

Is it time to discard the apo B:apo A-I ratio as a predictor of cardiovascular disease?

Original article Ingelsson E *et al.* (2007) Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA* 298: 776–785

SYNOPSIS

KEYWORDS apolipoproteins, cholesterol, coronary heart disease, lipids

BACKGROUND

There are conflicting data on whether the apolipoprotein (apo) B:apo A-I ratio is a better predictor of the risk of coronary heart disease (CHD) than more traditional lipid measures, such as LDL cholesterol or total cholesterol.

OBJECTIVE

To evaluate the relative effectiveness of different lipid measures for prediction of CHD risk.

DESIGN AND INTERVENTION

This was a prospective, population-based, cohort analysis of participants in the Framingham Offspring Study. Individuals who presented for examination in the fourth cycle (1987–1991) were eligible for inclusion. There were several exclusion criteria: prevalent cardiovascular disease (CVD) at baseline, serum triglycerides over 400 mg/dl, and age under 30 years or over 74 years. Venous blood samples were collected from participants after a 12 h fast and analyzed for total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, apo A-I, and apo B. Patients were followed-up from the time of first clinical examination until 31 December 2005.

OUTCOME MEASURE

The primary end point was occurrence of a CHD event, defined as CHD-related death, myocardial infarction, angina pectoris, or coronary insufficiency.

RESULTS

The study population included 3,322 individuals, of whom 53% were women. The mean

age for both sexes was 51 years (range 30–74 years). The mean systolic blood pressure was slightly higher in men than women (129 mmHg vs 124 mmHg). After a median follow-up of 15 years, there had been 291 CHD events, 32% of which occurred in women. Positive associations, all of a similar magnitude, were noted between CHD risk and several different lipid measures: total cholesterol:HDL cholesterol ratio (hazard ratio [HR] men = 1.39, women = 1.39), LDL cholesterol:HDL cholesterol ratio (HR men = 1.35, women = 1.36), apo B:apo A-I ratio (HR men = 1.39, women = 1.40), non-HDL cholesterol level (HR men = 1.22, women = 1.28), and apo B level (HR men = 1.37, women = 1.38). In men, increased levels of both HDL cholesterol and apo A-I were associated with a reduced risk of CHD, but only increased HDL cholesterol was indicative of reduced risk in women. There was no significant association between total cholesterol or LDL cholesterol and CHD risk in either sex individually, but the correlation became significant when data for the sexes were pooled. The measure with the highest level of discrimination for CHD events (C index) was the apo B:apo A-I ratio (men = 0.74; women = 0.76), although this discrimination measure was not significantly better than the other measures evaluated. Reclassification of 10-year CHD risk in men was significantly improved by use of the ratios for total cholesterol:HDL cholesterol and apo B:apo A-I, although neither was statistically superior to the other. Furthermore, multivariate analysis revealed that the apo B:apo A-I ratio did not add incremental benefit to predictive models that already included the total cholesterol:HDL cholesterol ratio.

CONCLUSION

The power of the apo B:apo A-I ratio for predicting CHD is similar to that of more established lipid ratios.

COMMENTARY

Justo Sierra-Johnson* and Rachel M Fisher

Currently, opinion in the scientific community is divided regarding the usefulness of the apo B:apo A-I ratio for the detection of CVD. While some physicians and researchers think of the apo B:apo A-I ratio as the *sine qua non* of cardiovascular risk, others question its use and consider cholesterol ratios to be better risk indicators. The study by Ingelsson *et al.* attempts to address this issue, but unfortunately it has a number of potential drawbacks.

Firstly, there were only 291 occurrences of the total composite end point, of which only 93 occurred in women who comprised the majority of the study population. Secondly, the definition of the 'composite end point' included CHD events with a diverse range of clinical severities, including angina, myocardial infarction, coronary insufficiency, and CHD-related death. Thirdly, Ingelsson *et al.* did not conduct analyses restricted to hard cardiovascular end points (death and CHD-related death)—probably because there were too few of these events—and did not report mortality data, thus limiting their potential conclusions. Finally, although the authors assessed model discrimination (using the C index), this useful tool cannot overcome methodological issues.¹

In a sense, Ingelsson *et al.*'s findings are in line with the results of other major clinical studies, such as AMORIS,² INTERHEART, ULSAM and MONICA/KORA. All these studies have shown that the apo B:apo A-I ratio is an independent risk predictor for CVD, as supported by a recent meta-analysis.³ Furthermore, elevated apo B:apo A-I ratio is an important feature of the metabolic syndrome in subjects with and without CHD.⁴ In the AMORIS trial,² the apo B:apo A-I ratio was a stronger predictor of CVD than the total cholesterol:HDL-cholesterol ratio, possibly because of a much greater number of fatalities than in the Ingelsson *et al.* study and the fact that the definition of 'cardiovascular events' was not as heterogeneous, allowing appropriate statistical comparisons to be made.⁵

The issue that weakens our overall enthusiasm for the Ingelsson *et al.* paper is the unfortunate

fact that the authors did not stratify their data by age. Total cholesterol and HDL cholesterol are more age-dependant variables than apolipoproteins, and age is by far the most powerful predictor of CVD. Recently, the AMORIS study reported that the superiority of the odds ratio for the apo B:apo A-I ratio over the total cholesterol:HDL-cholesterol ratio for predicting cardiovascular risk became progressively greater as the number of risk factors increased.⁵ Hence, the advantage of the apo B:apo A-I ratio is greatest in populations at highest risk of CVD.⁵ Use of conventional cholesterol ratios rather than the apo B:apo A-I ratio, therefore, results in frequent and substantial errors in the estimation of the lipoprotein-related risk of CVD. Nonetheless, there is an ongoing controversy in the US as to whether the apo B:apo A-I ratio should be included in clinical guidelines.

The evidence opposing the use of the apo B:apo A-I ratio in the paper by Ingelsson *et al.* is far from conclusive. Clearly, there is a need for more-definitive work. In particular, the results of lipid-lowering trials with clearly defined outcome measures will either strengthen or weaken the case for the apo B:apo A-I ratio. The final verdict is still to come.

References

- 1 Pencina MJ and D'Agostino RB (2004) Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* **23**: 2109–2123
- 2 Walldius G *et al.* (2001) High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* **358**: 2026–2033
- 3 Thompson A and Danesh J (2006) Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. *J Intern Med* **259**: 481–492
- 4 Sierra-Johnson J *et al.* (2006) Comparison of apolipoprotein-B/apolipoprotein-AI in subjects with versus without the metabolic syndrome. *Am J Cardiol* **98**: 1369–1373
- 5 Walldius G and Jungner I (2006) The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy—a review of the evidence. *J Intern Med* **259**: 493–519

J Sierra-Johnson is a Research Fellow and RM Fisher is an Associate Professor at Karolinska Institutet, Stockholm, Sweden. Dr Sierra-Johnson holds a dual appointment at the Mayo Clinic, Rochester, MN, USA.

Acknowledgments

The synopsis was written by Alexandra King, Associate Editor, Nature Clinical Practice.

Competing interests

The authors declared no competing interests.

Correspondence

*Atherosclerosis Research Unit
Department of Medicine
Karolinska Institutet
Karolinska University Hospital
S-171 76 Stockholm
Sweden
jusier@ki.se

Received 4 September 2007

Accepted 25 September 2007

Published online

6 November 2007

www.nature.com/clinicalpractice
doi:10.1038/ncpcardio1040

PRACTICE POINT

The data from Ingelsson *et al.* do not justify discarding the apolipoprotein B: apolipoprotein A-I ratio as a predictor of cardiovascular disease