Comparative Effectiveness of Generic Atorvastatin and Lipitor® in Patients Hospitalized with an Acute Coronary Syndrome

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Background—Although generic medications are approved based on bioequivalence with brand-name medications, there remains substantial concern regarding their clinical effectiveness and safety. Lipitor®, available as generic atorvastatin, is one of the most commonly prescribed statins. Therefore, we compared the effectiveness of generic atorvastatin products and Lipitor®.

Methods and Results—We conducted a population-based cohort study, using propensity score matching to minimize potential confounding of patients ≥65 years, discharged alive after acute coronary syndrome (ACS) hospitalization between 2008 and 2012 in Ontario, Canada, who were prescribed Lipitor® or generic atorvastatin within 7 days of discharge. The primary outcome was 1-year death/recurrent ACS hospitalization. Secondary outcomes included hospitalization for heart failure, stroke, new-onset diabetes, rhabdomyolysis, and renal failure. In the 7863 propensity-matched pairs (15 726 patients), mean age was 76.9 years, 56.3% were male, 87.6% had myocardial infarction, and all patients had complete follow-up. At 1 year, 17.7% of those prescribed generic atorvastatin and 17.7% of those prescribed Lipitor® experienced death or recurrent ACS (hazard ratio, 1.00; 95% CI, 0.93–1.08; P=0.94). No significant differences in rates of secondary outcomes between groups were observed. Prespecified subgroup analyses by age, sex, diabetes, atorvastatin dose, or admission diagnosis found no outcome difference between groups.

Conclusions—Among older adults discharged alive after ACS hospitalization, we found no significant difference in cardiovascular outcomes or serious, infrequent side effects in patients prescribed generic atorvastatin compared with those prescribed Lipitor® at 1 year. Our findings support the use of generic atorvastatin in ACS, which could lead to substantial cost saving for patients and health care plans without diminishing population clinical effectiveness. (J Am Heart Assoc. 2016;5:e003350 doi: 10.1161/JAHA.116.003350)

Key Words: acute coronary syndrome • comparative effectiveness • statin

Atorvastatin is a top-selling medication, with over 80 million prescriptions dispensed in the United States in 2014. In Canada, over 17 million prescriptions were filled for atorvastatin in 2012, totaling nearly $0.5 billion in sales.1,2 Generic atorvastatin was approved in Canada in June 2010, providing health care plans with an opportunity to save millions in medication costs.3 Once available in generic form in Canada, Ontario’s public prescription benefit program mandated universal substitution of any of the available generic atorvastatin products for all Lipitor® prescriptions. After this mandatory generic policy was implemented, Ontario’s public formulary atorvastatin costs dropped 74%, reducing atorvastatin expenditures from $316 million in 2009–2010 to $83 million in 2012–2013.4
Whereas most clinicians and patients welcome decreased generic drug costs, it is essential that safety and effectiveness is not compromised. Although generic drugs have identical active ingredients as brand-name drugs, they are not exact replicas because their inactive ingredients (excipients) differ. Health Canada, like the US Food and Drug Administration (FDA), requires bioequivalence studies for generic drug approval. Bioequivalence studies typically enroll a small number of healthy volunteers (minimum, 12) who are usually given one dose of brand-name and generic drug, and focus on drug absorption, only needing to show that a similar amount of the generic drug was absorbed at a similar rate as the brand-name drug. Statin efficacy was originally demonstrated with brand-name statins versus placebo in large, secondary prevention trials with thousands of patients, reducing major coronary events by 27% to 44%, mortality by 13% to 30%, and coronary death by 18% to 42% in those with heart disease. Given that generic medications are approved on the basis of bioequivalence with brand-name medications in healthy volunteers, rather than the target population with or at risk of cardiovascular disease, there remains a substantial uncertainty regarding their clinical effectiveness and safety, as well as the mandatory substitution policies that ensue following their approval. The few studies that have directly compared brand and generic atorvastatin in patients have evaluated lipid values rather than clinical outcomes. It is crucial to be able to provide strong clinical outcomes evidence regarding generic products in order to address concerns about their effectiveness and safety. The Ontario policy change affords a unique opportunity to compare clinical outcomes between generic atorvastatin preparations and Lipitor® in those with acute coronary syndromes (ACS), a population at the highest risk for adverse cardiac outcomes, at a time when Lipitor® was the most commonly prescribed statin, and during a period without other major competing health policy changes.

Methods

Design and Data Sources

We conducted a population-based observational study, creating a propensity-score–matched cohort by linking administrative health care databases for hospitalizations, prescription claims, and vital status using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (Toronto, Ontario, Canada). Data on diagnosis were from the Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database, outpatient medications dispensed were from the Ontario Drug Benefit prescription claims database, procedures were from the Ontario Health Insurance Plan and CIHI databases, vital status was from the Ontario Registered Persons Database, and neighborhood income was from Statistics Canada census data.

Study Population

Our cohort was comprised of patients 65 years and older, discharged alive and surviving at least 7 days after an ACS hospitalization between June 1, 2008 and June 30, 2012 in Ontario, Canada. ACS diagnosis was identified using International Classification of Disease, 10th Revision (ICD-10) codes I20, I21, I22, I24.0, I24.8, and I24.9. We excluded patients age >105 years, those with an invalid Ontario health card, with an index ACS coded as an in-hospital complication, or those hospitalized with ACS within the year preceding the index ACS. Patients who had multiple ACS admissions in the study period were identified based on their first ACS hospitalization. We categorized patients into 2 exposure groups based on receipt of a prescription of either generic atorvastatin or Lipitor® within 7 days of index discharge. From June 1, 2008 to June 30, 2012, eligible patients were included in the brand drug group, and after the mandatory generic automatic substitution policy change in June 2010, those eligible patients between June 1, 2010 and June 30, 2012 were included in the generic drug group (Figure 1 shows patient accrual). There were 9 generic atorvastatin products dispensed during our study (Apo-Atorvastatin, Co-Atorvastatin, Gd-Atorvastatin, Mylan-Atorvastatin, Novo-Atorvastatin, PMS-Atorvastatin, Ran-Atorvastatin, Ratio-Atorvastatin, and Sandoz-Atorvastatin).

Outcomes

The primary outcome was death or recurrent ACS hospitalization within 1 year. Secondary outcomes included hospitalization for heart failure, stroke, myopathy/rhabdomyolysis, renal insufficiency, and new-onset diabetes. ACS hospitalization and secondary outcomes were from discharge abstract data. Death was from the Ontario Registered Persons Database. Diabetes was ascertained using the Ontario Diabetes Mellitus Database (Table S1). Follow-up for ascertainment of outcomes began 7 days post-ACS discharge. Subjects who did not experience the event of interest were censored at the first occurrence of: switch from brand to generic (or vice versa) or after 1 year postindex date.

Statistical Analysis

To reduce potential confounding between treatment groups, we constructed a propensity-matched cohort as our primary analysis. The propensity score (the probability of receiving generic atorvastatin conditional on relevant baseline

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characteristics) was estimated using a multivariable logistic regression model. Variables in the propensity score model included those listed in Table 1.

To ensure balance between groups on key variables that may be associated with outcomes of interest and perform subgroup analysis, greedy nearest neighbor caliper matching without replacement was used to match each generic atorvastatin patient with a Lipitor®/C226 patient using the logit of the propensity score, and on age (±1 year), sex, diabetes, most responsible diagnosis at index admission (acute myocardial infarction [AMI] or angina), and statin daily dosage category (0–19, 20–39, and ≥40 mg). A caliper width of 0.2 of the SD of the logit of the propensity score in the overall sample was used. Generic atorvastatin patients without a suitable match were excluded from the cohort. To determine the degree of balance between the 2 groups in the matched cohort, we calculated standardized differences between groups for each of the measured baseline covariates, with a standardized difference of <0.1 indicative of good balance between groups for that covariate (Table 1).

In the propensity-score–matched cohort, Kaplan–Meier curves were estimated to compare survival between the treatment groups. Hazard ratios (HRs) and 95% CIs were calculated for the outcomes, including drug side effects, using Cox proportional hazard models with a robust sandwich-type variance estimator to account for the matched nature of the sample. Subgroup analyses, adjusted for covariates in the propensity score, were conducted for age (<75, ≥75 years), sex (male, female), past diabetes, Lipitor®/atorvastatin dose (<40 mg and ≥40 mg), and most responsible diagnosis (AMI or unstable angina). Pairs mismatched on age were excluded from the age subgroup analysis.

As a secondary analysis in the overall (nonpropensity score matched) cohort, we compared the primary outcome between generic atorvastatin preparations. We conducted a sensitivity analysis with the exposure of generic atorvastatin versus Lipitor® as a time-varying covariate, which allowed patients to switch between generic and brand atorvastatin without defining the grouping within 7 days of their ACS. To address concerns about the effect of secular trends in event rates, we reanalyzed our cohort limited to 1 year before and after the policy change. We also estimated mortality for the entire cohort at 7, 14, 30, and 365 days and examined for temporal trends by year. We estimated that with 7800

Figure 1. Distribution of patient accrual from June 2008 to June 2012.
| Characteristics                      | All Patients N=15,726 | Brand N=7,863 | Generic N=7,863 | Standardized Difference |
|--------------------------------------|-----------------------|---------------|-----------------|-------------------------|
| Age*, mean±SD, y                     | 76.87±7.66            | 76.88±7.66    | 76.87±7.67      | 0.00                    |
| Male* (%)                            | 8858 (56.3)           | 4429 (56.3)   | 4429 (56.3)     | 0.00                    |
| Income quintiles* (%)                |                       |               |                 |                         |
| 1 (lowest)                           | 3361 (21.4)           | 1670 (21.2)   | 1691 (21.5)     | 0.01                    |
| 2                                    | 3272 (20.8)           | 1645 (20.9)   | 1627 (20.7)     | 0.01                    |
| 3                                    | 3161 (20.1)           | 1601 (20.4)   | 1560 (19.8)     | 0.01                    |
| 4                                    | 3003 (19.1)           | 1498 (19.1)   | 1505 (19.1)     | 0.00                    |
| 5 (highest)                          | 2929 (18.6)           | 1449 (18.4)   | 1480 (18.8)     | 0.01                    |
| Rural* (%)                           | 2325 (14.8)           | 1151 (14.6)   | 1174 (14.9)     | 0.01                    |
| Most responsible diagnosis* (%)      |                       |               |                 |                         |
| Acute myocardial infarction          | 13,778 (87.6)         | 6889 (87.6)   | 6889 (87.6)     | 0.00                    |
| Angina                               | 1948 (12.4)           | 974 (12.4)    | 974 (12.4)      |                         |
| Most responsible diagnosis STEMI* (%)| 3776 (24.0)           | 1894 (24.1)   | 1882 (23.9)     | 0.00                    |
| Total length of stay, mean±SD, days  | 8.34±11.22            | 8.40±11.06    | 8.29±11.38      | 0.01                    |
| Median (IQR)                         | 5 (3–9)               | 5 (4–10)      | 5 (3–9)         | 0.01                    |
| Cardiovascular comorbidities* (%)    |                       |               |                 |                         |
| Angina                               | 667 (4.2)             | 354 (4.5)     | 313 (4.0)       | 0.03                    |
| Atrial fibrillation/flutter           | 1073 (6.8)            | 544 (6.9)     | 529 (6.7)       | 0.01                    |
| Diabetes                             | 5308 (33.8)           | 2654 (33.8)   | 2654 (33.8)     | 0.00                    |
| Heart failure                        | 2909 (18.5)           | 1461 (18.6)   | 1448 (18.4)     | 0.00                    |
| Hypertension                         | 12,235 (77.8)         | 6107 (77.7)   | 6128 (77.9)     | 0.01                    |
| Dyslipidemia                         | 5686 (36.2)           | 2843 (36.2)   | 2843 (36.2)     | 0.00                    |
| Peripheral vascular disease          | 599 (3.8)             | 308 (3.9)     | 291 (3.7)       | 0.01                    |
| Past myocardial infarction           | 1424 (9.1)            | 730 (9.3)     | 694 (8.8)       | 0.02                    |
| Cerebrovascular disease              | 764 (4.9)             | 374 (4.8)     | 390 (5.0)       | 0.01                    |
| Shock                                | 160 (1.0)             | 82 (1.0)      | 78 (1.0)        | 0.01                    |
| Medical comorbidities* (%)           |                       |               |                 |                         |
| Renal disease                        | 758 (4.8)             | 383 (4.9)     | 375 (4.8)       | 0.00                    |
| Cancer                               | 1294 (8.2)            | 646 (8.2)     | 648 (8.2)       | 0.00                    |
| Chronic obstructive pulmonary disease| 4422 (28.1)           | 2209 (28.1)   | 2213 (28.1)     | 0.00                    |
| Liver disease                        | 61 (0.4)              | 30 (0.4)      | 31 (0.4)        | 0.00                    |
| Peptic ulcer disease                 | 582 (3.7)             | 286 (3.6)     | 296 (3.8)       | 0.01                    |
| Anemia/blood disease                 | 1365 (8.7)            | 689 (8.8)     | 676 (8.6)       | 0.01                    |
| Cardiac invasive procedures* (%)     |                       |               |                 |                         |
| Coronary catheterization             | 1691 (10.8)           | 857 (10.9)    | 834 (10.6)      | 0.01                    |
| PCI                                  | 693 (4.4)             | 359 (4.6)     | 334 (4.2)       | 0.02                    |
| Coronary artery bypass grafting      | 187 (1.2)             | 98 (1.2)      | 89 (1.1)        | 0.01                    |
| Cardiac invasive procedures during hospitalization* (%) | | | | |
| Coronary catheterization             | 10,920 (69.4)         | 5447 (69.3)   | 5473 (69.6)     | 0.01                    |
| PCI                                  | 6921 (44.0)           | 3475 (44.2)   | 3446 (43.8)     | 0.01                    |
| Coronary artery bypass grafting      | 1383 (8.8)            | 685 (8.7)     | 698 (8.9)       | 0.01                    |
patients per group and a Lipitor® event rate of 17.7%, we would have 83% power to detect a 10% relative difference. SAS software (version 9.3; SAS Institute Inc., Cary, NC) was used to conduct statistical analyses. A 2-sided P<0.05 was considered statistically significant. Patient consent is not required for this retrospective study under the privacy rules.

Table 1. Continued

| Characteristics | All Patients | Brand | Generic | Standardized Difference |
|-----------------|-------------|-------|---------|-------------------------|
| **Most responsible physician annual volume of AMI/angina*** |            |       |         |                         |
| Mean±SD         | 34.05±32.05 | 34.20±31.70 | 33.91±32.40 | 0.01 |
| Median (IQR)    | 26 (9–48)   | 26 (9–48) | 26 (9–47) | 0.01 |
| **Most responsible physician type*** (%): |            |       |         |                         |
| Family physician | 3197 (20.3) | 1588 (20.2) | 1609 (20.5) | 0.01 |
| General internist | 5042 (32.1) | 2509 (31.9) | 2533 (32.2) | 0.01 |
| Cardiologist     | 6893 (43.8) | 3473 (44.2) | 3420 (43.5) | 0.01 |
| Other            | 594 (3.8)   | 293 (3.7) | 301 (3.8) | 0.01 |
| **Hospital annual volume of AMI/angina*** |            |       |         |                         |
| Mean±SD         | 464.27±328.43 | 463.60±327.83 | 464.94±329.04 | 0.00 |
| Median (IQR)    | 371 (214–757) | 385 (212–757) | 371 (214–757) | 0.00 |
| **Teaching hospital*** (%) |            |       |         |                         |
| None            | 8990 (57.2)  | 4505 (57.3) | 4485 (57.0) | 0.01 |
| Cath only or cath and PCI (%) | 1648 (10.5) | 805 (10.2) | 843 (10.7) | 0.02 |
| Cath, PCI, and OHS | 5088 (32.4) | 2553 (32.5) | 2535 (32.2) | 0.00 |
| **Medication use within 100 days before admission*** (%) |            |       |         |                         |
| Antiplatelet agents (Plavix)* | 1014 (6.4) | 494 (6.3) | 520 (6.6) | 0.01 |
| Any statin*     | 6293 (40.0) | 3104 (39.5) | 3189 (40.6) | 0.02 |
| Beta-adrenoreceptor antagonist* | 5062 (32.2) | 2538 (32.3) | 2524 (32.1) | 0.00 |
| ACEI/ARB*       | 8012 (50.9) | 3991 (50.8) | 4021 (51.1) | 0.01 |
| Nitrates*       | 1508 (9.6) | 771 (9.8) | 737 (9.4) | 0.01 |
| Calcium-channel blockers* | 4948 (31.5) | 2467 (31.4) | 2481 (31.6) | 0.00 |
| Furosemide*     | 2382 (15.1) | 1189 (15.1) | 1193 (15.2) | 0.00 |
| Spirolactone*   | 397 (2.5) | 199 (2.5) | 198 (2.5) | 0.00 |
| **Medication use within 7 days after discharge*** (%) |            |       |         |                         |
| Antiplatelet agents (Plavix) | 10 227 (65.0) | 5112 (65.0) | 5115 (65.1) | 0.00 |
| Beta-adrenoreceptor antagonist | 12 568 (79.9) | 6269 (79.7) | 6299 (80.1) | 0.01 |
| ACEI/ARB | 12 972 (82.5) | 6491 (82.6) | 6481 (82.4) | 0.00 |
| Nitrates | 3268 (20.8) | 1639 (20.8) | 1629 (20.7) | 0.00 |
| Calcium-channel blockers | 5415 (34.4) | 2682 (34.1) | 2733 (34.8) | 0.01 |
| Furosemide | 4129 (26.3) | 2049 (26.1) | 2080 (26.5) | 0.01 |
| Spirolactone | 698 (4.4) | 340 (4.3) | 358 (4.6) | 0.01 |
| **Dose per day within 7 days after index discharge*** |            |       |         |                         |
| Dose per day (mg), mean±SD | 47.43±24.09 | 47.69±24.15 | 47.16±24.03 | 0.02 |
| Median (IQR) | 40 (30–80) | 40 (30–80) | 40 (30–80) | 0.02 |

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; cath, catheterization; IQR, interquartile range; OHS, open heart surgery; PCI, percutaneous coronary intervention; PS, propensity score; STEMI, ST-elevation myocardial infarction.

*Included in PS model.
Generic Atorvastatin Effectiveness

Results

Study Cohort

Of 52,278 patients who met the eligibility criteria, were >65 years old, and were discharged alive after an ACS, we excluded 30,959 patients who within 7 days postindex discharge did not have a prescription for generic atorvastatin or Lipitor®, had both brand and generic atorvastatin dispensed, or died or were readmitted with ACS (Figure 2). In the final cohort of 21,319 patients, 9,666 patients received generic atorvastatin and 11,653 received Lipitor®. Of 9,666 patients who received generic atorvastatin, 7,863 (81%) were successfully matched to a patient who received Lipitor® using the matching and propensity score variables, creating 7,863 matched pairs in the cohort.

Propensity-Matched Cohort

The mean age of the propensity-score–matched cohort was 76.9 years, 56.3% were male, and 87.6% had a myocardial infarction (MI) as the index ACS diagnosis (Table 1). Common comorbidities included cardiovascular risk factors, such as diabetes (33.8%), hypertension (77.8%), and dyslipidemia (36.2%). Mean Lipitor®/atorvastatin dose was 47.7 mg and 47.2 mg/day, respectively. Mean 1-year medication possession ratio (adherence) was 88.4±23.3 for brand and 88.4±23.0 for generic atorvastatin. The most common generic atorvastatin product used in our study was Apo-atorvastatin (77.2%) followed by Ran-atorvastatin (7.8%), Ratio-atorvastatin (4.6%), Co-atorvastatin (3.8%), and Novo-atorvastatin (3.4%), with the remaining products each <2%. A comparison of the baseline characteristics of the treatment groups in the propensity-score–matched sample showed that the 2 groups were well balanced, with the standardized differences <0.1 (Table 1). Baseline characteristics of the unmatched cohort are presented in Table S2.

Figure 2. Study participant selection. AMI indicates acute myocardial infarction; MI, myocardial infarction.

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**Table 2. Primary and Secondary Outcomes in the Propensity-Matched Cohort**

| Outcomes                                      | Brand          | Generic        | Hazard Ratio (95% CI) | P Value |
|-----------------------------------------------|----------------|----------------|-----------------------|---------|
| 30 days after index discharge, n (%)*         |                |                |                       |         |
| Death                                         | 168 (2.2)      | 153 (1.9)      | 0.91 (0.73–1.12)      | 0.36    |
| Death/hospitalization for MI or angina         | 324 (4.2)      | 292 (3.7)      | 0.89 (0.76–1.04)      | 0.16    |
| Hospitalization for myocardial infarction or angina | 173 (2.2)      | 155 (2.0)      | 0.89 (0.71–1.10)      | 0.29    |
| Hospitalization for heart failure             | 159 (2.2)      | 149 (1.9)      | 0.93 (0.75–1.16)      | 0.53    |
| Hospitalization for ischemic/hemorrhagic stroke/TIA | 14 (0.2)       | 23 (0.3)       | 1.64 (0.84–3.13)      | 0.15    |
| 365 days after index discharge, n (%)*        |                |                |                       |         |
| Death                                         | 788 (11.6)     | 898 (11.6)     | 0.99 (0.90–1.09)      | 0.84    |
| Death/hospitalization for MI or angina         | 1218 (17.7)    | 1376 (17.7)    | 1.00 (0.93–1.08)      | 0.94    |
| Hospitalization for MI or angina              | 573 (8.6)      | 643 (8.6)      | 1.00 (0.89–1.12)      | 0.96    |
| Hospitalization for heart failure             | 436 (6.3)      | 491 (6.6)      | 1.03 (0.91–1.16)      | 0.67    |
| Hospitalization for ischemic/hemorrhagic stroke/TIA | 100 (1.6)      | 139 (1.9)      | 1.20 (0.93–1.56)      | 0.14    |

*Proportions are derived from the Kaplan–Meier curve with censoring at drug switch, end of follow up, or death (for outcomes that did not include death) whichever occurred first. MI indicates myocardial infarction; TIA, transient ischemic attack.

**Primary and Secondary Outcomes**

At 1 year, the rate of death or recurrent ACS hospitalization in the propensity-score–matched sample was 17.7% among those prescribed generic atorvastatin and 17.7% for Lipitor® (HR, 1.00; 95% CI, 0.93–1.08; P=0.94; Table 2; Figure 3). There were also no differences in the 30-day rates of death or recurrent ACS between generic atorvastatin (3.7%) and Lipitor® (4.2%) (HR, 0.89; 95% CI, 0.76–1.04; P=0.16). No significant differences in rates of heart failure or stroke between treatment groups were observed at 30 days or 1 year (Table 2; Figure S1). No differences were found in the primary outcome between the 9 different generic atorvastatin products (Figure 4).

As secondary outcomes, we also examined serious statin adverse events and found low 1-year rates for newly diagnosed diabetes (2.0% vs 1.9%; P=0.37) and rhabdomyolysis (P=0.39) in patients receiving generic atorvastatin and Lipitor®, respectively, with no difference between groups at 30 days or 1 year. Sensitivity analysis using the exposure of generic atorvastatin or Lipitor® as a time-varying covariate in the overall cohort also found similar results for primary and secondary outcomes (Table S3). For example, there was no difference in the primary outcome of death or recurrent ACS (HR, 0.99 [0.93–1.05]; P=0.668). The 1-year sensitivity analysis found consistent results for all outcomes. One-year mortality rates, adjusted for variables in the propensity score, did not show a declining trend over the study period: 11.7% for 2008; 8.9% for 2009; 11.6% for 2010; 12.0% for 2011; and 11.7% for 2012.

**Subgroup Analyses**

Prespecified subgroup analyses by age, sex, diabetes, atorvastatin dose, or admission diagnosis also found consistent results for the primary and secondary outcomes (Tables 3 and 4). For example, whereas absolute event rates were higher in the older age group at 1 year, no difference was found between generic atorvastatin and Lipitor® for the primary outcome of death or recurrent ACS in either the younger age group or the older age group (<75 years: HR, 0.97 [0.83–1.15]; ≥75 years: 1.00 [0.92–1.09]; P=0.90).

**Discussion**

Concerns about the effectiveness and safety of generic medications have led to the reluctance of prescribers and patients to use these medications.11,14,15 Our study, comparing Lipitor® and generic atorvastatin, one of the most common generic medications in use today, found no significant difference in clinical outcomes, with nearly 18% of patients in each group experiencing recurrent ACS or death within 1 year of drug initiation. Given the absence of a difference in major cardiovascular events between brand and generic atorvastatin in our large, population-based study, our study provides objective support that the benefits demonstrated by brand-name Lipitor® in clinical trials may indeed extrapolate to generic atorvastatin in clinical practice, offering patients and clinicians reassurance regarding the effectiveness of generic atorvastatin products as used in routine clinical practice in an ACS population.
Our study capitalized on a natural experiment within a large universal health system that was undergoing a mandatory policy change from Lipitor® to generic atorvastatin. We used this population-wide intervention to compare drug effectiveness in a high-risk ACS population who were prescribed an atorvastatin product within 7 days postdischarge. Lipitor® was automatically substituted to generic atorvastatin, as dictated by policy for the entire population. This policy mandate minimizes the chance of selection bias. Comparability between groups in our large cohort was also strengthened by use of a propensity-matched cohort that was well balanced for baseline prognostic characteristics. Additional strengths include the discrete intervention, patient-important clinical endpoints, and long-term follow-up. We conducted 2 sensitivity analyses, 1 that examined mortality in our cohort over the study period and 1 that restricted our analysis to 1-year pre- and postpolicy change to address potential secular trends in mortality over time and found no difference between groups, further strengthening our findings.

Our findings are important because bioequivalence studies are not designed to test clinical efficacy or effectiveness, given their samples sizes of typically <50 patients, single-dose

**Figure 3.** Cumulative incidence of primary endpoint and death according to study group. Cumulative incidence of the primary endpoint and death in brand and generic groups are displayed in Kaplan–Meier curves, reported as event-free rates as a percentage shown over time in days.
administration, investigation of drug absorption properties rather than clinical outcomes, and use of healthy volunteers.5,8,9,26 Meta-analyses of studies comparing brand-name and generic cardiovascular medications have found no difference between statins for lipid-level endpoints.16 Direct comparison of clinical outcomes with brand and generic statins is limited to 1 study with simvastatin that found no difference in cardiovascular outcomes.16–20,27–29 As such, our study is the first to compare the effectiveness of clinical outcomes between generic atorvastatin and Lipitor.

Quality control in generic manufacturing facilities has recently been questioned as drug recall notices have risen.30,31 Generic drug recalls, continued expansion of, and limited regulatory oversight for, overseas generic drug manufacturing facilities have raised public concern about the perceived safety and effectiveness of generic products. Reassuringly, we found no outcome differences between the 9 generic products, including some of the most common generic atorvastatin products used worldwide, Apo-atorvastatin and Ran-atorvastatin.30–33

A robust generic drug industry, producing effective therapies, coupled with a sufficient number of manufacturers to induce competitive pricing, is essential to support a sustainable health care system.34,35 We previously projected that the introduction of generic atorvastatin in the United States would reduce expenditures by $4.5 billion in 2014, a 77% savings.36 Comparable savings were found for Ontario’s public prescription benefit program, where total atorvastatin costs declined by 74% after the mandatory generic atorvastatin policy was instituted.4

High drug costs are also an essential consideration in selecting drug therapy given that they may pose a barrier to medication adherence.37,38 Gagne recently found that Medicare patients initiating a generic statin (lovastatin, pravastatin, or simvastatin) were more likely to adhere, which may have translated into improved clinical outcomes.39 Our study, demonstrating the effectiveness of generic atorvastatin versus Lipitor®, may reassure patients and clinicians about these generic products, potentially improving medication adherence, and may also support policy makers in their promotion of generic substitution policies.

**Limitations**

Our study has some limitations. We were able to create a well-balanced cohort through the use of propensity score methods. However, some risk factors (eg, smoking, physical activity) were not available. It is unlikely these factors were imbalanced enough in our cohort to impact our results. Because most in the brand group were from 2008 to 2010, and in the generic group from 2010 to 2012, there is possible confounding attributed to a temporal improvement in outcomes. In our propensity-matched cohort, baseline patient characteristics, medications within 7 days of index ACS discharge, and interventional cardiovascular procedures occurring during the ACS hospitalization were well balanced between groups, reducing the likelihood of confounding. In addition, our sensitivity analysis restricted to 1 year pre- and postpolicy change found similar results.

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**Table 1.**

| Manufacturer          | No. of Patients | Hazard Ratio (95% CI) |
|-----------------------|-----------------|----------------------|
| APO-ATORVASTATIN      | 607             | Reference            |
| RAN-ATORVASTATIN      | 612             | 0.50 (0.30-0.81)     |
| RATIO-ATORVASTATIN    | 381             | 0.95 (0.79-1.14)     |
| CO-ATORVASTATIN       | 296             | 1.07 (0.85-1.35)     |
| NOVO-ATORVASTATIN     | 279             | 0.57 (0.47-0.68)     |
| SANDOZ-ATORVASTATIN   | 136             | 0.73 (0.60-0.89)     |
| PMK-ATORVASTATIN      | 87              | 0.90 (0.73-1.10)     |
| MYLAN-ATORVASTATIN    | 22              | 0.90 (0.79-1.02)     |
| GI-AMLODIPINE/ATORVASTATIN | 8           | 1.50 (0.95-2.38)     |

*Adjusted for variables included in the propensity score cohort creation.

**Figure 4.** Adjusted primary outcome compared between generic atorvastatin products.
Furthermore, analysis of mortality rates indicated no significant changes during our study’s 4-year time frame. Our study is limited to an older cohort of patients ≥65 years. Smaller between-group differences are likely in younger patients. Although we found no significant difference in severe side effects, such as rhabdomyolysis and diabetes between the generic atorvastatin and Lipitor groups, we were unable to evaluate common side effects, such as myalgias and gastrointestinal symptoms associated with statins given that they are not captured adequately in Table 3.

| Subgroup | N Pairs | Brand No. of Events (%) | Generic No. of Events (%) | HR (95% CI) Brand vs Generic | P Value for Interaction |
|----------|---------|-------------------------|---------------------------|-----------------------------|------------------------|
| **Death** |         |                         |                           |                             |                        |
| <75 years | N=3233  | 137 (5.0)               | 140 (4.4)                 | 0.88 (0.70–1.12)            | 0.36                   |
| ≥75 years | N=4529  | 640 (16.4)              | 748 (16.7)                | 1.01 (0.91–1.12)            |                        |
| **Death/hospitalization for MI or angina** | |                          |                           |                             |                        |
| <75 years | N=3233  | 284 (10.1)              | 315 (9.9)                 | 0.97 (0.83–1.15)            | 0.90                   |
| ≥75 years | N=4529  | 917 (23.2)              | 1041 (23.2)               | 1.00 (0.92–1.09)            |                        |
| **Sex** |         |                         |                           |                             |                        |
| **Death** |         |                         |                           |                             |                        |
| Female N=3434 | 408 (13.7) | 454 (13.4) | 0.97 (0.85–1.10) | 0.61 |
| Male N=4429 | 380 (9.9) | 444 (10.2) | 1.02 (0.89–1.16) |               |
| **Death/hospitalization for MI or angina** | |                          |                           |                             |                        |
| Female N=3434 | 601 (20.0) | 666 (19.6) | 0.98 (0.88–1.09) | 0.63 |
| Male N=4429 | 617 (15.9) | 710 (16.2) | 1.02 (0.92–1.12) |               |
| **Past diabetes** | |                          |                           |                             |                        |
| **Death** |         |                         |                           |                             |                        |
| Diabetic N=2654 | 354 (15.6) | 431 (16.5) | 1.05 (0.92–1.20) | 0.21 |
| Nondiabetic N=5209 | 434 (9.6) | 467 (9.1) | 0.93 (0.83–1.06) |               |
| **Death/hospitalization for MI or angina** | |                          |                           |                             |                        |
| Diabetic N=2654 | 534 (23.3) | 651 (24.8) | 1.08 (0.96–1.19) | 0.07 |
| Nondiabetic N=5209 | 684 (14.9) | 725 (14.1) | 0.93 (0.85–1.03) |               |
| **Dose of brand or generic atorvastatin** | |                          |                           |                             |                        |
| **Death** |         |                         |                           |                             |                        |
| <40 mg N=2113 | 293 (16.2) | 353 (16.9) | 1.04 (0.90–1.20) | 0.37 |
| ≥40 mg N=5750 | 495 (9.9) | 545 (9.6) | 0.96 (0.85–1.08) |               |
| **Death/hospitalization for MI or angina** | |                          |                           |                             |                        |
| <40 mg N=2113 | 404 (22.1) | 494 (23.6) | 1.09 (0.95–1.23) | 0.11 |
| ≥40 mg N=5750 | 814 (16.0) | 882 (15.5) | 0.95 (0.87–1.04) |               |
| **Primary diagnosis** | |                          |                           |                             |                        |
| **Death** |         |                         |                           |                             |                        |
| MI N=6889 | 720 (12.0) | 829 (12.2) | 1.00 (0.91–1.10) | 0.49 |
| Angina N=974 | 68 (8.3) | 69 (7.2) | 0.87 (0.63–1.20) |               |
| **Death/hospitalization for MI or angina** | |                          |                           |                             |                        |
| MI N=6889 | 1090 (18.0) | 1238 (18.2) | 1.00 (0.93–1.09) | 0.77 |
| Angina N=974 | 128 (15.3) | 138 (14.4) | 0.96 (0.76–1.22) |               |

HR indicates hazard ratio; MI, myocardial infarction.
our data sources. We also do not have data on race/ethnicity. Our study did not evaluate the impact of generic versus brand drug copay because the generic copay does not differ in Ontario.

In conclusion, our large, population-based study found that there is no difference in major adverse cardiovascular outcomes at 1 year in older ACS patients prescribed generic atorvastatin products after hospitalization compared with those prescribed Lipitor®. Our findings support the use of generic atorvastatin in ACS, which could lead to substantial cost saving without diminishing population clinical effectiveness.

Table 4. Prespecified Subgroup Analysis of Primary Outcome and Death From Baseline to 30 Days

| Subgroup | N Pairs | Brand | Generic | HR (95% CI) Brand vs Generic | P Value for Interaction |
|----------|---------|-------|---------|-----------------------------|-------------------------|
| Age      |         |       |         |                             |                         |
| Death    |         |       |         |                             |                         |
| <75 years | N=3233  | 137 (5.0%) | 140 (4.4%) | 0.88 (0.70–1.12)            | 0.36                    |
| ≥75 years | N=4529  | 640 (16.4%) | 748 (16.7%) | 1.01 (0.91–1.12)            |                         |
| Death/hospitalization for MI or angina |         |       |         |                             |                         |
| <75 years | N=3233  | 284 (10.1%) | 315 (9.9%) | 0.97 (0.83–1.15)            | 0.90                    |
| ≥75 years | N=4529  | 917 (23.2%) | 1041 (23.2%) | 1.00 (0.92–1.09)            |                         |
| Sex      |         |       |         |                             |                         |
| Death    |         |       |         |                             |                         |
| Female   | N=3434  | 408 (13.7%) | 454 (13.4%) | 0.97 (0.85–1.10)            | 0.61                    |
| Male     | N=4429  | 380 (9.9%) | 444 (10.2%) | 1.02 (0.89–1.16)            |                         |
| Death/hospitalization for MI or angina |         |       |         |                             |                         |
| Female   | N=3434  | 601 (19.9%) | 666 (19.6%) | 0.98 (0.88–1.09)            | 0.63                    |
| Male     | N=4429  | 617 (15.9%) | 710 (16.2%) | 1.02 (0.92–1.12)            |                         |
| Past diabetes | |       |         |                             |                         |
| Death    |         |       |         |                             |                         |
| Diabetic | N=2654  | 354 (15.6%) | 431 (16.5%) | 1.05 (0.92–1.20)            | 0.21                    |
| Nondiabetic | N=5209 | 434 (9.6%) | 467 (9.1%) | 0.93 (0.83–1.06)            |                         |
| Death/hospitalization for MI or angina |         |       |         |                             |                         |
| Diabetic | N=2654  | 534 (23.3%) | 651 (24.8%) | 1.08 (0.96–1.19)            | 0.07                    |
| Nondiabetic | N=5209 | 684 (14.9%) | 725 (14.1%) | 0.93 (0.85–1.03)            |                         |
| Dose of brand or generic atorvastatin |         |       |         |                             |                         |
| Death    |         |       |         |                             |                         |
| <40 mg   | N=2113  | 293 (16.2%) | 353 (16.9%) | 1.04 (0.90–1.20)            | 0.37                    |
| ≥40 mg   | N=5750  | 495 (9.9%) | 545 (9.6%) | 0.96 (0.85–1.08)            |                         |
| Death/hospitalization for MI or angina |         |       |         |                             |                         |
| <40 mg   | N=2113  | 404 (22.1%) | 494 (23.6%) | 1.09 (0.95–1.23)            | 0.11                    |
| ≥40 mg   | N=5750  | 814 (16.0%) | 882 (15.5%) | 0.95 (0.87–1.04)            |                         |
| Primary diagnosis |             |       |         |                             |                         |
| Death    |         |       |         |                             |                         |
| MI       | N=6889  | 720 (12.0%) | 829 (12.2%) | 1.00 (0.91–1.10)            | 0.49                    |
| Angina   | N=974   | 68 (8.3%) | 69 (7.2%) | 0.87 (0.63–1.20)            |                         |
| Death/hospitalization for MI or angina |         |       |         |                             |                         |
| MI       | N=6889  | 1090 (18.0%) | 1238 (18.2%) | 1.00 (0.93–1.09)            | 0.77                    |
| Angina   | N=974   | 128 (15.3%) | 138 (14.4%) | 0.96 (0.76–1.22)            |                         |

HR indicates hazard ratio; MI, myocardial infarction.
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| Outcome                         | ICD-10 Code                                                                 |
|--------------------------------|-----------------------------------------------------------------------------|
| Ischemic stroke/hemorrhagic stroke/TIA | I630 I631 I632 I633 I634 I635 I637 I638 I639 I64 H341 I60 I61 G450 G451 G452 G453 G455 G456 G457 G458 G459 H340 |
| Heart failure                  | I50                                                                         |
| Rhabdomyolysis                 | G210 M628 T796                                                              |
| Diabetes                       | ICES-derived Ontario Diabetes Database definition\textsuperscript{21}       |
| Acute renal insufficiency      | N17 N19 R34                                                                 |
Table S2. Baseline and Treatment Characteristics of the Cohort Prior to Propensity Matching

| Characteristics                                      | All patients | Brand | Generic | P-value |
|------------------------------------------------------|--------------|-------|---------|---------|
|                                                      | N=21,319     | N=11,653 | N=9,666 |         |
| Age, mean ± SD, years                                | 77.13 ± 7.87 | 77.08 ± 7.77 | 77.19 ± 7.99 | 0.323  |
| Male                                                 | 11,884 (55.7%) | 6,457 (55.4%) | 5,427 (56.1%) | 0.282  |
| Income quintiles                                     |              |       |         |         |
| 1 (lowest)                                           | 4,630 (21.7%) | 2,564 (22.0%) | 2,066 (21.4%) | 0.764  |
| 2                                                    | 4,421 (20.7%) | 2,397 (20.6%) | 2,024 (20.9%) |         |
| 3                                                    | 4,253 (19.9%) | 2,302 (19.8%) | 1,951 (20.2%) |         |
| 4                                                    | 4,064 (19.1%) | 2,224 (19.1%) | 1,840 (19.0%) |         |
| 5 (highest)                                          | 3,951 (18.5%) | 2,166 (18.6%) | 1,785 (18.5%) |         |
| Rural                                                | 3,117 (14.6%) | 1,682 (14.4%) | 1,435 (14.8%) | 0.397  |
| Most responsible diagnosis                           |              |       |         |         |
| Acute myocardial infarction                          | 18,012 (84.5%) | 9,763 (83.8%) | 8,249 (85.3%) | 0.002  |
| Angina                                               | 3,307 (15.5%) | 1,890 (16.2%) | 1,417 (14.7%) |         |
| Most responsible diagnosis STEMI                     | 4,838 (22.7%) | 2,532 (21.7%) | 2,306 (23.9%) | <.001  |
| Total length of stay, mean ± SD, days                | 8.27 ± 10.84 | 8.36 ± 10.85 | 8.15 ± 10.83 | 0.151  |
| Median (IQR)                                         | 5 (3-9)      | 5 (4-10)   | 5 (3-9)   | <.001  |
| Cardiovascular comorbidities                         |              |       |         |         |
| Angina                                               | 1,284 (6.0%) | 874 (7.5%) | 410 (4.2%) | <.001  |
| Atrial fibrillation/flutter                          | 1,631 (7.7%) | 958 (8.2%) | 673 (7.0%) | <.001  |
| Diabetes                                             | 7,547 (35.4%) | 4,107 (35.2%) | 3,440 (35.6%) | 0.601  |
| Heart failure                                        | 4,293 (20.1%) | 2,459 (21.1%) | 1,834 (19.0%) | <.001  |
| Hypertension                                         | 16,779 (78.7%) | 9,193 (78.9%) | 7,586 (78.5%) | 0.469  |
| Dyslipidemia                                         | 7,817 (36.7%) | 4,196 (36.0%) | 3,621 (37.5%) | 0.028  |
| Peripheral vascular disease                          | 929 (4.4%)   | 561 (4.8%) | 368 (3.8%) | <.001  |
| Prior myocardial infarction                          | 2,247 (10.5%) | 1,410 (12.1%) | 837 (8.7%) | <.001  |
| Cerebrovascular disease                              | 1,089 (5.1%) | 607 (5.2%) | 482 (5.0%) | 0.463  |
| Shock                                                | 231 (1.1%)   | 120 (1.0%) | 111 (1.1%) | 0.405  |
| Medical comorbidities                                |              |       |         |         |
| Renal disease                                        | 1,194 (5.6%) | 716 (6.1%) | 478 (4.9%) | <.001  |
| Cancer                                               | 1,805 (8.5%) | 1,002 (8.6%) | 803 (8.3%) | 0.447  |
| Chronic obstructive pulmonary disease                 | 6,136 (28.8%) | 3,372 (28.9%) | 2,764 (28.6%) | 0.583  |
| Liver disease                                        | 96 (0.5%)    | 61 (0.5%) | 35 (0.4%) | 0.08   |
| Peptic ulcer disease                                 | 817 (3.8%) | 456 (3.9%) | 361 (3.7%) | 0.499  |
| Anemia/blood disease                                 | 1,996 (9.4%) | 1,128 (9.7%) | 868 (9.0%) | 0.081  |
| Cardiac invasive procedures                          |              |       |         |         |
| Coronary catheterization                             | 2,594 (12.2%) | 1,561 (13.4%) | 1,033 (10.7%) | <.001  |
| Percutaneous coronary intervention                   | 1,085 (5.1%) | 691 (5.9%) | 394 (4.1%) | <.001  |
| Coronary artery bypass grafting                      | 287 (1.3%) | 171 (1.5%) | 116 (1.2%) | 0.092  |
| Cardiac invasive procedures during hospitalization    |              |       |         |         |
### Characteristics

| Characteristics                                      | All patients | Brand N=11,653 | Generic N=9,666 | P-value |
|------------------------------------------------------|--------------|----------------|----------------|---------|
| Coronary catheterization                             | 14,299 (67.1%) | 7,539 (64.7%)  | 6,760 (69.9%)  | <.001   |
| Percutaneous coronary intervention                    | 8,953 (42.0%)  | 4,533 (38.9%)  | 4,420 (45.7%)  | <.001   |
| Coronary-artery bypass grafting                       | 1,793 (8.4%)   | 983 (8.4%)     | 810 (8.4%)     | 0.88    |
| Most responsible physician annual volume of AMI/angina|              |                |                |         |
| Mean ± SD                                            | 33.50 ± 31.70  | 33.21 ± 31.48  | 33.84 ± 31.95  | 0.15    |
| Median (IQR)                                         | 26 (9-47)     | 25 (9-47)      | 26 (9-47)      | 0.29    |
| Most responsible physician type                      |              |                |                |         |
| Family physician                                     | 4,411 (20.7%)  | 2,465 (21.2%)  | 1,946 (20.1%)  | <.001   |
| General internist                                    | 6,930 (32.5%)  | 3,908 (33.5%)  | 3,022 (31.3%)  |         |
| Cardiologist                                         | 9,104 (42.7%)  | 4,758 (40.8%)  | 4,346 (45.0%)  |         |
| Other                                                | 874 (4.1%)     | 522 (4.5%)     | 352 (3.6%)     |         |
| Hospital annual volume of AMI/angina                 |              |                |                |         |
| Mean ± SD                                            | 459.13 ± 327.10 | 447.41 ± 322.44 | 473.27 ± 332.10 | <.001   |
| Median (IQR)                                         | 371 (212-757) | 363 (212-647)  | 385 (214-757)  | <.001   |
| Teaching hospital                                    | 6,136 (28.8%)  | 3,272 (28.1%)  | 2,864 (29.6%)  | 0.01    |
| Hospital facilities                                  |              |                |                |         |
| None                                                 | 12,288 (57.6%) | 6,912 (59.3%)  | 5,376 (55.6%)  | <.001   |
| Cath only or cath and PCI                            | 2,272 (10.7%)  | 1,200 (10.3%)  | 1,072 (11.1%)  |         |
| Cath, PCI, and OHS                                   | 6,759 (31.7%)  | 3,541 (30.4%)  | 3,218 (33.3%)  |         |
| Medication use within 100 days prior index admission |              |                |                |         |
| Anti-platelet agents (Plavix)                        | 1,572 (7.4%)   | 835 (7.2%)     | 737 (7.6%)     | 0.20    |
| Any statin                                           | 8,977 (42.1%)  | 4,978 (42.7%)  | 3,999 (41.4%)  | 0.05    |
| Beta-adrenoreceptor antagonist                       | 7,257 (34.0%)  | 4,109 (35.3%)  | 3,148 (32.6%)  | <.001   |
| ACEI/ARB                                             | 11,146 (52.3%) | 6,220 (53.4%)  | 4,926 (51.0%)  | <.001   |
| Nitrates                                             | 2,451 (11.5%)  | 1,504 (12.9%)  | 947 (9.8%)     | <.001   |
| Calcium channel blockers                             | 6,991 (32.8%)  | 3,909 (33.5%)  | 3,082 (31.9%)  | 0.01    |
| Furosemide                                           | 3,554 (16.7%)  | 2,057 (17.7%)  | 1,497 (15.5%)  | <.001   |
| Spironolactone                                       | 580 (2.7%)     | 335 (2.9%)     | 245 (2.5%)     | 0.13    |
| Medication use within 7 days after discharge         |              |                |                |         |
| Anti-platelet agents (Plavix)                        | 13,485 (63.3%) | 7,778 (66.7%)  | 5,707 (59.0%)  | <.001   |
| Beta-adrenoreceptor antagonist                       | 16,989 (79.7%) | 9,362 (80.3%)  | 7,627 (78.9%)  | 0.01    |
| ACEI/ARB                                             | 17,530 (82.2%) | 9,657 (82.9%)  | 7,873 (81.5%)  | 0.01    |
| Nitrates                                             | 4,900 (23.0%)  | 2,940 (25.2%)  | 1,960 (20.3%)  | <.001   |
| Calcium channel blockers                             | 7,690 (36.1%)  | 4,333 (37.2%)  | 3,357 (34.7%)  | <.001   |
| Furosemide                                           | 5,885 (27.6%)  | 3,351 (28.8%)  | 2,534 (26.2%)  | <.001   |
| Spironolactone                                       | 981 (4.6%)     | 534 (4.6%)     | 447 (4.6%)     | 0.88    |
| Dose per day within 7 days after index discharge     |              |                |                |         |
| Dose per day (mg), mean ± SD                         | 45.60 ± 25.50  | 44.25 ± 24.64  | 47.22 ± 26.40  | <.001   |
| median (IQR)                                         | 40 (25-80)     | 40 (20-80)     | 40 (29-80)     | <.001   |
|                | Unadjusted | Adjusted<sup>a</sup> | Time dependent variable, unadjusted<sup>b</sup> | Time dependent variable, adjusted<sup>a,b</sup> |
|----------------|------------|----------------------|-----------------------------------------------|-----------------------------------------------|
|                | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| **30 days**    |            |         |            |         |            |         |            |         |
| Death          | 1.04 (0.86-1.27) | 0.69 | 1.08 (0.88-1.32) | 0.44 | 1.05 (0.87-1.27) | 0.63 | 1.09 (0.89-1.32) | 0.39 |
| Death / MI or angina | 0.88 (0.77-1.01) | 0.07 | 0.94 (0.82-1.08) | 0.38 | 0.88 (0.77-1.01) | 0.08 | 0.94 (0.82-1.09) | 0.40 |
| Hospitalization for MI or angina | 0.76 (0.63-0.92) | 0.01 | 0.84 (0.69-1.02) | 0.07 | 0.76 (0.63-0.92) | 0.01 | 0.84 (0.69-1.02) | 0.07 |
| Hospitalization for HF | 0.94 (0.78-1.15) | 0.58 | 1.00 (0.82-1.22) | 1.00 | 0.95 (0.79-1.16) | 0.64 | 1.01 (0.83-1.22) | 0.94 |
| Hospitalization for ischemic/hemorrhagic stroke/TIA | 1.56 (0.87-2.78) | 0.14 | 1.59 (0.88-2.86) | 0.13 | 1.56 (0.87-2.78) | 0.13 | 1.59 (0.88-2.86) | 0.13 |
| **365 days**   |            |         |            |         |            |         |            |         |
| Death          | 0.95 (0.88-1.03) | 0.21 | 1.00 (0.93-1.09) | 0.95 | 0.95 (0.88-1.03) | 0.21 | 1.00 (0.93-1.09) | 0.96 |
| Death / MI or angina | 0.93 (0.87-0.99) | 0.02 | 0.99 (0.93-1.05) | 0.69 | 0.93 (0.87-0.99) | 0.02 | 0.99 (0.93-1.05) | 0.67 |
| Hospitalization for MI or angina | 0.88 (0.80-0.96) | 0.01 | 0.96 (0.87-1.05) | 0.41 | 0.88 (0.79-0.96) | 0.01 | 0.96 (0.87-1.05) | 0.38 |
| Hospitalization for HF | 0.93 (0.83-1.03) | 0.17 | 0.99 (0.88-1.10) | 0.80 | 0.93 (0.83-1.03) | 0.18 | 0.99 (0.88-1.10) | 0.82 |
| Hospitalization for ischemic/hemorrhagic stroke/TIA | 1.16 (0.93-1.47) | 0.18 | 1.22 (0.97-1.54) | 0.09 | 1.16 (0.93-1.45) | 0.18 | 1.22 (0.97-1.54) | 0.09 |

HR = hazard ratio; MI = myocardial infarction; HF = heart failure; TIA = transient ischemic attack
<sup>a</sup> Adjusted for age, sex, income, rural residence, most responsible diagnosis, cardiovascular comorbidities, medical comorbidities, cardiac invasive procedures, medications (anti-platelet agents, beta adrenoreceptor antagonist, ACEI/ARB, nitrates, calcium channel blockers, furosemide, spironolactone), hospital level characteristics
<sup>b</sup> Time dependent variable analysis conducted on the full cohort (N = 21,319)
Figure S1. Cumulative Incidence of Secondary Endpoints According to Study Group

**Figure S1a. Hospitalization for HF**

- **Event-free (%)**
- **Time (days)**

**Figure S1b. Hospitalization for ischemic/Hemorrhagic Stroke/TIA**

- **Event-free (%)**
- **Time (days)**

**Figure S1c. Hospitalization for MI or Angina**

- **Event-free (%)**
- **Time (days)**