Prevalence of lipid abnormalities and cholesterol target value attainment in Egyptian patients presenting with an acute coronary syndrome

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Abstract
Background: Effective management of hyperlipidemia is of utmost importance for prevention of recurring cardiovascular events after an acute coronary syndrome (ACS). Indeed, guidelines recommend a low-density lipoprotein cholesterol (LDL-C) level of <70 mg/dL for such patients. The Dyslipidemia International Study II (DYSIS II) – Egypt was initiated in order to quantify the prevalence and extent of hyperlipidemia in patients presenting with an ACS in Egypt.

Methods: In this prospective, observational study, we documented patients presenting with an ACS at either of two participating centers in Egypt between November 2013 and September 2014. Individuals were included if they were over 18 years of age, had a full lipid profile available (recorded within 24 h of admission), and had either been taking lipid-lowering therapy (LLT) for ≥3 months at time of enrollment or had not taken LLT. Data regarding lipid levels and LLT were recorded on admission to hospital and at follow-up 4 months later.

Results: Of the 199 patients hospitalized for an ACS that were enrolled, 147 were on LLT at admission. Mean LDL-C at admission was 127.1 mg/dL, and was not significantly different between users and non-users of LLT. Only 4.0% of patients had an LDL-C level of <70 mg/dL, with the median distance to this target being 61.0 mg/dL. For the patients with LDL-C information available at both admission and follow-up, LDL-C target attainment rose from 2.8% to 5.6%. Most of the LLT-treated patients received statin monotherapy (98.6% at admission and 97.3% at follow-up), with the mean daily statin dose (normalized to atorvastatin) increasing from admission (30 mg/day) to follow-up (42 mg/day).

Conclusions: DYSIS II revealed alarming LDL-C goal attainment, with none of the patients with follow-up information available reaching the target of LDL-C <70 mg/dL, either at hospital admission or 4 months after their ACS event. Improvements in guideline adherence are urgently needed for reducing the burden of cardiovascular disease in Egypt. Strategies include the effective use of statins at high doses, or combination with other agents recommended by guidelines.

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1. Introduction

Patients suffering from an acute coronary syndrome (ACS) are considered to be at very high risk of experiencing further cardiovascular events. Effective management of associated risk factors such as dyslipidemia, hypertension, and diabetes mellitus is essential for limiting adverse outcomes in these patients. This is of particular importance in Egypt, where the number of deaths due to
cardiovascular disease is significantly higher than those for other countries in the region.²

Hyperlipidemia is highly prevalent in patients with an ACS, with previous studies reporting high low-density lipoprotein cholesterol (LDL-C) levels on admission to hospital.³,⁴ In the Get With The Guidelines (GWTG) study, Javed et al. reported that only 20.3% of patients were found to have a value of <70 mg/dL,² in line with the TARGET study, in which a mere 16.2% of ACS patients presented with LDL-C at this level, with over 50% having a value of >130 mg/dL.⁶ Initiation of intensive statin therapy is advised for all patients experiencing an ACS,³ with patients having been shown to benefit from such treatment even if they have an LDL-C level <80 mg/dL.⁷ However, studies show wide variability in statin use between treating physicians.⁸,⁹

DYSIS II was designed to obtain details on the management of cholesterol in patients suffering an ACS. This was a multinational, observational study that employed standardized methodology to enable evaluation of the prevalence of lipid abnormalities in patients from countries throughout the world. Here, we present the results collected in Egypt, providing an overview of the extent of hyperlipidemia in ACS patients, and how LLT is used in a real-world setting.

2. Methods

2.1. Study design and patients

Patients were enrolled at two centers within Egypt from November 2013 to September 2014. Individuals were included if they were over 18 years of age, hospitalized for an ACS (ST-segment elevation myocardial infarction [STEMI]/left bundle branch block myocardial infarction [LBBB MI], non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]) at the time of enrollment and had a full lipid profile available (recorded within 24 h of admission). Patients were excluded if they died during the hospital stay or if they were participating in a clinical trial at the same time as the study. If a patient was receiving LLT, the duration of treatment had to be ≥3 months prior to admission. Data were collected on admission to hospital for ACS, and at 4 months (±15 days) post-admission.

All included patients provided written informed consent. The study received ethical approval from the relevant committees at each participating center as per local regulations, and was performed in accordance with the Declaration of Helsinki.

2.2. Documentation

Data were recorded on a standardized case report form (CRF) and later entered into a central web-based database maintained at the Institut für Herzinfarktforschung, Ludwigshafen, Germany. At the time of admission to hospital, patient demographics, cardiovascular history, comorbidities, lipid profile and current medications were recorded. Demographic and clinical variables collected at admission included age, gender, race/ethnicity, body mass index (BMI), hypertension, type 2 diabetes mellitus, sedentary lifestyle, smoking status, documentation of coronary heart disease (CHD), previous myocardial infarction (MI), chronic renal failure (CRF), chronic kidney disease (CKD), stroke, peripheral vascular disease (PVD), and family history of CHD. Obesity was defined as BMI >30 kg/m². Diabetes was defined as current treatment for diabetes, a previous diagnosis of diabetes, or a fasting plasma glucose level of ≥126 mg/dL. Likewise, hypertension was defined as current treatment, a previous diagnosis, or having blood pressure >140/90 mmHg. A sedentary lifestyle was defined as <20–30 minutes of walking on <3–4 days per week. Stroke could be ischemic or hemorrhagic. Use of selected classes of cardiovascular medications (e.g., beta-blockers, calcium channel blockers, diuretics, ACE inhibitors, antiplatelet agents) and laboratory values of HbA1c and blood glucose at admission were also recorded.

Patients were divided into subgroups based on treatment status at admission: LLT users and LLT non-users. Use of LLTs at the time of the lipid test was determined at admission and by patient report at follow-up. The following classes of LLT were assessed: statin monotherapy, non-statin monotherapy, statin plus ezetimibe, and statin plus other non-statin therapy (‘other’ non-statin included nicotinic acid, fibrates, omega-3 fatty acids, and other less common agents). The statins assessed were atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, and simvastatin. Atorvastatin dose equivalents were based on clinical trial data on the LDL-C-lowering efficacy of various statins.¹⁰

A full lipid profile was recorded within 24 h of admission. The lipid profile included measurements of serum levels of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides. Pre-admission cardiovascular risk status (very high, high, moderate, or low) was determined for all patients, and goal attainment according to this classification was based on the lipid values determined at admission. Targets for LDL-C for very high-risk, high-risk, moderate-risk, and low-risk patients were defined according to the 2011 joint European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines as <70 mg/dL, <100 mg/dL, <115 mg/dL, and <130 mg/dL, respectively. Of note, very high- and high-risk patient groups have clearly set target values based on comorbidity, whereas for moderate and low risk, additional risk factors or markers such as obesity or high C-reactive protein (CRP) are taken into account. At 4 months (±15 days) post-admission, any lipid profiles available from the follow-up period were collected, and the medications that the subjects were receiving at this time were documented. The median distance to the LDL-C target was calculated for patients who had not attained the LDL-C target on the date of the lipid profile. Any occurrence of cardiovascular-related adverse events (rehospitalization, MI, stroke, percutaneous coronary intervention [PCI], and coronary artery bypass grafting [CABG]) during the follow-up period was recorded. These outcomes were not mutually exclusive.

2.3. Statistics

The study followed patients on LLT at admission through to the follow-up time point. Unless otherwise stated, throughout the text, the terms ‘treated’ and ‘on LLT’ refer to the treatment status at admission. Data are presented as means with standard deviations (SD), medians with interquartile ranges (IQR), or absolute values with percentages. Statistical significance was determined using the chi-squared test or the Mann–Whitney–Wilcoxon test. LDL-C target attainment was assessed first by risk classification and then, in the subgroup of patients with LDL-C data at both admission and follow-up. Data were analyzed using SAS version 9.3 (Cary, NC, USA) and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients

A total of 199 patients fulfilled the eligibility criteria. Their mean (SD) age was 58.0 years (±11.5) and 77.4% were male (Table 1). A high proportion of patients were classed as being obese (59.3%), and cardiovascular risk factors and comorbidities were common. In particular, 69.8% reported a sedentary lifestyle, 47.7% had hypertension, and 46.2% had type 2 diabetes mellitus.
Of the 199 enrolled patients, 147 (73.9%) were receiving LLT on admission to hospital (Table 1). These patients were older than those not receiving LLT (59.0 vs. 55.1 years; \( p < 0.05 \)), and more were classified as being obese (63.3% vs. 48.1%; \( p < 0.05 \)). Comorbidities were more common in the LLT patients than those not receiving LLT, in particular, hypertension (53.1% vs. 32.7%; \( p < 0.05 \)), and type 2 diabetes mellitus (50.3% vs. 34.6%; \( p < 0.05 \)).

A diagnosis of STEMI or LBBB MI was made for 52.4% of patients with LLT and 75.0% of patients not on LLT (\( p < 0.01 \)). An NSTEMI was the diagnosis for 28.6% and 11.5% of patients with and without LLT, respectively (\( p < 0.001 \)), acetylsalicylic acid (67.3% vs. 7.7%; \( p < 0.0001 \)), and nitrates (52.4% vs. 5.8%; \( p < 0.0001 \)).

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### 3.3. Treatment target attainment

Only 4.0% of patients had an LDL-C level below 70 mg/dL, with no significant difference in achievement of this value between the LLT-treated and not treated patients. When the LLT-treated patients were divided according to pre-admission risk level, 5.1% of those at very high risk, 27.3% of those at high risk, 32.3% of those at moderate risk, 14.3% of those at low risk were at their respective LDL-C target (Fig. 1). As per the ESC/EAS guidelines, all patients were classed as being at very high risk on admission, owing to their presentation with an ACS. The median distance to the target LDL-C level of <70 mg/dL for the overall population was 61.0 mg/dL (37.0, 84.0), with that for the patients treated with LLT prior to admission being 67.0 mg/dL (39.0, 84.0), and that for those not treated being 49.0 mg/dL (22.0, 77.0).

For the subgroup of patients with lipid values available at both baseline and follow-up, target attainment rose from 2.8% to 5.6% (Fig. 2). However, none of the patients treated with LLT prior to admission reached the goal at either time point, although it should be noted that only 36 patients had a lipid profile available from the follow-up period.

### 3.4. Lipid-lowering treatment

LLT for patients treated prior to hospital admission (\( n = 147 \)) consisted primarily of statin monotherapy (98.6%; Table 3), with
atorvastatin as the most frequently used statin (54.4%). In terms of non-statin therapy, no patients were being treated with ezetimibe, while 2 (1.4%) were taking a fibrate. A total of 110 treated patients had treatment data available at follow-up, 1.8% of whom were no longer receiving LLT. Treatment distributions at follow-up were broadly similar to those at admission, but atorvastatin use increased to 86.1% and rosuvastatin use increased to 13.0%. The mean atorvastatin dose equivalent increased from 30 mg/day at admission to 42 mg/day at follow-up.

3.5. Events during follow-up

Follow-up information (4 months) was available for 152 patients. Only one of these patients (LLT group) died and no patients suffered an MI or stroke. Rehospitalization rates were low for both groups (14.7% and 4.9% for LLT and no LLT, respectively; p = 0.10).

4. Discussion

Hyperlipidemia is highly prevalent in patients experiencing an ACS, even in those being treated with statins prior to presentation. Few of the LLT-treated high risk patients included in the Egyptian population of DYSIS II attained their target LDL-C level, thereby indicating inadequate use of LLT.

The patients who were being treated with LLT prior to admission with an ACS were older (59.0 vs. 55.1 years) and reported had treatment data available at follow-up, 1.8% of whom were no longer receiving LLT. Treatment distributions at follow-up were broadly similar to those at admission, but atorvastatin use increased to 86.1% and rosuvastatin use increased to 13.0%. The mean atorvastatin dose equivalent increased from 30 mg/day at admission to 42 mg/day at follow-up.

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| Table 2 | Lipid profile (within 24 h of admission). |
|----------------|---------------------------------|
| **Total N = 199** | **LLT N = 147 (73.9%)** | **No LLT N = 52 (26.1%)** | **p-value (LLT vs. no LLT)** |
| **LDL-C (mg/dL)** | mean ± SD | 127.1 ± 36.2 | 128.1 ± 32.2 | 1240 ± 46.0 | 0.16 |
| | median (IQR) | 130.0 (102.0, 151.0) | 136.0 (109.0, 154.0) | 115.5 (91.0, 146.5) | <0.001 |
| **HDL-C (mg/dL)** | mean ± SD | 39.9 ± 14.3 | 38.1 ± 13.2 | 45.1 ± 6.0 | <0.05 |
| | median (IQR) | 38.0 (30.0, 45.0) | 35.0 (29.0, 43.0) | 42.0 (35.0, 49.0) | <0.05 |
| **TC (mg/dL)** | mean ± SD | 192.8 ± 42.7 | 195.3 ± 39.6 | 185.8 ± 50.3 | 0.13 |
| | median (IQR) | 200.0 (158.0, 214.0) | 204.0 (162.0, 211.0) | 183.0 (150.0, 221.5) | <0.05 |
| **Triglycerides (mg/dL)** | mean ± SD | 148.9 ± 55.0 | 152.2 ± 50.1 | 152.0 (122.0, 171.0) | <0.05 |
| | median (IQR) | 150.0 (119.0, 171.0) | 152.0 (122.0, 171.0) | 121.0 (95.0, 175.0) | <0.05 |
| **Non-HDL-C (mg/dL)** | mean ± SD | 152.9 ± 45.2 | 157.2 ± 41.6 | 140.7 ± 52.7 | <0.05 |
| | median (IQR) | 157.0 (118.0, 183.0) | 162.0 (122.0, 184.0) | 131.5 (105.5, 178.0) | <0.05 |
| **LDL-C < 70 mg/dL** | % (n/N) | 4.0 (6/199) | 4.1 (6/147) | 3.8 (2/52) | 0.94 |
| **Distance to LDL-C < 70 mg/dL** | median (IQR) | 61.0 (37.0, 84.0) | 67.0 (30.0, 84.0) | 49.0 (22.0, 77.0) | – |

LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; SD, standard deviation; IQR, interquartile range. P-values calculated using chi-squared test.

| Table 3 | Lipid-lowering treatment among ACS patients treated with LLT at admission. |
|----------------|---------------------------------|
| **Hospital admission** | **N = 147** | **4-month follow-up** | **N = 110** |
| **LLT** | 100.0 (147/147) | 100.0 (147/147) | 98.2 (108/110) |
| **Statin therapy (%)** | 100.0 (147/147) | 100.0 (147/147) | 100.0 (108/108) |
| **Atorvastatin** | 54.4 (80/147) | 86.1 (93/108) | 86.1 (93/108) |
| **Fluvastatin** | 0.7 (1/147) | 0.0 (0/108) | 0.0 (0/108) |
| **Rosuvastatin** | 3.4 (5/147) | 13.0 (14/108) | 13.0 (14/108) |
| **Simvastatin** | 1.4 (2/147) | 0.9 (1/108) | 0.9 (1/108) |
| **Unknown** | 40.1 (59/147) | 0.0 (0/108) | 0.0 (0/108) |
| **Statin dose – atorvastatin eq. (mg/day)** | 30 ± 13 (n = 88) | 30 ± 13 (n = 88) | 42 ± 21 (n = 108) |
| **Ezetimibe (%)** | 0 (0/147) | 0 (0/108) | 0 (0/108) |
| **Fibrate (%)** | 1.4 (2/147) | 0.9 (1/108) | 0.9 (1/108) |
| **Statin monotherapy (%)** | 98.6 (145/147) | 99.1 (107/108) |
| **Non-statin monotherapy (%)** | 0.0 (0/147) | 0.0 (0/108) | 0.0 (0/108) |
| **Statin + ezetimibe (%)** | 0.0 (0/147) | 0.0 (0/108) | 0.0 (0/108) |
| **Statin + other non-statin (%)** | 1.4 (2/147) | 0.9 (1/108) | 0.9 (1/108) |
| **LLT discontinued after hospital discharge (%)** | – | 1.8 (2/110) |

Goals set according to ESC/EAS 2011 guidelines.[1] 

4 Dose equivalents calculated according to Ref. [10]. Data presented as mean ± standard deviation or percentage (n/N).
more comorbidities than those who had not been receiving LLT. Accordingly, higher proportions of the LLT patients were additionally being treated with non-LLT medications. Lower proportions of the LLT group had a sedentary lifestyle (68.7% vs. 73.1%) or were current smokers (38.1% vs. 50.0%), indicating that they had made some attempt at improving their lifestyle after being identified as needing statin treatment. The use of LLT appeared to affect the type of MI that the patients suffered, with significantly fewer of the treated group experiencing a STEMI (52.4% vs. 75.0%). In addition to lowering LDL-C levels, statins have also been shown to stabilize atherosclerotic plaque and to improve endothelial cell function. Therefore, the prior statin treatment may have reduced the occurrence of total vessel occlusion through diminishing the extent of plaque rupture and thrombus formation, thereby making a STEMI less likely. Dong et al. reported significant differences in plaque characteristics between STEMI and NSTEMI patients, with the former experiencing more plaque rupture. Furthermore, they noted that fewer of the STEMI patients were being treated with statins on admission (19.2% vs. 38.3% for NSTEMI). Spencer et al. also found a higher rate of STEMI in ACS patients that had been previously treated with LLT in comparison to those that had not (22.2% vs. 41.4%). This may have significant implications for inhospital mortality, which has been shown to be slightly higher for STEMI patients in comparison to NSTEMI. Another point of note is that the lower risk of total vessel occlusion produced by statin treatment may be particularly relevant for decreasing the incidence of LBBB MI, which is associated with high short- and long-term mortality.

At admission, very few patients had an LDL-C level corresponding to that recommended for very high or high-risk patients, even for those who had been receiving LLT. Furthermore, the distance to the <70 mg/dL target was extremely large, especially for the LLT group. This suggests that the statin treatment that was being prescribed to the LLT group prior to admission was insufficient for decreasing the risk of a cardiovascular event. Inadequate cholesterol lowering in Egypt was previously reported by El Etriby et al. for the first DYSIS population, with 28.3% of statin-treated very high-risk patients achieving an LDL-C level of <70 mg/dL. In the Egyptian cohort of the Centralized Pan-Middle East Survey on the under-treatment of hypercholesterolemia (CEPHEUS), Reda et al. found that only 10.7% of very high-risk patients, as defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III 2004 guidelines, had an LDL-C level of <70 mg/dL, despite the majority being treated with a statin.

It has been demonstrated that more intensive statin therapy reduces the occurrence of cardiovascular events in comparison to moderate treatment. In these previous studies, the intensive therapy generally consisted of the use of atorvastatin at 80 mg per day (160 mg per day simvastatin equivalent). While atorvastatin was the most commonly prescribed statin for the LLT patients in our analysis, the mean daily atorvastatin-equivalent dose was only 30 ± 13 mg (59 ± 26 mg simvastatin equivalent). However, while higher statin doses would have gone some way to lowering LDL-C levels, the extremely large distance to the <70 mg/dL target suggests that this would not have been sufficient for many patients. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), it was shown that LDL-C levels were reduced to a greater extent with the use of ezetimibe in combination with simvastatin (93.8–53.7 mg/dL during the trial) than with simvastatin alone (93.8–69.5 mg/dL during the study). Furthermore, the 2011 ESC/EAS guidelines state that the addition of a cholesterol absorption inhibitor such as ezetimibe to statin therapy can be considered if the required LDL-C target is not reached using statin monotherapy; however, no patient in the present study was prescribed ezetimibe. Greater use of statin/non-statin combination therapy therefore represents an opportunity for improving LDL-C target attainment in this population.

In the present analyses, the mean atorvastatin-equivalent dose increased from hospital admission to follow-up, thereby indicating that the LLT was intensified in a proportion of patients as a result of the ACS; however, the consistently poor target achievement found at follow-up suggests that further increases may have been appropriate. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22), patients with an ACS who were treated with intensive statin therapy had a superior outcome in terms of cardiovascular events in comparison to the patients that received standard therapy. Similar results were found in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study, where a trend towards lower incidence of cardiovascular events was reported for ACS patients receiving intensive statin therapy. In our analysis, the relatively small population meant that insufficient adverse events were recorded to allow accurate conclusions regarding the effect of LLT on cardiovascular outcome to be made. The apparently widespread underuse of intensive LLT in ACS patients, as demonstrated in the present study, was also identified by Javed et al. in the GWTG database, and by Arnold et al. in the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients’ Health Status (TRIUMPH) registry. This may be due to the disinclination of physicians to prescribe high doses of statins, which may be as a result of the potential for treatment-related adverse events such as myopathy and elevated liver enzymes. A further point of note is that there was no case of treatment intensification through the addition of a non-statin agent to statin therapy. In the ACS patients included in the IMPROVE-IT study, not only was LDL-C lowering superior in those treated with ezetimibe plus simvastatin, but cardiovascular outcome was better, with a 2% lower rate of primary endpoint (cardiovascular death, non-fatal MI, UA requiring hospitalization, coronary revascularization, or non-fatal stroke) achievement. It is likely that improved physician knowledge of current guidelines may result in less under-prescribing of LLT.

4.1. Limitations

A major limitation to this analysis is the low number of patients with a full lipid profile at the follow-up point. This prevents us from establishing a true picture of the effects of post-ACS LLT. However, it also demonstrates a lack of monitoring of patients after hospital discharge, which is contrary to guidelines. A second issue is the missing information regarding the details of the statin treatment in the LLT group at admission, with the specific type of statin used unavailable for approximately 40% of patients. The relatively small size of the population, in addition to the short follow-up time, resulted in few adverse events being recorded. Therefore, no conclusions could be drawn concerning the effect of LLT on cardiovascular outcome. A further limitation is that patients were recruited from only two centers, potentially reducing the applicability of the findings to the overall Egyptian population.

5. Conclusions

After an ACS event, statin doses were increased in patients treated for hyperlipidemia. Despite this, LDL-C levels were found to be consistently high and the lack of LDL-C target attainment for very high-risk ACS patients was alarming. It appears that significant under-treatment of hyperlipidemia exists for patients in Egypt who have suffered an ACS. Greater use of high-intensity statins and combination therapy could reduce the incidence of major cardiovascular events in these at-risk patients.
Conflict of interest

Mohamed Sobhy has received consultancy fees and research funds from Merck & Co. Ltd.

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Amany El Nashar is an employee of MSD Egypt.

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