ESC European Society of Cardiology

European Heart Journal (2017) **00**, 1–13
doi:10.1093/eurheartj/ehx549

CURRENT OPINION

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

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Received 24 June 2017; revised 24 July 2017; editorial decision 4 September 2017; accepted 11 September 2017

Preamble

The first randomized controlled data from cardiovascular outcomes trials with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have now been reported.[1,2] This ESC/EAS Task Force met to consider the impact on practical guidance for the use of these novel agents. This updated clinical guidance provides novel clinical decision algorithms when considering a PCSK9 inhibitor, and monitoring treatment efficacy to statin, ezetimibe and PCSK9 inhibitor. Gaps in knowledge for PCSK9 inhibition are also discussed.

Introduction

The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial (with evolocumab, a fully human monoclonal PCSK9 antibody) in 27 564 patients with atherosclerotic cardiovascular disease (ASCVD) was the first to be completed.[1] The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE)-1 and -2 trials were, however, stopped early following termination of bococizumab development due to effects specific to this antibody (*Box 1*).[2,3] In FOURIER, lowering of low-density lipoprotein

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Box 1 Key reasons for termination of bococizumab

The development of bococizumab was discontinued by Pfizer in late 2016.[a] The key reasons for this were a high level of immunogenicity and wide variability in the low-density lipoprotein cholesterol (LDL-C) lowering response.

- *Immunogenicity*: In statin-treated patients, PCSK9 inhibition with bococizumab reduced LDL-C levels by 55–60% in the short-term, but this effect was attenuated over time in 10–15% of patients due to the development of antidrug antibodies. It is important to note that this effect was specific to bococizumab, a partially humanized monoclonal antibody, which is characterized by substitution of rodent DNA sequences for <5% of human DNA sequences. It is thought that this substitution may have directly affected the immunogenicity of the antibody. This effect has not been reported for either evolocumab or alirocumab, which are fully human monoclonal antibodies. This immunogenicity may also explain the higher rate of injection site reactions (~10%) observed with bococizumab compared with either alirocumab or evolocumab (<5%).
- *Variability in LDL-C lowering response*: Irrespective of the presence or absence of antidrug antibodies, there was wide individual variability in the LDL-C lowering response with bococizumab; about 1 in 10 showed no reduction in LDL-C levels.

[a]Press release Tuesday, 1 November 2016. Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor.

cholesterol (LDL-C) levels by 59% (from 2.4 mmol/L to 0.78 mmol/L) significantly reduced the risk of major cardiovascular events (absolute event rates 9.8% vs. 11.3% on placebo over 2.2 years, relative risk reduction of 15%). The clinical benefit of PCSK9 inhibitor treatment was due to reduction of nonfatal events, largely driven by reduction in myocardial infarction (MI) and coronary revascularization. This benefit was generally consistent across all major patient subgroups, including age, sex, and type of clinical presentation of ASCVD [coronary artery disease (CAD) with history of MI, ischaemic stroke and symptomatic peripheral arterial disease (PAD)], and accrued over time.[1] Compared with the Cholesterol Treatment Trialists' (CTT) Collaboration for cardiovascular benefit per mmol/L reduction in LDL-C, which is based on average response over 5 years on statin therapy, the observed benefit in FOURIER was shown to fall below the regression line. When adjusted for duration of treatment, however, as the benefit of a cholesterol lowering therapy in the first year of treatment is less than in the following years, the results from FOURIER were superimposable with those observed with statin therapy (*Figure 1*).[4] Evidence from studies involving variants in the genes encoding PCSK9 and 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase provides further support for the concept that a similar risk reduction per unit LDL-C reduction is to be expected.[5]

Insights from these trials reinforce that the key determinants of clinical benefit are the absolute cardiovascular risk, the absolute magnitude of LDL-C reduction, and the absolute LDL-C level. In all trials, patients were at very high risk as defined by guidelines,[6,7] with a history of clinical ASCVD (either MI, stroke, or symptomatic PAD) and additional cardiovascular risk factors, including, in the SPIRE trials, clinically diagnosed familial hypercholesterolaemia (FH).[1,2] Patients had elevated LDL-C levels despite maximally tolerated lipid lowering therapy (the vast majority received high to moderate intensity statin therapy). In SPIRE-2, patients had higher LDL-C levels (mean at baseline 3.4 mmol/L or 133 mg/dL vs. 2.4 mmol/L or ~90 mg/dL in FOURIER and SPIRE-1).[1,2] Thus, despite progressive attenuation of LDL-C lowering with bococizumab due to the formation of neutralizing antibodies,[3] there was still significant clinical benefit in SPIRE-2 within 12 months (absolute event rates for major cardiovascular events 3.32% vs. 4.19% on placebo, relative risk reduction of 21%, $P = 0.02$). SPIRE-1 did not reveal a significant difference in cardiovascular events, however, as patients had lower LDL-C levels and the duration of treatment was short (7 months).[2]

Two key issues are pertinent when interpreting the results of FOURIER. The first issue relates to the rather short duration of the trial. It is important to emphasize that as the trial was event- and not time-driven the short duration was due to trial design. Allowing for a possible lag in treatment benefit, as seen in the statin trials, FOURIER planned for a median duration of ~43 months to allow for accrual of 1630 key secondary end points (a composite of cardiovascular death, MI, or stroke), which would provide 90% power to detect a relative reduction of at least 15% for this endpoint.[8] In reality, the observed event rate was higher and therefore the trial was completed after a median of 26 months at which time 1829 key secondary endpoints had occurred.[1]

The second issue relates to the lack of significant benefit on cardiovascular and all-cause mortality. As noted above, the FOURIER data show that the predominant effect of PCSK9 inhibition was prevention of non-fatal cardiovascular events, mainly driven by MI and coronary revascularization; fatal MI or stroke accounted for only 5–10% of all MI or stroke events.[1] These findings are consistent with trials evaluating high- vs. low-dose statin therapy, none of which showed reduction in cardiovascular death. Added to this, a meta-analysis of four high- vs. low-dose statin trials indicated a reduction mainly in non-fatal cardiovascular events in patients allocated to the high-dose regimen.[9] Moreover, while reduced mortality was observed in earlier statin trials (e.g. the Scandinavian Simvastatin Survival Study, 4S),[10] this was only seen after prolonged treatment and not after 2.2 years against a background of contemporaneous, predominantly high-dose statin therapy as in FOURIER. It will therefore be of great interest to see whether longer follow-up of patients treated with a PCSK9 inhibitor results in reduction in mortality.

Together with definitive evidence that LDL is causal for ASCVD,[11] the results of the FOURIER and SPIRE trials constitute a key step forward in addressing unanswered questions about PCSK9 inhibition in the previous Task Force document.[12] It should, however, be noted that while the FOURIER and SPIRE-1 and SPIRE-2 protocols permitted enrolment of patients with mild to moderate chronic kidney disease, there are currently no available data on which to base recommendations for the use of PCSK9 inhibitors. Furthermore, while there is reassurance regarding the safety of very low LDL-C levels that can be attained on PCSK9 inhibitor therapy,[13,14] this Task Force recognizes that these data are limited in large part to the short observation period of the currently available clinical trials.

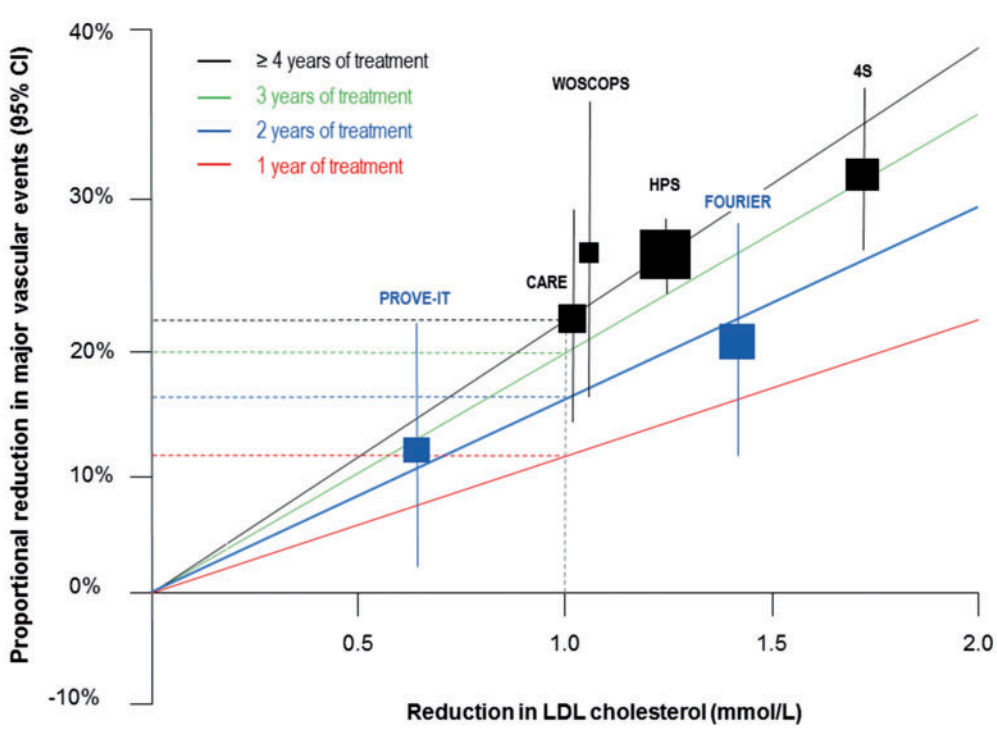


Figure 1 Cholesterol Treatment Trialists' Collaboration regression lines by duration of statin therapy. The lines represent the average expected proportional risk reduction for any given absolute low-density lipoprotein cholesterol (LDL-C) reduction by duration of statin therapy calculated using data from the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis of statin trials. The red line represents the expected clinical benefit of statins after 1 year of treatment, the blue line represents the expected clinical benefit after 2 years of treatment, the green line represents the expected clinical benefit after 3 years of treatment, and the black line represents the expected clinical benefit after 4 or more years of treatment. The lines are calculated from the CTT data (see Panel below). Column 2 of this Panel shows the proportional risk reduction per mmol/L reduction in LDL-C observed during each year of treatment with a statin. The proportional risk reduction per mmol/L reduction in LDL-C for any duration of statin therapy is calculated as an inverse-variance weighted meta-analysis of the effect of statin therapy during each year of treatment up to and including the year of interest (Panel, column 4). The CTT regression line for each duration of therapy is then plotted as a line through this estimate of the proportional risk reduction per mmol/L reduction in LDL-C for each duration of therapy with each line forced to pass through the origin (using the same methods as used by the CTT Collaborators). The black boxes represent the results of trials (CARE, WOSCOPS, HPS, and 4S) that had an average duration of follow-up of 5 years or more, while the blue boxes represent the results of trials (PROVE-IT and FOURIER) that had an average duration of follow-up of approximately 2 years. The figure shows that the point estimate from FOURIER (with a median follow-up of 2.2 years) is superimposable on the blue CTT regression line corresponding to the effect of 2 years of treatment with a statin.

Panel Proportional risk reduction per mmol/L reduction in LDL-C based on CTT Collaboration meta-analysis of statin trials

Year of treatment	CTT hazard ratio (95% CI) per mmol/L reduction in LDL-C during each year of treatment	Cumulative duration of treatment (years)	CTT hazard ratio (95%) per mmol/L reduction in LDL-C for each duration of treatment
0–1	0.88 (0.84–0.93)	1	0.88 (0.84–0.93)
1–2	0.77 (0.73–0.82)	2	0.83 (0.80–0.86)
2–3	0.73 (0.69–0.78)	3	0.80 (0.77–0.83)
3–4	0.72 (0.68–0.77)	4	0.78 (0.76–0.81)
4–5	0.77 (0.72–0.83)	5	0.78 (0.76–0.80)
>5	0.76 (0.69–0.85)	6	0.78 (0.76–0.80)
Overall	0.78 (0.76–0.80)	Mean 5.1	0.78 (0.76–0.80)

CI, confidence interval; CARE, Cholesterol And Recurrent Events; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HPS, Heart Protection Study; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; 4S, Scandinavian Simvastatin Survival Study; WOSCOPS, West of Scotland Coronary Prevention Study.

The remit for this European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Task Force is to consider the impact of this new evidence on recommendations for practical guidance for the use of PCSK9 inhibitors in clinical practice. While the scientific evidence for PCSK9 inhibition reducing nonfatal cardiovascular outcomes in ASCVD patients with LDL-C levels >1.8 mmol/L (70 mg/dL) at baseline is strong,[1] this Task Force also recognizes that the affordability of this treatment varies between countries. What is new to this updated Task Force guidance is inclusion of (i) an appraisal of recent cardiovascular outcomes data for PCSK9 monoclonal antibody therapy in the context of the clinical benefit observed with statin therapy and by duration of therapy; (ii) new clinical decision algorithms, which differentiate three LDL-C thresholds for consideration of PCSK9 inhibitor therapy; (iii) indices of increased cardiovascular risk including imaging relevant for patient risk stratification; and (iv) discussion of remaining gaps in evidence concerning PCSK9 inhibitor therapy. The LDL-C threshold values were based on consideration of absolute cardiovascular risk and the absolute LDL-C reduction required, key determinants of absolute cardiovascular risk reduction as supported by evidence from the CTT Collaboration,[4] as well as the magnitude of LDL-C reduction to be expected with PCSK9 inhibition. Thus, the selected LDL-C thresholds identify patients at high absolute risk with substantially elevated LDL-C levels despite statin with or without ezetimibe therapy, who are likely to derive maximum benefit from the addition of a PCSK9 inhibitor and attain LDL-C goal as a consequence of at least 50% lowering of LDL-C levels. A summary of terms used in this document is provided in *Box 2*.[1,6,7,15–17] This document provides guidance for clinicians in identifying those very high risk patients with substantially elevated LDL-C levels who are likely to benefit most from treatment with a PCSK9 inhibitor, taking into account cost issues.

Defining patients considered for treatment with a proprotein convertase subtilisin/kexin type 9 inhibitor

On the basis of currently available evidence, this Task Force recommends that a PCSK9 inhibitor should be considered in the following patient groups.

- Patients with ASCVD, by definition at very high risk,[6,7] who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, and thus are considered at particularly high risk of an adverse prognosis.
- Patients with ASCVD and at very high risk who do not tolerate appropriate doses of at least three statins and thus have elevated LDL-C levels.
- Familial hypercholesterolaemia patients without clinically diagnosed ASCVD, at high or very high cardiovascular risk, and with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy.

Patients with clinical atherosclerotic cardiovascular disease

As exemplified by FOURIER, patients with documented clinical ASCVD are at very high cardiovascular risk, with an annual absolute risk of a major cardiovascular event >3%.[1,16] The recommended first approach to the management of elevated LDL-C levels in these patients is intense statin therapy.[7] Clinicians should allow sufficient time to achieve the maximum tolerated regimen of statin therapy with concomitant ezetimibe, depending on clinical judgement and local guidance.[18] Since all statins, as well as ezetimibe, will be available as generic treatment before mid-2018, it is reasonable to strive for intense statin therapy with ezetimibe in all ASCVD patients. The Task Force does, however, recognize that while add-on ezetimibe provides a further 19–23% reduction in LDL-C levels,[19,20] this may be insufficient in very high risk patients who typically require more than 50% reduction to attain the recommended LDL-C goal.[7]

In these very high risk patients, this Task Force recommends an LDL-C threshold for consideration of PCSK9 inhibitor treatment of >3.6 mmol/L (140 mg/dL), despite statin with or without ezetimibe therapy or inability to tolerate appropriate doses of at least three statins. Reduction of LDL-C levels by 50% with this treatment offers the possibility of attainment of the guideline-recommended LDL-C goal (<1.8 mmol/L or 70 mg/dL), resulting in >1% annual reduction in absolute cardiovascular risk.[16] The mode of action of a PCSK9 inhibitor is complementary to statin and ezetimibe (*Figure 2*). The Task Force recognizes that the presence of additional indices of risk severity, such as rapidly progressive ASCVD, in particular after an acute coronary syndrome, diabetes mellitus, or complex multivessel or polyvascular atherosclerotic disease, exacerbates absolute risk.[6,21]Therefore, a lower LDL-C threshold is recommended for consideration of PCSK9 inhibition (>2.6 mmol/L or 100 mg/dL) in these patients (*Figure 3*).

It is important to bear in mind that ASCVD patients often have multiple vascular territories affected and thus have poorer outcome, requiring more intense treatment.[22,23] Where available in routine practice, imaging may help to identify those patients with severe and/or extensive ASCVD who are at particularly high risk. Simple non-invasive measures could be used to assess generalized large vessel atherosclerosis. Carotid artery scanning, usually ultrasound assessment, is used for diagnosis of carotid artery plaque (defined as either focal wall thickening > 50% compared with the surrounding vessel wall or a focal region with an intima-media thickness measurement ≥1.5 mm).[6] Coronary calcium score provides a global measure of coronary atherosclerosis and a score of >400 reflects significant and possibly high-risk CAD.[24] Coronary computed tomography angiography (CTA) directly visualizes the extent, severity, location, and composition of coronary atherosclerosis. Various characteristics on coronary CTA may be helpful in identifying high-risk patients (*Box 3*).[25,26] In addition, colour Doppler scanning of carotid vessels and more complex magnetic resonance angiography imaging can be used to confirm ASCVD in the carotid or peripheral arteries, as well as to detect renal artery stenosis.[6]

- A PCSK9 inhibitor should be considered in ASCVD patients with substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, or inability to tolerate appropriate doses of at least three statins, especially if there are additional indices of risk severity, i.e. familial hypercholesterolaemia, multivessel, or polyvascular disease or with rapidly progressive ASCVD (refer to *Figure 3*).

Box 2 Glossary of terms

Term	Explanation
Additional indices of risk severity	Markers of increased cardiovascular risk severity. These are defined for patients with clinical ASCVD as the concomitant presence of FH; diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; severe or extensive ASCVD; or rapid progression of ASCVD (repeated acute coronary syndrome, unplanned coronary revascularizations or ischaemic stroke within 5 years of the event). These definitions are derived from the 6th Joint Societies Guidelines for Prevention of CVD,[6] the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia,[7] and the 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension.[15] For FH patients without clinical ASCVD, additional indices of risk severity are diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; lipoprotein(a) >50 mg/dL; major risk factors such as smoking, marked hypertension; >40 years without treatment; premature ASCVD (<55 years in males and <60 years in females) in first degree relatives; and imaging indicators of increased risk. These definitions are derived from the 6th Joint Societies Guidelines for Prevention of CVD,[6] the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia,[7] the 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension,[15] and the SAFEHEART registry database.[17]
Clinical benefit	This is defined as reduction in major cardiovascular events, the primary endpoint of the FOURIER study,[1] a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. In FOURIER, clinical benefit was attributable to reduction in non-fatal events, largely driven by decreases in nonfatal MI and coronary revascularization.
LDL-C goal	This is the aim of therapeutic intervention, as recommended by the 6th Joint Societies Guidelines for Prevention of CVD,[6] and the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia.[7]
LDL-C threshold	This is the starting LDL-C value on which treatment decisions for a PCSK9 inhibitor are based, in patients on statin with or without ezetimibe treatment.
LDL-C threshold in ASCVD patients	In patients with clinical ASCVD the LDL-C threshold has been defined as > 3.6 mmol/L (140 mg/dL); reduction of LDL-C levels by 50% offers the possibility of attainment of the guideline-recommended LDL-C goal (70 mg/dL),[6,7] and >1% annual reduction in absolute cardiovascular risk.[16] The LDL-C threshold is lower (>2.6 mmol/L or 100 mg/dL) in ASCVD patients with additional indices of risk severity, defined by the 6th Joint Societies Guidelines for Prevention of CVD,[6] and the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia,[7] as the absolute risk of a recurrent event is higher.
LDL-C threshold in FH patients without ASCVD	In FH patients without clinical ASCVD the LDL-C threshold has been defined as > 4.5 mmol/L (180 mg/dL); reduction of LDL-C by at least 50% offers the possibility of attainment of the guideline-recommended LDL-C goal (<2.6 mmol/L or 100 mg/dL). As shown by the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia,[7] and the SAFEHEART Registry,[17] FH patients with additional indices of risk severity are at higher absolute risk. Consequently in these patients, the LDL-C threshold has been set lower (>3.6 mmol/L or 140 mg/dL).
Very high risk	Very high risk patients are defined by the 6th Joint Societies Guidelines for Prevention of CVD,[6] and the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia,[7] as those patients 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, 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.

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; ESH, European Society of Hypertension; FH, familial hypercholesterolaemia; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Familial hypercholesterolaemia patients without clinically diagnosed atherosclerotic cardiovascular disease

In routine clinical practice, FH is typically diagnosed using approaches such as the Dutch Lipid Clinic Network criteria based on familial or personal history of premature ASCVD, clinical signs such as tendon xanthoma or corneal arcus, and elevated LDL-C levels, with or without genetic testing, as recommended in the previous Task Force statement.[12] The elevated cardiovascular risk of undertreated heterozygous FH patients is well recognized,[27–30] with up to eight-fold higher risk in patients with an FH-causative mutation compared with unaffected relatives.[28] Furthermore, despite long-term, high-intensity statin treatment to lower LDL-C levels, asymptomatic FH patients often have evidence of an increased plaque burden in multiple vascular territories.[31] As there are no clinical outcomes studies specifically in FH patients, estimates of absolute cardiovascular risk are based on data from clinical trials and registries such as the Spanish SAFEHEART registry.[17,32] With maximally tolerated statin therapy plus ezetimibe (the recommended treatment in FH),[7,27] annual cardiovascular event rates are estimated at 1%, increasing with the presence of additional risk factors (such as marked hypertension, smoking, lipoprotein(a) >50 mg/dL, and the presence of premature cardiovascular disease in first-degree relatives).[17]

Treatment decisions are currently guided by the LDL-C level and the presence of additional indices of risk severity.[12] Clinicians should

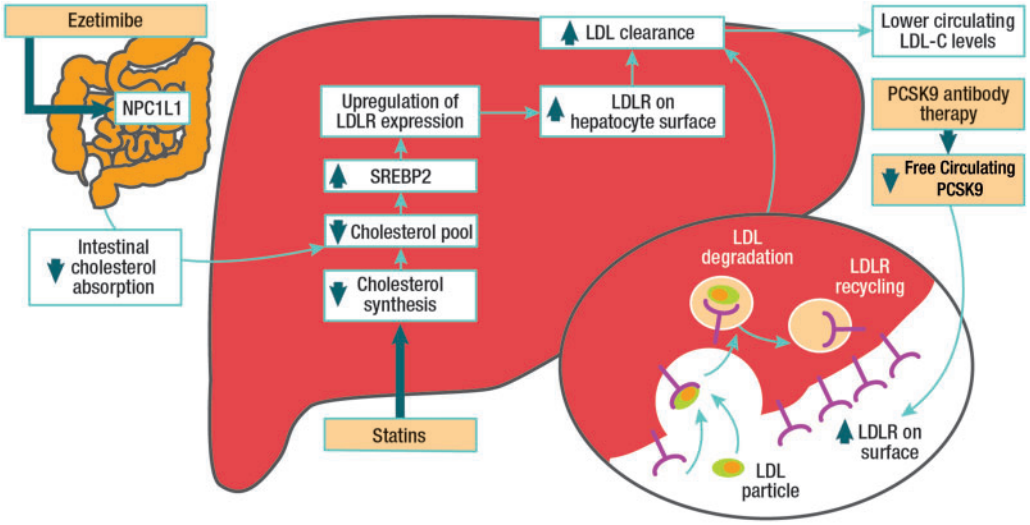


Figure 2 The modes of action of PCSK9 monoclonal antibody therapy, statin and ezetimibe are complementary. The low-density lipoprotein receptor (LDLR) at the hepatocyte surface binds circulating LDL particles; the LDLR-LDL complex is then internalized by endocytosis within clathrin-coated vesicles. Internalization of the LDLR, separation from bound LDL in the endosome complex and subsequent recycling of the LDLR to the plasma membrane is a continuous process (see inset).The level of expression of the *LDLR* gene (and thus LDLR activity) is sensitive to intracellular cholesterol levels; when cellular cholesterol levels are low, for example, as a result of statin-mediated inhibition of hepatic cholesterol synthesis, or as a result of reduced flux of chylomicron cholesterol from the intestine to the liver subsequent to ezetimibe-mediated inhibition of cholesterol absorption through the Niemann Pick C1-like 1 protein (NPC1L1) on the jejunal enterocyte brush border, then *LDLR* expression is upregulated by the sterol regulatory element binding transcription factor 2 (SREBP2). Expression of the PCSK9 gene is equally upregulated by SREBP2. Circulating PCSK9 interacts with and promotes cellular degradation of the LDLR with reduced LDLR recycling to the hepatocyte membrane; this results in reduced availability of LDLR, leading to higher plasma levels of LDL cholesterol (LDL-C). By binding to free circulating PCSK9, PCSK9 monoclonal antibodies prevent the association between PCSK9 and LDLR, resulting in enhanced recycling, increased LDLR availability and reduced plasma LDL-C levels. Thus, inhibition of HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) by statins, inhibition of intestinal cholesterol absorption by ezetimibe, and PCSK9 inhibition by monoclonal antibodies, exhibit complementary mechanisms of action and can be used in combination for highly efficacious lipid lowering therapy.

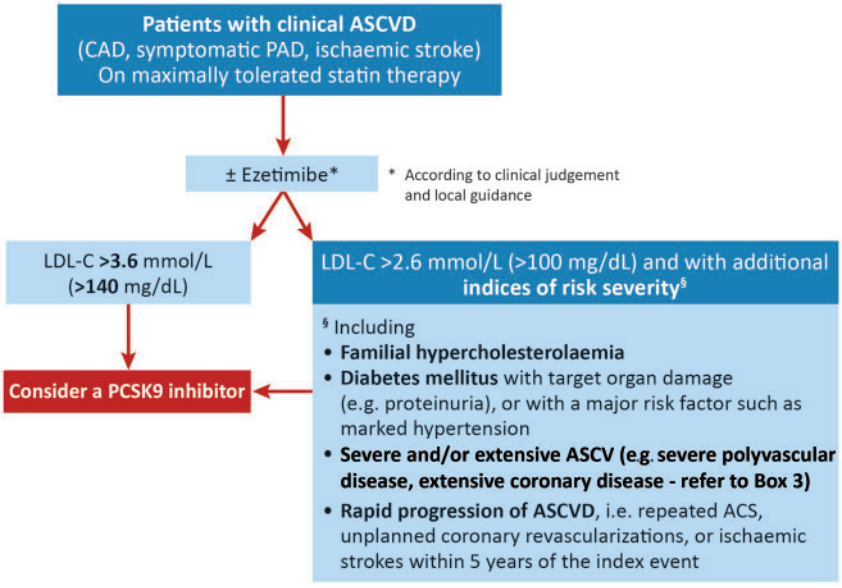


Figure 3 Clinical decision algorithm for the use of a PCSK9 inhibitor in patients with atherosclerotic cardiovascular disease (ASCVD) and with substantially elevated low-density lipoprotein cholesterol (LDL-C) levels despite maximally tolerated statin with or without ezetimibe therapy. Refer to *Box 2* for the rationale for selection of LDL-C thresholds. Note: Marked hypertension is defined by a blood pressure ≥160/100 mmHg, in accordance with 2013 ESH/ESC guidelines for the management of arterial hypertension.[15] The use of add-on ezetimibe is recommended according to clinical judgement and local guidance. ACS, acute coronary syndrome; CAD, coronary artery disease; PAD, peripheral artery disease.

Box 3 Markers of high risk with coronary computed tomography angiography (CTA)

Global high-risk markers on coronary CTA:
- Left main disease
- Proximal LAD disease
- 3-vessel disease

Focal high-risk markers on coronary CTA:
- Stenosis severity: >50% luminal obstruction
- Lesion composition: Mixed or non-calcified (reflecting earlier, unstable atherosclerosis)

CTA, computed tomography angiography; LAD, left anterior descending artery.

make every effort to ensure achievement of the maximally tolerated statin dose regimen plus ezetimibe, in accordance with current guidance.[18] Imaging may also have a role in guiding therapy, as evidence of increased plaque burden with ultrasound evaluation or CTA has been shown to be indicative of premature ASCVD and high risk for cardiovascular events.[33,34]

Taking account of recent evidence from SAFEHEART,[17] this Task Force recommends that an LDL-C threshold of >4.5 mmol/L (180 mg/dL) despite maximally tolerated statin plus ezetimibe identifies patients at high risk likely to derive maximum benefit from PCSK9 inhibition. A lower LDL-C threshold (>3.6 mmol/L or >140 mg/dL) is recommended when patients have additional indices of risk severity, as identified in *Box 2* and in *Figure 4*.[6,17] This approach can reduce the need for lipoprotein apheresis, a costly and invasive procedure which is inconvenient to patients and their caregivers.[35]

As in the previous Task Force document, evolocumab is recommended as an additional therapeutic option to reduce LDL-C levels in patients with homozygous FH, with or without apheresis. Given the mode of action of PCSK9 inhibition, some level of LDL receptor activity is required for efficacy. Consequently, treatment with a PCSK9 inhibitor is not recommended in patients with negative/negative *LDLR* mutations which have LDL receptor activity below 2%, as supported by evidence from the TESLA B and TAUSSIG studies.[12,36,37] With the very high risk of these patients due to the cumulative burden of very high LDL-C levels, most are likely to have already experienced clinical events.

- A PCSK9 inhibitor may be considered in heterozygous FH patients without clinically diagnosed ASCVD with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy.
- The LDL-C threshold for consideration of PCSK9 inhibition is lower if there are additional indices of risk severity (refer to *Figure 4*).

Monitoring low-density lipoprotein cholesterol lowering response

Response to initiation or dose adjustment of lipid lowering treatment (statin or add-on ezetimibe) can be assessed at 4 weeks.[7] As a minimum, LDL-C levels should be monitored, but a comprehensive lipid profile may facilitate better management decisions, given effects on triglycerides (median reduction ~16%) and high-density lipoprotein cholesterol (mean increase ~5%) observed with evolocumab in FOURIER.[1] Failure to attain LDL-C goal may be due to a number of factors including pharmacogenetic effects associated with reduced responsiveness, an inability to tolerate adequate statin doses and lack of adherence.[7,12] Consequently, if the patient is not at LDL-C goal on maximally tolerated statin therapy, adherence should be first checked and the clinician should reinforce the importance of treatment compliance as a determinant of improved cardiovascular outcome.[38] If adherence is shown to be satisfactory, the clinician should consider add-on ezetimibe treatment, in accordance with local guidance. If after 4 weeks the LDL-C lowering response is still inadequate and the patient is adherent with treatment, addition of a PCSK9 inhibitor should be considered (*Figure 5*).

Following a single injection of alirocumab or evolocumab, complete PCSK9 inhibition occurs rapidly and is sustained for 3–4 days with the nadir in LDL-C lowering response at 11–15 days.[39,40] This response is similar for either regimens of alirocumab (75/150 mg every 2 weeks) or evolocumab (140 mg every 2 weeks or 420 mg every month).[41] Information documenting the inter-individual variability in the LDL-C lowering response to PCSK9 inhibition is, as yet, limited. This is a pertinent issue, in the light of evidence from the SPIRE programme, in which the development of antidrug antibodies in a proportion of patients was associated with loss of LDL-C lowering efficacy and no cardiovascular benefit, as opposed to a significant cardiovascular benefit in patients who did not develop antidrug antibodies and had a persistent LDL-C lowering response (see *Box 1*).[3] There are limited data for alirocumab or evolocumab. In an analysis of trial data from more than 4700 patients treated with alirocumab for up to 78 weeks, 1.2% of patients developed persistent antidrug antibodies with the 150 mg 2-weekly regimen and 1.8% with the 75/150 mg 2-weekly regimen.[42] Antidrug antibodies were developed by 0.3% of patients allocated to evolocumab in FOURIER, and 0.3% (4 patients) in the Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER-1) extension study (two patients each who were initially allocated to standard of care or evolocumab, and then received the alternative treatment during long-term follow-up).[1,14] In the absence of extensive documentation of variability in the inter-individual response, this Task Force recommends that clinicians should monitor the LDL-C lowering response to alirocumab or evolocumab as indicated below and in *Figure 5*.

- Monitor the LDL-C lowering response to statin and ezetimibe at 4 weeks and check adherence before considering a PCSK9 inhibitor.
- Assess the LDL-C lowering response to the PCSK9 inhibitor at 2 weeks after first injection of either the monthly or 2-weekly regimen (before the next injection).

Future perspectives and gaps in knowledge

Despite this new evidence from the FOURIER and SPIRE trials, gaps remain in our knowledge regarding the use of PCSK9 inhibition in clinical practice (*Box 4*). The Evaluation of Cardiovascular Outcomes

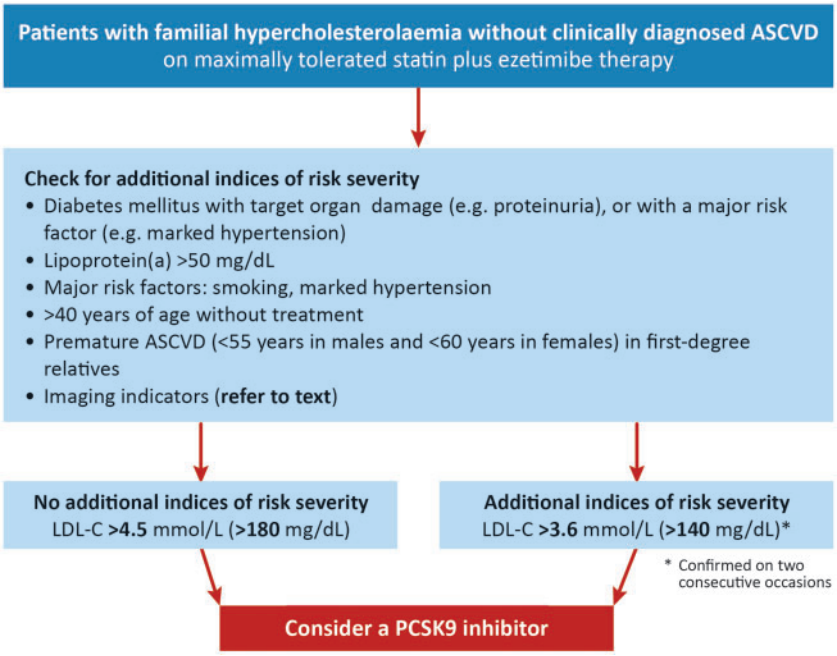


Figure 4 Clinical decision algorithm for the use of a PCSK9 inhibitor in familial hypercholesterolaemia patients without clinically diagnosed atherosclerotic cardiovascular disease (ASCVD) and with substantially elevated low-density lipoprotein cholesterol (LDL-C) levels despite maximally tolerated statin plus ezetimibe therapy. Refer to *Box 2* for the rationale for selection of LDL-C thresholds. Note: Marked hypertension is defined by a blood pressure ≥160/100 mmHg, in accordance with 2013 ESH/ESC guidelines for the management of arterial hypertension.[15]

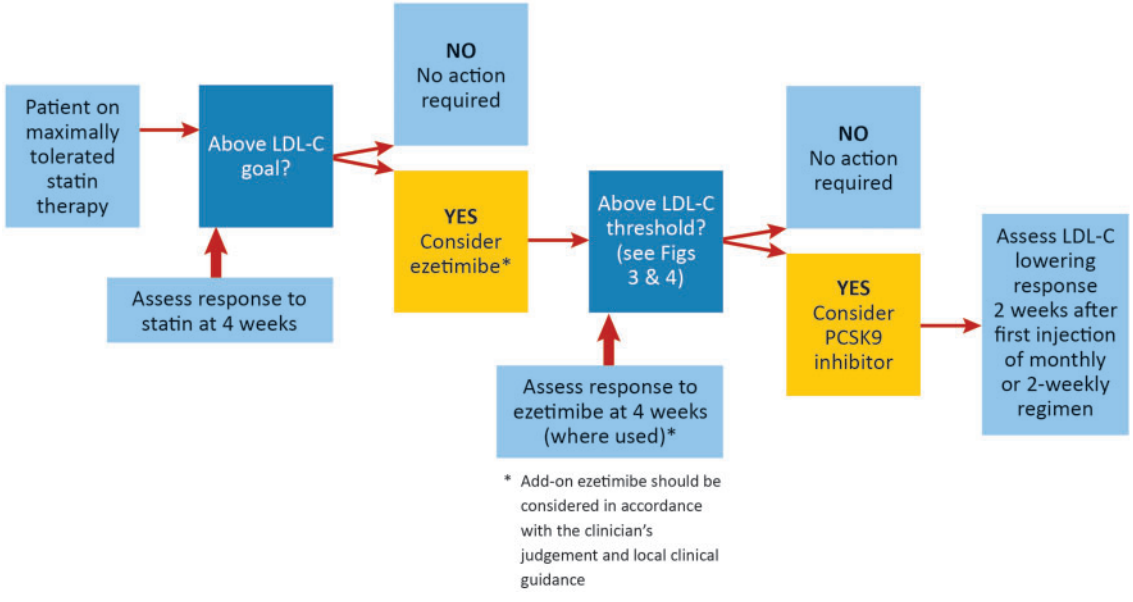


Figure 5 Monitoring the low-density lipoprotein cholesterol (LDL-C) lowering response to statin, ezetimibe and a PCSK9 inhibitor. Note: LDL-C goal is the aim of therapeutic intervention, with LDL-C levels as recommended by the 6th Joint Societies Guidelines for Prevention of Cardiovascular Disease,[6] and the 2016 ESC/EAS Guidelines for Management of Dyslipidaemia.[7] In contrast, LDL-C threshold is the starting LDL-C value on which treatment decisions for a PCSK9 inhibitor are based, in patients on statin plus ezetimibe treatment (*Box 2*).

Box 4 Gaps in knowledge concerning proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy

- Inter-individual variability in low-density lipoprotein cholesterol (LDL-C) lowering response to alirocumab and evolocumab
- Dedicated trials in patients with recent (<1 month) cardiovascular events
- Impact of PCSK9 inhibition in patients with chronic kidney disease (not requiring dialysis)
- Long-term efficacy and safety of PCSK9 inhibitors in clinical use
- Long-term safety of very low LDL-C levels
- Long-term impact of PCSK9 inhibition on disability and cardiovascular mortality
- Long-term evaluation of risk for type 2 diabetes
- Impact of sustained and marked LDL-C lowering to very low levels on plaque composition and stability
- Long-term impact of reduction in elevated lipoprotein(a) with PCSK9 inhibition
- Cost-effectiveness of PCSK9 inhibition added to maximally tolerated statin with or without ezetimibe therapy.

After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trial will provide additional information in patients treated with a PCSK9 inhibitor within 1–12 months (median 2.6 months, interim data) of an acute coronary syndrome.[43,44]

As with all novel treatments, long-term safety remains to be established. To date there are exposure data for up to 4 years' treatment with a PCSK9 inhibitor, including patients with heterozygous FH, predominantly involving a background of concomitant statin therapy.[14,45,46] Potential injection site reactions occurred in <5% of patients, and were mainly of very mild intensity with no evidence of a cumulative effect. When the PCSK9 inhibitor was compared with standard of care (statin with or without ezetimibe), annualized event rates for muscle symptoms, (4.7% vs. 8.5% with standard of care), and new-onset diabetes (2.8% vs. 4.0%, respectively) appear similar; Mendelian randomization studies do, however, indicate a potential risk for diabetes.[5,14] Clearly, there is a need for longer observation to assess potential effects on glucose control. There is no evidence to suggest an increase in the risk of haemorrhagic stroke with the addition of a PCSK9 inhibitor to statin treatment, as the point estimate of evolocumab compared with usual care (statin) reported in FOURIER was similar to that observed in the CTT meta-analysis of statin vs. placebo monotherapy trials.[1,4]

The safety of very low LDL-C levels merits special consideration, given that one in four patients treated with evolocumab in FOURIER attained LDL-C levels less than 0.52 mmol/L or 20 mg/dL.[1] Evidence to date, including patients with rare genetic traits associated with very low LDL-C levels, suggests no detrimental impact on steroid hormone production, enterohepatic circulation of bile acids, or neuronal cell function.[47] Indeed, these LDL-C levels are also consistent with the very low levels observed in newborns which, despite the physiological and developmental demands of infancy, are compatible with normal development.[48]

Irrespective of diabetes status at baseline, very low LDL-C levels (less than 0.65 mmol/L or 25 mg/dL) with alirocumab did not appear to affect mean glycated haemoglobin levels over time. There was also no excess risk for diabetes in patients with LDL-C levels <0.65 mmol/L.[47] Similar findings were reported with evolocumab.[14] Additionally, in patients with diabetes mellitus treated with insulin, there was no change in glycated haemoglobin or fasting plasma glucose during alirocumab treatment.[49] As previously discussed, however, Mendelian randomization studies indicate an increase in lifetime risk for diabetes with carriage of PCSK9 loss-of-function variants.[5] Clearly, this question will have to be evaluated further with additional large-scale trial data over a longer observation period.

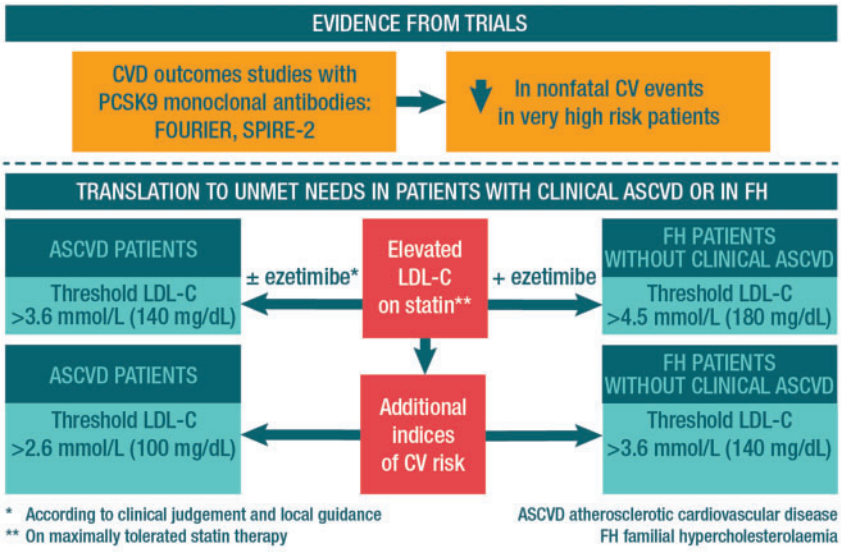
Additionally, data from the ODYSSEY and PROFICIO programmes, FOURIER and 6-year follow-up from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed no increase in adverse events including severe muscle symptoms, liver enzyme elevation, cognitive adverse events, or haemorrhagic stroke with very low LDL-C levels.[1,13,46] The Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects (EBBINGHAUS) trial, a substudy of FOURIER in 1204 patients (mean age 63 years), specifically evaluated effects on cognitive function using a robust well-validated testing platform [Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessment]. This study showed no detriment, even in patients attaining LDL-C levels <0.65 mmol/L (<25 mg/dL).[50] Long-term evaluation, especially in older patients (>75 years), is nonetheless warranted.

- In summary, this Task Force concludes that the available limited evidence for the safety of PCSK9 inhibition, and specifically for very low LDL C levels attained on treatment, is reassuring although further long-term surveillance is clearly indicated.

Health economics

The introduction of innovative therapeutic agents for the treatment of chronic disease states in large patient populations has important health economic implications. Patient groups at very high cardiovascular risk are likely to be a priority for treatment, although access is ultimately determined by the societal willingness-to-pay threshold based on quality-adjusted life-years gained.

Detailed discussion of cost-effectiveness analyses of PCSK9 inhibition in the proposed priority groups is beyond the remit of this Task Force. While some have concluded that the cost of treatment far exceeds the societal willingness - to - pay threshold,[51] others have argued that about one-half of this cost would be saved by reduction in direct and indirect disease-related costs.[52] It is important to bear in mind that absolute cardiovascular risk together with absolute LDL-C levels are the key determinants of the number needed to treat (NNT) to prevent a cardiovascular event. In patients with ASCVD, who have substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy, or inability to tolerate statins, data from FOURIER suggest that adding a PCSK9 inhibitor to lower LDL-C levels by 50% might be expected to reduce the 5-year



Summary Figure. Results of the first cardiovascular outcomes studies with PCSK9 monoclonal antibody therapy (FOURIER with evolocumab and SPIRE-2 with bococizumab) showed that lowering low-density lipoprotein cholesterol (LDL-C), on average by 60%, reduced non-fatal cardiovascular events in very high risk patients on statin therapy (with or without ezetimibe). Translation of these data to the management of very high risk patients with substantially elevated LDL-C levels was based on consideration of absolute cardiovascular risk and the absolute LDL-C reduction required, key determinants of absolute cardiovascular risk reduction, as well as the magnitude of LDL-C reduction to be expected with PCSK9 inhibition. On this basis, the Task Force has identified LDL-C levels (thresholds) for consideration of a PCSK9 inhibitor in very high risk patients not adequately controlled on statin plus ezetimibe, specifically those with clinical atherosclerotic cardiovascular disease (ASCVD), as well as in patients with familial hypercholesterolaemia (FH) without clinical events. Patients with indices of risk severity are at higher risk and therefore the recommended LDL-C thresholds are lower. CVD, cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; SPIRE-2, Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects-2.

NNT to ≤30 in patients with a baseline LDL-C >3.6 mmol/L (140 mg/dL).[1,16] Bearing in mind evidence of a continued or legacy benefit from 5 years treatment with a statin in the West of Scotland Coronary Prevention Study,[53] however, it would be presumptive to model the impact of adding a PCSK9 inhibitor on the NNT until longer-term follow-up data are available to assess the potential of these treatments to modify the trajectory of ASCVD.

Recommendations for cost-effectiveness analysis relating to the judicious use of innovative treatments are also evolving.[54] As highlighted by the EAS Consensus Panel Statement on LDL causality, the impact of therapy on lifetime cardiovascular risk also needs to be considered.[11] Prioritizing the use of a PCSK9 inhibitor in the very high risk patient groups defined in this Task Force statement, with substantially elevated LDL-C levels despite maximally tolerated statin wth or without ezetimibe therapy or inability to tolerate statins, may therefore have the potential to be cost efficient. Obviously, as these patients typically have multiple risk factors beyond elevated LDL-C, incorporation of simple preventive strategies, such as lifestyle interventions, smoking cessation, and blood pressure control, which have additive effects, is essential.

Conclusions

Having appraised the evidence from the first of the cardiovascular outcomes studies with PCSK9 inhibitors, this Task Force concludes that addition of a PCSK9 inhibitor should be considered in patients with ASCVD, and in FH patients without a prior clinical event, who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, or inability to tolerate appropriate doses of at least three statins (*Summary Figure*). Low levels of LDL-C attained on a PCSK9 inhibitor appear to be safe within the observation period of clinical trials performed so far. Prioritizing the use of this efficacious therapy in these patient groups may help reduce cardiovascular outcomes and the impact of the associated physical and/or psychological disability.

Funding

Funding for travel to participate in Task Force meetings was provided by the European Atherosclerosis Society.

Conflict of interest: J.J.B. has received unrestricted research grants from Medtronic, Biotronik, Boston Scientific, and Edwards Lifesciences. Reimbursement is made to the Department of Cardiology, Leiden University Medical Center, The Netherlands. J.J.F.B. has received honoraria for lectures from the European Atherosclerosis Society and Amgen. J.B. has received honoraria for consultancy and lectures from Amgen, AstraZeneca, Eli Lilly, Merck, Novo-Nordisk, Pfizer, and Regeneron/Sanofi. A.L.C. has received research grants to his institution from Amgen, AstraZeneca, Merck, Regeneron/Sanofi, and Sigma Tau, and honoraria for advisory boards, consultancy or speaker bureau from Abbott, Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Merck/MSD, Mylan, Pfizer, Rottapharm and Sanofi-Regeneron. M.J.C. has received research grants

from MSD, Kowa, Pfizer, and Randox, and honoraria for consultancy/lectures from Amgen, Kowa, Merck, Sanofi, Servier, Regeneron and Unilever. M.F. has received honoraria for consultancy from Amgen, Merck, Sanofi/Regeneron, Abbott, Eli Lilly, Pfizer, Astra Zeneca, Roche, Kowa, Servier, Mylan and Akcea/Ionis. B.A.F. has received research grants from Merck, Amgen and Esperion Therapeutics; and honoraria for lectures, consulting and/or advisory board membership from Merck, Amgen, Esperion, Ionis, and the American College of Cardiology. S.G. has received grants for educational events from Sanofi, Amgen and Berlin Chemie, honoraria for lectures and/or advisory boards from Sanofi and Amgen, and a travel grant from Amgen. I.G. has received honoraria for lectures and/or consultancy from MSD, Pfizer and Amgen. D.F.G. has received institutional research support and travel reimbursement from Pfizer. K.G.H. has received honoraria for consultancy from Amgen, Genzyme, Merck, Pfizer, Roche and Sanofi-Regeneron. U.L. has received honoraria for lectures and/or advisory boards from Amgen, Medicines Company, Berlin Chemie, Sanofi and Abbott. T.F.L. has received honoraria from Amgen and Sanofi and research grants from Amgen and AstraZeneca. M.F.P. has received honoraria for speaker bureau from Amgen. K.K.R. has received research grants from Sanofi, Regeneron, Pfizer, Amgen and MSD, and honoraria for lectures, advisory boards or as a steering committee member from Sanofi, Amgen, Regeneron, Lilly, Medicines Company, AstraZeneca, Pfizer, Kowa, IONIS, Esperion, Takeda, and Boehringer Ingelheim. E.S.S. has received reimbursement to his institution for honoraria for lectures/advisory boards from Amgen, Merck, IONIS, Chiesi, Sanofi-Regeneron, and Athera. JKS has received an honorarium for consultancy from Aegerion. L.T. has received research funding, and/or honoraria for advisory boards, consultancy or speaker bureau from Abbott, Actelion, Amgen, AstraZeneca, Bayer, Merck, Mylan, Novartis, Pfizer, Recordati, Sanofi-Regeneron and Servier. O.W. has received honoraria for lectures from Sanofi, Amgen, MSD, and AstraZeneca. S.W. has received research grants from Biotronik, Boston Scientific, Bracco Pharmaceutical, Edwards Lifesciences, Medtronic, Terumo Inc, St Jude Medical, and honoraria for consultancy from Boston Scientific and Daiichi Sankyo. J.L.Z. has received honoraria for speakers bureau from Amgen and Sanofi. P.A., and F.P., report no conflict of interest.

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