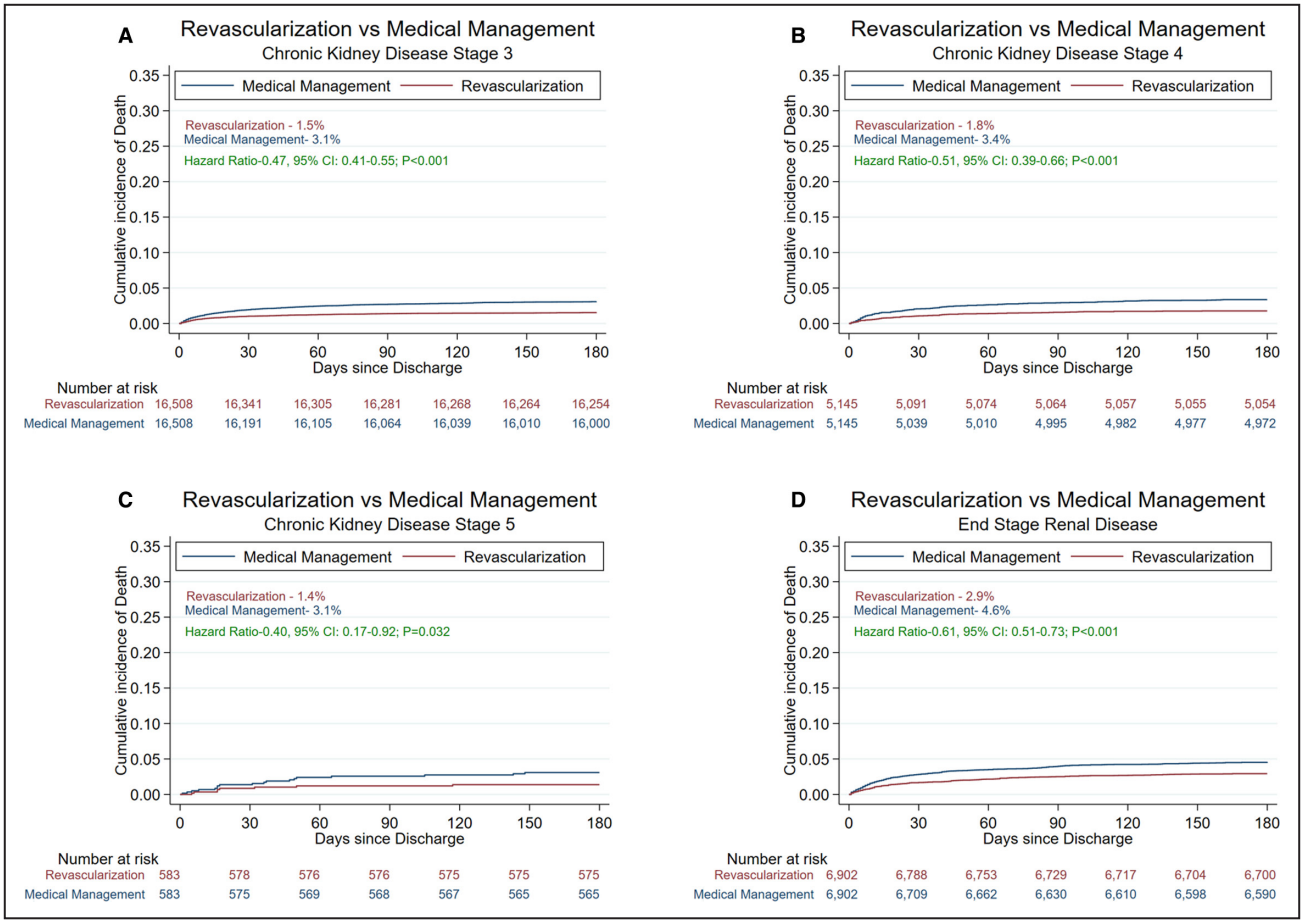

Figure 4. Kaplan-Meier graph plotting readmission mortality in revascularization vs medical management.
A, Chronic kidney disease Stage 3. **B**, Chronic kidney disease Stage 4. **C**, Chronic kidney disease Stage 5. **D**, End-stage renal disease.

care in heart disease evaluated according to recommended therapies (SWEDEHEART) registry demonstrated lower mortality at 1 year with the early invasive management in CKD stage 3 but no difference in advanced CKD stages (stage 4, 5, or ESRD) compared with medical management in patients with NSTEMI.[32] However, the SWEDEHEART study did not have enough power to detect the mortality difference in advanced CKD stages (CKD 4 sample 572, CKD 5/ESRD sample 278), and patients who underwent CA without intervention within 14 days of admission were included in the medical management group. As expected, we found that invasive management in a subgroup of patients who underwent revascularization (CAR) was associated with a significant reduction in mortality, MACE, MI, need for revascularization, and better efficacy outcomes in CKD stage 3, but also in CKD stage 4, 5, and ESRD. In contrast, the ISCHEMIA-chronic kidney disease (ISCHEMIA-CKD) randomized clinical trial did not find any difference for death or MI between the 2 strategies in patients with moderate to severe ischemia on stress testing.[33] However, the trial excluded very symptomatic patients, patients with heart failure or recent acute coronary syndromes, or an ejection fraction of <35%. This study included real-world patients with non–ST-segment–elevation acute coronary syndrome. Additionally, ischemic preconditioning might be the reason why no difference was found in the primary outcome between the 2 strategies in the ISCHEMIA-CKD trial.

Unmeasured confounders have the potential to affect the results in observational studies. However, we validated our results using falsification end point analysis and E-value analysis. The successful falsification analysis assures a balance of unmeasured confounders between 2 groups and claims the causality between intervention and study outcomes. Additionally, a higher E-value for various outcomes suggested a lesser likelihood for unmeasured confounders to overcome the association between study intervention and outcomes over current covariates adjustment. Thus, our results bring the evidentiary gap closer by reporting that patients with advanced stages of CKD and ESRD with NSTEMI benefit from an invasive approach compared with medical management, with a mild increase in the risk of renal outcomes.

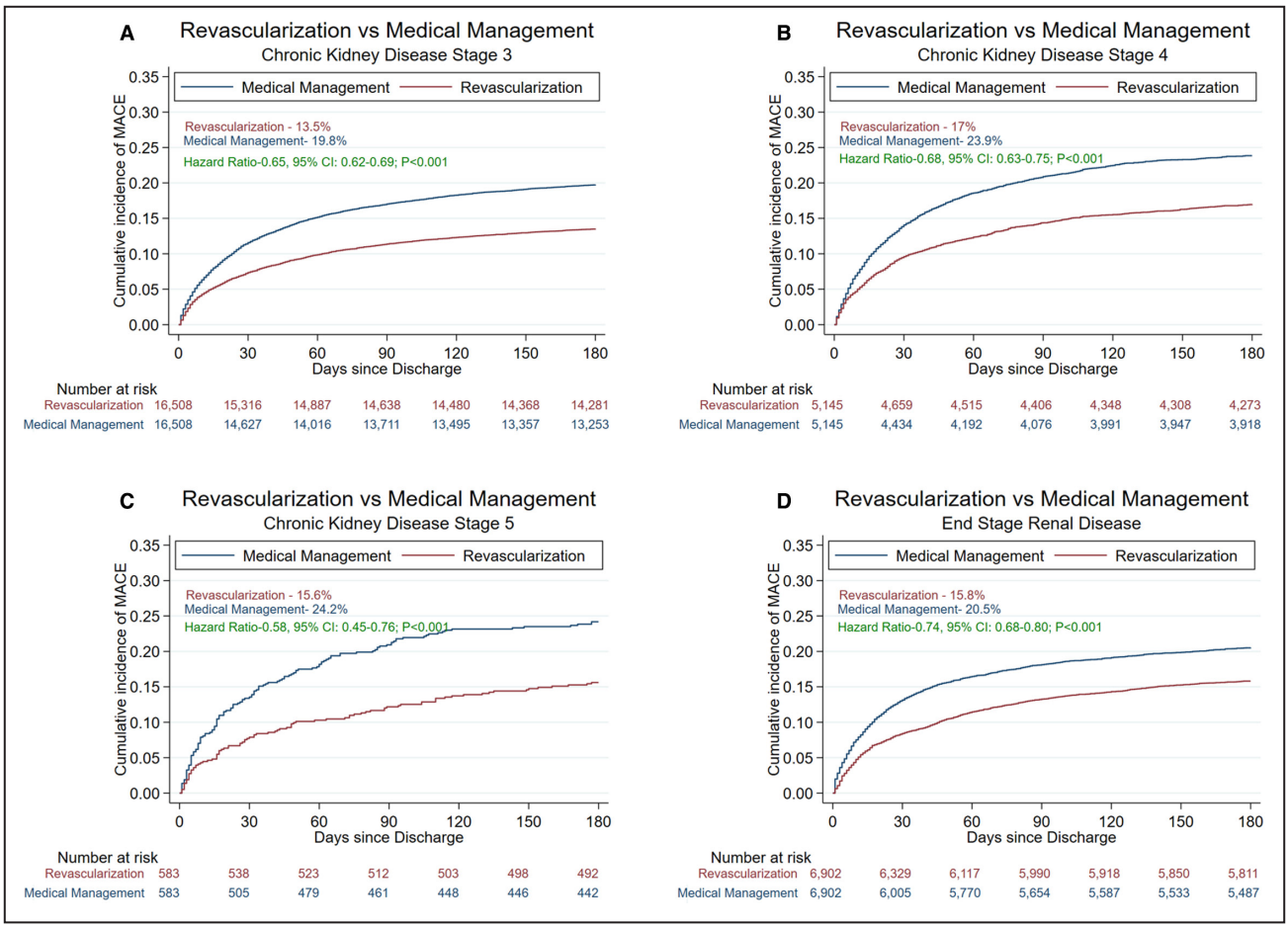

Figure 5. Kaplan-Meier graph plotting major adverse cardiovascular events (MACE) in revascularization vs medical management.
A, Chronic kidney disease Stage 3. **B**, Chronic kidney disease Stage 4. **C**, Chronic kidney disease Stage 5. **D**, End-stage renal disease. MACE are a composite of all-cause mortality, myocardial infarction readmission, stroke readmission, or heart failure readmission.

Although additional studies are needed, our results suggest that diagnostic coronary angiography was not associated with increased AKI; hence, an invasive strategy should be offered to all patients with NSTEMI-CKD, and revascularization should be a shared decision after discussing the risks and benefits with patients. CKD is associated with an increased risk of adverse ischemic and bleeding events, and a higher risk of AKI. Nonetheless, the mortality and major adverse cardiac and cerebrovascular events benefit of the invasive strategy outweighs the risk of adverse outcomes. Moreover, adverse renal outcomes will be even lower when adequate measures to reduce AKI risk are taken before, during, and after the procedure. Because clinical severity was not available in the current study, it would be essential to see future studies evaluating the impact of an invasive strategy on disease severity.

Our study has some limitations. First, the inherent nature of a retrospective cohort study makes it very difficult to avoid selection bias that could have confounded our results. Some patients may have opted out of invasive management, given the risk of dialysis dependency. Nevertheless, by propensity-score matching and using falsification outcome and E-value analysis, we intended to minimize the risk of bias and ascertain more robust results. However, the possibility of selection bias remains, given the observational nature of the study. Second, we did not have information about the exact glomerular filtration rate, and the analysis was based on coding, which may include errors in characterizing CKD stages and lead to information bias. However, we suspect that there may be minimal overlap between CKD groups, and given a large number of patients in each group, the results may not be any different, as evidenced by similar results across all stages of CKD. Third, the database lacks information on the amount of contrast used, the type of contrast used, and who received crystalloids before the procedure. Fourth, the database lacks information about nephrotoxic medication use before or during admission, and information on discharge medications. Finally, we may have missed events (ie, bleeding or death) that might have occurred outside the hospital, resulting in the

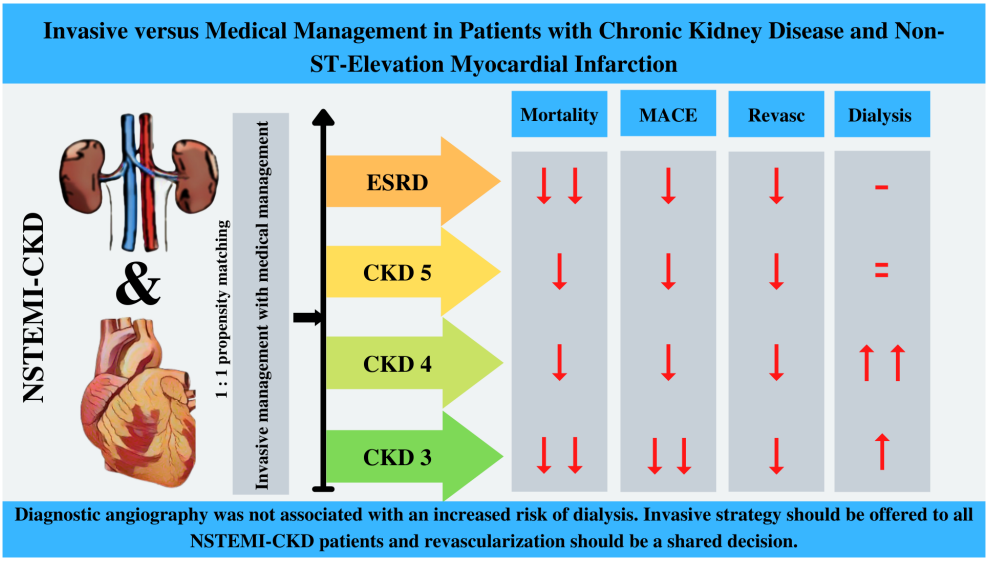

Figure 6. Invasive vs medical management in patients with NSTEMI and CKD.
The - indicates null effect of invasive management compared with medical management, = indicates equivocal effect, ↓ indicates a lower strength of association and ↑ indicates a higher strength of association for invasive management. MACE are a composite of all-cause mortality, myocardial infarction readmission, stroke readmission, or heart failure readmission. CKD indicates chronic kidney disease; dialysis, in-hospital acute kidney injury requiring dialysis; ESRD, end-stage renal disease; MACE, major adverse cardiovascular events; NSTEMI, non–ST-segment–elevation myocardial infarction; and Revasc, need for revascularization.

underrepresentation of events; however, this would be the case for both groups. Because we aimed to compare 2 groups, the ratio is a better measure of effect.

CONCLUSIONS

In patients with NSTEMI and advanced CKD stages, invasive management was associated with lower mortality, MACE, MI, need for revascularization, and better efficacy outcome along with the minimal increased risk of in-hospital dialysis, major bleeding, and similar post-discharge safety outcome (vascular complication, major bleeding, or AKI) at 6 months compared with medical management alone. The need for postprocedure dialysis during index hospitalization increased only when revascularization was performed in the invasive group (and not for the diagnostic CA-only group). Thus, invasive management should be offered to patients presenting with NSTEMI-CKD, and the risk of dialysis and major bleeding should be discussed before revascularization.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S4

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Supplemental Material

Table S1. ICD-10 CM codes used to identify comorbidities.

	ICD 10 CM codes
Comorbidities	**Secondary diagnosis field**
Hypertension	I10, I11, I12, I13, I15, I16
Diabetes	E08, E09, E10, E11, E13
Hyperlipidemia	E78.0, E78.1, E78.2, E78.4, E78.5
history of TIA or stroke	I69.3, Z86.73
Ischemic cardiomyopathy	I24.8, I24.9, I25.1, I25.10, I25.11, I25.110, I25.111, I25.118, I25.119, I25.2, I25.5, I25.6, I25.8, I25.810, I25.89, I25.9, I25.82, I25.83, I25.84, I25.41, I25.42, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.790, I25.791, I25.798, I25.799
Carotid Artery Disease	I65.2
Peripheral vascular disease	E08.5, E09.5, E10.5, E11.5, E13.5, I73, T82.856, Z98.62, Z95.820
Prior PCI	Z98.61
Prior CABG	Z95.1
Heart failure	I0981,I501,I5020,I5021,I5022,I5023,I5030,I5031,I5032,I5033,I5040,I5041,I5042, I5043,I50810,I50811,I50812,I50813,I50814,I5082,I5083,I5084,I5089,I509
Atrial Fibrillation	I48, I48.0, I48.1, I48.2, I48.4, I48.91
Chronic Pulmonary Disease	J40,J410,J411,J418,J42,J430,J431,J432,J438,J439,J440,J441,J449,J4520,J4521,J4522,J4530,J4531,J4532,J4540,J4541,J4542,J4550,J4551,J4552,J45901,J45902,J45909,J45990,J45991,J45998,J470,J471,J479,J60,J61,J620,J628,J630,J631,J632,J633, J634,J635,J636,J64,J660,J661,J662,J668,J670,J671,J672,J673,J674,J675, J676,J677,J678,J679,J684
Anemia	D50, E60, D61, D62, D63, D64, D46.0, D46.1, D46.2, D46.4, O99.0
Smoker	F17, Z87.891, Z72.0, O99.33, T65.2
Obesity	E66, Z68.3, Z68.4
Coagulopathy	D65,D66,D67,D680,D681,D682,D68311,D68312,D68318,D6832,D684,D688,D689,D691,D693,D6941,D6942,D6949,D6951,D6959,D696,D7582,O99111,O991112,O99113,O99119,O9912,O9913
History of Non-adherence to Medication	Z91.12, Z91.13, Z91.14, Z91.19

Table S2. ICD-10 CM codes used to identify exposures and outcomes.

Intervention	**ICD-10 PCS codes**
	Primary or secondary procedural field
Coronary angiogram	B200, B201, B206, B210, B211, B212, B216, B240ZZ3, B241ZZ3, B244ZZ3, B245ZZ3, B246ZZ3
PCI	02703, 02704, 02713, 02714, 02723,02724, 02733, 02734, 02H03, 02H04, 02H13, 02H14, 02H23, 02H24, 02H33, 02H34
CABG	02100, 02110, 02120, 02130
Invasive	composite of PCI, or CABG, or coronary angiogram
Coronary angiography with Revascularization	composite of PCI or CABG
Coronary angiography without Revascularization	Coronary angiography alone, PCI and CABG excluded
Cohort	**ICD-10 CM codes in secondary diagnosis field**
Non-ST segment Elevation MI	I21.4, I22.2 (primary diagnosis field)
Chronic Kidney Disease 3	N18.3
Chronic Kidney Disease 4	N18.4
Chronic Kidney Disease 5	N18.5
End Stage Renal Disease	N18.6
Outcomes	
All-cause mortality	**All-cause mortality during readmission is provided by NRD.**
	ICD-10 CM codes
	Primary diagnosis field during readmission for Diagnosis code and Primary or secondary procedural field during readmission for procedure code
MI readmission	I21, I22
Stroke readmission	I60, I61, I62, I690, I691, I692, I63, G46, G45, I6781, I6782, I97810, I97811, I97820, I97821
Heart failure	I0981, I110, I130, I132, I50
Acute Kidney Injury	N170, N171, N172, N178, N179, N19, N990, R34
Vascular complication	T817, S15, S25, S35, S45, S55, S65, S75, S85, S95, S090 02Q, 03Q, 04Q, 05Q, 06Q, 0GQ6, 0GQ7, 0GQ8, 0GQ9, 0GQD, 03L, 04L
Post-operative bleeding	I97418, I97618, I97620, I97621, I97638, D62, L7602, L7622, L7632, M96811, M96831, M96841
Hemoperitoneum	K66.1
Gastrointestinal Bleeding	K2211, K250, K252, K254, K256, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K260, K262, K264, K266, K270, K272, K274, K276, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K51011, K51211, K51311, K51411, K51511, K51811, K51911, K50011, K50111, K50811, K50911, K625, K5521
Hematuria	R31.0, R31.9
Hemoptysis	R04.2
Blood Transfusion	30243N0, 30243N1, 30243P0, 30243P1, 30243H0, 30243H1, 30240N0 30240N1, 30240P0, 30240P1, 30240H0, 30240H1, 30230H0, 30230H1, 30230N0, 30230N1, 30230P0, 30230P1, 30233N0, 30233N1, 30233P0, 30233P1

Major bleeding	composite of post-operative bleeding, hemoperitoneum, GI bleeding, hematuria, hemoptysis ‘AND’ blood transfusion
Revascularization- (PCI and/or CABG)	02703, 02704, 02713, 02714, 02723,02724, 02733, 02734, 02H03, 02H04, 02H13, 02H14, 02H23, 02H24, 02H33, 02H34, 02100, 02110, 02120, 02130

Table S3. Baseline Characteristics of Invasive vs Medical Management across different stages of Chronic Kidney Disease before Propensity score-matching.

	CKD 3 (n=81,281)					CKD 4 (n=23,831)					CKD 5 (n=2,991)					ESRD (n=32,949)				
	Invasive		Medical Management		p-value	Invasive		Medical Management		p-value	Invasive		Medical Management		p-value	Invasive		Medical Management		p-value
	n=51654		n=29627			n=10,811		n=13,020			n=1271		n=1720			n=22,330		n=10,619		
Age	72.8±10.8		78.9±11.2		<0.001	72.3±10.8		78.1±11.2		<0.001	68.0±11.5		75.0±12.4		<0.001	65.8±11.3		69.0±12.7		<0.001
Sex																				
Male	33107	64.1%	16221	54.8%		6292	58.2%	6960	53.5%		812	63.9%	920	53.5%		13589	60.9%	5980	56.3%	
Female	18547	35.9%	13406	45.2%	<0.001	4519	41.8%	6060	46.5%	<0.001	459	36.1%	800	46.5%	<0.001	8741	39.1%	4639	43.7%	<0.001
Comorbidities																				
History of Nonadherence to Medications	2991	5.8%	1804	6.1%	0.081	570	5.3%	738	5.7%	0.182	90	7.1%	138	8.0%	0.337	1434	6.4%	825	7.8%	<0.001
Hypertension	49529	95.9%	27749	93.7%	<0.001	10446	96.6%	12424	95.4%	<0.001	1246	98.0%	1665	96.8%	0.039	21848	97.8%	10260	96.6%	<0.001
Diabetes	31773	61.5%	15635	52.8%	<0.001	7690	71.1%	8150	62.6%	<0.001	959	75.5%	1153	67.0%	<0.001	16961	76.0%	7447	70.1%	<0.001
Hyperlipidemia	40302	78.0%	19403	65.5%	<0.001	8081	74.7%	8480	65.1%	<0.001	936	73.6%	1060	61.6%	<0.001	15087	67.6%	6190	58.3%	<0.001
History of stroke/TIA	5414	10.5%	4063	13.7%	<0.001	1223	11.3%	1652	12.7%	0.001	134	10.5%	222	12.9%	0.048	2664	11.9%	1511	14.2%	<0.001
Ischemic Cardiomyopathy	47937	92.8%	20830	70.3%	<0.001	9966	92.2%	9450	72.6%	<0.001	1164	91.6%	1143	66.5%	<0.001	20446	91.6%	7556	71.2%	<0.001
Carotid artery disease	2691	5.2%	1000	3.4%	<0.001	605	5.6%	395	3.0%	<0.001	45	3.5%	35	2.0%	0.012	719	3.2%	192	1.8%	<0.001
Peripheral vascular disease	11713	22.7%	6699	22.6%	0.829	2519	23.3%	2846	21.9%	0.008	265	20.8%	316	18.4%	0.09	4967	22.2%	2244	21.1%	0.023
Prior PCI	11169	21.6%	4948	16.7%	<0.001	2305	21.3%	2236	17.2%	<0.001	227	17.9%	247	14.4%	0.01	4694	21.0%	1853	17.4%	<0.001
Prior CABG	8973	17.4%	6178	20.9%	<0.001	1865	17.3%	2756	21.2%	<0.001	159	12.5%	306	17.8%	<0.001	3546	15.9%	1968	18.5%	<0.001
Chronic Heart failure	31301	60.6%	21198	71.5%	<0.001	7968	73.7%	10120	77.7%	<0.001	941	74.0%	1301	75.6%	0.317	15889	71.2%	7520	70.8%	0.526
Atrial Fibrillation	10383	20.1%	6947	23.4%	<0.001	2101	19.4%	2717	20.9%	0.006	186	14.6%	265	15.4%	0.559	4106	18.4%	2051	19.3%	0.044
Chronic Pulmonary Disease	14632	28.3%	8815	29.8%	<0.001	3003	27.8%	3811	29.3%	0.011	295	23.2%	393	22.8%	0.816	5238	23.5%	2724	25.7%	<0.001
Anemia	3624	7.0%	2552	8.6%	<0.001	1090	10.1%	1333	10.2%	0.906	145	11.4%	205	11.9%	0.877	1283	5.7%	624	5.9%	0.274
Smoker	18388	35.6%	9077	30.6%	<0.001	3521	32.6%	3763	28.9%	<0.001	397	31.2%	453	26.3%	0.003	6352	28.4%	2724	25.7%	<0.001
Obesity	13817	26.8%	4543	15.3%	<0.001	2935	27.1%	2099	16.1%	<0.001	351	27.6%	294	17.1%	<0.001	4750	21.3%	1559	14.7%	<0.001
Coagulopathy	5284	10.2%	2530	8.5%	<0.001	1190	11.0%	1155	8.9%	<0.001	155	12.2%	138	8.0%	<0.001	3071	13.8%	1392	13.1%	0.11
Hospital Characteristics																				
Bedsize					<0.001					<0.001					<0.001					<0.001
Small	5785	11.2%	5592	18.9%		1093	10.1%	2193	16.8%		114	9.0%	229	13.3%		1995	8.9%	1522	14.3%	
Medium	15220	29.5%	9386	31.7%		3217	29.8%	4173	32.1%		329	25.9%	502	29.2%		6083	27.2%	3366	31.7%	
Large	30650	59.3%	14649	49.4%		6501	60.1%	6654	51.1%		828	65.1%	989	57.5%		14252	63.8%	5731	54.0%	
Hospital Teaching Status					<0.001					<0.001					<0.001					<0.001
Nonteaching	14325	27.7%	11258	38.0%		2846	26.3%	4801	36.9%		280	22.0%	573	33.3%		5548	24.8%	3347	31.5%	
Teaching	37329	72.3%	18369	62.0%		7965	73.7%	8219	63.1%		991	78.0%	1147	66.7%		16782	75.2%	7272	68.5%	
Hospital Location					0.131					<0.001					0.008					0.168
Non-urban	24524	47.5%	14228	48.0%		4740	43.8%	6210	47.7%		475	37.4%	725	42.2%		8461	37.9%	3940	37.1%	
Urban	27130	52.5%	15399	52.0%		6071	56.2%	6810	52.3%		796	62.6%	995	57.8%		13869	62.1%	6679	62.9%	
Admission Day					<0.001					0.099					0.639					0.054
Weekdays	38320	74.2%	21475	72.5%		7989	73.9%	9498	72.9%		928	73.0%	1269	73.8%		16913	75.7%	7938	74.8%	

Weekend	13334	25.8%	8152	27.5%		2822	26.1%	3522	27.1%		343	27.0%	451	26.2%		5417	24.3%	2681	25.2%	
Primary Payer					<0.001					<0.001					<0.001					<0.001
Medicare	40348	78.1%	25586	86.4%		8510	78.7%	11153	85.7%		886	69.7%	1359	79.0%		18095	81.0%	8810	83.0%	
Medicaid	2757	5.3%	1377	4.6%		655	6.1%	611	4.7%		130	10.2%	146	8.5%		1641	7.3%	802	7.6%	
Private Insurance	6326	12.2%	1784	6.0%		1218	11.3%	889	6.8%		211	16.6%	150	8.7%		1972	8.8%	723	6.8%	
Median Household income category by patient Zip code					0.002					0.184					0.126					0.002
0-25th percentile	14715	28.5%	8180	27.6%		3123	28.9%	3913	30.1%		364	28.6%	555	32.3%		7515	33.7%	3599	33.9%	
26-50th percentile	14562	28.2%	8326	28.1%		3025	28.0%	3619	27.8%		344	27.1%	473	27.5%		5993	26.8%	2704	25.5%	
51-75th percentile	12737	24.7%	7313	24.7%		2608	24.1%	3023	23.2%		291	22.9%	348	20.2%		5017	22.5%	2356	22.2%	
76-100th percentile	8868	17.2%	5411	18.3%		1910	17.7%	2299	17.7%		243	19.1%	318	18.5%		3471	15.5%	1806	17.0%	

CKD – Chronic Kidney Disease, ESRD – End stage Kidney Disease, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Graft, IQR – Interquartile range

Figure S1A: CKD 3: Standardized differences in Overall and Propensity matched Cohort (invasive approach vs medical management)

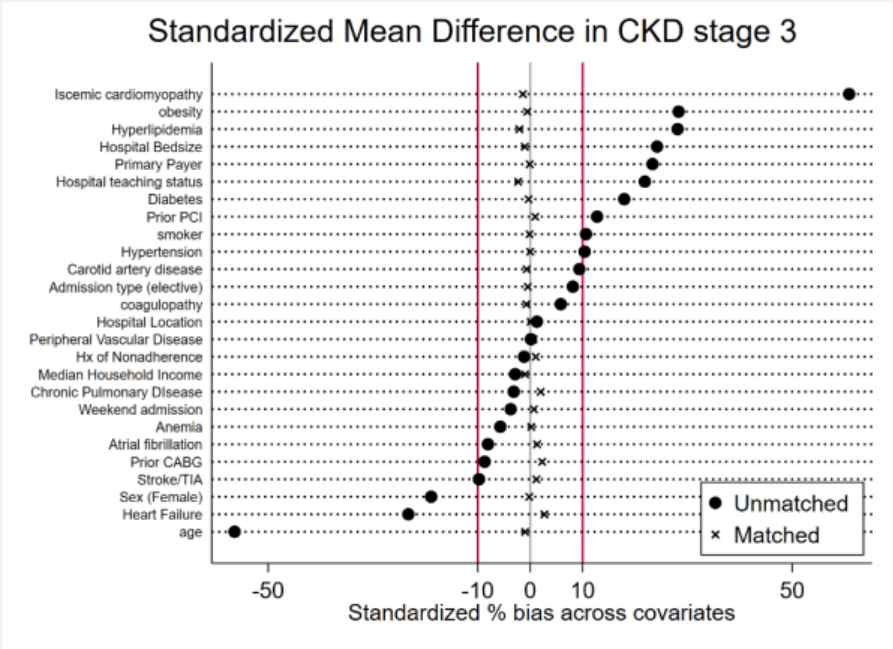


Figure S1B: CKD 4: Standardized differences in Overall and Propensity matched Cohort (invasive approach vs medical management)

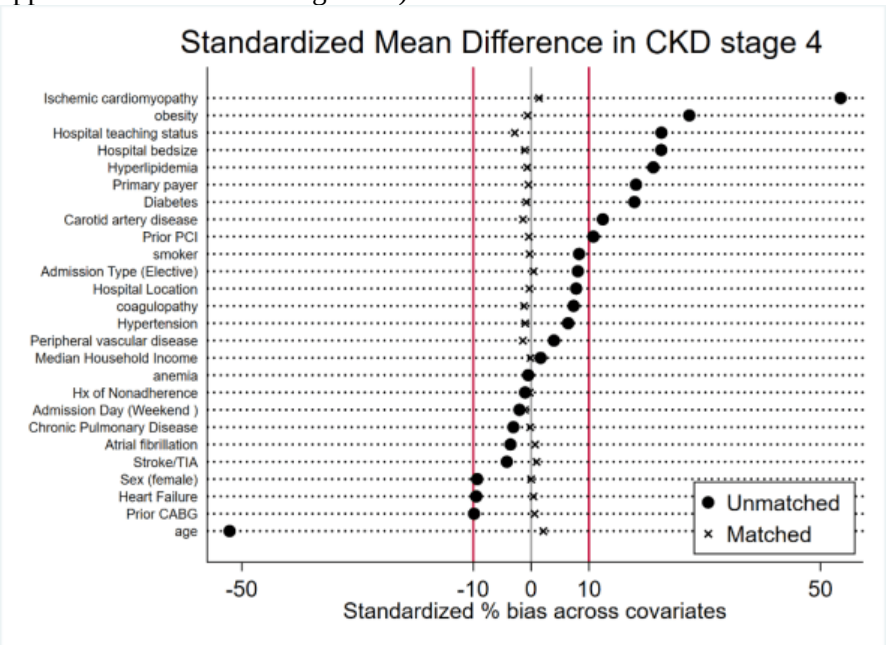


Figure S1C: CKD 5: Standardized differences in Overall and Propensity matched Cohort (invasive approach vs medical management)

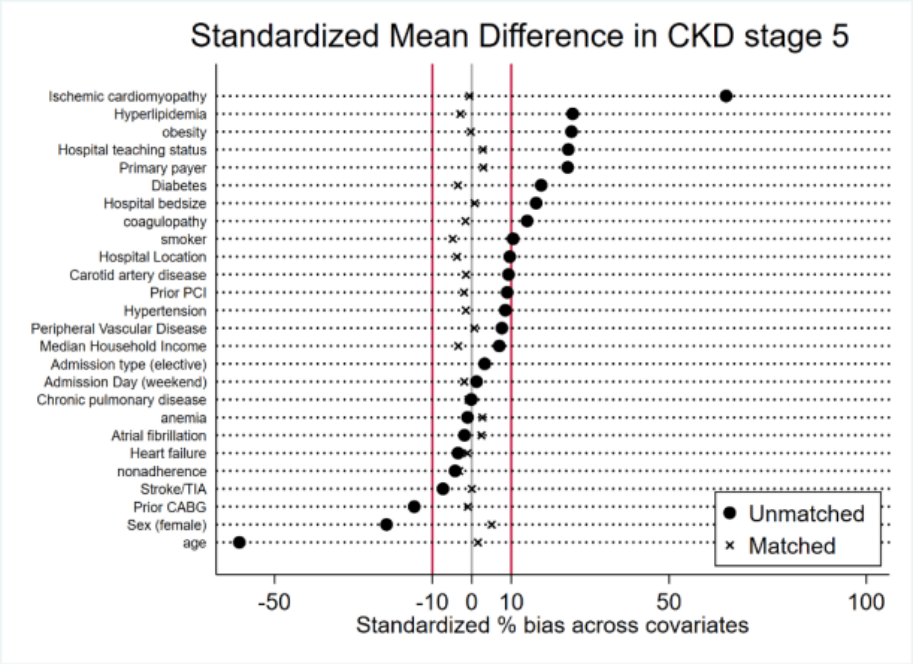


Figure S1D: ESRD: Standardized differences in Overall and Propensity matched Cohort (invasive approach vs medical management)

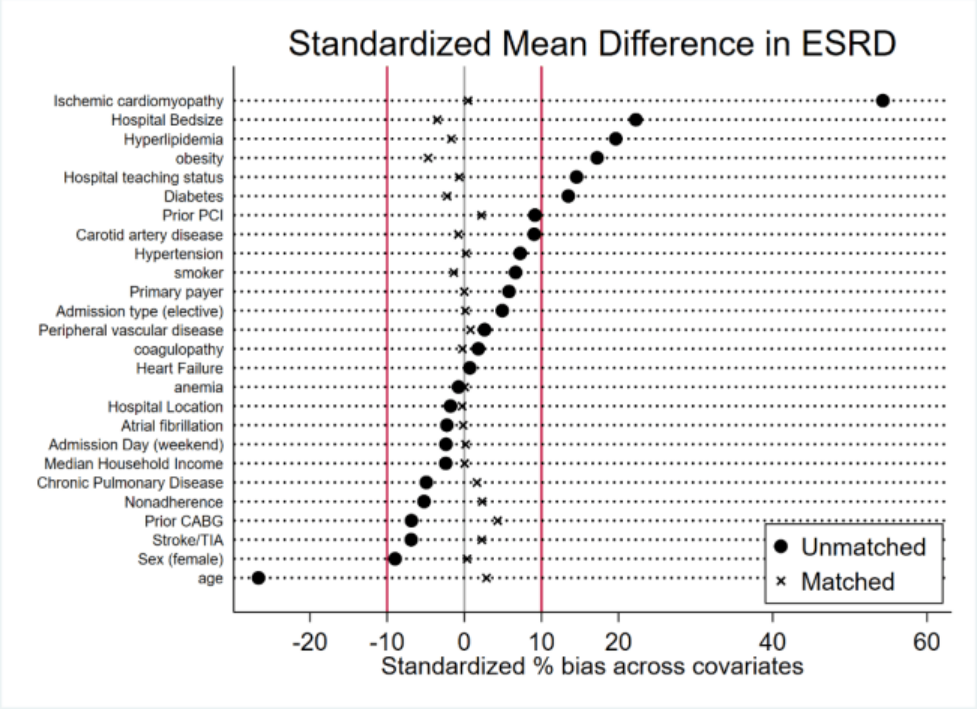


Figure S2A: CKD 3: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography with revascularization (CAR) approach vs medical management)

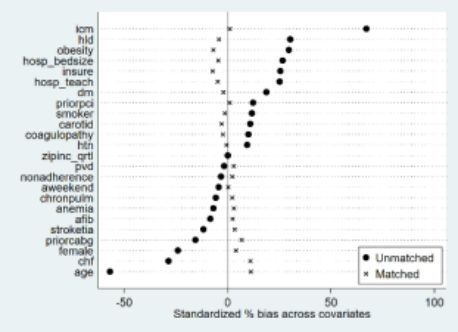


Figure S2B: CKD 4: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography with revascularization (CAR) approach vs medical management)

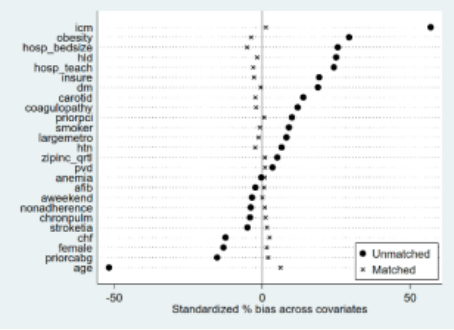


Figure S2C: CKD 5: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography with revascularization (CAR) approach vs medical management)

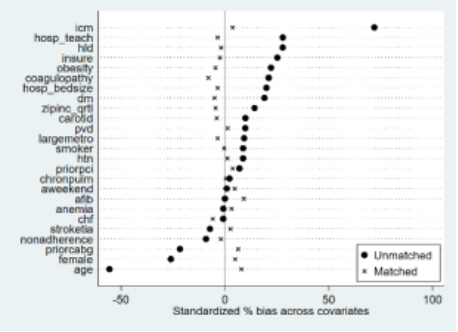


Figure S2D: ESRD: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography with revascularization (CAR) approach vs medical management)

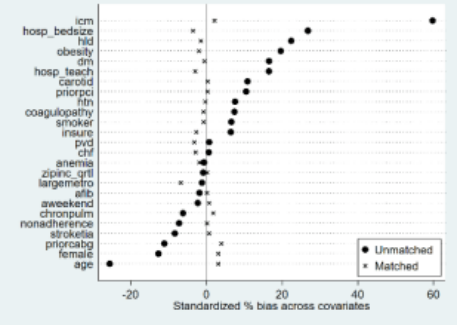


Figure S3A: CKD 3: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography without revascularization (CAWR) approach vs medical management)

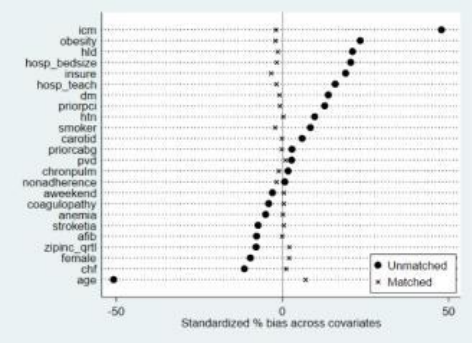


Figure S3B: CKD 4: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography without revascularization (CAWR) approach vs medical management)

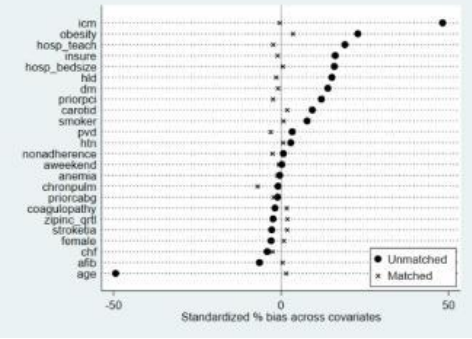


Figure S3C: CKD 5: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography without revascularization (CAWR) approach vs medical management)

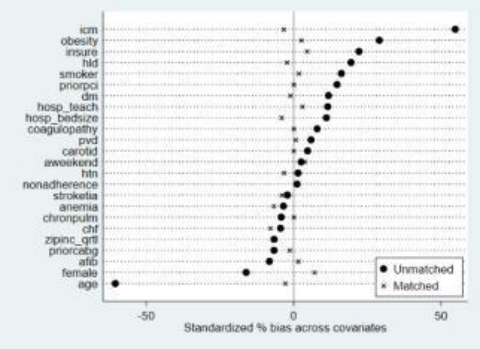
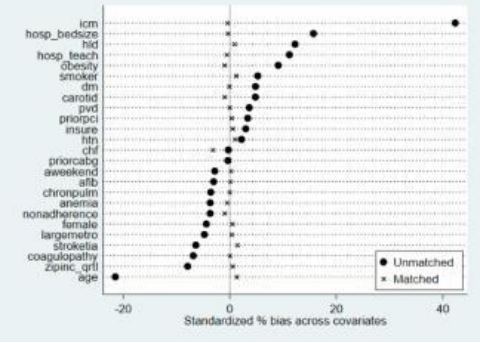


Figure S3D: ESRD: Standardized differences in Overall and Propensity matched Cohort (Coronary angiography without revascularization (CAWR) approach vs medical management)



icm – ischemic cardiomyopathy, hld-hyperlipidemia, insure – primary expected payer, hosp_bedsize – large vs medium/small hospital based on bedsize, hosp_teach – teaching status of hospital, dm – diabetes,

htn – hypertension, carotid – carotid artery disease, pvd – peripheral vascular disease, zipinc_qrtl – median household income by patient zipcode, chronpulm – chronic pulmonary disease, aweekend – weekend or weekday admission

Figure S4. Predictors of Invasive strategy in CKD/ESRD.