A Comparative Study of High-intensity Rosuvastatin Versus Atorvastatin Therapy Post-acute Coronary Syndrome Using Real-world Data

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Abstract: A high-intensity statin is recommended for the secondary prevention of cardiovascular diseases (CVD). However, real-world evidence of the effectiveness of rosuvastatin following acute coronary syndrome (ACS) is scarce. This retrospective cohort study included patients diagnosed with ACS to compare between the 2 high-intensity statin therapies (rosuvastatin vs atorvastatin) in
terms of a primary composite outcome of CVD-associated death, non-fatal ACS, and non-fatal stroke at 1 month and 12 months post discharge. The primary effectiveness outcome did not differ between the 2 groups at 1 month (1.3% vs 1%; aHR = 1.64, 95% CI 0.55-4.94, \( P = 0.379 \)) and at 12 months (4.8% vs 3.5%; aHR = 1.48, 95% CI 0.82-2.67, \( P = 0.199 \)). Similarly, the 2 groups had comparable safety outcomes. In conclusion, the use of high-intensity rosuvastatin compared to high-intensity atorvastatin therapy in patients with ACS had resulted in comparable cardiovascular effectiveness and safety outcomes. (Curr Probl Cardiol 2021;00:100956.)

Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVD) are a leading cause of death worldwide and lots of efforts have been made to reduce the mortality and morbidity associated with CVD.\(^1\) Drug therapy remains the cornerstone of CVD management with many treatment options, including statin therapy that was proven to have mortality benefit among patients with established coronary artery disease (CAD).\(^2,3\) According to the American Heart Association/American College of Cardiology (AHA/ACC) 2018 and 2013 guidelines for dyslipidemia, all patients who are 75 years or younger with atherosclerotic cardiovascular disease (ASCVD) should be treated with a high-intensity statin therapy as a secondary prevention with a goal of achieving \( \geq 50\% \) reduction in low-density lipoprotein cholesterol (LDL-C).\(^2,3\) High-intensity statins are defined as statin doses that can reduce LDL-C by at least 50%, which include atorvastatin 40 mg and 80 mg, and rosuvastatin 20 mg and 40 mg.\(^2,3\) However, the above clinical practice guidelines do not favor the use of one of the high-intensity statin over the other, and the onus of selecting a specific evidence-based high-intensity statin is left to the decision and preference of the treating physician.

The guidelines recommendations are based on landmark trials and a large meta-analysis of the statin landmark trials, such as Intensive vs Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE IT) trial, Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease (TNT) trial, Incremental Decrease through Aggressive Lipid Lowering (IDEAL) trial, and a few other randomized controlled trials, which showed that the use of high-intensity statin therapy, mainly atorvastatin, reduced the incidence of many important clinical outcomes, including acute
coronary syndrome (ACS), revascularization, and ischemic stroke compared to moderate or low intensity statin therapy.4–7

To the best of our knowledge, a few clinical studies evaluated the LDL-C lowering effects of the 2 high-intensity statins (atorvastatin vs rosuvastatin), without assessing CV-related outcomes for secondary prevention. For instance, the Comparison of Lipid-Modifying Efficacy of Rosuvastatin vs Atorvastatin in Patients with Acute Coronary Syndrome (LUNAR) study compared rosuvastatin (20 mg or 40 mg) to atorvastatin 80 mg, and it showed that rosuvastatin 40 mg was more effective in decreasing the LDL-C level at 12 weeks compared to atorvastatin 80mg (46.8% vs 42.7% LDL-C decrease, \( p = 0.02 \)).8 Similar findings were demonstrated by the Efficacy and Safety of Rosuvastatin 40 mg vs Atorvastatin 80 mg in High-Risk Patients with Hypercholesterolemia (POLARIS) study, which showed that rosuvastatin 40 mg can lower LDL level more than atorvastatin 80mg at 8 weeks (56% vs 52% LDL-C decrease, \( P < 0.001 \)).9 In addition, high-intensity doses of rosuvastatin were evaluated for both LDL-C reduction and primary prevention of cardiovascular events as demonstrated in the Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER) trial, where rosuvastatin was compared to placebo, but not for the cardiovascular secondary prevention benefit.10 However, the effectiveness and safety of rosuvastatin following ACS has not been widely studied, especially in real-world context.

In view of the lack of head-to-head trials comparing atorvastatin and rosuvastatin in terms of CV secondary prevention benefit and lack of real-world evidence of the effectiveness of rosuvastatin in patients post-ACS, we conducted a retrospective observational study aimed to compare the effectiveness and safety of the 2 high-intensity statin therapies (rosuvastatin vs atorvastatin) in patients with ACS postdischarge using real-world data.

**Methods**

**Study Setting**

This study was conducted at Heart Hospital in Qatar. The hospital is a 116-bed tertiary cardiology center under Hamad Medical Corporation (HMC), which is the principal public healthcare provider in the country.11

**Study Design and Population**

We conducted a retrospective cohort study involving patients admitted with ACS and discharged on either high-intensity rosuvastatin or high-
intensity atorvastatin using real-world data from the Heart Hospital. The study was approved by HMC Medical Research Centre and the Institutional Review Board (MRC-01-20-256). The study comprised 3 stages: (1) determining the primary composite outcome of CVD-associated death, non-fatal ACS, and nonfatal stroke within 1 month and 12 months of discharge among high-intensity statin naïve patients admitted with ACS and discharged on either high-intensity rosuvastatin or atorvastatin, along with determining the secondary effectiveness outcomes within 1 month and 12 months of discharge between the 2 study arms; (2) determining the effect of the 2 high-intensity regimens (atorvastatin vs rosuvastatin) on achieving a goal of reducing LDL-C by ≥ 50% from baseline or LDL-C < 70 mg/dL and; (3) assessing the safety outcomes, including the occurrence of myopathy, rhabdomyolysis, and elevation of liver enzymes to 3 times the upper limit of normal (ULN).

All patients admitted with the diagnosis of ACS to Heart Hospital, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA) during 1 January 2017 and 31 December 2018 were screened for potential inclusion in the study. All patients who met the inclusion criteria and discharged on high-intensity statin (either atorvastatin [40 mg or 80 mg] or rosuvastatin [20 mg or 40 mg] per oral once daily) were identified. Patients who were discharged on rosuvastatin were included in the rosuvastatin group (rosuvastatin users), while those discharged on atorvastatin were included in the atorvastatin group (atorvastatin users).

**Eligibility Criteria**

Patients were included in the study if they fulfilled the following criteria: (1) adult patients younger than 75 years; (2) diagnosed with ACS (STEMI, NSTEMI, or UA); (3) were either statin-naïve or on a low-to-moderate intensity statin therapy prior to admission and; (4) were discharged on either atorvastatin (40 mg or 80 mg per oral once daily) or rosuvastatin (20 mg or 40 mg per oral once daily). Patients were excluded if they had one of the following: (1) a known hypersensitivity to any statin; (2) active liver disease or hepatic dysfunction defined as a level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of more than 3 times the ULN; (3) pregnancy or breast-feeding; (4) receiving proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitor; (5) receiving ezetimibe; (6) already receiving a high-intensity statin prior to ACS diagnosis and hospitalization.
**Outcome Measures and Follow-up**

The effectiveness outcome measures included: (1) a primary composite outcome of CVD-associated death, non-fatal ACS, and non-fatal stroke within 1 month and within 12 months of discharge among the high-intensity statin naive patients who were discharged on either high-intensity rosuvastatin or atorvastatin; (2) secondary effectiveness outcomes, including, all-cause mortality, CV-related mortality, fatal or non-fatal stroke, fatal or nonfatal ACS, coronary revascularization, stent thrombosis, and stent restenosis within 1 month and 12 months postdischarge and; (3) lowering LDL-C by ≥ 50% from baseline or LDL-C < 70 mg/dL. On the other hand, the safety outcome measures of the study included: (1) myopathy, defined as muscle pain that was documented in any of the reviewed electronic medical records and was either attributed to statin use or warranted stopping statin therapy or reducing its dose; (2) rhabdomyolysis, defined as myopathy with a documented rise in creatine kinase by at least 5 times the ULN; (3) elevation of ALT or AST by more than 3 times ULN and; (4) any adverse drug event requiring the discontinuation of statin therapy. Patients were followed-up for 1-year postdischarge after the index event.

**Covariates**

The results of the effectiveness outcomes were adjusted for clinically relevant patient-, disease-, and medication-related variables that were associated with ACS, including: gender, age, smoking status, family history of CVD, dyslipidemia, diabetes, chronic kidney disease (CKD), peripheral artery disease (PAD), CAD, index event of STEMI, percutaneous coronary intervention (PCI), type of stent, level of baseline LDL-C, and use of aspirin, P2Y12 inhibitors, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB).

**Data Collection Procedures**

The baseline characteristics of the study participants and the outcomes of interest, including the primary and secondary outcomes as well as patient-, disease-, and medication-related factors, were collected from the HMC electronic medical records system (Cerner®) mainly by reviewing the physicians notes documented during admission for ACS, outpatient cardiology clinic visits, emergency visits to Heart Hospital, and the results of all laboratory and diagnostic investigations done during the study follow-up period. Moreover, we reviewed the encounters between
the patients and other healthcare providers in HMC as all facilities within the corporate have an integrated electronic system. Data collection was conducted during 1 June 2020 to 31 December 2020. Relevant data were manually extracted using a pretested data collection form.

**Statistical Analyses**

Data analyses were performed using the Statistical Package for Social Sciences program version 24.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY). The primary analysis was designed to test whether high-intensity rosuvastatin was equivalent to high-intensity atorvastatin, as evaluated using Cox proportional hazards modeling. Descriptive statistics were reported in the form of frequencies and percentages for categorical variables, mean ± standard deviation (SD) for normally distributed continuous variables, and median with interquartile range (IQR) for skewed continuous variables. Chi-square test was used to compare categorical variables between the 2 groups (rosuvastatin users vs atorvastatin users), Student’s t-test was used to compare the normally distributed continuous variables between the groups, and Mann–Whitney U test was applied to compare the skewed continuous variables between the groups.

Cox proportional hazard regression analysis was used to assess the association between the 2 high-intensity statin regimens and time-to-primary composite outcome and secondary effectiveness outcomes at 1 month and 12 months following discharge. The 1-month and 12-month Cox proportional hazard models were adjusted for clinically relevant variables. The results were presented as unadjusted hazard ratio (HR) and adjusted hazard ratio (aHR) with 95% confidence intervals (CIs). A P-value of < 0.05 was used to indicate statistical significance.

**Results**

**Subject Selection**

During the study period (1 January 2017 to 31 December 2018), we identified through the electronic pharmacy record system a total of 14,488 patients who were newly prescribed or prescribed refill prescriptions of a high-intensity statin either rosuvastatin 20 mg or 40 mg (n = 7116) or atorvastatin 40 mg or 80 mg (n = 7372). Of these, 4208 were admitted to our facility with ACS. Of these, 1253 patients met the study eligibility criteria. The eligible patients were classified into 2 groups: rosuvastatin group (n = 627) and atorvastatin group (n = 626).
Baseline Characteristics

The baseline characteristics comparisons between the 2 study groups are presented in Table 1. About 96% of the patients included in the analyses were male. The mean age of the patients in the rosuvastatin group was 52 ± 10 years vs 50 ± 9 years in the atorvastatin group, while the mean weight of the patients in the rosuvastatin group was 74 ± 13 Kg vs 77 ± 14 Kg in atorvastatin group. About 77% of the patients originated from Asia, while 20% originated from the Middle East. The prevalence of risk factors for cardiovascular diseases including smoking, family history of CAD, hypertension, dyslipidemia and diabetes among the patients included in the analysis were 47.4%, 15.2%, 39.6%, 16.5%, and 45%, respectively. These characteristics were balanced between the 2 study groups, except for dyslipidemia which was significantly more prevalent in the rosuvastatin group compared to the atorvastatin group (20.6% vs 12.5%; \( P < 0.001 \)). Among the study participants, the median (IQR) baseline LDL-C level was 114 (55) mg/dL. The baseline levels of LDL-C and liver enzymes were comparable between the study groups.

About 60% of the study population was admitted with STEMI and 39.9% underwent primary PCI, while 35.1% was admitted with NSTEMI. Significantly more patients in the rosuvastatin group underwent PCI compared to the atorvastatin group (86.9% vs 78.3%; \( P < 0.001 \)). Conversely, patients in the atorvastatin group had more drug eluting stents deployed than the rosuvastatin group (65.7% vs 56.0%; \( P < 0.001 \)), while the rosuvastatin group compared to the atorvastatin group had a significantly higher prevalence of bare metal stent (24.1% vs 13.1; \( P < 0.001 \)). The proximal left anterior descending artery was the most commonly identified culprit lesion among the patients who underwent PCI followed by the middle left anterior descending artery with proportions of 36.2% and 30.6 %, respectively.

Most of the study patients received the recommended pharmacological therapy for secondary prevention of cardiovascular events, including dual antiplatelet therapy, beta-blocker, and ACE inhibitor or ARB, with no differences between the study groups (Table 2). Rosuvastatin 20 mg was prescribed for 98.7% of the patients in the rosuvastatin arm, while atorvastatin 40 mg was prescribed for 75.9% of those in the atorvastatin arm.

Effectiveness Outcomes

There was no statistically significant difference between the rosuvastatin and the atorvastatin groups in terms of the primary composite endpoint of CVD-associated death, non-fatal ACS and non-fatal stroke at 1
Table 1. Baseline characteristics of postacute coronary syndrome patients receiving 2 different high-intensity statin therapies (N = 1253)

| Characteristic                  | All patients (N = 1253) | Rosuvastatin users (N = 627) | Atorvastatin users (N = 626) | P-value |
|--------------------------------|-------------------------|-------------------------------|-------------------------------|---------|
|                                | n (%)                   | n (%)                         | n (%)                         |         |
| Male gender                    | 1200 (95.8)             | 594 (94.7)                    | 606 (96.8)                    | 0.069   |
| Age*                           | 51 ± 10                 | 52 ± 10                       | 50 ± 9                        | <0.001  |
| Weight*                        | 76 ± 13                 | 74 ± 13                       | 77 ± 14                       | <0.001  |
| Region of origin               |                         |                               |                               | 0.005   |
| Asia                           | 969 (77.3)              | 514 (82.0)                    | 455 (72.7)                    |         |
| Middle East                    | 249 (19.9)              | 97 (15.5)                     | 152 (24.3)                    |         |
| Africa                         | 24 (1.9)                | 11 (1.8)                      | 13 (2.1)                      |         |
| Europe                         | 4 (0.3)                 | 2 (0.3)                       | 2 (0.3)                       |         |
| North America                  | 6 (0.5)                 | 3 (0.5)                       | 3 (0.5)                       |         |
| South America                  | 1 (0.1)                 | 0 (0)                         | 1 (0.2)                       |         |
| Smoking                        |                         |                               |                               | 0.008   |
| Smokers                        | 594 (47.4)              | 301 (48.0)                    | 293 (46.8)                    |         |
| Ex-smokers                     | 108 (8.6)               | 60 (9.6)                      | 48 (7.7)                      |         |
| Never smokers                  | 459 (36.6)              | 208 (33.2)                    | 251 (40.1)                    |         |
| Alcohol                        | 78 (6.2)                | 32 (5.1)                      | 46 (7.3)                      | <0.001  |
| Family history of CAD          | 190 (15.2)              | 93 (14.8)                     | 97 (15.5)                     | 0.206   |
| Ejection fraction              |                         |                               |                               | 0.578   |
| ≤ 40%                          | 216 (17.2)              | 114 (18.2)                    | 102 (16.3)                    |         |
| > 40%                          | 1034 (82.5)             | 512 (81.7)                    | 522 (83.4)                    |         |
| LDL-C (mg/dL)†                 | 114 [55]                | 114 [57]                      | 114 [53]                      | 0.708   |
| TC (mg/dL)†                    | 182 [62]                | 178 [71]                      | 182 [58]                      | 0.022   |
| HDL (mg/dL)†                   | 35 [10]                 | 35 [10]                       | 35 [10]                       | 0.132   |
| HbA1c                          |                         |                               |                               | <0.001  |
| ≤ 10%                          | 1028 (82.0)             | 523 (83.4)                    | 505 (80.7)                    |         |
| > 10%                          | 158 (12.6)              | 86 (13.7)                     | 72 (11.5)                     |         |
| ALT (U/L)†                     | 28 [20]                 | 28 [20]                       | 29 [20]                       | 0.927   |
| AST (U/L)†                     | 29 [22]                 | 29 [21]                       | 28 [22]                       | 0.287   |
| Hypertension                   | 496 (39.6)              | 242 (38.6)                    | 254 (40.6)                    | 0.474   |
| Dyslipidemia                   | 207 (16.5)              | 129 (20.6)                    | 78 (12.5)                     | <0.001  |
| Diabetes mellitus              | 564 (45.0)              | 286 (42.7)                    | 296 (47.3)                    | 0.106   |
| Chronic kidney disease         | 28 (2.2)                | 13 (2.1)                      | 15 (2.4)                      | 0.699   |
| Hyperthyroidism                | 2 (0.2)                 | 1 (0.2)                       | 1 (0.2)                       |         |
| Hypothyroidism                 | 20 (1.6)                | 10 (1.6)                      | 10 (1.6)                      | 0.997   |
| Peripheral artery disease      | 6 (0.5)                 | 4 (0.6)                       | 2 (0.3)                       | 0.687†  |
| Coronary artery disease        | 147 (11.7)              | 74 (11.8)                     | 73 (11.7)                     | 0.938   |
| Index event                    |                         |                               |                               |         |
| STEMI                          | 744 (59.4)              | 367 (58.5)                    | 377 (60.2)                    | 0.514   |
| NSTEMI                         | 440 (35.1)              | 230 (36.7)                    | 210 (33.5)                    | 0.301   |
| Unstable Angina                | 69 (5.5)                | 30 (4.8)                      | 39 (6.2)                      | 0.403   |
| PCI                            | 1053 (82.6)             | 545 (86.9)                    | 490 (78.3)                    | <0.001  |
| Primary PCI                    | 500 (39.9)              | 248 (39.6)                    | 252 (40.3)                    | 0.800   |
| CABG                           | 39 (3.1)                | 22 (3.5)                      | 17 (2.7)                      | 0.419   |
| Drug eluting stent             | 762 (60.8)              | 351 (56.0)                    | 411 (65.7)                    | <0.001  |
| Bare metal stent               | 234 (18.7)              | 151 (24.1)                    | 83 (13.3)                     | <0.001  |

(continued)
month and at 12 months of discharge, as shown in Table 3. At 1 month, 8 events occurred in the rosuvastatin group compared to 6 events in the atorvastatin group (1.3% vs 1%, HR = 1.38, 95% CI 0.48-3.96; \(P = 0.555\)). After adjusting for clinically relevant variables associated with ACS, there was still no difference in the primary composite endpoint between the study groups (aHR = 1.64, 95% CI 0.55-4.94; \(P = 0.379\)). Similarly, at 12 months of discharge, the primary composite endpoint did not differ significantly between the rosuvastatin and atorvastatin groups. A total of 30 events occurred in the rosuvastatin group compared to 22 events in the atorvastatin group at 12 months (4.8% vs 3.5%, HR = 1.36, 95% CI 0.78-2.36; \(P = 0.274\) and aHR = 1.48, 95% CI 0.82–2.67; \(P= 0.199\)). Likewise, there was no statistically significant difference between the study groups in the secondary effectiveness endpoints of all-cause mortality, cardiovascular mortality, fatal or non-fatal stroke, fatal or non-fatal ACS, coronary revascularization, stent thrombosis, and stent

| Characteristic | All patients (N = 1253) | Rosuvastatin users (N = 627) | Atorvastatin Users (N = 626) | \(P\)-value |
|---------------|-------------------------|-----------------------------|-----------------------------|-----------|
| Culprit lesions | | | | |
| Left main | 60 (4.8) | 27 (4.3) | 33 (5.3) | 0.424 |
| Proximal LAD | 454 (36.2) | 228 (36.4) | 226 (36.1) | 0.923 |
| Middle LAD | 383 (30.6) | 200 (31.9) | 183 (29.2) | 0.306 |
| Distal LAD | 89 (7.1) | 57 (9.1) | 32 (5.1) | 0.006 |
| Proximal LCx | 240 (19.2) | 145 (23.1) | 95 (15.2) | <0.001 |
| Proximal RCA | 230 (18.4) | 118 (18.8) | 112 (17.9) | 0.671 |
| Middle RCA | 250 (20) | 118 (18.8) | 132 (21.1) | 0.315 |
| Distal RCA | 124 (9.9) | 66 (10.5) | 58 (9.3) | 0.455 |
| Number of stents | | | | 0.066 |
| 0 | 290 (23.1) | 140 (22.3) | 150 (24.0) | |
| 1 | 704 (56.2) | 376 (60.0) | 328 (52.4) | |
| 2 | 209 (16.7) | 88 (14.0) | 121 (19.3) | |
| 3 | 38 (3.0) | 17 (2.7) | 21 (3.4) | |
| 4 | 11 (0.9) | 5 (0.8) | 6 (1.0) | |
| 5 | 1 (0.1) | 1 (0.2) | 0 (0) | |

*Values are expressed as mean ± SD.
†Values expressed as median [interquartile range].
‡\(P\)-value was calculated using Fisher’s Exact test; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CAD: coronary artery disease; CABG: coronary artery bypass grafting; HDL: high-density lipoproteins; HbA1c: glycated hemoglobin; LAD: left anterior descending artery; LCx: circumflex artery; LDL: low-density lipoproteins; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction; TC: total cholesterol.
restenosis at both 1 month and 12 months post-discharge, as shown in Table 4.

Table 2. Concurrent medications prescribed among postacute coronary syndrome patients receiving 2 different high-intensity statin therapies (N = 1233)

| Medication Class                  | All patients (N = 1253) n (%) | Rosuvastatin users (N = 627) n (%) | Atorvastatin users (N = 626) n (%) | P-value |
|------------------------------------|-------------------------------|-----------------------------------|-----------------------------------|---------|
| Aspirin                            | 1250 (99.8)                   | 624 (99.5)                        | 626 (100)                        | 0.249*  |
| P2Y12 inhibitor                    | 1246 (99.4)                   | 623 (99.4)                        | 623 (99.5)                        | 0.706   |
| List of P2Y12 inhibitors           |                               |                                   |                                   | 0.155   |
| Clopidogrel                        | 1148 (91.6)                   | 583 (93.0)                        | 565 (90.3)                       |         |
| Ticagrelor                         | 98 (7.8)                      | 40 (6.4)                          | 58 (9.3)                         | 0.308   |
| ACE inhibitor or ARB               | 918 (73.3)                    | 468 (72.9)                        | 450 (70.3)                       | 0.027   |
| List of ACE inhibitors             |                               |                                   |                                   |         |
| Lisinopril                         | 532 (42.5)                    | 292 (46.6)                        | 240 (38.3)                       |         |
| Enalapril                          | 16 (1.3)                      | 4 (0.6)                           | 12 (1.9)                         |         |
| Ramipril                           | 225 (18.0)                    | 108 (17.2)                        | 117 (18.7)                       |         |
| Perindopril                        | 63 (5.0)                      | 26 (4.1)                          | 37 (5.9)                         |         |
| Fosinopril                         | 2 (0.2)                       | 1 (0.2)                           | 1 (0.2)                          |         |
| List of ARBs                       |                               |                                   |                                   | 0.234   |
| Valsartan                          | 68 (5.4)                      | 35 (5.6)                          | 33 (5.3)                         |         |
| Losartan                           | 6 (0.5)                       | 1 (0.2)                           | 5 (0.8)                          |         |
| Irbesartan                         | 5 (0.4)                       | 1 (0.2)                           | 4 (0.6)                          |         |
| Candesartan                        | 1 (0.1)                       | 0 (0)                             | 1 (0.2)                          |         |
| Beta-blocker                       | 1154 (92.1)                   | 577 (92.0)                        | 577 (92.2)                       | 0.923   |
| List of beta-blockers              |                               |                                   |                                   | 0.023   |
| Bisoprolol                         | 689 (55.0)                    | 372 (59.3)                        | 317 (50.6)                       |         |
| Metoprolol                         | 457 (36.5)                    | 201 (32.1)                        | 256 (40.9)                       |         |
| Carvedilol                         | 14 (1.1)                      | 7 (1.1)                           | 7 (1.1)                          |         |
| Atenolol                           | 1 (0.1)                       | 0 (0)                             | 1 (0.2)                          |         |
| Propranolol                        | 1 (0.1)                       | 1 (0.2)                           | 0 (0)                            |         |
| Ivabradine                         | 20 (1.6)                      | 9 (1.4)                           | 11 (1.8)                         | 0.650   |
| Nitrate                            | 349 (27.9)                    | 154 (24.6)                        | 195 (31.2)                       | 0.009   |
| High intensity statin dose         |                               |                                   |                                   |         |
| 20 mg                              | –                              | 619 (98.7)                        | –                                 |         |
| 40 mg                              | –                              | 8 (1.3)                           | 475 (75.9)                       |         |
| 80 mg                              | –                              | –                                 | 151 (24.1)                       |         |

*P-value was calculated using Fisher’s Exact test; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker

About 45% of the patients in the rosuvastatin group compared to 43.2% of the patients in the atorvastatin group were able to achieve LDL-C reduction by ≥50% from baseline (P = 0.672). However, LDL-C levels after discharge were missing for around 60% of the study participants in both groups.
Safety Outcomes

A total of 19 adverse events were reported across the study population. There were no significant differences between the 2 study groups with regards to the reported safety outcomes, as shown in Table 4. Myopathy occurred in 0.5% of patients in the rosuvastatin group compared to 0.8% in the atorvastatin group. The rate of rise of ALT to > 3 times the ULN was 0.2% in the rosuvastatin group compared to 0.8% in the atorvastatin group, while the rate of rise of AST to >3 times the ULN was 0.3% in the rosuvastatin group compared to 0.5% in the atorvastatin group. Rhabdomyolysis was not reported in either groups. One patient discontinued rosuvastatin secondary to adverse events, while atorvastatin was discontinued in 3 patients secondary to adverse events.

Discussion

In this retrospective cohort study, we found that the use of high-intensity rosuvastatin, mainly 20mg, for the secondary prevention of CVDs after ACS resulted in similar cardiovascular outcomes (CVD-associated death, non-fatal ACS, and non-fatal stroke) compared to high intensity atorvastatin at 1 month and 12 months after hospital discharge.
Rosuvastatin 20 mg and 40 mg, as well as atorvastatin 40 mg and 80 mg, are considered high-intensity statins, and they are recommended by the AHA/ACC 2018 and 2013 guidelines for dyslipidemia in patients with CAD for secondary prevention of cardiovascular events.\(^2\),\(^3\) The guidelines recommendations are based on a few large randomized controlled trials like PROVE-IT, TNT, IDEAL, etc. that used atorvastatin as the

Table 4. Secondary outcomes of 2 different high-intensity statin therapies in patients post-acute coronary syndrome (N = 1253)

| Outcome                              | Rosuvastatin users (N = 627) | Atorvastatin users (N = 626) | Adjusted hazard ratio 95% CI | P-value |
|--------------------------------------|-----------------------------|-----------------------------|-----------------------------|---------|
|                                      | n (%)                       | n (%)                       |                             |         |
| Secondary effectiveness endpoints at 1 mo |                             |                             |                             |         |
| All-cause mortality                  | 1 (0.2)                     | 2 (0.3)                     | 0.78 (0.01-51.36)           | 0.909   |
| Cardiovascular mortality             | 1 (0.2)                     | 2 (0.3)                     | 0.78 (0.01-51.36)           | 0.909   |
| Fatal or nonfatal stroke             | 2 (0.3)                     | 0 (0)                       | 1 (0.06-18.08)              | 1.0     |
| Fatal or nonfatal ACS                | 7 (1.1)                     | 5 (0.8)                     | 1.56 (0.43-5.59)            | 0.496   |
| Coronary revascularization           | 4 (0.6)                     | 2 (0.3)                     | 4.93 (0.49-49.75)           | 0.176   |
| Stent thrombosis                     | 0 (0)                       | 0 (0)                       | —                           | —       |
| Stent restenosis                     | 0 (0)                       | 0 (0)                       | —                           | —       |
| Secondary effectiveness endpoints at 12 months |                             |                             |                             |         |
| All-cause mortality                  | 4 (0.6)                     | 2 (0.3)                     | 4.41 (0.66-29.60)           | 0.126   |
| Cardiovascular mortality             | 4 (0.6)                     | 2 (0.3)                     | 4.41 (0.66-29.60)           | 0.126   |
| Fatal or nonfatal stroke             | 7 (1.1)                     | 4 (0.6)                     | 2.06 (0.55-7.75)            | 0.283   |
| Fatal or nonfatal ACS                | 26 (4.1)                    | 16 (2.5)                    | 1.69 (0.85-3.38)            | 0.137   |
| Coronary revascularization           | 12 (1.9)                    | 8 (1.3)                     | 1.90 (0.69-5.23)            | 0.212   |
| Stent thrombosis                     | 1 (0.2)                     | 0 (0)                       | 1 (0.02-58.56)              | 1.0     |
| Stent restenosis                     | 3 (0.5)                     | 3 (0.5)                     | 1.43 (0.18-11.12)           | 0.734   |
| Lipid lowering outcomes*             |                             |                             |                             |         |
| LDL-C (mg/dL)                        | 54 [39]                     | 60 [39]                     | —                           | 0.074†  |
| LDL-C < 70 mg/dL                     | 173 (60.9)                  | 151 (60.4)                  | —                           | 0.565†  |
| Reduction of LDL-C by 50%            | 126 (45.0)                  | 104 (43.2)                  | —                           | 0.672‡  |
| Safety outcomes                      |                             |                             |                             |         |
| Myopathy                             | 3 (0.5)                     | 5 (0.8)                     | —                           | 0.506‖   |
| ALT > 3 ULN                          | 1 (0.2)                     | 5 (0.8)                     | —                           | 0.124‖   |
| AST > 3 ULN                          | 2 (0.3)                     | 3 (0.5)                     | —                           | 0.678‖   |
| Rhabdomyolysis                       | 0 (0)                       | 0 (0)                       | —                           | —       |
| Adverse drug event requiring statin discontinuation | 1 (0.2)                     | 3 (0.5)                     | —                           | 0.374‖   |

LDL-C, low-density lipoproteins cholesterol.

*Missing data for ~60% of study participants in both arms.

†Values expressed as median (interquartile range).

‡ P-value was obtained using Mann Whitney test.

‡‡ P-value was obtained using Chi-square test.

‖ P-value was obtained using Fisher’s Exact test; ACS, acute coronary syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase
high-intensity statin therapy.\textsuperscript{5--7} The 2013 AHA/ACC guidelines for dyslipidemia did not recommend a target of LDL-C; instead, it focused on the idea of using high-intensity statin rather than moderate or low intensity, while in the AHA/ACC 2018 guidelines, reducing LDL-C by 50\% was recommended for the patients who have ASCVD, and a target of LDL-C less than 70 mg/dL was recommended for those who were judged to have a very high risk ASCVD.\textsuperscript{2,3}

The effectiveness of rosuvastatin for the primary prevention of cardiovascular events is already proven and well-established. For instance, the JUPITER trial that included more than 17,000 healthy volunteers with LDL-C level less than 130 mg/dL had assessed the effect of rosuvastatin compared to placebo on primary prevention.\textsuperscript{10} The study was stopped after 1.9 year of follow-up as it showed clear reduction in major cardiovascular events, including myocardial infarction, stroke, arterial revascularization, hospitalization for UA and death from cardiovascular causes with the use of rosuvastatin compared to placebo (HR = 0.56; 95\% CI, 0.46-0.69; \( P < 0.001 \)).\textsuperscript{10} Nevertheless, the evidence of benefit of rosuvastatin in cardiovascular secondary prevention is very limited and most of the secondary prevention literature focusses on high intensity atorvastatin. To the best of our knowledge, there is paucity of studies that compared rosuvastatin with atorvastatin for secondary prevention in terms of cardiovascular clinical outcomes. Two virtual trials using the Archimedes model, which is an individual-based simulation of human pathophysiology and treatment intervention, were conducted to compare the clinical outcomes of rosuvastatin vs atorvastatin for cardiovascular secondary prevention.\textsuperscript{12,13} Interestingly, Colivicchi et al. found that the number needed to treat (NNT) to prevent 1 major adverse cardiovascular event (MACE) at 5 years for secondary prevention was 70 for rosuvastatin 20 mg compared to atorvastatin 40 mg and 63 for rosuvastatin 40 mg compared to atorvastatin 80 mg.\textsuperscript{12} Conversely, Schuetz et al. found that rosuvastatin 20 mg and 40 mg reduced MACE more than atorvastatin 40 mg and 80 mg. Among patients with ACS, the trial showed that when rosuvastatin 20 mg was compared to atorvastatin 40 mg, the 5-year NNT to prevent one MACE was 55, while it was 51 with rosuvastatin 40 mg compared to atorvastatin 80 mg.\textsuperscript{13} Although these results vary from our findings of similar secondary prevention benefit with the use of rosuvastatin vs atorvastatin post-ACS, the above mentioned trials were virtual studies using the Archimedes model and their follow up period was longer than the present study. Therefore, it is possible that the primary outcomes may differ between the 2 agents over a long period of time. However, this notion warrants further investigations.
In the current study, both rosuvastatin and atorvastatin had the same effect on achieving an LDL-C level of less than 70 mg/dL and in reducing LDL-C to less than 50% of the baseline. Our study findings differ from the previous studies that showed a better reduction in LDL-C with the use of rosuvastatin compared to atorvastatin. For example, the VOYAGER meta-analysis showed that 71% of patients treated with rosuvastatin 40 mg and 57% of those treated with rosuvastatin 20mg achieved the more than 50% reduction in LDL-C compared to 59% and 40% for atorvastatin 80mg and 40 mg, respectively. Additionally, the LUNAR study showed that the LDL-C reduction was significantly greater with rosuvastatin 40 mg compared to atorvastatin 80mg (46.8% vs 42.7% decrease, \( P = 0.02 \)), while the LDL-C reduction with rosuvastatin 20 mg was similar to that of atorvastatin 80mg. Similarly, the STELLAR trial found that rosuvastatin 10 to 80 mg reduced LDL-C by a mean of 8.2% more than atorvastatin 10 to 80 mg. In addition, the POLARIS study reported that rosuvastatin 40 mg reduced LDL-C significantly more than atorvastatin 80mg (56% vs 52%; \( P < 0.001 \)) and a cost-effectiveness analysis in terms of cost per percentage reduction in LDL-C estimated saving of 2.5 million dollars for every 10,000 patients treated with rosuvastatin 40mg instead of atorvastatin 80mg, an amount of money enough to treat additional 2700 patients for one year. However, it is worthwhile to mention here that around 60% of our study population did not have LDL-C level recorded during the follow-up. This is most likely attributed to the fact that the study review period was from the beginning of 2017 till the end of 2018, and the 2018 ACC/AHA guidelines that recommended treatment with high-intensity statin to achieve a target LDL-C of less than 70 mg/dL was not published till late 2018. Prior to that, the 2013 AHA/ACC guidelines did not recommend a target LDL for secondary prevention. We believe that this may have resulted in the difference between our study findings and the previous trials.

Both statin groups demonstrated a similar safety profile with less than 1% of patients developing liver toxicity, myopathy, or rhabdomyolysis and an overall discontinuation of statin therapy due to adverse events of less than 1%. These findings are consistent with findings from previous large randomized clinical trials.

This study was an observational retrospective study that has its limitations. First, the retrospective nature of the study and the dependence on the electronic medical records only to obtain all the study data carries the inherent risk of missing important information regarding the participants’ background, laboratory data, or even some of the outcomes that may not be appropriately documented in the medical records. Second, a regular follow up in fixed intervals could not be guaranteed in view of the
retrospective nature of the study; nevertheless, the study was conducted in the main cardiovascular tertiary center in the country and the medical records system is integrated between all the major centers in the country. Consequently, we believe that none of the primary outcomes have been missed as the occurrence of any of them will warrant a referral to our center. Third, the follow-up period was only one year, which is relatively short compared to prospective studies that looked for cardiovascular outcomes which could explain the low rate of events in the present study; however, this low rate was similar in both groups. Lastly, because of the low event rates observed in a recent experience assessing the effectiveness of atorvastatin 40 mg vs 80 mg in our center which showed an event rate of CVD-related outcomes of 3.2% vs 4.0% at 12 months, respectively,17 and the small population in our country, power analysis could not be applied as it would require a larger sample; rather, we used whole population sampling, where we included all the participants who fulfilled the eligibility criteria during the study period.

This retrospective cohort study, despite the previous limitations, had a good number of participants with an equal number and almost balanced baseline characteristics in the 2 groups. In addition, and most importantly, the study tried to answer a unique question and fill a gap in the existing literature to determine whether rosuvastatin has a similar clinical effectiveness as atorvastatin in CVD secondary prevention post-ACS, a question that we believe our study answered.

**Conclusion**

This study suggests that the use of high-intensity rosuvastatin, mainly 20mg, in secondary prevention post-ACS has a comparable effectiveness and safety to high-intensity atorvastatin over a one-year follow-up period, which may provide a clinician with evidence-based reassurance and more flexibility in the selection of a high-intensity statin therapy. With the existing evidence of rosuvastatin advantages in reducing LDL compared to atorvastatin, larger randomized prospective trials with a longer follow-up period are warranted to confirm the findings of the current study.

**Author Declarations**

**Ethics Approval and Consent to Participate**

The study was approved by HMC Medical Research Centre and the Institutional Review Board (MRC-01-20-256).
Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors’ Contributions

AR, FK, AM, SY, and ARA conceived the study.
AR, FK, BO, SC, OA, MSA, OO, AAA, MA, and AHA were involved in the data collection process.
AR, FK, and AA analyzed and interpreted the data.
AR, FK, BO, SC, OA, MSA, OO, AAA, MA, AM, AA, AHA, YA, SY and ARA interpreted the results.
AR, FK, BO, and AA wrote the manuscript.
All authors revised the manuscript and approved the final manuscript for submission.

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