What’s new in lipid lowering therapies in diabetes?

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Abstract
Diabetes can lead to myriad of microvascular and macrovascular complications - with the leading cause of mortality in diabetes being cardiovascular disease (CVD). Low-density lipoprotein cholesterol (LDL-C), along with non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TGs) are proven, modifiable risk factors for CVD. This article will focus on lipid lowering agents in individuals with diabetes. It will summarise relevant changes in the latest guidelines for dyslipidemia, and will also review the mechanisms of action of lipid lowering agents along with the latest cardiovascular outcomes data specific to individuals with diabetes. Older agents such as statins, ezetimibe, fibrates and nicotinic acid will be reviewed with a focus on new diabetes-specific evidence. Similarly, a relatively novel agent proprotein-convertase subtilisin-kexin type 9 (PCSK9) will be reviewed and details around the Pharmaceutical Benefits Scheme (PBS) criteria governing its usage in Australia will be included. Finally, this review will touch on agents still on the horizon such as icosapent ethyl, high-density lipoprotein (HDL) mimetics, bempedoic acid, omega-3 free fatty acids, bromodomain and extra-terminal proteins (BET) inhibitors and inclisirin - a long-acting RNA interference agent. In the appropriately selected population of individuals with diabetes, these agents can assist to further improve lipid profile and reduce cardiovascular events.
**What’s new in lipid lowering therapies in diabetes?**

Diabetes confers an independent risk to cardiovascular disease (CVD), but also shares many common comorbidities such as hypertension and dyslipidaemia. CVD remains the commonest cause of death in individuals with diabetes. Therefore, individuals with diabetes need to be monitored and offered aggressive treatment for reversible risk factors. Low-density lipoprotein cholesterol (LDL-C) is a reversible risk factor that should be reduced to the lowest tolerable level (1). However, although LDL-C reduction is the primary target, accumulating evidence suggest that other lipid measurements can add predictive value to CVD risk. Non-High-density-cholesterol (Non-HDL) (calculated as total cholesterol – HDL cholesterol) reflects both LDL-C and triglyceride (TG)-rich lipoproteins. European Guidelines suggest that Non-HDL-C can be an alternative target to LDL-C, particularly in individuals with high TGs (2). Non-HDL-cholesterol also has the added benefit of not requiring patients to be in a fasted state prior to collection. Target levels are <2.6mmol/l, <3.3mmol/l and <3.8mmol/l with very high, high and low-to-moderate CVD risk, respectively. Although these targets provide a guide as to what high risk patients should be aiming for, the latest perspective on LDL-C and Non-HDL-C targets suggests there is no evidence for an optimal target, and that the focus should be on maximising lipid-lowering-therapy even when suggested lipid targets have been reached as CVD events can be further reduced (1). Recent cardiovascular outcome trials have demonstrated that alongside older agents such as statins and fibrates, lipid-lowering therapies such as ezetimibe and monoclonal antibodies inhibiting proprotein-convertase subtilisin-kexin type 9 (PCSK9) lower LDL-C, Non-HDL-C and reduce CVD risk further (3). Being aware of the therapeutic benefit of classes of lipid-lowering therapies which are available or on the horizon are therefore important in clinical practice.

**Statins**
Statins lower LDL-C with reductions in the range of 30-63% (4) and remain first line pharmacological therapy to address elevated CV risk (5) (Table 1). They competitively inhibit hydroxymethylglutaryl-CoA-reductase, the rate-limiting step in cholesterol biosynthesis (6) (Figure 1).

A randomised controlled trial involving 2,383 individuals with type 2 diabetes (T2D) and at least one other risk factor, randomised participants to atorvastatin 10 mg per day or to placebo (7). Atorvastatin resulted in a 36% reduction in acute CV events. The study ended prematurely due to the benefits observed. The number needed to treat (NNT) at four years for the composite primary endpoint was 31. The reduction in CV events was consistent with a mean difference in LDL-C of 1.20mmol/L between the two groups, suggesting that individuals with T2D with additional CV risk factors should be considered to receive statin therapy regardless of their baseline LDL-C levels.

Pitavastatin is a newer statin available in Europe and Asia. In phase III and IV studies pitavastatin 1 to 4 mg once daily was no less effective than presumed equipotent dosages of atorvastatin and simvastatin (including in patients with T2D) and was superior to pravastatin in lowering LDL-C levels (8). It was generally well tolerated and, in several studies, it did not appear to adversely affect glucose metabolism. In fact, when used in combination with lifestyle modification in an open label, longer-term study, it was associated with a significant reduction in the risk of progression from impaired glucose tolerance to diabetes relative to lifestyle modification advice alone (9). However, a recent Korean study did not show any difference between pitavastatin and other statins in respect to glucose tolerance (10) and genetic studies (8) suggest that reduced activity of HMGCo-A reductase per se is associated with increased diabetes risk. Therefore, these findings should be regarded with some caution.

**Statin intolerance**
Documented rates of severe statin side effects are low (11) however, in clinical experience it is not uncommon for patients to describe symptoms whilst on therapy. Recognizing the true cases of statin intolerance is essential in order to avoid unnecessary cessation. In true statin intolerance, low doses can still be used and if tolerated, should be gradually increased to achieve the highest tolerable dose - as even low doses do provide a reasonable degree of lipid-lowering effect (12).

A current RCT (13) aims to determine if treatment with 180mg of bempedoic acid versus placebo decreases the risk of CV events in patients who are statin intolerant. Bempedoic acid inhibits adenosine triphosphate-citrate-lyase, an enzyme involved in fatty-acid and cholesterol synthesis. If this study’s result shows promise, bempedoic acid may potentially be an alternative lipid-lowering option for this high-risk population.

Ezetimibe

Ezetimibe targets the Niemann–Pick C1–like 1 (NPC1L1) protein, thus decreases cholesterol absorption from the ileum (Figure 1) (14). The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT, n= 18, 144) including 5,000 individuals with diabetes and acute coronary syndrome (ACS), demonstrated that the addition of ezetimibe to statin therapy reduced the composite primary endpoint (cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke) (14). Ezetimibe reduced LDL-C levels by an additional 24% when added to statins. There was a statistically significant increased benefit in individuals with diabetes compared to individuals without - 14% vs 0.6% reduction in the primary endpoint (P=0.023)(14). The NNT at seven years for the combined primary end-point was 50. There were no differences between the two groups in regards to adverse events.

Ezetimibe in conjunction with statins is therefore particularly effective in individuals with diabetes with suboptimal lipid levels despite maximal dose statin therapy, individuals unable
to tolerate maximum statin doses or as monotherapy in patients completely intolerant of statin therapy (15).

**PCSK9 inhibitors**

PCSK9 is a protein encoded by the PCSK9 gene involved in the regulation of LDL-receptors on the surface of hepatocytes. LDL-C are removed from the circulation via LDL-receptors. Normally the LDL:LDL-receptor-complex is internalized, the LDL is degraded enzymatically, and the receptor is re-cycled to the cell surface. PCSK9 binds to the LDL:LDL-receptor-complex, marking the LDL receptor for degradation and so preventing receptor re-cycling (16). PCSK9 inhibition increases LDL-receptor number and clearance of LDL from the circulation (16).

Evolocumab and alirocumab are fully human monoclonal antibodies that inhibit PCSK9. Evolocumab is currently the only PCSK9 inhibitor available in Australia on the Pharmaceutical Benefits Scheme (17). PCSK9 inhibitors lead to a significant reduction in LDL-C when used in conjunction with statins (3). Despite the efficacy of PCSK9 inhibitors in lowering LDL-C and CV events, their high cost means that PBS reimbursement in Australia is highly restricted. Currently, only evolocumab is reimbursed for patients with familial hypercholesterolemia and inadequately controlled LDL-C (17). Alirocumab was approved by the Australian Therapeutic Goods Administration in 2016 but at the time of writing has not received PBS approval (17).

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial (3) is a randomised trial. The primary composite end-point included cardiovascular death, myocardial infarct, stroke, hospitalisation for unstable angina or cardiac revascularisation. Participants (n=27,564, 36.6% with T2D) had LDL-C levels of ≥1.8mmol/L, were already receiving statin therapy and were randomised to either
evolocumab or placebo with a median of 2.2 year follow-up. At 48 weeks, evolocumab in addition to statin therapy, lowered LDL-C levels by 59% with a significant risk reduction of the composite primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; HR, 0.85; 95% CI, 0.79 to 0.92; P<0.001, NNT=67).

A sub-analysis of FOURIER examined the effect of evolocumab on cardiovascular events by diabetes status at baseline (18). Individuals with diabetes (n=11,031, 97.2% T2D) and individuals without diabetes (n=16,533) had similarly reduced cardiovascular outcomes, (HR 0.83, CI 0.75-0.93), and (HR 0.87, CI 0.79-0.96), (p=0.60). The only significant difference in adverse effects is that of injection site reactions in the evolocumab group (3).

Although currently not available in Australia, alirocumab has recently been shown to reduce cardiovascular risk in high-risk individuals already on high-intensity statin therapy after ACS. This was a large RCT (19) involving 18,924 patients who had an ACS 1 to 12 months earlier, had an LDL <1.8mmol/L, a non-HDL of ≥2.6mmol/L or an apolipoprotein-B level of ≥80mg/dL. 28.5% of individuals had diabetes in the alirocumab arm and 29.1% in the placebo arm. The median duration of follow up was 2.8 years. The composite primary end point of CV events occurred in 903 (9.5%) in the alirocumab group vs. 1052 (11.1%) in the placebo group, (HR=0.85, 95% CI, 0.78-0.93, p<0.001). The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group).

These studies demonstrate the potential benefit of PSK9 inhibitors in high-risk patients, including individuals with diabetes and those with known ACS. However, its high cost is likely to limit its clinical use for the foreseeable future.

**Fibrates**
Fibrates bind and activate peroxisome proliferator-activated receptor alpha (PPAR alpha), a member of the family of nuclear-hormone-receptors that are activated by lipids (Figure 1). Fibrates lower plasma triglyceride (TG) levels by decreasing very-low-density-lipids (VLDL) production and by increasing the clearance of TG rich lipoproteins (20).

In the Fenofibrate intervention and event lowering in diabetes (FIELD) study, 9795 participants with T2D and a TG level of 1.0–5.0 mmol/L were randomised to fenofibrate or placebo. Fenofibrates did not reduce the risk of the primary outcome (coronary heart disease death or non-fatal myocardial infarction)(21). Similarly, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study, 5518 individuals with T2D were randomised to either simvastatin with fenofibrate, or simvastatin with placebo. The mean follow-up was 4.7 years. The primary CV outcome rate at one year was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79 to 1.08; P = 0.32) suggesting combination of fenofibrate and simvastatin did not reduce the rates of CV outcomes (22).

In a subgroup analysis of FIELD (23), participants with marked dyslipidemia (elevated TG ≥2.3 mmol/L, HDL cholesterol of <1.08mmol/L) and T2D were found to be highest risk of CVD (17.8% over five years). They also had the most significant reduction in CV risk when treated with fenofibrate. There was a 27% relative risk reduction observed (95% CI 9-42, P= 0.005; NNT= 23) (23).

A new fibrate – pemafibrate is currently undergoing phase III trials to determine if administering a dose of 0.2mg twice a day in patients with T2D and hypertriglyceridemia will delay the time to first occurrence of the clinical composite end point of non-fatal MI, non-fatal stroke, hospitalisation for unstable angina requiring unplanned coronary revascularisation, or CV death (24).
Fenofibrate can be considered in individuals with significantly elevated hypertriglyceridemia and low HDL and in patients with high CV risk, but should not replace statins (table 2).

Fenofibrate also reduces diabetic retinopathy (DR) progression in T2D (25, 26). Several mechanisms have been proposed including anti-inflammatory, anti-angiogenic, and cell-signalling effects (27). The ACCORD-EYE study (26) observed significantly reduced progression of DR score, need for laser photocoagulation or vitrectomy in the fenofibrate plus statin group (6.5%) versus the statin alone group (10.2%) (OR, 0.60; 95% CI 0.42 to 0.87; P = 0.006). The ACCORDION-Eye-Study on the other hand, an observational study eight years following the completion of the ACCORD trial, found no significant difference in DR progression: 11.8% versus 10.2% (OR 1.13, 95% CI 0.71–1.79, P = 0.60), demonstrating lack of “metabolic memory” for lowering triglycerides (25) (table 3). Metabolic memory is a phenomenon whereby early, intensive metabolic control has potential enduring beneficial effects (28). This suggests that fenofibrate treatment may need to be ongoing to maintain benefit.

**Nicotinic acid (niacin)**

Nicotinic acid/niacin and its analogues inhibit the synthesis and secretion of VLDL, increases HDL and has been shown to lower lipoprotein(a) levels by 25% (29). However, there is currently no evidence that lowering Lp(a) with nicotinic acid leads to reduced CV events. A large RCT (29) involving 3414 patients with established CVD, low HDL, hypertriglyceridemia, and treated with a statin to a mean LDL of 1.8mmol/L observed no additional benefits with niacin treatment. Furthermore, the utility of niacin is limited by its poor tolerability. At the standard dose, 80% of users describe flushing and 20% describe pruritis, paraesthesia and nausea (29).
Pipeline therapies

Icosapent ethyl

Icosapent ethyl is a highly purified eicosapentaenoic acid (EPA) ethyl ester that is de-esterified to EPA after oral ingestion. EPA, like docosahexaenoic acid (DHA), is a long chain omega-3 fatty acid and has recently been shown to have potential beneficial effects in lowering TGs (figure 2). In a recent Japanese study (30), 18,645 patients with hypercholesterolemia were randomised to low intensity statin plus 1.8g of EPA daily or statin therapy alone. The risk of major coronary events was 19% lower, in the group that received EPA plus statin therapy than in the group that received statin therapy alone. In another recent RCT (31) involving 8179 participants with elevated TGs, established CVD or with diabetes (T2D N= 4730, T1D N=57) and other risk factors who were randomised to icosapent etyl 2g twice daily or placebo. The authors observed that ischemic events, including cardiovascular death, was significantly lower among those who received icosapent ethyl compared with placebo (17.2% vs. 22.0%; HR=0.75; 95% CI, 0.68-0.83; P<0.001). The mechanism behind these benefits is not yet known, but is thought to consist of stabilization or regression of coronary plaques and potentially an anti-inflammatory effect. The findings of this study are of particular significance as it stands apart from the earlier described trials of omega 3 fatty acids which did not observe a reduced rate of cardiovascular events when administered in addition statins.

HDL mimetics

HDL has been associated with a potential protective effect against atherosclerosis. However, despite the evidence from epidemiological association studies, raising HDL levels has not been proven to reduce CV event risk (32). This has led to a shift in focus towards the functional properties of HDL (particularly its role in reverse cholesterol transport) rather
than raising HDL levels. There are three mains steps to reverse cholesterol transport: 1) Cholesterol efflux, where HDL/apolipoprotein A-1 (apoA-1) remove excess cholesterol from cells, 2) lipoprotein remodelling, where HDL undergoes structural modifications and 3) hepatic lipid intake, where HDL releases cholesterol to the liver for final excretion (33). Several HDL mimetics have been tested in humans. Recombinant apoA-I Milano is based on a naturally occurring mutation where carriers are characterised by exceptionally low prevalence of CVD due to increased induction of reverse cholesterol transport. Unfortunately, a recent RCT involving 122 post-ACS patients failed to demonstrate incremental regression of coronary atherosclerosis (33).

CER-001 is a negatively charged lipoprotein complex that consists of recombinant human apoA-I and two naturally occurring phospholipids. Preliminary studies showed CER-100 can rapidly mobilise large amounts of cholesterol into the HDL fraction. However, once again larger safety and efficacy trials did not observe any differences in atheroma regression in the CER-100 group (33).

CSL-112 is a reconstituted HDL particle consisting of native apoA-I and phospholipids. It appears to be safe after two phase I trials and was associated with a dose-dependent increase in apoA-I levels post infusion and also significantly enhanced and increased cholesterol efflux (33). A large phase III study is currently underway with the aim to determine the potential benefit of CSL-112 in reducing CV events.

**Inclisiran**

PCSK9 antibodies have a short duration of effect and therefore require second weekly or monthly subcutaneous injections (17). Inclisiran is a long-acting RNA interference therapeutic agent that inhibits the synthesis of PCSK9 and therefore lowers LDL-C. This interfering molecule engages the RNA-induced-silencing-complex resulting in cleavage of
the messenger RNA molecule encoding PCSK9, preventing PCSK9 protein translation and therefore results in reduced levels of PCSK9 protein with longer lasting effects (34) (table 4).

**Bromodomain extra-terminal protein (BET) inhibitors**

Another potential novel target is the selective inhibition of bromodomain and extra-terminal proteins (BET). Apabetalone affects biological processes which are important in atherosclerosis and acute coronary events via selective inhibition of BET proteins. These regulate gene transcription via an epigenetic mechanism and may reduce CV risk by modulating pathways including reverse cholesterol transport, vascular inflammation, coagulation, and complement (figure 2). ApaBetalone has been shown to effectively downregulate the complement cascade, atherosclerosis and ApoE levels in rodents. The BETonMACE study (35) will focus on the effects of apabetalone in the prevention of subsequent MACE in >2400 individuals with CAD, T2D, low HDL-C levels on a background of statin therapy.

**Diet and Omega-3**

Unfortunately, there is no single ideal diet for all people with diabetes. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and plant-based diets are examples of healthy eating patterns recommended by the 2018 Standards of Medical Care in Diabetes (36).

Omega-3 fatty acids are thought to reduce hepatic production of TG-rich VLDL and increase the removal of other TG-rich lipoproteins (figure 2). Although a large number of studies have been performed to evaluate the impact of omega-3 fatty acids on a range of surrogate and clinical cardiovascular measures, most have failed to demonstrate benefit (37). However, many of these trials involved administration of low doses (eg, 1 g daily) of omega-3 fatty acids using formulations with variable bioavailability (38).
carboxylic acid) is a mix of omega-3 free fatty acids (both EPA and DHA) which has shown to decrease TGs, and has approval from the USA FDA as an adjunct to diet in individuals with severe hypertriglyceridemia. Unlike conventional omega-3 ethyl esters, it does not require hydrolysis by pancreatic lipase, allowing for better bioavailability. The effects of Epanova are currently being investigated in the Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) trial (38). This RCT aims to determine whether 4g of Epanova daily will reduce the rate of CV events in 13,000 statin-treated patients with hypertriglyceridemia and low HDL-C, many of whom have diabetes. The outcome will not be known for several years.

**Conclusion**

Diabetes is a significant risk factor for CVD and the lipid profile needs to be addressed in all patients with diabetes. Statins should always be considered first line. Ezetimibe in combination with statins can result in incremental lowering of LDL-C levels and further improve cardiovascular outcomes. Fibrates have a role in patients with high triglycerides and low HDL and fenofibrate should also be considered in patients with T2D and retinopathy. Finally, PCSK9 inhibitors are a novel class of lipid-lowering medications that could be integrated into the management of individuals with diabetes and dyslipidemia. They can be used in addition to statins, ezetimibe and fibrates. In appropriately selected individuals with diabetes, these new agents can assist to further improve lipid profile and reduce cardiovascular events, but their current use is limited by their cost. Many new agents are currently in development and provide great potential for further improving management of dyslipidemia in the future.
References


Table 1: Efficacy of different statins* (4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rosuvastatin</th>
<th>Atorvastatin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
<th>Fluvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL reduction</td>
<td>52-63% (10-40mg)</td>
<td>38-54% (10-80mg)</td>
<td>28-41% (10-40mg)</td>
<td>19-40% (10-40mg)</td>
<td>17-33% (20-80mg)</td>
</tr>
</tbody>
</table>

*The range of LDL reduction (%) depends on the dose of the medication (mg/day)

Table 2: Comparison of different LDL lowering agents (4, 14, 39)

<table>
<thead>
<tr>
<th>Agent</th>
<th>LDL lowering</th>
<th>TG lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>30-63%</td>
<td>14-33%</td>
</tr>
<tr>
<td>Ezetimibe + statins</td>
<td>Additional 23-24%</td>
<td>-</td>
</tr>
<tr>
<td>Fibrates</td>
<td>6-20%, 41-53%</td>
<td></td>
</tr>
<tr>
<td>PCSK9 inhibitor + statin</td>
<td>Additional 60%</td>
<td>12-31%</td>
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</table>
Table 3: Eye benefits in T2D individuals prescribed fenofibrates

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial type</th>
<th>Number</th>
<th>Diabetes type</th>
<th>Drug</th>
<th>Doses</th>
<th>Follow up</th>
<th>Eye outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIELD</td>
<td>RCT</td>
<td>9795</td>
<td>T2D</td>
<td>Fenofibrate vs placebo</td>
<td>Fenofibrate: 200mg</td>
<td>5 years</td>
<td>535 (61%) courses of laser treatment on placebo vs. 337 (39%) patients on fenofibrate (HR, 0.6; 95% CI, 0.5-0.8; p=0.0003). 342 (62%) vs 218 (39%) laser treatments for maculopathy (HR, 0.7; 95% CI, 0.5-0.9; p=0.002) and 193 (62%) vs 119 (38%) laser treatments for proliferative retinopathy (HR, 0.6; 95% CI, 0.4-0.9; p=0.009)</td>
</tr>
<tr>
<td>ACCORD-EYE</td>
<td>RCT</td>
<td>2856</td>
<td>T2D</td>
<td>Fenofibrate + statin vs statin alone</td>
<td>Fenofibrate: 160mg, Simvastatin: 20-40mg</td>
<td>4 year</td>
<td>Patients who progressed with their DR score or requiring laser photocoagulation or vitrectomy being 6.5% in the fenofibrate plus statin group versus 10.2% in the statin alone group (OR, 0.60; 95% CI 0.42 to 0.87; P = 0.006)</td>
</tr>
<tr>
<td>ACCORDION Eye study</td>
<td>RCT (follow on study from ACCORD-EYE)</td>
<td>1310</td>
<td>T2D</td>
<td>Nil</td>
<td>Fenofibrate: 160mg, Simvastatin: 20-40mg ceased 8 years ago</td>
<td>8 years from ACCORD-EYE completion</td>
<td>At eight years following the end of the trial, there was no significant difference in DR progression between fenofibrate and placebo groups, 11.8% versus 10.2% (OR 1.13, 95% CI 0.71–1.79, P = 0.60)</td>
</tr>
</tbody>
</table>
FIELD: Fenofibrate intervention and event lowering in diabetes; RCT: randomised control trial; T2D: type 2 diabetes; ACCORD-EYE: Action to Control Cardiovascular Risk in Diabetes eye study; ACCORDION Eye study: Action to Control Cardiovascular Risk in Diabetes follow-on study

Table 4: Pipeline Therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial type</th>
<th>Number</th>
<th>CVD risk</th>
<th>Drug</th>
<th>Mode of action</th>
<th>Doses</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ray et al, 2017</td>
<td>RCT (phase 2)</td>
<td>501</td>
<td>Yes</td>
<td>Inclisiran vs. placebo</td>
<td>a single dose of placebo or 200, 300, or 500 mg of inclisiran or two doses (at days 1 and 90) of placebo or 100, 200, or 300 mg of inclisiran</td>
<td>The mean reductions in LDL cholesterol levels at 180 days were 27.9-41.9% after a single dose of inclisiran and 35.5-52.6% after two doses (P&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Bhatt et al, 2019</td>
<td>RCT</td>
<td>8179</td>
<td>Yes</td>
<td>Icosapent ethyl vs. placebo</td>
<td>Stabilisation or regression of coronary plaques</td>
<td>2g twice daily</td>
<td>Ischemic events, including cardiovascular death, was significantly lower among those who received icosapent ethyl compared with placebo (17.2% vs. 22.0%; HR=0.75; 95% CI, 0.68-0.83; P&lt;0.001)</td>
</tr>
<tr>
<td>Nicholls et al, 2018</td>
<td>RCT</td>
<td>13086</td>
<td>Yes</td>
<td>Epanova/statin vs. cornoil/statin</td>
<td>Reduce hepatic production of TG-rich VLDL and increase the removal of other TG-rich lipoproteins</td>
<td>4g daily</td>
<td>Trial ongoing</td>
</tr>
<tr>
<td>Clinical</td>
<td>RCT (phase)</td>
<td>&gt;2400</td>
<td>Yes</td>
<td>Bromodomain</td>
<td>Affects biological processes</td>
<td>Trial ongoing</td>
<td></td>
</tr>
</tbody>
</table>

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Trials.gov 3) extra terminal protein inhibitor vs. placebo which are important in atherosclerosis and acute coronary events 100mg twice daily

| RCT (phase 2b) | 1267 | Yes | CSL112 mimetic low dose vs. high dose | Reconstituted HDL particle consisting of native apoA-I and phospholipids | Low and high dose | Trial ongoing |

RCT: randomised control trial; CVD: cardiovascular disease;

Figure 1: Lipid-lowering agents and their mechanisms of action

Legend: A) Statins; inhibit cholesterol synthesis by inhibiting hydroxymethylglutaryl CoA reductase (HMG CoA reductase), B) Ezetemibe; inhibits cholesterol absorption in the ileum via Niemann–Pick C1–like 1 (NPC1L1) protein, C) Fibrates; activate peroxisome proliferator-activated (PPAR-α) receptors leading to increased high density lipoprotein (HDL) and reduced triglycerides (TG), very low density lipoprotein (VLDL) and low density lipoprotein (LDL), D) Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors; prevent degradation of LDL receptors, hence increasing clearance of LDL.

Figure 2: Lipid lowering agents on the horizon and their mechanisms of action
Legend: Omega-3 fatty acids increase the clearance of triglyceride-rich (TG-rich) lipoproteins and reduce hepatic production of TG-rich very low-density lipoproteins (VLDL). They are also thought to have anti-inflammatory and plaque and membrane stabilising properties. Epanova and Icosapent ethyl are both omega-3 fatty acids that have been shown to effectively lower TG levels. Apabetalone is a bromodomain and extra-terminal protein (BET) protein inhibitor. By blocking BET protein if affects transcription regulation and modulating pathways that underly CVD.
Abstract

Diabetes can lead to myriad of microvascular and macrovascular complications - with the leading cause of mortality in diabetes being cardiovascular disease (CVD). Low-density lipoprotein cholesterol (LDL-C), along with non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TGs) are proven, modifiable risk factors for CVD. This article will focus on lipid lowering agents in individuals with diabetes. It will summarise relevant changes in the latest guidelines for dyslipidemia, and will also review the mechanisms of action of lipid lowering agents along with the latest cardiovascular outcomes data specific to individuals with diabetes. Older agents such as statins, ezetimibe, fibrates and nicotinic acid will be reviewed with a focus on new diabetes-specific evidence. Similarly, a relatively novel agent proprotein-convertase subtilisin-kexin type 9 (PCSK9) will be reviewed and details around the Pharmaceutical Benefits Scheme (PBS) criteria governing its usage in Australia will be included. Finally, this review will touch on agents still on the horizon such as icosapent ethyl, high-density lipoprotein (HDL) mimetics, bempedoic acid, omega-3 free fatty acids, bromodomain and extra-terminal proteins (BET) inhibitors and inclisirin - a long-acting RNA interference agent. In the appropriately selected population of individuals with diabetes, these agents can assist to further improve lipid profile and reduce cardiovascular events.
Omega-3 fatty acids (EPA/DHA)
- ↑ removal of TG rich lipoproteins
- ↓ hepatic production of VLDL
- *Other properties
  - Anti-inflammatory
  - Antioxidative
  - Plaque-stabilizing
  - Membrane-stabilizing

Apabetalolone
- Inhibits BET proteins
  - *Affects transcription regulation and modulating pathways that underly CVD
  - ↑ Reverse cholesterol transport
  - ↓ Vascular inflammation
  - Downregulate complement cascade

Icosapent ethyl
EPANOVA

Good feasibility

IMJ_14291_Figure 2.tif
What’s new in lipid lowering therapies in diabetes?

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