Rationale for using apolipoprotein B and apolipoprotein A-I as indicators of cardiac risk and as targets for lipid-lowering therapy

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Introduction

Although low density lipoprotein (LDL) is recognized as the primary lipid-related risk factor, and therefore the primary target for lipid-lowering therapy,¹–⁴ there are in fact several limitations of only using LDL cholesterol (LDL-C) as the primary risk variable.⁵,⁶ New data are accumulating which speak in favour of apolipoproteins (apo) as more informative risk indicators/factors. ApoB, which indicates the number of potentially atherogenic lipoprotein particles, and apoA-I, which reflects anti-atherogenic high density lipoprotein (HDL) particles, may be additional lipid-related variables that more accurately indicate cardiovascular (CV) risk than LDL-C. Thus, several studies have shown that apoB and apoA-I are strong predictors of myocardial infarction (MI).⁷–⁹ The two largest of these studies are the AMORIS⁷ and the INTERHEART⁹ studies which both show a very strong direct relation between a high apoB/apoA-I ratio and an increased risk of fatal MI⁷ and acute MI (AMI).⁹ Meisinger et al.¹⁰ add another piece of important information along the same lines.

Physiological and pathophysiological aspects of apoB and apoA-I metabolism

ApoB is present in very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), large buoyant LDL, and small dense LDL (sd-LDL), with one molecule of apoB in each of these atherogenic particles. Thus, total apoB reflects the total number of atherogenic particles (Figure 1). It is the apoB in the particles that leads to entrapment of these lipoproteins in the arterial wall. ApoB produced in the liver also stabilizes and allows the transport of cholesterol and triglycerides in plasma VLDL, IDL, large buoyant LDL, and sd-LDL (Figure 1). In addition, apoB serves as the ligand for the apoB and apoB,E receptors thereby facilitating the uptake of cholesterol in peripheral tissues and the liver.⁶

Usually >90% of all apoB in blood is found in LDL. In cases where LDL-C is in the normal/low range, high apoB levels may indicate an increased number of sd-LDL particles, which are the most atherogenic particles because they are easily oxidized and promote an inflammatory response and the growth of plaques.⁶

Larger apoB-containing particles, such as VLDL and IDL, can also enhance the risk of atherothrombosis by inhibiting the fibrinolytic system and by stimulating cytokine production and inflammatory reactions.⁶

ApoA-I is the major apolipoprotein in HDL particles and has a central role in the 'reverse cholesterol transport'. ApoA-I can 'pick up' excess cholesterol from peripheral cells and transfer it back to the liver in the HDL particles. ApoA-I also manifests anti-inflammatory and antioxidant effects.⁶ The anti-atherogenic properties of apoA-I were recently documented.¹¹
The ratio of apoB to apoA-I reflects the balance of cholesterol transport in a simple way. The higher the value of the apoB/apoA-I ratio, the more cholesterol is likely to be deposited in the arterial wall, thereby provoking atherogenesis and hence also increasing CV risk.6

Epidemiological results—prospective studies

The AMORIS (Apolipoprotein-related MOrtality RISk) study has shown that high levels of apoB are strongly related to increased CV risk, whereas apoA-I was protective both in males and females over a wide age range.7 In this prospective study performed in more than 175 000 Swedish males and females followed for an average of 98 months, almost 2000 subjects died from an MI. ApoB was also found to be a stronger marker of CV risk than LDL-C at any LDL-C level, but especially in subjects having even down to LDL-C levels 2 mmol/L.3 Newer direct methods for determining LDL-C are not yet standardized in all countries world-wide. The apoB/apoA-I ratio was the strongest of all conventional risk factors in predicting AMI.9

Several other studies have confirmed that either apoB and/or apoA-I levels are closely related to increased intima-media thickness in the carotid artery and the rate of its progressive increase in patients with the metabolic syndrome, 13 or to CV risk determined either as a first MI or a recurrent MI.6,8

ApoB, apoA-I, and prediction of MI in the MONICA/KORA Augsburg study

This study was performed in 1414 men and 1436 women aged 35–64 years and without a prior MI. The median follow-up period was 13 years. During follow-up, 114 men and 31 women experienced coronary events, 71 were fatal and 74 were non-fatal MI. The main result was the strong direct relationship between high apoB levels and increased risk for MI, which in multivariate models showed a 49 and 73% increase in risk for one standard deviation higher apoB values in men and women, respectively. Similarly, the age-adjusted risk for MI was also increased significantly, and with about the same magnitude, for both the apoB/apoA-I and the TC/HDL-C ratios in both genders. By contrast, high apoA-I concentrations were not significantly associated with low risk for MI. The results for apoB levels and the apoB/apoA-I ratio remained significant even when adjusted for age, smoking, alcohol, body mass index (BMI), diabetes, and hypertension.

These results are in line with the findings in the INTERHEART study, which was based on almost 15 000 AMI compared with 15 000 age- and sex-matched controls.9 In that study the apoB/apoA-I ratio was the strongest of all risk factors including smoking, hypertension, abdominal obesity, diabetes, alcohol, psycho-social stress, vitamin intake, and exercise. The results were independent of age, gender, and ethnicity. Furthermore, the apoB/apoA-I ratio also remained the strongest of all risk factors in multivariate analyses.

Clearly, the present findings from the MONICA/KORA study are in line with the results from the INTERHEART study since both showed that the apoB/apoA-I ratio was an independent risk factor. Although there were very few fatal events in the MONICA/KORA study, the results are also in line with the findings of the AMORIS study.6,7 However, in AMORIS the apoB/apoA-I ratio was a stronger risk factor than the TC/HDL-C ratio due to a much larger number of fatalities enabling proper statistical comparisons.6,8,12

ApoB and apoA-I—methodological advantages and experience from lipid-lowering trials

The preceding discussions show that there is an increasing knowledge indicating the power of using apoB and apoA-I as CV risk markers. This is further supported by several methodological advantages for these new tests. ApoB and apoA-I are measured directly, compared with LDL-C, which is usually calculated from measurements of TC, triglycerides (TG), and HDL-C, using the Friedewald formula, which is valid only if TG values are <4.5 mmol/L. To be able to use this formula the patients have to be fasted. Furthermore, the errors of that method are 5–20%, especially in subjects with LDL-C levels <2.5 mmol/L.5,6 This is a critical problem, since today’s target levels for lipid-lowering therapy must be accurately determined even down to LDL-C levels <2 mmol/L. Newer direct methods for determining LDL-C are not yet standardized internationally.6,12 In contrast, methods for determining apoB and apoA-I are internationally standardized and the errors of the methods are <5%. ApoB can adequately measure the number of apoB-containing particles, especially the sd-LDL, which is an advantage in patients...
with the metabolic syndrome and manifest diabetes.\textsuperscript{6,8,13} Furthermore, the methods can easily be automated; analyses are cheap, can be used on frozen sera, and, importantly, can be made on non-fasted samples.\textsuperscript{6–8} ApoB and apoA-I are also useful indicators of the effects of lipid-lowering therapy.\textsuperscript{6–8} Statins decrease apoB by 15–50% and they increase apoA-I by 5–15%, with greatest effects for rosuvastatin.\textsuperscript{6} Fibrates reduce apoB less than statins,\textsuperscript{6} whereas the apoA-I-raising effects of fibrates may be equally good or better than that of statins.\textsuperscript{6} In recent reviews it was shown that changes in apo concentrations during statin therapy were, if anything, more closely related to outcome than changes in lipids, lipoproteins, or lipid ratios.\textsuperscript{6–8}

A new approach to predict lipid-related CV risk – the apoB/apoA-I ratio paradigm

Obviously, results from both prospective risk studies, including the presently reported MONICA/KORA study, and from lipid-lowering trials indicate that the apoB/apoA-I ratio is a useful summary index of risk and that it is at least as good as, and often better than, the conventionally used LDL-C, and various other lipid ratios. There are a number of user-friendly reasons for adopting this ratio into clinical practice. Since the analyses can be made on non-fasted samples this is of great practical advantage for patients and physicians over the other methods, which usually need fasting. Furthermore, the results can be expressed as one number for the ratio only, rather than by many values for LDL-C, HDL-C, TG, and lipid ratios.

Clearly more data, especially from lipid-lowering trials, will strengthen the use of apoB and apoA-I. The available knowledge has already led to an update of guidelines in Canada.\textsuperscript{4} Cut and target values have already been proposed.\textsuperscript{2,6} Based upon the new knowledge it is now time to update guidelines to include apoB and apoA-I as primary risk variables of equal importance to LDL-C and HDL-C. It is therefore proposed that values indicating level of risk should be developed, taking the conventional risk factors into consideration as well as the prevalence and incidence of CV disease within different geographical and socio-economic areas. The apoB/apoA-I ratio could be a simple, robust, precise risk indicator of great value in health screening and during lipid-lowering therapy.

References

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