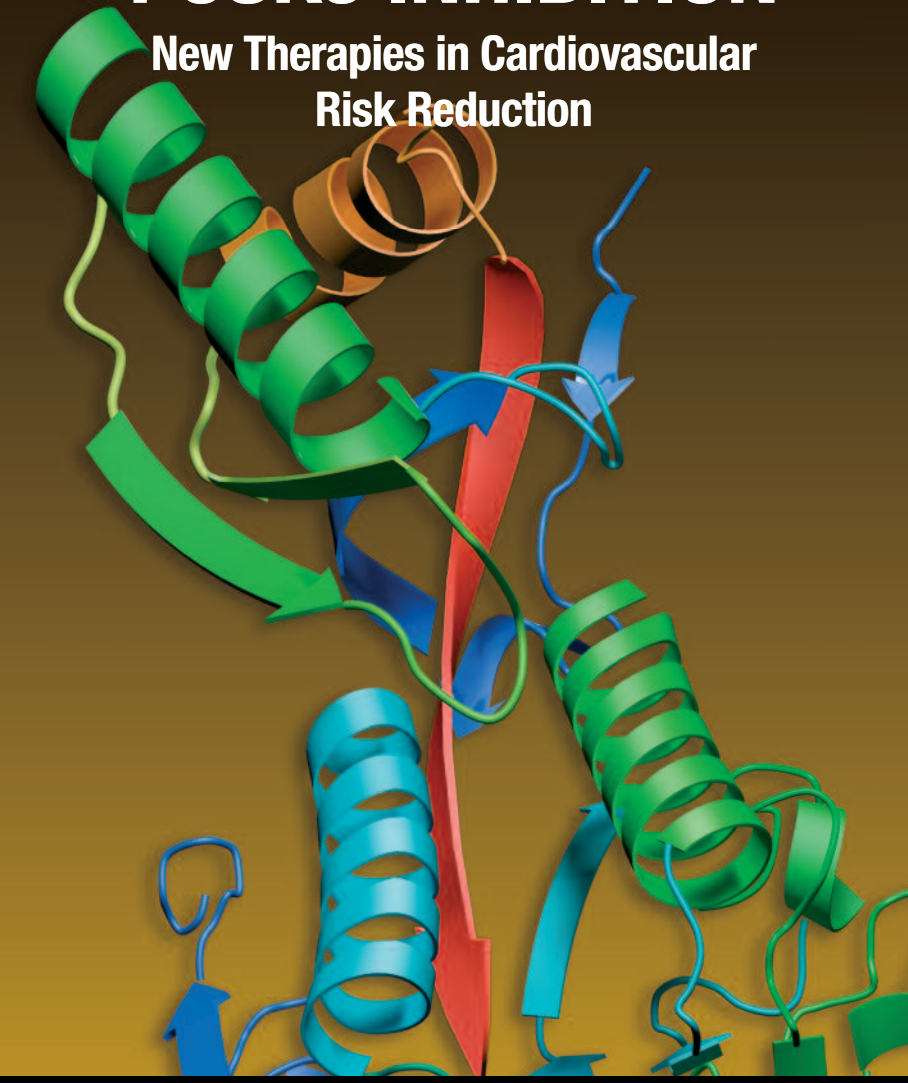
UPDATED SECOND EDITION

INTRODUCTORY GUIDE

PCSK9 INHIBITION

New Therapies in Cardiovascular Risk Reduction



PCSK9FORUM
EDUCATION AND RESEARCH

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Why we wrote this Handbook

Elevated LDL cholesterol remains an important driver of atherosclerotic vascular disease, a primary cause of premature cardiovascular mortality and morbidity. An exciting new treatment for marked reduction of LDL cholesterol levels is now on the horizon: the PCSK9 inhibitors, a new class of biologics. This Handbook seeks to summarise the rationale and current evidence base supporting the use of PCSK9 inhibition for the improvement of long-term cardiovascular outcomes.

Many randomised, controlled trials have proven the utility of statins in reducing LDL cholesterol and cardiovascular disease during the last 25 years, but we need to go beyond the limitations of statins. The next generation of treatments to control elevated LDL cholesterol must address the substantial residual cardiovascular risk remaining after even intensive statin-based therapy, the unpredictability of the response to a statin in an individual patient, and the frequent occurrence of statin intolerance.

The elucidation of the role of PCSK9 in the control of LDL metabolism launched worldwide research efforts that culminated in the approval in 2015 of the first novel agents targeting PCSK9. This Handbook summarises the current state of knowledge on this groundbreaking new therapy.

1. Continuing burden of death and disability from high LDL cholesterol

Circulatory diseases remain the leading cause of death in the developed world

Recent (2013) data from the USA showed that about one death in four occurred as a result of diseases of the heart or cerebral circulation, with the majority due to coronary heart disease (CHD) (Figure 1.1).[1] In Europe, 1.8 million deaths occurred each year as a result of coronary heart disease, stroke or other cardiovascular disease, accounting for about two-fifths of all deaths (data for 2004–2010).[2]

Improvements in the diagnosis and management of cardiovascular risk factors, heart disease and stroke have led to an encouraging reduction in death rates from atherothrombotic disease in recent decades.[1,3] Nevertheless, the burden of mortality from cardiovascular or cerebrovascular events remains unacceptably high. Cardiovascular disease not only reduces the duration of life, but also its quality: even survivors of a myocardial infarction or stroke face a high risk of recurrent events, and often face years of disability or other long-term adverse consequences, such as congestive heart failure.

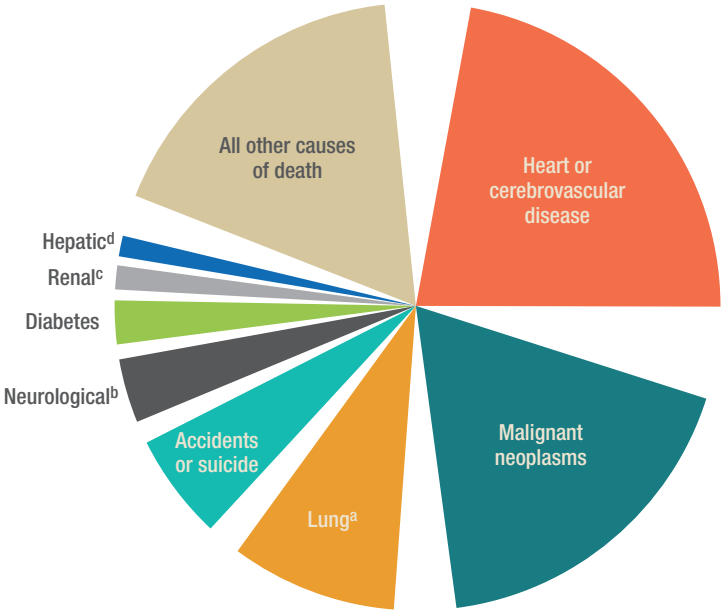
We need to intervene in the progression of cardiovascular risk to prevent atherosclerotic damage to the vasculature that leads to clinical cardiovascular disease. PCSK9 inhibition is an exciting new approach to the management of cardiovascular risk that will reach the clinic in the coming years, with major potential to reduce the burden of atherosclerotic vascular disease.

LDL cholesterol remains the key target of lipid-modifying therapy

European and US guidelines continue to identify LDL-C as the main target for lipid-modifying therapy, with the aim of improving long-term cardiovascular prognosis (Table 1.1).[4,5]

Overwhelming evidence, summarised in these guidelines, continues to identify elevated LDL cholesterol as a clinically important source of accelerated atherosclerosis and elevated cardiovascular risk.[6] Recently, the technique of Mendelian randomisation was used to study 312,231 subjects

Figure 1.1. Burden of mortality (age-adjusted mortality rates) due to diseases of the heart or of the cerebrovascular circulation (USA, 2013)



Drawn from data presented by the Centers for Disease Control and Prevention (2015). [a]Chronic lower respiratory disease, influenza, pneumonia, or pneumonitis; [b]Parkinson's disease or Alzheimer's disease; [c]nephritis, nephrotic syndrome, nephrosis; [d]chronic liver disease, cirrhosis.

with or without polymorphisms of genes which control cholesterol metabolism and which confer naturally lower levels of LDL cholesterol.[7] The control group (without these polymorphisms) received statins during adulthood over a short period (about 5 years) to achieve similar reductions in LDL cholesterol. The reduction in the risk of CHD for each 1 mmol/L lifelong reduction in LDL cholesterol was 54% greater for the group with *vs.* without the polymorphisms. Thus, lowering elevated LDL cholesterol early in life is more effective than intervention with similar lipid-lowering efficacy applied later in life. Importantly, the impact on cardiovascular risk was independent of the mechanism of lowering LDL cholesterol.[8]

Familial hypercholesterolaemia and the lifetime burden of elevated LDL cholesterol

Familial hypercholesterolaemia is the most common genetic condition known to medical science, with a population prevalence that may be as high as

Table 1.1. Current focus on LDL-C as the main target for lipid-modifying therapy for reduction of cardiovascular risk

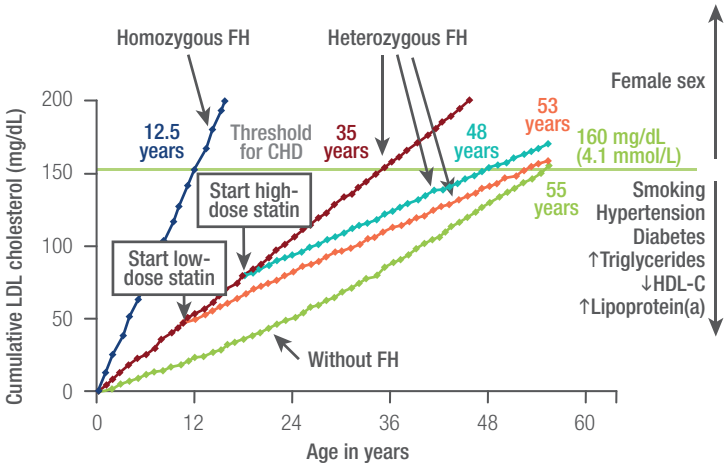
European guideline: European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)[4]	"LDL-C is recommended as the primary target for treatment. TC should be considered as the treatment target if other analyses are not available."
US guideline: American College of Cardiology (ACC) and American Heart Association (AHA)[5]	"The members of the Expert Panel acknowledge the important contributions arising from decades of genetic and biochemical studies, observational epidemiologic and ecological studies, and in vitro and animal experiments that associated higher low-density lipoprotein cholesterol (LDL–C) levels with greater ASCVD risk. These studies provided the rationale for RCTs, which in turn demonstrated that lowering cholesterol levels reduced ASCVD events and thereby established a central, causal role of atherogenic cholesterol-containing lipoprotein particles, particularly LDL, in the genesis of CHD and ASCVD."

ASCVD: atherosclerotic cardiovascular disease; LDL: low-density lipoprotein; RCT: randomised, controlled trial; TC: total cholesterol.

about 1:200.[9,10] Patients with familial hypercholesterolaemia have severely elevated LDL cholesterol levels from early in life. They typically develop atherosclerotic vascular disease in childhood followed by clinical CHD by their twenties (homozygous familial hypercholesterolaemia) or before middle age (heterozygous familial hypercholesterolaemia).

The concept of the lifetime burden of elevated LDL cholesterol accounts for the early development of CHD in these patients.[10,11] The severity and duration of hypercholesterolaemia act together with additional cardiovascular risk factors such as other lipid abnormalities, smoking and diabetes, with a substantial risk of CHD occurring once the patient has reached a cumulative exposure to 160 mmol of LDL cholesterol (Figure 1.2). Phenotypic and/or genotypic differences between subjects alter the actual threshold at which any individual presents with a high risk of CHD.[10]

Figure 1.2. Clinical importance of the concept of a lifetime burden of elevated LDL cholesterol



Female sex increases the cumulative threshold of LDL cholesterol for CHD, while cardiovascular risk factors (smoking etc.) decrease it so that CHD appears at an earlier age. FH: familial hypercholesterolaemia. Reproduced with permission from Nordestgaard *et al.*[10] (original concept from Vuorio *et al.*[11]).

Treatment with a statin delays the age at which CHD presents, by reducing the circulating level of LDL cholesterol and thus reducing exposure to LDL cholesterol over time. It is clear from Figure 1.2 that it is better to intervene earlier, rather than later, to address elevated LDL cholesterol, especially in a patient at severely elevated cardiovascular risk due to familial hypercholesterolaemia.[10,12]

There are clear clinical benefits from therapeutic intervention to counter the high cardiovascular risk associated with elevated LDL cholesterol in subjects with familial hypercholesterolaemia:

- By age 45 years, untreated **patients with familial hypercholesterolaemia have the LDL cholesterol burden of a 70-year-old without familial hypercholesterolaemia**.[13]
- Standardised (all-cause) excess mortality rates for people aged 20–39 years with familial hypercholesterolaemia in the UK were 8,975 for men and 16,039 for women (with no significant difference between genders), compared with people without familial hypercholesterolaemia.[14]
- Even today, **people with familial hypercholesterolaemia die 15 years earlier**, on average, than their counterparts without this condition[15] (see also Figure 1.2).

- **People with familial hypercholesterolaemia gain 3 years of life, on average, from being diagnosed and treated** to address their high LDL cholesterol.[16]
- **People with FH bear a heavy burden of recurrent cardiovascular events after their initial event**, as shown by a retroactive chart analysis in the USA, where the interval between cardiovascular events in people with familial hypercholesterolaemia was only 5 years on average.[17] **Intensive treatment to lower their LDL cholesterol increased this interval to an average of 7 years** – promising, but **clearly indicating there is much work to do to prolong and improve the lives of this population**.

Clinical algorithms for managing cardiovascular risk due to hypercholesterolaemia differ in Europe (Table 1.2) and in the USA (Table 1.3).[4,5] Expert groups in the USA have moved away from recommending goal values for LDL cholesterol and focus on the required intensity of statin treatment. This in itself, however, is determined to an important extent by the patient's LDL cholesterol level before treatment: high-intensity statin treatment is expected to reduce LDL-C by at least 50%, compared with 30–50% for moderate-intensity statin treatment. Statins remain the mainstay of treatment to control LDL cholesterol.

Table 1.2. European recommendations for control of LDL cholesterol

Patients at…	LDL cholesterol goal
Very high cardiovascular risk Established cardiovascular disease, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe chronic kidney disease or 10-year cardiovascular risk ≥10%[a]	<1.8 mmol/L (<70 mg/dL) and/or a ≥50 % LDL-C reduction when the target level cannot be reached
High cardiovascular risk Markedly elevated individual cardiovascular risk factors, a 10-year cardiovascular risk level ≥5% to <10%[a]	Consider controlling to <2.5 mmol/L (<100 mg/dL)
Moderate cardiovascular risk 10-year cardiovascular risk >1 to ≤5%[a]	Consider controlling to <3.0 mmol/L (<115 mg/dL)

[a]Determined using the SCORE cardiovascular risk calculator.

Table 1.3. Overview of US recommendations for control of LDL cholesterol to improve long-term cardiovascular outcomes

…**with established atherosclerotic cardiovascular disease** (acute coronary syndromes, prior myocardial infarction, angina, prior revascularisation, atherosclerotic cerebrovascular or peripheral arterial disease presumed to be of atherosclerotic origin) without class II-IV heart failure or end-stage renal disease	**High-intensity** statin (age ≤75 years if not a candidate for moderate intensity on other criteria) or Moderate-intensity (age >75 years if not a candidate for high intensity on other criteria)
…**with LDL-C ≥4.9 mmol/L (190 mg/dL)**	**High intensity**
…**aged 40–75 years with diabetes and LDL-C 1.8–4.9 mmol/L (70–189 mg/dL)** without established atherosclerotic cardiovascular disease	**High intensity** (if 10-year cardiovascular risk ≥7.5%), otherwise **moderate intensity**
...aged 40–75 years without atherosclerotic cardiovascular disease or diabetes, with LDL-C 1.8–4.9 mmol/L (70–189 mg/dL) and 10-year cardiovascular risk ≥7.5%	**Moderate-to-high intensity**

Cardiovascular risk scoring by Pooled Cohort Equations (see reference 5).

KEY POINTS

- Elevated LDL cholesterol accelerates atherosclerosis and increases the likelihood of death or disability due to cardiovascular disease
- LDL cholesterol remains the key target of lipid-modifying therapy
- The lifetime burden of the severity *and* duration of hypercholesterolaemia combines to damage the arterial wall: lower is better for LDL cholesterol – the sooner the better

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2. Limitations of current management of patients at high cardiovascular risk due to elevated LDL cholesterol

The challenge of familial hypercholesterolaemia

Underdiagnosis

Familial hypercholesterolaemia is the most common genetic disorder in the world and yet >99% of patients worldwide never receive the diagnosis that would facilitate intensive therapy to reduce their LDL cholesterol; this is largely due to a lack of awareness of the disease and uncertainty about how best to screen for cases.[1,2] Recent evidence that the prevalence of familial hypercholesterolaemia is more likely to be 1:200 rather than the previously quoted 1:500 exacerbates the magnitude of this problem.[1]

Improvements in screening, diagnosis and management are needed urgently for people with familial hypercholesterolaemia (and, indeed, for other patients with elevated cardiovascular risk due to hypercholesterolaemia). The following section considers the limitations of currently available therapeutic strategies.

Undertreatment

Achieving treatment goals with statins in patients with familial hypercholesterolaemia is challenging, even when they are diagnosed and treated. The introduction of these agents into clinical practice has seen a reduction in LDL cholesterol in this population and an improvement in outcomes.[3,4] All patients with familial hypercholesterolaemia should receive a statin,[2] but 79% of patients with heterozygous familial hypercholesterolaemia in The Netherlands did not achieve their goal for LDL cholesterol (<2.5 mmol/L [100 mg/dL]), despite 96% receiving a statin.[5] A second study showed that 81% of patients with familial hypercholesterolaemia did not achieve LDL cholesterol <2.6 mmol/L (100 mg/dL) despite maximal statin treatment plus a second lipid-modifying agent.[3]

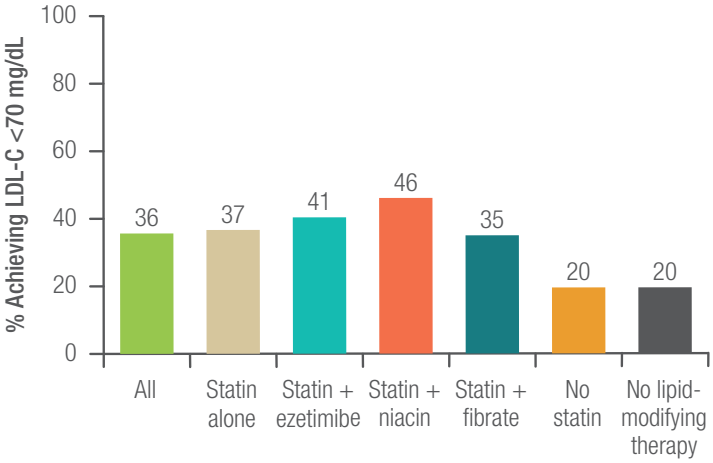
In general, monotherapy with a statin is not usually sufficient to get a patient with familial hypercholesterolaemia to goal LDL cholesterol and adding further therapies (ezetimibe, a bile acid sequestrant and possibly nicotinic acid or a fibrate) will provide an additional reduction in LDL cholesterol.[1,2] Indeed, a considerable burden of cardiovascular risk remains after intervention with a statin, even in populations without familial hypercholesterolaemia.[6] Other treatments (lipid apheresis, mipomersen and lomitapide) are pharmacological treatment options for patients with homozygous familial hypercholesterolaemia.[1,2]

Overall, few patients with familial hypercholesterolaemia achieve LDL cholesterol goals on current therapy.

Low rates of LDL cholesterol goal attainment in other populations at elevated cardiovascular risk

Many patients with elevated LDL cholesterol not due to familial hypercholesterolaemia do not achieve LDL cholesterol goals with current treatments. A survey of 9,950 high-risk patients with CHD showed that more than half did not achieve LDL cholesterol <1.8 mmol/L (70 mg/dL) either with a statin alone, or with a statin combined with other lipid-modifying agents (Figure 2.1).[7] Similarly, about half of patients with CHD did not achieve LDL cholesterol <2.5 mmol/L in the pan-European

Figure 2.1. Low rates of LDL cholesterol goal achievement in patients with coronary artery disease on lipid-modifying therapy



Drawn from data presented by Karalis *et al.*[7]

EUROASPIRE III survey of people with a history of cardiovascular disease.[8] Recent data from the EUROASPIRE IV survey confirm and extend these findings: only 58% and 21% achieved an LDL cholesterol level of 2.5 mmol/L or 1.8 mmol/L, respectively.[9]

Variable LDL cholesterol responses and non-adherence to statins

Although high-potency statins provide reductions in LDL cholesterol there is considerable variation between individuals in the response to statin treatment, even when a high-potency statin is prescribed: one study estimated that it would be necessary to treat to a mean LDL cholesterol of 1.5–1.6 mmol/L to maintain LDL cholesterol continuously below 2.0 mmol/L.[10] Poor adherence to statin therapy is common (the majority of patients stop taking their statin within a year)[11] and this is an important cause of the variable therapeutic response.[12] Indeed, these phenomena are probably linked, as pharmacokinetic and other factors may underlie to some extent the inter-individual variability in the response to a statin and also the extent to which this treatment is tolerated (see below).[13]

An analysis from the Treating to New Targets trial showed that visit-to-visit variability of LDL cholesterol in statin-treated patients was a significant predictor of subsequent events (16% increase in risk for each additional standard deviation increase in LDL cholesterol variability).[14] A number of reports have identified a possible genetic basis for this variable treatment response,[15] although the magnitude of effect of common genetic variants has been questioned.[16]

The problem of intolerance to statins

The incidence of adverse events attributable to statins in randomised clinical trials is low.[17] However, side-effects in muscle occurred in up to 29% of statin-treated patients in observational studies, presenting a potential barrier to treatment.[13] It is important that patients remain on a statin whenever possible, in order to reduce their exposure to hypercholesterolaemia and to reduce their risk of an adverse cardiovascular outcome (see Figure 1.2, above). A switch to a different agent in the same class, or to a lower statin dose as part of a combination regimen, helps most patients to remain on statin-based therapy.[13,18] Pharmacogenetic studies have detected a gene that may identify patients at risk of statin-induced myopathy (*SLCO1B1*, a member of the solute carrier organic anion transporter family).[16]

KEY POINTS

- Familial hypercholesterolaemia is the most common genetic disorder in the world and yet >99% of patients worldwide never receive the diagnosis that would facilitate intensive therapy to reduce their LDL cholesterol
- Few patients with familial hypercholesterolaemia (or other causes of hypercholesterolaemia) achieve LDL cholesterol goals on current therapy
- Statin intolerance is an important barrier to the delivery of statin-based therapy for a substantial minority of patients
- More effective treatments are required to go beyond the limitations of current therapies for managing cardiovascular risk due to elevated LDL cholesterol

Summary of unmet needs in the management of hypercholesterolaemia

The introduction of statins has revolutionised the management of patients at increased cardiovascular risk due to elevated LDL cholesterol. As described above, these agents provide marked (if variable) reductions in LDL cholesterol and clinically significant reductions in cardiovascular event rates in patients at high cardiovascular risk. Nevertheless, most patients do not achieve their goal LDL cholesterol on these agents, particularly people with the severe hypercholesterolaemia associated with familial hypercholesterolaemia. Also, statins reduce the risk of a cardiovascular event by only up to about 50% at most, leaving a substantial burden of cardiovascular morbidity and mortality even after treatment.[6] There remains a need for a consistently effective, well-tolerated treatment that will provide reductions in LDL cholesterol beyond those available with a statin, with reductions in other atherogenic lipoproteins, including VLDL cholesterol, lipoprotein remnants and lipoprotein(a) that will address the residual risk after treatment with a statin.[19]

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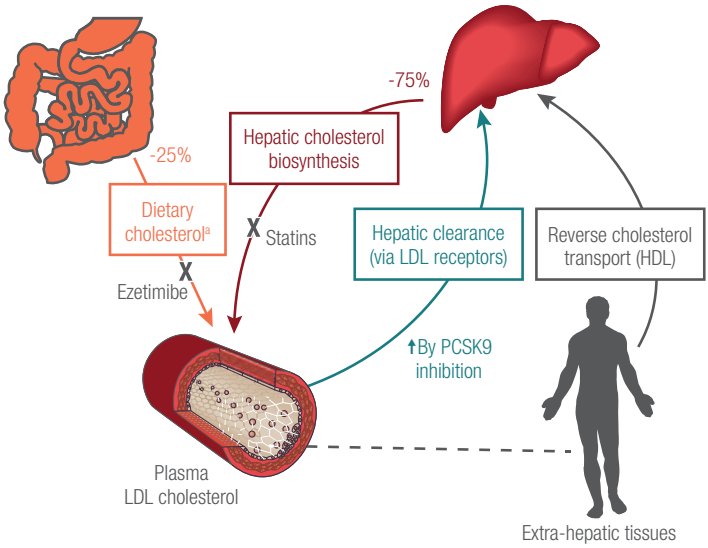
3. PCSK9 inhibition as a strategy for addressing unmet needs in the management of cardiovascular risk

PCSK9, the LDL receptor and plasma cholesterol

Figure 3.1 provides a simplified overview of the main sources of plasma LDL cholesterol. Most cells in the body have the capacity to synthesise cholesterol. However, the majority of circulating LDL cholesterol is synthesised in the liver, by HMG-CoA reductase and the principal means of removal of LDL cholesterol from the circulation is via a family of hepatic LDL receptors. Current therapies are targeted at reducing the rate of cholesterol biosynthesis (the main effect of statins) or reducing the rate of absorption of cholesterol into the circulation (ezetimibe, bile acid sequestrants or plant sterols/stanols) derived from food and/or from bile.

Figure 3.1. Overview of cholesterol metabolism and transport



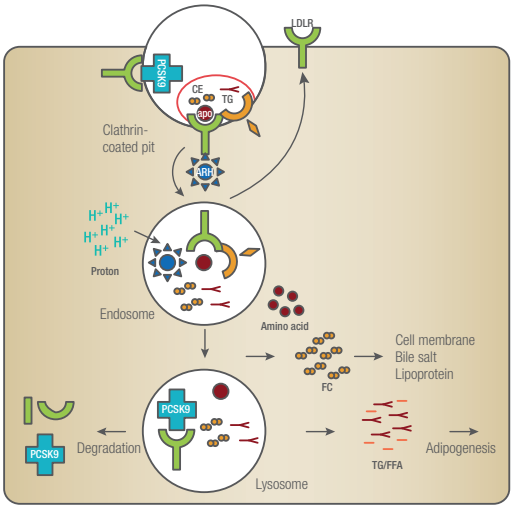
[a]Via chylomicrons or chylomicron remnants processed by the liver; PCSK9: proprotein convertase subtilisin/kexin type 9.

The LDL receptor on the surface of liver cells is an essential component of the machinery for regulating levels of LDL cholesterol.[1] Once an LDL particle binds to this receptor, it is rapidly bound at a coated pit and taken up within an intracellular endosome, and then catabolised within a lysosome, where the LDL particle is dissociated from the LDL receptor at acid pH. The lipid and protein content of the LDL particle is then degraded (Figure 3.2). The LDL receptor protein then recycles back to the cell surface. Most (90–95%) patients with familial hypercholesterolaemia have mutations in the *LDLR* gene that result in reduced or abolished LDL receptor function or a reduced number of LDL receptor protein molecules on the cell surface. Heterozygous familial hypercholesterolaemia is the most common form of the disease, with potential for loss of up to 50% of LDL receptor activity.

What is PCSK9 and how does it influence circulating levels of LDL-C?

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition is a novel therapeutic concept based on reduction of plasma LDL cholesterol through increased hepatic clearance (see Figure 3.1).[2,3] The binding of the PCSK9 protein to the LDL receptor increases the probability of the LDL receptor then being diverted to a lysosome, where it is degraded, rather than being recycled to the cell membrane as usual (Figure 3.2).[4]

Figure 3.2. Role of the LDL receptor in the regulation of serum cholesterol



Apo: apolipoprotein; ARH: low-density lipoprotein receptor adapter protein; CE: cholesteryl ester; FC: free cholesterol; LDLR: LDL receptor; TG: triglyceride. See text for a description of LDL receptor recycling.

Adapted with permission from *Yale Journal of Biology and Medicine*.[1]

A number of mutations and polymorphisms[a] of the *PCSK9* gene have been identified, which support its importance in the regulation of LDL cholesterol. These include "loss of function" and "gain of function" mutations that reduce and increase, respectively, the activity of PCSK9 (Table 3.1).[5,6] Common loss-of-function mutations in PCSK9 in humans are associated with lower LDL cholesterol and a reduced frequency of adverse cardiovascular events, compared with subjects with wild-type PCSK9. For example:

- 2.6% of Black subjects in the Atherosclerosis Risk in Communities (ARIC) study in the USA had a nonsense (loss of function) mutation in the *PCSK9* gene (0.8% for the Y142X allele and 1.8% for the C679X allele). Their mean LDL cholesterol was reduced by 28% (p=0.008) *vs.* non-carriers of these mutations, and this was associated with an 88% lower risk of coronary heart disease (age-and gender-adjusted hazard ratio [HR] 0.11 [95%CI 0.02 to 0.81]; p=0.03).
- 3.2% of White subjects in the ARIC study had the R46L loss of function mutation of *PCSK9*, which reduced mean LDL cholesterol by 15% and the risk of coronary heart disease by 47% (adjusted HR 0.50 [95%CI 0.32 to 0.79]; p=0.003) *vs.* non-carriers.[7]
- 2.6% of 45,699 subjects pooled from three observational studies in Denmark had the R46L loss of function mutation of *PCSK9*; a reduction in LDL cholesterol of 11–16% was associated with a 30% reduction in the risk of ischaemic heart disease for carriers *vs.* non-carriers.[8] The improvement in cardiovascular outcomes was larger than predicted by the reduction in LDL cholesterol, which the authors attributed to the *PCSK9* genotype being a better predictor of lower lifetime LDL cholesterol levels than a point measurement of LDL cholesterol made in adulthood.

These findings confirm the observations described above (Section 1) that lifetime exposure to lower LDL cholesterol markedly improves cardiovascular outcomes, and extend this concept specifically to the actions of PCSK9 on levels of LDL cholesterol. Moreover, the subjects with loss-of-function PCSK9 mutations appeared to be generally healthy,

[a]Mutations differ from polymorphisms as follows. A mutation is any change in a DNA sequence from normal (where there is a normal allele that is prevalent in the population and the mutation changes this to a rare and abnormal variant); a polymorphism is a common DNA sequence variation, where no single allele is regarded as the standard sequence. Source: Wellcome Trust (http://genome.wellcome.ac.uk/doc_WTD020780.html, accessed May 2015).

with no apparent adverse pathological consequences arising from their PCSK9 mutation. Loss of function PCSK9 variants also did not appear to influence markers of glucose homeostasis, such as fasting plasma glucose or insulin levels, or risk for type 2 diabetes.[9]

These observations have fuelled considerable interest among researchers in cardiovascular medicine in the prospect of pharmacological inhibition of PCSK9 as a therapeutic strategy for the management of dyslipidaemia and cardiovascular risk. PCSK9 inhibitors are the latest in a series of new discoveries of biological therapies to address unmet clinical needs in chronic, non-communicable diseases.

Table 3.1. Examples of polymorphisms of PCSK9 that influence circulating levels of LDL-C

Mutation	Effect on PCSK9 activity
S127R P216L D374Y D374Y + N157K (double mutation in one patient) C(–161)T I474V	**Gain of function** (resulting in **fewer LDL receptors** and **higher LDL cholesterol**)
Y142X, C679X R46L L108R D35Y	**Loss of function** (resulting in **more LDL receptors** and **lower LDL cholesterol**)

Compiled from information presented by Abifadel *et al.*[5] and De Castro-Orós *et al.*[6]

KEY POINTS

- The hepatic LDL receptor is the most important mechanism of removal of LDL cholesterol from the circulation
- Reducing the activity or expression of PCSK9 increases the number of LDL receptors, which reduces circulating LDL cholesterol
- People with mutations of the *PCSK9* gene that *decrease* its activity have lifelong low LDL cholesterol and a lower risk of cardiovascular events than the general population
- Mutations of the *PCSK9* gene that *increase* its activity can give rise to the familial hypercholesterolaemia phenotype

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4. Clinical experience with PCSK9 inhibitors in the management of high LDL cholesterol and cardiovascular risk

PCSK9 inhibitors: current status

Monoclonal antibody therapy

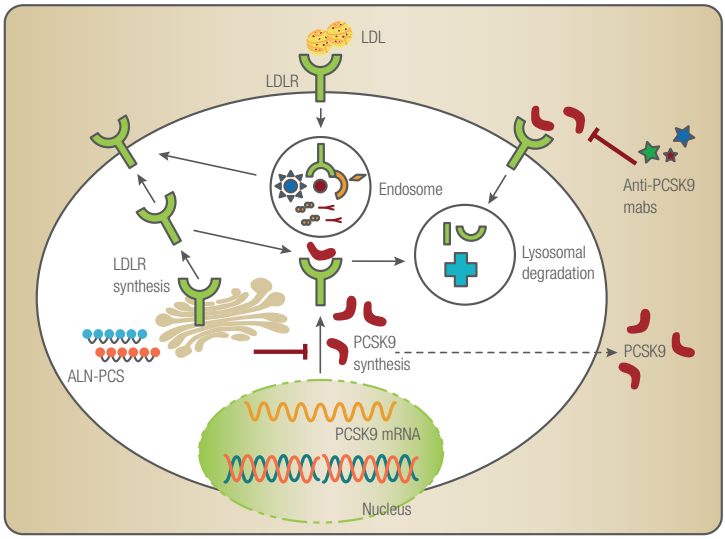
Monoclonal antibody therapy targeting PCSK9 has led the field in clinical development. The first of these agents, alirocumab (Praluent, Sanofi/Regeneron) and evolocumab (Repatha, Amgen), received regulatory approval in Europe and the USA in 2015. Both agents are licensed for the management of adult patients with hypercholesterolaemia or mixed dyslipidaemia; evolocumab is also licensed for the treatment of adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia. These agents are given by subcutaneous injection and have a long duration of action requiring infrequent administration (either 2-weekly for alirocumab or monthly or 2-weekly for evolocumab) compared with current therapies. Another monoclonal antibody targeting PCSK9, bococizumab (Pfizer) is in Phase III clinical evaluation (the SPIRE trial programme).

Other approaches

Beyond monoclonal antibody therapy, other approaches for targeting PCSK9 are also being investigated. These include an RNA interference (RNAi) molecule (ALN-PCSsc, Alnylam and The Medicines Company), small molecule candidates, which in general are orally available, as well as vaccine candidates. To date, there are 8 preclinical drugs and a total of 7 in clinical trials with the associated mechanism of action of 'PCSK9 inhibitor'.

Of these novel agents, ALN-PCSsc has attracted attention following encouraging Phase I results. This first-in-class RNAi therapeutic inhibits PCSK9 gene expression, typically by causing the destruction of specific messenger RNA (mRNA) molecules, thus inhibiting PCSK9 synthesis (Figure 4.1). In multiple subcutaneous dosing in hypercholesterolaemic

Figure 4.1. Inhibition of PCSK9 may be achieved by blocking PCSK9 binding to the LDL receptor (as for PCSK9 monoclonal antibody therapy), or by blocking PCSK9 synthesis. The latter approach has been adopted with a first-in-class RNAi therapeutic (ALN-PCSsc), which inhibits PCSK9 gene expression by causing the destruction of specific messenger RNA (mRNA) molecules.



Adapted from presentation given by Fitzgerald *et al* (2015).[1]

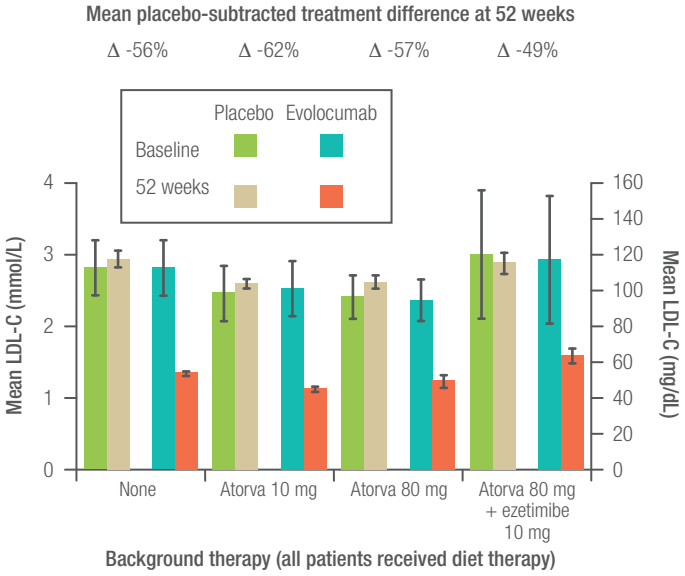
patients on or off statins, ALN-PCSsc lowered LDL cholesterol by up to 83% (least squares mean change up to 54%). This response was durable, suggesting the possibility of injecting every 6 months. The treatment was also well tolerated.[1] ALN-PCSsc is now in Phase II development (ORION programme).

This section summarises efficacy data for the most advanced PCSK9 inhibitors - alirocumab, evolocumab and bococizumab.

Marked reductions in LDL cholesterol

A one-year evaluation of evolocumab demonstrates the marked reductions in LDL-C that result from PCSK9 inhibition, irrespective of the nature of background lipid-modifying therapy (Figure 4.2).[2] Mean reductions from baseline in LDL-C approaching 50%, or greater, were seen in patients on background diet therapy, low- or high-intensity statin

Figure 4.2. Substantial reductions in LDL-C with evolocumab irrespective of background intensity of lipid-modifying therapy



Δ: mean treatment difference *vs.* placebo. Atorva: atorvastatin. Patients are stratified according to lipid-lowering treatment before randomisation. Drawn from data presented by Blom *et al.*[2]

treatment, or high-intensity statin plus ezetimibe. A reduction in LDL cholesterol of comparable magnitude was seen in a Phase III study in which alirocumab was compared with ezetimibe in patients with hypercholesterolaemia (Figure 4.3).[3]

The results of other Phase III studies with evolocumab and alirocumab are shown in Table 4.1.[4-17] PCSK9 inhibition was highly effective in lowering LDL cholesterol in patients with heterozygous familial hypercholesterolaemia, on top of maximally tolerated statin with or without other lipid-modifying therapy. Evolocumab was also shown to lower LDL cholesterol by 30.9% (placebo-corrected) in patients with homozygous familial hypercholesterolaemia. Additionally, both alirocumab and evolocumab were effective in non-familial hypercholesterolaemia, including patients with statin intolerance. In the MENDEL-2 trial, a higher proportion of patients attained LDL cholesterol goal on evolocumab compared with ezetimibe (Figure 4.4).[4] Additionally, in the ODYSSEY trials programme, adding alirocumab to statin led to greater LDL cholesterol

Table 4.1. Phase III studies that evaluated PCSK9 inhibitors

Alirocumab

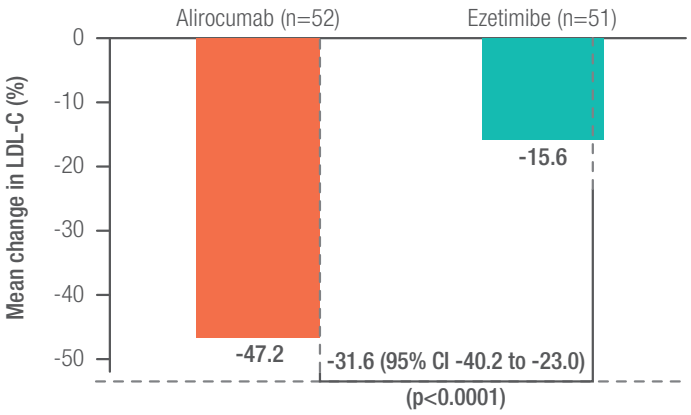
Drug (study)	Patient population	N, duration	Effect on LDL-C
ODYSSEY-FH I[9]	Heterozygous FH	486, 78 w	Δ –58% *vs.* EZE
ODYSSEY-FH II[9]	Heterozygous FH	249, 78 w	Δ –51% *vs.* EZE
ODYSSEY-High FH[10]	Heterozygous FH, LDL-C >4.0 mmol/L or 160 mg/dL	106, 24 w	–46% vs. placebo (standard of care)
ODYSSEY-COMBO I[11]	HC	316, 24 w	–46% vs. placebo (standard of care)
ODYSSEY-COMBO II[12]	High CV risk on maximal statin therapy	707, 104 w	Δ –51% vs. baseline, Δ –30% vs. EZE (each at w 24)
ODYSSEY OPTIONS I[13]	HC, on ATOR 20 or 40 mg	355, 24 w	–44-54% vs. -21–23% on EZE, –4.8-5.0% doubling ATOR dose, –21% switching to ROS 40 (ATOR 40 only)
ODYSSEY OPTIONS II[14]	HC, on ROS 10 or 20 mg	305, 24 w	–38-51% vs. –11-14% on EZE, –16% switching ROS dose
ODYSSEY CHOICE I[15]	HC ± statin	803, 24 w	–52-59% vs. placebo
ODYSSEY CHOICE II[16]	HC, + EZE, fenofibrate or diet alone	233, 24 w	– 56% vs. placebo
ODYSSEY ALTERNATIVE[17]	Statin intolerant	361 (placebo run-in) 314 (randomized), 24 w	–45% vs. –14.6% with EZE

Evolocumab

Drug (study)	Patient population	N, duration	Effect on LDL-C
TESLA-B[5]	Homozygous FH	49, 12 w	Δ –30.9% *vs.* placebo
RUTHERFORD-2[6]	Heterozygous FH	331, 12 w	Δ –59% to –66% *vs.* placebo for 2-weekly or monthly administration
LAPLACE-2[7]	HC	2,067, 12 w	Δ –63% to –75% *vs.* placebo for 2-weekly or monthly administration with moderate- or high-intensity statin
GAUSS-2[8]	Statin-intolerant	307, 12 w	Δ –63% to –75% *vs.* placebo, Δ – 37% to –39% *vs.* EZE, each for 2-weekly or monthly administration
MENDEL-2[4]	HC not previously on drug treatment	614, 12 w	Δ –55% to –57% *vs.* placebo, Δ – 38% to –40% *vs.* EZE, each for 2-weekly or monthly administration

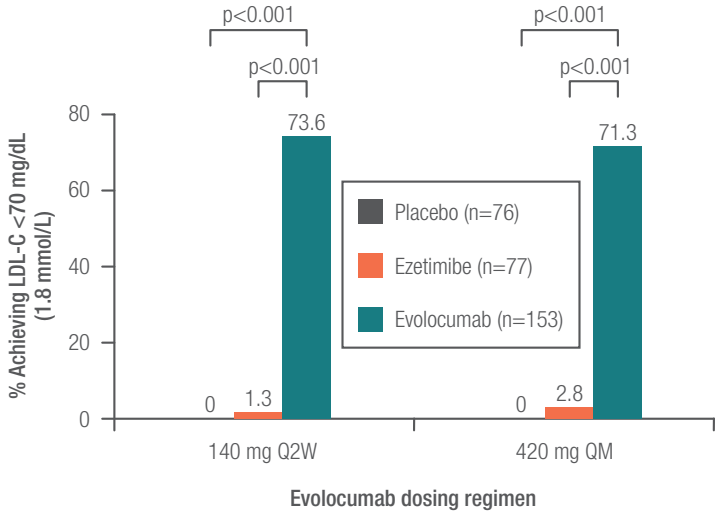
It is important to note that the magnitude of LDL-C reductions in people with familial hypercholesterolaemia depends on the density and function of their LDL receptors: while mean changes in LDL-C demonstrate that PCSK9 inhibitors were effective in reducing LDL-C in each patient, these values should not be used to compare efficacy between trials. Δ: mean change from baseline relative to treatments stated; FH: familial hypercholesterolaemia; HC: hypercholesterolaemia; ATOR: atorvastatin; EZE: ezetimibe; ROS: rosuvastatin. See also the study by Blom *et al.*[2]

Figure 4.3. Effects of 24 weeks of treatment with alirocumab *vs.* ezetimibe on LDL cholesterol in patients with hypercholesterolaemia



Drawn from data presented by Roth *et al.*[3] Doses given were 75 mg s.c. Q2W for alirocumab and 10 mg QD for ezetimibe. Patients were not receiving other lipid-lowering treatment.

Figure 4.4. Proportions of patients achieving LDL-C <70 mg/dL (1.8 mmol/L) in the MENDEL-2 study

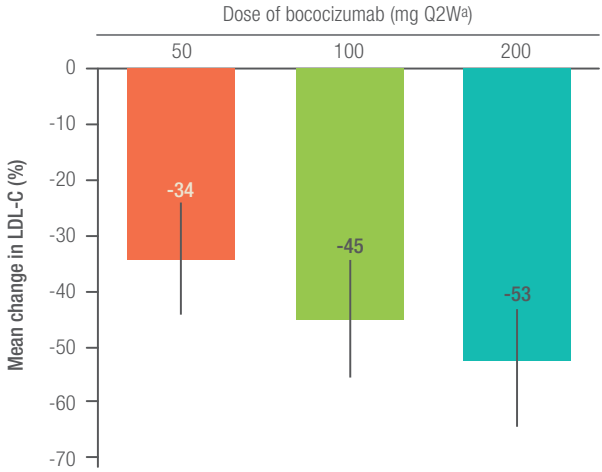


Q2W: dosing every two weeks; QM: monthly dosing. Numbers of patients: n=153 for each evolocumab group, n=76–78 for other groups. Drawn from data presented by Koren *et al.*[4]

reduction compared with other therapeutic approaches, including adding ezetimibe, doubling the dose of statin or switching to a higher-intensity statin.

Bococizumab has also demonstrated reductions in LDL cholesterol of similar magnitude. Figure 4.5 summarises the effects of this agent on LDL cholesterol from a 23-week study in statin-treated patients with hypercholesterolaemia.[18]

Figure 4.5. Effect of bococizumab on LDL cholesterol in a 12-week study in statin-treated patients with hypercholesterolaemia



Ballantyne *et al.*[18] [a]Effects of monthly dosing omitted for clarity (mean placebo-adjusted changes from baseline to 12 weeks of –28 mg/dL [200 mg QM] and –45 mg/dL [300 mg QM]).

Impact on other atherogenic lipoproteins

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein that is closely associated with increased risk of cardiovascular disease independently of levels of LDL cholesterol or non–HDL cholesterol. Lp(a) should be controlled to below the 80th percentile of the population, which is about 50 mg/dL, according to the EAS, who have also developed an App for mobile devices based on their Consensus Position Paper on this topic.[19,20]

PCSK9 inhibition has been shown to reduce Lp(a) in the studies summarised in Table 4.1. In combined analyses, treatment with alirocumab or evolocumab reduced Lp(a) by 25-30% as a function of baseline levels.[21,22]

Incidentally, treatment with ALN-PCSsc also reduced Lp(a) by up to 44% (multiple dosing).[1]

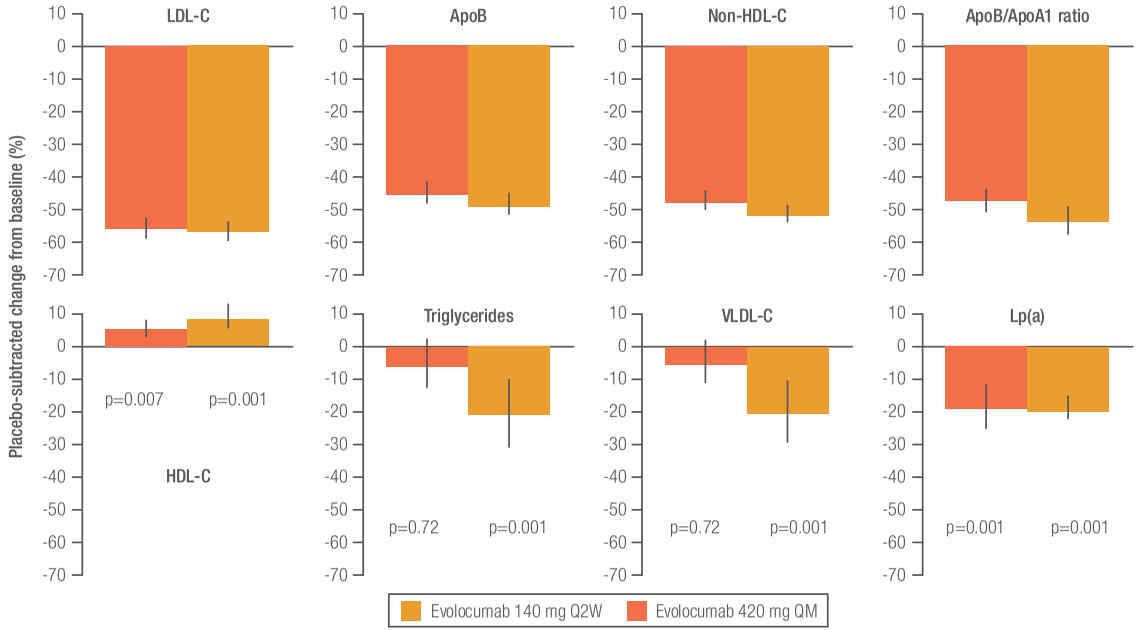
PCSK9 inhibition was effective in reducing levels of ApoB and non-HDL cholesterol, and the ratio of ApoB to ApoAI, in addition to LDL cholesterol (as shown for the MENDEL-2 study in Figure 4.6).[4] Significant reductions in levels of triglycerides and VLDL cholesterol, and increases in HDL cholesterol, were also observed, depending on the dosing regimen.

Cardiovascular outcomes trials in progress

The circulating level of LDL-C is accepted as a surrogate marker of the risk of adverse cardiovascular outcomes. The substantial lowering of LDL-C by PCSK9 inhibitors therefore holds considerable therapeutic promise for improving long-term cardiovascular prognosis in high-risk patients. As with any cardiovascular therapy, however, the ultimate test of the utility of these agents will be in their ability to reduce the frequency of morbid cardiovascular events. Large, randomised outcomes studies with these agents are underway:

- The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study is comparing evolocumab *vs.* statin therapy in about 22,500 patients with dyslipidaemia and a history of cardiovascular disease who are at high risk of a recurrent event (ClinicalTrials.gov NCT01764633). This trial is expected to report at the end of 2016.
- The ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (LONG TERM) study is comparing alirocumab with placebo (ClinicalTrials.gov NCT01663402).[23] Most of the 18,000 patients in this study have well controlled LDL cholesterol (<1.8 mmol/L [70 mg/dL]) on maximal lipid-modifying therapy with a recent acute coronary syndrome. The trial is expected to complete in 2017.
- Two placebo-controlled outcomes studies are underway with bococizumab in patients at high risk of a cardiovascular event:
  - The Evaluation of Bococizumab (PF-04950615) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE-1) study (ClinicalTrials.gov NCT01975376) is underway in 17,000 patients with LDL cholesterol relatively well controlled by lipid-modifying treatment (1.8–2.6 mmol/L [70–100 mg/dL]). Completion is expected in April 2018.

Figure 4.6. Effects of PCSK9 inhibition on LDL-C and other components of the lipid profile



Q2W: dosing every two weeks; QM: monthly dosing. Bars are 95%CI. Drawn from data presented in the MENDEL-2 study (Koren *et al*).[4]

– The Evaluation of Bococizumab (PF-04950615) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE-2) study (ClinicalTrials.gov NCT01975389) is underway in 9,000 patients with dyslipidaemia despite lipid-modifying treatment (LDL cholesterol ≥2.6 mmol/L [100 mg/dL] or non–HDL cholesterol ≥3.4 mmol/L [130 mg/dL]). Completion is expected in January 2018.

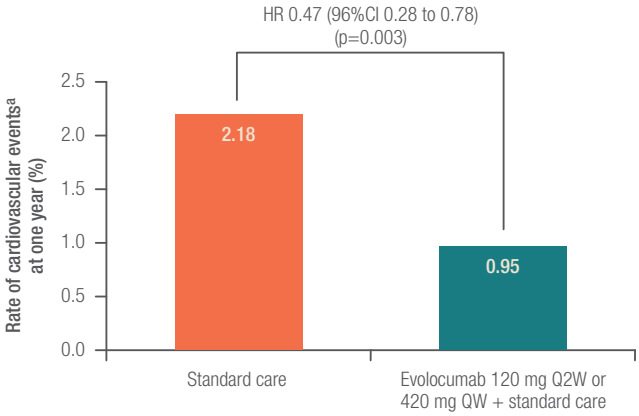
Preliminary outcomes data for PCSK9 inhibitors

Preliminary data are available to suggest that evolocumab and alirocumab may reduce the frequency of cardiovascular events in patients at elevated cardiovascular risk.

An exploratory analysis (pooled analysis of the randomised OSLER-1 and OSLER-2 trials) evaluated the effects of evolocumab on cardiovascular outcomes (Figure 4.7).[23] The addition of evolocumab *vs.* standard of care alone reduced LDL cholesterol by 61%, and was associated with a 53% reduction in cardiovascular events, over a median follow-up of 11 months.

A pre-specified preliminary analysis of the ODYSSEY LONG TERM trial (Table 4.2) reported data from 2,341 patients. Treatment with alirocumab on top of statin and other lipid-modifying therapy reduced LDL cholesterol

Figure 4.7. Effect of evolocumab on cardiovascular outcomes in a pooled analysis of the OSLER-1 and OSLER-2 trials



[a]Composite of death, myocardial infarction, hospitalisation for unstable angina, coronary revascularisation, stroke, transient ischaemic attack, or hospitalisation for heart failure. Drawn from data presented by Sabatine *et al.*[23]

by 62% *vs.* placebo. There was also a 48% reduction in major adverse cardiovascular events over 78 weeks (HR 0.52, 95% CI 0.31 to 0.90).[24] Additionally, a meta-analysis of 24 Phase II and III studies evaluating PCSK9 monoclonal antibody therapy reported reductions in all-cause mortality (odds ratio [OR] 0.45, 95% CI 0.23 to 0.86, p=0.015) and cardiovascular mortality (OR 0.50, 95% CI 0.23 to 1.10, p=0.084).[25]

Table 4.2. Cardiovascular events in the ODYSSEY LONG TERM study with alirocumab in patients at high cardiovascular risk receiving a statin

	Alirocumab (n=1,550)	Placebo (n=788)	p
Non-fatal myocardial infarction	0.9	2.3	0.01
Death from coronary heart disease[b]	0.3	0.9	0.26
Fatal or non-fatal ischaemic stroke	0.6	0.3	0.35
Hospitalisation for CHF	0.6	0.4	0.76
Coronary revascularisation due to ischaemia	3.1	3.0	1
All positively adjudicated cardiovascular events[c]	0.46	0.51	0.68
Adjudicated major adverse cardiac events[a] (%)	1.7	3.3	0.02

[a]Includes deaths from unknown cause. [b]Includes all events listed above. [c]Composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation, from a post-hoc analysis not specified in the trial protocol. All other outcomes are listed as cardiovascular adverse events of interest. Adapted from Robinson JG *et al. N Engl J Med* (2015).[24]

These data are exciting, but at present only hypothesis-generating. A fuller understanding of the effects of PCSK9 inhibition on cardiovascular outcomes must await the completion of the randomised outcomes trials described above.

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KEY POINTS

- PCSK9 inhibitors reduced LDL cholesterol by >50% in randomised trials in high cardiovascular-risk patients with hypercholesterolaemia
- Similar substantial reductions in LDL cholesterol were also seen in patients with familial hypercholesterolaemia
- PCSK9 inhibitors are effective when added to other lipid-modifying treatment, including high-intensity statin therapy
- Preliminary data from exploratory analyses suggest a reduced frequency of adverse cardiovascular outcomes associated with PCSK9 inhibitor treatment in high-risk patients with hypercholesterolaemia

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5. Tolerability and safety of PCSK9 inhibitors

PCSK9 inhibitors appear to be well tolerated. A recent meta-analysis of four Phase II evaluations of evolocumab included data from 1,359 patients (see Table 5.1). The overall incidence of adverse events was similar with evolocumab or placebo. There was a slight excess of injection site reactions and muscle-related events with evolocumab.[1]

Long-term safety data are available from the OSLER trials with evolocumab (n=4,465, median follow-up 11.1 months) and ODYSSEY LONG TERM with alirocumab (n=2,341, 78 week treatment duration).[2,3] In both reports, adverse events were reported with similar frequency with the PCSK9 inhibitor compared with the comparator (standard of care in OSLER versus evolocumab, and placebo in ODYSSEY LONG TERM versus alirocumab). Summary adverse event data for evolocumab are provided in Table 5.1 and for alirocumab in Fig 5.1.[1-3]

Table 5.1. Summary of adverse event (AE) data (%) for evolocumab in Phase II studies and OSLER

	Evolocumab	Comparator
Phase II data		
Patients with:		
Any AE	57	49
AE leading to discontinuation	0.7	1.5
Injection site reactions	4.1	3.3
Muscle-related	6.0	3.9
OSLER	**Evolocumab**	**Standard of care**
Patients with:		
Any AE	69	65
AE leading to discontinuation	2.4	NA
Injection site reactions	4.3	NA
Muscle-related AE	6.4	6.0

NA = Not applicable; patients receiving standard of care only did not receive placebo injections and thus AEs at injection sites did not occur

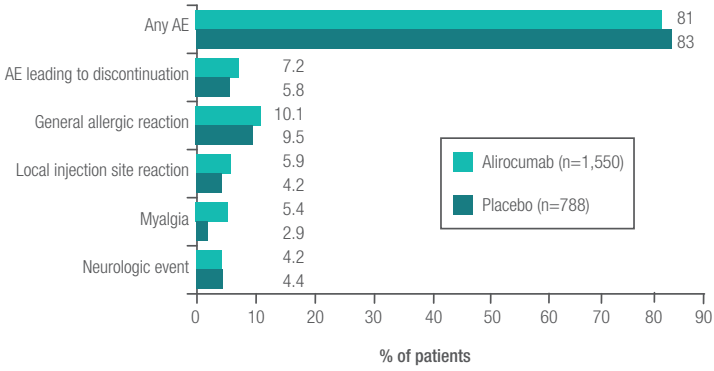
The US Food and Drug Administration (FDA) has raised concerns regarding the possibility of adverse effects on cognition with PCSK9 inhibitors. It is not clear at present whether these concerns are relevant specifically to these agents or to lowering of LDL-C *per se*, as previously expressed for statins.[4] Furthermore, it is important to bear in mind that these monoclonal antibodies are large molecules and therefore are unlikely to cross the blood-brain barrier. The incidence of any neurocognitive event in a pooled analysis of phase 2/3 trials was 0.8% for alirocumab (N=2,476) and 0.7% for placebo (N=1,276), when added to a statin.[5] Similarly, data from a pooled analysis of integrated data from phase 2/3 trials showed no increase in the incidence of neurocognitive effects, which were reported as 0.1% with evolocumab (n= 3,946) versus 0.3% in the control groups (n=2,080).[6]

However, it is important to bear in mind that none of these trials have rigorously evaluated neurocognitive effects. An ongoing trial (EBBINGHAUS, a substudy of the FOURIER outcomes study with evolocumab) is addressing this issue.

Recent findings have extended our knowledge about the safety of PCSK9 monoclonal antibody therapy.

- Two recent meta-analyses, each involving over 10,000 patients treated with alirocumab or evolocumab, have provided further reassurance on the safety of PCSK9 inhibition.[8,9]

Figure 5.1. Tolerability profile in the ODYSSEY LONG TERM trial: adverse events of interest



To date, there are limited published data for bococizumab, the third PCSK9 inhibitor being evaluated in outcomes studies. In a phase II study, adverse events were similar across placebo and bococizumab groups.[7]

- We now have evidence that treatment with evolocumab for up to 52 weeks did not influence plasma levels of gonadal hormones and adrenocorticotrophic hormone (ACTH), or erythrocyte vitamin E concentration.[10] This is pertinent given that vitamin transport and steroidogenesis are closely linked to LDL cholesterol metabolism.
- Importantly, the available data do not indicate any increase in the risk of new-onset type 2 diabetes with either alirocumab or evolocumab, highly relevant given the target patient population.[11,12]
- Finally, anti-drug binding or neutralizing antibodies to these agents do not appear to be an issue, with evidence suggesting that these are transient and affect 0.1–0.7% of patients.[5,6,13]

Ultimately, we await the results of ongoing outcomes studies with alirocumab, evolocumab and bococizumab to fully evaluate the long-term safety and tolerability of these novel agents.

KEY POINTS

- PCSK9 inhibitors have been generally well tolerated in clinical trials
- The main side-effects associated with these agents are injection site reactions, which is unsurprising for an injectable treatment
- The tolerability and safety profiles of these agents so far support long-term administration for lifelong conditions such as hypercholesterolaemia

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6. Conclusions: potential future role for PCSK9 inhibition in cardiovascular care

Treatment with a statin, however intensive, leaves a high level of residual cardiovascular risk; such risk arises from both modifiable (*eg* lipid profile, blood pressure) and non-modifiable (*eg* age, gender) risk factors. Combination therapies with statins are already widely used in high-risk patients in order to attain LDL cholesterol goals, with addition of ezetimibe and resins to further lower LDL cholesterol and fibrates and fish oils/omega-3 fatty acids to lower triglycerides. While improvements in the management of cardiovascular risk have reduced the burden of cardiovascular disease to some extent, future progress will depend on the implementation of new treatment strategies that are able to make inroads into this residual risk. A wealth of evidence associates elevation of circulating levels of atherogenic lipoproteins, particularly LDL cholesterol, with an increased risk of adverse cardiovascular outcomes.

Observational evidence links reduced activity of PCSK9 closely with a reduced level of LDL cholesterol, together with a reduced burden of atherosclerosis and cardiovascular events. We already know that the administration of a PCSK9 inhibitor can at least halve the level of LDL cholesterol even when added to statin-based lipid-modifying therapy. Moreover, these agents appear from short-term clinical trials, at least, to be sufficiently well tolerated to support long-term administration to patients with hypercholesterolaemia. The initial data on cardiovascular outcomes presented recently provide an intriguing hint of a possible improvement in long-term cardiovascular prognosis with these agents.

Randomised outcome trials with these agents are in progress, with doubtless more to come. In principle, any patient at elevated risk of an adverse cardiovascular outcome due to elevated LDL cholesterol could benefit from treatment with a PCSK9 inhibitor, particularly people with the severe hypercholesterolaemia phenotype associated with familial hypercholesterolaemia (Box 6.1). The approval of the first agents in this new class of PCSK9 biologics may provide a dramatic improvement in our

ability to get high-risk patients to their LDL cholesterol goal. We will find out in the coming years whether pharmacological inhibition of PCSK9 can take us beyond the statin era, as the next major advance in cardiovascular care.

Box 6.1 People at high cardiovascular risk who are likely to benefit from treatment with a PCSK9 inhibitor

- **People with familial hypercholesterolaemia**
  - Lifelong exposure to very high levels of LDL cholesterol and other atherogenic lipoproteins, such as Lp(a), causes early onset of cardiovascular disease
  - Low likelihood of achieving optimal control of LDL-cholesterol on current therapies
- **People with statin intolerance**
  - Intensity of statin treatment limited by side-effects
  - Problem of low adherence to LDL cholesterol-lowering therapy among this population
- **People at high cardiovascular risk who are not at their LDL cholesterol goal**
  - Urgent need to control their LDL cholesterol to prevent a first or recurrent morbid cardiovascular event