Appropriateness of cholesterol and triglycerides reporting checked by External Quality Assessment programs

Sandra Secchiero*, Laura Sciacovelli, Lorena Zardo, Mario Plebani

Centro di Ricerca Biomedica, Via Ospedale, 18, 31033 Castelfranco Veneto, Treviso, Italy

Abstract

Background: The recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention and the third Adult Treatment Panel report (ATPIII) released by the National Cholesterol Education Program are based on accumulating evidence concerning the contribution of lipoproteins and other risk factors in the development of coronary heart disease (CHD). The laboratories play an important role in the successful adoption of these guidelines. Methods: In External Quality Assessment (EQA) programs managed by the Center of Biomedical Research, results and respective reference intervals (RI) are sent as laboratory’s medical form. We assessed how well the 200 participants to EQA scheme 2002 for clinical biochemistry reported total cholesterol (TC) and triglycerides (TGs) results according to either European or National Cholesterol Education Program (NCEP) guidelines. Results: Only 18% of laboratories reported total cholesterol concentrations correctly in terms of desirable, borderline-high, and high risk for the CHD development, 12% reported a single desirable value (180, 190, or 200 mg/dl), and 70% reported the RI (85 laboratories in the whole interval, 34 are the only upper reference limit and 15 are the desirable value in addition to RI). The upper reference limit was 200 mg/dl in 65% of cases, but 32% of laboratories presented higher limits, reaching values as high as 250–260 mg/dl. Only the 3.7% of laboratories reported triglyceride concentrations in terms of risk-oriented ranges for the CHD development, 6.8% the single desirable value, and 89.5% the RI. Conclusion: Our study demonstrates that the current practice of reporting results for cholesterol and triglycerides does not follow the guidelines, and appropriate changes are required to be made.

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1. Introduction

Cardiovascular diseases, of which coronary heart disease (CHD) is the most common, are the major causes of death in adults in their middle years and older in most European countries as well as in the United States [1,2].

Lipids are closely associated with the clinical endpoints of cardiovascular diseases. The epidemiological data demonstrate that the relation between total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels and the incidence of CHD is continuous and increasing in all the range of their plasmatic concentrations; at the same time, there is a negative correlation, which is continuous and decreasing, between high-density lipoprotein-cholesterol (HDL-C) level and the probability of CHD [3]. While preventing coronary artery diseases by lowering high
blood cholesterol levels is based on conclusive scientific evidence [4–8], instead, if the increase of triglyceride (TG) level is associated with an increased CHD risk this has been a subject of a long-drawn controversy, even if there is an emerging international consensus in increased emphasis on the risk associated with high TGs [9–13].

Recently, some guidelines have been published on the control of TC and LDL-C aiming at preventing the coronary heart diseases in clinical practice. The most authoritative documents [14–18] show some important and significant conceptual analogies.

They suggest, in fact, that the patient’s diagnostic iter should begin with a complete fasting lipoprotein panel or profile (TC, LDL-C, HDL-C, and TGs), together with the evaluation of his absolute coronary heart disease risk.

As coronary heart disease is multifactorial in origin, it is important in healthy individuals to estimate the absolute risk (the risk of developing coronary heart disease, either a nonfatal event or coronary death, over the next 10 years) by taking into account all the major risk factors: smoking, hypertension, lipids (raised TC and LDL-C, low HDL-C and raised TC), raised blood glucose, family history of premature CHD, and advancing age, as well as lifestyle risk factors: overweight/obesity, physical inactivity, and atherogenic diet. Subjects at highest multifactorial risk can be identified and targeted for lifestyle intervention and, where appropriate, drug therapies [19,20]. The European Task Force was the first to introduce the use of the coronary risk chart to estimate CHD risk [18]. The third Adult Treatment Panel report (ATPIII), released in May 2001 by the National Cholesterol Education Program (NCEP) [14], in comparison to previous APTII [21], introduces a new calculated marker (non-HDL-C) and changes in the medical decision cut-points for LDL-C (100 mg/dl = 2.58 mmol/l), HDL-C (40 mg/dl = 1.03 mmol/l), and TGs (150 mg/dl = 1.70 mmol/l), while it has not changed the cut-point for TC (200 mg/dl = 5.17 mmol/l).

The Second Joint Task Force of European and other Societies on Coronary Prevention [16] recommends, as biochemical goals, a TC consistently below 190 mg/dl (5.00 mmol/l) and an LDL-C below 115 mg/dl (3.00 mmol/l) and indicates, as markers of increased coronary risk, an HDL-C <40 mg/dl (1.03 mmol/l) and fasting TGs>180 mg/dl (2.03 mmol/l). Beyond these formal differences between the two guidelines, there are some important analogies and conceptual convergences that allow us to conclude that their basic principles are, nowadays, widely shared inside the international scientific community. In fact, the preliminary evaluation of “absolute coronary risk,” the adoption of the concept of “target values” in the clinical management of TC and LDL-C, and the adoption of diversified values according to the subject’s risk profile, as shown in the two documents, represent the fundamental concepts, by now shared, on which to base a correct clinical management of the alterations of the lipidemia.

A further analogy among guidelines is the need of standardization of lipoprotein reporting.

ATPIII declares that the successful implementation of the guidelines will require that clinical laboratories shall be able to provide accurate results to the clinician in an appropriate and readily interpreted format [14,22]. In addition, the Italian guideline for the reporting of the plasmatic levels of lipids and lipoproteins [23], based on the document of the European Task Force, declares that the reporting style must specify carefully the meaning to attribute to the values at the side of the determination.

Laboratories play an important role in successful adoption of guidelines for the prevention of cardiovascular diseases. In laboratory routine practice, more attention to accuracy and standardization of the measurements is required to achieve reliable patient classifications, while in reporting formats, appropriate changes are necessary because the information of the laboratory can have a practical use in the clinical management of the patient.

The aim of our work is to evaluate the state of this issue in Italian laboratories using data from External Quality Assessment (EQA) scheme for clinical biochemistry managed by the Center of Biomedical Research (CRB) [24], which is accredited by the Clinical Pathology Accreditation (CPA) Program for EQA Scheme Accreditation [25] and has more than 200 participants.

As a general rule, an EQA program can provide valid indications on the state of the analytical quality reached by laboratories; the EQA program of the CRB, requiring participants to send results in the medical report form in use in each laboratory [26], becomes a privileged observatory and can also pro-
provide reliable indications on the degree of appropriateness of reporting.

2. Methods

To evaluate the total analytical variability of TC and TGs determinations, we reviewed all data from the last three cycles of the EQA scheme for clinical biochemistry managed by the CRB. The mean interlaboratory variability was calculated on data from 24 control samples, distributed in 12 different surveys, with a wide range of concentration. The number of results for each survey ranged from a minimum of 163 to a maximum of 184.

In the EQA program of CRB, for each constituent overall, method and diagnostic system-related data are analysed using the nonparametric method. The median, the robust standard deviation [SD_{rob}, 75th–25th/1.349] and the interlaboratory variability (which is expressed as coefficient of variation, CV%) are estimated after the exclusion of outliers (defined as results falling outside the range: median ± 3 SD_{rob}) [27].

The mean interlaboratory variability was obtained by the CV% observed in each survey for overall participants’ results, independently from the method they used.

To verify the appropriateness of TC and TGs reporting, we examined 190 medical reports from a survey of the last EQA (October 2002). We assessed how well the laboratories reported their results according to the published guidelines, paying particular attention to consistency of numeric reference ranges and linguistic terminology. Moreover, we studied the units of measure employed by laboratories.

3. Results

3.1. Interlaboratory variability

Regarding TC determinations, the results of the last three cycles of EQA showed a mean CV% of 4.1%, with a trendline nearly constant in the wide range of concentration ranging from 3.3 to 8.8 mmol/l (from 127 to 340 mg/dl) (Fig. 1). This variability is below the analytical goal used in EQA program of CRB, which is 6.3% [28–30].

Regarding TG determinations, in an analytical interval ranging from 0.5 to 3.0 mmol/l (from 44.0 to 265 mg/dl), a mean CV% of 5.4% was found. This variability, although not remarkable, denoted the presence of great systematic differences among methods, and the trendline showed a reduction of variability related to more elevated concentrations (Fig. 2). Even for TGs, however, the interlaboratory variability is widely below the analytical goal of 15.5% used in the EQA program [28–30].

3.2. Units of measure

Eighty percent of laboratories used milligrams per deciliter, and only 2% used the SI unit [31,32] that is millimoles per liter. Eighteen percent of participants used the two units, and precisely 15% reported results first in milligrams per deciliter and then in millimoles.
per liter, and 3% first in SI unit and then in the traditional unit.

By using the two units of measure, values after the transformation can differ slightly, one from the other, according to the number of decimal points of the conversion factor employed or to the selected approximations; for example, 200 mg/dl of TC was found to correspond to 5.00, 5.16, 5.17, 5.18, and 5.20 mmol/l, while 170 mg/dl of TGs was found to correspond to 1.87, 1.90, and 1.92 mmol/l. However, the greatest risk is to indicate a cutoff value with a system and a completely different one with the other unit if an incorrect factor of conversion is used, as we observed in some cases both for TC (the value of 200 mg/dl was transformed in 5.70 mmol/l that corresponds to 220 mg/dl) and TGs (the value of 170 mg/dl was transformed in 2.26 mmol/l that corresponds to 200 mg/dl) [33,34].

3.3. Total cholesterol and triglycerides reporting

3.3.1. Total cholesterol

A total of 70.5% of the medical reports examined (134 laboratories over 190) presented the reference interval (RI), and precisely 85 laboratories the whole interval, 34, only the upper reference limit, and 15, in addition to RI, reported the desirable value (13 laboratories), two (1 laboratory) or three risk-oriented ranges (1 laboratory).

About 11.6% (22 laboratories) reported the single desirable value, while the remaining 17.9% (34 laboratories), the risk-oriented ranges, and precisely 28 laboratories presented TC concentrations correctly in terms of desirable, borderline and high risk, 1 laboratory as desirable and borderline risk, 3 laboratories in terms of borderline and high risk, and 2 as desirable and high risk for the development of CHD.

Analyzing the RIs reported by the 134 laboratories, we observed significant differences (Fig. 3), also among the laboratories using the same analytical method (data not reported in figure). We found 42 different RIs. The more commonly used RI (33 laboratories) was 0–200 mg/dl, followed by the RI of 140–200 mg/dl used by 12 laboratories.

About 65% of laboratories used a value of 200 mg/dl (5.18 mmol/l) as upper limit, but 32% of laboratories used upper limits higher than 190 or 200 mg/dl (respectively, the so-called “desirable value” by the Task Force of European and other Societies on Coronary Prevention and the ATPIII), reaching values as high as 250 or 260 mg/dl (Fig. 4).

Among the 35 reported desirable values (22 from laboratories who presented the single desirable value and 13, the RI, too) they were found to be 180 mg/dl (1 laboratory), 190 mg/dl (9 laboratories), or 200 mg/dl (25 laboratories). Thirteen laboratories indicated desirable values according to age: for subjects under 20, the desirable value was 185, 180, and 170 mg/dl for 4, 2, and 1 laboratories, respectively, while 6 laboratories indicated a desirable value of 180 mg/dl for subjects under 30.

From the analysis of the reports with two or three risk-oriented ranges (recommended by ATPIII), it is deduced that 23.5% (8 out of 34) presented limits different from the guideline (those marked with an asterisk in Fig. 5).

3.3.2. Triglycerides

About 89.5% of the reports examined (170 laboratories over 190) presented the reference interval
Fig. 3. Total cholesterol: RIs (grey shapes) reported by 134 laboratories. The number of laboratories that use the same RI is reported in the abscissa.
(RI), and precisely 148 laboratories, the whole interval, 21, only the upper reference limit, and 1 reported the desirable value in addition to RI. Two laboratories indicated the range for male and female subjects, and other two declared that the values are dependent on age.

Some 6.8% (13 laboratories) reported a single desirable value, while only 3.7% (7 laboratories) presented triglyceride concentrations in terms of two (desirable and high), three (desirable, borderline and high or borderline, high and very high) or four (desirable, borderline, high and very high) risk-oriented ranges.

Analyzing the RIs adopted by the 170 laboratories, we observed a wide variability (Fig. 6). We even found 61 different RIs without a prevailing interval. In the figure, we pointed with an arrow the intervals more frequently used: 40–160, 40–170, 50–170 mg/dl.

Analyzing the upper limit of the RIs, we observed a much greater dispersion in comparison to that of TC. The values of the upper limit ranged from 150 to 250 mg/dl, and the more frequently used upper limit had a value of 170 mg/dl (Fig. 7).

Among the 14 laboratories that reported a desirable value, it was found to be 170 mg/dl (2 laboratories), 180 mg/dl (8 laboratories), or 200 mg/dl (4 laboratories). No laboratory used as desirable value the one recommended by ATPIII, which is 150 mg/dl; instead, 8 laboratories used the value recommended by the European Task Force, which is 180 mg/dl. Finally, none of the reports presenting more risk-
Fig. 6. Triglycerides: RIs (grey shapes) reported by 134 laboratories. The number of laboratories that use the same RI is reported in the abscissa.
oriented levels followed the American recommendations (Fig. 8).

In addition, the linguistic terminology used to indicate the ranges presented differences among participants. For example, for total cholesterol, the desirable value was also called decisional level, optimal value, a value to be hoped for and recommended value; the borderline range was also called interval of attention, moderated risk, moderated increase, low atherogenic risk, and range of suspect; the value of high risk was also indicated as decisional limit, elevated risk, elevated increase, high atherogenic risk, and pathological value.

Finally, no laboratory reported or acknowledged risk factor. Only 1 laboratory over 190 in the report wrote that for values of total cholesterol higher than 4.9 mmol/l, the clinician must refer to the coronary risk chart to estimate CHD risk.

4. Conclusion

The recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention and the third Adult Treatment Panel report released by the National Cholesterol Education Program are in agreement and suggest for screening a complete fasting lipoprotein profile (TC, LDL-C, HDL-C, and TGs), together with the evaluation of the absolute coronary heart disease risk of the subject.

Accurate and precise measurement of TC, HDL-C, LDL-C, and TGs, therefore, will continue to be highly important in achieving appropriate classification of patients according to the cut-points of the above recommendations.

In the past year clinical laboratories have continued to improve the methods for lipid testing [35,36], and the results of the last three cycles of EQA scheme
for clinical biochemistry of CRB showed a satisfactory interlaboratory variation for TC and TGs determinations. For both, in fact, the mean CV% was below their analytical goal [28–30]. The modification of some lipid cut-points and the recommendation to calculate CHD risk both require significant changes in the format of medical reports.

The results of this study show that the participants in EQA scheme of CRB do not follow, if not in minimal part, the changes in TC and TGs cut-points required by the above guidelines. The greatest part of laboratories still use reference intervals (RI) instead of risk-oriented ranges.

Moreover, we observed a huge variation in RIs. The use of different RIs, which does not seem justified by analytical variation, causes a paradoxical situation in which the same values lead to a different clinical interpretation (for example, a sample with a mean value of 6.8 mmol/l would have been “normal” according to some laboratories and “pathological” according to others) [37].

Even among a few laboratories that correctly use the risk-oriented ranges instead of RIs, great differences are shown in linguistic terminology, but above all, from a numerical point of view.

Finally, our study, similar to another one [38], shows that no laboratory provides indications on the risk factors. The current status of lipid panel reports, therefore, seems to be inappropriate.

Certainly, the transition from a situation in which the therapeutic decisions had to be based on the TC, LDL-C, and HDL-C cut-points to another in which the same decisions had to be based on risk levels—to their definition, the values of lipids contribute, together with other biochemical, anamnestic, and clinical-nature parameters that in a laboratory, up to now, are not possible to be obtained with safety and reliability—makes the lipid reports a problematic issue.

In the literature, recent examples of standardized medical report format exist [23,38], and there is one who suggests including for the physician, who has the necessary clinical information, a link to the risk calculator on the NCEP web page.

We do not suggest an ideal medical report format, but through EQA schemes, we can encourage laboratories to critically examine the validity of their reports and support them to take the appropriate changes in order to follow recent and actual guidelines. Full implementation of guidelines on prevention of coronary heart disease requires, in fact, education of physicians and other medical professionals including biochemists. The huge variability in reference ranges and failure to list risk factors can only cause confusion. Laboratory reports that include inaccurate reference ranges and ignore risk factors fail to communicate, hinder risk assessment, and hamper implementation of treatment.

Correcting lipid report, laboratories provide an opportunity to improve communication with the clinicians and recording of risk factors, with the hope of reducing morbidity and mortality due to coronary heart disease. In fact, the laboratory medicine is an integral part of the process of the patient’s care, and the clinical laboratories must not be limited to produce simple data, but must contribute to improve the clinical outcome.

References

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