## Title

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## Journal

Circulation Cardiovascular Quality and Outcomes, 12(4)

## ISSN

1941-7713

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## Publication Date

2019-04-01

## DOI

10.1161/circoutcomes.118.004942

Peer reviewed

Published in final edited form as:

*Circ Cardiovasc Qual Outcomes*. 2019 April ; 12(4): e004942. doi:10.1161/CIRCOUTCOMES.118.004942.

# Association between Secondary Prevention Medication Use and Outcomes in Frail Older Adults after Acute Myocardial Infarction

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## Abstract

**Background:** Secondary prevention medications are often not prescribed to frail, older adults following acute myocardial infarction (AMI), potentially due to the absence of data to support use, perceived lack of benefit, and concern over possible harms. We examined the effect of using more guideline-recommended medications post-AMI on mortality, rehospitalization, and functional decline in the frailest and oldest segment of the U.S. population—long-stay nursing home (NH) residents.

**Methods and Results:** We conducted a retrospective cohort study of NH residents aged ≥65 years using 2007–2010 national U.S. Minimum Data Set clinical assessment data and Medicare claims. Exposure was the number of secondary prevention medications (antiplatelets, beta-

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Disclosures

The authors have no relevant financial, personal, or professional relationships to disclose.

blockers, statins, and renin-angiotensin-aldosterone system inhibitors) initiated post-AMI. Outcomes were 90-day death, rehospitalization, and functional decline. We compared outcomes for new-users of 2 versus 1 and 3 or 4 versus 1 medications using inverse probability of treatment-weighted odds ratios (OR) with 95% confidence intervals (CI). The cohort comprised 4,787 residents, with a total of 509 death, 820 functional decline, and 1,226 rehospitalization events. Compared to individuals who initiated 1 medication, mortality ORs were 0.98 (95% CI, 0.79–1.22) and 0.74 (95% CI, 0.57–0.97) for users of 2 and 3 or 4 medications, respectively. Rehospitalization ORs were 1.00 (95% CI, 0.85–1.17) for 2 and 0.97 (95%CI, 0.8–1.17) for 3 or 4 medications. Functional decline ORs were 1.04 (95% CI, 0.85–1.28) for 2 and 1.12 (95% CI, 0.89–1.40) for 3 or 4 medications. In a stability analysis excluding antiplatelet drugs from the exposure definition, more medication use was associated with functional decline.

**Conclusions:** Use of more guideline-recommended medications post-AMI was associated with decreased mortality in older, predominantly frail adults, but no difference in rehospitalization. Results for functional decline from the main and stability analyses were discordant and did not rule out an increased risk associated with more medication use.

### Keywords

Aging; Secondary Prevention; Quality and Outcomes; Mortality/Survival; Myocardial Infarction; Geriatrics; Comparative Effectiveness; Nursing Home; Pharmacoepidemiology

## INTRODUCTION

Acute myocardial infarction (AMI) remains a major cause of morbidity and mortality in the U.S., with about 790,000 Americans experiencing a new or recurrent AMI every year.[1] Four classes of medication are recommended by guidelines[2–4] for the secondary prevention of AMI: antiplatelets, β-blockers, statins, and renin-angiotensin-aldosterone system (RAAS) inhibitors. Each of the four medication classes improve clinical outcomes when initiated post-AMI.[5–8]

With the average age of first AMI being 65.3 years for males and 71.8 years for females, older adults represent a large portion of patients requiring secondary prevention medications.[1] Optimal use of these medications has a proven mortality benefit post-AMI in older community-dwelling adults.[9, 10]

While understanding the risks and harms of individual medication classes after AMI is important, focusing on the total number of medications prescribed captures additional information about the outcomes associated with overall intensity of treatment. It also provides a greater understanding of the cumulative benefits and risks that can occur when multiple medications are used in the same patient, which can lead to complex interactions between drugs and with the patient's physiology.[11] These issues are of special importance for older adults in late life, in whom polypharmacy and debate over the risks and harms of intensive treatment are central issues.[11]

Frailty is the decreased ability of individuals to recover from physiologic insults, and often presents with the phenotype of weight loss, sarcopenia, or the lack of independence in

activities of daily living.[12–14] Secondary prevention medications are often not prescribed to frail, older adults, especially those residing in the nursing home (NH) long-term, which is the frailest and oldest subpopulation in the U.S.[15–17] The lack of prescribing may be in part due to perceived lack of benefit, concern over potential harms, and lack of data as NH residents are rarely included in clinical trials of medications.[16, 17] Given the deviations from clinical guidelines for older adults in the NH setting, understanding how these medications affect outcomes in the NH population may influence and optimize future prescribing. Data on how treatment effects vary across subgroups defined by age, cognition, and functional status (proxies for life expectancy) would be particularly useful to guide prescribing since older, frailer individuals may benefit less from receiving more secondary prevention medications.

We examined the association between prescribing more versus fewer guideline-recommended medications post-AMI in older NH residents and functional decline, mortality, and rehospitalization outcomes. Our investigation can help inform whether prescribing fewer medications is appropriate in frail older adults due to the limited life expectancy and other relevant characteristics of the population. Furthermore, it can help identify which groups would be most likely to benefit from receiving more secondary prevention medications after AMI.

## METHODS

### Study Design and Data Sources

The data are subject to a data use agreement with the Centers for Medicare and Medicaid Services and cannot be made available to other researchers for purposes of reproducing the results or replicating the procedures.

This was a retrospective new-user cohort study that linked the following national datasets: Medicare fee-for-service denominator (eligibility) information, Medicare Part A inpatient hospital claims, Medicare Part D prescription drug claims, and Minimum Data Set (MDS) 2.0. The MDS is a comprehensive, clinical assessment instrument used to document health status of NH residents, including demographic, medical, functional status, psychological, and cognitive status information. The MDS assessments are federally mandated for all residents in NHs certified to receive Medicare or Medicaid funding. Online Survey Certification and Reporting (OSCAR) data were used for facility-level information, including NH characteristics, staffing levels, and quality measures. A previously validated algorithm was used to track the timing and location of health service use.[18]

### Study Population

The study population was previously established[16, 17, 19, 20] national cohort of long-stay NH residents aged ≥65 years without a history of AMI who were hospitalized for AMI (ICD-9 codes 410.XX or 411.1 in principal or secondary position on inpatient claim), had not taken antiplatelet, β-blocker, statin, or RAAS inhibitor medications for at least 4 months before their AMI, and were readmitted to a U.S. NH directly after hospital discharge between May 1, 2007 and December 31, 2010 (Supplementary Figure S1). Long-stay NH residents are a

predominantly frail population, thus we did not apply specific inclusion criteria to isolate long-stay residents that met a particular definition of frailty. However, we excluded patients with extremely poor functional status before the AMI hospitalization (ADL score ≥24) because they had little opportunity for further functional decline (see "Outcomes" below).[19, 21] We selected previous non-users to permit an evaluation of the decision to initiate secondary prevention medications after AMI, distinct from the decision to continue these agents in patients who had already been taking them before their AMI. Additional details of the cohort have been previously described.[16, 17, 19]

## Exposure and Contrasts of Interest

Oral antiplatelet, β-blocker, statin, and RAAS inhibitor medications, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers (Supplementary Table S1), were identified according to generic name in Medicare Part D prescription drug claims.[22] The categorical secondary prevention medication use variable had 3 distinct levels: 1, 2, and 3 or 4 medication classes used. There were few individuals who received 4 medications, so they were grouped with those who received 3 medications. Individuals who received zero medications were excluded to minimize confounding bias because they represent a distinct group from all others. These individuals tend to be much sicker and less likely to benefit from medications, so significant confounding by prognosis is a concern for any comparisons with them. The effects of different combinations of medication classes were not examined because the sample size precluded such analyses and the focus of this study was on the potential value associated with prescribing more guideline-recommended medications (i.e., increasing medication burden).

The contrasts of interest were defined as the effect of initiating 3 or 4 versus 2 versus 1 secondary prevention medications in the immediate post-AMI period, regardless of subsequent treatment discontinuations, switches, or additions among the treatment groups (i.e., the intention-to-treat estimand).[23–25] This is analogous to emulating a multi-arm pragmatic trial that compares the incremental benefits and harms of more versus less guideline-concordant prescribing.

## Outcomes

The three outcomes were death, all-cause rehospitalization, and functional decline. We used data from Medicare Part A and Medicare enrollment files to identify hospital admissions and date of death. Functional decline was defined as an increase of 3 points on the validated 28-point MDS Morris scale of independence in Activities of Daily Living between the prehospital baseline assessment and the first available assessment after hospitalization up to 3 months after discharge.[21, 26] This measure indicates the degree of dependence on staff assistance in seven areas of ADL function (bed mobility, transfer, locomotion, dressing, eating, toilet use, personal hygiene), which are summed to create a validated score that ranges from 0 (no assistance required) to 28 (total dependence in ADL functioning).[21] Increases in this score over time have been validated as an important marker of functional decline, and a 3-point increase corresponds to a major loss of independence in one ADL or incremental losses in two or more ADLs.[19, 26]

### Follow-up

We excluded individuals who died or were hospitalized within 14 days of hospital discharge because reliable ascertainment of secondary prevention medication use is difficult in such short-stay situations. Follow-up therefore started on day 14 (index date) after hospital discharge and continued for 90 days.[19] For the rehospitalization outcome, at the end of the 90-day follow-up, participants were classified as alive without rehospitalization, having had a rehospitalization, or having died without a rehospitalization. For the functional decline outcome, at the end of the 90-day follow-up, participants were classified as alive without functional decline, having had functional decline documented on an MDS assessment in that period, or having died without evidence of functional decline on the MDS. For the death outcome, individuals were simply categorized as alive or dead at 90 days.

### Baseline Characteristics

Variables that could potentially confound the relationship between the number of secondary prevention medications prescribed and outcomes were prespecified and all measured prior to the index date. A complete list of these 89 characteristics and details about their measurement are provided in Supplementary Table S2.

### Statistical Analyses

We adjusted for confounding by baseline covariates using methods that rely on estimating the propensity score (i.e., the joint probabilities of receiving 2 medications versus 1 and 3 or 4 medications versus 1, conditioned on covariates). We estimated the propensity score via a multinomial logistic regression model that used the aforementioned 89 baseline variables (Supplementary Table S2) to predict the number of secondary prevention medications used. The propensity scores were used to construct stabilized inverse probability of treatment weights (IPTW), which resulted in good covariate balance across treatment groups based on standardized mean differences (Supplementary Table S3).

We used IPT-weighted *binomial* logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) comparing more versus less secondary prevention medication use for the outcome of death. We used IPT-weighted *multinomial* logistic regression models for the rehospitalization and functional decline outcomes in order to account for the competing risk of death.[27] In all outcome models, use of 1 medication was the reference exposure level.

We conducted several stability analyses (e.g., IPTW truncation; exclusion of antiplatelet users from treatment definition) to test the robustness of our treatment effect estimates to analytic decisions (Supplemental Material). In one stability analysis, we excluded users of antiplatelet agents because aspirin is a recommended antiplatelet agent (in addition to clopidogrel, or more rarely, as an alternative), but is available without a prescription and thus underascertained in Medicare claims, which could result in biased estimates.

We considered $P < .05$ to be statistically significant.

### Subgroup Analyses

In separate analyses to evaluate whether the association between prescribing more versus less secondary prevention medications and outcomes varied across participant characteristics (i.e., effect measure modification[28]), we included interaction terms between the exposure and characteristic (i.e., multiplied the two independent variables). These baseline characteristics included levels of age (≤85 versus >85)[29], cognitive function (moderate to severe impairment versus no to mild impairment), and functional status (moderate to severe impairment versus no to mild impairment). We also examined sex and race/ethnicity, though these subgroup characteristics were of secondary interest. The IPTW were re-estimated for subgroup analyses to ensure covariate balance between treatment groups within subgroups, which was examined using standardized mean differences.

### Software

Data were analyzed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC) and Stata, version 14.0 (Stata Corp., College Station, TX), software.

### Ethics Approval

The institutional review boards of Brown University; the University of California San Francisco; and the San Francisco VA Health Care System approved the study protocol.

## RESULTS

### Study Cohort

Our study cohort included 4,787 NH residents, of which 1,825 (38.1%) received 1 medication, 1,572 (32.8%) received 2 medications, and 1,390 (29%) received 3 or 4 medications post-AMI (Supplementary Figure S1). The different combinations of medication classes are shown in Supplementary Table S4. The mean (SD) age of the study cohort was 84 (8) years and the majority were female (n=3,269; 68%) and white race (n=4,014; 84%). Approximately 50% of the cohort had moderate to severe cognitive impairment (n=2,373) and 74% of the cohort required extensive or greater assistance with their ADLs (n=3,542). On average, residents were actively taking 11 medications (SD=5). Hypertension (n=2,706; 56.5%) and heart failure (n=2,437; 50.9%) were the most common chronic conditions. The median pre-AMI length of NH stay was 352 days (interquartile range [IQR] 81–1,081).

The prevalence of baseline characteristics by treatment group are shown in Table 1 and accompanying standardized differences in Supplementary Table S3. Age differed markedly across treatment groups before IPT weighting, with older NH residents being less likely to receive more secondary prevention medications. Residents receiving fewer secondary prevention medications were also less likely to have hyperlipidemia, diabetes, or hypertension, but were more likely to have atrial fibrillation. Notably, residents receiving more medications had a better functional status, less severe cognitive impairment, and shorter pre-AMI lengths of NH stay.

During follow-up, 509 of 4,787 participants died (10.6%); 820 (17.1%) experienced a functional decline event; and 1,226 (25.6%) were rehospitalized.

### Outcomes of Secondary Prevention Medication Use

Prescribing 3 or 4 medications was associated with a significant decrease in mortality compared to patients who received 1 medication post-AMI (OR 0.74, 95% CI 0.57–0.97), but no significant difference in functional decline (OR 1.12, 95% CI 0.89–1.40) or all-cause rehospitalization (OR 0.97, 95% CI 0.80–1.17)(Table 2). Prescribing 2 medications instead of 1 was not associated with significant decrease in mortality (OR 0.98, 95% CI 0.79–1.22), functional decline (OR 1.04, 95% CI 0.85–1.28), or rehospitalization (OR 1.00, 95% CI 0.85–1.19).

### Treatment Effects in Subgroups

In a subgroup analyses stratifying patients by age greater than 85 or less than or equal to 85 years, no notable differences were observed for the associations between more versus less secondary prevention medications and mortality, rehospitalization, or functional decline outcomes (Supplementary Table S5). No significant differences were observed for any outcome between treatment groups when patients were stratified on their cognitive performance (Table 3) or functional status (Table 4) at baseline. No sex- or race/ethnicity-based differences were observed (data not shown).

### Stability Analyses

Weight truncation did not meaningfully alter the results (Supplementary Table S6). Additional adjustment for covariates in the IPTW outcome models also did not alter the results (Supplementary Table S7). Results from analyses excluding antiplatelet drugs from the exposure definition were generally consistent with the main results, but more medication use was significantly associated with functional decline (OR 1.27, 95% CI 1.07–1.53 for 2 medications; OR 1.30, 95% CI 1.03–1.63 for 3 medications)(Supplementary Table S8).

## DISCUSSION

In this national retrospective cohort study, we found that use of more guideline-recommended secondary prevention medications post-AMI was associated with a decrease in mortality in older, predominantly frail residing in NHs. Residents receiving 3 or 4 secondary prevention medications had a 26% lower risk of mortality compared to residents receiving 1 medication. Use of more guideline-recommended medications did not appear to influence the risk of rehospitalization. The main and stability analysis results for functional decline were discordant and suggested that more medication might be associated with an increased risk of functional decline. The associations between secondary prevention medication use and outcomes did not markedly vary across subgroups defined by age, cognitive status, or functional status. Prior studies have demonstrated that less prescribing of secondary prevention medications is common among older NH residents and may be attributable to the absence of data demonstrating the benefits of using more guideline-recommended medications after AMI in NH residents.[16] Our findings suggest that

prescribing more guideline-recommended medications is indicated for frail, older adults who wish to maximize longevity after AMI.[19, 30]

Although data on the use of more versus fewer secondary prevention medications in frail, older adults is lacking, our study is consistent with two studies using older data to examine the associations between secondary prevention medications and mortality in older community-dwelling adults.[10, 31] The non-U.S. populations in these studies are younger and much less frail than our population of NH residents. However, they offer the most comparable published data to our own, highlighting the severe lack of information on the effects of using more secondary prevention medications among frail, older adults. The first study demonstrated that individuals receiving all 4 medication classes, or 3 if a fourth class was contraindicated, had significantly lower one-year mortality compared with participants receiving 0 or 1 medications at discharge (adjusted OR 0.54, 95% CI 0.36–0.81).[10] The second study suggested that the use of all four guideline concordant medications is associated with decreased mortality compared to 0 medications (HR=0.40, 95% CI 0.21–0.95).[31] Little is also known about the effects of individual cardiovascular medication classes in highly vulnerable older adults, but our findings are generally consistent with another study that found new use of beta-blockers versus non-use after AMI was associated with a mortality benefit (HR=0.74, 95% CI 0.67–0.83) among older NH residents.[19]

Our study contributes to the literature on more versus less secondary prevention medication use by studying a much frailer and older population than has been previously examined. It does so with more recent data, a larger and nationally representative U.S. sample, a richer set of covariates, and functional and rehospitalization outcomes for which data was not previously available. Additionally, to provide data that helps providers to tailor treatment decision-making to individual patients, we performed subgroup analyses by patient-specific factors that are associated with life expectancy, including age, cognition, and functional status at baseline. Ultimately, we found that the association between more secondary prevention medication use and outcomes did not markedly vary across subgroups defined by age, cognition, or functional status at baseline. In our study, individuals who were older, cognitively impaired, and functionally dependent were all still likely to derive a mortality benefit from being prescribed more secondary prevention medications after AMI, which agrees with prior literature on beta-blockers in the same population of older NH residents.[19] These results support the conclusion that the average time to mortality benefit (TTB) associated with prescribing more medications may be shorter than the average life expectancy of many NH residents after AMI.[32, 33] In turn, the results support prescribing more secondary prevention medications post-AMI for older, predominantly frail adults who wish to maximize their longevity. However, for older adults who do not wish to maximize longevity, our results also highlight an opportunity to reduce polypharmacy through deprescribing—the process of tapering or stopping medications under medical supervision.[11]

Despite the possibility that using more medications provides a mortality benefit, it is important to weigh the potential risks, several of which are unexaminable in our data. Use of more secondary prevention medications increases polypharmacy for older adults while increasing the complexity of medication management for caregivers, including NH staff.

Taking more medications may also increase the risk of drug-drug interactions and adverse drug events. For example, use of more guideline-recommended medications after an acute coronary syndrome was associated with greater risk of falls among women who were frail, but not among those who were robust.[9] While the TTB of taking more secondary preventions may be weeks to months, the risk of drug-drug interactions and adverse events may increase in just hours to days. This is especially true among NH residents due to the altered pharmacokinetics and pharmacodynamics that arise with advanced age and frailty.[34, 35] Potential and empirically unverified risks of using more medications should not be an absolute barrier to prescribing in frail, older adults. Rather, the potential risks should be considered in the harm-benefit calculus before prescribing, monitored for, and appropriately managed if they arise (e.g., through deprescribing or dose reduction).[36]

The findings of our study must be interpreted in light of several limitations. First, because our study was observational, we cannot rule out the possibility of residual confounding. One plausible mechanism for confounding is that individuals with a more severe AMI are likely to receive a greater number of secondary prevention medications because of the stronger perceived indication for aggressive management. Another plausible mechanism is that individuals who were frailer, had a worse prognosis, or were generally sicker were less likely to receive more secondary prevention medications because providers perceived extensive treatment as futile. However, several factors support the robustness of our findings. The two proposed overarching mechanisms of confounding would bias results in opposite directions and thus cancel, at least in part. We also obtained good balance on almost 90 measured baseline covariates across treatment groups after IPTW. Furthermore, in prior work, we conducted a companion validation study using national data from the Department of Veterans Affairs, which contains information on vital signs, laboratory test results, and measures of cardiac function that was missing from our linked Medicare and MDS data.[19] That work suggested that these variables would not substantially alter the observed results.

A second limitation is that the inclusion of RAAS inhibitors may have increased residual confounding because they are indicated after AMI primarily for patients with heart failure, left ventricular systolic dysfunction, hypertension, and diabetes.[3, 37] Although we adjusted for most of those variables in our propensity score estimation models, residual bias due to missing ejection fraction information is still a concern. Similarly, we were unable to accurately differentiate ST-elevation MI (STEMI) from non-ST-elevation MI (NSTEMI), which may have influenced the prescribing of more versus fewer secondary prevention medications.

Third, due to the nature of our data, we were unable to conduct analyses of medication dose (e.g., statin intensity), to examine some other outcomes that were of interest (e.g., cognition), to assess etiologically relevant follow-up periods beyond 90 days, to include aspirin use in the exposure definition, or to examine the effect of different combinations of medication classes. Future studies should aim to address those important questions. Finally, sample sizes for many subgroups were limited in this study and thus a barrier to detecting small or moderate magnitude effects. Our larger (N=10,992) prior study suggested that the effects of beta-blockers on functional decline differed significantly across subgroups.[19]

### Conclusions

In summary, the use of more guideline-recommended medications post-AMI was associated with decreased mortality in older, predominantly frail adults, but no difference in rehospitalization. The mortality benefit was consistently observed across subgroups defined by baseline age, cognition, and functional status. Results for functional decline were discordant and did not rule out an increased risk associated with more medication use. Additional research is necessary to evaluate whether more secondary prevention medication use among frail, older adults truly does result in functional harms and how information on type of infarct may influence the results. While residual confounding remains a concern and plausible alternative explanation for all findings, the results suggest that use of more secondary prevention medications after AMI is indicated for frail, older adults who wish to maximize their longevity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

The authors would like to thank HCR ManorCare, Inc., for generously providing data used in the study. Drs. Zullo, Shah, Rudolph, Wu, and Steinman are U.S. Government employees; the views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

Sources of Funding

Drs. Zullo and Shah are supported by an Agency for Healthcare Research and Quality award (5K12HS022998). Dr. Zullo is also supported by a Veterans Affairs Office of Academic Affiliations Advanced Fellowship in Health Services Research and Development. Financial support for this study was also provided by the National Heart, Lung, and Blood Institute (5R01HL111032) and National Institute on Aging (K24AG049057).

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**What is Known**

- Four classes of medication are recommended for the secondary prevention of acute myocardial infarction and have a mortality benefit in non-frail, older adults: antiplatelets, β-blockers, statins, and renin-angiotensin-aldosterone system (RAAS) inhibitors.
- Secondary prevention medications are often not prescribed to frail, older adults, especially those residing in nursing homes long-term. Prescribing fewer medications is due in part to perceived lack of benefit, concern over potential harms, and lack of supporting data.

**What this Study Adds**

- Prescribing 3 or 4 secondary prevention medications to predominantly frail, older adults was associated with a 24% relative decrease in mortality compared to individuals who received 1 medication after acute myocardial infarction, but no notable difference in all-cause rehospitalization, and effects did not differ by age, sex, race/ethnicity, cognition, or functional status.
- Use of more secondary prevention medications was associated with a 30% relative increase in functional decline after excluding antiplatelet drugs from the exposure definition, but not when considering all medications.

**Table 1.**

Characteristics of users of 1, 2, and 3 or 4 secondary prevention medications.

| | No. (%) | | |
|---|---|---|---|
| **Characteristics** | **1 (n=1825)** | **2 (n=1572)** | **3 or 4 (n=1390)** |
| Age, mean (SD), years | 84.7 (8.3) | 83.4 (8.1) | 81.9 (8.0) |
| Female sex | 1271 (69.6) | 1100 (70.0) | 898 (64.6) |
| Race | | | |
| White | 1545 (84.7) | 1327 (84.4) | 1142 (82.2) |
| African American | 197 (10.8) | 170 (10.8) | 172 (12.4) |
| Other | 83 (4.5) | 75 (4.8) | 76 (5.4) |
| Body Mass Index, mean (SD), $kg/m^2$ | 25.3 (6.5) | 26.0 (6.6) | 26.3 (6.1) |
| Chronic Conditions | | | |
| Hyperlipidemia | 173 (9.5) | 241 (15.3) | 347 (25.0) |
| Diabetes | 399 (21.9) | 394 (25.1) | 439 (31.6) |
| Hypertension | 945 (51.8) | 876 (55.7) | 885 (63.7) |
| Heart Failure | 866 (47.5) | 853 (54.3) | 718 (51.7) |
| Atrial fibrillation | 510 (28.0) | 435 (27.7) | 296 (21.3) |
| Peripheral vascular disease | 124 (6.8) | 117 (7.4) | 130 (9.4) |
| Depression | 217 (11.9) | 196 (12.5) | 187 (13.5) |
| COPD | 467 (25.6) | 396 (25.2) | 374 (26.9) |
| Arthritis | 236 (12.9) | 191 (12.2) | 165 (11.9) |
| PVD | 124 (6.8) | 117 (7.4) | 130 (9.4) |
| Elixhauser comorbidity score, median (IQR) | 3.1 (1.3) | 3.2 (1.3) | 3.2 (1.3) |
| ADL scale (28-point) before hospitalization, mean (SD) | 16.7 (7.3) | 15.9 (7.2) | 15.5 (7.2) |
| ADL status (categorical) before hospitalization * | | | |
| Independent to limited assistance required | 600 (32.9) | 569 (36.2) | 522 (37.6) |
| Extensive assistance required | 538 (29.5) | 497 (31.6) | 478 (34.4) |
| Extensive dependency | 687 (37.6) | 506 (32.2) | 390 (29.0) |
| Cognitive status before hospitalization | | | |
| Intact or borderline intact | 518 (28.4) | 485 (30.9) | 480 (34.5) |
| Mild to moderate dementia | 935 (51.2) | 799 (50.8) | 720 (51.8) |

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| | No. (%) | | |
|---|---|---|---|
| **Characteristics** | **1 (n=1825)** | **2 (n=1572)** | **3 or 4 (n=1390)** |
| Moderately severe to very severe dementia | 372 (20.4) | 288 (18.3) | 190 (13.7) |
| CHESS score before hospitalization, mean (SD) † | 0.6 (0.8) | 0.7 (0.8) | 0.6 (0.8) |
| Geriatric symptoms before hospitalization | | | |
| Falls | 392 (21.5) | 284 (18.1) | 237 (17.1) |
| Dyspnea | 141 (7.7) | 117 (7.4) | 100 (7.2) |
| Number of medications before hospitalization, median (IQR) | 10 (7–14) | 11 (8–14) | 11 (8–14) |
| Medication use before hospitalization | | | |
| Warfarin | 180 (9.9) | 102 (6.5) | 78 (5.6) |
| Calcium channel blocker | 224 (12.3) | 173 (11.0) | 157 (11.3) |
| Thiazide diuretic | 82 (4.5) | 62 (3.9) | 50 (3.6) |
| Loop diuretic | 559 (30.6) | 385 (24.5) | 264 (19.0) |
| Nitrate | 230 (12.6) | 161 (10.2) | 119 (8.6) |
| Length of nursing home stay before hospitalization, median (IQR), d | 453 (104–1,160) | 344 (80–1,092) | 249 (70–930) |
| Length of hospital stay for AMI, median (IQR), d | 7 (5–10) | 6 (4–10) | 6 (4–9) |
| No. of days in ICU or CCU | | | |
| None | 783 (42.9) | 642 (40.8) | 473 (34.0) |
| 1–2 | 467 (25.6) | 390 (24.8) | 426 (30.7) |
| ≥3 | 575 (31.5) | 540 (34.4) | 491 (35.3) |
| Nursing home care pathway after hospitalization | | | |
| Skilled nursing facility benefit | 1,360 (74.5) | 1,226 (78.0) | 1,088 (78.3) |
| Long-term care | 465 (25.5) | 346 (22.0) | 302 (21.7) |

Abbreviations: SD, standard deviation; IQR, interquartile range; COPD; chronic obstructive pulmonary disease; CHESS, Changes in Health, End-stage Disease, Signs, and Symptoms; PVD, peripheral vascular disease; ADL, activities of daily living; AMI, acute myocardial infarction; ICU, intensive care unit; CCU, coronary care unit.

*Measured by the Morris 28-point scale of independence in ADLs, and categorized as 0 to 14 (independent to limited assistance required), 15 to 19 (extensive assistance required), and 20 or higher (extensive dependency).

†Scores ranging from 0 to 5, with higher scores indicating greater health instability.

**Table 2.**

Effect of the number of medication classes on outcomes among nursing home residents after myocardial infarction.

| Outcome | No. of Medications | Events / n | Risk (%) | Crude OR (95% CI) | IPTW OR (95% CI) |
|---|---|---|---|---|---|
| Mortality | 1 | 228 / 1825 | 12.5 | Reference | Reference |
| | 2 | 178 / 1572 | 11.3 | 0.89 (0.73–1.10) | 0.98 (0.79–1.22) |
| | 3 or 4 | 103 / 1390 | 7.4 | 0.56 (0.44–0.72) | 0.74 (0.57–0.97) |
| Rehospitalization | 1 | 450 / 1825 | 24.7 | Reference | Reference |
| | 2 | 414 / 1572 | 26.3 | 1.06 (0.91–1.24) | 1.00 (0.85–1.19) |
| | 3 or 4 | 362 / 1390 | 26.0 | 1.00 (0.85–1.18) | 0.97 (0.80–1.17) |
| Functional Decline | 1 | 259 / 1825 | 14.2 | Reference | Reference |
| | 2 | 274 / 1572 | 17.4 | 1.26 (1.05–1.52) | 1.04 (0.85–1.28) |
| | 3 or 4 | 287 / 1390 | 20.7 | 1.48 (1.23–1.79) | 1.12 (0.89–1.40) |

Abbreviations: OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment-weighted.

*Circ Cardiovasc Qual Outcomes*. Author manuscript; available in PMC 2020 April 01.

**Table 3.**

Effect of the number of medication classes on outcomes among nursing home residents after myocardial infarction stratified by cognitive impairment

| Outcome | Cognitive Performance Categories* | No. of Medications | Events / n | Risk (%) | Crude OR (95% CI) | IPTW OR (95% CI) | P for Effect Modification† |
|---|---|---|---|---|---|---|---|
| Mortality | No to Mild Impairment | 1 | 103 / 844 | 12.2 | Reference | Reference | 0.24 |
| | | 2 | 73 / 790 | 9.2 | 0.73 (0.53–1.01) | 0.83 (0.59–1.15) | |
| | | 3 or 4 | 45 / 780 | 5.8 | 0.44 (0.31–0.64) | 0.60 (0.40–0.90) | |
| | Moderate to Severe Impairment | 1 | 125 / 981 | 12.7 | Reference | Reference | |
| | | 2 | 105 / 782 | 13.4 | 1.06 (0.80–1.40) | 1.13 (0.85–1.51) | |
| | | 3 or 4 | 58 / 610 | 9.5 | 0.72 (0.52–1.00) | 0.88 (0.62–1.26) | |
| Rehospitalization | No to Mild Impairment | 1 | 239 / 844 | 28.3 | Reference | Reference | 0.57 |
| | | 2 | 231 / 790 | 29.2 | 1.00 (0.81–1.25) | 0.96 (0.76–1.21) | |
| | | 3 or 4 | 230 / 780 | 29.5 | 0.98 (0.79–1.22) | 0.96 (0.75–1.25) | |
| | Moderate to Severe Impairment | 1 | 210 / 981 | 21.4 | Reference | Reference | |
| | | 2 | 182 / 782 | 23.3 | 1.10 (0.87–1.38) | 1.06 (0.84–1.35) | |
| | | 3 or 4 | 131 / 610 | 21.5 | 0.95 (0.74–1.22) | 0.97 (0.72–1.31) | |
| Functional Decline | No to Mild Impairment | 1 | 150 / 844 | 17.8 | Reference | Reference | 0.49 |
| | | 2 | 170 / 790 | 21.5 | 1.22 (0.95–1.57) | 0.97 (0.73–1.27) | |
| | | 3 or 4 | 194 / 780 | 24.9 | 1.42 (1.12–1.81) | 1.09 (0.81–1.46) | |
| | Moderate to Severe Impairment | 1 | 109 / 981 | 11.1 | Reference | Reference | |
| | | 2 | 104 /782 | 13.3 | 1.24 (0.93–1.66) | 1.17 (0.86–1.60) | |
| | | 3 or 4 | 93 / 610 | 15.3 | 1.38 (1.02–1.87) | 1.18 (0.84–1.66) | |

Abbreviations: OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment-weighted.

*Measured by the Cognitive Performance Scale and dichotomized as 0 to 2 (intact cognition to mild impairment) and >3 (moderate to severe impairment)

†Presented for the IPTW estimates only.

**Table 4.**

Effect of the number of medication classes on outcomes among nursing home residents after myocardial infarction stratified by functional impairment

| Outcome | Functional Impairment Categories | No. of Medications | Events / n | Risk (%) | Crude OR (95% CI) | IPTW OR (95% CI) | P for Effect Modification * |
|---|---|---|---|---|---|---|---|
| Mortality | No to Mild Impairment | 1 | 67 / 600 | 11.2 | Reference | Reference | 0.79 |
| | | 2 | 51 / 569 | 9.0 | 0.78 (0.53–1.15) | 0.92 (0.62–1.37) | |
| | | 3 or 4 | 32 / 522 | 6.1 | 0.52 (0.34–0.81) | 0.80 (0.49–1.29) | |
| | Moderate to Severe Impairment | 1 | 161 / 1,225 | 13.1 | Reference | Reference | |
| | | 2 | 127 / 1,003 | 12.7 | 0.96 (0.75–1.23) | 1.02 (0.78–1.33) | |
| | | 3 or 4 | 71 / 868 | 8.2 | 0.59 (0.44–0.79) | 0.72 (0.52–0.99) | |
| Rehospitalization | No to Mild Impairment | 1 | 134 / 600 | 22.3 | Reference | Reference | 0.65 |
| | | 2 | 140 / 569 | 24.6 | 1.11 (0.84–1.46) | 1.11 (0.83–1.49) | |
| | | 3 or 4 | 128 / 522 | 24.5 | 1.07 (0.81–1.41) | 1.13 (0.83–1.55) | |
| | Moderate to Severe Impairment | 1 | 315 / 1,225 | 25.7 | Reference | Reference | |
| | | 2 | 273 / 1,003 | 27.2 | 1.05 (0.87–1.27) | 0.95 (0.78–1.17) | |
| | | 3 or 4 | 233 / 868 | 26.8 | 0.98 (0.80–1.20) | 0.89 (0.70–1.14) | |
| Functional Decline | No to Mild Impairment | 1 | 46 / 600 | 7.7 | Reference | Reference | 0.44 |
| | | 2 | 71 / 569 | 12.5 | 1.67 (1.13–2.48) | 1.47 (0.96–2.28) | |
| | | 3 or 4 | 68 / 522 | 13.0 | 1.70 (1.14–2.53) | 1.45 (0.92–2.29) | |
| | Moderate to Severe Impairment | 1 | 213 / 1,225 | 17.4 | Reference | Reference | |
| | | 2 | 203 / 1,003 | 20.2 | 1.20 (0.97–1.50) | 0.95 (0.74–1.20) | |
| | | 3 or 4 | 219 / 868 | 25.2 | 1.52 (1.22–1.88) | 1.02 (0.79–1.32) | |

Abbreviations: OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment-weighted.

* Presented for the IPTW estimates only.