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Editorial

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# Apolipoprotein A2 Isoforms: New Insight into the Risk of Myocardial Infarction

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Apolipoproteins, which are located in a cholesterol-containing phospholipid monolayer on the particle surface, confer structural integrity to high-density lipoprotein (HDL) assembly and direct its metabolism by binding to lipid transporters, lipid transfer proteins, lipophilic enzymes, and lipoprotein receptors[1]. Apolipoprotein A2 (ApoA2) is the second most abundant protein in HDL particles, accounting for ~20% of total HDL protein[2]. Similar to the most abundant HDL protein, apolipoprotein A1 (ApoA1), ApoA2 contains a tandem array of amphipathic helices. The cardioprotective action of ApoA1 is well-established and largely related to its key role in reverse cholesterol transport[3]. However, the role of ApoA2 is less clear, particularly regarding whether it is an antiatherogenic or proatherogenic protein, with data from experimental studies[4, 5] and epidemiological studies[6, 7] concerning its pathophysiological role not being in agreement. A patient with an ApoA2 deficiency has been previously described[8]. This deficiency seems to have little influence on the lipid and lipoprotein profiles and the occurrence of coronary artery disease, suggesting that the role of ApoA2 may be redundant with that of the other exchangeable apolipoproteins, such as ApoA1[9].

There is undoubtedly significant functional redundancy between the different exchangeable types of apolipoproteins[9]. Owing to their close protein homology and genetic relatedness[2], each apolipoprotein may have evolved to also have a unique function. Investigating the separate structural isoforms of ApoA2 may thus lead to a better understanding of the specific pathophysiological role of ApoA2. In this issue of Journal of Atherosclerosis and Thrombosis, Kihara *et al.*[10] conducted a nested case-control study from the Japan Public Health Center-based Study (JPHC Study) to test the hypothesis that the levels of three major ApoA2 isoforms (ApoA2-ATQ/ATQ, ApoA2-ATQ/AT, and ApoA2-AT/AT) are inversely associated with the risk of myocardial infarction. Although a novel sandwich enzyme-linked immunosorbent assay provides for robust and rapid analysis of these ApoA2 isoforms, few studies have investigated their association with cardiovascular disease risk. In the present study, the authors found that one of the ApoA2 isoforms (ApoA2-AT/AT) was inversely associated with risk of myocardial infarction in a crude model, but the association became statistically insignificant after adjustment for traditional cardiovascular risk factors. Thus, the authors concluded that none of the three ApoA2 isoforms showed any significant associations with the risk of myocardial infarction.

The strength of the present study is that the authors reported an association of ApoA2 isoforms with the risk of myocardial infarction for the first time. Although the effect of three major isoforms of ApoA2 was evaluated based on the risk of myocardial infarction, total ApoA2 concentrations or other ApoA2 isoforms (ApoA2-AT/A and ApoA2-A/A) and their associations with the risk of myocardial infarction remain unclear in the present study. The nested case-control study design and its limited sample size may be the reasons for the absence of significant associations between ApoA2 isoforms and myocardial infarction risk. There has been continued uncertainty about the relationship between ApoA2 levels and risk of cardiovascular diseases; thus, the present findings clearly do not support previous controversies regarding

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potential anti- or pro-atherogenic effects of ApoA2, which warrants further investigation.

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## Conflict of Interest

None.

## References

1) Lund-Katz S and Phillips MC: High density lipoprotein structure-function and role in reverse cholesterol transport. Subcell Biochem, 2010; 51: 183-227
2) Segrest JP, Garber DW, Brouillette CG, Harvey SC and Anantharamaiah GM: The amphipathic alpha helix: a multifunctional structural motif in plasma apolipoproteins. Adv Protein Chem, 1994; 45: 303-369
3) Curtiss LK, Valenta DT, Hime NJ and Rye KA: What is so special about apolipoprotein AI in reverse cholesterol transport? Arterioscler Thromb Vasc Biol, 2006; 26: 12-19
4) Johnson WJ, Kilsdonk EP, van Tol A, Phillips MC and Rothblat GH: Cholesterol efflux from cells to immunopurified subfractions of human high density lipoprotein: LP-AI and LP-AI/AII. J Lipid Res, 1991; 32: 1993-2000
5) Warden CH, Hedrick CC, Qiao JH, Castellani LW and Lusis AJ: Atherosclerosis in transgenic mice overexpressing apolipoprotein A-II. Science, 1993; 261: 469-472
6) Birjmohun RS, Dallinga-Thie GM, Kuivenhoven JA, Stroes ES, Otvos JD, Wareham NJ, Luben R, Kastelein JJ, Khaw KT and Boekholdt SM: Apolipoprotein A-II is inversely associated with risk of future coronary artery disease. Circulation, 2007; 116: 2029-2035
7) Xiao J, Zhang F, Wiltshire S, Hung J, Jennens M, Beilby JP, Thompson PL, McQuillan BM, McCaskie PA, Carter KW, Palmer LJ and Powell BL: The apolipoprotein AII rs5082 variant is associated with reduced risk of coronary artery disease in an Australian male population. Atherosclerosis, 2008; 199: 333-339
8) Deeb SS, Takata K, Peng RL, Kajiyama G and Albers JJ: A splice-junction mutation responsible for familial apolipoprotein A-II deficiency. Am J Hum Genet, 1990; 46: 822-827
9) Remaley AT: Apolipoprotein A-II: still second fiddle in high-density lipoprotein metabolism? Arterioscler Thromb Vasc Biol, 2013; 33: 166-167
10) Kihara T, Yamagishi K, Honda K, Ikeda A, Yatsuya H, Saito I, Kokubo Y, Yamaji T, Shimazu T, Sawada N, Iwasaki M, Iso H, Tsugane S; for the JPHC Study Group: Apolipoprotein A2 Isoforms in Relation to the Risk of Myocardial Infarction: A Nested Case-Control Analysis in the JPHC Study. J Atheroscler Thromb, 2021; 28: 483-490