

REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

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Abstract. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, John Chapman M, Couture P, de Graaf J, Durrington PN, Faergeman O, Fronlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Srinath Reddy K, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KMS (Heart Research Institute, Sydney, NSW, Australia; Baylor College of Medicine, Houston, TX, USA; Hospital Clinico Universitario, Valencia, Spain; St Franciscus Gasthuis, Rotterdam, the Netherlands; Hôpital de la Pitié, Paris, France; Centre Hospitalier Universitaire de Québec, Québec, Canada; Radboud University Nijmegen Medical Center, Nijmegen, the

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Rochester, NY, USA; All India Institutes of Medical Sciences, New Delhi, India; Northwestern University, Chicago, IL, USA; Isfahan Cardiovascular Research Center, Isfahan, Iran; McGill University Health Sciences Centre, Montreal, Quebec, Canada; Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA; Monash University, Victoria, Australia; and King Gustaf V Research Institute and Karolinska Institute, Stockholm; Sweden). Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel (Review). *J Intern Med* 2006; **259**: 247–258.

There is abundant evidence that the risk of atherosclerotic vascular disease is directly related to plasma cholesterol levels. Accordingly, all of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol. This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable. On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of chole-

sterol in these lipoprotein fractions. Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins. Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy. On the basis of this evidence, we believe that apo B should be included in all guidelines as an indicator of cardiovascular risk. In addition, the present target adopted by the Canadian guideline groups of an apo B <90 mg dL⁻¹ in high-risk patients should be reassessed in the light of the new clinical trial results and a new ultra-low target of <80 mg dL⁻¹ be considered. The evidence also indicates that the apo B/apo A-I ratio is superior to any of the conventional cholesterol ratios in patients without symptomatic vascular disease or diabetes to evaluate the lipoprotein-related risk of vascular disease.

Keywords: apo B, coronary heart disease, guidelines, LDL cholesterol, lipid-lowering therapy.

Background

Guidelines are a critical tool to improve clinical practice; but to remain evidence based, they must be modified as new information is acquired. All the ATP reports are based on the proposition that LDL cholesterol is the most clinically useful lipoprotein-related index of the risk of vascular disease. That there is a positive relation between the plasma level of LDL cholesterol and the risk of coronary heart disease and that reduction of LDL cholesterol reduces clinical cardiovascular events are both indisputable [1]. But LDL cholesterol is not the only framework in which these relations can be expressed.

We submit that there is a more useful alternative to consider: the atherogenic lipoprotein particle paradigm. This newer paradigm is based on multiple fundamental cell and animal biological studies, epidemiological studies and clinical trials. Many of the most important of these are summarized elsewhere [2–8]. Our purpose is to present its logic and the evidence for it in a form that is accessible to

clinicians as well as to researchers and then to outline our recommendations for changes in the guidelines.

The atherogenic lipoprotein particle paradigm

In brief, this paradigm posits that the total number of atherogenic particles is a more important determinant of the risk of vascular disease than any of the conventional lipid measures. This is the case because the number of particles within any lipoprotein fraction determines the likelihood of any member of that class entering and lodging within an arterial wall. The conventional lipid indices equate the risk due to a specific lipoprotein fraction to the plasma lipid concentration of that fraction. Thus, triglycerides are the estimate of the risk due to VLDL, LDL cholesterol the estimate of the risk due to LDL, and non-HDL cholesterol the estimate of the combined risk of VLDL, IDL, LDL and Lp(a). But there is an error in this equation. The lipid composition of the principal atherogenic lipoproteins differs substantially amongst

individuals. Therefore, lipid levels do not automatically equal lipoprotein particle levels.

By contrast, each VLDL, IDL, LDL, and Lp(a) lipoprotein particle contains one molecule of apo B100 [4, 9]. Because each of these atherogenic lipoprotein particles contains one molecule of apo B100 and because the lipid composition of VLDL, IDL and LDL differs so substantially, there is no precise relation between the lipid concentration of a specific lipoprotein fraction and the number of particles within that fraction. Each chylomicron and chylomicron remnant contains one molecule of apo B48. Clinical assays measure both apo B100 and apo B48. Total plasma apo B – the sum of the total apo B100 and apo B48 lipoprotein particles – yields the best current estimate of total atherogenic particle number, which represents the lipoprotein atherogenic burden.

apo B has been shown to be superior to LDL cholesterol in predicting the risk of vascular events and the progression of vascular disease in a series of prospective epidemiological studies. These include the 5 and 13 year reports of the Quebec Cardiovascular Study [10, 11], the AMORIS study [12], the Thrombo Study [13], the Thrombo Metabolic Syndrome Study, [14], the Northwick Park Heart Study [15], the Nurses' Health Study [16] and amongst patients with type 2 diabetes in the Health Professionals' Follow-up Study [17]. Similar results have been reported when atherogenic particle number has been measured by nuclear magnetic resonance [18, 19]. The other recent report of interest, the ARIC study [20], did not directly compare LDL cholesterol and apo B and therefore is not relevant in this regard. However, such comparisons are available within the placebo wings of several major statin clinical trials such as 4S [21], AFCAPS/TexCAPS [22] and LIPID [23]. In all, apo B was more informative than LDL cholesterol as an index of the risk of cardiovascular events. Moreover, atherogenic particle number has been shown to be superior to LDL cholesterol in judging the residual clinical risk on therapy in a number of the statin clinical trials such as AFCAPS/TexCAPS [22], the Leiden Heart Study [24] and LIPID [23]. Taken together, this constitutes a very substantial body of evidence demonstrating apo B is superior to LDL cholesterol in recognizing the risk of cardiovascular disease [10–23] and in judging the adequacy of statin therapy [22–24].

LDL cholesterol versus LDL particle number

Except in the uncommon circumstance of type III hyperlipoproteinaemia, even in hypertriglyceridaemic patients, more than 90% of total plasma apo B is associated with LDL particles [25, 26]. Therefore, total plasma apo B is, for practical purposes, a reflection of LDL apo B. If the lipid composition of LDL particles were fixed, LDL cholesterol would necessarily represent fully the risk resulting from LDL. In practice, this is not the case. Although all LDL particles contain one molecule of apo B, they differ substantially in their cholesterol content across the full density range from which they can be isolated [3, 4]. In healthy individuals, for example, the molar ratio of cholesterol to apo B in LDL varies from 2750 : 1 in LDL with a hydrated density of 1.026 g mL⁻¹ to 2100 : 1 in denser LDL with a hydrated density of 1.041 g mL⁻¹ – a difference of almost 25% [4].

Most studies divide LDL into only two subclasses: large and buoyant LDL particles that are relatively enriched in cholesterol (LB-LDL) and small and dense LDL that contain less cholesterol (SD-LDL). Whilst useful, this is an oversimplification and it is biologically and clinically more accurate to recognize at least three subclasses: very large LDL (LDL I), large LDL (LDL II) and small LDL (LDL III) [4, 27, 28] (Fig. 1). Indeed, none of us have just one subclass, although one does tend to predominate at any time. A correspondence between the predominant LDL subclass and disease was noted first by Teng *et al.* [5]. Low-risk individuals were characterized by a lower than average number of LDL particles and

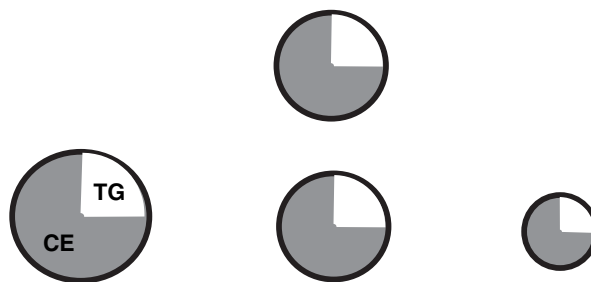


Fig. 1 LDL subclasses. This figure illustrates the three major LDL subclasses: LDL I, LDL II and LDL III. Each has one molecule of apo B. The relative amounts as well as the proportions of cholesterol ester and triglyceride are indicated for each. As the particles become smaller and denser, the total amount of core lipid and in particular, cholesterol ester, decreases.

the dominant LDL subclass was LDL II. Patients with familial hypercholesterolaemia (FH) were characterized by markedly increased numbers of LDL I and LDL II, whereas patients with hyperTg hyperapo B were characterized by markedly increased numbers of LDL II, particularly LDL III particles [5].

Because the amount of LDL cholesterol per LDL particle varies substantially both between and within individuals, LDL cholesterol does not necessarily equal the most critical variable, the total number of LDL particles. This is the key point.

Regulation of LDL composition and particle number

Several recent reviews detail the metabolic processes that regulate LDL particle number and LDL composition [2, 3, 6, 7, 29–31]. We will summarize only the most important points. The number of LDL particles is determined by the rate at which LDL particles are cleared from plasma and the rate at which they are produced. FH and familial defective apo B100 (FDB) are two monogenic disorders characterized by impaired specific receptor-mediated clearance of LDL from plasma [32]. In both, there are markedly increased numbers of cholesterol-enriched LDL I in plasma and extensive premature coronary atherosclerosis. Polygenic hypercholesterolaemia in which LDL cholesterol levels are increased due to overproduction of LDL is much more common than FH or FDB [33]. Nevertheless, hypercholesterolaemia *per se*, that is, elevated LDL cholesterol as defined by ATPII as levels >75th percentile of the population, [34] is much less common in patients with coronary disease than hypertriglyceridaemia – plasma triglyceride >133 mg L⁻¹ (1.5 mmol L⁻¹) – or low HDL cholesterol [35–38].

However, to conclude that LDL is not as important as these two other abnormalities would be wrong. If apo B is taken into account, the picture alters dramatically. Increased numbers of SD-LDL due to increased secretion of triglyceride-rich VLDL appear to be the single most frequent abnormality in patients with premature coronary artery disease [7, 8]. This phenotype – hyperTg hyperapo B – is also amongst the commonest abnormalities in patients with insulin resistance and type 2 diabetes mellitus [7] and is also the hallmark phenotype of familial combined hyperlipidaemia, the commonest familial dyslipoproteinaemia, which is associated

with premature coronary artery disease [39]. Indeed, accurate diagnosis of familial combined hyperlipidaemia depends on measuring apo B and not just plasma or lipoprotein lipids [40]. Moreover, the clearest *in vivo* data pointing to increased flux of fatty acids to the liver as producing increased VLDL secretion also come from metabolic studies in familial combined hyperlipidaemia (FCHL) [41, 42].

There is a predictable relationship between plasma triglycerides and LDL composition such that SD-LDL become the dominant LDL fraction as plasma triglycerides increase above 133 mg dL⁻¹ (1.5 mmol L⁻¹) [30, 43]. However, the relationship is far from perfect and no single triglyceride level produces a perfect separation of the dominant LDL subclasses. The association is the consequence of two processes: first, the progressive hydrolysis of larger, triglyceride-rich VLDL particles and second, the exchange and transfer of the two principal core lipids – triglyceride and cholesterol ester – amongst HDL, VLDL and LDL. These transfers and exchanges are mediated by cholesterol ester transfer protein and produce a triglyceride-enriched LDL particle. The triglyceride is then hydrolysed by hepatic lipase, and perhaps also by phospholipase A2, to produce an SD-LDL particle with less cholesterol ester per particle and therefore a lower cholesterol/apo B ratio [2, 3, 30, 43].

SD-LDL particles are at least as atherogenic as LB-LDL particles, even though they contain less cholesterol [3, 43]. It is not the mass of cholesterol circulating in plasma in LDL particles that is most important; rather, it is the number of atherogenic particles that are trapped within the arterial wall that counts the most. Indeed, is it not self-evident that arterial injury from atherogenic particles occurs only after they contact the endothelium or penetrate the arterial wall?

Smaller LDL particles enter the arterial wall more easily because they are smaller than larger LDL particles [44, 45]. They also have greater affinity for the glycoproteins of the arterial wall [46, 47] and therefore greater likelihood of binding to them and being trapped within the arterial wall. In addition, they have a greater propensity to oxidation [48–50], and therefore provide greater drives to thrombosis, inflammation and endothelial dysfunction [51–53]. Not surprisingly, a series of cross-sectional and prospective studies have shown that risk is higher when SD-LDL are the predominant fraction, although in most of these studies, they do not

remain independently predictive when other parameters such as triglyceride or total/HDL cholesterol ratio are taken into account [18, 19, 53–60]. Contrary reports have appeared indicating that risk is higher in those with LB-LDL. However, these studies were cross-sectional in design and the selection criteria excluded most patients with SD-LDL [61, 62]. SD-LDL are the most common profile in patients with vascular disease and reduction in SD-LDL is clearly associated with clinical benefit [63–65]. Moreover, the 13-year follow-up report of the Quebec Cardiovascular found that the cholesterol levels in LB-LDL were not associated with an increased risk of IHD, whereas those in SD-LDL were [11].

Nevertheless, it appears that LDL particle number is more important than LDL composition. Thus, in the vast majority of patients with hypertriglyceridaemia, SD-LDL are the dominant subclass, but only a portion of these patients have an elevated apo B [25, 66]. The evidence from multiple cross-sectional and prospective studies demonstrates clearly that the risk of vascular disease in patients with hypertriglyceridaemia relates to the level of apo B [15, 67–72].

apo B, chylomicrons and non-HDL cholesterol

Whilst each chylomicron and chylomicron remnant particle contains one molecule of apo B48 and these will all be included in the conventional apo B assay, this does not present a problem. Once again, except in type III hyperlipoproteinaemia, there are so few chylomicron particles compared even to VLDL particles, that they do not significantly influence total plasma apo B levels [7]. From this follows one major practical advantage of measurement of apo B over LDL cholesterol: patients do not need to be fasting to measure apo B, whereas they must be, or perhaps, even worse, must be assumed to be, fasting to calculate LDL cholesterol.

Non-HDL cholesterol is not a clinically accurate surrogate for apo B. The two are highly correlated but only moderately concordant [73]. Thus, at any level of non-HDL cholesterol, there will be considerable variation in apo B levels. The converse is also true: at any level of apo B, there will be substantial variation in non-HDL cholesterol. Non-HDL cholesterol and apo B represent different measures. Non-HDL cholesterol is the sum of the cholesterol in VLDL, IDL, LDL and Lp(a). Of the total plasma apo B,

approximately 90% are IDL and LDL particles with almost the remainder VLDL particles. Except for type III hyperlipoproteinaemia, VLDL particles make up a relatively constant portion of the total apo B particle number. Not so for VLDL cholesterol, which can easily range from 10% to 25% or more of non-HDL cholesterol, with the result that there is much greater variance in VLDL cholesterol as a percentage of non-HDL cholesterol than there is of VLDL apo B as a percentage of total apo B.

Moreover, VLDL particles are substantially larger than IDL or LDL particles and therefore less likely to enter the arterial wall. Veniant and Young examined the relationship between risk and lipoprotein size and showed in an experimental model that even when particle numbers are equivalent, LDL is associated with more extensive vascular disease than VLDL [74]. Not surprisingly therefore, most of the available evidence from epidemiological studies [8, 75], noninvasive studies [76, 77] and clinical trials [22–24] demonstrates that apo B is superior to non-HDL cholesterol as a marker of vascular risk and as an index of the adequacy of LDL-lowering therapy [8, 78, 79]. In two studies [17, 80], they have been equivalent. One of these [80] studied a low-risk population of healthy women in whom a high incidence of SD-LDL would not be expected. By contrast, in a study in men, a higher risk group, apo B was clearly superior to non-HDL cholesterol [81]. Furthermore, apo B has been also shown to be superior to non-HDL cholesterol in predicting vascular risk in a recently completed study of type 2 diabetes mellitus [82]. Of interest, the number of LDL particles or apo B is more closely associated with insulin resistance or markers of the metabolic syndrome than either LDL [83–85] or non-HDL cholesterol [73, 86].

In summary, whilst non-HDL cholesterol and apo B correlate, they are not the same, biologically or clinically. Furthermore, non-HDL cholesterol adds complexity to the LDL cholesterol-based system: which parameter is primary in importance? Moreover, there is no evidence that non-HDL cholesterol has yet broadly penetrated clinical practice or even been widely accepted by practitioners.

Methodological advantages of apolipoproteins

Clinical practice at the moment demands the patient be fasting for all estimates of lipid values. So long as

LDL cholesterol is calculated, that cannot be changed. Direct measures of LDL cholesterol are available, but they are not standardized and worse yet, they have the same biological limitations as calculated LDL cholesterol. Therefore, they add expense and complexity, but no more information.

The measurement of apoproteins has been standardized by the IFFC/WHO [87, 88], is automated, and fasting samples are not required, features that are accepted by authorities in the field [89]. Furthermore, the error in calculating LDL cholesterol increases as plasma triglyceride levels increase such that it must be abandoned at levels $>400 \text{ mg dL}^{-1}$ (4.50 mmol L^{-1}). In these patients, who are not infrequent, either no estimate of LDL can be made or nonstandardized, direct, determinations of LDL cholesterol must be performed, creating further complexity and expense. The methodological advantages alone of apo B and apo A-I would transform clinical practice. Because the technology is already developed, not complex and not expensive, there should be no cost impediment to its widespread introduction.

apo B versus LDL cholesterol in judging the adequacy of LDL-lowering therapy

As apo B is superior to LDL cholesterol in identifying the risk of vascular disease in untreated individuals, it would seem to follow that apo B will also be better in judging residual risk and therefore the adequacy of therapy. Statins are the overwhelmingly popular choice of reducing LDL cholesterol and apo B. However, it is not widely appreciated they lower LDL cholesterol more than apo B. For example, in a study of patients with SD-LDL treated with a statin, the decrease in LDL cholesterol was 15% greater than the decrease in apo B [90], a difference that was even greater in the patients with diabetes in the CARDS study in which LDL cholesterol was reduced by 40% (CI 39–41%), whereas apo B was lowered by only 23% (CI 22–24%) [91]. As SD-LDL are so common in type 2 diabetes, this suggests the degree to which there is discordance in the reduction in LDL cholesterol and apo B may be more pronounced when SD-LDL are the dominant LDL subclass. Moreover, the differences noted are mean differences. For individual patients, the discordance may be even larger.

Reliance on LDL cholesterol will lead to serious under-treatment of these patients. As statins, on

average, reduce LDL cholesterol more than they lower apo B, it is necessarily true that apo B on statin therapy will be relatively higher than LDL cholesterol. That is, the number of atherogenic lipoprotein particles will be higher than the LDL cholesterol suggests. Indeed, this has been demonstrated to occur in large subsets of both normotriglyceridaemic and hypertriglyceridaemic subjects treated with statins [92].

It follows that on-treatment apo B should be a more reliable index of the residual risk of vascular disease than on-treatment LDL cholesterol and this is exactly what has been observed in the statin trials in which the prognostic value of LDL cholesterol has been compared with apo B. Indeed, in most of the major statin trials, with the exception of 4S [21], the on-treatment level of LDL cholesterol was not significantly predictive of the residual risk of vascular disease. By contrast, in 4S [21], LIPID [23], AFCAPS/TexCAPS [22], the Leiden Heart Study [24] and the Thrombo Study [13], on-treatment apo B was predictive of the residual risk of vascular events.

It is true that in these studies LDL cholesterol was the primary criterion for selecting patients and the primary parameter for assaying the lipid response. But it is also true that apo B was a prespecified analyte. In addition, most of the major trials to date have used fixed dose therapies. None have been designed to produce a targeted level of either LDL cholesterol or apo B. Rather, they have tested specific doses of specific statins. It should also be noted that the first of the modern interventional trials – the FATS trial – used apo B as the primary criterion by which patients were selected [93].

Second, how do LDL cholesterol and apo B compare in predictive power at lower levels for each? The AMORIS study [12] demonstrated that apo B was even more predictive in those with LDL cholesterol levels below the 50th percentile than in those with values above this limit. That is to say, the difference in predictive power between apo B and LDL cholesterol is greater in the lower than in the upper half of the distribution of values.

Third, what is the relationship between LDL cholesterol and apo B in patients with an LDL cholesterol $<130 \text{ mg dL}^{-1}$? Figure 2 displays these results in 2159 consecutive patients with levels of LDL cholesterol $<130 \text{ mg dL}^{-1}$ and triglycerides $<400 \text{ mg dL}^{-1}$ (4.5 mmol L^{-1}) attending the University of Laval Lipid Clinic. The laboratory methods

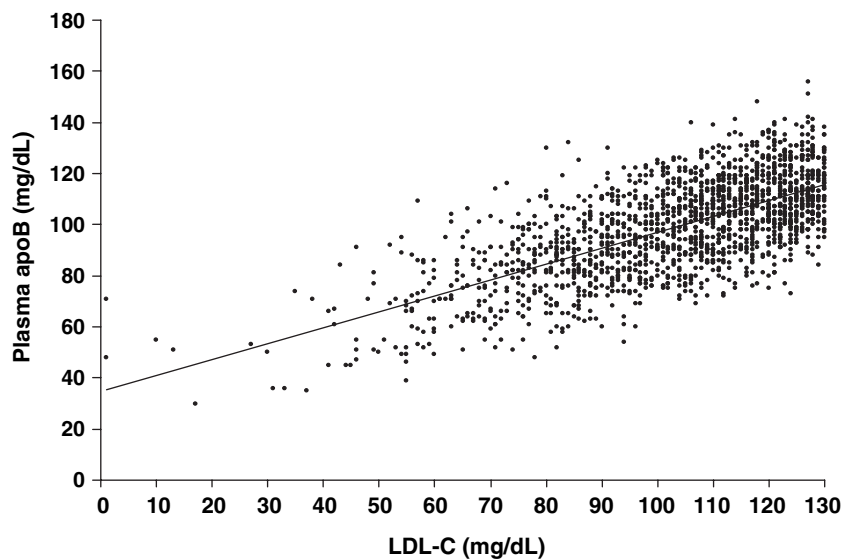


Fig. 2 LDL cholesterol and apo B. This figure illustrates the relationship between LDL cholesterol (*x*-axis) and apo B (*y*-axis) in 2159 patients all of whom had an LDL cholesterol <130 mg dL⁻¹ who were attending the Lipid Clinic at the University of Laval. No clinically useful relationship between these two measures is present.

are well established and standardized and the sample size is large. Notwithstanding that, there is a statistically significant relationship between the two measures, the dispersion around the line of identity is so pronounced that the relation is clinically meaningless for individuals. These results demonstrate that in dyslipidaemic patients, at levels of LDL cholesterol below the 50th percentile of the population, the level of apo B in individual patients cannot be inferred from the level of LDL cholesterol. The choice then is between a variable that is calculated and has not been shown to relate to clinical outcome at lower levels – LDL cholesterol – and a variable that is measured and has been related to prognosis – apo B.

The apo B/apo A-I ratio versus the TC/HDL C ratio

Currently, the lipoprotein-related risk of vascular disease is based on total and HDL cholesterol. The AMORIS study was the first to demonstrate that the apo B/apo A-I ratio was significantly more informative of cardiovascular risk than any of the conventional cholesterol indices: TC/HDL C, LDL C/HDL C or non-HDL C/LDL C. The most recent AMORIS results [75] also demonstrate that none of the lipids add significant predictive information to the apo B/apo A-I ratio. The differences in predictive power of the apoprotein ratio versus cholesterol ratio are substantial. Figure 3 illustrates this in both males and females from the AMORIS study. As risk

increases, the superiority of the apo B/apo A-I ratio compared with the conventional TC/HDL C ratio becomes more and more obvious. A substantial number of other reports supporting the superiority of the apo B/apo A-I as the best overall lipoprotein-related risk of vascular disease have already been published [13, 15, 22–24] and more should appear shortly. Of interest, the apo B/apo A-I ratio has been shown to be a significant predictor of the risk of heart failure, whereas LDL and HDL cholesterol were not [94].

The INTERHEART study has massively extended the data on the predictive power of the apo B/apo A-I ratio [95]. Conducted in 52 countries, involving 30 000 subjects, the INTERHEART study has established that the same core risk factors operate in different ethnic groups with different dietary intakes. Moreover, there was a remarkable linear relationship between the apo B/apo A-I ratio and risk, such that this single index accounted for just over 50% of cardiovascular events. These results are unprecedented in terms of their scope and clarity and lend potent support to the change we are advocating.

Recommendations

We recognize that any substantial change will require time to implement not least because it will take time to educate other healthcare professionals and patients as to the advantages of change and to make apolipoprotein measurements widely

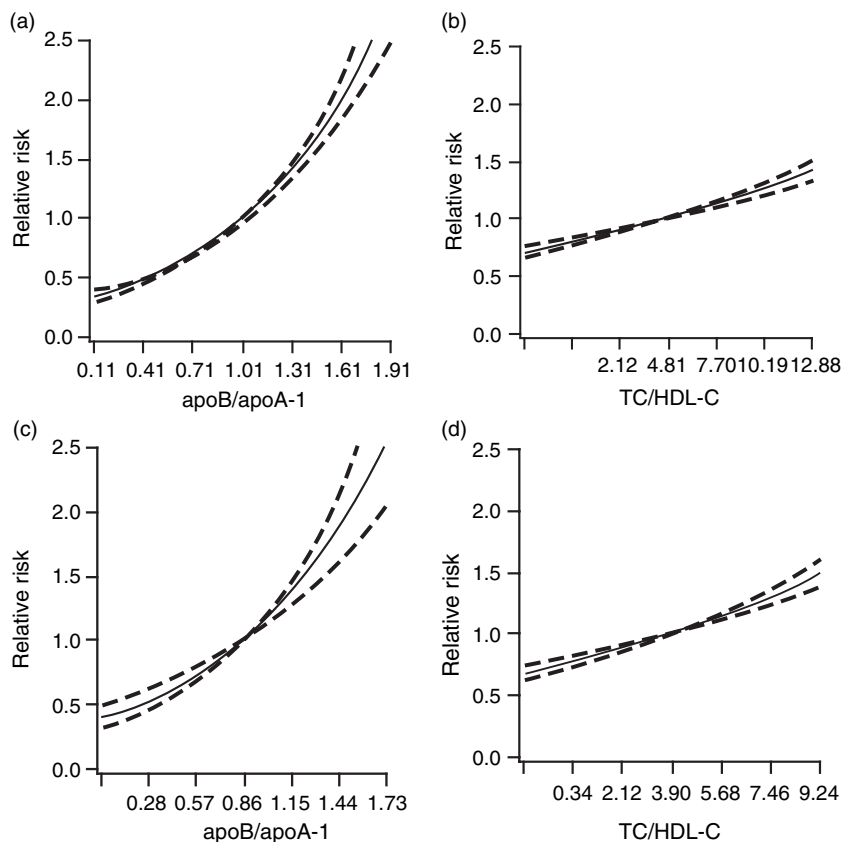


Fig. 3 apo B/apo A-I ratio versus TC/HDL C ratio in the AMORIS study. Panels (a) and (b) depict the relationship in males between vascular risk and the apo B/apo A-I and TC/HDL C ratios respectively. Panels (c) and (d) present the same data for females. The difference in slopes represents the difference in predictive power between the two ratios.

available. Therefore, we believe the first step is to introduce apolipoproteins as alternatives to the conventional indices. Accordingly, we believe that all guideline groups should recommend that:

- 1 the apo B/apo A-I ratio be accepted as an alternative to the TC/HDL C ratio to calculate the lipoprotein-related risk of vascular disease; and
- 2 target levels of apo B be adopted as alternatives to LDL or non-HDL cholesterol.

Summary

We believe that introduction of apo B into clinical practice represents a balanced and logical progression of the changes brought in by ATPIII [96]. This has become the position of the three major Canadian guideline groups [97–99] and we propose that their decisions deserve to be more broadly promoted. The latest European Guidelines acknowledge the value of apo B, but highlight the current problem of restricted laboratory availability [100]. Were the value of apo B as an alternative to the cholesterol indices to be more generally endorsed, laboratory availability

would certainly increase. The objective therefore should be to ensure that apo B is included in all the guidelines and that target values are specified.

It is, arguably, even more urgent to implement apolipoproteins into clinical practice in the developing countries in which the healthcare infrastructures are less developed and in which the need for simple, accurate indices of risk and of the adequacy of therapy may be even greater than in the developed countries of the world. But decisions for these countries must be based on data from these countries.

One of the cardinal virtues of guidelines is that they simplify and codify. However, diseases do not always precisely fit their first formulations. apo B is an extension of what came before, a more precise and more practical measure to improve clinical practice and treatment outcomes. As clinicians and researchers, we believe that, when evidence based, guidelines should endorse alternatives such as apo B so that doctors can modify their clinical practice. Otherwise, advances in clinical care, and therefore in clinical benefit, may, inadvertently, be delayed by the guideline process.

Key points

- apo B measures total atherogenic particle number in plasma and is superior to LDL cholesterol as an index of the lipid-related risk of vascular disease and as a guide to the adequacy of LDL-lowering therapy.
- Measurement of apo B is simple, standardized and does not require fasting plasma.
- apo B is a better guide than any of the cholesterol indices for judging the adequacy of LDL-lowering therapy.
- The apo B/apo A-I ratio appears to be superior to any of the cholesterol ratios for quantifying the lipoprotein-related risk of vascular disease.

Conflict of interest

R.C., M.C.-C., P.C., J.D.-G., P.N.D., O.F., J.F., C.D.F., C.G., S.M.H., S.E.H., I.J., R.M.K., P.K., S.M., C.J.P., T.A.P., K.S.-R., N.S., A.F.S., E.S., P.J.T., G.W. and K.M.S.W. declare that they have no conflict of interest.

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