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CLINICAL INVESTIGATIONS

Acute kidney injury requiring dialysis and in-hospital mortality in patients with chronic kidney disease and non–ST-segment elevation acute coronary syndrome undergoing early vs delayed percutaneous coronary intervention: A nationwide analysis

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Background: Chronic kidney disease (CKD) is a well-known risk factor for coronary artery disease and is associated with poor outcomes following an acute coronary syndrome (NSTE-ACS). The optimal timing of an invasive strategy in patients with CKD and NSTE-ACS is unclear.

Hypothesis: Timing of PCI in CKD patients will not affect the risk of mortality or incidence of dialysis.

Methods: We queried the National Inpatient Sample database (NIS) to identify cases with NSTEMI and CKD. Patients who underwent percutaneous coronary intervention (PCI) day 0 or 1 vs day 2 or 3 after admission were categorized as early vs delayed PCI, respectively. The primary outcomes of the study were in-hospital mortality and acute kidney injury requiring hemodialysis (AKI-D). The secondary outcomes were length of stay and hospital charges. Baseline characteristics were balanced using propensity score matching (PSM).

Results: After PSM, 3708 cases from the delayed PCI group were matched with 3708 cases from the early PCI group. The standardized mean differences between the 2 groups were substantially reduced after PSM. All other recorded variables were balanced between the 2 groups. In the early and delayed PCI groups, the incidence of AKI-D (2.5% vs 2.3%; $P = 0.54$) and in-hospital mortality (1.9% vs 1.4%; $P = 0.12$) was similar. Hospital charges and length of stay were higher in the delayed PCI group.

Conclusions: The incidence of AKI-D and in-hospital mortality among patients with CKD and NSTE-ACS were not significantly affected by the timing of PCI. However, delayed PCI added significant cost and length of stay. A prospective randomized study is required to validate this concept.

KEYWORDS

Acute Coronary Syndrome, Cardiac Catheterization/Diagnostic, Interventional, Kidney Disease

1 | INTRODUCTION

The optimal timing of coronary angiography and revascularization for patients with chronic kidney disease (CKD) presenting with an acute non–ST-segment elevation acute coronary syndrome (NSTE-ACS) is controversial. There are no studies examining the effect of an early vs delayed strategy for these patients on short-term outcomes such as in-hospital mortality and acute kidney injury requiring dialysis (AKI-D). Although the current non–ST-segment elevation myocardial infarction (NSTEMI) guidelines recommend an invasive strategy for patients with CKD and no other serious comorbidity or

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contraindication to the procedure, there are no specific recommendations on optimal timing.[1] The European guideline recommends an early invasive strategy for the high-risk patient, wherein moderate to severe renal dysfunction is considered an intermediate risk factor.[2]

Many studies have shown that an early invasive strategy, compared with a delayed invasive treatment strategy, reduces the incidence of cardiovascular death and myocardial infarction (MI), whereas others have demonstrated no significant difference.[3–10] The concern with an immediate strategy is that early intervention on unstable plaque can lead to coronary emboli and microvascular obstruction. The concern with a delayed invasive approach is that it places patients at risk for recurrent ischemia and infarction. Very recently, a published meta-analysis concluded that an early invasive strategy does not reduce the risk for death of MI compared with a delayed strategy.[11] However, none of the published studies examined the effect of an early vs delayed strategy on outcomes in patients with CKD. To assess the value of early vs delayed percutaneous coronary intervention (PCI) in patients with CKD and NSTEMI, we analyzed a large national database, comparing the incidence of AKI-D and in-hospital mortality.

2 | METHODS

We queried the National Inpatient Sample (NIS) from 2010 to 2014 to identify patients with CKD and NSTEMI. The NIS is part of the Healthcare Cost and Utilization Project (HCUP) and represents approximately 20% of all inpatient admissions from participating hospitals.[12] The publicly available database contains de-identified patient information. It provides *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) diagnoses, procedure codes, demographic information, and patient discharge status. It also contains Clinical Classification Software (CCS), which are clusters of similar diagnoses that can be used to identify diagnoses or procedures. Conditions such as obesity, hypertension, peripheral vascular disease, depression, fluid and electrolyte disorders, coagulopathy, chronic pulmonary disease and diabetes mellitus (DM) are also included in the database as Elixhauser comorbidities. Refer to Table 1 for the ICD-9-CM and CCS diagnosis and procedure codes used in the study.

We identified a cohort of patients with CKD who underwent PCI for NSTEMI. Patients with CKD were identified using ICD-9-CM codes 585.1, 585.2, 585.3, 585.4, 585.5, and 585.9. We included patients age ≥ 18 years with NSTE-ACS who underwent PCI with bare-metal or drug-eluting stent(s). Patients with concomitant diagnosis of ST-segment elevation myocardial infarction (STEMI) were excluded. We restricted our cohort to those undergoing PCI. Patients undergoing PCI on day 0 or 1 after admission were categorized as the early PCI group; patients undergoing PCI on day 2 or 3 after admission were categorized as the delayed PCI group. Patients undergoing cardiac surgery during the same admission were excluded. When a patient underwent PCI on 2 separate days, the first day of stenting was considered the index day of the procedure. Patients whose index procedure day of stenting was on or after the fourth day of admission or patients who had staged PCI anytime after the index PCI during the same hospitalization were also excluded from the study. Elective admissions and cases with missing values for age, race, mortality data, and timing of PCI were excluded (Table 2).

There is no single ICD-9-CM code for contrast-induced nephropathy (CIN). To identify patients with CIN requiring dialysis, we used ICD-9-CM codes for AKI plus ICD-9-CM codes for dialysis. We excluded patients who only had the ICD-9-CM code for end-stage

TABLE 1 Diagnosis and procedure codes

Diagnosis or Procedure	ICD-9-CM or CCS Codes
Inclusion criteria	
NSTEMI	410.7, 410.70–410.72, 411.1
CKD	585.1–585.5, 585.9
BMS and DES	36.06, 36.07
Exclusion criteria	
ESRD	585.6
Dialysis	39.95, 54.98
Valvular or CABG surgery	Procedure CCS: 43 and 44
STEMI	410.x1 (410.01–410.91)
Comorbidities	
Prior MI	412
Smoking	V15.82, 305.1
Dyslipidemia	CCS code: 53
Acute CVA	CCS code: 109
Prior revascularization	V45.81, V45.82
Chronic ASA use	V58.66
AKI	584, 585.4–585.9
Family history of CAD	V17.3
Cardiogenic shock	785.51
Ventricular arrhythmias	427.1, 427.4, 427.41, 427.42

Abbreviations: AKI, acute kidney injury; ASA, acetylsalicylic acid (aspirin); BMS, bare-metal stents; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Clinical Classification Software; CKD, chronic kidney disease; CVA, cerebrovascular accident; DES, drug-eluting stents; ESRD, end-stage renal disease; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

TABLE 2 Inclusion and exclusion criteria

Inclusion criteria
Age ≥ 18 y
CKD
PCI
NSTEMI
Exclusion criteria
Missing information for in-hospital mortality data and timing of PCI
Elective admissions
ESRD without mention of AKI
STEMI
Valvular surgery or CABG during the same admission
Pre-admission, index PCI on or after fourth day of admission
Repeat procedure (staged PCI) after index procedure

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; ESRD, end-stage renal disease; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

renal disease or a procedure code for dialysis without the mention of AKI. The primary outcomes of interest were in-hospital mortality and AKI-D. The secondary outcomes were total charges and length of stay.

2.1 | Statistical analysis

The statistical analyses was performed using SPSS software, version 24 (IBM Corp., Armonk, NY). For propensity score matching (PSM), we used 1:1, logistic algorithm, nearest neighbor variable within caliper width of 0.01. Cases were matched for "Delayed" with "Early" group. The following variables were entered in the PSM algorithm: age, race, sex, weekend admission, prior history of MI, smoking, dyslipidemia, DM, acute cerebrovascular accident, prior history of revascularization, chronic aspirin use, AKI, cardiogenic shock, chronic lung disease, coagulopathy, depressive disorders, hypertension, obesity, ventricular arrhythmias, fluid and electrolyte disorders, and peripheral vascular disease. Because we analyzed ≥1 year of data, we included years 2010 to 2014 into PSM to control for year-to-year variations. We used unweighted, matched cases for further analysis and reported both before and after PSM data. Categorical and continuous variables were analyzed with the χ^2 and Mann–Whitney *U* test. A 2-sided *P* value of <0.05 was considered statistically significant. The categorical variables were reported as percentages, and continuous variables were reported as median with interquartile range.

3 | RESULTS

3.1 | Baseline characteristics and PSM analysis

The initial cohort prior to PSM included 7705 unweighted cases in the early PCI group and 3946 cases in the delayed PCI group. After PSM, 3708 cases were selected out of 3946 cases (94%) and were matched with 3708 cases from the early PCI group (Table 3). The median age of the patients for both groups was 73 years. A higher proportion of patients admitted on weekends was more likely to have delayed PCI (34.9% vs 17%; *P* < 0.001). Before PSM, Caucasians,

TABLE 3 Patient characteristics before and after PSM

	Before PSM			After PSM		
	Early PCI	Delayed PCI	*P* Value	Early PCI	Delayed PCI	*P* Value
Variables	n = 7705	n = 3946		n = 3708	n = 3708	
Age, y, median (IQR)	73 (64–80)	73 (65–81)	0.003	74 (65–81)	73 (65–81)	0.26
Caucasian, %	70.7	72.5	<0.001	73.1	72.1	0.76
Weekend admission, %	17.0	34.9	<0.001	30.6	30.9	0.76
Female sex, %	35.5	37.1	0.1	37.7	36.9	0.49
Chronic pulmonary disease	22.4	25.1	0.001	24.8	24.8	0.98
Coagulopathy	4.9	5.3	0.26	5.4	5.3	0.84
Depression	8.7	8.8	0.79	8.9	9.0	0.87
HTN	88.6	88.2	0.52	87.9	88.3	0.64
Fluid and electrolyte disorders	20.9	28.6	<0.001	26.8	27.8	0.36
Acute CVA	0.8	0.9	0.65	1.0	0.9	0.81
Obesity	20.5	20.8	0.68	21.0	20.9	0.93
PVD	20.9	22.3	0.08	21.7	22.0	0.76
DM	57.0	59.9	0.003	59.1	59.5	0.74
Prior MI	19.5	19.4	0.9	18.2	19.3	0.25
Smoking	34.0	33.2	0.39	34.1	33.3	0.46
Dyslipidemia	76.8	73.4	<0.001	72.9	74.1	0.23
Prior revascularization	33.8	34.1	0.76	33.3	33.8	0.59
Chronic ASA use	19.8	19.5	0.68	19.9	19.6	0.75
Family history of CAD	8.1	7.6	0.39	7.6	7.6	1.00
Ventricular arrhythmia	4.7	5.0	0.54	5.1	4.8	0.56
Cardiogenic shock	3.3	2.1	<0.001	2.2	2.1	0.81
AKI	31.8	39.9	<0.001	39.3	38.6	0.52
Year						
2010	14.2	13.5	0.34	13.5	13.3	0.84
2011	19.1	18.4		18.9	18.6	
2012	20.6	21.3		20.7	21.5	
2013	22.6	23.6		22.7	23.5	
2014	23.5	23.2		24.2	23.1	

Abbreviations: AKI, acute kidney injury; ASA, acetylsalicylic acid (aspirin); CAD, coronary artery disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PSM, propensity score matching; PVD, peripheral vascular disease.

weekend admissions, AKI, chronic pulmonary disease, fluid and electrolyte disorders, and DM were proportionally higher in the delayed PCI group. The presence of dyslipidemia and cardiogenic shock was higher in patients in the early PCI group. Otherwise, remaining variables, including year-to-year grouping, were not statistically significant between the 2 groups (Table 3). After PSM, there was no statistical difference between the 2 groups, and standardized mean differences substantially reduced for all variables (<5%).

3.2 | Outcomes

Before PSM, there was no statistically significant difference between the early and delayed PCI groups for in-hospital mortality (1.8% vs 1.5%; $P = 0.19$) or AKI-D (2.2% vs 2.3%; $P = 0.83$). The secondary outcomes, median total hospital costs, and length of stay were higher in the delayed PCI group ($77 616 vs $68 413, $P < 0.001$; and 4 vs 3 days, $P < 0.001$, respectively). After PSM, there was no statistically significant difference for in-hospital mortality (1.9% vs 1.4%; $P = 0.12$) or AKI-D (2.5% vs 2.3%; $P = 0.54$). The delayed PCI group had higher median cost ($77 529 vs $70 554; $P < 0.001$) and longer length of stay (4 vs 3 days; $P < 0.001$; Table 4).

4 | DISCUSSION

Among the cohort of patients with CKD and NSTE-ACS identified in this large national database, early PCI was not associated with a significant increase in the incidence of AKI-D or in-hospital mortality compared with delayed PCI. Early PCI was associated with reduced hospital costs and length of stay. Patients with CKD are more likely to have significant comorbidities including DM, prior heart failure, prior MI, peripheral arterial disease, and prior revascularization compared with patients with normal renal function.[13] Among patients undergoing PCI, these comorbidities are associated with a high risk of adverse events including severe bleeding, the need for dialysis, and in-hospital mortality.[13–15]

Patients with CKD are a vital group to examine because CKD is strongly associated with in-hospital mortality and bleeding in NSTEMI patients undergoing PCI.[13–15] A subgroup analysis of the Treat Angina With Aggrastat and Determine the Cost of Therapy With Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction (TACTICS-TIMI 18) study examined the interaction between creatinine (Cr) clearance, outcomes, and the use of an early invasive management strategy. The authors found that in patients with a mild to moderate decrease in renal function, early invasive management was superior to a conservative approach.[16] The study was, however, limited to patients with Cr <2.5 mg/dL, as the original trial excluded patients with serum Cr >2.5 mg/dL. In the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial, early intervention improved the composite outcome of mortality, MI, and stroke at 6 months.[5] However, renal function was not identified in this study. We did not observe any mortality benefit based on timing of PCI. Although the early PCI group had higher prevalence of cardiogenic shock, there was no difference in the unadjusted mortality rate between the 2 groups (3.3% vs 2.1%). After adjusting for cardiogenic shock, the mortality difference between the 2 groups was not significant. We believe that low incidence, and 1.1% absolute difference of cardiogenic shock patients between both groups, would not have significantly impacted the mortality. Moreover, comorbidity burden between the 2 groups is statistically insignificant, except for DM, dyslipidemia, and AKI, suggesting that the patient population in the 2 groups is similar.

CKD is the greatest risk factor for CIN.[17–20] AKI after angiography is a significant risk factor for long-term mortality and end-stage renal disease requiring dialysis.[19] Utilizing the National Cardiovascular Data Registry (NCDR) Cath-PCI registry, Tsai et al. reported that CKD was associated with a 2-fold to 28-fold increased risk of AKI-D.[17] Their study reported a 0.07% incidence of AKI-D post-PCI in patients with normal renal function, compared with 4.3% in patients with severe CKD. Importantly, they observed that AKI-D after PCI was associated with increased mortality.[17] We observed a lower

TABLE 4 Outcomes of patients before and after PSM

Before PSM				
Variables	Early Stenting, n = 7705	Delayed Stenting, n = 3946	OR (95% CI)	*P* Value
Died	1.8	1.5	0.81 (0.60-1.11)	0.19
Dialysis, %	2.2	2.3	1.03 (0.80-1.33)	0.83
Total charge in USD (IQR)	68 413 (48 400–98 889)[a]	77 616 (55 914–111 156)[b]	—	<0.001
LOS, d (IQR)	3 (2–4)[a]	4 (3–6)[b]	—	<0.001
After PSM				
Variables	Early Stenting, n = 3708	Delayed Stenting, n = 3708	OR (95% CI)	*P* Value
Died	1.9	1.4	0.75 (0.53-1.08)	0.12
Dialysis, %	2.5	2.3	0.91 (0.68-1.23)	0.54
Total charge in USD (IQR)	70 554 (50 187–101 885)[c]	77 529 (55 820–110 470)[d]	—	<0.001
LOS, d (IQR)	3 (2–5)[c]	4 (3–6)[d]	—	<0.001

Abbreviations: CI, confidence interval; IQR, interquartile range; LOS, length of stay; OR, odds ratio; PSM, propensity score matching; USD, US dollars.

[a] n = 7568.

[b] n = 3890.

[c] n = 3638.

[d] n = 3655.

incidence of AKI-D because our cohort consisted of all stages of CKD. The American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines recommend hydration for 3 to 12 hours prior to undergoing angiography with contrast media.[14] Hydration and minimizing the dose of contrast administered are proven to reduce the risk of CIN.[21] A prospective study showed a very low (2.4%) incidence of CIN in patients who received guideline-recommended hydration prior to contrast administration. None of their 747 patients required dialysis. On the contrary, a recently published randomized trial showed that the rates of CIN were identical between patients who received intravenous (IV) hydration vs those who did not.[22] They also found that IV hydration added to hospital cost and length of stay. A single-center retrospective cohort study of patients undergoing PCI found that participants with a high ratio of hydration volume to weight actually had higher rates of CIN-AKI and worse outcomes overall.[23] Their findings challenge the established concept that IV hydration prevents CIN and suggest that it may even cause harm. However, these studies did not disclose whether they analyzed patients with CKD. Many experts still insist that IV hydration remains the standard of care in patients with CKD.[24] Though we could not determine if patients in the delayed PCI group received adequate hydration, the delay did not reduce the incidence of post-PCI AKI-D.

There are no randomized controlled trials evaluating the value of an early vs a delayed invasive strategy in patients with NSTEMI and CKD. The Optimised Procedure in Patients with NSTEMI and CKD (NSTEMI-CKD) trial was attempted (NCT02543177), but it was terminated early due to poor enrollment.[25] Our retrospective analysis of a large population of patients with NSTEMI and CKD suggests cardiac catheterization and PCI should not be delayed because of renal dysfunction. A prospective randomized trial will be required to test this hypothesis.

4.1 | Study limitations

There are important limitations to this study. The study was based on a database that may have errors in the assignment of appropriate diagnosis and procedure codes. Although we used PSM to correct for confounding factors, the result may have been influenced by the non-randomized assignment and inability to correct for confounding factors that were not included in the algorithm. We could not determine the clinical reasons influencing the timing of PCI. The delayed PCI group included patients with a significantly higher proportion of comorbidities including DM, fluid and electrolyte disorders, AKI, and weekend admission. The Cr level or glomerular filtration rate at the time of PCI is a critical piece of information that is not provided in the database. Furthermore, a large proportion of patients had "unspecified" CKD (ICD-9-CM code 585.9); therefore, a subgroup analysis of CKD stages was not practical. These factors could have influenced the timing of cardiac catheterization. One of the determinants of AKI-D is the volume of contrast. We could not control this variable because the information was not available in the database. All these limitations may have been minimized by PSM. After PSM, the net difference between the groups was significantly reduced, measured by standardized mean difference, mitigating the influence of the comorbidities on the timing of PCI.

5 | CONCLUSION

Among patients with CKD and NSTE-ACS, the incidence of AKI-D and in-hospital mortality was not significantly affected by the timing of PCI. However, delayed PCI added significant hospital cost and length of stay. These findings suggest early PCI in patients with NSTEMI and CKD may be a preferred strategy. A prospective randomized study will be required to validate this concept.

Conflicts of interest

Dr. Bavry is a contractor for the American College of Cardiology. The authors declare no other potential conflicts of interest.

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