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Lipid optimisation in lower extremity peripheral arterial disease

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**Abstract**

**Aims:**

This review aims to explore the current guidance and issues surrounding lipid optimisation of patients with peripheral arterial disease (PAD).

**Methods:**

A narrative review of the global PAD guidance, specifically focusing on low density lipoprotein cholesterol (LDL-C) reduction methods including; 'treating to target', 'fire and forget' and LDL-C percentage reduction. Advanced literature searches were carried out in Pubmed and Google Scholar databases comparing most recent PAD lipid guidance.

**Results:**

PAD lipid guidance could be improved internationally to help clinicians implement the best lipid-reduction strategies for their patients and challenge the arbitrary 1.4mmol/L LDL-C target in line with novel proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK-9i) trials. By educating primary and secondary care staff on the benefits of maximal lipid-reduction therapies, we can reduce major adverse cardiovascular events (MACE) and major adverse limb events (MALE). Championing PAD community clinics may lead to earlier prevention. Research comparing lipid-reduction strategies in practice is needed to improve outcomes internationally, and ongoing practice audited to understand the extent of under-prescribing in PAD.

**Conclusions:**

This review highlights the current PAD lipid-reduction treatments and the clarity issues of global guidance. Further research is needed to tackle ongoing mortality and morbidity rates in PAD patients against their better off cardiovascular disease (CVD) peers.

**MESH Key Terms:** "Cholesterol", "Hydroxymethylglutaryl-CoA Reductase Inhibitors", "Ezetimibe", "Evolocumab", "Alirocumab", "Peripheral Arterial Disease", "Vascular Disease", "Atherosclerosis", "Secondary Prevention", "Lipoprotein, LDL".

## Lipid Conversions

Table 1. Lipid conversions adapted from (1)

## Introduction

This review aims to explore the current guidance and issues surrounding lipid optimisation of patients with lower extremity peripheral arterial disease (PAD).

## Lower Extremity Peripheral Arterial Disease

Peripheral arterial disease (PAD) has multiple aetiologies (2). The majority of PAD cases are caused by atherosclerotic plaque accumulation in the lower limb arterial tree leading to a reduction in arterial blood flow (3). Clinically this manifests as intermittent claudication which can progress to chronic limb threatening ischaemia (4).

Additional causes include thrombo-embolic disease, vasculitis and extrinsic compression. Important clinical risk factors include smoking, black ethnicity, diabetes, hypertension, hypercholesterolaemia, decreased eGFR and poor lifestyle (2,5).

## Prevalence of PAD

Globally, PAD affects approximately 5.6% of people over 25 (6,7) and represents over a quarter of cardiovascular disease worldwide (8). PAD is often defined as an ankle-brachial pressure index (ABPI) of less than or equal to 0.9 at rest (9,10). This may exclude patients with calcified arteries, where ABPI may be greater than 1.3 (11). Diabetes, heavy smoking and chronic kidney disease can all increase arterial stiffening. An estimated 41% of PAD patients also have type 2 diabetes mellitus

(12). Several previous studies have cited the greater prevalence of PAD in men (13,14). However, it is now suspected that women may be of equal prevalence, and present 10-20 years later than men (15–18). Patients living with PAD can present to general practice or directly to secondary care with symptoms ranging from intermittent claudication (IC) to chronic limb threatening ischaemia (CLTI).

**Secondary Prevention**

Both symptomatic and asymptomatic PAD patients carry an increased risk of cardiovascular events (19). Although patients suffering with PAD may be most concerned about amputation, major adverse cardiovascular events (MACE) occur more frequently in PAD patients than limb loss (20–22). Their ten-year risk of amputation stands at 10%, whereas, their five-year risk of MACE (defined in the Secondary Manifestations of ARTerial disease (SMART) study as nonfatal MI, nonfatal stroke, and vascular mortality) is 13.2% (21–24). In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk (FOURIER) trial, PAD patients without previous MI or stroke had 10.3% (MACE) verses 2.6% major adverse limb events (MALE) across a two and half year follow up period (25).

PAD patients were also found to be at a higher risk of cardiovascular events than patients with coronary artery disease (CAD) or patients with previous myocardial infarction (MI) (25, 26). In the SMART study statins were prescribed to 74% of the CAD patients, compared to 53% of PAD patients (25). Aspirin was used by 89% of CAD patients as opposed to 65% of PAD patients, see table 2. Women with PAD were also found to be the least medically optimised, compared to male post-MI patients who were the most well medicated (25). Overall PAD patients had a higher mortality and an increased event rate of ischaemic coronary events than patients with CAD and up to four times higher the risk of vascular death than patients with angina or cardiovascular disease (CVD) (25). In PAD patients, previous angina or MI does not predict mortality (26).

*Table. 2 Comparison between PAD and CVD (previous MI patients) adapted from results from the SMART trial (n= 3563) (25).*

Persistent PAD under-prescribing at the secondary prevention stage as found by the PINNACLE registry analysis and other studies, demonstrates the need for specific solutions for this patient group (6,27–29). Current literature commonly focuses on adverse cardiac outcomes, with PAD as part of a subgroup analysis (30).

**Lifestyle modification**

All PAD patients should have documented smoking cessation which is followed up regularly (11,31,32). Peripheral bypass in smokers carries a threefold risk of graft failure according to a meta-analysis of 29 studies (33). Patients with intermittent claudication who continue to smoke also have an increased risk of amputation (34). A review of the most effective treatments for smoking specifically in PAD patients found that clinician advice did encourage patients to quit, and thus holds an important part in the vascular consultation (35).

Exercising to the point of maximal pain is recommended by UK NICE (National Institute for Clinical Excellence), ESC (European Society of Cardiology) and ESVS (European Society of Vascular Surgery) and improves claudication symptoms and overall walking distance (11,32). Supervised exercise, although more effective at improving walking distance than unsupervised exercise, is not available in many countries (36–39). Un-supervised patients are advised to walk for at least 30 mins, two to three times a week for 12 weeks (11,36,40). However, participants in one study reported that they avoided exercise following vascular intervention because they believed that the pain on walking causes “damage to their muscles and legs” (20). Thus, indicating the future benefit of qualitative studies in PAD.

## UK NICE guidance summary

In the socialised UK National Health Service (NHS), evidence based, cost effective treatments are recommended by the National Institute for health and Care Excellence (NICE). UK NICE PAD Guidelines recommend smoking cessation, diabetic control, lipid management, hypertension management, antiplatelet therapy, diet and unsupervised exercise in claudicants, managed by primary care physicians / general practitioners (11). PAD diagnosis should be by vascular examination and measurement of ankle brachial pressure index (ABPI). The majority of imaging should only be requested if an intervention is planned. Patients with severe lifestyle limiting short distance claudication or CLTI should be referred to a vascular surgeon. Since 2014, NICE has recommended high-intensity statin prescription and measurement of a full lipid profile (total cholesterol, HDL-C, non-HDL-C and triglycerides) in PAD patients (11). Lipid levels should then be re-checked at three months. Newer UK NICE lipid-specific guidance (April 2020), places increasing emphasis on low-density lipoprotein cholesterol (LDL-C) reduction targets of 40% from baseline or below 1.8mmol/L for all patients diagnosed with PAD (41). UK NICE guidance advises symptomatic PAD patients to be prescribed high-intensity statin therapy as per secondary prevention algorithms, see figure 3 (41).

## Statins

*Penicillium citrinum*, a species of fungi, aided the production of the first statin in 1976. It produced a substance with molecular similarities to 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) (42,43). HMG-CoA reductase catalyses the reaction of HMG-CoA into Mevalonic acid at the start of the cholesterol synthesis pathway in the liver, see figure 1. The substance acted as a competitive inhibitor for HMG-CoA. The substance ‘compactin’, an early version of today’s

pravastatin, inspired scientists to find similar compounds, which were effective at lowering cholesterol in humans (42, 43).

*Fig.1 Statin inhibition in the cholesterol synthesis process*

**Statin Types and Lipid Reduction**

*Fig. 2 Adapted from (44), Chemical structure of statin types used for cholesterol reduction*

High-intensity statin therapy is defined by NICE as causing an LDL-C reduction of >40% and includes: atorvastatin 20mg or above and rosuvastatin 10mg or above, or ezetimibe 10mg alongside the maximum tolerated statin dose (41). Patients with PAD who were prescribed appropriate high-intensity statin dosing over moderate-intensity statin dosing had a 15% lower risk of mortality and a 22% decrease in amputation risk over 5.9 years average follow-up (45).

Simvastatin 80mg does meet the LDL-C reduction target at 42%, however is contraindicated due to the high risk of muscle toxicity (41). Pravastatin caused a maximum effect of 29% reduction and is classed as a low-intensity statin (41). Fluvastatin 80mg had a medium-intensity effect at 33% reduction and thus, is not suitable for secondary prevention (41). Only the five types of statin mentioned above are available on NHS prescription, see figure 2 (46). High-intensity dosing, or the 'fire and forget' method, may not be sufficient and should be paired with repeat full lipid screening, with follow up of ezetimibe 10mg if the target of LDL-C <1.8mmol/L, or a 40% reduction in LDL-C is not met. It is also important for clinicians to record adherence to statins, lifestyle advice and acknowledgement of lipid treatment targets (41). However, there is a lack of clarity globally on lipid targets and statin treatment strategies, as the ESC now recommend a lower LDL-C treatment target of 1.4mmol/L (see global LDL-C summary in table 5) (47). Recent proprotein convertase

subtilisin/kexin type 9 inhibitors (PCSK-9I) trials, have started to challenge these arbitrary LDL-C targets by showing ongoing cardiovascular benefit below 10mg/dL (0.26 mmol/L) LDL-C (25).

**Statin Intolerance**

*Fig. 3 Adapted from (48), UK NICE Statin intolerance algorithm June 2020*

UK NICE produced a statin intolerance algorithm in June 2020, after increasing concerns of negative media coverage of statin muscle side effects, see figure 3 (48). The 'nocebo' effect may have added to statin discontinuation in three quarters of patients who stop taking their statins after two years (48). Real world statin intolerance reaches up to 18%, compared to just 5% in randomised blinded controlled trials (49). Statin-related muscle toxicity presents as "symmetrical pain and/or weakness in large proximal muscle groups, worsened by exercise", which are similar to claudication symptoms in PAD. True statin intolerances can be tackled by de-challenge and re-challenge approaches set out by UK NICE; providing the creatinine kinase (CK) does not exceed four times the upper limit of normal. A CK above this would require specialist assessment for statin-induced rhabdomyolysis, which has an average incidence of four per 100,000 patients (48). Patients with genuine statin intolerance may be suitable for ezetimibe or PCSK-9i (41,48).

Other side effects such as statin-induced diabetes and haemorrhagic stroke (atorvastatin) are rare, with up to 100 and 10 patients per 10,000 respectively experiencing these adverse events (50,51). The pleiotropic benefits of statins outweigh these risks (50). 'Alternative dosing' is recommended by ESC/ European atherosclerosis society (EAS) and American College of Cardiology (ACC)/ American Heart Association (AHA), where statins are taken on alternative days to reduce patient symptoms and increase adherence to medication (47,52). NICE statin intolerance pathway advocates for a de-challenge and re-challenge approach, starting patients on lower doses, monitoring their CK levels if symptomatic and changing statin type (48). UK NICE also recommends discussing adherence with

patients if their LDL-C target is not met after three months on high-intensity dosing (48). Timing of statins is also important as previous studies have suggested that simvastatin is more potent at night due to its short-half life (53). Patients may also find the large size of statin tablets difficult to swallow; more qualitative research is needed into the adherence of statins to understand the patient-perspective.

**Non-statin Lipid Reduction Therapies**

**Ezetimibe**

Instead of inhibiting HMG-CoA reductase, ezetimibe targets niemann–pick C1-like 1 protein (NPC1L1) in the jejunum and liver (54). NCP1L1 aids absorption of micelles into enterocytes and hepatocytes (54). Newer studies have proposed that ezetimibe promotes reverse cholesterol transport in the liver, by exposing the hepatocytes to lower cholesterol levels (55). Ezetimibe is metabolised separately to statins, and there is little evidence of any major interactions with drugs used regularly for lipid-reduction (56).

Despite the success of the IMProved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) trial in patients with acute coronary syndrome, the Ezetimibe and Simvastatin in Hypercholesterolemic Enhances Atherosclerosis Regression (ENHANCE) study found no benefits of ezetimibe plus simvastatin over simvastatin alone in carotid stenosis patients (57,58). However, a smaller study of 100 patients with carotid stenosis, ezetimibe plus atorvastatin over atorvastatin alone showed lower non-HDL-C levels and decrease in artery plaque area (59).

Studies specifically for the use of ezetimibe in the PAD patient population remain scarce and of poor quality. 67 PAD patients on simvastatin 40mg, whom when added ezetimibe, showed further progression in their atherosclerotic plaques (60). The authors admitted the study was hugely underpowered (72%), and after a year of simvastatin 40mg and ezetimibe, the LDL-C reached 1.75

mmol/L (32, 41). Narrowly hitting the current 2020 UK NICE target of 1.8mmol/L LDL-C but missing the ESC/ESVS target of less than 1.4mmol/L (41). NICE classifies simvastatin 40mg as medium-intensity statin dosing, which is now unsuitable for secondary prevention of cardiovascular events; the study was completed in 2011 (41). The Effect of Lipid Modification on Peripheral Artery Disease after Endovascular Intervention (ELIMIT) trial with 102 PAD patients also reported no difference between simvastatin 40mg and ezetimibe over simvastatin alone in 2013 (61). A third study did find a difference between LDL-C in ezetimibe and simvastatin 40mg and simvastatin alone after two years: 1.7 mmol/L compared to 2.4 mmol/L respectively. But, found no corresponding differences between tissue perfusion and exercise limits in the groups (62).

Ezetimibe, when used in conjunction with statins, has been shown to provide an additive benefit reduction of 23-24% in LDL-C levels in patients with coronary artery disease (41). Novel NICE guidance recommends addition of ezetimibe if non-HDL-C levels have not reduced by over 40% from baseline after three months (41). Doubling of statin dose is also less likely to achieve higher rates of non-HDL-C/LDL-C reduction than adding in ezetimibe (48). In statin intolerant patients, ezetimibe may be prescribed as monotherapy (41,52,63).

**PCSK-9 inhibitors**

Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors are monoclonal antibodies that target the PCSK-9 protein which promotes degradation of low-density lipoprotein receptor (LDL-R) in hepatocytes (64,65). LDL-C attaches onto LDL-R and is absorbed intercellularly. By interfering with the degradation of LDL-R caused by PCSK-9, LDL-C can continue to be absorbed from the blood (64,66). Statins have also been shown to be less effective in patients with high PCSK-9 activity (66).

Familial Hypercholesterolemia (FH) a genetically inherited condition which affects around 1 in 200-500 people, is mainly caused by a mutation in LDL-R (67,68). However, it can also be caused by

PCSK-9 gain of function mutations (69). These mutations prevent hepatic regulation of LDL-C, causing early death from atherosclerotic conditions (66). UK NICE only offers evolocumab, a PCSK-9i, to specific patient populations outlined in table 3 (70).

*Table 3. Adapted from NICE Evolocumab guidance, showing which patient groups may receive Evolocumab (70). FH= Familial Hypercholesterolemia. High Risk= Includes PAD. Very High Risk= polyvascular disease.*

Unfortunately, due to these therapies costing up to £4,400 ($6,045, €5,016) per patient per annum, only patients who are very high risk may be able to benefit (71).

The FOURIER trial demonstrated that lipid reduction beyond current targets of 1.8 or 1.4mmol/L LDL-C had added cardiovascular benefit with no short-term side effects (25). Evolocumab also reduced the risk of MALE (defined as ALI, amputation, or urgent revascularisation) by 42% in PAD patients (n=3642) (65). There were also no significant differences in major adverse side effects when compared to placebo (1.3% Evolocumab versus 1.5% placebo, P=0.57) (65). Evolocumab also drove lipoprotein(a) levels down 20-30%, where patients with greater reductions appeared to gain more coronary benefit (72). This is interesting as potentially 90% of a person's lipoprotein(a) is inherited (73,74). Further research is needed into the link between lipoprotein(a) and cardiovascular risk alongside LDL-C (72).

Alirocumab in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) trial (n= 18 924) when combined with statin in recent CAD patients produced a 15% relative risk reduction in the end point (defined as cardiovascular death, non-fatal MI, non-fatal stroke, or unstable angina) (75). Unfortunately, there was no PAD cohort to support MALE figures from the FOURIER trial. Potential long-term effects are yet to come to light (72). However, bococizumab, another potential PCSK-9i, had to be discontinued after trials showed

a decrease in LDL-C lowering and production of autoantibodies (76). The PCSK-9i studies were limited by the lack of ezetimibe prescriptions (75).

**Lipid Management Guidance for PAD**

While there are some areas of agreement between newer UK NICE lipid guidance, European and American societies; there is much controversy surrounding lipid targets and statin use globally, as illustrated by table 5. With non-HDL-C targets set to anywhere between 2.2-2.6 mmol/L and none, it is understandable that there are treatment differences between clinicians (9,32,41,77). UK NICE 2020 lipid management guidance sets out clear lipid targets for general cardiovascular prevention which encourages doctors to perform a full lipid screen at baseline and annually with repeats every three months if statin is titrated (41). It also outlines the LDL-C reduction capabilities for each statin, highlighting the need for initial treatment on high-intensity dose statins with over 40% LDL-C reduction (9,31). The lipid specific European and American guidance sets out a more ambitious LDL-C reduction target of over 50% (47,52).

The additive combination effects of ezetimibe and PCSK-9i are starting to be implemented in practice (25,75). However, with a single PCSK-9i Quality of Life Year (QALY) costing up to $450,000 (£325,000) (€370,000), it is not currently cost effective to start all PAD patients on extreme lipid lowering therapies (31,52). Even though 95% of patients given Evolocumab hit LDL-C targets when paired with high-intensity statin therapy in ACS patients (78). See table 3 for UK NICE PSCK-9i treatment boundaries.

However, there appears to be key differences over the risk category of PAD patients. Both UK NICE 2020 and ESC/EAS 2019 lipid specific guidance put PAD patients in the ‘very high risk’ category for secondary cardiovascular prevention (32,41). Whereas ACC/AHA in 2018 decided that ‘very high risk’ patients must have previous multiple atherosclerotic cardiovascular disease (ASCVD)

conditions or any major ASCVD event to be eligible for LDL-C reduction >1.8mmol/L (52). Despite this, ACC/AHA guidance takes a harsher approach with secondary prevention in general, citing that all ASCVD patients should be on high-intensity statin doses which reduce their LDL-C by over 50%, compared to the 40% target of UK NICE lipid guidance (41,52). The Asia-Pacific society of atherosclerosis and vascular diseases stated no specific lipid reduction targets or intensity of statin dosing in relation to LDL-C reduction (79).

UK NICE guidance on lipid management of PAD falls in line with general cardiovascular prevention (31, 41). It is not specific to patients with PAD. Lipid screening does not mention LDL-C measurement in initial screening recommendations 1.3.4 UK NICE 2014 or in the required blood tests before statins 1.3.13 (41). However, it does advise that statins should be started on high-intensity doses, such as atorvastatin 80mg or rosuvastatin 40mg, for secondary prevention purposes. UK NICE advises a repeat lipid profile at three months and recommends an annual lipid screen to inform annual prescription reviews. Non-HDL-C should have a 40% reduction, if not reached, clinicians should increase statin dose, consider lifestyle changes, and discuss adherence to medication (41). Ezetimibe is mentioned only in relation to hypercholesterolaemia, which was last reviewed in 2018, despite having an additional effect of up to 24% LDL-C reduction in the IMPROVE-IT trial (41,58). However, UK NICE guidance released in April 2020, includes lipid measurements; total cholesterol, HDL-C, non-HDL-C, LDL-C, triglycerides (41). Only excluding the HDL-C/LDL-C ratio.

**Treatment strategies for lowering LDL-C**

Two different statin treatment strategies have been previously discussed in cardiovascular literature. 'Fire and forget (F&F)' consists of prescribing a low to moderate dose statin, but without any lipid screening or clinician follow-up or consequent statin titration (80,81). Those for this strategy argue that giving 10mg of atorvastatin to eight patients is four times as effective as giving 80mg to one person from a dose-responsive perspective (81). No lipid screening means less phlebotomy visits

and less statin side effects (81). One paper suggested that further cholesterol reduction in patients with already reduced levels may only have limited vascular benefits and therefore further reductions may be “overly zealous” (82). However, more recent trials have suggested that benefits increase below 10mg/dL or 0.2mmol/L of LDL-C (25,83).

The ‘treating to target’ (T2T) method allows more individualised patient care by prescribing a statin and re-checking lipid levels after three months or annually and titrating the statin up as necessary (80). A study looking at the two different statin treatment strategies found that treating to target LDL-C level with follow up, significantly increased adherence to statins, and patients had lower cardiovascular disease event rates (80). This suggests that despite the initial cost-effectiveness of the F&F method, patients are cardiovascularly worse off.

A potential third lipid reduction strategy is the use of personalised reduction targets, where their LDL-C target is set at a 50% of their baseline. LDL-C percentage reduction is mentioned frequently in global guidance, but there remains a lack of comparison between strategies and implementation in practice. This enables major clinical differences in the management of hyperlipidaemic PAD patients, as those with higher base line LDL-C may not achieve the lower threshold targets set by the ESC of 1.4 mmol/L, as seen in table 4.

*Table 4. Percentage reduction verses named targets*

*Table 5. Current global PAD and Lipid guidance summary. UK NICE= National Institute for Health and Care Excellence. ESC= European Society of Cardiology. ESVS= European Society of Vascular Surgery. ACC= American College of Cardiology. AHA= American Heart Association. EAS= European Atherosclerosis Society. VHR= Very High Risk. *Alternative Dosing, taking statins on alternative days.*

## Under-prescribing of Statins in PAD

Under-prescribing in PAD is well documented in the literature, where patients receive inadequate statin dosing, antiplatelet or anticoagulation medicines compared to comparator groups with coronary or cerebral vascular atherosclerosis (22,84-87). A Canadian vascular clinic study (n=208), where half had PAD, found that of the 88% of patients taking a statin, 43% were moderate intensity only (84). 32% of patients did not reach an LDL-C target of <2 mmol/L (84). An Irish study of 180 vascular patients found 86% were on statin therapy, but failed to segregate by dose and type, and nevertheless urged that vascular surgeons take on more responsibility for medical management (86).

More recently, a larger study by UK Vascular and Endovascular Research Network (VERN) n=440, found that PAD patients in ten vascular care centres across the UK had suboptimal care against UK and European guidance (87). The study found that only 11% of patients were on high-dose statin therapy and 39% anti-thrombotic agent; PAD patients also had a mean LDL-C of 2.7 mmol/L (87). Importantly, they found that medical optimisation of this cohort would lead to an absolute risk reduction of the ten-year cardiovascular risk by 29% (87).

In contrast, 83% of CAD patients were prescribed statins in the UK carotid interventions audit (88,89). Simple interventions could be the answer in improving statin prescription, and one study highlighted ‘untapped’ quality improvement lead by vascular junior doctors, which achieved an in-patient statin prescription rate of 100% (88). Teaching of the juniors included 20-minute presentations, a statin compliance form added to patient notes and senior positive input to remember statin prescription (88). This intervention could easily be applied to CLI and ALI inpatients, to ensure patients are discharged on high-intensity statins.

## Recommendations

There is much room for change within global guidance. Firstly, to bring down lipid targets to 1.4mmol/L falling in line with ESC guidance or lower based on the emerging data from the PCSK-9i trials (47). Increasing clarity of the guidance specifically for PAD patients to be on high-intensity statins, using the T2T method, see figure 4 with appropriate adjunctive use of ezetimibe and PCSK-9i.

*Fig. 4 Treat to Target recommendation by Sucharitkul et al., March 2021*

Further research into PCSK-9i will give the scientific community a greater understanding of the long-term risks and benefits for patients. Additionally, the long-term effects of decreasing LDL-C to zero may provide evidence to support treating LDL-C to below 1.8mmol/L. Furthermore, comparative research between lipid-reduction strategies in PAD should be made a priority, as it is unknown which is superior. Qualitative studies of statins in PAD are needed to address statin adherence and intolerance.

UK and European guidance should be audited to understand the scale of the under prescribing of statins and other medications in PAD patients, including under-represented groups. Overall an international effort is needed to evaluate the medical care of PAD patients.

## Conclusion

This review highlights the current lipid lowering treatments in patients suffering with PAD and advocates a T2T approach. All clinicians treating patients with PAD should prioritise lipid optimisation, however, further research is needed to determine the optimal lipid reduction strategy in PAD.

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**REVISED FIGURES: 21st March 2021**
**Sucharitkul Et al. Lipid optimisation in peripheral arterial disease**

| To Convert from mmol/L to mg/dL | |
|---|---|
| Total/HDL-C/LDL-C mmol/L | *38.67 = mg/dL |
| For Triglycerides mmol/L | *88.57 = mg/dL |
| **To Convert from mg/dL to mmol/L** | |
| Total/HDL-C/LDL-C mg/dL | /38.67 = mmol/L |
| For Triglycerides mg/dL | /88.57 = mmol/L |

***Table 1. Lipid conversions adapted from (1)***

| SMART trial | CVD patients | PAD patients |
|---|---|---|
| **Statin prescription** | **74%** | **53%** |
| **Aspirin prescription** | **89%** | **65%** |
| **Annual risk of vascular events** | **3.10%** | **3.20%** |

***Table 2. Comparison between peripheral arterial disease patients (PAD) and cardiovascular disease (CVD). Adapted from results from the Secondary Manifestations of ARTerial disease (SMART) trial (n= 3563) (22).***

| | Without CVD | With CVD | |
|---|---|---|---|
| | | High Risk | Very High Risk |
| **Primary non-FH or Mixed dyslipidaemia** | Not recommended | Only if LDL-C >4mmol/L | Only if LDL-C >3.5 mmol/L |
| **Primary heterozygous FH** | Only if LDL-C >5.0mmol/L | Only if LDL-C >3.5 mmol/L | |

***Table 3. Adapted from NICE Evolocumab guidance, showing which patient groups may receive Evolocumab (70). FH= Familial Hypercholesterolemia. High Risk= Includes PAD. Very High Risk= polyvascular disease (disease in multiple vascular beds).***

| Baseline LDL-C mmol/L | >50% reduction mmol/L | Meets ESC target of <1.4mmol/L? |
|---|---|---|
| **7** | <3.5 | No |
| **5** | <2.5 | No |
| **3** | <1.5 | No |
| **2** | <1.0 | Yes |

***Table 4. Percentage reduction verses named targets. ECS= European Society of Cardiology.***

| PAD/Lipid guidance | LDL-C Target | Non-HDL-C Target | Statin type/dose | Statin Intolerance | Ezetimibe | PCSK-9i |
|---|---|---|---|---|---|---|
| **NICE PAD 2008/2014 (11)** | Refers to CVD guidance | Refers to CVD guidance | Refers to lipid guidance | Refers to lipid guidance | Refers to lipid guidance | Refers to lipid guidance |
| **ESC/ESVS PAD 2017 (32)** | <1.8mmol OR greater than or equal to 50% | Not mentioned | Not mentioned, 'Statin' only | Not mentioned | is beneficial | Fourier trial noted- awaiting further trials |
| **ACC/AHA PAD 2016 (77)** | No Target | No Target | Not mentioned | Not mentioned | Not mentioned | Not mentioned |
| **Asia-Pacific 2018 (79)** | No target | No target | Not mentioned, 'Statin' only | Not mentioned | Not mentioned | Not mentioned |
| **Lipid specific NICE 2020 (41)** | Reduce LDL-C by 40% OR <1.8mmol/L | <2.5mmol/L | Atorvastatin 80mg OR Rosuvastatin 40mg | De-challenge and Re-Challenge | Add after 3mth if targets not met | LDL-C >3.5mmol/L AND VHR on max ezetimibe/statin PAD=**VHR** |
| **Lipid specific ESC/EAS 2019 (47)** | <1.4 mmol/L Reduce LDL greater or equal to 50% of baseline | <2.2mmol/L | Statins which reduce LDL by more than 50% | Alternative dosing* | Add if target not achieved on max statin | Add if target not achieved on max statin PAD=**VHR** |
| **Lipid specific ACC/AHA 2018 (52)** | Reduce LDL-C by 50% in ASCVD OR <1.8 mmol/L if **VHR** | <2.6mmol/L | High-intensity statins which reduce LDL-C by more than 50% | Alternative dosing* or re-challenge | Add if target not achieved on max statin | Add if target not achieved on max statin. But consider long term unknown side effects |
| **Lipid Specific Taiwan 2018 (90)** | <2.5 mmol/L for **PAD only** <1.4mmol/L (ACS and DM) | <2.5mmol/L | High-intensity statins which reduce LDL-C by more than 50% | Not mentioned | Add if target not achieved on max statin | Consider for statin intolerant/statin resistant or FH |

***Table 5. Current global PAD and Lipid guidance summary. UK NICE= National Institute for Health and Care Excellence. ESC= European Society of Cardiology. ESVS= European Society of Vascular Surgery. ACC= American College of Cardiology. AHA= American Heart Association. EAS= European Atherosclerosis Society. VHR= Very High Risk. *Alternative Dosing, taking statins on alternative days***

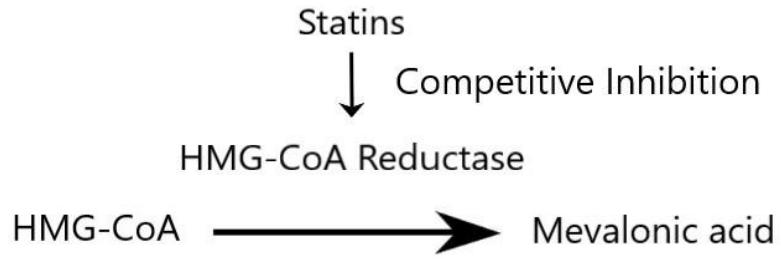



***Figure 1. Statin inhibition in the cholesterol synthesis process***

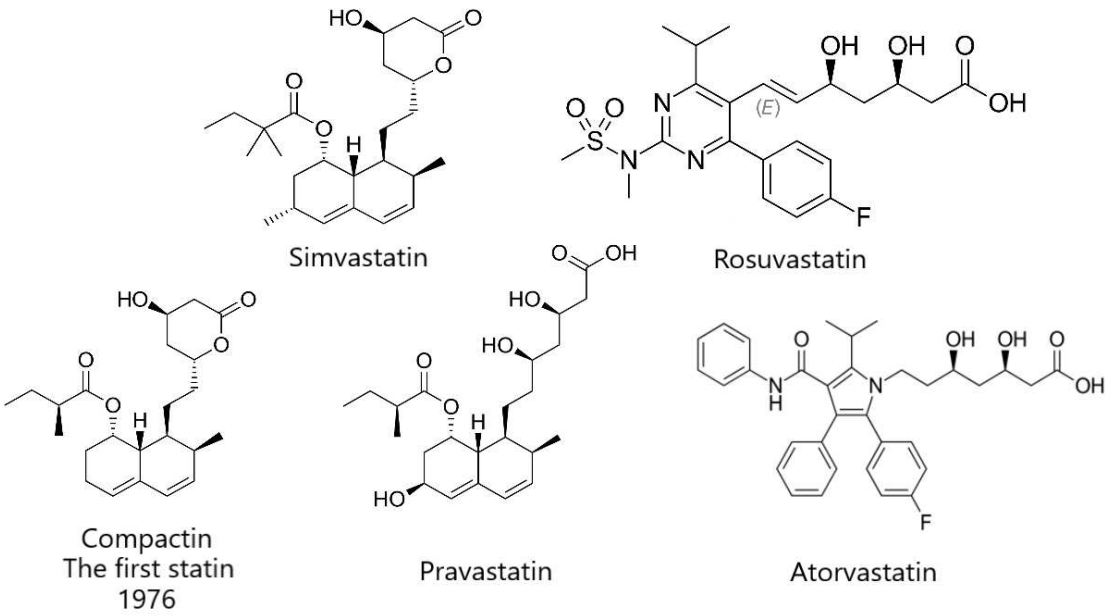



***Figure 2. Chemical structure of statin types used for cholesterol reduction. Adapted from (44).***

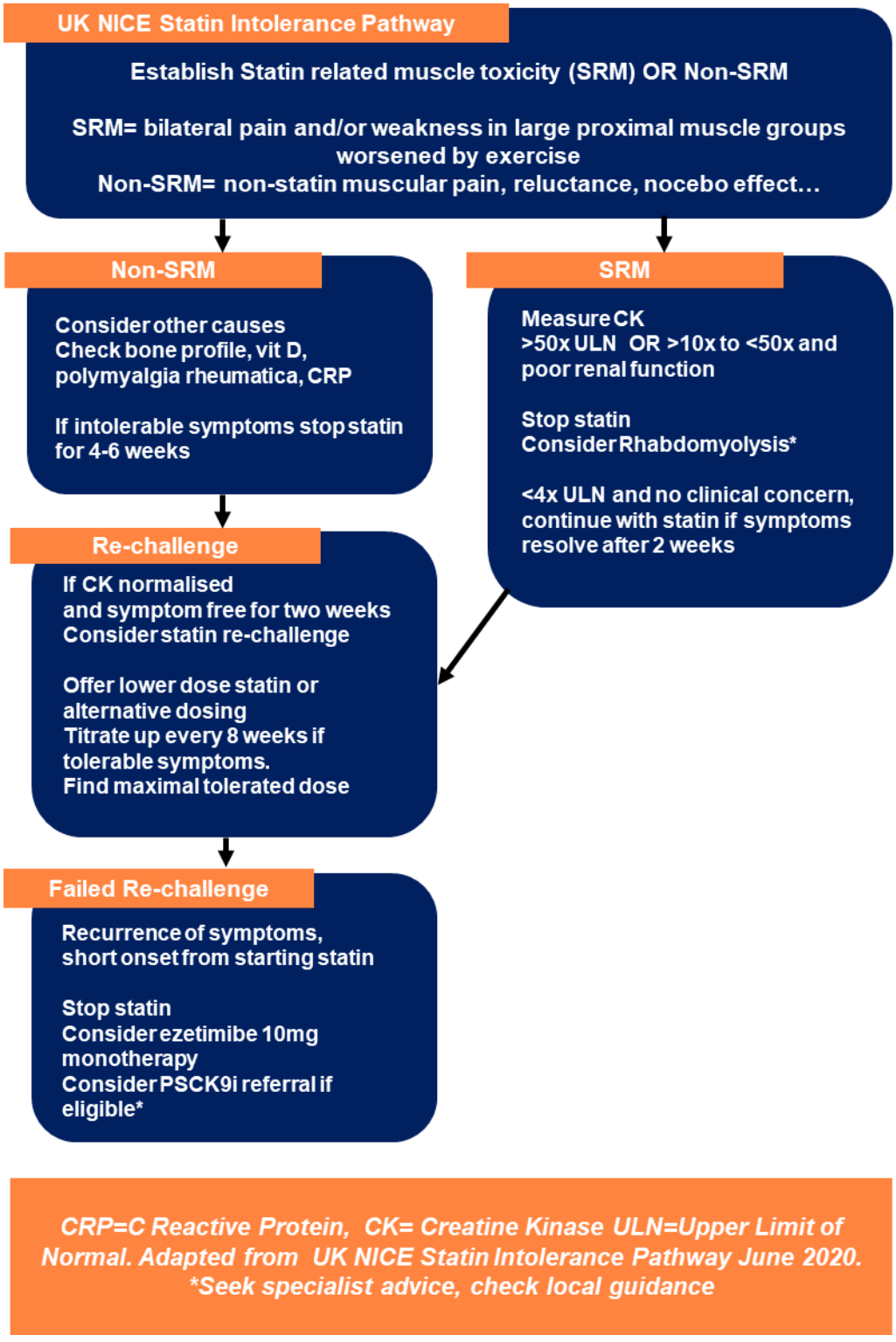
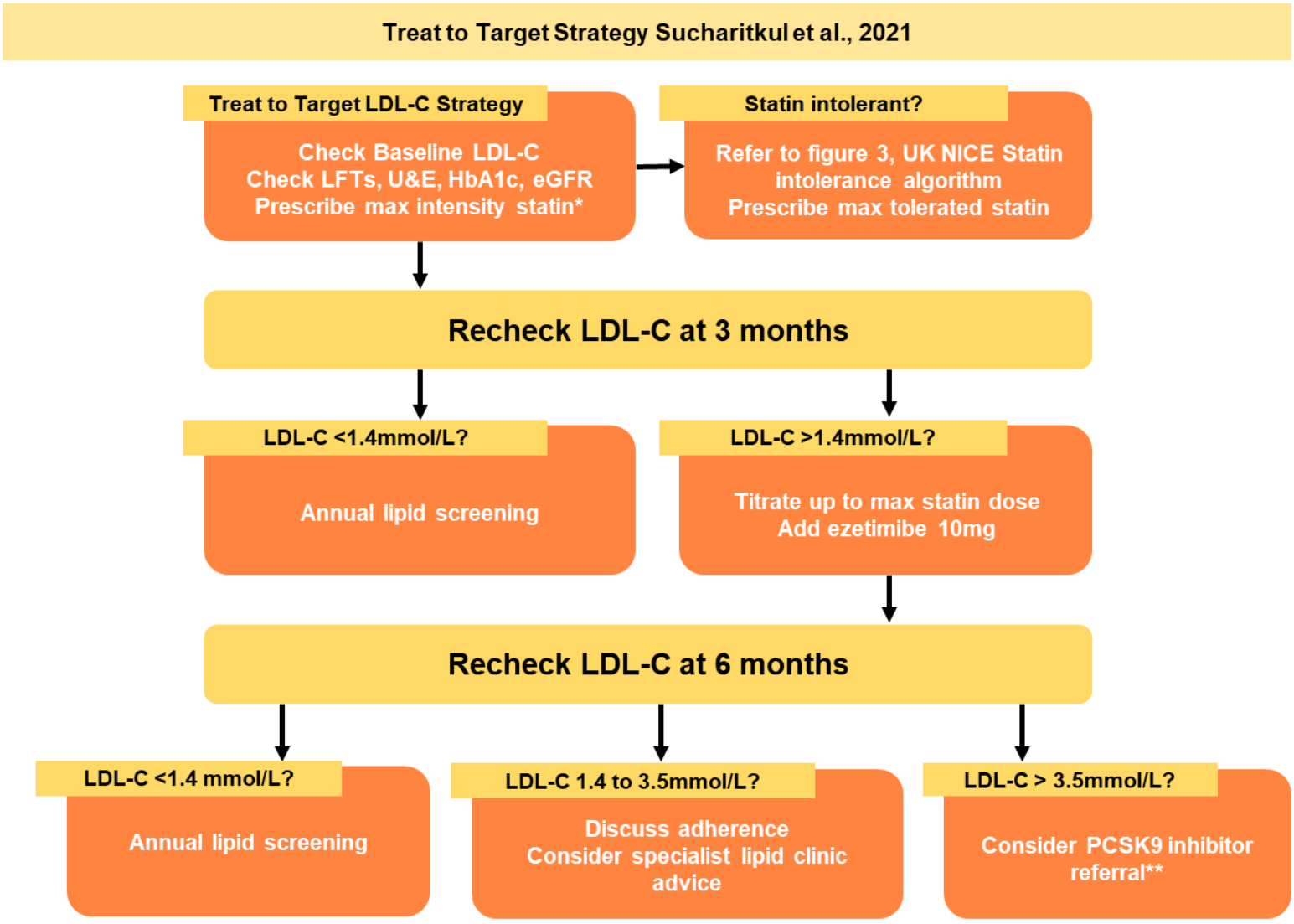



***Figure 3. Summary of UK NICE Statin intolerance algorithm June 2020. Adapted from (48).***




*LDL-C = Low-Density Lipoprotein cholesterol, LFT= Liver Function Tests, U&E= Urea and Electrolytes, HbA1c= Glycated haemoglobin, eGFR= Estimated Glomerular Filtration Rate*

**if eGFR <60 mL/min/1.73 m² offer up to atorvastatin 20mg*
*Max intensity= atorvastatin 80mg or rosuvastatin 40mg, LDL-C reduction of greater than 40% (41)*

***Check local guidance, LDL-C 3.5>mmol/L PCSK9i threshold based on UK NICE lipid guidance 2020 (41)*

***Figure 4. Treat to Target recommendation by Sucharitkul et al., March 2021. LDL-C= Low-density lipoprotein cholesterol. PCSK9i= Proprotein convertase subtilisin/kexin type 9. Based on (11, 41, 32, 47, 52, 80).***