Hypercholesterolemia and laboratory report

Joint document of the Italian Society of Cardiology (SIC) and the Italian Society of Clinical Biochemistry-Laboratory Medicine (SIBioC)

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ABSTRACT

Elevated plasma concentration of cholesterol bound to LDL (LDL-C) is the predominant risk factor for cardiovascular (CV) diseases. An important number of clinical trials demonstrated that the use of statins to reduce LDL-C is beneficial in terms of prevention of CV events in the entire population. Over time, specific LDL-C targets to be achieved have been established to guarantee the best outcome for the patient from the therapeutic intervention. The fundamental role of the clinical laboratory in diagnosis and treatment monitoring of dyslipidemias, requires that harmonization in the different phases of the laboratory process be pursued and achieved in order to allow the correct management of patients. The harmonization process has been the subject of national and international recommendations over time; however, a further recommendation is essential, considering that some recent evidences testify to a sub-optimal adoption of the indications by a non-negligible number of laboratories, confirming the need to repeat training and information activities. Aim of this joint document is to analyze the importance of the therapeutic targets to be achieved and the critical elements of laboratory diagnostic related to dyslipidemia, in order to provide indications for the harmonization of the reporting of the lipid profile. According to these recommendations, the lipid parameters should be reported accompanied by the therapeutic goals differentiated by the risk categories for LDL-C and non-HDL-C and by the threshold values for the other parameters. The use of comparison terms like Reference values or Normal values in the laboratory report must be definitely abandoned.

Key word: *harmonization, laboratory report, lipoproteins*

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INTRODUCTION

Dyslipidemia is one of the main cardiovascular (CV) risk factors for the development of atherosclerotic disease and its control: recognized therapies with proven effectiveness guarantee optimal control of this risk over time (1,2). The most recent international guidelines (2) have identified increasingly stringent therapeutic goals for LDL cholesterol (LDL-C), which depend on the CV risk class of the individual patient. For the clinician and the patient, these targets represent a mandatory goal to achieve in order to optimize long-term prognosis.

To this aim, the laboratory reports relating to plasma lipid parameters, and mainly the reference values included in the reports, must comply with the recommendations of the guidelines, differentiating by risk class, so that each patient can recognize her/himself in her/his specific target to avoid misunderstandings, with the risk of discontinuing the lipid-lowering treatment, within a correct multidisciplinary context.

The aim of this joint consensus document between the Italian Society of Cardiology (SIC) and the Italian Society of Clinical Biochemistry and Clinical Molecular Biology - Laboratory Medicine (SIBioC) is to analyze the importance of the CV risk estimate, of the therapeutic targets to be achieved and the critical elements of laboratory diagnostic related to dyslipidemia, as well as to provide a proposal for the harmonization of the reporting of the lipid profile parameters to be applied in all clinical contexts to which the patient belong

Dyslipidemia as cardiovascular risk factor

The atherosclerotic disease is the main component of the CV diseases which, as a whole, account for over 4 million deaths in Europe every year (1,2). These deaths are due to prolonged exposure to multiple CV risk factors; among them, dyslipidemia is certainly one of the most relevant (1). Dyslipidemias or dyslipoproteinemias indicate quantitative changes in the plasma concentrations of total and lipoprotein cholesterol, or triglycerides (1). These variations can originate from primary alterations in the metabolism of lipoproteins, caused by genetic factors (primary dyslipidemias), or can be the consequence of environmental factors or other pathologies (secondary dyslipidemias). The presence of dyslipidemia is strictly correlated to the onset of atherosclerosis; therefore; early recognition and treatment of this condition may reduce the risk of CV disease. The most proven correlation with the development and progression of atherosclerotic disease is certainly the hypercholesterolemia. LDL-C has evolved from an abnormality or artifact called “protein X” from the Pedersen study, to the most relevant marker of atherosclerotic disease and become one of the most important causal risk factor for atherosclerotic disease (3).

Low-density lipoproteins bind glycosaminoglycans and remain trapped into the arterial wall where they undergo oxidation; oxidized LDL are recognized by scavenger receptors on macrophages and internalized by endocytosis, transforming macrophages into foam cells. These, in turn, release cytokines that trigger inflammatory processes. In response, smooth muscle cells in the arterial intima proliferate and produce collagen, leading to vascular alterations such as intimal thickening, atherosclerotic plaque formation, and possible rupture (4). Over 200 studies, including more than 2 million individuals, have demonstrated an association between LDL-C exposure and the risk of atherosclerotic CV disease (3). Initially, obesity and a sedentary lifestyle were considered responsible for high LDL-C levels, but subsequent research has also highlighted a significant role of heredity and genetic mutations.

Epidemiological studies such as the Seven Countries Study (5), the Framingham Heart Study (6), and the Münster Heart Study (PROCAM) (7) have clearly identified risk factors for CV disease and highlighted the importance of elevated LDL-C and total cholesterol levels in the development of atherosclerotic disease. The first and most important study to estimate this correlation was the Scandinavian Simvastatin Survival Study (4S) (8) which demonstrated how the reduction of LDL-C and total cholesterol levels with simvastatin in secondary prevention significantly reduced CV mortality and mortality from all causes. This study paved the way for a series of studies on statins, which confirmed the association between reduction of LDL-C levels and improved survival, as well as the reduction of major adverse CV events (MACE). A meta-analysis that included 10 studies with 79 494 patients showed that statins reduce the incidence of coronary events, stroke and overall mortality without affecting non-coronary mortality and that both sexes benefit of the reduction, regardless of diabetes, hypertension and smoking (9). Another meta-analysis of 27 randomized controlled trials with 174 149 subjects demonstrated that statins reduce the risk of major coronary events and coronary revascularization procedures by 24% and stroke by 15%, for every 1.0 mmol/L (~40 mg/dL) decrease of LDL-C (10). The analysis of these data highlights that the association between plasma LDL-C concentration and the risk of atherosclerotic disease meets all causality criteria. Indeed, prospective epidemiological studies, Mendelian randomization studies, and randomized intervention studies, all confirm a consistent dose-dependent relationship between the absolute magnitude of LDL-C plasma concentration and the risk of atherosclerotic disease. Furthermore, they demonstrate that the effect of LDL-C on the risk of atherosclerotic disease increases with the duration of exposure to hypercholesterolemia. The consistency between several lines of evidence, especially between genetic data and the results of numerous randomized intervention trials employing different pharmacological treatments to reduce LDL-C, provides significant clinical evidence that these lipoproteins cause atherosclerosis and that reducing LDL-C reduce the risk of CV events.

Estimation of cardiovascular risk and cholesterol targets recommended by the guidelines

The prevention of CV events plays a fundamental role in managing health at population level. In order

to maximize the benefits associated with the use of preventive strategies for the control of CV risk factors, it is crucial to identify those categories of subjects who can benefit most from prevention programs. In general, the greater the absolute risk of developing a CV event, the greater the benefit deriving from the reduction of risk factors and the smaller the number of subjects to be treated in a given population in order to prevent a single event in a certain time frame. The recent 2021 guidelines of the European Society of Cardiology (ESC) on CV prevention (11), confirm the estimate of CV risk as an essential tool for CV prevention programs. In primary prevention, the CV risk estimate utilizes the SCORE2 (Systemic Coronary Risk Estimation) algorithm; for each of the four regional clusters (European populations at low, moderate, high or very high risk of developing CV events, respectively), it is possible to identify a risk map which, through the combination of factors such as sex, smoking, systolic blood pressure and non-HDL-C (no longer total cholesterol, as in previous versions of the guidelines), allows estimating the risk of developing fatal and non-fatal CV events in subjects aged between 40 and 69 years in 10 years. A SCORE2 >7.5% in individuals aged <50 years and a SCORE2 >10% in individuals aged between 50 and 69 years, identify a very high risk of developing CV events, and consequently the indication to start, as soon as possible, aggressive therapy to control risk factors. Subjects aged >70 (the elderly) deserve specific attention, as the SCORE2 algorithm tends to overestimate the CV risk in this category of patients, because the relationship between the classic risk factors, such as lipids and blood pressure, and the risk of developing CV disease, attenuates with age; furthermore, CV disease-free survival progressively dissociates from overall survival with increasing age, in relation to the increased risk of death not related to CV events (the so-called competing risk). In these patients, an adapted SCORE2 algorithm, the so-called SCORE2-OP (older persons), is to be used; according to SCORE2-OP, the very high-risk category is identified for score values >15%. The 2021 guidelines include alternative predictive models for patients suffering from diabetes mellitus (ADVANCE and DIAL). These models, however, show some limitations: they were developed considering the data from a small number of studies and with a limited sample size, and are not statistically adapted to the current rates of CV diseases. They are also poorly suited to be used in the European context, as they do not consider the substantial variations in risk between countries and consequently can erroneously lead to an under- or over-estimation of CV risk. The need to identify a more adequate risk estimate for patients with diabetes, led to the introduction, in the new ESC 2023 guidelines (12), to a specific algorithm, the SCORE2-Diabetes algorithm, which integrates the elements already present in the SCORE2 with specific parameters of type 2 diabetes mellitus, such as glycated hemoglobin, estimated glomerular filtration rate (eGFR) and age at diagnosis of diabetes, identifying at very high risk, individuals with a SCORE2-Diabetes >20%, or with established CV disease or with severe organ damage. Patients suffering from familial hypercholesterolemia (FH) and chronic kidney disease (CKD) also belong to categories worthy of a different CV risk assessment in primary prevention. Individuals affected by FH fall into the high-risk category in the absence of CV disease, and are considered at very high risk, in the presence of CV disease or of an additional risk factor. Patients with CKD are considered at high risk if they have moderate CKD (eGFR between 30 and 44 mL/min/1.73 m^2 and urine albumin/creatinine ratio (ACR) <30 or eGFR between 45 and 59 mL/min/1.73 m^2 and ACR between 30−300, or, again, for eGFR ≥60 mL/min/1.73 m^2 and ACR >300). Subjects with severe CKD (eGFR<30 mL/min/1.73 m^2 or eGFR between 30 and 44 mL/min/1.73 m^2 and ACR >30) fall into the very high-risk category. The same therapeutic targets of individuals in secondary prevention are thus assigned to a number of subjects in primary prevention considered at very high risk; these include diabetic subjects with organ damage and/or multiple risk factors or subjects suffering from CKD, and carriers of subclinical atherosclerosis or suffering from peripheral arterial disease as well. This ESC initiative can be considered unique in the world. Actually, it reflects the attempt of the guidelines to cope with a shift in the prevention current paradigm highlighted by the “Rose paradox”. The majority of subjects who will suffer a major unexpected CV event in the future are indeed included in these categories. The prevention strategies will therefore concentrate progressively and precisely in these subjects.

For the four risk categories, the ESC guidelines recommend achieving and/or exceeding the following LDL-C targets: <3.00 mmol/L (116 mg/dL), in low-risk subjects; <2.60 mmol/L (100 mg/dL), in subjects at moderate risk; <1.80 mmol/L (70 mg/dL), in high-risk subjects; <1.40 mmol/L (55 mg/dL), in subjects at very high risk and <1.04 mmol/L (40 mg/dL), in subjects at particularly high risk (i.e. individuals who have experienced a second CV event in the two years following the first). The achievement of these goals is necessary for long-term primary and secondary prevention and must represent for professionals in the field and for patients, an imperative and unavoidable objective to be achieved through targeted pharmacological treatments.

LABORATORY DIAGNOSTICS

The fundamental role of the clinical laboratory in diagnosis, treatment monitoring and in assessing the achievement of the therapeutic targets in dyslipidemia, requires that harmonization be pursued and achieved in clinical laboratories in order to allow correct management of patients, providing them the best possible outcome. Harmonization concerns all phases of the laboratory process (pre-analytical, analytical, post-analytical). Each of these phases has been the subject of national and international recommendations over time (13-15) whose contents are still (with few exceptions) valid. However, a further recommendation is essential, considering that some evidence (16-18) testifies to a sub-optimal adoption of the indications into the daily practice of a non-negligible number of laboratories, confirming the need to repeat training and information activities.

Table 1 summarizes the main indications, which are detailed below.

Table 1
Indications for the harmonization of the pre-and post-analytical phase

Pre-analytical phase				Post-analytical phase		
Analyst	Essential	Recomended	Suggested	Sample	Units of measurements	Comparison
Total Cholesterol	X			Heparinized plasma (P) or Serum (S)	mmol/L and/or mg/dL	Threshold values
LDL-Cholesterol	X			Heparinized plasma (P) or Serum (S)	mmol/L and/or mg/dL	Treatment goals
HDL-Cholesterol	X			Heparinized plasma (P) or Serum (S)	mmol/L and/or mg/dL	Threshold values
Triglycerides	X			Heparinized plasma (P) or Serum (S)	mmol/L and/or mg/dL	Threshold values
Non-HDL Cholesterol		X		Estimate	mmol/L and/or mg/dL	Treatment goals
Remnant Cholesterol		X		Estimate	mmol/L and/or mg/dL	Threshold values
Apolipoprotein B			X	Heparinized plasma (P) or Serum (S)	g/L	Threshold values
Lipoprotein (a)			X	Heparinized plasma (P) or Serum (S)	nmol/L (recommended) mg/dL (not recommended)	Threshold values

Non-fasting blood sampling: optional

Pre-analytical phase

What parameters to measure for the lipid profile?

Given that it is difficult (if not impossible) for the individual laboratory to deviate from the execution of what is prescribed in the request, it is however highly recommended that the laboratories also maintain methods for measuring lipoprotein parameters not commonly requested or that, alternatively, these samples can be sent to other more specialized centers. On the other hand, since some of the parameters considered important for risk assessment (non-HDL-C, remnants cholesterol) are calculated parameters, which do not require additional measures (and therefore costs), these should be introduced in the report automatically.

The standard lipid profile includes the determination of total cholesterol (TC) and lipoprotein cholesterol (HDL-C and LDL-C) and triglycerides (TG). As mentioned before, to these parameters should be added the non-HDL cholesterol (non-HDL-C, obtained by subtracting HDL-C from TC) and, if LDL-C is measured directly[1], also remnants cholesterol (C-remnants, obtained by subtracting HDL-C and LDL-C from TC), at least in patients with TG <1.90 mmol/L (170 mg/dL). These two parameters estimate the cholesterol bound to IDL and VLDL fractions which carry a non-negligible amount of atherogenic cholesterol and constitute an additional risk factor (15).

Lipoprotein(a) [Lp(a)] should be measured at least once in an adult's life (15,19); given the difficulties of its accurate measurement, it is possible to consider sending the samples to specialized centers that can assemble an adequate number of tests and use apo(a) isoform-insensitive assays. Apo B determination is considered more informative than the measurement of TC and non-HDL-C for the evaluation of an individual's exposure to atherogenic lipoproteins (14-15) and could represent a secondary therapeutic target especially in patients with hypertriglyceridemia (15,3); however, the clinical evidence, which derives from clinical studies in which this parameter has been rarely used, is not yet considered sufficiently robust to introduce its determination into international recommendations, nor there is a shared therapeutic target. It is therefore rarely requested and consequently few laboratories offer this measurement.

Is fasting relevant?

The possibility of carrying out a lipid profile even if the subject (or the patient) has not fasted for the classic 8-12 hours, has been examined and proposed in some

[1]*If the LDL-C is calculated by the Friedewald formula, the C-remnants value is equal to TG/2.2 (when reported in mmol/L) or to TG/5 (when reported in mg/dL) and therefore does not constitute additional information*

consensus documents (15,20); really, the recent intake of foods only affects the concentration of TG (and even this in a not particularly significant amount). This possibility is not offered by many laboratories (18), probably because blood sampling is frequently performed for other parameters in addition to those of the lipid profile. Furthermore, in case of abnormal values, patients must undergo a second fasting sample to check the plausibility of the results. However, it is an interesting possibility that can be usefully offered within screening programs carried out in places other than the clinical laboratory, such as the workplace, schools, city squares on the occasion of *ad hoc* campaigns. A further possibility consists in offering the opportunity of a non-fasting blood sampling to those patients who need to measure only their LDL-C to monitor the achievement of therapeutic goals.

Analytical phase

The standardization of the measurement of classical parameters (including apo B) of the lipid profile has reached acceptable levels; it is therefore sufficient for the individual laboratory to use reagents that are in line with the level of standardization achieved (14).

For the measurements of Lp(a), because of the molecular heterogeneity of the lipoprotein, it is advisable to use methods that are not affected by the specific isoform of the sample (size-insensitive) and that the result is expressed in nmol/L. The limited diffusion of these methods to date and the lack of a sufficiently accurate conversion coefficient that allows the values obtained in mg/dL to be transformed into nmol/L[2], make it difficult for the individual laboratory to satisfy a limited number of requests by providing accurate results. For this reason, it is probably advantageous to concentrate the measurements in second level laboratories (19).

Shall we measure or estimate LDL cholesterol?

A still much debated question concerns the choice whether to measure LDL-C with direct methods or to calculate it by formulas. There are no definitive indications on the matter; the decision of the individual laboratory depends considerably on the internal organization of the laboratory. If the Friedewald formula is used in samples with TG values >2.25 mmol/L (200 mg/dL) (non-fasting samples), the LDL-C result is progressively underestimated. Similarly, the accuracy of the data is not optimal in case of particularly low LDL-C values (<1.8 mmol/L, 70 mg/dL) (15). In these events, the EFLM guidelines suggest using the Martin-Hopkins formula (15) which, however, does not currently seem to be particularly widespread in Italian laboratories (18). If the Martin-Hopkins formula is not used, the use of direct LDL-C measurement is preferable for non-fasting samples and is necessary for the calculation of the C-remnants value; furthermore, direct measurement is indicated in all cases of TG >4.5 mmol/L (400 mg/dL). It must be underlined, however, that neither the direct method nor the estimation methods are able to ensure an accurate measurement of LDL-C in every patient, given the strict dependence of the LDL-C value on the plasma concentration of TG.

Post-analytical phase

The improvement of this specific phase of the laboratory process, should cope with the harmonization of the following aspects (21,22):

- terminology
- units of measurement
- reference intervals and decision values

The terminology to identify the lipid profile parameters, is not a main issue since it is commonly used and standardized (Cholesterol, LDL-Cholesterol, HDL-Cholesterol, Triglycerides). Furthermore, they can be determined both on serum (S-) and on heparinized plasma (P-) (15).

Regarding the units of measurement, the 1967 IFCC recommendation (21) encouraging the transition to SI units (mmnol/L) in Clinical Chemistry reports, was followed in Northern Europe, while in Italy it was largely disregarded (6). While the reasons behind this recommendation remain still valid, a campaign to encourage its use today seems unlikely. The decision to include in the report both units (mmol/L and mg/dL), while on the one hand could encourage the adoption of SI units, on the other hand it is perhaps not particularly effective, as clinicians will read the units they are used to (i.e. mg/dL), ignoring the results expressed in SI units, with little likelihood of encouraging their use. However, despite these problems, the use of SI units should be recommended.

The adoption of the correct comparison term for the specific analyte (reference intervals or decision values) is fundamental for an adequate evaluation of the laboratory result (22). In the case of lipid parameters, including the reference values in the report is the most inappropriate method as numerous epidemiological investigations, issued many years ago (23) but also recent (24) have demonstrated that in the Western world, concentrations of lipids and lipoproteins linked to CV risk, are so widespread that a large part of the population shows values that are within the reference intervals despite being linked to a high CV risk. As a consequence, in this event, it is likely that a value is perceived as “normal” when actually it is not. The reference values are therefore not only completely useless but also misleading and therefore should never be reported. Decisional values linked to the amount of CV risk conveyed by CT, HDL-C and TG and the therapeutic goals for LDL-C should be used instead. Failure to adopt this reporting method could be, at least in part, the cause of patients’ lack (or partial) adherence to therapy (25).

[2]*The definition of a conversion factor is in fact impossible as the molecular weights of the various isoforms of Lp(a) are different and each individual possesses her/his specific isoforms; it is therefore only possible to indicate a factor based on an average molecular weight which, however, in the individual subject, may not be correct at all.*

INDICATIONS FOR REPORTING LIPID PROFILE PARAMETERS

Considering what has been illustrated in the above paragraphs, to ensure that the report related to lipid diagnostics is unambiguous, understandable by both the patient and the referring clinician, and does not give rise to misinterpretations, it is advisable to follow the indications contained in Table 1. Regarding the comparison terms to be used, detailed indications based on robust evidence derived from clinical intervention and epidemiological studies are those reported by the 2019 ESC guidelines (in association with the European Atherosclerosis Society - EAS) (1), by the 2020 EAS consensus document on the dyslipidemia management (in association with the European Federation of Laboratory Medicine - EFLM) (15), and by 2021 ESC guidelines on the CV diseases prevention (11). These documents report the therapeutic goals for non-HDL-C and LDL-C based on different risk categories (1,11), as well as the thresholds values linked to the association of the lipid parameters with the CV risk (15). Regarding Lp(a), two important consensus documents have recently been published (26,27). The values to be included in the report are listed in Table 2. It is important to emphasize that the therapeutic targets indicated for LDL-C and non-HDL-C are differentiated into the risk classes in which the individual patient is placed, based on his clinical situation (presence or absence of diabetes, systolic hypertension, renal disease, previous CV events); the laboratory obviously does not have this information available, so the values differentiated by risk class must all be listed in the report.

Table 2
Thresholds values and decisional values (therapeutic goals) to be included in the laboratory report

Analyte	Thresholds values SI units; traditional units	Therapeutic goals SI units; traditional units
Total Cholesterol	<5.0 mmol/L; <190 mg/dL	
Triglycerides	<1.70 mmol/L; <150 mg/dL	
HDL-Cholesterol	M >1,0 mmol/L; >40 mg/dL F >1.20 mmol/L; >45 mg/dL	
LDL-Cholesterol		Patients at CV risk low: <3.0 mmol/L; <116 mg/dL moderate: <2.6 mmol/L; <100 mg/dL high: <1.81 mmol/L; <70 mg/dL very high: <1.42 mmol/L; <55 mg/dL
non-HDL-Cholesterol		Patients at CV risk: moderate <3.4 mmol/L; <131 mg/dL high <2.6 mmol/L; <100 mg/dL very high <2.2 mmol/L; <85 mg/dL
Remnants Cholesterol	<0.8 mmol/L; <30 mg/dL	
Lipoprotein (a)	<75 nmol/L (values 75-125 nmol/L indicate an moderate CV risk, values >125 nmol/L indicate an elevated CV risk	
Apolipoprotein A-1	>1.25 g/L; >125 mg/dL	
Apolipoprotein-B	<1.0 g/L; <100 mg/dL	

Table 3
Critical values for lipids

Analyte	Value	Interpretative comment
LDL Cholesterol	>13 mmol/L; 500 mg/dL >5 mmol/L; 190 mg/dL	Consider homozygous FH Consider heterozygous FH
Triglycerides	>10 mmol/L; 890 mg/dL	Severe hypertriglyceridemia with high risk of acute pancreatitis

FH, familial hypercholesterolaemia

The referring clinician will then be able to assess whether or not the therapeutic goal has been achieved for that specific patient.

A final indication concerns the laboratory reporting of critical values. The issue has already been addressed in Italy a few years ago (14) in a consensus document and taken up more recently at an international level by the joint document of EAS and EFLM (15). Critical values are unexpected results that must be reported promptly to the clinician because they require attention and rapid intervention. In the context of dyslipidemia, the concept of timely reporting can apply to LDL-C values indicative of FH and to TG values indicative of risk of acute pancreatitis. These values must be reported appropriately on the report, possibly with a specific flag or a note and eventually communicated to the referring clinician. The critical values for dyslipidemia are shown in Table 3.

TAKE HOME MESSAGE

It is strongly recommended that the indications for the harmonization of the laboratory report included in this document be followed and adopted by each laboratory as soon as possible: the adoption of the indications does not involve any additional expenditure, but only a moderate organizational effort. If the laboratory management system prevents or makes it difficult to associate the relative value (or values) with each parameter, a footnote can be introduced in the report, listing the different values.

It should be stressed that persisting in labeling the comparison system for lipid parameters as “Reference values” or even worse “Normal values” could lead the patient (or the non-specialist clinician) to consider the value present on the report as “normal” when instead that value may be associated with a high and unacceptable CV risk for the clinical conditions of that particular patient, with the possibility of inducing harmful behaviors such as the abandon of the pharmacological treatment.

CONFLICT OF INTEREST

None

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