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# **A Practical Case-Based Approach to Dyslipidaemia in Light of the European Guidelines**

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Additional information is available at the end of the chapter

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## **1. Introduction**

The European Atherosclerosis Society and the European Society of Cardiology have made new recommendations regarding the treatment of dyslipidaemia (1). Such recommendations build upon the "Joint European Societies' Task Force Guidelines on the Prevention of CVD in Clinical Practice" of 2007 [1, 2]. The most important changes include the redefinition of the risk categories and the addition of a 'very high-risk' category. For these new risk categories, the LDL-C targets have been redefined. In the highest risk individuals, the lowering of LDL to 70 mg/dl is recommended. Furthermore, HDL-c has been added to the new SCORE risk chart and non-HDL cholesterol is now considered to be a secondary target.

In this study, we illustrate how these guidelines can be used in clinical practice. We also give some tips on how to make them more user-friendly for clinicians (Figure 1). The discussed case (Clinical Case 1) was developed to combine a series of difficulties in therapeutic decision-making. We accepted the principle that any correctable secondary causes of dyslipidaemia had been excluded and that the patient had already received all the care to improve the other risk factors but without real (enough) success. These risk factors included smoking cessation, weight loss and/or blood pressure reduction. Unfortunately, this case is far from an exception. The reality is that it is often more difficult to quantitatively reduce risk factors, than it is to reduce cholesterol levels.

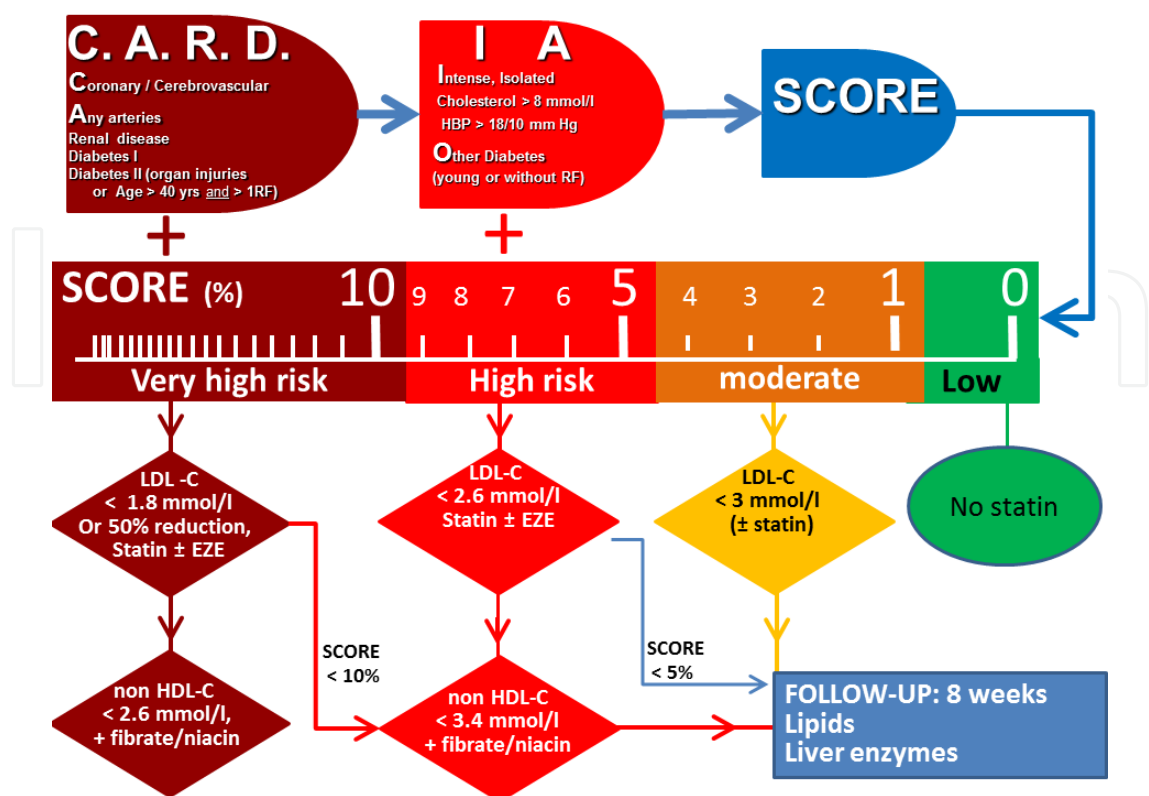


Figure 1. Algorithm of dyslipidaemia management in cardiovascular prevention.

Clinical Case 1. Presentation.

The patient, a woman of 59 years of age, has come to visit her doctor because she has reached the same age as when her sister suffered from a heart attack (two years ago).

**Personal history:** Without particularity.

**Family history:** Her mother is obese and has been treated for diabetes since the age of 60 years. Her sister has undertaken a coronary bypass surgery following a heart attack at 59 years of age.

**Lifestyle-dietary habits.** Smokes (15 cigarettes per day), sedentary (works in an office, does not practice sport and only engages in interior recreation).

**Clinical examination.** Weight: 92 kg; height: 1,74 m (Body mass index – BMI : 30,5 kg/m<sup>2</sup>); waist circumference: 99 cm ; blood pressure: 145 / 85 mm Hg, no xanthoma, no corneal arcus.

**Biology:** Total cholesterol: 5.8 mmol/l; HDL cholesterol (HDL-C) : 1.0 mmol/l; triglycerides (TG): 3.5 mmol/l; cholesterol LDL (LDL-C) : 3.2 mmol/l (tableau 1); glycaemia : 112 mg/dl ; hs-CRP= 1,2 mg/dL; normal levels of creatinin, hepatic enzymes and thyroid hormones.

## Clinical Case 2. What is the Cardiovascular Risk of this Patient?

*Our patient has no cardiovascular history, diabetes or any severe risk factors. Thus, we should calculate the risk SCORE, i.e., the risk of cardiovascular mortality in 10 years (we should take into consideration that we are a country with a high-risk population).*

*- Based on the classical risk factors (gender, age, systolic blood pressure and total cholesterol levels) and according to the classical SCORE table, the risk SCORE is 4% (Figure 2).*

*- Based on the new way to calculate the risk, the risk of our patient is quite high. After adjusting the HDL-C (near 1 mmol/l), using the four tables or using multipliers plus the reference chart, the SCORE reached should be 6-6,4%. Given her family history (her sister, a woman of 60 years), this must be multiplied by 1.7 (Figure 2). Thus, the calculation is 10-11%. In addition, the presence of other risk factors (high levels of triglycerides, obesity, sedentariness and high hs-CRP) justifies the multiplication by 1.5 (~1.46=1.1 x 1.1 x 1.1 x 1.1). This gives us 15-16% (let us take 15% as a base to facilitate later calculations). Thus, in total, we estimate that the risk of the patient dying of cardiovascular disease in 10 years is likely to be 15 % (Table 1). The patient is, therefore, in the category of risk labelled very high. The global risk (fatal and non-fatal) can be calculated by multiplying this by three (as the patient is a woman of nearly 60 years of age), giving a value of ~ 45%, which is very high.*

## 2. First question: What is the cardiovascular risk of this patient?

To determine whether the patient is in the highest/high-risk category, we propose the acronym "C.A.R.D.I.A.SCORE". This will make it easy to remember (Figure 1).

### 2.1. Acronym « C.A.R.D.I.A. SCORE »

If there is an history of cardiovascular (« C ») disease, coronary, cerebrovascular or any artery injuries (« A ») in general (peripheral arteries, aneurism, etc.); if there is renal insufficiency (« R ») defined by a glomerular filtration below 60 ml/min/1,73 m<sup>2</sup>; if there is diabetes (« D »), either type I or II complicated of organ injuries (microalbuminuria) or type II without complications; if the patient is older than 40 years of age and displaying other risk factors (notice that, in diabetes, the three conditions of « complication, age and risk factor give the acronym « CAR »), the patient should be considered as « very high-risk ».

For patients who show an isolated, yet severe, risk factor (« I »), like diabetes, without any other risk factor, severe hypercholesterolemia (cholesterol > 7.5 mmol/l and/or familial hypercholesterolemia) or severe hypertension (>180 mm Hg), they should be considered as « **high-risk** ». Furthermore, patients who have been diabetic since a young age (« I ») should also be considered as « **high-risk** ».

All other individuals who do not present one of the above characteristics should be examined using SCORE (6).

## 2.2. SCORE with two novelties

**First novelty.** It is now possible to qualify the risk SCORE quantitatively, according to the presence of a family history of early cardiovascular disease and the level of HDL cholesterol (1, 3 and 4). We can do this by using either the four specific tables (one for each of the four HDL-C levels) (1) or the HDL-C specific multipliers to adjust the SCORE risk based on one reference table (the table for HDL-C = 0.8 mmol/l) (6) (Figure 2). In addition, we should consider the patient as higher risk if other risk factors are present (high levels of triglycerides, obesity, sedentariness, etc.). For these factors, the guidelines do not provide any multipliers but, as a rule of thumb, we should accept a minimum value of 1.1 as a multiplier for each additional factor. Indeed, in epidemiological studies, it is rare that a parameter can be identified as statistically independent and a clinically meaningful risk factor if it does not increase the risk to a minimum of 10%, after adjusting for other risk factors.

**Second novelty.** Patients should not be categorized according to a single "frontier of risk" (below or above 5%). Instead, they should be categorized based on the three "frontiers of risk": 1%, 5% and 10%. Thus, the risk SCORE should be defined as "**low**" if it is less than 1%, "**moderate**" if it is between 1% and 5%, "**high**" if it is between 5% and 10% and "**very high**" if it is over 10% (Figure 1).

Our case (Clinical Case 2) illustrates how a "moderate" 4% risk can be significantly enhanced in refining the other risk factors such as HDL-C, family history and so on. It is possible to calculate the global risk (fatal and non-fatal) simply by multiplying by three for men, by four for women and by a little less for older people. Taking this into consideration, for our female patient of 59 years, we should multiply by three. Thus, the overall risk is 45%. This is another way of expressing the CVD risk (with a higher number!). It should be used to increase our patient's awareness of CVD and encourage her to be more motivated to follow the regime and take her medication.

## 3. Second question, how do we treat this patient?

The LDL-C remains the primary target, as in the previous guidelines. The target LDL-C is determined as a function of the patient's risk. For each risk category, there is a different LDL GOAL. There is also a simplified chart to calculate the LDL reduction percentage to reach that goal. The evidence to decrease LDL-C to such low levels is supported by previous studies that indicate a possible regression of atherosclerotic plaques (i.e., a "rejuvenation" of the arteries) in this condition.

What if the level of LDL-C is unavailable because it is non-computable by the Friedewald formula (when TG levels are above 4.5 mmol/l)? In this case, we should use another target. The alternative target is not the level of total cholesterol, as proposed in the previous guidelines. Instead, it is the level of non HDL-C that will become, in this case, the primary target (see §4).



## High Risk Population

FEMALES											MALES										
Non-smokers					Smokers					Non-smokers					Smokers						
Age					Age					Age					Age						
180	11	12	13	15	16	22	24	26	28	31	16	18	21	24	28	26	30	34	39	45	
160	9	9	10	12	13	17	19	20	22	25	11	13	15	18	21	19	22	25	29	34	
140	7	7	8	9	10	13	14	16	18	19	8	9	11	13	15	14	16	19	22	26	
120	5	6	6	7	8	10	11	12	14	15	6	7	8	9	11	10	12	14	16	19	
Systolic blood pressure (mmHg)											Systolic blood pressure (mmHg)										
180	5	6	6	7	8	11	12	13	14	16	11	13	15	18	21	19	22	25	30	35	
160	4	4	5	6	6	8	9	10	11	12	8	9	11	13	15	14	16	19	22	26	
140	3	3	4	4	5	6	7	8	9	10	6	7	8	9	11	10	12	14	16	19	
120	2	3	3	3	4	5	5	6	7	7	4	5	6	7	8	7	8	10	12	14	
Total Cholesterol (mmol/l)											Total Cholesterol (mmol/l)										
180	3	3	4	4	5	6	7	8	8	9	7	9	10	12	15	13	15	18	21	25	
160	2	3	3	3	4	5	5	6	6	7	5	6	7	9	11	9	11	13	15	19	
140	2	2	2	2	3	4	4	4	5	6	4	4	5	6	8	7	8	9	11	14	
120	1	2	2	2	2	3	3	3	4	4	3	3	4	5	6	5	6	7	8	10	
HDL-C (mmol/l)											HDL-C (mmol/l)										
180	1	2	2	2	2	3	3	3	4	4	5	5	7	8	9	8	10	12	14	17	
160	1	1	1	1	2	2	2	2	3	3	3	4	5	6	7	6	7	8	10	12	
140	1	1	1	1	1	2	2	2	2	3	2	3	3	4	5	4	5	6	7	9	
120	1	1	1	1	1	1	1	2	2	2	2	2	2	3	4	3	4	4	5	6	
Multiply SCORE by											Multiply SCORE by										
HDL-C (mmol/l)											HDL-C (mmol/l)										
0.8 (31)											0.8 (31)										
x 1,0											x 1,0										
0.9 (35)											0.9 (35)										
x 0,9											x 0,9										
1.0 (39)											1.0 (39)										
x 0,8											x 0,8										
1.1 (43)											1.1 (43)										
x 0,7											x 0,7										
1.2 (46)											1.2 (46)										
x 0,7											x 0,7										
1.3 (50)											1.3 (50)										
x 0,6											x 0,6										
1.4 (54)											1.4 (54)										
x 0,5											x 0,5										
1.6 (62)											1.6 (62)										
x 0,4											x 0,4										
1.8 (70)											1.8 (70)										
x 0,4											x 0,5										
Familial history of early CV disease											Familial history of early CV disease										
présent x 1,7											présent x 2										
Others RF											Others RF										
Triglyc. > 150 mg/dL											Triglyc. > 150 mg/dL										
Waist circ. > 80 cm											Waist circ. > 94 cm										
Sedentary											Sedentary										
Social precarity											Social precarity										
Plaque at US											Plaque at US										
Lp(a) > 30 mg/dL											Lp(a) > 30 mg/dL										
Hs-CRP > 0,9 mg/dl											Hs-CRP > 0,9 mg/dl										
Each											Each										
X > 1,1											X > 1,1										

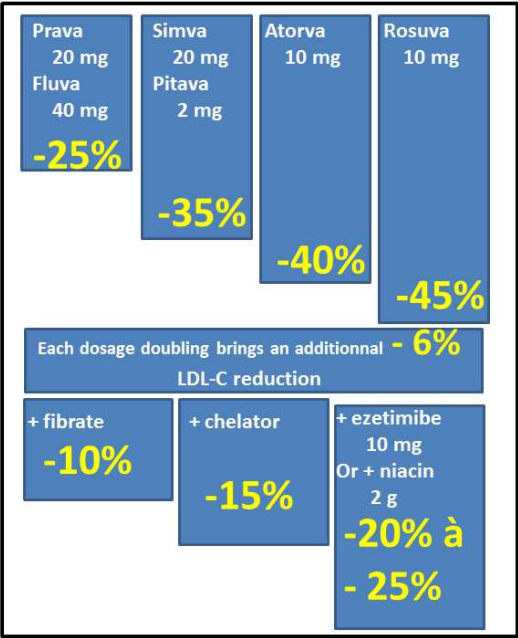
(a)

## Low Risk Population

FEMALES										MALES										
Non-smokers					Smokers					Non-smokers					Smokers					
Age					Age					Age					Age					
180	6	6	7	7	8	12	13	13	15	16	9	10	12	14	16	16	18	20	23	27
160	4	5	5	6	6	9	10	10	11	12	6	7	8	10	12	11	13	15	17	20
140	3	4	4	4	5	7	7	8	9	10	5	5	6	7	8	8	9	11	12	15
120	2	3	3	3	4	5	6	6	7	7	3	4	4	5	6	6	6	8	9	11
Systolic blood pressure (mmHg)										Systolic blood pressure (mmHg)										
180	3	3	3	4	4	6	6	7	8	8	6	7	8	9	11	10	12	14	16	19
160	2	2	3	3	3	4	5	5	6	6	4	5	6	7	8	7	8	10	11	14
140	2	2	2	2	2	3	4	4	4	5	3	3	4	4	5	5	6	7	8	10
120	1	1	2	2	2	3	3	3	3	4	2	2	3	3	4	4	4	5	6	7
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	2	2	2	2	2	3	3	4	4	5	4	4	5	6	7	7	8	9	11	13
160	1	1	1	1	2	2	2	3	3	4	3	3	4	4	5	5	6	8	9	11
140	1	1	1	1	1	2	2	2	3	3	2	2	3	3	4	4	4	5	6	8
120	1	1	1	1	1	1	2	2	2	2	1	2	2	2	3	3	3	4	5	6
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	1	1	1	1	1	2	2	2	3	3	4	4	5	6	7	7	8	9	11	13
160	1	1	1	1	1	2	2	2	2	2	3	3	4	4	5	5	6	8	9	11
140	1	1	1	1	1	1	1	1	2	2	2	2	3	3	4	4	4	5	6	8
120	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Total Cholesterol (mmol/l)										Total Cholesterol (mmol/l)										
180	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
140	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1			

3.1. Which Statin, What Dose and How Fast

Statin should always be the first line treatment (even for dyslipidaemia mixed with elevations of cholesterol and triglycerides, as we will demonstrate below (§4)). We should begin by prescribing a statin at a dosage that is the most likely to be effective in obtaining the correct reduction target. The rationale to choose the statin type and dosage is quite mathematical and is based on the baseline level, the LDL-C target and knowledge of the different statins' power (Figure 3). In terms of power (for a same dosage), these are fluvastatin < pravastatin < simvastatin < pitavastatin < atorvastatin < rosuvastatin [5]. Another rule is that, on average, doubling each of the statin dosage leads to a further decline in the rate of LDL-C of 4% to 6%. Another way to intensify the treatment is to associate the statin with one of the other anti-dyslipidaemia drugs (Figure 3). Among these, ezetimibe has the largest (20% to 25%) additional reduction of LDL-C. When the risk is high and the target is not reached, it is important to adjust the treatment as quickly as possible. The compliance and satisfaction of the patient, as well as the physician, depends on it.



**Figure 3.** The choice and the statin dose should be based on a near mathematical criterion: the target reduction of LDL-C. The necessary reduction is easily estimated by the difference between the baseline LDL-C level and its target (according to the risk level) divided by the baseline LDL-C. The figure displays the power of different treatments in reducing LDL-C. For better precision of atorvastatin, we should use the following rule (dosage→ % LDL-C reduction): 10 mg → 38%, 20 mg → 45%, 40 mg → 49%, 80 mg → 52%). Other drugs also influence the HDL-C and TG levels. Statins have a small effect on the levels of HDL-C (slight ↑) and triglycerides (slight ↓). Fluva: fluvastatin; prava: pravastatin; pita: pitavasatin; simva: simvastatin; rosuva:rosuvastatin; atorva: atorvastatin.

3.2. Before prescribing a statin, we will check

Before the initiation of treatment, it is important to ensure that the CK (creatine phosphokinase) levels are not too high. If they are very high (> 5 times the upper limit of normal), it is better to delay and to check again six weeks later. Furthermore, it is important to determine the cause of these levels (intense physical exercise, trauma or recent intramuscular injection). To reduce

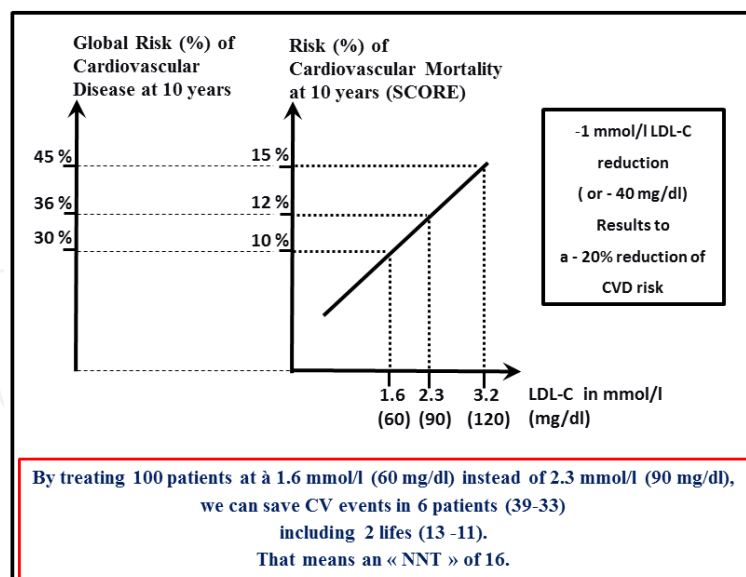
the risk of muscle side effects, we have to be more vigilant in elderly patients or in cases where the simultaneous use of treatment is interfering (via cytochrome P 450) with the metabolism of the proposed statin. We also have to be particularly careful if the patient has previously suffered from hepatic or renal insufficiencies.

For our patient in the very high-risk category, the LDL-C target is below 1.8 mmol/l. To achieve this target, we should reduce the patient's LDL-C by 40% (Clinical Case 3).

### Clinical Case 3. How do we Treat Cholesterol in this Patient?

For our patient with a very high-risk,

- The target is  $< 1.8 \text{ mmol/l}$
- The necessary LDL-C reduction is:  $3.0 \text{ mmol/l} - 1.8 \text{ mmol/l} = 1.2 \text{ mmol/l}$ , which requires a reduction of 40% of the LDL-C ( $1.2 / 3.0 = 40\%$ ).
- The statins that are able to achieve a 40% reduction (Figure 3) are, for example, 40 mg simvastatin or 20 mg atorvastatin (there is very little chance of achieving such a reduction with pravastatin, even with 20 mg simvastatin).
- Prior to prescribing the drug, we should first verify the levels of CPK and liver enzymes, if this has not already been achieved.



**Figure 4.** Shows how various LDL reductions decrease the risk of cardiovascular mortality up to 10 years (SCORE) and the risk of global cardiovascular risk (fatal and non-fatal) up to 10 years (this is calculated by multiplying the risk SCORE by three). (1) The current 0.9 mmol/l reduction of LDL-C relatively reduces CV events by 18%. Hence, the absolute risk of mortality CV decreases from 15% to 12%. Similarly, the global CV risk (multiplied by 3, see above) decreases from 45% to 36%. (2) A greater reduction below the target of 1.8 mmol/l allows a relative reduction in the amount of CV events by 32%. Hence, the absolute risk of mortality CV decreases from 15% to 10% and the CV global risk decreases from 45% to 30%.

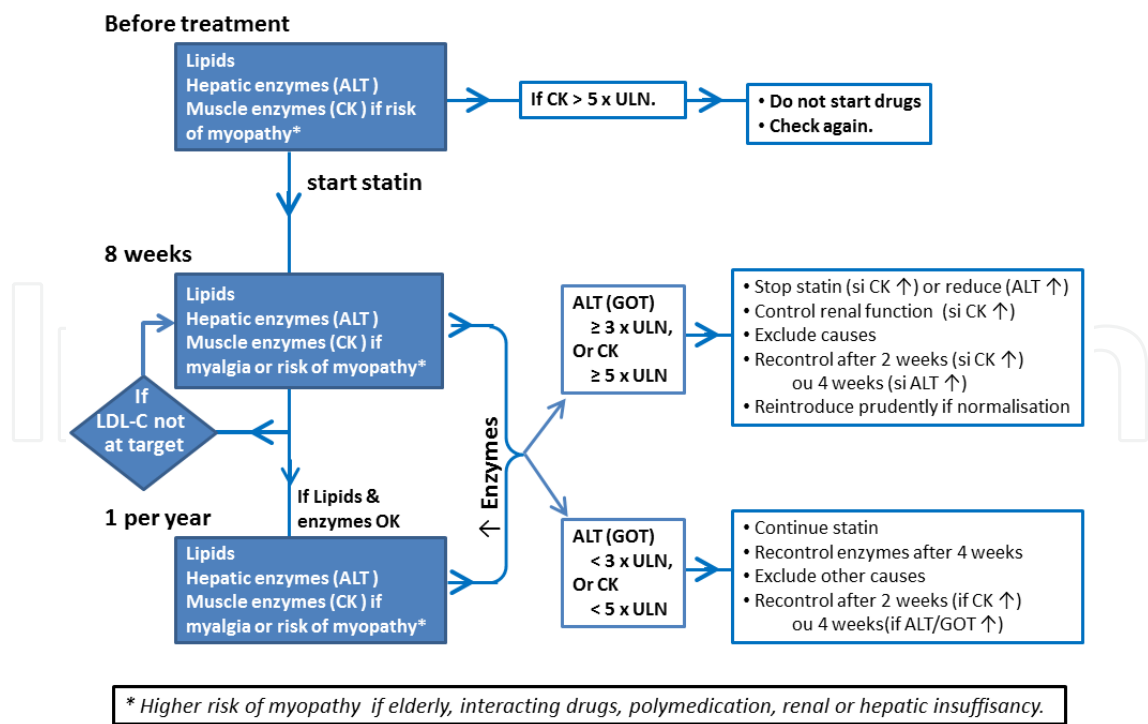


4. Third question, how to follow up the patient?

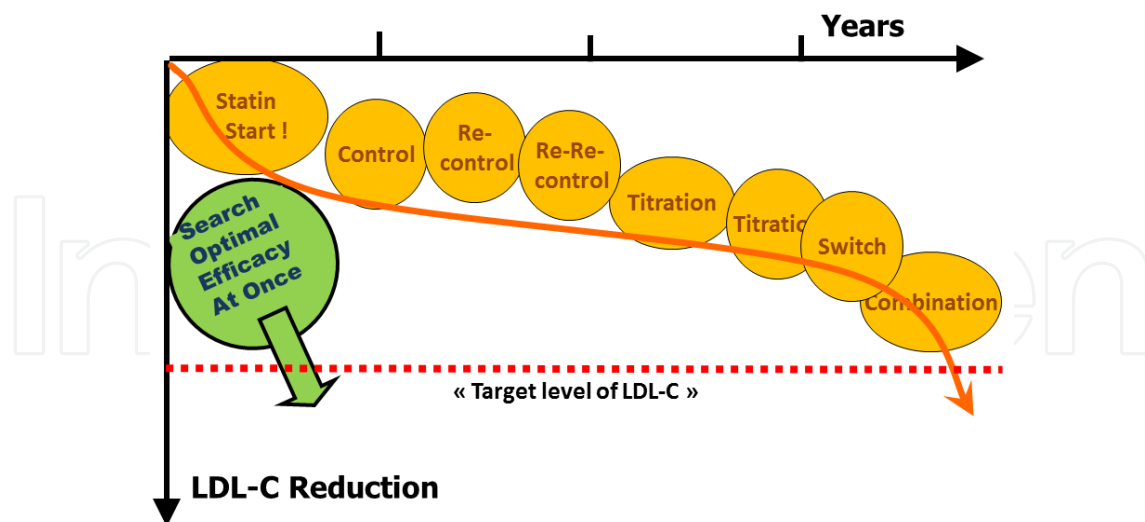
In order to verify the effectiveness and safety of the patient’s prescription, the improved guidelines recommend a patient follow up eight weeks later. Once the lipid levels have reached the target levels (according to the risk of the patient) and a safe level is maintained, an annual follow up will suffice.

4.1. Tolerance monitoring

Throughout the therapy, the monitoring of liver enzymes (Figure 5) is required. In subjects complaining of muscle pain, the muscle enzymes should be analysed. As long as the enzymes are not too high ( $< 3 \times$  the upper limit of normal or ULN), we should continue the statin. However, if the enzymes exceed by  $3 \times$  ULN for liver enzymes or  $5 \times$  ULN for muscle enzymes (Figure 5), the statins should be stopped. Furthermore, the enzymes should be checked four to six weeks later (or two weeks later if the CK is very high). For high elevation of the CK, we should check the renal function. When the enzymes return to a normal value, treatment (or an alternative treatment) should be carefully reintroduced. In all cases, other common causes of the elevation of these enzymes should be excluded. In the instance of high CK, this means intensive muscle efforts and injuries (including intramuscular injections, etc.). For cases of high ALT, this means weight gain, excess of sugar, fat or alcohol, steatosis, hepatitis, lithiasis migration and other medications, etc.



**Figure 5.** Biological monitoring of liver and muscle enzymes. CK: Creatine kinase. ALT. Alanine aminotransferase (also called SGPT).



**Figure 6.** In the intensity of treatment, a rapid escalation is more beneficial than a slow progression.

## 4.2. Efficacy monitoring

If the target is not achieved and, especially, if the observed reduction is lower than expected, as is the case here (Clinical Case 4), we should first check whether the patient has been compliant. We know that, after one year, approximately half of patients do not correctly take their medication [6]. If the patient has been compliant with her medication, it is possible that the inadequate response is due to a resistance to the statin. This occurs in 10% of patients. If this is the case, we should adapt the treatment.

### Clinical Case 4. How do we Follow up the Patient?

*Eight weeks after the prescription of 40 mg simvastatin, the patient is not complaining of myalgia. CPK levels have not been controlled and the GOT rates are normal. However, we are slightly disappointed with the lipid profile of the patient, which has become (Table 1):*

*Total cholesterol: 4.8 mmol/l; LDL-C: 2, 3 mmol/l; HDL-C: 1.1 mmol/l; Triglycerides: 3.1 mmol/l*

*The treatment appears to be well tolerated but the target has not been reached. Curiously, the reduction has not achieved the expected 40% (but only 28%!).*

#### 4.2.1. Why is it important that the target is reached?

In a recent meta-analysis of the results of 118,000 subjects from 26 intervention trials with statins, there was evidence of a relationship between the reduction of LDL-C and the reduction

of the incidence of CV disease in 4-5 years. Every decrease of 1 mmol/l for LDL - C by a statin (Figure 4) was associated with a relative reduction in about 20% coronary events, stroke and heart deaths [7]. This relationship was universal (regardless of age, sex and other risk factors). Furthermore, it was almost linear over the range of studied LDL-C levels.

The absolute benefit produced by statins not only depends on their capacity to lower LDL-C but also, on the initial CV risk. Thus, the greater the initial CV risk, the greater the reduction of absolute risk. In such cases, it is crucial to ensure the reduction of LDL-C. For our patient (Clinical Case 4 and Figure 4), we calculated that a reduction of LDL-C to 1.6 mmol/l (below the target of 1.8 mmol/l), instead of the current reached level of 2.3 mmol/l (Clinical Case 4), should reduce the risk of mortality from 12% to 10% CV. This should also reduce the CV global risk (multiplied by three) from 36% to 30% (Figure 4). This means that if this target was not achieved in 100 patients, six (30-36%) patients would experience a CV event and two patients would die (10%-12%). This highlights the importance of achieving values below the target, even if it sometimes seems difficult.

#### 4.2.2. What to do if the target is not reached?

In our patient's case (Clinical Case 5), we should try to obtain her compliance by reassuring her. If, in spite of this, the target is still not reached, we should adapt the treatment. This can be achieved by increasing the dosage of the statin (doubling each = 6% further LDL reduction) or replacing it with a more powerful statin. Another option is to combine the treatment with Ezetimibe (with an additional reduction of 20-25%) (Figure 3). The latter option is particularly useful when the observed reduction appears lower than expected, despite the patient's compliance with the treatment. Indeed, this suggests that the patient has a resistance to the statins. This usually affects all statins at all doses (the effect of each doubling statin dose does not allow the patient to achieve more than 4% or even 3%).

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#### Clinical Case 5. What do we do if the Target is not Reached?

*Due to the disappointing result at the second visit, we ask the patient about her resistance to comply. The patient says that she is scared of the side effects of the medication and thus, she only takes half a pill and tends to forget to take her medication. We answer all of her questions. We put the patient's mind at ease and encourage her to correctly take her medicine. Thus, the patient finally complies. This is confirmed at her third visit. However, at this visit, the patient's LDL-C still remained above 1.8 mmol/l. This means that we should adapt the statin (Table 1).*

*Eight weeks later (visit 4, Table 1), the lipid profile of the patient becomes (Table 1):*

*Total cholesterol: 4.0 mmol/l; LDL-C : 1.6 mmol/l; HDL-C : 1.2 mmol/l; Triglycerides: 2.8 mmol/l.*

*The target of LDL - C (less than 1.8 mmol/l) has now been reached. However, elevated levels of triglycerides and low level of HDL - C still remain! Should we be concerned about them?*

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#### 4.2.3. *Reach the target« ASAP<sup>2</sup> ».*

As mentioned above, the benefit of the LDL-C reduction can be seen within the first year treatment. The goal of "as quickly as possible" is all the more important in patients that are considered as high-risk. In a patient such as ours, there is a 15% risk of her dying from CVD in the next 10 years. Furthermore, there is a 45% (almost a "chance" on 2) risk of her having a global (fatal and non-fatal) CV event in the next 10 years. This means that there is a respective 1.5% risk and 4.5% (almost a "chance" on 20) risk of CV mortality and global CV risk per year. Although this may seem like a relatively small number, the delay in the necessary reduction of LDL-C for a year in 100 individuals (like our patient) would result in at least four to five CV events (including one death). However, in our practice, we should take note of the excuses given by the patient or by ourselves (anniversary cake, Christmas or Easter celebration, carnivals, holidays in all-inclusive hotels, etc., are a few days before blood sampling!). Such legions delay treatment adaption and obtaining satisfactory results. Taking this into consideration, it is clear that a more honest escalation in treatment would be more beneficial for the patient (Figure 6).

### 5. Fourth question: Should we go beyond LDL?

This leads us to three questions: (1) under statin therapy, does the patient still have a residual CV risk? (2) Is it necessary to target HDL-C and triglycerides? (3) Finally, is there scientific evidence that suggests further intervention would be beneficial? To answer these three questions, the guidelines respond affirmatively. Even after the reduction of LDL-C under the correct value target, a residual risk persists (between 60 and 80% of the initial risk). Part of this residual risk is attributed to the persistence of other alterations in a lipid profile.

Thus, if after the LDL-C correction, the patient still displays a high or very high-risk and has combined dyslipidaemia (triglycerides [TG] high > 1.7 mmol/l and HDL cholesterol [HDL - C] too low < 1.2 mmol/l for men or < 1.4 mmol/l for women), she may benefit from further improvement in her lipid profile.

The next question is: at this stage, how should a therapeutic target be set? Should we correct these levels of HDL-C and triglycerides or should we seek another target? In practice, it is often impossible to completely correct TG and HDL-C levels to achieve levels of 1.7 mmol/l for TG or 1.2 mmol/l in men and 1.4 mmol/l in women for HDL-C. On the one hand, TG levels vary too much from one day to the next. On the other hand, HDL-C levels are difficult to increase. For example, a baseline HDL-C at 0.8 mmol/l gives a rise of 20%, equivalent to 0.16 mmol/l. This only allows the HDL-C levels to reach 1 mmol/l - a difference barely perceptible, given the limited accuracy of laboratory measurements. Thus, the new guidelines recommend a more realistic target: the level of **non-HDL cholesterol** (non-HDL-C). This level is measured by a simple calculation:

$$\text{Non-HDL-C} = \text{total cholesterol} - \text{HDL-C}$$

In fact, as we can understand from the formula of Friedewald, this non-HDL-C is the sum [LDL-C + VLDL cholesterol]. The originality of this parameter is that it integrates all the potentially atherogenic lipoproteins, namely LDL and VLDL. These have a particularly high presence of low HDL-C and high TG (e.g., in the metabolic syndrome) [8].

The conditions and level of non-HDL-C targets are easy to deduct from the target levels of LDL-C. This is because they integrate the target value of LDL-C ( $< 1.8$  or  $< 2.5$  mmol/l) plus the ideal value of VLDL-C ( $< 0.8$  mmol/l; 0.8 is obtained by dividing the ideal 1.7 mmol/l level of TG by 2.2, see the Friedewald formula). Consequently, the level of non-HDL-C should be less than 2.5 mmol/l or 3.3 mmol/l as the risk is very high or high, respectively (Clinical Case 6).

### Clinical Case 6. Should we go Further in Correcting the Dyslipidaemia?

*The presence of high levels of triglycerides and low levels of HDL-C signal the calculation of the level of cholesterol non-HDL and the examination of the patient's residual risk.*

*At this stage, the calculated risk SCORE (with a total cholesterol of 4 mmol/l) is still very high. The SCORE is equal to 10.4%, taking into account the SCORE, HDL-C and family history, as well as the other risk factors such as TG, obesity, sedentariness and high hs-CRP (Table 1). Another way to calculate this risk is by considering the initial risk SCORE of 15% and removing the CV risk reduction produced by the LDL-C reduction (Figure 4). This leads to the same result.*

*Non-HDL cholesterol, which is equal to 2.8 mmol/l (tot chol – HDL-C = 4.0 – 1.2), should certainly be reduced below 2.5 mmol/l (= target for very high-risk). To do so, we can either strengthen the power of the statin or add ezetimibe to further reduce LDL-C. Another option is to add a fibrate or niacin to reduce TG (and LDL for niacin). Although these alternatives result in approximately the same reduction of the non-HDL cholesterol, they lead to different final lipid patterns (Table 1).*

	Visit 1	Visit 2	Visit 4	Visit 5 (2 alternatives)	
Time line	0	2 months	6 months	10 months	
Therapeutic target(s)		LDL-C $< 1.8$ mmol/l $< 70$ mg/dl	Second attempt to correct LDL-C	Non HDL-C $< 2.5$ mmol/l ( $\downarrow$ LDL-C)	Alternative to $\downarrow$ non HDL-C $< 2.5$ mmol/l ( $\downarrow$ VLDL-C)
Current treatment	Baseline	Simva 40 mg	- Better compliance - Atorva 40 mg or rosuva 20 mg	Same as visit 4 + ezetimibe 10 mg	Same as visit 4 + fenofibrate 145 mg
Total cholesterol	5.8 mmol/l (224 mg/dl)	4.8 mmol/l (185 mg/dl)	4.0 mmol/l (156 mg/dl)	3.6 mmol/l (140 mg/dl)	3.7 mmol/l (141 mg/dl)



	Visit 1	Visit 2	Visit 4	Visit 5 (2 alternatives)	
HDL-C	1,0 mmol/l (39 mg/dl)	1,1 mmol/l (42 mg/dl)	1,2 mmol/l (45 mg/dl)	1,2 mmol/l (47 mg/dl)	1,3 mmol/l (49 mg/dl)
Triglycerides	3,5 mmol/l (308 mg/dl)	3,1 mmol/l (271 mg/dl)	2,8 mmol/l (246 mg/dl)	2,6 mmol/l (232 mg/dl)	2,0 mmol/l (172 mg/dl)
LDL-C	3,2 mmol/l (124 mg/dl)	2,3 mmol/l (89 mg/dl)	1,6 mmol/l (62 mg/dl)	1,2 mmol/l (46 mg/dl)	1,5 mmol/l (58 mg/dl)
Non HDL-C	5,8-1,0=4,8 mmol/l (224-39=185 mg/dl)	4,8-1,1=3,7 mmol/l (185-42=143 mg/dl)	4,0-1,2=2,9 mmol/l (156-45=111 mg/dl)	3,6-1,2=2,4 mmol/l (140-47=93 mg/dl)	3,7-1,3=2,4 mmol/l (141-49=92 mg/dl)
LDL reduction (from baseline level)		-0,9 mmol/l (-28%) (- 35 mg/dl)	-1,6 mmol/l (-50%) (- 62 mg/dl)	-2,0 mmol/l (-63%) (- 77 mg/dl)	-1,7 mmol/l (-53%) (- 66 mg/dl)
Relative risk reduction (Absolute risk reduction or ARR)		- 18% (- 2,7%)	- 32% (- 4,8%)	- 40% (- 6,0%)	> - 34%* (>- 5,1%)*
SCORE evolution calculated from the initial SCORE and the subsequent ARR	15,0%	12,3%	10,2%	9,0%	<9,9%
SCORE evolution estimated from SCORE Chart (see Figure 2).	15,9%	12,2%	10,4%	10,4%	8,1%

The relative risk reduction (RRR) is calculated from the CTT regression (every LDL-C reduction of 1 mmol/l LDL-C leads to a 20% CVD risk reduction). \* The effect associated with the combination of statin and fibrate is expected to be greater than the effect of the LDL reduction. According to a recent study of diabetes (ACCORD), the addition of fibrate to statin in patients (including non-diabetic patients) with high TG and low HDL-C brings an additional 30% reduction in the risk of CVD. In our SCORE calculation, the smaller risk (8-9%) is due to the increase in HDL-C (the multiplier is 0.6 instead of 0.7) and the suppression of TG amongst the "other risk factors" (only obesity, sedentariness and hs-CRP remain, therefore, the multiplier for the other risk factor is  $1.1 \times 1.1 \times 1.1 = 1.3$  instead of 1.5). Simva: simvastatin; rosuva: rosuvastatin; atorva: atorvastatin.

**Table 1.** The evolution of the lipid profiles and CV risk in relation to our patient's increased treatment.

The reduction in the level of non-HDL-C should be achieved by an additional lowering of the LDL-C level. There are a number of ways to do this, including the prescription of a higher statin dosage, a stronger statin, a combination with ezetimibe (if intolerant) or by lowering the level of TG (and therefore, VLDL-C) via the association of the statin with fibrate or niacin (Clinical Case 6).

## 6. Conclusions

The new recommendations offer a practical approach. They are more precise in supporting the lipid profile of CV prevention. The four levels of risk and the possible adjustment of the new targets (non-HDL-C or apoB) next to the traditional targets of the LDL-C and HDL-C rate will allow better prescriptions of appropriate therapeutic drugs.

The present case illustrates step by step (visit by visit) the rationale for escalating treatment in order to achieve the best cardiovascular prevention. We hope that such an example can help give a better understanding of the EAS/ESC guidelines. The rigorous mathematical reasoning is, of course, only displayed here to better quantify the benefit of the various therapeutic choices. It is unlikely that it would be used in clinical practice. It is important to note that the practical implementation of guidelines requires the intuitive clinical skill of the practitioner, as well as open discussions with the patient. We would also like to highlight that, if the correction of the lipid profile is accepted as the cornerstone of CV prevention, the importance of lifestyle change (smoking, diet and physical activity) and the need to correct other risk factors should not be forgotten.

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