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Revascularization in Patients With Non-ST Elevation Myocardial Infarction and Advanced Chronic Kidney Disease

Fu-Chih Hsiao; Chien-Te Ho; Chia-Pin Lin; Chiu-Yi Hsu; Chi-Jen Chang, MD; and Pao-Hsien Chu, MD

Abstract

Objective: To investigate the impact of revascularization on long-term survival and renal outcome in non−ST-elevation myocardial infarction (NSTEMI) patients with severe chronic kidney disease (CKD).

Patients and Methods: This study includes NSTEMI patients with an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, including those on chronic hemodialysis who were identified from the multicenter Chang Gung Research Database from January 1, 2007, to December 31, 2017. Inverse probability of treatment weighting was used to generate comparable groups. The survival and the risk of progression to chronic hemodialysis between those receiving revascularization, either percutaneous coronary intervention or coronary artery bypass graft, and those receiving medical therapy during index hospitalization were compared.

Results: A total of 2821 NSTEMI patients with severe CKD, including 1141 patients on chronic hemodialysis, were identified. Of these, 1149 patients received revascularization and 1672 received medical therapies. The differences in demographics, comorbidities, and presentations between groups were balanced after inverse probability of treatment weighting. After a mean follow-up of 1.82 years, revascularization was associated with a lower risk of all-cause mortality (adjusted HR, 0.61; 95% CI, 0.54-0.70). For non−dialysis-dependent patients who had survival to discharge, revascularization had a higher risk of progression to chronic hemodialysis (adjusted HR, 1.83; 95% CI, 1.49-2.26) after a mean follow-up of 2.3 years.

Conclusion: Revascularization was associated with a lower risk of all-cause mortality in NSTEMI patients with severe CKD. For non−dialysis-dependent patients who survived to discharge, revascularization was associated with a higher risk of progression to chronic hemodialysis.

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Chronic kidney disease (CKD) is strongly associated with an increased risk of incident myocardial infarction (MI).[1] Moreover, CKD is an independent predictor of mortality in patients with non−ST-segment elevation myocardial infarction (NSTEMI).[2] In addition, NSTEMI patients with severe CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min per 1.73 m^2), including dialysis-dependent patients, have an even higher risk of in-hospital and long-term mortality than those with mild-to-moderate CKD (eGFR of 30 to 60 mL/min per 1.73 m^2).[3,4]

Revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) have been shown to be beneficial for patients with NSTEMI.[5,6] However, patients with severe CKD are more likely to be treated only medically in real-world practice.[7,8] In patients with severe CKD, the benefit of revascularization may be compromised by revascularization procedure-related adverse renal events, particularly those requiring renal replacement therapy.[9,10] In

From the Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan City, Taiwan (F.-C.H., C.-T.H., C.-P.L., C.-J.C., P.-H.C.); and the Center for Big Data Analytics and Statistics, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan City, Taiwan (C.-Y.H.).

addition, revascularizations for NSTEMI patients with severe CKD were shown to be associated with an increased risk of bleeding compared with those with normal renal function or CKD of less severity,[4] which are associated with increased mortality.[11]

Currently, the impact of revascularization on long-term survival and renal outcomes in NSTEMI patients with concomitant severe CKD is unclear. Several previous studies[3,4,12] included this specific group of patients. However, they accounted for only less than 10% of the entire study cohort included in these studies; less than 20% of those patients received invasive therapies. Furthermore, the findings were inconsistent between studies.

Thus, this study aimed to investigate the impact of revascularization on in-hospital and long-term mortality and renal outcome in NSTEMI patients severe CKD (including those on chronic hemodialysis) using a multicenter database.

PATIENTS AND METHODS

Data Source

Patients were identified from the Chang Gung Research Database for analysis. This database is derived from the original patient-level electronic medical records of Chang Gung Memorial Hospital, which is the largest health care provider in Taiwan with seven institutes. Since 2000, the database has collected, integrated, and standardized the electronic medical records of 1.3 million patients (6% of Taiwan's population) without specific selection criteria. The diagnoses were coded according to the International Classification of Disease Ninth Revision Clinical Modification (ICD-9-CM) codes before 2016 and ICD-10-CM revision codes afterward. The medication and procedure codes are unique and can be mapped to the World Health Organization Anatomical Therapeutic Chemical codes and ICD-9-CM procedure codes, respectively. One advantage of this database is that it includes detailed laboratory and examination results. Thus, we were able to identify important covariates at baseline, such as cardiac troponin, serum creatinine, and hemoglobin, for the present study. The data structure and representativeness have been reported in detail, and many diagnostic codes have been validated before.[13-15]

Patients who were identified from this database after applying the inclusion and exclusion process were linked to the National Health Insurance Research Database to track longitudinal all-cause mortality. The National Health Insurance Research Database is a single-payer compulsory insurance program that covered 99.9% of the entire population in Taiwan in 2014 and included almost all medical visits and hospitalizations.[16] Thus, all mortality events would be captured. Each patient's personal information was de-identified using a consistent encryption procedure; therefore, informed consent was waived for the present study. The institutional review board of Chang Gung Memorial Hospital, Linkou (201800819B0) approved this study.

Study Design

From January 1, 2007, to December 31, 2017, patients with severe CKD who had been hospitalized for NSTEMI were identified from the Chang Gung Research Database. The cohort entry date was defined as the date of admission. Cases of NSTEMI were confirmed if both of two criteria were met: 1) a principal inpatient diagnosis of NSTEMI; and 2) elevated cardiac troponin-I level above the 99th percentile of the upper reference limit (>0.3 ng/mL by Beckman Coulter assay) with increase and/or decrease during index hospitalization. Severe CKD was defined by two consecutive outpatient eGFRs of less than 30 mL/min per 1.73 m^2 or having regular hemodialysis before the cohort entry date. If serum creatinine data were unavailable before the cohort entry date, the first data point after admission was defined as the baseline value. Patients who had no documented serum creatinine levels at baseline or during hospitalization were excluded. We used the Modification of Diet in Renal Disease formula to calculate eGFR.

TABLE 1. Baseline Demographics and Clinical Characteristics of NSTEMI Patients With Severe CKD Who Had Revascularization vs Medical Therapies[a,b]

	Inverse probability of treatment weighting					
	Before			After		
	Revascularization n=1149	Medical therapy n=1672	ASMD	Revascularization	Medical therapy	ASMD
Demographics						
Age, y	69.0±10.6	73.4±11.8	0.39	70.7±10.1	71.3±10.6	0.05
Male	690 (60.1)	884 (52.9)	0.15	55.6	56.2	0.01
Smoking	232 (20.2)	268 (16)	0.11	18.3	18.1	0.01
Comorbidities						
DM	647 (56.3)	880 (52.6)	0.07	56.8	54.1	0.06
Hypertension	695 (60.5)	996 (59.6)	0.02	63.7	59.9	0.08
Dyslipidemia	457 (39.8)	590 (35.3)	0.09	40.3	37.5	0.06
Known CAD or prior PCI	453 (39.4)	568 (34)	0.11	41.0	36.9	0.08
Prior CABG[c]	6 (0.5)	4 (0.2)	0.05	0.3	0.3	0.00
Prior MI	147 (12.8)	193 (11.5)	0.04	13.6	12.1	0.05
HFrEF	223 (19.4)	368 (22)	0.06	20.8	20.9	0.00
AF	92 (8)	164 (9.8)	0.06	9.0	9.1	0.00
Prior ischemic stroke	242 (21.1)	502 (30)	0.21	20.2	20.9	0.02
Lower extremity arterial disease	307 (26.7)	416 (24.9)	0.04	24.8	26.0	0.03
Dementia	31 (2.7)	105 (6.3)	0.17	5.0	4.8	0.01
Cancer	108 (9.4)	218 (13)	0.12	10.1	13.0	0.09
Chronic hemodialysis	531 (46.2)	610 (36.5)	0.20	42.8	40.8	0.04
Clinical presentations						
Cardiac arrest	72 (6.3)	141 (8.4)	0.08	5.6	7.3	0.07
Invasive ventilator	406 (35.3)	551 (33)	0.05	28.6	33.1	0.10
Unstable hemodynamics	428 (37.2)	584 (34.9)	0.05	30.3	35.1	0.10
Inotropes/ vasopressors	401 (34.9)	583 (34.9)	0.00	28.5	34.9	0.14
IABP	158 (13.8)	23 (1.4)	0.48	10.7	2.1	0.36
ECMO	21 (1.8)	6 (0.4)	0.14	1.4	0.6	0.09
Bacteremia	31 (2.7)	83 (5)	0.12	2.9	3.4	0.03
Intracranial hemorrhage	1 (0.1)	15 (0.9)	0.12	0.1	0.6	0.08
Gastrointestinal bleeding	30 (2.6)	120 (7.2)	0.21	5.8	5.5	0.01
Blood transfusion	718 (62.5)	912 (54.5)	0.16	52.3	57.2	0.10
Medication						
Aspirin	1093 (95.1)	1356 (81.1)	0.44	94.8	85.7	0.31
P2Y12 inhibitors	1139 (99.1)	1485 (88.8)	0.44	99.2	91.9	0.36
Anticoagulant	1121 (97.6)	1131 (67.6)	0.86	79.9	79.8	0.00
Statin	855 (74.4)	938 (56.1)	0.39	65.2	63.4	0.04
ACEI or ARB	875 (76.2)	968 (57.9)	0.40	66.6	64.9	0.04
Beta blocker	947 (82.4)	1178 (70.5)	0.29	77.1	75.4	0.04
Laboratory and echocardiographic data						
BUN, mg/dL	59.4±31.1	70.0±41.1	0.28	57.8±31.0	69.3±34.0	0.37
Creatinine, mg/dL	6.6±3.7	5.5±3.4	0.31	6.2±3.7	5.8±3.0	0.10
Troponin-I, ng/mL[d]	4.2 (1.4-13.5)	2.8 (1.1-8.3)	0.18	3.0 (1.0-10.6)	3.2 (1.2-9.7)	0.00
Hemoglobin, g/dL[e]	8.2±1.7	8.1±1.9	0.07	8.3±1.8	8.1±1.5	0.09
Platelet, mL[e]	156.0±69.2	151.0±75.5	0.07	166.9±78.5	152.9±61.3	0.21
CRP, mg/L[d]	77.1 (29.9-162.0)	77.9 (30.3-160.5)	0.04	58.1 (21.3-143.6)	78.5 (30.5-160.0)	0.14

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TABLE 1. Continued

	Inverse probability of treatment weighting					
	Before			After		
	Revascularization n=1149	Medical therapy n=1672	ASMD	Revascularization	Medical therapy	ASMD
Laboratory and echocardiographic data, continued						
LVEF, %	53.3±14.9	52.9±15.8	0.04	52.6±15.2	53.1±13.0	0.02
Total hospital stays, d	18.8±14.2	16.6±13.7	0.16	17.5±13.2	17.4±12.0	0.01
ICU stays, d	7.3±6.2	6.8±6.3	0.08	5.8±6.2	5.7±5.3	0.01

[a]ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASMD, absolute standardized mean differences; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; HFrEF, heart failure with reduced ejection fraction; IABP, intra-aortic balloon pump; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

[b]Values are mean ± SD, median (IQR), and n (%) as appropriate.

[c]Prior CABG was compared by Fisher Exact test.

[d]Troponin-I and CRP are the peak value and presented as median (IQR), which are compared by Mann-Whitney Test.

[e]Hemoglobin and platelet are presented as the nadirs.

Patients who received revascularization (PCI or CABG) during index hospitalization were compared with those who received only medical therapies. The PCI and CABG procedures were identified using in-hospital procedure codes.

Covariates

Covariates included two parts: 1) demographics and comorbidities at baseline; and 2) in-hospital clinical data, including clinical presentations (cardiac arrest, shock, respiratory failure, bleeding events, and bacteremia), medications, laboratory test results, and left ventricular ejection fraction (LVEF) by transthoracic echocardiography. Smoking status was identified from the nursing records at index hospitalization. Comorbidities were defined as any inpatient or two outpatient diagnoses identified at baseline. In addition to diagnostic codes, an LVEF <40% on echocardiography was required to define heart failure with reduced ejection fraction (HFrEF). Cancer was defined only if the diagnoses were identified within 3 years prior to the cohort entry date. Prior PCI or CABG was extracted from the inpatient data using procedure codes at baseline.

Cardiac arrest was defined as the procedure code for cardiopulmonary resuscitation. Respiratory failure was identified using the procedure code of the mechanical ventilator. Unstable hemodynamics were defined as the use of inotropics or vasopressors (norepinephrine, epinephrine, and dopamine) or having procedure codes for intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO).

In-hospital intracranial bleeding or gastrointestinal bleeding was defined as a relevant discharge diagnosis. In-hospital blood transfusions were identified using procedure codes. Bacteremia was defined as positive blood cultures and receiving parenteral antibiotics. Troponin-I and C-reactive protein levels are expressed as the median of peak values. Serum hemoglobin and platelet counts are expressed as nadirs during hospitalization. Details regarding the codes for diagnoses and procedures are summarized in Supplementary Table 1 (available online at http://www.mayoclinicproceedings.org).

Outcomes

The in-hospital outcomes investigated were all-cause mortality and acute kidney injury requiring newly initiated hemodialysis. The double lumen catheter was the only vascular access for newly initiated hemodialysis after acute kidney injury in Chang Gung Memorial Hospitals. Therefore, we used the procedure code for double lumen catheter

insertion to identify patients who developed in-hospital acute kidney injury requiring hemodialysis.

Long-term outcomes after discharge include all-cause mortality and progression to chronic hemodialysis. All-cause mortality was analyzed in the entire study population. Only non—dialysis-dependent patients who had survival to discharge were included to investigate the long-term risk of progression to chronic hemodialysis. Progression to chronic hemodialysis was defined by having at least three procedure codes for outpatient or inpatient hemodialysis after discharge.

The follow-up period for all-cause mortality was the time from the cohort entry date until mortality or May 31, 2018, whichever had been earlier. The follow-up period for progression to chronic hemodialysis was the time from the cohort entry date until first hemodialysis, mortality, last clinical visit, or May 31, 2018, whichever occurred first.

Statistical Analysis

To compare the in-hospital outcomes and the long-term all-cause mortality between patients who received revascularization and those who received medical therapies alone, we used inverse probability of treatment weighting (IPTW) based on the propensity score derived from multivariable logistic regression to generate comparable groups. The propensity score was calculated using the values of the covariates in Table 1, except covariates with missing data (blood urea nitrogen, C-reactive protein, and in-hospital LVEF), substantial differences (aspirin and P2Y12 inhibitors), and total hospital and intensive care unit (ICU) stay. After excluding patients on chronic hemodialysis at baseline and patients who had in-hospital mortality, a CKD-IPTW cohort was generated based on the propensity score calculated with the values of covariates in Supplementary Table 2 (available online at http://www.mayoclinicproceedings.org), except aspirin, P2Y12 inhibitors, blood urea nitrogen, and LVEF. Absolute standardized mean differences (ASMDs) were calculated to evaluate the differences between the two groups. An ASMD of less than 0.1 indicates a negligible difference. Baseline characteristics are presented as number and percentage, mean and SD, or median and IQR, as appropriate.

The estimated risk of all-cause mortality between the two groups after IPTW adjustment was compared using a Cox proportional hazards model. For progression to chronic hemodialysis, the risk between the two groups in the CKD-IPTW cohort was compared using the Fine and Gray method to consider all-cause mortality as a competing risk. Hazard ratios are reported with 95% CI and as: 1) crude HR without any adjustment; 2) adjusted for all covariates in Table 1 (for in-hospital and long-term mortality) and Supplementary Table 2 (for acute kidney injury requiring hemodialysis and progression to chronic hemodialysis). Hazard ratios after adjusting for covariates with ASMD greater than 0.01 in the IPTW and CKD-IPTW cohorts were presented in Supplementary Table 3 (available online at http://www.mayoclinicproceedings.org).

Subgroup analysis was performed to determine whether the risk difference of all-cause mortality between the revascularization and medical therapy group was consistent among the subgroups, including age (<80 or ≥80 years), sex, and the presence or absence of known coronary artery disease/prior PCI/prior CABG, prior MI, HFrEF, atrial fibrillation, chronic hemodialysis, cardiac arrest, unstable hemodynamics, or respiratory failure.

All statistical analyses were performed using the SAS Enterprise Guide 8.2. (SAS Institute Inc). All statistical tests were two-sided, and *P* values of less than .05 were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 2821 patients with an eGFR of <30 mL/min per 1.73 m^2, including 1141patients (40.5%) on chronic hemodialysis who were hospitalized for NSTEMI, were identified from the Chang Gung Research Database between January 1, 2007, and December 1, 2017. Among them, 1149

patients received revascularization with either PCI (n=1046) or CABG (n=103), and the remaining 1672 patients received medical therapies alone. Table 1 shows the baseline characteristics and in-hospital data of both groups before and after IPTW adjustment. Before adjustment, patients who received revascularization were younger (69.0 vs 73.4 years) and more likely to be male (60.1% vs 52.9%). More patients in the revascularization group had prior PCI or known coronary artery disease (39.4% vs 34.0%, ASMD=0.11) and received chronic hemodialysis at baseline (46.2% vs 36.5%, ASMD=0.20). A history of ischemic stroke, dementia, or cancer was more common among patients who received medical therapies. Overall, 340 patients (12.1%) had prior MI, 591 patients (21.0%) had heart failure, 723 patients (25.6%) had lower extremity arterial disease, and 256 patients (9.1%) had atrial fibrillation, all of which were comparable between groups.

Approximately one-third of the patients in both groups were complicated by respiratory failure or unstable hemodynamics. Mechanical circulatory support, including ECMO (1.8% vs 0.4%) and IABP (13.8% vs 1.4%) were more commonly used in the revascularization group. In the 181 patients (52.5%) who received IABP, it was used for hemodynamic support because of shock at presentation. In 56 patients (30.9%), prophylactic IABP was applied under stable hemodynamic conditions for supporting high-risk PCI procedures or supporting patients with high-risk anatomy before CABG. In the remaining 30 patients, IABP was used due to development of unstable hemodynamics during PCI.

The occurrence of cardiac arrest during hospitalization was found to be comparable in both groups. Intracranial bleeding and gastrointestinal bleeding occurred more frequently among patients who received medical therapy alone. However, patients in the revascularization group were more likely to have blood transfusions during hospitalization (62.5% vs 54.5%). Among patients who had PCI, 58.9% of them had PCI for one vessel and the remaining 41.1% had PCI for two or three vessels. The coronary anatomy of patients receiving CABG is described in Supplementary Table 4 (available online at http://www.mayoclinicproceedings.org).

A dynamic increase and/or decrease pattern of the troponin-I values were observed in both groups (Supplementary Table 5, available online at http://www.mayoclinicproceedings.org), and the peak value was higher in the revascularization group (4.2 vs 2.8 ng/mL, ASMD=0.18). The peak C-reactive protein values (77.1 vs 77.9 mg/L), nadirs of hemoglobin (8.2 vs 8.1 g/dL), and LVEF (53.3% vs 52.9%) during hospitalization were comparable between both groups. All guideline-recommended medications for NSTEMI were more frequently prescribed in the revascularization group.

After IPTW adjustment, all demographics, comorbidities, unstable presentations, coexisting in-hospital events (bleeding and bacteremia), peak troponin-I, nadirs of hemoglobin, and LVEF values were well balanced in both groups with ASMDs less than 0.1. However, more patients in the revascularization group received aspirin (94.8% vs 85.7%, ASMD=0.31) and P2Y12 inhibitors (99.2% vs 91.9%, ASMD=0.36). Among those who received P2Y12 inhibitors, 23.8% and 12.5% had ticagrelor in the revascularization and medical therapies group, respectively. The remaining patients received clopidogrel.

The length of ICU stay was comparable between the groups (7.3 vs 6.8 days). However, the revascularization group had a longer total hospital stay (18.8 vs 16.6 days, ASMD=0.16).

Supplementary Table 2 reports the baseline characteristics of the non−hemodialysis-dependent subgroup (excluding those with in-hospital mortality) before and after IPTW adjustment. After IPTW adjustment, most covariates were balanced. However, more patients in the revascularization group received aspirin and P2Y12 inhibitors and had prior MI.

Outcomes

Table 2 shows the clinical outcomes of patients receiving revascularization and medical therapies alone. The in-hospital mortality rate was

TABLE 2. Clinical Outcomes of NSTEMI Patients With Severe CKD Who Had Revascularization vs Medical Therapies in the IPTW Adjusted Cohort[a,b]

Outcomes	Revascularization	Medical therapy	HR (95% CI)	*P*	Adjusted HR (95% CI)[c]	*P*
In hospital all-cause mortality	9.8	25.1	0.40 (0.32-0.50)	<.001	0.62 (0.47-0.81)	.001
Long-term all-cause mortality	63.8	77.0	0.59 (0.53-0.65)	<.001	0.61 (0.54-0.70)	<.001
In hospital newly-initiated hemodialysis	15.5	10.0	1.59 (1.26-2.01)	<.001	1.63 (1.23-2.17)	.001
Progression to chronic hemodialysis[d,e]	50.8	36.1	1.51 (1.30-1.76)	<.001	1.83 (1.49-2.26)	<.001

[a]CKD, chronic kidney disease; IPTW, inverse probability of treatment weighting; NSTEMI, non-ST segment elevation myocardial infarction.
[b]Values shown are percentages.
[c]Adjusted for all covariates in Table 1 (for in-hospital outcomes and long-term mortality) and Supplementary Table 2 (for progression to chronic hemodialysis).
[d]Non–dialysis-dependent patients who survived NSTEMI to discharge, after IPTW adjustment (as in Supplementary Table 2).
[e]Fine and Gray method to consider all-cause mortality as a competing risk.

significantly lower in the revascularization group (9.8% vs 25.1%; adjusted HR, 0.62; 95% CI, 0.47 to 0.81). However, revascularization was associated with a higher risk of in-hospital acute kidney injury requiring newly initiated hemodialysis (15.5% vs 10.0%; adjusted HR, 1.63; 95% CI, 1.23 to 2.17).

The mean follow-up period was 1.82 years for the total cohort and 2.3 years for the subgroup of patients who were not dialysis-dependent at baseline and had survival to discharge. As shown in Table 2 and Figures 1 and 2, revascularization was associated with a lower risk of long-term mortality (adjusted HR, 0.61; 95% CI, 0.54 to 0.70) in the total cohort. However, in the subgroup of non–dialysis-dependent patients who had survival to discharge, revascularization was associated with a higher risk of progression to chronic hemodialysis (adjusted HR, 1.83; 95% CI, 1.49 to 2.26). The findings were consistent if outcomes were adjusted for covariates with ASMD greater than 0.01 in the IPTW and CKD-IPTW cohorts as shown in Supplementary Table 3.

Subgroup Analysis

Figure 3 shows the subgroup analysis of long-term mortality stratified by selected baseline characteristics. The effect of revascularization on reducing long-term mortality was consistent, irrespective of age, sex, in-hospital cardiac arrest, respiratory failure, unstable hemodynamics, or the presence or absence of chronic hemodialysis, diabetes, HFrEF, prior MI, prior coronary artery disease/PCI/CABG, and atrial fibrillation at baseline.

DISCUSSION

The key findings of this multicenter database study on NSTEMI patients with severe CKD (including patients on chronic hemodialysis) are as follows: 1) revascularization was associated with lower in-hospital and long-term mortality; 2) revascularization was associated with a higher risk of in-hospital newly initiated hemodialysis; and 3) for non–dialysis-dependent patients who survived to discharge, revascularization was associated with a higher risk of progression to chronic hemodialysis during follow-up.

In our study, the findings regarding in-hospital outcomes are consistent with those of previous studies. In a large nationwide database study, Bhatia et al[17] reported that in NSTEMI patients with stage 4 or 5 CKD, the PCI-treated group had a 39% and 59% lower likelihood of in-hospital all-cause mortality, respectively, compared with the

propensity score-matched medically treated group. However, PCI was associated with a higher incidence of acute kidney injury requiring hemodialysis (7.28% vs 4.3%, $P<.001$) in patients with stage 4 CKD. In another national database study,[7] patients with MI (including both NSTEMI and ST-elevation MI) and stage 4-5 CKD or on chronic hemodialysis, revascularizations were shown to be associated with 37% and 44% lower risk of in-hospital mortality, respectively, compared with those treated medically.

In terms of long-term outcomes, substantial evidence supports that revascularization with either PCI or CABG reduces mortality and recurrent ischemic events compared with medical therapies alone for patients with NSTEMI, especially for those with higher risk.[5,6] Chronic kidney disease with eGFR less than 60 mL/min per 1.73 m^2 in patients with NSTEMI is a risk factor for adverse events, and revascularization is recommended according to guidelines.[18,19] However, the benefit of revascularization for patients with co-existing advanced CKD remained unclear. Patients with eGFR less than 30 mL/min per 1.73 m^2 were excluded from most randomized trials. Several registries included this specific group of patients. However, only a small proportion of those patients enrolled in those registries received invasive therapies.[3,4,12] Szummer et al[3] analyzed the outcome of patients with NSTEMI and CKD (eGFR < 60 mL/min per 1.73 m^2) enrolled in the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry from 2003 to 2006 and reported that in the subgroup of patients with advanced CKD (n=757), the 1-year mortality did not differ between those who received revascularization and those received medical therapies alone. However, only 29 of 757 patients underwent PCI or CABG. Holzmann et al[12] reported that in the subgroup of patients with stage 4 CKD (n=1031) among those enrolled in the SWEDEHEART registry from 2011 to 2014, those who were treated with PCI (n=146) had a lower risk of death (HR, 0.54; 95% CI, 0.38 to 0.77) at a mean follow-up of 3.2 years. Wong et al[4] analyzed the pooled data from Canadian Acute Coronary Syndromes I, Acute Coronary Syndromes II, and Canadian Global Registry of Acute Coronary Events registries in which 639 patients with severe CKD were enrolled and reported that in-hospital revascularization was independently associated with lower 1-year all-cause mortality, irrespective of eGFR. In the present study, we focused on investigating the outcome of NSTEMI patients with stage 4-5 CKD (including patients on chronic hemodialysis) and included a total of 2821 patients, among whom 40% received revascularization. We have shown that revascularization was associated with a lower risk of long-term all-cause mortality (adjusted weighted HR, 0.61) at a mean follow-up of 1.82 years. The findings of this study may be more generalizable to this specific group of patients. We further showed that the improvement of survival by revascularization was associated with increased risk of progression to chronic hemodialysis during long-term follow-up. When treating this specific group

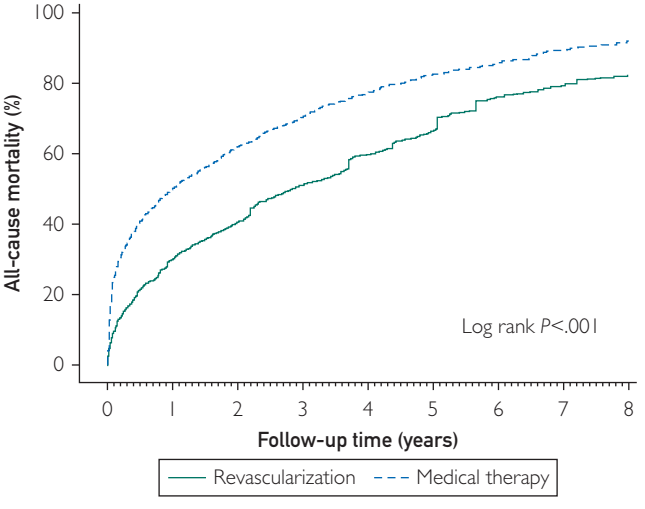

FIGURE 1. Kaplan-Meier survival estimates for all-cause mortality. Plot of survival function of all-cause mortality for patients with revascularization versus medical therapies in the inverse probability of treatment weighting cohort.

of patients, the choice between treatment in favor of longer survival or longer hemodialysis-free interval may depend on the age, frailty, comorbidity, and economic burden.

Among the patients included in our study, 35.9% (1,012 patients) had unstable hemodynamics; and 42% of them (428 patients) received revascularization therapy. The subgroup analysis showed that the benefit of revascularization in improving long-term survival was consistent irrespective of the presence or absence of unstable hemodynamics. In NSTEMI patients who presented with unstable hemodynamics or cardiogenic shock (or unstable hemodynamic), revascularization was recommended according to guidelines.[18,19] However, in a retrospective nation-based study, invasive strategies with coronary angiography, PCI, and mechanical circulatory support were reported to be less often applied in those NSTEMI patients with co-existing CKD compared with those without.[20] Among the patients included in our study, 35.9% had unstable hemodynamics; 42% of them were treated with PCI or CABG. The subgroup analysis showed that the benefit of revascularization in improving long-term survival was consistent irrespective of the presence or absence of unstable hemodynamics. The findings of our study suggest that the benefit of revascularization for NSTEMI patients who presented with shock remains in patients with co-existing severe CKD.

In the present study, we used IPTW to generate more homogenous and comparable groups and reported the HR for mortality after adjusting for variable covariates to mitigate selection bias. The only noticeable difference after IPTW adjustment was that aspirin and P2Y12 inhibitors were more commonly prescribed in the revascularization group compared with the medical therapy group. Most patients received at least one antiplatelet agent in both groups. However, the prevalence of dual antiplatelet therapy was lower in the medical therapy group compared with the revascularization group (76.8% vs 94.5%). Current guidelines recommend dual antiplatelet therapy for patients with NSTEMI with or without CKD.[5] However, patients with CKD are commonly deprived of standard treatment in the real world.[21,22] The most plausible explanation for this is the presence of bleeding or the physician's concerns about the high bleeding risk in this cohort. Dual antiplatelet therapy might not be prescribed or might be terminated prematurely in particular for patients not receiving stent implantation. Although the findings of the current study were consistent before and after adjusting for antiplatelet prescriptions, the potential impact of difference in the prevalence of antiplatelet use could not be excluded.

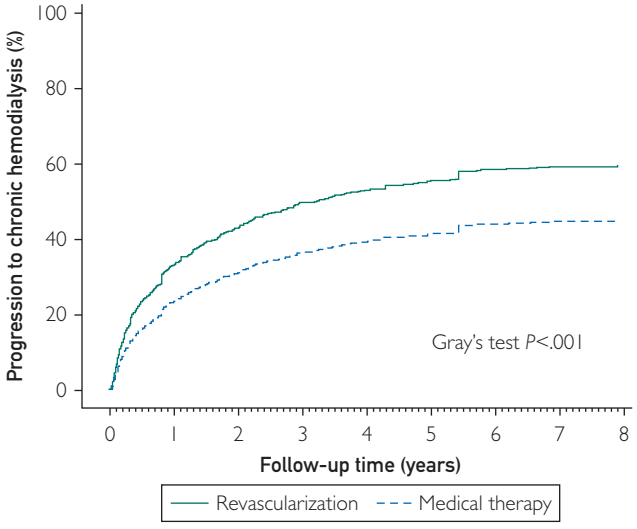

FIGURE 2. Cumulative incidence function of progression to chronic hemodialysis. Plot of cumulative incidence function of progression to chronic hemodialysis (in non—dialysis-dependent patients who survived non-ST segment elevation myocardial infarction to discharge) for patients with revascularization versus medical therapies in the inverse probability of treatment weighting cohort.

Study Limitations

First, certain important data for NSTEMI risk assessment were not available, including electrocardiography, blood pressure, heart rate, and Killip classification. Second, the prevalence of type 2 MI among the included patients and the differences in the prevalence between the treatment groups were unknown. The benefit of revascularization

Characteristic strata	Treatment strategy		Hazard ratio (95% confidence intervals)	*P for interaction*
	Revascularization	Medical therapy		
Age				**0.884**
<80	60.05%	72.70%	0.57 (0.49-0.67)	
≥80	78.67%	87.95%	0.83 (0.64-1.08)	
Sex				**0.552**
Male	63.01%	79.90%	0.64 (0.53-0.77)	
Female	64.36%	74.81%	0.56 (0.46-0.68)	
DM				**0.591**
No	64.10%	73.93%	0.60 (0.49-0.73)	
Yes	63.50%	79.69%	0.76 (0.64-0.90)	
HFrEF (heart failure with reduced LVEF <40%)				**0.267**
No	64.72%	75.21%	0.61 (0.52-0.70)	
Yes	60.12%	83.96%	0.64 (0.48-0.85)	
Old MI				**0.851**
No	63.54%	76.19%	0.61 (0.53-0.70)	
Yes	65.17%	83.21%	0.77 (0.49-1.19)	
Previous CABG, CAD or PCI				**0.931**
No	65.91%	79.95%	0.63 (0.53-0.75)	
Yes	62.26%	75.34%	0.62 (0.50-0.77)	
AF				**0.257**
No	63.36%	76.63%	0.62 (0.54-0.71)	
Yes	67.87%	81.20%	0.56 (0.32-1.00)	
Chronic hemodialysis				**0.346**
No	60.65%	77.58%	0.57 (0.48-0.69)	
Yes	67.93%	76.25%	0.79 (0.64.-0.96)	
Cardiac Arrest				**0.511**
No	61.92%	75.35%	0.62 (0.54-0.71)	
Yes	95.04%	98.60%	1.28 (0.74-2.20)	
Respiratory failure requiring invasive ventilator				**0.548**
No	61.20%	72.78%	0.62 (0.52-0.74)	
Yes	70.15%	85.63%	0.70 (0.56-0.86)	
Shock				**0.299**
No	59.07%	70.08%	0.72 (0.60-0.85)	
Yes	74.57%	89.94%	0.64 (0.52-0.78)	

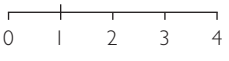

FIGURE 3. Subgroup analysis of long-term all-cause mortality by selected baseline characteristics in the inverse probability of treatment weighting—adjusted cohort. AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; DM, diabetes mellitus; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention

may differ among different types of MI. Third, the coronary angiographic characteristics and the completeness of revascularization were not available. These are important determinants of outcome after revascularization. Fourth, we did not investigate the effect of revascularization on the other major cardiovascular event

including repeat revascularization and recurrent myocardial infarction, which are also of clinical importance. Fifth, the majority of patients in the revascularization group received PCI with only 9.0% received CABG. Therefore, the findings of this study may not be extrapolated to all patients treated with CABG.

CONCLUSION

Revascularization with either PCI or CABG were associated with lower in-hospital and long-term mortality in patients with advanced CKD. In patients with non–dialysis-dependent severe CKD who had survival to discharge, revascularization was associated with an increased risk of progression to chronic hemodialysis during follow-up. Randomized trials are required to further corroborate the findings of this retrospective analysis.

POTENTIAL COMPETING INTERESTS

The authors report no potential competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ASMD,** absolute standardized mean differences; **CABG,** coronary artery bypass graft; **CKD,** chronic kidney disease; **HFrEF,** heart failure with reduced ejection fraction; **IPTW,** inverse probability of treatment weighting; **LVEF,** left ventricular ejection fraction; **NSTEMI,** non-ST segment elevation myocardial infarction; **PCI,** percutaneous coronary intervention

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Correspondence: Address to Chi-Jen Chang, MD, The Cardiology Division, Department of Internal Medicine, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, 199 Tun-Hwa North Road, Taipei 105, Taiwan. (chijenformosa@gmail.com); or Chi-Jen Chang, MD and Pao-Hsien Chu, MD are joint corresponding authors (taipei.chu@gmail.com).

ORCID

Chia-Pin Lin: https://orcid.org/0000-0001-7959-7804;
Chiu-Yi Hsu: https://orcid.org/0000-0001-7171-3532;
Pao-Hsien Chu: https://orcid.org/0000-0003-0361-6348

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