Is Lipoprotein(a) Ready for Prime-Time Use in the Clinic?

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KEYWORDS

• Lipoprotein(a) • Atherosclerotic cardiovascular disease • Pharmacotherapy • Risk assessment • Models of care

KEY POINTS

- Lipoprotein(a), a polymorphic lipoprotein, is a potent heritable risk factor for atherosclerotic cardiovascular disease and aortic stenosis.
- The causal role for lipoprotein(a) in atherosclerotic cardiovascular disease is well-supported by genetic, epidemiologic, and experimental studies.
- Several therapies can lower Lipoprotein(a), but none have been tested for their effects on cardiovascular disease outcomes in patients selected for having elevated plasma Lipoprotein(a).
- There is only a moderate level of evidence supporting routine screening for elevated Lipoprotein(a), but conditional recommendations can be made for testing certain groups of patients.
- Whether Lipoprotein(a) remains a risk factor for atherosclerotic cardiovascular disease after low-density lipoprotein cholesterol is decreased to very low levels remains an issue.

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like particle covalently bound to a hydrophilic glycoprotein called apolipoprotein(a) [apo(a)] that is under potent genetic control. Plasma levels of Lp(a) vary by up to 1000-fold among individuals, with 1 in 4 having levels that may increase the risk of atherosclerotic cardiovascular disease (ASCVD; **Fig. 1**).[1] Several new sources of evidence support a causal role for Lp(a) in (ASCVD) and aortic valve stenosis (reviewed in[2]). Individuals with elevated Lp(a) have a high life-time burden of ASCVD. This notion is important for coronary prevention. However, is Lp(a) ready for prime-time use in coronary prevention clinics?

BIOLOGY AND EPIDEMIOLOGY OF LIPOPROTEIN(a)

For full details of this topic the reader is referred to a recent review.[2] The structure of the Lp(a) particle is shown in **Fig. 2**. The LDL-like moiety contains 1 apoB-100 molecule indistinguishable from LDL per se, with apo(a) linked to apoB-100 by a single disulphide bond.[3] The apo(a) gene (*LPA*) has sequence homology with plasminogen.[4] Plasma Lp(a) concentration and isoform size are highly heritable, and largely determined by genetic variation in the *LPA* gene. The kringle 4 type-2 (KIV_2) copy number variant gives rise to at least 40 different sized apo(a) isoforms and explains on average between 30% and 70% of the variation in Lp(a) concentration. Mendelian randomization and genome-wide association studies

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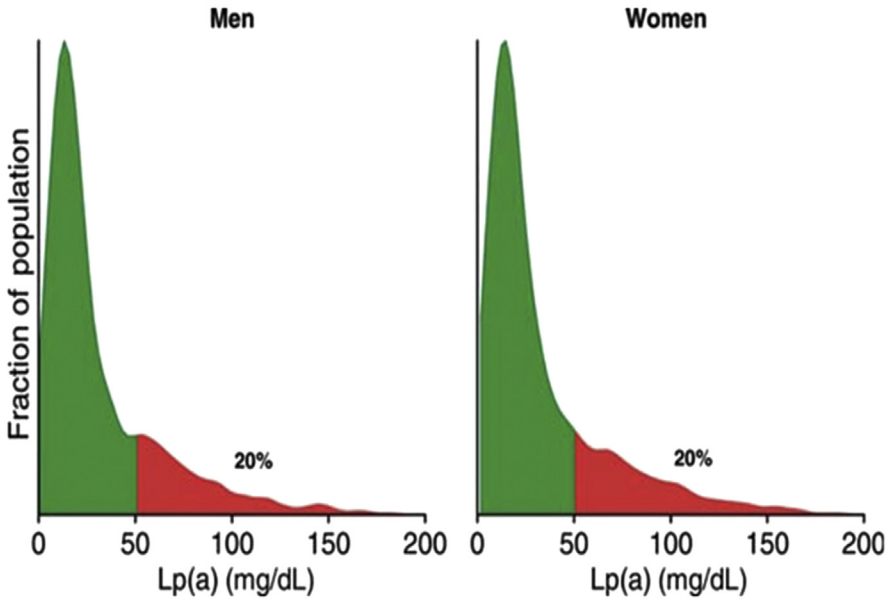

Fig. 1. The population distribution of serum lipoprotein(a) (Lp[a]) concentrations. Levels are positively skewed, with approximately 20% of individuals have elevated Lp(a) of 50 mg/dL or greater. (*From* Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010;31(23):2845; with permission.)

have elucidated the role of Lp(a) in ASCVD and aortic stenosis.[2] Although the main site of Lp(a) catabolism is the liver, several distinct cellular receptors have been proposed to mediate Lp(a) clearance, including the LDL receptor (LDLR) and other members of the LDLR family, scavenger receptor class B type 1

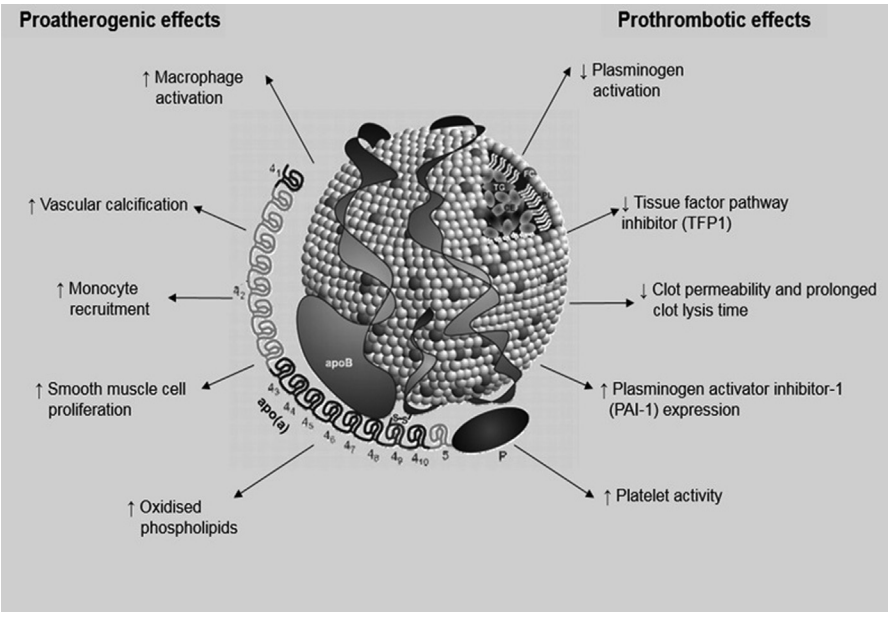

Fig. 2. Structure and pathobiology of lipoprotein(a) (Lp[a]). Lp(a) consists of a low-density lipoprotein (LDL)-like moiety bound to apo(a). Apo(a) contains 10 types of KIV, followed by a kringle 5-linke sequence (KV) and an inactive protease-like domain (P). The number of kringle 4 type-2 repeats determines Lp(a) isoform size. Many potential pathogenic effects have been ascribed to Lp(a), largely from in vitro studies, and almost all of which have been directly ascribed to apo(a). The majority of these functions must be considered speculative at present. (*From* Boffa MB, Koschinsky ML. Update on lipoprotein(a) as a cardiovascular risk factor and mediator. Curr Atheroscler Rep 2013;15(10):360; with permission.)