Abstract
This review discusses recent advances in lipid management, focusing on a new class of drugs known as pcsk9i (proprotein convertase subtilisin/kexin 9 inhibitors). It describes the basic and clinical pharmacology of these drugs.

Keywords: Alirocumab, Bococizumab, Evolocumab, LDL cholesterol, Familial hypercholesterolaemia.

Introduction
Dyslipidaemia is a commonly encountered clinical condition, which may occur alone or in conjunction with other aspects of the metabolic syndrome. Dyslipidaemia is an important predictor of cardiovascular disease as well. In spite of statin therapy, not all patients are able to achieve target LDL-C (low-density lipoprotein cholesterol) targets. Even in those who do achieve adequate LDL-C lowering, there does remain a significant amount of residual cardiovascular risk. Yet others are unable to tolerate statin therapy, and require other forms of treatment. A small proportion of patients may have heterozygous (HeFH) or homozygous familial hypercholesterolaemia (HoFH), and are unable to achieve optimal LDL-C goals with statin monotherapy.

These clinical situations represent therapeutic challenges which cannot be met by statins alone. These challenges, all of which may lead to adverse cardiovascular outcomes if left untreated, warrant the development of newer classes of drugs to control LDL-C.

Cholesterol Biology
The primary target of lipid lowering therapy is LDL-C, even though definitions of metabolic syndrome prefer to include low HDL-C (high density lipoprotein cholesterol) and high triglycerides in their diagnostic criteria. Serum LDL C binds to LDL receptors (LDL R), which are located on the surface of hepatocytes. LDL C is then carried to the cytoplasm of the hepatocytes, where it is degraded in the lysosomes, leaving the LDLR free to be recycled back to the cell surface for use.

Normally, a physiological mechanism exists to maintain this homeostasis. When the serine protease PCSK9 (proprotein convertase subtilisin/kexin type 9) binds to LDLR at the surface, it ensures lysosomal degradation of the LDLR as well. PCSK 9 activity is up regulated during statin therapy by a positive feedback mechanism, initiated by lowered cholesterol levels. This homeostatic mechanism prevents statins from exerting their full LDL lowering effects.

PCSK9 Inhibition
PCSK9 is a relatively recently discovered protein. Gain-of-function mutations in PCSK9 have been linked with hypercholesterolaemia, while loss-of-function mutation are associated with markedly lower levels of LDL-C. PCSK9 inhibition thus becomes an apposite strategy for lipid lowering therapy.

Various pharmaceutical means are being developed to inhibit PCSK9. These include small monocodies, oral peptides, antisense oligonucleotides, and small interfering ribonucleic acid (SIRNA). All these, however, are still in early stages of development. This review focuses on monoclonal antibodies to PCSK9, which have recently been approved for use in European Union, USA, and other markets. Two fully human IgG2 monoclonal antibodies to PCSK9, i.e., alirocumab and evolocumab, are currently approved for use. A humanized monoclonal antibodies, bococizumab is presently in phase 3 randomized clinical trials.

Mechanism of Action
The PCSK9 inhibiting antibodies, i.e., alirocumab and evolocumab, bind with high affinity to PCSK9, preventing it from binding to LDLR, and thus preventing PCSK9-mediated degradation of LDLR. This allows lysosomal degradation of LDL to continue unimpeded, while keeping LDLR free to be recycled back to the hepatocyte cell surface, to continue transporting LDL C for degradation.

Both alirocumab and evolocumab are eliminated by two pathways: a saturable target mediated binding to PCSK9,
followed by lysosomal degradation; and nonspecific clearance by the reticulo-endothelial system.

The PCSK9 inhibitors are not eliminated by hepatic metabolism or renal clearance. This allows them to be used without dose adjustment in mild to moderate hepatic or renal impairment. As data is currently lacking, the drugs should be used with caution in severe hepatic or severe renal impairment.

**Clinical Pharmacology**

Both alirocumab and evolocumab have demonstrated efficacy, safety, and tolerability as lipid lowering agents in various patient populations.

**Alirocumab**

As part of the ODYSSEY programme, alirocumab has been evaluated in ten randomized, double-blind, multinational, phase III, studies either as monotherapy or in combination with other Lipid lowering therapy (LLT), and included patients with heterozygous familial hypercholesterolaemia (HeFH) and non-FH patients who had clinical atherosclerotic cardiovascular disease.

Alirocumab monotherapy provided significantly greater reductions in LDL-C from baseline to week 24 than ezetimibe, with a treatment difference of -31.6%. When added to statin-based therapy in patients with hypercholesterolaemia and high CV risk, alirocumab generally provided significant reductions in LDL-C from baseline to week 24 relative to all comparators, with treatment differences of -61.9% (LONG TERM) and -45.9% (COMBO I) versus add-on placebo, -23.6 to -36.1% versus add-on ezetimibe (COMBO II, OPTIONS I, and OPTIONS II) and -20.3 to -49.2% versus modified statin therapy. In all of these trials, the LDL-C-lowering benefits of alirocumab were observed by week 4 and sustained to week 24, 52, or 78 of treatment.

Additionally, a post hoc analysis of CV events in LONG TERM demonstrated a 48% reduction in the risk of an adjudicated major adverse CV event (composite endpoint of CHD death, non-fatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) with add-on alirocumab versus add-on placebo (1.7 vs. 3.3%; hazard ratio 0.52; 95% CI 0.31-0.90; nominal p = 0.02). Alirocumab recipients also experienced significant reductions from baseline in apoB, non-HDL-C, and Lp (a) compared with patients receiving control treatment (placebo or ezetimibe), irrespective of whether they were receiving background statins. Fasting TGs were also significantly reduced with alirocumab versus placebo when combined with statin therapy. When added to statin-based treatment, alirocumab was associated with significant increases in HDL-C and apoA1 relative to placebo or ezetimibe.

Subcutaneous alirocumab, as monotherapy or in combination with other LLT, was generally well tolerated in patients with hypercholesterolaemia, including those with HeFH or statin intolerance in the ODYSSEY trials.

**Evolocumab**

Evolocumab has been studied in heterozygous familial hypercholesterolaemia (RUTHERFORD-2), primary hypercholesterolaemia/mixed dyslipidaemia as combination therapy with statin (LAPLACE-2, MENDEL-2), primary hypercholesterolaemia/mixed dyslipidaemia in Japanese (YUKAWA-2), statin intolerants patients (GAUSS-2) and primary hypercholesterolaemia/mixed dyslipidaemia as monotherapy (MENDEL-2). The LDL-C levels were lowered by 54.8% to 76.3% in these trials, indicating the efficacy of evolocumab in various clinical situations. A target LDL-C of <1.8 mmol/l was achieved in 85.8% to 94.5% of all evolocumab recipients, as compared to only 16.7% to 62.3% of those receiving ezetimibe, and 1.9% to 38.9% of those on placebo on a background therapy of moderate or high intensity statin in the LAPLACE-2 trial. A pooled analysis of all these trials, PROFICIO, reported consistent LDL-C reductions in all subgroups, including those aged >65y and <65y, men and women, those with and without type 2 diabetes, those with and without metabolic syndrome, and those with low, moderate or high risk of CVD.

**Pharmacodynamics**

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<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
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<tbody>
<tr>
<td>Time of maximum suppression of free PCSK9</td>
<td>4-8 hours</td>
<td>4 hours (85-95%)</td>
</tr>
<tr>
<td>Time to nadir of LDL-C</td>
<td>15 days</td>
<td>14 days with 140mg; 21 days with 420 mg</td>
</tr>
<tr>
<td>Reduction on LDL-C</td>
<td>58% with 150 mg</td>
<td>64% with 420 mg</td>
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**Pharmacokinetics**

<table>
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<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
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<tbody>
<tr>
<td>Bioavailability</td>
<td>85%</td>
<td>72%</td>
</tr>
<tr>
<td>C_{max}</td>
<td>8.18 mg/L with 75 mg in abdomen</td>
<td>130 µg/ml with 140mg; 46.0µg/ml</td>
</tr>
<tr>
<td>Time to C_{max}</td>
<td>3-7 days (median)</td>
<td>3-4 days (median)</td>
</tr>
<tr>
<td>Time to steady state</td>
<td>4-6 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.04 - 0.05 L/kg</td>
<td>3.3L</td>
</tr>
<tr>
<td>Half life</td>
<td>17-20 days (12 days with statin co-administration)</td>
<td>11-17 days</td>
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lipoprotein cholesterol (HDL-C) apolipoprotein A1, triglycerides, lipoprotein a, non-HDL-C, and total cholesterol. The drug also showed significant reduction in free PCSK9 levels ranging from 12.7 to 61.1%. It is noteworthy that PCSK9 has been identified as a significant cardiovascular risk factor, independent of LDL-C concentrations.

Longer trials, including DESCARTE, OSLER-1 and OSLER-2 have assessed the long term efficacy and safety of evolocumab, at 52, 124 and 48 weeks respectively. OSLER-1 and OSLER-2 have demonstrated cardiovascular benefit with evolocumab, as compared to standard of care therapy. Evolocumab-treated subjects were less likely to experience “all cardiovascular events”, and major adverse cardiovascular events at one year (hazard ratio 0.47; 95% CI 0.28-0.78 for both).

Evolocumab has been studied in homozygous familial hypercholesterolaemia, in phase 3 and long term trials. The TESLA Part B trial revealed efficacy of evolocumab, which varied according to the genetic cause. Patients with defective mutations in both LDLR alleles experienced -46.9% change in LDL, those with defective mutations in one /both LDLR alleles had -40.8% change in LDL, while those with defective/negative LDLR status had -24.5% reduction. All these reductions, however, were statistically significant. There was one non responder out of 33 subjects: this subject had a negative/negative LDLR status. Interim results of the ongoing TAUSSIG study reveal an 18.6% reduction in LDL-C at 48 weeks, with 15% subjects having been able to discontinue or reduce the frequency of apheresis.

Summary
In conclusion, both alirocumab and evolocumab, given by subcutaneous injection, can further lower LDL-cholesterol levels significantly in patients with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease already taking maximally tolerated doses of a statin. Limited posthoc data suggest that they may decrease the incidence of cardiovascular events as well. The drugs appear to be safe and well tolerated, with its adverse event profile being similar to that of placebo.

References