Safety and efficacy of high-potency statin in Chinese patients with established cardiovascular disease

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ABSTRACT

Clinical guidelines recommend the use of high-intensity statins in patients with acute coronary syndrome (ACS). Yet, most clinical trials were conducted in mainly Caucasian population. This study investigated the relationship between statin intensity (low, moderate or high potency), low-density lipoprotein cholesterol (LDL-C) goal attainment and safety outcomes within 1 year of statin therapy in Chinese ACS patients. A retrospective study was conducted at the Prince of Wales Hospital during 1 August 2010 to 13 November 2014. Efficacy outcomes include percentage LDL reduction, target lesion revascularization (TLR) and ACS-related accident & emergency department (AED) readmission. Composite safety outcomes include myopathy, liver function test derangement and impaired glycemic control were evaluated. A total of 357 ACS patients were recruited. Low-, moderate- and high-intensity statins can achieve 21% (95% CI: 11.1% to 30.9%), 32.8% (95% CI: 26.9% to 38.7%), 57.8% (95% CI: 48.1% to 67.4%) LDL-C reduction respectively. Using high-intensity statins is more likely than moderate-intensity statins to achieve ≥50% LDL-C reduction respectively (OR: 9.437, 95% CI: 4.028 to 22.107) (p < 0.0001). High-intensity statins are more likely to achieve LDL-C <1.8mmol/L than moderate-intensity statins (OR: 6.398, 95% CI: 2.716 to 15.072) (p < 0.0001). Low-intensity statins are not significantly different from moderate-intensity to achieve LDL-C <1.8mmol/L (OR: 0.559, 95% CI: 0.305 to 1.026) (p = 0.061). The relationship between statin intensity and LDL-C goal attainment was adjusted for age, gender, smoking status, alcohol consumption, family history of ACS, baseline LDL-C and regular exercise of subjects. High-intensity statin users were more likely than moderate-intensity statin users to have impaired fasting blood glucose and Haemoglobin A1C (OR: 2.495, 95% CI: 1.048 to 5.94; OR: 2.805, 95% CI: 1.143 to 6.883) (p = 0.039; p = 0.024). A total of 42 (11.8%) TLR or ACS-related AED readmission were recorded. There was no significant difference in the composite endpoint between low-potency statin users and moderate-potency statin users (OR 0.61, 95% CI 0.24-1.55, P=0.298) or between high-potency statin users and moderate-potency statin users (OR 0.42, 95% CI 0.09-1.92, P=0.263). High-intensity statins are more likely than moderate-intensity statins to have impaired fasting blood glucose (OR: 2.495, 95% CI: 1.048 to 5.94; p= 0.039) and HbA1c (OR: 2.805, 95% CI: 1.143 to 6.883; p = 0.024). The present study showed that high-intensity statins result in greater LDL-C reduction and more adverse effects than statins of lower intensity. However, statin intensity and LDL-C goal attainment have no significant effects on the incidence and time-to-event of the efficacy outcomes.

Keywords: *Acute coronary syndrome, Lipid management, statins, Low-density cholesterol, Safety, Efficacy.*

INTRODUCTION

Serum LDL level is known to be associated with atherosclerotic cardiovascular disease (ASCVD) including acute coronary syndrome (ACS) for decades.[1,2] HMG-CoA reductase inhibitors (statins) are commonly used drugs to lower serum LDL cholesterol (LDL-C) level to prevent ASCVD. In recent years, international guidelines recommend more stringent LDL-C levels. In US, for patients that have a history of ASCVD, the new guideline recommends the use of high-intensity statin for secondary prevention, which on average reduces LDL-C

by at least 50%.[3] In European and Canadian guidelines base their recommendations on "the lower, the better" approach. These guidelines recommend targeting a very low absolute LDL-C level with statins to reduce the total cardiovascular risk. Both guidelines recommend an LDL-C target of less than 1.8 mmol/L for very high-risk patients including patients with history of ASCVD.[4,5] In our previous pilot study, Hong Kong patients were using statin doses lower than recommended for secondary prevention of ASCVD in western guidelines but did not automatically translate into worse clinical outcomes.[6] Similar findings were observed in Korean and Japanese studies[7,8,9] All these findings lead to a doubt of whether taking high-intensity statins is beneficial for Chinese or Asian patients for secondary prevention of ASCVD. In addition, since majority of the subjects involved in the clinical trials of statin therapy which are taken into consideration by treatment guidelines are Caucasians, the efficacy of achieving absolute LDL-C level of < 2.6 and 1.4 mmol/L recommended by western guidelines should be further studied in local eastern situation.

Statins are one of the safest cholesterol-lowering drugs, but still there are concerns regarding their risk of hepatotoxicity, increased risk of myopathy and increased risk of new onset of diabetes mellitus (DM). For hepatotoxicity, the National Institute of Health Guidelines defined drug-induced liver injury by alanine aminotransferase (ALT) level of three times the upper limit of normal (ULN). However, the actual incidence of elevated ALT level is rare. As reported by a meta-analysis published in 2003, the incidence of ALT elevation more than three times ULN was found to be 1.3% with statins and 1.1% with placebo with no case of acute liver failure.[10] Another commonly reported adverse effect of statins is statin-associated muscle symptoms (SAMS). Statistics from patient registries and clinical experience show that 7% to 29% of patients complain of SAMS.[11-15] However, in randomized controlled trials, the incidence of SAMS is substantially lower than that reported in observational studies. In The Effects of Statins on Muscle Performance (STOMP) study, 9.4% of the naïve atorvastatin 80mg-treated and 4.6% of control subjects met the study definition of myalgia after 6 months.[16] This may indicate the problem of lacking a consensus on the definitions of SAMS. Therefore, the European Atherosclerotic Society (EAS) published a consensus statement on SAMS in 2015. **Table 1** lists out the definitions of SAMS proposed by EAS.[17] As for the increased new onset of DM after taking statins, there are evidence that statins can modestly increase plasma glucose level. A meta-analysis combining 13 studies with total 91,140 patients shows that it takes treating 255 patients with statins for 4 years to have one extra case of new onset DM.[18] Thus, statins provide excellent benefit-to-risk profile in preventing ASCVD. Despite the safe profile of statins, there are still some concerns about the safety of targeting very low LDL-C level with statin therapy. One study found that there is an increased risk of non-cardiovascular death in very aggressive treatment to LDL of less than 40 mg/dL (~1.03 mmol/L).[19] Another study, which is a post-hoc analysis of JUPITER trial found that more diabetes mellitus, hematuria, hepatobiliary disorders, and insomnia were resulted when targeting LDL of less than 30 mg/dL (~0.78 mmol/L).[20] Based on the above findings, some research gaps are identified for further investigation more specifically in the Chinese population. As a result, this study aimed to investigate whether high-intensity statins are safe and efficacious in the Hong Kong Chinese population.

METHODS

This study was a retrospective observational cohort study. The study site was at the Prince of Wales Hospital (PWH). Patients naive to statins who were admitted to PWH due to ACS and had out-patient follow-up at the Cardiology Clinic of PWH are the target population. The actual sample includes the cohort of patients in the target population who were newly started on statin with an index date from 1 August 2010 to 13 November 2014. The list of patients was acquired through the Clinical Data Analysis and Reporting System (CDARS). Included subjects should be naïve to statin therapy and are required to have at least one year of unchanged statin therapy after the index date. Patients taking drugs that interact with statins with clinical significance are excluded because the interacting drugs may affect the LDL-C control or affect the incidence of myopathy, liver function test derangement or new-onset DM. Clinically significant interactions with statins are defined according to a review article.[21] Only when the interaction meets the criteria of clinical significance will the case be excluded. Examples of drugs that can induce secondary dyslipidemia include corticosteroids, anabolic steroids, progestins and protease inhibitors.[22] Patients taking these drugs concurrently with statins should be excluded because secondary dyslipidemia may affect the control of LDL-C by statins. On the other hand, some diseases can also induce secondary dyslipidemia. Examples include nephrotic syndrome, hypothyroidism, obstructive liver disease and chronic renal failure requiring hemodialysis and transplantation.[22] Apart from the above, patients who have documented fatty liver or non-alcoholic steatohepatitis (NASH) are excluded because they can also cause liver function test (LFT). Included subjects were then classified based on four criteria – statin intensity, achievement of ≥50% LDL-C reduction in one year and achievement of ultra-low LDL-C level (<1.8 and 2.6 mmol/L) after one year. Among the sub-groups under each category, efficacy and safety outcomes were compared. During the study period, the latest LDL-C goal of 1.4 mmol/L was not published yet, therefore, we evaluated the impact of the target of LDL-C goal of 1.8 mmol/L.

Table 1. Patients' Demographics

	Overall (N=357)	High-potency statins (N=42)	Moderate-potency statins (N=246)	Low-potency statins (N=69)	P-value
Demographic characteristic / Family history of ACS					
Gender - Male - Female	 268 (75.1%) 89 (24.9%)	 35 (83.3%) 7 (16.7%)	 186 (75.6%) 60 (24.4%)	 47 (68.1%) 22 (31.9%)	0.187
Mean age at index event	66.6 ± 11.8	60 ± 10	66.3 ± 11.5	71.7 ± 11.6	<0.0001
Mean BMI (n)	25.5 ± 3.27 (n= 50)	25.0 ± 2.97 (n = 10)	25.9 ± 3.42 (n = 31)	24.3 ± 3 (n = 9)	0.383
Family history of ACS - Yes - No - Unknown	 7 (2.0%) 10 (2.8%) 340 (95.2%)	 2 (4.8%) 2 (4.8%) 38 (90.5%)	 4 (1.6%) 8 (3.3%) 234 (95.1%)	 1 (1.4%) 0 (0%) 68 (98.6%)	0.201
Lifestyle					
Smoking history - Active smoker - Ex-smoker - Non-smoker - Unknown	 96 (26.9%) 87 (24.4%) 157 (44.0%) 17 (4.8%)	 15 (35.7%) 5 (11.9%) 20 (47.6%) 2 (4.8%)	 70 (28.5%) 60 (24.4%) 103 (41.9%) 13 (5.3%)	 11 (15.9%) 22 (31.9%) 34 (49.3%) 2 (2.9%)	0.091
Alcohol drinking history - Active drinker - Social drinker - Ex-drinker - Non-drinker - Unknown	 27 (7.6%) 12 (3.4%) 6 (1.7%) 144 (40.3%) 168 (47.1%)	 6 (14.3%) 1 (2.4%) 0 (0%) 14 (33.3%) 21 (50.0%)	 17 (6.9%) 9 (3.7%) 5 (2.0%) 97 (39.4%) 118 (48.0%)	 4 (5.8%) 2 (2.9%) 1 (1.4%) 33 (47.8%) 29 (42.0%)	0.717
Regular exercise - Yes - No - Unknown	 33 (9.2%) 9 (2.5%) 315 (88.2%)	 5 (11.9%) 3 (7.1%) 34 (81.0%)	 22 (8.9%) 5 (2.0%) 219 (89.0%)	 6 (8.7%) 1 (1.4%) 62 (89.9%)	0.326
At index event					
Index event					<0.0001
STEMI	142 (39.8%)	27 (64.3%)	98 (39.8%)	17 (24.6%)	
NSTEMI	132 (37.0%)	9 (21.4%)	97 (39.4%)	26 (37.7%)	
Unstable angina	83 (23.2%)	6 (14.3%)	51 (20.7%)	26 (37.7%)	
Mean baseline LDL-C	3.03 ± 0.905	3.84 ± 1.04	3.04 ± 0.822	2.51 ± 0.72	<0.0001
Coronary catheterization - Yes - No	 304 (85.2%) 53 (14.8%)	 40 (95.2%) 2 (4.8%)	 213 (88.6%) 33 (13.4%)	 51 (73.9%) 18 (26.1%)	0.005
Primary PCI - Yes - No	 246 (85.2%) 111 (14.8%)	 34 (81.0%) 8 (19.8%)	 176 (71.5%) 70 (28.5%)	 36 (52.2%) 33 (47.8%)	0.002
Primary CABG - Yes - No	 20 (5.6%) 337 (94.4%)	 3 (7.1%) 39 (92.9%)	 12 (4.9%) 234 (95.1%)	 5 (7.2%) 64 (92.8%)	0.550
Thrombolytic - Yes - No	 52 (14.6%) 305 (305%)	 10 (23.8%) 32 (76.2%)	 34 (13.8%) 212 (86.2%)	 8 (11.6%) 61 (88.4%)	0.175
Comorbidities / Past medical history					
Hypertension - Yes - No	 177 (49.6%) 180 (50.4%)	 14 (33.3%) 28 (66.7%)	 115 (46.7%) 131 (53.3%)	 48 (69.6%) 21 (30.4%)	<0.0001
Hyperlipidemia - Yes - No	 72 (20.2%) 285 (79.8%)	 8 (19.0%) 34 (81%)	 55 (22.4%) 191 (77.6%)	 9 (13.0%) 60 (87%)	0.230
Diabetes mellitus - Yes - No	 52 (14.6%) 305 (85.4%)	 1 (2.4%) 41 (97.6%)	 36 (14.6%) 210 (85.4%)	 15 (21.7%) 54 (78.3%)	0.020
Past ACS - Yes - No	 18 (5.0%) 339 (95%)	 3 (7.1%) 39 (92.9%)	 12 (4.9%) 234 (95.1%)	 3 (4.3%) 66 (95.7%)	0.697
Past CVA - Yes - No	 10 (2.8%) 347 (97.2%)	 0 (0.00%) 42 (100%)	 9 (3.7%) 237 (96.3%)	 1 (1.4%) 68 (98.6%)	0.468
CHF - Yes - No	 11 (3.1%) 346 (96.9%)	 0 (0.00%) 42 (100%)	 10 (4.1%) 236 (95.9%)	 1 (1.4%) 68 (98.6%)	0.385
PAD - Yes - No	 1 (0.3%) 356 (99.7%)	 0 (0.00%) 42 (100%)	 1 (0.4%) 245 (99.6%)	 0 (0.00%) 69 (100%)	1.000

BMI = Body-mass index, STEMI = ST-elevation myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, PCI = Percutaneous coronary intervention, CABG = Coronary artery bypass grafting, CVA = cerebrovascular accidents (including stroke or TIA), CHF = Congestive heart failure, PAD = Peripheral arterial disease. *Values of continuous variables are reported as mean ± standard deviation. Categorical variables are reported as n (%).

The primary outcomes of the current study included the change of LDL-C levels and the safety outcomes related to the use of statin therapy. The LDL-C level measured during admission was collected as baseline LDL level. The LDL-C level measured between 12 months after admission was collected. The percentage of LDL-C reduction was calculated by baseline LDL and 1-year LDL. 1-year LDL was used to determine whether the patient attained an absolute LDL target such as <2.6mmol/L or <1.8mmol/L. The safety outcomes related to the use of statin therapy included derangement of LFT, muscle symptoms, elevation of serum creatine kinase (CK) levels and new onset of fasting blood glucose (FBG) elevations. Derangement of LFT was defined as elevated liver transaminase (more than 3 times the upper limit of normal) on 2 or more occasions.[23,24] Both reported muscle symptoms and elevation of serum CK to more than 10 times the upper limit of normal (ULN) were measured since these two presentations are regarded as myopathy when they happen concurrently.[24] New-onset Type-2 diabetes mellitus was measured as new-onset FBG ≥7mmol/L or new-onset HbA1c≥6.5%. Due to the very low incidence of adverse effects in our pilot study, a composite endpoint of all the above adverse effects was tested.

The secondary outcomes included the time-to- target lesion revascularization (TLR) and time to ACS related Accident & Emergency Department (AED) readmission (time-to-AED) were collected. Survival analyses on time-to-TLR and time-to-AED were performed for each target %LDL reduction (10%, 20%, 30%, 40%, 50%, 60% and 70%) by comparing the group attaining the goal and the group not attaining. Target lesion revascularization is defined as repeated percutaneous coronary intervention (PCI) that was done to previously stented vessel. TLR was done when the patient was admitted due to clinical symptoms or restenosis was found in previously stented vessel during repeated coronary angiography.

STATISTICAL ANALYSIS

Baseline comparison, categorical baseline characteristics were expressed in percentage proportions while numerical continuous characteristics were expressed in mean ± standard deviation. Chi-square test or Fisher's exact test was used to investigate the association between categorical baseline characteristics and study sub-groups. One-way ANOVA with subsequent post-hoc comparisons or independent sample t-test was used to compare the means of numerical continuous characteristics among different study sub-groups. For primary outcome analysis, mean percentage LDL-C reduction among study sub-groups were compared using two-way ANOVA to adjust for interaction from other covariates. The relationship between binary categorical outcomes and their predictors are analyzed using binary logistic regression to control for other covariates. For secondary outcome analysis, Kaplan-Meier survival curves and log-rank tests are used to compare the time-to-secondary outcome among different LDL-C goal attainment. All statistical tests are based on level of significance of 5% (α= 0.05). Microsoft Excel 2010 and IBM SPSS Statistics 22 were adopted for statistical analysis in this study.

RESULTS

A total of 592 patient records were reviewed and among them 235 cases were excluded based on the exclusion criteria **(Figure 1)**. Therefore, the final recruited patients were 357 for the current study. Baseline characteristics between groups of statin potencies were compared in **Table 1**. The mean age, type of index event, mean baseline LDL-C, rate of coronary catheterization, rate of percutaneous coronary intervention (PCI), rate of preexisting hypertension and rate of preexisting diabetes mellitus were significantly different among the group of high-potency, moderate-potency, and low-potency statin. No significant differences in other baseline characteristics were detected among the three groups. Binary logistic regression demonstrated that statin intensity has a significant impact on the probability of achieving ≥50% LDL-C reduction from baseline after 1 year of statin therapy. Using low- and high-intensity statins is less likely and more likely than moderate-intensity statins to achieve ≥50% LDL-C reduction respectively (OR: 0.212, 95% CI: 0.09 to 0.498; OR: 9.437, 95% CI: 4.028 to 22.107) ($p < 0.0001$; $P < 0.0001$). As covariates, it is found that active smokers are less likely than non-smokers to achieve ≥50% LDL-C reduction (OR: 0.362, 95% CI: 0.177 to 0.742) ($p = 0.005$). Age (OR: 0.996, 95% CI: 0.972 to 1.02) ($p = 0.734$), gender (OR: 0.991, 95% CI: 0.514 to 1.912) ($p = 0.979$), alcohol consumption ($p = 0.789$) and regular exercise ($p = 0.522$) have no significant effect on the probability of achieving ≥50% LDL-C reduction. Regarding the LDL-C goal of < 1.8 mmol/L, high-intensity statins are more likely to achieve LDL-C <1.8mmol/L than moderate-intensity statins (OR: 6.398, 95% CI: 2.716 to 15.072) ($p < 0.0001$). However, low-intensity statins are not significantly different from moderate-intensity to achieve the goal (OR: 0.559, 95% CI: 0.305 to 1.026) ($p = 0.061$). Apart from statin intensity, baseline LDL-C also has a significant effect on the probability of achieving the LDL-C goal (OR: 0.479, 95% CI: 0.355 to 0.647) ($p < 0.0001$). In other words, it is less likely to achieve LDL-C <1.8 mmol/L with higher baseline LDL-C. Active smokers are also less likely to achieve the goal compared to non-smokers (OR: 0.46, 95% CI: 0.242 to 0.872) ($p = 0.017$).

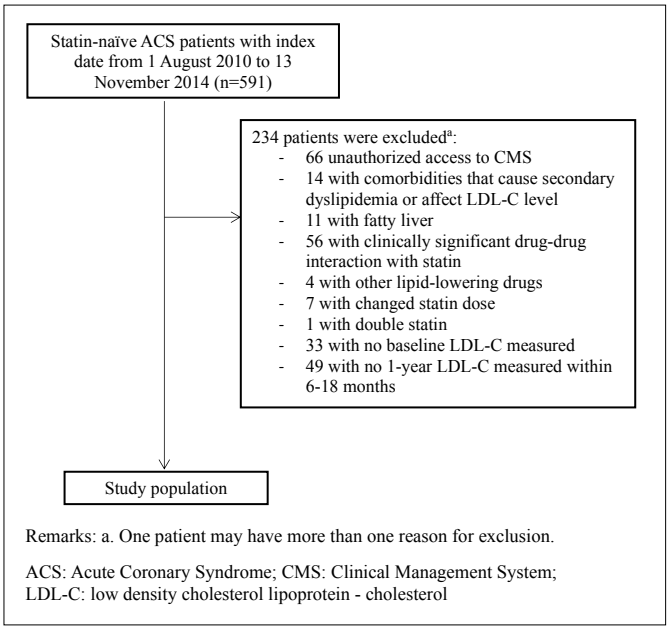

***Figure 1**: Study flow*

The safety outcomes related to statin therapy in the current study is summarized in **Table 2**. There were none or only very limited number of cases with CK >10 ULN, muscle symptoms and LFT derangement (defined as ALT >3ULN on 2 or more occasions). A composite endpoint of liver function test derangement, muscle symptoms, elevated creatine kinase (>10 ULN), new-onset impaired fasting blood glucose (FBG≥7mmol/L) or new-onset HbA1c (≥6.5%) was used in logistic regression. High-potency statin users were more likely to have either one of the above adverse effects than moderate-potency statin users (OR 2.86, 95% CI 1.33-6.18, P=0.007). However, there was no significant difference between low-potency and moderate potency (OR 0.83, 95% CI 0.40-1.72, P=0.613). In addition, the effect of statin potency on fasting blood glucose and HbA1c was separately studied after excluding the patients with pre-existing diabetes mellitus. High-potency statin was more likely to cause new-onset impaired FBG (≥7mmol/L) than moderate-intensity statin (OR 2.50, 95% CI 1.05-5.94, P=0.039). However, there was no significant difference between the effect of low-potency and moderate-potency statin (OR 0.96, 95% 0.40-2.31, P=0.924). Regarding HbA1c, high-potency statin was more likely to cause new-onset impaired HbA1c (≥6.5%) than moderate-potency statin (OR 2.80, 95% CI 1.14-6.89, P=0.024) but there was no significant difference between low-potency statin and moderate-potency statin (OR1.22, 95% CI 0.54-2.79, P=0.635). High-intensity statin users were more likely than moderate-intensity statin users to have impaired fasting blood glucose (OR: 2.495, 95% CI: 1.048 to 5.94) (p = 0.039). Low-intensity statin users were not significantly different from moderate-intensity in likelihood of causing impaired FBG (OR: 0.958, 95% CI: 0.398 to 2.305) (p = 0.924). It is found that achievement of LDL-C <2.6mmol/L, <1.8mmol/L and ≥50% LDL-C reduction from baseline have no significant effects on the incidence of impaired fasting BG in patients without prior history of DM (OR: 1.308, 95% CI: 0.416 to 4.111; OR: 1.123, 95% CI: 0.605 to 2.087; OR: 1.391, 95% CI: 0.687 to 2.814) (p = 0.646; p = 0.713; p = 0.359).

The cardiovascular outcomes in this study included TLR and ACS-related AED re-admission within 1 year of statin therapy. Logistic regression shows that achievement of ≥50% LDL-C reduction has no significant effect on the probability of TLR (OR: 1.344, 95% CI: 0.229 to 7.873) (p = 0.743) and ACS-related AED re-admission (OR: 0.561, 95% CI: 0.224 to 1.405) (p = 0.217) within 1 year of statin therapy. The same result appears in the composite outcome of TLR or ACS-related AED re-admission (OR: 0.79, 95% CI: 0.347 to 1.8) (p = 0.574).

Table 2. The safety outcomes related to statin therapy.

		Statin			Total (n=357)
		High-potency (n=42)	**Moderate- potency (n=246)**	**Low-potency (n=69)**	
Deranged LFT	Yes	0 (0%)	3 (1.2%)	0 (0%)	3 (0.8%)
	No	42 (100%)	243 (98.8%)	69 (100%)	354 (99.2%)
Muscle symptoms	Yes	0 (0%)	1 (0.4%)	0 (0%)	1 (0.3%)
	No	42 (100%)	245 (99.6%)	69 (100%)	356 (99.7%)
Elevated creatine kinase	Yes	0 (0%)	1 (0.4%)	0 (0%)	1 (0.3%)
	No	42 (100%)	245 (99.6%)	69 (100%)	356 (99.7%)
New-onset Impaired FBG	Yes	13 (31%)	37 (15.0%)	9 (13.0%)	59 (16.5%)
	No	28 (66.7%)	173 (70.3%)	45 (65.2%)	246 (58.9%)
	Having pre-existing DM	1 (2.4%)	36 (14.6%)	15 (21.7%)	52 (14.6%)
New-onset Impaired HbA1c	Yes	11 (26.2%)	31 (12.6%)	11 (15.9%)	53 (14.8%)
	No	30 (71.4%)	179 (72.8%)	43 (62.3%)	252 (70.6%)
	Having pre-existing DM	1 (2.4%)	36 (14.6%)	15 (21.7%)	52 (14.6%)

LFT: liver enzyme test; FBG: fasting blood glucose; DM: diabetes mellitus; HbA1c: Hemoglobin A1c

DISCUSSION

The current project confirmed that statin intensity has significant effect on attainment of some of the LDL-C goals of patients. It was shown that high-intensity statins are more likely than moderate-intensity statins to achieve ≥50% LDL-C reduction. Secondly, high-intensity statins are also more likely than moderate-intensity statins to achieve the absolute LDL-C goal of <1.8mmol/L. However, low-intensity statins are not significantly different from moderate-intensity statins to achieve LDL-C <1.8mmol/L. However, statin intensity has no significant effect on the probability of achieving absolute LDL-C goal of <2.6mmol/L. This may be explained by all statin intensity groups have similarly high likelihood in achieving LDL-C of <2.6mmol/L since it is not a very aggressive target. Hence there is no significant difference in the probability of goal attainment of LDL-C <2.6mmol/L. Apart from statin intensity, baseline LDL-C is shown to significantly affect the probability of achieving absolute LDL-C goal of <2.6 and <1.8mmol/L. Similar findings were observed in a Taiwanese retrospective study.[25] With increasing baseline LDL-C, it is less likely to achieve the two absolute LDL-C goals since the percentage LDL-C reduction required would become larger and make the goal attainment more difficult. Hence, for all statin intensity groups, baseline LDL-C is also an important covariate of the absolute LDL-C goal attainment.

The current study confirmed that LDL-C goal attainment of ≥50% reduction, <2.6mmol/L and <1.8mmol/L did not have significant effects on the incidence of impaired FBG. Yet, it showed that high-intensity statin users were more likely to result in impaired FBG and HbA1c than moderate-intensity statins. Ex-smokers also had significantly lower likelihood of having impaired FBG than non-smokers. The cause-and-effect relationship between statin therapy and impaired glycemic control is well documented. It was shown in a meta-analysis that 9% (OR: 1.09, 95% CI 1.02 to 1.17) more patients receiving statins were diagnosed with DM than those receiving placebo.[18] However, the incidence of new DM due to statins was very low. The meta-analysis also showed that it takes treating 255 (95% CI: 150 to 852) patients for 4 years to detect 1 extra case of DM.[18] In addition, a cross-sectional study showed the positive association between aging and elevated HbA1c levels after adjusting for gender, BMI, FBG, and 2-hour post-load glucose values.[26] From linear regression, it was found that for every 1 unit increase in age, HbA1c level increases for 0.012 units in non-diabetic patients. This is consistent with the findings of the present study. Past epidemiologic and cross-sectional studies showed that smoking can induce insulin resistance.[27-29] Several studies showed that current smokers have higher HbA1c levels than non-smokers, regardless of ethnicity.[30-35] However, it was shown in a multi-ethnic and multi-centre cross-sectional study that there is no significant difference in FBG among never-smokers, ex-smokers, and current smokers for fasting blood glucose.[36] Another meta-analysis involving over 35,000 patients also show that there is no significant difference in FBG between current and never-smokers.[37] These results are different from what has been found in the present study probably because of the large and unexplained heterogeneity of the effects in different populations.

For the safety outcomes, it was found that high-intensity statins are more likely than moderate-intensity statins to result in the composite adverse effects of CK elevation >10 ULN, muscle symptoms, LFT derangement and impaired glycemic control in the current study. Previously, a meta-analysis showed that the incidence of CK elevation >10 ULN is only 1 per 1000 to 1 per 10000 people per year.[38] In addition, The Effects of Statins on Muscle Performance (STOMP) study shows that 9.4% of atorvastatin 80mg-treated patients versus 4.6% placebo-treated patients developed myalgia.[16] Therapeutically, most patients complained of statin-associated muscle symptom (SAMS) with one statin can tolerate another statin well.[14,39] Therefore, SAMS may not be generalized to other statins and may even have other causes apart from statins. For LFT derangement, large trials of statins involving more than 48,000 patients have shown that there is no significant difference in the incidence of ALT > 3 ULN in statin group versus placebo group.[23] Same with SAMS, LFT derangement usually subsides if the statin is continued without interruption.[40] In the present study, only 3 cases of LFT derangement were detected and all of them were in the moderate-intensity group. It is worth to note that most patients in Hong Kong were in the moderate-intensity group.

In the current study, no significant effect was observed for the time-to-TLR and time-to-AED readmission among the three target LDL-C goals. For TLR, it was previously demonstrated that the overall incidence of TLR after PCI with drug-eluting stent is 3.8% at 2 years and 82.5% of the TLR occur within the first year after stenting.[41] There is also a study regarding incidence rate of TLR in the Chinese Han population. The incidence of TLR as shown is numerically higher than that in western population.[42] At only 7 months after drug-eluting stent implantation, there are already 5.5% patients have TLR. However, in the present study, there are only 7 cases of TLR in the whole sample of 357 patients within the follow-up period of 1 year (incidence rate = 1.96%), which indicates that the incidence rate of TLR is generally lower in the current study. Therefore, either a larger sample size or longer follow-up period is required to have more cases in each comparison group for an accurate comparison of time-

to-TLR using Kaplan-Meier analysis because study has shown that Kaplan-Meier analysis is likely inaccurate in small number of cases.[43] Therefore, no conclusive results can be obtained for the effect of LDL-C goal attainment on time-to-TLR in our Chinese population from the present study.

For ACS-related AED readmission, a large clinical study in the United States showed the incidence rate and time-to-event of ACS-related AED readmission within 1 year after starting statin therapy was 6.8% with a mean time-to-event of 4.9 months.[44] In the present study, the overall incidence rate is 10.4% (37 cases over 357 subjects) with a mean time-to-event of 87.4 days. Therefore, the incidence rate found in the current study in the study population was higher than the previously published US population. The mean time-to-event was also shorter numerically than the US population. But for the effect of LDL-C goal attainment on time-to-event, the number of readmissions in each comparison group was too small that led to inconclusive relationship between LDL-C goal attainment and time-to-A&E readmission in the current study.

Several limitations exist in the present study. Firstly, this was a single-centre study in one of the major acute public hospitals in Hong Kong. The results may not truly reflect the actual safety and efficacy profile of different intensities of statins and LDL-C goals in Hong Kong or Chinese population. Secondly, information including medication adherence and lifestyle modifications could not be obtained from the consultation notes of physicians with the retrospective nature of the study. Thirdly, a subject selection bias may exist in the present study because only subjects who remained on the same statin regimen throughout the 1-year therapy were included. Therefore, subjects who have switched their therapies due to unresponsiveness or over-responsiveness of their statin therapies were excluded. As a result, our analysis may over-estimate the efficacy of lower intensity statins & underestimate the efficacy of higher intensity statins.

CONCLUSION

The present study showed that high-intensity statins result in greater LDL-C reduction and more adverse effects than statins of lower intensity. However, statin intensity and LDL-C goal attainment have no significant effects on the incidence and time-to-event of the efficacy outcomes.

Conflict of Interest:

All authors declared that there was no conflict of interest during the study and the preparation of the manuscript.

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CE Questions Answer for 302(D&T)

Review of Monoclonal Antibodies for the Treatment of Crohn's Disease

1. C 2. D 3. A 4. C 5. B 6. D 7. C 8. B 9. A 10. B