European Heart Journal (2016) **0**, 1–11
doi:10.1093/eurheartj/ehw480

CURRENT OPINION

European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk

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Received 4 May 2016; revised 8 August 2016; accepted 15 August 2016

Introduction

Atherosclerotic cardiovascular disease (ASCVD) underlies the thrombotic events intimately associated with myocardial infarction, a significant proportion of ischaemic strokes, as well as critical limb ischaemia. Such events confer substantial mortality, physical and/or mental disability, and cost for the individual and society.[1] Indeed, no finite value can be attributed to the cost to the individual, although survival and subsequent quality of life are critical factors, especially in young individuals with ASCVD.[2] Although the advent of precision medicine and innovative treatments have been the driver for an individualized approach to patient management and prevention, the ever-increasing financial restraints in healthcare systems worldwide often require clinical benefit to be balanced with the cost of a given intervention.

The causality of plasma low-density lipoprotein-cholesterol (LDL-C) and reduced LDL receptor-mediated LDL uptake in the pathophysiology of ASCVD has been established beyond any reasonable doubt.[3] For patients at very high risk of premature ASCVD, including those with familial hypercholesterolaemia (FH) without ASCVD, elevated LDL-C is a common risk factor.[4,5] Indeed, high LDL-C levels are prevalent in both FH and non-FH patients in the acute secondary prevention setting.[6] In the case of the latter, polygenic effects may account for an elevated LDL-C concentration as reflected by genetic risk scores.[7]

The key clinical issue is attainment of guideline-recommended LDL-C levels (<1.8 mmol/L or 70 mg/dL) for patients at very high cardiovascular risk.[4] Even with high-intensity statin treatment, a substantial proportion of these patients will remain above this LDL-C goal due to <50% lowering of LDL-C levels, in part as result of

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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pharmacogenetic effects that underlie wide inter-individual variability in statin response.[8] This eventuality emphasizes the need for additional LDL-C reduction with new therapeutic approaches which target these atherogenic particles.

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a key role in the regulation of hepatic LDL receptor activity.[9] Subjects with sequence variants in the gene coding for PCSK9 (loss-of-function) that are associated with lower levels of LDL-C have a substantially reduced risk of coronary disease;[10] conversely, subjects heterozygous for a gain-of-function mutation of *PCSK9* present with a phenotype consistent with FH.[11] These findings have set the stage to investigate PCSK9 inhibition as an innovative therapeutic approach to improve control of elevated LDL-C levels.

Several clinical studies with different monoclonal antibodies against circulating PCSK9, either alone or in addition to statin therapy, have confirmed profound reductions of LDL-C levels (by up to ~60%).[12–15] Evidence to date indicates that these PCSK9 inhibitors are generally well tolerated, with injection site reactions typically reported by about 5% of patients in clinical trials,[14,15] and no increase in the frequency of creatine kinase (CK) elevations, myalgia or muscle symptoms.[13] A recent meta-analysis has suggested a possible signal for increased frequency of neurocognitive events,[12] although it should be borne in mind that reporting of neurocognitive symptoms was not systematically defined in these trials, and the absolute numbers of events were low. Although larger and longer-term studies are needed to further establish safety and efficacy for reduction of cardiovascular events in patients at high and very high cardiovascular risk, one *post hoc* analysis with alirocumab and one prespecified exploratory analysis with evolocumab have reported a reduced rate of major adverse cardiovascular events associated with PCSK9 inhibition.[14,15] These data have to be interpreted with caution, because the number of cardiovascular events in each study was low; definitive large randomized trials on the efficacy and safety of this novel therapeutic approach to reduce cardiovascular events are ongoing.[16,17] Moreover, further data on the safety of PCSK9 antibody therapy with respect to neurocognitive effects are awaited from the EBBINGHAUS study with evolocumab, as well as planned studies with alirocumab and bococizumab.[18]

As two antibodies are already approved in Europe (see *Box 1*) and in clinical use, the main purpose of this consensus document is to discuss the appropriate clinical use of PCSK9 antibodies in patients at very high cardiovascular risk who have substantially elevated LDL-C levels on maximal statin/ezetimibe therapy. The LDL-C threshold values for considering PCSK9 monoclonal antibody therapy were agreed based on consideration of absolute cardiovascular risk and the absolute LDL-C reduction required. This approach is supported by the Cholesterol Treatment Trialists' Collaboration, which showed that absolute LDL-C reduction is one of the key determinants of absolute cardiovascular risk reduction.[19]

Consistent with European guidelines,[4,5] this consensus document focuses on three priority groups: (i) patients at very high risk not at LDL-C goal, i.e. with documented ASCVD (clinical or unequivocal on imaging, with plaque on coronary angiography or carotid ultrasound), including those with progressive ASCVD [i.e. repeated acute coronary syndromes (ACSs), repeated unplanned coronary revascularizations, or repeated ischaemic strokes within 5 years of the index event], or diabetes mellitus with target organ damage or with a major risk factor such as marked hypercholesterolaemia or marked hypertension; (ii) patients with FH without ASCVD; and (iii) patients in any of these groups with statin intolerance. Although patients with severe chronic kidney disease (glomerular filtration rate <30 mL/min/1.73 m^2) are by definition also at very high risk,[4] to date this group has been excluded from clinical trials with PCSK9 inhibitors and therefore no recommendations can be made at this time. This document offers decision algorithms to assist the clinician in identifying those very high risk patients who are likely to approach LDL-C goal as a consequence of at least 50% lowering of LDL-C levels and thus likely derive a relevant reduction in absolute cardiovascular risk. These recommendations aim to provide support in appropriately allocating a highly effective LDL-C lowering therapy, while also taking account of financial restraints within healthcare budgets. Hence, the recommended patient selection is more conservative than the approved treatment indications.

Patients with very high cardiovascular risk

For patients at very high risk, lowering LDL-C levels to the goal of <1.8 mmol/L (<70 mg/dL) and/or achieving $\geq 50\%$ LDL-C reduction when this goal cannot be reached is a Class IA recommendation.[4,5] In guidelines, statins are indisputably the mainstay of LDL-C

Box 1 Approved indications for alirocumab and evolocumab in Europe

Indication	PCSK9 inhibitor
Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:	Alirocumab[a]
–in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,	Evolocumab[a]
–alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated.	
Adults and adolescents $\geq$12 years with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies	Evolocumab[b]

Sources: http://www.medicines.org.uk/emc/medicine/30628; http://www.medicines.org.uk/emc/medicine/30956.
[a]The initial dose for alirocumab is 75 mg once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks. Evolocumab is given 140 mg every 2 weeks or 420 mg once monthly.
[b]The initial recommended dose is 420 mg once monthly, uptitrated after 12 weeks to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

lowering, although the benefit of treatment will only be replicated in real life if patients are treated appropriately, and adhere to the prescribed treatment regimen. Data from registries show that this is a major issue, as only 35–40% of patients with a recent ACS or with stable coronary artery disease prescribed a statin attain LDL-C goal.[20,21] Real-world goal attainment may be even lower; in EUROASPIRE IV only 19% of all coronary artery disease patients had LDL-C levels below goal.[22] Thus, the importance of adherence with statin treatment should be emphasized in discussions between the clinician and patient, before consideration of additional treatment.

Several clinical studies have established the efficacy of PCSK9 monoclonal antibody therapy in lowering LDL-C levels in high to very high risk patients not at LDL-C goal on maximally tolerated efficacious statin therapy (i.e. using atorvastatin 40–80 mg or rosuvastatin 20–40 mg), including those with type 2 diabetes.[13,23] Unfortunately, in the majority of studies PCSK9 inhibitors have been second-line therapy on top of maximally tolerated statins, whereas in the clinical setting, ezetimibe is typically recommended as combination therapy with statins in selected patients when a specific LDL-C goal is not reached with the maximally tolerated dose of a statin.[4,5,24] Furthermore, definitive results must be awaited from ongoing outcomes studies in patients with a recent ACS (ODYSSEY OUTCOMES study with alirocumab); with a myocardial infarction, ischaemic stroke, or symptomatic peripheral artery disease (FOURIER study with evolocumab), or at high risk of a cardiovascular event and with LDL-C levels $\geq$1.8 or $\geq$ 2.6 mmol/L (SPIRE-1 and SPIRE-2 studies, respectively, with bococizumab).[16,17,25,26] Similarly, the impact on progression of coronary atherosclerosis, on top of statin therapy, evaluated by intravascular ultrasound, will give further insights (GLAGOV study with evolocumab).[27]

On the basis of available evidence, this Task Force recommends that a PCSK9 inhibitor may be considered in the defined very high risk patients, i.e. with ASCVD (clinical or unequivocal on imaging), or diabetes mellitus (with target organ damage or with a major cardiovascular risk factor),[4] who despite recommended maximally tolerated statin plus ezetimibe therapy require more than 50% reduction in LDL-C levels (i.e. with LDL-C levels >3.6 mmol/L or > 140 mg/dL) to reach the recommended goal (<1.8 mmol/L or <70 mg/dL) (*Figure 1*).[4] This threshold LDL-C value was selected as this Task Force agreed that the absolute LDL-C reduction is one of the determinants of the absolute cardiovascular risk reduction. Patients with LDL-C >3.6 mmol/L will have >50% reduction in LDL-C levels after PCSK9 inhibition, i.e. an absolute LDL-C reduction of > 1.8 mmol/L. Recognizing that patients with rapidly progressive ASCVD are at even higher risk, a lower LDL-C threshold of > 2.6 mmol/L or > 100 mg/dL was considered for initiation of a PCSK9 inhibitor (*Figure 1*). The Task Force recognizes that ASCVD patients with additional factors indicating a particularly high absolute cardiovascular risk and with LDL-C levels between 2.6 and 3.4 mmol/L (100 and 140 mg/dL) may be considered for PCSK9 inhibition on an individual basis according to the attending clinician's judgement of the absolute risk of the patient.

The recommendations aim to identify patients at highest risk who are most likely to derive profound absolute LDL-C reduction and therefore the greatest benefit from PCSK9 inhibition, while also taking into account the financial restraints within healthcare budgets.

Standardized screening for FH in patients with substantially elevated LDL-C levels is also recommended. The modified Dutch Lipid Clinic Network Criteria, in which a score is derived from the LDL-C level, the family and personal history of premature ASCVD, and the presence of tendon xanthomas or corneal arcus, is one possible approach (*Box 2*).[28] Although genetic testing (a component of the Dutch Lipid Clinic Network Criteria) is not considered mandatory, where available or accessible, this can be clinically helpful, within the context of cascade screening, for clinical management at the family level.

Patients with familial hypercholesterolaemia

Familial hypercholesterolaemia is an autosomal co-dominant inherited disorder, characterized by elevated serum LDL-C levels and increased risk for ASCVD, which has been sub-classified into heterozygous (He) and homozygous (Ho) forms depending on the presence of one or two affected alleles in genes encoding the LDL receptor, apolipoprotein B or PCSK9.[29–31] Although FH is one of the most common inherited conditions, evident in about 1 in 200–250 individuals in the general population,[32,33] the vast majority of HeFH patients are undetected, with clinical diagnosis often after the acute event.[6,34] Despite conflicting data for the residual cardiovascular risk in FH patients on lipid lowering treatment, mainly statin, almost all have ASCVD at the time of death.[35–38]

As the nature of the causative gene defect may have variable impact on the severity of HeFH, treatment decisions are currently guided by the LDL-C level and the presence of other risk factors that indicate a very high cardiovascular risk. These include diabetes mellitus, lipoprotein(a) >50 mg/dL, marked hypertension, and premature familial ASCVD (<55 years in males and <60 years in females), as defined by the Sixth Joint Task Force (2016)[4] and the European Atherosclerosis Society Consensus Panel on FH.[29,30] Treatment should be initiated as early as possible, as the age of starting treatment is a key determinant of later phenotypic severity.[39] Patients should be titrated to the maximally tolerated dose of efficacious statin (preferably atorvastatin or rosuvastatin); if LDL-C levels are still above recommended goals (<1.8 mmol/L or < 70 mg/dL in patients with ASCVD, and <2.6 mmol/L or < 100 mg/dL in patients without ASCVD), addition of ezetimibe is recommended before consideration of a PCSK9 inhibitor.[5,29,40]

Despite statin–ezetimibe combination therapy, however, a significant proportion of patients fail to attain LDL-C goal.[41,42] This panel recognizes that addition of a PCSK9 inhibitor is a very attractive and efficacious new option for HeFH patients who typically need 50–60% incremental LDL-C reductions to achieve LDL-C goal.[43,44] However, until results from major outcomes trials are reported, the panel proposes that PCSK9 inhibitor treatment may be considered for severe FH patients with ASCVD (as discussed above), as well as those without ASCVD (clinical or on imaging) and LDL-C levels >5.0 mmol/L or > 200 mg/dL despite maximally tolerated statin/ezetimibe therapy. For patients with additional risk factors as defined above [diabetes mellitus, elevated lipoprotein(a) >50 mg/dL, marked hypertension, and premature familial ASCVD (<55 years in males and <60 years in females)], the LDL-C threshold is lower, i.e. >4.5 mmol/L or > 175 mg/dL (see *Box 3* and *Figure 2*). These suggested LDL-C

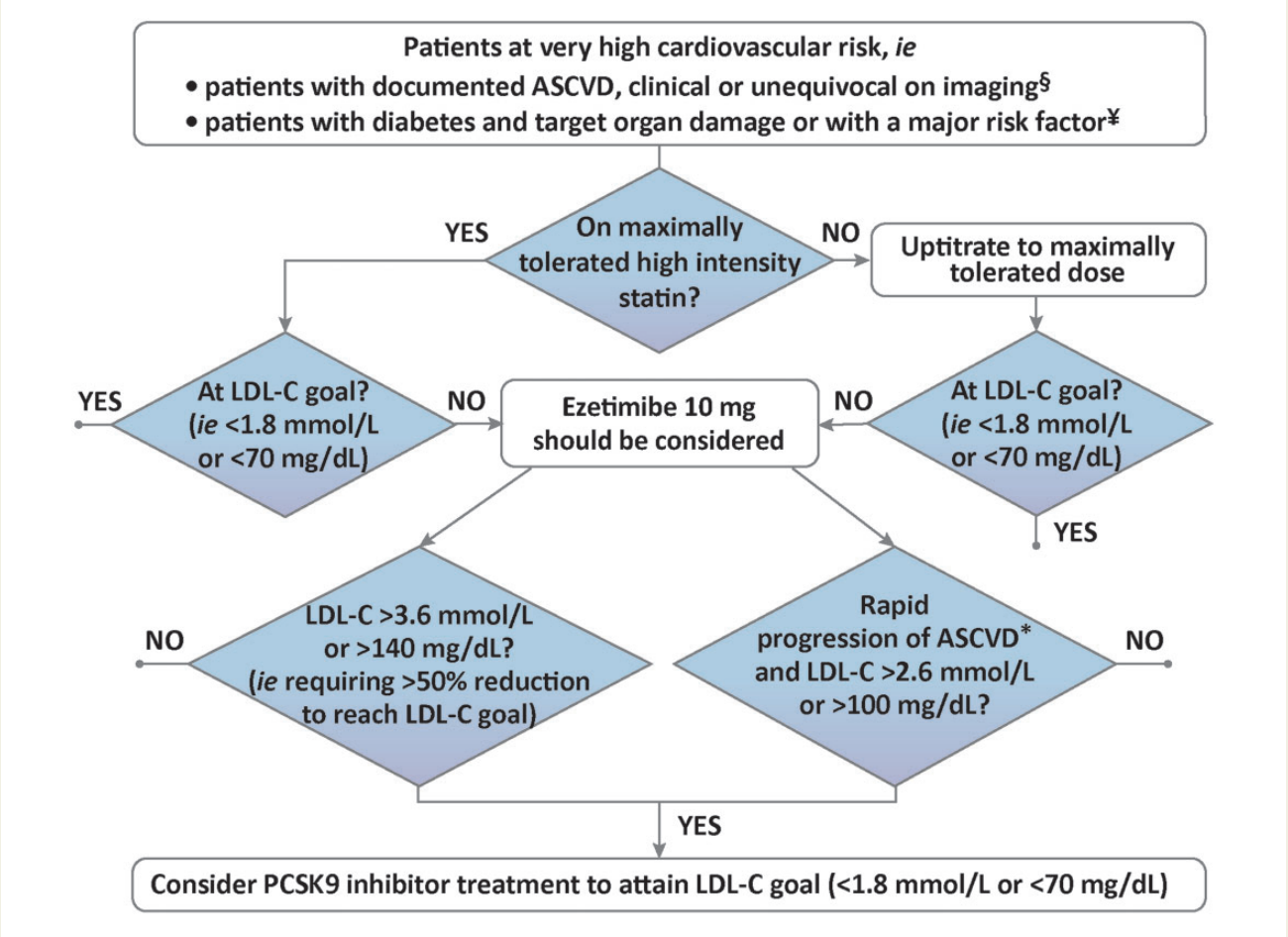

Figure 1 Algorithm for consideration of proprotein convertase subtilisin/kexin type 9 inhibitor treatment in very high risk patients, i.e. with atherosclerotic cardiovascular disease (ASCVD), or diabetes mellitus (with target organ damage or a major cardiovascular risk factor), as defined by the Sixth Joint Task Force (2016).[4]

§Documented clinical ASCVD includes previous acute myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, stroke and transient ischaemic attack, aortic aneurysm, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes plaque on coronary angiography or carotid ultrasound. It does not include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery.

¥Diabetes mellitus with target organ damage such as proteinuria, or with a major risk factor such as marked hypercholesterolaemia or marked hypertension.

*Rapid progression of ASCVD is defined as repeated acute coronary syndromes, repeated unplanned coronary revascularizations, or repeated ischaemic strokes within 5 years of the index event. The suggested threshold for these patients is based on the consensus of this Joint ESC/EAS Task Force and represents a compromise between selection of patients at highest risk who are most likely to benefit from PCSK9 inhibition and justification of the cost of treatment given financial restraints within healthcare budgets. The Task Force recognizes that ASCVD patients with additional factors indicating a particularly high absolute cardiovascular risk (i.e. anticipated absolute risk reduction of > 2%/year), and with LDL-C levels between 2.6 and 3.4 mmol/L (100 and 140 mg/dL) may be considered for PCSK9 inhibition on an individual basis according to the attending clinician's judgement of the absolute risk of the patient. This means that in this LDL-C range at present only patients with a 5-year risk of major adverse cardiovascular events >20% would be recommended to be considered for PCSK9 inhibition, so that the anticipated absolute risk reduction can reach >2%/year (based on the relation between absolute LDL-C reduction and prevented major adverse cardiac events in the Cholesterol Treatment Trialists' Collaboration analysis). Here, both the absence of data from randomized clinical outcome trials at present and considerations for cost-effectiveness had to be taken into account.

thresholds are based on the consensus of this Task Force and also take into account the financial restraints within healthcare budgets.

For HoFH patients, lipid-lowering therapy, including LDL apheresis where available, should be started as early as possible.[30,31] To date, only evolocumab has been evaluated in HoFH, providing up to ~30% reduction in LDL-C levels.[45] As expected, evolocumab induced greater LDL-C decreases in patients with defective/defective and defective/negative LDL receptor (*LDLR*) mutations, but had very little effect in rare patients with negative/negative *LDLR* mutations. On this basis, the Task Force recommends considering evolocumab

Box 2 Dutch Lipid Clinic Network Criteria for diagnosis of heterozygous familial hypercholesterolaemia in adults[a]

	Points
Group 1: Family history	
(i) First-degree relative with known premature coronary heart disease: men < 55 years and women < 60 years),	1
OR	
(ii) First-degree relative with known LDL-C >95th percentile by age and gender for country	1
(iii) First-degree relative with tendon xanthoma and/or corneal arcus	2
OR	
(iv) Child(ren) <18 years with LDL-C >95th percentile by age and gender for country	2
Group 2: Clinical history	
(i) Subject has premature coronary heart disease (<55 years in men; <60 years in women)	2
(ii) Subject has premature cerebral or peripheral vascular disease (<55 years in men; <60 years in women)	1
Group 3: Physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person < 45 years	4
Group 4: Biochemical results (LDL-C)	
>8.5 mmol/L (>325 mg/dL)	8
6.5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: Molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the *LDLR*, *APOB*, or *PCSK9* genes	8
Likely diagnosis	Point score
Definite FH	≥8
Probable FH	6–7
Possible FH	3–5
Unlikely	<3

[a]Adapted from Hovingh *et al.* (2013).[28]

treatment for HoFH patients except those with confirmed negative/negative *LDLR* mutations for whom lomitapide may be a preferred option (see *Box 3*).

Patients with statin intolerance

Although statin therapy undoubtedly represents the first-line pharmacotherapy for LDL-C lowering for prevention and treatment of premature ASCVD, a proportion of patients report adverse effects. Many of these effects have not been confirmed in controlled trials (e.g. cataract, cancer, peripheral neuropathy, insomnia, fatigue, and neurocognitive symptoms), or have no clinically significant relevance (e.g. proteinuria, mild hepatic enzyme elevation). Two adverse effects are of particular concern; a moderately increased risk of developing type 2 diabetes,[46] and, predominantly, statin-associated muscle symptoms (SAMS), which appear much more common in real world practice than in the published large trials.[47] The latter has attracted most attention, given the well-established consequences of increased cardiovascular events and mortality associated with statin discontinuation.[48]

Definitions of statin intolerance with emphasis on SAMS given by consensus groups and used in clinical trials with alirocumab and evolocumab have varied (*Box 4*).[47,49–54] Although the aetiology is not fully elucidated, a proportion of patients treated with a statin manifest symptoms that remit after withdrawal and re-occur with rechallenge. It is noteworthy, however, that in both the ODYSSEY ALTERNATIVE and GAUSS trials, at least 50% of patients considered 'statin intolerant' were in fact tolerant of lower or intermittent dosing strategies with statin rechallenge. Nevertheless, the clinical effectiveness of such dosing regimens is not known.

Recommendations for management of SAMS in very high risk patients, further developed from a recent EAS Consensus Panel,[47] are shown in *Figure 3*. Patients who complain of muscle symptoms and have a CK level <10-fold the upper limit of normal (ULN) should be interviewed and receive counselling from their clinician to emphasize the clinical benefits of statin therapy. After a statin washout, patients with CK ≥ 4 × ULN but <10 × ULN at baseline and with recurrent symptoms should successively undertake two dechallenges/rechallenges with separate statins, started at the lowest recommended daily dose; an additional statin challenge is recommended for patients with CK either normal or < 4 × ULN at baseline. Patients with no symptoms after statin washout should continue statin treatment. All patients should be uptitrated to the maximally tolerated statin dose wherever possible, and ezetimibe should be considered in patients not at LDL-C goal.

This Task Force recommends that very high risk patients (as defined in the previous sections) intolerant of at least two statins at any dose, with muscle symptoms and/or CK elevation, and with substantially elevated LDL-C levels despite ezetimibe therapy (as defined previously in this document and in *Figure 3*) may be considered for treatment with a PCSK9 inhibitor. Furthermore, due to the complexity in establishing true statin intolerance and the risk of overdiagnosis of SAMS, the panel recommends centralization of this evaluation to ensure that the PCSK9 inhibitor is used appropriately. The role of the physician is especially important to best manage SAMS and encourage, wherever possible, statin as the recommended therapy for the prevention and treatment of ASCVD.

Cost vs. benefit

Based on the approved indications for alirocumab and evolocumab and estimates from EUROASPIRE IV,[22] up to 80% of ASCVD patients in Europe would theoretically represent the patient pool for PCSK9 inhibitor therapy in secondary prevention, which is at present clearly not sustainable for health services given the cost of treatment. The UK National Institute for Health and Care Excellence approvals for alirocumab and evolocumab incorporated a model for a cost–benefit analysis, with LDL-C lowering as a surrogate to link to cardiovascular events.[55,56] The incremental cost-effectiveness ratios were lowest for those groups proposed for consideration of PCSK9 inhibition in this consensus statement, e.g. with severe FH with CVD (<£25 000

Box 3 Very high risk patient groups for whom proprotein convertase subtilisin/kexin type 9 inhibitors may be considered

Patient group	Pre-treatment	Criteria for consideration of PCSK9 inhibition
ASCVD[a] or diabetes mellitus with target organ damage or a major risk factor[b]	Maximally tolerated efficacious statin (preferably atorvastatin or rosuvastatin) + ezetimibe	• LDL-C > 3.6 mmol/L (140 mg/dL) • Rapid progression of ASCVD[c] and LDL-C > 2.6 mmol/L or > 100 mg/dL
Severe FH without ASCVD		
Heterozygous FH	maximally tolerated efficacious statin (preferably atorvastatin or rosuvastatin) + ezetimibe	• LDL-C > 5.0 mmol/L or > 200 mg/dL • ≥1 additional risk factor indicative of very high cardiovascular risk[d] and LDL-C > 4.5 mmol/L or > 175 mg/dL
Homozygous FH	maximally lipid lowering therapy, including LDL apheresis	All patients EXCEPT those with negative–negative *LDLR* mutations
Statin intolerant	Ezetimibe	Any of the above categories

The suggested thresholds for patients with rapid progression of ASCVD and FH are based on the consensus of this Joint ESC/EAS Task Force and represent a compromise between selection of patients at highest risk who are most likely to benefit from PCSK9 inhibition and justification of the cost of treatment given the financial restraints within healthcare budgets.

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia.

[a]Consistent with guidelines,[4] documented clinical ASCVD includes previous acute myocardial infarction, acute coronary syndrome (ACS), coronary revascularization and other arterial revascularization procedures, stroke and transient ischaemic attack, aortic aneurysm, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes plaque on coronary angiography or carotid ultrasound. It does not include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery.

[b]Consistent with guidelines,[4] diabetes mellitus with target organ damage such as proteinuria, or with a major risk factor such as smoking, marked hypercholesterolaemia, or marked hypertension.

[c]Rapid progression of ASCVD defined as repeated ACSs, repeated unplanned coronary revascularizations, or repeated ischaemic strokes within 5 years of the index event. The Task Force recognizes that ASCVD patients with additional factors indicating a particularly high absolute cardiovascular risk (i.e. anticipated absolute risk reduction of > 2%/year), and with LDL-C levels between 2.6 and 3.4 mmol/L (100 and 140 mg/dL) may be considered for PCSK9 inhibition on an individual basis according to the attending clinician's judgement of the absolute risk of the patient. This means that in this LDL-C range at present only patients with a 5-year risk of major adverse cardiovascular events >20% would be recommended to be considered for PCSK9 inhibition, so that the anticipated absolute risk reduction can reach >2%/year (based on the relation between absolute LDL-C reduction and prevented major adverse cardiac events in the Cholesterol Treatment Trialists' Collaboration analysis). Here, both the absence of data from randomized clinical outcome trials at present and considerations for cost-effectiveness had to be taken into account.

[d]Risk factors indicating a very high cardiovascular risk include diabetes mellitus, lipoprotein(a) > 50 mg/dL, marked hypertension, premature familial ASCVD (<55 years in males and <60 years in females), as defined by the Sixth Joint Task Force (2016),[4] and the European Atherosclerosis Society Consensus Panel on FH.[29,30]

per QALY gained when added to statin plus ezetimibe), and in the setting of non-FH at very high risk of progression of CVD (between £19 300 and £34 000, and <£30 000 per QALY gained at an LDL-C level of 3.5 mmol/L). However, it is important to bear in mind that LDL-C is a surrogate measure and cardiovascular outcomes data are needed to provide accurate measures of the effects of PCSK9 inhibition in preventing CVD. Moreover, cost–benefit analyses are also dependent on the cost of these treatments, which remain under negotiation in several European countries. Until the results from outcomes studies are available, the findings from such reports are to be regarded with caution. Identification of individuals at highest risk of an (recurrent) event is paramount, as they will potentially benefit to the greatest degree.

Gaps and unanswered questions

There remain a number of unanswered questions regarding the clinical use of PCSK9 monoclonal antibody therapy, including long-term safety (see *Box 5*). More data are also needed in patients with coronary disease with comorbidities, including moderate-to-severe chronic kidney disease. An important question is whether and to what extent these treatments, added to statins, reduce ASCVD events in very high risk patients who do not attain LDL-C goal.

Conclusion

This ESC/EAS Task Force consensus document provides clinicians with practical guidance for the use of PCSK9 inhibitor treatment in patients at very high risk of (recurrent) cardiovascular events with poorly controlled LDL-C levels (see Box 3). This Joint Task Force recommends that treatment with a PCSK9 monoclonal antibody may be considered in very high risk patients with ASCVD (clinical or unequivocal on imaging[4,5]), including those with progressive ASCVD, or diabetes mellitus (with target organ damage or a major cardiovascular risk factor); or in patients with severe FH without ASCVD with substantially elevated LDL-C levels despite maximal statin/ezetimibe therapy. Patients in these groups with verified statin intolerance (SAMS) may be also considered for PCSK9 inhibition. These recommendations identify a patient population who are likely to derive most potential benefit from this novel therapy, while also taking account of the financial restraints within healthcare budgets. This document is based on current evidence for PCSK9 monoclonal antibody therapy, and will be re-evaluated with the availability of data from large, randomized cardiovascular outcomes studies evaluating the impact of these novel agents on ASCVD and related thromboembolic events.

Conflict of interest: Panel members have received research funding, and/or honoraria for advisory boards, consultancy or speaker

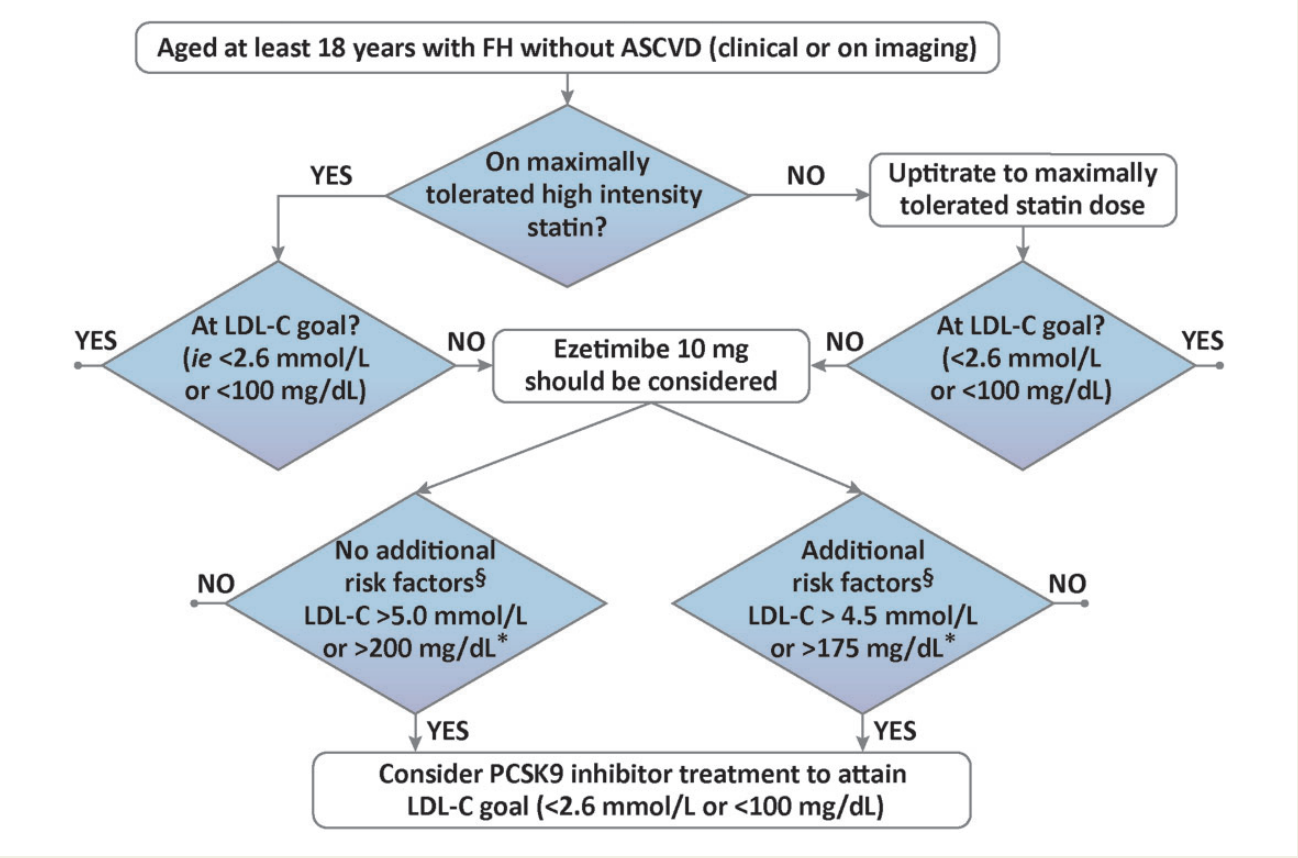

Figure 2 Algorithm for consideration of proprotein convertase subtilisin/kexin type 9 inhibitor treatment in severe familial hypercholesterolaemia patients without atherosclerotic cardiovascular disease (ASCVD) (as defined in *Box 3*).
§Additional risk factors that indicate a very high cardiovascular risk include diabetes mellitus, elevated lipoprotein(a) > 50 mg/dL, marked hypertension, and premature familial ASCVD (<55 years in males and <60 years in females), as defined by the Sixth Joint Task Force (2016),[4] and the European Atherosclerosis Society Consensus Panel on FH.[29,30]
*The suggested thresholds for these patients are based on the consensus of this Joint ESC/EAS Task Force and represent a compromise between selection of patients at highest risk who are most likely to benefit from PCSK9 inhibition, and justification of the cost of treatment given financial restraints within healthcare budgets.

Box 4 Definitions for statin-associated muscle symptoms

Consensus group	Definition
EAS Consensus Panel[47]	Clinical diagnostic definition, based on assessment of the probability of SAMS being due to a statin, taking into account the nature of the muscle symptoms, the elevation in CK levels and their temporal association with statin initiation, discontinuation, and rechallenge
Statin Muscle Safety Task Force[50]	Statin intolerance is a real phenomenon that manifests mostly as an array of muscle-related symptoms (aching, stiffness, proximal motor weakness, fatigue, and back pain) Definition is based on symptoms plus the magnitude of elevation in CK
Trial	
ODYSSEY ALTERNATIVE[51]	Intolerance to ≥ 2 statins, including one at the lowest approved starting dose A placebo run-in and statin rechallenge arm were included in an attempt to confirm intolerance
GAUSS[52]	Intolerance to at least one statin because of muscle-related events
GAUSS-2[53]	Intolerance to ≥ 2 statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects
GAUSS-3[54]	Intolerance to ≥ 3 statins or 2 statins (one of which was atorvastatin ≤10 mg/day) or with a history of marked CK elevation accompanied by muscle symptoms while on a statin

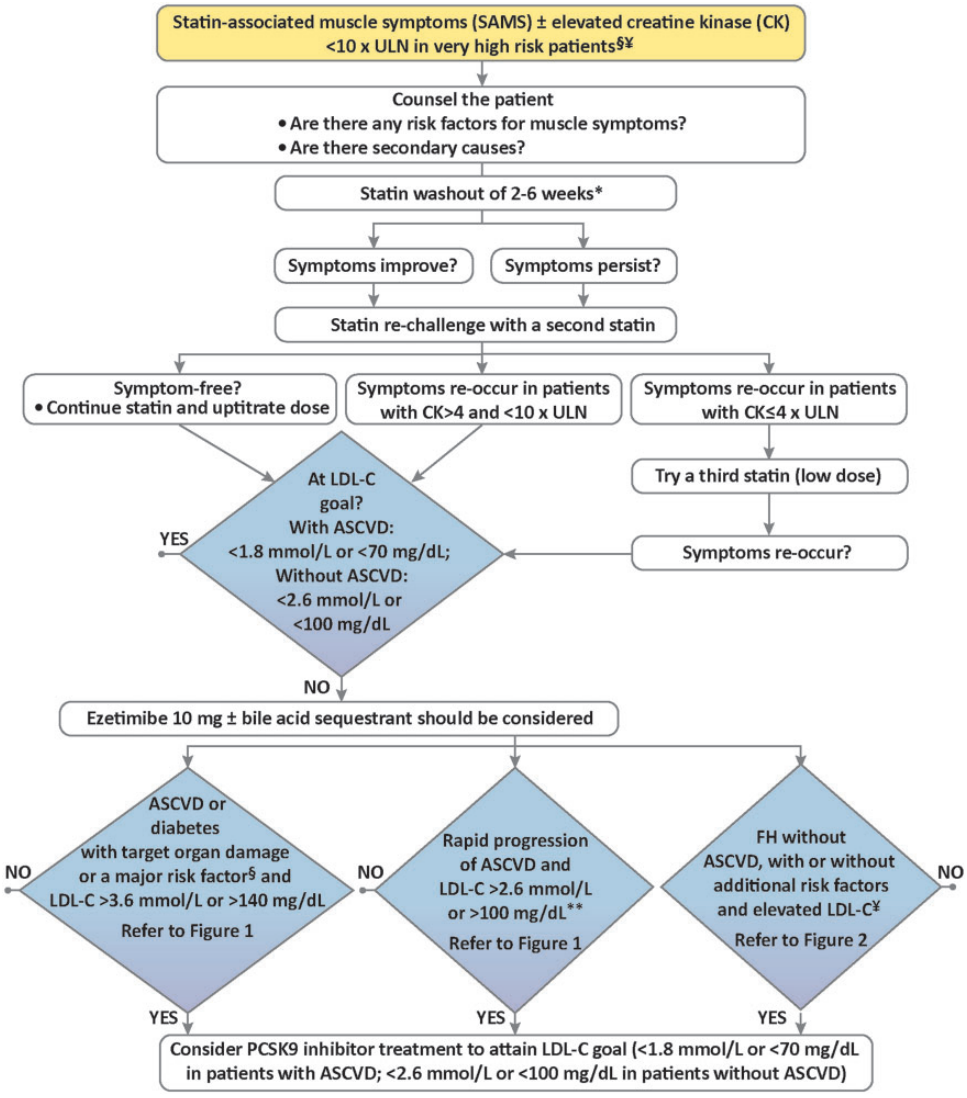

Figure 3 Algorithm for consideration of proprotein convertase subtilisin/kexin type 9 inhibitor treatment in very high risk patients with statin-associated muscle symptoms (SAMS), further developed from a recent consensus recommendation.[47] ASCVD, atherosclerotic cardiovascular disease.

§Very high risk defined by the Sixth Joint Task Force (2016)[4] as documented clinical ASCVD (previous acute myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, stroke and transient ischaemic attack, aortic aneurysm, and peripheral arterial disease); and unequivocally documented ASCVD on imaging (plaque on coronary angiography or carotid ultrasound; it does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery). Patients with diabetes mellitus with target organ damage such as proteinuria, or with a major risk factor such as marked hypercholesterolaemia or marked hypertension are also considered as very high risk.

¥Additional risk factors that indicate a very high cardiovascular risk include diabetes mellitus, elevated lipoprotein(a) $>$ 50 mg/dL, marked hypertension, and premature familial ASCVD ($<$55 years in males and $<$60 years in females), as defined by the Sixth Joint Task Force (2016),[4] and the European Atherosclerosis Society Consensus Panel on FH.[29,30]

*Suggested statin washout is dependent on creatine kinase (CK) elevation, i.e. 2–4 weeks if CK elevation is $<$ 4 $\times$ ULN, and 6 weeks if CK elevation is $>$ 4 $\times$ ULN.

**Rapid progression of ASCVD is defined as repeated acute coronary syndromes, repeated unplanned coronary revascularizations, or repeated ischaemic strokes within 5 years of the index event. The suggested threshold for these patients is based on the consensus of this Joint ESC/EAS Task Force and represents a compromise between selection of patients at highest risk who are most likely to benefit from PCSK9 inhibition and justification of the cost of treatment given financial restraints within healthcare budgets. The Task Force recognizes that ASCVD patients with additional factors indicating a particularly high absolute cardiovascular risk (i.e. anticipated absolute risk reduction of $>$ 2%/year), and with LDL-C levels between 2.6 and 3.4 mmol/L (100 and 140 mg/dL) may be considered for PCSK9 inhibition on an individual basis according to the attending clinician's judgement of the absolute risk of the patient. This means that in this LDL-C range at present only patients with a 5-year risk of major adverse cardiovascular events $>$20% would be recommended to be considered for PCSK9 inhibition, so that the anticipated absolute risk reduction can reach $>$2%/year (based on the relation between absolute LDL-C reduction and prevented major adverse cardiac events in the Cholesterol Treatment Trialists' Collaboration analysis). Here, both the absence of data from randomized clinical outcome trials at present and considerations for cost-effectiveness had to be taken into account.

Box 5 Unanswered questions about proprotein convertase subtilisin/kexin type 9 inhibitor treatment

- Impact on regression vs. progression of atherosclerotic plaque, and plaque stability
- Impact on cardiovascular outcomes
- Long-term safety, including neurocognitive and immunogenic effects
- Lower and upper age limits for treatment
- Cost-effectiveness in patient populations at different levels of cardiovascular risk

bureau from Abbott Mylan (M.F., L.T., J.L.Z.), Actelion (L.T.), Aegerion (A.L.C., L.T.), Amgen (A.L.C., M.J.C., M.F., G.K.H., U.L., T.F.L., L.T., O.W.), AstraZeneca (A.L.C., M.J.C., M.F., L.T.), Bayer (U.L., L.T.), Berlin-Chemie (U.L.), Boehringer (L.T.), Daiichi-Sankyo (L.T.), Eli Lilly (A.L.C., M.F.), Genzyme (A.L.C., M.F., G.K.H.), GlaxoSmithKline (L.T.), Kowa (M.J.C., M.F.), Mediolanum (A.L.C.), Menarini (L.T.), Merck or MSD (A.L.C., M.F., G.K.H., U.L., L.T., O.W., J.L.Z.), Novartis (L.T.), Pfizer (A.L.C., M.J.C., M.F., G.K.H., U.L., L.T., J.L.Z.), Philips (J.L.Z.), Recordati (A.L.C.), Roche (M.F., G.K.H., U.L.), Rottapharm (A.L.C.), Sanofi (S.G.), Sanofi-Regeneron (A.L.C., M.J.C., M.F., G.K.H., U.L., T.F.L., L.T., O.W.), Servier (M.F., L.T.), Sigma-Tau (A.L.C.). B.G. and D.S. report no disclosures.

References

1. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J* 2006;**27**:1610–1619.
2. Matza LS, Stewart KD, Gandra SR, Delio PR, Fenster BE, Davies EW, Jordan JB, Lothgren M, Feeny DH. Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Serv Res* 2015;**15**:173.
3. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* 2015;**161**:161–172.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
5. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J* 2016; pii: ehw272. [Epub ahead of print].
6. De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein JJ, Kotseva K, Ray K, Reiner Ž, Wood D, De Bacquer D, EUROASPIRE Investigators. Prevalence and management of familial hypercholesterolaemia in coronary patients: an analysis of EUROASPIRE IV, a study of the European Society of Cardiology. *Atherosclerosis* 2015;**241**:169–175.
7. Lüscher TF. Improving prevention: risk scores, imaging, and PCSK9 inhibitors. *Eur Heart J* 2016;**37**:499–501.
8. Ridker PM, Mora S, Rose L, JUPITER Trial Study Group. Per cent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. *Eur Heart J* 2016;**37**:1373–1379.
9. Seidah NG, Awan Z, Chrétien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. *Circ Res* 2014;**14**:1022–1036.
10. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;**354**:1264–1272.
11. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;**34**:154–156.
12. Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC, Torguson R, Brewer HB Jr, Waksman R. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. *Eur Heart J* 2016;**37**:536–545.
13. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, Brockmeyer M, Kandzari DE, Kubica JM, D'Agostino RBS, Kubica J, Volpe M, Agewall S, Kereiakes DJ, Kelm M. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med* 2015;**163**:40–51.
14. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Eng J Med* 2015;**372**:1489–1499.
15. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA, Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Eng J Med* 2015;**372**:1500–1509.
16. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby JF, Tricoci P, White H, Zeiher A, Steg PG. 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.
17. Sabatine MS, Giugliano RP, Keech A, Honarpour N, Wang H, Liu T, Wasserman SM, Scott R, Sever PS, Pedersen TR. Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. *Am Heart J* 2016;**173**:94–101.
18. Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects (EBBINGHAUS). ClinicalTrials.gov Identifier: NCT02207634. https://clinicaltrials.gov/ct2/show/NCT02207634 (28 September 2016).
19. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
20. Gencer B, Auer R, Nanchen D, Räber L, Klingenberg R, Carballo D, Blum M, Vogt P, Carballo S, Meyer P, Matter CM, Windecker S, Lüscher TF, Mach F, Rodondi N. Expected impact of applying new 2013 AHA/ACC cholesterol guidelines criteria on the recommended lipid target achievement after acute coronary syndromes. *Atherosclerosis* 2015;**239**:118–124.
21. Gitt AK, Drexel H, Feely J, Ferrières J, Gonzalez-Juanatey JR, Thomsen KK, Leiter LA, Lundman P, da Silva PM, Pedersen T, Wood D, Jünger C, Dellea PS, Sazonov V, Chazelle F, Kastelein JJP, DYSIS Investigators. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. *Eur J Prev Cardiol* 2012;**19**:221–230.
22. Reiner Ž, De Backer G, Fras Z, Kotseva K, Tokgözoglu L, Wood D, De Bacquer D, EUROASPIRE Investigators. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries—Findings from the EUROASPIRE IV survey. *Atherosclerosis* 2016;**246**:243–250.
23. Sattar N, Preiss D, Robinson JG, Djedjos CS, Elliott M, Somaratne R, Wasserman SM, Raal FJ. Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. *Lancet Diabetes Endocrinol* 2016;**4**:403–410.
24. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting

without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
25. The Evaluation of Bococizumab (PF-04950615;RN316) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE-1). ClinicalTrials.gov Identifier: NCT01975376. https://clinicaltrials.gov/ct2/show/NCT01975376 (28 September 2016).
26. The Evaluation of Bococizumab (PF-04950615; RN316) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE-2). ClinicalTrials.gov Identifier: NCT01975389. https://clinicaltrials.gov/ct2/show/NCT01975389 (28 September 2016).
27. GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound (GLAGOV). ClinicalTrials.gov Identifier: NCT01813422. https://clinicaltrials.gov/ct2/show/NCT01813422 (28 September 2016).
28. Hovingh GK, Davidson MH, Kastelein JJ, O'connor AM. Diagnosis and treatment of familial hypercholesterolaemia. *Eur Heart J* 2013;**34**:962–971.
29. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J* 2013;**34**:3478–3490.
30. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjærg-Hansen A, Watts GF, Averna M, Boileau C, Borén J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ, European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;**35**:2146–2157.
31. Gidding SS, Ann Champagne M, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, Lopes-Virella M, Watts GF, Wierzbicki AS, American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation* 2015;**132**:2167–2192.
32. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016;**37**:1384–1394.
33. Do R, Stitziel NO, Won HH, Jørgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, NHLBI Exome Sequencing Project, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Hovingh GK, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT, Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Cupples LA, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'donnell CJ, Altshuler D, Gabriel S, Kathiresan S. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature* 2015;**518**:102–106.
34. Nanchen D, Gencer B, Auer R, Räber L, Stefanini GG, Klingenberg R, Schmied CM, Cornuz J, Muller O, Vogt P, Jüni P, Matter CM, Windecker S, Lüscher TF, Mach F, Rodondi N. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *Eur Heart J* 2015;**36**:2438–2445.
35. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heeringa J, Witteman JC, Lansberg PJ, Kastelein JJ, Sijbrands EJ. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;**337**:a2423.
36. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, Seed M, Humphries SE, on behalf of the Simon Broome Familial Hyperlipidaemia Register Group. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J* 2008;**29**:2625–2633.
37. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierød MB, Leren TP, Retterstøl K. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992-2010. *J Am Heart Assoc* 2014;**3**:e001236.
38. Krogh HW, Mundal L, Holven KB, Retterstøl K. Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death. *Eur Heart J* 2016;**37**:1398–1405.
39. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Steinhagen-Thiessen E, Stroes ES, Taskinen MR, Tybjærg-Hansen A, Wiklund O, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;**36**:2425–2437.
40. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
41. Béliard S, Carreau V, Carrié A, Giral P, Duchêne E, Farnier M, Ferrières J, Fredenrich A, Krempf M, Luc G, Moulin P, Bruckert E. Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: can we do better? Analysis of results obtained during the past two decades in 1669 French subjects. *Atherosclerosis* 2014;**234**:136–141.
42. Perez de Isla L, Alonso R, Watts GF, Mata N, Saltijeral Cerezo A, Muñiz O, Fuentes F, Diaz-Diaz JL, de Andrés R, Zambón D, Rubio-Marin P, Barba-Romero MA, Saenz P, Sanchez Muñoz-Torrero JF, Martinez-Faedo C, Miramontes-Gonzalez JP, Badimón L, Mata P,, Safeheart I. Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-Year SAFEHEART Registry follow-up. *J Am Coll Cardiol* 2016;**67**:1278–1285.
43. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, Blom D, Civeira F, Krempf M, Lorenzato C, Zhao J, Pordy R, Baccara-Dinet MT, Gipe DA, Geiger MJ, Farnier M. ODYSSEY FH I and FH II: 78-week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Eur Heart J* 2015;**36**:2996–3003.
44. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, Langslet G, Scott R, Olsson AG, Sullivan D, Hovingh GK, Cariou B, Gouni-Berthold I, Somaratne R, Bridges I, Scott R, Wasserman SM, Gaudet D, RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:331–340.
45. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA, TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA part B): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:341–350.
46. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;**375**:735–742.
47. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN, European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;**36**:1012–1022.
48. Kim MC, Cho JY, Jeong HC, Lee KH, Park KH, Sim DS, Yoon NS, Yoon HJ, Kim KH, Hong YJ, Park HW, Kim JH, Jeong MH, Cho JG, Park JC, Seung KB, Chang K, Ahn Y. Impact of postdischarge statin withdrawal on long-term outcomes in patients with acute myocardial infarction. *Am J Cardiol* 2015;**115**:1–7.
49. Guyton JR, Bays HE, Grundy SM, Jacobson TA, The National Lipid Association Statin Intolerance Panel. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol* 2014;**8(3 Suppl)**:S72–S81.
50. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel, Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol* 2014;**8(3 Suppl)**:S58–S71.
51. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, Du Y, Pordy R, Gipe DA, ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs

ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015;**9**:758–769.
52. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, Wasserman SM, Stein EA. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA* 2012;**308**:2497–2506.
53. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M, GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;**63**:2541–2548.
54. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceška R, Lepor N, Ballantyne CM, Gouni-Berthold I, Elliott M, Brennan DM, Wasserman SM, Somaratne R, Scott R, Stein EA, GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA* 2016;**315**:1580–1590.
55. National Institute for Health and Care Excellence. Hypercholesterolaemia (primary) and dyslipidaemia (mixed)—alirocumab [ID779]. NICE in development [GID-TAG512]. https://www.nice.org.uk/guidance/indevelopment/gid-tag512 (28 September 2016).
56. National Institute for Health and Care Excellence. Hypercholesterolaemia (primary), dyslipidaemia (mixed)—evolocumab [ID765]. NICE technology appraisal guidance [TA394]. https://www.nice.org.uk/guidance/indevelopment/gid-tag498 (28 September 2016).