ORIGINAL ARTICLE

# Low-density Lipoprotein Cholesterol Target Attainment in Patients with Stable or Acute Coronary Heart Disease in the Philippines: Results from the Dyslipidemia International Study II

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## ABSTRACT

**Objective.** To quantify the extent of hyperlipidemia and its treatment in patients with stable coronary heart disease (CHD) or an acute coronary syndrome (ACS) in the Philippines.

**Methods.** The Dyslipidemia International Study (DYSIS) II was an observational, multinational study conducted in patients aged ≥18 years with stable CHD or being hospitalized with an ACS. A full lipid profile was evaluated at baseline, and for the ACS cohort, at 4 months after discharge from hospital. Achievement of low-density lipoprotein cholesterol (LDL-C) targets and the use of lipid-lowering therapy (LLT) were assessed.

**Results.** A total of 232 patients were enrolled from 10 centers in the Philippines, 184 with stable CHD and 48 being hospitalized with an ACS. The mean LDL-C level for the CHD patients was 88.0±40.1 mg/dL, with 33.3% achieving the target of <70 mg/dL recommended for very high-risk patients. For the ACS cohort, the mean LDL-C level was 109.0±48.5 mg/dL, with target attainment of 25.0%. The majority of the CHD cohort was being treated with LLT (97.3%), while 55.3% of the ACS patients were receiving LLT prior to hospitalization, rising to 100.0% at follow-up. There was little use of non-statins.

**Conclusions.** For these very high-risk patients from the Philippines, LDL-C target attainment was poor. Opportunities for better monitoring and treatment of these subjects are being missed.

*Key Words: cholesterol, statins, coronary heart disease, acute coronary syndrome, myocardial infarction*

## INTRODUCTION

The continuing rise in the prevalence of cardiovascular disease is a serious global problem. Approximately half of the cases of this class of disease are located in Asia, with huge variations in associated mortality between the countries of the region.[1] In the Philippines, a national

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survey demonstrated increasing numbers of people with atherosclerosis-related risk factors, including dyslipidemia, diabetes and hypertension.[2] Furthermore, mortality due to cardiovascular disease has been reported to be higher in the Philippines than the majority of other Southeast Asian countries.[1] Adequate management of the cardiovascular risk factors in this country is therefore essential.

Lipid abnormalities, including high levels of low-density lipoprotein cholesterol (LDL-C), contribute greatly to the development and progression of cardiovascular disease. A study in Asia found that for every 1 mmol/L (39 mg/dL) increase in total cholesterol (TC), there was an increase in the risk of coronary death of around 35%.[3] The main focus of strategies to address hyperlipidemia has been the lowering of LDL-C levels, with the guidelines of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) advocating a value of <70 mg/dL (1.8 mmol/L) for patients at very high cardiovascular risk, such as those that have suffered an acute coronary syndrome (ACS).[4] In order to attain such a level, patients require lipid-lowering therapy (LLT), the mainstay of which is statins. These drugs have been shown to significantly lower LDL-C levels and reduce cardiovascular events.[5] If the target cholesterol value cannot be reached using this approach, drugs such as ezetimibe or fibrates may be used. Indeed, in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the addition of ezetimibe to simvastatin therapy resulted in greater lowering of LDL-C and a superior cardiovascular outcome compared to the statin alone.[6] Many patients being treated with LLT fail to achieve their recommended target LDL-C level. Of the 57,885 statin-treated subjects in the Dyslipidemia International Study (DYSIS), only 21.7% of those at very high cardiovascular risk had an LDL-C value of <70 mg/dL.[7] In Asia specifically, the Centralized Pan-Asian Survey on the Undertreatment of Hypercholesterolemia (CEPHEUS) demonstrated higher target attainment for very high-risk LLT-treated hypercholesterolemic patients, at 34.9%.[8] However, the study also demonstrated variations between the included countries in terms of the guidelines that were used and the resulting rates of target achievement for different risk categories. There is a clear need to evaluate hyperlipidemia on a national level.

DYSIS II was a global observational study established to quantify hyperlipidemia and the achievement of guideline-recommended lipid levels in patients with chronic and acute coronary heart disease (CHD). It further aimed to assess how LLT was being used in such patients.

## METHODS

### Study design and patients

DYSIS II was an observational, cross-sectional, multinational study. Patients in the Philippines were enrolled at 10 sites across the country from July 2013 to September 2014. Individuals over 18 years of age were recruited if they were attending a physician visit for stable CHD or if they were being hospitalized due to an ACS. CHD was defined as stenosis of >50%, diagnosed by either coronary angiography or cardiac CT; prior percutaneous coronary intervention (PCI); prior coronary artery bypass grafting (CABG); or documentation of an ACS more than 3 months prior to the appointment. ACS was defined as an ST-segment elevation myocardial infarction or left bundle branch block myocardial infarction (STEMI/LBBB-MI), a non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). Patients were excluded if they were participating in a clinical trial at the same time as the study, and for the ACS cohort, if they did not survive up until hospital discharge. Subjects were required to have a full lipid profile available. For the CHD cohort this was taken from the most recent blood test within the previous 12 months. For the ACS cohort, it was derived from blood taken within 24 h of hospital admission. Patients were divided according to whether or not they were being treated with LLT. In order to be included in the LLT groups, treatment duration had to be at least 3 months by the time of the lipid test. Data on the CHD patients were collected at the physician visit, while those for the ACS patients were collected at hospital admission and during a telephone interview 4 months later.

The study received approval from the ethics committee at each site and was conducted in accordance with the Declaration of Helsinki and its amendments.

### Documentation

A standardized case report form (CRF) was used for data collection. Details were then entered into an online database maintained at the Institut für Herzinfarktforschung, Ludwigshafen, Germany. Demographic and clinical variables were documented at the baseline physician visit for the CHD cohort and at hospital admission for the ACS cohort. These factors included age, gender, and body mass index (BMI); the presence of hypertension, diabetes mellitus, chronic kidney disease (CKD) or congestive heart failure (CHF); documentation of prior stroke or myocardial infarction (MI); and the presence of cardiovascular risk factors, including smoking, a sedentary lifestyle and a family history of CHD. Obesity was defined as a BMI of >30 kg/m$^2$. Hypertension was defined as current blood-pressure-lowering treatment, a previous diagnosis of hypertension, or a blood pressure reading of >140/90 mm Hg. Diabetes was defined as current treatment for diabetes, a previous diagnosis of diabetes, or a fasting plasma glucose level of ≥126 mg/dL. A sedentary lifestyle was defined as <20–30 minutes of walking on <3–4 days per week.

The lipid profile that was constructed for each patient contained measurements of serum LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, TC, and triglycerides. The proportions of patients that displayed an LDL-C level of <70 mg/dL, the ESC/EAS target for very

high-risk patients, were calculated for both cohorts.[9] For the ACS cohort, a pre-admission risk level was determined from the data collected at baseline. Achievement of the corresponding LDL-C levels was then calculated. The respective targets for the very high, high, moderate, and low-risk patients were <70 mg/dL, <100 mg/dL, <115 mg/dL, and <130 mg/dL.[9] At the 4-month follow-up point, any lipid profiles available from the period since hospital discharge were collected. LDL-C target attainment was again determined, with all patients considered to be at very high-risk, owing to their ACS.

Any LLT that the patients were being treated with was detailed on the CRF at baseline, and for the ACS cohort, at the 4-month follow-up. The statins evaluated were atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The non-statins included ezetimibe, nicotinic acid, fibrates, and omega-3 fatty acids. Both monotherapy and combination therapies were detailed. In order to allow comparisons to be made between the different statins, dosages were normalized to atorvastatin potency according to clinical trial data regarding the lipid-lowering abilities of the different statins.[10]

For the ACS cohort, any adverse events, including death or rehospitalization, were documented at the 4-month follow-up.

### Statistical analysis

SAS version 9.3 (Cary, NC, USA) was used for all the statistical analyses. Continuous variables are presented as means and standard deviations (SDs) or medians and interquartile ranges (IQRs), and categorical variables are presented as patient numbers and percentages. Differences between LLT-treated and not treated patients were analyzed using a chi-square or Mann–Whitney–Wilcoxon test. All the statistical comparisons were two-tailed and considered to be significant if the p-value was calculated to be <0.05. Multivariate logistic regression was carried out to determine factors that increased the likelihood of an LLT-treated patient achieving an LDL-C level of <70 mg/dL. The covariables included in the model were age, gender, obesity, current smoking, sedentary lifestyle, stable angina, hypertension, CKD, type 2 diabetes mellitus, history of CHF and statin dose.

## RESULTS

### Patients

A total of 232 patients were enrolled from 10 centers in the Philippines, 184 attending a physician visit for stable CHD and 48 being hospitalized with an ACS.

The CHD cohort had a mean age of 63.2 ± 11.5 years and 77.2% were male (Table 1). Of these, 97.3% were being treated with LLT at the time of their latest lipid test. There were no significant differences between the LLT-treated and not treated patients in terms of age, gender, BMI or comorbidities. Hypertension and type 2 diabetes mellitus were highly prevalent (80.4% and 57.1%, respectively). A lower percentage of the LLT patients were current smokers compared to those in the no LLT group (2.2% vs. 20%; p < 0.05).

**Table 1.** Patient characteristics – stable CHD cohort

| | All patients mean ± SD or % (n/N) (N = 184) | LLT mean ± SD or % (n/N) (N = 179) | No LLT mean ± SD or % (n/N) (N = 5) | p-value (LLT vs. no LLT) |
|---|---|---|---|---|
| Age (years) | 63.2 ± 11.5 | 63.3 ± 11.6 | 59.4 ± 5.7 | 0.32 |
| Male | 77.2 (142/184) | 77.1 (138/179) | 80.0 (4/5) | 0.88 |
| BMI (kg/m$^2$) | 26.4 ± 4.2 | 26.4 ± 4.2 | 25.7 ± 2.2 | 0.76 |
| BMI > 30 kg/m$^2$ | 17.9 (33/184) | 18.4 (33/79) | 0.0 (0/5) | 0.29 |
| Comorbidities and CV risk factors | | | | |
| Type 2 diabetes mellitus | 57.1 (105/184) | 58.1 (104/179) | 20.0 (1/5) | 0.09 |
| Hypertension | 80.4 (148/184) | 80.4 (144/179) | 80.0 (4/5) | 0.98 |
| CKD | 15.8 (29/184) | 15.6 (28/179) | 20.0 (1/5) | 0.79 |
| Prior stroke* | 9.3 (17/182) | 9.0 (16/177) | 20.0 (1/5) | 0.41 |
| PAD | 3.9 (7/181) | 4.0 (7/176) | 0.0 (0/5) | 0.65 |
| Current smoker | 2.7 (5/184) | 2.2 (4/179) | 20.0 (1/5) | <0.05 |
| Sedentary lifestyle | 43.7 (79/181) | 43.2 (76/176) | 60.0 (3/5) | 0.46 |
| Family history of CHD | 58.3 (102/175) | 58.8 (100/170) | 40.0 (2/5) | 0.40 |
| Type of CHD | | | | |
| Coronary angiography (stenosis >50%) | 48.4 (89/184) | 47.5 (85/179) | 80.0 (4/5) | 0.15 |
| Cardiac CT (stenosis >50%) | 0.0 (0/184) | 0.0 (0/179) | 0.0 (0/5) | --- |
| Prior PCI | 34.8 (64/184) | 35.8 (64/179) | 0.0 (0/5) | 0.10 |
| Prior CABG | 33.2 (61/184) | 34.1 (61/179) | 0.0 (0/5) | 0.11 |
| History of ACS# | 35.3 (65/184) | 34.6 (62/179) | 60.0 (3/5) | 0.24 |

*Legend: *Includes ischemic and hemorrhagic stroke; #>3 months prior to enrollment. LLT, lipid-lowering therapy; BMI, body mass index; CV, cardiovascular; CHD, coronary heart disease; CKD, chronic kidney disease; PAD, peripheral artery disease; CT, computed tomography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome.*

**Table 2.** Patient characteristics – ACS cohort

| | All patients mean ± SD or % (n/N) (N = 48) | LLT mean ± SD or % (n/N) (N = 26) | No LLT mean ± SD or % (n/N) (N = 22) | p-value (LLT vs. no LLT) |
|---|---|---|---|---|
| Age (years) | 64.8 ± 10.7 | 65.1 ± 10.9 | 64.5 ± 10.6 | 0.92 |
| Male | 64.6 (31/48) | 57.7 (15/26) | 72.7 (16/22) | 0.28 |
| BMI (kg/m$^2$) | 24.9 ± 4.4 | 24.6 ± 4.5 | 25.1 ± 4.4 | 0.41 |
| BMI > 30 kg/m$^2$ | 8.5 (4/47) | 12.0 (3/25) | 4.5 (1/22) | 0.36 |
| Comorbidities & CV risk factors | | | | |
| Type 2 diabetes mellitus | 33.3 (15/45) | 26.9 (7/26) | 42.1 (8/19) | 0.29 |
| Hypertension | 62.5 (30/48) | 61.5 (16/26) | 63.6 (14/22) | 0.88 |
| CKD | 6.3 (3/48) | 3.8 (1/26) | 9.1 (2/22) | 0.45 |
| History of stroke* | 2.2 (1/46) | 3.8 (1/26) | 0.0 (0/20) | 0.38 |
| PAD | 0.0 (0/46) | 0.0 (0/26) | 0.0 (0/20) | - |
| Current cigarette smoker | 20.8 (10/48) | 11.5 (3/26) | 31.8 (7/22) | 0.08 |
| Sedentary lifestyle | 47.9 (23/48) | 26.9 (7/26) | 72.7 (16/22) | <0.01 |
| Family history of CHD | 34.0 (16/47) | 23.1 (6/26) | 47.6 (10/21) | 0.08 |
| ACS diagnosis | | | | |
| STEMI/LBBB MI | 31.3 (15/48) | 19.2 (5/26) | 45.5 (10/22) | 0.05 |
| NSTEMI | 66.7 (32/48) | 80.8 (21/26) | 50.0 (11/22) | <0.05 |
| Unstable angina | 2.1 (1/48) | 0.0 (0/26) | 4.5 (1/22) | 0.27 |

*Legend: *Includes ischemic and hemorrhagic stroke. BMI, body mass index; CV, cardiovascular; CHD, coronary heart disease; CKD, chronic kidney disease; LLT, lipid-lowering therapy; ACS, acute coronary syndrome; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction; LBBB MI, myocardial infarction with left bundle branch block; NSTEMI, non-ST-elevation myocardial infarction.*

**Table 3.** Lipid profile at baseline

| | Stable CHD | | | | ACS | | | |
|---|---|---|---|---|---|---|---|---|
| | All patients mean ± SD or median (IQR) or % (n/N) (N = 183) | LLT mean ± SD or median (IQR) or % (n/N) (N = 178) | No LLT mean ± SD or median (IQR) or % (n/N) (N = 5) | p-value (LLT vs. no LLT) | All patients mean ± SD or median (IQR) or % (n/N) (N = 48) | LLT mean ± SD or median (IQR) or % (n/N) (N = 26) | No LLT mean ± SD or median (IQR) or % (n/N) (N = 22) | p-value (LLT vs. no LLT) |
| LDL-C (mg/dL) | 88.0 ± 40.1 | 87.0 ± 39.4 | 126.4 ± 50.4 | 0.07 | 109.0 ± 48.5 | 98.3 ± 46.8 | 121.5 ± 48.4 | 0.12 |
| HDL-C (mg/dL) | 43.0 (37.0, 51.0) | 43.0 (38.0, 51.0) | 36.0 (36.0, 40.0) | 0.18 | 43.0 (32.0, 51.0) | 45.0 (33.0, 56.0) | 41.5 (32.0, 50.0) | 0.34 |
| Non-HDL-C (mg/dL) | 105.5 (82.0, 131.0) | 105.0 (81.0, 131.0) | 172.0 (124.0, 196.0) | <0.05 | 134.5 (92.5, 169.5) | 111.5 (84.0, 167.0) | 151.0 (104.0, 177.0) | 0.15 |
| TC (mg/dL) | 157.4 ± 45.4 | 156.0 ± 44.2 | 206.4 ± 65.3 | 0.07 | 176.6 ± 50.6 | 167.4 ± 48.4 | 187.5 ± 52.1 | 0.26 |
| Triglycerides (mg/dL) | 123.0 (89.0, 161.0) | 121.0 (89.0, 159.0) | 175.0 (130.0, 198.0) | 0.21 | 104.0 (75.0, 142.0) | 96.5 (74.0, 143.0) | 112.0 (75.0, 142.0) | 0.78 |
| LDL-C < 70 mg/dL* | 33.3 (61/183) | 33.7 (60/178) | 20.0 (1/5) | 0.52 | 25.0 (12/48) | 30.8 (8/26) | 18.2 (4/22) | 0.32 |
| Distance to LDL-C < 70mg/dL | 25.5 (12.0, 46.0) | 25.0 (11.0, 44.0) | 81.5 (47.0, 97.5) | 0.05 | 58.5 (23.5, 84.0) | 56.0 (19.0, 81.0) | 63.0 (33.0, 96.0) | 0.30 |

*Legend: *Target for very high-risk patients.[9] LLT, lipid-lowering therapy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; SD, standard deviation; IQR, interquartile range*

The mean age of the ACS cohort was 64.8 ± 10.7 years and 64.6% were male (Table 2). At the time of hospital admission, 54.2% of subjects were being treated with some form of LLT. Age, gender and BMI did not vary depending on whether or not a patient was being treated with LLT. Comorbidities were common, with 62.5% of the overall cohort having hypertension and 33.3% having type 2 diabetes mellitus. Of all the cardiovascular risk factors, the only one that varied between the LLT group and the no LLT group was a sedentary lifestyle, which was less common in the treated patients (26.9% vs. 72.7%; p < 0.01). A STEMI was less frequently diagnosed for the LLT-treated patients (19.2% vs. 45.5%; p = 0.05), with an NSTEMI being more common (80.8% vs. 50.0%; p < 0.05).

## Lipid profiles

For the CHD cohort, the mean LDL-C level calculated from the most recent lipid test was 88.0 ± 40.1 mg/dL (Table 3). The value for the LLT group was numerically lower than that for the no LLT group (87.0 vs. 126.4 mg/dL); however, the difference was not found to be statistically significant (p = 0.07). The median level of non-HDL-C was also lower in the treated group (105.0 vs. 172.0; p < 0.05). On the other hand, median HDL-C (43.0 vs. 36.0 mg/dL; p = 0.18) and triglyceride (121.0 vs. 175.0 mg/dL; p = 0.21) levels did not vary significantly between groups. A total of 33.3% of CHD patients had an LDL-C level below the 70 mg/dL target for very high-risk patients, with no significant difference between the LLT and no LLT groups (33.7% vs.

20.0%; p = 0.52). However, the median distance to target for the patients not at goal was much lower for the treated patients (25.0 mg/dL) that those not treated (81.5 mg/dL). In the multivariate regression analysis, no variables were found to be associated with an LLT-treated CHD patient achieving an LDL-C level of <70 mg/dL (Table 4).

For the ACS cohort, the mean LDL-C level calculated from blood taken within 24 h of hospital admission was 109.0 ± 48.5 mg/dL (Table 3). The LLT-treated patients appeared to have a lower value than those not treated (98.3 vs. 121.5 mg/dL); however, the difference was not statistically significant (p = 0.12). Levels of non-HDL-C (111.5 vs. 151.0 mg/dL; p = 0.15), HDL-C (45.0 vs. 41.5 mg/dL; p = 0.34) and triglycerides (96.5 vs. 112.0 mg/dL; p = 0.78) did not vary significantly between the two groups. Overall, 25.0% of the ACS cohort had an LDL-C level below 70 mg/dL, including 30.8% of the LLT group and 18.2% of the no LLT group. When the patients were sub-divided according to their risk category prior to suffering the ACS, 66.0% were determined to be at very high risk, with only 25.8% of these patients displaying an LDL-C level of <70 mg/dL, the target for patients in that specific risk category (Figure 1). None of the variables entered into the logistic regression model were found to be associated with an LLT-treated ACS patient having an LDL-C level of <70 mg/dL (Table 4).

Only four ACS patients had their lipid levels re-tested during the 4-month follow-up period; therefore, there was insufficient data to calculate LDL-C target attainment at follow-up.

## Use of lipid-lowering therapy

At the outpatient clinic visit, 97.3% of the CHD patients were documented to have been treated with LLT for at least 3 months prior to their latest lipid test (Table 5). All but one of the patients were taking a statin as part of their therapy, with atorvastatin the most commonly prescribed (57.9%). Statin monotherapy was the treatment

**Table 4.** Predictors for LDL < 70 mg/dl in patients treated with LLT

| | Stable CHD | | ACS* | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age ≥ 70 years | 1.661 (0.781–3.533) | 0.188 | 7.035 (0.538–91.968) | 0.137 |
| Female | 0.868 (0.387–1.946) | 0.730 | 0.296 (0.030–2.928) | 0.298 |
| Obesity† | 0.548 (0.212–1.418) | 0.215 | ‡ | ‡ |
| Current smoking | 1.001 (0.086–11.68) | 0.999 | <0.001 (<0.001–>999.9) | 0.966 |
| Sedentary lifestyle | 0.777 (0.388–1.556) | 0.477 | 0.497 (0.373–65.574) | 0.225 |
| Stable angina | 0.596 (0.300–1.186) | 0.140 | 0.219 (0.018–2.684) | 0.235 |
| CKD | 0.875 (0.345–2.222) | 0.779 | ‡ | ‡ |
| T2DM | 1.532 (0.757–3.101) | 0.235 | 1.897 (0.127–28.278) | 0.642 |
| History of CHF | 0.872 (0.395–1.927) | 0.735 | ‡ | ‡ |
| Hypertension | 1.793 (0.706–4.554) | 0.219 | 0.212 (0.010–4.631) | 0.324 |
| Statin dose (>20 mg/day atorvastatin eq.) | 0.986 (0.966–1.006) | 0.163 | ‡ | ‡ |

*Legend: *At baseline; †BMI >30 kg/m²; ‡variables omitted due to insufficient data. CHF, congestive heart failure; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus.*

**Table 5.** Use of lipid-lowering therapy

| | CHD | ACS | |
|---|---|---|---|
| | % (n/N) or mean ± SD (N = 184) | Admission % (n/N) or mean ± SD (N = 48) | 4-month follow-up % (n/N) or mean ± SD (N = 27) |
| LLT | 97.3 (179/184) | 54.2 (26/48) | 100.0 (21/21) |
| Statin therapy | 99.4 (178/179) | 100.0 (26/26) | 100.0 (21/21) |
| Atorvastatin | 57.9 (103/178) | 61.5 (16/26) | 47.6 (10/21) |
| Fluvastatin | 0.0 (0/178) | 0.0 (0/26) | 4.8 (1/21) |
| Lovastatin | 0.0 (0/178) | 0.0 (0/26) | 0.0 (0/21) |
| Pitavastatin | 0.0 (0/178) | 0.0 (0/26) | 0.0 (0/21) |
| Pravastatin | 1.1 (2/178) | 0.0 (0/26) | 0.0 (0/21) |
| Rosuvastatin | 23.6 (42/178) | 19.2 (5/26) | 38.1 (8/21) |
| Simvastatin | 17.4 (31/178) | 19.2 (5/26) | 4.8 (1/21) |
| Unknown | 0.0 (0/178) | 0.0 (0/26) | 4.8 (1/21) |
| Statin daily dose – atorvastatin eq. (mg/day)* | 29 ± 19 (n = 178) | 48 ± 30 (n = 26) | 45 ± 26 (n = 20) |
| Statin monotherapy | 77.7 (139/179) | 92.3 (24/26) | 94.7 (18/19) |
| Non-statin monotherapy | 0.6 (1/179) | 0.0 (0/26) | 0.0 (0/19) |
| Statin + ezetimibe | 7.8 (14/179) | 0.0 (0/26) | 0.0 (0/19) |
| Statin + other non-statin† | 14.0 (25/179) | 7.7 (2/26) | 5.3 (1/19) |

*Legend: *Statin dose normalized to atorvastatin potency;[10] †includes fibrates, nicotinic acid and omega-3 fatty acids.*

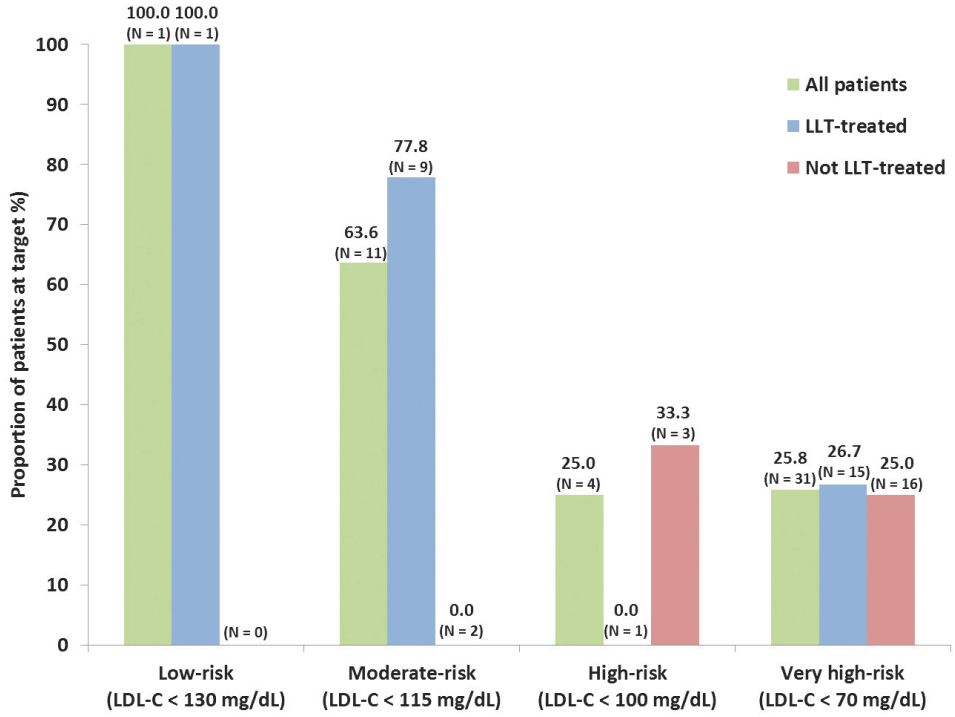


**Figure 1.** Target LDL-C attainment in ACS patients at baseline, by pre-ACS risk level

*Legend: Risk categories and LDL-C targets defined as per ESC/EAS 2011 guidelines.*[9]

regimen for 77.7% of patients, with 7.8% taking a statin in combination with ezetimibe and 14.0% taking a statin with another non-statin, predominantly a fibrate. The mean atorvastatin-equivalent daily statin dosage was 29 ± 19 mg.

At hospital admission, 54.2% of the ACS patients were being treated with LLT, with this including a statin in all cases. Atorvastatin was again the most popular statin (61.5%). Most patients were taking the statin as monotherapy (92.3%), with 7.7% taking it in combination with a non-statin. No patients were being treated with non-statin monotherapy or with ezetimibe. The mean atorvastatin-equivalent daily statin dose was 48 ± 30 mg.

At the 4-month follow-up point, all patients were being treated with LLT. Of these, all were taking a statin, with only one taking it in combination with a non-statin (5.3%). Again, there was no use of ezetimibe. The mean atorvastatin-equivalent daily statin dosage was 45 ± 26 mg.

### Adverse cardiovascular events during follow-up for the ACS cohort

Four of the ACS patients died in the period between hospital discharge and the 4-month follow-up point. No non-fatal cardiovascular events were recorded during this time.

## DISCUSSION

LDL-C target attainment was found to be low for both the stable CHD and ACS cohorts from the Philippines, in particular for patients not being treated with LLT. Although many of these subjects were prescribed such therapy, it appears that its use was not optimized for a high proportion of patients. A number of potential opportunities for better management of these very high-risk subjects are not being exploited.

The CHD cohort displayed high rates of comorbidities and cardiovascular risk factors, in particular, hypertension and type 2 diabetes mellitus. A sedentary lifestyle was also common; however, hardly any subjects were current smokers. Very few patients were not taking LLT at the time of their latest lipid test, making it difficult to evaluate any differences in the characteristics and comorbidities of patients with and without such treatment.

Hypertension and diabetes were also common in the ACS cohort, although they were found at lower rates than in the CHD patients. A further difference was the higher prevalence of smoking, with over 30% of the patients not treated with LLT prior to the ACS being current smokers. A sedentary lifestyle was also significantly more common in the no LLT group. These findings suggest that these two modifiable risk factors may have been addressed by patients in response to initiation of LLT treatment and increased attention to their poor state of health. Subjects in the LLT group were less likely to be diagnosed with a STEMI than those in the no LLT group, with an NSTEMI following the opposite trend. This is likely due to the alterations in atherosclerotic plaque characteristics that are caused by statin treatment.[11,12]

The mean LDL-C level for the CHD cohort was only 18 mg/dL higher than the recommended value of <70 mg/dL; however, only a third had attained this target. This is similar to the value reported for the LLT-treated Pan-Asian cohort of CEPHEUS (34.9%), but higher than that found for the global cohort (22.8%).[13] For the patients being treated with LLT in the present study, the distance to target for those that had not achieved it was 25 mg/dL, suggesting that slight improvements in the management of these patients could greatly increase goal attainment. On the other hand, the patients not treated with LLT displayed a higher LDL-C level and a huge distance to target, indicating significant under-treatment. Furthermore, these patients appeared to have lower HDL-C and higher triglyceride levels compared to the treated patients, although these differences did not reach statistical significance, which may have been affected by the small number of subjects in the no LLT group.

The ACS cohort displayed a higher mean LDL-C level of 109.0 mg/dL, with the LLT-treated patients having a slightly lower value than those not treated. Target attainment was low, at 25.0%, and not hugely different between the LLT and no LLT groups, although this may have achieved significance with a higher number of patients. The distance to target for those that had not reached it was high for both groups. As 66% of the subjects in the ACS cohort were classified as being at very high risk prior to the ACS event, most of whom were not at target, this suggests that many patients were not being adequately treated. In the 4 months after discharge from hospital, only 4 patients had their lipid levels re-checked. This could be because of the costs of such analysis being high, with patients often having to pay for it themselves,[14] but may also be due to physicians not always requesting such tests when they are appropriate. Current and past guidelines from the Philippine Heart Association and the Philippine Lipid and Atherosclerosis Society highlight the importance of monitoring lipid levels for evaluation of treatment response in patients with established atherosclerotic cardiovascular disease, all of whom should be receiving LLT.[15,16] This is mirrored in the European guidelines, which advise lipid re-testing 4–6 weeks after an ACS.[4,9] Therefore, greater monitoring of patients after an ACS may help to improve LDL-C target attainment. However, although access to lipid testing is expanding as a result of changes in the healthcare insurance system of the Philippines,[17] many patients continue to miss out on regular screening owing in part to its financial burden,[14] but also to poor patient and physician compliance with recommendations.

When evaluating use of LLT in the CHD cohort, almost all patients were reported to be receiving such treatment, in agreement with the guidelines.[15,16] However, the atorvastatin-equivalent daily statin dosage was of only moderate intensity, which may account for the low LDL-C target attainment. As high-intensity statin therapy is recommended for all patients with established CHD and elevated LDL-C in the Philippines,[16] it appears that administered doses were sub-optimal. It is also likely that the fear of potential adverse effects of high statin doses of both patients and physicians may have contributed to the medication not being maximized. Quite a high proportion of patients were taking a non-statin in combination with a statin, with this being a fibrate in half of cases. This may be due to the high prevalence of low HDL-C levels and high triglyceride levels in the Philippines.[18]

For the ACS cohort, 55.3% of patients were being treated with LLT prior to hospital admission, with this rising to 100.0% by follow-up. The atorvastatin-equivalent daily statin dosage was relatively high at both time points (48 and 45 mg, respectively); however, this does not correlate with the low level of LDL-C target attainment. It is possible that, despite high prescription rates of statins, many patients were not adhering to their treatment regimen. The national health insurance scheme of the Philippines aims to provide cover for the entire population; however, only limited outpatient treatment is included in care packages.[14] Simvastatin is the only statin currently included on the list of outpatient medications that will be paid for by the insurance scheme.[17] It is therefore surprising that atorvastatin is the most commonly prescribed statin in both the CHD and ACS cohorts of the present study. It is possible that the higher cost of atorvastatin resulted in poor adherence and dose-reduction by the patients themselves, making the medication less effective at lowering LDL-C levels. Use of non-statins varied significantly between the CHD and ACS cohorts. For the CHD patients, ezetimibe and fibrates were used in relatively high proportions of patients when compared with Asian studies on patients with cardiovascular disease[19] or dyslipidemia.[8,20] On the other hand, none of the ACS patients was treated with ezetimibe either prior to hospital admission or at the 4-month follow-up, with use of a statin plus non-statin combination in very few cases. It is known that many physicians choose combination LLT only when LDL-C target values are not reached at a follow-up visit. However, the addition of ezetimibe to statin therapy has been shown to both improve LDL-C levels and reduce the rate of cardiovascular events after an ACS. Learning from the IMPROVE-IT study, patients suffering from an ACS event could particularly benefit from the use of ezetimibe as part of their LLT.

There were some limitations to the present study. Firstly, the number of lipid profiles available from the follow-up of the ACS patients was extremely low. This prevents us from assessing any relationship between lipid levels and LLT. However, this finding also demonstrated the poor monitoring of these patients, highlighting a potential opportunity for increasing LDL-C target attainment. A further limitation was the small size of the ACS cohort, which reduced the accuracy of the comparisons between the LLT and no LLT group, as well as the results of the multivariate analysis. Finally, medication adherence was not evaluated; therefore, the effects of LLT on lipid levels may have been underestimated.

## CONCLUSIONS

The patients in the Philippines that were enrolled in DYSIS II displayed low levels of LDL-C target attainment, despite high use of LLT. The data indicate that significant improvements need to made in the treatment and monitoring of these very high-risk patients.

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### Statement of Authorship

All authors approved the final version submitted.

### Author Disclosure

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