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The apoB/apoA-I Ratio is a Strong Predictor of Cardiovascular Risk

Göran Walldius

1. Introduction

In the present paper the rationale for including apolipoprotein (apo)B and apoA-I into clinical practice is reviewed. ApoB and apoA-I are the two major apolipoproteins involved in lipid transport and in the processes causing atherosclerosis and its complications. ApoB is the major protein in Very Low Density (VLDL), Intermediate Density (IDL) and Low Density Lipoproteins (LDL), one protein per particle (1). ApoA-I is the major protein in High Density Lipoprotein (HDL) particles **(Figure 1)**. The apoB number indicates the total number of atherogenic particles, the higher the number the higher is the cardiovascular (CV) risk.

ApoA-I reflects the anti-atherogenic potential in HDL particles, the higher the value the better protection of CV risk. The apoB/apoA-I ratio (apo-ratio) indicates the balance between atherogenic and anti-atherogenic particles, the higher the value, the higher is the CV risk. In previous papers we (2-6) and others (7-12) have reviewed the importance of apolipoproteins, mainly apoB and apoA-I, but also other apolipoproteins like apoC-II and apoCIII, apoE, and Lp(a) as markers of atherogenic risk. In this review many new data on apoB, apoA-I and the apo-ratio and their relations to cardiovascular (CV) risk are presented. The majority of these studies were published in the last 6 year period.

The debate today (mid 2012) is about whether LDL-C should remain as the primary variable for CV risk evaluation and target for lipid-lowering therapy. During the last few years non-HDL-C has been found and proposed to be the next primary target for CV risk evaluation and target for treatment (9-11,13,14). Notably, although LDL-C and non-HDL-C are considered the best CV risk markers most large studies of CV risk have shown that the lipid ratios, i.e. the TC/HDL-C, the LDL-C/HDL-C and the non-HDL-C/HDL-C ratios, are stronger than any specific single lipid fraction (2,3,4,6,15). The major aim of this paper is therefore to review papers on apoB, apoA-I and the apo-ratio related to risk of atherosclerosis

and various clinical complications like myocardial infarction (MI), stroke and other severe events to find out if there is evidence for using apoB and apoA-I, and especially the apoB/apoA-I ratio (apo-ratio) motivating clinical use of these risk markers/predictors. Both similarities, but mainly differences between apos and conventional lipids to predict CV risk, will be highlighted. Methodological aspects and the role of apoB and apoA-I, the two determinants of the apo-ratio, will first be commented. The major part of the paper describes the role of the apo-ratio as a CV risk marker/predictor. The overall conclusion from this paper will be that apoB, apoA-I and the apo-ratio merit to be included in future guidelines in order to be recognized and used in clinical practice.
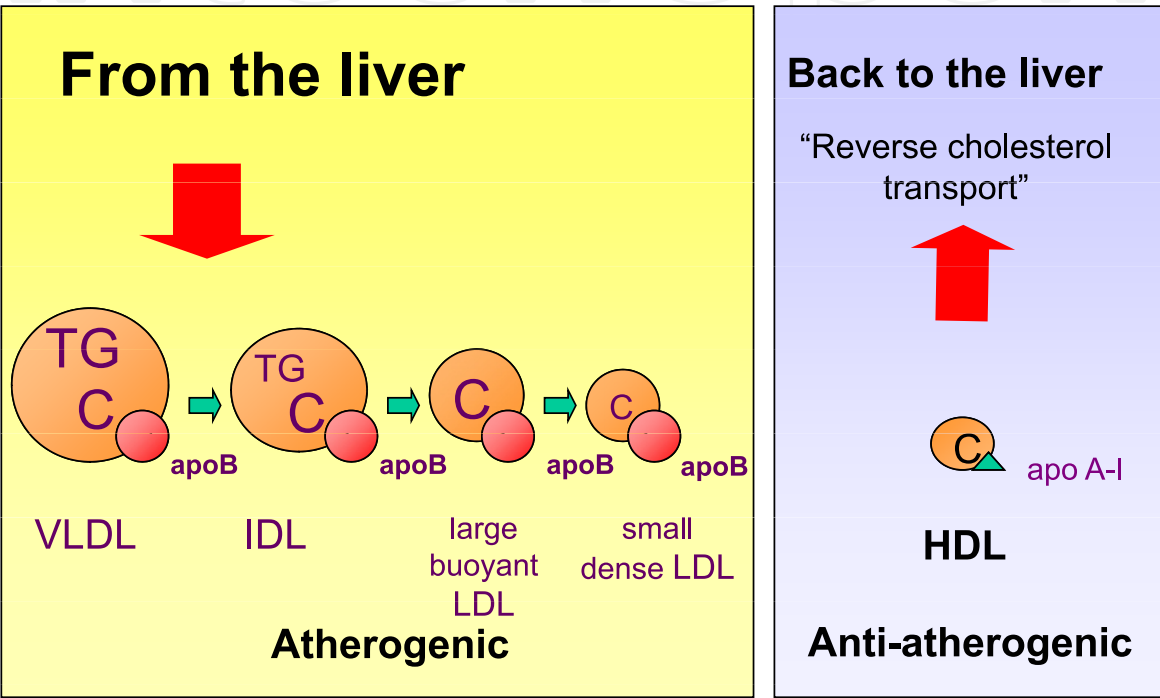

Figure 1. The figure shows the atherogenic particles containing one apoB protein per VLDL, IDL, large buoyant LDL, small dense LDL particles and the anti-atherogenic lipoproteins containing apoA-I. The balance between apoB and apoA-I, i.e., the apoB/apoA-I ratio, reflects the balance between the "bad cholesterol particles and the good cholesterol particles". This apo-ratio is strongly related to cardiovascular risk, the higher the ratio, the higher is the risk. (From reference 3).

2. Methodological pros and cons for using apoB, apoA-I and the apo-ratio versus conventional lipids

2.1. Methodological problems for various lipids

The most commonly used method world-wide to measure LDL-C is based on the Friedewald formula (16). However, errors are common and the methodological problems and shortcomings are not commonly recognized but have been discussed in many papers (17-25). Thus, the formula (LDL-C = TC – HDL-C – TG/5) is not valid for blood samples having triglycerides (TG) above 3.5-4 mmol/L, for patients with type III hyperlipoproteinemia or chylomicronemia or non-fasting specimens (17-19). The errors for

LDL-C can be false positive in the range of 2-17% or false negative between 12-15% if TG levels are very low or closer to 4 mmol/L. This may create large problems for both clinicians and patients since patients may be misclassified as being at risk or not at risk according to guidelines. Similarly, it may be difficult for the clinician to evaluate if a patient has been adequately treated to the target of LDL-C. Newer so called ''direct LDL-C methods'' have been developed and they are homogeneous methods, that is, assays that do not require a preliminary separation step, such as ultracentrifugation, or manual manipulation of the sample for determining LDL-C (9,18-20). However, these methods, although standardized at a given laboratory, do not always correlate well over the whole range of lipid values, and they are not even internationally standardized like those for apolipoproteins.

The practical problems of measuring HDL-C are also of concern and correlation between various methods are sometimes even worse than those for LDL-C (18,19,26). Consequently, the values for non-HDL-C (TC minus HDL-C) may also be subject to large variations due to the errors mainly for measuring HDL-C. However, there is an advantage for non-HDL-C over LDL-C determined by the Friedewald formula since non-HDL-C is not subject to influence of non-fasting that may distort the TG levels and make it difficult to obtain a correct value for LDL-C (27). Furthermore, non-HDL-C contains C from all atherogenic fractions i.e. VLDL, IDL and various forms of LDL. Thus, non-HDL-C which indicates the total mass of C is more likely to reflect the variation of atherogenic particle set up for many patients with various genotypes and phenotypes. Such patients may have a greater chance to be correctly identified as risk individuals based on non-HDL-C, rather than to an imprecise measure of only LDL-C. For the interested reader of methods and concerns of validity, see further excellent reviews (18,19,26,27).

2.2. Methodological advantages for apolipoproteins

There are methodological advantages of using apoB and apoA-I compared to LDL-C and HDL-C since the apo-methods have been internationally standardized according to WHO-IFCC already in 1990-ies (26,28,29). The standardization initiatives for apo B have proceeded more quickly and more successfully than for LDL-C. The WHO-IFCC collaboration has resulted in the development of secondary reference material to ensure traceability of manufacturer calibrators to an approved standard. The bias and imprecision for 22 immunonephelometric and immunoturbidimetric assays ranged were usually below 5%. These errors are commonly smaller than that for calculated LDL-C and lipid ratios. Costs for measuring apos can be much reduced if apos are introduced as routine methods. However, pedagogical aspects (education of physicians, patients and laymen), and the well documented and cemented LDL-paradigm will make it difficult to convince guideline committees to introduce apoB and apoA-I as CV risk predictors. Importantly, this should not invalidate that apos are accepted as strong risk markers especially since so many other methods determining LDL-C and HDL-C are accepted in guidelines despite rather weak correlations between various methods due to incomplete standardizations.

3. Physiological and pathophysiological aspects of apoB

3.1. ApoB production, circulation and distribution

ApoB-100 is produced in the liver and apoB-48 is synthesized in the gut (3,12). ApoB-100 is the dominating protein in plasma compared with minute amounts of apoB-48 even in the postprandial state. In most conditions, more than 90% of all apoB in blood is found in LDL. There are excellent reviews of how apoB-100 assembles VLDL in the liver, more details on VLDL composition (12), and some comments on the genetics of apoB (30-33). ApoB is present in VLDL, IDL large buoyant LDL, and small dense LDL (sdLDL), with one molecule of apoB in each of these atherogenic particles (1). Importantly, apoB does not occur on HDL particles. Thus, total apoB reflects the total number of potentially atherogenic particles **(Figure 1).** This is principally different from non-HDL-C which indicates the total mass of C. ApoB produced in the liver stabilizes and allows the transport of C and TG in plasma VLDL, IDL, large buoyant LDL and sdLDL**.** ApoB also serves as the ligand for the apoB and apoB,E receptors thereby facilitating uptake of C in peripheral tissues and in the liver as reviewed (2,3,12). ApoB may provoke atherogenesis since it can be entrapped in the arterial wall of the coronary arteries and also as exemplified by findings in femoral plaques (12,34,35) where it may be modified, oxidized and glucosylated and therefore also contribute in the process of plaque formation. In this process LDL-C with apoB infiltrates the arterial wall and many factors like adhesion molecules, cytokines, growth factors are involved in oxidation processes leading to inflammation and growth of plaques unless HDL bound apoA-I can neutralize these processes (see elsewhere in this paper). Interestingly, already in 1976 Hoff presented data showing that apoB and apoA-I were found in the arterial wall of the coronary and carotid arteries as well as in the aorta (35). Olofsson et al (12) discuss the intra-arterial metabolism of apoB and apoA-I and also Fogelstrand and Borén (36).

3.2. Plasma levels of apoB and target values for therapy

The levels of apoB in plasma may vary from 0.2 to above 3 g/L, with highest values for those with hereditary hypercholesterolemias. In the "normal case" the values for males and females do not differ much. Reference values have been published by Cantois et al. already in 1996 (37). The values slowly increase from childhood to adult life (2,3). Those who live to ages above 75 years commonly have relatively low apoB values since those with higher values may have died due to various CV events. During lipid-lowering therapy apoB targets have been recommended to be < 0.90 g/L for those at moderate risk and < 0.80 for those at a high risk, see further below (3,9,11,38). Values should be given in two decimals.

3.3. ApoB versus LDL-C and risk for CV events

One of the first publications on clinical risks during the course of myocardial infarction (MI) related to apoB and also to apoA-I was presented by Avogaro already in 1978 (39,40). In 1980 Sniderman et al. presented data indicating that hyperapoB with normal C levels was related to coronary atherosclerosis (41). Since then many reports have been published indicating that apoB is involved in atherogenesis and its complications like MI. In 1996 Lamarche et al. (42) showed that apoB was strongly associated with onset of coronary heart

disease in 2,155 men aged 45–76 years followed for 5 years (Quebec Cardiovascular Study). The predictive effect of apoB remained after adjustment for TG, HDL-C and TC/HDL-C. ApoA-I was protective, but not as strong as the harmful apoB in multivariate analysis. In the 10-year follow up of the Atherosclerosis Risk in Communities (ARIC) study, apoB was measured in 12,339 middle-aged participants (43) and had predictive power above that of LDL-C, TG and HDL-C. However, despite strong univariate associations for apoB and LDL-C, apoB did not contribute to risk prediction in subgroups with elevated TG, with lower LDL-C, or with high apoB relative to LDL-C. This may be due to the error for apoB determination which was estimated at 17% which is considerably higher than the approximate 5% that is common in most recent trials.

Importantly, apoB has been found to have a stronger relation with CV risk than LDL-C in several other studies as reported in coming sections. These include the AMORIS study (44), especially at low values of LDL-C (see below), the Thrombo Study (45), the Thrombo Metabolic Syndrome Study (46), the Northwick Park Heart Study (47), the Nurses' Health Study (48) and amongst patients with type 2 diabetes in the Health Professionals Follow-up Study (49).

In the Copenhagen City Heart Study Benn et al. (50) studied 9,231 asymptomatic women and men from the Danish general population followed prospectively for 8 years and observed the following incident events: ischemic heart disease 591, MI 278, ischemic cerebrovascular disease 313, ischemic stroke 229, and any ischemic CV event 807. ApoB, adjusted for multiple common confounding risk factors, had a higher predictive ability than LDL-C in all these various ischemic events (p < 0.03 to < 0.001). They suggested that prediction of future ischemic cardiovascular events could be improved by measuring apoB.
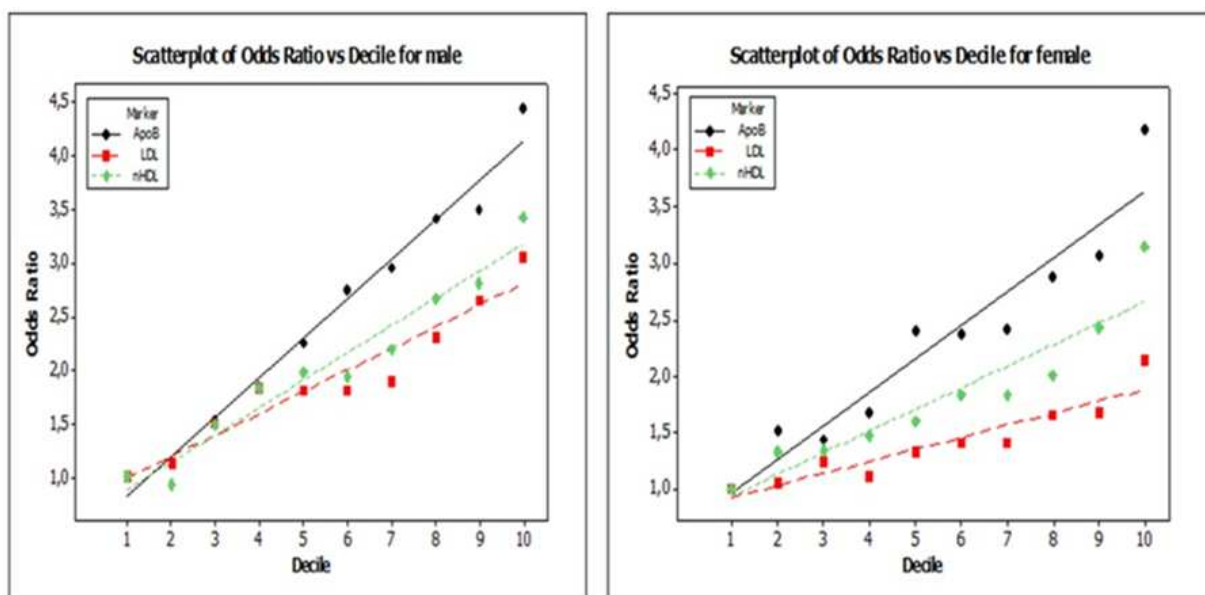

Figure 2. The AMORIS study; apoB, non-HDL-C and LDL-C (x-axis, deciles) versus risk of myocardial infarction (Odds Ratio) (y-axis) in males (left) and females (right).

In addition, in the placebo groups of several major statin clinical trials such as 4S (51), AFCAPS/TexCAPS (52,53) and LIPID (54) apoB was more informative than LDL-C as an index of the risk of CV events. Taken together, this strongly indicates that apo B is superior to

LDL-C in recognizing the risk of CV disease and effects of statin therapy. Additional results (55) also favor apoB over LDL-C, and others are also reported in the section on the apo-ratio below. Such major studies are the AMORIS (3,44,56,57). In our study we found the steepest risk-relationship for MI with increasing values of apoB followed by non-HDL-C and the lowest increase in relation to LDL-C values with similar risk progressions for men and women **(Figure 2 and Figure 3 left).** Also in the INTERHEART (58,59) and ISIS-studies (60) as well as those summarized in the ERFC-meta-analyses (8,10) apoB was strongly related to risk of MI. In meta-analyses similar strong findings for apoB versus LDL-C are summarized by a large number of international scientists and clinicians in more detail (4,13,61,62).

4. ApoB versus non-HDL-C

ApoB indicates the number of atherogenic particles whereas non-HDL-C indicates the C mass from all atherogenic fractions like VLDL, IDL and the large buoyant LDL and the most atherogenic sdLDL fractions. But is apoB similar to or better than non-HDL-C in predicting risk? Although there is a similarity between apoB and non-HDL-C, they may have different metabolic fate and thus impact on risk. The rationale for using non-HDL-C is based on the fact that there is a close relationship between non-HDL-C and apoB values. Usually the correlation is about 0.80–0.85. However, correlation is not the same as concordance. In fact, two variables can be highly correlated but also be highly discordant, i.e. they do not correspond well. Either they are too high or too low compared with the other variable. Importantly, discordance produces major errors in the middle of the population distribution. Sniderman has frequently presented data with explanations of the advantages of apoB over LDL-C and non-HDL-C (4,13,14,21,62,63). Commonly, the sdLDL-particles contribute much to the large numbers of atherogenic particles, i.e. the apoB number is high and these small particles can easily penetrate into the arterial wall. However, in conditions with high non-HDL-C due to high VLDL-C and high large buoyant LDL-C the sdLDL-particles may be rather low in numbers indicating comparatively low numbers of apoB particles. These larger cholesterol-containing VLDL and IDL particles, although rich in C, do not easily penetrate into the arterial wall.

Of interest, the number of apoB is more closely associated with insulin resistance or markers of the metabolic syndrome than either LDL-C or non-HDL-C (3,62,63). Thus, in patients with hypertriglyceridaemia with normal, or even low LDL-C values, i.e. patients with the metabolic syndrome (MetS), and in patients with overt diabetes, apoB has been shown to be superior to non-HDL-C in predicting vascular risk (3,62,63). Again, even if non-HDL-C and apoB correlate, they are not the same biologically or clinically. In most cases apoB is associated with a higher CV risk than non-HDL-C as well as LDL-C. Furthermore, non-HDL-C may not be that easy to understand or explain for the clinician or the patient once they have learnt that the bad C is LDL-C.

Many studies and clinical trials have been published showing that apoB has a stronger capacity to identify all different phenotypes and to better predict CV risk than both LDL-C and non-HDL-C (3,11,61-63). Sniderman et al. (62) have published a convincing meta-analysis of results from published epidemiological studies that contains estimates of the

relative risks of LDL-C, non-HDL-C and apoB of fatal or non-fatal ischemic CV events. Twelve reports including 23,455 subjects and 22,950 events, were analyzed. Whether analyzed individually or in head-to-head comparisons, apoB was the most potent marker of CV risk RR = 1.43; (95% CI, 1.35-1.51), LDL-C was the least RR = 1.25; (1.18-1.33), and non-HDL-C was intermediate RR = 1.34; (1.24-1.44). Only HDL-C accounted for any substantial portion of the variance of the results among the studies. They commented that in patients in whom LDL composition is normal, the cholesterol markers and apoB are equivalent markers of risk, i.e. correlation between the three markers is high. However, when the markers are discordant, that is, when LDL-C is normal but LDL-particles (P)(= apoB) is high or, alternatively, when LDL-C is high but LDL-P are normal, then apoB and non-HDL-C are better markers of risk than LDL-C. They calculated the number of clinical events prevented by a high-risk treatment regimen of all those >70th percentile of the US adult population using each of the 3 markers. Over a 10-year period, a non-HDL-C strategy would prevent 300,000 more events than an LDL-C strategy, whereas an apoB strategy would prevent 500,000 more events than a non-HDL-C strategy. These examples emphasize the greater potential for using apoB rather than non-HDL-C and LDL-C.

However, in another major meta-analysis by Boekholdt et al. (64) they studied 62,154 patients enrolled in 8 statin trials published between 1994 and 2008. Among 38,153 statin treated patients 158 developed fatal MI, 1,678 non-fatal MI, 615 fatal events from other coronary artery disease, 2,806 hospitalizations for unstable angina, and 1,029 fatal or nonfatal strokes occurred during follow-up. The adjusted HRs for major CV events per 1-SD increase were 1.13 (95% CI, 1.10-1.17) for LDL-C, 1.16 (1.12- 1.19) for non-HDL-C, and 1.14 (1.11-1.18) for apoB. These HRs were significantly higher for non-HDL-C than LDL-C (p = 0.002) and apoB (p = 0.02). Thus, from both these meta-analyses non-HDL-C stands out as a stronger predictor of CV diseases than LDL-C. The explanation for the different findings of apoB in these two meta-analyses is unclear but may be explained by the fact that the first study is based on data from a prospective risk studies, whereas the second study reflects effects of statins on lipid and lipoprotein metabolism. Further comments are given in the discussion.

5. Physiological and pathophysiological aspects of apoA-I

There are many subgroups of particles of HDL with different lipid and apo compositions (3,12,29). Beyond apoA-I there are other apos such as apoA-II, apoA-III, apoC-III, apoD and apoM. ApoA-I is the major protein in HDL and this protein is taken to represent HDL metabolism since it occurs almost exclusively in HDL particles. By measuring HDL-C the amount of C transported in blood is indicated to represent the reverse cholesterol transport (RCT), a major protective aspect of HDL metabolism – by laymen named "the good cholesterol". ApoA-I initiates the RCT process in peripheral tissues. ApoA-I has also many other functions beyond RCT since apoA-I is involved in anti-inflammation, anti-oxidation, anti-infectious activity, anti-proteas activity, anti-apoptotic, and anti-thrombotic functions (3). Furthermore, apoA-I can initiate the endothelial production of nitric oxide that is of vital help in producing vasodilation (3). Furthermore apoA-I may help to regulate glucose-insulin homeostasis. Thus, by measuring apoA-I you may get additional "protective" effects

above those given only by the HDL-C number. For methodological reasons Warnick and others prefer to use apoA-I rather than HDL-C methods (19). HDL and apoA-I metabolism are reviewed in more detail, see ref. (3,12,29,65-67).

5.1. Plasma levels of apoA-I and target values for therapy

The plasma concentration of apoA-I can vary from 0.1 to over 3 g/L. Reference values have been published by Cantois et al. already in 1996 (37). There is little variation with fasting-non-fasting (68). Normally women have 0.1-0.3 g/L higher apoA-I values than men, similar to the higher HDL-C values for women. After menopause apoA-I values commonly decrease in parallel with HDL-C. However, there have been few published recommendations regarding what should be a "normal apoA-I value". A normal value for any adult should be at least close to 1 g/L or above. So far, there have been few recommendations on valid cut values indicating increased CV risk and target values. Values should be given in two decimals. For further comments, see the section on the apo-ratio.

5.2. Biological variation of apoA-I

ApoA-I and ApoA-II may also enter the cerebrospinal flow via the choroid plexus (69). Reduction in the HDL apoA-I/apoC-III ratio, changes in the HDL subpopulation distribution and an increase in HDL oxidation potential correlated with the development of MI in young patients (70). In a Korean study of 15,154 healthy subjects higher CRP levels were associated with significantly lower HDL-C and apoA-I levels, and also higher apoB values (71). In a US population of 8,708 apparently healthy population apoA-I was strongly positively associated, whereas apoB was significantly reduced with alcohol intake. Similarly the transaminases AST, ALT and gamma-GT increased with higher alcohol consumption (72).

5.3. ApoA-I and risk for CV events

Already in 1978,1979, Avogaro et al. (39,40) showed that apoA-I was as good as lipids in predicting myocardial infarction (MI) in those under 50 years of age but apoA-I was a better predictor in those over 60 years of age. In the Swedish APSIS study (73) Held et al. in 1994 studied patients with angina pectoris. During a median follow-up time of 3.3 years (2,663 patient years), 37 patients suffered a CV death, 30 suffered a non-fatal MI and 100 underwent a revascularization. Apo-I and TG were predictors of CV death or non-fatal MI in univariate analyses, but only apoA-I remained as an independent predictor in multivariate analyses. All lipid variables except LDL-C were related to the risk of revascularization in univariate analyses, but only apoA-I and apoB were independent predictors of such events. They concluded that apolipoprotein levels were better predictors of CV events than other lipid parameters in patients with stable angina pectoris.

Many studies have shown an inverse relationship between apoA-I and MI (3,44,74,52,53,59,60). In a study of Japanese Americans apoA-I predicted coronary heart disease only at low concentrations of HDL (75). High apoA-I values have been found to correlate with low risk for MI in AMORIS as indicated **(Figure 3, right).** Luc et al. also found

that apoA-I is the best prospective risk marker of several other apoproteins in HDL (76). In the large INTERHEART case-control study apoA-I had a greater protective effect of MI at a wider range of apoA-I values than HDL-C (58,59). Patel et al. (77) found that ApoA-I levels are a consistent discriminator of atherosclerotic burden among patients with stable CAD.
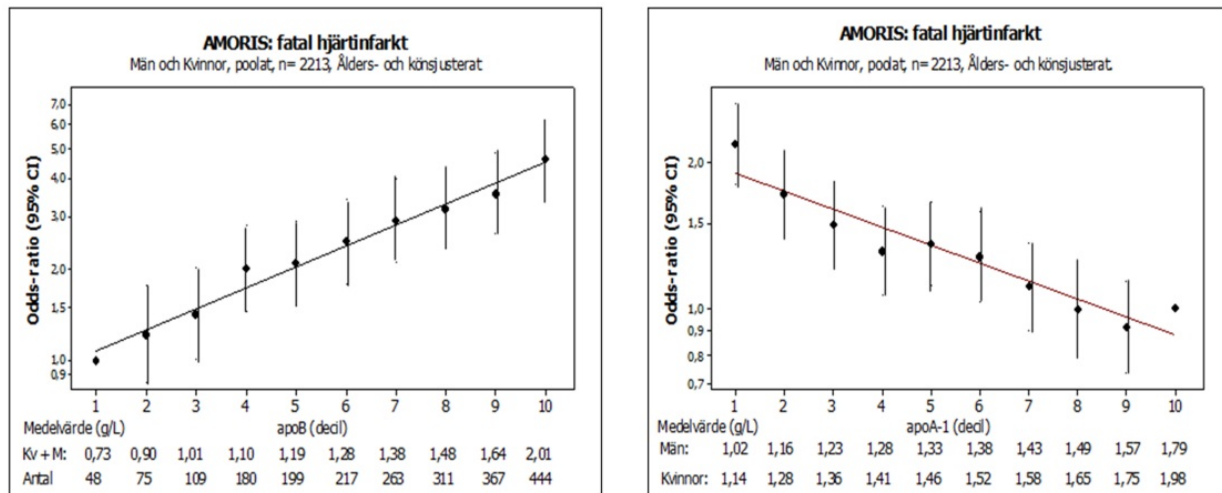

Figure 3. Left; The AMORIS study: Fatal myocardial infarction (Odds Ratio) is related to increasing values of apoB. The values are adjusted for age, TC and TG. Right; The AMORIS study: Fatal myocardial infarction is related to decreasing values of the apoA-I. The values are adjusted for age, gender, TC and TG. Similar pattern for men (män) and women (kvinnor).

In the CORONA study performed in patients with severe heart failure (placebo versus rosuvastatin) apoA-I, in univariate analysis, was the second best (after apoB plus apoA-I) of all different lipid fractions in predicting total death and MACE (MAjor Coronary Events). Furthermore, in a multivariate stepwise analysis apoA-I ranked fifth, better than high sensitivity CRP (hsCRP), of all 14 predictors of outcome where no conventional lipid fraction was significant. The best predictor was pro-BNP (78).

In a study of risk of stroke in Taiwan it was shown that apoA-I but not apoB levels may serve as an effect modifier of hypertension for the risk of stroke events (79).

In the combined analysis of data from the IDEAL statin trial and the Epic-Norfolk case-control study (80) very high HDL-C due to enlarged HDL-particles values were associated with increased rather than decreased CV risk. However, in contrast, apoA-I appears not to turn into a significant risk factor at high plasma concentrations. They conclude that apoA-I is associated with CHD risk independently from HDL size suggesting that the cardioprotective role of large HDL might be more closely related to its apoA-I content than to HDL size per se. These observations may have important consequences for future CAD risk assessment and novel treatment strategies. Indeed, several experimental studies have pointed to a crucial role for apoA-I in protection against atherosclerosis (3,12,65,81).

In the AFCAPS /TexCAPS statin trial (placebo versus lovastatin) multivariate analysis showed that apoA-I was better than HDL to predict outcome (52,53). In addition, the apo-ratio was the best of all lipids and apo-fractions to explain CV risk reduction, see further below.

6. General comments on the validity of using a ratio as a primary marker of risk

Lipid and lipoprotein ratios like TC/HDL-C and LDL-C/HDL-C have been used in various international guidelines for decades to define CV risk. However, LDL-C has in the vast number of guidelines dominated as the primary risk marker why ratios rarely are used today in clinical practice. One major reason why the lipid ratios are questioned as relevant risk markers is due to the fact that HDL-C is included in the value for TC, so HDL-C occurs both in the nominator and denominator of the ratio. Similarly, since LDL-C most commonly is derived by the Friedewald formula, HDL-C is involved as a factor for calculating LDL-C and therefore also indirectly in the nominator and denominator of that ratio. Therefore physicians are hesitant to the mathematical way of dividing various lipid numbers to obtain a mathematical, but, in their mind, not a biologically relevant ratio. When so called direct methods are used for measuring LDL-C this problem is less. In recent years non-HDL-C has been recommended as the next primary risk variable and the new non-HDL-C/HDL-C ratio has been defined. Interestingly, this ratio gives the same final number of risk as that of the TC/HDL-C ratio.

Most researchers and guidelines recommend the use the TC/HDL-C ratio since calculation of this ratio is not dependent on that blood sampling has been performed in the fasted state. This is the same argument as for using non-HDL-C rather than calculated LDL-C. The challenge now is can the apo-ratio, which summarizes the CV risk related to all atherogenic and all anti-atherogenic variables into one number, be the next rational choice as a primary risk variable? Does the apo-ratio add to information already obtained by lipids and lipid ratios? And are the values for apoB, apoA-I and especially the apo-ratio much influenced by other confounding risk factors? These and many other questions are addressed in the sections below based on a vast number of publications.

7. Prospective cardiovascular risk studies – Relations to apoB, apoA-I and the apoB/apoA-I-ratio

7.1. The AMORIS prospective study and risk of myocardial infarction (MI)

The Swedish AMORIS (Apolipoprotein-related MOrtality RISk) study is the largest of all studies in which apoB and apoA-I have been measured in more than 175.000 individuals followed prospectively for up to 25 years. The participating subjects were recruited from health check-ups during 1985-1996. Their age ranged from below 10 years to above 90 years. In these years health screening was very common in Sweden. Subjects included in the database called AMORIS were mainly healthy, not acutely ill or hospitalized and no subject participated in clinical trials. They were all treated by their general practitioners in the greater Stockholm area and they constitute a valid socio-economical cohort of the greater Stockholm population as indicated in several of our papers presented below. Large blood screening programs were used including some 8,000 determinations of LDL-C according to Friedewald. Simultaneously apoB and apoA-I were analyzed by automated immunoturbidimetric methods in all 175.000 subjects according to the WHO-IFCC protocol and in collaboration with their representatives (82). LDL-C was calculated according to the

Jungner formula (44). The Jungner formula yields the same LDL-C values as those obtained by using the Friedewald formula (16) as confirmed by Talmud et al. (47). Also HDL-C values were determined by the Friedewald formula once LDL-C was calculated by the Jungner formula. All analyses in the AMORIS laboratory database (confounding clinical risk factors like hypertension, diabetes and obesity were available in cohorts) were performed by automated methods at the same CALAB laboratory headed by Ingmar Jungner. Several papers were published describing the apoB, apoA-I and the apo-ratio characteristics of the population and the methods (3,21,44,82-85). In an early AMORIS study we have previously noted that patients with type IIB dyslipidemias, i.e. combined hypercholesterolemia and hypertriglyceridemia, had the highest apo-ratio (86). The subsequent CV manifestations were related to the laboratory variables obtained at the first visit to the physician.

In 2001 we presented the first endpoint paper based on 98,722 men and 76,831 women in the Lancet (44). We found a strong direct relationship between apoB and an indirect inverse relationship between apoA-I and risk of MI (men = 864, women = 359) **(Figure 3)**. Furthermore, apoB was a stronger risk factor than LDL-C especially at low values of LDL-C. The apo-ratio was the strongest lipid-related factor **(Figure 4).** In the left part of the figure the values for apoB and apoA-I divided into quartiles are displayed in a three dimensional way. Thus, in those with highest values of apoB and in those with lowest apoA-I values the risk increased about 6-fold in a stepwise fashion compared to those with lowest apoB and highest apoA-I values. The highly significant results were similar for men and women and remained after adjusting for age, TC and TG. The figure clearly illustrate that the risk is about the same for those with an increased apoB at highest apoA-I levels, as the risk for those with lowest apoA-I levels but with low apoB values. Thus the figure illustrates the importance of measuring both apoB and apoA-I to get correct information on MI risk level. In the right part of the figure the same results can also be depicted as a straight line (semi-log scale) showing the impact of higher apo-ratio versus increased risk of MI. We also found that apoB was significantly better to predict risk than LDL-C especially for those with low values for LDL-C.
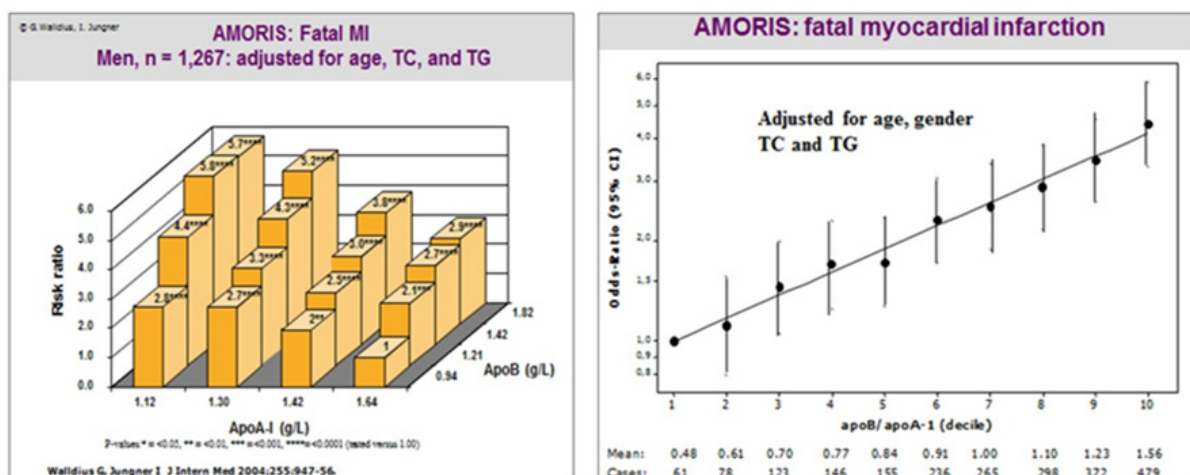

Figure 4. Left; The AMORIS study: Fatal myocardial infarction (Risk ratio) is related to increasing values of apoB and decreasing values of apoA-I. The values are adjusted for age, TC and TG. Similar pattern is seen for men and women (reference 3). Right; The AMORIS study: Fatal myocardial infarction is related to increasing values of the apoB/apoA-I ratio. The values are adjusted for age, gender, TC and TG. (Both figures from reference 3).

With increasing values of the apo-ratio there was a parallel increase in apoB, LDL-C, non-HDL-C and TG **(Figure 5, left)** and a decrease in apoA-I and HDL-C values **(Figure 5, right).** This figure illustrates that an increasing apo-ratio indirectly also indicate the contribution of the other lipids as risk factors. In multivariate analyses the apo-ratio is the strongest of all lipid-related variables and is thus the best summarizing risk variable.
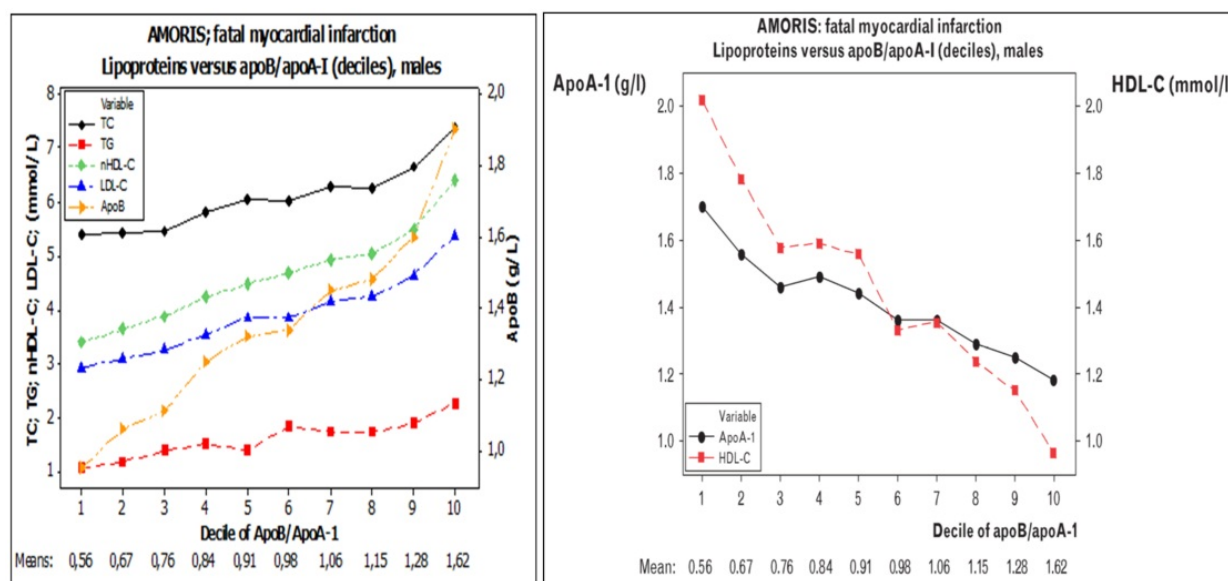

Figure 5. Left; the apo-ratio in deciles (x-axis) versus different atherogenic lipid fractions (y-axis). Right; the apo-ratio in deciles (x-axis) versus values for HDL-C and apoA-I (y-axis). Both figures from the AMORIS study (in reference 3).

In collaboration with Sniderman we have also published data from AMORIS showing that the apo-ratio has a significantly stronger relation with MI than any other lipid-based ratio (3,4,21).

In another AMORIS cohort including 69,029 men and 57,167 women who were followed for a mean of 10.3 years we determined LDL size as reflected by the LDL-C/apoB ratio (87). Because LDL size did not add predictive information to the apo-ratio, it appears that this apo-ratio also captures the risk related to LDL size. These findings add to our previously published results from AMORIS that indicates that the apo-ratio is the best single lipid-related summary index of risk and that TC, TG, non-HDL-C, and LDL-C do not add significant predictive power to the apo-ratio.

7.2. The apo-ratio and inflammatory risk factors – relations to MI, stroke and heart failure in the AMORIS study

The risk relation to age during prolonged follow-up was also studied in an AMORIS population (n = 149,121) free of previous MI at blood sampling. They were followed from 1985 to 2002 with respect to n = 6,794 first cases of MI. The mean value of the apo-ratio for men was 1.0 and for women 0.85 at baseline. In collaboration with Holme we found that the apo-ratio was somewhat stronger for those developing non-fatal than fatal MI (88). The risk was also stronger associated with the apo-ratio in those < 65 years of age than above, but

risk remained significantly related to the apo-ratio also in the older population. In multivariate analyses the apo-ratio was a better predictor than TC/HDL-C. Furthermore, the apo-ratio added clinically significant information to TC/HDL-C in men as reflected by a net reclassification improvement (NRI) of 9.4% (P < 0.0001). Furthermore, also in patients developing heart failure, a common complication after MI, the apo-ratio is the best lipid-related variable to classify risk especially in men (89).

Subsequently we have shown that for the inflammation marker haptoglobin (Hp) has strong relations with MI, stroke and heart failure in the AMORIS cohort (90). There were 11,216 men and 4,291 women who had a first MI, 8,463 men and 6,072 women who had a first stroke, and 4,670 and 3,634 who had a first heart failure, respectively. Based on 4,254 MI cases the risk of MI was about 4.5 times higher in the upper joint quartile of the apo-ratio as compared to the lower, whereas this relative risk for Hp was about 4.1. However, the attributable risk for the apo-ratio is higher since more subjects were classified into the top joint quartile of TC and the apo-ratio (12.8%) than that of TC and Hp (8.8%) and into the lower joint quartiles (12.1%) and (6.4%), respectively.

In another AMORIS-based cohort of 65,050 subjects Holme et al. (91) developed an inflammatory score comprising white blood cell count, haptoglobin and in a subgroup also CRP. After 11.8 years follow-up 3,649 MI, 2,663 stroke, 2,690 heart failure, in total 7, 456 MACE, occurred. In multivariate Cox proportional hazards analysis the inflammatory scores added predictive information over and above classical lipids such as TC and TG. Based on the apo-ratio, which was a stronger marker of CVD risk than conventional lipids, the inflammatory score added significant information value measured by net reclassification improvement, especially for those with the higher values for these variables. However, there was no statistically significant biological interaction between lipoproteins and the inflammatory markers. These data indicate that routinely used markers of inflammation in combination with the apo-ratio could be used in daily medical practice to assess CV risk.

We have also published data of lipid- and the apo-ratio from three cultures (Sweden, Iran, US) showing that the apo-ratio is highest in the Swedes (the AMORIS cohort) but similar in the Americans (NHANES) and Iranians (92). By contrast, the TC/HDL-C ratio is highest in the Iranians, intermediate in the Americans and lowest in the Swedes. There were similar associations of the pro-atherogenic and anti-atherogenic lipoproteins between the genders and variation with age in these three different cultures. These data indicate that complete characterization of lipoproteins requires measurement of apoB and apoA-I as well as lipoprotein lipids.

7.3. The apo-ratio in relation to chronic kidney disease and MI risk in the AMORIS study

Some previous studies have shown apoB to be increased and apoA-I to be decreased in patients with renal insufficiency. In the much larger AMORIS study Holzmann et al. (93) performed in 142,394 middle-aged mainly healthy men and women it was shown that the apo-ratio, the TC/HDL-C ratio, and non-HDL-C all are strong predictors of first MI, among

both men and women, with or without chronic kidney disease (CKD). Those with the lowest glomerular filtration rate (estimated GFR mL/min/1.73 m², n = 5,838) had the highest apo-ratio. In Receiver Operator Characteristics (ROC) analysis the area under the curve (AUC) for the apo-ratio was 0.77 for men and 0.83 for women without CKD, and 0.65 and 0.74 among men and women with CKD, respectively analyses. These and other data reflect a certain advantage in the prediction of MI for the apo-ratio as compared to conventional lipids. Furthermore, the findings also indicate the presence of severe atherosclerosis both in the kidney and in the coronary arteries.

7.4. The apo-ratio and risk of stroke in the AMORIS study

High LDL-C is a major risk factor for MI. However, LDL-C is rarely increased in those who suffer any type of stroke. A low HDL-C and some abnormalities in either apoB and/or apoA-I have previously been found in patients with ischaemic stroke (94-99). In 2006 Walldius et al. published the first report on risk of stroke based on the AMORIS-population (100). The relationships between different types of fatal stroke and the lipid fractions, apoB, apoA-I and the apo-ratio were examined in 98,722 men and 76,831 women followed for a mean of 10.3 years. High apoB and low apoA-I values were significantly related to risk of stroke. The odds ratio comparing the upper 10th vs. the 1st decile of the apo-ratio for all strokes adjusted for age, gender, TC and TG was 2.07 (95% CI: 1.49–2.88, p < 0.0001). The apo-ratio was linearly related to the risk of stroke although the slope was less than observed for the risk of fatal MI (**Figure 6, left**). Low apoA-I was a common abnormality in all stroke subtypes including subarachnoidal and haemorrhagic strokes. In multivariate analyses the apo-ratio was a significantly stronger risk predictor than TC/HDL-C and LDL-C/HDL-C ratios.

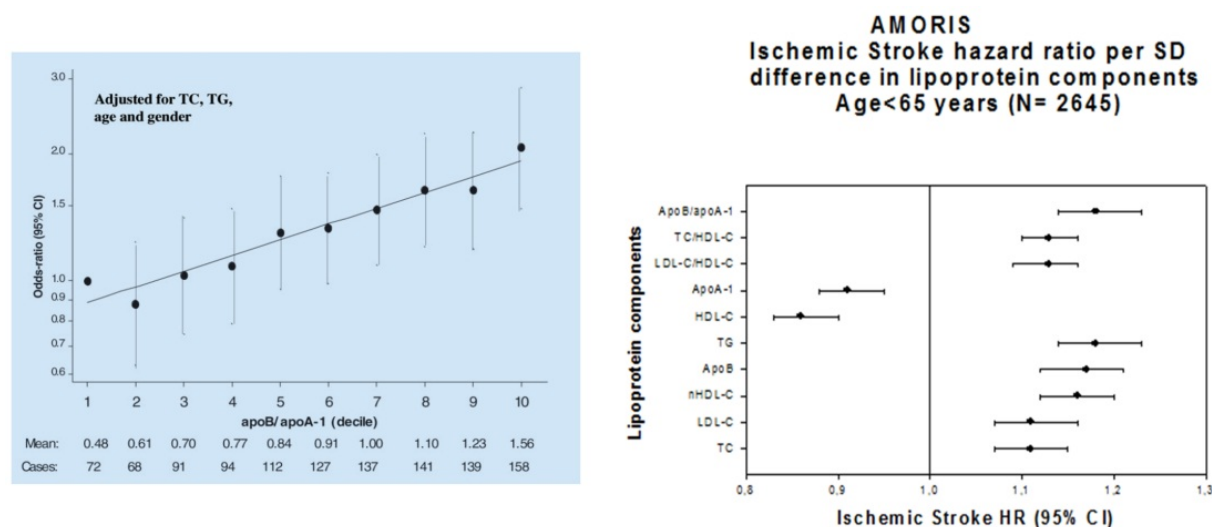**Figure 6.** Risk of total stroke (left) (reference 3 and 100) and ischemic stroke (right) (reference 101). Both figures from the AMORIS study.

In a prospective follow-up study (mean observation age 11.8, range 7–17 years) based on the AMORIS population (n = 148,600). Holme et al. focused on risk of fatal and non-fatal ischaemic and haemorrhagic stroke in relation to all lipids and apos (101). Hazard ratio of

non-fatal and fatal ischaemic and haemorrhagic stroke for 1 SD difference in lipoprotein components was calculated by gender, adjusted for age, MI, diabetes and hypertension. Ischaemic stroke was more common than haemorrhagic stroke (5:1), but case fatality was higher in haemorrhagic stroke. The apo-ratio, non-HDL-C and TG as well as low HDL-C and a high TC/HDL-C ratio were all predictors of ischemic stroke **(Figure 6, right)** and all cerebrovascular events (n=7,480) with somewhat stronger relations for non-fatal than fatal events. The apo-ratio was significantly stronger than the TC/HDL-C ratio in the patients with ischaemic stroke as reflected by chi-squared information value, adjusted for hypertension, diabetes, AMI, age and gender. The strongest association was for ischaemic stroke in those < 65 years of age and also for those with LDL-C < 3.0 mmol/L. There were no lipid relations to risk of haemorrhagic stroke other than a high apo-ratio related to risk in women.

7.5. Other findings from AMORIS indicating that the apo-ratio predicts CV risk

In addition, the risk of death from aortic aneurysms (n = 241) was significantly related to the apo-ratio (p< 0.0039) (3) adding to the importance of the apo-ratio as a predictor of severe ischaemic complications related to atherosclerosis. In that paper we also noted that, there was no relationship between the apo-ratio and risk of cancer (n = 4,423), motor vehicle accidents (n =100) or dementia (n = 255).

8. The apo-ratio in case-control CV risk studies

8.1. The INTERHEART study and risk of MI

The largest case-control study which has been performed is the INTERHEART study (58) comprising 15,152 patients with a first MI compared to 14,820 subjects from 52 countries world-wide matched for age, gender, ethnicity and continent. The aim of the study was to investigate which of the nine most common risk factors had the strongest relation to risk of MI and also which of the factors was most prevalent (highest Population Attributable Risk). These factors were: lipids primarily measured as the apoB/apoA-I ratio, smoking, diabetes, hypertension, abdominal obesity, psychosocial, fruits and vegetables, exercise, and alcohol. They found that all these risk factors were statistically related to risk.

The strongest **(Figure 7, left, (Table 1, left)** and also the most prevalent risk factor **(Table 1, right)**, was the apo-ratio both in men and women in each of the 52 countries worldwide. The apo-ratio plus smoking variables explained 70% of the entire risk which amounted to 90% for all nine risk factors taken together.

In a subsequent paper (59) they also showed that the apo-ratio had the strongest relation to MI-risk of all other measured lipids **(Figure 7, right, top panel).** They also showed a significantly stronger relationship to MI risk for the apo-ratio than the TC/HDL-C ratio **(Figure 7, right; bottom panel).** It was also shown that apoA-I had better diagnostic power than HDL-C over a wider range of low to high values.

Based on the findings and impact of these risk factors on risk of MI the INTERHEART Modifiable Risk Score (IHMRS) was developed based on age, the apo-ratio, smoking –

present, smoking – second hand, diabetes and hypertension with a range of points from 0-32 (102).
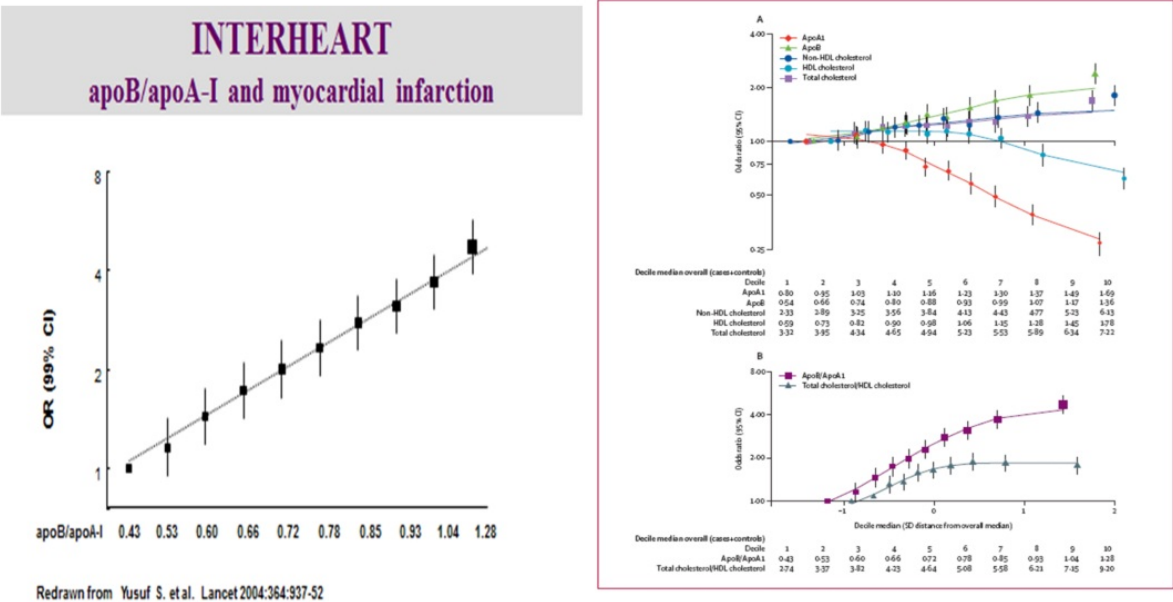

Figure 7. The INTERHEART study. Risk (Odds ratio, y-axis) versus the apoB/apoA-I ratio (left) (reference 58), and single lipids, apolipoproteins and their ratios (right) (reference 59).

INTERHEART Risk of AMI in relation to common risk factors (Yusuf S et al. Lancet 2004;364:937)		**INTERHEART** Risk of AMI in relation to common risk factors (Yusuf S et al. Lancet 2004;364:937)	
Risk factor adj. for all	**OR (99 % CI)**	**Risk factor adj. for all**	**PAR (99 % CI)**
ApoB/apoA-I	3.25 (2.81-3.76)	ApoB/apoA-I	49.2 (43.8-54.5)
Smoking	2.87 (2.58-3.19)	Smoking	35.7 (32.5-39.1)
Diabetes	2.37 (2.07-2.71)	Diabetes	9.9 (8.5-11.5)
Hypertension	1.91 (1.74-2.10)	Hypertension	17.9 (15.7-20.4)
Abd.obesity	1.62 (1.45-1.80)	Abd.obesity	20.1 (15.3-26.0)
Psychosocial	2.67 (2.21-3.22)	Psychosocial	32.5 (25.1-40.8)
Veg.&Fruits	0.70 (0.62-0.79)	Fruits & Veg.	13.7 (9.9-18.6)
Exercise	0.86 (0.76-0.97)	Exercise	12.2 (5.5-25.1)
Alcohol	0.91 (0.82-1.02)	Alcohol	6.7 (2.0-20.2)
Combined	**129 (90-185)**	**Combined**	**90 (88-92)**

Table 1. The INTERHEART study. Risk of myocardial infarction (AMI); Odds ratios for nine conventional risk factors (left) and Population Attributable Risk for nine conventional risk factors (right) (booth tables reprinted from reference 58).

The IHMRS was positively associated with incident MI in a large cohort of people at low risk for CV disease (12% increase in MI risk with a 1-point increase in score). The data were internally validated and the discrimination was tested (ROC c-statistic 0.69, 95% CI: 0.64-0.74) or even higher values up to 0.79 in certain global areas. Results were consistent across ethnic groups and geographic regions. A non-laboratory-based score has also been supplied. The IHMRS demonstrated clinical credibility, evidence of accuracy, and evidence of generality.

In an analysis of 15,780 patients from the INTERHEART study (103) it was shown that HbA1c was a useful diagnostic tool of risk and the levels increased with increasing apo-ratio from 0.75-0.84 for each quintile increase of HbA1c from <5.4 – >6.12% (p < 0.0001). Most of the MI patients had values in the highest HbA1c quintile. The advantage of using the apo-ratio in India (104), Latin America (105), Puerto Rico (106), and Africa (107) based on the INTERHEART study designs has been useful for evaluating CV risk and should be valuable in treating risk in these countries but also elsewhere in the world.

8.2. The INTERSTROKE study

The standardized INTERSTROKE case-control study was performed in 22 countries worldwide (108). Cases were patients with acute first stroke (within 5 days of symptoms onset and 72 hours of hospital admission). Controls had no history of stroke, and were matched with cases for age and sex. In 3,000 cases (n = 2,337, 78%, with ischaemic stroke; n = 663, 22% with intracerebral haemorrhagic stroke) and 3,000 controls, significant risk factors for all stroke were: history of hypertension, current smoking, waist-to-hip ratio, diet risk score, regular physical activity, diabetes mellitus, alcohol intake, psychosocial stress and depression, cardiac causes, and the apo-ratio in falling order. Together, these risk factors accounted for 88.1% of the population attributable risk for all stroke. Increased concentration of non-HDL-C was not associated with risk of ischaemic stroke, but was associated with reduced risk of intracerebral haemorrhagic stroke, whereas increased concentration of apoB was associated with increased risk of ischaemic stroke, but was not associated with risk of intracerebral haemorrhagic stroke. The apo-ratio was a stronger predictor of ischaemic stroke than was ratio of non-HDL-C/HDL-C.

8.3. Other studies on stroke and atherosclerosis in the carotid arteries

Kostapanos et al. (109) studied 163 patients aged 70 years (88 men) with a first-ever acute ischemic/non-embolic stroke and 166 volunteers (87 men) with no history of CV disease. Compared with subjects with an apo-ratio in the lowest quartile, those within the highest quartile had a 6.3-fold increase in the odds of suffering an ischemic stroke (p<0.001). This association remained significant after controlling for sex, age, smoking status, body mass index, waist circumference, glucose and insulin levels, the presence of hypertension and diabetes mellitus, and lipid profile parameters (adjusted OR = 3.02; 95% CI 5.16-7.83; p = 0.02). The findings support elevated apo-ratio as an independent predictor of ischemic stroke in individuals over age 70.

Park et al. (110) studied 464 statin or fibrate naïve Korean patients with acute ischemic stroke: intracranial (ICAS, n = 236), extracranial (n = 44), and no cerebral atherosclerotic stenosis (n = 184). The ICAS group showed a significantly higher apo-ratio than the other two groups. The apo-ratio of 0.93 was substantially increased in patients with advanced ICAS (3 or more intracranial stenoses), the highest quartile of the apo-ratio was an independent predictor of ICAS (OR, 2.13; 95% CI, 1.05 - 4.33). A dose–response relationship (multivariate analysis) was observed between the presence of advanced ICAS and the apo-ratio quartiles (ORs, 4.03, 4.88,

and 7.79, for the fourth quartile versus the first quartile). Patients having more metabolic syndrome components indicating MetS were more likely to have ICAS, advanced ICAS, and a higher apo-ratio (p < 0.001 for all). Thus, a higher apo-ratio is a predictor of ICAS rather than of extracranial atherosclerotic stenosis or no cerebral atherosclerotic stenosis. The apo-ratio might be a biomarker for ICAS in Asian patients with stroke.

8.4. The ISIS-study relating the apo-ratio to risk of MI

This ISIS case–control study was conducted among 3,510 acute MI patients (without prior vascular disease, diabetes, or statin use) in UK hospitals and 9,805 controls (60). Relative risks (age, sex, smoking, and obesity-adjusted) were more strongly related to apoB than to LDL-C and, given apoB, more strongly negatively related to apoA-I than to HDL-C. The apo-ratio was substantially more informative about risk than LDL-C/HDL-C, TC/HDL-C, non-HDL-C, and TC. Relative risks within several subgroups of patients showed no clear heterogeneity of effect with respect to sex, smoking, or BMI. The strongest effects were seen in those aged 30-49 years but even at ages 70-79, a 2SD higher apo-ratio was associated with a highly significant (P < 0.00001) relative risk. Furthermore, the apo-ratio, if untreated, is stable over time. Given the usual value of apoB, the usual value of LDL-C (indicating sdLDL particles) the risk was significantly higher. They concluded that single measurements of apoB and apoA-I are more predictive than single measurements of LDL-C and HDL-C and that the apo-ratio is the single best predictor of all lipid fractions is consistent with previously reviewed results including the AMORIS study (3,44).

9. Other studies showing strong prediction of CV risk by the apo-ratio

In our previous review from 2006 (3) we commented results from several prospective risk studies all showing an important diagnostic improvement of CV risk using apos and the apo-ratio over conventional lipids most commonly also adjusted for other confounders. The Dutch EPIC-Norfolk study (111) published in 2007 was performed in 1,511 apparently healthy controls and in 869 cases who had developed a non-fatal or fatal MI. They showed that in a head to head analysis of TC/HDL-C ratio versus the apo-ratio the Odds ratio for linear trend for quartiles was non-significant for the lipid-ratio but strongly significant for the apo-ratio, p < 0.006. These analyses were adjusted for sex, age, and time of enrollment and was adjusted for diabetes (yes or no), body mass index, smoking status (yes or no), systolic blood pressure, C-reactive protein level, and log-transformed triglyceride level. The apo-ratio added significant predictive value above that of the Framingham risk score since the area under the receiver-operating characteristic curve was 0.594 for Framingham risk score alone vs. 0.613 for Framingham risk score plus the apo-ratio, p < 0.001. Despite the fact that the difference was strongly significantly in favor of the apo-ratio the authors concluded that this was only a small increase. However, the authors pointed out that the apo-ratio is also useful since it can be applied in non-fasting samples.

The German MONICA/Kora Augsburg study (112) showed that in 1,414 men and 1,436 women without prior MI and a median follow up of 13 years the TC/HDL-C ratio predicted

MI risk. In addition, the apo-ratio was significantly related to increased risk of MI adjusted for age, smoking, alcohol, BMI, diabetes and hypertension.

In the American Thrombo study and its follow-up (113) both high apoB and low apoA-I predicted risk of re-infarction. In a follow-up they found that apoB was the strongest risk factor in those who manifested the MetS (114). However, in the German GRIPS (115), the results were negative in that LDL-C in multivariate analysis was found to be a stronger determinant of risk than apoB and the apo-ratio. This is, in fact, one of the very few studies to be found that shows LDL-C to be significantly better than apos in predicting risk. In the South Wales Cearphilly studies (116), although significant prediction was seen for apoB and apoA-I, the addition of apos did not improve prediction MI. In both of these two studies the number of events was below 300.

In the Swedish ULSAM studies (117,118) they showed that the risk of MI increased in parallel with increasing values of the apo-ratio. In those who had values for the ratio of <0.67 the incidence of MI was 9.5%, those who had ratios of 0.67–0.86 had an incidence of 17.7%, those with ratios of 0.87–1.23 had an incidence of 30.7%, and those with apo-ratio values >1.24 had an incidence of 44.8%. These risk values correspond well with those found in the AMORIS study (3,44). A risk prediction score was derived from one half of the population sample from the ULSAM cohort including systolic blood pressure, smoking, family history of MI, serum pro-insulin, and the apo-ratio. The score was highly predictive for future MI in the other half of the population that was not used for generating the score. The ULSAM score performed slightly better than the Framingham and PROCAM scores (evaluated as areas under the receiver operating curves; Framingham, 61%; PROCAM, 63%; ULSAM, 66%; p < 0.08). The authors also reported from the 30-year follow up of patients in the ULSAM study that ECG abnormalities were risk markers after the first 20 years of follow up but also that the apo-ratio and blood pressure remained significant risk predictors over three decades (118).

Ingelsson et al. (119) in the US Framingham study found that after a median follow-up of 15.0 years, 291 participants, 198 of whom were men, developed various manifestations of CHD. In multivariate models adjusting for non-lipid risk factors, the apo-ratio predicted CHD (HR per SD increment, 1.39; 95% CI 1.23-1.58 in men and HR, 1.40; 1.16-1.67 in women), but risk ratios were similar for the TC/HDL-C ratio (HR, 1.39; 1.22- 1.58 in men and HR, 1.39; 1.17-1.66 in women) and for LDL-C/HDL-C (HR, 1.35; 1.18-1.54 in men and HR, 1.36; 1.14-1.63 in women). In both genders, models using the apo-ratio were comparable with but not better than that for other lipid ratios. The apo-ratio did not predict CHD risk in a model containing all components of the Framingham risk score including the TC/HDL-C ratio. They concluded that the apo-ratio adds no incremental utility over this lipid ratio. Notably, there were few hard events in this small study, a fact that may restrict the interpretation of the results.

In India Goswami et al. (120) studied 100 patients with MI who were age-matched with 100 healthy control subjects. The exponential value of the regression coefficient beta for the apo-ratio was 11.9, as compared to 4.4 for the LDL-C/HDL-C ratio, 3.5 for the TC/HDL-C ratio and 2.2 for the TC/HDL-C ratio. The findings suggested that the apo-ratio is a better

discriminator of CAD risk in the atherosclerosis-prone Indian population, than any of the conventional lipid ratios. They suggested that the apo-ratio should be an alternative to other lipid ratios in the risk assessment in patients with CAD.

In a comparative observational study by Agoston-Coldea et al. (121) on 289 subjects were divided into two groups: 144 subjects with old MI, and 145 subjects without CHD, but with CV risk factors. The multivariate analysis indicated that apoB over 1.7 g/L are closely correlated with MI (p = 0.001) independent of age, smoking, diabetes, hypertension, lipid TC/HDL-C and the LDL-C/HDL-C ratio. The protective effect of apoA-I was also significant (p = 0.004) in multivariate analysis. They concluded that the predictive value of the apo-ratio is superior to that of serum lipid fractions and that the apo-ratio therefore should be introduced in current clinical practice.

In the prospective case-cohort study (PREVEND cohort) (122) 6,948 subjects without previous CHD they studied the risk factors predicting major coronary events. The age- and sex-adjusted HR was 1.37 (95% CI, 1.26-1.48) for the apo-ratio and 1.24 (1.18-1.29) for the TC/HDL-C ratio (both p < 0.001). The risks of the two ratios were only marginally attenuated by additional controlling for traditional risk factors TG, hypertension, diabetes, obesity and smoking), hs-CRP and albuminuria.

In a Korean study by Kim et al (123) they studied the association between plasma lipids, and apolipoproteins and coronary artery disease: a cross-sectional study in a low-risk Korean population in 544 subjects. In the lowest quartile of TC, TG and LDL-C, and the highest quartile of HDL-C, only the apo-ratio was associated with CAD in both men and women. They concluded that the apo-ratio is the only variable that differentiates the patients with CAD from those without and, furthermore, gives additional information to that supplied by traditional lipid risk factors in a low-risk Korean population.

Agoston-Coldea et al. (124) studied 208 patients (100 men and 108 women), with and without previous MI by coronary angiography. They showed that the apo-ratio had a stronger correlation with MI than the TC/HDL-C ratio. Multivariate analysis performed with adjustments for conventional risk factors, showed that the levels of apoB, the apo-ratio and Lp(a), are significant independent CV risk factors. Therefore they recommend that the apo-ratio and Lp(a) should be included in clinical practice.

10. Meta-analysis of studies on CV risk

In 2006 Thomson and Danesh published a meta-analysis based on data from 23 relevant prospective studies in which apoB, apoA-I and the apo-ratio were associated with risk of MI (8). They compared risk in the top versus the bottom tertile of baseline values. The relative risks were; apoB 1.86 (95% CI 1.55-2.22, cases n = 6,320), apoA-I 1.62 (1.43-1.83, cases n = 6,333), and the apo-ratio 1.86 (1.55-2.22, cases n = 3,730). ApoB and the apo-ratio were directly related to risk, whereas apoA-I was protective. In that study no results were given for any lipids.

In 2009 the Emerging Risk Factor Collaboration (ERFC) published an extended meta-analysis in which they included 302,430 men and women without previous vascular disease

from 68 long-term prospective studies, mostly in Europe and North America (10). During 2.79 million person-years of follow-up, there were 8,857 nonfatal MI, 3,928 coronary heart disease deaths, 2,534 ischemic strokes, 513 hemorrhagic strokes, and 2,536 unclassified strokes. Half of the studies included less than 100 events, and the largest study (ARIC) included 871 cases. In 22 studies on risk of MI and in 8 studies on risk of ischemic stroke they had also measured apoB, apoA-I and the apo-ratio. In 91,307 individuals with 4,499 MI and in 8 studies with 60,571 individuals and 1,192 cases they could compare how well the TC/HDL-C ratio and apoB, apoA-I and the apo-ratio were related to these CV events. In all of these comparisons non-HDL-C, HDL-C, the non-HDL-C/HDL-C ratio, apoB, apoA-I and the apo-ratio, adjusted for age and sex, were significantly related to risk of both MI and ischemic stroke. When additionally adjusted also for blood pressure, smoking, BMI, hypertension, and other lipid markers the HR was 1.50 (95%CI, 1.38-1.62) for the non-HDL-C/HDL-C ratio and 1.49 (1.39-1.60) for the apo-ratio. Interestingly, adjusting for these confounders changed the HR only marginally. These data show that the lipid- and apo-ratios give similar and significant prediction of risk. Furthermore they also found that apoB had similar risk as non-HDL-C, and apoA-I had similar risk as HDL-C. The ERFC authors concluded that both lipid- and apo-ratios can be used even in the non-fasted state since the apo-ratio and the lipid ratio give similar information. Furthermore, they also discuss that there may be important advantages for using apolipoproteins.
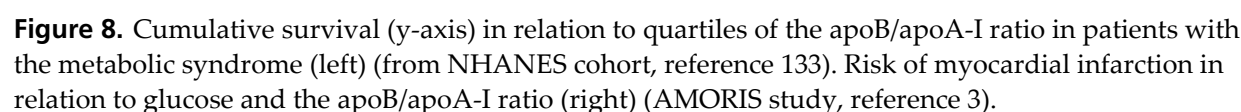
Importantly, the ERFC did not include the three largest studies on risk of MI and stroke related to lipids, apos and the apo-ratio. These are the studies; AMORIS, n = 6,794 first cases of AMI (88), and n = 4,470 first ischemic stroke (101), INTERHEART, cases n = 15, 152 for first MI (59), n = 2,337 for first stroke (108), and the ISIS study, n = 3,510 for first MI (60). These studies were excluded because a complete set of confounding variables were not available (AMORIS), or that two studies were case-control studies (INTERHEART and ISIS). The findings in ERFC are therefore restricted to the results based on only prospective studies with many fewer number of events (total n = 5,691) compared to these much larger studies also covering a world-wide population (AMORIS, INTERHEART, INTERSTROKE and ISIS) (total n = 32,263). So adding all these results to those obtained in the ERFC studies the advantages of the apo-ratio as risk predictor may be even more compelling. Such advantages for clinical use are commented in several sections below and are summarized in the discussion. Results from a recent ERFC publication are also included and discussed in page 39.

11. Relations between the apo-ratio and the metabolic syndrome, glucose - insulin metabolism and diabetes - Risk predictors for CV manifestations

11.1. Metabolic syndrome (MetS) and diabetes

In subjects with the MetS and in patients with diabetes several studies have been performed indicating advantages of using apos, especially apoB, over conventional lipids. In our previous review (3) we summarized these results from Stewart et al. (125), Korean studies (126-128) and studies from India (129) and Canada (130). In these papers the highest values

for the apo-ratio were found in those who had most manifestations of the MetS. The apo-ratio was also related to atherosclerosis verified by angiography even if LDL-C values were low. In the Swedish ULSAM study (131) at the 26.8 year follow-up 462 patients had developed MI. The apo-ratio was highest in those who developed a MetS, and their apo-ratio was inversely related to glucose disposal. These findings were independent of LDL-C and smoking. Both the apo-ratio and MetS independently predicted MI.

Sierra-Johnson et al. (132) studied 2,955 adults (mean age 47 years; 1,457 women) without diabetes from the US NHANS III population. The apo-ratio was an independent predictor of insulin resistance after adjustment for age and race, and remained significant after further adjustment for MetS components including TG, HDL-C, traditional and inflammatory risk factors. They recommended that the apo-ratio should be recognized and implemented in future clinical guidelines. In the follow-up paper (133) of a multi-ethnic representative subset of 7,594 US adults (mean age 45 years; 3,881 men, 3,713 women) there were 673 CV deaths of which 432 were from CHD. Both the apo-ratio (HR 2.14, 95% CI, 1.11 – 4.10) and the TC/HDL-C ratio (HR 1.10, 1.04 – 1.16) were related to CHD death. Only apoB (HR 2.01, 1.05 – 3.86) and the apo-ratio (HR 2.09, 1.04 – 4.19) remained significantly associated with CHD death after adjusting for CV risk factors **(Figure 8 left)**. This suggested that the measurement of apolipoproteins has superior clinical utility over traditional risk markers such as the TC/HDL-C ratio in identifying subjects at risk for fatal CV disease. In addition, the combined elevation of glucose and a high apo-ratio increases the risk of MI as documented in the AMORIS study (3) **(Figure 8, right)**.

Zhong et al. (134) found also in China that the apo-ratio increased significantly with number of MetS components. Belfki et al (135) have shown in a Tunisian population that the apo-ratio increased significantly with each of the components as well as with increasing numbers of components of the MetS after adjusting for age and gender. Similarly, the apo-ratio was associated with insulin resistance.

Figure 8. Cumulative survival (y-axis) in relation to quartiles of the apoB/apoA-I ratio in patients with the metabolic syndrome (left) (from NHANES cohort, reference 133). Risk of myocardial infarction in relation to glucose and the apoB/apoA-I ratio (right) (AMORIS study, reference 3).

Based on the findings in subjects with MetS Sniderman and Faraj (136) have argued for including both apoB and apoA-I as stronger risk markers especially compared to LDL-C (often low in MetS), TG and HDL-C. These apos also have strong relations to glucose and insulin homeostasis. Therefore the apo-ratio should be a valid component of the MetS especially since the apo-ratio has so strong predictive value of CV risk. The apo-ratio also summarizes the risk for individuals with MetS into one simple and predictive risk number. In another paper Sniderman et al. (137) have also analyzed pros and cons for using the apo-ratio.

Bruno et al. (138) studied diabetic subjects and they found that apoB and the apo-ratio were associated with CV mortality independently of non-HDL-C. They recommended that apoB and apoA-I should be measured routinely in all people with diabetes, particularly in the elderly.

Bayu et al. (139) studied 224 diabetic patients (85 type 1 and 139 type 2). After adjusting for age, sex, diabetes duration, systolic blood pressure and diabetes medications they found that the apo-ratio was the best predictor of diabetic retinopathy. Traditional lipids improved the ROC area by only 1.8 % whereas the apo-ratio improved the area by 8.2 %.

Enkhma et al. (140) have studied several ethnic groups of European and African Americans and developed a CV risk score which was found to be significantly increased across tertiles of the apo-ratio. They concluded that the apo-ratio differed across ethnicities and was associated with presence of the MetS in both groups. Among African Americans, an elevated apo-ratio independently predicted a greater risk of CAD.

Ounis et al. (141) studied thirty-two obese 13 years old children with 16 subjects who participated in a 8-week training period and 16 subjects serving as a control group. The apo-ratio was positively correlated with TG (r = 0.46, p < 0.01), blood glucose (r = 0.48, p < 0.01), waist circumference (r = 0.34, p < 0.01), systolic (r = 0.31, p < 0.01) or diastolic (r = 0.29, p < 0.05) blood pressure and was negatively correlated with HDL-C (r = 0.51, p < 0.01), Fat max (r = 0.45, p < 0.01) and VO^2 peak (r = 0.39, p < 0.01). When adjusted for pubertal stage, the relationships between the apo-ratio and other variables were not significantly altered. The multiple regression analysis showed that the change in total HDL-C is the most significant predictor of the change of the apo-ratio explaining 82% of the variance of its change over the training program.

Gatz et al. (142) studied thirty same-sex twin pairs in which both members were assessed at baseline and one twin subsequently developed dementia, at least 3 years subsequent to the baseline measurement, while the partner remained cognitively intact for at least three additional years. Eighteen of the 30 cases were diagnosed with Alzheimer's disease. Baseline assessments were conducted when twins' average age was 70.6 (SD = 6.8) years. Which twin would develop dementia was predicted by less favorable lipid values defined by higher apoB and higher apo-ratio, poorer grip strength, and — to a lesser extent — higher emotionality on the EAS Temperament Scale. Given the long preclinical period that characterizes Alzheimer's disease, these findings may suggest late life risk factors for dementia. Alternatively, there may be early development of atherosclerosis in critical cerebral arteries based on an elevated apo-ratio over time.

Carnevale-Schianca et al. (143) enrolled 616 patients with normal glucose tolerance (NGT) (273 men and 343 women), and measured insulin resistance, lipid profile, the apo-ratio and the factors compounding the MetS. An unfavorable apo-ratio (> 0.90 for males and > 0.80 for females) was present in 13.9 % of 108 patients with LDL-C < 100 mg/dL. Compared to subjects with lower apo-ratio, they had more elements of MetS and their lipid profile strongly correlated with high CV risk. In NGT individuals with LDL-C < 100 mg/dL, a higher apo-ratio indicated an atherogenic lipid profile, suggesting that LDL-C alone is insufficient to define CV risk. This study demonstrates that the apo-ratio is at least complementary to LDL-C in identifying a more correct CV risk profile of asymptomatic NGT subjects.

Wen et al. (144) measured high sensitive hsCRP, apoB, apoA-I, and the profiles of coronary angiograms, echocardiography and oral glucose tolerance tests (OGTT)s as well as traditional risk factors in 1,757 cardiology patients. The hsCRP or the apo-ratio were significantly correlated with the presence and severity of angiographic profiles, the levels of left ventricular (LV) ejection fraction, LV mass and LV mass index, and the presence of abnormal OGTT. The combination of the apo-ratio and hsCRP had greater correlation with abnormal glucose metabolism than its individual components in patients with normal fasting glucose, and was an independent predictor for coronary artery disease.

12. The apo-ratio and relations to atherosclerosis, vascular functions and inflammation

In many clinical conditions coronary arteriography, carotid ultrasound (CIMT), endothelial function, calcium scoring (CAC) and even more recently Intra Vascular Ultrasound (IVUS) studies of the coronary arteries has been related to lipid- and apo-abnormalities. Coronary and femoral plaques also contain apos (34-36). Many of these studies indicate that apos are more closely related to the amount of atherosclerosis than conventional lipids. Relevant studies are commented below.

In the Uppsala PIVUS study by Andersson et al. (145) the prevalence of carotid plaque was investigated. In 942 free living 70 year old men (n = 469) and women (n = 473) an ultrasound was performed. A plaque was defined by at least 50% increase of the intima-media thickness (IMT). Plaques were slightly more prevalent in men (n = 322) than in women (n = 293). Individuals with plaques had significantly higher the apo-ratio (p = 0.013), LDL-C/HDL-C-ratio (p = 0.04), LDL-C (p = 0.02), higher levels of fasting blood glucose (p = 0.02), Framingham risk score (p < 0.0001), higher levels of systolic blood pressure, (p < 0.0001), and also a higher average of pack-years of cigarette smoking (p = 0.008) after adjustment for gender and statin use. No significant differences were seen for HDL-C, diastolic blood pressure or BMI. The inflammatory markers oxidized LDL, TNF alpha, and leucocyte count as well as insulin resistance (HOMA) were increased.

In another subsample of 70 years old men (n = 124) and women (n = 123) who did not use lipid-lowering drugs from the PIVUS study (146) were investigated whether the amount of visceral (VAT) or subcutaneous adipose tissue (SAT) independently of the other can determine the apo-ratio. VAT and SAT areas were assessed using magnetic resonance

imaging. Their adipose tissue areas were related to their levels of apoB, apoA-I and the apo-ratio. ApoA-I levels were independently related to the VAT area (r = −0.33, p < 0.0001) whereas the apoB levels were not (r = 0.102, p = 0.07). The VAT area was independently significantly (r = 0.25, p = 0.001) related to the apo-ratio in the multiple regression analysis whereas the SAT area was not. This observation may indicate that VAT is metabolically active possibly through decreased adiponectin levels. The VAT metabolism seems more related to abnormalities in the apo-ratio which also may be a consequence of abnormal glucose-insulin metabolism as discussed above in other studies on the MetS.

Schmidt and Wikstrand (147) reported that in a multi-variable analysis including all baseline variables only the apo-ratio (p = 0.003) and serum insulin (p = 0.026) were significantly related to IMT composite progression rate indicating that the apo-ratio is an important risk factor for predicting atherosclerotic progression rate during very long-term follow-up in clinically healthy middle-aged men.

Reis et al (148) have studied factors that may influence MetS and development of obesity. They performed weighted Pearson partial correlation coefficients for waist circumference, log-transformed leptin, and insulin vs. metabolic, inflammatory, and thrombogenic CV risk factors among men and women aged 40 years and older, NHANES III. They found that apoB was positively correlated with waist, leptin and insulin both in men and women, whereas apoA-I was significantly and negatively related to these risk markers. These findings may indicate that the apo-ratio can summarize the lipid abnormalities into one number. The results were adjusted for age, ethnicity, smoking, physical activity, alcohol intake and time of fasting.

Junyent et al. (149) assessed carotid intima-media thickness (CIMT) and plaque in relation to classical risk factors and apoA-I and apoB levels in 131 unrelated patients with familial hypercholesterolemia (FCHL), 27 with prior CVD and 190 age- and sex-matched control subjects. By multivariate analysis in a model with all risk factors, inclusive of the MetS, independent associations of CIMT were age, the apo-ratio, systolic blood pressure, fasting glucose, family history of CVD and TC/HDL-C ratio (r^2 = 0.475, p < 0.001). The strongest determinant of IMT was the apo-ratio (β = 0.422, p < 0.001). The findings support the atherogenicity of the lipid phenotype in FCHL beyond associated risk factors. They also have implications for diagnosis and management of CVD risk in this condition.

Vladimirova-Kitova et al. (150) have found that carriers of a LDL-receptor defective gene have a higher carotid IMT and apo-ratio than non-carriers, whereas no difference between the groups was found with respect to the level of other lipid parameters, ADMA, total homocysteine, cell adhesion molecules, and % flow mediated dilation. Thus the apo-ratio is a predictor of IMT in carriers of this LDL-receptor gene.

Dahlen et al. (151) performed the CARDIPP-1 primary care study a study in 247 patients with type 2 diabetes, aged 55-66 years. They found that there was a significant association between the apo-ratio and CIMT in middle-aged patients with in type 2 diabetes. The association was independent of conventional lipids, hsCRP, glycaemic control and use of statins.

In the study by Rasouli et al. (152) 138 men and 126 women aged 40-70 years, were classified as CAD cases or controls, according to the results of coronary angiography. The severity of CAD was scored on the basis of the number and extent of lesions in coronary arteries. The results indicate that the apo-ratio, apoB and Lp(a) are independent risk factors for CAD and are superior to any of the cholesterol ratios. They suggested using the apo-ratio as the best marker of CAD in clinical practice.

Smith et al. (153) compared the body composition and the apo-ratio in migrant Asian Indians white Caucasians in Canada. Indian men and women had a higher apo-ratio than Caucasians (p = 0.0003)]. Of interest, there were also significant correlations between the apo-ratio and WHR in all groups, except the Indian women.

Both in children and adults obesity either defined by BMI or waist/hip ratio has been found to be directly related to apoB and the apo-ratio, and indirectly to apoA-I levels (154-156).

In the Cardiovascular Risk in Young Finns Study (157) they measured CIMT and brachial endothelial function in 879 subjects. They determined whether apoB and apoA-I measured in childhood and adolescence could predict atherosclerosis in adulthood. In subjects aged 12 to 18 years at baseline, apoB and the apo-ratio were directly (p < 0.001) related and apoA-I was inversely (p = 0.01) related with adulthood IMT. In subjects aged 3 to 18 years at baseline, apoB (p = 0.02) and the apo-ratio (p < 0.001) were inversely related, and apoA-I (p = 0.003) was directly related to adulthood flow mediated dilatation. Adjustment for age, gender, blood pressure, BMI, TG, insulin, CRP and brachial diameter at baseline did not change these relations. The apo-ratio measured in adolescence was stronger than the LDL-C/HDL-C or non-HDL-C/HDL-C ratios (c-values, 0.623 vs. 0.569, p = 0.03) in predicting increased CIMT in adulthood. The authors concluded that apoB and apoA-I measured in children and adolescents reflect an abnormal lipoprotein profile that may predispose to the development of subclinical atherosclerosis later in life. These markers are therefore useful in pediatric lipid risk assessment.

In a cross-sectional and 6-year prospective data from the cardiovascular risk in young Finns study (aged 24 to 39 years) (158) they studied metabolic risk variable MetS and their associations with CIMT. ApoB, CRP, and type II secretory phospholipase A2 enzyme activity were significantly higher and apoA-I lower in subjects with MetS (n = 325) than in subjects without MetS (n=858) indicating that the apo-ratio may summarize the risk into one number. In prospective analysis both MetS and high apoB predicted (p < 0.0001) incident high CIMT. The association between MetS and incident high CIMT was attenuated by about 40% after adjustment with apoB. Adjustments with apoA-I, CRP, or type II secretory phospholipase A2 did not diminish the association. Thus, the atherogenicity of MetS in this population assessed by incident high CIMT is mainly mediated by elevated apoB, but not inflammatory markers.

In the Swedish study Wallenfeldt et al. studied the relationships between abnormalities in lipoprotein concentrations in 338 apparently healthy 58-year-old men with manifestations of the MetS (159). Those who had an apo-ratio > 0.74, irrespective of blood pressure and smoking, had a significant progression (untreated) of the IMT values of the carotids over a

3-year period. Thus CIMT is a non-invasive simple, sensible and useful method to follow dynamic progression of atherosclerosis. Furthermore, the level of the apo-ratio is a strong predictor of these atherosclerotic changes in the arterial wall. Thus, values of the apo-ratio > 0.74 may alert the treating doctor to the need of adequate lipid-lowering therapy.

In a Japanese study (160) sixty-six type 2 diabetic patients with carotid atherosclerosis and 66 age- and sex-matched patients without carotid atherosclerosis were compared. They concluded that the combination of apoB and HOMA-R is a superior marker of carotid atherosclerosis compared with LDL-C alone in patients with type 2 diabetes.

Kim et al. (161) have studied 757 stroke patients undergoing coronary artery bypass grafting. They found that prevalence of asymptomatic carotid stenosis > 50% and > 70% was 26.4 % and 8.6%, respectively. In multivariate analysis, plasma levels of the apo-ratio and homocysteine were independently associated with carotid stenosis. Receiver operating characteristic curve (ROC) analysis indicated area under the curve values of 0.708 (the apo-ratio), 0.678 (Lp(a)), and 0.689 (homocysteine).

Ajeganova et al. (162) have studied patients with rheumatoid arthritis (RA) that commonly are affected by premature atherosclerosis including development of xanthomas. They studied 114 patients, age 50.6 years, 68.4% women, with recent RA (< 12 months after symptoms onset) and they were assessed at 0, 3, 12, 24 and 60 months after RA diagnosis. Plaque detection was positively associated with age and smoking (ever). After adjustment, a longitudinal approach demonstrated an independent positive prediction of CIMT by the apo-ratio (p = 0.030), but negative prediction by apoA-I (p = 0.047). Higher levels of the pro-atherogenic apo-ratio and apoB and low anti-PC (IgM antibodies against phosphorylcholine) were independently associated with bilateral carotid plaque p = 0.002, 0.026 and 0.000, respectively). Both baseline and longitudinal levels of other inflammatory/disease-related factors failed to show significant associations with the study outcomes.

13. Effects of lipid-lowering therapy on change of apoB, apoA-I and the apo-ratio

The mode of actions of statins and their effects on lipids and apos is reviewed in more detail elsewhere (163-165). The most commonly used drugs today are the statins that can reduce apoB synthesis and increase apoA-I synthesis and turnover. In clinical practice simvastatin and pravastatin are the most commonly used statins since they are now available as generics. They can reduce apoB up to about 20% and increase apoA-I by about 2-5% and a bit more for simvastatin. The most effective apoB-reducing statins are atorvastatin and rosuvastatin which lower the apoB-values by about 40-45% and 45-50%, respectively. Best increase in apoA-I concentrations is obtained by rosuvastatin which can increase the value by about 10-15% depending on baseline values, the lower the higher is the increase (163-165). Commonly for all statins there is a strong dose-response relationship, except for atorvastatin where higher doses commonly result in lowering of HDL-C and apoA-I values. The strongest lowering effects of the apo-ratio is obtained by rosuvastatin which lowers this ratio by about 50 %, followed by atorvastatin about 40-45 %, and simvastatin and pravastatin up to 30 %.

14. Prediction of outcome in statin trials using LDL-C or the apo-ratio

LDL-C has been the primary focus in lipid-lowering trials for more than two decades. A vast number of studies, both in primary and secondary prevention, have shown that there is a close relationship between LDL-C and CV event rates, the lower the LDL-C, the lower is the risk (163-165). In several of these trials also apoB, apoA-I and the apo-ratio have been measured. When explaining the relationship of each lipid fraction and each apo-fraction to CV event reduction virtually all lipids as well as apoB and apoA-I and the apo-ratio are significantly related to outcome. However, LDL-C is much weaker predictor than apoB and any lipid ratio. The best relationship with CV risk reduction is the apo-ratio. Examples from several trials are presented below.

In the AFCAPS/TexCAPS study (52,53), lovastatin 20-40 mg/d or placebo were given to 3,304 patients with rather normal LDL-C but low HDL-C values. ApoB decreased by 18.9 % and apoA-I increased by 7.2 %. At 5 years, there was a 37 % decrease in the relative risk for having a first acute coronary event in the lovastatin versus placebo group. In a head to head analysis it was found that apoB was better than LDL-C, $p < 0.01$, apoA-I was better than HDL-C, $p < 0.01$, and the apo-ratio was better than the TC/HDL-C ratio, $p < 0.01$ in explaining the event reduction **(Figure 9, left).** In this study it made no difference to which treatment group the patients were assigned, conventional diet – placebo or the lovastatin group. The apo-ratio value on treatment was the only lipid-related marker that was significantly related to outcome **(Figure 9, right).**
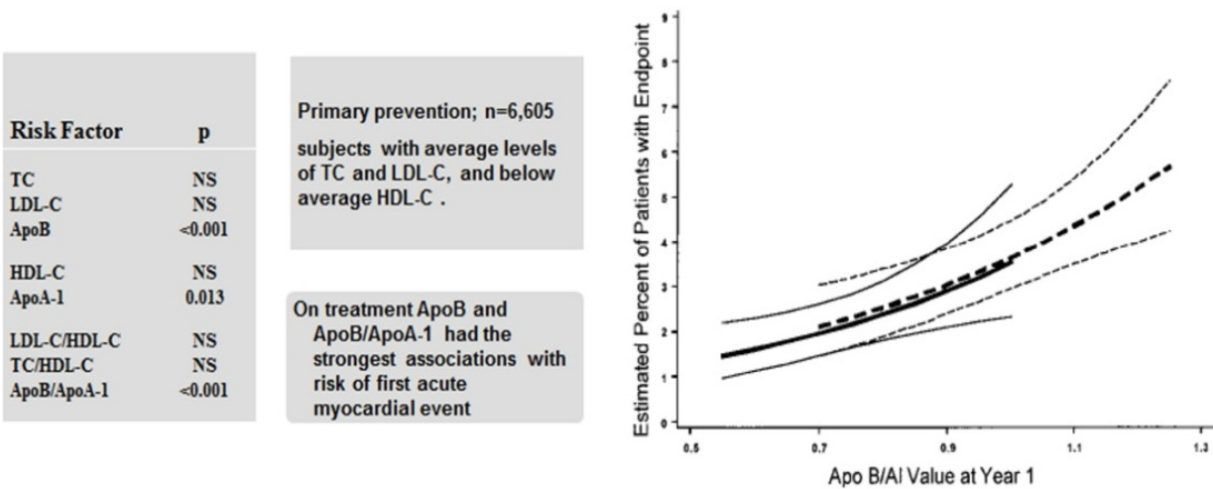

Figure 9. The AFCAPS/TexCAPS study. The apoB/apoA-I ratio was the best predictor of outcome expressed in head to head analyses versus lipids (left) (reference 52). Risk remaining during treatment (lovastatin versus placebo) in relation to obtained values for the apoB/apoA-I ratio (right) (reference 53).

In the LIPID trial pravastatin reduced CHD mortality by 24 % and total mortality by 22 % (3,4,54). The TC/HDL-C and the apo-ratios on treatment were considerably better in explaining outcome than either LDL-C or HDL-C. The values of the apo-ratio had strongest relations to event reduction.

To which target LDL-C values should lipid-lowering aim? In the ACCESS study (166) therapy reduced LDL-C levels to 'normal – target levels'. However, such therapy only

reached apoB levels to about the 50th percentile of a population. This means that the patients were not optimally treated by using LDL-C at recommended guideline levels. These results may illustrate that apoB would be a better target if proper target levels have been proposed.

To reach targets in guidelines has been further investigated in a more recent paper by Vodnala et al. (167). They applied the ATP III guidelines, including Framingham Risk Scores to determine whether patients met non-HDL-C goals upon referral. In order to reach targets for non-HDL-C among patients (n = 5,692) most high- and many intermediate-risk patients goals would require more aggressive treatment to reach either the TC/HDL-C = 3.5 or the apo-ratio = 0.50 goals. Thus, a more intense therapy using better target goals, i.e. apoB or the apo-ratio, than the conventional LDL-C or non-HDL-C would most likely add clinical value and better treatment effects.

Van den Bogaard et al. (168) studied 9,247 patients (mean age 61 years, 81% males), participating in the Treatment to New Targets (TNT) trial in which the effects of 80 mg versus 10 mg atorvastatin was compared. The association between lipoprotein components and the risk of cerebrovascular events after the first year into the trial was investigated. All lipoprotein components, except LDL-C, showed a significant gradient for incidence of cerebrovascular events with increasing quartiles of the lipoprotein component. If the lipoprotein components were treated as continuous variables, the adjusted HR for cerebrovascular events for 1 SD difference in 1-year lipoprotein components were for LDL-C 1.13 (95%CI, 1.02–1.25), for HDL-C 0.86 (0.76–0.97), for apoB 1.17 (1.04–1.28), for apoA-I 0.83 (0.74–0.94), for TC / HDL-C 1.22 (1.10–1.34) and for the apo-ratio 1.24 (1.12–1.37). The apo-ratio was superior to TC/ HDL-C, because adding the apo-ratio to TC/HDL-C improved prediction, whereas adding TC/HDL-C to the apo-ratio did not. These findings are consistent with the AMORIS study linking the apo-ratio to risk of stroke (99,100), and are also similar to results from the combined data of TNT and IDEAL showing that TC⁄HDL-C and the apo-ratios are more closely associated with CVD than any of the individual lipoprotein parameters. They concluded that in coronary heart disease patients receiving intensive lipid-lowering treatment, the on-treatment apo-ratio provides the strongest association with incidence of cerebrovascular events followed by TC / HDL-C. They also stated that as current European and US guidelines only acknowledge LDL-C as a therapeutic target and HDL-C and triglycerides as risk markers it will be up to future guideline committees to implement these new parameters as risk predictors and to define new treatment targets based on these apolipoproteins.

Kastelein et al. (169) showed in a post hoc analysis that combined data from 2 prospective, randomized clinical trials in which 10 001 TNT and 8,888 ("Incremental Decrease in End Points through Aggressive Lipid Lowering"- IDEAL) patients with established coronary heart disease were assigned to atorvastatin 10 mg/d or atorvastatin 80 mg/d. In models with LDL-C, non-HDL-C and apoB were positively associated with cardiovascular outcome, whereas a positive relationship with LDL-C was lost. In a model that contained non-HDL-C and apoB, neither was significant owing to collinearity. Inclusion of measurements of apoA-I further strengthened the relationships. The TC/HDL-C and the apo-ratio in particular were

each more closely associated with outcome than any of the individual pro-atherogenic lipoprotein parameters **(Table 2).** In a pair-wise COX model comparison of the two ratios the TC/HDL-C was non-significant but the apo-ratio was significant, $p<0.001$. However, the authors mainly conclude that these data support the use of non-HDL-C or apoB as novel treatment targets for statin therapy, but do not believe that the apo-ratio is yet a valid risk variable because of uncertainness of the impact of risk of HDL-C and apoA-I. Furthermore, they state that in the absence of interventions that have been proven to consistently reduce CVD risk through raising plasma levels of HDL-C or apoA-I, it seems premature to consider the ratio variables as clinically useful. These conclusions merit further comments in the discussion. However, clearly the apo-ratio comes out as the best CVD predictor as manifested by their data when all head-to-head comparisons are performed between various lipids and apos.

LDL cholesterol	0.95	0.87–1.05	0.33	Apolipoprotein B	0.94	0.85–1.04	0.26
Apolipoprotein B	1.24	1.13–1.36	<0.001	Apolipoprotein B/A-I	1.30	1.20–1.39	0.001
Non-HDL cholesterol†	1.00	0.93–1.07	0.94	Total/HDL cholesterol	1.00	0.92–1.10	0.91
Apolipoprotein B/A-I	1.24	1.17–1.32	0.001	Apolipoprotein B/A-I	1.24	1.13–1.36	0.001

Table 2. TNT-IDEAL pooled data. Head to head comparisons between various lipids, apolipoproteins and ratios (redrawn from reference 169).

Holme et al. (170) studied the ability of apolipoproteins to predict new-onset of congestive heart failure (HF) in statin-treated patients with coronary heart disease (CHD) in the IDEAL study based on 8,326 patients of whom 185 subjects had a HF event. Variables related to LDL-C carried less predictive information than those related to HDL-C, and apoA-I which was the single variable most strongly associated with HF. LDL-C was less predictive than both non-HDL-C and apoB. The apo-ratio was most strongly related to HF after adjustment for potential confounders, among which diabetes had a stronger correlation with HF than did hypertension. The apo-ratio was 2.2 times stronger associated than that of diabetes. Calculation of the net reclassification improvement (NRI) index revealed that about 3.7 % of the patients had to be reclassified into more correct categories of risk once the apo-ratio was added to the adjustment factors. The reduction in risk by intensive lipid-lowering treatment as compared to usual-dose simvastatin was well predicted by the difference in apo-ratio on-treatment levels mostly through the reductions in apoB. Thus, both apoB, apoA-I and the apo-ratio had additional clinical value above lipids in predicting risk of HF.

Holme et al. (171) also looked into the ability of apoB, apoA-I or the apo-ratio to predict new coronary heart disease (CHD) events in patients with CHD on statin treatment in the IDEAL trial comparing the effects of atorvastatin 80 mg/d to that of simvastatin 20-40 mg/d to prevent CHD subsequent major coronary events (MACE). Variables related to LDL-C

carried more predictive information than those related to HDL-C, but LDL-C was less predictive than both non-HDL-C and apoB. Of all lipoprotein variables, the apo-ratio was the best predictor of MACE during statin treatment. The apo-ratio carried as much information as apoB, apoA-I, LDL-C, and HDL-C together. However, for estimating differences in relative risk reduction between the treatment groups, apoB and non-HDL-C were the strongest predictors. They recommended that measurements of apoB and apoA-I should be more widely available in clinical praxis.

Results from the recently published ASTEROID Trial (172) showed that in patients with acute coronary syndromes treated with rosuvastatin 40 mg daily for 2 years a significant (p < 0.001) regression was found of the atherosclerotic burden in the coronary arteries (intravascular ultrasound). In these patients LDL-C was reduced from 3.35 mmol/L (130 mg/dl) to 1.55 mmol/L (60 mg/dl), p < 0.001 and the apo-ratio was reduced from high 0.95 to low 0.49, p < 0.001. These results indicate that the risk related to the apo-ratio risk was reduced from the eighth risk decile to the first decile, i.e. to normality.

Nicholls et al. (173) presented data based on 4 studies in which IVUS was used in 1,455 coronary patients. They were given lipid-lowering with either atorvastatin, simvastatin, pravastatin and rosuvastatin (strongest lipid-lowering). A highly significant regression of coronary atheroma volume over a two year period was recorded. They stated that "Reducing the ratio of apoB to apoA-I was the strongest lipid predictor of changes in atheroma burden in patients treated with a statin". Thus, even small, but clinically important changes in atheroma volume, can be identified by IVUS techniques and also by closely related changes in the strongest marker of lipoprotein metabolism, i.e. the apo-ratio.

Tani et al. in Japan performed a 6-month prospective study of 64 patients with coronary artery disease treated with pravastatin (174). The plaque volume, assessed by IVUS, decreased by 12.6% (p < 0.0001). A significant decrease of 6.4 % and 14.6 % was found in the serum level of apoB and the apo-ratio (p < 0.0001 and p <0.0001, respectively, vs baseline), and apoA-I increased by 14.0 % (p < 0.0001). A stepwise regression analysis revealed that the change in the apo-ratio was an independent predictor of the change in coronary plaque volume (p < 0.0023). They concluded that a decrease in the apo-ratio is a simple predictor for coronary atherosclerotic regression: the lower the apo-ratio, the lower the risk of coronary atherosclerosis.

Taskinen et al. studied diabetic patients treated with fenofibrate (the FIELD study,175). Lipid ratios and the apo-ratio performed significantly better than any single lipid or apolipoprotein in predicting CVD risk during treatment. In the placebo group, the variables best predicting CVD events were non-HDL-C/HDL-C, TC/HDL-C (HR 1.21, p < 0.001 for both), the apo-ratio (HR 1.20, p < 0.001), LDL-C/HDL-C (HR 1.17, p < 0.001), HDL-C (HR 0.84, p < 0.001) and apoA-I (HR 0.85, p < 0.001). In the fenofibrate group, the first four predictors were very similar (the apo-ratio was fourth), followed by non-HDL-C and apoB.

In the JUPITER primary prevention trial (176) rosuvastatin 20 mg versus placebo was given to patients with initial LDL-C levels < 3.4 mmol/L and hsCRP > 2 mg/dL. Already after a medium time of treatment of 1.9 years, the trial was stopped for safety reasons since the actively treated patients benefitted by a highly significant risk reduction in MACE by 50 %. It should be pointed out that several thousand patients, those first recruited into the trial, participated for

more than three to four years in the trial. LDL-C was reduced to 1.4 mmol/L and the apo-ratio was reduced from 0.95 to 0.49, p < 0.001. This indicates that "normal values" for the apo-ratio should be in the order of < 0.50 in order to obtain as low future risk as possible.

In a recent publication from JUPITER the authors reported that LDL-C, non-HDL-C, apoB and lipid-ratios as well as the apo-ratio had about similar predictive value of remaining risk during treatment with rosuvastatin (177). However, in subgroup analyses they reported that apoA-I had a greater capacity to define remaining risk than HDL-C. Furthermore, they also found that any lipid-related ratios had a greater predictive value than single values of LDL-C, non-HDL-C or apoB. In addition, if LDL-C values reached < 100 mg/dL or < 70 mg/dL, or if non-HDL-C targets were reached < 130 mg/dL or < 100 mg/dL, the only lipid-related variable or ratio that still was associated with remaining significant risk was the apo-ratio. These data, although the number of events is small in the sub-cohorts, indicate that the apo-ratio is a realistic and a valid predictor of risk and may be better than conventional lipids. However, the authors indicated that differences were small and that LDL-C and non-HDL-C were still sufficiently good as targets for treatment despite the fact that the results were in favor of the apo-ratio.

15. Treating CV risk patients to new targets using apolipoproteins

The apo-ratio, as shown in this paper, has commonly been shown to predict CV risk equally well or, in fact, more commonly even significantly better than conventional lipids in both prospective and treatment studies. So, which cut levels and targets of the apo-ratio should be recommended in the clinic to indicate CV risk before and after treatment? Since there is an almost linear increase (semi-log scale) in risk with increasing values of the apo-ratio from both AMORIS and the INTERHEART studies **(Figure 10)** it is clear that at values of the apo-ratio > 0.90 (values should be given in two decimals in order not to lose important information) there is a considerable increase in risk, whereas values from 0.70 to about 0.90 are indicative of a moderate risk. Values for men < 0.70 and for fertile females < 0.60 can be more normal especially if no other risk factors are present. The "ideal-biologically normal values" are rather < 0.50 as also documented in lipid-lowering trials in which CV events have been successfully reduced (176,177). So the target values during therapy must focus on these levels, the lower the apo-ratio the better is the therapy.

Lipids and apos are commonly correlated as also manifested in the AMORIS study (3 and others). In order to simplify for the physicians to learn what a value of LDL-C corresponds to regarding apoB **(Figure 11, left)**, a table has been compiled based on data from AMORIS also for the relationship between LDL-C and the apo-ratio **(Figure 11, right)**. A value of the apo-ratio of 0.80 roughly corresponds to a value for LDL-C of 3.0 mmol/L, and an apo-value of about 0.50 corresponds to LDL-C value 1.6 mmol/L for men and about 0.1 units lower for females. Notably, there is a large deviation from this correlation line. Those having a higher apoB or a higher apo-ratio at all levels of LDL-C (above the line) in general have a much higher CV risk than those below the line. Further details and relations between apolipoproteins, lipids and their relations to CV risk, and cut- and target levels of apoB and apoA-I have been reviewed (3). Since the target level for LDL-C according to many guidelines is set at LDL-C < 1.6 mmol/L, a target and normal value of the apo-ratio < 0.50 seems to be a realistic number.
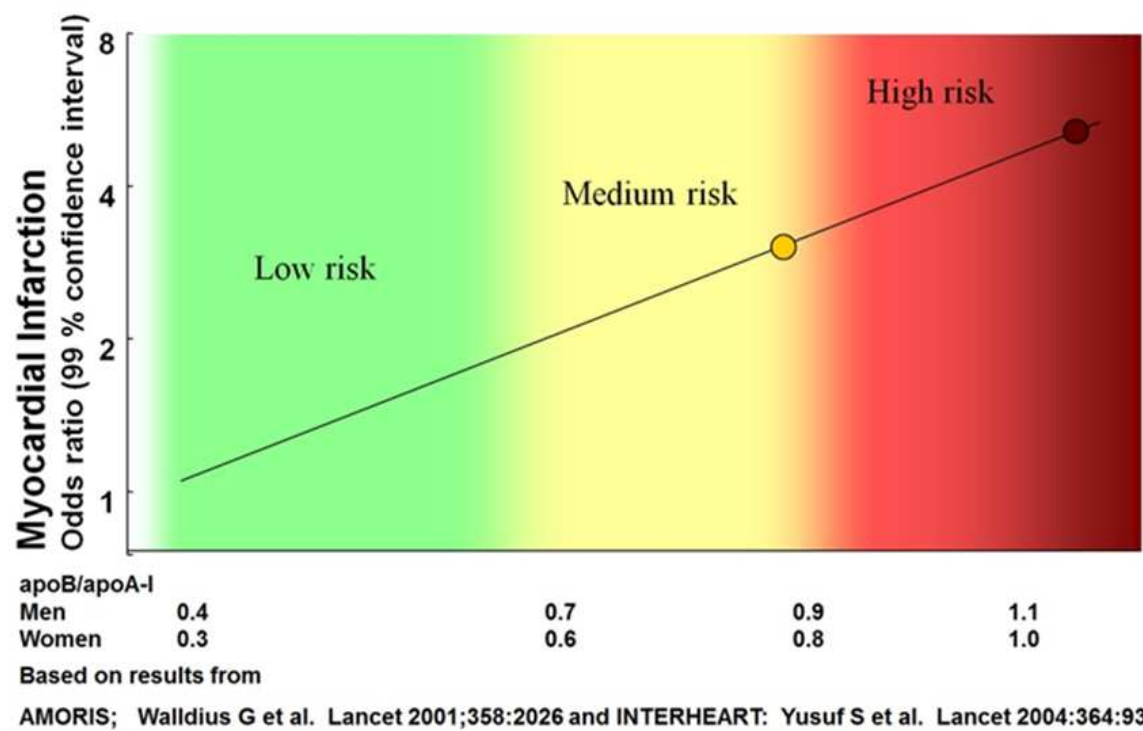
Figure 10. This line of risk of myocardial infarction is based on the findings in the AMORIS (reference 3) and the INTERHEART (reference 58) studies. Tentative cut-values are indicated in green (low risk), yellow (medium risk), and red (high risk). Values for a particular patient can be indicated by the dots on the line. During lipid-lowering treatment it is easy to monitor how a patient moves upwards or downwards in the risk line for the apo-ratio.
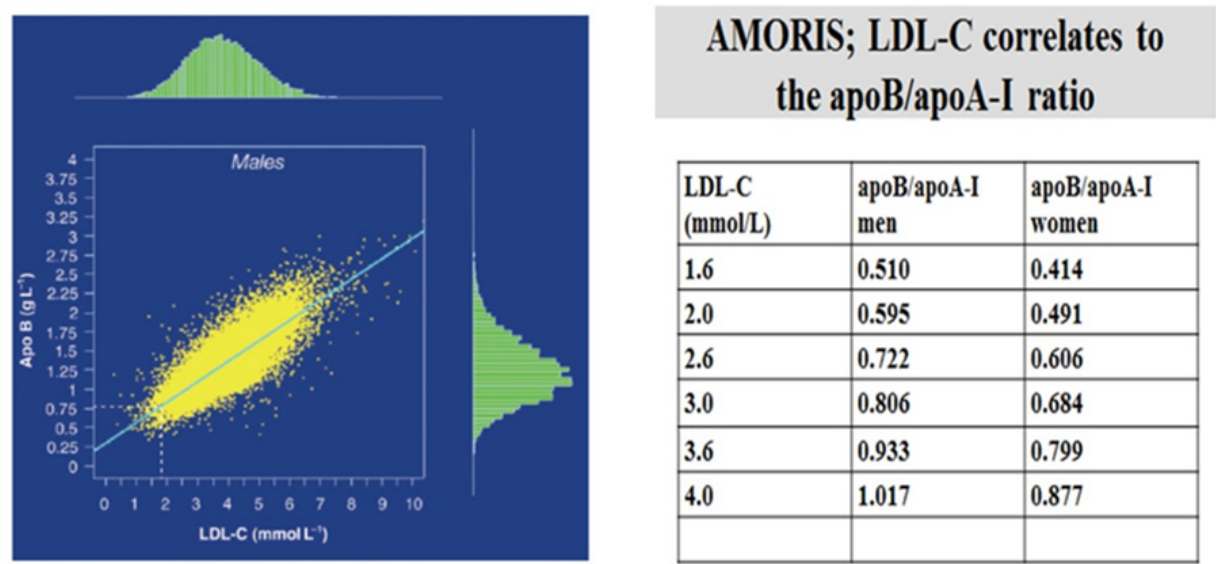

AMORIS; LDL-C correlates to the apoB/apoA-I ratio

LDL-C (mmol/L)	apoB/apoA-I men	apoB/apoA-I women
1.6	0.510	0.414
2.0	0.595	0.491
2.6	0.722	0.606
3.0	0.806	0.684
3.6	0.933	0.799
4.0	1.017	0.877

Figure 11. Data from the AMORIS study. Relations between LDL-C and apoB (left), and LDL-C and the apoB/apoA-I levels (right). Various cut-levels of LDL-C correspond to apoB and apoB/apoA-I values (both figures from reference 3).

How much can effective lipid-lowering therapy reduce apoB and the apo-ratio and how much can apoA-I be increased? Physical exercise and diet, if effective and longstanding, can reduce

apoB by 5-10 % at the most and the apo-ratio by about 5% and increase apoA-I by about 5%. For more information see reference 3 and data on effects of statins in section 13 above.

16. Discussion

Today, LDL-C, non-HDL-C and lipid ratios are prioritized in international guidelines although apoB has also been mentioned in a few guidelines (9,18,38,178-180). In this review evidence is given indicating that apoB, apoA-I, and especially the apo-ratio, are at least equally good, or often even better than conventional lipids to predict CV risk prospectively and during lipid-lowering treatment. Much of this new information has not yet been included in any previously published meta-analyses. It is therefore of importance to review these data obtained from countries in the whole world in order to get the full information of what apolipoproteins can deliver for CV risk prediction and evaluation. These findings and advantages are summarized below and also briefly in **Table 3 (I) and (II)**.

The biological relevance of using apoB and apoA-I as markers of CV risk is convincing since these proteins are carriers of lipids in the circulation and deliver C to peripheral tissues including the arterial wall (mediated by apoB). ApoA-I can remove C from the subendothelial space for breakdown and removal through the bile and further GI excretion. ApoA-I has also my other protective actions as summarized above and can thereby modify or inhibit inflammation and atherogenesis provoked by oxidation and modification of LDL-C with apoB (3,64). Thus, both apoB and apoA-I are biologically and patho-physiologically strongly active in normal biology and in plaque formation.

There are also methodological advantages of using these apos (3,23,28,65). Direct measurements of apoB and apoA-I by internationally standardized methods are available, analysis can be performed even if taken from patients in the non-fasted state, apos can be trustfully analyzed on frozen samples, the errors of the methods are not dependent on TG levels, and the methodological errors are usually low. Furthermore, costs for the direct analysis can be low as is the case in many countries. Importantly, the apo-ratio reflects the whole lipoprotein spectrum of virtually all phenotypes (type III patients need additional definition of risk) into one number. No sort like mg/dL or mmol/L has to be given for the ratio, which may otherwise be difficult to convert to understandable numbers in different countries. In summary, just one number of the apoB/apoA-I ratio indicates the risk level, similar numbers in all parts of the world. The higher the number, the higher is the risk (3) as also supported by a vast number of studies summarized in this paper. The cardiovascular risk line related to increasing value of the apo-ratio seems to be very similar world-wide **(Figure 10)**.

ApoB, which indicates the number of potentially atherogenic particles, mainly sdLDL particles, has in a majority of publications been shown to be a better predictor of CV risk than LDL-C (9,11,13,14,44,59-62,88,89 and others) but in several instances apoB and non-HDL-C seem to indicate similar CV risk (10). One explanation why apoB may be better than non-HDL-C in risk prediction may be due to the fact that larger VLDL- and IDL-C-containing particles may have less potential to penetrate into the arterial walls than

Biological relevance

ApoB and apoA-I are carriers of lipids into and out of the arterial wall. Major pathophysiological mechanims are dependent on these proteins and how they can be modified (apoB) and be protective due to defensive actions.

Methodological advantages

Methods for apoB and apoA-I internationally standardized. Methodological errors of apoB and apoA-I are generally <5%. Fasting is not needed. High TG does not interfere. Frozen samples can be analyzed. The apo-ratio; no sort like mmol/L or mg/dL is needed. One number indicates the "cholesterol balance", easy to remember and act upon. Identifies sdLDL particle numbers. The apo-ratio reflects the risk associated with an imbalance between atherogenic and anti-atherogenic lipoproteins.

Relations to CV diseases

Strong predictors of myocardial infarction, stroke, heart failure, and also related to risk of renal failure and aortic aneurysms

Table 3 (I)

_____

Relations to CV risk factors

Strong associations with abdominal obesity, metabolic syndrome and both diabetes

Relations to CV risk in univariate and multivariate analyses

Risk relationships for individual apos ant the apo-ratio commonly remained after adjustment for multiple conventional risk factors.

Relations to lipids and lipoproteins as predictors of CV risk

Lipids and lipid-based ratios are rarely significantly better than apos or the apo-ratio. However, apos and the apo-ratio are at least as good as lipids and lipid ratios, but commonly significantly better than lipids to predict CV risk

Relations to atherosclerosis

Strong associations with atherosclerosis in carotid arteries (IMT), coronary atherosclerosis (angiography and IVUS), femoral plaques and impaired endothelial function. Predicts progression and regression of carotid and coronary atherosclerosis

Relations to lipid-lowering treatment

Predicts outcome in statin trials equally well or commonly better than conventional lipids and lipoproteins

Table 3 (II)

Table 3. (I) and (II). Summary of findings supporting the use of apoB, apoA-I and the apo-ratio.

sdLDL particles. In fact, in a number of large publications including meta-analyses apoB has been shown to be a stronger predictor than the next best predictor non-HDL-C (9,11,13,14,61,62). LDL-C is only the third best predictor of future CV risk according to major analyses (9,62) and so also during statin treatment (169-171). However, in another meta-analysis they found non-HDL-C to be better than LDL-C and apoB during statin treatment (64). In a majority of these studies data have been adjusted for age and gender as well as other confounding risk factors like blood pressure, smoking, obesity and commonly also diabetes and other lipids.

Direct comparative data of HDL-C versus apoA-I is more sparse and is still much debated due to the complexity of HDL metabolism. ApoA-I has often similar predictive value as HDL-C as presented in the ERFC meta-analysis (10). However, especially in the large INTERHEART study, apoA-I over the whole range of HDL-values was a better predictor of risk than HDL-C (59). Similarly, in the AFCAPS/TexCAPS statin study apoA-I was a stronger determinant of risk than HDL-C (52,53).

What about the lipid-ratios versus the apo-ratio, which has strongest relations to CV risk? Importantly, all ratios and especially the apo-ratio predict prospective risk better than any single lipid variable (3,4,7,22,44,52,53,56,59,60,80,88,89,100,101,169-171 and others). Similarly, during statin treatment ratios also beat single lipoproteins in predicting risk (168-171,174). That should be obvious since ratios has a greater potential to find subjects at risk in whom the anti-atherogenic capacity of HDL-C or apoA-I are deranged. These data are also obtained when controlling for confounders i.e. conventional risk factors. Thus, the apo-ratio may have a better potential to identify subjects with different phenotypes than a single lipoprotein fraction. These strong findings in favor of any ratio, especially the apo-ratio, are strangely enough, not considered important in any international guideline despite the fact that ratios virtually in all studies in which ratios have been used outperform the results obtained by single lipoprotein fractions. Why this unscientific approach by guidelines committees?

Results from meta-analyses are generally well trusted but can also be questioned regarding selection criteria for including studies, acceptance of analytical and diagnostic methods used in each of the studies, primary and secondary variables used as major endpoints as well as the general conclusions drawn from the analyses. The results from the first ERFC meta-analysis have been taken to indicate that the apo-ratio and the TC/HDL-C ratio are equally good predictors of risk (10) and that apoB is equally good as risk predictor as non-HDL-C and apoA-I is equally predictive as HDL-C. The authors also open for future use of apolipoproteins especially in evaluation of risk of MI. In these risk conditions they found that apoB and apoA-I could be more useful in men than women, and in subjects with high TC, in those with low HDL-C, in individuals with hypertension, and in those with intermediate CV risk (Framingham risk score) apos can also be useful. They also found that the apo-ratio was a better predictor of CHD than stroke. However, in a recent publications in JAMA they conclude that the TC/HDL-C ratio had stronger predictive power than the apo-ratio when these ratios were added to conventional risk factors.

Two major critical views against these JAMA (see footnotes a/ and b/ below) papers may be raised that unfavorably affect the trust of using apos as risk predictors. Many early studies on apos included in these meta-analyses had large methodological errors (not internationally standardized) which may affect the conclusions on the credibility to use apos as risk predictors. This is unfair to the modern apo-technology which has much lower methodological errors.

Furthermore, in the ERFC studies they pooled non-fatal MI, all CHD fatalities, peripheral vascular diseases, and even all strokes, especially haemorrhagic stroke and unidentified stroke in very old people, into the primary variable "cardiovascular events". Such pooling of events considerably dilute the potential of adequate information yielded by an appropriately measured apos and the apo-ratio. This is especially the case for patients with risk of MI and in those suffering ischemic strokes in which positive diagnostic values have been obtained for apos as summarized in previously commented studies.

The authors also discuss some potential problems with introduction of apos such as need for education, lack of availability of apo-methods in the most laboratories, standardization problems as well as additional costs for such methods. All these aspects and possible problems must obviously be considered when new diagnostic tests shall be introduced for clinical use in risk evaluation. Yes, education is mandatory and may take time, but such problems must not over shade the importance of innovation of analytical tools. Costs can be significantly reduced if apo-tests become standard analyses. In fact, many biochemists already now favor these analyses over conventional lipids as documented previously in this paper.

Another criticism of the ERFC-studies is related to which studies were excluded (lack of confounding variables or case-control studies) from the meta-analyses in ERFC. Thus, major studies like AMORIS (44), INTERHEART (58) and ISIS (60) were not included in the ERFC meta-analysis. Neither were their positive results commented in the discussion on risk of MI despite the fact that these three studies have six times as many well defined events than those in the ERFC studies. In all these large studies apoB, apoA-I and especially the apo-ratio, due to their large number of events, were each significantly stronger predictors than conventional lipids. In ERFC there were many studies, but few of these studies showed significant differences between lipids and apos due to few well defined hard events. Neither did ERFC point out that the apo-ratio also seems to be the best variable to describe the remaining CV risk after statin treatment. This has been shown especially in the statin trials like AFCAPS/TexCAPS (52,53), IDEAL (169-171), TNT (168-170), CARDS (181), and JUPITER (176) as well as in studies on regression of atherosclerosis during lipid-lowering therapy (172-174) as pointed out above. In most of these studies the data were also adjusted for age, gender, conventional lipids and lipoproteins as well as other major risk factors like blood pressure, smoking, obesity and diabetes. Grundy simply concludes in the JAMA editorial

a/ The Emerging Risk Factors Collaboration. Lipid-Related Markers and Cardiovascular Disease Prediction. JAMA. 2012;307(23):2499-2506.

b/ Scott M. Grundy. Editorial: Use of Emerging Lipoprotein Risk Factors in Assessment of Cardiovascular Risk. 2012;307(23):2540-2541.

that conventional risk factors plus LDL-C, and possibly one more risk factor, is enough as tools for prediction of risk – a very conservative approach which is so (too!) common in US!

How much do confounders/risk factors impact on the results from all these CV risk studies? Importantly, in ERFC (10) and also in the majority of studies cited above, the impact of adjusting for major confounders was very small and only changed the risk (HR, RR or OR) to a minor degree. In fact, the apolipoproteins added value, measured as net reclassification index (NRI) in several large studies (88,91,170). This indicates that apolipoproteins, especially the apo-ratio, could change the numbers of individuals either to a higher or a lower CV risk compared to conventional lipids. Newly developed risk algorithms based on the apo-ratio have also been developed showing at least equal predictive or even better values than conventional risk algorithms (102,117,118). Thus, apoB, apoA-I and the apo-ratio can already now be used in clinical settings.

In the present review the apo-ratio has been shown to be closely related to many different types of CV events in prospective studies. These common diseases are myocardial infarction, stroke, especially ischemic stroke, heart failure, renal failure, aortic aneurysms, development of diabetes, including retinopathy **(Table 3 I and II)**. However, in the meta-analyses published so far only CV events have been chosen as endpoints and other manifestation of CV risk related to atherosclerosis have been excluded.

Is the apo-ratio useful in predicting various metabolic and inflammatory conditions commonly underlying atherosclerosis and its future consequences? In fact, the apo-ratio has also been found to be a valuable summarizing index of lipid-abnormalities and their complications in a large number of studies of the MetS and/or diabetes (125-139,143,144). In addition, the apo-ratio values are also increased in patients with hypertension, obesity, in pubertal children and in those with heredity for CV diseases (130,141). The apo-ratio is also more closely than lipids related to atherosclerosis in a large number of studies in which different techniques like coronary angiography, arterial wall thickness obtained by ultrasound techniques in the carotid arteries (CIMT values) or even in the coronary arteries by intravascular ultrasound (IVUS) and arterial abnormalities such as the endothelial dysfunction have been used (145-162). Thus, in all these disease or risk situations the apo-ratio may identify those at an increased risk even better than what is currently performed by using LDL-C or the recently recommended non-HDL-C.

The newest research data on the apo-ratio have not yet been reviewed by international guideline committees. Thus, so far, in the newest guidelines developed over the last few years non-HDL-C and apoB are mentioned, and accepted for clinical use, whereas the apo-ratio is still waiting for acceptance (9,35,178,179).

In conclusion; with all the new knowledge presented in this paper about the strong relations between apoB, apoA-I, and the apo-ratio, and CV risk as well as other disease manifestations, it is proposed, as many researchers have already done, that these strong risk predictors/factors/markers are included in new guidelines. In many disease conditions and manifestations of atherosclerosis apolipoproteins are at least equally informative, and often better than LDL-C, non-HDL-C and lipid ratios in predicting risk. It is realized that there

will be pedagogical hurdles, but it should be possible to educate physicians, patients and health providers to understand that these apolipoproteins are markers of normal and abnormal cholesterol metabolism. The apo-ratio simply reflects the "balance between the bad cholesterols and the good cholesterols" technically measured by apolipoproteins. The apo-ratio is a valid cardiovascular risk index (CRI) that reflects the level of CV risk for virtually all patients with different lipid phenotypes, the higher the value of the apo-ratio, the higher is the risk. Finally, targeting lower values (about 0.50) of the apo-ratio during therapy may more correctly identify who is at risk or not at risk, and how high is the risk? Does the risk depend on the atherogenic apoB, or the anti-atherogenic apoA-I or rather on the most informative value i.e. the apo-ratio which summarizes the level of risk in a simple way? Since physicians usually only manage to effectively evaluate and trust one laboratory marker, the apo-ratio is such a valid marker. By simply plotting the value for a given patient on the risk line you can easily follow improvement during therapy and also motivate the patient to improve values to normal levels **(Figure 10**). New guidelines should at least contain equally objective information (cut-values and target values) on how to use apoB, apoA-I, and the apo-ratio as on lipids so that physicians can choose whichever diagnostic marker of risk they prefer. Gradually this new apolipoprotein-based risk classification with a focus on the apoB/apoA-I ratio may, or rather should be, introduced in clinical practice.

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Abbreviations

apos	apolipoproteins
apoB	apolipoprotein B
apoA-I	apolipoprotein A-I
apo-ratio	apoB/apoA-I ratio
C	cholesterol

CV	cardiovascular
VLDL	Very Low Density Lipoprotein
IDL	Intermediate Density Lipoprotein
LDL	Low Density Lipoprotein
sdLDL	small dense LDL
TC	total cholesterol
HDL	high density lipoprotein
hsCRP	high sensitivity CRP (C-reactive protein)
IVUS	intravascular ultrasound
CIMT	carotid intima media thickness
CRI	Cardiovascular Risk Index
HR	Hazards Ratio
NRI	Net Reclassification Index
MACE	Major Coronary Events
RR	Relative Risk

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