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Review article

# New cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention?

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ABSTRACT

Elevated low-density lipoprotein cholesterol (LDL-C) is a principally modifiable cause of atherosclerotic cardiovascular disease; accordingly, recent European and US multisociety dyslipidaemia guidelines emphasise the importance of lowering LDL-C to reduce cardiovascular risk. This review provides perspectives on established and emerging agents that reduce LDL-C to help providers synthesize the abundance of new evidence related to prevention of cardiovascular disease. We provide hypothetical cases of patients with different cardiovascular risk factors and medical histories to illustrate application of current lipid-lowering guidelines in various clinical settings. As a core focus of preventive therapy, both European and US lipid management guidelines emphasise the importance of identifying patients at very high cardiovascular risk and treating to achieve LDL-C levels as low as possible, with European guidelines setting a goal of <1.4 mmol/L (<55 mg/dL) in patients with very high-risk cardiovascular disease. The proprotein convertase subtilisin/kexin type 9 inhibitors are now included in the guidelines and may fulfil an important unmet need for very high-risk patients who are not able to achieve LDL-C goals with conventional agents. The recently approved bempedoic acid and other promising agents under development will add to the armamentarium of lipid-lowering drugs available for clinicians to help patients meet their treatment goals.

## 1. Introduction

Substantial new evidence has accumulated in the area of dyslipidaemia treatment, leading to the revision of guidelines in both Europe and the US. There is extensive evidence showing that low-density lipoprotein cholesterol (LDL-C) and apoprotein B–containing lipoproteins are causal in cardiovascular disease (CVD) and should be primary targets in the treatment of dyslipidaemia. There has been a general trend towards more intensive LDL-C lowering and treating below lower thresholds, especially for secondary prevention, as the risk to the patient increases with increasing LDL-C, and the risk reduction achieved depends on the absolute LDL-C reduction [1–3]. In late 2018, the American College of Cardiology (ACC) and American Heart Association (AHA) published a multisociety guideline for the management of blood

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cholesterol [2]. The US guideline introduced definitions of high-risk and very high-risk (VHR) atherosclerotic CVD (ASCVD) and recommended lipid-lowering therapy accordingly. For patients with VHR ASCVD, the recommended LDL-C goal is ≤ 1.8 mmol/L (≤70 mg/dL) (Table 1) [2]. More recently, in September 2019, the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) published a new guideline and introduced updated recommendations, including recommending that LDL-C be lowered as much as possible, specifically a goal of <1.4 mmol/L (<55 mg/dL) in patients with VHR, including those with established CVD or familial hypercholesterolaemia (FH) with ASCVD or another risk factor (Table 1) [1]. Supplementary Table S1 provides a more detailed comparison of European and US lipid-lowering guidelines.

Several recent reviews provide comprehensive overviews of the pathophysiology of atherosclerosis and coronary artery disease (CAD) and pharmacologic lipid modification therapies [4–6]. To help cardiologists and other providers synthesize the abundance of new evidence related to the prevention of CVD and apply the guidelines in clinical practice, we focused on established and emerging agents that reduce LDL-C for patients with different cardiovascular risk factors and medical histories in various disease states. In addition, we briefly review other agents in the cardiovascular risk–reduction landscape, including those commonly prescribed to patients with type 2 diabetes mellitus (T2DM) and hypertriglyceridaemia [7]. Agents very early in clinical development and agents without outcomes data (e.g. fibrates) were considered beyond the scope of this review, as was cost-effectiveness in light of the differing pricing, access and reimbursement policies worldwide.

## 2. Approved LDL-C–lowering therapies

Statins (3-hydroxy-3-methylglutaryl-coenzyme [HMG-CoA] inhibitors) are the cornerstone of therapy among LDL-C–lowering drugs; other LDL-lowering drugs include ezetimibe, bile acid sequestrants and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [2]. The sites and targets of traditional and newer lipid-lowering therapies are outlined schematically in Fig. 1.

There is extensive evidence showing that LDL-C is one of the most important causal factors for CVD. For this reason, LDL-C is the primary target in dyslipidaemia guidelines, yet a recent meta-analysis revealed a potential important role of other plasma lipids, including triglycerides [8]. Most lipid-lowering therapies in use today increase LDL receptor expression and therefore increase LDL clearance. There are also agents such as lomitapide that decrease LDL-C synthesis, but these agents are only indicated for homozygous FH, have numerous side effects, and are used mainly by lipid specialists.

Statins block HMG-CoA reductase activity, which decreases intrahepatic cholesterol concentration and upregulates the LDL receptor, leading to an increase in the clearance of hepatic LDL particles, ultimately lowering LDL-C levels [9]. Statin monotherapy reduces LDL-C levels by approximately 30–50% [2,10]. Statin therapy intensity is divided into three categories according to the AHA/ACC guidelines: high intensity, moderate intensity and low intensity based on typical LDL-C lowering (approximately 50%, 40% and 30%, respectively) [2].

The most commonly used non-statin drug is ezetimibe [2], which inhibits cholesterol absorption in the small intestine through the Niemann-Pick C1-like protein 1 receptor, causing an indirect increase in LDL receptor synthesis, and typically lowers LDL-C by approximately 20% [6,11]. Despite guideline-directed use as a second-line agent to lower LDL-C levels, ezetimibe may not be potent enough to achieve target LDL-C goals in all patients, particularly those with markedly elevated LDL-C levels [12,13].

Bile acid sequestrants such as cholestyramine, colestipol and colesevelam decrease the enterohepatic pool of cholesterol and indirectly increase LDL receptor synthesis, reducing LDL-C levels by 15–30% depending on the dose [2,6,11]. These agents are not absorbed and do not cause systemic adverse effects, but they can bind to other drugs and cause gastrointestinal adverse effects, including constipation, and can exacerbate hypertriglyceridaemia (fasting triglyceride levels need to be < 3.4 mmol/L [<300 mg/dL] in patients initiating bile acid sequestrant treatment) [2,11].

A new pathway to decrease LDL-C levels involves inhibiting PCSK9. There are different ways to inhibit PCSK9, but most experience to date is with the monoclonal antibodies alirocumab and evolocumab. These agents bind to and prevent circulating PCSK9 from binding to the LDL receptor, increasing the number of LDL receptors available to clear circulating LDL-C [6,11]. PCSK9 inhibitors, the most innovative lipid-lowering therapies since statins, are potent drugs that have been observed to lower LDL-C levels by 43–64% [2,6,11]. Although target LDL-C goals are achieved with statin monotherapy in some patients (e.g. 38% of patients with acute coronary syndrome [ACS]) [14], high-risk patients or patients with very high LDL-C levels need additional (combination) treatment. Patients who are not able to tolerate higher statin doses may also require non-statin alternatives and/or combination therapy to achieve target LDL-C goals. PCSK9 inhibitors are useful in selected high-risk patients, such as those with FH, or statin-intolerant patients who are not able to achieve target LDL-C goals with conventional treatments [2,6].

Data from the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial indicate that PCSK9 inhibitors are also useful for individuals with advanced disease or high plaque burden, such as patients with diabetes mellitus, polyvascular disease and post–coronary artery bypass graft following recent ACS [15–17]. A recent meta-analysis of clinical trials of alirocumab or evolocumab reported that use of PCSK9 inhibitors was associated with significantly lower risk of myocardial infarction (MI; by 20%; $p < 0.0001$), ischaemic stroke (by 22%; $p = 0.0005$) and coronary revascularisation (by 17%; $p < 0.0001$) compared with controls (placebo and/or other lipid-lowering drugs) [18]. There were no significant differences in all-cause or cardiovascular death between PCSK9 inhibitors and controls.

Table 2 summarises the hypothetical LDL-C values that patients might achieve on different lipid-lowering therapies and combinations. For example, in a patient with an LDL-C level of 3.9 mmol/L (150 mg/dL), high-intensity statin therapy would be expected to reduce LDL-C by 50% to 1.9 mmol/L (75 mg/dL); addition of ezetimibe would result in incremental LDL-C reduction to 1.6 mmol/L (60 mg/dL), or a 60% overall reduction in LDL-C from the starting point (3.9 mmol/L [150 mg/dL]). For the same starting LDL-C, treatment with a moderate-intensity statin plus ezetimibe plus a PCSK9 inhibitor would be expected to reduce LDL-C by 80% from 3.9 mmol/L (150 mg/dL) to 0.8 mmol/L (30 mg/dL).

Meta-analyses of major lipid-lowering studies by the Cholesterol Treatment Trialists' (CTT) Collaboration have shown that the reduction in risk for major cardiovascular events is proportional to absolute LDL-C reduction. In an analysis of statins *versus* controls, for example, each 1 mmol/L (39 mg/dL) reduction in LDL-C was associated with a 21% risk reduction in major vascular events [3] (Supplementary Table S2). Further reduction in major cardiovascular events is observed with more intensive statin regimens compared with less intensive statin regimens [3]. This reduction in major cardiovascular events is observed in patients with diabetes [19], in patients with chronic kidney disease [20] and across all cardiovascular risk groups, even among those with a low 5-year risk (<5% or ≥5% to <10%) [21]. These results emphasise the criticality of LDL-C lowering to reduce cardiovascular risk, as well as the consistent benefit across different risk populations.

## 3. Guidelines in clinical practice

To illustrate the application of the European and US lipid-lowering guidelines in a variety of clinical settings, we have included three hypothetical secondary prevention cases of patients with different cardiovascular risk factors and medical histories. Adjusting the

**Table 1**
LDL-C goals and thresholds from European and US lipid-lowering guidelines.

| CV risk category | ESC/EAS 2019 [1] | AHA/ACC 2018 [2] |
|---|---|---|
| Definition | | |
| VHR | Documented ASCVD, includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation, stroke and TIA, and PAD.<br>DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years).<br>Severe CKD (eGFR <30 mL/min/1.73 $m^2$)<br>SCORE ≥10% for 10-year risk of fatal CVD<br>FH with ASCVD or with another major risk factor. | History of multiple major ASCVD events (recent ACS within the past 12 months, history of MI or ischaemic stroke, symptomatic PAD) or one major ASCVD event and multiple high-risk conditions[a]. |
| High risk | Markedly elevated single risk factors, in particular, total cholesterol >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL) or BP ≥ 180/110 mmHg.<br>Patients with FH without other major risk factors.<br>Patients with DM without target organ damage with DM duration ≥10 years or another additional risk factor.<br>Moderate CKD (eGFR 30–59 mL/min/1.73 $m^2$).<br>SCORE ≥5% and <10% for 10-year risk of fatal CVD. | AHA/ACC cardiovascular risk calculator estimate ≥20% for 10-year risk for ASCVD.<br>Patients with severe hypercholesterolaemia (≥4.9 mmol/L [≥190 mg/dL]).<br>Patients with DM and LDL-C ≥1.8 mmol/L (≥70 mg/dL). |
| Moderate risk | Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration <10 years, without other risk factors.<br>SCORE ≥1% and <5% for 10-year risk of fatal CVD. | AHA/ACC cardiovascular risk calculator estimate 5% to <7.5% (borderline); 7.5% to <20% (intermediate) for 10-year risk for ASCVD.<br>Patients without DM and LDL-C levels ≥1.8 mmol/L (≥70 mg/dL). |
| Low risk | SCORE <1% for 10-year risk of fatal CVD. | AHA/ACC cardiovascular risk calculator estimate <5% for 10-year risk for ASCVD. |
| **Treatment threshold for LDL-C reduction** | | |
| VHR | Reduce LDL-C levels ≥50% and LDL-C goal of <1.4 mmol/L (<55 mg/dL).<br>Goal LDL-C of <1.0 mmol/L (<40 mg/dL) for patients with ASCVD who experience a second vascular event within 2 years while taking maximally tolerated statin therapy. | LDL-C <1.8 mmol/L (<70 mg/dL). |
| High risk | Reduce LDL-C levels ≥50% and LDL-C goal ≥1.8 mmol/L (≥70 mg/dL). | LDL-C <2.6 mmol/L (<100 mg/dL).<br>Reduce levels ≥50% in patients with DM and LDL-C ≥1.8 mmol/L (≥70 mg/dL). |
| Moderate risk | LDL-C <2.6 mmol/L (<100 mg/dL). | Clinician-patient risk discussion before starting statin.<br>Reduce LDL-C levels by ≥ 30% in patients without DM and LDL-C levels ≥1.8 mmol/L (≥70 mg/dL). |
| Low risk | LDL-C <3.0 mmol/L (<116 mg/dL). | Clinician-patient risk discussion. |
| **Recommended pharmacologic treatment** | | |
| VHR | Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe.<br>In patients with ACS and LDL-C levels not at goal despite maximally tolerated statin plus ezetimibe, early initiation of PCSK9 inhibitor should be considered.<br>PCSK9 inhibitor may be considered in patients at VHR not achieving target LDL-C goal on maximally tolerated statin and ezetimibe. | Maximally tolerated statin to lower LDL-C levels by ≥ 50%.<br>Add ezetimibe to maximally tolerated statin when LDL-C level remains ≥1.8 mmol/L (≥70 mg/dL).<br>Add PCSK9 inhibitor to maximally tolerated statin when LDL-C level remains ≥1.8 mmol/L (≥70 mg/dL). |
| High risk | Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe. | High-intensity statin therapy.<br>Add ezetimibe to high-intensity statin if LDL-C level remains ≥1.8 mmol/L (≥70 mg/dL). |
| Moderate risk | Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe. | Clinician-patient risk discussion before starting statin.<br>Moderate-intensity statin in patients with DM and LDL-C ≥1.8 mmol/L (≥70 mg/dL); reasonable to add ezetimibe or bile acid sequestrant in patients who would benefit from more aggressive LDL-C lowering.<br>In patients with borderline risk, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin. |
| Low risk | Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe. | Clinician-patient risk discussion. |

ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, Systematic Coronary Risk Estimation; T1DM/T2DM, type 1/2 diabetes mellitus; TIA, transient ischaemic attack; VHR, very high risk.

[a] Multiple high-risk conditions include age ≥65 years, heterozygous FH, history of congestive heart failure, prior coronary artery bypass graft or percutaneous coronary intervention, DM, hypertension, CKD, current smoking, persistently elevated LDL-C ≥2.6 mmol/L (≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe.

pharmacologic interventions based on guideline recommendations helped the patients improve their lipid profile and reduce their cardiovascular risk. We also provide two primary prevention example cases, one in a person with FH and one in an elderly person (Supplementary Fig. S1 and S2).

### 3.1. Case 1: VHR - hypothetical secondary prevention in a VHR patient with ACS and prior angina/percutaneous coronary intervention

Despite advances in interventional and pharmacologic strategies, ACS is associated with a high rate of major adverse cardiovascular events (MACE) [22]. Early aggressive use of statin therapy (atorvastatin) in patients with ACS showed significant reduction in plaque volume (−13% *versus* +9% for controls; $p < 0.0001$) at 6 months as measured by volumetric intravascular ultrasound [23]. The degree of reduction in plaque volume was positively correlated with LDL-C reduction (by 42%), even in patients with low baseline LDL-C (<3.2 mmol/L [<125 mg/dL]). Adding a non-statin lipid-modifying agent, such as ezetimibe, to statin therapy has been shown to further lower the LDL-C levels and to improve cardiovascular outcomes [24].

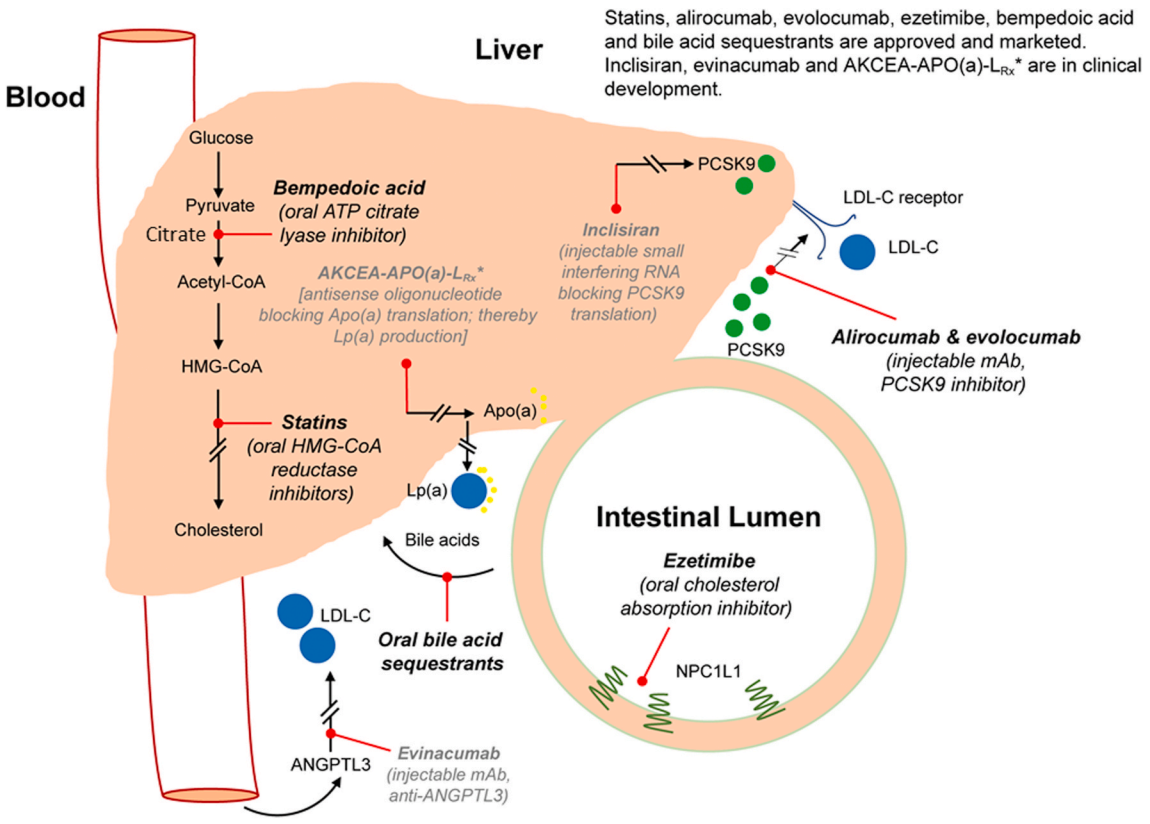


**Fig. 1.** Sites and targets of lipid-lowering therapies.
Approved drugs/drug classes are in black font; agents under development are in grey font. *Also known as TQJ230. ANGPTL3, angiopoietin-like 3 protein; Apo(a), apolipoprotein A; ATP, adenosine triphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); mAb, monoclonal antibody; NPC1L1, Niemann-Pick C1-like protein 1; PCSK9, proprotein convertase subtilisin/kexin type 9.

PCSK9 monoclonal antibodies possess potential anti-inflammatory and antithrombotic mechanisms associated with PCSK9 inhibition, along with influence on plaque composition and instability that might confer benefits during the early phase of ACS, when the risk of event recurrence is highest [25]. Data from the large ODYSSEY OUTCOMES trial in over 18,000 patients after an ACS showed significant reductions in major cardiovascular events in several risk groups following treatment with alirocumab, including patients with diabetes mellitus, polyvascular disease and post–coronary artery bypass graft [15–17].

Data from the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial also show that patients with a more recent MI (within 2 years), multiple MIs, peripheral artery disease (PAD), or residual multivessel coronary disease tended to benefit the most from evolocumab treatment [26]. Evolocumab lowered LDL-C levels by approximately 60%, regardless of subgroup, and reduced the risk of the primary endpoint (cardiovascular death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation) by 20% in those with a more recent MI, by 18% in those with prior multiple MIs and by 21% in those with multivessel disease. The recently conducted **EVO**locumab for Early Reduction of LDL-cholesterol Levels in **P**atients With **A**cute **C**oronary **S**yndromes (EVOPACS) study assessed the impact of evolocumab, administered within 24–72 h of symptom onset, on LDL-C levels after 8 weeks in patients already receiving high-intensity statin therapy who presented with ACS [27]. EVOPACS also assessed the effect of evolocumab on inflammatory biomarkers, platelet reactivity, coronary plaque composition and myocardial and acute kidney injury following coronary interventions. In 308 patients hospitalised for ACS in EVOPACS, evolocumab 420 mg every 4 weeks significantly reduced LDL-C from baseline to week 8 relative to placebo (−77% *versus* −35%; $p < 0.001$) on top of high-intensity statin, and a higher percentage of patients achieved a target LDL-C goal of <1.8 mmol/L (<70 mg/dL) in the evolocumab group (96% *versus* 38%) [14]. Evolocumab was well tolerated and had a neutral effect on C-reactive protein levels, consistent with previous studies [14].

For patients with an ACS, the new European lipid-lowering guidelines recommend adding a PCSK9 inhibitor early after the event in patients whose LDL-C levels are not already at goal despite maximally tolerated statin plus ezetimibe [1]. The US guidelines consider patients with ACS within 12 months as VHR, in which an LDL-C level >1.8 mmol/L (>70 mg/dL) would indicate adding ezetimibe [2]; adding a PCSK9 inhibitor in this setting is reasonable according to US guidelines. Fig. 2 describes the risk assessment and treatment of a VHR patient with ACS and prior angina and percutaneous coronary intervention.

### 3.2. *Case 2: VHR - hypothetical VHR patient with dyslipidaemia, diabetes and multiple cardiovascular events*

Patients with documented ASCVD and/or a history of multiple major ASCVD events are at VHR for additional cardiovascular events. Moreover, CVD is the most important cause of morbidity and mortality in individuals with T2DM, and cardiovascular risk may be substantially reduced by addressing multiple ASCVD risk factors in patients with T2DM [28]. Thus, among VHR patients with prior cardiovascular events and T2DM who are not achieving LDL-C treatment goals per current guidelines, addition of a PCSK9 inhibitor to maximally tolerated statin plus ezetimibe warrants consideration. Fig. 3 describes the risk assessment and treatment of a middle-aged woman with dyslipidaemia, diabetes and a history of cardiovascular events which progressed to an acute MI. With the addition of evolocumab to a statin plus ezetimibe, she met her LDL-C treatment goals and remained stable without further cardiovascular events 1 year later.

**Table 2**
Hypothetical LDL-C values achievable with different intensities of lipid-lowering therapies and combinations [10][a].

| Lipid-lowering therapy (monotherapy or combination) | Theoretical % LDL-C reduction [10] | Theoretical LDL-C value achievable with treatment, mmol/L (mg/dL) | | |
|---|---|---|---|---|
| | | Patient with baseline LDL-C of 3.9 mmol/L (150 mg/dL) | Patient with baseline LDL-C of 3.4 mmol/L (130 mg/dL) | Patient with baseline LDL-C of 2.6 mmol/L (100 mg/dL) |
| Statin monotherapy | | | | |
| Low intensity | 30% | 2.7 (105) | 2.4 (91) | 1.8 (70) |
| Moderate intensity | 40% | 2.3 (90) | 2.0 (78) | 1.6 (60) |
| High intensity | 50% | 1.9 (75) | 1.7 (65) | 1.3 (50) |
| Non-statin monotherapy | | | | |
| Ezetimibe | 20% | 3.1 (120) | 2.7 (104) | 2.1 (80) |
| PCSK9 inhibitor | 60% | 1.6 (60) | 1.4 (52) | 1.0 (40) |
| Statins + ezetimibe | | | | |
| Low intensity | 44% | 2.2 (84) | 1.9 (73) | 1.4 (56) |
| Moderate intensity | 52% | 1.9 (72) | 1.6 (62) | 1.2 (48) |
| High intensity | 60% | 1.6 (60) | 1.4 (52) | 1.0 (40) |
| Statins + PCSK9 inhibitor | | | | |
| Low intensity | 72% | 1.1 (42) | 0.9 (36) | 0.7 (28) |
| Moderate intensity | 76% | 0.9 (36) | 0.8 (31) | 0.6 (24) |
| High intensity | 80% | 0.8 (30) | 0.7 (26) | 0.5 (20) |
| Statins + ezetimibe + PCSK9 inhibitor | | | | |
| Low intensity | 78% | 0.9 (33) | 0.8 (29) | 0.6 (22) |
| Moderate intensity | 80% | 0.8 (30) | 0.7 (26) | 0.5 (20) |
| High intensity | 84% | 0.6 (24) | 0.5 (21) | 0.4 (16) |

[a]Note that hypothetical values differ slightly from those noted in the European guidelines (see Supplementary Table S3); LDL-C reductions reported in the European guidelines that differ from the values in this table include ≈30% for moderate-intensity statin, ≈65% for high-intensity statin plus ezetimibe, ≈75% for PCSK9 inhibitor plus high-intensity statin and ≈85% for PCSK9 inhibitor plus high-intensity statin plus ezetimibe [1].
Low-, moderate- and high-intensity statins defined by Stone et al. (2014) [68].
Grey shading represents reductions/goals meeting US [2] (but not European [1]) LDL-C goals for patients with VHR ASCVD; blue shading represents reductions/goals meeting both US and European LDL-C goals for patients with VHR ASCVD.
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; VHR, very high risk.

### *3.3. Case 3: VHR - MI in a hypothetical VHR patient with polyvascular disease*

Elevated LDL-C is a risk factor for both CAD and PAD. In patients with CAD, the prevalence of concomitant PAD varies depending on risk factors, including age, smoking and diabetes. In patients with PAD, approximately 60% have concomitant CAD [29]. Patients who have symptomatic CAD and PAD, called polyvascular disease, are at approximately 50–80% increased risk of MACE compared with either disease state alone [30], and concomitant diabetes is additive [29]. In the IMPROVE IT trial, patients with polyvascular disease and diabetes had an event rate for the composite of cardiovascular death, MI or stroke of ~50% at 7 years, even in patients who achieve a mean LDL-C concentration of 1.8 mmol/L (69.9 mg/dL) [29]. In addition to MACE risk, patients with PAD are at heightened risk of major adverse limb events (MALE), including acute limb ischaemia and major amputation [31]. There are few medical therapies that reduce the risk of MALE, which is a major cause of morbidity in PAD [31]. In the FOURIER trial [32], LDL-C lowering with evolocumab (median LDL-C, 0.8 mmol/L [31 mg/dL] at 48 weeks) reduced the risk of major cardiovascular events (by 21% [$p = 0.0098$] and 14% [$p < 0.001$], respectively) and MALE (by 37% [$p = 0.063$] and 63% [$p = 0.0197$], respectively) in patients both with and without PAD. Patients with PAD had a larger absolute risk reduction than patients without PAD due to their higher risk. In addition, there was a 42% reduction in MALE (0.27% *versus* 0.45%; hazard ratio [HR], 0.58; 95% confidence interval, 0.38–0.88; $p = 0.0093$). A roughly linear relationship between achieved LDL-C and MALE risk that extended below 0.26 mmol/L (10 mg/dL) was observed, thus demonstrating that LDL-C is an important risk factor for MALE and can be modified by LDL-C lowering. When looking at composite MACE or MALE in patients with PAD, including those without prior MI or stroke, the number needed to treat with evolocumab for 2.5 years was only 16.

Identifying PAD and polyvascular disease in patients with ACS is a simple and potent marker of risk for MACE and MALE, and for finding a population that derives a robust benefit from intensive lipid lowering. Fig. 4 illustrates a hypothetical case of acute MI in a VHR patient with polyvascular disease. This older woman with dyslipidaemia, diabetes and a history of smoking had an acute MI 2 years after stenting of the

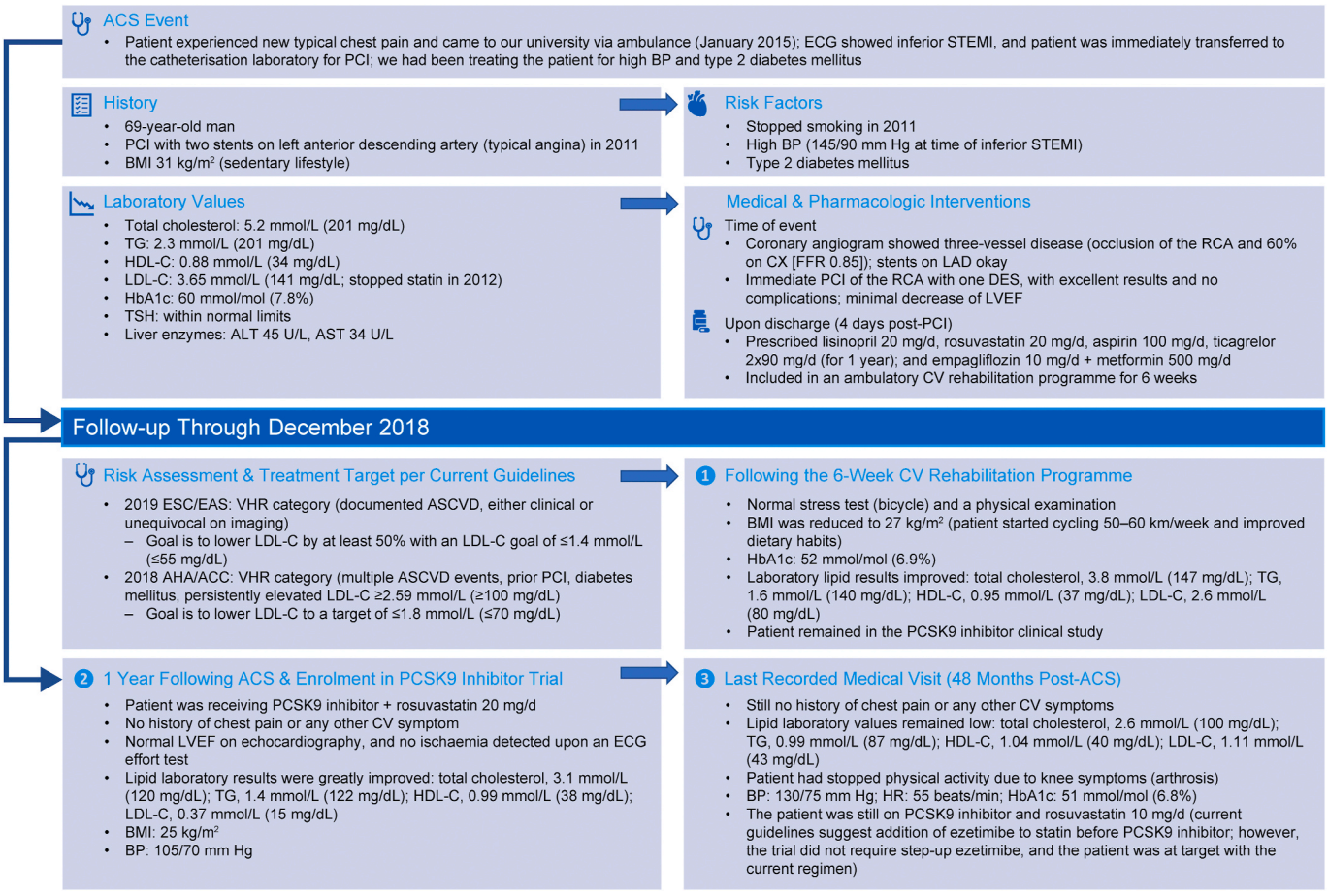


**Fig. 2.** Hypothetical secondary prevention in a VHR patient with ACS and prior angina/PCI.
ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CV, cardiovascular; CX, chest x-ray; DES, drug-eluding stent; EAS, European Atherosclerosis Society; ECG, electrocardiogram; ESC, European Society of Cardiology; FFR, fractional flow reserve; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LAD, left anterior descending coronary artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; TG, triglyceride; TSH, thyroid-stimulating hormone; VHR, very high risk.

superficial femoral artery. With the addition of a PCSK9 inhibitor to a statin and ezetimibe regimen, plus cardiovascular rehabilitation, she was able to meet her LDL-C treatment goals and remained stable without further cardiovascular events or MALE 1 year after her MI.

## 4. Non–LDL-C cardiovascular landscape

### *4.1. Dyslipidaemia/hypertriglyceridaemia*

Patients with established ASCVD remain at increased risk for major cardiovascular events even in the setting of optimal lipid-lowering treatment. Elevated triglyceride levels contribute to that residual risk [33]. Very low–density lipoproteins and chylomicrons are the major triglyceride-rich lipoproteins. The US lipid-lowering guidelines note two categories of hypertriglyceridaemia: moderate (triglyceride levels 2.0–5.6 mmol/L [175–499 mg/dL]) and severe (triglyceride levels ≥5.6 mmol/L [≥500 mg/dL]); both can be a risk factor for ASCVD, and severe hypertriglyceridaemia also increases the risk of acute pancreatitis [2]. In both instances, the guidelines indicate that it is reasonable to reduce triglyceride levels to reduce ASCVD risk. The European guidelines recommend initiating treatment to reduce triglyceride levels in high-risk individuals with hypertriglyceridaemia (>2.3 mmol/L [>200 mg/dL] or between 1.5 and 5.6 mmol/L [between 135 and 499 mg/dL] despite statin treatment in high-risk or above patients at LDL-C goal) [1].

Omega-3 fatty acids such as icosapent ethyl, which is composed of eicosapentaenoic acid, 1.8 g/day plus low-intensity statin have been shown to significantly reduce the risk of major coronary events by 19% *versus* statin therapy alone in a large Japanese study in patients with total cholesterol ≥6.5 mmol/L (≥250 mg/d) [34]. Recently, results from the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) reported that treatment with icosapent ethyl 4 g/day significantly reduced the risk of major cardiovascular total events by 25% ($p < 0.0001$) and major cardiovascular first events by 30% ($p < 0.0001$) in high-risk patients receiving statin therapy (established CVD or diabetes mellitus and ≥1 additional risk factor; triglyceride level 1.7–5.6 mmol/L [150–499 mg/dL] and LDL-C level 1.1–2.6 mmol/L [41–100 mg/dL], median follow-up, 4.9 years) [35]. Icosapent ethyl was recently approved in the US as an adjunctive (secondary) therapy to maximally tolerated statin therapy to reduce cardiovascular risk in adults with elevated triglyceride levels (>1.7 mmol/L [>150 mg/dL]) and established CVD or diabetes mellitus and two or more additional cardiovascular risk factors [36]. Results from these studies indicate that icosapent ethyl confers additional residual risk reduction beyond statin therapy. However, additional analyses suggest that the reduction in cardiovascular risk is not solely due to triglyceride lowering and pleotropic mechanisms. Reduction in vascular inflammation and antithrombotic effects may be responsible for the cardioprotective benefit of icosapent ethyl. In fact, increased rates of bleeding supporting an

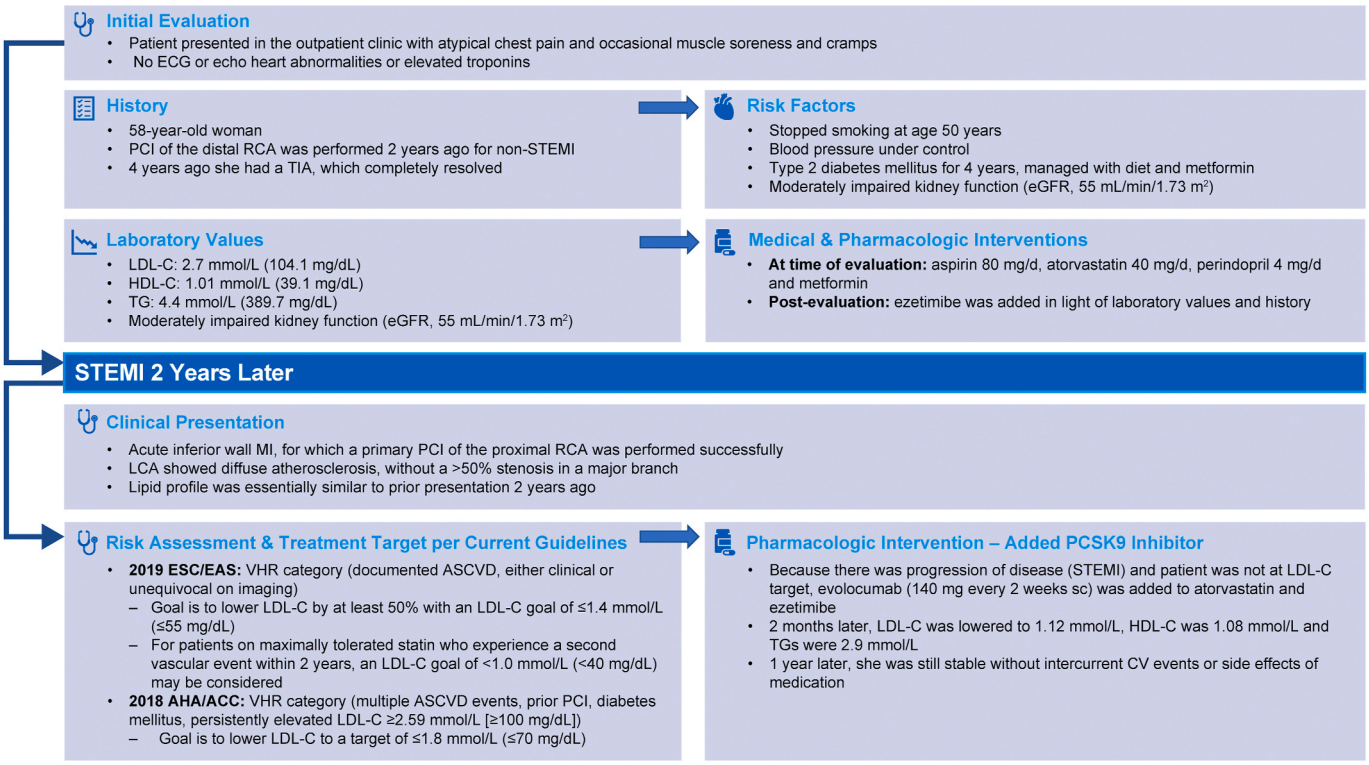


**Fig. 3.** Hypothetical VHR patient with dyslipidaemia, diabetes and multiple cardiovascular events.
ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; EAS, European Atherosclerosis Society; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HDL-C, high-density lipoprotein cholesterol; LCA, left coronary artery; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RCA, right coronary artery; sc, subcutaneous; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack; TG, triglyceride; VHR, very high risk.

antithrombotic effect were observed. An unexpected safety finding was an increased risk of clinically identified atrial fibrillation. The biology and clinical implications of this observation are unclear [33]. A large meta-analysis of 10 trials involving 77,917 participants demonstrated no significant association between supplementation with low dose omega-3 fatty acids and reductions in fatal or nonfatal coronary heart disease or any major vascular events [37]. Whether the beneficial effects of omega-3 fatty acids are caused by the higher doses (3–4 g/d) remains to be assessed.

Orphan drug volanesorsen for the treatment of familial chylomicronaemia syndrome (FCS) is beyond the general scope of this review due to its restricted availability in certain regions/nations. Emerging LDL-C-lowering therapy evinacumab on trial for homozygous FH is also excluded for similar reason.

### 4.2. *Diabetes/metabolic syndrome*

Cardiovascular disease is the most important cause of morbidity and mortality in individuals with T2DM, and substantial reduction in cardiovascular risk is seen when multiple ASCVD risk factors are addressed in patients with T2DM [28]. The recent American Association of Clinical Endocrinologists/American College of Endocrinology guidelines for lipid lowering in patients with diabetes recommend a target LDL-C goal of <1.4 mmol/L (<55 mg/dL) in patients with extreme risk for ASCVD (i.e. established clinical CVD, stage 3 or 4 chronic kidney disease and/or heterozygous FH) [7]. Until recently, management of cardiovascular risk in patients with T2DM has focused on optimisation of comorbidities, such as hypertension and hyperlipidaemia. The treatment paradigm has shifted with the publication of data from recent trials, such as Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) [38] and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) [39], which demonstrate that agents developed to lower HbA1c are efficacious for reducing cardiovascular risk.

### 4.3. *Elevated lipoprotein(a)*

Elevated lipoprotein(a) [Lp(a)] levels are associated with an increased risk of CVD, aortic stenosis, and to some extent venous thrombosis, particularly when levels are >125 nmol/L (50 mg/dL) [40,41]. A recent Icelandic population study found that molar concentration of Lp(a), rather than apolipoprotein(a) particle size, explained the association between Lp(a) and cardiovascular risk [42]. In addition, people with Lp(a) concentrations in the bottom 10% of the population had increased risk for T2DM. Lp(a) is also associated with more extensive atherosclerotic burden manifesting as PAD [43], as well as worse outcomes in patients with PAD [44], including higher rates of amputation [45]. In the FOURIER trial in over 25,000 patients, higher baseline Lp(a) levels were associated with an increased risk of major cardiovascular events; these patients experienced greater absolute reductions in Lp(a) with evolocumab treatment and tended to derive greater clinical benefit [41]. Patients with Lp(a) levels above the median experienced a 23% reduction in major cardiovascular events compared with a 7% reduction in events in patients with Lp(a) levels below the median. Moreover, the study reported a significant relationship between Lp(a) reduction and risk of major cardiovascular events of 15% ($p = 0.0199$) per 25 nmol/L (10 mg/dL) reduction in Lp(a). A large pooled analysis of alirocumab phase 3 trials reported that Lp(a) was significantly reduced, and there was a 12% reduction in the relative risk of major cardiovascular events per 25% reduction in Lp(a) ($p = 0.0254$) [40]. However, this observation was no longer significant after adjustment for LDL-C reduction [40]. In the ODYSSEY OUTCOMES study, the risk of major cardiovascular events

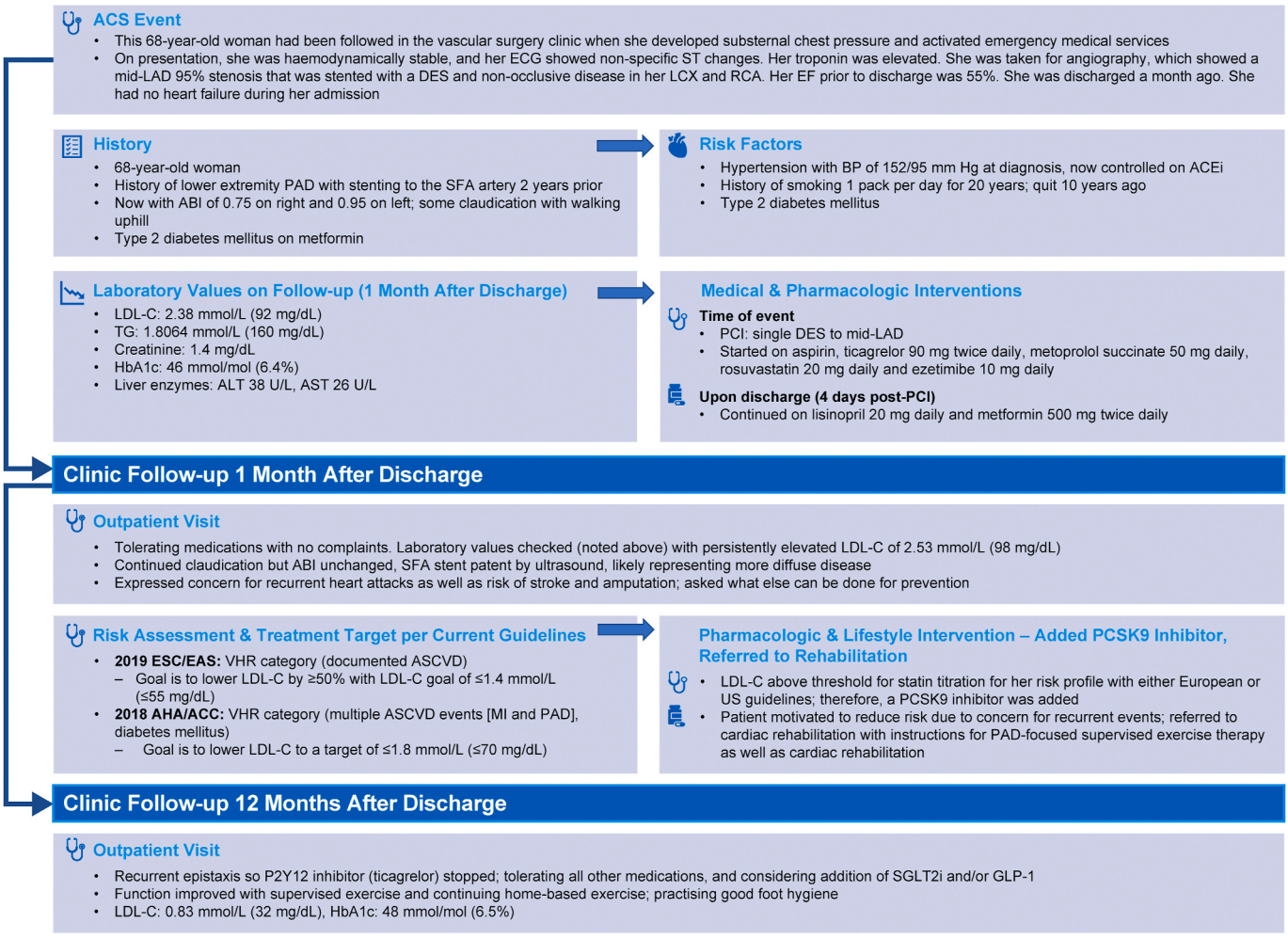


**Fig. 4.** Hypothetical VHR patient with polyvascular disease and recent MI.
ABI, ankle-brachial index; ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AHA, American Heart Association; ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BP, blood pressure; DES, drug-eluting stent; EAS, European Atherosclerosis Society; ECG, electrocardiogram; EF, ejection fraction; ESC, European Society of Cardiology; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RCA, right coronary artery; SFA, superficial femoral artery; SGLT2i, sodium-glucose cotransporter-2 inhibitor; ST, sinus tachycardia; TG, triglyceride; VHR, very high risk.

was greater with increasing Lp(a) levels, and absolute risk reduction for these events was greater at higher baseline Lp(a) levels exceeding 2% in the upper two quartiles [$p = 0.0011$ for interaction across Lp(a) quartiles] [46]. Further analysis showed that alirocumab reduced Lp(a) levels and major cardiovascular events independently of LDL-C levels. These results suggest that patients with higher baseline Lp(a) levels may derive enhanced benefit from treatment with PCSK9 inhibitors relative to those with lower Lp(a) levels.

The technologies of antisense oligonucleotide inhibition and of small interfering RNA aim to degrade gene mRNA transcripts and reduce protein production and plasma lipoprotein levels, respectively. AKCEA-APO(a)-$L_{Rx}$ (also known as TQJ230), an antisense oligonucleotide developed to lower Lp(a), significantly and dose-dependently lowered Lp(a) levels by 35–80% from baseline in a recent phase 2 study in 286 patients with screening Lp(a) levels of at least 150 nmol/L (60 mg/dL) [47]. The direct evidence for Lp(a) reduction as a path to lowering risk of CVD will have to wait for completion of appropriate CV outcomes trials.

### 4.4. Chronic kidney disease

Chronic kidney disease is associated with an increased risk of CVD and cardiovascular and overall mortality [2,48]. In patients with chronic kidney disease with at least one serum creatinine measurement ≥150 μmol/L (≥1.7 mg/dL) in men and ≥130 μmol/L (≥1.5 mg/dL) in women, simvastatin plus ezetimibe significantly reduced the risk of major cardiovascular events by 17% ($p = 0.021$) [49]. Ischaemic stroke was reduced by 28% ($p = 0.0073$) and coronary revascularisation procedures were reduced by 27% ($p = 0.0027$), while the risk of any coronary event (non-fatal MI or coronary death) was reduced by 8% ($p = 0.37$). For patients with chronic kidney disease, there was an estimated 19% reduction in major atherosclerotic events per 1 mmol/L (39 mg/dL) reduction in LDL-C. Many patients with chronic kidney disease have poor tolerability of high dose statins. Furthermore, in patients undergoing regular hemodialysis treatment, rosuvastatin lowered the LDL-C level but had no significant effect on CVD outcomes [50].

### 4.5. Antithrombotics

Platelets play an important role in the pathogenesis of atherothrombotic complications [4]. Antiplatelet therapy has been shown to improve cardiovascular outcomes both in ACS and in stable secondary prevention settings, where benefits generally exceed the bleeding hazards [4]. Recently, rivaroxaban, a selective direct factor Xa inhibitor, when used at a lower dose of 2.5 mg twice daily in combination with

aspirin, significantly reduced the risk of major cardiovascular events by approximately 25% in high-risk patients with stable atherosclerotic vascular disease enriched for polyvascular disease (CAD, PAD or both) [51–53].

## 5. Emerging LDL-C–lowering therapies

The sites and targets of emerging lipid-lowering therapies, including inclisiran, bempedoic acid and evinacumab, are outlined in Fig. 1. Bempedoic acid is a small-molecule prodrug that lowers LDL-C by inhibiting adenosine triphosphate citrate lyase, a key enzyme in the cholesterol biosynthesis pathway upstream from HMG-CoA reductase [54]. In two studies involving statin-intolerant patients, bempedoic acid significantly reduced LDL-C *versus* placebo at week 12 (−21% with bempedoic acid in addition to background non-statin therapy; −29% with bempedoic acid plus background non-statin therapy including ezetimibe) [55,56]. A 52-week study in patients with ASCVD on maximally tolerated statin therapy, heterozygous FH, or both, showed that bempedoic acid 180 mg daily significantly reduced LDL-C (placebo-corrected differences) by 18% at week 12, 16% at week 24 and 14% at week 52 [54]. Bempedoic acid 180 mg daily plus ezetimibe 10 mg daily added to maximally tolerated statin therapy in patients at high risk for CVD significantly reduced LDL-C by 36% at week 12 compared with 17% for bempedoic acid alone or 23% for ezetimibe alone; similar results were observed with non–HDL-C, total cholesterol and apolipoprotein B (ApoB) [16]. A trial assessing the effect on lipid levels of bempedoic acid added to maximally tolerated statins in patients with ASCVD reported significant placebo-corrected reductions in LDL-C (by 17% and 10% at weeks 12 and 52, respectively), non–HDL-C (13% and 10%), total cholesterol (11% and 8%) and ApoB (13% and 10%) [57]. In February 2020, bempedoic acid received FDA approval as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH or established ASCVD who require additional lowering of LDL-C [58]. In addition, a bempedoic acid and ezetimibe fixed-dose combination therapy was also approved [59]. These therapies were subsequently approved by the European Medicines Agency [60,61]. A large cardiovascular outcomes study with bempedoic acid is underway (NCT02993406). A meta-analysis of the available phase 2 and phase 3 clinical studies showed that bempedoic acid seems to have unfavorable effects on serum uric acid, creatinine level and the incidence of gout [62].

Inclisiran is a small interfering RNA that produces sustained interference with the expression of hepatocyte-specific PCSK9; the drug showed LDL-C reductions of approximately 50% at day 180 after administration of two 300-mg doses on days 1 and 90, as well as reductions in Lp(a) of approximately 25% [63]. The drug showed significant reductions in other atherogenic lipoproteins, including ApoB, non–HDL-C and very-low-density lipoprotein cholesterol [64], as well as similar LDL-C reductions in patients with and without diabetes [65]. LDL-C reduction was sustained at 1 year following one dose (200, 300 or 500 mg on day 1) or two doses (100, 200 or 300 mg on days 1 and 90) of inclisiran [66]. Time-averaged LDL-C levels were reduced by 30–39% in the group that received one dose of inclisiran and by 30–46% in the group that received two doses; moreover, a 50% LDL-C reduction was maintained for at least 6 months in the two-dose 300-mg group. A large phase 3 trial assessing the effect of inclisiran on major cardiovascular events is underway (ORION-4 trial; NCT03705234).

## 6. Summary and implications

Multiple lines of evidence have established that elevated LDL-C is a principally modifiable cause of ASCVD and that throughout the range of LDL-C levels, “lower is better” with no apparent lower threshold, at least down to about 1 mmol/L (40 mg/dL). Accordingly, recent European and US multisociety dyslipidaemia guidelines stress the importance of lowering LDL-C and other cholesterol-rich apolipoproteins to reduce cardiovascular risk. This review focused on established and emerging agents that reduce LDL-C in various disease states, risk profiles and event types to help cardiologists and other healthcare providers synthesize the abundance of new evidence related to the prevention of CVD and to apply the guidelines in clinical practice. The 2019 ESC/EAS and 2018 AHA/ACC guidelines place particular emphasis on identifying patients at very high cardiovascular risk and modifying established risk factors. Such VHR patients have established ASCVD and/or a combination of other risk factors, including diabetes, hypertension, PAD, chronic kidney disease or other dyslipidaemias such as hypertriglyceridaemia. Both European and US guidelines underscore the importance of treating to achieve LDL-C levels as low as possible, with European guidelines setting a goal of <1.4 mmol/L (<55 mg/dL) in patients with VHR CVD (<1.8 mmol/L [<70 mg/dL] in the US blood cholesterol guideline). Both guidelines recommend at least a 50% reduction, in addition to risk-specific LDL-C goals. Many patients, however, are unable to achieve LDL-C goals with conventional agents; therefore, the availability of the potent LDL-C–lowering drugs, the PCSK9 inhibitors, will help fulfil an unmet need, further reducing cardiovascular risk when added to statin-based therapy. Moreover, the EVOPACS study supports the use of PCSK9 inhibitor therapy, specifically evolocumab, in the in-patient setting immediately after ACS. In light of this combined knowledge base, current treatment protocols and resources may have to be expanded to adopt the necessary changes in clinical practice.

Although outcomes data for the recently approved bempedoic acid/bempedoic acid + ezetimibe combination are not yet available and these therapies are not yet addressed in dyslipidaemia guidelines, bempedoic acid represents a new non-statin alternative that has potential relevance in both primary and secondary prevention settings, perhaps particularly for statin-intolerant patients who require modest LDL-C lowering [67]. Other promising agents under development will also add to the armamentarium of lipid-lowering drugs available for clinicians to help patients meet their treatment goals. Evinacumab, inclisiran and agents that target Lp(a) represent exciting new approaches that hopefully will further expand our therapeutic armamentarium and may enable a more tailored and individualised approach to cardiovascular risk reduction. The non–LDL-C therapies, including agents that reduce triglycerides, clearly can reduce cardiovascular risk in certain patients; however, the residual risk of elevated LDL-C remains an important consideration for a holistic treatment approach.

Unmet needs for CVD prevention include further clarification on the use of ApoB and Lp(a) for risk stratification, more evidence for long-term use of PCSK9 inhibitors in specific populations, and the use of statin-based therapy in older patients. Observational data on attainment of recommended LDL-C goals in real-world practice will also be an important piece of evidence to validate the proposed thresholds and perhaps support further alignment of LDL-C treatment goals worldwide. With the establishment of the benefits and safety of very low LDL-C concentrations, new treatment paradigms can be considered, including (i) starting LDL-C lowering at earlier ages to diminish the cumulated/accrued overall exposure, (ii) treating to much lower goals using triple-combination therapy in patients with established atherosclerotic disease and (iii) continuing the quest for new pharmacologic mechanisms for LDL-C lowering.

## Author contributions

D.A., B.M. and C.C. conceived the idea for the manuscript, contributed to interpretation of the data, critically revised the manuscript for important intellectual content and provided oversight. J.W.J., P.R.T., S. G., F.M., L.T. and M.P.B. contributed to interpretation of the data, drafted or critically revised sections of the manuscript and reviewed critically for important intellectual content. J.U. and A.K. contributed to interpretation of the data and revised the manuscript critically for important intellectual content. All authors approved the submitted version of the manuscript and agree to be accountable for all aspects of

the work ensuring integrity and accuracy.

## Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:D. A. reports speaker's honoraria and consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, Merck, Novartis and Sanofi-Regeneron; and research funding to his institution from Bristol Myers Squibb, Pfizer, Medtronic and Roche Diagnostics. J.W.J. reports receiving research grants and/or was a speaker for meetings sponsored by Amgen, Athera, AstraZeneca, Biotronik, Boston Scientific, Daiichi Sankyo, Eli Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Roche, Sanofi-Aventis, The Medicine Company, the Netherlands Heart Foundation, CardioVascular Research Netherlands (CVON), the Netherlands Heart Institute and the European Community Framework KP7 Programme. P.R.T. reports consultancy fees from Amgen, Amarin, Janssen, Boehringer Ingelheim, Novo Nordisk, Esperion and Sanofi-Regeneron and research funding from Amgen; is also a stockholder for Epirium Bio. S.G. reports financial support from MEXT/JSPS KAKENHI 17K19669, 18H01726 and 19H03661, independent research grant support from Bristol Myers Squibb (33999603), grant support from Vehicle Racing Commemorative Foundation and Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering and grants from Sanofi, Pfizer and Ono; also reports personal fees from the American Heart Association as an Associate Editor for *Circulation* and from Thrombosis Research Institute as a member of steering committee for GARFIELD-AF and VTE project. F.M. declares no conflict of interest. J.U. reports personal fees from Alexion, Amarin, Ambry, Amgen, Esperion, Regeneron and Sanofi. A.K. reports receiving honoraria, consultancy fees and research funding from Amgen, and support for an educational activity and honoraria from Mylan and Novartis; also reports receiving honoraria and consultant fees from AstraZeneca, Sanofi and Bayer, SDMC sitting fees from Kowa, and honoraria from Pfizer. L.T. reports personal fees from Abbott, Actelion, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Merck Sharp & Dohme, Mylan, Novartis, Novo Nordisk, Sanofi, Servier, Pfizer and Recordati. M. P.B. reports grants and personal fees (through Brigham and Women's Hospital and/or UCHealth University of Colorado Hospital) from Amgen, AstraZeneca, Bayer, Novo Nordisk, Pfizer and Sanofi, and personal fees (through Brigham and Women's Hospital and/or UCHealth University of Colorado Hospital) from Janssen, Merck and Regeneron. B. M. and C.C. are Amgen employees and stockholders.

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## Appendix A. Supplementary data

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