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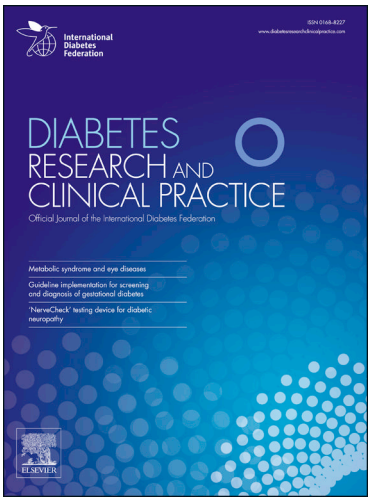

Invited review

The future of new drugs for diabetes management

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The future of new drugs for diabetes management

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Abstract

The future of the newer classes of glucose-lowering drugs, namely dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium/glucose co-transporter-2 (SGLT-2) inhibitors, is being redefined by the large prospective cardiovascular outcome trials (CVOTs). These trials have more than confirmed cardiovascular (CV) safety: indeed, various cardio-renal parameters have improved during some of the trials with GLP-1RAs and SGLT-2 inhibitors in type 2 diabetes. Benefits have included reductions in major adverse cardiovascular events such as fatal and non-fatal myocardial infarction and stroke, decreased hospitalization for heart failure, a slower decline in glomerular filtration rate and reduced onset and progression of albuminuria. In consequence, the CVOTs have raised expectations that newer glucose-lowering agents should offer advantages that extend beyond glycaemic control and weight management to address complications and comorbidities of type 2 diabetes, particularly cardio-renal diseases. Although large prospective outcome trials incur a high cost which may prompt reconsideration of their design, these trials are generating evidence to enable more exacting and more effective management of type 2 diabetes and its accompanying cardio-renal diseases.

Keywords:
Type 2 diabetes; glucose-lowering agents; glycaemic control, cardio-renal disease, outcome trials

Introduction

Despite extensive public health messaging and prevention programmes, the diabetes epidemic continues to escalate, largely with type 2 diabetes fuelled by obesity. Lifestyle measures have had limited impact, leaving a major challenge for pharmacological interventions. This review will focus on the expanding role for recently available and possible new glucose-lowering agents to manage type 2 diabetes.

Cardio-renal-metabolic disease

The diverse metabolic disturbances of type 2 diabetes coupled with the associated micro- and macro-vascular complications are collectively considered to represent a cardio-renal-metabolic disease entity (Figure 1) [1]. The metabolic disturbances, which are manifest by hyperglycaemia and dyslipidaemia, are typically consequent to over nutrition, insulin resistance, defects of insulin secretion and other endocrine abnormalities. Collectively, these and other cardiovascular (CV) risk factors such as inflammation and a pro-coagulant state contribute to the increased occurrence of athero-thrombotic diseases which account for up to half of all deaths amongst type 2 diabetes patients [2-5]. Chronic kidney disease (CKD; based on an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or albuminuria) affects up to about 40% of people with type 2 diabetes and increases mortality risk [6, 7].

Treatment of type 2 diabetes is fundamentally concerned with optimising glycaemic control, facilitating weight control and managing CV risk [8-10]. To address concerns over the CV safety of new glucose-lowering agents the US Food and Drug Administration (FDA) introduced large prospective post-marketing cardiovascular outcome trials (CVOTs) [11-13]. These trials have confirmed the CV safety of glucose-lowering agents (noted in pre-approval (phase 2 and 3) studies) and raised expectations that some of these agents might offer protection against CV and renal complications beyond the benefits conferred by glycaemic control alone [13]. However, metformin remains the first-line glucose-lowering agent of choice for most type 2 diabetes patients, due to its antihyperglycaemic efficacy with very low risk of hypoglycaemia or weight gain, and decades of evidence that associates metformin with reduced long-term CV risk and useful pleiotropic actions [9, 10, 14, 15].

Interpreting CVOTs

The CVOTs are designed to assess CV safety by comparing major adverse CV events in groups of type 2 diabetes patients treated with particular glucose-lowering agents versus control (placebo), the latter group receiving 'usual care' with other classes of glucose-lowering therapies (Table 1) [16-32]. Ideally (if theoretically) this will achieve similar blood glucose values (so-termed glycaemic equipoise) between the groups, thereby excluding the effect of glycaemic control per se. However, glycaemic equipoise has rarely been achieved in the CVOTs and there have been many other differences between the active and control groups that could affect CV disease, including changes in body weight and the use of antihypertensive and lipid-lowering agents. Comparisons between the trials are frustrated by varying inclusion and exclusion criteria such as randomization of different populations with different combinations of CV risk factors, ranging from all patients having recently suffered an acute CV event to groups in which less than 50% of patients have had a prior CV event [12,13,33]. Additionally, evaluation of CV events has not been identical across the trials. Consequently, the main composite endpoint (time to the first event of a 3-point composite of major adverse CV events (MACE) comprising CV death, non-fatal myocardial infarction (MI), non-fatal stroke) has accrued from different adverse CV events at different rates in different trials. Also, hierarchical statistical testing has complicated the evaluation of secondary endpoints in some trials. Thus it is difficult to compare between trials or agents, or to identify drug class effects. However, analyses of sub-populations from within the CVOTs and analyses of similar smaller trials have controlled for some of the discrepancies within the larger and more heterogeneous trials: these analyses have reduced statistical power but they have provided useful insights, as discussed below [12, 13, 33]. Reassuringly, information about CV events in case-controlled studies and interrogations of uncontrolled 'real life' databases have provided similar information to the prospective CVOTs [34-36].

From CVOTs to guidelines

CVOTs have been undertaken with dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium/glucose co-transporter-2 (SGLT-2) inhibitors. The mode of action, glycaemic efficacy and other effects of these agents, including risk of hypoglyaemia, have been reviewed previously [8-10, 37]. The AACE/ACE consensus statement of 2017 suggests a priority sequence for the choice of initial and additional glucose-lowering agents taking account of patient characteristics, therapeutic efficacy, safety profile and emerging evidence from CVOTs [10]. The importance of lifestyle interventions is reiterated, and the preferred initial pharmacological therapy for most patients is metformin, swiftly followed by combination therapy with a GLP-1RA or SGLT-2 inhibitor or insulin for patients with particularly severe or symptomatic disease [10].

The more recent ADA/EASD consensus statement (2018) extends the AACE/ACE approach by proposing that the choice of additional therapy (beyond lifestyle and metformin) should be guided by the absence or presence of atherosclerotic cardiovascular disease (ASCVD), heart failure or CKD [9]. Presence of ASCVD and/or advanced CKD favours use of a GLP-1RA, while heart failure or less severe renal disease might suggest preference for an SGLT-2 inhibitor, noting important efficacy caveats regarding use of the latter class in advanced renal impairment. DPP-4 inhibitors are suggested when GLP-1RAs are not tolerated or advanced CKD is a concern. After considering the presence of ASCVD, heart failure or CKD, selection of second-line glucose-lowering therapy is guided principally by avoidance of hypoglycaemia risk, achievement of weight control, and finally cost [Figure 2]. Sulfonylureas, meglitinides and thiazolidinediones (TZDs) are the low-cost options: sulfonylureas and meglitinides are recognized to carry risk of hypoglycaemia and weight gain, and their CV effects are still unclear, while TZDs are disadvantaged by weight gain and risk of oedema, heart failure and bone fractures. However, some trial evidence has suggested beneficial effects of pioglitazone in ASCVD, especially stroke [38-41]. Alpha-glucosidase inhibitors and other agents with glucose-lowering indications in the USA (bromocriptine, colesevelam and pramlintide) do not feature as part of the main algorithm in this consensus.

DPP-4 inhibitors

Since their introduction in 2006, DPP-4 inhibitors, which enhance the endogenous incretin effect, have become widely used, especially as add-on to metformin [37, 42, 43] Although glucose-lowering potency may be limited, particularly for individuals with excessive hyperglycaemia consequent to inadequate residual beta-cell function, these agents incur little risk of hypoglycaemia or weight gain. CVOTs based on FDA requirements have affirmed the CV safety of DPP-4 inhibitors [16-18] including omarigliptin (a once-weekly tablet used in Japan) (Tables 1 and 1A). The omarigliptin CVOT was terminated early when it was decided not to submit a marketing application in the USA

[32]. Vildagliptin has not been tested in an 'FDA CVOT', but there are similar data from meta-analyses (see table 1A) [31, 44-46].

Although DPP-4 inhibitors have not altered the rates of MI and stroke in the CVOTs, a possible association of some members of the class with more hospitalization for heart failure cannot be excluded [17, 18]. DPP-4 inhibitors can be used in patients with deteriorating renal function (linagliptin without dose reduction due to its hepatic elimination) [20, 47, 48], and recent experimental studies suggest that DPP-4 inhibition might confer some protection against renal fibrosis, but the long-term clinical impact of this has not been studied [49]. Possible risk of pancreatitis is appreciated, and appropriate patient selection (eg. caution if a history of pancreatitis) offers an approach to lower an already very low risk [50, 51]. Overall, DPP-4 inhibitors have shown good tolerability and a good safety profile with convenient dosing and without need for additional monitoring – features that enhance prescriber confidence and patient acceptance.

For the future, the AACE/ACE and ADA/EASD consensus statements affirm that the greater glucose-lowering and weight-lowering potencies of GLP-1RAs plus additional cardio-renal benefits favour GLP-1RAs over DPP-4 inhibitors in obese and more severely hyperglycaemic type 2 diabetes patients. However subcutaneous injections, nausea and the cost of GLP-1RAs leave DPP-4 inhibitors as an ideal add-on to metformin for patients who are modestly above their glycaemic target. As experience grows with SGLT-2 inhibitors, this class may gain preference as add-on to metformin in more severely hyperglycaemic and obese individuals, especially when heart failure is a factor for consideration. Indeed a fixed-dose combination tablet comprising metformin + a DPP-4 inhibitor + an SGLT-2 inhibitor (Qternmet) has recently been approved by the US FDA.

GLP-1RAs

GLP-1RAs were introduced in 2005: they are either exendin-like peptides (exenatide and lixisenatide) or more homologous GLP-1 analogues that are structurally adapted and formulated to reduce degradation by DPP-4 [52-54]. Current GLP-1RAs are administered by subcutaneous injection and act via the GLP-1 receptor to enhance the incretin effect. Their glucose-lowering effect, which carries a low risk of hypoglycaemia is related to the administration schedule (once- or twice-daily or once-weekly), such that short-acting agents can target prandial glucose excursions and longer-acting agents can provide a protracted incretin effect. The weight-lowering and metabolic credentials of GLP-1RAs may owe as much to their satiety effect and glucagon suppression as to potentiation of prandial insulin secretion. Experimental studies have suggested that GLP-1RAs may preserve pancreatic beta-cell mass partly by protecting against destructive cytokines [55, 56]. GLP-1RAs have been used effectively in combination with metformin and insulin, and may defer the use of insulin in some advanced stages of type 2 diabetes [57, 58].

The CVOTs have confirmed the CV safety of GLP-1RAs and several members of the class have shown significant benefits to the MACE and/or its various components including CV mortality [21-27]. Between-trial variability has hampered identification of class effects as well as comparison between individual agents. The benefits of GLP-1RAs on MACE have emerged slowly in the trials but with little reduction of hospitalization for heart failure, suggesting that GLP-1RAs are more likely to improve ASCVD [12, 13, 33]. This could be mediated in part through reductions in body weight, insulin resistance, sodium retention and BP, and small alterations to the lipid profile. There is also evidence that GLP-1RAs directly affect endothelial function to increase vascular compliance and act on the myocardium to increase contractility [59-61]. Sub-group analyses of the CVOTs suggest that the CV benefits of GLP-1RAs can occur in individuals with and without a prior CV history (ie primary and secondary prevention), although events may accrue more slowly amongst those with no prior CV history. These differences in the CV effects between GLP-1RAs do not appear to relate to differences in drug structure or administration schedule, and are independent of well recognized variables within the trial populations, including age, ethnicity, baseline HbA1c and estimated glomerular filtration rate (eGFR).

The degradation of GLP-1RAs by circulating peptidases enables these agents to be used in renal impairment, typically with eGFR down to 30 ml/min/1.73m^2, and lower with caution. Recent evidence from the CVOTs suggests that GLP-1RAs can reduce the onset and progression of macroalbuminuria [62]. This may be due in part to reductions in blood pressure, inflammation and oxidative stress, but also appears to involve altered intra-renal haemodynamics which affect filtration, although the mechanisms are unclear [63-65].

Future prospects for GLP-1RA therapy have been enhanced by the positive CVOTs for several members of the class and their positioning in the AACE-ACE and ADA-EASD consensus reports as a preferred add-on to metformin for obese type 2 diabetes patients, especially those with existing ASCVD [9, 10]. The need for subcutaneous injection, especially if once weekly, seems to be less of a barrier as devices have improved, but dose-related nausea remains an issue for patient persistence, despite this side effect usually decreasing with time. Concerns about the risk of acute pancreatitis have been mitigated by judicious patient selection and appreciation of the low incidence rate, but the ability to predict non-responders to GLP-1RAs remains a challenge, particularly given the high cost of these medicines.

Fixed-ratio combinations of a GLP-1RA with insulin reduces insulin dose, weight gain and hypoglycaemia risk, providing an appealing option for overweight insulin-requiring type 2 diabetes patients. The recent filing for regulatory approval of an orally administered GLP-1RA (semaglutide)

will be welcomed by patients uncertain about injections. It is also noted that several potential future hybrid and chimeric peptides contain GLP-1RA components, and that GLP-1RAs are receiving clinical evaluation for improved bone health and neuroprotective effects against Alzheimer's disease and Parkinson's disease [66, 67]. Overall, reassuring safety evidence and potential further opportunities have secured a more prominent position for GLP-1RAs in the future management of type 2 diabetes.

SGLT-2 inhibitors

Introduced in 2012, the SGLT-2 inhibitors are widely used as second and third line glucose-lowering agents with low risk of hypoglycaemia plus weight-lowering and blood pressure-lowering effects. Their insulin-independent glucosuric action differs from other glucose-lowering agents enabling use in combination with any other drug class at any stage in the natural history of type 2 diabetes, provided there is adequate renal function [68].

The CVOTs have confirmed the CV safety profile of SGLT-2 inhibitors, and the rapid reduction of MACE noted in the EMPA-REG and CANVAS trials suggests that the effects of SGLT-2 inhibition on the CV system are unlikely to be generated through a gradual change in the progression of ASCVD [13, 28-30,]. Each of the SGLT-2 inhibitors tested in large trials to-date has reduced hospitalization for HF, and this effect has been greater amongst patients with prior known CV disease than in those without prior CV disease [69-71]. Accordingly, the ADA-EASD consensus report has recommended SGLT-2 inhibitors as a preferred add-on to metformin for type 2 diabetes patients with heart failure. Whilst the diuretic, antihypertensive and weight-lowering actions of SGLT-2 inhibitors could improve the CV prognosis of these patients, additional effects on myocardial energetics, electrolyte balance and haemodynamics have been proposed which could at least partially explain a reduction in MACE [13, 72] (Table 2).

SGLT-2 inhibitors have consistently improved measures of long-term renal function during the CVOTs and other relevant trials [73, 74]. SGLT-2 inhibition appears to protect the glomerulus through increased tubulo-glomerular feedback in which increased sodium is delivered along the nephron into the upper ascending limb of the loop where it prompts the juxtaglomerular apparatus to increase adenosine signalling [75]. This causes constriction of the afferent glomerular vessels and reduces glomerular pressure. Coupled with lower blood pressure and a reduction in plasma volume during SGLT-2 inhibitor therapy, these adjustments reduce the risk of hyperfiltration and reduce damage to glomerular endothelial cells and podocytes, accounting for the reductions in onset and progression of micro- and macro-albuminuria [76, 77]. Although therapy with an SGLT-2 inhibitor is initially associated with a small fall in eGFR (typically by about 2-5 ml/min/1.73m^2) and attributed mostly to the diuresis and blood pressure lowering, the eGFR gradually recovers over the next 3-6

months. Thereafter, eGFR declines less rapidly than in individuals not receiving an SGLT-2 inhibitor [28-30, 76, 77]. The combination of an SGLT-2 inhibitor to reduce afferent glomerular perfusion and an ACE inhibitor to reduce efferent glomerular pressure may provide added renal protection, but it has been noted that reduced efferent perfusion can increase the risk of lower oxygen supply to the loop of Henle [75]. Whether SGLT-2 inhibitors should be adopted for their cardio-renal benefits in diabetic individuals with low eGFR (when there is little glucose lowering efficacy) remains under investigation [78].

Genital mycotic infections, which commonly occur during the first few months of therapy with an SGLT-2 inhibitor can usually be remedied by self treatment with an antifungal cream as soon as symptoms are experienced [79]. Fournier's gangrene, though very rare, has been reported as an increased risk with SGLT-2 inhibitor therapy [80]. Debate continues regarding reports of an increased risk of lower limb amputation, and significant peripheral artery disease warrants caution with SGLT-2 inhibitors pending further evidence [79]. However, the risk of atypical 'non-hyperglycaemic'/euglycaemic diabetic ketoacidosis (DKA) must be appreciated, particularly in insulin-treated patients who reduce their insulin dose (some of whom may be misdiagnosed type 1 diabetes patients). It is noted that SGLT-2 inhibitors are now receiving indications as adjunctive therapy to insulin in type 1 diabetes where the risk of DKA is much higher (up to 4% per annum) than in type 2 diabetes (<0.1% in clinical trials) [81]. Overall, the broad utility of SGLT-2 inhibitors offers growing applications for this class in the treatment of type 2 diabetes and its cardio-renal comorbidities.

Future therapies

The many different pathogenic components of type 2 diabetes provide a variety of therapeutic targets that enable agents with different modes of action to act in combination to enhance glycaemic control [82, 83]. Indeed, low doses of two or more differently acting glucose-lowering agents can achieve similar or greater efficacy than high doses of one agent, and often with fewer adverse effects [84]. Given the importance of early effective glycaemic control the early use of combination therapy is a key feature of the AACE/ACE consensus of 2017 and an accepted mechanism to individualise treatment in most current guidelines [8-10]. The increasing availability of fixed-dose oral and fixed-ratio injectable combinations simplifies combination therapy by reducing the pill/injection burden, which can increase adherence [85, 86].

Despite the benefits of early, effective and sustained glycaemic control in type 2 diabetes being well recognized, a large proportion of type 2 diabetes patients (typically 30-60% in occidental societies) fail to achieve or maintain glycaemic targets. The occurrence of complications remains unacceptably

high, illustrating the need for yet further differently-acting glucose-lowering agents and strategies to address clinical inertia and poor adherence to treatment [87, 88]. Many new chemical entities with glucose-lowering activity have been identified and evaluated in preclinical studies but very few have attracted initial clinical assessment. Of these few have been pharmacokinetically eligible, free of unwanted side effects and sufficiently specific and potent to proceed into large phase 3 trials which consume most of the estimated average cost of > 2.5 billion US dollars over the 10 years or so that it takes to bring a drug to market [89, 90].

Several potential new approaches to enhance insulin secretion have been evaluated: these include glucokinase (GK) activators which enhance glucose metabolism, agonists of fatty acid-stimulated G-protein-coupled receptors which raise intracellular calcium or activate adenylate cyclase, and other routes to increase cyclic AMP [91-93]. However, to date none of these has successfully completed clinical development. The tetrahydrotriazine imeglimin is advanced in phase 3 development: it alters cellular energetics via effects on mitochondrial permeability transition pores (PTPs), enhances insulin secretion, decreases hepatic glucose production and increases glucose disposal. Initial clinical trials with several hybrid and chimeric peptides have shown substantial glucose-lowering and weight-lowering effects: examples include tirzepatide, a peptide agonist at receptors for GLP-1 and gastric inhibitory peptide (GIP), and MEDI0382, an agonist at GLP-1 and glucagon receptors [94, 95]. Chimeric peptides that interact with various combinations of receptors, notably GLP-1, GIP, glucagon, gastrin and xenin have improved glycaemic and weight control in preclinical studies, and improved beta-cell viability [93].

Small non-peptide molecules that mimic or potentiate the action of insulin have shown promising glucose-lowering properties in preclinical studies, but most of these have yet to receive clinical evaluation [91, 92]. Vanadium compounds that enhance insulin action have shown antihyperglycaemic efficacy in clinical studies but the therapeutic index is narrow. Dietary supplements containing micronutrients and vitamins that are often deficient in type 2 diabetes have produced beneficial effects in some patients, but these are not pharmacological interventions. Many other novel agents to improve glycaemic control in type 2 diabetes have been considered: these include glucagon receptor antagonists, fibre supplements, leptin analogues, adiponectin receptor agonists, analogues of fibroblast growth factor-21, selective peroxisome proliferator-activated receptor modulators, hydroxysteroid dehydrogenase-1 inhibitors, adenosine monophosphate-activated protein kinase (AMPK) activators, sirtuins and a list of agents that can alter the activity of enzymes and co-factors affecting nutrient metabolism [91, 92]. Clinical trials have been undertaken with some of these agents but they have yet to proceed through a full phase 3 trials programme and their CV and renal effects are little known.

Conclusions

The evolution of treatment guidance for type 2 diabetes has sought to improve the selection of therapy for the individual, moving from a generalized algorithm to one that is stratified by group and then refined to provide a more personalized approach [8-10]. The CVOTs, though designed to confirm CV safety, have enabled further refinement and raised expectations that glucose-lowering agents can provide significant benefits beyond glycaemic control and weight management. Prescribers are now looking for properties that will additionally address complications and co-morbidities, particularly cardio-renal diseases and other conditions that commonly accompany diabetes. Large prospective outcome trials such as the CVOTs are very costly (probably in the range of 200-500 million US dollars) and if regulators require CVOTs to continue in their current form this might deter pharmaceutical companies from investing in entirely novel high risk agents [96]. Accordingly, simpler protocols, wider inclusion opportunities and more 'pragmatic' trial designs are being explored to reduce the costs and increase the information generated by these types of trials [96]. Other approaches might involve extensions to exclusivity periods for marketing or more extensive interrogation of 'real world' databases [97]. However, the future of new drugs for diabetes management is poised to provide greater opportunity to intervene earlier, more effectively and more selectively with agents that confer a broader spectrum of effects to improve glycaemic control and address some of the associated complications of type 2 diabetes.

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Legends to Figures

Figure 1. Type 2 diabetes may be considered as a cardio-renal-metabolic disease that develops through the interaction of a variable mix of genetic and environmental factors that disturb metabolic homeostasis and give rise to cardiovascular (CV), renal and other complications. Although the pathogenic process is highly heterogeneous, it typically involves a prodromal period of prediabetes (impaired glucose tolerance and/or impaired fasting glucose) associated with emergent insulin resistance, compensatory hyperinsulinaemia and other alterations to the endocrine control of nutrient metabolism. Prediabetes progresses into frank type 2 diabetes when pancreatic beta-cell function is unable to compensate for insulin resistance, and the diagnostic thresholds of hyperglycaemia are exceeded. The clinical scenario frequently includes an accompanying cluster of CV risk factors

including dyslipidaemia, raised blood pressure and pro-inflammatory and pro-coagulant features that conspire to precipitate premature atherothrombotic CV disease and heart failure. Persistent glucotoxicity gives rise to microvascular, profibrotic and neural complications that manifest as the typical nephropathies, retinopathies and autonomic and peripheral neuropathies of type 2 diabetes. ACS, acute coronary syndrome; BP, blood pressure; eGFR, estimated glomerular filtration rate; Hb haemoglobin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ROS, reactive oxygen species.

Figure 2. A summary of the main decision points in an algorithm for the management of hyperglycaemia in type 2 diabetes set out in the ADA-EASD consensus report of 2018 [9]. Initial and continuing treatment of hyperglycaemia involves lifestyle, advice and support, and the first pharmacological intervention will usually be metformin. Intensification of treatment by addition of a second glucose-lowering agent could be guided by the absence or presence of atherosclerotic cardiovascular disease (ASCVD), heart failure or chronic kidney disease (CKD). Presence of ASCVD favours consideration of a glucagon-like peptide-1 receptor agonist (GLP-1RA), while presence of heart failure favours a sodium/glucose co-transporter-2 (SGLT-2) inhibitor. Presence of advanced CKD may enable use of a GLP-1RA although an SGLT-2 inhibitor may be considered in earlier stages of CKD. Dipeptidyl peptidase-4 (DPP-4) inhibitors are considered in circumstances when GLP-1RAs are not tolerated. After consideration of ASCVD, heart failure and CKD the selection of a second glucose-lowering agent can be guided by the need to minimize risk of hypoglycaemia, achieve and maintain an appropriate body weight, and then minimize cost. Agents to minimize risk of hypoglycaemia favour GLP-1RAs, SGLT-2 inhibitors, DPP-4 inhibitors and thiazolidinediones: agents for weight control favour GLP-1RAs and SGLT-2 inhibitors before DPP-4 inhibitors, while the cost sensitive choices would be a thiazolidinedione or sulfonylurea. If the foregoing does not enable adequate glycaemic control, then a third glucose-lowering agent, which may be insulin, should be considered.

Tables - titles and footnotes

Table 1. A. Key baseline characteristics and results of large prospective post-marketing cardiovascular outcome trials (CVOTs) undertaken with newer classes of glucose-lowering drugs, namely dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium/glucose co-transporter-2 (SGLT-2) inhibitors. B. Baseline characteristics and

results of large cardiovascular studies undertaken with the DPP-4 inhibitors vildagliptin (propensity score matching database analysis) and omarigliptin (prospective trial terminated early for commercial reasons).

Footnotes to table 1:

[a]Elixa and Tecos trials were initiated before the FDA guidance on CV requirements and each had a primary endpoint that was a 4-point composite MACE (3-point MACE plus hospitalization for angina).

[b]the Sustain 6 and Pioneer 6 trials were extended pre-approval studies so do not have the same statistical power as the others.

[c]CANVAS was originally designed for up to 9 years, but amended to end when enough MACE events had accumulated between the CANVAS and CANVAS-R studies**.** Now referred to as the CANVA S Program

*Statistically significant; [+]Fatal and non-fatal stroke; [#]hospitalised for unstable angina
[++]hospitalisation for heart failure or CV death

[z]3pt MACE + hospitalisation for angina/unstable angina

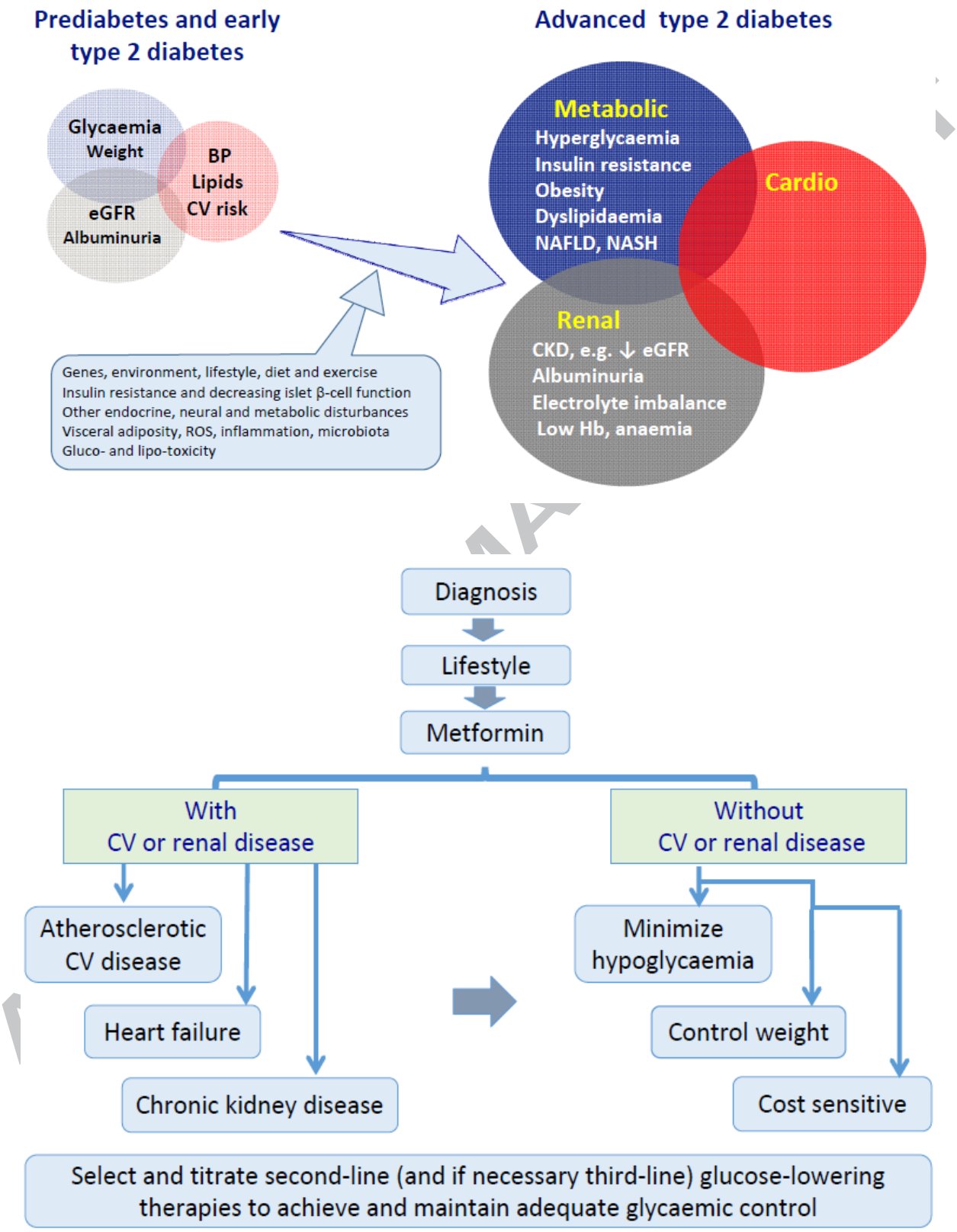
Worse than usual care

Better than usual care

Ang H – hospitalised for angina; CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; BP = blood pressure; GLD = glucose lowering drugs; HHF = hospitalised for heart failure; MACE = Major Adverse Cardiac Event (composite of cardiovascular death, non-fatal MI and non-fatal stroke); MI– myocardial infarction, UA= unstable angina

Table 2. Potential mechanisms through which glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium/glucose co-transporter-2 (SGLT-2) inhibitors exert cardio-renal protective effects beyond glucose-lowering and weight-lowering effects.

Footnote to Table 2. The cardiovascular protection mediated by GLP-1RAs appears to be mostly through a reduction in fatal atherosclerotic events, while the protection mediated by SGLT-2 inhibitors is mostly by a reduction in the onset and progression of heart failure. SGLT-2 inhibitors can reduce the long-term decline in glomerular filtration rate and reduce the onset and progression of albuminuria, while the renal effects of GLP-1RAs are less pronounced and appear to involve intra-renal haemodynamic adjustments that alter filtration. *A decrease in intra-glomerular pressure is mediated by a combination of reduced plasma volume, reduced blood pressure and increased tubulo-glomerular feedback (TGF). TGF is increased by tubular sodium which activates macula densa cells to release ATP which is converted to adenosine. Adenosine causes contraction of afferent glomerular vessels and the reduced intra-glomerular pressure reduces filtration.
↑ increase; ↓ decrease; Δ change, → leading to.



Trial [www.clinical trials.gov ID]	Start - End & Follow up	Patient No & Age	Baseline Characteristics: T2DM Duration & BMI (kg/m²)	HbA1c (%) & % Insulin ± GLD	% Prior CVD & High BP	CV type CVD = coronary/cerebro/ peripheral vascular disease	ry end-point (⁰1)	met by all studies	Non-Fatal +includes fatal: MI	Non-Fatal +includes fatal: Stroke	HHF	CV death	All cause death	
								Hazard Ratio and 95% Confidence Intervals						
[a]TECOS[16] sitagliptin [NCT00790205]	2008 – 2015 3yrs	14671 65yrs	11.6yrs 30.2	7.2 23	100 86	≥50y ± CVD	3 pt MACE + AngH	Yes **0.98**[z] 0.89, 1.08	**0.95**[+] 0.81, 1.11	**0.97**[+] 0.79, 1.19	**1.00** 0.83, 1.20	**1.03** 0.89, 1.19	**1.01** 0.90, 1.14	TEcos
EXAMINE[17] alogliptin [NCT00968708]	2009 – 2013 1.5yrs	5380 61yrs	7.2yrs 28.7	8.0 30	100 83	≥18y, ACS ≤90 days	3 pt MACE	Yes **0.96** Upper ≤1.16	**1.08** 0.88, 1.33	**0.91** 0.55, 1.50	**1.07** 0.79, 1.46	**0.79** 0.60, 1.04	**0.88** 0.71, 1.09	Examine
SAVOR[18] saxagliptin [NCT01107886]	2010 – 2013 2.1yrs	16492 65yrs	10.3yrs 31.1	8.0 41	78 81	≥40y + CVD or ≥55y + ≥1 CV risk factor	3 pt MACE	Yes **1.0** 0.89, 1.12	**0.95** 0.80, 1.12	**1.11** 0.88, 1.39	**1.27*** 1.07, 1.51	**1.03** 0.87, 1.22	**1.11** 0.96, 1.27	Savor
CAROLINA[19] linagliptin vs glimepiride [NCT01243424]	2010 - 2018 6.3yrs	6033 64yrs	? 30.1	7.2 0	34 88	≥40yrs + CVD or end organ damage, or ≥70yrs, or ≥2 CV risk factors	3 pt MACE	Yes **0.98** 0.84, 1.14	**1.01**	**0.87**		**1.0** 0.81, 1.24		Carolina
CARMELINA[20] linagliptin [NCT01897532]	2013 - 2019 2.2yrs	6979 66yrs	15.0yrs 31.4	7.9 58.8	57 90.8	≥18yrs + micro/macro albuminuria + CVD, &/or CKD (pre-defined UACR)	3 pt MACE	Yes **1.02** 0.89, 1.17	**1.15** 0.91, 1.45	**0.88** 0.63, 1.23	**0.90** 0.74, 1.08	**0.96** 0.81, 1.14	**0.98** 0.84, 1.13	Carmelina

[a]ELIXA[21] lixisenatide [NCT01147250]	2010 – 2015 2.1yrs	6068 60yrs	9.3yrs 30.1	7.7 39	100 76.4	≥30y, ACS/MI <180 days	3 pt MACE + UA	Yes **1.02** [z] 0.89, 1.17	**1.03** [+] 0.87, 1.22	**1.12** [+] 0.79, 1.58	**0.96** 0.75, 1.23	**0.98** 0.78, 1.22	**0.94** 0.78, 1.13	Elixa
LEADER[22] liraglutide [NCT01179048]	2010 – 2016 3.8yrs	9340 64.3yrs	12.8yrs 32.5	8.7 44	92	≥50y + CVD (inc HF) or CKD, or ≥60y + ≥1 CV risk factor	3 pt MACE	Yes **0.87** * 0.78, 0.97	**0.88** 0.75, 1.03	**0.89** 0.72, 1.11	**0.87** 0.73, 1.05	**0.78*** 0.66, 0.93	**0.85*** 0.74, 0.97	Leader
EXSCEL[23] exenatide QW [NCT01144338]	2010 – 2017 3.2yrs	14752 63yrs	12yrs BMI?	8.0 46	73	≥18y ± CVD	3 pt MACE	Yes **0.91** 0.83, 1.00	**0.97**[+] 0.85, 1.10	**0.85** [+] 0.70, 1.03	**0.94** 0.78, 1.13	**0.88** 0.76, 1.02	**0.86** 0.77, 0.97	Exscel
REWIND[24] dulaglutide [NCT01394952]	2011 – 2018 5.4yrs	9901 66.2yrs	10.5yrs 32.3	7.3 24	31.5 93	≥50yrs + CVD, or ≥55yrs + subclinical vasc dis, or ≥60yrs + ≥2 CV risk factors	3 pt MACE	Yes **0.88** * 0.79, 0.99	**0.96** 0.79, 1.16	**0.76*** 0.61, 0.95	**0.93** 0.77, 1.12	**0.91** 0.78, 1.06	**0.90** 0.80, 1.01	Rewind
[b]SUSTAIN 6[25] semaglutide sc qw [NCT01720446]	2013 – 2016 2.1yrs	3297 64.6 yrs	14.2yrs 37.8	8.7 58	83 92.8	≥50y + CVD (inc HF) or CKD, or ≥60y + ≥1 CV risk factor	3 pt MACE	Yes **0.74** * 0.58, 0.95	**0.74** 0.51, 1.08	**0.61*** 0.38, 0.99	**1.11** 0.77, 1.61	**0.98** 0.65. 1.48	**1.05** 0.74, 1.50	Sustain 6
HARMONY[26] albiglutide [NCT02465515]	2015 – 2018 1.6yrs	9463 64.1yr	14.1yrs 32.3	8.76 60	70 86	≥40yrs+ CVD	3 pt MACE	Yes **0.78** * 0.68, 0.90	**0.75*** 0.61, 0.90	**0.86*** 0.66, 1.14	**0.85**[++] 0.70, 1.04	**0.93** 0.73, 1.19	**0.95** 0.79, 1.16	Harmony
[b]PIONEER 6[27] semaglutide oral [NCT02692716]	2017 – 2018 1.3yrs	3183 66yrs	14.7yrs 32.3	8.2 ?	35 94	≥50yrs + CVD or moderate CKD, or ≥60yrs +≥ 1 CV risk	3 pt MACE	**0.79*** 0.57, 1.11	1.18 0.73, 1.90	**0.74** 0.35 1.57	**0.86** 0.48, 1.55	**0.49** 0.27, 0.92	**0.51** 0.31, 0.84	Pioneer 6

[c]CANVAS[28] [NCT01032629] canagliflozin (CANVAS-R*) [(NCT01989754)]	2009 - 2017 3.1yrs 2014 - 2017	10142 63.3yrs	13.5yrs 32.0	8.2 50	65 90	≥30 yrs + CVD, or ≥50 yrs + ≥2 CV risk factors	3 pt MACE	Yes **0.86*** 0.75, 0.97	**0.85** 0.69, 1.05	**0.90** 0.71, 1.15	**0.67** 0.52, 0.87	**0.87** 0.72, 1.06	**0.87** 0.74, 1.01	Canvas
EMPA-REG[29] = C-SCADE 8 empagliflozin [NCT01131676]	2010 – 2015 3.1yrs	7020 63yrs	57% >10yr 30.6	8.1 48	99 94	≥18 yrs + CVD	3 pt MACE	Yes **0.86*** 0.74, 0.99	**0.87** 0.70, 1.09	**1.24** 0.92, 1.67	**0.65*** 0.50, 0.85	**0.62*** 0.49, 0.77	**0.68*** 0.57, 0.82	Empa R
DECLARE[30] dapagliflozin [NCT01730534]	2013 – 2018 4.2yrs	17160	11.0yrs 32.1	8.3 41.6	40.5 89	≥40yrs + high CV risk	3pt MACE Co-primary CV Death or HHF	Yes **0.93** 0.84, 1.03	**0.89** 0.77, 1.01	**1.01** 0.84, 1.21	**0.73*** 0.61, 0.88	**0.98** 0.82, 1.17	**0.93** 0.82, 1.04	Declare

Table 1A. Summary of patient characteristics and main cardiovascular outcomes30-39

[a]Elixa and Tecos trials were initiated before the FDA guidance on CV requirements and each had a primary endpoint that was a 4-point composite MACE (3-point MACE plus hospitalization for angina).

[b]the Sustain 6 and Pioneer 6 trials were extended pre-approval studies so do not have the same statistical power as the others.

[c]CANVAS was originally designed for up to 9 years, but amended to end when enough MACE events had accumulated between the CANVAS and CANVAS-R studies**.** Now referred to as the CANVAS Program

*Statistically significant; [+]Fatal and non-fatal stroke; [#]hospitalised for unstable angina
[++]hospitalisation for heart failure or CV death

[z]3pt MACE + hospitalisation for angina/unstable angina

Worse than usual care

Better than usual care

Ang H – hospitalised for angina; CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; BP = blood pressure; GLD = glucose lowering drugs; HHF = hospitalised for heart failure; MACE = Major Adverse Cardiac Event (composite of cardiovascular death, non-fatal MI and

non-fatal stroke); MI– myocardial infarction, QW = once weekly; sc = subcutaneous; UA = unstable angina.

Table 1A. Summary of patient characteristics and main cardiovascular outcomes

Table 1B. Summary of patient characteristics and main cardiovascular outcomes with vildagliptin and omarigliptin

	Baseline characteristics												
Trial [www.clinical trials.gov ID]	**Start - End & Follow up**	**Patient No & Age**	**T2DM Duration & BMI (kg/m²)**	**HbA$_{1c}$ (%) & Insulin ± GLD %**	**% Prior CVD & High BP**	**CV type** CVD = coronary/cerebro/peripheral vascular disease	**Primary end-point (^{0}1)**	**^{0}1 met by all studies**	**Non-Fatal $^+$includes fatal**		**HHF**	**CV death**	**All cause death**
									MI	**Stroke**			
								Hazard Ratio and 95% Confidence Intervals					
Vildagliptin[31] Database analysis	2011-2013 9.9mo	3,750 68.3yrs	11.8yrs ?	? 50.8	13.3 ?	≥40yr ACS/ ischaemic stroke ≤3 months	3 pt MACE	Yes **0.90** 0.72, 1.11	**0.79** 0.46, 1.36	**0.96** 0.74, 1.24	**0.81** 0.53, 1.22	**0.93** 0.56, 1.52	**0.82** 0.59 1.13
Omarigliptin[32] QW [NCT01703208]	2012-2016 1.8yrs	4,202 63.7yrs	12.0 31.2	8.0 36.6	100 95	≥40yr + CVD	3 pt MACE + HHF	Yes **1.00** 0.77, 1.29	**0.87**$^+$ 0.60, 1.26	**0.94**$^+$ 0.58, 1.52	**0.60** 0.35, 1.05	**1.06** 0.66, 1.68	**1.28** 0.88, 1.85

	GLP-1 receptor agonists	SGLT-2 inhibitors
Cardiovascular	**Mostly decrease ASCVD**	**Mostly decrease heart failure**
	↓ Blood pressure (but ↑ heart rate)	↓ Blood pressure
	↑ Vasodilatation (endothelium-mediated ?)	↓ Plasma volume (due to diuresis)
	↓ Angiotensin II (renin activity unchanged ?)	↓ Arterial stiffness (mechanism unclear)
	↑ Natriuresis (↓ renal Na/H exchanger ?)	↑Myocardial energy substrate (ketones)
	↓ Improved lipid profile (↓ TC, ↓ LDL, ↓ TG)	↑ Myocardial BCAA catabolism (→ ↑ PDH)
	↓ Inflammatory and atherotthrombotic markers (↓ CRP, ↓eNOS, ↓ ICAM-1, ↓PAI-1)	↑Myocardial energetics (↓ Na/H exchanger → ↑mitochondrial calcium)
		↑ Angiotensin 1-7 (mechanism unclear)
		↓ Uric acid (↑ renal urate excretion)
Renal	**Decrease in albuminuria**	**Decrease CKD and albuminuria**
	Δ Intra-renal haemodynamics (mechanisms unclear)	↓ Intra-glomerular pressure*
	↓ Angiotensin II activity in glomerulus (effect unclear)	↑ Tubulo-glomerular feedback

	↓ Inflammation (partly by ↓ adiposity)	↓ Hyperfiltration
	↓ Oxidative stress (partly by ↓ glucotoxicity)	↓ Inflammation (partly by ↓ adiposity)
		↓ Oxidative stress (partly by ↓ glucotoxicity)