




# Relationship between lipoproteins, thrombosis, and atrial fibrillation

Wern Yew Ding <sup>1†</sup>, Majd B. Proty <sup>2†</sup>, Ian G. Davies <sup>3</sup>, and Gregory Y.H. Lip<sup>1,4\*</sup>

<sup>1</sup>Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, UK; <sup>2</sup>Systems Immunity University Research Institute, Cardiff University, Cardiff, UK; <sup>3</sup>Research Institute of Sport and Exercise Science, Liverpool John Moores University, Liverpool, UK; and <sup>4</sup>Department of Clinical Medicine, Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark

Received 21 October 2020; revised 14 December 2020; accepted 12 January 2021; online publish-ahead-of-print 23 January 2021

## Abstract

The prothrombotic state in atrial fibrillation (AF) occurs as a result of multifaceted interactions, known as Virchow's triad of hypercoagulability, structural abnormalities, and blood stasis. More recently, there is emerging evidence that lipoproteins are implicated in this process, beyond their traditional role in atherosclerosis. In this review, we provide an overview of the various lipoproteins and explore the association between lipoproteins and AF, the effects of lipoproteins on haemostasis, and the potential contribution of lipoproteins to thrombogenesis in AF. There are several types of lipoproteins based on size, lipid composition, and apolipoprotein category, namely: chylomicrons, very low-density lipoprotein, low-density lipoprotein (LDL), intermediate-density lipoprotein, and high-density lipoprotein. Each of these lipoproteins may contain numerous lipid species and proteins with a variety of different functions. Furthermore, the lipoprotein particles may be oxidized causing an alteration in their structure and content. Of note, there is a paradoxical inverse relationship between total cholesterol and LDL cholesterol (LDL-C) levels, and incident AF. The mechanism by which this occurs may be related to the stabilizing effect of cholesterol on myocardial membranes, along with its role in inflammation. Overall, specific lipoproteins may interact with haemostatic pathways to promote excess platelet activation and thrombin generation, as well as inhibiting fibrinolysis. In this regard, LDL-C has been shown to be an independent risk factor for thromboembolic events in AF. The complex relationship between lipoproteins, thrombosis and AF warrants further research with an aim to improve our knowledge base and contribute to our overall understanding of lipoprotein-mediated thrombosis.

## Keywords

Atrial fibrillation • Lipids • Lipoproteins • Low-density lipoprotein • Very low-density lipoprotein • High-density lipoprotein • Oxidized lipoprotein • Lipoprotein(a) • Incidence • Haemostasis • Thrombosis • Thromboembolism • Stroke

## 1. Introduction

Atrial fibrillation (AF) is a multi-systemic condition that is associated with serious complications including thromboembolism, dementia, and heart failure, resulting in impaired quality of life, significant morbidity, and increased mortality.<sup>1–5</sup> The prevalence of AF rises with age and concomitant comorbidities.<sup>6,7</sup> At present, there is an upward trajectory to the global incidence and prevalence of AF.<sup>8,9</sup> Indeed, every individual has a one-in-four lifetime risk of developing this condition,<sup>10,11</sup> with a greater burden amongst those with risk factors.<sup>12</sup> By 2060, it is projected that at least 17.9 million people in Europe will be affected by AF.<sup>13,14</sup>

The mechanism by which AF occurs is complex but has previously been described in detail.<sup>15</sup> Management of patients with the condition is primarily focused on the prevention of thromboembolism due to the presence of a prothrombotic state with this arrhythmia. The prothrombotic or hypercoagulable state in AF occurs as a result of multifaceted interactions, known as Virchow's triad of hypercoagulability, structural abnormalities, and blood stasis.<sup>16</sup> Despite considerable research in this area, the precise mechanisms by which AF contributes to a prothrombotic state remains ill-defined.

There is emerging evidence that lipoproteins are implicated in thrombogenesis, beyond their traditional role in atherosclerosis. In this review,

<sup>†</sup> These authors are Joint first authors.

\* Corresponding author. Tel: +44 0151 794 9020, E-mail: gregory.lip@liverpool.ac.uk

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

we provide an overview of the various lipoproteins and explore their relationship with AF, haemostasis, and the potential contribution to thrombogenesis.

## 2. Lipoproteins

Lipids (also known as ‘fat’) are naturally occurring compounds serving numerous biological functions including the formation of plasma membranes or signalling molecules, and as a source of energy. They exist in several forms including free fatty acids, glycerolipids (GL), glycerophospholipids (GPL), sphingolipids, and sterol lipids. Each of these lipid subtypes have different molecular structures and basic properties (Figure 1). As a brief overview, fatty acids form the fundamental category of biological lipids and therefore the basic building blocks of more complex lipids. Their chemistry consists of a hydrocarbon chain with a terminal carboxylic acid group and may be defined as saturated or unsaturated depending on the maximum possible number of bonds or hydrogen atoms.<sup>17,18</sup> GL consist of a single glycerol molecule which acts as the backbone for attachment to fatty acid chains. The most relevant example of GL are triglycerides (TG), which contain three fatty acid chains and play an important role in metabolism as energy sources and sources of dietary fat.<sup>18,19</sup> Sterol lipids consist of four fused rings of hydrocarbon to which other molecules attach. A major type of sterol lipid is cholesterol which serves as a precursor for the synthesis of other steroids as well as serving as structural support for plasma membranes.<sup>20,21</sup> Dietary cholesterol is often stored and transported in the form of a cholesterol ester (CE), which chemically represents a cholesterol molecule joined to a fatty acid via an ester bond.<sup>22</sup>

One common feature that lipids share as a group is their insolubility in water. Consequently, they must be transported with proteins in the circulation (‘lipoproteins’).<sup>23</sup> Lipoproteins are complex structures consisting of a central hydrophobic core primarily composed of CE and TG which is surrounded by a hydrophilic membrane comprising of GPL, free cholesterol, and apolipoproteins.<sup>23,24</sup> There are several types of lipoproteins based on size, lipid composition, and apolipoprotein category, namely: chylomicrons, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), intermediate-density lipoprotein, and high-density lipoprotein (HDL). When elevated, all lipoproteins confer a pro-atherogenic risk, apart from HDL which is anti-atherogenic.<sup>23</sup> Each lipoprotein contains numerous types of lipid species and proteins, whose composition varies even between individual lipoproteins of the same type (Figure 2).

LDL is the main transporter for cholesterol in the circulation and every LDL particle contains one apolipoprotein B100 molecule. LDL exists in a spectrum that varies in size and density with the three major density subclasses being small dense LDL (sdLDL), intermediate LDL, and large buoyant LDL.<sup>25</sup> Small dense LDLs are considered more atherogenic and pro-coagulant compared to the other subtypes of LDL for various features as they have decreased affinity for LDL receptors and hence remain longer in the circulation, more readily enter the arterial intima where they are engulfed by macrophages to become foam cells, and are more susceptible to oxidation than its larger counterpart.<sup>26–28</sup> There is also increasing evidence that the number of ApoB-rich particles or the concentration of apolipoprotein B may contribute to atherogenic risk.<sup>29</sup>

Modern lipidomic techniques, with the aid of liquid chromatography coupled to mass spectrometry, have allowed for detailed characterization of the LDL lipidome.<sup>30</sup> This has revealed over 300 different lipid species residing within the interior or phospholipid membrane of the LDL

particle. Each of these may have specific associations with various pathologies and interactions with traditional risk factors, thereby adding to its complexities.<sup>31,32</sup> Oxidative modification of LDL, predominantly by non-enzymatic processes, leads to the formation of oxidized LDL (OxLDL) particles. These particles have altered structure and content, containing oxidized proteins and lipids (particularly GPL), and leading to a more atherogenic phenotype.<sup>33</sup> Furthermore, the susceptibility of LDL to aggregation and proteoglycan binding has provided a deeper insight into the atherogenicity of LDL.<sup>34</sup>

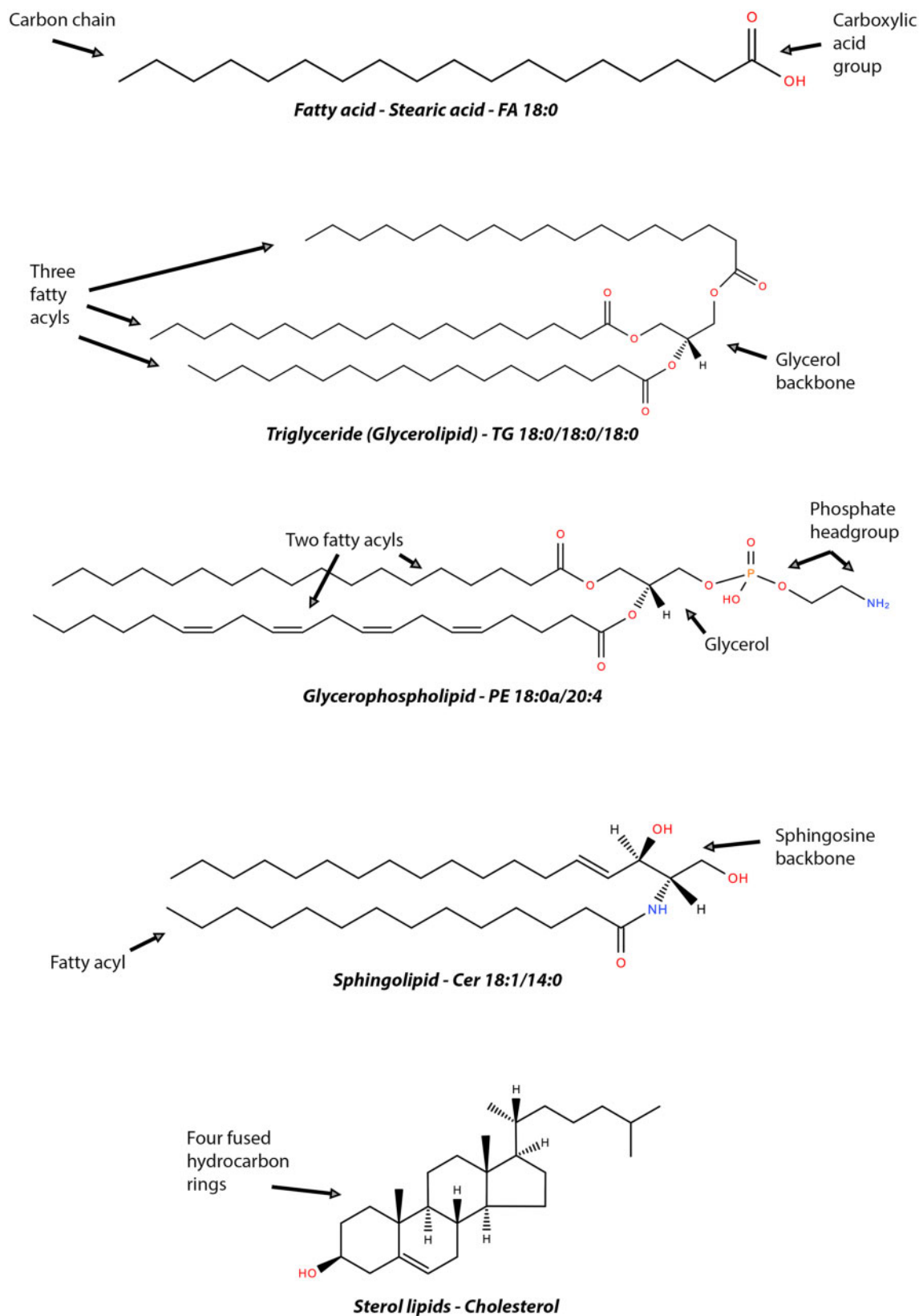
Lipoprotein(a) [Lp(a)] is a specialized form of LDL assembled in the liver from LDL and apolipoprotein(a) attached to apolipoprotein B100 via a disulphide bridge (Figure 2).<sup>35</sup> Lp(a) has been implicated in atherogenesis by enhancing endothelial cell adhesion and molecule expression, promoting the formation of foam cells by binding to macrophages with high affinity and interfering with vascular permeability.<sup>36</sup> Furthermore, the Lp(a) constituent, apolipoprotein(a), shares many structural similarities with plasminogen which has been reported to cause interference with the physiological fibrinolysis process and to contribute to a pro-thrombotic phenotype.<sup>37</sup>

## 3. Lipoproteins and atrial fibrillation

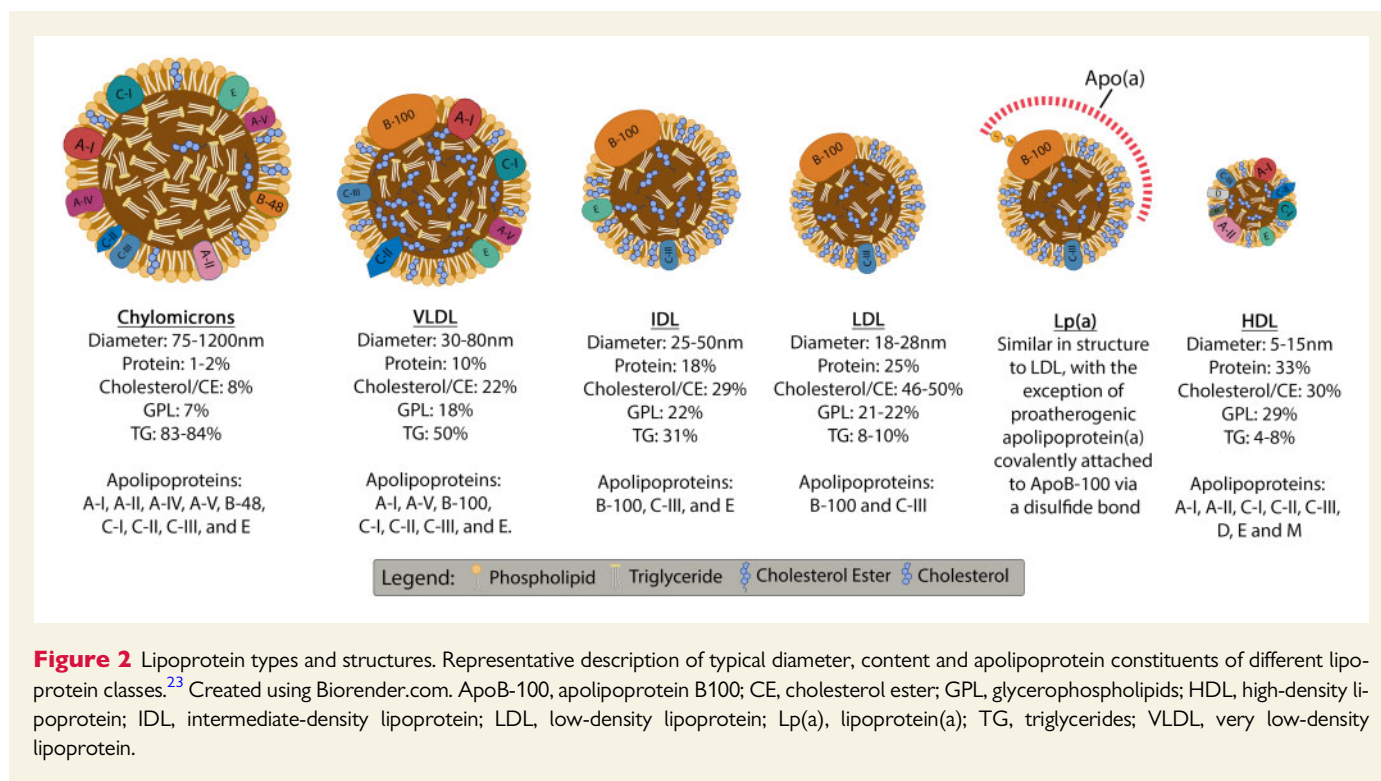
### 3.1 The paradoxical inverse relationship between cholesterol and the incidence of AF

The association between serum cholesterol and coronary heart disease has been described since early 1964.<sup>38</sup> There is an increased risk of coronary heart disease with elevated total cholesterol (TC) and LDL cholesterol (LDL-C), and reduced HDL cholesterol (HDL-C) levels.<sup>39,40</sup> A longitudinal analysis over a 35-year period of patients from the Framingham study confirmed that long-term exposure to these lipid abnormalities led to a greater risk of atherosclerotic cardiovascular disease and mortality.<sup>41</sup> Moreover, both the LDL particle and LDL-C are now considered causal for atherosclerotic cardiovascular disease.<sup>42</sup> In turn, atherosclerotic disease is an established independent risk factor for incident AF.<sup>43,44</sup> As such, elevated levels of TC and LDL-C may have been expected to increase the risk of incident AF. However, current evidence does not support this and in contrast, several well-conducted observational studies have described a paradoxical inverse relationship between TC and LDL-C, and incident AF (Table 1).

A health survey performed by Iguchi *et al.*<sup>61</sup> found that hypercholesterolaemia, defined by TC >220 mg/dL or the use of cholesterol-lowering agents, was related to reduced new-onset AF. Reduced levels of LDL-C has also been linked to increased prevalence of AF.<sup>56</sup> In one study of 88 785 patients, for example, TC and LDL-C levels were inversely linked to incident AF over a follow-up period of 7 years.<sup>48</sup> The authors reported no significant association between incident AF, and HDL-C or TG. However, the overall incidence of AF was extremely low at 0.52 per 1000 person-years.<sup>48</sup> Similar findings were described in the ARIC (Atherosclerosis Risk in Communities) cohort which was validated even when analysing lipid levels as time-dependent variables.<sup>59</sup> An ancillary study to ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) demonstrated that low HDL-C was associated with a significant increase in incident AF.<sup>62</sup> In a Japanese cohort, Watanabe *et al.*<sup>60</sup> also found that both TC and LDL-C were inversely related to incident AF. Furthermore, reduced levels of HDL-C was



**Figure 1** Representative schematic of lipid subtypes. Example structures from each LIPID MAPS category of lipids are shown in this figure highlighting their structural features. Fatty acids (FA), which may be saturated or unsaturated, form the basic building blocks of lipids, with each class having specific defining feature. Chemical structures are from PubChem and LIPID MAPS.



independently associated with greater incidence of AF in females, but not males. The former had a 28% higher risk of AF with each 10% decrease in HDL-C. Results from the SPCCD (Swedish Primary Care Cardiovascular Database) showed that each unit (mmol/L) increase in TC and LDL-C were associated with a 19% and 16% lower risk of incident AF, respectively; also, HDL-C and TG were not related to incident AF. In contrast to the previous study, Mourtzin *et al.*<sup>49</sup> found no sex-specific differences in outcomes based on lipid abnormalities.

The relationship (or lack of) between the aforementioned measures of lipid abnormalities and incident AF has also been demonstrated among patients with ST-elevation myocardial infarction<sup>46</sup> and chronic heart failure.<sup>50</sup> In a small study of patients who had AF ablation, TC and LDL-C were inversely associated with a higher risk of AF recurrence.<sup>65</sup> However, subgroup analysis demonstrated that these factors were only significant in females but not males. The levels of HDL-C and TG were not related to AF recurrence post-ablation.<sup>65</sup> The inverse relationship between AF, and TC and LDL-C are further supported by the fact that use of lipid-lowering medications does not reduce the risk of incident AF.<sup>59,66</sup>

It is worth noting that conflicting results have been demonstrated in few studies. A combined analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) and Framingham Heart Study cohorts found that raised HDL-C and TG were independently associated with a lower risk of new-onset AF.<sup>57</sup> However, the authors reported that TC and LDL-C were not important risk factors for new-onset AF. In a community-based cohort of Korean males, Kim *et al.*<sup>52</sup> found that although the presence of metabolic syndrome led to greater incidence of AF over a follow-up period of 8.7 years, this was driven primarily by central obesity, and neither TG or HDL-C were risk factors for incident AF. Similar results were obtained from a historical Japanese population.<sup>53</sup>

Different study designs, populations, lifestyles and age ranges may partly explain some of the inconsistencies of previous studies.

Nonetheless, the current literature strongly indicates that both TC and LDL-C have an inverse relationship with incident AF. This is supported by a recent meta-analysis of nine large cohort studies.<sup>67</sup> Overall, these findings are important as they imply that a reduction in TC and LDL-C, may have unintended consequences for the risk of incident AF. The role of TG and HDL-C, and whether there are sex-specific responses to lipid abnormalities with regards to AF need further investigation.

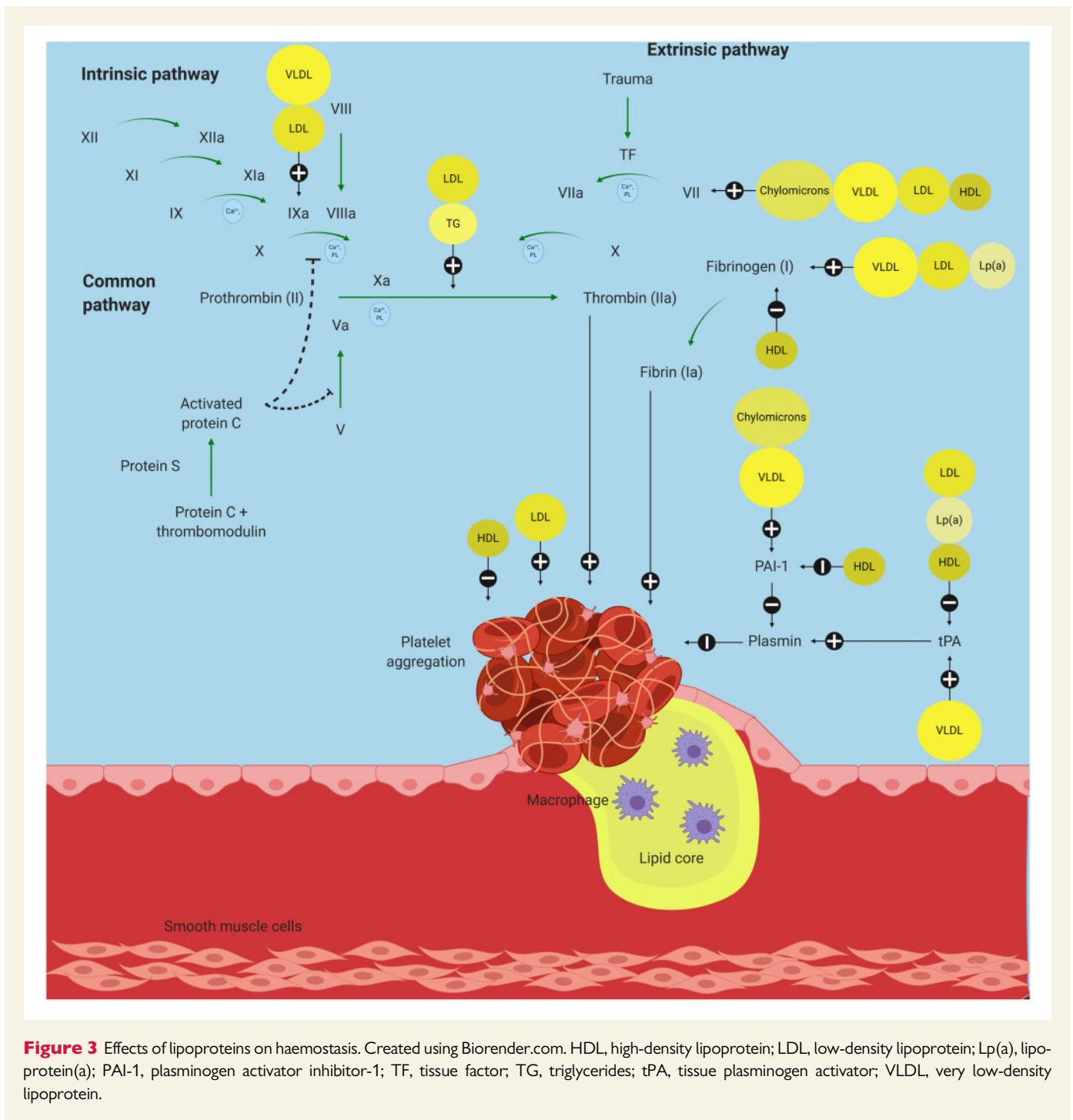
In addition to the measures of lipids described above, several others have been explored in relation to incident AF. Aronis *et al.*<sup>54</sup> found that Lp(a) levels above 50 mg/dL (compared to <10 mg/dL) were not associated with incident AF. Monocyte to HDL-C ratio has also been described as a novel biomarker of inflammation that may be useful to predict new-onset AF in patients undergoing percutaneous coronary intervention<sup>51</sup> or coronary artery bypass grafting.<sup>55</sup>

### 3.2 Underlying mechanisms

In general, there is limited research on mechanisms that underpin the relationship between lipoproteins and AF. In a report from the Women's Health Study, Mora *et al.*<sup>58</sup> conjectures that the inverse relationship may be due to the stabilizing effect of cholesterol on myocardial cell membranes. This may occur through the effects of cholesterol on the regulation of ion channels and sensitivity of volume-regulated anion current to osmotic gradients.<sup>68-71</sup> Furthermore, cholesterol depletion has been found to impair cardiomyocyte contractility by deregulation of calcium handling, adrenergic signalling and the myofibrillar architecture.<sup>72</sup>

The link between cholesterol levels and development of AF may also be related to inflammation. It has been shown that TC, LDL-C and HDL-C levels were decreased while TG was increased during inflammation.<sup>73</sup> Therefore, reduced levels of cholesterol may be reflective of underlying inflammatory processes within the host that contributes to AF. Furthermore, lipoproteins influence the course of sepsis by binding to





bacterial endotoxins and attenuate the harmful effects of inflammatory responses.<sup>74</sup>

It was reported that the effects of lipoproteins on incident AF extended beyond the cholesterol content to include the number of lipoprotein particles for LDL and VLDL.<sup>58</sup> In this regard, it was the smaller particles for each of these lipoproteins that were the actual driving force contributing to the inverse relationship with AF as larger cholesterol-rich LDL-particles, total HDL-C, Lp(a) and TG were not associated with incident AF.<sup>58</sup> In a small study of female patients undergoing catheter ablation, those with AF had smaller lipoprotein particles with increased oxidation, glycation and TG content compared to controls in sinus

rhythm.<sup>75</sup> Similar findings have been reported elsewhere among male patients.<sup>76</sup> Overall, these changes resulted in enhanced foam cell formation via accelerated phagocytosis by macrophages, and reduced antioxidant ability of HDL.<sup>75</sup> These changes are important as HDL particles have been shown to be more protective against cardiovascular events,<sup>77,78</sup> which are known to contribute to AF. Furthermore, foam cells are known to initiate a wide range of bioactivities including inflammatory processes<sup>79–81</sup> that may be linked to the pathogenesis of AF.

Sex differences in the association of lipoproteins and AF that were observed in some studies may be attributable to hormones, especially oestrogen, and differences in body fat distribution or insulin sensitivity.<sup>82–84</sup>

**Table 1** Impact of lipoprotein abnormalities on incidence or prevalence of atrial fibrillation

Author, year (ref)	Study type	Population	n	Follow-up (months)	Finding(s) in relation to incidence or prevalence of AF
Harrison, 2020 <sup>45</sup>	Prospective	Community-based cohort	13 724	NA	<p>↑ TC: PR 0.61 (95% CI 0.49–0.75)</p> <p>↑ LDL-C: PR 0.60 (95% CI 0.48–0.75)</p> <p>↑ HDL-C: PR 0.58 (95% CI 0.46–0.74)</p> <p>↑ non-HDL-C: PR 0.63 (95% CI 0.51–0.78)</p> <p>↑ LDL-C/HDL-C ratio: PR 0.75 (95% CI 0.61–0.94)</p>
Xue, 2019 <sup>46</sup>	Prospective	STEMI	985	31	<p>↑ TC: HR 0.54 (95% CI 0.32–0.90)</p> <p>↑ LDL-C: HR 0.56 (95% CI 0.31–1.00)</p> <p>TG or HDL-C not found to be risk factors</p>
Choe, 2018 <sup>47</sup>	Retrospective	Population-based cohort	22 886 661	65	<p>↑ TG: HR 1.12 (95% CI 1.12–1.13)</p> <p>↑ HDL: HR 1.24 (95% CI 1.23–1.25)</p>
Li, 2018 <sup>48</sup>	Prospective	Community-based cohort	88 785	85	<p>↑ TC: HR 0.60 (95% CI 0.43–0.84)</p> <p>↑ LDL-C: HR 0.60 (95% CI 0.43–0.83)</p> <p>TG or HDL-C not found to be risk factors</p>
Mourtzinis, 2018 <sup>49</sup>	Retrospective	Hypertensive	51 020	42	<p>↑ TC: HR 0.84 (95% CI 0.78–0.92)</p> <p>↑ LDL-C: HR 0.86 (95% CI 0.79–0.97)</p> <p>TG or HDL-C not found to be risk factors</p>
Liu, 2018 <sup>50</sup>	Prospective	Chronic heart failure	308	36	<p>↑ TC: HR 0.99 (95% CI 0.97–1.00)</p> <p>↑ LDL-C: HR 0.98 (95% CI 0.97–1.00)</p> <p>HDL-C not found to be risk factor</p>
Ulus, 2018 <sup>51</sup>	Prospective	Elderly (>65 years) with ACS undergoing PCI	308	NA	<p>↑ MHR: OR 1.10 (95% CI 1.05–1.15)</p>
Kim, 2018 <sup>52</sup>	Retrospective	Community-based cohort of males	21 981	104	TG or HDL-C not found to be risk factors
Kokubo, 2017 <sup>53</sup>	Prospective	Community-based cohort	6898	166	TC, TG or HDL-C not found to be risk factors
Aronis, 2017 <sup>54</sup>	Prospective	Community-based cohort	9908	167	↑ Lp(a) not found to be risk factor
Saskin, 2017 <sup>55</sup>	Retrospective	Isolated CABG	662	0.23	↑ MHR: OR 11.5 (95% CI 1.25–106.67)
Krittayaphong, 2016 <sup>56</sup>	Retrospective	Hypertensive	13 207	NA	↑ LDL-C: OR 0.53 (95% CI 0.37–0.78)
Alonso, 2014 <sup>57</sup>	Prospective	Community-based cohort	7142	115	<p>↑ HDL-C: HR 0.64 (95% CI 0.48–0.87)</p> <p>↑ TG: HR 1.60 (95% CI 1.25–2.05)</p> <p>TC and LDL-C not found to be risk factors</p>
Mora, 2014 <sup>58</sup>	Prospective	Healthy female healthcare professionals	23 738	197	<p>↑ LDL-C: HR 0.72 (95% CI 0.56–0.92)</p> <p>↑ VLDL-particles: HR 0.78 (95% CI 0.61–0.99)</p> <p>↑ LDL-particles: HR 0.77 (95% CI 0.60–0.99)</p> <p>↑ Cholesterol-poor small LDL: HR 0.78 (95% CI 0.61–1.00)</p> <p>↑ Small VLDL particles: HR 0.78 (95% CI 0.62–0.99)</p> <p>Larger cholesterol-rich LDL-particles, total HDL-C, Lp(a) and TG not found to be risk factors</p>
Lopez, 2012 <sup>59</sup>	Prospective	Community-based cohort	13 044	224	<p>↑ LDL-C: HR 0.90 (95% CI 0.85–0.96)</p> <p>↑ TC: HR 0.89 (95% CI 0.84–0.95)</p> <p>HDL-C, TG and use of lipid-lowering medications not found to be risk factors</p>
Watanabe, 2011 <sup>60</sup>	Prospective	Community-based cohort	28 449	54	<p>↑ HDL-C in females: HR 0.35 (95% CI 0.18–0.67)</p> <p>↑ HDL-C in males not found to be risk factor: HR 0.74 (95% CI 0.42–1.30)</p>

Continued

**Table 1 Continued**

Author, year (ref)	Study type	Population	n	Follow-up (months)	Finding(s) in relation to incidence or prevalence of AF
Iguchi, 2010 <sup>61</sup>	Prospective	Community-based cohort	30 449	NA	↑ TC: HR 0.94 (95% CI 0.90–0.97) ↑ LDL-C: HR 0.92 (95% CI 0.88–0.96) Hypercholesterolaemia, as defined by TC >220 mg/dL or the use of cholesterol-lowering agents: OR 0.75 (95% CI 0.58–0.96)
Haywood, 2009 <sup>62</sup>	Prospective	Hypertensive	39 056	NA	↑ HDL-C: OR 0.77 (95% CI 0.62–0.95)
Rosengren, 2009 <sup>63</sup>	Prospective	Community-based cohort of males	6903	412	TC not found to be risk factor
Frost, 2005 <sup>64</sup>	Prospective	Population-based cohort without endocrine or cardiovascular diseases at baseline	47 589	68	(Females) ↑ TC: HR 0.57 (95% CI 0.42–0.78) TC not found to be a risk factor in males

ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass graft; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MHR, monocyte- to high-density lipoprotein cholesterol ratio; NA, not applicable; OR, odds ratio; PCI, percutaneous coronary intervention; PR, prevalence ratio; STEMI, ST-elevation myocardial infarction; TC, total cholesterol; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.

Moreover, a fall in testosterone levels among ageing males may influence oxidative modification of LDL-C.<sup>85</sup>

It is worth mentioning that the effects of specific lipoproteins may vary under certain conditions. For example, injection of VLDL extracted from patients with metabolic syndrome into mice resulted in excess lipid accumulation and apoptosis in the atria, and significantly greater left atrial dilatation compared to VLDL from healthy volunteers.<sup>86</sup> Thus, VLDL may contribute to the development of atrial cardiomyopathy and subsequent vulnerability to AF through direct cytotoxicity, altered action potentials, disrupted calcium regulation, delayed conduction velocities, modulated gap junctions and derangements in sarcomere proteins (Figure 4).<sup>87</sup> This highlights the fact that focusing on the quantity of lipoproteins on its own may limit our understanding of the mechanisms underlying the paradoxical inverse relationship of lipoproteins and AF.

## 4. Lipoproteins and thrombosis

The role of lipoproteins in modulating thrombosis and haemostasis to produce fibrin clots is well described.<sup>88</sup> LDL and VLDL have been shown to increase thrombin generation and inhibit fibrinolysis.<sup>89,90</sup> An inverse relationship of VLDL to fibrin clot permeability and fibre mass-length ratio has previously been demonstrated.<sup>91</sup>

In addition to the coagulation system, platelets seem to be affected by lipoproteins as well. To start with, there is evidence that patients with excessive LDL, such as those in familial hypercholesterolaemia that is characterized by lack or defective LDL receptors, display enhanced platelet reactivity with increased  $\alpha$ -granule secretion,<sup>92</sup> fibrinogen binding,<sup>93</sup> and aggregation.<sup>94</sup> In contrast, patients with abetalipoproteinaemia that is characterized by a lack of all apolipoprotein B-containing lipoproteins (chylomicrons, VLDL and LDL) have reduced platelet activation.<sup>95</sup> Furthermore, LDL has been shown to promote excess platelet activation which may contribute to the higher incidence of thrombosis in hyperlipidaemia.<sup>96,97</sup>

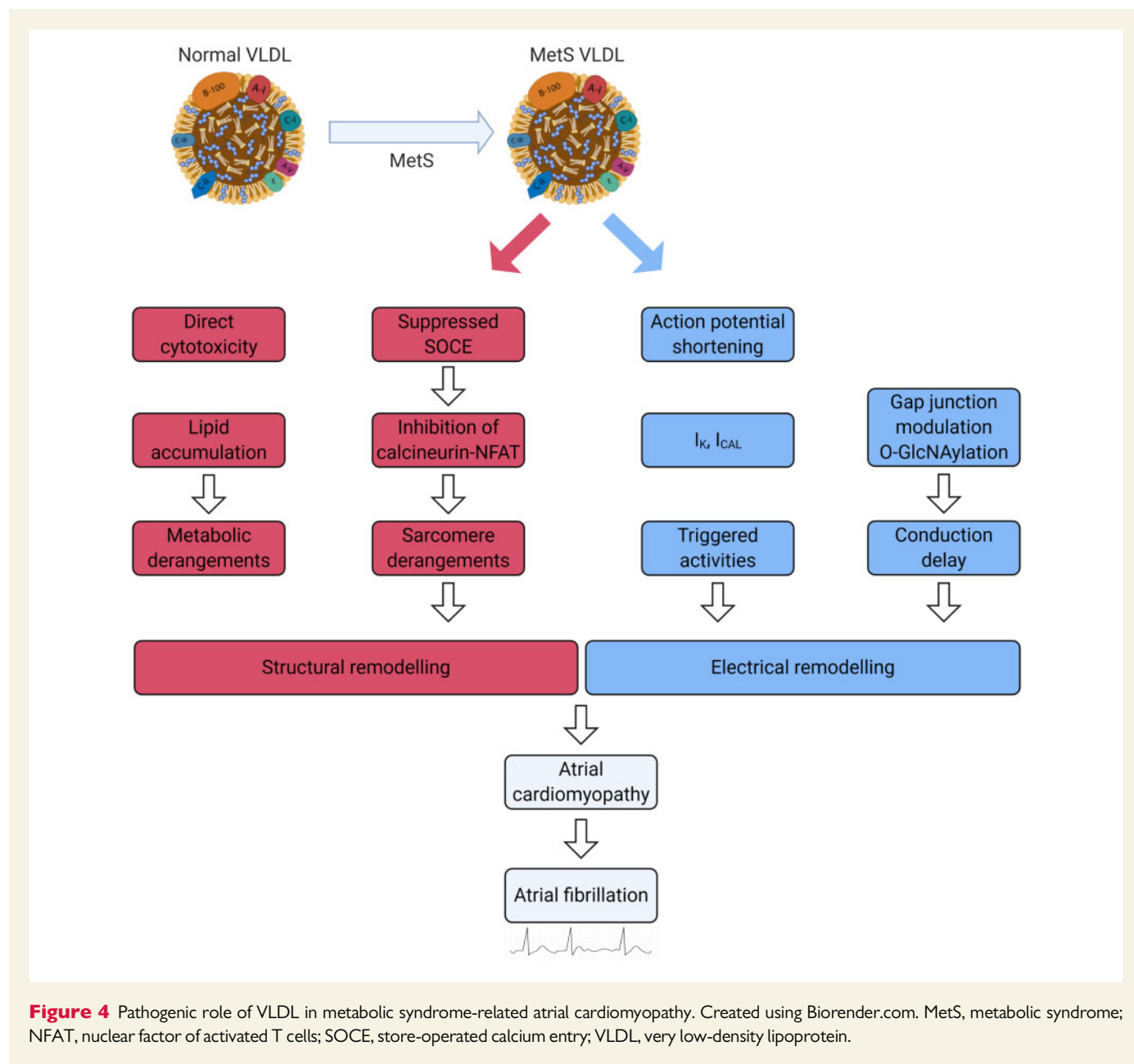
Certain subclasses of LDL may be more harmful than others. For instance, sdLDL was shown to be independently associated with both

thrombotic and haemorrhagic strokes.<sup>98</sup> A potential mechanism could include increased susceptibility to oxidation which leads to a substantial increase in thrombin generation compared to the larger native LDL.<sup>99,100</sup> In addition to identifying the lipid subclasses and oxidative states, evaluating the effects of individual lipid species may be of importance. For instance, Klein et al.<sup>101</sup> demonstrated that VLDL was capable of activating the contact pathway in the presence of platelets, thereby causing an increase in the rate and amount of thrombin generation. A subsequent detailed lipoprotein analyses revealed that this was driven by phosphatidylethanolamine (PE). Interestingly, PE is also responsible for oxLDL-induced thrombin generation.<sup>102</sup>

### 4.1 OxLDL and haemostasis

Despite many decades of research into oxLDL, definitions of what it contains and method of detection vary between groups and publications.<sup>33</sup> Perhaps the most encompassing definition for oxLDL is 'A particle derived from circulating LDL that may have peroxides or their degradation products generated within the LDL molecule or elsewhere in the body associated with the particle'.<sup>33</sup> Such particles therefore may include lipid peroxides, hydroxides or aldehydes such as malondialdehyde in addition to protein oxidation products. These biochemical changes give oxLDL altered properties which may facilitate its detection and separation on the basis of density, negative charge and monoclonal antibody (mAb). The latter method utilizes antibodies to oxidized epitopes on the surface of oxLDL such as EO6 for oxidized phosphatidylcholine (oxPC)<sup>103</sup> and 4E6 for oxidized apoB.<sup>104</sup> Given the variation in detection methods of oxLDL and possible consequences on interpretation of the evidence, this review specifies the method of detection of oxLDL where appropriate.

Elevated oxLDL levels (detected by 4E6 mAb) are independently associated with several cardiovascular risk factors including increasing age, male gender, raised body mass index, abdominal obesity, hypertension, raised C-reactive protein, renal dysfunction, hyperuricaemia, and smoking.<sup>105</sup> These risk factors are important in AF, which has also been shown to be directly associated with elevated 4E6-measured oxLDL levels.<sup>106–109</sup>



Oxidized LDL (4E6 mAb) correlates to thrombogenesis by interfering with the coagulation system and clot formation. In this regard, patients with acute coronary syndrome demonstrate a positive correlation between oxLDL and tissue factor levels in plasma.<sup>110</sup> Activation of T lymphocytes by oxLDL, prepared by chemical oxidation of native LDL with copper sulfate, via the lectin-type oxLDL receptor 1 (LOX-1) has also been shown to increase the expression of tissue factor on the surface of leukocytes.<sup>111</sup> Furthermore, oxLDL generated with copper oxidation was noted to inhibit fibrinolysis, modify fibrin clot structure and increase thrombin generation.<sup>102,112</sup> Finally, oxLDL (detected by 4E6) correlated to reduced clot permeability and prolonged clot lysis time.<sup>113</sup>

OxLDL generated *in vitro* by copper oxidation has been shown to cause activation and aggregation of platelets via CD36 and LOX-1,<sup>114–116</sup> as well as impair endothelial regeneration by reducing the release of nitric oxide.<sup>117</sup> Furthermore, platelet reactivity in cardiovascular disease can be

related to dyslipidaemia,<sup>118,119</sup> which is characterized by accumulation of oxLDL as measured by LDL isolation, lipid extraction and subsequent high performance liquid chromatography.<sup>120</sup> In turn, platelet reactivity is an important determinant of fibrin clot structure and effective platelet inhibition is associated with a weaker, more permeable fibrin network.<sup>121</sup> Therefore, oxLDL may indirectly influence fibrin clot properties through its effects on platelet reactivity. To complicate matters, recent evidence suggests that oxLDL activation of platelets promotes further oxLDL uptake by platelets (detected with the polyclonal orb10973 anti-oxLDL antibody), augmenting the pro-oxidative thrombogenic phenotype.<sup>122</sup> Finally, there is evidence suggesting that activated platelets contribute to the formation of oxLDL species and modification of lipoprotein function.<sup>123</sup> Putting it together, the evidence points towards a cycle of oxLDL-induced platelet activation leading to further oxLDL formation and uptake by platelets.



**Table 2** Clinical studies describing association of lipoproteins with thrombotic conditions

Author, year (ref)	Study design	Population	n	Finding(s) in relation to thrombosis
Morelli, 2017 <sup>133</sup>	Case-control	Recent venous thrombosis	5107	↓ ApoB: OR 1.35 (95% CI 1.12–1.62) ↓ ApoA1: OR 1.50 (95% CI 1.25–1.79)
Grifoni, 2012 <sup>134</sup>	Cross-sectional	First episode venous thromboembolism	747	↑ Lp(a): OR 2.6 (95% CI 1.7–4.0)
Kamstrup, 2012 <sup>131</sup>	Community-based cohort	White Danish descent	41 231	↑ Lp(a): OR 1.21 (95% CI 1.10–1.33) for risk of myocardial infarction (coronary atherothrombosis) No association between Lp(a) and venous thrombosis
Ohira, 2006 <sup>135</sup>	Cohort	No history of stroke	14 448	↑ Lp(a): OR 1.42 (95% CI 1.10–1.83) for non-lacunar strokes, No association between Lp(a) and lacunar or cardioembolic strokes
Tsimikas, 2005 <sup>35</sup>	Cross-sectional	Coronary artery disease	504	↑ oxLDL: ApoB100 ratio: OR 3.12 ( $P < 0.01$ ) ↑ Lp(a): OR 3.64 ( $P < 0.01$ )
Deguchi, 2005 <sup>136</sup>	Cross-sectional	Men with venous thrombosis	98	↓ HDL: OR 6.5 (2.3–19) ↓ ApoA1: OR 6.0 (2.1–17) ↑ IDL: OR 2.7 (1.0–6.8, $P < 0.05$ ) ↑ sdLDL: OR 3.1 (1.3–7.4)
Doggen, 2004 <sup>137</sup>	Case-control	Post-menopausal women with first venous thrombosis	2463	↑ HDL-C: OR 0.71 (95% CI 0.52–0.97) ↑ TG: OR 2.13 (95% CI 1.34–3.37)
Marcucci, 2003 <sup>138</sup>	Case-control	History of venous thromboembolism	1033	↑ Lp(a): OR 2.1 (95% CI 1.4–3.2)
von Depka, 2000 <sup>139</sup>	Case-control	History of venous thromboembolism	951	↑ Lp(a): OR 3.2 (95% CI 1.9–5.3)
Holvoet, 1998 <sup>140</sup>	Case-control	Coronary artery disease	270	↑ oxLDL in acute coronary syndrome than stable angina ( $r^2$ 0.65, $P < 0.01$ )
Kawasaki, 1997 <sup>141</sup>	Case-control	Confirmed deep vein thrombosis	218	↑ TC: OR 4.5 (95% CI 2.4–8.3) ↑ TG: OR 2.4 (95% CI 1.3–4.6)

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; Lp(a), lipoprotein(a); OR, odds ratio; OxLDL, oxidized low-density lipoprotein; sdLDL, small dense low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

## 4.2 Lp(a) and haemostasis

In addition to its recognized atherogenic properties,<sup>124</sup> Lp(a) appears to have a direct prothrombotic effect by interfering with platelets and the fibrinolysis system. Although it has been found to interact with platelets, the target receptor remains unclear.<sup>125</sup> Furthermore, literature surrounding the nature of interaction between Lp(a) and platelets is conflicting, with evidence to suggest that it may have both activating and inhibiting effects.<sup>126</sup>

Lp(a) has been shown to facilitate platelet activation through thrombin-related activating hexapeptide, but not thrombin or adenosine diphosphate.<sup>127</sup> On the contrary, some studies reported an inhibitory effect of Lp(a) to platelet activation by collagen or thrombin.<sup>125</sup> Less controversial is the ability of Lp(a) to impair platelet-mediated fibrinolytic reactions by interfering with the binding of plasminogen, which shares structural similarities to apolipoprotein(a), and tissue plasminogen activator to the platelet surface.<sup>128</sup> This is compounded by the ability of Lp(a) to inactivate tissue factor pathway inhibitor which may promote thrombosis through the extrinsic coagulation pathway.<sup>129</sup> However, evidence in genetic studies on the contribution of Lp(a) to venous thrombosis

have been negative,<sup>130,131</sup> suggesting that the primary prothrombotic effects of Lp(a) may be limited to atherothrombosis (arterial) or anti-fibrinolysis.<sup>132</sup> Additional studies describing the association between lipoproteins and thrombotic conditions are summarized in Table 2.

## 4.3 The effects of lipid-modifying therapy on thrombosis and haemostasis

The role of lipoproteins in haemostasis is further supported by the fact that application of lipid-modifying therapy is associated with changes in haemostasis.<sup>142</sup> Specifically, atorvastatin may exert antiplatelet effects by interfering with redox signalling.<sup>143</sup> It has also been shown that statins are able to reduce fibrin clot lysis time, independent of warfarin.<sup>144</sup> For example, a randomized controlled trial by Undas *et al.*<sup>145</sup> confirmed the effects of statins and also showed similar results with the use of other lipid-modifying therapy, specifically fenofibrate. The authors reported increased fibrin clot permeability and reduced lysis time with the use of these agents compared to pre-treatment values, potentially through its effects on thrombin generation. Turbidity analysis also showed that use

**Table 3** Effects of lipoproteins on thromboembolic outcomes in atrial fibrillation

Author, year (ref)	Study type	Population	n	Follow-up (months)	Finding(s)
Liu, 2020 <sup>161</sup>	Retrospective	Non-valvular AF	2345	26	↑ LDL-C in low-risk: HR 2.60 (95% CI 1.26–5.37) for ischaemic stroke ↑ LDL-C in high-risk: HR 2.50 (95% CI 1.10–5.70) for ischaemic stroke
Yan, 2019 <sup>162</sup>	Retrospective	Non-valvular AF with low CHA <sub>2</sub> DS <sub>2</sub> -VASc score	595	NA	↑ Lipoprotein(a): OR 1.02 (95% CI 1.01–1.03) for thromboembolic events
Pol, 2018 <sup>163</sup>	Prospective	AF with at least 1 stroke/SE risk factor	14 884	23	↑ Apolipoprotein A1: HR 0.81 (95% CI 0.73–0.90) for composite risk of ischaemic stroke, SE, MI and CV death Apolipoprotein B was not associated with composite risk of ischaemic stroke, SE, MI and CV death
Qi, 2017 <sup>164</sup>	Retrospective	AF ± ischaemic stroke	815	NA	↑ LDL-C: OR 2.00 (95% CI 1.62–2.47) for ischaemic stroke
Aronis, 2017 <sup>54</sup>	Prospective	Community-based cohort	10 127	190	↑ Lipoprotein(a) was not associated with stroke risk in patients with AF
Wu, 2017 <sup>165</sup>	Retrospective	Non-valvular AF	2470	NA	↑ LDL-C: OR 1.27 (95% CI 1.08–1.49) for ischaemic stroke
Igarashi, 1998 <sup>166</sup>	Prospective	Chronic AF	150	NA	↑ Lipoprotein(a) was an independent risk factor for LA thrombus (standardized coefficient of 0.300)

AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable or available; OR, odds ratio; SE, systemic embolism.

of these drugs resulted in thicker fibres that were more prone to effective fibrinolysis.

A further randomized controlled trial of patients with type 1 diabetes mellitus and dyslipidaemia found that the beneficial effects of statins on fibrin clot properties may be related to reduced expression of glycoprotein IIIa, tissue factor, and P-selectin.<sup>146</sup> Finally, the use of statins has been associated with risk reduction of both venous and arterial thromboembolisms.<sup>147–151</sup> Therefore, it is tempting to speculate that the statin-induced protective effects may be related to its influence on reduction of pro-coagulant lipoproteins or enhancement of anti-coagulant lipoproteins.<sup>90</sup>

A prospective, case-controlled study of patients with stable coronary artery disease and hypercholesterolaemia found that use of pravastatin was associated with reduced thrombus formation at both high and low shear rates.<sup>152</sup> As expected, there was a significant decrease in TC and LDL-C levels with pravastatin. Thrombus formation was also assessed after 1 week of treatment with pravastatin, prior to any significant reduction in TC and LDL-C levels, and it was found that this was unchanged compared to pre-treatment. As a result, the authors concluded that the beneficial effects of pravastatin on thrombogenicity was due to its effects on lipids/lipoproteins.<sup>152</sup> Interestingly, other studies have reported that the anti-coagulant effects of statin therapy, in terms of thrombin generation and platelet activation, were seen as early as 3 days following treatment.<sup>153,154</sup>

Nonetheless, it should be noted that there currently remains insufficient evidence to conclude whether the protective effects of statins are related to its lipid-modifying effects or otherwise.<sup>148</sup> In contrast to the aforementioned studies, Dangas *et al.*<sup>155</sup> showed a reduction in thrombogenicity among patients after 6 months of treatment with pravastatin, regardless of change in LDL-C. Furthermore, despite a similar reduction

in LDL-C between subgroups of patients treated with pravastatin compared to dietary advice only, the anti-thrombotic benefit was only demonstrated among those receiving pravastatin. Additionally, a study by Undas *et al.*<sup>156</sup> found that the use of simvastatin was associated with a reduction in thrombin generation, independent of changes in lipid profile. Overall, there may be various pathways by which lipid-modifying therapy, in particular statins, may interact with the haemostatic process.

## 5. Lipoproteins and thromboembolism in AF

Given the effects of lipoproteins on haemostasis, their contribution to thromboembolic events may be expected. Indeed, lipoprotein abnormalities have been shown to be an independent risk factor for stroke and venous thromboembolism.<sup>157–160</sup> However, few studies have explored this relationship in the context of AF (Table 3).

### 5.1 Low-density lipoprotein cholesterol

LDL-C has been implicated in thromboembolic events among patients with AF. Wu *et al.*<sup>165</sup> found that LDL-C was an independent risk factor for both a history of ischaemic stroke and future stroke risk among patients with AF. Similar findings were reported in a case-controlled study, whereby raised LDL-C was shown to be an independent predictor of ischaemic stroke in patients with AF, irrespective of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>164</sup> Furthermore, this association demonstrated a dose-response pattern. A later study confirmed the relationship between LDL-C and ischaemic stroke, and observed that lowering LDL-C may be particularly beneficial among AF patients with a low CHA<sub>2</sub>DS<sub>2</sub>-VASc score (less than two in males and three in females).<sup>161</sup>

Interestingly, LDL-C appears to have an opposite influence on the risk of incident AF and subsequent thromboembolic risk which highlights the importance of regular monitoring and treatment adjustments in clinical practice.

## 5.2 Lipoprotein(a)

There are conflicting reports on the effects of Lp(a) on thromboembolic risk in AF. Igarashi et al.<sup>166</sup> demonstrated that serum Lp(a) was an independent risk factor for left atrial thrombus detected on transoesophageal echocardiogram in patients with chronic AF. Additionally, left atrial thrombus was present in 48% of AF patients with a Lp(a) level  $\geq 30$  mg/dL, suggesting that this may be a useful biomarker to identify patients at high risk of thromboembolism. However, a limitation of this study was that relatively few patients (19%) were on anticoagulation therapy.<sup>166</sup>

More recently, higher Lp(a) levels were found to be independently associated with clinically confirmed thromboembolic events in non-valvular AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of less than two.<sup>162</sup> Curiously, Aronis et al.<sup>54</sup> found that elevated levels of Lp(a) was associated with an increased stroke risk among non-AF patients, but not in those with AF. In support of the latter, we previously demonstrated that there was no correlation between Lp(a) and D-dimer, as a marker of thrombogenesis.<sup>167</sup> Overall, the inconsistent results on Lp(a) may suggest the existence of different Lp(a) phenotypes that contribute differently to thrombogenesis<sup>168</sup> and therefore, sole measurement of total Lp(a) levels may be inadequate for this purpose. In this regard, the measurement of oxidized lipids may have an important role to increase our understanding on the potential impact of Lp(a) on atrial function and risk of AF.<sup>169–171</sup>

## 5.3 Other measures of lipoproteins

In a sub-study of the ARISTOTLE trial, higher levels of Apolipoprotein A1 were independently associated with a lower composite risk of ischaemic stroke, systemic embolism, myocardial infarction, and cardiovascular mortality.<sup>163</sup> When analysed separately, Apolipoprotein A1 was found to be a risk factor for each of the individual outcomes apart from myocardial infarction. In reverse, the authors reported that Apolipoprotein B was not associated with the risk of composite outcomes but that it was a risk factor for myocardial infarction. Decker et al.<sup>172</sup> demonstrated that low HDL and high TG were not independently associated with ischaemic stroke among AF patients over a follow-up period of 14.8 years, though there was a trend for the former [hazard ratio (HR) 1.47, 95% confidence interval (CI) 0.99–2.20;  $P = 0.06$ ].

The relationship between lipoproteins and thromboembolism in AF is further indicated by studies that have explored the impact of statins, as medications that are known to regulate lipoproteins. A subgroup analysis comprising of 1446 AF patients with ischaemic stroke found that higher statin adherence during 5-year follow-up predicted a reduced risk of stroke recurrence [HR 0.59 (95% CI 0.43–0.81)].<sup>173</sup> In this context, the effects of statins may be related to a reduction of oxLDL levels that promote its anti-inflammatory properties,<sup>174,175</sup> which has been shown to reduce the endogenous thrombin potential in patients with AF.<sup>176</sup> He et al.<sup>177</sup> found that prior use of statins resulted in lower plasma oxLDL levels at baseline and at 3-month follow-up among patients presenting with an ischaemic stroke. Furthermore, pre-stroke statin use was associated with reduced short-term mortality [odds ratio (OR) 0.38 (95% CI 0.16–0.91) and major disability (OR 0.38 (95% CI 0.15–0.99)].

## 6. Gaps and limitations

Despite a wealth of evidence on the role of lipoproteins in thrombosis and AF, it is recognized that these molecules are heterogeneous, containing numerous subclasses and lipid species with variable effects.<sup>178</sup> In this regard, much of the conflicting evidence and paradox in prior studies may be due to the usage of crude methods of classification that undermines the complexity of lipoproteins. Given recent advancements in our ability to accurately analyse lipoprotein subclasses and lipid species, future studies should focus on identifying the relationship of these molecules with incident AF and thromboembolic complications. Moreover, the mechanism by which this occurs also warrants further investigation. With better understanding in this area, the development of targeted treatment approaches for high-risk subgroups may be possible. Furthermore, ongoing clinical trials such as the Lp(a)HORIZON study (ClinicalTrials.gov NCT04023552) are examining novel agents targeting Lp(a) levels and may provide more data on the association of Lp(a), incident AF and thrombotic events.

One group of lipids which is emerging as a key player in haemostatic reactions is oxidized GPL. These molecules have been shown to play a role in thrombotic disorders and are primarily generated enzymatically by platelets and leukocytes.<sup>179,180</sup> The presence of these molecules in lipoproteins has not been conclusively studied, particularly in light of newer lipidomic technologies. The majority of previous studies of oxidized GPL in lipoproteins had relied on antibodies that bind oxPC, demonstrating their presence as a defining feature of oxLDL<sup>181</sup> and Lp(a).<sup>182</sup> It is not known whether the presence of oxPC, or other oxidized GPL, on lipoproteins enhance coagulation reaction in a similar way to enzymatically-generated oxPC on the surface of activated cells.<sup>179</sup> The growth in the lipidomics field and availability of increasingly sensitive techniques may pave the way for studies in this area.

Moving forward, the role of genetics in lipoproteins should also be considered. Elevated Lp(a) is prevalent in approximately 20% of the population,<sup>183</sup> and strongly influenced by genetic variability.<sup>184</sup> Much of the variation is related to the apo(a) protein, which consists of kringle domains that vary in molecular weight and therefore size of the Lp(a) particle.<sup>185,186</sup> The genetic variation in the *LPA* locus has enabled Mendelian randomization studies to demonstrate that both the Lp(a) concentration and the smaller apo(a) isoform are independently causal for some cardiovascular diseases.<sup>183,187–191</sup> While a large UK-based population study by Zanetti et al.<sup>188</sup> found no causal relationship between Lp(a) and AF, further Mendelian randomization studies are needed to confirm this finding in other cohorts.

## 7. Conclusion

There is a paradoxical relationship between TC and LDL-C, and incident AF. The mechanism by which this occurs is poorly defined but may be related to changes in the regulation of ion channels and inflammatory processes. To complicate matters, excess lipoproteins promote thrombin generation, inhibit fibrinolysis and enhance platelet activation. In this regard, LDL-C has been shown to be an independent risk factor for thromboembolic events in AF. Overall, the complex relationship between lipoproteins, thrombosis and AF warrants further research. An improved knowledge base in this area may unlock important mechanistic pathways that contribute to our overall understanding of haemostasis and guide our clinical approach in the treatment of prothrombotic conditions.

## Data availability

The data that support the findings of this review are available from the corresponding author upon reasonable request.

## Acknowledgements

We thank Professor Valerie O'Donnell for her constructive comments on our manuscript.

**Conflict of interest:** W.Y.D., I.G.D., and M.B.P.: none declared. G.Y.H.L.: consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

## References

- Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y-H, McAnulty JHJ, Zheng Z-J, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–847.
- Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946–952.
- Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–364.
- Thrall G, Lane D, Carroll D, Lip GYH. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med* 2006;**119**:448.e1–448.e19.
- Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, Van Gilst WH, Van Gelder IC, Rienstra M. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. *J Am Coll Cardiol* 2015;**66**:1000–1007.
- Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *J Am Med Assoc* 1994;**271**:840–844.
- Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;**155**:469–473.
- Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. *Int J Clin Pract* 2018;**72**:e13070.
- Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;**114**:119–125.
- Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, Stijnen T, Lip GYH, Witteman JCM. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;**27**:949–953.
- Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042–1046.
- Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng L-C, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ* 2018;**361**:k1453.
- Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, Witteman JCM, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;**34**:2746–2751.
- Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: european perspective. *Clin Epidemiol* 2014;**6**:213–220.
- Wijesurendra RS, Casadei B. Mechanisms of atrial fibrillation. *Heart* 2019;**105**:1860.
- Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. *Heart* 2020;**106**:1463–1468.
- Burdge GC, Calder PC. Introduction to fatty acids and lipids. *World Rev Nutr Diet* 2014;**112**:1–16.
- Dowhan W, Bogdanov M. Chapter 1: Functional roles of lipids in membranes. *New Comprehensive Biochemistry*. Elsevier. Vol. 36, pp. 1–35. [https://doi.org/10.1016/S0167-7306\(02\)36003-4](https://doi.org/10.1016/S0167-7306(02)36003-4).
- Yen C-LE, Stone SJ, Koliwad S, Harris C, Farese RVJ. Thematic review series: glycerolipids. DGAT enzymes and triacylglycerol biosynthesis. *J Lipid Res* 2008;**49**:2283–2301.
- Cerqueira N, Oliveira EF, Gesto DS, Santos-Martins D, Moreira C, Moorthy HN, Ramos MJ, Fernandes PA. Cholesterol biosynthesis: a mechanistic overview. *Biochemistry* 2016;**55**:5483–5506.
- Baila-Rueda L, Cenarro A, Civeira F. Non-cholesterol sterols in the diagnosis and treatment of dyslipidemias: a review. *CMC* 2016;**23**:2132–2145.
- Buhman KF, Accad M, Farese RV. Mammalian acyl-CoA:cholesterol acyltransferases. *Biochim Biophys Acta* 2000;**1529**:142–154.
- Feingold KR, Grunfeld C. Introduction to lipids and lipoproteins. South Dartmouth (MA): Endotext, 2018.
- Mahley RW, Innerarity TL, Rall SCJ, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. *J Lipid Res* 1984;**25**:1277–1294.
- Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. *Oxid Med Cell Longev* 2017;**2017**:1–10.
- Tanaga K, Bujo H, Inoue M, Mikami K, Kotani K, Takahashi K, Kanno T, Saito Y. Increased circulating malondialdehyde-modified LDL levels in patients with coronary artery diseases and their association with peak sizes of LDL particles. *Arterioscler Thromb Vasc Biol* 2002;**22**:662–666.
- Packard CJ, Demant T, Stewart JP, Bedford D, Caslake MJ, Schwertfeger G, Bedynek A, Shepherd J, Seidel D. Apolipoprotein B metabolism and the distribution of VLDL and LDL subfractions. *J Lipid Res* 2000;**41**:305–318.
- Hayashi T, Koba S, Ito Y, Hirano T. Method for estimating high sdLDL-C by measuring triglyceride and apolipoprotein B levels. *Lipids Health Dis* 2017;**16**:21.
- Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, Ference BA. Apolipoprotein B particles and cardiovascular disease: a narrative review. *JAMA Cardiol* 2019;**4**:1287–1295.
- Reis A, Rudnitskaya A, Blackburn GJ, Mohd Fauzi N, Pitt AR, Spickett CM. A comparison of five lipid extraction solvent systems for lipidomic studies of human LDL. *J Lipid Res* 2013;**54**:1812–1824.
- Saeed A, Feofanova EV, Yu B, Sun W, Virani SS, Nambi V, Coresh J, Guild CS, Boerwinkle E, Ballantyne CM, Hoogeveen RC. Remnant-like particle cholesterol, low-density lipoprotein triglycerides, and incident cardiovascular disease. *J Am Coll Cardiol* 2018;**72**:156–169.
- Reis A, Rudnitskaya A, Chariyavilaskul P, Dhaun N, Melville V, Goddard J, Webb DJ, Pitt AR, Spickett CM. Top-down lipidomics of low density lipoprotein reveal altered lipid profiles in advanced chronic kidney disease. *J Lipid Res* 2015;**56**:413–422.
- Parthasarathy S, Raghavamenon A, Garelnabi MO, Santanam N. Oxidized low-density lipoprotein. *Methods Mol Biol* 2010;**610**:403–417.
- Ruuth M, Nguyen SD, Vihervaara T, Hilvo M, Laajala TD, Kondadi PK, Gisterå A, Lähteenmäki H, Kittilä T, Huusko J, Uusitupa M, Schwab U, Savolainen MJ, Sinisalo J, Lokki M-L, Nieminen MS, Jula A, Perola M, Ylä-Herttula S, Rudel L, Öörni A, Baumann M, Baruch A, Laaksonen R, Ketelhuth DFJ, Aittokallio T, Jauhiainen M, Käkälä R, Borén J, Williams KJ, Kovonen PT, Öörni K. Susceptibility of low-density lipoprotein particles to aggregate depends on particle lipidome, is modifiable, and associates with future cardiovascular deaths. *Eur Heart J* 2018;**39**:2562–2573.
- Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, Witztum JL, Berger PB. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med* 2005;**353**:46–57.
- Ferretti G, Bacchetti T, Johnston TP, Banach M, Pirro M, Sahebkar A. Lipoprotein(a): a missing culprit in the management of atherothrombosis? *J Cell Physiol* 2018;**233**:2966–2981.
- Romagnuolo R, Marcovina SM, Boffa MB, Koschinsky ML. Inhibition of plasminogen activation by apo(a): role of carboxyl-terminal lysines and identification of inhibitory domains in apo(a). *J Lipid Res* 2014;**55**:625–634.
- Kannel WB, Dawber TR, Friedman GD, Glennon WE, McNamara PM. Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease; the Framingham study. *Ann Intern Med* 1964;**61**:888–899.
- Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837–1847.
- Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sortie PD, Catellier D, Patsch W. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001;**104**:1108–1113.
- Duncan MS, Vasan RS, Xanthakis V. Trajectories of blood lipid concentrations over the adult life course and risk of cardiovascular disease and all-cause mortality: observations from the Framingham study over 35 years. *J Am Heart Assoc* 2019;**8**:e011433.
- Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskiran M-R, Tokgozöglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459–2472.
- Chyou JY, Hunter TD, Mollenkopf SA, Turakhia MP, Reynolds MR. Individual and combined risk factors for incident atrial fibrillation and incident stroke: an analysis of 3 million at-risk US patients. *J Am Heart Assoc* 2015;**4**:e001723.



44. Brunner KJ, Bunch TJ, Mullin CM, May HT, Bair TL, Elliot DW, Anderson JL, Mahapatra S. Clinical predictors of risk for atrial fibrillation: implications for diagnosis and monitoring. *Mayo Clin Proc* 2014;**89**:1498–1505.
45. Harrison SL, Lane DA, Banach M, Mastek M, Kasperczyk S, Józwiak JJ, Lip GYH; LIPIDOGram2015 Investigators. Lipid levels, atrial fibrillation and the impact of age: results from the LIPIDOGram2015 study. *Atherosclerosis* 2020;**312**:16–22.
46. Xue Y, Zhou Q, Shen J, Liu G, Zhou W, Wen Y, Luo S. Lipid profile and new-onset atrial fibrillation in patients with acute ST-segment elevation myocardial infarction (an Observational Study in Southwest of China). *Am J Cardiol* 2019;**124**:1512–1517.
47. Choe WS, Choi EK, Do Han K, Lee EJ, Lee SR, Cha MJ, Oh S. Association of metabolic syndrome and chronic kidney disease with atrial fibrillation: a nationwide population-based study in Korea. *Diabetes Res Clin Pract* 2019;**148**:14–22.
48. Li X, Gao L, Wang Z, Guan B, Guan X, Wang B, Han X, Xiao X, Bin Waleed K, Chandran C, Wu S, Xia Y. Lipid profile and incidence of atrial fibrillation: a prospective cohort study in China. *Clin Cardiol* 2018;**41**:314–320.
49. Mourtzinis G, Kahan T, Bengtsson Boström K, Schiöler L, Cedstrand Wallin L, Hjerpe P, Hasselström J, Manhem K. Relation between lipid profile and new-onset atrial fibrillation in patients with systemic hypertension (from the Swedish Primary Care Cardiovascular Database [SPCCD]). *Am J Cardiol* 2018;**122**:102–107.
50. Liu C, Geng J, Ye X, Yuan X, Li A, Zhang Z, Xu B, Wang Y. Change in lipid profile and risk of new-onset atrial fibrillation in patients with chronic heart failure: a 3-year follow-up observational study in a large Chinese hospital. *Medicine (Baltimore)* 2018;**97**:e12485.
51. Ulus T, Isgandarov K, Yilmaz AS, Vasi I, Moghanchizadeh SH, Mutlu F. Predictors of new-onset atrial fibrillation in elderly patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Aging Clin Exp Res* 2018;**30**:1475–1482.
52. Kim Y-G, Choi K-J, Han S, Hwang KW, Kwon CH, Park G-M, Won K-B, Ann SH, Kim J, Kim S-J, Lee S-G, Nam G-B, Kim Y-H. Metabolic syndrome and the risk of new-onset atrial fibrillation in Middle-Aged East Asian Men. *Circ J* 2018;**82**:1763–1769.
53. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kusano K, Miyamoto Y. Development of a basic risk score for incident atrial fibrillation in a Japanese General Population—the Suita Study. *Circ J* 2017;**81**:1580–1588.
54. Aronis KN, Zhao D, Hoogeveen RC, Alonso A, Ballantyne CM, Guallar E, Jones SR, Martin SS, Nazarian S, Steffen BT, Virani SS, Michos ED. Associations of lipoprotein(a) levels with incident atrial fibrillation and ischemic stroke: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Heart Assoc* 2017;**6**:e007372.
55. Saskin H, Serhan Ozcan K, Yilmaz S. High preoperative monocyte count/high-density lipoprotein ratio is associated with postoperative atrial fibrillation and mortality in coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg* 2017;**24**:395–401.
56. Krittayaphong R, Rangsri R, Thinkhamrop B, Hurst C, Rattanamongkolgul S, Sripaiboonkij N, Yindeengam A. Prevalence and associating factors of atrial fibrillation in patients with hypertension: a nation-wide study. *BMC Cardiovasc Disord* 2016;**16**:57.
57. Alonso A, Yin X, Roetker NS, Magnani JW, Kronmal RA, Ellinor PT, Chen LY, Lubitz SA, McClelland RL, McManus DD, Soliman EZ, Huxley RR, Nazarian S, Szklo M, Heckbert SR, Benjamin EJ. Blood lipids and the incidence of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study. *J Am Heart Assoc* 2014;**3**:e001211.
58. Mora S, Akinouli AO, Sandhu RK, Conen D, Albert CM. Paradoxical association of lipoprotein measures with incident atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;**7**:612–619.
59. Lopez FL, Agarwal SK, Maclellan RF, Soliman EZ, Sharrett AR, Huxley RR, Konety S, Ballantyne CM, Alonso A. Blood lipid levels, lipid-lowering medications, and the incidence of atrial fibrillation: the atherosclerosis risk in communities study. *Circ Arrhythm Electrophysiol* 2012;**5**:155–162.
60. Watanabe H, Tanabe N, Yagihara N, Watanabe T, Aizawa Y, Kodama M. Association between lipid profile and risk of atrial fibrillation: niigata preventive medicine study. *Circ J* 2011;**75**:2767–2774.
61. Iguchi Y, Kimura K, Shibasaki K, Aoki J, Kobayashi K, Sakai K, Sakamoto Y. Annual incidence of atrial fibrillation and related factors in adults. *Am J Cardiol* 2010;**106**:1129–1133.
62. Haywood LJ, Ford CE, Crow RS, Davis BR, Massie BM, Einhorn PT, Williard A. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). *J Am Coll Cardiol* 2009;**54**:2023–2031.
63. Rosengren A, Hauptman PJ, Lappas G, Olsson L, Wilhelmsen L, Swedberg K. Big men and atrial fibrillation: effects of body size and weight gain on risk of atrial fibrillation in men. *Eur Heart J* 2009;**30**:1113–1120.
64. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Med* 2005;**118**:489–495.
65. Shang Y, Chen N, Wang Q, Zhuo C, Zhao J, Lv N, Huang Y. Blood lipid levels and recurrence of atrial fibrillation after radiofrequency catheter ablation: a prospective study. *J Interv Card Electrophysiol* 2020;**57**:221–231.
66. Adabag AS, Mithani S, Al Aloul B, Collins D, Bertog S, Bloomfield HE. Efficacy of gemfibrozil in the primary prevention of atrial fibrillation in a large randomized controlled trial. *Am Heart J* 2009;**157**:913–918.
67. Guan B, Li X, Xue W, Tse G, Bin Waleed K, Liu Y, Zheng M, Wu S, Xia Y, Ding Y. Blood lipid profiles and risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Clin Lipidol* 2020;**14**:133–142.e3.
68. Dart C. Lipid microdomains and the regulation of ion channel function. *J Physiol* 2010;**588**:3169–3178.
69. Abi-Char J, Maguy A, Coulombe A, Balse E, Ratajczak P, Samuel J-L, Nattel S, Hatem SN. Membrane cholesterol modulates Kv1.5 potassium channel distribution and function in rat cardiomyocytes. *J Physiol* 2007;**582**:1205–1217.
70. Levitan I, Christian AE, Tulenko TN, Rothblat GH. Membrane cholesterol content modulates activation of volume-regulated anion current in bovine endothelial cells. *J Gen Physiol* 2000;**115**:405–416.
71. Goonasekara CL, Balse E, Hatem S, Steele DF, Fedida D. Cholesterol and cardiac arrhythmias. *Expert Rev Cardiovasc Ther* 2010;**8**:965–979.
72. Hissa B, Oakes PW, Pontes B, Ramírez-San Juan G, Gardel ML. Cholesterol depletion impairs contractile machinery in neonatal rat cardiomyocytes. *Sci Rep* 2017;**7**:43764.
73. Khovidhunkit W, Kim M-S, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* 2004;**45**:1169–1196.
74. Berbée JFP, Havekes LM, Rensen PCN. Apolipoproteins modulate the inflammatory response to lipopolysaccharide. *J Endotoxin Res* 2005;**11**:97–103.
75. Kim S-M, Lee J-H, Kim J-R, Shin D-G, Lee S-H, Cho K-H. Female patients with atrial fibrillation have increased oxidized and glycated lipoprotein properties and lower apolipoprotein A-I expression in HDL. *Int J Mol Med* 2011;**27**:841–849.
76. Kim S-M, Kim J-M, Shin D-G, Kim J-R, Cho K-H. Relation of atrial fibrillation (AF) and change of lipoproteins: male patients with AF exhibited severe pro-inflammatory and pro-atherogenic properties in lipoproteins. *Clin Biochem* 2014;**47**:869–875.
77. Albers JJ, Slee A, Fleg JL, O'Brien KD, Marcovina SM. Relationship of baseline HDL subclasses, small dense LDL and LDL triglyceride to cardiovascular events in the AIM-HIGH clinical trial. *Atherosclerosis* 2016;**251**:454–459.
78. Rizzo M, Otvos J, Nikolic D, Montalto G, Toth PP, Banach M. Subfractions and subpopulations of HDL: an update. *CMC* 2014;**21**:2881–2891.
79. Maguire EM, Pearce SWA, Xiao Q. Foam cell formation: a new target for fighting atherosclerosis and cardiovascular disease. *Vascul Pharmacol* 2019;**112**:54–71.
80. Wang D, Yang Y, Lei Y, Tzvetkov NT, Liu X, Yeung AWK, Xu S, Atanasov AG. Targeting foam cell formation in atherosclerosis: therapeutic potential of natural products. *Pharmacol Rev* 2019;**71**:596–670.
81. Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, Doran AC, Vickers KC. The role of lipids and lipoproteins in atherosclerosis. South Dartmouth (MA): Endotext; 2000.
82. Palmisano BT, Zhu L, Eckel RH, Stafford JM. Sex differences in lipid and lipoprotein metabolism. *Mol Metab* 2018;**15**:45–55.
83. Wang X, Magkos F, Mittendorfer B. Sex differences in lipid and lipoprotein metabolism: it's not just about sex hormones. *J Clin Endocrinol Metab* 2011;**96**:885–893.
84. Regitz-Zagrosek V. Unsettled issues and future directions for research on cardiovascular diseases in women. *Korean Circ J* 2018;**48**:792–812.
85. Barud W, Palusiński R, Beltowski J, Wójcicka G. Inverse relationship between total testosterone and anti-oxidized low density lipoprotein antibody levels in ageing males. *Atherosclerosis* 2002;**164**:283–288.
86. Lee H-C, Lin H-T, Ke L-Y, Wei C, Hsiao Y-L, Chu C-S, Lai W-T, Shin S-J, Chen C-H, Sheu S-H, Wu B-N. VLDL from metabolic syndrome individuals enhanced lipid accumulation in atria with association of susceptibility to atrial fibrillation. *IJMS* 2016;**17**:134.
87. Lee H-C, Lin Y-H. The pathogenic role of very low density lipoprotein on atrial remodeling in the metabolic syndrome. *IJMS* 2020;**21**:891.
88. Deguchi H, Elias DJ, Griffin JH. Minor plasma lipids modulate clotting factor activities and may affect thrombosis risk. *Res Pract Thromb Haemost* 2017;**1**:93–102.
89. Olufadi R, Byrne CD. Effects of VLDL and remnant particles on platelets. *Pathophysiol Haemost Thromb* 2006;**35**:281–291.
90. Ouweneel AB, Van Eck M. Lipoproteins as modulators of atherothrombosis: from endothelial function to primary and secondary coagulation. *Vascul Pharmacol* 2016;**82**:1–10.
91. Fatah K, Silveira A, Tornvall P, Karpe F, Blomback M, Hamsten A. Proneness to formation of tight and rigid fibrin gel structures in men with myocardial infarction at a young age. *Thromb Haemost* 1996;**76**:535–540.
92. Betteridge DJ, Cooper MB, Saggerson ED, Pritchard BN, Tan KC, Ling E, Barbera G, McCarthy S, Smith CC. Platelet function in patients with hypercholesterolaemia. *Eur J Clin Invest* 1994;**24**:30–33.
93. DiMinno G, Silver MJ, Cerbone AM, Rainone A, Postiglione A, Mancini M. Increased fibrinogen binding to platelets from patients with familial hypercholesterolemia. *Arteriosclerosis* 1986;**6**:203–211.
94. Elisaf M, Karabina SA, Bairaktari E, Goudevenos JA, Siamopoulos KC, Tselepis AD. Increased platelet reactivity to the aggregatory effect of platelet activating factor, *in vitro*, in patients with heterozygous familial hypercholesterolaemia. *Platelets* 1999;**10**:124–131.
95. Surya II, Mommersteeg M, Gorter G, Erkelens DW, Akkerman JW. Abnormal platelet functions in a patient with abetalipoproteinemia. *Thromb Haemost* 1991;**65**:306–311.



96. Shen M-Y, Chen F-Y, Hsu J-F, Fu R-H, Chang C-M, Chang C-T, Liu C-H, Wu J-R, Lee A-S, Chan H-C, Sheu J-R, Lin S-Z, Shyu W-C, Sawamura T, Chang K-C, Hsu CY, Chen C-H. Plasma L5 levels are elevated in ischemic stroke patients and enhance platelet aggregation. *Blood* 2016;**127**:1336–1345.
97. Korpolaar SJA, Akkerman J-WN. Platelet activation by low density lipoprotein and high density lipoprotein. *Pathophysiol Haemos Thromb* 2006;**35**:270–280.
98. Zhao CX, Cui YH, Fan Q, Wang PH, Hui R, Cianflone K, Wang DW. Small dense low-density lipoproteins and associated risk factors in patients with stroke. *Cerebrovasc Dis* 2009;**27**:99–104.
99. Verhoye E, Langlois MR. Circulating oxidized low-density lipoprotein: a biomarker of atherosclerosis and cardiovascular risk? *Clin Chem Lab Med* 2009;**47**:128–137.
100. Rota S, McWilliam NA, Baglin TP, Byrne CD. Atherogenic lipoproteins support assembly of the prothrombinase complex and thrombin generation: modulation by oxidation and vitamin E. *Blood* 1998;**91**:508–515.
101. Klein S, Spannagl M, Engelmann B. Phosphatidylethanolamine participates in the stimulation of the contact system of coagulation by very-low-density lipoproteins. *Arterioscler Thromb Vasc Biol* 2001;**21**:1695–1700.
102. Zieseniss S, Zahler S, Muller I, Hermetter A, Engelmann B. Modified phosphatidylethanolamine as the active component of oxidized low density lipoprotein promoting platelet prothrombinase activity. *J Biol Chem* 2001;**276**:19828–19835.
103. Hörkkö S, Bird DA, Miller E, Itabe H, Leitinger N, Subbanagounder G, Berliner JA, Friedman P, Dennis EA, Curtiss LK, Palinski W, Witztum JL. Monoclonal autoantibodies specific for oxidized phospholipids or oxidized phospholipid-protein adducts inhibit macrophage uptake of oxidized low-density lipoproteins. *J Clin Invest* 1999;**103**:117–128.
104. Trpkovic A, Resanovic I, Stanimirovic J, Radak D, Mousa SA, Cenic-Milosevic D, Jevremovic D, Icenovic ER. Oxidized low-density lipoprotein as a biomarker of cardiovascular diseases. *Crit Rev Clin Lab Sci* 2015;**52**:70–85.
105. Langlois MR, Rietzschel ER, De Buyzere ML, De Bacquer D, Bekaert S, Blaton V, De Backer GG, Gillebert TC. Femoral plaques confound the association of circulating oxidized low-density lipoprotein with carotid atherosclerosis in a general population aged 35 to 55 years: the Asklepios Study. *Arterioscler Thromb Vasc Biol* 2008;**28**:1563–1568.
106. Polovina M, Petrovic I, Brkovic V, Asanin M, Marinkovic J, Ostojic M, Petrovic I, Brkovic V, Asanin M, Marinkovic J, Ostojic M. Oxidized low-density lipoprotein predicts the development of renal dysfunction in atrial fibrillation. *Cardiorenal Med* 2017;**7**:31–41.
107. Polovina MM, Ostojic MC, Potpara TS. Relation of biomarkers of inflammation and oxidative stress with hypertension occurrence in lone atrial fibrillation. *Mediators Inflamm* 2015;**2015**:653026.
108. Duni A, Liakopoulos V, Rapsomanikis K-P, Dounousi E. Chronic kidney disease and disproportionately increased cardiovascular damage: does oxidative stress explain the burden? *Oxid Med Cell Longev* 2017;**2017**:1–15.
109. Florens N, Calzada C, Lyasko E, Juillard L, Soulage CO. Modified lipids and lipoproteins in chronic kidney disease: a new class of uremic toxins. *Toxins (Basel)* 2016;**8**:376.
110. Emekli-Alturfan E, Basar I, Alturfan AA, Ayan F, Koldas L, Balci H, Emekli N. The relation between plasma tissue factor and oxidized LDL levels in acute coronary syndromes. *Pathophysiol Haemos Thromb* 2007;**36**:290–297.
111. Cimmino G, Cirillo P, Conte S, Pellegrino G, Barra G, Maresca L, Morello A, Cali G, Loffredo F, R De P, Arena G, Sawamura T, Ambrosio G, Golino P. Oxidized low-density lipoproteins induce tissue factor expression in T-lymphocytes via activation of lectin-like oxidized low-density lipoprotein receptor-1. *Cardiovasc Res* 2020;**116**:1125–1135.
112. Azizova OA, Roitman EV, Dement'eva II, Nikitina NA, Gagaeva EV, Lopukhin YM. Effects of low-density lipoproteins on blood coagulation and fibrinolytic activity. *Bull Exp Biol Med* 2000;**129**:541–544.
113. Lados-Krupa A, Konieczynska M, Chmiel A, Undas A. Increased oxidation as an additional mechanism underlying reduced clot permeability and impaired fibrinolysis in type 2 diabetes. *J Diabetes Res* 2015;**2015**:456189.
114. Ardlie NG, Selley ML, Simons LA. Platelet activation by oxidatively modified low density lipoproteins. *Atherosclerosis* 1989;**76**:117–124.
115. Podrez EA, Byzova TV. Prothrombotic lipoprotein patterns in stroke. *Blood* 2016;**127**:1221–1222.
116. Chen K, Febbraio M, Li W, Silverstein RL. A specific CD36-dependent signaling pathway is required for platelet activation by oxidized low-density lipoprotein. *Circ Res* 2008;**102**:1512–1519.
117. Vanhoutte PM. Regeneration of the endothelium in vascular injury. *Cardiovasc Drugs Ther* 2010;**24**:299–303.
118. Pawlowska Z, Swiatkowska M, Krzeslowska J, Pawlicki L, Cierniewski CS. Increased platelet-fibrinogen interaction in patients with hypercholesterolemia and hypertriglyceridemia. *Atherosclerosis* 1993;**103**:13–20.
119. Carvalho AC, Colman RW, Lees RS. Platelet function in hyperlipoproteinemia. *N Engl J Med* 1974;**290**:434–438.
120. Colas R, Sassolas A, Guichardant M, Cugnet-Anceau C, Moret M, Moulin P, Lagarde M, Calzada C. LDL from obese patients with the metabolic syndrome show increased lipid peroxidation and activate platelets. *Diabetologia* 2011;**54**:2931–2940.
121. Knowles RB, Lawrence MJ, Ferreira PM, Hayman MA, D'Silva LA, Stanford SN, Sabra A, Tucker AT, Hawkins KM, Williams PR, Warner TD, Evans PA. Platelet reactivity influences clot structure as assessed by fractal analysis of viscoelastic properties. *Platelets* 2018;**29**:162–170.
122. Chatterjee M, Rath D, Schlotterbeck J, Rheinlaender J, Walker-Allgaier B, Alnaggar N, Zdanyle M, Müller I, Borst O, Geisler T, Schäffer TE, Lämmerhofer M, Gawaz M. Regulation of oxidized platelet lipidome: implications for coronary artery disease. *Eur Heart J* 2017;**38**:1993–2005.
123. Blache D, Gautier T, Tietge UJF, Lagrost L. Activated platelets contribute to oxidized low-density lipoproteins and dysfunctional high-density lipoproteins through a phospholipase A2-dependent mechanism. *FASEB J* 2012;**26**:927–937.
124. Chapman MJ, Huby T, Nigon F, Thillet J. Lipoprotein (a): implication in atherothrombosis. *Atherosclerosis* 1994;**110**:S69–S75.
125. Tsironis LD, Mitsios JV, Milionis HJ, Elisaf M, Tselepis AD. Effect of lipoprotein (a) on platelet activation induced by platelet-activating factor: role of apolipoprotein (a) and endogenous PAF-acetylhydrolase. *Cardiovasc Res* 2004;**63**:130–138.
126. Labudovic D, Kostovska I, Toshihka Trajkovska K, Cekovska S, Brezovska Kavrakova J, Topuzovska S. Lipoprotein(a)—link between atherogenesis and thrombosis. *Prague Med Rep* 2019;**120**:39–51.
127. Rand ML, Sangrar W, Hancock MA, Taylor DM, Marcovina SM, Packham MA, Koschinsky ML. Apolipoprotein(a) enhances platelet responses to the thrombin receptor-activating peptide SFLLRN. *Arterioscler Thromb Vasc Biol* 1998;**18**:1393–1399.
128. Ezratty A, Simon DI, Loscalzo J. Lipoprotein(a) binds to human platelets and attenuates plasminogen binding and activation. *Biochemistry* 1993;**32**:4628–4633.
129. Caplice NM, Panetta C, Peterson TE, Kleppe LS, Mueske CS, Kostner GM, Broze GJ, Simari RD. Lipoprotein (a) binds and inactivates tissue factor pathway inhibitor: a novel link between lipoproteins and thrombosis. *Blood* 2001;**98**:2980–2987.
130. Helgadottir A, Gretarsdottir S, Thorleifsson G, Holm H, Patel RS, Gudnason T, Jones GT, van Rij AM, Eapen DJ, Baas AF, Tregouet D-A, Morange P-E, Emmerich J, Lindblad B, Gottsäter A, Kiemeny LA, Lindholt JS, Sakalihasan N, Ferrell RE, Carey DJ, Elmore JR, Tsao PS, Grarup N, Jørgensen T, Witte DR, Hansen T, Pedersen O, Pola R, Gaetani E, Magnadottir HB, Wijmenga C, Tromp G, Ronkainen A, Ruigrok YM, Blankenstein JD, Mueller T, Wells PS, Corral J, Soria JM, Souto JC, Peden JF, Jalilzadeh S, Mayosi BM, Keavney B, Strawbridge RJ, Sabater-Lleal M, Gertow K, Baldassarre D, Nyyssönen K, Rauramaa R, Smit AJ, Mannarino E, Giral P, Tremoli E, de Faire U, Humphries SE, Hamsten A, Haraldsdottir V, Olafsson I, Magnusson MK, Samani NJ, Levey AI, Markus HS, Kostulas K, Dichgans M, Berger K, Kuhlenbäumer G, Ringelstein EB, Stoll M, Seedorf U, Rothwell PM, Powell JT, Kuivaniemi H, Onundarson PT, Valdimarsson E, Matthiasson SE, Gudbjartsson DF, Thorgerisson G, Quyyumi AA, Watkins H, Farrall M, Thorsteinsdottir U, Stefansson K. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. *J Am Coll Cardiol* 2012;**60**:722–729.
131. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Genetic evidence that lipoprotein(a) associates with atherosclerotic stenosis rather than venous thrombosis. *Arterioscler Thromb Vasc Biol* 2012;**32**:1732–1741.
132. Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? *J Lipid Res* 2016;**57**:745–757.
133. Morelli VM, Lijfering WM, Bos MHA, Rosendaal FR, Cannegieter SC. Lipid levels and risk of venous thrombosis: results from the MEGA-study. *Eur J Epidemiol* 2017;**32**:669–681.
134. Grifoni E, Marcucci R, Ciuti G, Cenci C, Poli D, Mannini L, Liotta AA, Miniati M, Abbate R, Prisco D. The thrombophilic pattern of different clinical manifestations of venous thromboembolism: a survey of 443 cases of venous thromboembolism. *Semin Thromb Hemost* 2012;**38**:230–234.
135. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley THJ, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke* 2006;**37**:2493–2498.
136. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High-density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men. *Circulation* 2005;**112**:893–899.
137. Doggen CJM, Smith NL, Lemaitre RN, Heckbert SR, Rosendaal FR, Psaty BM. Serum lipid levels and the risk of venous thrombosis. *Arterioscler Thromb Vasc Biol* 2004;**24**:1970–1975.
138. Marcucci R, Liotta AA, Cellai AP, Rogolino A, Gori AM, Giusti B, Poli D, Fedi S, Abbate R, Prisco D. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. *Am J Med* 2003;**115**:601–605.
139. von DM, Nowak-Göttl U, Eisert R, Dieterich C, Barthels M, Scharrer I, Ganser A, Ehrenforth S. Increased lipoprotein (a) levels as an independent risk factor for venous thromboembolism. *Blood* 2000;**96**:3364–3368.
140. Holvoet P, Vanhaecke J, Janssens S, Van de Werf F, Collen D. Oxidized LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable coronary artery disease. *Circulation* 1998;**98**:1487–1494.
141. Kawasaki R, Kambayashi J, Ariyoshi H, Sakon M, Suehisa E, Monden M. Hypercholesterolemia as a risk factor for deep-vein thrombosis. *Thromb Res* 1997;**88**:67–73.
142. Zolcinski M, Ciesla-Dul M, Undas A. Effects of atorvastatin on plasma fibrin clot properties in apparently healthy individuals and patients with previous venous thromboembolism. *Thromb Haemost* 2012;**107**:1180–1182.

143. Violi F, Carnevale R, Pastori D, Pignatelli P. Antioxidant and antiplatelet effects of atorvastatin by Nox2 inhibition. *Trends Cardiovasc Med* 2014;**24**:142–148.
144. Zabczyk M, Majewski J, Karkowski G, Malinowski KP, Undas A, Zabczyk M, Majewski J, Karkowski G, Malinowski KP, Undas A. Vitamin K antagonists favourably modulate fibrin clot properties in patients with atrial fibrillation as early as after 3 days of treatment: relation to coagulation factors and thrombin generation. *Thromb Res* 2015;**136**:832–838.
145. Undas A, Celinska-Lowenhoff M, Lowenhoff T, Szczeklik A. Statins, fenofibrate, and quinapril increase clot permeability and enhance fibrinolysis in patients with coronary artery disease. *J Thromb Haemost* 2006;**4**:1029–1036.
146. Tehrani S, Mobarrez F, Antovic A, Santesson P, Lins P-E, Adamson U, Henriksson P, Wallen NH, Jorneskog G. Atorvastatin has antithrombotic effects in patients with type 1 diabetes and dyslipidemia. *Thromb Res* 2010;**126**:e225–e231.
147. Colli S, Eligini S, Lalli M, Camera M, Paoletti R, Tremoli E. Vastatins inhibit tissue factor in cultured human macrophages. A novel mechanism of protection against atherothrombosis. *Arterioscler Thromb Vasc Biol* 1997;**17**:265–272.
148. Undas A, Brummel-Ziedins KE, Mann KG. Anticoagulant effects of statins and their clinical implications. *Thromb Haemost* 2014;**111**:392–400.
149. Glynn RJ, Danielson E, Fonseca FAH, Genest J, Gotto AMJ, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Ridker PM. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 2009;**360**:1851–1861.
150. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;**166**:1814–1821.
151. Ray JG, Mamdani M, Tsuyuki RT, Anderson DR, Yeo EL, Laupacis A. Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med* 2001;**161**:1405–1410.
152. Lacoste L, Lam JY, Hung J, Letchacovski G, Solymoss CB, Waters D. Hyperlipidemia and coronary disease. Correction of the increased thrombogenic potential with cholesterol reduction. *Circulation* 1995;**92**:3172–3177.
153. Undas A, Celinska-Löwenhoff M, Brummel-Ziedins KE, Brozek J, Szczeklik A, Mann KG. Simvastatin given for 3 days can inhibit thrombin generation and activation of factor V and enhance factor Va inactivation in hypercholesterolemic patients. *Arterioscler Thromb Vasc Biol* 2005;**25**:1524–1525.
154. Sanguigni V, Pignatelli P, Lenti L, Ferro D, Bellia A, Carnevale R, Tesaro M, Sorge R, Lauro R, Violi F. Short-term treatment with atorvastatin reduces platelet CD40 ligand and thrombin generation in hypercholesterolemic patients. *Circulation* 2005;**111**:412–419.
155. Dangas G, Smith DA, Unger AH, Shao JH, Meraj P, Fier C, Cohen AM, Fallon JT, Badimon JJ, Ambrose JA. Pravastatin: an antithrombotic effect independent of the cholesterol-lowering effect. *Thromb Haemost* 2000;**83**:688–692.
156. Undas A, Celinska-Löwenhoff M, Domagala TB, Iwaniec T, Dropinski J, Löwenhoff T, Szczeklik A. Early antithrombotic and anti-inflammatory effects of simvastatin versus fenofibrate in patients with hypercholesterolemia. *Thromb Haemost* 2005;**94**:193–199.
157. Luo Y, Li J, Zhang J, Xu Y. Low HDL cholesterol is correlated to the acute ischemic stroke with diabetes mellitus. *Lipids Health Dis* 2014;**13**:171.
158. Dentali F, Gessi V, Marcucci R, Gianni M, Grandi AM, Franchini M. Lipoprotein(a) as a risk factor for venous thromboembolism: a systematic review and meta-analysis of the literature. *Semin Thromb Hemost* 2017;**43**:614–620.
159. Li S, Gao Y, Ma W, Wang H, Zhou G, Guo W, Liu Y. The relationship between serum lipoprotein (a) levels and ischemic stroke risk: a cohort study in the Chinese population. *Inflammation* 2014;**37**:686–693.
160. Boden-Albala B, Kargman DE, Lin I-F, Paik MC, Sacco RL, Berglund L. Increased stroke risk and lipoprotein(a) in a multiethnic community: the Northern Manhattan Stroke Study. *Cerebrovasc Dis* 2010;**30**:237–243.
161. Liu W, Xiong N, Xie K, Wu B, Qi Z, Zhou P, Gao W, Bao L, Gao X, Qiu Z, Gong H, He G, Cao B, Shi H, Luo X, Li J. A stricter control of low-density lipoprotein is necessary for thrombosis reduction in 'lower thrombosis risk' patients with atrial fibrillation: a multicenter retrospective cohort study. *J Thromb Thrombolysis* 2020;**50**:849–857.
162. Yan S, Li Q, Xia Z, Yan S, Wei Y, Hong K, Wu Y, Li J, Cheng X. Risk factors of thromboembolism in nonvalvular atrial fibrillation patients with low CHA2DS2-VASc score. *Medicine (Baltimore)* 2019;**98**:e14549.
163. Pol T, Held C, Westerbergh J, Lindback J, Alexander JH, Alings M, Erol C, Goto S, Halvorsen S, Huber K, Hanna M, Lopes RD, Ruzyllo W, Granger CB, Hijazi Z. Dyslipidemia and risk of cardiovascular events in patients with atrial fibrillation treated with oral anticoagulation therapy: insights from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *J Am Heart Assoc* 2018;**7**:e007444.
164. Qi Z, Chen H, Wen Z, Yuan F, Ni H, Gao W, Shen J, Li J, Lin Y, Shan Y, Jin B, Yan P, Shi H, Luo X. Relation of low-density lipoprotein cholesterol to ischemic stroke in patients with nonvalvular atrial fibrillation. *Am J Cardiol* 2017;**119**:1224–1228.
165. Wu M, Zhou XH, Ruozha B, Song SF, Li YD, Zhang JH, Xing Q, Lu YM, Tang BP. [The relationship between LDL-C and ischemic stroke in 2 470 patients with non-valvular atrial fibrillation in Xinjiang region]. *Zhonghua Nei ke za Zhi* 2017;**56**:258–262.
166. Igarashi Y, Yamaura M, Ito M, Inuzuka H, Ojima K, Aizawa Y. Elevated serum lipoprotein(a) is a risk factor for left atrial thrombus in patients with chronic atrial fibrillation: a transesophageal echocardiographic study. *Am Heart J* 1998;**136**:965–971.
167. Lip GY. Lipoprotein(a) in atrial fibrillation. *Am Heart J* 2000;**139**:555–556.
168. Enkhaa B, Anuurad E, Zhang W, Tran T, Berglund L. Lipoprotein(a): genotype-phenotype relationship and impact on atherogenic risk. *Metab Syndr Relat Disord* 2011;**9**:411–418.
169. Prinsns JK, Nannankeril PJ, Sidorova TN, Yermalitskaya LV, Boutaud O, Zagolkapitte I, Barnett JV, Murphy MB, Subati T, Stark JM, Christopher IL, Jafarian-Kerman SR, Saleh MA, Norlander AE, Loperena R, Atkinson JB, Fogo AB, Luther JM, Amarnath V, Davies SS, Kirabo A, Madhur MS, Harrison DG, Murray KT. Highly reactive isolevuglandins promote atrial fibrillation caused by hypertension. *JACC Basic Transl Sci* 2020;**5**:602–615.
170. Aschner M, Nguyen TT, Sinitskii AI, Santamaria A, Bornhorst J, Ajsuvakova OP, da Rocha JBT, Skalny AV, Tinkov AA. Isolevuglandins (isoLGs) as toxic lipid peroxidation byproducts and their pathogenetic role in human diseases. *Free Radic Biol Med* 2020;**S0891-5849(20)31298-3**.
171. Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. *Nat Rev Cardiol* 2019;**16**:305–318.
172. Decker JJ, Norby FL, Rooney MR, Soliman EZ, Lutsey PL, Pankow JS, Alonso A, Chen LY. Metabolic syndrome and risk of ischemic stroke in atrial fibrillation: ARIC study. *Stroke* 2019;**50**:3045–3050.
173. Flint AC, Conell C, Ren X, Kamel H, Chan SL, Rao VA, Johnston SC. Statin adherence is associated with reduced recurrent stroke risk in patients with or without atrial fibrillation. *Stroke* 2017;**48**:1788–1794.
174. Ndrepepa G, Braun S, von BN, Mehili J, Gorchakova O, Vogt W, Schomig A, Kastrati A. Oxidized low density lipoproteins, statin therapy and severity of coronary artery disease. *Clin Chim Acta* 2005;**360**:178–186.
175. Obermayer G, Afonyushkin T, Binder CJ. Oxidized low-density lipoprotein in inflammation-driven thrombosis. *J Thromb Haemost* 2018;**16**:418–428.
176. van Kuilenburg J, Lappegard KT, Sexton J, Plesiewicz I, Lap P, Bouwels L, Sprong T, Mollnes TE, Verheugt F, van Heerde WL, Pop GA. Persisting thrombin activity in elderly patients with atrial fibrillation on oral anticoagulation is decreased by anti-inflammatory therapy with intensive cholesterol-lowering treatment. *J Clin Lipidol* 2011;**5**:273–280.
177. He L, Xu R, Wang J, Zhang L, Zhang L, Zhao W, Dong W. Prestroke statins use reduces oxidized low density lipoprotein levels and improves clinical outcomes in patients with atrial fibrillation related acute ischemic stroke. *BMC Neurol* 2019;**19**:240.
178. Pechlaner R, Tsimikas S, Yin X, Willeit P, Baig F, Santer P, Oberhollenzer F, Egger G, Witztum JL, Alexander VJ, Willeit J, Kiechl S, Mayr M. Very-low-density lipoprotein-associated apolipoproteins predict cardiovascular events and are lowered by inhibition of APOC-III. *J Am Coll Cardiol* 2017;**69**:789–800.
179. Lauder SN, Allen-Redpath K, Slatter DA, Aldrovandi M, O'Connor A, Farewell D, Percy CL, Molhoek JE, Rannikko S, Tyrrell VJ, Ferla S, Milne GL, Poole AW, Thomas CP, Obaji S, Taylor PR, Jones SA, Groot PG, de Urbanus RT, Horkko S, Uderhardt S, Ackermann J, Jenkins VP, Brancale A, Kronke G, Collins PW, O'Donnell VB. Networks of enzymatically oxidized membrane lipids support calcium-dependent coagulation factor binding to maintain hemostasis. *Sci Signal* 2017;**10**:ean2787.
180. Slatter DA, Percy CL, Allen-Redpath K, Gajisiewicz JM, Brooks NJ, Clayton A, Tyrrell VJ, Rosas M, Lauder SN, Watson A, Dul M, Garcia-Diaz Y, Aldrovandi M, Heurich M, Hall J, Morrissey JH, Lacroix-Desmazes S, Delignat S, Jenkins PV, Collins PW, O'Donnell VB. Enzymatically oxidized phospholipids restore thrombin generation in coagulation factor deficiencies. *JCI Insight* 2018;**3**:3.
181. Itabe H. Oxidized low-density lipoproteins: what is understood and what remains to be clarified. *Biol Pharm Bull* 2003;**26**:1–9.
182. Tselepis AD. Oxidized phospholipids and lipoprotein-associated phospholipase A2 as important determinants of Lp(a) functionality and pathophysiological role. *J Biomed Res* 2018;**31**:13–22.
183. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. *J Am Coll Cardiol* 2019;**74**:54–66.
184. Zekavat SM, Ruotsalainen S, Handsaker RE, Alver M, Bloom J, Poterba T, Seed C, Ernst J, Chaffin M, Engreitz J, Peloso GM, Manichaikul A, Yang C, Ryan KA, Fu M, Johnson WC, Tsai M, Budoff M, Vasan RS, Cupples LA, Rotter JI, Rich SS, Post W, Mitchell BD, Correa A, Metspalu A, Wilson JG, Salomaa V, Kellis M, Daly MJ, Neale BM, McCarroll S, Surakka I, Esko T, Ganna A, Ripatti S, Kathiresan S, Natarajan P, NHLBI TOPMed Lipids Working Group. Deep coverage whole genome sequences and plasma lipoprotein(a) in individuals of European and African ancestries. *Nat Commun* 2018;**9**:2606.
185. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol* 2017;**69**:692–711.
186. Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res* 2016;**57**:1339–1359.
187. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res* 2016;**57**:1953–1975.
188. Zanetti D, Gustafsson S, Assimes TL, Ingelsson E. Comprehensive investigation of circulating biomarkers and their causal role in atherosclerosis-related risk factors and clinical events. *Circ Genomic Precis Med* 2020;**13**:e002996.

189. Enas EA, Varkey B, Dharmarajan TS, Pare G, Bahl VK. Lipoprotein(a): An independent, genetic, and causal factor for cardiovascular disease and acute myocardial infarction. *Indian Heart J* 2019;**71**:99–112.
190. Pan Y, Li H, Wang Y, Meng X, Wang Y. Causal effect of Lp(a) [lipoprotein(a)] level on ischemic stroke and Alzheimer disease: a mendelian randomization study. *Stroke* 2019;**50**:3532–3539.
191. Saleheen D, Haycock PC, Zhao W, Rasheed A, Taleb A, Imran A, Abbas S, Majeed F, Akhtar S, Qamar N, Zaman KS, Yaqoob Z, Saghir T, Rizvi SNH, Memon A, Mallick NH, Ishaq M, Rasheed SZ, Memon F-U-R, Mahmood K, Ahmed N, Frossard P, Tsimikas S, Witztum JL, Marcovina S, Sandhu M, Rader DJ, Danesh J. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 2017;**5**:524–533.