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Review Article

The revolution in cholesterol management: putting PCSK9 Inhibitors into practice

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Introduction

Of an estimated 58 million deaths globally from all causes in 2005, cardiovascular disease (CVD) accounted for 30%. This proportion is equal to that due to infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined **(1)**. It is important to recognize that a substantial proportion of these deaths (46%) were of people under 70 years of age, in the more productive period of life; in addition, 79% of the disease burden attributed to cardiovascular disease is in this age group **(2)**.

One of the cardiovascular disease (CVD) risk factors is atherosclerosis: caused when high levels of low density lipoprotein (LDL-C) in the blood build up in the inner walls of arteries, thickening them and provoking an inflammatory response, it can lead to heart attack or stroke. Levels of LDL-C are therefore often used as a surrogate marker for the risk of having a cardiovascular event **(3)**.

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. Overwhelming evidence, summarized in these guidelines, continues to identify elevated LDL cholesterol as a clinically important source of accelerated atherosclerosis and elevated cardiovascular risk.

Familial hypercholesterolemia and the lifetime burden of elevated LDL-cholesterol

Familial hypercholesterolemia is the most common genetic condition known to medical science, with a population prevalence that may be as high as about 1:200 **(4)**. Patients with familial hypercholesterolemia have severely elevated LDL cholesterol levels from early in life. They typically develop atherosclerotic vascular disease in childhood followed by clinical coronary heart disease (CHD) by their twenties (homozygous familial hypercholesterolemia) or before middle age (heterozygous familial hypercholesterolemia). The concept of the lifetime burden of elevated LDL cholesterol accounts for the early development of CHD in these patients. The severity and duration of hypercholesterolemia 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. Phenotypic and/or genotypic differences between subjects alter the actual threshold at which any individual presents with a high risk of CHD **(4)**.

Achieving treatment goals in patients with familial hypercholesterolemia is challenging, even when they are diagnosed and treated. Only few patients with familial hypercholesterolemia achieve LDL cholesterol goals on current

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therapy. On the other hand; many patients with elevated LDL cholesterol not due to familial hypercholesterolemia 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 single lipid modifying drug, or combination therapy **(5)**. Similarly, about half of patients with CHD did not achieve LDL cholesterol <2.5 mmol/L in the pan-European EUROASPIRE III survey of people with a history of cardiovascular disease **(6)**. 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 **(7)**.

Statins

By now you've heard of statins, also known as HMG-CoA reductase inhibitors. Statins are the cornerstone of treatment to help regulate cholesterol production. Available since the late 1980's, statins include well-known agents like atorvastatin (Lipitor), simvastatin (Zocor), and rosuvastatin (Crestor). Statins work so well because they inhibit an enzyme involved in the making of cholesterol in the liver and boost the number of low density lipoprotein receptors (LDL-R) to help clear the body of LDL ("bad cholesterol). However, although hugely successful in terms of sales — Pfizer's atorvastatin (Lipitor) is the bestselling drug of all time — for many, statins are ineffective or the side effects are intolerable **(8)**. Very low levels of LDL-C are not achievable in the majority of patients.

There are a number of problems encountered clinically with the use of 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 **(9)**. Also, poor adherence to statin therapy is common (the majority of patients stop taking their statin within a year) and this is an important cause of the variable therapeutic response. 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 **(10)**.

Another important aspect to address here; is the problem of intolerance to statins; where despite the fact that the incidence of adverse events attributable to statins in randomized clinical trials is low **(11)**; however, side-effects in muscle occurred in up to 29% of statin-treated patients in observational studies, presenting a potential barrier to treatment **(12)**. It is important that patients remain on a statin whenever possible, in order to reduce their exposure to hypercholesterolemia and to reduce their risk of an adverse cardiovascular outcome. 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)**. Pharmaco-genetic 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) **(14)**.

Pcsk9 a promise to fulfill

However, a new class of drugs may change the face of lowering LDL cholesterol. Hoping to address this unmet need, the drug development pipelines of some biopharmaceutical companies feature novel candidates to lower LDL-C. Perhaps the most eagerly anticipated are the PCSK9 inhibitors, several of which have been shown to reduce LDL-C levels in clinical trials.

Cholesterol metabolism

Before proceeding into the story of PCSK9; we have to go quickly through this simplified review of the main sources of plasma LDL cholesterol; most cells in the body have the

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capacity to synthesize cholesterol. However, the majority of circulating LDL cholesterol is synthesized 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.

The LDL receptor on the surface of liver cells is an essential component of the machinery for regulating levels of LDL cholesterol. 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 catabolized 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. The LDL receptor protein then recycles back to the cell surface. Most (90–95%) patients with familial hypercholesterolemia 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 hypercholesterolemia is the most common form of the disease, with potential for loss of up to 50% of LDL receptor activity.

The discovery

In 2003, French researchers identified high levels of a protein in a family with familial hypercholesterolemia, an inherited disease that leads to dangerously high blood cholesterol and, consequently, increased risk of cardiovascular disease **(15)**. The protein, called proprotein convertase subtilisin/kexin type 9 (PCSK9), had been discovered earlier that year by Canadian researchers **(16)**.

Inhibition of this protein is a novel therapeutic concept based on reduction of plasma LDL cholesterol through increased hepatic clearance. 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 **(17)**.

A number of mutations and polymorphisms 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 (Table1) **(18)**.

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) **(19)**.

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(Table 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** & **higher LDL cholesterol**)
• Y142X • C679X • R46L • L108R • D35Y	- Loos of function (resulting in **more LDL receptors** & **lower LDL cholesterol**)

• 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 **(19)**.

• 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 ischemic 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 **(20)**.

These findings confirm the observations described above 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, 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 **(21)**. These observations have fueled considerable interest among researchers in cardiovascular medicine in the prospect of pharmacological inhibition of PCSK9 as a therapeutic strategy for the management of dyslipidemia 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.

A series of experiments from different laboratories subsequently showed that high levels of PCSK9 stopped the low density lipoprotein (LDL) receptors from functioning. Three years later after the French researchers identified PCSK9 protein; the results of a large community study mapping LDL cholesterol (LDL-C) levels and the incidence of coronary heart disease against mutations in the PCSK9 gene were released **(22)**. Those with genetic variations linked to reduced PCSK9 function were found to have significantly lower LDL-C levels and lower risk of coronary heart disease.

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The hypothesis that inhibiting PCSK9 activity could reduce cholesterol became an important research topic. This led to experimental studies in animal models showing that inhibition of PCSK9 was a potent way to reduce cholesterol levels in blood.

Pcsk9 inhibitors unveil

The year 2015 had been a big year for cardiology. Attendees of that year's American College of Cardiology (ACC) meeting were buzzing about the clinical-trial sessions highlighting the breakthrough in cardiology - the PCSK9 inhibitors. Cardiologists and general practitioners alike are excited about the two PCSK9 inhibitors, alirocumab and evolocumab, in late-stage clinical development, because of their ability to lower LDL-C in patients for whom other treatments have been ineffective.

Approach: 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 hypercholesterolemia or mixed dyslipidemia; evolocumab is also licensed for the treatment of adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia. 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. Bococizumab; is a drug that was in development by Pfizer targeting PCSK9 to reduce LDL cholesterol. Pfizer withdrew the drug from development in November 2016, after completion of 6 "phase 3" studies; determining that it was "not likely to provide value to patients, physicians or shareholders" **(23)**.

Another investigational product; LY3015014 (LY) by Lilly; a neutralizing antibody of proprotein convertase subtilisin/kexin type 9 (PCSK9), administered every 4 or 8 weeks in patients with primary hypercholesterolemia, when added to a background of standard-of-care lipid-lowering therapy, including statins **(23)**.

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. In multiple subcutaneous dosing in hypercholesterolemia 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 **(24)**. ALN-PCSsc is now in Phase II development (ORION program).

Do we need guidelines?

The availability of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab and evolocumab, for use has highlighted the need for practical guidance. In response, practice guidelines have been issued to aid clinicians in the appropriate use of these novel treatments. In balancing the clinical need for these treatments with their cost, a conservative approach has to be considered.

In May 2017; an Expert Panel convened by the National Lipid Association was charged with updating the recommendations on the use of

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proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy that were provided by the 2015 National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia; current update provides the Expert Panel's evidence-based recommendations on the clinical utility of PCSK9 inhibitors in patients with stable ASCVD, progressive ASCVD, familial hypercholesterolemia phenotype/low-density lipoprotein cholesterol ≥190 mg/dL, and very-high-risk patients with statin intolerance **(25)**.

ASCVD

1. PCSK9 inhibitor therapy should be considered for ASCVD risk reduction in patients with stable atherosclerotic cardiovascular disease, particularly in those with additional ASCVD risk factors, on maximally-tolerated statin therapy ± ezetimibe, with on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength A, Quality: High
2. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with progressive atherosclerotic cardiovascular disease on maximally-tolerated statin therapy ± ezetimibe, and on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength B, Quality: Moderate

Phenotypic FH/LDL-C ≥190 mg/dL

3a PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients ages 40 to 79 years with phenotypic FH, pretreatment LDL-C ≥190 mg/dL, no uncontrolled ASCVD risk factors, or other key additional high-risk markers*, and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥130 mg/dL on maximally-tolerated statin therapy ± ezetimibe. Strength B, Quality: Moderate

3b PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 40 to 79 years with phenotypic FH, pretreatment LDL-C ≥190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers*, or genetic confirmation of FH, and on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL on maximally-tolerated statin ± ezetimibe. Strength: B, Quality: Moderate

3c PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 18 to 39 years with phenotypic FH, pre-treatment LDL-C ≥190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers*, or genetic confirmation of FH, and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥130 mg/dL on maximally-tolerated statin ± ezetimibe. Strength: E, Quality: Low

3d PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with homozygous familial hypercholesterolemia, either of unknown genotype, or those known to be LDL receptor defective, on maximally-tolerated statin therapy ± ezetimibe with LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength B, Quality: Moderate

Very-high-risk/statin intolerance

4. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in selected very-high-risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid-lowering therapies. Strength C, Quality: Low

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLA, National Lipid Association; PCSK9, proprotein convertase subtilisin/kexin type 9.

*Including history of uncontrolled high blood pressure, diabetes, current cigarette smoking, or family history of premature ASCVD; or additional high-risk markers (coronary calcium ≥300 Agatston units [or ≥75th percentile for the patient's age, gender, and ethnicity]; Lp(a) ≥ 50 mg/dL using an isoform insensitive assay, hs-CRP ≥ 2 mg/L or CKD including albumin/creatinine ratio ≥ 30 mg/g).

(Figure 1) 2017 Recommendations of the NLA Expert Panel on treatment with PCSK9 inhibitors

Tolerability and safety of pcsk9 inhibitors

The PCSK9 inhibitors appear to be generally well-tolerated, but long-term safety data are needed as well as long-term outcomes studies (Table 2). A meta-analysis of 20 randomized controlled trials, further confirmed the significant effect of PCSK9 inhibitors in decreasing LDL-C with good safety and tolerability. 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 **(26)**.

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) **(27,28)**. 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).

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(Table 2) Clinical trials involving alirocumab and evolocumab

Alirocumab	Evolocumab
ODYSSEY LONG TERM	DESCARTES
ODYSSEY COMBO II	RUTHERFORD-2
ODYSSEY FH I	TESLA
ODYSSEY FH II	OSLER
	MENDEL-2
	LA PLACE-2
	FOURIER

The US Food and Drug Administration (FDA) have raised concerns regarding the possibility of adverse effects on cognition with PCSK9 inhibitors. It was not clear whether these concerns were relevant specifically to these agents or to lowering of LDL-C per se, as previously expressed for statins **(29)**. 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 neuro-cognitive 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 **(30)**. Similarly, data from a pooled analysis of integrated data from phase 2/3 trials showed no increase in the incidence of neuro-cognitive effects, which were reported as 0.1% with evolocumab (n= 3,946) versus 0.3% in the control groups (n=2,080) **(31)**. However, a recent study that addressed this issue; "Evaluating PCSK9 Binding Antibody Influence On Cognitive Health in High Cardiovascular Risk Subjects EBBINGHAUS", a sub-study of the FOURIER outcomes study with evolocumab was presented in the ACC 2017 earlier in March which evaluated change over time in neurocognitive testing in subjects receiving statin therapy in combination with evolocumab (AMG 145), compared with subjects receiving statin therapy in combination with placebo; and the researchers found no evidence that adding the PCSK9 inhibitor evolocumab on top of statin treatment causes memory loss or other cognitive issues **(32)**.

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 **(33,34)**.

• We now have evidence that treatment with evolocumab for up to 52 weeks did not influence plasma levels of gonadal hormones and adreno-cortico-trophic hormone (ACTH), or erythrocyte vitamin E concentration **(35)**. 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 **(36)**.

• Finally, anti-drug binding or neutralizing antibodies to these agents do not appear to be an issue, with evidence suggesting that these

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are transient and affect 0.1–0.7% of patients **(37)**.

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

Pcsk9 inhibitors: a technology worth paying for

Finally; in order to be cost-effective for patients, providers, and payers, the new proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors would need to cost around $2400 per year, a mark that is strikingly lower than what manufacturers are currently charging for the two available drugs. Using a "willingness-to-pay" threshold of $50,000 per quality-adjusted life-year (QALY) gained, the PCSK9 inhibitors would need to cost $2100 per year for the familial hypercholesterolemia (FH) patient population. For secondary-prevention patients with LDL-cholesterol levels >70 mg/dL despite taking a maximally tolerated statin, a cost of $2400 per year would render the new monoclonal antibodies cost-effective. Finally, for statin-intolerant patients with CVD and an LDL-cholesterol level >70 mg/dL, the drugs would be cost-effective at the same willingness-to-pay threshold if priced at $2600 per year **(38)**.

At present evolocumab (Repatha, Amgen) and alirocumab (Praluent, Sanofi/Regeneron), cost $14,100 and $14,600 in the US, respectively, for a year-long supply of the LDL-cholesterol–lowering medication. In Europe, evolocumab, the only agent approved by the European Commission, costs $6800 per year in the UK and $8200 and $8800 per year in Austria and Finland, respectively. The new report, conducted by the Institute for Clinical and Economic Review (ICER), an independent, non-profit research group, evaluated the potential cost-effectiveness of the new drugs "to support dialogue needed for successful action to improve the quality and value of healthcare for all patients" **(38)**.

Conclusion

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 hypercholesterolemia. The initial data on cardiovascular outcomes presented recently provide an intriguing hint of a possible improvement in long-term cardiovascular prognosis with these agents.

Randomized 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 hypercholesterolemia phenotype associated with familial hypercholesterolemia. 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.

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