European Heart Journal Advance Access published June 10, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv239

REVIEW

Clinical Update

Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes

Ele Ferrannini[1]* and Ralph A. DeFronzo[2]

[1]Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy; and [2]Diabetes Division, University of Texas Health Science Center, San Antonio, TX, USA

Received 7 April 2015; revised 5 May 2015; accepted 16 May 2015

Type 2 diabetes mellitus (T2DM) is characterized by multiple pathophysiologic abnormalities. With time, multiple glucose-lowering medications are commonly required to reduce and maintain plasma glucose concentrations within the normal range. Type 2 diabetes mellitus individuals also are at a very high risk for microvascular complications and the incidence of heart attack and stroke is increased two- to three-fold compared with non-diabetic individuals. Therefore, when selecting medications to normalize glucose levels in T2DM patients, it is important that the agent not aggravate, and ideally even improve, cardiovascular risk factors (CVRFs) and reduce cardiovascular morbidity and mortality. In this review, we examine the effect of oral (metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP4 inhibitors, SGLT2 inhibitors, and α-glucosidase inhibitors) and injectable (glucagon-like peptide-1 receptor agonists and insulin) glucose-lowering drugs on established CVRFs and long-term studies of cardiovascular outcomes. Firm evidence that in T2DM cardiovascular disease can be reversed or prevented by improving glycaemic control is still incomplete and must await large, long-term clinical trials in patients at low risk using modern treatment strategies, i.e. drug combinations designed to maximize HbA_{1c} reduction while minimizing hypoglycaemia and excessive weight gain.

Keywords Type 2 diabetes • Glucose-lowering drugs • Cardiovascular disease • Cardiovascular risk

Natural history and pathophysiology of type 2 diabetes

Type 2 diabetes (T2DM) is a systemic disease characterized by multiple pathophysiologic disturbances.[1] Individuals destined to develop T2DM manifest moderate–severe insulin resistance in muscle and liver, impaired β-cell glucose sensitivity, and increased insulin secretion.[1–3] With time, β-cells fail to secrete sufficient amounts of insulin to offset the insulin resistance[4,5] and normal glucose tolerant individuals progress to impaired glucose tolerance (IGT) and then to overt T2DM.[1,6–10] In addition to the core defects of insulin resistance and β-cell failure, T2DM individuals manifest at least five other pathophysiologic abnormalities: (i) adipocyte insulin resistance, leading to accelerated lipolysis and elevated circulating free fatty acid (FFA) levels.[11] Increased plasma FFA,[12,13] in concert with increased deposition of toxic lipid metabolites (diacylglycerol, FattyAcid-CoAs, and ceramides) in muscle, liver, and, possibly, β-cells (lipotoxicity)[14] worsen the insulin resistance in liver/muscle and aggravate β-cell failure; (ii) impaired incretin effect,[15] primarily due to β-cell resistance to the insulin-stimulatory effects of both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[16–18]; (iii) increased glucagon secretion and enhanced hepatic sensitivity to glucagon,[19,20] resulting in an increased rate of hepatic and renal glucose production[1]; (iv) increased renal glucose reabsorption[21]; and (v) brain insulin resistance and altered neurotransmitter function leading to dysregulation of appetite and weight gain[22] (*Figure 1*). From this brief overview of the pathophysiology, it is clear that multiple drugs used in combination will eventually be required to normalize glucose homeostasis in the majority of T2DM patients, including those initially well controlled on monotherapies. Furthermore, because T2DM is a progressive disease, with time more and more glucose-lowering medications will need to be added to maintain normoglycaemia.[23–25] Because T2DM is associated with a markedly increased incidence of cardiovascular complications (see below), it is advantageous that the medications used to restore normoglycaemia not aggravate known cardiovascular risk factors (CVRFs), not accelerate the underlying atherogenic process and, optimally, reduce cardiovascular risk. It is pertinent to recall here that in the Look AHEAD trial[26] intensive lifestyle intervention in overweight/obese T2DM patients failed to

* Corresponding author. Department of Clinical and Experimental Medicine, Via Roma, 67, 56100 Pisa, Italy. Tel: +39 50 553272, Fax: +39 50 553235, Email: ferranni@ifc.cnr.it

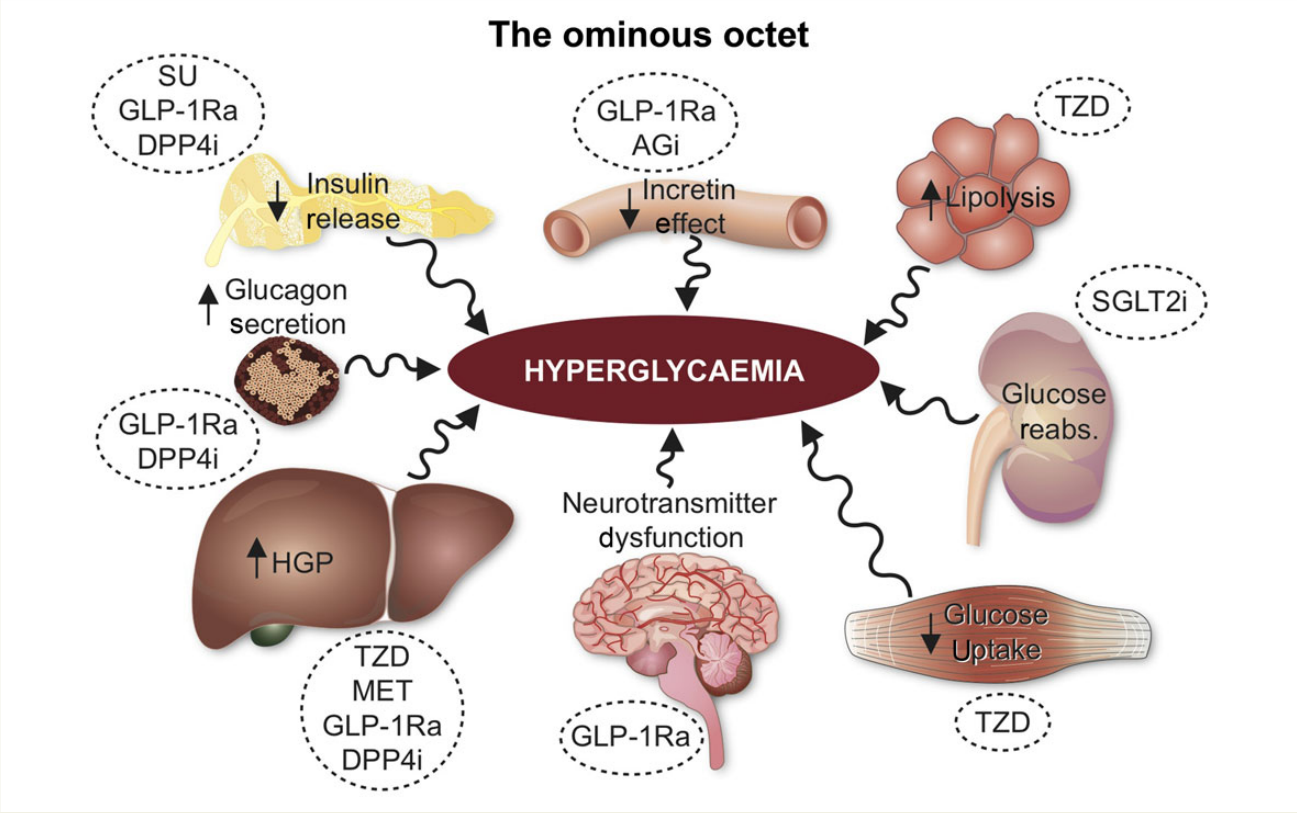

Figure 1 Mechanistic contribution of different tissues to hyperglycaemia. The arrows indicate the direction of change in function; site and mode of action of glucose-lowering drugs are shown in the dotted circles. HGP, hepatic glucose production; GLP-1Ra, GLP-1 receptor agonists; TZDs, thiazolidinediones; DPP4i, DPP4 inhibitors; SGLT2i, SGLT2 inhibitors; SU, sulfonylureas; AGi, α-glucosidase inhibitors.

affect cardiovascular disease (CVD) outcome after 9.6 years of median follow-up despite improved biomarkers of glucose and lipid control and other health benefits. Therefore, to examine the impact of glucose-lowering drugs on CVD is of full clinical relevance.

Type 2 diabetes and atherosclerotic cardiovascular disease

It is conclusively established that the microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy) are directly related to the severity and duration of hyperglycaemia, as reflected by the HbA_{1c}.[25,27] However, macrovascular complications are the primary cause of mortality, with myocardial infarction (MI) and stroke accounting for 80% of all deaths in T2DM patients.[28] In a Finnish cohort of T2DM patients without prior MI, the 7-year incidence of MI was double that of non-diabetic subjects and similar to that of non-diabetic subjects with a prior MI.[29] Recurrence of major atherosclerotic events in T2DM individuals with a prior MI is very high, ~6% per year,[30] and death rate in T2DM patients is approximately two-fold greater than in matched non-diabetic individuals,[31–33] even after adjustment for other CVRFs.[34,35] Further, the relationship between glycaemia and increased CV risk starts within the normal blood glucose range without evidence of a threshold effect.[34–38] In a population-based study of health claims in Ontario (379 003 with diabetes and 9 018 082 without diabetes), the transition from low-to-high CVD risk occurred 14.6 years earlier in the diabetic group.[39]

The load of CVRFs includes hypertension, dyslipidaemia (reduced HDL-cholesterol, elevated triglycerides, and small dense LDL particles), obesity (especially visceral), physical inactivity, sub-clinical inflammation, and endothelial dysfunction. This cluster, referred to as *metabolic* or *insulin resistance* syndrome,[40–42] consistently predicts atherosclerotic CVD (ATCVD).[43–48] Many studies have reported an association between insulin resistance/hyperinsulinaemia and ATCVD in the general population.[45,49–67] Moreover, in cross-sectional analyses insulin treatment in T2DM patients is consistently associated with the presence of ATCVD even after adjusting for multiple CVRFs.[68] However, in most studies insulin resistance was not measured directly and control for statistical confounding was incomplete. Thus, in a cohort of carefully phenotyped non-diabetic subjects baseline insulin resistance (as measured by the euglycaemic insulin clamp technique) was independently associated with a small increment in the intima-media thickness of the common carotid artery (Copenhagen Insulin and Metformin Therapy, C-IMT)—an antecedent of CVD[69] and a measure of the atherosclerotic burden in T2DM[70]—in men but not in women.[71] Also, in a study of 11 644 T2DM patients attending hospital-based diabetes clinics insulin treatment was not an independent predictor of incident CVD.[72]

Finally, in the ORIGIN trial in 12 537 T2DM patients with prior CVD or CVRFs insulin treatment for a median of 6.2 years had a neutral effect on CVD outcomes[73] and modestly reduced C-IMT progression.[74]

Cardiovascular disease and diabetes are among the leading global and regional causes of death; between 1990 and 2016 CVD deaths increased by 25%.[75,76] In a recent comparative assessment of the global burden of metabolic risk factors for CVD, 60% of worldwide CVD deaths in year 2010 was attributable to four modifiable cardiometabolic risk factors[77]: high BP, blood glucose, BMI, and serum cholesterol. These findings are similar to those reported in the INTERHEART study in 2004.[78]

Implications for choice of glucose-lowering agents in type 2 diabetes

In examining the effect of currently approved glucose-lowering drugs on established CVRFs and, where available, on CV mortality and morbidity, two preliminary considerations are important. First, micro- and macrovascular T2DM complications often coexist in the same patient but have partially different pathophysiology and risk factors. Also, the dose–response relation of hyperglycaemia to microvascular complications is significantly steeper than to macrovascular disease.[79,80] Secondly, the vast majority of epidemiologic studies and clinical trials is based on major adverse cardiac events (MACE) as the outcome, which includes CV death, non-fatal MI, and non-fatal stroke (sometimes, also unstable angina requiring hospitalization, amputation, and revascularization procedures are included). These outcomes, however, represent the tip of the iceberg of a gamut of manifestations of CVD (*Figure 2*) including the most common cardiac problem in T2DM, i.e. heart failure, and chronic kidney disease, a potent CVD predictor.[81] Therefore, while MACE is a practical and well-established 'hard' endpoint, its ability to track the natural history of CVD is limited. Finally, although T2DM confers an equivalent risk to ageing 15 years,[39] the beneficial effects of improved glycaemic control on CVD prevention may require >10 years to become manifest.[82,83] Therefore, prevention of CVD in T2DM patients demands a multifactorial approach to improve/normalize glycaemia and correct multiple the classical CVRFs, as shown in the survey by Anselmino *et al.*[84] and prospectively implemented in the Steno-2 Study.[85]

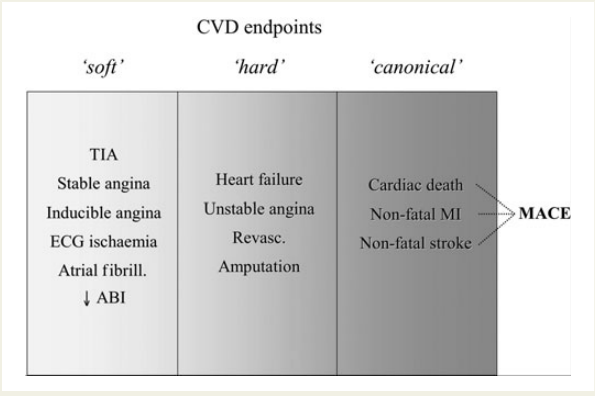

Figure 2 Major adverse cardiac events and other major adverse cardiovascular events are the tip of the iceberg of atherosclerotic cardiovascular disease. ABI, ankle-brachial index.

Glucose-lowering drugs

Metformin

Metformin is the most commonly prescribed oral glucose-lowering agent worldwide and is recommended as first-line therapy by the American Diabetes Association (ADA), European Association for the Study of Diabetes, and International Diabetes Federation.[86] Metformin has been used for over 50 years and it safety profile is well known.[87] In the UKPDS, metformin significantly reduced MI, coronary deaths, and all-cause mortality by 39, 50, and 36%, respectively, in newly diagnosed T2DM patients with low CVD risk whose body weight was >120% of the ideal weight.[88] In the 10-year follow-up of UKPDS,[82] metformin-treated obese T2DM patients continued to show a reduction in MI (33%) and death from any cause (33%). However, the number of subjects in this study was small ($n = 342$) and they were all obese; also, the lack of lipid lowering drugs and modern blood pressure and kidney preserving drugs diminishes the relevance of this observation for present-day treatment.

Many retrospective analyses of large databases have concluded that metformin reduces the incidence of cardiovascular events.[89–96] However, in most of these studies sulfonylureas were the comparator,[89–91,93–95] and it is not possible to determine whether sulfonylureas increased[96] or metformin decreased CVD outcomes. In one of the few prospective trials, Hong *et al.*[97] randomized 304 T2DM patients with a history of coronary artery disease (CAD) to glipizide or metformin for a median follow-up of 5 years. The hazard ratio (HR) (0.54) for the composite endpoint (CV death, any cause mortality, MI, non-fatal stroke, and arterial revascularization) was significantly reduced in the metformin group. Two retrospective analyses[98,99] in diabetic patients with CAD with or without heart failure concluded that metformin improves survival independent of glycaemic control. Two ongoing randomized, double-blind clinical trials [Metformin in CABG trial, MetCAB (NCT01438723) and Glycometabolic Intervention as Adjunct to Primary Percutaneous Intervention in ST Elevation Myocardial Infarction Trial, GIPS-III (NCT01217307)[100] will help to elucidate whether metformin can reduce infarct size and improve left ventricular function after ischaemia-reperfusion injury. More definitive evidence on the issue will have to await the Glucose-Lowering in Non-diabetic Hyperglycaemia trial [GLINT (ISRCTN34875079)], which will randomize 12 000 high-risk patients with dysglycaemia, but without overt diabetes, to metformin or placebo for 5 years.

Regarding the effect of metformin on CVD proxies, in 118 T2DM patients followed for >3 years metformin was associated with a small, but significant decrease in the rate of C-IMT progression compared with placebo.[101] Similar results were reported in a small group ($n = 40$) of patients with the metabolic syndrome[102] and in 200 Japanese T2DM patients followed for 2 years.[103] However, in the Carotid Atherosclerosis: Metformin for Insulin Resistance (CAMERA) study,[104] metformin had no effect on C-IMT

progression over 18 months in 173 non-diabetic patients. However, in contrast to the Katakami[101] and Meaney study,[102] all subjects in CAMERA were on statin therapy, which could have minimized any effect of metformin. Two ongoing trials [C-IMT trial (NCT00657943) and Reducing with Metformin Vascular Adverse Lesions in Type 1 Diabetes Trial (REMOVAL, NCT014883560)] will examine the effect of metformin on C-IMT in 950 T2DM patients and in 500 type 1 diabetic patients, respectively. In these trials, statin therapy will be monitored closely to dissect out any anti-atherogenic effect of metformin.

Potential mechanisms for the putative protective effect of metformin include improved glycaemic control,[82,88,105,106] reduction in methylglyoxal levels,[107] decrease in VLDL secretion and plasma triglyceride levels, and reduced postprandial lipaemia.[108–115] Plasma LDL- and HDL-cholesterol levels are either unchanged or change minimally with metformin.[116] Improved endothelial dysfunction and reduced plasminogen-activator inhibitor 1 (PAI-1) levels also have been reported.[117] Cumulative exposure to obesity is a CVD risk factor,[118] and modest weight loss (~2–3 kg) is common in T2DM patients treated with metformin.[86,119] The weight loss is explained by the anorectic effect of the biguanide and its gastrointestinal side effect profile (diarrhoea, abdominal discomfort, and flatulence).[86] With regard to insulin resistance, a systematic review of euglycaemic insulin clamp studies in T2DM patients has established that metformin is not an insulin sensitiser,[120] its effect being confined to liver and gut.[121]

In summary, the weight of available evidence indicates that metformin does not exert adverse effects on CVD in T2DM patients; because it improves some CVRFs, metformin *may* reduce CVD morbidity and mortality.

Sulfonylureas

Sulfonylureas have been used to treat T2DM patients for over 60 years. Their main mechanism of action is to enhance insulin secretion by β-cells[1]; the resultant hyperinsulinaemia overcomes, in part, the insulin resistance in liver and muscle, leading to a decrease in HbA_{1c}. *In vitro* studies have demonstrated that sulfonylureas accelerate β-cell failure[122–124]; furthermore, they fail to improve CVRFs,[125] promote weight gain, and cause hypoglycaemia,[125] the latter two adverse effects being associated with increased CVD risk.[126,127] In the ADVANCE trial, severe hypoglycaemia was associated with a significant increase in major macrovascular events and death from a cardiovascular cause.[128]

Concerns about the association between sulfonylureas and increased cardiovascular mortality first arose in 1970 with the controversial University Group Diabetes Program,[129] which resulted in the Food and Drug Administration (FDA) inserting a warning label in the prescribing information for sulfonylurea drugs. Many studies, mostly retrospective analyses of large databases[94–100,130–134] but some prospective,[101] have demonstrated an increased CVD risk in T2DM patients treated with sulfonylureas. Amongst the sulfonylureas, the incidence of adverse cardiovascular events appears to be greatest with glibenclamide (glyburide).[131–136] However, UKPDS,[25] ADVANCE,[137] and ACCORD[138] failed to demonstrate an increase in either CVD mortality or morbidity in sulfonylurea-treated T2DM patients. Recent meta-analyses also have generated conflicting results with some purporting to show an increase in cardiovascular mortality,[100,130] while another concluded that there was no increase in CV disease.[139] The study by Monami *et al.*[96] reported an increase in mortality, most likely cardiovascular in origin, but no increase in other CV events. While part of this controversy may be resolved by the Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with Type 2 Diabetes (CAROLINA) (NCT01243424),[140] the issue is further complicated by reports that combination therapy with a sulfonylurea plus metformin may increase cardiovascular risk.[88,141,142] Because glibenclamide interferes with ischaemic preconditioning,[143,144] causes more hypoglycaemia,[145] and may be associated with an increased incidence of CVD compared with other sulfonylureas,[131–136] if a sulfonylurea is to be used, an agent other than glibenclamide is preferable.

In summary, it remains unclear at the present time whether or not sulfonylureas are associated with an increased CVD risk. With the exception of the ongoing CAROLINA study,[140] we are unaware of planned prospective studies that might resolve this controversy.

Meglitinides

Repaglinide and nateglinide are short-acting insulin secretagogues that bind to both the sulfonylurea receptor and a distinct site on the β-cell. This confers a different pharmacodynamic profile to these agents, which therefore must be given prior to each meal.[146] Unlike sulfonylureas whose major effect is to reduce fasting plasma glucose concentrations, the major action of the meglitinides is to reduce postprandial glucose excursions.[146] Because of their short action, meglitinides are associated with less hypoglycaemia and weight gain compared with sulfonylureas.[147,148] Neither repaglinide nor nateglinide[149,150] has any effect on classic CVRFs, although a decrease in Lp(a) has been reported with repaglinide.[150] In a 30-day follow-up of 740 repaglinide-treated T2DM patients who had a hospital admission for ischaemic heart disease, no increase in CV mortality or events was observed compared with 5543 T2DM patients treated with glibenclamide or gliclazide.[151]

Thiazolidinediones

The thiazolidinediones (TZDs, pioglitazone, and rosiglitazone) exert their metabolic and cardiovascular effects via activation of peroxisome proliferator-activated receptors-γ.[152,153] In 2011, the use of rosiglitazone in the USA was restricted by the FDA[154] and the drug was removed from Europe because of concern about increased CVD risk, especially MI. In a literature review, Scherntaner and Chilton[155] found that rosiglitazone consistently was associated with an HR of >1.0 for CVD events. More recently, the FDA re-examined the RECORD study[156] and concluded that there was no increase in overall CV risk. On this basis, the FDA lifted its restriction on rosiglitazone; however, the drug has not re-gained traction in the USA and has not been reintroduced in Europe.

Thiazolidinediones are the only true insulin-sensitising agents, exerting their effects in skeletal[153] and cardiac muscle,[157] liver,[158–160] and adipose tissue.[159] Although not commonly appreciated, pioglitazone[161–165] as well as rosiglitazone[162,166] act on the β-cell to augment insulin secretion and preserve β-cell function. Pioglitazone exerts beneficial effects on a number of CVRFs: (i) increases plasma HDL-cholesterol,[167–171] (ii) reduces plasma triglyceride and FFA

levels,[159] (iii) is neutral on LDL-cholesterol levels,[167–171] and converts small dense LDL-cholesterol particles into larger, more buoyant particles,[167–171] (iv) reduces BP,[172,173] (v) improves endothelial dysfunction,[174,175] (vi) ameliorates insulin resistance,[153] (vii) decreases visceral fat,[14,152] (viii) increases adiponectin and reduces PAI-1, C-reactive protein (CRP) and tumour necrosis factor-α (TNF-α) levels,[176,177] and (ix) improves non-alcoholic steatohepatitis.[178] Rosiglitazone produces metabolic effects similar to those of pioglitazone with two notable exceptions: the drug increases plasma LDL-cholesterol and triglyceride levels.[170,171] Because they enhance renal sodium and water reabsorption,[179] TZDs can cause congestive heart failure (CHF), especially in patients with diastolic dysfunction. However, pioglitazone has been shown to improve diastolic dysfunction, to enhance myocardial insulin sensitivity and to be neutral to left ventricular function.[180]

In a large prospective study (PROactive) involving 5238 T2DM patients with a previous CV event or multiple CVRFs,[181] an increased incidence of serious CHF was observed but CHF patients did not experience increased all-cause mortality.[182] In this study, pioglitazone improved several CVRFs (HDL-cholesterol, BP, and HbA_{1c}), and reduced the second principal MACE endpoint (cardiovascular mortality, MI, and stroke) by 16%. In a subgroup of 2445 patients with previous MI, pioglitazone reduced likelihood of subsequent MI by 16% [183] and in 984 patients with previous stroke, it caused a 47% reduction in recurrent stroke.[184]

However, in PROactive the composite primary endpoint (mortality, non-fatal MI, silent MI, stroke, acute coronary syndrome, coronary artery bypass grafting/percutaneous coronary intervention, leg amputation, and leg revascularization) did not reach statistical significance because of a higher number of leg revascularization procedures in the pioglitazone group.[181] Leg revascularization typically is excluded from CV intervention trials. Subsequent PROactive analyses confirmed that pioglitazone has no beneficial effect on peripheral vascular disease.[185] Consistent with PROactive, a meta-analysis of all published pioglitazone studies (excluding PROactive) demonstrated a 25% decrease in CV events.[186]

Three studies have demonstrated that pioglitazone slows anatomical progression of ATCVD. In PERISCOPE,[187] T2DM patients with established CAD were randomized to pioglitazone or glimepiride for 1.5 years. In the glimeperide-treated group, atheroma volume progressed, while it regressed in the pioglitazone-treated group. In CHICAGO[188] and in a similarly designed study,[189] pioglitazone halted C-IMT, which progressed in the glimepiride-treated group (both $P < 0.01$). In PERISCOPE and CHICAGO, the reduction in C-IMT was correlated with the increase in HDL-cholesterol, while in the study of Lagenfeld *et al.*[189] it correlated with the improvement in insulin sensitivity. Diabetic individuals with renal impairment are at increased risk for CV disease/mortality.[81] In PROactive, pioglitazone significantly reduced MACE in patients with and without reduced GFR.[190]

In a retrospective analysis of the UK General Practice Database (including 91 511 T2DM patients with a follow-up of 7.1 years), pioglitazone was associated with a 31–39% reduction in all-cause mortality compared with metformin, while sulfonylureas were associated with a significant increase in mortality.[191] In 27 451 metformin-treated patients who had pioglitazone as add-on, the HR for all-cause mortality (0.70) and MACE (0.75) was significantly reduced.[192]

All in all, PROactive, studies reported to the FDA, assessing C-IMT, those demonstrating regression of coronary atheroma,[189] and a systematic review of the literature suggest that pioglitazone may slow the progression of atherogenesis and reduces CV events.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP4i) block the degradation of GLP-1, GIP, and a variety of other peptides, including brain natriuretic peptide.[193] This class of drugs has a modest effect to reduce HbA_{1c} and is weight neutral.[194,195] In clinical trials, DPP4i have not been shown to exert any meaningful BP-lowering effect.[195,196] A meta-analysis of 17 clinical trials with various DPP4i demonstrated a small, ~6 mg/dL, decline in total cholesterol.[197] No consistent changes in fasting levels of LDL-cholesterol, HDL-cholesterol, or triglycerides have been demonstrated.[198] In contrast, DPP4i reduce postprandial lipaemia as evidenced by reductions in plasma triglyceride, apolipoprotein B-48, and apolipoprotein B-100 levels following a mixed meal.[199,200] Sitagliptin has been reported to reduce hsCRP[201] and improve endothelial dysfunction.[202,203] Animal studies have demonstrated that DPP4i reduce ischaemia-reperfusion injury.[204]

Pooled and/or meta-analyses with individual DPP4i demonstrated a significant reduction in CV events: sitagliptin,[205,206] vildagliptin,[207] saxagliptin,[208,209] alogliptin,[210] and linagliptin.[211] A pooled analysis of all DPP4i[208,212] also demonstrated a significant CVD reduction. However, these analyses were all retrospective and were not specifically designed to examine the effect of DPP4i on CVD incidence. Recently, the results of two large prospective CV outcome trials have been published. In SAVOR-TIMI,[213] 16 492 T2DM patients who had a history of, or were at high risk for, CV events were randomized to placebo or saxagliptin and followed for a median of 2.1 years. The primary endpoint (MACE) occurred in 7.3 and 7.2% (HR = 1.00) of saxagliptin and placebo-treated subjects, respectively; the major secondary endpoint (MACE plus hospitalization for unstable angina/coronary revascularization/heart failure) occurred in 12.8 and 12.4%, respectively. An unexpected finding in this study was a 3.5% incidence of hospitalization for CHF (vs. 2.8% in the placebo arm, $P = 0.007$), but this was not associated with an increase in mortality. The reason(s) for the increased CHF incidence is unknown but DPP4 degrades a multitude of vasoactive peptides, including brain natriuretic peptides, the levels of which are markedly elevated in patients with CHF.[214] Further studies to define whether the increased hospitalization for CHF was a chance finding or was causally related to DPP4i therapy are warranted. In EXAMINE,[215] 5380 T2DM patients with an acute MI or hospitalization for unstable angina in the prior 15–90 days were randomized to alogliptin or placebo and followed for a median of 18 months: 11.3% of patients treated with alogliptin and 11.8% treated with placebo (HR = 0.96) experienced the primary endpoint (MACE). SAVOR-TIMI and EXAMINE are remarkable in that prior meta-analyses with these DPP4i suggested a reduction in CV events.[201–203] It should be noted, however, that the treatment period (1.5–2.1 years) was very short in both SAVOR-TIMI and EXAMINE. Furthermore, the difference in HbA_{1c} level between DPP4i treatment and placebo groups was relatively small (0.3–0.4%) and the majority of patients were receiving statins, antiplatelet, and anti-hypertensive agents, which could have obscured differences. Ongoing trials with

sitagliptin (TECOS)[216] and linagliptin (CAROLINA)[140] will help to clarify whether the DPP4i have any potential against CV events.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) mimic the action of endogenous GLP-1 and are both short-acting (4–6 h) [exenatide (Byetta®) and lixisenatide (Lyxumia®), intermediate-acting (24 h) (liraglutide (Victoza®) and long-acting (7 days) (exenatide (Bydureon®), dulaglutide (Trulicity®), and semaglutide). Glucagon-like peptide-1 receptor agonists enhance glucose homeostasis through: (i) stimulation of insulin secretion; (ii) inhibition of glucagon secretion; (iii) direct and indirect suppression of endogenous glucose production; (iv) suppression of appetite; (v) enhanced insulin sensitivity secondary to weight loss; (vi) delayed gastric emptying, resulting in decreased postprandial hyperglycaemia.[1,217,218] Importantly, the reduction in HbA_{1c} is maintained in excess of 3 years because of a durable effect on the β-cell to enhance insulin secretion.[219]

Glucagon-like peptide-1 receptors have been demonstrated in cardiomyocytes, kidney, vascular endothelium, and arterial smooth muscle cells,[220] suggesting that GLP-1RAs may reduce CV risk. Glucagon-like peptide-1 receptor agonists exert beneficial effects on a number of CVRFs, and have been found to have cardioprotective properties in animal studies.[214,221] In a variety of preclinical models (pig, dog, rat) of CHF, GLP-1RAs have been shown to improve glucose utilization and increase LV contractility, stroke volume, and cardiac output.[222–225] Glucagon-like peptide-1 receptor agonists also have been shown to reduce infarct size. In pigs, exenatide caused a striking 40% reduction in infarct area, improved LV output, enhanced recovery of myocardial wall thickening, and improved the molecular mechanisms involved in the apoptosis of ischaemic myocardial cells.[226] Similar cardioprotective effects of native GLP-1[227] and liraglutide have been observed in a murine model of ischaemia following coronary artery occlusion.[228]

Several small studies have evaluated the effect of GLP-1 in both diabetic and non-diabetic humans with CHF. In 12 patients with NYHA III–IV, GLP-1 infusion for 5 weeks significantly improved left ventricular ejection fraction (LVEF), maximal ventilation oxygen consumption, and 6-min walk distance.[229] Similar beneficial effects on LV function have been observed in other[230,231] but not all[232] studies. Several studies also have demonstrated beneficial effects of GLP-1 infusion in humans with ischaemic heart disease. A 72-h GLP-1 infusion initiated in patients with acute MI increased LVEF and infarct-zone-related wall motion.[231] Intravenous GLP-1 prior to dobutamine stress echocardiography in humans with CAD reduced ischaemic LV dysfunction during coronary balloon occlusion and mitigated stunning.[233] The same investigators demonstrated protection against ischaemic LV dysfunction and myocardial stunning after coronary baboon occlusion in non-diabetic individuals.[234] In a large ($n = 172$) randomized, double-blind, placebo-controlled study, exenatide infusion started prior to the onset of reperfusion in patients undergoing angioplasty for STEMI significantly reduced ischaemia, and the myocardial salvage index (quantitated by cardiac MRI) was increased 3 months later.[235]

Glucagon-like peptide-1 receptor agonists also exert beneficial effects on multiple CV risk factors and the metabolic syndrome. All GLP-1RAs are associated with weight loss[236,237] and a decrease in visceral as well as subcutaneous fat.[238] Recently, high-dose liraglutide (3.0 mg/day) has been approved by the FDA for treatment of obesity in diabetic and non-diabetic subjects.[239] Glucagon-like peptide-1 receptor agonists consistently cause modest reductions in systolic (4–5 mmHg) and diastolic (1–2 mmHg) BP.[240–242] The reduction in BP is observed prior to significant weight loss, although weight loss likely contributes to the long-term maintenance of BP reduction. With regard to this, GLP-1 infusion acutely enhances urinary sodium excretion in a dose-dependent manner.[243] Glucagon-like peptide-1 receptor agonists cause a small increase in heart rate (2–3 beats/min), which likely is related to the presence of GLP-1 receptors in the SA node.[244] Glucagon-like peptide-1[245] and GLP-1RAs[246,247] also improve endothelial dysfunction in T2DM patients. In particular, using venous occlusion plethysmography Basu *et al.*[246] demonstrated that GLP-1 induced acetylcholine-mediated vasodilation, which could be blocked by administration of glybenclamide but not glimepiride. Glucagon-like peptide-1 and GLP-1RAs reduce postprandial lipaemia as indexed by decreases in Apo-B48, triglycerides, remnant lipoprotein triglycerides, and remnant lipoprotein cholesterol.[248,249] Glucagon-like peptide-1 also reduces postprandial as well as fasting plasma FFA levels by 30–40%.[249] Liraglutide, exenatide, dulaglutide, and albiglutide all-cause modest reductions in total cholesterol, LDL-cholesterol, triglycerides, and FFA, and a modest increase in HDL-cholesterol.[232,250–254] The beneficial effect of GLP-1RAs is related to two factors: (i) delayed gastric emptying[255] and (ii) direct effect to inhibit ApoB-48 secretion, as demonstrated in cultured hamster enterocytes.[256] Animal studies have suggested a direct inhibitory effect of GLP-1 on VLDL synthesis/secretion,[257] although controversy exists over this effect. Finally, GLP-1 and GLP-1RAs reduce inflammatory markers that are strongly associated with ATCVD, most notably hsCRP.[258,259] Glucagon-like peptide-1 receptor agonists also lower plasma levels of TNF-α and PAI-1[260–262] and stimulate adiponectin synthesis in adipocytes.[263]

Large, long-term prospective studies currently are underway to examine whether GLP-1RAs affect CV outcome in high-risk individuals; these studies will start to report in late 2015 (*Table 1*). A meta-analysis of independently adjudicated *post hoc* MACE from all phase II/III studies from the liraglutide clinical development program[264] has reported an HR of 0.70 for liraglutide vs. all comparator drugs. A retrospective analysis of the LifeLink Database[265] of medical claims from 2005 to 2009 for patients without history of MI in the preceding 9 months identified 39 275 T2DM patients treated with exenatide and 381 218 patients treated with other glucose-lowering drugs. Exenatide-treated patients were less likely to have a CVD event (HR = 0.81), CVD-related hospitalization (HR = 0.88), and all-cause hospitalization (HR = 0.88). Although encouraging, a definitive answer concerning the CV impact of GLP-1RAs awaits the completion of LEADER (liraglutide), EXSCEL (exenatide LR), ELIXA (lixisenatide), SUSTAIN 6 (semaglutide), and REWIND (dulaglutide) (*Table 1*).

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) represent the newest class of oral agents approved for the treatment of T2DM in

Table 1 Cardiovascular outcome trials in type 2 diabetes

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4i	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin	Linagliptin
Comparator	Placebo	Placebo	Placebo	Sulfonylurea	Placebo
Number	16 500	5400	14 000	6000	8300
Results	Ref. 213	Ref. 215	ADA 2015	2018	2018
	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP-1RA	Liraglutide	Lixisenatide	Semaglutide	Exenatide LR	Dulaglutide
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Number	8754	6000	6000	9500	9600
Results	2018	ADA 2015	2016	2018	2018
	EMPA-REG	CANVAS	DECLARE	NCT01986881	
SGLT2i	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	
Comparator	Placebo	Placebo	Placebo	Placebo	
Number	7300	7000	22 200	3900	
Results	2015	2017	2019	2020	

the USA and Europe. Their mechanism of action is inhibition of the SGLT2 transporter and reduction of the threshold for glucose spillage into the urine leads to an increase in urinary glucose excretion in the range of 60–100 g/day.[266–268] The resultant decline in plasma glucose concentrations leads to the amelioration of glucotoxicity resulting in improved β-cell function and decreased insulin resistance.[269–272] With a baseline of ~8.0%, SGLT2i reduce HbA_{1c} by ~0.8–1.0, i.e. similar to that observed with metformin, for up to 2 years.[273–276] Because of their unique mechanism of action, the SGLT2i can be combined with all glucose-lowering medications including insulin.

In addition to improving insulin resistance, SGLT2i affect important CVRFs. By inhibiting sodium reabsorption in the proximal tubule, they lead to mild intravascular volume depletion and decrease in BP of 4–6/1–2 mmHg.[267,268] Sodium-glucose co-transporter-2 inhibitors consistently cause a weight loss of 2.5–3.0 kg over the 6–12 months after initiation of therapy, which persists for up to 2 years.[273–277] Small increases in plasma LDL- and HDL-cholesterol, without change in their ratio, and modest decreases in plasma triglycerides have been observed with dapagliflozin, canagliflozin, and empagliflozin. Because these lipid changes are small, their clinical significance is unclear. Uric acid and sodium are cotransported in the proximal tubule. Consequently, decrements in serum uric acid of 0.8–1.0% consistently have been observed with all SGLT2i.[265–277]

A prospectively planned meta-analysis of phase II/III dapagliflozin clinical trials included 5261 and 3021 patients in the dapagliflozin and comparator groups, respectively. The HR for the composite endpoint of MACE plus hospitalization for unstable angina was 0.82 in favour of dapagliflozin.[277]

α-Glucosidase inhibitors

α-Glucosidase inhibitors (AGIs) (acarbose, miglitol, and voglibose) inhibit the breakdown of complex carbohydrates in the gastrointestinal tract, leading to delayed carbohydrate absorption and reduction in postprandial hyperglycaemia.[278] They also increase plasma GLP-1 levels[279] and alter the gut microbiome.[280] HbA_{1c} reduction with the AGIs is in the range of 0.5–0.7% with a baseline HbA_{1c} of 8.0%.[281] The AGIs reduce postprandial triglycerides[282,283] but their effect on fasting triglycerides as well as on LDL- and HDL-cholesterol levels is inconsistent and clinically insignificant.[282–287] In T2DM patients, AGIs do not significantly affect BP or body weight.[281]

There are no long-term studies examining the effect of AGIs on CVD. In STOP-NIDDM, 1429 subjects with IGT were randomized to acarbose or placebo and followed for 3.3 years. Acarbose reduced the risk of developing T2DM by 25% and delayed the onset of hypertension.[288] Subjects in the acarbose group ($n = 15$) experienced a 49% relative risk reduction in macrovascular events compared with the placebo group ($n = 32$).[289] However, the total number of events ($n = 47$) was small and the study was not powered to draw any conclusion about CVD protection. A large ($n = 7000$) secondary-prevention trial is assessing the effects of acarbose when added to optimized usual cardiovascular care in patients with coronary heart disease and IGT (ISRCTN Number: 91899513).[290]

Insulin

Multiple insulin preparations (rapid, intermediate, and long acting) are available and, when used in combination, insulin can normalize HbA_{1c} in virtually all T2DM patients.[291] However, the improvement in glycaemic control is not without side effects, especially weight gain and hypoglycaemia.[292] Normalization of HbA_{1c} conclusively has been shown to prevent/slow the progression of microvascular complications in both T2DM[82] and T1DM.[83] In the T1DM patients in the Diabetes Control & Complications Trial (DCCT), 42 units/day of insulin also reduced the incidence of CV events.[105] As previously mentioned, the ORIGIN study[73] in people with new-onset or early T2DM, IGT, or IFG (with either a prior CV event or at high risk for CVD) reported no reduction in macrovascular events (HR =

1.0) despite maintaining an excellent glycaemic control (HbA_{1c} = 6.2%) throughout the 6 years of the trial with a mean insulin dose of 28 units/day. In the sulfonylurea/insulin arm of the UKPDS study[25] as well as its 10-year follow-up,[83] there was no indication that insulin use was associated with an excess of incident CVD.

In contrast to this trial evidence, many retrospective or case–control studies of insulin treatment have reported a higher prevalence of CVD in insulin-treated patients.[293–298] The opposite indication from epidemiological studies and randomized controlled trials remains problematic. The biology of insulin's action on the vasculature is ambivalent. In fact, insulin can promote atherogenesis through several mechanisms. The hormone promotes *de novo* lipogenesis and augments hepatic VLDL synthesis[299,300] via stimulation of sterol regulatory-element-binding protein-1c and inhibition of acetyl-CoA carboxylase.[301] In cultured arterial smooth muscle cells, insulin augments LDL-cholesterol transport, augments collagen synthesis, stimulates proliferation, and turns on multiple genes involved in inflammation.[302–306] *In vivo* studies in dogs,[307] rabbits,[308] and chickens[309] provided evidence for an atherogenic potential of insulin. Rats chronically (7–10 days) infused with insulin while maintaining euglycaemia become markedly resistant to the stimulation of glucose uptake and suppression of plasma FFA by insulin and develop hypertension.[310] In humans with normal glucose tolerance, insulin infusion to raise fasting plasma insulin from 57 to 104 pmol/L for 3 days produced detectable insulin resistance.[311] On the other hand, there is abundant biological[312] and physiological evidence supporting an anti-atherosclerotic effect of insulin via mechanisms mainly involving nitric oxide release,[313,314] suppression of pro-apoptotic signals,[312] and inhibition of platelet aggregation.[315,316] In the context of hugely complex, interacting networks,[312] the net balance of anti- and pro-atherosclerotic effects of insulin may depend on specific experimental or physiological circumstances.

From the clinical standpoint, it is reasonable to assume that in T2DM patients, the positive association between the pharmacological use of insulin and ATCVD may be explained by the cross-sectional, retrospective nature of many studies,[293–298] and by a strong indication bias (e.g. insulin is most often used in long-standing, complicated diabetes). At the same time, it must be considered that longitudinal[72] and trial (UKPDS and ORIGIN) evidence, if less abundant, consistently fails to show that insulin treatment *per se* enhances ATCVD risk. Conservatively, it is possible that any pro-atherogenic potential of exogenous insulin may be overrun by the beneficial effects of improved glycaemic control; the reduction in incident CVD[105] and long-term mortality[317] associated with 7 years of intensified insulin treatment of T1DM patients lends further support to this side of the argument. It must be emphasized, however, that factors such as background CVD risk, degree of insulin resistance, insulin dose, extent of weight gain, frequency of hypoglycaemia, and even strategy of insulin administration (basal-bolus, premix formulations, etc.) may impart unpredictable variability to the CVD outcome.

Cardiovascular outcome trials

The magnitude of vascular protection potentially afforded by glucose-lowering agents can be gauged from the UKPDS as well as the epidemiological data of randomized clinical trials. A sustained ~1% decrement in HbA_{1c} can be expected to reduce coronary risk by 10–15%.[27] Three recent prospective trials—ADVANCE,[137] ACCORD,[138] and VADT[318]—in high-risk T2DM patients tested the ability of intensified glycaemic control to protect against CVD. Baseline HbA_{1c} was 7.2% in ADVANCE, 8.1% in ACCORD, and 9.4% in VADT. After intensive therapy, HbA_{1c} dropped to 6.4% in ACCORD and ADVANCE and to 6.9% VADT; after standard therapy,

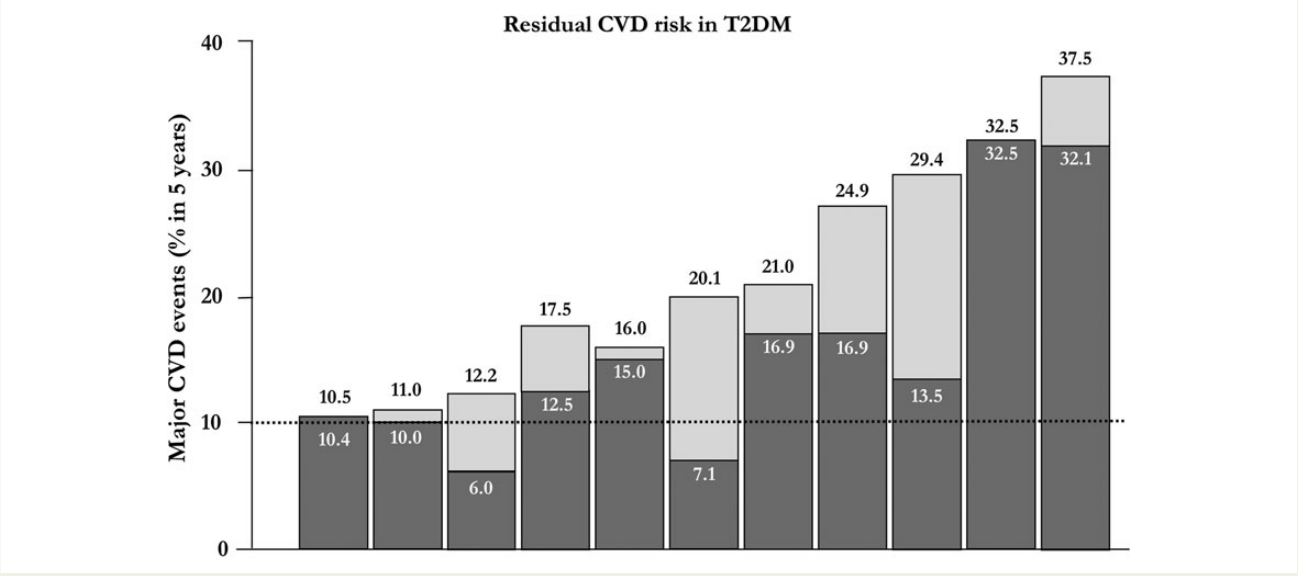

Figure 3 Five-year risk of major cardiovascular events in the diabetic cohorts of randomized trials of anti-hypertensive treatment. The height of each bar is the baseline risk in rank order from lowest to highest, the light grey areas are the median treatment-induced risk reduction. The dark grey bars show that the residual cardiovascular disease risk is generally higher than the baseline risk. Redrawn from Ref.[324].

the values were 7.5, 7.0, and 8.4%, respectively. None of these studies showed a decrease in incident CVD. Despite a significant reduction in ischaemic cardiac events (MI, revascularization, and unstable angina)[319] in the intensive treatment group, ACCORD was stopped prematurely because of increased mortality. In general, this failure can be explained by multiple factors. First, follow-up was relatively short (3–6 years) viz. the fact that in UKPDS it took 10 years to observe the benefit of intensive glycaemic control in newly diagnosed T2DM.[82] Secondly, regression of atherosclerosis is possible, but advanced lesions—such as unstable/disrupted plaques with a higher lipid content[320]—may be unaffected by modest reductions in glycaemic exposure, thereby posing a continual threat of MACE (*Figure 2*). Thirdly, the rates of hypoglycaemia and weight gain were greater in the intensive-therapy arm in all three trials,[128,321,322] very likely due to the high daily insulin doses required to lower HbA_{1c} below 7%. Hypoglycaemia also occurred frequently in ORIGIN (42 and 14% of patients in the glargine and standard therapy groups, respectively); severe hypoglycaemia was associated with a greater risk for all-cause mortality, CV death, and arrhythmic death.[322] Finally, the possibility that high doses of insulin (>80–100 units/day) in long-standing T2DM patients may accelerate the progression of vascular damage cannot be conclusively ruled out (*Figure 3*).[323]

For the newer glucose-lowering agents (DPP4i, GLP-1RAs, and SGLT2i), a number of CV outcome trials currently are in progress involving thousands of high-risk patients (*Table 1*); although they are all designed as safety trials, they will no doubt provide further insight into the reversibility of CVD risk in complicated diabetes. However, the overarching notion emerging from the accumulated experience of intervention trials[324] is that in high-risk patients CVD risk reduction is indeed greater than in low-risk subjects but their *residual risk* remains high (and higher than in low-risk subjects). In other words, residual risk[325] appears to be roughly proportional to baseline risk. Therefore, the evidence reviewed here can be interpreted to indicate that the last word on the prevention of CVD by glucose-lowering agents must await large, long-term clinical trials in patients at low risk using modern treatment strategies, i.e. drug combinations designed to maximize HbA_{1c} reduction while minimizing hypoglycaemia and excessive weight gain.[326]

Conflict of interest: none declared.

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