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Association of secondary prevention medication use after myocardial infarction with mortality in hemodialysis patients

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ABSTRACT

Background. Mortality after myocardial infarction (MI) among patients undergoing dialysis is high. However, studies investigating the use of secondary prevention medications after MI and clinical outcomes in dialysis patients are lacking. This study aimed to examine the association of the number of guideline-recommended medications (antiplatelets, β-blockers, statins and renin–angiotensin–aldosterone system inhibitors) with all-cause mortality after MI in hemodialysis (HD) patients.

Methods. We conducted a nationwide cohort study of incident HD patients who were admitted for MI between 1 January 2010 and 31 December 2014 and were followed up until 31 December 2015, using Taiwan’s national health insurance research database.

Results. Of 1471 patients (mean age 68 years, 41.9% women) included in the analysis, 281 (19.1%) were treated with one cardioprotective medication, 406 (27.6%) with two, 490 (33.3%) with three and 294 (20%) with four. During a median follow-up of 1.0 years, 458 (31.1%) patients died. In a multivariable Cox model, each additional use of guideline-recommended therapies was associated with a significant 12% reduction in the risk of mortality [hazard ratio (HR) 0.88 [95% confidence interval (CI) 0.80–0.97]]. Similar results were obtained in the analysis with the inverse probability of treatment weighting [HR 0.84 (95% CI 0.77–0.92)] and in the propensity score–matched subcohort [HR 0.87 (95% CI 0.77–0.98)]. The decreased mortality risk was consistently observed across all subgroups.

Conclusions. The use of more evidence-based medications for secondary prevention after MI was associated with a lower risk of all-cause mortality in HD patients.
INTRODUCTION

Chronic kidney disease (CKD) is a risk factor for myocardial infarction (MI) [1–3]. After MI, the risk of subsequent adverse cardiovascular disease (CVD) events is elevated in patients with CKD. Patients with end-stage kidney disease (ESKD) requiring dialysis are more likely to experience cardiac arrest and in-hospital death after MI than the nondialysis population [2, 4]. In addition, 1-year and 2-year mortality rates after MI in dialysis patients were 59% and 73%, respectively, which were much higher than in the general population [2].

Evidence-based medications, including antiplatelet agents, β-blockers, statins and renin-angiotensin–aldosterone system (RAAS) inhibitors, are recommended by the current guidelines for secondary prevention after MI [5–7]. Each of the four types of medications improves the clinical outcomes in patients with MI. However, the benefits associated with the use of these medications have been largely identified in studies involving patients with preserved kidney function [8]. A recent analysis showed that patients with CKD remain underrepresented in contemporary CVD clinical trials [9]. Moreover, despite the increased risk of adverse outcomes, patients with advanced CKD are less likely to receive these guideline-recommended therapies [1, 4, 10]. There is a lack of information on the effect of guideline-recommended treatments in CKD patients with MI.

In the present study we aimed to examine whether the use of more guideline-recommended secondary prevention medications after MI reduces long-term mortality among ESKD patients receiving hemodialysis (HD) in a national population-based cohort.

MATERIALS AND METHODS

Data source

We performed a retrospective, observational cohort study of incident HD patients with MI. Patient data were retrieved from Taiwan’s National Health Insurance Research Database (NHIRD), which contains healthcare data gathered prospectively for 99% of the Taiwanese population (~23 million people) [11]. The de-identified information recorded in the NHIRD includes demographic information (e.g. date of birth, sex, area of residence) and clinical information (e.g. diagnostic codes from the International Classification of Diseases, 9th Revision–Clinical Modification (ICD-9-CM), drug prescriptions and medical procedures). The institutional review board of the Taipei Tzu Chi Hospital approved the study and granted a waiver for the need to obtain informed consent.

Study design and population

From the NHIRD, we included incident HD patients who were then admitted to hospitals for a first MI event between 1 January 2010 and 31 December 2014. Incident HD patients were identified as those who were newly diagnosed with ESKD and initiated maintenance HD for at least 90 days. Patients with ESKD...
Enrollment procedure

We excluded patients who were <20 years of age, had switched to PD or had undergone kidney transplantation before the index MI. Patients were also excluded if they died before or within 90 days after discharge from the MI event, were rehospitalized within 90 days after discharge or were lost to follow-up within 30 days after discharge. Patients who did not receive any of the four types of secondary prevention medications were also excluded because they tended to be more critically ill and less likely to be prescribed and/or benefit from these preventive medications. Significant confounding by progression would thus be a concern regarding any comparisons involving them.

Exposure

Oral antiplatelet agents, β-blockers, statins and RAAS inhibitors, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and direct renin inhibitors, were determined by analyzing the prescriptions given at the first outpatient follow-up visit after hospital discharge according to the Anatomical Therapeutic Chemical classification (Supplemental Table 1). The number of secondary prevention medications was categorized into four groups: one, two, three or four medications. Patients prescribed one medication were treated as the reference group.

Covariates

Variables that were thought to potentially confound the relationship between the number of secondary prevention medications prescribed and outcomes were prespecified and included demographic characteristics (age, sex, dialysis vintage, calendar year, geographic location), comorbidities, pattern of acute MI (AMI), type of revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)] and bleeding events during the index hospitalization (gastrointestinal or intracranial bleeding). Comorbid conditions diagnosed during any hospitalization before the index hospitalization, during the index hospitalization or at more than two outpatient visits within 365 days were identified by the presence of the relevant ICD-9-CM codes and included hypertension (ICD-9 codes 401–405), dyslipidemia (272), diabetes mellitus (250), heart failure (428), stroke (430–437), peripheral arterial occlusive disease (440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8 and 447.9), chronic obstructive pulmonary disease (COPD; 490–496) and cancer (140–208). The Charlson Comorbidity Index (CCI) was used to quantify overall systemic health [15].

Outcome measures

The outcome of interest was all-cause mortality. We defined the 91st day after discharge from hospitalization for the MI event as the index date for study entry. The study population was censored at the time a patient switched to PD, a patient underwent kidney transplantation or at the end of follow-up on 31 December 2015.

Statistical analyses

Categorical data are presented as frequencies and percentages and were compared with the chi-squared test. Continuous data with a normal distribution are presented as mean ± standard deviation (SD) and were compared by one-way analysis of variance. To account for the nonrandomized treatment selection and to reduce the effects of confounders, three statistical approaches were considered: multivariable Cox model (adjusted for the above covariates), inverse probability of treatment weighting (IPTW) and propensity score (PS) matching. We assessed the proportional hazards assumption using a time-dependent covariate test, which was met for all models.

We estimated the individual PSs using a multivariable logistic regression model that incorporated 24 a priori selected covariates (all baseline characteristics in Table 1, excluding the four cardioprotective medications) (Supplemental Table 2). For the IPTW approach, we calculated the IPTW for each patient using the PS to minimize the selection bias. IPTW-adjusted Cox regression models were then fitted to compare the treatment effects. Patients treated with two, three or four medications were PS matched to patients treated with one medication using a 1:1 nearest-neighbor approach [16]. This procedure was repeated separately for each group to create a PS-matched subcohort [17]. The four PS-matched groups of patients were then compared using a multivariable Cox model. Effect modification of the association between each additional prescription of secondary prevention medications and mortality by eight clinically important variables that may affect prognosis [age ≥60 versus <60 years, sex, dyslipidemia, diabetes, heart failure, comorbidities (CCI score <5 versus ≥5), revascularization (yes versus no) and patterns of MI (STEMI versus non-STEMI)] was also tested by including multiplicative interaction terms in the multivariable model. Two-tailed P-values <.05 were considered statistically significant. All statistical analyses were carried out using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of study population

Among 2272 incident HD patients who experienced MI, 1471 (64.7%) were included in the final analyses (Figure 1). Of these, 616 (41.9%) were women and the mean age was 68 years (SD 11). Baseline characteristics of individuals in all groups are shown in Table 1. A total of 281 (19.1%) received one medication after discharge, 406 (27.6%) received two, 490 (33.3%) received three and 294 (20.0%) received four. The medications were antiplatelet agents, β-blockers, statins or RAAS inhibitors. In
Table 1. Baseline characteristics of study patients before propensity score matching

| Characteristics                        | 1 (n = 281) | 2 (n = 406) | 3 (n = 490) | 4 (n = 294) | P-value |
|----------------------------------------|-------------|-------------|-------------|-------------|---------|
| Age (years), mean ± SD                 | 69.3 ± 11.4 | 68.9 ± 11.6 | 67.4 ± 11.1 | 65.0 ± 10.6 | <.001   |
| Age group (years), n (%)               | 10 (2.5)    | 17 (3.5)    | 12 (4.1)    |             |         |
| 20–44                                  |             |             |             |             |         |
| 45–64                                  |             |             |             |             | <.001   |
| 65–74                                  |             |             |             |             |         |
| 75–100                                 |             |             |             |             |         |
| Sex, n (%)                             |             |             |             |             | .721    |
| Male                                   | 158 (56.2)  | 231 (56.9)  | 289 (59.0)  | 177 (60.2)  |         |
| Female                                 | 123 (43.8)  | 175 (43.1)  | 201 (41.0)  | 117 (39.8)  |         |
| HD vintage (years), mean ± SD          | 2.1 ± 1.3   | 2.1 ± 1.4   | 1.9 ± 1.3   | 2.1 ± 1.3   | .168    |
| Geographic location, n (%)             |             |             |             |             | .018    |
| Northern Taiwan                        | 137 (48.8)  | 156 (38.5)  | 218 (44.5)  | 147 (50.2)  |         |
| Central Taiwan                         | 53 (18.9)   | 102 (25.2)  | 94 (19.2)   | 46 (15.7)   |         |
| Southern Taiwan                        | 86 (30.6)   | 132 (33.6)  | 166 (33.9)  | 96 (32.8)   |         |
| Eastern Taiwan and islands             | 5 (1.8)     | 11 (2.7)    | 18 (3.7)    | 4 (1.4)     |         |
| Comorbidities, n (%)                   |             |             |             |             | .333    |
| Hypertension                           | 278 (98.9)  | 402 (99.0)  | 489 (99.8)  | 292 (99.3)  |         |
| Dyslipidemia                           | 169 (60.1)  | 259 (63.8)  | 328 (66.9)  | 210 (71.4)  | .028    |
| Diabetes mellitus                      | 229 (81.5)  | 351 (86.5)  | 408 (83.3)  | 253 (86.1)  | .242    |
| Heart failure                          | 183 (65.1)  | 259 (63.8)  | 287 (58.6)  | 163 (55.4)  | .041    |
| Stroke                                 | 84 (29.9)   | 98 (24.1)   | 111 (22.7)  | 67 (22.8)   | .121    |
| PAOD                                   | 66 (23.5)   | 106 (26.1)  | 104 (21.2)  | 59 (20.1)   | .209    |
| COPD                                   | 97 (34.5)   | 127 (31.3)  | 120 (24.5)  | 66 (22.5)   | .001    |
| Cancer                                 | 31 (11.0)   | 25 (6.2)    | 36 (7.4)    | 18 (6.1)    | .074    |
| CCI score, n (%)                       | 13 (4.6)    | 24 (5.9)    | 32 (6.5)    | 23 (7.8)    |         |
| ≤3                                     | 102 (36.3)  | 144 (35.5)  | 195 (39.8)  | 124 (42.2)  |         |
| 4–5                                    | 166 (59.1)  | 238 (58.6)  | 263 (53.7)  | 147 (50.0)  |         |
| ≥6                                     | 5.89 ± 1.53 | 5.85 ± 1.51 | 5.63 ± 1.46 | 5.51 ± 1.40 | .003    |
| Pattern of MI, n (%)                   | 13 (4.6)    | 42 (10.3)   | 52 (10.6)   | 26 (8.8)    | .030    |
| STEMI                                  | 268 (95.4)  | 364 (89.7)  | 438 (89.4)  | 268 (91.2)  |         |
| Revascularization, n (%)               | 134 (47.7)  | 228 (56.2)  | 315 (64.3)  | 202 (68.7)  | <.001   |
| PCI                                    | 12 (4.3)    | 27 (6.7)    | 18 (3.7)    | 16 (5.4)    | .203    |
| CABG                                   | 15 (5.3)    | 21 (5.2)    | 29 (5.9)    | 14 (4.8)    | .911    |
| In-hospital bleeding events, n (%)     |             |             |             |             |         |
| Medication before entry, n (%)         |             |             |             |             |         |
| Aspirin                                | 137 (48.8)  | 213 (52.5)  | 218 (44.5)  | 148 (50.3)  | .107    |
| Clopidogrel                            | 70 (24.9)   | 115 (28.3)  | 126 (25.7)  | 79 (26.9)   | .745    |
| Ticlopidine                            | 7 (2.5)     | 15 (3.7)    | 10 (2.0)    | 6 (2.0)     | .404    |
| Cilostazol                             | 48 (17.1)   | 68 (16.8)   | 56 (11.4)   | 44 (15.0)   | .077    |
| β-blocker                              | 114 (40.6)  | 192 (47.3)  | 283 (57.8)  | 194 (66.0)  | <.001   |
| RAAS inhibitor                         | 107 (38.1)  | 193 (47.5)  | 252 (51.4)  | 174 (59.2)  | <.001   |
| Calcium-channel blocker                | 152 (54.1)  | 247 (60.8)  | 326 (66.5)  | 209 (71.1)  | <.001   |
| Diuretics                              | 87 (31.0)   | 155 (38.2)  | 187 (38.2)  | 118 (40.1)  | .106    |
| Statin                                 | 70 (24.9)   | 135 (33.3)  | 158 (32.2)  | 149 (50.7)  | <.001   |
| Proton pump inhibitor                  | 49 (17.4)   | 73 (18.0)   | 102 (20.8)  | 54 (18.4)   | .605    |
| NSAlD                                  | 73 (26.0)   | 86 (21.2)   | 111 (22.7)  | 66 (22.5)   | .524    |
| Medication after discharge, n (%)      |             |             |             |             |         |
| Antiplatelets                          | 237 (84.3)  | 390 (96.1)  | 482 (98.4)  | 294 (100.0) | <.001   |
| β-blocker                              | 17 (6.1)    | 154 (37.9)  | 400 (81.6)  | 294 (100.0) | <.001   |
| RAAS inhibitor                         | 17 (6.1)    | 142 (35.0)  | 346 (70.6)  | 294 (100.0) | <.001   |
| Statin                                 | 10 (3.6)    | 126 (31.0)  | 242 (49.4)  | 294 (100.0) | <.001   |

NSAID, nonsteroidal anti-inflammatory drug; PAOD, peripheral arterial occlusive disease.

general, patients prescribed fewer medications were older, were more likely to have heart failure and COPD and had higher CCI scores. Patterns of MI were also different among the four groups. Notably, patients receiving more medications were more likely to have undergone PCI during the index hospitalization. PS matching yielded a population of 776 patients (194 in each of the four treatment groups). In the matched subcohort, 325 (41.9%) were women and the mean age was 67 years (SD 11). Baseline characteristics were well balanced after matching among the four groups (Table 2).
Mortality

After a median follow-up of 1.0 years (interquartile range (IQR) 0.3–1.9), 458 (31.1%) patients had died. Kaplan–Meier curves for time to the primary outcome are depicted in Supplementary Figure 1. As the number of medications used for secondary prevention after MI increased, the risk of mortality decreased (incidence 31.0, 28.8, 20.5 and 19.0 events per 100 patient-years in patients receiving one, two, three and four medications, respectively) (Table 3). Each additional use of guideline-recommended therapies was associated with a 17% lower risk of all-cause death in the unadjusted Cox model [hazard ratio (HR) 0.83 [95% confidence interval (CI) 0.75–0.91]; P < .001]. This association remained significant after multivariable adjustment [HR 0.88 (95% CI 0.80–0.97); P = .011]. Findings were also similar in the IPTW-adjusted Cox model [HR 0.84 (95% CI 0.77–0.92); P < .001]. In the PS-matched subcohort, the median follow-up time was 1.0 years (IQR 0.4–2.0). Compared with individuals who initiated one medication, the HRs for mortality were 0.85 (95% CI 0.59–1.21; P = .353), 0.69 (95% CI 0.47–1.01; P = .059) and 0.68 (95% CI 0.47–0.98; P = .039) for those who used two, three and four medications, respectively. Consistent with this finding, an increase in the number of guideline-recommended medications was found to be associated with a reduced risk of mortality [HR 0.87 (95% CI 0.77–0.98); P = .023]. The reduction in the risk of mortality with the increasing number of guideline-recommended medications was consistent across all clinically relevant subgroups (Figure 2).
Table 2. Baseline characteristics of study patients after propensity score matching

| Characteristic                          | 1 (n = 194) | 2 (n = 194) | 3 (n = 194) | 4 (n = 194) | P-value |
|----------------------------------------|-------------|-------------|-------------|-------------|---------|
| Age (years), mean ± SD                 | 67.1 ± 11.3 | 66.5 ± 11.8 | 65.8 ± 11.1 | 66.8 ± 10.3 | .672    |
| Age group (years), n (%)               |             |             |             |             | .407    |
| 20–44                                  | 3 (1.6)     | 9 (4.6)     | 9 (4.6)     | 5 (2.6)     |         |
| 45–64                                  | 85 (43.8)   | 71 (36.6)   | 77 (39.7)   | 74 (38.1)   |         |
| 65–74                                  | 52 (26.8)   | 68 (35.1)   | 63 (32.5)   | 68 (35.1)   |         |
| ≥75                                    | 54 (27.8)   | 46 (23.7)   | 45 (23.2)   | 47 (24.2)   |         |
| Sex, n (%)                             |             |             |             |             | .885    |
| Male                                   | 114 (58.8)  | 114 (58.8)  | 115 (59.3)  | 108 (55.7)  |         |
| Female                                 | 80 (41.2)   | 80 (41.2)   | 79 (40.7)   | 86 (44.3)   |         |
| HD vintage (years), mean ± SD          | 2.1 ± 1.3   | 2.0 ± 1.4   | 2.0 ± 1.4   | 2.1 ± 1.2   | .887    |
| Geographic location, n (%)             |             |             |             |             | .944    |
| Northern Taiwan                        | 95 (49.0)   | 88 (45.4)   | 87 (43.5)   | 94 (48.5)   |         |
| Central Taiwan                         | 33 (17.0)   | 38 (19.6)   | 38 (19.6)   | 34 (17.5)   |         |
| Southern Taiwan                        | 62 (32.0)   | 64 (33.0)   | 68 (33.5)   | 63 (32.5)   |         |
| Eastern Taiwan and islands             | 4 (2.1)     | 4 (2.1)     | 1 (0.5)     | 3 (1.6)     |         |
| Comorbidities, n (%)                   |             |             |             |             | .502    |
| Hypertension                           | 194 (100.0) | 193 (99.5)  | 194 (100.0) | 193 (99.5)  | 1.000   |
| Dyslipidemia                           | 135 (69.6)  | 136 (70.1)  | 134 (69.1)  | 129 (66.5)  | .874    |
| Diabetes mellitus                      | 174 (89.7)  | 169 (87.1)  | 162 (83.5)  | 166 (85.6)  | .337    |
| Heart failure                          | 122 (62.9)  | 118 (60.8)  | 108 (55.7)  | 117 (60.3)  | .523    |
| Stroke                                 | 49 (25.3)   | 45 (23.2)   | 47 (24.2)   | 52 (26.8)   | .864    |
| PAOD                                   | 47 (24.2)   | 45 (23.2)   | 34 (17.5)   | 43 (22.2)   | .394    |
| COPD                                   | 61 (31.4)   | 51 (26.3)   | 43 (22.2)   | 53 (27.3)   | .230    |
| Cancer                                 | 11 (5.7)    | 14 (7.2)    | 15 (7.7)    | 13 (6.7)    | .871    |
| CCI score, n (%)                       |             |             |             |             | .502    |
| ≤3                                     | 8 (4.1)     | 13 (6.7)    | 15 (7.7)    | 13 (6.7)    |         |
| 4–5                                    | 69 (35.6)   | 75 (38.7)   | 79 (40.7)   | 66 (34.0)   |         |
| ≥6                                     | 117 (60.3)  | 106 (54.6)  | 100 (51.6)  | 115 (59.3)  |         |
| Mean ± SD                              | 5.92 ± 1.56 | 5.67 ± 1.40 | 5.57 ± 1.44 | 5.77 ± 1.41 | .106    |
| Pattern of MI, n (%)                   |             |             |             |             | .336    |
| STEMI                                  | 13 (6.7)    | 17 (8.8)    | 17 (8.8)    | 9 (4.6)     |         |
| NSTE MI                                | 181 (93.3)  | 177 (91.2)  | 177 (91.2)  | 185 (95.4)  |         |
| Revascularization, n (%)               |             |             |             |             | .502    |
| PCI                                    | 115 (59.3)  | 118 (60.8)  | 117 (60.3)  | 117 (60.3)  | .992    |
| CABG                                   | 9 (4.6)     | 12 (6.2)    | 12 (6.2)    | 11 (5.7)    | .901    |
| In-hospital bleeding events, n (%)     | 11 (5.7)    | 7 (3.6)     | 12 (6.2)    | 8 (4.1)     | .597    |
| Medication before entry, n (%)         |             |             |             |             | .502    |
| Aspirin                                | 102 (52.6)  | 105 (54.1)  | 85 (43.8)   | 96 (49.5)   | .185    |
| Clopidogrel                            | 54 (27.8)   | 47 (24.2)   | 47 (24.2)   | 61 (31.4)   | .317    |
| Ticlopidline                           | 3 (1.6)     | 10 (5.2)    | 5 (2.6)     | 6 (3.1)     | .215    |
| Cilostazol                             | 32 (16.5)   | 28 (14.4)   | 20 (10.9)   | 29 (15.0)   | .339    |
| \(β\)-blocker                         | 81 (41.8)   | 98 (50.5)   | 103 (53.1)  | 127 (65.5)  | <.001   |
| RAAS inhibitor                         | 78 (40.2)   | 97 (50.0)   | 107 (55.2)  | 112 (57.7)  | .003    |
| Calcium-channel blocker                | 121 (62.4)  | 131 (67.5)  | 137 (70.6)  | 124 (63.9)  | .313    |
| Diuretics                              | 71 (36.6)   | 76 (39.2)   | 76 (39.2)   | 70 (36.1)   | .879    |
| Statin                                 | 55 (28.4)   | 64 (33.0)   | 64 (33.0)   | 99 (51.0)   | <.001   |
| Proton pump inhibitor                  | 37 (19.1)   | 30 (15.5)   | 39 (20.1)   | 35 (18.0)   | .671    |
| NSAID                                  | 45 (23.2)   | 42 (21.7)   | 46 (23.7)   | 46 (23.7)   | .958    |
| Medication after discharge, n (%)      |             |             |             |             | .958    |
| Antiplatelets                          | 168 (86.6)  | 189 (97.4)  | 191 (98.5)  | 194 (100.0) | <.001   |
| \(β\)-blocker                          | 8 (4.1)     | 76 (39.2)   | 157 (80.9)  | 194 (100.0) | <.001   |
| RAAS inhibitor                         | 12 (6.2)    | 66 (34.0)   | 147 (75.8)  | 194 (100.0) | <.001   |
| Statin                                 | 6 (3.1)     | 57 (29.4)   | 87 (44.9)   | 194 (100.0) | <.001   |

NSAID, nonsteroidal anti-inflammatory drug; PAOD, peripheral arterial occlusive disease.

We investigated the association between each cardioprotective treatment and mortality (Table 4). With respect to the use of \(β\)-blockers, RAAS inhibitors and statins, there were significantly decreased risks of all-cause mortality in the unadjusted models. However, this association remained significant after adjustment only for RAAS inhibitors [HR 0.82 (95% CI 0.68–0.99); P = .039]. To assess the reliability of our findings, we did sensitivity analyses to minimize exposure misclassification bias, using
Table 3. Cox proportional hazards models investigating the association of the number of secondary prevention medications with the risk of mortality

| Model                  | Events (n/N) | Incidencea | HR (95% CI) | P-value |
|------------------------|--------------|------------|-------------|---------|
| Unadjusted             |              |            |             |         |
| 1 medication           | 108/281      | 31.0       | 1 (Reference) | –       |
| 2 medications          | 149/406      | 28.8       | 0.93 (0.73–1.19) | .571    |
| 3 medications          | 129/490      | 20.5       | 0.66 (0.51–0.85) | .001    |
| 4 medications          | 72/294       | 19.0       | 0.61 (0.45–0.82) | .001    |
| Per medication         | 458/1471     | 27.3       | 0.83 (0.75–0.90) | <.001   |
| Adjustedb              |              |            |             |         |
| 1 medication           | 108/281      | 31.0       | 1 (Reference) | –       |
| 2 medications          | 149/406      | 28.8       | 1.00 (0.78–1.30) | .975    |
| 3 medications          | 129/490      | 20.5       | 0.75 (0.57–0.98) | .032    |
| 4 medications          | 72/294       | 19.0       | 0.76 (0.56–1.04) | .084    |
| Per medication         | 458/1471     | 27.3       | 0.88 (0.80–0.97) | .011    |
| IPTW adjustedb         |              |            |             |         |
| 1 medication           | 108/281      | 31.0       | 1 (Reference) | –       |
| 2 medications          | 149/406      | 28.8       | 0.87 (0.67–1.12) | .267    |
| 3 medications          | 129/490      | 20.5       | 0.67 (0.52–0.86) | .002    |
| 4 medications          | 72/294       | 19.0       | 0.64 (0.47–0.86) | .003    |
| Per medication         | 458/1471     | 27.3       | 0.84 (0.77–0.92) | <.001   |
| PS matchedb            |              |            |             |         |
| 1 medication           | 72/194       | 29.2       | 1 (Reference) | –       |
| 2 medications          | 59/194       | 22.0       | 0.85 (0.59–1.21) | .353    |
| 3 medications          | 44/194       | 17.3       | 0.69 (0.47–1.01) | .059    |
| 4 medications          | 49/194       | 18.5       | 0.68 (0.47–0.98) | .039    |
| Per medication         | 224/776      | 21.7       | 0.87 (0.77–0.98) | .023    |

aIncidence rate per 100 patient-years.
bAdjusted for age, sex, dialysis vintage, geographic location, calendar year, pattern of AMI, PCI, CABG, in-hospital bleeding events, baseline comorbid conditions (hypertension, dyslipidemia, diabetes mellitus, congestive heart failure, stroke, peripheral arterial occlusive disease, COPD, cancer) and CCI score.

Table 4. Associations of individual cardioprotective medication classes with all-cause mortality

| Treatment       | Crude HR (95% CI) | P-value | Adjusted HRa (95% CI) | P-value |
|-----------------|-------------------|---------|-----------------------|---------|
| Antiplatelets   |                   |         |                       |         |
| Treated         | 0.85 (0.57–1.25)  | 0.396   | 0.82 (0.55–1.23)      | 0.347   |
| Untreated       | Reference         | Reference | Reference             |         |
| β-blocker       |                   |         |                       |         |
| Treated         | 0.79 (0.66–0.95)  | 0.011   | 0.92 (0.76–1.11)      | 0.395   |
| Untreated       | Reference         | Reference | Reference             |         |
| RAAS inhibitor  |                   |         |                       |         |
| Treated         | 0.75 (0.62–0.90)  | 0.002   | 0.82 (0.68–0.99)      | 0.039   |
| Untreated       | Reference         | Reference | Reference             |         |
| Statin          |                   |         |                       |         |
| Treated         | 0.79 (0.65–0.95)  | 0.013   | 0.85 (0.70–1.03)      | 0.091   |
| Untreated       | Reference         | Reference | Reference             |         |

aAdjusted for age, sex, dialysis vintage, geographic location, calendar year, pattern of AMI, PCI, CABG, in-hospital bleeding events, baseline comorbid conditions (hypertension, dyslipidemia, diabetes mellitus, congestive heart failure, stroke, peripheral arterial occlusive disease, COPD, cancer) and CCI score.

time intervals of 30 and 60 days after discharge from MI as the index date (Supplementary Table 1). Furthermore, patients without any medications were included as the reference group (Supplementary Table 2). The results of the analyses were consistent with the main findings.

DISCUSSION

In this nationwide retrospective cohort study, we found that the use of more guideline-recommended secondary prevention medications after MI was associated with a decreased risk of mortality during a median of 1 year of follow-up in an incident HD population. Specifically, the use of one additional...
guideline-recommended medication was associated with a 12% lower risk of mortality.

CKD has been identified as an adverse prognostic factor in patients with MI. Patients with progressively more severe CKD had higher rates of mortality and patients with ESKD had the worst prognosis [18, 19]. Wright et al. [18] observed that, compared with patients with normal kidney function, the risk of post-discharge mortality was 2.4-, 2.2-, 1.9- and 5.4-fold higher in patients with mild (creatinine clearance \(>50\)–\(\leq 75\) ml/min), moderate (creatinine clearance \(>35\)–\(\leq 50\) ml/min) and severe kidney dysfunction (creatinine clearance \(\leq 35\) ml/min) and ESKD, respectively. Similar findings have been described by Szummer et al. [19]. They demonstrated that more advanced CKD stages were associated with a higher 1-year mortality rate in a cohort of 23,262 consecutive patients with NSTEMI in Sweden. Several mechanisms have been proposed to explain the clinically unfavorable association between ESKD and MI. Patients with ESKD have higher rates of preexisting traditional CVD risk factors and more advanced atherosclerosis on presentation with acute coronary syndrome, which may predispose this population to higher CVD mortality. In addition, novel risk factors such as chronic inflammation, calcium and phosphorus abnormalities, sodium and volume overload and endothelial dysfunction associated with the uremic environment may lead to kidney-specific pathophysiology and partially contribute to their worse clinical outcomes [20]. Baber et al. [21] showed differences in the extent of coronary atherosclerosis and coronary plaque morphology between patients with and without CKD in a cohort of acute coronary syndrome patients undergoing PCI. Compared with patients without CKD, patients with CKD had longer lesions with greater luminal encroachment and a higher plaque burden; the coronary atherosclerotic plaque composition in the lesions in patients with CKD also involved larger necrotic cores and dense calcium deposits with less fibrous tissue [21].

Suboptimal management of MI in the ESKD population may be one of the most important andmodifiablecauses of the worse prognosis. Numerous studies have reported that patients with more severe CKD are less likely to receive guideline-recommended therapies [1, 4, 10, 19]. Underutilization of cardioprotective medications in dialysis patients may be driven partly by the lack of clinical trial evidence supporting their efficacy. The present study was the first, to the best of our knowledge, to investigate the association between exposure to a number of cardioprotective medications after MI and the long-term mortality risk among patients with ESKD. Very few studies have evaluated specific individual therapies as secondary prevention for MI in patients with ESKD. Berger et al. [22] showed that ESKD patients \(>65\) years of age are far less likely than non-ESKD patients to be treated with aspirin, \(\beta\)-blockers and angiotensin-converting enzyme inhibitors during an admission for AMI, and the lower rates of usage for these medications, particularly aspirin, may contribute to the increased 30-day mortality using the ESRD database and the Cooperative Cardiovascular Project database. Chung et al. [23] reported that moderate to high-intensity statin lowers the risk of all-cause mortality by 24% in dialysis patients who had no prior use of statins after an AMI during a 4-year follow-up in a national cohort study. Our observations of the survival benefit of RAAS inhibitors were in line with those made by Evans et al. [24], who reported that the use of RAAS inhibitors was associated with a significantly lower 3-year mortality rate in a large Swedish registry, which was consistent across all kidney function subgroups, including dialysis patients. However, we did not observe the survival benefit of the other three medications. The contradictory results may be due to differences in study population, diagnosis criteria, follow-up period and drug intensity. Although there was a lack of a significant association of individual cardiovascular drug use, other than RAAS inhibitors, with reduced mortality, our results suggest that patients with ESKD may benefit from combined treatment with multiple drugs after MI.

Despite the possibility that the use of more cardioprotective medications may provide a survival benefit, it is important to weigh the potential risks. Polypharmacy is a common problem among dialysis patients [25]. It increases not only the complexity of care, but also the risks of adverse drug reactions, drug interactions and morbidity and mortality because of the altered pharmacokinetics and pharmacodynamics in this population. For example, a recent meta-analysis found that the use of dual antiplatelet agents was associated with a higher bleeding risk in HD patients [26]. Therefore there are important considerations when seeking to provide the greatest protection while limiting the chance of possible harm [27]. Preferably the potential risks should be incorporated into decision-making regarding prescriptions, monitored carefully and managed properly if they occur.

Our study has several limitations. First, given the nature of observational studies, we cannot rule out the possibility of confounding by indication as an alternative explanation for our findings. One potential confounder is that patients with more severe MI are likely to receive a greater number of cardioprotective medications for secondary prevention. Another plausible confounder is that physicians are less likely to prescribe more secondary prevention medications to patients who face more serious medical problems, who are more critically ill or who have a worse prognosis. However, these two possible confounders would bias the results in opposite directions and therefore at least partly alleviate each other. Second, the number of cardioprotective treatments was based on the first prescription following hospital discharge, thus we cannot be certain whether there was treatment deviation. Third, we did not have information on the severity of MI or information on health-related factors such as smoking status, dietary habits and physical activity. Fourth, the cause of death in each patient could not be retrieved from the NHIRD. Fifth, we included patients who survived at least 90 days after MI, so our findings could only reasonably be applied to the early survivors after a MI. Finally, although randomized controlled studies are needed to confirm our findings, it may not be feasible to perform clinical trials to test the efficacy of cardioprotective medications in high-risk ESKD patients. Hence observational data may be the highest level of evidence that will ever be available regarding this condition.

CONCLUSION

In incident HD patients hospitalized for MI who survived for \(>90\) days, our study demonstrated that the use of more guideline-recommended secondary prevention medications after discharge was associated with a lower risk of long-term all-cause mortality. Our results have important therapeutic implications, suggesting that more aggressive medical treatment may improve the quality of care for HD patients with MI and should be considered in this population.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.
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DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST STATEMENT

None declared.

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