Lipid and lipoprotein profiles disparities with statin therapy among acute coronary syndrome patients

Disparités de profils lipidiques et lipoprotéiques avec un traitement par statine chez des patients atteints d'un syndrome coronarien aigu

Zeynab Jebberi, Hédi Ben Slima, Hanene Aoua*, Wassim Dali, Ali Ben Khalfallah

Cardiology department, Menzel Bourguiba Regional Hospital, Faculty of medicine of Tunis, University of Tunis El Manar, Tunisia.
**Bioactive substances laboratory, Faculty of Sciences of Bizerte, University of Tunis El Manar, Tunisia.*

Résumé

Introduction: De larges essais cliniques ont prouvé que les statines représentent un traitement hypolipémiant efficace. Le LDL-C est principalement évalué dans le cadre de la prévention secondaire des maladies cardiovasculaires.

Méthodes: La population à l'étude était composée de 100 patients atteints de syndromes coronariens aigus et sans antécédents de prise de statines. Des échantillons de sang ont été prélevés afin d'évaluer les lipides et les lipoprotéines à l'admission, puis pendant le suivi jusqu'à la visite de 18 mois. Le cadre comprenait le LDL-C en tant que paramètre simple, puis quatre paramètres composés : l'indice de Castelli, le coefficient athérogène, l'indice athérogène non logarithmique du plasma et le Cholindex. Quatre sous-groupes ont été évalués séparément : Sujets à taux de triglycérides élevés, taux de LDL-C élevé, sujets à très faible taux de LDL-C et taux de HDL-C élevés.

Résultats: La réponse globale aux statines était négative aussi bien pour le LDL-C que pour les paramètres composés. Cependant, les patients avec des taux de triglycérides élevés et des taux de C-LDL élevés ont présenté de meilleurs résultats pour la plupart des paramètres.

Conclusion: La réponse LDL- cholestérol au traitement par les statines peut être aléatoire en fonction de divers facteurs. Cependant, les paramètres composés peuvent indépendamment aider à discuter de la prochaine étape : Intensification du traitement par statine ou association de médicaments synergiques.

Mots-clés
Statine, LDL-C, indice de Castelli, coefficient athérogène, indice athérogène du plasma, Cholindex

Summary

Background: Large clinical trials approved statin as an effective lipid-lowering therapy. LDL-C are first evaluated within the cardiovascular disease secondary prevention.

Methods: The study population consisted of 100 acute coronary syndromes patients and statin-naive. Blood sampling were taken for lipid and lipoprotein evaluation on admission and then during follow-up till the 18-month visit. The framework included the LDL-C as a simple parameter and then four compound parameters; The Castelli index, the atherogenic coefficient, the non-logarithmic atherogenic index of plasma and the CHOLINDEX. Four sub-groups were evaluated separately; High Triglycerides levels subjects, high LDL-C levels, very low LDL-C and high HDL-C levels subjects.

Results: The overall response to statin was negative including LDL-C and the compound parameters. Although, patients with high triglycerides levels and high LDL-C levels did have better results on most of these parameters.

Conclusion: Statin therapy LDL-C response may be random depending on various factors. However, the compound parameters may independently help to discuss the next step; Intensifying the statin therapy or synergic drug association.

Keywords
Statin, LDL-C, Castelli index, AC, AIP, CHOLINDEX

Correspondance
Hédi Ben Slima
Service des Maladies Cardio-Vasculaires. Hôpital Régional Menzel Bourguiba,
7050– TUNISIE
Tél : 00 216 22 870 088
E-mail : drbenslima.hedi@yahoo.fr

INTRODUCTION

Statin therapy is an evidence-based therapy in cardiovascular disease prevention [1]. The clinical benefit is nowadays approved. The biochemical effect is, however, inhomogeneous in the out-clinic patients. Lipid levels and lipoprotein levels are not a likely influenced with statins. Though, we conducted a small study among acute coronary syndromes (ACS) patients from a north Tunisian community in order to search for a correlative parameter in such diverse biochemical response.

METHODS

We conducted an observational study in the cardiology department of Menzel Bourguiba Hospital in collaboration with the Bioactive substances' laboratory from the faculty of sciences of Bizerte in Tunisia. The study population consisted in100 patients initially admitted to the cardiac care unit for ACS within the period of January 2013 till January 2016. All patients were statin-naive. The clinical characteristics are reported on *(Table 1)*.

Table 1: The clinical characteristics of the subjects

Clinical characteristics	Percentage
Gender	
Males	83%
Females	17%
Diabetes	31%
Smoking	76%
Arterial hypertension	32%
Dyslipidemia	
On diet	2%
Fibrates	3%
Morbid obesity	2%
Chronic kidney disease	
CC > 30 ml/mn	6%
CC < 30 ml/mn	2%
Coronary artery disease	
No significant stenosis	3%
One-vessel	51%
Two-vessels	27%
Three-vessels	19%
Statin therapy prescribed	
Simvastatin	40%
Atorvastatin	52%
Rosuvastatin	8%

Blood samplings were taken after fasting for 8 hours. «T0» as the first sample was taken during the first 48 hours of hospitalization. «T1» as the second sampling was taken on the 6-month visit, «T2» on the 12-month visit and «T3» on the 18-month visit. All tests were run in the Faculty's Laboratory using the standard methods for lipids and lipoproteins measurement. Lipids and lipoproteins evaluated in the study were considered as the lipido-lipoprotein profile of each patient. These parameters were classified as simple and compound parameters. The Triglycerides level (TG), the Cholesterol level (CL), the Low-Density Lipoprotein level (LDL-C) and the High-Density Lipoprotein level (HDL-C) were all considered simple. The compound parameters were the Castelli index, the atherogenic coefficient (AC), the non-logarithmic atherogenic index of plasma (AIP) and the CHOLINDEX *(Table 2)*.

Table 2: The calculated parameters

Parameter	Calculation method
LDL-C (mmol/L)	(CL) – (HDL-C) – (TG/2.2)
Non-HDL-C (mmol/L)	(CL)-(H.DL-C)
Castelli index I	(CL) / (HDL-C)
Castelli index II	(LDL-C) / (HDL-C)
Atherogenic coefficient (AC)	(Non-HDL-C) / (HDL-C)
Non-logarithmic atherogenic index of plasma (AIP)	(TG) / (HDL-C)
CHOLINDEX (mmol/L)	(LDL-C) – (HDL-C) if TG < 4.5 mmol/L (LDL-C) – (HDL-C) + (TG/2.2) if TG > 4.5 mmol/L

Forty-four subjects were assorted into 4 groups according to their initial lipid values. The first group encountered patients with high initial TG (>2.25 mmol/L). A second group with high LDL-C (>4.9 mmol/L), a third group with very low LDL-C (<1.3 mmol/L) were also considered. The fourth group encountered those with high initial HDL-C (>2.32 mmol/L).

Biochemical concerns:

All results are in mmol/L. The conversion factor for TG was 88.57. For LDL-C and HDL-C, it was 38.67.

TG were obtained with enzymatic reactions as already described by Fossati and Prencipe [2]. CL were measured as Allain et al. indicated [3]. Friedewald formula was used for LDL-C [4]. HDL-C was measured by Tietz's method [5].

We defined the Castelli index (= LDL-C / HDL-C) as the «Castelli index II» that has been described in the primary prevention reports *(Table II)*. The atherogenic index (=Non-HDL-C / HDL-C) would represent the atherogenic effect of the plasma lipoproteins [6]. AIP is the ratio TG / HDL-C and would be inversely related to the diameter of the LDL particles [7]. The CHOLINDEX ((LDL-C) – (HDL-C)) is the

only compound parameter already validated for hypertriglyceridemia [8]. In such cases (TG > 4.5 mmol/L) it is calculated as (LDL-C) -(HDL-C) -(TG/2.2).

Statistical analysis:
Data were summarized as means with standard deviation (SD). Statistical significance was defined as *p<0.05*. Only the LDL-C was analysed in the simple parameters' category. The four compound parameters were analysed for all the subjects. Changes in lipids and lipoproteins values were signed as positive response to statin if the mean value decreases. The response is considered negative otherwise.

RESULTS

Hundred patients were enrolled in this study with a mean age of 65.15+/-10 years old. Males were predominant *(Table 1)*. Rosuvastatin was prescribed for 8 patients. Atorvastatin and simvastatin were prescribed for 52 and 40 patients respectively.
The mean value for LDL-C was 2.55+/-0.71 mmol/L at T0. The Castelli index was 4+/-3.9, the AC was 4.91+/-4.49. The AIP was 2.11+/-2.38 and the CHOLINDEX at 1.53+/-1.57.
The response to statin was meanly negative with LDL-C as it increases to 3.42+/-2.31 mmol/L at T3 (with non-significant *p=0.07*). The same negative results were found for the Castelli index as it increases from 4+/-3.9 to 4.21+/-6.94 at T3. However, taking the fact for high value of the SD, the Castelli index medians were relatively decreased at T3 (2.9 at T0 and 2.33 at T3).
For the AC and the AIP, the results were also negative with patchy SD.

Groups 'results:
1-TG > 2.25 mmol/L:
Fourteen patients had TG more than 2.25 mmol/L on admission. Their mean age was 68.43+/-8.65 and the sex-ratio was 1.8. Their initial mean LDL-C was 2.52+/-1.16 mmol/L. The compound parameters had patchy SD expect for the CHOLINDEX that was 1.76+/-1.3 mmol/L *(Table 2)*.
The response to statin with the compound parameters was positive in this group. The Castelli index decreased by 12.8% at one year of follow-up and the AC by 38.3%. Diabetics were at best with the Castelli index at 36.9% (43.5% with atorvastatin and 32.5% with simvastatin) and the AC at 52.3% (53.3% for atorvastatin and 52% for simvastatin). This subgroup of diabetics had decreased their AIP by 26.4% with atorvastatin and 74% with simvastatin. However, the non-diabetics in this group were at best with the CHOLINDEX.

2-LDL-C > 4.9 mmol/L:
Seven patients were assigned to this group. Only one was diagnosed with probable familial hypercholesterolemia (FHC). The mean age was 68.6+/-6.37 years old. They were all males. Three were diabetics, two had a chronic kidney disease and a history of stroke. Atorvastatin was assorted for the diabetics and simvastatin for the non-diabetics.
The initial LDL-C for the patient with suspected FHC was 6.91 mmol/L, the other six had a mean at 5.95+/-0.72 mmol/L.
The mean value for the Castelli index was 6.31+/-2.3. For the AC, it was 6.9+/-2.67 and for the API 1.29+/-1. The CHOLINDEX was not reported as though results were ill-assorted.
The only positive response for the LDL-C was observed in

Table 3: Initial lipid and lipoprotein levels assorted by groups

	OVERALL POPULATION	TG > 2.25 (mmol/L)	LDL-C (mmol/L)		HDL-C > 2.32 (mmol/L)
			> 4.9	< 1.3	
Simple parameters					
					1.29
TG (mmol/L)	1.39	3.02	1.13	1.25	2.86
LDL-C (mmol/L)	2.55	2.52	5.95	_	5.31
CL (mmol/L)	4.90	4.93	7.55	2.74	2.65
HDL-C (mmol/L)	1.02	0.87	1.08	1.24	
Compound parameters					
					1.08
CASTELLI INDEX	4.00	4.76	6.31	_	1.03
ATHEROGENIC COEFFICIENT	4.91	6.92	6.90	1.79	0.49
AIP	2.11	5.02	1.29	1.47	0.21
CHOLINDEX (mmol/L)	1.53	1.76	4.86	_	2.66
Non-HDL-C (mmol/L)	3.12	4.04	6.47	1.49	

this group. The mean value decreased by 56.7% for the diabetics at the 18-month visit and by 42.2% for the non-diabetics. The response for the compound parameters was also positive in this group. The Castelli index decreased by 52% at the 18-month visit and the AC by 39%. Moreover, these responses were better with atorvastatin (65.8% and 55.8% respectively). The AIP decreased by 27%. In comparison with subjects non assigned to this group, the correlative positive response was observed especially with diabetics on Atorvastatin.

3-LDL-C< 1.3 mmol/L:

Eighteen patients had an initial LDL-C less than 1.3 mmol/L. Their mean age was 67.8+/-7.7 years old. The sex-ratio was 9. One third were diabetics, two had a history of chronic kidney disease and two with stroke.

These minimal LDL-C values were only considered to enrol subjects in this group noting that the Friedewald formula was not validated for such values. Therefore, we did not consider the Castelli index and the CHOLINDEX if the LDL-C within is as low.

The initial mean value for the AC was 1.79+/-1.88 and for the AIP 1.47+/-1.84.

The response to statin was negative in this group. LDL-C values increased during the follow-up. All the compound parameters increased with no difference in effect between diabetics and non-diabetics. The CHOLINDEX was 3 times higher at the end of follow-up.

4-HDL-C > 2.32 mmol/L:

Five patients had an initial HDL-C more than 2.32 mmol/L. Their mean age was 60.2+/-9.5 years old. There was one woman in this group. They all had no comorbidity. Four took atorvastatin and one rosuvastatin.

The initial LDL-C mean value was 2.86+/-1.44 mmol/L (higher than the overall population). On admission, this group had the lower values for the compound parameters. However, all the responses to statin were also negative in this group. Even though, there was only significant correlation with the Castelli index (*p=0.016*) and the CHOLINDEX (p=0.025).

DISCUSSION

Mixed evaluation of lipids and lipoproteins levels reinforce the need for early institution of lipid-lowering therapies. The compound parameters encountering these different components were evaluated and validated in the primary prevention field of cardiovascular diseases (CVD). However, they lack recommendations for their use in the secondary prevention field. Accordingly, we conducted a small study within ACS patients to evaluate the different results of these compound parameters with statin intake. Hundred patients were enrolled from a semi-rural community in the north of Tunisia, considered as a middle-income country. The compound parameters assessed were the Castelli index, the AC, the API and the CHOLINDEX.

An initial estimation of lipid and lipoprotein levels (LDL-C, HDL-C, TG, CL) showed a negative response to statin. Overall, LDL-C didn't decrease. Hence, we evaluated the cohort according to their initial lipid levels. The group with TG more than 2.25 mmol/L and the group with LDL-C more than 4.9 mmol/L had their compound parameters decreased on statin therapy. Diabetics were especially more prone to better response. Unlikely, the group with LDL-C less than 1.3 mmol/L and HDL-C more than 2.32 mmol/, although hypothetically less atherogenic profiles, they had a negative response to statin.

These compound parameters rely on lipids and lipoproteins metabolism interactions. Among our cohort that had negative response to statin on the simple parameters, we were able to discern a probable positive response on the metabolism framework.

Two indexes of Castelli were proposed. The Castelli index I uses the CL and the Castelli index II uses the LDL-C. These indexes were appraised in many studies as the Framingham Heart Study, AFCAPS/TexCAPS study, Helsinky study and the Coronary Primary Prevention trial [9]. These variables highlight the interaction between the atherogenic and non-atherogenic lipids. Nonetheless, they are limited because they lack the TG which is a key element in Atherogenesis. Thereby, the AIP and AC may offer a better overview.

The AC evaluates the amount of cholesterol in the lipoproteins (Very-Low, Intermediate and Low-Density Lipoproteins) [10].

The AIP is related to the predominant LDL particles volume [11]. Therefore, it might mirror the lipoproteins' metabolic pathway [11]. Cut-off values were suggested for primary CVD prevention [12]. The authors proposed 1.65 for females and 2.75 for males [12]. Its increase was correlated to the increase of the Small-Dense LDL (sdLDL) and the larger Very-Low-Density Lipoprotein (VLDL) [13]. Thus, the AIP might be more compelling with the CVD prevention and especially when TG are high [14, 15].

The CHOLINDEX was proposed by Akpinar et al. [8]. It was considered as a better predictor for CVD than LDL.

The ESC guidelines recommend the use of these compound parameters to estimate the CVD risk in primary prevention [1]. Our thoughts were about evaluating their utility within the statin therapy for secondary CVD prevention. We only discussed the biochemistry aspect of this assessment and not the clinical benefits on follow-up. First, the results of our study were less deceiving with these compound parameters than the simple lipid and lipoprotein parameters especially with the groups with high TG and high LDL-C. Second, we highlighted the fact that the less

atherogenic lipid profile as classified with the simple parameters is actually «pseudo-less» or a «false-less» atherogenic. So how about considering these compound parameters when optimal LDL-C doesn't prevent all cardiovascular events. Third, we speculate that negative response on the compound parameters should prone for the next step in therapy decision making. In such cases, more intensive statin therapy and lifestyle modifications might be the solution. Otherwise, it is the association with a synergic lipid-lowering therapy.

Study limitations

Our results were inherently limited by the small number of the population and its inhomogeneous lipid and lipoprotein profile. Hence, the SD were patchy for most of the compound parameters. Negative values were observed with the CHOLINDEX doubting though its reliability.

The LDL-C were above the cut-off values which might be related first to the limited intensive statin therapy and second to less strict lifestyle modifications. Noting otherwise that the study was designed as observational and the cohort had limited access to healthcare.

CONCLUSIONS

Our observational study showed random response to statin therapy for ACS patients. The evaluation of LDL-C compared to compound lipid and lipoprotein parameters was ill-assorted. These latter are probably more sensitive when the baseline profile is very atherogenic and less sensitive with the pseudo-non-atherogenic profiles. Therapy decision making should consider these changes to indicate a synergic drug association or more intensive regimen as simpler parameters might not be the optimal utensil.

No conflict interest

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