Which should be the goals of apolipoprotein A1? Analysis of a healthy population in Argentina

WALTER MASSON[MTSAC 1], DANIEL SINIAWSKI[MTSAC1], PATRICIA SORROCHE[1], WALTER SCORDO[1]

ABSTRACT

Background
Recent studies have demonstrated that apolipoprotein A1 (ApoA) is a better predictor of cardiovascular risk than HDL-C. However, the definite goals of this new marker have not been clearly defined.

Objective
The objective of this study was to infer the goals of ApoA from a healthy population.

Methods
The distribution of ApoA and HDL-C in 304 blood donors was analyzed according to gender. ApoA goals were assumed using two strategies: 1) a simple linear regression model, and 2) percentile analyses.

Results
In the percentile analyses, ApoA levels of 126 and 147 mg/dL corresponded to recommended goals for HDL-C in men and women, respectively. The linear regression model showed that 40 and 50 mg/dL HDL-C corresponded to 140 and 158 mg/dL ApoA in men and women, respectively.

Conclusion
The findings of this study suggest that previously postulated ApoA goals should be reviewed in both genders.

REV ARGENT CARDIOL 2012;80:XXX-XXX.

Key words > Apolipoproteins - Lipids – Risk factors

Abbreviations >

AApoA:	apolipoprotein A1		**SD:**	standard deviation
HDL-C:	high density lipoprotein cholesterol		**CI:**	confidence interval
ATP III:	Adult Treatment Panel III			

BACKGROUND

Cardiovascular disease is the leading cause of morbimortality. In this context, it is thus very relevant to identify and rectify population risk factors. Although multiple epidemiological studies have demonstrated that HDL-C is inversely and independently associated with the risk of coronary events[1-2], other investigations have suggested that increasing HDL-C values do not necessarily reduce this risk. [3-6] This paradox could be partly explained by the fact that measuring "quantity" is not the same as assessing "quality".[6]

Apolipoprotein A1 (ApoA) is the main HDL protein, reflecting to a great extent the anti-atherogenic ability of HDL-C. In recent years, ApoA has been found to independently predict cardiovascular risk more accurately than conventional lipid measurements.[7-9] However, ApoA goals have not been clearly defined. Previously, we have suggested apolipoproein B goals from LDL-C preestablished therapeutic objectives in a healthy population.[10] Including new patients to this population, a new analysis was performed to obtain ApoA goals, using two strategies: 1) Development of a linear regression between ApoA and HDL-C plasmatic concentrations: 2) Comparison of ApoA percentiles with the corresponding HDL-C goals

already established in the literature.

METHODS

A descriptive-observational transverse study was undertaken in blood samples obtained from consecutive blood donors.

Inclusion criteria: Any subject accepted as blood donor by the hemotherapy department.

Exclusion criteria: 1) prior cardiovascular disease; 2) history of diabetes or hypertension; 3) previous hypolipemic therapy.

ApoA level was measured by kinetic immunonephelometry and HDL-C level was obtained by direct enzymatic method.

A simple linear regression model was performed between ApoA levels and HDL-C concentrations. ApoA percentiles were calculated according to gender and compared with the percentiles corresponding to accepted HDL-C goals (50 mg/dL in women and 40 mg/dL in men).

Continuous data between two groups were analyzed with a t test when variable distribution was normal, or else with the Wilcoxon test. Categorical data were analyzed with a chi-square test. Pearson's correlation coefficient was used to analyze the correlation between HDL-C and ApoA. A p value < 0.05 was considered statistically significant.

The study was performed following the Helsinki Declaration, Good Clinical Practice Guidelines and local ethical committee recommendations for medical research in human subjects.

RESULTS

Data from 304 subjects (with available ApoA and HDL-C levels) were analyzed. Mean age was 42 ± 14 years and 64% were men. Population characteristics are shown in Table 1.

Mean ApoA was 149 ± 32 mg/dL in the overall population. In the analysis according to gender mean ApoA was 141 ± 26 mg/dL in men and 165 ± 37 mg/dL in women (p<0.01).

Twenty fifth, 50th and 75th percentiles for ApoA in men were 123, 138 and 157 mg/dL, while in women the same percentiles were 141, 161 and 184 mg/dL. A good correlation was obtained between ApoA and HDL-C levels (r=0.83).

The cut-off HDL-C plasmatic levels defined by ATP III (Adult Treatment Panel III) as coronary risk factor in men and women (< 40 and < 50 mg/dL, respectively) corresponded to the 30th percentile in both genders. The same percentile for ApoA resulted in 126 and 147 mg/dL in men and women, respectively. Figure 1 shows the comparison between HDL-C and ApoA percentiles in men and women.

The linear regression model between ApoA and HDL-C plasmatic levels shown in Figure 2, revealed that in men 40 mg/dL HDL-C correlated with 140 mg/dL ApoA (ApoA=1.861723 * HDL-C + 65.87143). Similarly, in women 50 mg/dL HDL-C correlated with 158 mg/dL ApoA (ApoA=2.068239 * HDL-C + 54.78753).

DISCUSSION

Measurement of the lipid profile has some limitations. Measuring the plasmatic level of HDL-C does not reflect the biological and functional activity of this

Table 1. General population characteristics (n=304)

Categorical varibales	%
Men	64
Smokers	31
Continuous variables	**mean±SD**
Age, years	42±14
Body mass index, kg/m2	26,20±4,4
Apolipoprotein B, mg/dL	93±40
Apolipoprotein A1, mg/dL	149±32
Total Cholesterol, mg/dL	200±41
LDL-C, mg/dL	128±41
HDL-C, mg/dL	49±13
Triglycerides, mg/dL	112±93

complex lipoprotein. Several epidemiological studies have shown that ApoA is more strongly associated with cardiovascular events than HDL-C.[7-8] One study revealed that the increase in HDL-C adjusted by ApoA and other clinical variables was not associated with a lower rate of coronary events and even, at higher HDL-C values, a positive correlation with coronary risk was observed.[3] Conversely, ApoA preserved the inverse association independently of the its value and the rest of the analyzed variables.

In the American NHANES program, median ApoA in both genders was lower than in our study (133 vs. 138 mg/dL in men y 147 vs. 161 mg/dL in women).[11] Mean ApoA in our study (men 141 ± 26 mg/dL, women 165 ± 37 mg/dL) was near the 75th percentile of that survey. Moreover, mean values obtained in our study were slightly above those reported in a large Swedish study, where mean ApoA was 136 ± 22 mg/dL and 151 ± 24 mg/dL in men and women, respectively.[12]

In our study, HDL-C concentration was also higher than that of other reports with ApoA analysis, such as the Framingham Offsring Study, in which plasma values of 40 and 50 mg/dL corresponded approximately to the 50th percentile. [13] Differences with these reports might be explained by the younger and healthier population used in the present study.

ApoA reference values and goals are not yet well established, limiting the application of this new marker in the clinical context of cardiovascular prevention. Walldius et al proposed ApoA plasmatic levels < 115 mg/dL in men and <125 mg/dL in women as cut-off values associated with greater risk.[14] The new European guidelines for dyslipidemia management suggest values <120 y 140 mg/dL in men and women.[15] In our study, the 30th percentile for HDL-C corresponded approximately to plasmatic levels of 40 and 50 mg/dL, which are minimum goals suggested in the literature for men and women. The same percentile for ApoA resulted in values of 126 and 147 mg/dL in men and women, respectively.

The linear regression analysis showed that ApoA values equivalent to the same HDL-C goals were 140 and 158 mg/dL in men and women, respectively,

Fig. 1. Comparison of increasing HDL-C and ApoA percentiles. The darker columns represent the 30th percentile for HDL-C and ApoA. **A.** In men, the 30th percentile of HDL-C corresponds to the suggested goal (40 mg/dL). The 30th percentile of ApoA corresponds to 126 mg/dL. **B.** In women, the 30th percentile of HDL-C corresponds with the suggested goal (50 mg/dL). The 30th percentile of ApoA corresponds to 147 mg/dL. ApoA: apolipoprotein A1.

HDL-C: High density lipoprotein cholesterol. ApoA: Apolipoprotein A1
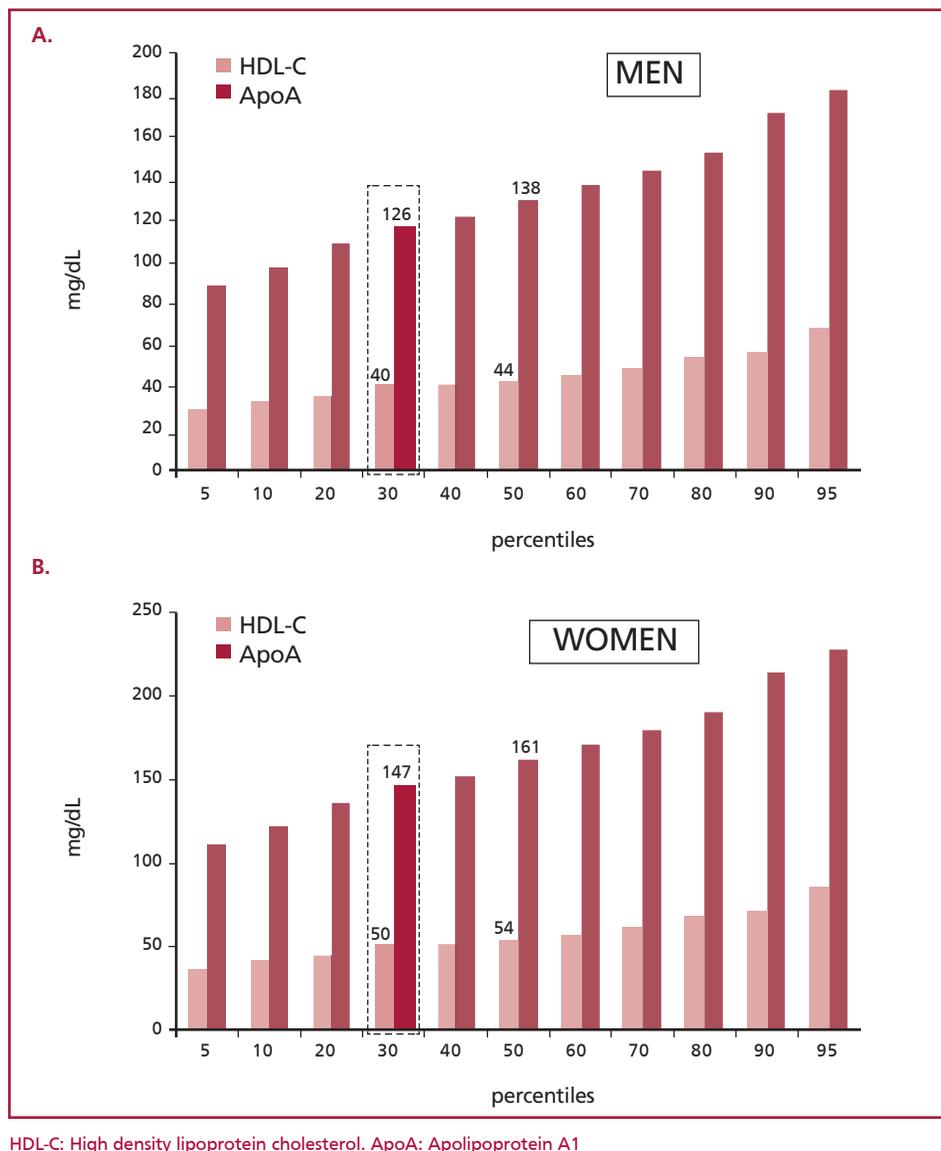
corresponding approximately to the 50th percentile.

It is important to point out that ApoA values obtained by means of both strategies (percentile analysis or linear regression model) were higher than those previously recommended and could be postulated as new lipid goals.

Limitations

A potential limitation of this study could be sample selection bias, since blood donor subjects do not represent the overall population

Assumed ApoA goals are completely empirical and exploratory, and should be tested in studies specially designed for this purpose.

Clinical implications

ApoA values of 126 and 147 mg/dL could be postulated as goals for men and women, respectively. A more ambitious value, greater than 140 or 158 in men and women could be established as an "optimal" goal in cardiovascular prevention.

CONCLUSIONS

The findings of this study suggest that previously postulated ApoA goals should be reviewed. New investigations will help to corroborate these results.

RESUMEN

¿Cuáles deberían ser las metas de apolipoproteína A1? Análisis de una población saludable de la Argentina

Introducción
Estudios recientes demostraron que el nivel de apolipoproteína A1 (ApoA) es un mejor predictor de riesgo cardiovascular que el HDL-C. Sin embargo, las metas definitivas de este nuevo marcador aún no se han definido claramente.

Objetivos
Inferir metas de ApoA analizando una población saludable.

Métodos
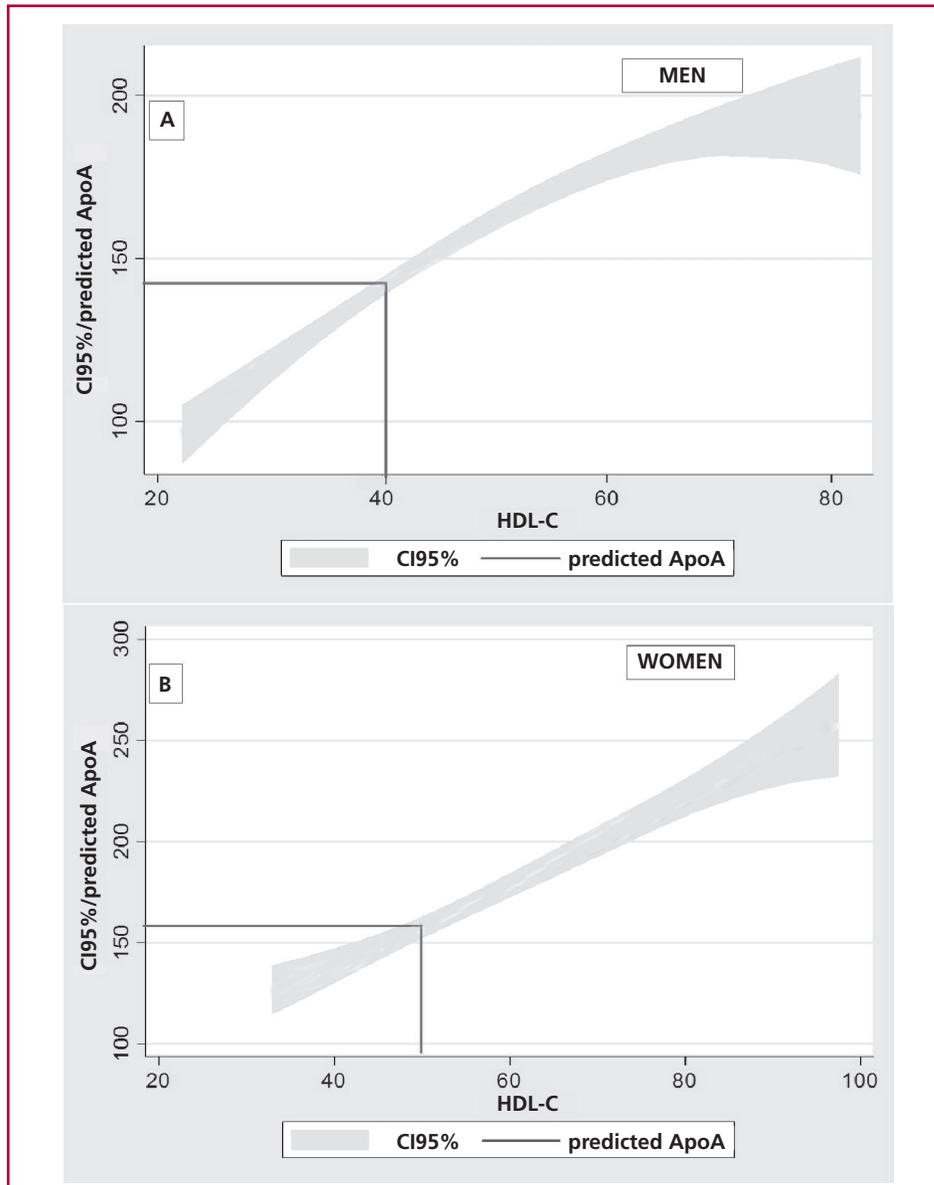Se analizó la distribución de ApoA y HDL-C en 304 donantes

Fig. 2. Linear regression model between ApoA and HDL-C concentrations. **A.** In men, 40 mg/dL HDL-C corresponded to 140 mg/dL ApoA. **B.** In women, 50 mg/dL HDL-C correlated with 158 mg/dL ApoA. ApoA: apolipoprotein A1; CI 95%: 95% confidence interval.se of aspirin inhibits COX-1 occurrence, which is present in new platelets when turnover is increased.

HDL-C: High density lipoprotein cholesterol. ApoA: Apolipoprotein A1. 95% CI: 95% confidence interval

de sangre según el sexo. Se infirieron metas de ApoA mediante dos estrategias: 1) un modelo de regresión lineal y 2) análisis de percentiles.

Resultados
En el análisis de percentiles, valores de ApoA de 126 y 147 mg/dl se correspondieron con metas recomendadas de HDL-C en hombres y mujeres, respectivamente. El modelo de regresión lineal mostró que 40 y 50 mg/dl de HDL-C se correspondieron con 140 y 158 mg/dl de ApoA en hombres y mujeres, respectivamente.

Conclusiones
Los hallazgos del presente estudio sugieren que los valores propuestos previamente como metas de ApoA en ambos sexos deberían revisarse.

Palabras clave > Apolipoproteínas - Lípidos - Factores de riesgo

REFERENCES

1. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et. al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8–15.
2. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA 2007;298:786–98.
3. van der Steeg WA, Holme I, Boekholdt SM, Larsen ML, Lindahl C, Stroes ES, et al. High-Density lipoprotein cholesterol, high density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk. The IDEAL and EPIC-Norfolk studies. J Am Coll Cardiol 2008;51:634-42.
4. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et.al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357:2109-22.
5. Briel M, Ferreira-Gonzalez I, You JJ, Karanicolas PJ, Akl EA, Wu P, et.al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality:

systematic review and meta-regression analysis. BMJ. 2009;338:b92.
6. Ansell BJ. The two faces of the 'good' cholesterol. Cleve Clin J Med. 2007;74:697-705.
7. Walldius G, Jungner I, Holme I, Aastveit AH, Werner Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001; 358:2026–33.
8. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet 2008; 372: 224–33.
9. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. Jounal of Internal Medicine 2006;259:481-92.
10. Siniawski D, Masson W, Bluro I, Sorroche P, Scordo W, Krauss J, et al. Niveles plasmáticos de apolipoproteínas en una población saludable de la Argentina: implicaciones en prevención cardiovascular. Rev Argent Cardiol 2010;78:123-8.
11. Bachorik PS, Lovejoy KL, Carroll MD, Johnson CL. Apolipoprotein B and AI distributions in the United States, 1988–1991: results of the National Health and Nutrition Examination Survey III (NHANES III). Clin Chem 1997;43:2364–78.
12. Jungner I, Marcovina SM, Walldius G, Holme I, Kolar W, Steiner E. Apoliprotein B and A-I values in 147 576 Swedish males and females, standardized according to the World Health Organization-International Federation of Clinical Chemistry First International Reference Materials. Clin Chem 1998; 44:1641-9.
13. ContoIs JH, Macnamara JR, Lammi-Keefe CJ, Wilson PW, Massov T, Schaefer EJ. Reference intervals for plasma apolipoprotein A-I determined with a standardized commercial immune turbidimetric assay: results from the Framingham Offspring Study. Clinical Chemistry 1996;42:507-14.
14. Walldius G, Jungner I. Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. J Intern Med 2004; 255:188–205.
15. Reiner Z, Catapano AL, De Becker G, Graham I, Taskinen MR, Wiklund O, et al. Guía de la ESC/EAS sobre el manejo de las dislipemias. Rev Esp Cardiol. 2011;64:1168:e1-e60.

Declaration of conflict of interest

The authors do not have a conflict of interests.