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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

Dyslipidemia Profiles in Patients with Peripheral Artery Disease

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Abstract

Purpose of Review This review of the literature aims to discuss the evidence linking different lipid and apolipoprotein measures to peripheral artery disease.

Recent Findings Measures of atherogenic dyslipidemia, including elevations in total cholesterol and total cholesterol/high-density lipoprotein cholesterol as well as low levels of high-density lipoprotein cholesterol, are strongly associated with future risk of peripheral artery disease. Compared to coronary artery disease, there are fewer data showing an association between low-density lipoprotein cholesterol and future risk of peripheral artery disease. Novel lipid measures, including nuclear magnetic resonance-derived lipoproteins and oxidized lipids, may lead to better assessments of future peripheral artery disease risk.

Summary These data highlight the important differences between lipid risk factors for peripheral and coronary artery disease. Improved understanding of these distinctions may lead to new therapeutic options for patients with peripheral artery disease.

Keywords Dyslipidemia · Lipoproteins · Atherosclerosis · Cholesterol · Apolipoproteins · Peripheral artery disease

Introduction

Lower-extremity peripheral artery disease (PAD) refers to atherosclerosis, thrombosis, and inflammation causing obstruction in one or more leg arteries [1]. PAD affects an estimated eight million adults in the USA and 200 million individuals worldwide [2, 3]. Although individuals with PAD are often asymptomatic, they remain at heightened risk of cardiovascular events [4]. Clinical manifestations of PAD include claudication and lower-extremity ulcers, and in severe cases, PAD may result in amputation and even death. Numerous epidemiologic studies have demonstrated an association between PAD and traditional cardiovascular risk factors, including diabetes, hypertension, tobacco use, and advanced age [4]. However, compared to coronary artery disease (CAD), there are fewer studies examining the role of lipids and apolipoproteins in the pathogenesis of PAD (Table 1). Among the data available, some important differences between the lipid profiles associated with PAD and CAD have also emerged. In this review of the literature, we detail the lipid profiles associated with PAD, discuss insights from studies of lipid-lowering therapies, and also discuss future directions in this field.

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Considerations when Comparing PAD Clinical Data

When discussing clinical studies of PAD, an important consideration is the clinical definition used to define PAD. Many studies define PAD based on symptoms suggestive of claudication using validated questionnaires such as the Rose questionnaire or San Diego Claudication Questionnaire [4]. Others

Table 1 Population-based studies of lipids and apolipoproteins in peripheral artery disease

Study	Sex of participants	Age of participants (years)	PAD definition	Lipids/apolipoproteins evaluated
Framingham Study [5]	Men and women	28–62	IC	TC
Framingham Offspring Study [6]	Men and women	≥ 40	IC, femoral bruits, ABI < 0.90	TC, HDL-C, triglycerides
Cardiovascular Health Study [7, 8]	Men and women	≥ 65	ABI < 0.90	TC, HDL-C, LDL-C, triglycerides
Rotterdam Study [9]	Men and women	≥ 55	ABI < 0.90	TC, HDL-C
Multi-Ethnic Study of Atherosclerosis [10]	Men and women	45–84	ABI ≤ 0.90	TC/HDL-C
Edinburgh Artery Study [11]	Men and women	55–74	IC, ABI, reactive hyperemia	TC, HDL-C, non-HDL-C, triglycerides
Reykjavik Study [12]	Men	34–80	IC	TC
Israeli Ischemic Heart Disease [13]	Men	40–65	IC	TC, non-HDL-C, TC/HDL-C
Honolulu Heart Program [14]	Men	> 70	ABI	TC, HDL-C, triglycerides
Physicians' Health Study [15]	Men	40–84	IC, LE revascularization	TC, HDL-C, LDL-C, triglycerides, TC:HDL-C, ApoA-I, $ApoB_{100}$
Women's Health Study [16, 17]	Women	≥ 45	IC, LE revascularization	TC, HDL-C, LDL-C, triglycerides, non-HDL-C, TC:HDL-C, ApoA-I, $ApoB_{100}$
Health Professionals Follow-Up Study [18]	Men	40–75	LE amputation or revascularization, ≥ 50% obstruction in LE artery, ABI < 0.9, or physician diagnosis of PAD	TC
Speedwell Study [19]	Men	45–59	IC	TC, HDL-C, triglycerides
Smith et al. [20]	Men and women	Median 65	Reduction in ABI > 0.14, CLI	TC, triglycerides

ABI ankle-brachial index, *Apo* apolipoprotein, *CLI* critical limb ischemia, *HDL-C* high-density lipoprotein cholesterol, *IC* intermittent claudication, *LDL-C* low-density lipoprotein cholesterol, *LE* lower extremity, *PAD* peripheral artery disease, *TC* total cholesterol

rely on the ankle-brachial index (ABI), which is the ratio of the highest brachial artery pressure to the highest ankle pressure in each limb. Although an ABI ≤ 0.90 is considered diagnostic of PAD, many studies utilize alternative thresholds [21]. Additional PAD endpoints include percutaneous or surgical revascularization, critical limb ischemia, or amputation. A debate of the merits of each clinical PAD endpoint is beyond the scope of this review, and we broach the topic simply to highlight this important consideration when comparing data from different studies.

Total Cholesterol

Total cholesterol is one of the most common lipid measures reported on standard lipid panels. Total cholesterol is a summary measure that includes different density fractions of cholesterol, including the high-density, low-density, and very low-density lipoprotein cholesterol circulating in the bloodstream, and it is measured directly from serum or plasma in the clinical chemistry laboratory. Among cholesterol measures, total cholesterol was assayed in some of the earliest epidemiologic cohorts of cardiovascular disease and has a positive risk association in many of these studies.

The original Framingham Heart Study followed 2336 men and 2873 women age 28–62 for up to 38 years [5]. Participants completed claudication questionnaires at 2-year intervals, and investigators identified 381 cases of incident claudication. Using a pooled logistic regression analysis, every 40-mg/dL increase in total cholesterol was associated with a relative risk of 1.2 for claudication (95% confidence interval 1.1–1.3) [5]. The Speedwell prospective heart study of British men age 45–59 found that baseline levels of total cholesterol were on average ~ 10 mg/dL higher among those who developed future claudication ($p < 0.05$) [19]. Finally, in a prospective cohort of 8045 Icelandic men with 76 incident cases of

intermittent claudication detected using the Rose questionnaire, total cholesterol was a stronger risk factor for PAD than for coronary heart disease [12].

Additional studies have examined the relationship between total cholesterol and ABI as an indicator of PAD. The Framingham Offspring Study prospectively followed 3313 men and women and collected data on claudication symptoms and ABI. Investigators found that hypercholesterolemia, defined as either having a total cholesterol level ≥ 240 mg/dL or actively taking a lipid-lowering drug, had a relative risk of 1.7 (95% confidence interval 1.1–2.4) for ABI < 0.9 in sex- and age-adjusted regression models [6]. Of note, however, this risk association was no longer statistically significant in multivariable models adjusting for additional cardiovascular risk factors. In the Cardiovascular Health Study, every 10-mg/dL increase in total cholesterol was associated with a 10% greater risk of an ABI < 0.9 [7]. Studies of older patients have found similar risk associations for total cholesterol and abnormal ABI [9, 14].

Several prospective cohorts have examined the association between total cholesterol and "hard" clinical PAD endpoints such as peripheral revascularization. The Health Professionals Follow-Up Study followed 44,985 men free of cardiovascular disease at baseline for a median of 24.2 years [18]. Investigators identified 537 cases of incident PAD, a composite outcome defined by limb amputation or revascularization, a peripheral angiogram showing obstruction ≥ 50% in at least one artery, ABI < 0.9, or a physician diagnosis of PAD. Self-reported hypercholesterolemia was associated with a 45% increased risk of PAD [18]. The Physicians' Health Study was a prospective cohort of 14,916 apparently healthy men age 40–84 who were free of cardiovascular disease at baseline [15]. PAD was defined as intermittent claudication or lower-extremity revascularization. In a nested case–control analysis of 140 individuals with incident PAD and 140 age- and smoking status-matched controls, those in the top quartile of total cholesterol had a relative risk of 3.1 (95% confidence interval 1.5–6.5) for incident PAD compared to those in the bottom quartile in multivariable-adjusted models (Fig. 1a) [15]. In 27,935 women enrolled in the Women's Health Study who had blood samples available for laboratory measurement, total cholesterol was not associated with incident PAD in either age-adjusted or multivariable-adjusted regression analyses (Fig. 1b) [16]. PAD was defined as intermittent claudication, confirmed using the Edinburgh Claudication Questionnaire, or peripheral artery revascularization, confirmed by physician review of medical records.

High-Density Lipoprotein Cholesterol

A low concentration of HDL-C is among the strongest lipoprotein risk markers for PAD. In the Framingham Offspring Study, every 5-mg/dL decrease in HDL-C was associated with a 10% increased risk of incident PAD [6]. Similarly, the Cardiovascular Health Study showed a 1% increased odds for every 1 mg/dL decrease in HDL-C [7]. The Rotterdam study included 6450 people age 55 and older, and defined PAD as an ABI < 0.9. HDL-C concentrations ≥ 35 mg/dL were associated with an odds ratio of 0.7 (95% confidence interval 0.5–0.8) for incident PAD compared to levels < 35 mg/dL [9]. Investigators in the Edinburgh Artery Study collected data on claudication, ABI, and reactive hyperemia in 1592 men and women age 55–74 [11]. Every 15.5-mg/dL increase in HDL-C was associated with a relative risk of 0.7 (95% confidence interval 0.5–1.0) for claudication and a 0.012 (± 0.006) unit increase in ABI in multivariable-adjusted models. In contrast to these data, the Speedwell study found no risk association for HDL-C and incident claudication [19].

Several studies of PAD have assessed the ratio of total cholesterol to HDL-C (TC/HDL-C), which has a high discriminatory capacity for other forms of atherosclerotic disease, even when each individual measure is within normal limits [22]. In a study of prevalent PAD diagnosed using the Edinburgh Claudication Questionnaire and ABI ≤ 0.90, mean TC/HDL-C among those with PAD was 1.4 units greater than among healthy controls ($p < 0.001$) [23]. Among participants in the Physicians' Health Study, TC/HDL-C was the strongest lipid, apolipoprotein, or inflammatory biomarker for incident PAD; the relative risk for the highest versus lowest quartile of TC/HDL-C was 3.9 (95% confidence interval 1.7–8.6) [15]. The investigators also concluded there was no benefit to additionally testing other lipid or apolipoprotein measures, including total cholesterol, HDL-C, LDL-C, triglycerides, apolipoprotein A-1, or apolipoprotein B_{100}, in terms of assessing future risk. The Multi-Ethnic Study of Atherosclerosis (MESA), which was a cross-sectional study of 6814 individuals free of cardiovascular disease at baseline, found that a TC/HDL-C measure > 5.0 was associated with a 58% increased risk of ABI ≤ 0.90 compared to TC:HDL-C ≤ 5.0 [10]. In the Women's Health Study, HDL-C and TC/HDL-C had similar, robust associations with incident PAD in multivariable-adjusted regression models (hazard ratio for extreme tertile comparison 3.33, 95% confidence interval 1.85–5.85 and 3.11, 95% confidence interval 1.67–5.81, respectively) [17]. Importantly, within this female population, low levels of HDL-C did identify women at greater risk for future PAD beyond TC/HDL-C alone.

Triglycerides

Although plasma triglyceride concentration is an important risk factor for atherosclerotic disease, the data showing an association with PAD are conflicting. Among 193 patients with diabetes and prevalent PAD based on both a claudication questionnaire and ABI < 0.90, every 89-mg/dL increase in triglycerides was associated with an increased risk of PAD

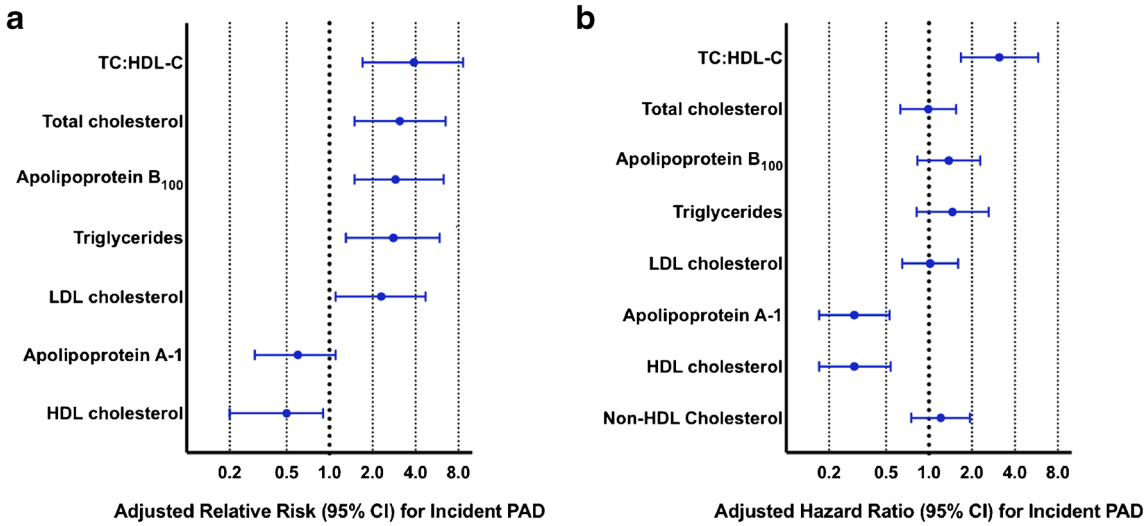

Fig. 1 **a** Risk associations between standard lipid and apolipoprotein measures and incident PAD in the Physicians' Health Study. Relative risk and 95% confidence intervals for the top versus bottom quartile of standard lipid and apolipoprotein measures, adjusted for age, smoking, diabetes, hypertension, family history of premature atherosclerosis, exercise frequency, and body mass index (**a** created using data from [15]). **b** Risk associations between standard lipid and apolipoprotein measures and incident PAD in the Women's Health Study. Hazard ratio and 95% confidence intervals for the top versus bottom tertile of standard lipid and apolipoprotein measures, adjusted for age, smoking pack-years, metabolic syndrome, hypertension, hormonal therapy, high-sensitivity C-reactive protein, lipid-lowering therapy, randomized treatment assignment, and body mass index (**b** created using data from [17]). PAD, peripheral artery disease; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol; LDL, low-density lipoprotein

compared to controls (risk ratio 1.006, 95% confidence interval 1.000–1.012) [24]. In the Speedwell heart study, triglyceride concentration was on average 29 mg/dL higher in those who developed claudication compared to controls ($p < 0.01$) [19]. Triglyceride concentration may also be associated with PAD progression. In a population of 415 active smokers with PAD defined by claudication and an ABI < 0.9, a triglyceride level ≥ 195 mg/dL was associated with a 70% greater risk of ABI decrease of at least 0.15 over time ($p = 0.003$) [20]. The Physicians' Health Study found a robust association between plasma triglycerides and incident PAD; the relative risk for extreme quartiles was 2.8 (95% confidence interval 1.3–5.9) in a multivariable-adjusted model [15]. Furthermore, clinical trial data also suggest that fibrate therapy may lead to reductions in claudication among individuals with PAD over time [25]. However, several other studies, including the Framingham Offspring Study, Edinburgh Artery Study, and Cardiovascular Health Study, have not found a significant association between triglycerides in PAD after adjusting for other traditional risk factors and lipid measures [6, 7, 11]. In contrast to the Physicians' Health Study, the Women's Health Study also found no significant association between triglycerides and incident PAD [17].

Low-Density Lipoprotein Cholesterol

In typical cholesterol panels, LDL-C is calculated using the Friedewald equation rather than directly measured [26]. The accuracy of this method is reduced in the non-fasting state or in individuals with elevated levels of plasma triglycerides [27]. Although there are methods of directly measuring LDL-C, this requires additional time and cost, thus limiting its role in the clinical setting. Numerous lines of evidence have documented the critical role LDL-C plays in the pathogenesis of atherosclerosis [28]. However, in contrast to CAD, data supporting a link between LDL-C and incident PAD are limited. Part of this gap in the literature is because many early cohorts did not include either calculated or measured values of LDL-C and instead relied on total cholesterol. Nonetheless, when LDL-C has been measured, its association with PAD in epidemiologic studies is inconsistent.

One retrospective analysis examined 467 men and 1444 women with a mean age ~ 81 and symptomatic PAD [29]. In this study, each 1-mg/dL increase in LDL-C was associated with a 1.9% increased risk of prevalent PAD. Of note, the diagnosis of PAD was based solely on chart review with an unvalidated and broad definition that included such criteria as skin and nail changes. In 6-year follow-up data from the Cardiovascular Health Study, heightened levels of LDL-C were associated with declining ABI [8]. Importantly, many individuals in this study had a history of atherosclerotic disease at baseline with a mean age at enrollment of 74, meaning some participants likely already had PAD at the time of enrollment. In the Physicians' Health Study, the relative risk for incident PAD among individuals in the highest compared to the lowest quartile of LDL-C was 2.3 (95% confidence interval 1.1–4.7) [15]. This is a similar risk association to that of

apolipoprotein B_{100}, a surrogate for atherogenic lipoprotein particles, and incident myocardial infarction (MI) in the same cohort [30]. There was no significant association between LDL-C and incident PAD in the Women's Health Study in either age-adjusted or multivariable-adjusted regression models [17]. This is in sharp contrast to the positive risk association observed between LDL-C and the composite endpoint of incident MI, coronary revascularization, ischemic stroke, or cardiovascular death in the same cohort [31].

Non-High-Density Lipoprotein Cholesterol

Non-HDL-C encompasses all atherogenic lipoproteins, including LDL-C, VLDL-C, intermediate-density lipoprotein cholesterol (IDL-C), lipoprotein(a), chylomicrons, and triglyceride-rich chylomicron remnant, and easily calculated by subtracting HDL-C from total cholesterol, both of which are measured in the standard lipid assay used by most clinicians. Several studies have shown that non-HDL-C is a powerful marker of future cardiovascular events and can help identify individuals at heightened cardiovascular risk, even though they may have a normal LDL-C [32–34].

Data on non-HDL-C and PAD are less clear. In an Israeli study of 8343 men free of symptomatic PAD and CAD at baseline who were followed for 5 years, non-HDL-C was the only lipid measure associated with incident claudication in multiple regression models that also adjusted for HDL-C and TC:HDL-C [13]. Similarly, in the Edinburgh Artery Study, every ~ 50-mg/dL increase in non-HDL-C was associated with a 60% increased risk of claudication and a 0.02-unit decrease in ABI [11]. In contrast, there was no significant association between non-HDL-C and incident PAD in the Women's Health Study [17].

Lipid-Lowering Therapy in PAD: Statins

Although the link between LDL-C and incident PAD in epidemiologic studies is inconsistent, statins reduce mortality and cardiovascular events in patients with PAD, and professional society guidelines recommend statin therapy in this patient population [21, 35]. There is a growing body of literature showing that LDL-C lowering can also reduce limb events in PAD. In the landmark Scandinavian Simvastatin Survival Study (4S) of 4444 men and women with a history of MI or angina, simvastatin led to a significant reduction in new or worsening claudication compared to placebo (2.3% vs. 3.6%, $p = 0.008$) but no change in the incidence of femoral bruits [36]. Of note, claudication was adjudicated without using a validated questionnaire, and 6% of the study population already reported claudication at enrollment [37]. In the Heart Protection Study, 20,536 high-risk patients, including 6748 with documented PAD, received either simvastatin 40 mg daily or placebo [38]. After a mean follow-up of 5 years, simvastatin led to a 16% relative reduction in the risk of PAD events. However, this was primarily due to a 20% reduction in non-coronary revascularization, which also included carotid interventions. Additionally, simvastatin did not reduce amputations.

An observational study of 155,647 patients with newly diagnosed PAD in the Veterans Affairs health system found that statin use significantly reduced rates of lower-extremity amputation compared to anti-platelet therapy alone, and that higher-intensity statin therapy had a greater effect on amputations (hazard ratio 0.67, 95% confidence interval 0.61–0.74) than lower- to moderate-intensity statins (hazard ratio 0.81, 95% confidence interval 0.75–0.86) [39]. However, it is not clear whether this benefit was purely due to overall LDL-C reduction or due to additional alterations in LDL particle number or size, or a reduction in inflammation. Recently, the FOURIER trial randomized 27,564 patients with known atherosclerotic disease already on statin therapy to either evolocumab, a monoclonal antibody against PCSK9 that dramatically lowers LDL-C, or placebo [40]. Evolocumab led to a 42% reduction in major adverse limb events compared to placebo [41••].

Lipid-Lowering Therapy in PAD: Non-Statin-Based Approaches

Earlier studies examined the effects of lipid lowering therapy on additional PAD-related outcomes, although the number of patients included in these studies is limited. One such study randomized 24 patients with claudication and either hypercholesterolemia or hypertriglyceridemia to active treatment with cholestyramine, nicotinic acid, or clofibrate versus usual care [42]. Those in the active treatment arm experienced less angiographic progression of their PAD after a mean duration of 19 months. The Cholesterol-Lowering Atherosclerosis Study (CLAS) randomized 162 individuals with a history of coronary artery bypass surgery to LDL-C-lowering therapy with colestipol hydrochloride (a bile acid sequestrant), HDL-C raising therapy with niacin, and diet compared to placebo and diet [43]. At 2 years, drug therapy reduced atherosclerotic plaque burden in the femoral arteries compared to placebo, although the change was less pronounced than that seen in either native coronary arteries or surgical bypass grafts. The Program on the Surgical Control of the Hyperlipidemias (POSCH) trial randomized 838 patients with a prior MI to either partial ileal bypass surgery or placebo [44]. After a mean follow-up of 9.7 years, surgical intervention reduced the incidence of both claudication ($p = 0.038$) and Doppler ultrasound evidence of PAD at 5 years ($p < 0.01$) [44].

Lipoprotein Particles and Triglyceride-Rich Lipoproteins

Standard lipid panels are unable to measure the concentration or size of lipoprotein particles and instead measure the overall cholesterol concentration within each particle class. However, lipoprotein particle size and number, as well as the cholesterol content of these particles, can vary significantly between individuals [31]. This is particularly relevant for triglyceride-rich lipoproteins like VLDL, which are typically not included in standard lipid panels and, therefore, have often been excluded from epidemiologic studies in PAD.

There are numerous methods that permit measurement of lipoprotein particle concentration and size, including gel chromatography, sequential ultracentrifugation, and nuclear magnetic resonance (NMR) spectroscopy. Recently, an analysis from the Women's Health Study used NMR spectroscopy to characterize the lipoprotein profile of incident PAD. Although LDL-C was not significantly associated with incident PAD, both total and small LDL particle concentrations were associated (p-trend across tertiles 0.02 for both) [17]. Other measures, including HDL particle size and concentrations of both medium and very large VLDL particles, were significantly associated with incident PAD. Overall, this analysis revealed that components of atherogenic dyslipidemia, including elevations in TC/HDL-C, triglyceride-rich lipoproteins, and small LDL particles as well as low levels of HDL particles, are more strongly associated with incident PAD than a composite of CAD and cerebrovascular disease (Fig. 2).

Apolipoproteins

Lipoprotein particles consist of not just cholesterol and triglycerides but also phospholipids and apolipoproteins. Apolipoproteins typically reside on the surface of these particles to provide structural support, act as enzymatic substrates, and bind lipoprotein receptors [45]. Apolipoprotein A–I is the primary lipoprotein in HDL particles, and each particle may contain several apolipoprotein A–I molecules. Apolipoprotein B_{100} is the primary apolipoprotein component of LDL, VLDL, and IDL particles, and there is typically only one copy of Apolipoprotein B_{100} in each of these particles. As discussed above, since the cholesterol content of lipoprotein particles can vary significantly, studies have also examined the link between apolipoprotein concentration and incident PAD as another way of estimating lipoprotein particle number.

In the Physicians' Health Study, apolipoprotein A-1 concentration was inversely associated with incident PAD [14]. Levels in the highest quartile were associated with a 40% risk reduction compared to levels in the lowest quartile, although this did not reach statistical significance. The risk association was even more pronounced in the Women's Health Study, which showed a 70% risk reduction for those in the highest tertile compared to the lowest tertile (p-trend across tertiles < 0.0001) [17].

An observational study of 18 patients with intermittent claudication not on statin therapy showed that overall apolipoprotein B levels were higher compared to controls [46]. In the Physicians' Health Study, apolipoprotein B-100 was one of the strongest markers of future PAD risk, only surpassed by total cholesterol and TC/HDL-C [15]. Individuals with levels in the highest quartile had a relative risk of 2.9 for incident PAD (95% confidence interval 1.5–6.3) compared to those in the lowest quartile. In contrast, apolipoprotein B_{100} was not significantly associated with incident PAD in either age-adjusted or multivariable-adjusted regression models in the Women's Health Study [17].

Oxidized Lipids

Although not measured in clinical assays, there is a growing body of research on the role of oxidized lipids in atherosclerotic disease. Data suggest that LDL particles themselves are not atherogenic; rather, they become atherogenic after traversing the endothelial barrier and undergoing oxidative modification by monocytes, endothelial cells, and macrophages [47, 48]. Both in vivo and in vitro data suggest oxidized LDL particles subsequently play an important role in atherosclerosis through monocyte recruitment, further uptake of LDL by monocytes, retention of monocytes in the subendothelial space, and potentiation of a local inflammatory response [47, 48]. There are clinical data further suggesting a link between oxidized lipids and PAD.

In the Edinburgh Artery Study, circulating lipid peroxides were higher in individuals with PAD compared to controls ($p = 0.001$), and every 1-μmol/L increase in lipid peroxides was associated with a 17% increased risk of PAD among nonsmokers [49]. There was no significant association when smokers were included in the analysis. Among 62 individuals with early-onset PAD requiring surgical intervention before age 50, circulating antibodies against oxidized LDL better discriminated cases versus controls than plasma triglycerides or apolipoprotein A–I [50]. The Bruneck prospective study followed 1510 men and women age 40–79 with ultrasound measures of carotid and femoral atherosclerosis and measured the concentration of antibodies against oxidized lipids in more than 90% of participants. After multivariable adjustment, antibody levels in the highest tertile were significantly associated with incident femoral and carotid atherosclerosis over a 5-year interval [51]. More recently, in a nested case–control analysis of 143 men with PAD from the Health Professionals Follow-up Study and 144 women with PAD from the Nurses' Health Study, each standard deviation increase in circulating antibodies to oxidized lipids was associated with a 51% increased risk of PAD in women (95% confidence interval 24–85%) and a

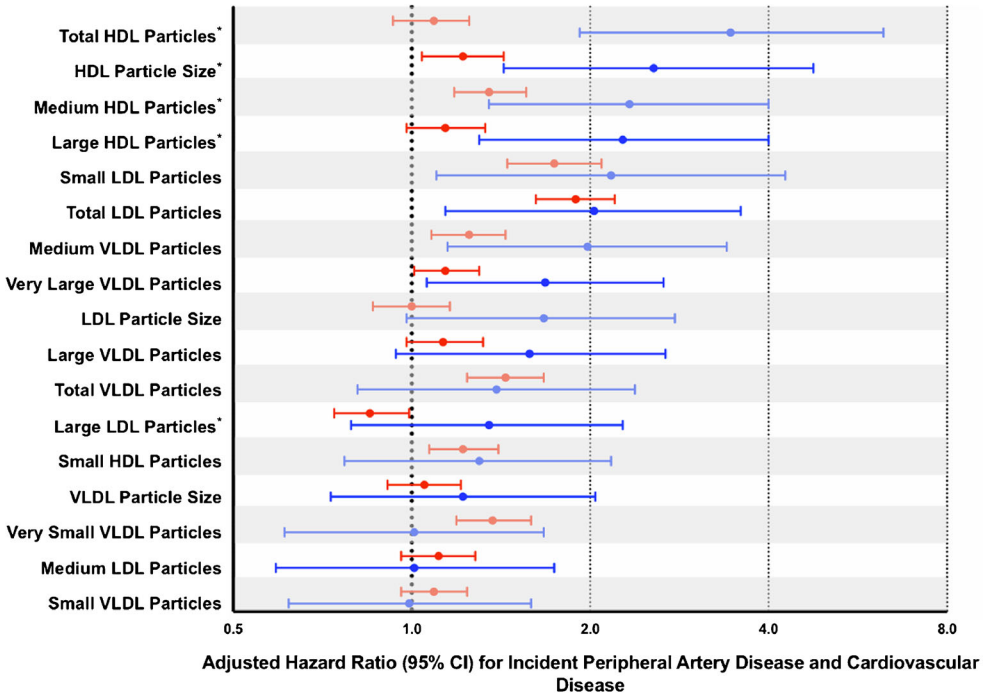

Fig. 2 Risk associations between nuclear magnetic resonance lipoprotein measures and incident peripheral artery disease versus incident cardiovascular disease in the Women's Health Study. Hazard ratios and 95% confidence intervals for the highest versus lowest tertile of lipoprotein measure and its association with incident peripheral artery disease (*blue*) and cardiovascular disease (*red*), adjusted for age, smoking pack-years, metabolic syndrome, hypertension, hormonal therapy, high-sensitivity C-reactive protein, lipid-lowering therapy, randomized treatment assignment, and body mass index. *Asterisk* denotes hazard ratios comparing lowest to highest tertile. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; CI, confidence interval (figure created using data from [17])

23% increased risk in men (95% confidence interval 0–52%) in multivariable-adjusted models [52].

Future Directions

Given the link between PAD and atherogenic dyslipidemia, several recent clinical trials are assessing drugs that may be particularly effective in PAD. The REDUCE-IT trial randomized more than 8000 high-risk individuals with a history of cardiovascular disease and hypertriglyceridemia to either high-dose eicosapentaenoic acid or placebo [53]. History of PAD was included as an enrollment criterion in the trial, and both lower-extremity revascularization and amputation were included as tertiary and exploratory outcomes. In the overall trial population, treatment with eicosapentaenoic acid led to no change in the rate of lower-extremity amputation compared to placebo (hazard ratio 1.04, 95% CI 0.57–1.89). However, additional analyses of limb-related outcomes have not yet been published. The PROMINENT trial (NCT03071692) is randomizing 10,000 participants with hypertriglyceridemia to either placebo or pemafibrate, a novel fibrate, in both primary and secondary prevention arms. New and worsening PAD is a secondary outcome of this trial, which is currently ongoing.

Conclusion

These data highlight the key lipid and apolipoprotein determinants of PAD. As discussed, many of these measures exhibit a distinct risk association from that of CAD, although atherosclerotic diseases in any arterial bed have historically been considered equivalent. Solely focusing on LDL-C as a therapeutic target may not fully address the risk of first or recurrent limb events in these patients. Hopefully, several ongoing clinical trials will not only lead to further insights into the lipoprotein profiles of PAD but also lead to new therapeutic options in this high-risk patient population.

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Compliance with Ethical Standards

Conflict of Interest Aaron W. Aday declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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