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ORIGINAL ARTICLE

Clinical outcomes of high-intensity doses of atorvastatin in patients with acute coronary syndrome: A retrospective cohort study using real-world data

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Aims: To compare the effectiveness and safety of 2 high-intensity atorvastatin doses (40 mg *vs* 80 mg) among acute coronary syndrome (ACS) patients.

Methods: This retrospective observational cohort study using real-world data included patients admitted with ACS to the Heart Hospital in Qatar between 1 January 2017 and 31 December 2018. The primary endpoint was a composite of cardiovascular disease-associated death, nonfatal ACS and nonfatal stroke. Cox proportional hazard regression analysis was used to determine the association between the 2 high-intensity atorvastatin dosing regimens and the primary outcome at 1 month and 12 months postdischarge.

Results: Of the 626 patients included in the analyses, 475 (75.9%) received atorvastatin 40 mg, while 151 (24.1%) received atorvastatin 80 mg following ACS. Most of the patients were Asian (73%), male (97%) with a mean age of 50 years and presented with ST-elevation myocardial infarction (60%). The incidence of the primary effectiveness outcome did not differ between the atorvastatin 40-and 80-mg groups at 1 month (0.8 *vs* 1.3%; adjusted hazard ratio = 0.59, 95% confidence interval 0.04–8.13, P = .690) and at 12 months (3.2 *vs* 4%; adjusted hazard ratio = 0.57, 95% confidence interval 0.18–1.80, P = .340). Similarly, the use of the 2 doses of atorvastatin resulted in comparable safety outcomes, including liver toxicity, myopathy and rhabdomyolysis with an event rate of <1% in both groups.

Conclusion: The use of atorvastatin 40 mg in comparison to atorvastatin 80 mg in patients with ACS resulted in similar cardiovascular effectiveness and safety outcomes.

KEYWORDS

acute coronary syndrome, atorvastatin, cardiovascular disease-associated death, high-intensity statin, secondary prevention of cardiovascular events

The authors confirm that the principal investigator for this paper is Ms. Alaa Rahhal.

1 | INTRODUCTION

A high-intensity statin, defined as atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg orally, which lowers low-density lipoprotein cholesterol (LDL-C) by ≥50%, is recommended by clinical practice guidelines for secondary prevention of cardiovascular (CV) events among patients who have an atherosclerotic CV disease (CVD; Class 1A).[1,2] Several clinical trials have demonstrated that statin use reduces major CV events.[3–10] Specifically, large randomized controlled clinical trials have established the efficacy and safety of statins for secondary prevention of CVDs.[8–10] The Intensive *vs* Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE IT) trial, which compared atorvastatin 80 mg to pravastatin 40 mg, demonstrated a risk reduction of 16% over 2 years in the composite endpoint of all-cause mortality, myocardial infarction, documented unstable angina requiring re-hospitalization, revascularization (performed at least 30 days after randomization), and stroke among patients with the acute coronary syndrome (ACS).[8] Additionally, the Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease (TNT) trial, which compared atorvastatin 80 mg to 10 mg, showed a risk reduction of 22% over 4.9 years in a major adverse CV event, defined as CV death, nonfatal myocardial infarction, resuscitation after cardiac arrest and fatal or nonfatal stroke.[9] Similarly, in the Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndrome (MIRACL) trial, the early use of atorvastatin 80 mg after ACS compared to placebo had resulted in a 16% significant reduction in a primary composite outcome of mortality, nonfatal myocardial infarction, and cardiac arrest with resuscitation over a follow-up period of 16 weeks.[10]

Therefore, the use of atorvastatin 80 mg among patients with coronary artery disease (CAD) had resulted in a risk reduction of 16–22% in major adverse CV event. However, to the best of our knowledge, the secondary prevention CV benefit of atorvastatin 40 mg compared to 80 mg in the setting of ACS has not yet been well-established. Although the CURE-ACS trial compared both doses among ACS patients in terms of LDL-C reduction[11], there is no head-to-head comparison between atorvastatin 40 and 80 mg to assess the CV secondary prevention effect of the 2 regimens. Moreover, Atorvastatin 40 mg could serve as an appropriate high-intensity statin alternative among patients who have partial statin intolerance (defined as inability to continue using a certain statin therapy due to side effects at a specific dose), especially as the Incremental Decrease through Aggressive Lipid Lowering (IDEAL) trial's protocol permitted down titration of atorvastatin 80 to 40 mg among patients who were unable to tolerate atorvastatin 80 mg, and hence 587 patients (13%) had their atorvastatin dose reduced to 40 mg.[12,13] Thus, clinicians might favour the use of atorvastatin 40 mg over 80 mg as an initial high-intensity statin therapy if they have concerns about safety. Therefore, this retrospective, observational cohort study aimed to compare using real-world data the effectiveness and safety of 2 high-intensity statin doses (atorvastatin 40 *vs* 80 mg) in patients with ACS at 1 and 12 months postdischarge, and to determine the predictors of prescribing 80 mg upon discharge.

What is already known about this subject

- A high-intensity statin is recommended for secondary prevention of cardiovascular diseases.
- The efficacy and safety of atorvastatin 80 mg for secondary prevention is well established.
- The effectiveness of atorvastatin 40 *vs* 80 mg following acute coronary syndrome (ACS) has not been widely studied in a real-world context.

What this study adds

- The use of 2 high-intensity doses of atorvastatin (40 and 80 mg) post-ACS was associated with similar cardiovascular outcomes at 1 and 12 months postdischarge.
- The 2 high-intensity doses of atorvastatin resulted in similar safety outcomes.
- Clinicians may use either high-intensity atorvastatin dose following ACS.
- However, clinicians might favor the use of atorvastatin 40 mg over 80 mg as an initial high-intensity statin therapy if they have concerns about safety.

2 | METHODS

2.1 | Study setting

This study was conducted at the Heart Hospital in Qatar. The hospital is a 116-bed tertiary cardiology centre under the Hamad Medical Corporation (HMC), and is the only national centre for CVDs in the country.[14]

2.2 | Study design and population

We conducted a retrospective, observational, cohort study using real-world data from Heart Hospital. The study was approved by HMC Medical Research Centre and Institutional Review Board in Qatar. The study comprised 4 stages: (i) determining the time to a primary composite outcome of CVD-associated death, nonfatal ACS, and nonfatal stroke within 1 month and 12 months of discharge among high-intensity statin naïve patients admitted with ACS, along with determining the time to secondary effectiveness outcomes within 1 month and 12 months of discharge; (ii) determining the effect of the 2 high-intensity statin dosing regimens (atorvastatin 40 *vs* 80 mg) in achieving a goal of reducing LDL-C by ≥50% from baseline or LDL-C <70 mg/dL; (iii) assessing the safety outcomes, including the occurrence of myopathy, rhabdomyolysis, and elevation of liver enzymes to 3× the upper limit of normal (ULN); and (iv) conducting a retrospective

analysis of the demographic and clinical characteristics of the atorvastatin 80 *vs* 40-mg users to identify the predictors of prescribing atorvastatin 80 mg among the ACS patients in our facility.

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

2.3 | Eligibility criteria

Patients were included in the study if they fulfilled all of the following eligibility criteria: (i) adult patients aged ≥18 years, but ≤75 years; (ii) diagnosed with ACS (STEMI, NSTEMI or UA); (iii) were either statin-naïve or on a low-to-moderate intensity statin therapy prior to admission; and (iv) were discharged on either atorvastatin 40 mg or atorvastatin 80 mg. Patients were excluded if they had 1 of the following: (i) a known hypersensitivity to any statin; (ii) active liver disease or hepatic dysfunction defined as a level of alanine aminotransferase (ALT) or aspartate aminotransferase of >3× ULN; (iii) pregnancy or breast-feeding; (iv) receiving proprotein convertase subtilisin/kexin type 9 inhibitor; (v) receiving ezetimibe; or (vi) already on a high-intensity statin prior to ACS diagnosis and hospitalization.

2.4 | Outcome measures and follow-up

The effectiveness outcome measures in this study included: (i) a primary composite outcome of CVD-associated death, nonfatal ACS and nonfatal stroke within 1 month and within 12 months of discharge among high-intensity statin naïve patients who were discharged on either atorvastatin 40 or 80 mg; (ii) secondary effectiveness outcomes, including, all-cause mortality, CV mortality, fatal or nonfatal stroke, fatal or nonfatal ACS, coronary revascularization, stent thrombosis, and stent restenosis within 1 month and 12 months postdischarge; and (iii) lowering LDL-C by ≥50% from baseline or LDL-C < 70 mg/dL. By contrast, the safety outcome measures of the study included: (i) myopathy, defined as any muscle pain or muscle weakness that was mentioned in any of the reviewed electronic documentations and was either attributed to statin use or warranted stopping statin or reducing the dose; (ii) rhabdomyolysis, defined as myopathy with a documented rise in creatine kinase by at least 5× ULN; (iii) elevation of ALT or aspartate aminotransferase >3× ULN; and (iv) any adverse drug event requiring statin discontinuation. Predictors of prescribing atorvastatin 80 mg among ACS patients, including several patient-, disease- and medication- factors, such as demographics, comorbid diseases and concomitant prescription drugs during hospitalization were also measured. Patients were followed-up for 1 year postdischarge date, or until the occurrence of the primary endpoint, or until censoring if they were lost to follow-up.

2.5 | Covariates

The results of the effectiveness outcomes were adjusted for clinically relevant patient-, disease- and medication-related variables that were associated with ACS, including: sex, age, geographical region of origin, smoking status, family history of CVD, hypertension, diabetes, chronic kidney disease, peripheral artery disease, CAD, index event of STEMI, index event of NSTEMI, index event of UA, primary percutaneous coronary intervention (PCI), number of deployed stents, type of stent, level of baseline LDL-C, and use of aspirin, P2Y12 inhibitors and β-blockers.

2.6 | Data collection procedures

Data needed for both the baseline participants characteristics 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 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. Additionally, we reviewed the documentation of any encounter between the patients and other healthcare providers in HMC as all facilities within the corporation have an integrated electronic system. Relevant data were manually extracted using a pretested data collection form.

2.7 | 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, USA). Descriptive statistics in the form of frequencies and percentages were reported for categorical variables and mean ± standard deviation for continuous variables. The χ^2 test was used to compare categorical variables between the 2 groups (atorvastatin 80-mg users *vs* atorvastatin 40-mg users), and Student *t*-test was used to compare continuous variables between the 2 groups.

Cox proportional hazard regression analysis was used to assess the association between atorvastatin doses 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 and adjusted hazard ratio (aHR) with 95% confidence intervals (CIs). A *P*-value of <.05 was used to indicate statistical significance.

Furthermore, multivariate logistic regression was used to determine the predictors of prescribing atorvastatin 80 mg among ACS patients. Sixteen clinically relevant variables were included in the logistic regression model, using the backward stepwise likelihood ratio with the probability of entry of 0.05 and removal of 0.10 at each step. The results are presented as adjusted odds ratio (aOR) with corresponding 95% CI. A *P*-value of <.05 was used for statistical significance.

3 | RESULTS

3.1 | Subject selection

We identified 7372 patients who were dispensed either atorvastatin 40 mg (*n* = 7009) or 80 mg (*n* = 363) through the Heart Hospital electronic pharmacy record system during the study period (1 January 2017 to 31 December 2018), suggesting that atorvastatin 40 mg is more commonly prescribed than atorvastatin 80 mg at our facility. Upon screening the potentially eligible patients above, 626 fulfilled the study's eligibility criteria and classified into 2: 475 (75.9%) in the atorvastatin 40-mg group and 151 (24.1%) in the atorvastatin 80-mg group.

3.2 | Baseline characteristics

The baseline characteristics comparisons between the atorvastatin 40-mg group (*n* = 475) and the atorvastatin 80-mg group (*n* = 151) are presented in Table 1. About 97% of the patients included in the analyses were male with a mean age of 50 ± 9 years. Most of the patients originate from Asia (72.7%) and the Middle East (24.3%; Table 1). In addition, diabetes, hypertension, history of smoking and family history of CAD were highly prevalent in the studied population with proportions of 47.3, 40.6, 46.8 and 15.5%, respectively. These characteristics were balanced between the 2 study groups. However, history of a previous CAD was significantly more prevalent in the atorvastatin 40-mg group compared to the 80-mg group (13.5 *vs* 6%; *P* = .012).

The mean LDL-C level in the atorvastatin 80-mg group was 130 ± 44.7 mg/dL compared to 110 ± 41.9 mg/dL in the atorvastatin 40-mg group (*P* < .001), while the baseline levels of liver enzymes were significantly lower in the atorvastatin 80-mg group (Table 1).

Sixty percent of the patients were admitted with the diagnosis of STEMI, while 33.5% had NSTEMI. Around 80% of the patients underwent PCI with the proximal left anterior descending artery as the most common identified culprit lesion (36.3%). The atorvastatin 80-mg group had a higher prevalence of STEMI events compared to the atorvastatin 40-mg group (76.8 *vs* 54.9%; *P* < .001). Similarly, more patients in the atorvastatin 80-mg group underwent PCI compared to the 40-mg group (87.4 *vs* 75.4%; *P* = .002). The implantation of drug-eluting stents was more frequent in the atorvastatin 80-mg arm compared to the 40-mg arm (74.2 *vs* 62.9%; *P* = .035).

The use of other medications for ACS was similar in both groups, as shown in Table 2. Almost 100% of the patients in both groups were prescribed aspirin and $P2Y_{12}$ inhibitors, while 71.4% of the patients in the atorvastatin 40-mg group compared to 66.9% of those in the atorvastatin 80-mg group were prescribed an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, and >90% of the patients in both groups received a β-blocker.

3.3 | Effectiveness outcomes

There was no statistically significant difference between the atorvastatin 40- and 80-mg groups in the primary composite outcome of CVD-associated death, nonfatal ACS and nonfatal stroke at 1 month (0.8 *vs* 1.3%, HR = 0.60, 95% CI 0.10–3.30; *P* = .551). After adjusting for variables that are associated with ACS, including sex, age, geographical region of origin, smoking status, family history of CVD, hypertension, diabetes, chronic kidney disease, peripheral artery disease, CAD, index event of STEMI, index event of NSTEMI, index event of UA, primary PCI, number of deployed stents, type of stent, baseline LDL-C value and concomitant medications for ACS, the primary composite outcome did not differ between the 2 groups (aHR = 0.59, 95% CI 0.04–8.13; *P* = .690). Similarly, within 1 year of discharge, the primary composite outcome did not significantly differ between the atorvastatin 40- and 80-mg groups (3.2 *vs* 4.0%, HR = 0.58, 95% CI 0.22–1.50; *P* = .243, aHR = 0.57, 95% CI 0.18–1.80; *P* = .340) as shown in Table 3.

Likewise, as shown in Table 4, there was no difference in the secondary outcomes of all-cause mortality, CV mortality, fatal or nonfatal stroke, fatal or nonfatal ACS, coronary revascularization, stent thrombosis, and stent restenosis at 1 month and at 12 months post-discharge. Although atorvastatin 40 and 80 mg appeared similar in reducing LDL-C to <70 mg/dL (24 *vs* 22.5%), atorvastatin 80 mg compared to the 40 mg significantly reduced the LDL-C by >50% from baseline (21.2 *vs* 15.2%; *P* = .022). However, we were able to obtain the LDL-C levels after discharge for around 40% of the patients in both groups.

3.4 | Safety outcomes

The frequency of adverse events related to the statin therapy was very low in both groups, with myopathy occurring in around 0.8% and increased ALT to >3× ULN in around 0.7% in both groups, as shown in Table 4. Only 3 patients (0.3%) in the atorvastatin 40-mg group and no patients in the 80-mg group discontinued the statin therapy secondary to adverse events.

3.5 | Predictors of prescribing atorvastatin 80 mg in ACS

As shown in Table 5, the likelihood of physicians prescribing atorvastatin 80 mg increased by around 4-fold in patients diagnosed with STEMI (aOR = 3.8, 95% CI 2.2–6.5; *P* < 0.001). The increase in

TABLE 1 Baseline characteristics of acute coronary syndrome patients receiving 2 different high-intensity atorvastatin doses (*n* = 626)

Characteristic	All patients (*n* = 626)	Atorvastatin 40-mg users (*n* = 475)	Atorvastatin 80-mg users (*n* = 151)	*P*-value
Male sex	606 (96.8)	457 (96.2)	149 (98.7)	.185*
Age	50 ± 9.14	50 ± 8.9	48 ± 9.7	.020
Weight	77 ± 14.52	77 ± 14.6	77 ± 14.2	.824
Region of origin				.015*
Asia	455 (72.7)	358 (75.4)	97 (64.2)	
Middle East	152 (24.3)	104 (21.9)	48 (31.8)	
Africa	13 (2.1)	10 (2.1)	3 (2.0)	
Europe	2 (0.3)	2 (0.4)	0	
North America	3 (0.5)	1 (0.2)	2 (1.3)	
South America	1 (0.2)	0	1 (0.7)	
Smoking	293 (46.8)	214 (45.1)	79 (52.3)	.376
Alcohol	46 (7.3)	27 (5.7)	19 (12.6)	.005
Family history of CAD	97 (15.5)	67 (14.1)	30 (19.9)	.091
Ejection fraction				>.999*
≤40%	102 (16.3)	77 (16.2)	25 (16.6)	
>40%	522 (83.4)	396 (83.4)	126 (83.4)	
LDL-C (mg/dL)	115 ± 43.4	110 ± 41.9	130 ± 44.7	<.001
TC (mg/dL)	185 ± 46.6	181 ± 45.4	196 ± 48.6	.001
HDL (mg/dL)	35 ± 9.9	34 ± 9.9	37 ± 9.7	.010
HbA1c (%)	7.2 ± 2.1	7.2 ± 2.1	7.3 ± 2.2	.624
ALT	33 ± 21.6	34 ± 23.6	30 ± 13.3	.043
AST	40 ± 42.3	43 ± 47.4	30 ± 14.9	.001
Hypertension	254 (40.6)	198 (41.7)	56 (37.1)	.316
Dyslipidaemia	78 (12.5)	61 (12.8)	17 (11.3)	.830*
Diabetes mellitus	296 (47.3)	228 (48.0)	68 (45.0)	.525
Chronic kidney disease	15 (2.4)	12 (2.5)	3 (2.0)	>.999*
Hyperthyroidism	1 (0.2)	1 (0.2)	0	>.999*
Hypothyroidism	10 (1.6)	8 (1.7)	2 (1.3)	>.999*
Peripheral artery disease	2 (0.3)	2 (0.4)	0	>.999*
Coronary artery disease	73 (11.7)	64 (13.5)	9 (6.0)	.012
Index event				
STEMI	377 (60.2)	261 (54.9)	116 (76.8)	<.001
NSTEMI	210 (33.5)	180 (37.9)	30 (19.9)	<.001
Unstable angina	35 (5.6)	30 (6.3)	5 (3.3)	.162
PCI	490 (78.3)	358 (75.4)	132 (87.4)	.002
Primary PCI	252 (40.3)	186 (39.2)	66 (43.7)	.501*
CABG	17 (2.7)	17 (3.6)	0	.023*
Drug eluting stent	411 (65.7)	299 (62.9)	112 (74.2)	.035*
Bare metal stent	83 (13.3)	68 (14.3)	15 (9.9)	.292*
Coronary angiography access				.347
Transradial	540 (86.3)	413 (86.9)	127 (84.1)	
Transfemoral	75 (12)	54 (11.4)	21 (13.9)	
Most common culprit lesions				
Proximal LAD	227 (36.3)	179 (37.7)	48 (31.8)	.142
Middle LAD	188 (30)	131 (27.6)	57 (37.7)	.039
Proximal LCx	98 (15.7)	80 (16.8)	18 (11.9)	.134

(Continues)

TABLE 1 (Continued)

Characteristic	All patients (*n* = 626)	Atorvastatin 40-mg users (*n* = 475)	Atorvastatin 80-mg users (*n* = 151)	*P*-value
Number of stents				.108
0	150 (24.0)	124 (26.1)	26 (17.2)	
1	328 (52.4)	248 (52.2)	80 (53.0)	
2	121 (19.3)	83 (17.5)	38 (25.2)	
3	21 (3.3)	16 (3.4)	5 (3.3)	
4	6 (1.0)	4 (0.8)	2 (1.3)	

Values are expressed as *n* (%) or mean ± standard deviation;
**P*-value was calculated using Fisher's exact test; CAD: coronary artery disease; LDL: low-density lipoproteins, TC: total cholesterol; HDL: high-density lipoproteins; HbA1c: glycated hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LAD: left anterior descending artery; LCx: circumflex artery.

TABLE 2 Concurrent medications prescribed among the acute coronary syndrome patients receiving 2 different high-intensity atorvastatin doses (*n* = 626)

Medication class	All patients (*n* = 626)	Atorvastatin 40-mg users (*n* = 475)	Atorvastatin 80-mg users (*n* = 151)	*P*-value
Aspirin	626 (100.0)	475 (100.0)	151 (100.0)	--
$P2Y_{12}$ inhibitor	623 (99.5)	472 (99.4)	151 (100.0)	>.999*
List of $P2Y_{12}$ inhibitors				0.011*
Clopidogrel	565 (90.3)	437 (92.0)	128 (84.8)	
Ticagrelor	58 (9.3)	35 (7.4)	23 (15.2)	
ACE inhibitor or ARB	440 (70.3)	339 (71.4)	101 (66.9)	.294
List of ACE inhibitors				0.916*
Lisinopril	240 (38.3)	185 (38.9)	55 (36.4)	
Enalapril	12 (1.9)	9 (1.9)	3 (2.0)	
Ramipril	117 (18.7)	91 (19.2)	26 (17.2)	
Perindopril	37 (5.9)	27 (5.7)	10 (6.6)	
Fosinopril	1 (0.2)	1 (0.2)	0	
List of ARBs				0.435*
Valsartan	33 (5.3)	27 (5.7)	6 (4.0)	
Losartan	5 (0.8)	5 (1.1)	0	
Irbesartan	4 (0.6)	2 (0.4)	2 (1.3)	
Candesartan	1 (0.2)	1 (0.2)	0	
Beta-blocker	577 (92.2)	433 (91.2)	144 (95.4)	.094
List of β-blockers				.660*
Bisoprolol	317 (50.6)	237 (49.9)	80 (53.0)	
Metoprolol	256 (40.9)	193 (40.6)	63 (41.7)	
Carvedilol	7 (1.1)	6 (1.3)	1 (0.7)	
Atenolol	1 (0.2)	1 (0.2)	0	
Ivabradine	11 (1.8)	7 (1.5)	4 (2.6)	.504*
Nitrate	195 (31.2)	156 (32.8)	39 (25.8)	.206*

Values are expressed as *n* (%).
**P*-value was calculated using Fisher's exact test; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker.

TABLE 3 Primary outcomes of 2 different high-intensity atorvastatin doses in patients with acute coronary syndrome (*n* = 626)

Outcome	Atorvastatin 40-mg users (*n* = 475)	Atorvastatin 80-mg users (*n* = 151)	Hazard ratio 95% CI	*P*-value	Adjusted hazard ratio 95% CI	P-value
Primary endpoint at 1 month	4 (0.8)	2 (1.3)	0.60 (0.10–3.30)	.551	0.59 (0.04–8.13)	.690
CVD-associated death, nonfatal ACS, and nonfatal stroke						
Primary endpoint at 12 months	15 (3.2)	6 (4.0)	0.58 (0.22–1.50)	.243	0.57 (0.18–1.80)	.340
CVD-associated death, nonfatal ACS, and nonfatal stroke						

Values are expressed as *n* (%). CVD: cardiovascular disease; ACS: acute coronary syndrome

TABLE 4 Secondary outcomes of 2 high-intensity atorvastatin doses in patients with acute coronary syndrome (*n* = 626)

Outcome	Atorvastatin 40-mg users (*n* = 475)	Atorvastatin 80-mg users (*n* = 151)	Adjusted hazard ratio 95% CI	*P*-value
Secondary effectiveness endpoints at 1 month				
All-cause mortality	0	2 (1.3)	1 (0.03–35.2)	>.999
Cardiovascular mortality	0	2 (1.3)	1 (0.03–35.2)	>.999
Fatal or nonfatal stroke	0	0		
Fatal or nonfatal ACS	5 (1.1)	0	1 (0.10–9.60)	>.999
Coronary revascularization	2 (0.4)	0	1 (0.03–37.45)	>.999
Stent thrombosis	0	0		
Stent restenosis	0	0		
Secondary effectiveness endpoints at 12 months				
All-cause mortality	1 (0.2)	1 (0.7)	1 (0.02–41.29)	>.999
Cardiovascular mortality	1 (0.2)	1 (0.7)	1 (0.02–41.29)	>.999
Fatal or nonfatal stroke	4 (0.8)	0	--	.577*
Fatal or nonfatal ACS	11 (2.3)	4 (2.6)	0.79 (0.18–3.41)	.749
Coronary revascularization	5 (1.1)	3 (2.0)	0.62 (0.09–4.31)	.632
Stent thrombosis	0	0		
Stent restenosis	2 (0.4)	1 (0.7)	1 (0.02–66.3)	>.999
Lipid lowering outcomes				
LDL-C <70 mg/dL[a]	114 (24.0)	34 (22.5)	--	.812**
Reduction of LDL-C by 50%[a]	72 (15.2)	32 (21.2)	--	.022**
Safety outcomes				
Myopathy	4 (0.8)	1 (0.7)	--	>.999*
ALT >3× ULN	4 (0.8)	1 (0.7)	--	>.999*
AST >3× ULN	3 (0.6)	0	--	>.999*
Rhabdomyolysis	0	0		
Adverse drug event requiring statin discontinuation	3 (0.3)	0	--	>.999*

Values are expressed as *n* (%).

*P-value was obtained using Fisher's exact test;

**P-value was obtained using χ^2 test;

[a]Missing data for ~60% of study participants in both arms; ACS: acute coronary syndrome; LDL-C: low-density lipoproteins cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN, upper limit of normal.

tendency to prescribe atorvastatin 80 mg was also observed in ACS patients who underwent PCI (aOR of 2.8, 95% CI 1.5–5.2; *P* = .001). Similarly, the use of bare metal stent was associated with around 2-fold increase in atorvastatin 80-mg prescription (aOR = 2.2, 95% CI 1.1–4.3; *P* = .024).

4 | DISCUSSION

In this retrospective observational cohort study, we found that the use of 2 high-intensity doses of atorvastatin (40 *vs* 80 mg) post-ACS was associated with similar CV outcomes, including CVD-related

TABLE 5 Predictors of atorvastatin 80 mg use

Characteristic	Adjusted odds ratio 95% CI	*P*-value
STEMI	3.8 (2.2–6.5)	<.001
PCI	2.8 (1.5–5.2)	.001
Bare metal stent	2.2 (1.1–4.3)	.024

STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention

death, nonfatal ACS, and nonfatal stroke at 1 month and 12 months postdischarge. In addition, the 2 high-intensity doses of atorvastatin resulted in similar safety outcomes. Since a high-intensity statin therapy, such as atorvastatin 40 mg or 80 mg, is recommended by clinical practice guidelines for secondary prevention post atherosclerotic CVD based on landmark trials that mainly evaluated the efficacy and safety of atorvastatin 80 mg,[1,2] it was hypothesized that atorvastatin 40 mg would result in comparable CV benefit post-ACS when compared to the atorvastatin 80 mg.

The CV benefit of high-intensity statin therapy was demonstrated in a meta-analysis of 5 randomized controlled trials evaluating more *vs* less intensive statin therapy among a total of 39 612 individuals.[15] The meta-analysis showed a significant reduction in the major adverse vascular events of 15% (95% CI 11–18; $P < .0001$), nonfatal myocardial infarction (MI) of 13% (95% CI 7–19; $P < .0001$), coronary revascularization of 19% (95% CI 15–24; $P < .0001$), and ischaemic stroke of 16% (95% CI 5–26; $P = .005$) with the use of high-intensity statin. The benefit of atorvastatin 80 mg post-ACS specifically was well established in the PROVE-IT and IDEAL trials.[8,12] In the PROVE-IT trial, the use of atorvastatin 80 mg compared to pravastatin 40 mg over 2 years had resulted in a significant reduction in a composite endpoint of all-cause mortality, MI, UA requiring hospitalization, revascularization and stroke (22.4 *vs* 26.3, 95% CI 5–26; $P = .005$).[8] In the IDEAL trial, atorvastatin 80 mg compared to simvastatin 20 mg reduced nonfatal MI significantly (6 *vs* 7.2%, HR = 0.83; 95% CI, 0.71–0.98; $P = .02$) over a follow-up period of 4.8 years among patients with previous history of MI.[12] Compared to the PROVE-IT and IDEAL trials, the present study reported a lower event rate of the CV outcomes, which might be explained by the shorter follow-up period of 12 months. Nevertheless, the current study demonstrated a novel and reassuring observation, that atorvastatin 40 mg has similar CV benefits post-ACS in comparison to atorvastatin 80 mg.

According to the 2018 American College of Cardiology and American Heart Association (ACC/AHA) guidelines for dyslipidaemia for secondary prevention of CV events among patients who have atherosclerotic CVD, a high-intensity statin is defined as a statin therapy that lowers LDL-C by ≥50%.[2] Liu *et al*. showed that in a population of Chinese patients with ACS, high-intensity statin therapy (a loading dose of atorvastatin 80 mg/d prior to PCI, followed by a maintenance dose of 40 mg/d for 3 months post-PCI) was more effective in achieving an LDL-C target of ≤1.81 mmol/L than a conventional moderate-intensity statin therapy (atorvastatin 20 mg).[16] In the current study, atorvastatin 80 mg was significantly better in lowering LDL-C by ≥50% compared to atorvastatin 40 mg which is consistent with the CURE-ACS trial that mainly aimed at evaluating the LDL-C lowering effects of atorvastatin 40 *vs* 80 mg and showed a greater reduction of LDL-C in the atorvastatin 80-mg group compared to the 40-mg group (27.5 *vs* 19.04%).[11] Despite the baseline LDL-C being significantly higher in the atorvastatin 80-mg group (130 ± 44.7 *vs* 110 ± 41.9 mg/dL; $P < .001$), both doses were able to reduce LDL-C to <70 mg/dL, which is the target LDL-C for patients with very high risk of atherosclerotic CVD as per the 2018 ACC/AHA guidelines for dyslipidaemia.[2] However, the follow-up data of LDL-C were only available for 40% of the study patients, which might be explained by the fact that 2013 ACC/AHA guidelines for dyslipidaemia for secondary prevention of CV events recommended using a high-intensity statin post-ACS regardless of LDL-C.[1] One study showed that, in patients undergoing coronary revascularization who achieved an LDL-C < 70 mg/dL or >50% reduction from baseline level, there was a lower risk of a primary outcome of a composite of cardiac death, myocardial infarction or stroke, in the high-intensity statin therapy group (atorvastatin 40 or 80 mg, and rosuvastatin 20 mg) compared to non–high-intensity statin therapy and concluded that lower major adverse CV outcomes with the use of the former was achieved regardless of LDL-C target achieved.[17] It is important to highlight that our study's review period was from 1 January 2017 to 31 December 2018 with 1-year follow-up, and the new AHA dyslipidaemia guidelines that recommended targeting a specific LDL-C was published in November 2018.[2] This might explain why our clinicians were not following-up the LDL-C postdischarge until the new guidelines were out and reversed the old recommendation. Therefore, this finding should be interpreted in the light of this limitation.

In addition to similar effectiveness between the 2 high-intensity doses of atorvastatin, this study demonstrated similar safety outcomes, including liver toxicity, myopathy, and rhabdomyolysis, with a very low event rate of <1%, which is consistent with high-intensity statin landmark trials.[8,10,12]

In the present study, we further investigated the predictors of prescribing atorvastatin 80 mg compared to 40 mg as the rate of prescribing 80 mg at our facility is low, which resulted in unbalanced study groups in terms of the number of the study participants. Upon conducting the screening of patients who were prescribed high-intensity atorvastatin doses at our facility during the study period, we found that atorvastatin 80 mg to 40 mg prescribing ratio was 1:19. The factors that were significantly associated with prescribing atorvastatin 80 mg were STEMI as an index event, PCI as the method of treatment of the index event, and bare metal stent implantation. These findings demonstrate the prescribing pattern of atorvastatin high-intensity doses at our facility, but do not present causality.

This study was a retrospective observational cohort study using real-world data that are susceptible to potential limitations. First, the study's follow-up period was only 1 year, which could be considered relatively short when compared with other CV prospective studies. Although a 1-year follow up might have been adequate for several of

the secondary outcomes, including stent thrombosis, stent restenosis, and for most of the safety outcomes, it might have underestimated the primary outcomes, which could explain the low event rate of primary outcome in our study. Second, the retrospective nature of the study and the reliance on the electronic medical records to collect the relevant data carries the possibility of missing some data, including laboratory values such as lipoprotein panel examination. However, the nonadherence of clinicians to monitoring lipid panel postdischarge could have been mainly due to changes in the AHA dyslipidaemia guidelines recommendation for targeting LDL-C while on high-intensity statin therapy. Additionally, we could not guarantee the patients' attendance to their regular follow-up visits as the study was a retrospective noninterventional study and attending the follow-up visits was at the patients' discretion. Nevertheless, we do not think that this limitation has affected our primary outcome or most of our secondary outcomes, as the study site is the primary CV tertiary care and referral centre in the country and the occurrence of any of the primary outcome and most of the secondary outcomes will warrant a transfer to our facility. Third, the effectiveness outcomes were adjusted for clinically significant patient and disease variables; however, there is a potential for other measured or unmeasured variables to influence the results. Fourth, the number of atorvastatin 40- and 80-mg users was relatively small, and the groups had an unequal number of participants due to the prescribing pattern of atorvastatin high-intensity doses at our facility, which might have affected the robustness of the analyses. Nevertheless, this retrospective observational cohort study aimed to answer a clinically important question that is faced by cardiologists in daily practice, and it could serve as a preliminary indicator for future prospective studies to assess the impact of atorvastatin 40 mg post-ACS on CV outcomes. Finally, power analysis was not applied due to the small patient population in our country and the facility where the study was conducted. Therefore, we used total population sampling, where we included all patients who fulfilled the study eligibility criteria during the pre-specified study review period.

In conclusion, the use of atorvastatin 40 mg in comparison to atorvastatin 80 mg after ACS had resulted in comparable effectiveness and safety outcomes over a follow-up period of 1 year. Therefore, following ACS, clinicians may use either high-intensity atorvastatin dose. However, larger studies with a longer follow-up period are warranted to confirm the findings of the present study.

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COMPETING INTERESTS

There are no competing interests.

CONTRIBUTORS

A.R., A.A., A.M. and A.R.A. conceived the study. A.R., F.K., A.H.A., Y.A., H.A., M.H. and I.A. were involved in the data collection process. A.R., F.K., A.R.A. and A.A. analysed and interpreted the data. A.R., F.K., A.M., S.A., A.A., A.H.A., Y.A., H.A., I.A. and A.R.A. interpreted the results. A.R., F.K., A.M., S.A. and A.A. wrote the manuscript. All authors revised the manuscript and approved the final manuscript for submission.

DATA AVAILABILITY STATEMENT

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.

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