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**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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## **2017 Update of ESC/EAS Task Force on Practical Clinical Guidance for PCSK9 inhibition in patients with ASCVD or in familial hypercholesterolaemia**

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## Introduction

The first data from cardiovascular outcomes trials with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have now been reported.<sup>1,2</sup> The FOURIER trial (with evolocumab, a fully human monoclonal PCSK9 antibody) in 27,564 patients with atherosclerotic cardiovascular disease (ASCVD) was completed.<sup>1</sup> The SPIRE-1 and 2 trials were, however, stopped early following termination of bococizumab due to effects specific to this humanized antibody (**Box 1**).<sup>2,3</sup> In FOURIER, lowering of low-density lipoprotein 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% versus 11.3% on placebo over 2.2 years, relative risk reduction of 15%,  $p < 0.001$ ). The clinical benefit of PCSK9 inhibitor treatment was largely consistent across all major patient subgroups, including age, sex, and type of clinical presentation of ASCVD (coronary artery disease with history of myocardial infarction [MI], ischaemic stroke and symptomatic peripheral arterial disease PAD)), and accrued over time.<sup>1</sup> The observed benefit in FOURIER was shown to fall below the Cholesterol Treatment Trialists' Collaboration (CTTC) regression line for cardiovascular benefit per mmol/L reduction in LDL-C, based on average response over 5 years on statin therapy. When compared for the same duration of treatment, however, the results were superimposable with that observed with statin therapy (**Figure 1**).<sup>4,5</sup> Evidence from studies involving variants in the genes encoding PCSK9 and HMGCoA reductase provides further support for the concept that a similar risk reduction per unit LDL-C reduction is to be expected.<sup>6</sup>

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 burden. In all trials, patients were at very high risk as defined by the 6<sup>th</sup> Joint Task Force guidelines,<sup>7</sup> with a history of clinical ASCVD (either MI, stroke or symptomatic PAD) and additional cardiovascular risk factors, including clinically diagnosed familial hypercholesterolaemia (FH) (SPIRE trials).<sup>1,2</sup> Patients had a substantial residual LDL-C burden despite maximally tolerated lipid lowering therapy (most were receiving high to moderate intensity statin). In SPIRE-2, patients had a higher residual LDL-C burden (mean LDL-C at baseline 3.4 mmol/L or 133 mg/dl versus 2.4 mmol/l or ~90 mg/dl in FOURIER and SPIRE-1).<sup>1,2</sup> Thus, despite progressive attenuation of LDL-C lowering with bococizumab due to the formation of neutralizing antibodies,<sup>3</sup> there was significant clinical benefit in SPIRE-2 within 12 months (absolute event rates for major cardiovascular events 3.32% versus 4.19% on placebo, relative risk reduction of 21%,  $p = 0.02$ ). In contrast, SPIRE-1 with lower residual LDL-C burden and shorter duration of treatment (7 months), did not show significant differences in cardiovascular events.<sup>2</sup>

Two key issues have been raised regarding FOURIER. The first issue relates to the rather short duration of the trial. It is important to emphasize that the trial was event- and not time-driven.

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 1,630 key secondary end points (a composite of cardiovascular death, MI or stroke), which would provide 90% power to detect a relative reduction of  $\geq 15\%$  for this endpoint.<sup>8</sup> In reality, the observed event rate was higher and therefore the trial was completed after a median of 2.2 years after 1,829 key secondary endpoints had occurred.<sup>1</sup>

The second issue relates to the lack of significant benefit on cardiovascular and all-cause mortality. Inspection of the FOURIER data shows that the predominant effect of PCSK9 inhibition was prevention of non-fatal cardiovascular events, including coronary revascularization; cardiovascular mortality was mainly attributed to reasons other than MI or stroke.<sup>1</sup> These findings are consistent with trials evaluating high- versus low-dose statin therapy, none of which showed reduction in cardiovascular death. Added to this, a meta-analysis of four high- versus low-dose statin trials indicated a reduction predominantly in non-fatal cardiovascular events.<sup>9</sup> Moreover, while reduced mortality was observed in earlier statin trials (e.g. 4S trial)<sup>10</sup>, this was only seen after prolonged treatment and not after 2.2 years against a background of current evidence-based therapy as in FOURIER. It will therefore be of great interest to see whether longer follow-up of patients treated with a PCSK9 inhibitor provides evidence of reduced mortality.

Together with definitive evidence that LDL is causal for ASCVD,<sup>11</sup> 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.<sup>12</sup> 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 is 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,<sup>13,14</sup> this Task Force recognizes that these data are limited in large part to the observation period of the clinical trials. Given the current high treatment cost, an acceptable cost versus benefit ratio will only be achieved in very high risk patients with substantial residual LDL-C burden, where the relative risk reduction with PCSK9 inhibition can be translated into a significant absolute risk reduction over the trajectory of ASCVD. The remit for this ESC/EAS Task Force, therefore, is to consider the impact of this new evidence on recommendations for practical guidance for the use of PCSK9 inhibitors in clinical practice.

### **Defining patients considered for treatment with a PCSK9 inhibitor**

On the basis of 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,<sup>7</sup> who have a substantial residual LDL-C burden despite maximally tolerated statin  $\pm$  ezetimibe therapy, and thus are

considered at particularly high risk of an adverse prognosis. In addition, patients with ASCVD who do not tolerate appropriate doses of at least three statins ( $\pm$  ezetimibe) and thus have a high residual LDL-C burden, should also be considered.

- In FH patients without clinically diagnosed ASCVD, at high or very high cardiovascular risk, and with substantial residual LDL-C burden despite maximally tolerated statin + ezetimibe therapy.

#### *Patients with ASCVD*

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  $>3\%$ .<sup>7,15</sup> The recommended first approach to management of elevated LDL-C levels in these patients is intense statin therapy.<sup>16</sup> Clinicians should allow sufficient time to achieve the maximum tolerated regimen of statin therapy;<sup>17</sup> FOURIER illustrates this in practice, with 69.3% of patients on high intensity statin and only 30.4% on moderate intensity statin.<sup>1</sup> While add-on ezetimibe provides a further 19-23% reduction in LDL-C levels,<sup>18,19</sup> this may be insufficient in very high risk patients who typically require  $>50\%$  reduction to attain the recommended LDL-C goal.

In these very high risk patients with substantial residual LDL-C burden ( $>3.6$  mmol/L or 140 mg/dl) despite statin  $\pm$  ezetimibe therapy or inability to tolerate appropriate doses of at least three statins ( $\pm$  ezetimibe), clinicians should consider addition of a PCSK9 inhibitor. Lowering LDL-C levels by at least 50% with this therapy will result in  $>1\%$  annual reduction in absolute cardiovascular risk.<sup>15</sup> This 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.<sup>7,20</sup> 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 2**). Where available in routine practice, imaging may help to identify patients with complex multivessel ASCVD who are at particularly high risk (**Box 2**). Simple non-invasive measures could be used, for example in a patient with MI detection of carotid disease using Doppler scanning, or PAD using Ankle brachial pressure index measurement could easily confirm or refute multivessel disease and the need for aggressive management.

*A PCSK9 inhibitor should be considered in ASCVD patients with substantial residual LDL-C burden despite maximally tolerated statin  $\pm$  ezetimibe therapy, or inability to tolerate appropriate doses of at least three statins ( $\pm$  ezetimibe), especially if there are additional indices of risk severity, i.e. FH, multivessel or polyvascular disease or with rapidly progressive ASCVD.*

### *FH patients without clinically diagnosed ASCVD*

In routine clinical practice, FH is typically diagnosed using approaches such as the Dutch Lipid Clinic Network criteria, with or without genetic testing, as recommended in the previous Task Force statement.<sup>12</sup> The elevated cardiovascular risk of undertreated heterozygous FH patients is well recognized.<sup>21-24</sup> As shown by the SAFEHEART registry, this risk increases >8-fold in patients with an FH-causative mutation compared with unaffected relatives,<sup>22</sup> and by 3-4 fold in patients with an FH-causative mutation and LDL-C levels >4.9 mmol/L (>190 mg/dl).<sup>25,26</sup> 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.<sup>25,27</sup> As there are no clinical outcomes studies in FH patients, estimates of absolute cardiovascular risk are based on data from clinical trials and registries such as SAFEHEART.<sup>28,29</sup> With maximally tolerated statin + ezetimibe therapy (the recommended treatment in FH)<sup>16,21</sup>, annual cardiovascular event rates are estimated at 1%, increasing with the presence of additional risk factors (such as marked hypertension, smoking, and lipoprotein(a) >50 mg/dl).<sup>28</sup>

Treatment decisions are currently guided by the LDL-C level and the presence of additional indices of risk severity.<sup>12</sup> Clinicians should make every effort to ensure achievement of the maximally tolerated statin dose regimen, in accordance with current guidance.<sup>17</sup> Imaging may also have a role in guiding therapy, as evidence of increased plaque burden with ultrasound evaluation or computed tomographic angiography has been shown to be indicative of premature ASCVD and high risk for cardiovascular events.<sup>30</sup>

Given their high absolute risk, FH patients with substantial residual LDL-C burden on maximally tolerated statin + ezetimibe therapy require at least 50% lowering of LDL-C levels to optimally impact cardiovascular risk. Taking account of recent evidence from SAFEHEART,<sup>28</sup> this Task Force recommends that clinicians should consider a PCSK9 inhibitor in FH patients without clinically diagnosed ASCVD, including young FH patients, when LDL-C levels are >4.5 mmol/L (>180 mg/dl) despite maximally tolerated statin + ezetimibe therapy. A lower LDL-C threshold (>4.0 mmol/L or >160 mg/dl) is recommended when patients have additional indices of risk severity (**Figure 3**). This approach can reduce the need for lipoprotein apheresis, a costly and invasive procedure which is rather inconvenient to patients and their carers.<sup>31</sup>

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, except in those with confirmed negative/negative *LDLR* mutations.<sup>12,32</sup> 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 clinically diagnosed ASCVD if there is substantial residual LDL-C burden despite maximally tolerated statin + ezetimibe therapy.*
- *The LDL-C threshold for consideration of PCSK9 inhibition is lower if there are additional indices of risk severity (refer to fig 3).*

#### *Monitoring LDL-C lowering response*

Response to initiation or dose adjustment of lipid lowering treatment (statin or add-on ezetimibe) can be assessed at 4-8 weeks.<sup>16</sup> As a minimum, LDL-C levels should be monitored, but a comprehensive lipid profile may facilitate better management decisions. 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.<sup>12,16</sup> 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.<sup>33</sup> If adherence is shown to be satisfactory, the clinician should consider add-on ezetimibe treatment. If after 4-8 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 4**).

Following a single injection of alirocumab or evolocumab, complete PCSK9 inhibition occurs within 3-4 days with the nadir in LDL-C lowering response at 11-15 days.<sup>34,35</sup> This response is similar for either regimens of alirocumab or evolocumab.<sup>36</sup> Information documenting the inter-individual variability in the LDL-C lowering response to PCSK9 inhibition is, however, limited. This is a pertinent issue, in the light of evidence from the SPIRE programme (see **Box 1**).<sup>3</sup> In an analysis of trial data from more than 4,700 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.<sup>37</sup> Antidrug antibodies were developed by 0.3% of patients allocated to evolocumab in FOURIER, and 0.3% (4 patients) in the open-label OSLER-1 extension study (2 patients each who were initially allocated to standard of care or evolocumab, and then received the alternative treatment during long-term follow-up).<sup>1,14</sup> 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 4**.

- *Monitor the LDL-C lowering response to statin ± ezetimibe at 4-8 weeks and check adherence before considering a PCSK9 inhibitor.*
- *Assess the LDL-C lowering response to the PCSK9 inhibitor at 10-14 days after first injection of either the monthly or 2-weekly regimen.*

#### **Future perspectives and gaps in knowledge**



Despite this new evidence from FOURIER and, to a lesser degree SPIRE, gaps remain in our knowledge regarding the use of PCSK9 inhibition in clinical practice (**Box 3**). ODYSSEY Outcomes 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.<sup>38,39</sup>

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.<sup>14,40,41</sup> Potential injection site reactions occurred in <5% of patients, and were mainly of very mild intensity with no evidence of a cumulative effect. Compared with standard of care (statin ±ezetimibe), the incidences of muscle-related symptoms, especially important in PAD, (8% versus 9%), and new-onset diabetes (4.1% versus 4.3%) on a PCSK9 inhibitor appear similar.<sup>14</sup> There is no evidence for an increase in the risk of haemorrhagic stroke, although the point estimate reported in FOURIER was similar to that observed in the CTT meta-analysis.<sup>1,4</sup>

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.<sup>1</sup> 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, and neuronal cell function.<sup>42</sup> Additionally, data from the ODYSSEY programme, FOURIER and 6-year follow-up from 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.<sup>1,13, 41</sup> The EBBINGHAUS trial, a substudy of FOURIER in 1,204 patients (mean age 63 years), specifically evaluated effects on neurocognitive 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).<sup>43</sup> Long-term evaluation, especially in older patients (>75 years), is nonetheless warranted.

*In summary, this Task Force concludes that available 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,<sup>44</sup> others have argued that about one-half of this cost would be saved by reduction in direct and indirect disease-related costs.<sup>45</sup> It is important to bear in mind that absolute cardiovascular risk and absolute LDL-C levels are the key determinants of the number needed to treat (NNT) to prevent a cardiovascular event. In patients with ASCVD, and in FH patients without a prior event, who have a substantial LDL-C burden despite maximally tolerated statin ± 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 NNT to  $\leq 30$ .<sup>1,15</sup> Bearing in mind evidence from WOSCOPS of a legacy benefit from statin therapy,<sup>46</sup> 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.<sup>47</sup> As highlighted by the European Atherosclerosis Society Consensus Panel Statement on LDL causality, the impact of therapy on lifetime cardiovascular risk needs to be considered, as in a recent analysis.<sup>11,48</sup> Prioritizing the use of a PCSK9 inhibitor in the very high risk patient groups defined in this Task Force statement, with a substantial residual LDL-C burden despite maximally tolerated statin ± 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 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 a substantial residual LDL-C burden despite maximally tolerated statin ± ezetimibe therapy, or inability to tolerate appropriate doses of at least three statins (± ezetimibe). Low levels of LDL-C attained on a PCSK9 inhibitor appear to be safe within the observation period of clinical trials; indeed, these LDL-C levels are comparable with those in newborns, even with the elevated physiological demands of infancy.<sup>49</sup> Prioritizing the use of this innovative therapy in these patient groups may also confer societal benefit when taking into account the impact of this treatment on lifetime cardiovascular risk.

## **Funding and disclosure statements**

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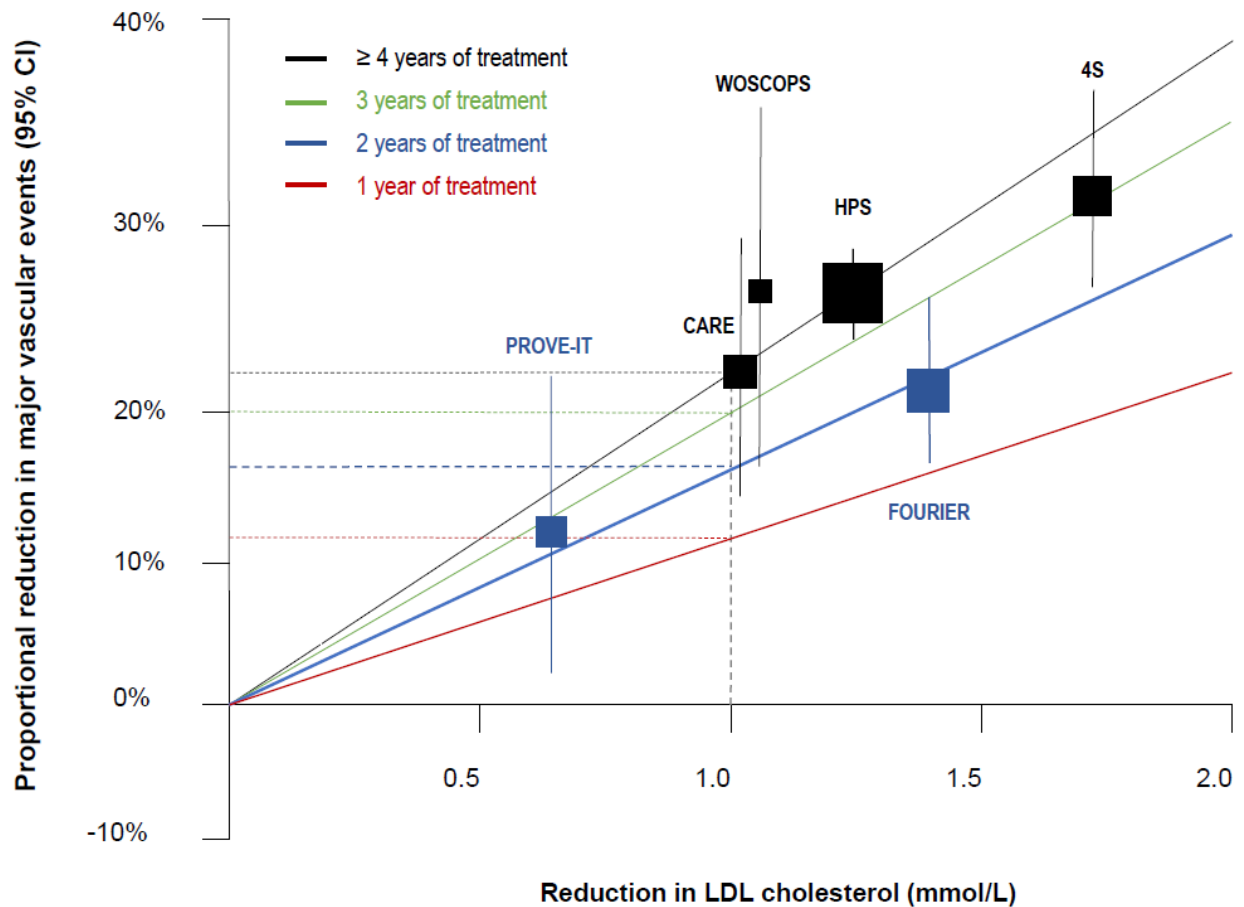
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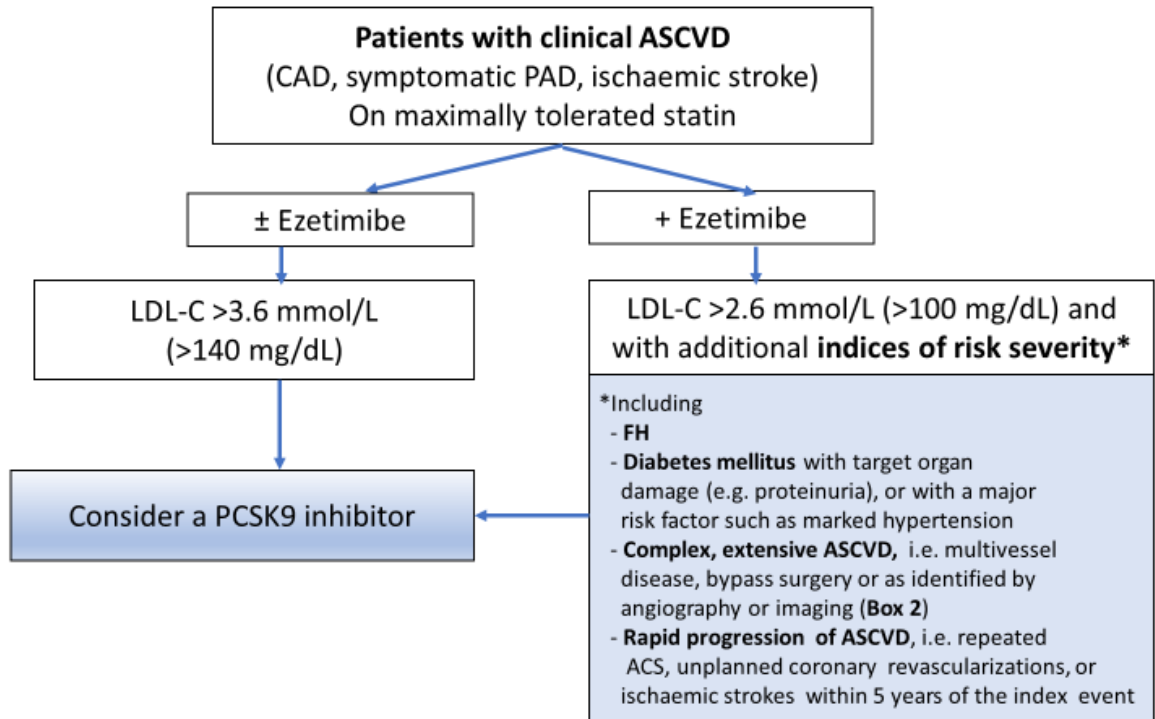
**Figure 1.** Comparison of the results of FOURIER and statin trials by duration of therapy.

The black line is the Cholesterol Treatment Trialists' regression line showing average effect of 5.1 years of treatment with a statin on the risk of major vascular events. It is calculated as a meta-analysis of the effect of statin therapy per mmol/L reduction in LDL-C during each year of treatment (column 2 of the Table). The average effect of treatment with a statin on the risk of major vascular events for a given duration of therapy is calculated by meta-analysing the effect of statin therapy during each year of treatment up to and including the duration of interest (as shown in column 4 of the Table). The figure shows that the point estimate from FOURIER (at a median of 2.2 years) is superimposable on the CTT regression line corresponding to the effect of 2 years of treatment with a statin. The CARE, WOSCOPS, HPS and 4S trials had a median duration of therapy of 5 years (and are shown in black), while the PROVE-IT and FOURIER trials had a median duration of therapy of approximately 2 years (and are shown in blue).

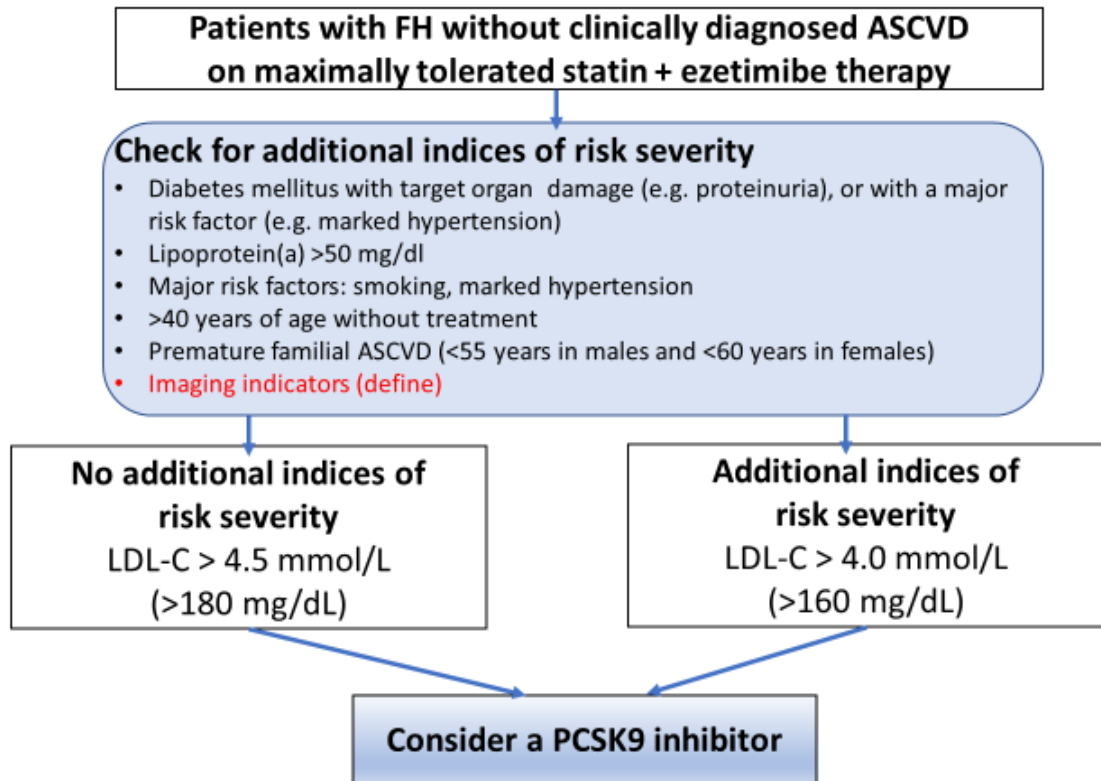


Year of treatment	HR (95% CI) per mmol/L reduction in LDL-C during each year of treatment in CTT	Cumulative duration of Treatment (years)	HR (95%) per mmol/L reduction in LDL-C for cumulative duration of statin treatment in CTT
<b>0-1</b>	0.88 (0.84-0.93)	<b>1</b>	0.88 (0.84-0.93)
<b>1-2</b>	0.77 (0.73-0.82)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

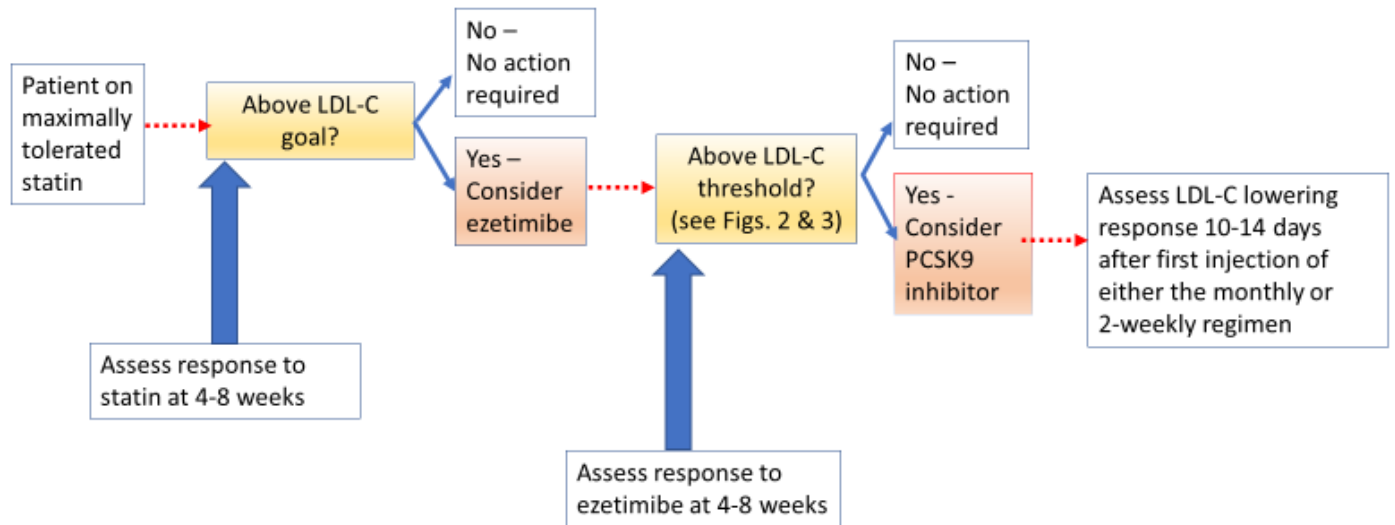
**Figure 2.** Clinical decision algorithm for the use of a PCSK9 inhibitor in patients with ASCVD and with substantial residual LDL-C burden despite maximally tolerated statin ± ezetimibe therapy



**Figure 3.** Clinical decision algorithm for the use of a PCSK9 inhibitor in FH patients without clinically diagnosed ASCVD and with substantial residual LDL-C burden despite maximally tolerated statin + ezetimibe therapy



**Figure 4.** Monitoring response to statin, ezetimibe and a PCSK9 inhibitor in patients with ASCVD or FH patients without clinically diagnosed ASCVD



### Box 1. Key reasons for termination of bococizumab

The development of bococizumab was discontinued by Pfizer in late 2016.\* The key reasons for this were a high level of immunogenicity and wide variability in the 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 anti-drug 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 LDL binding region of bococizumab. 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 anti-drug 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.

\* Press release Tuesday, 1st November 2016. Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor.

[http://www.pfizer.com/news/press-release/press-release-detail/pfizer\\_discontinues\\_global\\_development\\_of\\_bococizumab\\_its\\_investigational\\_pcsk9\\_inhibitor](http://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor)

### Box 2. Role of imaging in identifying patients with complex, extensive ASCVD

ASCVD is often asymptomatic, but yet is associated with CV events and mortality. Thus a patient who presents with MI, is likely to have some element of AS elsewhere eg carotid vessels, peripheral vessels. Outcome is poorer in those with multisystem ASCVD, and treatment should be aggressive in these cases. Detection of multisystem disease can be enhanced by simple non-invasive tests

- Ankle Brachial Pressure Index measurement in PAD. A ratio of <0.9 is diagnostic of PAD
- Colour Doppler scanning of carotid vessels allows degree of stenosis (if any), plaque type and blood flow to be assessed.
- More complex Magnetic Resonance Angiography (MRA) imaging confirms ASCVD in these 2 regions and also can be used to detect renal artery stenosis, again lesions associated with a poorer prognosis in terms of CV Events

**Box 3.** Gaps in knowledge

- Variability in 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
- 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 ± ezetimibe therapy