Can we achieve ESC 2019 guidelines LDL-cholesterol target in Tunisia?

Peut-on atteindre le LDL-cholestérol cible de l'ESC 2019 en Tunisie ?

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Abstract

Introduction: Dyslipidemias are a major cardiovascular risk factor. The control of LDLc level is one of the major targets in patients admitted for an acute coronary syndrome (ACS).

Aim: To study the lipid profile after ACS and to assess the degree of applicability of the European guidelines in Tunisia.

Methods: This was a prospective, multicentric, non-randomized study involving consecutive patients admitted for ACS between October 2019 and March 2020; for whom a lipid assessment was carried out on admission and checked after four to six weeks under high dose of statin.

Results: One hundred patients were included. The mean age of our population was 58.7 years and the sex ratio was 5.7. Obesity was present in 15%, Diabetes in 35%, hypertension in 34% and smoking in 61% of cases. Our patients presented with ST segment elevation myocardial infraction in 51%. The mean total plasma LDLc level was 1.04±0.26g/L. A reduction in LDLc levels of more than 50% was noted in 33% of patients. A value less than 0.55g/L of LDLc was noted in 46% of patients. The therapeutic target (LDLc<0.55g/L and reduction of by more than 50%) was achieved in 30% of patients. The only therapeutic alternative was the diet and lifestyle changes.

Conclusion: Our results demonstrate the difficulty of reaching the therapeutic target of LDLc after an ACS in Tunisia. Several factors can be identified, mainly the absence of therapeutics recommended in second and third line in Tunisia.

Key-words: Acute coronary syndrome, Therapeutics, Statin, Dyslipidemias, guidelines.

Résumé

Introduction : Les hypercholestérolémies et en particulier l'élévation du LDLc constituent un facteur de risque cardiovasculaire majeur. Leur contrôle constitue un élément important chez les patients présentant des syndromes coronaires aigus (SCA).

Objectif : Etudier le profil lipidique après un SCA et évaluer le degré d'applicabilité des recommandations européennes en Tunisie.

Méthodes : Il s'agissait d'une étude prospective, multicentrique non randomisée, portant sur une série de patients consécutifs hospitalisés pour un SCA entre octobre 2019 et mars 2020, pour lesquels un bilan lipidique a été réalisé à l'admission et contrôlé quatre à six semaines après le SCA sous forte dose de statine.

Résultats : Notre population était composée de 100 patients d'âge moyen de 58,7 ans avec un sexe ratio de 5,7. L'obésité était présente dans 15% des cas, le diabète dans 35%, l'hypertension artérielle dans 34% et le tabagisme dans 61% des cas. Nos patients avaient présenté un SCA avec sus décalage ST dans 51%. Le taux moyen du LDLc à l'admission était de 1,04±0,26g/L. La cible thérapeutique était atteinte dans seulement 30% des cas. La seule alternative thérapeutique était la majoration des mesures hygiéno-diététiques.

Conclusion : Nos résultats démontrent la difficulté de l'atteinte de la cible thérapeutique du LDLc après un SCA en Tunisie. Plusieurs facteurs peuvent être incriminés. La cause essentielle étant la non disponibilité des molécules recommandées en deuxième et troisième ligne en Tunisie.

Mots-clés : Syndrome coronarien aigue, Thérapeutique, Dyslipidémies, Statines, Recommandations.

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INTRODUCTION

Several studies and meta-analyzes have proven a dose-dependent reduction in cardiovascular (CV) disease with lipid-lowering agents (1–3). Patients who present with acute coronary syndrome (ACS) are at increased risk of recurrent CV events. For those patients, lipid management and control of LDLc level should be strict and obtained as soon as possible (4). Current European recommendations on the management of dyslipidemia emphasize on the importance of intensive treatment of LDLc in patients hospitalized for ACS. The therapeutic goal is an LDLc level< 0.55g/L and a reduction of LDLc >50% (4). If the LDLc goal is not achieved after four to six weeks despite maximal tolerated statin therapy a combination with Ezitimib is recommended, if it still not achieved after four to six weeks, addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is recommended (4). The aim of our study was to assess the applicability of European guidelines in Tunisian patients admitted for ACS.

METHODS

Patients were enrolled at the cardiology departments of Ariana Hospital, Nabeul Hospital and security forces hospital from October 2019 to March 2020. Patient admitted for ACS were included if they were over 18 years and were not receiving statins the month prior to the admission. The European Society of Cardiology (ESC) definition of ACS was adopted. Patients were excluded if they died during the hospitalization or in the month after discharge and if the level of LDLc could not be calculated by the Friedwald formula. A lipid profile screen was recorded within 24 hours of admission. Serum levels of Total cholesterol, Triglyceride and HighDensity Lipoprotein Cholesterol (HDL-C) were recorded from laboratory measurement and the LDLc level was calculated using the Friedwald formula. Demographic and clinical variables were collected using a data collecting sheet. All patients received a high dose statin (atorvastatin 40 or 80 mg or rosuvastatin 20 mg) since the first day of admission. A biological lipid control was obtained four to six weeks after the ACS and the LDLc level was calculated.

Statistics analysis

Data was entered using Excel 2013 © software. Statistical analysis was performed using SPSS software for Windows ver. 21.0. We calculated simple frequencies and relative frequencies (percentages) for the qualitative variables. We calculated means and standard deviations and determined the range (extreme values = minimum and maximum) for the quantitative variables. For the comparison between the groups, we used the Chi-squared test for the qualitative variables and the ANOVA test for the quantitative variables. In all cases the significance level was set at 0.05.

RESULTS

One hundred patients were included. The mean age was 58.7±11.5 years. The sex ratio was 5,7. Obesity was prevalent in 15%, hypertension in 34%, diabetes in 35%, and smoking in 61% of cases. Six percent of patients didn't have any cardiovascular risk factor (CVRF), 51% had only one CVRF, 30% had two CVRF, 11% had three CVRF and 2% had four CVRF. Echocardiography was performed in 88% of patients before discharge from hospital; mean left systolic function was 54,8%. Coronarography was performed in 92% and five percent had normal angiography, 39% had single vessel coronary artery disease (CAD), 33% had double vessel CAD and 15% had triple vessel CAD.

Our patients presented with an ST segment elevation myocardial infraction (STEMI) in 51% and a non-STEMI in 49% of cases. At admission the mean plasma total cholesterol (TC) level was 1.72±0.33 g/L, the mean plasma triglyceride (TG) level was 1.6±1.1 g/L, the mean High density lipoprotein cholesterol (HDL-C) level was 0.38±0.09 g/L and the mean LDLc level was 1.04±0.26 g/L. The lipid profile is resumed in table 1. All patients received a high dose of statin before discharge, 76% of patients received 80 milligrams of atorvastatin, 15% received 40 milligram of atorvastatin and 9% received 20 milligrams of rosuvastatin (figure 1). After four to six weeks of treatment: The mean plasma TC level was 1.21±0.29 g/L, the mean decrease in cholesterol level was 27.5±19% with extremes between a reduction of 85,7% and an increase of 18.7%.

The mean plasma TG level was 1.13±0.54 g/L, the mean decrease in TG levels was 21±32% with extremes between a reduction of 75% and an increase of 100%.

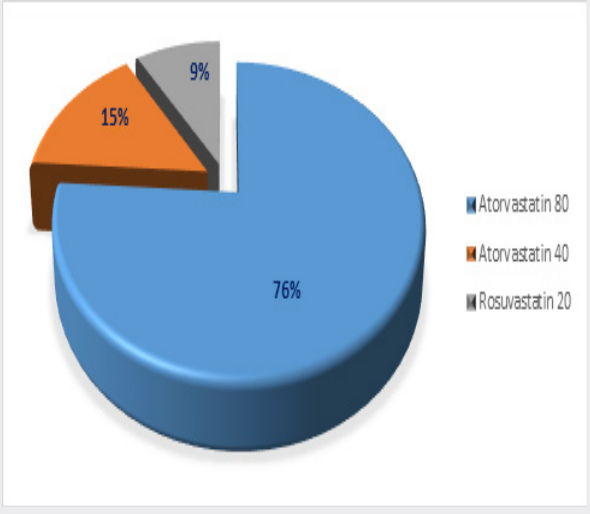

Figure 1. Distribution of patients according to the lipid-lowering treatment prescribed on discharge.

The mean HDL-C level was 0.37±0.1 g/L. The mean increase in HDLc was 6±30% with extremes between an increase of 49,46% and a reduction of 90,6%. The mean level of LDLc was 0.62±0.24 g/L with a maximum of 1.43g/L and a minimum of 0.17g/L. The mean decrease in LDLc was 38.2±22.1% with extremes between a decrease of 82.76% and an increase of 17.65% (Figure 2 and 3). The evolution of lipid profile is resumed in table 1. A reduction in LDLc levels of more than 50% was noted in 33% of patients. A value less than 0.55g/L of LDLc was noted in 46% of patients.

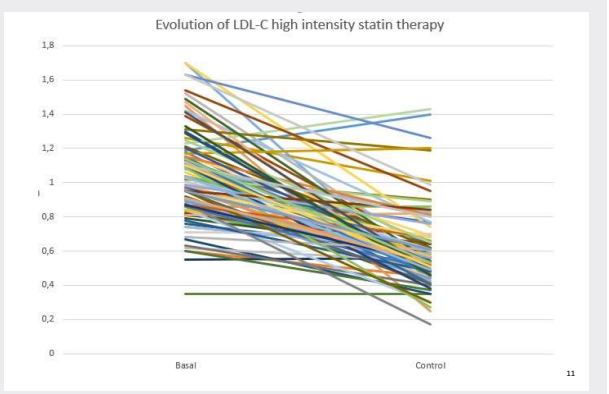

Figure 2. Distribution of LDL-C on admission and after 4-6 weeks of high intensity statin therapy.

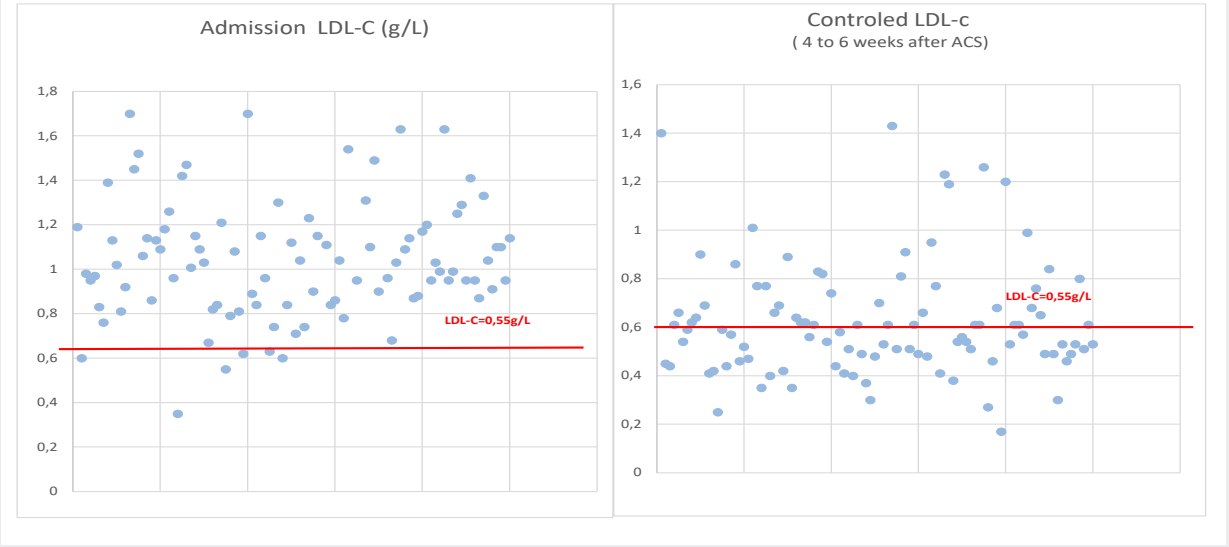

Figure 3. Evolution of LDL-C after four to six weeks of high intensity statin therapy.

Table 1. Comparison between lipid profile on admission and after statin treatment

	AT ADMISSION	AFTER 4-6 WEEKS	Modification (%)
TC	1.72±0.33 g/L	1.21±0.29 g/L	27.5±19 (decrease)
TG	1.6±1.1 g/L	1.13±0.54 g/L	21±32 (decrease)
HDL-C	0,38± 0.09 g/L	0.37±0.1 g/L	6 ±30 (increase)
LDLc	1.04±0.26 g /L	0.62±0.24 g/L	38.2±22.1 (decrease)

The therapeutic target LDLc (LDLc <0.55 g/L and reduction by more than 50%) was achieved in 30% patients. We didn't identify any predictive factor of target achievement, we compared age, gender, CVRF, type of ACS, clinical examination data, coronary involvement and lipid profile at admission. No significant difference was identified.

DISCUSSION

Several studies and meta-analyzes have proven the existence of a dose-dependent reduction in cardiovascular disease of atherosclerotic origin with lipid-lowering agents (1,5). Patients hospitalized for ACS are at high risk of recurrence and strict control of CVRF is part of the management. In this context, the ESC published new guidelines in 2019 about dyslipidemia (4). Target LDLc levels should be obtained as soon as possible after ACS. High dose statin treatment should be started in the first days of hospitalization and a laboratory check of LDLc levels should be done after four to six weeks. The therapeutic target for LDLc is a level below 0.55g/L and a reduction by more than 50% compared to the initial level (4). In our population, the therapeutic target was only reached in 30% of patients. A value less than 0.55 g/L of LDLc was noted in 46% of patients and a reduction by mor then 50% was noted in 33%.

the therapeutic target for the entire population but for this registry the LDLc target level after ACS was 0.7 g/L (data collected before the 2019 guidelines). For patients admitted for a STEMI the target was achieved in 32.4% of patients, for patients admitted for a non STEMI it was 29.9% and 27.8% for the patient followed up for stable angina, one year after inclusion (6). In the DYSIS II study (cohort that included more than 57,000 patients including more than 44,000 patients classified at least with a high cardiovascular risk), the therapeutic target was also considered according to the 2016 guidelines, the study population was divided into two large groups, the first for patients with stable coronary artery disease and the second for patients followed for ACS. The rate of achievement of the therapeutic target was calculated upon inclusion in the study and after four months (7). For the ACS group, the target was reached in 29.8% of cases for patients already taking lipid-lowering treatment and in 7.1% of cases for those with no prior lipid lowering treatment. For patients who did not reach the therapeutic target, the dose of the statin was doubled.

During the next four-month follow-up, the target was reached in 41.7% for the entire population, in 40.5% for patients who were already on lipid-lowering treatment and in 43.5% of cases for patients initially naive of statins (7). In our study, for the patients who did not reach the therapeutic target, the only alternative was to reinforce the hygieno-dietetic rules except for the patients taking 40 milligrams of atorvastatin in whom we opted for an increase to 80 milligrams. According to the ESC 2019 guidelines, the combination of high-dose statins with ezetimibe should be the next step. In the IMPROVE-IT study, the combination of simvastatin and ezetimibe was associated with a reduction of more than 6.4% in major adverse cardiac and cerebral events and an additional reduction of 24% in the LDLc level with a combination of simvastatin and ezetimibe compared to simvastatin alone.

The benefit of adding ezetimibe was consistent for several groups (8). In addition, several studies have proven the safety of this combination (5,13,14). In the DYSlipidemia International Study (DYSIS) II study, the combination of ezetimibe with a high dose of statin could increase the rate of achievement of the therapeutic target from 25% to 50% for the ACS group already taking lipid-lowering treatment during the Inclusion (10). This association led to a reduction in major cardiovascular events (11), stroke (8) and readmissions after ACS (12). This drug is not yet available in Tunisia and this is one of the reasons leading to the non-applicability of the European guidelines in our country. This is the same for PCSK9 inhibitors which are not available in our country and whose cost in other countries is very high, limiting their prescription.

CONCLUSION

Our results confirm the difficulty of reaching the new therapeutic targets of LDLc after an ACS. The unavailability of ezetimibe and PCSK9 inhibitors in Tunisia is a major concern and it should be noted that 70% of our patients should have been on a combination of statin plus ezetimibe. For these patients at least one of the cardiovascular risk factors is not controlled making the risk of recurrence of the ischemic event more important.

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