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Apolipoprotein(a) Isoforms and the Risk of Vascular Disease

Systematic Review of 40 Studies Involving 58,000 Participants

Sebhat Erqou, MD, PHD,* Alexander Thompson, PHD,* Emanuele Di Angelantonio, MD, PHD,* Danish Saleheen, MBBS, MPHIL,* Stephen Kaptoge, MSC, PHD,* Santica Marcovina, PHD, DSC,† John Danesh, DPHIL*

Cambridge, United Kingdom; and Seattle, Washington

Objectives The purpose of this study was to assess the association of apolipoprotein(a) (apo[a]) isoforms with cardiovascular disease risk.

Background Although circulating lipoprotein(a) (Lp[a]) is likely to be a causal risk factor in coronary heart disease (CHD), the magnitude of this association is modest. Lipoprotein(a) particles with smaller, rather than larger, apo(a) isoforms may be stronger risk factors.

Methods Information was collated from 40 studies published between January 1970 and June 2009 that reported on associations between apo(a) isoforms and risk of CHD or ischemic stroke (involving a total of 11,396 patients and 46,938 controls).

Results Thirty-six studies used broadly comparable phenotyping and analytic methods to assess apo(a) isoform size. These studies yielded a combined relative risk for CHD of 2.08 (95% confidence intervals [CI]: 1.67 to 2.58) for individuals with smaller versus larger apo(a) isoforms (corresponding approximately to 22 or fewer kringle IV type 2 repeats vs. >22 repeats or analogously an apo[a] molecular weight of <640 kDa vs. ≥640 kDa). There was substantial heterogeneity among these studies (I^2 = 85%, 80% to 89%), which was mainly explained by differences in the laboratory methods and analytic approaches used. In the 6 studies of ischemic stroke that used comparable phenotypic methods, the combined relative risk was 2.14 (1.85 to 2.97). Overall, however, only 3 studies made allowances for Lp(a) concentration.

Conclusions People with smaller apo(a) isoforms have an approximately 2-fold higher risk of CHD or ischemic stroke than those with larger proteins. Further studies are needed to determine whether the impact of smaller apo(a) isoforms is independent from Lp(a) concentration and other risk factors. (J Am Coll Cardiol 2010;55:2160–7)

Lipoprotein(a) (Lp[a]) is composed of a low-density lipoprotein (LDL) particle and a glycoprotein molecule known as apolipoprotein(a) (apo[a]) (1). Apolipoprotein(a) is structurally homologous to plasminogen and is responsible for the unique properties of Lp(a) (1,2). A collaborative analysis of individual data from 36 prospective studies, involving more than 126,000 individuals, has demonstrated that circulating Lp(a) concentration is continuously associated with risk of coronary heart disease (CHD) and stroke independent from several conventional risk factors (including total cholesterol) (3). The likelihood that Lp(a) is causally relevant to vascular disease risk has been increased by reports of highly significant associations of Lp(a)-related genetic variants with CHD risk (4–9). However, because the risk with Lp(a) concentration is only about one-quarter

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From the *Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; and the †Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, Washington. Dr. Erqou has been supported by the Gates Cambridge Trust. Drs. Erqou and Thompson have received consultancy payments from GlaxoSmithKline. Drs. Thompson and Di Angelantonio have been supported by UK Medical Research Council doctoral training grants. Dr. Saleheen has been supported by the Yousef Jameel Foundation. Dr. Danesh has received research funding from the British Heart Foundation, BUPA Foundation, diaDexus, European Union, Evelyn Trust, Fogarty International Center, GlaxoSmithKline, Medical Research Council, Merck Sharp and Dohme, National Heart, Lung and Blood Institute, National Institute of Neurological Disorders and Stroke, Novartis, Roche, UK Biobank, and Wellcome Trust.

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of that seen with LDL cholesterol (3), any clinical implications of this moderate association currently appear limited. Such considerations could change if specific Lp(a) subtypes were shown to confer importantly higher vascular risks. In particular, it has been proposed that Lp(a) particles with smaller apo(a) isoforms may be more pathogenic because they appear to have: 1) increased capacity to bind oxidized phospholipids; 2) greater propensity to localize in blood vessel walls through increased lysine-binding ability and interaction with fibrin; and 3) greater thrombogenic effect through increased inhibition of plasmin activity (10–13). It has also been suggested that smaller apo(a) isoforms may act synergistically with other factors such as small-dense LDL and oxidized LDL particles (10,13–15). The basis for apo(a) size heterogeneity relates to a copy-number variation in one of its protein domains, kringle IV type 2 (KIV_2), which exists in 5 to 50 identically repeated copies. This copy-number variation confers marked heterogeneity in the molecular mass of apo(a) isoforms, which can range between 200 and 800 kDa (Table 1) (1,16,17). Apolipoprotein(a) is encoded by the *LPA* gene, which contains a 5.6-kb segment existing in multiple repeats (KIV_2 repeat polymorphism) that is responsible for the apo(a) isoform variation (2,18).

Many studies (19–23) have reported on the association of apo(a) isoform size variations with the risk of vascular disease. Although they have reported apparently divergent relative risks (RRs), these studies have tended to be small and to involve wide confidence intervals. Their interpretation has been complicated by differences in relation to: 1) populations studied (e.g., people of European, Asian, or African ancestry) because apo(a) characteristics tend to vary by ethnicity (24); 2) methods used to measure apo(a) isoforms (e.g., genotypic vs. phenotypic methods, and among the latter, quantitative vs. semiquantitative approaches); 3) vascular disease outcomes recorded (e.g., myocardial infarction [MI], coronary stenosis, stroke); and 4) analytic approaches used (e.g., different cut-offs chosen to define smaller apo[a] size). Studies have also differed in adjustments for covariates, particularly in relation to circulating Lp(a) concentration, higher levels of which tend to be associated with smaller apo(a) isoforms (4,25,26).

Table 1 Relationship Between Various Approaches Used to Express apo(a) Isoform Sizes

Apo(a) Isoform Size Expressed as		
No. of KIV_2 Repeats	Gel Migration Speed	Molecular Weight
11–13	F	<400 kDa
14–16	B	460 kDa
17–19	S1	520 kDa
20–22	S2	580 kDa
23–25	S3	640–655 kDa
>25	S4	>700 kDa

For gel migration speed, F = mobility faster than apolipoprotein-B_{100} ($apoB_{100}$), B = mobility equal to $apoB_{100}$, and S1–S4 = different levels of mobility slower than $apoB_{100}$. Relevant references are provided in the Online Appendix.

apo(a) = apolipoprotein(a); KIV_2 = kringle IV type 2.

To help clarify the evidence, we have conducted a systematic review and meta-analysis of 40 relevant studies of apo(a) isoforms and coronary and ischemic stroke outcomes that involved a total of 11,396 cases and 46,938 controls.

Abbreviations and Acronyms

apo(a) = apolipoprotein(a)
CHD = coronary heart disease
KIV_2 = kringle IV type 2
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
MI = myocardial infarction
RR = relative risk

Methods

Study selection. Studies published between January 1970 and June 2009 that reported on associations between apo(a) isoforms and coronary or stroke outcomes were identified by systematic searches of MEDLINE, scanning of the reference lists of original reports, and discussions with investigators. Electronic searches used MeSH terms and free text related to vascular disease and apo(a) isoforms (e.g., "cardiovascular" [MeSH], "lipoprotein(a)" [MeSH], "protein isoforms" [MeSH], "apolipoprotein(a)," "isoforms," "coronary heart disease," and "stroke"). Studies were eligible for inclusion if they: 1) were broadly population based (i.e., did not select participants or controls on the basis of preexisting comorbidities or cardiovascular risk factors (such as end-stage renal disease, diabetes, or high LDL cholesterol levels); 2) had used a well-described assay to measure apo(a) isoforms; 3) recorded CHD (defined as MI, angina, coronary stenosis, or revascularization) or ischemic stroke outcomes using accepted criteria (i.e., MI using World Health Organization or similar criteria, coronary stenosis using quantitative angiography and typically defined as at least 1 coronary artery with ≥50% coronary stenosis, or ischemic stroke using brain imaging); and 4) provided findings that could be used to calculate an odds ratio for vascular disease. Retrospective and cross-sectional study designs were eligible for inclusion because apo(a) isoforms are determined by copy-number variation in the *LPA* gene (1,2) and are therefore unlikely to be altered by prevalent vascular disease. In cases of apparent duplicate publication, investigators were contacted to confirm whether such studies contained unique participants (lack of reply led to use of the report with the greatest number of participants). Forty unique studies were included (Fig. 1).

Data extraction. The following information was extracted from each article using a standardized abstraction form: study population (including population source and the sampling method employed), geographic location, year of baseline survey, age range of participants at baseline, percentage of male participants, mean duration of follow-up (for prospective studies), vascular disease outcome definition, assay methods and standards used, type of blood sample used, mean apo(a) isoform size and Lp(a) concentration, RR estimates for CHD or ischemic stroke, cut-off level used to categorize apo(a) isoforms as smaller or larger, and degree of statistical adjustment for any potential confounders used (+ = no adjustment; ++ = adjustment for age, sex, and