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Prevention of diabetes macrovascular complications and Heart Failure

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Key Words

Hypertension, LDL-cholesterol, obesity, countries, ethnicity, metformin, SGLT2i's, GLP-1RA's.

Key Points

- Glucose reduction per se lowers ASCVD risk modestly but multifactorial risk management, incorporating LDL-c and SBP reductions and smoking cessation, in addition to glucose management, can lead to substantial reductions in risk for ASCVD.
- Priority in low- and middle- income countries should be given towards sustainable supplies of cheap metformin, statin and BP medications to lower CV risks for people with diabetes.
- Large scale weight loss can lessen or reverse type 2 diabetes, but may also meaningfully lower ASCVD and HF risks – ongoing trials will refute or confirmation this notion in the next 5 years
- The SGLT2i and GLP-1RA class lower CV outcomes, with greater reductions in cardio-renal outcomes for the former and atherothrombotic outcomes (e.g., stroke and PAD) for the latter. Such benefits are independent of glycaemia and background metformin therapy. These findings have led to revisions of clinical guidelines.
- Further reductions in CV risk may stem from delaying diabetes in those at high risk, as well as from better messaging and adoption of sustainable lifestyle changes.

Synopsis (100 words or less)

CV mortality in diabetes has declined substantially over the last three decades in high income countries from a multifactorial approach targeting glucose, cholesterol, and blood pressure, and lower smoking rates. Additional CV gains may be achieved from large scale weight loss, which ongoing trials are testing, and from delaying diabetes in those at highest risk. Finally, recent outcome trials support a role for i) SGLT2i, which lower MACE but incident heart failure more strongly, and for ii) GLP-1RAs, which lower atherothrombotic outcomes more consistently, including stroke and peripheral arterial disease. The CV prevention toolbox in diabetes has expanded.

Introduction

As described previously, type 2 diabetes is associated with accelerated vascular risk which accounts for around half of the life years lost from diabetes.¹ However, in high income countries, many factors inclusive of earlier diagnosis and better management of several risk factors have driven down cardiovascular risks. Declining risk for atherosclerotic cardiovascular disease has led, in turn, to rising deaths from cancer in people with diabetes.² However, premature cardiovascular deaths from type 2 diabetes in many low- and middle-income countries are rising. At the same time, more people with diabetes in high income countries, such as the UK, now develop peripheral arterial disease or heart failure (HF) as their first ‘vascular’ presentation.³ This chapter will summarize the major therapeutic modalities to lessen cardiovascular outcomes and HF in people with type 2 diabetes. It will rely, wherever possible, on meta-analysis of outcome trials, supplemented by other outcome trials or best quality observational data. The data will show that good glycemia control per se lowers risk modestly but that multifactorial risk factor management, also targeting lipids, smoking and blood pressure, gives far greater protection against adverse vascular outcomes. In addition, it will describe recent gains from a series of landmark trials that have helped establish newer diabetes therapies – sodium-glucose cotransporter 2 inhibitors (SGLT2i’s) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) – as important in further lowering of ASCVD or cardiorenal risks in people with type 2 diabetes.

Impact of glucose lowering per se

Whilst diabetes is diagnosed based on elevated glucose or HbA1c levels above specific diagnostic criteria, both the pathophysiology of type 2 diabetes (excess weight / ectopic fat⁴) and patterns of risk factors in people with pre-diabetes (higher BMI, systolic blood pressure, abnormal lipids), indicate that many risk factors linked to ASCVD are already worsened before frank diabetes develops.⁵ Even so, once frank diabetes develops, further elevations in glucose levels independently add to adverse cardiovascular risk; keeping glucose lower will therefore protect against ASCVD.

Whilst the impact of intensive glucose lowering has been questioned, a meta-analysis which combined data from five major glucose lowering trials, employing differing glucose lowering regimens, showed that for each 0.9% lower HbA1c, there was a 17% reduction in events of non-fatal myocardial infarction (odds ratio 0.83, 95% CI 0.75-0.93) (Figure 1), and a 15% reduction in coronary heart disease (0.85, 0.77-0.93), although there was no impact on all-cause mortality (1.02, 0.87-1.19).⁶ Those in the intensive glucose arm did not have lower HF risks, however, and were on average 2.5kg heavier, linked to greater use of therapies known to increase weight (sulfonylureas and insulin, and pioglitazone in the proactive trial). The same meta-analysis⁶ also helped place these HbA1c findings into context by comparing how many events would be prevented should 200 people with diabetes have their glucose lowered versus typical benefits from statins or blood pressure medications (Figure 2). This figure helps reiterate the concept of multifactorial treatment as it shows blood pressure and LDL-cholesterol reductions can do more in the short term to lower cardiovascular risks than targeting glucose alone. Furthermore, whilst glucose lowering is important to protect against ASCVD, the benefits appear less than perhaps many first imagined, and take some years to emerge. Of course, it must be remembered most of the above trials were done in predominantly white individuals, who on average develop T2D later than many other ethnicities. It is therefore entirely possible that due to earlier development of T2D in other ethnic groups, and often with more rapid glycaemic deterioration, hyperglycemia has a greater weighting for ASCVD outcomes in many non-white groups. This speculation requires direct study.

Lipids lowering

LDL-c is causally related to adverse outcomes in all populations, and ample evidence supports statins lowering ASCVD outcomes in people with and without diabetes. In people with diabetes, the Cholesterol Treatment Trialists' (CTT) Collaborators showed that a 1 mmol/l reduction in LDL-c led to a 21% reduction in major vascular events and a 13% reduction in vascular mortality.⁷ For this reason, most guidelines around the world recommend statin use in people with type 2 diabetes, with lower targets for those with existing ASCVD; additional trial evidence shows that the lower the

achieved LDL-c, the greater the reduction in ASCVD outcomes. Furthermore, genetic data now confirms elevated apo B levels as the causal element in development of ASCVD.⁸

More recently, two other non-statin agents that lower LDL-c, have also shown to lower vascular risks in people with diabetes, as summarised in a recent article⁹ (Table 1). This includes the once daily oral agent, Ezetimibe, which seems to have a particularly good effect in people with diabetes, and PCSK9 inhibitors, which are given as injections every two of four weeks. Ezetimibe lowers LDL-c by around 24%, whereas PCSK9i lower LDL-c around 60%. Both agents are now licensed for use in diabetes, though PCSK9i remain expensive so their use is restricted to those at greatest risks and in whom statins or ezetimibe do not allow patients to reach reasonable LDL-c levels. Ezetimibe is, however, available in generic forms and lower cost makes it a good agent when maximally tolerated statin doses do not help patients achieve their LDL-c goals. The evidence for outcome benefit with other lipid lowering agents is either currently lacking (Bempedoic acid), or controversial (high dose fish oils & fibrates – more trials ongoing), though it appears more LDL-c lowering agents will be licensed soon, increasing the lipid- lowering armoury to help prevent or delay ASCVD.

Blood pressure lowering

In a recent paper which looked at differences in CV risk factors between people with and without type 2 diabetes by age of onset, systolic blood pressure was higher by around 7-9 mmHg across all ethnicities in those with diabetes diagnosed aged 20-39 years of age¹⁰. The link between diabetes and hypertension is highly robust and it may be that the processes that lead to development of type 2 diabetes – e.g., ectopic fat gain, excess caloric intake, lower activity levels - also lead to increments in SBP. For this reason, and as higher SBP is causally related to ASCVD and key microvascular complications, lowering blood pressure is another cornerstone in the management of people with type 2 diabetes. Blood pressure reduction lowers all major vascular outcomes in people with diabetes (a 10 mm Hg reduction in systolic blood pressure lowering risk by 12%, 95% CI: 6-28%) although the benefits appear be somewhat less in people with diabetes compared to those without for incident CHD (12% risk reduction) but similar for stroke (26% risk reduction)¹¹. Blood pressure reduction also lowers heart failure and all-cause mortality in people with diabetes (Figure 3).

Recent guidance on blood pressure reduction has advocated lower targets than previously, aiming for <130 mmHg for majority of people with T2DM, but less strict targets (typically to <150 mmHg) for those who are older or frail.¹² Likely, most physicians will aim for a SBP somewhere between 130-140 mmHg in their patients, though if they can tolerate levels <130 without side effects, then gains will be greater. Most favored blood pressure drugs are ACE inhibitors or ARBs (due to their effects to lessen albuminuria risks), followed by calcium channel blockers, diuretics and more recently spironolactone has come into favor. The emerging consensus for better SBP control is to use lower doses of two drugs than a larger dose of a single agent.

Lifestyle measures and ASCVD outcomes

Weight loss

Surprisingly, whilst modest weight loss protects against development of diabetes in those at elevated risk, and larger weight loss can lead many people with T2DM to undergo remission, trial evidence linking intentional weight loss to hard outcome benefits in T2DM is lacking. The Look AHEAD trial, a randomized trial of intensive lifestyle versus usual care in people with T2DM, did not establish outcomes benefits of modest weight loss.¹³ However, most considered this trial to have recruited too low a risk population to have sufficient power to see gains, and as noted, overall average weight loss was modest. A post hoc analysis from the same trial showed that those people who achieved a >10% weight loss in the first year, had a 21% (95% CI: 2% to 36%) lower risk of the primary outcome (composite of death from cardiovascular causes, non-fatal acute myocardial infarction, non-fatal stroke, or admission to hospital for angina¹⁴). This work allied to other trials which show modest weight loss does not lead to ASCVD outcome benefits in the short term (e.g., Locaserin in the CAMELLIA-TIMI 61 trial¹⁵), suggests larger weight loss may be needed to show outcome benefits.

In the DiRECT trial, which helped people with T2DM achieve around a 10kg weight loss, the number of adverse events, albeit admittedly low, was significantly lower by second year of follow-up in the control group.¹⁶ We were also able to show significant benefits in terms of lipids and blood pressure in the intervention group relative to controls. In unpublished data, we noted remarkable

improvements in a protein pattern associated incident cardiovascular outcomes by the end of the first year relative to control participants, in keeping with a significant reduction in future cardiovascular risk. Ongoing clinical outcome trials perhaps in particular SURPASS,¹⁷ which is comparing the effects of tirzepatide (dual GIP and GLP-1 receptor agonist) versus dulaglutide (GLP-1-RA with proven ASCVD benefits¹⁸). As the former drug is associated with sustainably greater weight loss, this trial should help gauge the benefits of intentional weight loss in people with T2DM.

Outside of randomized trials, a series of studies using bariatric surgery, have suggests even greater weight loss may give important CV outcome benefits in people with diabetes. For example, using the Swedish Diabetes Registry, we reported that gastric bypass surgery (GBP) was associated with remarkably lower risks for major outcomes in people with T2DM who had on average a BMI >40 at baseline. Risks for incident heart failure (hazard ratio [HR] 0.33 [95% CI 0.24, 0.46]) and CV mortality (HR 0.36 [(95% CI 0.22, 0.58)], were substantially lowered by GBP as were renal outcomes.¹⁹ In a linked study, we also showed GBP surgery to be associated with a lower risk for incident atrial fibrillation (AF), and to lower risk of mortality in people with T2DM who had prevalent HF.²⁰ Whilst such findings are of major interest, one must remember that these are not randomized trials and biases exist in people who chose to undergo bariatric surgery versus those who do not. Even so, the totality of findings suggest large weight loss may yield important cardiovascular outcome benefits in people with T2DM, extending beyond ASCVD to include AF, renal and HF benefits. With the advent of stronger incretin-based drugs for weight loss, and ongoing clinical outcome trials, the impact of large-scale weight loss (i.e., >10kg) on cardiovascular outcomes in people with T2D should soon be confirmed or refuted.

Other lifestyle measures

There is no dubiety smoking is a strong risk factor for ASCVD, and people with diabetes have as much reason not to smoke as those without diabetes. There are now excellent ways to help people stop smoking, including nicotine patches and a range of medications.²¹ Face to face support also appears more helpful than self-help materials. All people with T2DM who smoke should be encouraged to try to stop smoking and given the best possible help to achieve success.

In terms of activity, there are no randomized trials linked to CV outcomes, but clearly, greater activity levels help maintain muscle mass, keeps BMI, lipids, and blood pressure levels lower and may have additional benefits across a range of pathways (liver fat, inflammation etc). Perhaps the best recent data on activity and mortality comes from the UK Biobank, a general population study which included people with T2DM. Using data from wearable devices, Strain and colleagues were able to show greater physical activity energy expenditure (PAEE) was associated with lower all-cause mortality.²² More intense activity levels were also associated with lower risk for mortality, independent of amount of total activity volume. If we accept activity lessens CV outcomes, if people with T2DM can find sustainable ways to increase their activity levels, including even walking a little more, this could help offset CV disease. The manner in which health care professionals discuss activity with their patients can improve and perhaps needs to be more prescriptive. For example, as most people have iPhones, even simple targets of modest increase in steps (e.g., extra 500 per day on average, increasingly gradually) may allow people to focus on achievable changes.

Antihyperglycaemia agents (AHAs)

Aside from their glucose lowering abilities that lower vascular risk, albeit modestly and slowly, it is important to assess whether AHAs lower cardiovascular risk beyond their glucose lowering actions? A short summary of the quality of evidence for each agent is given below for each major AHA used in clinical care.

Metformin: Metformin is an excellent glucose lowering agent which does not cause weight gain or potentiate hypoglycaemia. The UKPDS trial identified a cardiovascular benefit for metformin but as this evidence stemmed from a subgroup analysis and involved low outcome numbers, many in the cardiovascular community remain sceptical. Subsequent meta-analyses have not added additional support for a metformin-associated CV benefit.

Sulfonylureas: There is no good evidence to suggest sulfonylureas lower cardiovascular risk, beyond their glucose lowering benefits. In a recent large, randomised trial (CAROLINA²³), there was no clear benefit of the DPP-4 inhibitor, linagliptin, versus the SU, glimepiride: primary outcome

occurred in 356 of 3023 participants (11.8%) in the linagliptin group and 362 of 3010 (12.0%) in the glimepiride group (HR, 0.98 [95.47% CI, 0.84-1.14]. As DPP-4 inhibitors have not been shown to lower ASCVD risk compared to placebo (see below), by extension, glimepiride is unlikely to do so either.

Insulin: The ORIGIN trial (n= 12,537 people) did not show insulin lowers cardiovascular risk compared to standard when given in early diabetes or pre-diabetes. Incident cardiovascular outcomes rates were 2.94 and 2.85 per 100 person-years in the insulin-glargine and standard-care groups, respectively, for the first coprimary outcome (hazard ratio, 1.02; 95% confidence interval [CI], 0.94 to 1.11; P=0.63).

DPP-4 inhibitors: Four DPP-4 inhibitor outcome trials testing alogliptin, saxagliptin, sitagliptin, and lingagliptin²⁴⁻²⁷ failed to demonstrate any superiority compared with placebo in patients with type 2 diabetes mellitus and high CV risk. In addition, there was an unexpected higher risk of hospitalization for heart failure was reported with saxagliptin in SAVOR-TIMI-53.

Pioglitazone: In the PROACTIVE trial, pioglitazone reduced the secondary outcome composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who had a high risk of cardiovascular events.²⁸ However, heart failure risk increased significantly. Pioglitazone also lowered stroke and MI risks in patients with pre-diabetes and insulin resistance in the IRIS trial.²⁹ However, as the drug causes weight gain, is linked to greater fracture risk and increases HF risk in people with diabetes, it is less favored compared to available alternatives. This trial showed helped generate idea that some drugs can have differential effects on ASCVD and HF, so that the pathophysiological processes can be differentially influenced dependent on the drugs actions.

SGLT2i's: The most notable results from recent CVOTs comes the SGLT2i and GLP-1RA classes. As reported in a recent meta-analysis of five SGLT2i outcome trials, this class lowers MACE risk modestly (around 10%), significant only in those with prior ASCVD (Figure 4a³⁰). However, more notable is a far greater reduction in the risk of incident HF hospitalisation in both those with (by 30%) and without (by 37%) prior ASCVD (Figure 4b). As noted in other papers, these drugs also lower

incident renal outcomes and slow decline in eGFR. It has also been established that such benefits do not relate to glucose lowering effects but to multiple other actions, chief amongst these likely to be haemodynamic effects leading to lessening of glomerular hyperfiltration and adverse cardiac remodelling.^{31–33} However, cellular changes arising from SGLT2i actions on nutrient fluxes may also play a role.³⁴ Whatever the mechanism, multiple ongoing mechanistic trials are underway to add more insights, so called reverse translation (**Figure 5³⁵**). Finally, this class has also been shown to lessen HF or CV death in people with HF with reduced ejection fraction (HFrEF) in two recent seminal trials that have established SGLT2i as foundational in the treatment of such patients, whether they have diabetes or not.³⁶ The SGLT2i drugs with the best benefits to safety ratio appear to empagliflozin and dapagliflozin, though canagliflozin is also licensed for some indications.

GLP-1RA's: The GLP-1RA class, mostly injectable therapies, but a recent oral drug introduced, has also shown outcome benefits but these appear more consistently in the ASCVD domain. A recent meta-analysis that included all seven outcome trials to date showed the class lessens MACE and CV death by 12%, MI risk by 9% and stroke risk by 16%³⁷ (**Figure 6**). These hazard ratios are likely modest underestimates as the meta-analysis included ELIXA, a universally null trial that tested the short acting GLP-1RA, lixisenatide. The agents with the best evidence include liraglutide, dulaglutide, albiglutide and semaglutide, though albiglutide has not been licensed for use. There is some evidence that these drugs may lessen incident HFH but far more modestly (9% reduction) than seen with SGLT2i's.

Side effect profiles of SGLT2i and GLP-1RA classes

The advantage of both classes over some other AHA agents is that they help weight loss, do not increase hypoglycaemia and lower blood pressure. The SGLT2i class does increase risk for genital infections and DKA but these can be minimised by patient education and better targeting of drugs to suitable patients. Genetical infections are also easily treated. The GLP-1RA class causes nausea and vomiting early on in treatment, an effect than can be minimised by starting low and escalating the doses slowly. Such effects tend to lessen with continued use.

Guideline implications of recent evidence

Due to their consistent results, the SGLT2i and GLP-1RA classes have been recommended in recent guidelines for treatment of patients with diabetes and existing ASCVD.^{38,39} The SGLT2i class is also recommended for patients with T2DM and HF and CKD. These two classes have also been variably suggested for patients at elevated risk for ASCVD, but, as we recently reviewed,⁴⁰ cardiovascular- and diabetes- led guidelines recommend somewhat different categories of at-risk patients who would merit treatment. However, all group now agree such classes can be used independently of glycaemia levels and increasing evidence shows that both classes work independently of background metformin therapy, as recently reviewed,⁴¹ so that there is no need to start with metformin in patients recommended for such therapies. This latter point remains somewhat debated in diabetes circles.

Greater outcome benefits in Asians?

Finally, in a recent meta-analysis of outcome trials where primary endpoints data for Asian ethnicity was able to be extracted, we showed that the GLP-1RA class may lessen MACE in people with diabetes more greatly in Asians than in whites (Figure 7). The same pattern seemed true for the SGLT2i class in lessening incident HFH / CV death in those with HFrEF. If these observations hold true, they are clinically important as over 60% of the world's population is Asian and it is here where diabetes rates are escalating most rapidly. However, more work is needed to validate these observations and, if validated, to test whether they apply to all Asians or only specific ethnicities within this large population.

Summary

Cardiovascular risk in people with T2DM has substantially declined in high income countries over the last 3-4 decades, with early gains achieved from a combination of glucose reductions, lipid lowering via statins, and blood pressure treatments, on the background of falling smoking rates. In low- and middle-income countries, CV risks remains high and the goals are for earlier diagnosis of diabetes, and pre-diabetes, so that more can be prevented from developing diabetes or it can be meaningfully

delayed. Thereafter, a reliable supply of cheap metformin, statin and blood pressure medications would do much to lessen CV risks in these countries. It is insufficient to target only glucose reduction.

In high income countries, cardiovascular improvements accrued over a few decades may have started to plateau in the last decade, perhaps due to a slowing or even reversal of risk factor improvements.

That noted, the last 10 years has seen a remarkable number of outcome trials that convincingly showed reductions in ASCVD and incident HF hospitalizations in people with diabetes using two newer classes of drugs. At the same time, there is growing interest in the benefits of large weight loss to further lessen risks of important CV outcomes in people with diabetes who are living with obesity or severe obesity. There is a parallel growing interest in helping recently diagnosed people with diabetes achieve remission, a process which should also lessen CV risks. Further strategies to test remission protocols in many countries are being widely tested or planned. Going forwards, the toolbox to help lessen CV outcomes in people with diabetes across its life course has expanded significantly (Figure 8), with gains at both ends of the diabetes life course.

Finally, despite all these medical advances, it is also important that health care professional do not forget to help their patients with diabetes achieve small but sustainable improvements in their diets and activity levels, even if trials are lacking to show the hard outcome benefits of such changes.

There is other ample evidence that lifestyle improvements can have profound benefits on future health, and the messaging of these needs to improve going forwards. Such points are particularly pertinent in the post COVID era as better lifestyles are needed to help offset all the metabolic and vascular harms imposed by the pandemic, effects that disproportionately impact people living with diabetes.

Clinics Care Points – *Bulleted list of evidence-based pearls and pitfalls relevant to the point of care*

- To help prevent important CV complications, it is critical to adopt a multifactorial risk factor approach and not just focus on glucose reduction.
- Many people with diabetes will be recommended for statins. The risk for myopathy associated with statin has been proven to be exaggerated in recent n-of-1 trials. Patients who claim to suffer muscle side effects (unless severe or associated with measurable CK elevations) should be encouraged to stop and restart statin, initially at same dose and then at a lower dose, or type of statin switched. If statins cannot be tolerated, ezetimibe should be recommended.
- When starting blood pressure treatments, it is better to consider dual therapy, each drug given at low dose.
- Give simpler messaging for lifestyle advice so that patients can try attempt achievable goals which must also be sustainable. If such advice fails to make a difference, multiple other options to help aid weight loss could be signposted.
- Discuss diabetes drug options with patients, pointing out the benefits and side effects and explain that some drugs can give meaningful CV benefits without necessarily altering glucose concentrations.
- If local resources allow, consider discussing the potential option for diabetes remission clinics in people with recently diagnosed diabetes as this can also lower CV risk.

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Figures, Tables:

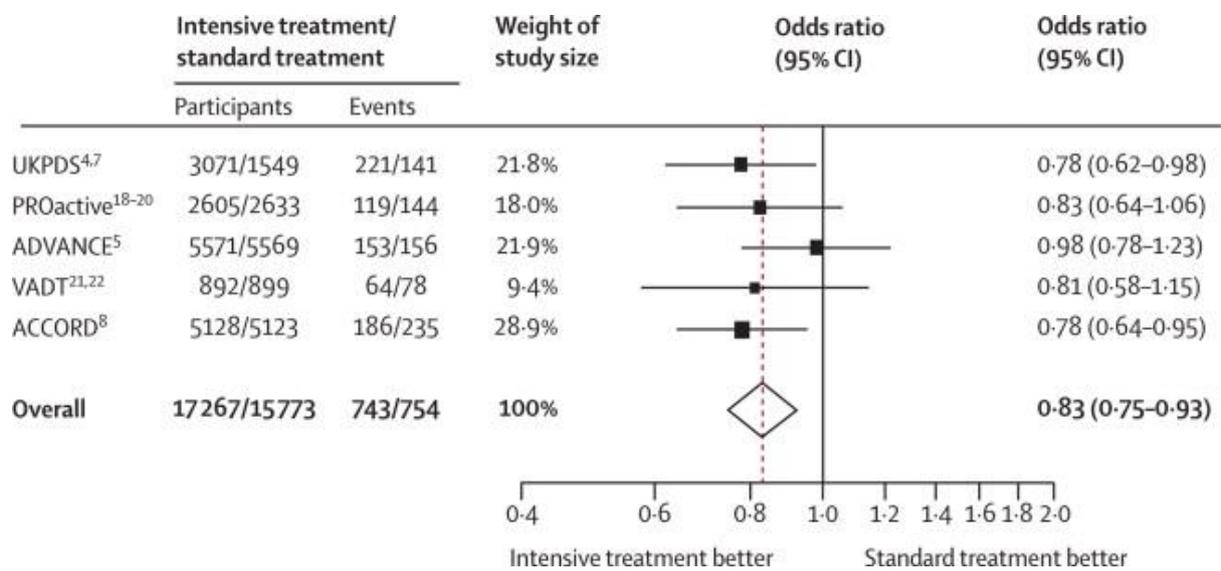


Figure 1. Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment. Reproduced with permission from ref.⁶

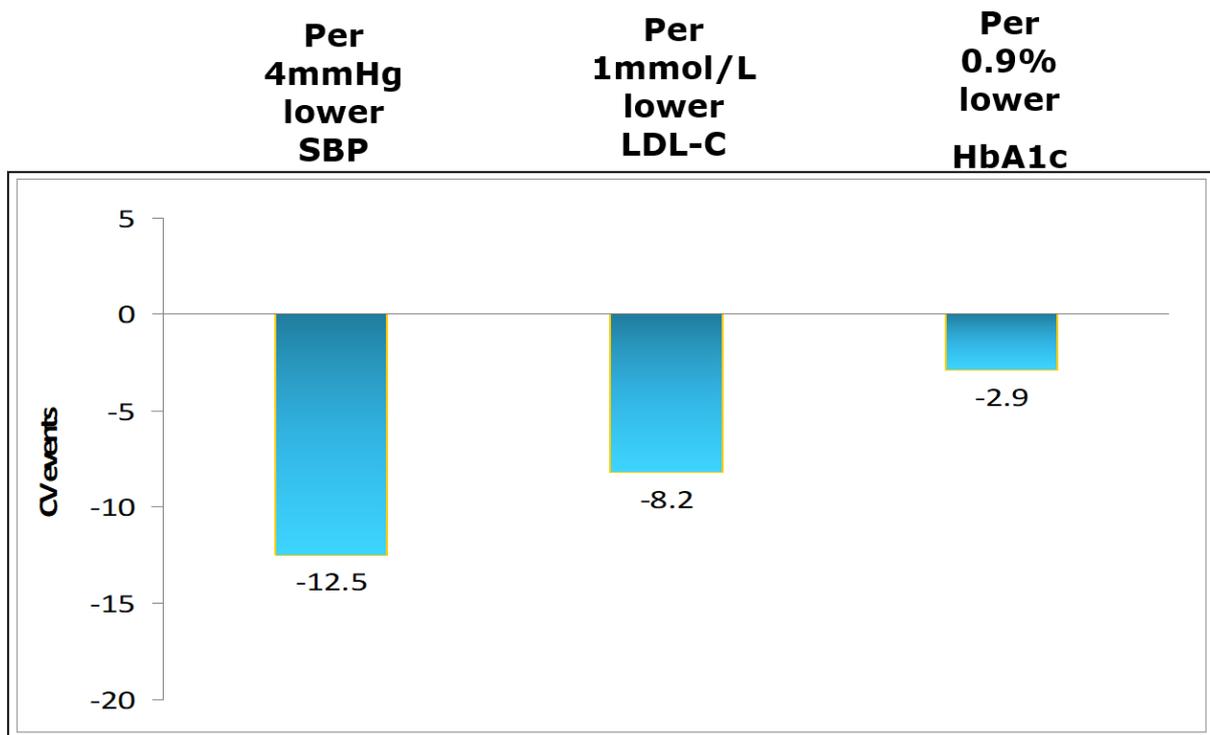


Figure 2 Developed from data in ref.⁶ Number of cardiovascular events prevented per every 200 individuals treated for 5 years with relevant agents in each class.

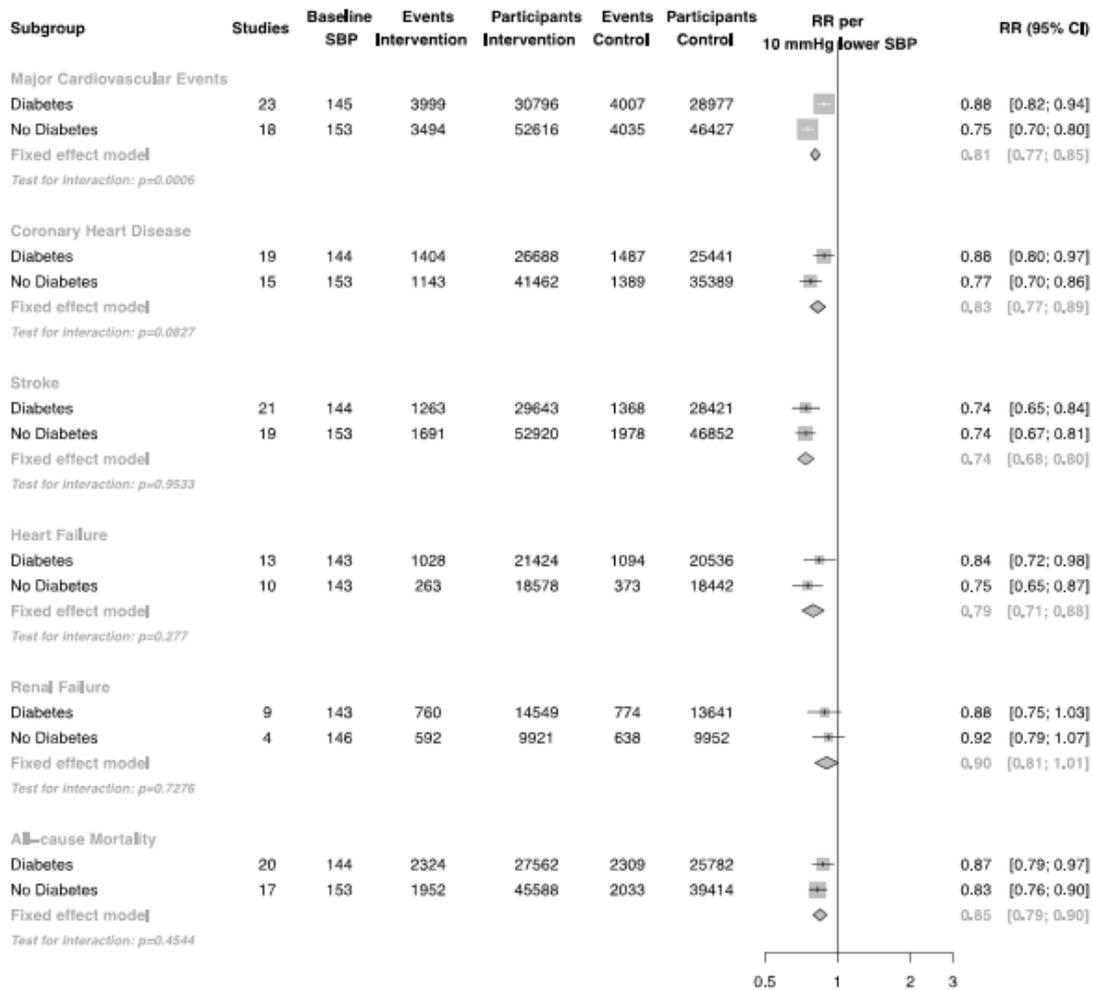
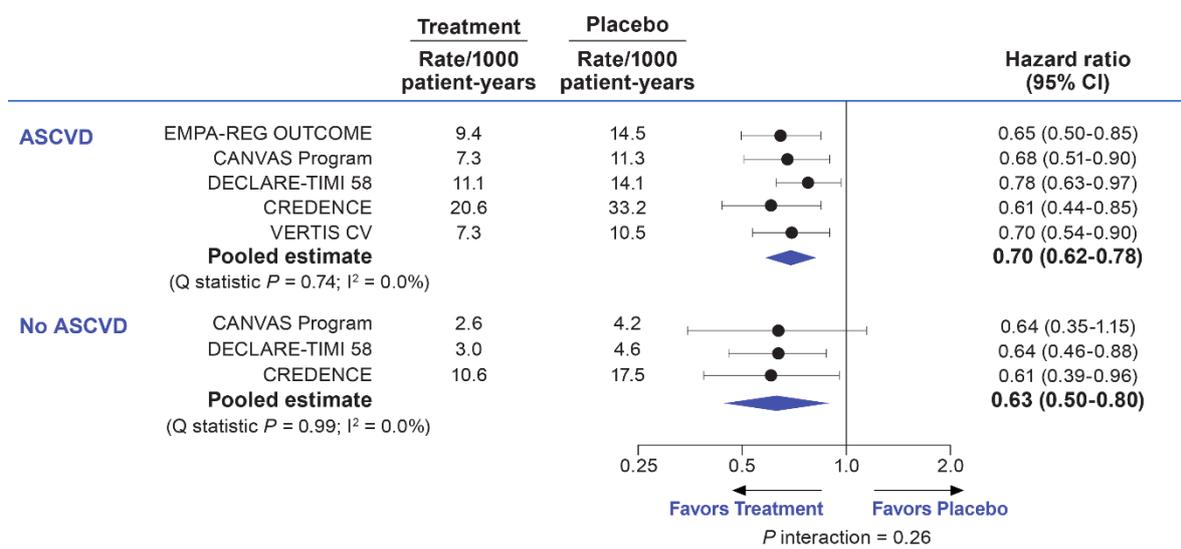
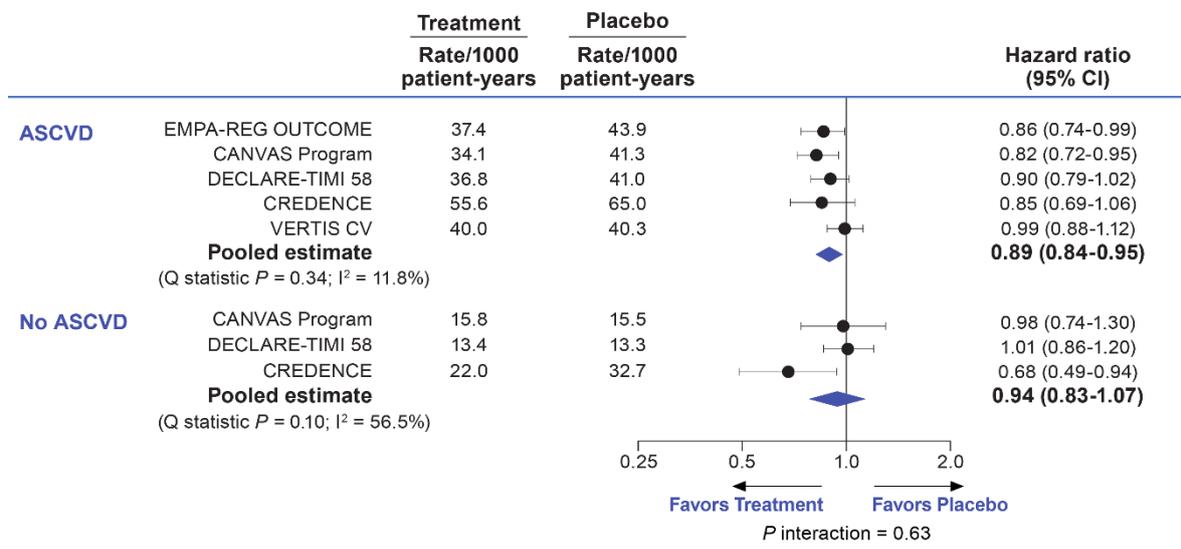


Figure 3. Reproduced with permission from ref.¹¹

Standardised effect of a 10 mm Hg reduction in systolic blood pressure (SBP) on the relative risk (RR) of major cardiovascular events, coronary heart disease, stroke, heart failure, renal failure, and all-cause mortality stratified by subgroups in which all (DM) or none (No DM) of the participants had diabetes mellitus at baseline.



Figures 4a and 4b.

Reproduced with permission from ref³⁰ The MACE (Fig 4a) and HFH (Fig 4b) benefits across people with diabetes with and without prevalent ASCVD in recent SGLT2i cardiovascular outcome trials.

Reverse translation



Figure 5. Reproduced with permission from³⁵ Reverse translation of the outcome benefits seen with SGLT2i and GLP-1RAs.

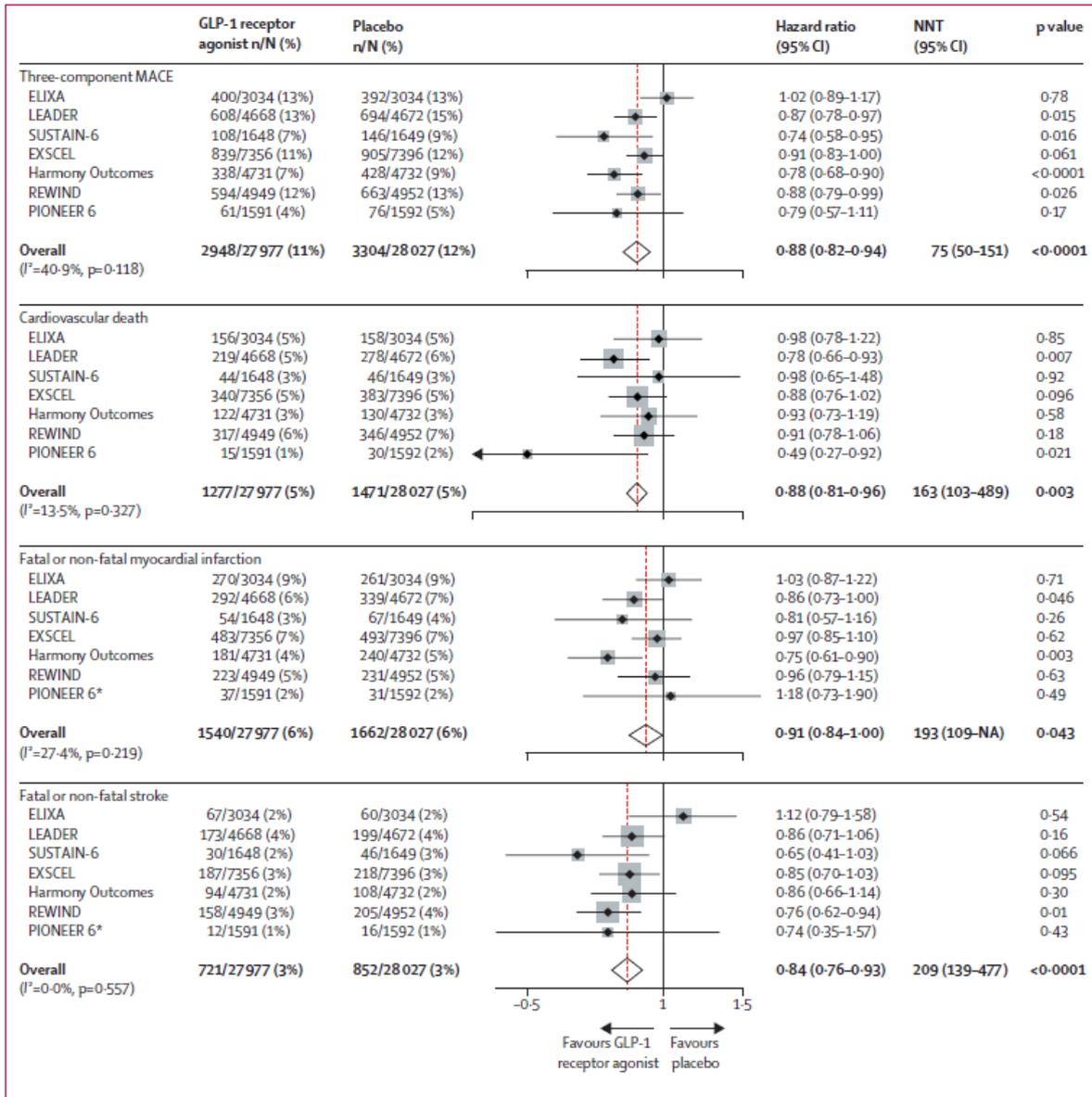


Figure 6.

Reproduced with permission from ref³⁷ Risk of MACE and each of its components. Three-component MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs are calculated over an estimated median follow-up of 3.2 years. MACE=major adverse cardiovascular events. GLP-1=glucagon-like peptide-1. NNT=number needed to treat.

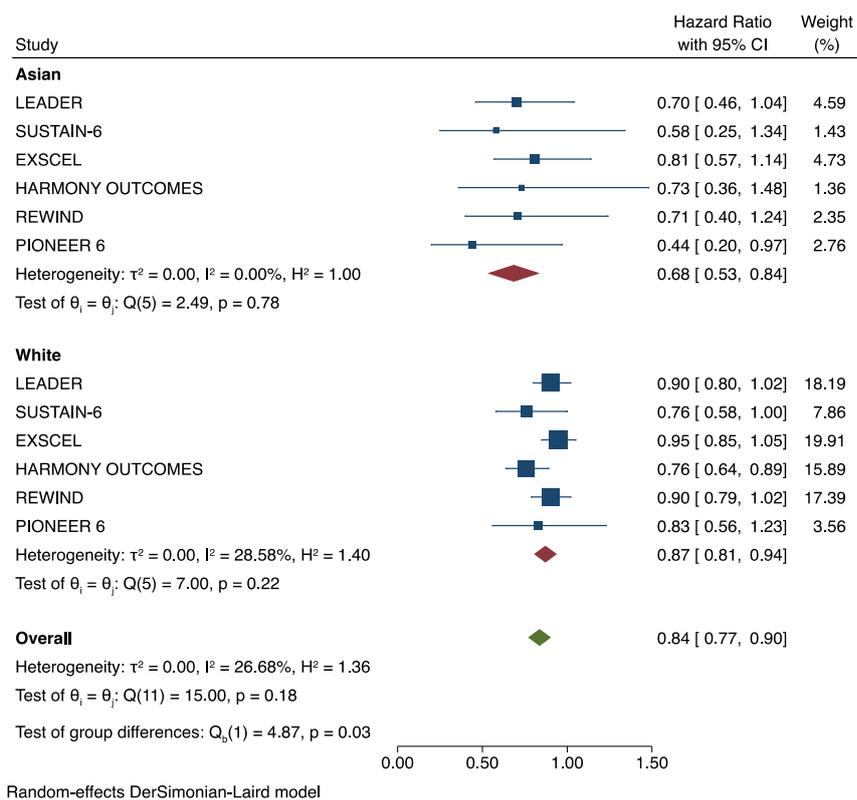


Figure 7. Reproduced with permission from⁴² GLP-1RA cardiovascular outcome trials reporting MACE outcome by race. GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event.

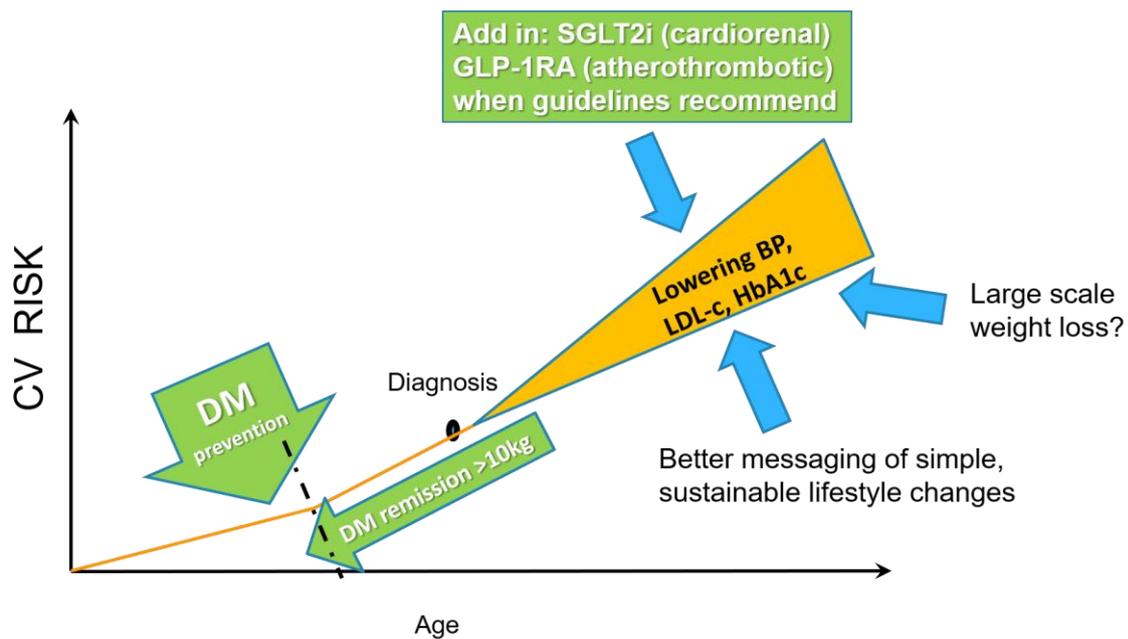


Figure 8.

This figure outlines different factors that are either fully proven to help lessen CV risk in people with diabetes or may be shown to do so in future. If diabetes can be prevented or delayed in those at higher risk, this delay can offset CV risk. Earlier diagnosis can also lower overall glycaemic exposure. Early after diagnosis, consideration of multifactorial risk factor management, targeting glucose, cholesterol, and blood pressure, as well as smoking cessation, will lead to considerable benefits. There are ongoing trials testing agents that yield substantial weight loss, and their CV outcomes are also eagerly awaited. Whether better messaging of lifestyle advice (or facilitating adoption of such changes) can lessen CV risks is not known but seems sensible. Finally, two newer classes of diabetes drugs have shown substantial CV benefits and, wherever possible (and affordable), should be initiated at some point in the diabetes life course, in line with national or local diabetes guidelines.

Table 1. Lipids lowering medications and their impacts in people with diabetes, and brief relevant clinical implications (adapted from ref⁹)

Classification of drug	Key trials	Findings	Clinical implications
Statins	CTT	LDL-C reduction of 1 mmol/L results in approximately 21% reduction in CV event. Intensive statin regimes result in statistically significant 15% further reduction in major vascular events, without significant side effects.	Statins as first line in patients with diabetes. Nowadays, the most used are atorvastatin and rosuvastatin. Both have greater benefits on TG reduction than the older simvastatin and pravastatin.
Ezetimibe	IMPROVE-IT	Reduced CV mortality, major CV event and stroke by 5.5% absolute RR (hazard ratio, 0.85; 95% confidence interval, 0.78–0.94) The largest relative reductions occurred in patients with DM were in MI (24%) and stroke (39%).	First add-on therapy if patients are not reaching targets for LDL-c or non-HDL-c despite maximally tolerated statin therapy
PCSK9 inhibitor	FOURIER	Evolocumab reduced cardiovascular outcomes in patients with diabetes: HR 0.83 (95% CI 0.75–0.93; $p = 0.0008$) for primary composite endpoint. Similar data for Alirocumab.	Currently reserved for patients at very high absolute risk for ASCVD. This includes patients with FH or existing ASCVD, with sustained elevations in LDL-c despite maximally tolerated statin therapy plus ezetimibe.
Fibrates	ACCORD	Modest changes seen in the reduction of TG levels and increase in HDL-C levels.	Add-on to statins for mixed hyperlipidemia, without robust evidence demonstrating improved outcomes in ASCVD risk. Further ongoing trials with newer fibrates.
Icosapent ethyl; Eicosapentaenoic acid (EPA) ethyl ester	REDUCE-IT	Primary endpoint event occurred in 17.2% of treated patients compared with 22.0% in placebo group (HR 0.75; 95% CI 0.68 to 0.83; $p < 0.001$)	Potential new therapy with modest lowering of TG levels. Outcome benefits may be largely independent of TG lowering. Other trials in same space were negative, lending some doubt on the REDUCE-IT trial result.
Bempedoic acid; ATP citrate lyase inhibitor	CLEAR-Harmony	Treatment reduced the mean LDL cholesterol level – 16.5% from baseline (difference vs. placebo in change from baseline, – 18.1 percentage points; 95% CI, – 20.0 to – 16.1; $p < 0.001$).	Potential new therapy for LDL cholesterol lowering. Can be combined to Ezetimibe to achieve LDL-c reduction equivalent to modest dose statin.

