Curr Treat Options Cardio Med (2019) 21: 94
DOI 10.1007/s11936-019-0791-7

Vascular Disease (M Weinberg, Section Editor)

Primary and Novel Lipid-Lowering Therapies to Reduce Risk in Patients With Peripheral Arterial Disease

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Published online: 17 December 2019

This article is part of the Topical Collection on *Vascular Disease*

Keywords Vascular disease · Peripheral arterial disease · Accelerated atherosclerotic cardiovascular disease

Abstract

Purpose of review The diagnosis of peripheral arterial disease (PAD) is a high-risk marker for accelerated atherosclerotic cardiovascular disease (ASCVD) and is associated with substantial morbidity and mortality. In addition to common, modifiable cardiovascular disease risk factors that contribute to PAD, which include hypertension, diabetes mellitus, and smoking, an elevation in concentrations of serum atherogenic lipoproteins (lipids) is an increasingly recognized contributor to premature atherosclerosis.
Recent findings The recognition and inclusion of PAD as a marker of higher-cardiovascular risk demonstrates the need to aggressively reduce elevations in atherogenic lipoproteins, particularly low-density-lipoprotein cholesterol. In addition to diet, lifestyle, and statin therapy, there is evidence that novel, pharmacologic lipid-lowering treatments improve specific outcomes in patients with PAD as primary and adjunctive therapy.
Summary In this review, we discuss the efficacy and evolving roles of statin and novel nonstatin therapies on outcomes in patients with PAD.

Introduction

Peripheral arterial disease (PAD) is defined as stenosis or occlusion of the arteries of the upper or lower extremities predominantly driven by atherosclerosis but also thrombosis, noncardiac emboli, and other inflammatory conditions [1]. Given the substantial morbidity and mortality that frequently follows its diagnosis, there is an increasing need to prevent the disease, identify affected individuals, and reduce the burden of disease among affected individuals. Traditional risk factors that contribute to its development include smoking, diabetes mellitus, and hypertension [2]. Recent evidence demonstrates that increase elevation of serum atherogenic lipoproteins (lipids) contributes to cardiovascular disease and PAD progression, particularly as the pool of atherogenic lipoproteins is increasing alongside the growing epidemic of obesity [2]. Aggressive changes in diet and lifestyle and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor (statin) therapy are the mainstay of treatment to reduce elevated lipids and improve disease outcomes in patients with PAD [3]. Studies are now demonstrating that the use of novel nonstatin therapies to aggressively reduce elevations in atherogenic lipoproteins, particularly low-density-lipoprotein cholesterol (LDL-c), improve outcomes in PAD [4, 5•]. Herein, we discuss the efficacy of these new agents and the evolving roles of statin and novel nonstatin therapies in the management of patients with PAD.

The role of statin therapy to improve outcomes in patients with PAD

The 2016 American Heart Association (AHA) and American College of Cardiology (ACC) guidelines on the management of patients with lower extremity PAD emphasize that patients with PAD are less likely to receive guideline-directed therapy than patients with other forms of cardiovascular disease [6•, 7, 8]. In addition to improved control of diabetes, hypertension, smoking, and the use of a single antiplatelet therapy (aspirin or clopidogrel alone), statins are a class IA-recommended therapy to reduce myocardial infarction (MI), stroke, and cardiovascular death in patients with symptomatic PAD [6•, 7].

Statins

Current guidelines recommend that all patients with PAD be treated with a maximally tolerated statin medication [8]. Statins inhibit HMG-CoA reductase, allowing for reduction of cholesterol biosynthesis, upregulation of LDL receptors on the cell surface, and pleotropic effects, such as reductions in inflammatory factors and isoprenoids, which act as lipid attachments for intracellular signaling molecules [9–11]. Statins also demonstrate the ability to stabilize atherosclerotic plaques, decrease thrombogenic response, and have a beneficial effect on endothelial function and blood flow [10, 11]. Statins have demonstrated reductions in major adverse cardiovascular events and mortality in several randomized controlled trials (RCTs) and observational data over the last three decades [12]. This section will focus on the benefits of statin therapy among patients with PAD.

Vascular events and mortality

In patients with PAD, there is a notable reduction in composite major vascular events, which include myocardial infarction (MI), coronary death, stroke, or revascularization [3, 13•].

In the Heart Protection Study (HPS), 20,536 patients in the UK were randomized to receive simvastatin 40 mg or placebo [3]. Among the 6748 study patients who had a diagnosis of PAD and received the study treatment, the time to first major vascular event demonstrated an absolute risk reduction (ARR) of 6.3% (NNT = 15, $p < 0.0001$) compared to those who received the placebo treatment [3]. Even after excluding patients who did not have a preexisting diagnosis of coronary artery disease (CAD), there was a significant reduction in time to first major cardiovascular event (5.8% ARR, heterogeneity $p = 0.9$). This finding was not confounded by pre-treatment LDL-c, and patients with prior peripheral revascularization and amputations had a similar reduction [3].

Kumbhani et al. examined patients enrolled in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, an international database encompassing over 68,000 patients from 44 countries [2]. This study stratified 5861 patients with symptomatic PAD and assessed the impact of statin use on outcomes [2]. In the treatment arm, there was a significant reduction (hazard ratio [HR] = 0.83, $p = 0.01$) in the primary composite outcome of cardiovascular death, myocardial infarction, and stroke compared to the placebo arm. Among secondary end points, which consisted of the individual endpoints of the primary composite outcome, there were reductions in the treatment arm in all-cause mortality (HR 0.83, $p = 0.014$), cardiovascular mortality (HR 0.84, $p = 0.05$), and nonfatal stroke (HR 0.74, $p = 0.016$) [2]. These findings demonstrated the superiority of high-intensity statins vs lower-intensity statins, which did not demonstrate similar efficacy in the PAD population in older meta-analyses [14].

Adverse limb events and mortality

Among patients with CAD and PAD, patients on statin therapy demonstrated improved cardiovascular and PAD outcomes, including reductions in adverse limb events and mortality. The HPS study showed a reduction in time to first peripheral vascular event ($p = 0.006$) with greater ARRs among patients with PAD [3]. This effect was mostly driven by reductions in non-coronary revascularizations ($p = 0.002$), including carotid endarterectomy, peripheral revascularization, and aneurysm repair procedures ($p = 0.0003$) [3]. There were no apparent effects on the incidence of aneurysm repairs, deaths, nor amputations [3].

Arya et al. examined different intensities of statin exposure within 1 year of the diagnosis of PAD in over 150,000 patients enrolled in the National Veteran Affairs Data Registry [15••]. The study found that the incidence of amputation and death was significantly lower with any statin use compared to exposure to no statin therapy irrespective of the use of antiplatelet therapy [15••]. The benefit was also greater when comparing patients on high-intensity statins in comparison to patients on moderate- and low-intensity statins ($p < 0.001$) [15••]. This data, similar to prior analyses, suggests that early initiation and high-intensity dosing of statin therapy improves outcomes within 1 year of diagnosis of PAD [15••, 16]. Notably, this population was predominantly male

(97.9%), white (82.6%), either a current or former smoker (29% and 26.4%, respectively), and 20.9% of the patients were on simvastatin 80 mg [15••].

In a retrospective study, Foley et al. examined outcomes of 909 patients with symptomatic PAD who underwent peripheral angiography and/or endovascular intervention [13•]. Patients on high-intensity statin use (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) demonstrated an association with improved survival at 3 years (adjusted HR 0.53, $p = 0.004$) and reduced MACE (adjusted HR 0.58, $p = 0.02$) compared to those on low-moderate statin use therapy. This study did not find a significant association with the mean LDL-c between the low-moderate intensity and high-intensity groups (80 mg/dl vs 87 mg/dL) ($p = 0.14$) [13•]. Although benefit was not observed when comparing amputation-free survival and major adverse limb events, they did observe an association between greater survival and reduction in MACE in patients with critical limb ischemia (CLI) on high-intensity statins with weighted data (HR 0.53, $p = 0.021$ and HR 0.54, $p = 0.039$, respectively) [13•].

International data also demonstrated improved outcomes among PAD patients on high-intensity statins. Analysis of REACH data provided evidence that PAD patients on statins had significantly fewer primary adverse limb outcomes at 4 years compared to patients not on statins (HR 0.82, $p = 0.0013$) [2]. This association between high-intensity use and improved outcomes was seen with improvements in claudication and incident critical limb ischemia (HR 0.82, $p = 0.0087$), incident lower extremity percutaneous or surgical revascularization procedures (HR 0.83, $p = 0.0079$), and incident ischemic amputations (HR 0.64, $p = 0.0027$) [2]. A Taiwanese study looking at patients with type 2 DM and PAD found that statin users had lower risks of lower extremity amputation (adjusted HR 0.75, $p = 0.003$), in-hospital cardiovascular death (adjusted HR 0.78, $p = <0.001$), and all-cause mortality (adjusted HR 0.73, $p = < 0.001$) [17•].

Perioperative data and critical limb ischemia

Statin use also demonstrates improved outcomes when examining outcomes of patients with CLI perioperatively. Vogel et al. investigated a Medicare beneficiary database for PAD diagnoses [18]. They found that preoperative statin use was associated with lower amputation rates at 30 days ($p = 0.0001$), 90 days ($p = <0.0001$), and 1 year ($p = <0.0001$) [18]. Use of preoperative statins also had improved limb salvage during 1 year for patients with claudication ($p = 0.003$) and for rest pain ($p = 0.061$) compared to patients who were not on statins preoperatively [18].

Regarding use of statins in the postoperative setting, one study found that postoperative statin use following lower extremity amputation demonstrated a mortality benefit for patients on moderate-intensity statin (HR 0.64, $p = 0.005$) and high-intensity statin (HR 0.56, $p = 0.032$) [19]. Importantly and consistent with other studies on underutilization of statin therapy, only 44.7% of patients were on statin therapy after 1 year [19].

Endovascular postprocedural outcomes and CLI were examined by Aiello et al. by analyzing patients on statin therapy at time of endovascular treatment. Statin use was associated with a higher rate of primary patency (ARR = 10.0%, $p = 0.007$), secondary patency ($p = 0.001$), limb salvage ($p = 0.001$), and overall survival ($p = 0.038$) at 24 months [20]. Notably, patients on statins at time of

Table 1. Impact of statin therapy on PAD outcomes

First author (ref. #)	Registry/study	Years	N	Statin (or intensity)	Outcome
HPS collaborative group [3]	HPS (randomized control trial)	1994–1997 (5 year follow-up)	20,536	Simvastatin 40 mg	Significant reduction in rate of first major vascular event and reduction of first peripheral event
Kumbhani et al. [2]	REACH Registry	2004–2008	Subset of 5861 from original 69,055	62.2% use of statins in population	Those on statins had lower risk of adverse limb outcomes and reduction of composite of cardiovascular death/MI/stroke
Arya et al. [15••]	Veterans Affairs Data/Observational Cohort	2003–2014	155,647	28% were not on statins, stratified use to low-moderate and high intensity	High-intensity statins are underused. Improved mortality and amputation with statin use, higher intensity with improved reduction
Foley et al. [13•]	University of California Davis Registry	2006–2013	909	Divided by intensity, high (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) vs moderate/low intensity	High-intensity statin had improved survival and decreased MACE
Hsu et al. [17•]	Taiwanese Study/ Observational Cohort	2000–2011	69,332	Divided into statin/nonstatin agents and no medication	Specifically assessed patients with diabetes and PAD. Those who used statins had lower risk of lower extremity amputation and mortality
Vogel et al. [18]	Medicare Claim Data	2007–2008	22,954	Identified statin use with diagnoses of claudication, rest pain, ulceration, gangrene, endovascular revascularization, and open surgery	Statin users vs nonusers had lower amputation rates, improved limb salvage

endovascular treatment had higher rates of diabetes, CAD, congestive heart failure, MI, and coronary bypass grafting, and similar lesion types, classifications, and primary procedures [20]. The association was found to be independent of LDL-c [20].

O'Donnell et al. examined 931 patients with CLI on either high-, moderate-, or low-intensity statin postoperatively after revascularization (endovascular or surgical) [21]. Although 77% were discharged on statin, 35% were on recommended guideline-based statin dosage [21, 22••]. Discharge on any statin was associated with lower mortality (HR 0.71, $p < 0.01$), and those on recommended high intensity had lower mortality (HR 0.73, $p < 0.05$) and MALE (HR 0.71, $p < 0.05$) [21].

Claudication

Studies also demonstrate symptomatic benefit with the utilization of statin therapy to improve claudication. One study noted that although maximal walking time did not change significantly, there was improvement in pain-free walking time after 12 months of treatment with atorvastatin 80 mg [23]. Pooled data from a Cochrane review noted improvement in total walking distance and pain-free walking distance but no significant impact on ABI scores [14] (Table 1).

Expanding the definition of high-risk cardiovascular disease to include PAD

Recent literature substantiates the marker of PAD as a heightened degree of systemic atherosclerosis potentiating a malignant vascular phenotype [24, 25]. In one study, based on the REACH registry, patients with polyvascular disease had substantially increased risk for all-cause mortality, nonfatal stroke, and nonfatal myocardial infarction (MI) [24, 26]. Additionally, a Canadian study which included 16,440 patients between 1985 and 1995 noted that the annual mortality of patients was higher among those with PAD (8.2%) than MI (6.3%), with 49% of patients dying within the 5.9 year follow-up [25].

The 2018 Cholesterol Clinical Practice Guidelines expanded the definition of very-high-risk atherosclerotic cardiovascular disease (ASCVD) [22••]. This was defined as either the presence of multiple major ASCVD events (which included symptomatic PAD as claudication with ABI < 0.85 or previous revascularization or amputation) or one major ASCVD event with multiple high-risk conditions. For secondary prevention, guidelines provided a class IA recommendation that patients be initiated on a high-intensity statin (with goal of achieving a 50% or greater reduction in LDL). For high-risk patients not at goal despite maximally tolerated statin therapy, the addition of ezetimibe was recommended (I, BNR), followed by proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor therapy if LDL-c still remained > 70 mg/dL. Among very-high-risk patients, despite maximally tolerated statin therapy, it was considered reasonable to add a PCSK9 inhibitor if the LDL-c was greater than or equal to 70 mg/dL or the non-HDL-c was greater than or equal to 100 mg/dL after discussing net benefit, safety, and cost (IIa-BR) [22••].

The role of novel lipid agents – ezetimibe and PCSK9 inhibitors – as primary and adjunctive therapy in PAD

Ezetimibe

Ezetimibe acts to reduce intestinal cholesterol absorption by targeting the Niemann-Pick C1-like protein [27]. In the Improved Reduction of Outcomes Vytorin Efficacy International Trial (IMPROVE-IT) which was a randomized control trial examining 18,144 patients after ACS randomized to ezetimibe (10 mg) in combination with simvastatin (40 mg) compared to simvastatin alone [27]. It demonstrated an ARR for MACE of 2% over 7 years [27]. The addition of ezetimibe also led to a statistically significant reduction of LDL to 53 mg/dL compared to 69.5 mg/dL in the simvastatin alone group [27]. About 5.7% of patients in the treatment arm had a diagnosis if PAD [27] (Table 2).

Similarly, the Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) Trial prospectively evaluated patients after percutaneous coronary intervention on atorvastatin plus ezetimibe or atorvastatin alone [30]. The study noted that combination therapy was associated with a statistically significant reduction in atheroma volume ($p = 0.001$) [30].

Table 2. Impact of adjunctive nonstatin therapy on PAD outcomes

First author (ref. #)	Study	Years	N	Medication used	Outcome
Ezetimibe					
Cannon et al. [27]	*IMPROVE-IT	6 years	18,144	Ezetimibe with simvastatin	Reduced LDL-c, improved composite of cardiovascular death, nonfatal MI, unstable angina, coronary revascularization, and stroke post cardiac event
PCSK9 inhibitors					
Schwartz et al. [5•]	ODYSSEY OUTCOMES	2.8 years	18,924	Alirocumab	Improved composite primary end point (death from CAD, nonfatal MI, fatal/nonfatal ischemic stroke, or unstable angina)
Szarek et al. [28••]	ODYSSEY OUTCOMES	2.8 years	18,924	Alirocumab	Reduction in nonfatal cardiac events and death after ACS
Sabatine et al. [4]	FOURIER Trial	2.2 years	27,564	Evolocumab	Improved composite primary end point (cardiovascular death, MI, stroke, hospitalization for unstable angina, coronary revascularization)
Bonaca et al. [29]	PAD in FOURIER trial	2.2 years	Subset of 3642	Evolocumab	Reduced composite of cardiovascular death, MI, stroke, hospital admission for unstable angina, or coronary revascularization reduced risk for MALE

Additional details: *studied outcomes after cardiac event, not PAD specifically

PCSK9 inhibitors

PCSK9 inhibitors are monoclonal antibodies that inhibit the PCSK9 protein, which functions to degrade the LDL receptor. This results in increased LDL receptors on the cell surface and marked reduction of LDL-c in the circulation [31]. As previously mentioned, in patients with very high ASCVD risk, PCSK9 inhibitors are recommended as third-line agents, after ezetimibe, for secondary prevention (I, BNR recommendation) [22••]. In certain cases, it is reasonable to consider these medications as second-line agents (IIa-BR) [22••].

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) [4] Trial, 27,654 patients with ASCVD on maximally tolerated statin therapy and an LDL-c greater than or equal to 70 mg/dL (or non-HDL-C greater than or equal to 100 mg/dL) on maximal statin therapy were randomized to evolocumab or placebo [4]. After 2.2 years, there was a decrease in LDL-c from median of 92 mg to 30 mg/dL ($p < 0.001$) [4]. It also showed a significant decrease in the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (HR 0.85, $p < 0.001$) and secondary end points of cardiovascular death, myocardial infarction, or stroke (HR 0.8, $p < 0.001$) [4].

Similarly, in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome (ODYSSEY) Trial, 18,924 patients with ASCVD on maximally tolerated statin therapy and an LDL-c greater than or equal to 70 mg/dL (or either non-HDL-C greater than or equal to

100 mg/dL or apolipoprotein B of at least 80 mg/dL) on maximally tolerated statin therapy were randomized to alirocumab or placebo [5, 28••]. After 2.8 years, there was a reduction of the primary composite end point of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization (HR 0.85, $p < 0.001$), and the benefit was greatest among patients who had a higher baseline LDL level [5•, 28••].

The FOURIER data was further analyzed to assess outcomes in patients specifically with PAD. This subgroup identified 3642 patients as having a diagnosis of PAD by either intermittent claudication with ABI of < 0.85 or prior peripheral vascular procedure or amputation secondary to atherosclerotic disease [29]. This analysis found that there was a reduction of the composite of cardiovascular death, MI, stroke, and hospital admission for unstable angina or cardiac revascularization (HR = 0.79, $p = 0.0098$) [29]. Those with PAD had larger ARRs (3.5% with PAD and 1.6% without PAD) [29]. This study also demonstrated a reduction in MALE, such as acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia, with reduction risk (HR 0.58, $p = 0.0093$) which correlated with the degree of reduction in LDL-c ($p = 0.026$) [29]. Patients with PAD but without prior MI or stroke demonstrated a reduction in the composite of MACE and MALE (HR 0.52 with ARR of 6.3%, NNT 16 $p = 0.0006$) [29].

In terms of side effects, no significant differences between groups were seen. Injection site reactions were rare, with the majority being mild [28••, 29]. There were no significant difference between experimental and placebo in terms of allergic reactions. Factors limiting the use of these medications are the lack of long-term data (these trials were limited to a few years), parenteral route of medication, and expense of monoclonal antibodies. The cost of PCSK9 inhibitors may not only limit eligibility from insurers but may also impede access and reduce long-term adherence [32, 33]. It should also be noted that both the FOURIER and ODYSSEY Trials were funded by pharmaceutical companies, and the data analyzing PAD outcomes specifically from the FOURIER data was a subgroup analysis limiting the interpretation of those results (Fig. 1).

Future directions

As we look to optimize the risk of patients with PAD, we must design studies that demonstrate the greatest reduction in adverse ASCVD outcomes. Diet and lifestyle will remain the basis for all effective strategies to reduce risk. Behavioral strategies that can decrease smoking, increase activity, and improve the quality of dietary consumption will promote the greatest reduction in ASCVD across populations. The latter carries particular importance, as the epidemic of diabetes and metabolic syndrome continues to rise. However, effective pharmacologic therapies that improve outcomes for individuals continue to prove their benefits. As the metabolic composition of patients with PAD changes so will the targets of therapy. Effective lipid-lowering studies should address elevations in triglyceride-rich lipoproteins that will contribute more to ASCVD than ever before with the pervasive and expanding metabolic syndrome phenotype.

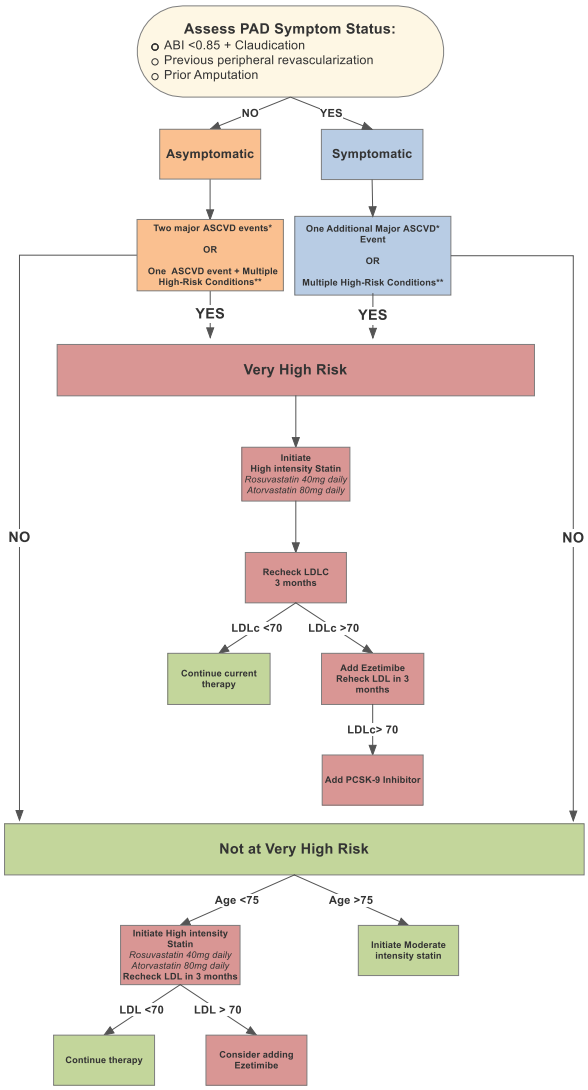

Fig. 1. Major ASCVD events include recent acute coronary syndrome (within the past 12 months), history of myocardial infarction (other than recent acute coronary syndrome event listed above), history of ischemic stroke, and symptomatic peripheral arterial disease (history of claudication with ankle brachial index). High-risk conditions include age ≥ 65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s), diabetes mellitus, hypertension, chronic kidney disease (eGFR 15–59 mL/min/1.73 m2), current smokings, persistently elevated LDL-c (LDL-c≥ 100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe, and history of congestive heart failure

Conclusion

PAD patients represent a group of patients at high risk for cardiovascular disease in addition to the significant complications deriving from PAD, including critical limb ischemia, amputations, and stroke. As demonstrated, aggressive

risk factor reduction is essential to reduce disease progression. It is imperative to initiate timely use of statin medications at the maximally tolerated dose to reduce risk. Additionally, with novel therapies to lower LDL-c, we are now seeing that the patient who demonstrates appropriate adherence to statin therapy or is intolerant of statin therapy may benefit from additional lipid-lowering therapy with the use of ezetimibe or PCSK9 inhibitors that have demonstrated reductions in adverse limb events in addition to reductions in major adverse cardiovascular events.

Compliance with Ethical Standards

Conflict of Interest

Benjamin Hirsh reports receiving consulting fees from and served on the advisory boards of Sanofi-Regeneron and AztraZeneca Pharmaceuticals.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Hiatt W, Goldstone J, Smith S, et al. Atherosclerotic peripheral vascular disease symposium II: nomenclature for vascular diseases. Circulation. 2008;118(25):2826–9.
2. Kumbhani D, Steg P, Cannon C, Eagle KA, Smith SC Jr, Goto S, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral arterial disease: insights from the REACH Registry. Eur Heart J. 2014;35:2864–72.
3. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007;45(4):645–54.
4. Sabatine M, Giugliano R, Keech A, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. NEJM. 2017;376(18):1713–22.
5.• Schwartz G, Szarek S, Bhatt D, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. NEJM. 2018;379(22):2097–10.

This is the FOURIER trial, which was a large RCT involving 27,564 patients which studied the effects of Evolocumab.

6.• Gerhard-Herman M, Gornik H, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary. Circulation. 2017;135:e686–72.

This is the ODYSSEY trial, which was a large RCT including 18,924 patients after an acute coronary syndrome, which studied the effects of Alirocumab.

7. Gerhard-Herman M, Gornik H, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease. JACC. 2017;69(11):e71–126.
8. Subherwal S, Patel M, Kober L, Peterson ED, Jones WS, Gislason GH, et al. Missed opportunities despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. Circulation. 2012;126:1345–54.
9. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med. 2001;5(4):378–87.
10. Liao J. Pleotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005;45:89–118.
11. Davignon J. Beneficial cardiovascular pleotropic effects of statins. Circulation. 2004;109(suppl III):III-29–43.
12. Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
13.• Foley T, Singh G, Kokkinidis D, et al. High-intensity statin therapy is associated with improved survival in patients with peripheral artery disease. J Am Heart Assoc. 2017;6:e00569.

This study assessed patients with symptomatic PAD and stratified statin intensity retrospectively, noting improved survival and decreased MACE with high intensity statin use.

14. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database Syst Rev. 2007;4:1–63.
15.•• Arya S, Khakharia A, Binney Z, et al. Association of statin dose with amputation and survival in patients with peripheral arterial disease. Circulation. 2018;136:1435–4.

This study is an observational cohort study involving 155,647 patients with PAD, which stratifying statin use by intensity. It noted improved mortality and lower amputation with statin use with higher intensity.

16. Hirsh B, Smilowitz N, Rosenson R, Fuster V, Sperling LS. Utilization of and adherence to guideline-recommended lipid lowering therapy after acute coronary syndrome. J Am Coll Cardiol. 2015;66:184–92.
17.• Hsu C, Chen Y, Su Y, et al. Statin therapy reduces future risk of lower-limb amputation in patients with diabetes and peripheral arterial disease. J Clin Endocrinol Metab. 2017;102:2373–8.

This is a retrospective Taiwanese study with 69,332 patients addressing PAD with Diabetes Mellitus which noted improved outcomes with statin use.

18. Vogel T, Dombrovskiy V, Galinanes E, Kruse R. Preoperative statins and limb salvage after lower extremity revascularization in the medicare population. Circ Cardiovasc Interv. 2013;6:694–700.
19. DeCarlo C, Scher L, Shariff S, Phair J, Lipsitz E, Garg K. Statin use and other factors associated with mortality after major lower extremity amputation. J Vasc Surg. 2017;66(1):216–5.
20. Aiello F, Khan A, Meltzer A, Gallagher KA, McKinsey J, Schneider DB. Statin therapy is associated with superior clinical outcomes after endovascular treatment of critical limb ischemia. *J Vasc Surg*. 2012;55:371–80.
21. O'Donnell T, Deery S, Darling J, et al. Adherence to lipid management guidelines is associated with lower mortality and major adverse limb events in patients undergoing revascularization for chronic limb threatening ischemia. J Vasc Surg. 2017;66(2):572–8.
22.•• Grundy S, Stone N, Bailey A, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. 2018 Cholesterol Clinical Practice Guidelines. 1–120.

This report is the most recent update regarding cholesterol clinical practice guidelines.

23. Mohler E, Hiatt W, Creager M. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation. 2003;108(12):1481–6.
24. Suarez C, Zeymer U, Limbourg T, et al. Influence of polyvascular disease on cardiovascular event rates. Insights from the REACH Registry. Vasc Med. 2010;15(4):259–65.
25. Caro J, Migliaccio-Walle K, Ishak K, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. BMC Cardiovasc Disord. 2005;5:14.
26. Bhatt D, Steg P, Ohman E, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180–9.
27. Cannon C, Blazing M, Giugliano R, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *NEJM*. 2015;372(25):2387–97.
28.•• Szarek M, White H, Schwartz G, et al. Alirocumab reduces total nonfatal cardiovascular and fatal events. The ODYSSEY OUTCOMES Trial. JACC. 2019;73(4):387–9.

This article is a subset analysis specifically addressing use of Evolocumab in the PAD population from FOURIER data.

29. Bonaca M, Nault P, Giugliano R, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease. Circulation. 2018;137:338–50.
30. Tsujita K, Suigyama S, Sumida H, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention. J Am Coll Cardiol. 2015;66:495–507.
31. Page M, Watts G. PCSK9 Inhibitors – mechanisms of action. Aust Prescr. 2016;39(5):164–7.
32. Hlatky M, Kazi D. PCSK9 Inhibitors: economics and policy. J Am Coll Cardiol. 2017;70:2677–87.
33. Kazi D, Moran A, Coxson P, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA. 2016;315(7):743–53.

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