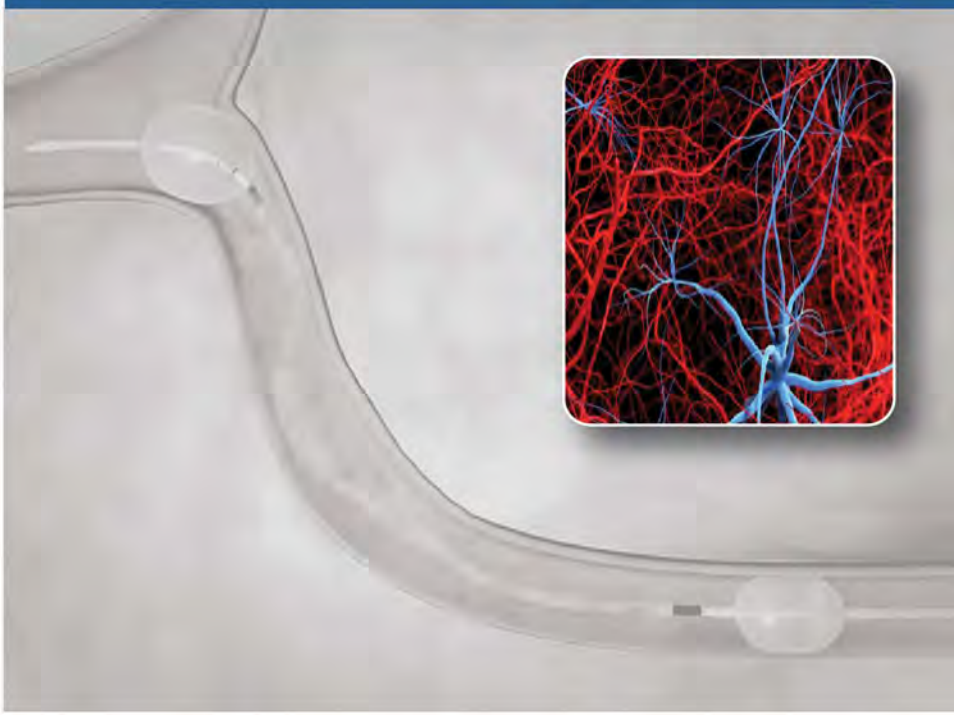
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YEARBOOK

Yearbook of Vascular and Endovascular Surgery

2016



R Sekhar

Foreword
Pradip K Datta

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CHAPTER

3

Statins in Peripheral Vascular Disease

Siddharth Rajput

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INTRODUCTION—LIPIDS, FATTY STREAKS, SIMPLE AND COMPLEX PLAQUES

Over the last 50 years or so, the relationship between dyslipidaemia and atherosclerosis has been an area of active research as the prevalence of atherosclerosis and associated cardiovascular complications increases in the developed and the developing world alike. Atherosclerosis is the sequelae of chronic arterial inflammation secondary to prolonged exposure to oxidative stressors and involves multiple cell types and cellular mediators. Circulating blood is in constant contact with endothelial cells (ECs) that separate circulating platelets, monocytes, and coagulation factors from the highly thrombogenic internal elastic lamina and basement membrane. Vascular ECs also separate vascular smooth muscle cells (VSMCs) in the media from circulating growth factors. Production of reactive oxygen species, such as those secondary to cigarette smoking or exposure to glycation end products, for example, damage the ECs, resulting in decreased nitric oxide (NO) production and activation of both platelets and circulating monocytes. The expression of inflammatory mediators induces monocyte adhesion and migration to the area of injury where oxidized low-density lipid particles (oxLDLs) are engulfed, changing the morphology of each macrophage to a lipid-filled foam cell. Vascular smooth muscle cells are also affected and change from a contractile to a proliferative and secretory phenotype. In areas of vessel injury, VSMCs migrate from the media across the internal elastic lamina to the intima, where they proliferate and deposit a collagen-rich extracellular matrix forming a vascular lesion, known as a fatty streak. The cycle of inflammatory factor release and the subsequent cellular response results in the development of an "atherosclerotic plaque".[1] This fibroatheroma contains a complex network of proliferating VSMCs, extracellular matrix proteins, and macrophages. Larger lesions contain a milieu of cells, matrix metalloproteinases, and inflammatory factors as well as alter luminal haemodynamics. A plaque may remain stable for many years, however, as the atheroma grows, the size of the lesion may

preclude perfusion by the vasa vasorum, compromising the delivery of nutrients to the plaque. The increased demand for oxygen and nutrients in the plaque leads to a relatively hypoxic environment, resulting in VSMC death, thinning the protective fibrous cap, and increasing the likelihood of rupture. Dyslipidaemia has long been recognized as an independent risk factor for atherosclerosis-related coronary artery and peripheral vascular disease and is the target for numerous interventions to attenuate the associated large disease burden. High levels of low-density lipoproteins (LDLs) and by products of oxidation reactions with LDL (i.e. oxLDL) injure ECs and promote monocyte adhesion, VSMC migration, and platelet activation—events that initiate the development of atherosclerotic plaque. In contrast, high levels of high-density lipoproteins (HDLs) have been independently shown to be atheroprotective, by providing an opposing effect to LDL. While LDL and HDL remain the 2 most studied lipoproteins with regard to atherosclerotic disease, very low-density lipoproteins (VLDLs) and triglycerides have also gained attention as potential targets for therapy in the cholesterol metabolism pathways.

STATINS: 3-HYDROXY-3-METHYLGLUTARYL-COENZYME A REDUCTASE INHIBITORS

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as statins, are the single most effective cholesterol reducing medications available today. Statins competitively inhibit HMG-CoA reductase, the key enzyme of cholesterol synthesis in the liver. Statins decrease levels of LDL production as well as remove existing LDL from circulation by increasing serum LDL uptake by the liver. Statins also increase uptake of very low-density lipoproteins (VLDLs) as well as decrease total cholesterol and triglycerides by the liver. Statins were first discovered in 1971 by Japanese biochemist Akira Endo when he isolated the agent mevastatin from the fungus *Penicillium citrinum*.[2] However, the first clinical application of a statin was by Merck & Co (Kenilworth, New Jersey) who isolated lovastatin from the *Aspergillus terreus* in 1976 and marketed the first commercially available statin in 1987 as Mevacor.[3] Since then, several other both synthetic and naturally occurring statins were created and/or isolated by competing pharmaceutical companies for therapeutic use. Statins have also been combined with other agents, including niacin and ezetimibe to create combination therapy in efforts to further decrease cholesterol levels in the circulation. Today, the Joint Task Force on Practice Guidelines[4] for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk in adults from the American College of Cardiology (ACC) and the American Heart Association (AHA) support the use of statins for the prevention of ASCVD in many higher risk primary and all secondary prevention individuals without heart failure. Moreover, their review of the literature shows that statin therapy reduces ASCVD events in individuals with LDL levels as low as 70 mg/dl, suggesting that statins are beneficial irrespective of initial LDL levels. To date, there has been no specific validated LDL target in the peripheral arterial disease (PAD) population. Furthermore, ethical issues preclude conducting

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prospective randomized placebo controlled trials of statins in patients with PAD. Despite these challenges, the Society of Vascular Surgery (SVS) recently published guidelines[5] for management of asymptomatic PAD, claudication, and cerebrovascular disease (CBD). They derive their recommendations from the ACC/AHA guidelines, which recommend that statins should be considered in all individuals with an estimated 10- year risk of major cardiovascular events >7.5%. Therefore, the SVS recommends their use in both symptomatic and asymptomatic noncoronary ASCVD. As a whole, most vascular surgeons and vascular medicine clinicians agree statin therapy is an essential component in the management of patients with atherosclerotic disease. The use of statins to modify lipid profiles in patients with noncoronary ASVCD is summarised subsequently.

Statins and Aortic Aneurysms

Atherosclerosis of the aorta results in subsequent aneurysmal degeneration and also has a pathophysiological role in dissections as well as other aortic degenerative disease. In a retrospective review of over 600 patients with thoracic aortic aneurysms, performed by the Yale group using multivariate analysis (after adjusting for age, gender, chronic obstructive pulmonary disease, cardiovascular disease, family history, aneurysm location, and aneurysm size), patients on statins had a decreased rate of rupture, dissection, repair, or death (mean follow-up of 3.5 years).[6] A subsequent study by the same group on a larger cohort of patients further supported the protective effects of statins on long-term outcomes for patients with thoracic aortic aneurysms; however, patients with aneurysms of the aortic root were still at risk, despite treatment with a statin.[7] Several other observational studies document nearly a 50% reduction in growth rates of abdominal aortic aneurysms in patients on statin therapy.[8-10] These studies also noted reduced mortality in outcomes of patients undergoing surgical intervention for their abdominal aneurysms, even when ruptured.[10,11] In summary, statins are associated with a slower progression of aortic atherosclerotic disease and aneurysm expansion; however, it should be noted that these studies are retrospective with a relatively smaller sample size.

Statins and PAD

Approximately 8–12 million people in the United States have PAD, ranging from claudication to critical limb ischemia (CLI).[12] PAD is also recognized as a sensitive marker for coronary artery disease (CAD), cerebrovascular disease (CBD), and cardiovascular mortality.[4] Patients with PAD have a relative risk of cardiovascular mortality ranging from 1.4 to 5.9 compared to patients without PAD.[13-15] These numbers stress the importance of identifying best medical therapies that modify the systemic effects of PAD. The benefit of statin therapy to attenuate or stabilise aortic atherosclerosis was known even in the 1990s.[16,17] More recently, 3 small clinical trials have evaluated the effects of statins and other pharmaceuticals on aortic atherosclerosis monitoring progression of disease with novel noninvasive imaging techniques.[18-20] In Japan, 108 patients

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with hypercholesterolaemia were randomized to atorvastatin, etidronate (a bisphosphonate used in treatment of osteoporosis), or both drugs daily.[20] Using magnetic resonance imaging (MRI), they found that atorvastatin monotherapy significantly reduced the amount of thoracic aortic plaque, while etidronate monotherapy reduced only abdominal aortic plaque.[20] Combination therapy of atorvastatin plus etidronate for 12 months significantly reduced both thoracic and abdominal aortic plaques.[20] A second US study found a dose-related relationship between statin therapy and reduction in atherosclerotic inflammation, as a rapid dose-dependent reduction in radiotracer uptake on positron emission tomography in the aorta occurred in patients on high-dose atorvastatin compared to lower doses.[19] The same dose-dependent effect was noted in patients taking rosuvastatin.[18]

The Heart Protection Study (HPS) from 2002 was the first large multicentre randomised controlled trial (RCT) of a statin (simvastatin 40 mg daily vs placebo) that included a large enough number of patients with PAD (6748 patients) to draw conclusions on the effects of statins in this population.[21] HPS found that patients with PAD allocated to simvastatin had a 22% relative reduction in the rate of first major vascular events (coronary events, strokes, or revascularisation) and that all (20,536) patients of the study had a 16% relative reduction. Furthermore, this effect was seen across all subgroups included in the study, irrespective of their pretreatment LDL cholesterol levels. Post-hoc analysis of the 1990s Scandinavian Simvastatin Survival Study (4S), performed on 4444 patients with CAD also showed that effective cholesterol lowering slows the progression of atherosclerosis in the periphery and results in less signs and symptoms of PAD.[22] Patients treated with statins had significantly lower relative risks of intermittent claudication, carotid bruit, femoral bruit, and angina pectoris than the placebo group. Newer prospective observational studies, such as the REduction of Atherothrombosis for Continued Health (REACH) Registry,[23] report the same findings. A total of 5861 patients with PAD were included in the registry, and only 62% of these patients were on a statin. The REACH Registry observed a significantly greater incidence of worsening claudication, new revascularization procedures (open or endovascular), and amputations in the nonstatin-treated group. They concluded that patients with PAD on statins have ~18% lower long-term risk of adverse limb outcomes when compared to those not on statin therapy.[23] These and many other studies support the use of statins in patients with PAD for primary and secondary prevention of ASCVD and adverse limb outcomes.[24-27]

In the early 2000s, 3 small prospective placebo-controlled randomized clinical trials were performed in patients with claudication to evaluate the effect of simvastatin[28,29] and atorvastatin[30] on exercise performance. At 3- to 6-month follow-up, patients in the statin therapy group were noted to have longer pain-free walking distance, increased total walking distance, and significantly improved ankle–brachial indexes (ABIs) both at rest and after exercise.[28-30] However, more recently, another small observational study shows that although ABIs improved in the statin treatment group, there was no difference in muscle perfusion, metabolism, nor exercise parameters over time in these patients.[31]

Further evidence is emerging regarding the effects of statins on patients undergoing infrainguinal bypass surgery for treatment of CLI. This group of

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patients is located on the opposite end of the spectrum of PAD, with severe atherosclerosis causing ischaemic rest pain, tissue loss, and limb loss. The studies showed that statin therapy was independently associated with fewer combined ASCVD complications, shorter hospital length of stay, improved long-term survival at 5.5 years,[32] increased graft patency and limb salvage rates.[33,34] Almost 10 years later, 2 more retrospective studies were published on the effects of statin therapy in patients with CLI undergoing infrainguinal bypass surgery and endovascular intervention.[35,36] Both studies found improved rates of survival in patients treated with statins. In the endovascular therapy observational cohort study, statins were associated with improved target lesion patency rates as well as decreased rates of stroke and MI.[35,36]

In summary, the scarce literature supporting the use of statin therapy in patients with claudication and CLI implies a strong association with increased primary prevention of ASCVD events, secondary prevention of adverse lower extremity events, and overall reduced mortality; however, these studies do not show that statins have any significant effect on the patency of infrainguinal bypasses.

Statins and Cerebrovascular Disease

About 87% of all strokes in the United States are ischaemic-type infarcts.[37] A major preventable cause of ischaemic stroke is atherosclerotic occlusive disease of the extracranial carotid artery. Initial studies only recruited patients with elevated LDL profiles, while later studies were all inclusive regarding the initial LDL levels, and measured early carotid atherosclerosis by B-mode ultrasonography of mean maximum intimal–medial thickness (IMT) of carotid artery walls.[38-43] The agents tested included lovastatin, pravastatin, atorvastatin, and simvastatin. All 6 studies showed significant reductions in IMT in patients with hypercholesterolaemia and asymptomatic early carotid atherosclerosis. Once established that statins had beneficial effect on patients with all types of ASCVD, not just coronary heart disease, further studies emerged assessing the impact of statins on stroke incidence. The first of these studies to include stroke as a prescribed end point was the Cholesterol and Recurrent Events (CARE) trial. The CARE investigators found a 32% reduction in all-cause strokes and a 27% reduction in stroke or TIA in patients with a recent MI (within the past 10 months of study enrolment) when treated with pravastatin.[44] Pravastatin was studied in 2 other international multicentre trials. The first of these was a secondary prevention trial of pravastatin known as LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) that included over 9000 patients.[45] The other was a primary prevention trial in >6500 males with hypercholesterolemia known as WOSCOPS (West of Scotland Prevention Coronary Prevention Study).[46] Pooled data from the CARE, LIPID, and WOSCOPS trials showed that pravastatin reduced the risk of stroke over a wide range of lipid values, including those with LDL <100 mg/dl prior to treatment initiation among patients with documented coronary disease.[47] Larger scale prospective data demonstrating that cholesterol lowering statin therapy reduces the risk of stroke was elicited from the landmark HPS.[21] Results of the HPS trial were similar to the CARE trial with a

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25% overall stroke reduction, including fatal stroke. Interestingly, this study also showed a 50% reduction in intervention with carotid endarterectomy or carotid artery stenting.

Once the safety and efficacy of statins in secondary prevention were established, clinical trials began to focus on primary prevention of major cardiovascular events in patients at risk of stroke without previous coronary events. The WOSCOPS mentioned previously, was the first of the primary prevention studies to show a trend toward reduction in incidence of all strokes in 1995. By the end of the 2000s, over 10 RCTs including Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in 2004; all concluded that statins reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by 20% per 18 mg/dl reduction in LDL cholesterol.[48,49] Of note, this finding holds true irrespective of initial LDL levels. Furthermore, the dose of statin has also been studied by The Treating to New Targets (TNT) study where it was found that higher dose statin therapy reduced both stroke and all cerebrovascular events by an additional 20–25% compared to the lower dose.[50]

In 2006, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators studied the effectiveness of high-dose atorvastatin in prevention of fatal or nonfatal stroke in patients who had suffered either a stroke or TIA within 6 months of study enrolment. This secondary prevention study found that statins reduced the overall incidence of strokes as well as all cardiovascular events in patients with previous stroke.[51] However, these effects were marginal, with only a 5-year absolute risk reduction of 2.2% [51] and contrasted with results of the HPS study, which found no reduction in the risk of stroke among patients with prior CBD.[21] Analysis of the studies would later show that patients in the HPS study with a prior stroke or TIA were enrolled at a time point greater than 4 years after their stroke, despite the fact that most recurrent strokes usually occur within the first year after the index event. These findings imply that initiation of statin therapy in the immediate post-stroke period may be effective secondary prevention of another stroke but that statins have little to no effect when initiated later.

Finally, the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial looked at patients on rosuvastatin with normal LDL levels but known elevated C-reactive protein levels and also found a 51% reduction in ischaemic strokes (P ¼ .004), again suggesting that statins are protective against stroke, despite a normal LDL profile.[52] An important adverse event associated with the statin treatment group in the SPARCL trial was the increased incidence of haemorrhagic stroke.[51] This effect was also noted in the HPS study. In 2011, a meta-analysis and systematic review of 23 randomised trials and 19 observational studies of statins and stroke comprising a total of 248,391 patients and 14,784 intracerebral haemorrhages was published. The authors found no evidence that statins were actually associated with intracerebral haemorrhage.[53]

In summary, statin therapy is effective for the primary and secondary prevention of stroke and TIAs in patients with and without coronary manifestations of ASCVD, without increased risk of haemorrhagic stroke.

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Statins and Atherosclerotic Renovascular and Chronic Kidney Disease

Atherosclerotic renovascular hypertension is a form of secondary hypertension due to renal artery stenosis and the introduction of statins and angiotensin receptor blocking agents (ARBs) has converted this pathology into a slowly progressive disease.[54] Small retrospective studies on the effects of statins in patients with atherosclerotic renal artery disease have been published with little to no long-term follow-up data.[54,55] One study showed an improvement in overall mortality as well as a slower rate of progression of renal insufficiency.[56] Three large-scale RCTs, the Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR), the Angioplasty and Stenting for Renal Artery Stenosis (ASTRAL), and the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), performed in the 2000s all compared endovascular surgical intervention to best medical therapy for atherosclerotic renal artery disease.[57-59] An angiotensin receptor blocker (ARB), a statin, and an antiplatelet agent comprised thee medical regimen. All 3 studies showed no evidence of clinical benefit from revascularisation in patients with renovascular disease compared to best medical therapy alone.[57-59] Since then, statins have been studied in select subgroups of patients with renovascular disease. In Canada, in a cohort study on elderly patients with renovascular disease, statins were associated with improved overall prognosis.[60] Despite having a larger burden of both cardiovascular and renal comorbidity, the group of patients treated with a statin had a significantly lower incidence of MI, stroke, heart failure, acute renal failure, dialysis, and death compared to those not on statin therapy.[41] These beneficial effects were not similarly observed in patients with chronic kidney disease (CKD), although CKD is considered to be an independent risk factor for recurrent cardiovascular events, and patients with end-stage renal disease (ESRD) have the highest incidence of ASCVD.[37,61,62] The Kidney Disease Outcomes Quality Initiative (KDOQI) has established guidelines for the management of dyslipidaemia in patients with CKD because of this population's increased risk of both symptomatic and asymptomatic ASCVD. Since then, 2 randomised placebo-controlled trials have been published evaluating the safety and efficacy of statins in patients with ESRD. The first of these trials, the Deutsche Diabetes Dialyse Studie (4D), was performed in Germany solely on diabetic patients with ESRD. Despite the cholesterol-lowering effects of atorvastatin, no difference occurred in the incidence of the individual or combined end point of cardiac death, nonfatal MI, or stroke.[63] Surprisingly, they found a 2-fold increase in the incidence of fatal stroke in the treatment group. The second trial performed in the United States, a Study to Evaluate the Use of Rosuvastatin in Subjects On Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events (AURORA), was conducted on varied patients with ESRD on haemodialysis.[64] With almost 4 years of follow-up, no difference was found between rosuvastatin-treated groups and controls with respect to nonfatal MI, nonfatal stroke, or death from cardiovascular sources. The negative outcomes of the 4D and AURORA trials left many questions unanswered, specifically about the

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effectiveness and safety of statins in patients with early-stage CKD. In 2011, the Study of Heart and Renal Protection (SHARP) looked exclusively at patients with CKD, including patients with ESRD and treated them with a statin in combination with ezetimibe.[65] The end point was a composite of nonfatal MI, cardiac death, stroke, and any revascularization procedure. The SHARP trial found a 17% reduction in the composite end point for those in the treatment arm.[65] When subgroup analysis was performed on the different stages of CKD, the ESRD group showed no difference in the rate of primary outcome further proving that targeting a reduction in mortality with statins in this group of patients may be futile.[65] In summary, statin therapy is beneficial and should be prescribed for primary and secondary prevention of cardiovascular events in the CKD population; however, patients with ESRD may not share the same benefits of therapy.

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