Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Lipid-lowering treatment in peripheral artery disease

Niki Katsiki[1], Athanasios D Giannoukas[2], Vasilios G Athyros[1] and Dimitri P Mikhailidis[3]

Peripheral artery disease (PAD) is characterized by increased cardiovascular (CV) risk, limb morbidity and all-cause mortality. According to the current guidelines (2016) of the American Heart Association/American College of Cardiology on the management of PAD patients, statin therapy is recommended for PAD patients in order to treat dyslipidemia and reduce CV risk.The present narrative review discusses the use of statins and other lipid-lowering drugs such as ezetimibe, fibrates, niacin, anacetrapib and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in PAD patients in terms of both CV and limb outcomes. The clinical implications of hypolipidemic drug therapy in special patient populations including those with metabolic syndrome, non-alcoholic fatty liver disease, chronic kidney disease and type 2 diabetes mellitus, which may frequently co-exist with PAD, are also considered.

Addresses
[1] Second Department of Propaedeutic Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippocration Hospital, Thessaloniki, Greece
[2] Department of Vascular Surgery, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[3] Department of Clinical Biochemistry, Royal Free Hospital Campus, University College London Medical School, University College London (UCL), London, UK

Corresponding author: Mikhailidis, Dimitri P (MIKHAILIDIS@aol.com)

Current Opinion in Pharmacology 2018, **39**:19–26

This review comes from a themed issue on **Cardiovascular and renal**

Edited by **Dimitris Tousoulis** and **Evangelos Oikonomou**

For a complete overview see the Issue and the Editorial

Available online 4th February 2018

https://doi.org/10.1016/j.coph.2018.01.003

Introduction

Peripheral artery disease (PAD) represents a coronary heart disease (CHD) equivalent as recognized by the 2001 National Cholesterol Education Program Adult Treatment Panel III [1]. In this context, PAD is characterized by increased cardiovascular (CV) morbidity and mortality as well as total mortality [2,3•]. The most common risk factors for PAD are advanced age, type 2 diabetes mellitus (T2DM) and smoking, followed by dyslipidemia and hypertension [4]. Of note, dyslipidemia is frequently underdiagnosed and undertreated in PAD patients [5,6]. Apart from CHD, PAD has been associated with non-cardiac vascular diseases such as stroke, abdominal aortic aneurysms (AAA), carotid disease and atherosclerotic renal artery stenosis [7–10]. Links between PAD and metabolic diseases, including the metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD), as well as chronic kidney disease (CKD) have also been reported [11–14]. These disorders may further increase CV risk [15–18].

According to the current guidelines (2016) of the American Heart Association (AHA)/the American College of Cardiology (ACC) on the management of PAD patients [19•], several drugs may be used to improve CV risk factors and reduce CV risk in these patients including antiplatelet, antihypertensive and hypolipidemic agents.

The present narrative review discusses the use of lipid-lowering drugs in PAD patients in terms of both CV and lower extremity outcomes. The use of these drugs in special patient populations such as those with MetS, NAFLD, CKD, and T2DM is also considered.

Statins

Statins remain the first-line lipid-lowering therapy to treat PAD patients as recommended by the current AHA/ACC guidelines [19•]. Statins may beneficially affect not only the quantity but also the quality of LDL-C, as they have been reported to reduce the number of small dense LDL (sdLDL) particles [20,21]. Furthermore, statins can improve HDL functionality [22]. The clinical significance of these lipid abnormalities has been discussed elsewhere [23•,24]. Apart from improvements in the lipid profile, statins exert pleiotropic properties including plaque stabilization, regression of atheroma and anti-inflammatory effects, thus minimizing CV risk in PAD patients [25•,26].

Statins in PAD patients

Statins were shown to decrease CV and limb morbidity as well as all-cause death in a cohort study of 1107 patients with intermittent claudication [27]. In patients with critical limb ischemia (CLI), statins reduced total mortality and CV events and increased amputation-free survival [28,29]. Similar benefits were observed in the First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH) registry following statin treatment; increased amputation-free survival was seen in several

populations of statin-treated patients including those with T2DM, CKD and older than 75 years as well as those undergoing endovascular therapy or bypass revascularization [30•]. Statin therapy also decreased total mortality in PAD patients with atrial fibrillation [31]. Furthermore, statin users had reduced CV mortality and fewer lower-extremity amputations in a nationwide database of PAD patients with T2DM [32]. Similarly, in the REACH registry, statin therapy was associated with lower rate of limb outcomes such as worsening symptoms, amputations and revascularization [33]. Improved limb salvage at one year was also observed in PAD patients undergoing endovascular or surgical interventions who were treated with a statin preoperatively [34]. Similar benefits were observed in those administered a statin postoperatively [35]. Furthermore, in patients with both above-knee and below-knee amputations, statins decreased one-year mortality [36]. However, there are studies not reporting reductions in amputation rate following statin treatment in PAD patients [37].

Achievement of LDL-C < 70 mg/dl at a short-term follow-up period (mean duration 4.8 months) after endovascular intervention for PAD was associated with reduced all-cause mortality and CV morbidity [38•]. Apart from lowering CV risk, attaining LDL-C targets in PAD patients can also improve limb symptoms [39]. Of note, high-intensity statin use (i.e. atorvastatin 40–80 mg or rosuvastatin 20–40 mg) was related to fewer CV events and improved survival compared with low-moderate statin therapy in patients with symptomatic PAD, despite similar LDL-C levels [40•].

Statins are recommended in PAD patients undergoing endovascular interventions as they can reduce revascularization rates and postoperative CV events [37]. Lower restenosis rates have been reported in statin-treated patients undergoing stent implantation in the femoropopliteal arteries [41]. Overall, statins may improve perioperative and long-term morbidity and mortality rates as well as infrainguinal bypass graft patency rates, graft restenosis and amputation incidence in PAD patients [42•,43]. Statins may also prolong pain-free walking time or distance and improve quality of life in PAD patients [37,44,45].

PAD patients are suboptimally treated with statins, although statin therapy is indicated in these high-risk individuals [46–48]. In this context, PAD patients (as well as those with ischemic stroke and DM) were less likely to receive statin therapy compared with CHD patients [49]. Admission to a vascular surgery department can increase prescription of statins at discharge [50,51]. Furthermore, PAD patients involved in a guideline-recommended risk-reduction educational program that promoted the use of drugs reducing CV risk such as statins, were reported to have fewer CV and limb events at the end of the seven-year follow-up period [52]. These findings strongly support the need to intensify the implementation of current guidelines, and especially statin use, in PAD patients.

Statins in PAD patients with comorbidities

CKD is frequently present in PAD patients, leading to increased limb and CV morbidity and mortality as well as worse outcomes following endovascular or surgical interventions [53,54]. Statins may improve renal function in different patient populations including those with CHD, MetS, T2DM, CKD, and PAD [55•,56–59]; these conditions often coexist. Statins have also been shown to decrease the risk of vascular events in patients with advanced CKD [60] and the risk of contrast-induced acute kidney injury (CI-AKI), an important side effect of contrast media administration [61•,62]. CI-AKI has been linked to increased CV and renal morbidity, total mortality and prolonged hospitalization [63].

Statins are beneficial in several patient populations including those with MetS, NAFLD, and T2DM. In these patients, statins can not only improve lipids but also decrease CV risk [64,65•,66]. In T2DM patients, statins may also reduce the risk for diabetic complications [67], whereas in NAFLD patients they can improve hepatic biochemical and histological features [15,17,65•]. Therefore, in PAD patients with these cardiometabolic comorbidities, statins may exert several beneficial effects and should be administered.

PAD patients are more likely to develop AAA [68,69]. Therefore, current AHA/ACC guidelines recommend performing a screening duplex ultrasound for AAA in patients with symptomatic PAD [19•]. Statins have been shown to lower CV mortality and slow AAA growth in patients with AAA but further evidence is needed to establish these associations as there are conflict reports [70,71].

Despite several beneficial effects, statins may increase the risk for new-onset diabetes (NOD) [72], especially in individuals at risk of developing T2DM such as women, obese, older (>70 years), of Asian ethnicity and those with prediabetes or MetS [73,74]. The statin-related risk for NOD depends on statin type and dose as well as duration of therapy [75]. Several molecular mechanisms have been proposed to explain the diabetogenic effect of statins [76]. There is a need to establish whether PAD patients are more prone to NOD development because in these patients several risk factors for NOD may coexist including older age, prediabetes, and MetS.

Ezetimibe

Ezetimibe has been reported to improve the lipid profile and exert anti-atherogenic, antioxidant, and anti-inflammatory properties, thus further reducing CV risk [77•].

Ezetimibe may also improve LDL quality by decreasing sdLDL particles [78], thus representing an attractive therapeutic option for patients with mixed dyslipidemia such as those with T2DM, MetS, or NAFLD [67,79–81]. Ezetimibe may be used as monotherapy in statin intolerant patients [82].

In patients with acute coronary syndrome as well as in those with advanced CKD, the combination of simvastatin plus ezetimibe was shown to significantly decrease the rate of CV events compared with simvastatin monotherapy in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [83] and compared with placebo in the Study of Heart and Renal Protection (SHARP) [60], respectively. Of note, 5.5% of patients in the IMPROVE-IT trial had PAD. These findings strongly support the use of ezetimibe in such high-risk patients in order to achieve maximum CV benefit. Furthermore, based on the results of the IMPROVE-IT trial, the American Diabetes Association current (2017) guidelines recommend the use of ezetimibe plus statin combination in T2DM patients with LDL-C levels > 50 mg/dl after an acute coronary syndrome [84].

The effects of ezetimibe on PAD progression remain controversial; previous studies in PAD patients reported no benefit in terms of local atherosclerosis (vessel wall, lumen and volumes) and exercise performance following ezetimibe treatment when compared with statin monotherapy despite effective LDL lowering and improvements in the ankle-branchial index [85–87].

Fibrates

Fibrates are useful drugs to treat mixed (atherogenic) dyslipidemia as they target not only TG metabolism but also increase HDL-C and decrease small dense LDL particles [88]. Therefore, fibrates may be considered in patients with T2DM, MetS or NAFLD who frequently have atherogenic dyslipidemia [89,90]. Especially, in T2DM patients, fenofibrate was shown to reduce CV events in those with elevated TG and low HDL-C levels as reported in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial [91] and the ACCORDION [92], whereas in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate was found to decrease the rate of total CV events and nonfatal myocardial infarction as well as microvascular complications, including nephropathy, in T2DM patients [93]. Furthermore, fenofibrate treatment was associated with a lower risk of amputation in T2DM patients in the FIELD study [94], thus highlighting its potential protective role also in PAD patients. Interestingly, a previous meta-analysis found that fibrates significantly reduced albuminuria as well as CV morbidity and mortality in CKD patients [95]. These benefits may be of clinical importance in fibrate-treated PAD patients. However, fibrates may raise serum creatinine levels by up to 30%, leading to an acute reduction in estimated glomerular filtration rate (eGFR), possibly due to an increase in the production of creatinine or vasodilatory prostaglandins, thus not causing true kidney dysfunction [96]. This effect can be reversible and may mask an underlying renal benefit [95].

In PAD patients, fibrates may be considered in patients with low HDL and elevated TG levels to treat atherogenic dyslipidemia as suggested by previous guidelines [97]. Furthermore, in the Lower Extremity Arterial Disease Event Reduction (LEADER) trial [98] bezafibrate significantly reduced CHD morbidity in elderly men with PAD. More research is needed to elucidate the effects of fibrates on PAD outcomes.

Niacin

Niacin can increase HDL-C levels but this benefit was not related to reduced CV risk [99] as reported in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial [100] and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [101]. Due to these negative results in terms of CV risk as well as niacin-induced serious adverse events (gastrointestinal, musculoskeletal, and skin-related), niacin was withdrawn from the EU market [102].

Limited data exist on the use of niacin in PAD patients. In the Cholesterol Lowering Atherosclerosis Study (CLAS), colestipol plus niacin led to TG decreases and HDL-C increases, along with LDL-C reductions; these lipid improvements were associated with a slower atherosclerosis progression in femoral arteries [103]. However, in the Effect of Lipid Modification on Peripheral Artery Disease after Endovascular Intervention Trial (ELIMIT), no changes were observed in vessel wall, lumen and volumes of the femoral arteries following niacin therapy (combined with ezetimibe and simvastatin) in PAD patients [86]. Furthermore, in such patients, no benefits were recorded in terms of treadmill walking time and claudication onset time after niacin treatment [104]. Of note, coagulation factors were significantly decreased in niacin-treated PAD patients as reported in the Arterial Disease Multiple Intervention Trial (ADMIT) [105]. Niacin was also shown to promote recovery of limb function and revascularization in mice with peripheral ischemia [106].

Cholesteryl ester transfer protein (CETP) inhibitors

CETP inhibitors were developed as HDL-C-raising drugs [107]. However, torcetrapib was associated with increased CV morbidity and mortality probably due to off-target effects in the Investigation of Lipid Level

Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial [108], whereas dalcetrapib and evacetrapib had neutral CV effects in the dal-OUTCOMES study [109] and the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial [110], respectively, leading to discontinuation of their development [111–113]. In contrast, anacetrapib is the only CETP inhibitor that was reported to significantly decrease the incidence of major coronary events in patients with CV disease in the recently published phase 3 Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial [114]. Of note, approximately 8% of these patients had PAD. However, anacetrapib was found to slightly increase blood pressure (by 0.7/0.3 mmHg for systolic/diastolic blood pressure) and to accumulate in adipose tissue [114]. Significantly more patients had estimated glomerular filtration rate <60 ml/min/1.73 m^2 in the anacetrapib group compared with placebo (11.5 versus 10.6%; $p = 0.04$) [114]. It should be noted that anacetrapib is not available in the market yet and the manufacturing company decided against filing for approval of the drug [115].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

PCSK9 inhibitors are a novel class of lipid-lowering drugs administered subcutaneously every two weeks or once a month [116,117]. These drugs have been reported to significantly reduce LDL-C up to 73% when co-administered with a statin ± ezetimibe as well as improve other lipid parameters including lipoprotein (a) [118]. There are two PCSK9 inhibitors approved by both the Food and Drug Administration (FDA) and the European Medicine Agency (EMA): evolocumab and alirocumab. Previous analyses reported potential CV benefits following treatment with these drugs [119,120]. Furthermore, evolocumab was shown to significantly reduce CV morbidity in patients with CV disease and baseline LDL-C $\geq$70 mg/dl (1.8 mmol/l) treated with a statin and/or ezetimibe in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial [121]. Of note, 13.2% of the patients had symptomatic PAD. Furthermore, evolocumab did not affect glucose metabolism and exerted its CV benefits to a similar extent in patients with and without T2DM [122]. The results of the ongoing randomized, placebo-controlled, double-blind CV outcome clinical trial with alirocumab [the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial] will further elucidate the effects of PCSK9 inhibitors on CV risk [123]. With regard to safety, adverse events were tolerable and minimal following treatment with PCSK9 inhibitors, although currently available data are limited in terms of both absolute numbers and follow-up time [124]. A recent meta-analysis did not find an increased rate of musculoskeletal and neurocognitive side effects with PCSK9 inhibitors [125]. Further trials are needed to establish the safety of these drugs as well as their efficacy in special patient populations such as those with PAD, CKD, MetS and NAFLD.

Interestingly, PCSK9 inhibitors can significantly decrease lipoprotein (a) [Lp(a)] levels [126]. Elevated Lp(a) concentrations have been associated with increased CV risk [127] as well as with the presence of AAA [128,129]. As PAD patients have a higher prevalence of AAA than the general population (as discussed above), the use of drugs may minimize the risk for developing AAA by lowering Lp(a) levels. This may represent an attractive therapeutic option.

Conclusions

Statin therapy is recommended for PAD patients in order to treat dyslipidemia and reduce CV risk. Statins may also improve limb morbidity and outcomes after vascular interventions, pain-free walking distance and quality of life, as well as decrease all-cause mortality in these patients. Furthermore, statins exert beneficial pleiotropic effects in patients with T2DM, MetS, NAFLD, and CKD. These metabolic disorders may frequently co-exist with PAD, thus highlighting the clinical implications of statin treatment in these high-risk patients. Ezetimibe may be used in combination with statins, especially in patients with mixed dyslipidemia. Fibrates can also be used with statins but some degree of caution is required. Further research is needed to elucidate the efficacy and safety of other lipid-lowering drugs such as anacetrapib and PCSK9 inhibitors in PAD patients.

Conflict of interest statement

This review was written independently; no company or institution supported the authors financially or by providing a professional writer. NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Elpen, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and Win Medica. ADG has nothing to declare. VGA has given talks, attended conferences and participated in trials sponsored by MSD, Angelini, Sanofi, and Amgen. DPM has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest

1. **Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)**. *JAMA* 2001, **285**:2486-2497.

2. Subherwal S, Patel MR, Kober L, Peterson ED, Bhatt DL, Gislason GH, Olsen AM, Jones WS, Torp-Pedersen C, Fosbol EL: **Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study**. *Eur J Prev Cardiol* 2015, **22**:317-325.

3. • Sigvant B, Lundin F, Wahlberg E: **The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease**. *Eur J Vasc Endovasc Surg* 2016, **51**:395-403.
A recent meta-analysis on the disease progression of PAD.

4. Olin JW, Sealove BA: **Peripheral artery disease: current insight into the disease and its diagnosis and management**. *Mayo Clin Proc* 2010, **85**:678-692.

5. Poussa H, Strandberg TE, Tikkanen I, Kauhanen P, Lepäntalo M: **Diagnosis and treatment of dyslipidemia are neglected in patients with peripheral artery disease**. *Scand Cardiovasc J* 2007, **41**:138-141.

6. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM: **Oxford vascular study: population-based study of incidence, risk factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention**. *Circulation* 2015, **132**:1805-1815.

7. Banerjee A, Fowkes FG, Rothwell PM: **Associations between peripheral artery disease and ischemic stroke: implications for primary and secondary prevention**. *Stroke* 2010, **41**:2102-2107.

8. Takagi H, Umemoto T: **ALICE (All-Literature Investigation of Cardiovascular Evidence) group: association of peripheral artery disease with abdominal aortic aneurysm growth**. *J Vasc Surg* 2016, **64**:506-513.

9. Long TH, Criqui MH, Vasilevskis EE, Denenberg JO, Klauber MR, Fronek A: **The correlation between the severity of peripheral arterial disease and carotid occlusive disease**. *Vasc Med* 1999, **4**:135-142.

10. Leertouwer TC, Pattynama PM, van den Berg-Huysmans A: **Incidental renal artery stenosis in peripheral vascular disease: a case for treatment?** *Kidney Int* 2001, **59**:1480-1483.

11. Zou Y, Li X, Wang C, Wang J, Wang F, Ma L, You W, Li C: **Association between non-alcoholic fatty liver disease and peripheral artery disease in patients with type 2 diabetes**. *Intern Med J* 2017, **47**:1147-1153.

12. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, Djoussé L, Sutton-Tyrrell K, Newman AB *et al.*: **Metabolic syndrome and risk of incident peripheral artery disease: the cardiovascular health study**. *Hypertension* 2014, **63**:413-419.

13. Garimella PS, Hirsch AT: **Peripheral artery disease and chronic kidney disease: clinical synergy to improve outcomes**. *Adv Chronic Kidney Dis* 2014, **21**:460-471.

14. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP: **Characteristics other than the diagnostic criteria associated with metabolic syndrome: an overview**. *Curr Vasc Pharmacol* 2014, **12**:627-641.

15. Katsiki N, Mikhailidis DP, Mantzoros CS: **Non-alcoholic fatty liver disease and dyslipidemia: an update**. *Metabolism* 2016, **65**:1109-1123.

16. Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP: **Editorial: should chronic kidney disease be considered as a coronary heart disease equivalent?** *Curr Vasc Pharmacol* 2012, **10**:374-377.

17. Athyros VG, Tziomalos K, Katsiki N, Doumas M, Karagiannis A, Mikhailidis DP: **Cardiovascular risk across the histological spectrum and the clinical manifestations of non-alcoholic fatty liver disease: an update**. *World J Gastroenterol* 2015, **21**:6820-6834.

18. Katsiki N, Athyros VG, Karagiannis A, Wierzbicki AS, Mikhailidis DP: **Should we expand the concept of coronary heart disease equivalents?** *Curr Opin Cardiol* 2014, **29**:389-395.

19. • Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S *et al.*: **2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines**. *Circulation* 2017, **135**:e686-e725.
Current guidelines for PAD management by ACC/AHA.

20. Clementi A, Kim JC, Floris M, Cruz DN, Garzotto F, Zanella M, Nalesso F, Brendolan A, Giavarina D, Soffiati G *et al.*: **Statin therapy is associated with decreased small, dense low-density lipoprotein levels in patients undergoing peritoneal dialysis**. *Contrib Nephrol* 2012, **178**:111-115.

21. Rizos CV, Kostapanos MS, Rizos EC, Tselepis AD, Elisaf MS: **The effect of rosuvastatin on low-density lipoprotein subfractions in patients with impaired fasting glucose**. *J Cardiovasc Pharmacol Ther* 2015, **20**:276-283.

22. Gomaraschi M, Adorni MP, Banach M, Bernini F, Franceschini G, Calabresi L: **Effects of established hypolipidemic drugs on HDL concentration, subclass distribution, and function**. *Handb Exp Pharmacol* 2015, **224**:593-615.

23. • Mikhailidis DP, Elisaf M, Rizzo M, Berneis K, Griffin B, Zambon A, Athyros V, de Graaf J, März W, Parhofer KG *et al.*: **European panel on low density lipoprotein (LDL) subclasses: a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses: executive summary**. *Curr Vasc Pharmacol* 2011, **9**:531-532.
An expert panel statement on the clinical significance of small dense LDL particles.

24. Otocka-Kmiecik A, Mikhailidis DP, Nicholls SJ, Davidson M, Rysz J, Banach M: **Dysfunctional HDL: a novel important diagnostic and therapeutic target in cardiovascular disease?** *Prog Lipid Res* 2012, **51**:314-324.

25. • Chiesa ST, Papageorgiou N, Charakida M: **Statins in peripheral arterial disease**. *Curr Pharm Des* 2017. September 26 [Epub ahead of print].
A recent review on statin use in PAD patients.

26. Kitrou P, Katsanos K, Karnabatidis D, Reppas L, Brountzos E, Spiliopoulos S: **Current evidence and future perspectives on anti-platelet and statin pharmacotherapy for patients with symptomatic peripheral arterial disease**. *Curr Vasc Pharmacol* 2017, **15**:430-445.

27. Kumakura H, Kanai H, Hojo Y, Iwasaki T, Ichikawa S: **Long-term survival and fate of the leg in de novo intermittent claudication**. *Eur Heart J Qual Care Clin Outcomes* 2017, **3**:208-215.

28. Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, Pevec WC, Amsterdam EA, Laird JR: **Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia**. *J Am Coll Cardiol* 2014, **63**:682-690.

29. Suckow BD, Kraiss LW, Schanzer A, Stone DH, Kalish J, DeMartino RR, Cronenwett JL, Goodney PP, Vascular Study Group of New England: **Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival**. *J Vasc Surg* 2015, **61**:126-133.

30. • Stavroulakis K, Borowski M, Torsello G, Bisdas T: **CRITISCH collaborators: association between statin therapy and amputation-free survival in patients with critical limb ischemia in the CRITISCH registry**. *J Vasc Surg* 2017, **66**:1534-1542.
The present study highlights the beneficial effects of statins on limb survival in patients with CLI.

31. Proietti M, Raparelli V, Laroche C, Dan GA, Janion M, Popescu R, Sinagra G, Vijgen J, Boriani G, Maggioni AP *et al.*: EORP-AF Gen Pilot Investigators: **Adverse outcomes in patients with atrial fibrillation and peripheral arterial disease: a report from the EURObservational research programme pilot survey on atrial fibrillation**. *Europace* 2017, **19**:1439-1448.

32. Hsu CY, Chen YT, Su YW, Chang CC, Huang PH, Lin SJ: **Statin therapy reduces future risk of lower-limb amputation in patients with diabetes and peripheral artery disease**. *J Clin Endocrinol Metab* 2017, **102**:2373-2381.

33. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I *et al.*: REACH Registry Investigators: **Statin therapy and long-term adverse limb outcomes in patients with peripheral artery**

disease: insights from the REACH registry. *Eur Heart J* 2014, **35**:2864-2872.

34. Vogel TR, Dombrovskiy VY, Galiñanes EL, Kruse RL: **Preoperative statins and limb salvage after lower extremity revascularization in the Medicare population**. *Circ Cardiovasc Interv* 2013, **6**:694-700.

35. Klingelhoefer E, Bergert H, Kersting S, Ludwig S, Weiss N, Schönleben F, Grützmann R, Gäbel G: **Predictive factors for better bypass patency and limb salvage after prosthetic above-knee bypass reconstruction**. *J Vasc Surg* 2016, **64** 380–388.e1.

36. 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**:216-225.

37. Harris SK, Roos MG, Landry GJ: **Statin use in patients with peripheral arterial disease**. *J Vasc Surg* 2016, **64**:1881-1888.

38. • Lee JH, Ko YG, Shin DH, Kim JS, Kim BK, Choi D, Hong MK, Jang Y: **Attainment of low-density lipoprotein cholesterol goal after endovascular treatment is associated with reduced cardiovascular events in patients with peripheral arterial disease**. *J Vasc Surg* 2016, **63**:756-763.
This study supports the achievement of LDL-C goals to improve CV risk in PAD patients.

39. Daskalopoulou SS, Daskalopoulos ME, Mikhailidis DP, Liapis CD: **Lipid management and peripheral arterial disease**. *Curr Drug Targets* 2007, **8**:561-570.

40. • Foley TR, Singh GD, Kokkinidis DG, Choy HK, Pham T, Amsterdam EA, Rutledge JC, Waldo SW, Armstrong EJ, Laird JR: **High-intensity statin therapy is associated with improved survival in patients with peripheral artery disease**. *J Am Heart Assoc* 2017, **6**.
A review that highlights the importance of high-intensity statin therapy to reduce CV risk and mortality rates in PAD patients.

41. Kim W, Gandhi RT, Peña CS, Herrera RE, Schernthaner MB, Acuña JM, Becerra VN, Katzen BT: **The influence of statin therapy on restenosis in patients who underwent nitinol stent implantation for de novo femoropopliteal artery disease: two-year follow-up at a single center**. *J Vasc Interv Radiol* 2016, **27**:1494-1501.

42. • Paraskevas KI, Giannoukas AD, Mikhailidis DP: **Statins and infrainguinal vascular bypass procedures**. *Curr Vasc Pharmacol* 2013, **11**:51-57.
A review that summarizes data on improved perioperative and long-term mortality and morbidity rates in statin-treated PAD patients.

43. Paraskevas KI, Athyros VG, Briana DD, Kakafika AI, Karagiannis A, Mikhailidis DP: **Statins exert multiple beneficial effects on patients undergoing percutaneous revascularization procedures**. *Curr Drug Targets* 2007, **8**:942-951.

44. Poredos P, Jezovnik MK: **Do the effects of secondary prevention of cardiovascular events in PAD patients differ from other atherosclerotic disease?** *Int J Mol Sci* 2015, **16**:14477-14489.

45. Gargiulo G, Giugliano G, Brevetti L, Sannino A, Schiattarella GG, Serino F, Carbone A, Scudiero F, Ferrone M, Corrado R *et al.*: **Use of statins in lower extremity artery disease: a review**. *BMC Surg* 2012, **12**:S15.

46. Meltzer AJ, Sedrakyan A, Connolly PH, Ellozy S, Schneider DB, Vascular Study Group of Greater New York: **Risk factors for suboptimal utilization of statins and antiplatelet therapy in patients undergoing revascularization for symptomatic peripheral arterial disease**. *Ann Vasc Surg* 2017. June 8 [Epub ahead of print].

47. O'Donnell TFX, Deery SE, Darling JD, Shean KE, Mittleman MA, Yee GN, Dernbach MR, Schermerhorn ML: **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**:572-578.

48. Argyriou C, Saleptsis V, Koutsias S, Giannoukas AD: **Peripheral arterial disease is prevalent but underdiagnosed and undertreated in the primary care setting in central Greece**. *Angiology* 2013, **64**:119-124.

49. Steen DL, Khan I, Becker L, Foody JM, Gorcyca K, Sanchez RJ, Giugliano RP: **Patterns and predictors of lipid-lowering therapy in patients with atherosclerotic cardiovascular disease and/or diabetes mellitus in 2014: insights from a large US managed-care population**. *Clin Cardiol* 2017, **40**:155-162.

50. Thiney M, Della Schiava N, Feugier P, Lermusiaux P, Ninet J, Millon A, Long A: **How admission to a vascular surgery department improves medical treatment in patients with lower extremity peripheral arterial disease**. *Ann Vasc Surg* 2017, **40**:85-93.

51. Steenhof N, Le Piane F, Leblanc K, Eisenberg NR, Kwan Y, Malmberg C, Papadopoulos A, Roche-Nagle G: **Vascular quality of care pilot study: how admission to a vascular surgery service affects evidence-based pharmacologic risk factor modification in patients with lower extremity peripheral arterial disease**. *Vasc Health Risk Manag* 2014, **10**:333-340.

52. Hussain MA, Al-Omran M, Mamdani M, Eisenberg N, Premji A, Saldanha L, Wang X, Verma S, Lindsay TF: **Efficacy of a guideline-recommended risk-reduction program to improve cardiovascular and limb outcomes in patients with peripheral arterial disease**. *JAMA Surg* 2016, **151**:742-750.

53. Paraskevas KI, Giannoukas AD, Mikhailidis DP: **Renal function impairment in peripheral arterial disease: an important parameter that should not be neglected**. *Ann Vasc Surg* 2009, **23**:690-699.

54. Paraskevas KI, Giannoukas AD, Mikhailidis DP: **The impact of impaired renal function on long-term outcomes in patients with peripheral arterial disease**. *Angiology* 2010, **61**:415-416.

55. • Nikolic D, Banach M, Nikfar S, Salari P, Mikhailidis DP, Toth PP, Abdollahi M, Ray KK, Pencina MJ, Malyszko J *et al.*: Lipid Blood Pressure Meta-Analysis Collaboration Group: **A meta-analysis of the role of statins on renal outcomes in patients with chronic kidney disease. Is the duration of therapy important?** *Int J Cardiol* 2013, **168**:5437-5447.
A meta-analysis on statin-induced renal benefits in patients with CKD.

56. Alnaeb ME, Alobaid N, Seifalian AM, Mikhailidis DP, Hamilton G: **Statins and peripheral arterial disease: potential mechanisms and clinical benefits**. *Ann Vasc Surg* 2006, **20**:696-705.

57. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP: **The role of statins in the treatment of type 2 diabetes mellitus: an update**. *Curr Pharm Des* 2014, **20**:3665-3674.

58. Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP: **Statins can improve proteinuria and glomerular filtration rate loss in chronic kidney disease patients, further reducing cardiovascular risk. Fact or fiction?** *Expert Opin Pharmacother* 2015, **16**:1449-1461.

59. Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, Tziomalos K, Ganotakis ES, Elisaf M: **Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study**. *Nephrol Dial Transplant* 2007, **22**:118-127.

60. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, *et al.*: SHARP Investigators: **The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial**. *Lancet* 2011, **377**:2181-2192.

61. • Briasoulis A, Pala M, Telila T, Merid O, Akintoye E, Vogiatzi G, Oikonomou E, Tousoulis D: **Statins and contrast-induced nephropathy: a systematic review and meta-analysis**. *Curr Pharm Des* 2017. September 13 [Epub ahead of print].
A recent meta-analysis on the protective role of statins against CI-AKI.

62. Wang N, Qian P, Yan TD, Phan K: **Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and trial sequential analysis**. *Int J Cardiol* 2016, **206**:143-152.

63. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP: **Contrast-induced nephropathy: an "all or none" phenomenon?** *Angiology* 2015, **66**:508-513.

64. Bragg DA, Walling A: **Metabolic syndrome: hyperlipidemia**. *FP Essent* 2015, **435**:17-23.

65. • Athyros VG, Alexandrides TK, Bilianou H, Cholongitas E, Doumas M, Ganotakis ES, Goudevenos J, Elisaf MS, Germanidis G, Giouleme O *et al.*: **The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An Expert Panel Statement**. *Metabolism* 2017, **71**:17-32.

A recent expert panel statement on the use of statins in NAFLD patients.

66. Khavandi M, Duarte F, Ginsberg HN, Reyes-Soffer G: **Treatment of dyslipidemias to prevent cardiovascular disease in patients with type 2 diabetes**. *Curr Cardiol Rep* 2017, **19**:7.

67. Katsiki N, Purrello F, Tsioufis C, Mikhailidis DP: **Cardiovascular disease prevention strategies for type 2 diabetes mellitus**. *Expert Opin Pharmacother* 2017, **18**:1243-1260.

68. Gray C, Goodman P, Cullen P, Badger SA, O'Malley K, O'Donohoe MK, McDonnell CO: **Screening for peripheral arterial disease and carotid artery disease in patients with abdominal aortic aneurysm**. *Angiology* 2016, **67**:346-349.

69. Paraskevas KI, Mikhailidis DP, Giannoukas AD: **Additional issues on screening, prevention, and treatment of abdominal aortic aneurysms**. *Am J Mens Health* 2013, **7**:472-474.

70. Weiss N, Rodionov RN, Mahlmann A: **Medical management of abdominal aortic aneurysms**. *VASA* 2014, **43**:415-421.

71. Dunne JA, Bailey MA, Griffin KJ, Sohrabi S, Coughlin PA, Scott DJ: **Statins: the holy grail of Abdominal Aortic Aneurysm (AAA) growth attenuation? A systematic review of the literature**. *Curr Vasc Pharmacol* 2014, **12**:168-172.

72. Vlachopoulos C, Ioakeimidis N, Aznaouridis K, Lazaros G, Tousoulis D: **Statins in diabetes mellitus**. *Curr Pharm Des* 2017. August 15 [Epub ahead of print].

73. Betteridge DJ, Carmena R: **The diabetogenic action of statins – mechanisms and clinical implications**. *Nat Rev Endocrinol* 2016, **12**:99-110.

74. Chrysant SG: **New onset diabetes mellitus induced by statins: current evidence**. *Postgrad Med* 2017, **129**:430-435.

75. Katsiki N, Rizzo M, Mikhailidis DP, Mantzoros CS: **New-onset diabetes and statins: throw the bath water out, but, please, keep the baby!** *Metabolism* 2015, **64**:471-475.

76. Banach M, Malodobra-Mazur M, Gluba A, Katsiki N, Rysz J, Dobrzyn A: **Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance**. *Curr Pharm Des* 2013, **19**:4904-4912.

77. • Katsiki N, Theocharidou E, Karagiannis A, Athyros VG, Mikhailidis DP: **Ezetimibe therapy for dyslipidemia: an update**. *Curr Pharm Des* 2013, **19**:3107-3114.

A review summarizing the beneficial effects of ezetimibe as a lipid-lowering drug.

78. Winkler K, Jacob S, Müller-Schewe T, Hoffmann MM, Konrad T: **Ezetimibe alone and in combination lowers the concentration of small, dense low-density lipoproteins in type 2 diabetes mellitus**. *Atherosclerosis* 2012, **220**:189-193.

79. Simon TG, Corey KE, Chung RT, Giugliano R: **Cardiovascular risk reduction in patients with nonalcoholic fatty liver disease: the potential role of ezetimibe**. *Dig Dis Sci* 2016, **61**:3425-3435.

80. Iqbal J, Al Qarni A, Hawwari A, Al Ghanem AF, Gasmelseed A: **Metabolic syndrome, dyslipidemia and regulation of lipoprotein metabolism**. *Curr Diabetes Rev* 2017. July 5 [Epub ahead of print].

81. Katsiki N, Tentolouris N, Mikhailidis DP: **Dyslipidaemia in type 2 diabetes mellitus: bad for the heart**. *Curr Opin Cardiol* 2017, **32**:422-429.

82. Katsiki N, Athyros VG, Karagiannis A: **Exploring the management of statin intolerant patients: 2016 and beyond**. *Curr Vasc Pharmacol* 2016, **14**:523-533.

83. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, *et al.*: IMPROVE-IT Investigators: **Ezetimibe added to statin therapy after acute coronary syndromes**. *N Engl J Med* 2015, **372**:2387-2397.

84. http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf.

85. West AM, Anderson JD, Meyer CH, Epstein FH, Wang H, Hagspiel KD, Berr SS, Harthun NL, DiMaria JM, Hunter JR *et al.*: **The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline**. *Atherosclerosis* 2011, **218**:156-162.

86. Brunner G, Yang EY, Kumar A, Sun W, Virani SS, Negi SI, Murray T, Lin PH, Hoogeveen RC, Chen C *et al.*: **The Effect of Lipid Modification on Peripheral Artery Disease after Endovascular Intervention Trial (ELIMIT)**. *Atherosclerosis* 2013, **231**:371-377.

87. West AM, Anderson JD, Epstein FH, Meyer CH, Wang H, Hagspiel KD, Berr SS, Harthun NL, Weltman AL, Dimaria JM *et al.*: **Low-density lipoprotein lowering does not improve calf muscle perfusion, energetics, or exercise performance in peripheral arterial disease**. *J Am Coll Cardiol* 2011, **58**:1068-1076.

88. Katsiki N, Nikolic D, Montalto G, Banach M, Mikhailidis DP, Rizzo M: **The role of fibrate treatment in dyslipidemia: an overview**. *Curr Pharm Des* 2013, **19**:3124-3131.

89. Kushner PA, Cobble ME: **Hypertriglyceridemia: the importance of identifying patients at risk**. *Postgrad Med* 2016, **128**:848-858.

90. Gandhi N, Lenton R, Bhartia M, Abbas A, Raju J, Ramachandran S: **Effect of fibrate treatment on liver function tests in patients with the metabolic syndrome**. *Springerplus* 2014, **3**:14.

91. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J *et al.*: **Effects of combination lipid therapy in type 2 diabetes mellitus**. *N Engl J Med* 2010, **362**:1563-1574.

92. Elam MB, Ginsberg HN, Lovato LC, Corson M, Largay J, Leiter LA, Lopez C, O'Connor PJ, Sweeney ME, Weiss D *et al.*: ACCORDION Study Investigators: **Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes**. *JAMA Cardiol* 2017, **2**:370-380.

93. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P *et al.*: FIELD Study Investigators: **Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial**. *Lancet* 2005, **366**:1849-1861.

94. Rajamani K, Colman PG, Li LP, Best JD, Voysey M, D'Emden MC, Laakso M, Baker JR, Keech AC, FIELD Study Investigators: **Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial**. *Lancet* 2009, **373**:1780-1788.

95. Jun M, Zhu B, Tonelli M, Jardine MJ, Patel A, Neal B, Liyanage T, Keech A, Cass A, Perkovic V: **Effects of fibrates in kidney disease: a systematic review and meta-analysis**. *J Am Coll Cardiol* 2012, **60**:2061-2071.

96. Sica DA: **Fibrate therapy and renal function**. *Curr Atheroscler Rep* 2009, **11**:338-3342.

97. Pollak AW, Kramer CM: **LDL lowering in peripheral arterial disease: are there benefits beyond reducing cardiovascular morbidity and mortality?** *Clin Lipidol* 2012, **7**:141-149.

98. Meade T, Zuhrie R, Cook C, Cooper J: **Bezafibrate in men with lower extremity arterial disease: randomised controlled trial**. *BMJ* 2002, **325**:1139.

99. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP: **High-density lipoprotein, vascular risk, cancer and infection: a case of quantity and quality?** *Curr Med Chem* 2014, **21**:2917-2926.

100. AIM-HIGH Investigators: Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W: **Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy**. *N Engl J Med* 2011, **365**:2255-2267.

101. HPS2-THRIVE Collaborative Group: Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R *et al.*: **Effects of extended-release niacin with laropiprant in high-risk patients**. *N Engl J Med* 2014, **371**:203-212.

102. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/01/news_detail_001694.jsp&mid=WC0b01ac058004d5c1.

103. Blankenhorn DH, Azen SP, Crawford DW, Nessim SA, Sanmarco ME, Selzer RH, Shircore AM, Wickham EC: **Effects of colestipol–niacin therapy on human femoral atherosclerosis**. *Circulation* 1991, **83**:438-447.

104. Hiatt WR, Hirsch AT, Creager MA, Rajagopalan S, Mohler ER, Ballantyne CM, Regensteiner JG, Treat-Jacobson D, Dale RA, Rooke T: **Effect of niacin ER/lovastatin on claudication symptoms in patients with peripheral artery disease**. *Vasc Med* 2010, **15**:171-179.

105. Chesney CM, Elam MB, Herd JA, Davis KB, Garg R, Hunninghake D, Kennedy JW, Applegate WB: **Effect of niacin, warfarin, and antioxidant therapy on coagulation parameters in patients with peripheral arterial disease in the Arterial Disease Multiple Intervention Trial (ADMIT)**. *Am Heart J* 2000, **140**:631-636.

106. Pang DK, Nong Z, Sutherland BG, Sawyez CG, Robson DL, Toma J, Pickering JG, Borradaile NM: **Niacin promotes revascularization and recovery of limb function in diet-induced obese mice with peripheral ischemia**. *Pharmacol Res Perspect* 2016, **4**:e00233.

107. Mohammadpour AH, Akhlaghi F: **Future of cholesteryl ester transfer protein (CETP) inhibitors: a pharmacological perspective**. *Clin Pharmacokinet* 2013, **52**:615-626.

108. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD *et al.*: ILLUMINATE Investigators: **Effects of torcetrapib in patients at high risk for coronary events**. *N Engl J Med* 2007, **357**:2109-2122.

109. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, *et al.*: dal-OUTCOMES Investigators: **Effects of dalcetrapib in patients with a recent acute coronary syndrome**. *N Engl J Med* 2012, **367**:2089-2099.

110. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, *et al.*: ACCELERATE Investigators: **Evacetrapib and cardiovascular outcomes in high-risk vascular disease**. *N Engl J Med* 2017, **376**:1933-1942.

111. Kosmas CE, DeJesus E, Rosario D, Vittorio TJ: **CETP inhibition: past failures and future hopes**. *Clin Med Insights Cardiol* 2016, **10**:37-42.

112. Katsiki N, Athyros VG, Mikhailidis DP: **The DEFINE study: a bright future for CETP inhibitors?** *Expert Opin Investig Drugs* 2011, **20**:311-314.

113. https://investor.lilly.com/releasedetail.cfm?releaseid=936130.

114. HPS3/TIMI55-REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD, Cannon CP, Braunwald E, Sammons E *et al.*: **Effects of anacetrapib in patients with atherosclerotic vascular disease**. *N Engl J Med* 2017, **377**:1217-1227.

115. http://investors.merck.com/news/press-release-details/2017/Merck-Provides-Update-on-Anacetrapib-Development-Program/default.aspx.

116. Katsiki N, Athyros VG, Mikhailidis DP, Mantzoros C: **Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors: shaping the future after the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) trial**. *Metabolism* 2017, **74**:43-46.

117. Alkindi M, Siminovitch KA, Gupta M, Genest J: **Monoclonal antibodies for the treatment of hypercholesterolemia: targeting PCSK9**. *Can J Cardiol* 2016, **32**:1552-1560.

118. Ferdinand KC, Nasser SA: **PCSK9 inhibition: discovery, current evidence, and potential effects on LDL-C and Lp(a)**. *Cardiovasc Drugs Ther* 2015, **29**:295-308.

119. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M *et al.*: ODYSSEY LONG TERM Investigators: **Efficacy and safety of alirocumab in reducing lipids and cardiovascular events**. *N Engl J Med* 2015, **372**:1489-1499.

120. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM *et al.*: Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators: **Efficacy and safety of evolocumab in reducing lipids and cardiovascular events**. *N Engl J Med* 2015, **372**:1500-1509.

121. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM *et al.*: FOURIER Steering Committee and Investigators: **Evolocumab and clinical outcomes in patients with cardiovascular disease**. *N Engl J Med* 2017, **376**:1713-1722.

122. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS *et al.*: **Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial**. *Lancet Diabetes Endocrinol* 2017. September 14 [Epub ahead of print].

123. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW *et al.*: **Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial**. *Am Heart J* 2014, **168**:682-689.

124. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP: **PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease**. *Cochrane Database Syst Rev* 2017, **4**:CD011748.

125. Khan AR, Bavishi C, Riaz H, Farid TA, Khan S, Atlas M, Hirsch G, Ikram S, Bolli R: **Increased risk of adverse neurocognitive outcomes with proprotein convertase subtilisin-kexin type 9 inhibitors**. *Circ Cardiovasc Qual Outcomes* 2017, **10**.

126. Schulz R, Schlüter KD: **PCSK9 targets important for lipid metabolism**. *Clin Res Cardiol Suppl* 2017, **12**:2-11.

127. Katsiki N, Al-Rasadi K, Mikhailidis DP: **Lipoprotein (a) and cardiovascular risk: the show must go on**. *Curr Med Chem* 2017, **24**:989-1006.

128. Alexandrou AT, Tsimikas S: **Elevated Lp(a) and abdominal aortic aneurysm**. *Angiology* 2017, **68**:96-98.

129. Kotani K, Sahebkar A, Serban MC, Ursoniu S, Mikhailidis DP, Mariscalco G, Jones SR, Martin S, Blaha MJ, Toth PP *et al.*: Lipid Blood Pressure Meta-analysis Collaboration (LBPMC) Group: **Lipoprotein(a) levels in patients with abdominal aortic aneurysm**. *Angiology* 2017, **68**:99-108.