Cardiovascular and kidney risks in persons with type 2 diabetes: contemporary understanding with greater emphasis on excess adiposity

Short title: Cardiovascular risks in diabetes: role of adiposity

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X (Twitter): Using epidemiological, genetic, drug and disease pattern data, we explain how excess adiposity is a more important factor for cardiovascular complications type 2 diabetes than previously thought.

Article Highlights

- **Why did we undertake this study?**

To review the understanding of the causes of diabetes complications.

- **What is the specific question(s) we wanted to answer?**

Have we underestimated the impact of excess weight on cardiovascular-kidney-metabolic complications in persons with T2DM?

- **What did we find?**

Patterns in complications over time (including rising HF rates in younger type 2 new), newer epidemiology and genetic data, all suggest that excess adiposity may be more important for incident diabetes complications than previously understood.

- **What are the implications of our findings?**

Interventions that target excess weight or pathways linking obesity to complications might better prevent diabetes and/or its multiple cardiovascular-kidney-metabolic complications as well as multiple other common co-occurring conditions.

Abstract

In high income countries, rates of atherosclerotic complications in type 2 diabetes have declined markedly over time due to better management of traditional risk factors including lipids, blood pressure and glycaemia levels. Population wide reductions in smoking have also helped lower atherosclerotic complications. However, as excess adiposity is a stronger driver for heart failure, and obesity levels have remained largely unchanged, heart failure risks have not declined as much and may even be rising in the increasing number of people developing type 2 diabetes at younger ages. Excess weight is also an under recognized risk factor for chronic kidney disease. Based on evidence from a range of sources, we explain how excess adiposity must be influencing most risks well before diabetes develops, particularly in younger onset diabetes which is linked to greater excess adiposity. We also review potential mechanisms linking excess adiposity to heart failure and chronic kidney disease and speculate on how some of the responsible pathways – e.g., hemodynamic, cellular overnutrition and inflammatory - could be favorably influenced by intentional weight loss (via lifestyle or drugs). On the basis of available evidence, we suggest that the cardiorenal outcome benefits seen with SGLT2i may partially derive from their interference of some of these same pathways. We also note that many other complications common in diabetes (e.g., hepatic, joint disease, perhaps mental health) are also variably linked to excess adiposity. All such observations suggest a greater need to tackle excess adiposity earlier in type 2 diabetes.

Cardiovascular risk in persons with type 2 diabetes

Type 2 diabetes is associated with an approximate doubling in cardiovascular (CV) risk compared with those without type 2 diabetes after adjusting for traditional risk factors (1, 2). This two-fold excess risk reflects the influence of hyperglycemia, adiposity and other features of type 2 diabetes not captured by traditional CV risk profiling. Type 2 diabetes is the chronic disease most closely linked to excess adiposity, with >10-20 fold higher risk for incident diabetes for those with BMI >35 kg/m^2 vs 23 kg/m^2(3), and is associated with a 2-3 fold greater risk for coronary artery disease, peripheral arterial disease (PAD) and heart failure (HF)(4) compared with those without diabetes, and increases risk for chronic kidney disease (CKD) (5), that in turn, further increases CV risk (6, 7).

Pathways for excess cardiovascular / kidney risks in persons with type 2 diabetes: exploring diabetes pathophysiology.

Excess fat deposited ectopically – albeit accumulated at differing BMIs and differing rates dependent on age, race, sex and genetic background - contributes to the pathogenesis of type 2 diabetes (8) and, critically, is upstream of the many metabolic/hormonal defects in type 2 diabetes (9). For persons with excess weight, ectopic fat distributes throughout the peritoneum (reflected by waist circumference, a better predictor of CV outcomes than BMI) (10), and into liver, pancreas, heart, skeletal muscle, around blood vessels, and into the circulation in the form of triglycerides and free fatty acids (**Figure** 1). This ectopic fat, plus other concomitants of excess caloric intake such as higher salt intake and lower physical activity, are associated with many pathways (some 'hidden') influencing CV risk often years before diabetes is diagnosed. In line with this, analyses from the UK Biobank revealed that people with pre-diabetes by HbA1c criteria were on average 3 years older, had a 3-unit higher BMI, 6 mmHg higher systolic blood pressure (SBP) and a higher total cholesterol:HDL-c

ratio versus those with normoglycemia (11). Persons with pre-diabetes often progress to type 2 diabetes with further weight gain and/or as they lose muscle mass with age, adding the additional CV risk factor of diabetes-range hyperglycemia (11) (**Figure 2**).

Type 2 diabetes was previously considered a CV risk equivalent (12), but such risk in persons with newly diagnosed type 2 diabetes, especially those diagnosed at a young age, is well below that in people with prior myocardial infarction (MI) (13). Nevertheless, coronary heart disease (CHD) risk increases with longer diabetes duration and aggregated exposure to hyperglycemia and associated risk factors (excess weight, higher BP, dyslipidemia), such that type 2 diabetes approaches a CHD risk equivalent after around 10-15 years duration (13) (**Figure 2**).

Impact of weight loss on type 2 diabetes and associated CHD risk factors

Robust randomized trial evidence demonstrates that intentional weight loss can lead to remission of type 2 diabetes (14), with approximately 5% remission incidence over the first 1-2 years for each 1% of weight loss in those with diabetes duration <6 years (15). Among other benefits, diabetes remission is associated with improvements in lipids, most notably triglycerides, liver steatosis, and blood pressure (BP) (16). However, whether remission of diabetes, if sustained over time, lowers CV risk remains unproven; improvements in glucose levels, BP, weight and lipids suggest CV risk should be lowered, but the extent likely depends on the magnitude of weight loss and whether the remission is into pre-diabetes or normal HbA1c range. Support for a possible CV benefit from intentional weight loss comes from results of *post hoc* epidemiological analyses of the Look AHEAD trial (17); observational studies of bariatric surgery in persons with type 2 diabetes (18); and from

analyses of mutable proteomic changes that 'capture' changes in CV risk (19); but definitive evidence remains elusive.

Genetic evidence for the importance of obesity and related risk factors beyond hyperglycemia to CV risk in persons with and without type 2 diabetes

A series of studies using Mendelian randomization analyses have assessed the connection between cardiometabolic risk factors and CV risk independent of diabetes status. Consistent with a large body of observational data (2), analyses of polymorphisms for BMI or fat mass suggest adiposity is independently associated with and likely causal for HF, atrial fibrillation, hypertension, CHD and a range of other CV outcomes, and that the association between lifelong higher BMI and risk for HF is greater in magnitude than for CHD (20).

Another way to explore the independent associations between lifelong modest isolated hyperglycemia from a genetic perspective is to evaluate CV risk in persons with heterozygous, inactivating glucokinase (GCK) mutations who have mild fasting hyperglycemia from birth (21), but with no influence on weight or BP. Results of an observational analyses of such a cohort, that despite a median duration of 48.6 years of modest hyperglycemia (median HbA1c=6.9%), the prevalence of microvascular and macrovascular complications among persons with a GCK mutation was not different to controls. However, those who developed type 2 diabetes at the same age were heavier, had higher BP and worsening HbA1c over time, and suffered substantial kidney and vascular complications (21).

Among persons with type 2 diabetes, polymorphisms associated with BMI and SBP predicted multiple CV complications (22). By contrast, polymorphisms associated with

hyperglycemia/type 2 diabetes had only modest independent associations with adjusted CV risk (20).

Associations between adiposity and heart failure, chronic kidney disease and coronary heart disease in persons with type 2 diabetes

Excess adiposity is associated with HF and CKD in persons with type 2 diabetes, more so than for ASCVD. In results from analyses evaluating 20-year trends in CV complications among persons with type 2 diabetes in Sweden, higher BMI was almost linearly associated with substantially higher risk for incident hospitalization for heart failure (HFH), whereas its association with incident MI was modest (2). By contrast, LDL-c was linearly associated with incident acute MI, whereas it was flat for incident HF (**Figure 3a**), and higher HbA1c was associated with both outcomes. These patterns illustrate the large increase in HF risk with type 2 diabetes and obesity, and that CV risk factors are differentially associated with different diabetes comorbidities.

With regard to CKD, among persons with type 2 diabetes who already have an increased risk for CKD, high BMI was independently associated with even higher risk for CKD (5), findings supported as likely causal by genetic data (23).

Type 2 diabetes is associated with accelerated ASCVD associated with many risk factors including excess adiposity, physical inactivity, high BP, dyslipidemia, and other perturbances, many of which onset before diabetes is diagnosed. By contrast, analyses of covariates associated with risk for HF and CKD, while overlapping to some extent with ASCVD risk factors, include a greater role for excess adiposity linked to excess ectopic fat in multiple tissues (**Figure 3b**). The key ‘hidden’ pathways that link excess adiposity to HF and

CKD risks are far from established but speculatively also include hemodynamic and cellular 'over-nutrition' stressors that adversely influence myocardial and nephron health. Whatever the mechanisms, while considerable efforts have been directed at targeting established CV risks factors of BP, LDL-c and glucose levels in persons with type 2 diabetes, far less attention has been paid to targeting excess weight (or non-traditional risk pathways that link excess adiposity to outcomes). It follows that earlier targeting of weight in diabetes should particularly help attenuate HF and CKD complications in diabetes, as well as multiple other complications of obesity (including metabolic, mechanical and potentially mental health outcomes), as also partially nicely suggested by recent reviews (24, 25).

Changing trends in CV risks in persons with diabetes: impact of addressing traditional risk factors

Given the patterns of risk, the progressive increase in statin and antihypertensive therapy in people with type 2 diabetes from the late 1990s onwards, combined with progressively earlier diagnosis of diabetes, and reductions in smoking, have markedly driven down cardiovascular event rates in the cohort with diabetes and in the general population (26, 27). Data from the USA showed a pattern of substantially declining rates for MI and stroke in people with diabetes over the last two decades (28), though such events still remained far in excess of those seen in individuals without diabetes.

Results from analyses from the Swedish National Diabetes Registry investigated CV disease trends between 2001 to 2019 in a study comparing persons with type 2 diabetes and matched controls (**Figure 4**). Results revealed that the incidence of ASCVD and HF had generally decreased over time among persons with type 2 diabetes, although HF gains had plateaued in recent years. A difference in excess risk for HF in type 2 diabetes by age was noted with

higher relative risks among younger persons with type 2 diabetes relative to controls, particularly more recently (2). Other data from the UK published in 2015 showed HF (14.1%) and PAD (16.2%) to be the two most common first 'vascular' outcomes in people with type 2 diabetes, with myocardial infarction and stroke now less frequent (29); the latter observations suggest less people with diabetes are dying from CV complications and thus are able to develop other outcomes. Hence, in general, as ASCVD events (mostly) and deaths have declined, a diversification in CV and other non-CV outcomes experienced by people with type 2 diabetes in high income countries has occurred and will likely continue particularly if more younger people develop type 2 diabetes.

Heart failure in persons with type 2 diabetes: time to up our game

HF with preserved (HFpEF) or reduced ejection fraction (HFrEF) is more common in persons with versus without type 2 diabetes, with risks around 2 to 3-fold higher than in the general population (30). Given recent trends in HF incidence and prevalence, guidelines now recommend clinicians consider HF signs and ask about the symptoms of HF in their patients with type 2 diabetes (31). If clinical suspicions arise, measurement of NT-proBNP as a screening test, and additional workup as needed is appropriate (31, 32). Routine testing of NT-proBNP in all persons with type 2 diabetes, however, is unaffordable in most healthcare systems. Yet, on the plus side, discussed in greater detail below, progressively greater use of SGLT2i in persons with type 2 diabetes use may offset rises in HF going forwards.

Changing patterns in the causes of death in type 2 diabetes

The reductions in CV events and CV deaths in persons with type 2 diabetes have been so marked over recent decades that cancer may soon be the leading cause of deaths among persons with diabetes in the UK (33, 34) and Sweden (35). Similarly, USA data from 1988 to 2015 reported the percentage of total deaths due to CV causes declined from around 48% to 34% in people with diabetes, and from 45% to 31% in those without (36). The percent of deaths due to cancer was stable in both groups so that proportionately more deaths were due to non-vascular and non-cancer causes (36). The consequence of such changes is a rise in life expectancy for people with type 2 diabetes and this, more than changes in incidence, has increased type 2 diabetes prevalence in high income countries. The other consequence of greater life expectancy is that more people with type 2 diabetes now develop multiple long-term conditions linked to progressively greater aggregated exposure to excess adiposity (e.g., NASH, osteoarthritis) or hyperglycemia (e.g., dementia) or both (e.g., CKD). Unless obesity is prevented, more people living with or without type 2 diabetes will develop multiple chronic conditions leading to rising health costs, and declining quality of life (25).

Challenges in managing diabetes-related cardiovascular risk in low- and middle-income countries.

In low- and middle-income countries, the clinical challenges are different but greater. In Mexico, for example, diabetes mortality rates were several-fold higher than in high-income countries between 1998 to 2004 (37) and, though some improvements have occurred, substantial opportunities to improve outcomes remain (38). At the basic level, frequent delays in diagnoses mean that many are exposed to years of ectopic fat and related risk factors including hyperglycemia and their clinical consequences. The challenge in such countries is to ensure the sustained availability of cheap statins, antihypertensive medications and

metformin, a combination that can substantially reduce diabetes-associated CV risks. Unfortunately, industrialization is changing lifestyles (lower activity, cheaper calories), leading to more adiposity and type 2 diabetes with resultant increases in CV and CKD risks. In these countries, if weight is not targeted, more with type 2 diabetes will rapidly develop multiple long-term conditions in part as premature CV deaths decline with dire impacts for individuals, society, and economic progress.

Heterogeneity in complication risks: which factors matter?

Much has been written about the heterogeneity in diabetes pathogenesis, which may also relate to differential risks for specific CV and kidney outcomes. A few simple characteristics (with differential adiposity patterns) that determine risks for various outcomes are worth highlighting, however, such as age of type 2 diabetes onset and race /ethnicity.

Younger age of onset of type 2 diabetes is more damaging than type 2 diabetes diagnosed later in life, linked in part to obesity.

As the obesity epidemic has expanded, the number of people with type 2 diabetes under the age of 40 has increased globally; in the UK <1000 had type 2 diabetes in the 1970s rising to >130,000 by 2018 (39). This is concerning as lower age at diagnosis is linked to life years lost from diabetes (40). Indeed, results from a study across 19 high-income countries using two large data sources showed that at age 50, those with diabetes diagnosed at age 30, 40, and 50 years died, on average, 14, 10, and 6 years earlier, respectively, than counterparts without diabetes (41). Thus, every decade of earlier diagnosis is associated with about four years of lower life expectancy.

This higher mortality risk in younger-onset type 2 diabetes is in part linked to obesity: younger people must gain more weight (and so more ectopic fat) to overcome either their more resilient pancreatic beta-cell reserve or their higher muscle mass compared with older people to develop type 2 diabetes. In a UK study of persons diagnosed with type 2 diabetes between the ages of 20-39 years, men were around 33 pounds (15kg), and women 53 pounds (24kg) heavier than their age and sex-similar counterparts without diabetes (42). In both sexes, such weight differentials narrowed as the age of diagnosis increased (**Figure 5**). This higher weight at younger ages is also associated with greater differences in systolic BP and triglyceride levels relative to matched counterparts without type 2 diabetes (42). Younger onset of type 2 diabetes, particularly in men, may also be accompanied by longer delays in type 2 diabetes diagnosis (as estimated from higher HbA1c levels at diagnosis compared with people diagnosed later in life (Figure 5)). Furthermore, younger onset diabetes is accompanied by faster glycemic deterioration than when type 2 diabetes develops in later life (43, 44). All these factors, in turn, suggest people developing diabetes earlier in life will have a greater and longer aggregated exposure to i) hyperglycemia, ii) excess adiposity and iii) associated risk factors than if diabetes develops later in life.

The accelerated CV risks associated with the above factors is compounded by less aggressive LDL-c and BP management in younger people with type 2 diabetes (43) in part because 10-year calculated CV risks are lower due to younger ages. This suggests a need to develop better lifetime risk scores in people with type 2 diabetes that could also usefully capture risks of multiple complications simultaneously. Furthermore, excess weight at younger ages is often linked to lower socioeconomic status, more complex adverse societal and mental health issues (45), or disrupted family architecture, making effective interventions challenging. The higher levels of obesity in younger persons with type 2 diabetes also contributes to the greater

relative risks for HF when compared with older people developing type 2 diabetes (40), given excess weight is a stronger risk factor for HF than for myocardial infarction (46). Collectively, inferior cardiometabolic risk factor management plus greater obesity likely explain why CV risks have decreased least over recent years in younger people with type 2 diabetes, and why HF rates may even be worsening in this group (2). Many countries are considering how they meet the considerable challenge of rising numbers with younger onset type 2 diabetes, including even in children.

Race (ethnicity) and cardiovascular risks in persons with type 2 diabetes: differing weightings of risk factors?

In contrast to considerable data on CV risks in type 2 diabetes in mostly White populations, far less data exists for non-White populations. Of note, many races develop type 2 diabetes at lower average BMIs than in White persons, and often a decade or so earlier in life, meaning an extra decade of hyperglycemia, and other diabetes risk factors (11). This lower BMI "threshold" to develop type 2 diabetes explains the much higher type 2 diabetes prevalence in many non-White races (42). However, the mechanisms behind these patterns across races are not homogeneous but variably include a faster ectopic fat gain for a given BMI (e.g., in South Asian) (47) or more rapid beta cell deterioration (e.g. Black and South Asian) (48). The reasons to mention these differences is that they may drive different patterns of CV risks with potentially a greater role for earlier and often more rapid glycemic deterioration towards more non-fatal MI and CKD risks in some races (49). That noted, South Asian and Black individuals with type 2 diabetes in the UK tend to have fewer life-years lost associated with type 2 diabetes than do White individuals (50), the explanation for which is not fully understood. More work is required to better describe and understand diabetes-associated complication risks by race (or ethnicity), and how these may be shifting over time.

Better understanding of the results of CV outcomes trials in type 2 diabetes from recent pathophysiological perspectives including role of excess adiposity

For many years, the three main classes of medications available to treat hyperglycemia for persons with type 2 diabetes were metformin, sulfonylureas, and insulin. Intensive glucose lowering does lower cardiovascular risk but only very modestly in the short term as suggested by a meta-analysis of intensive glucose lowering trials (51). In this meta-analysis, major cardiovascular events were lowered by 9% (HR 0.91, 95% CI 0.84-0.99) in the more intensive arm, primarily because of a 15% reduced risk of myocardial infarction (HR 0.85, 95% CI 0.76-0.94). However, trial evidence suggests that metformin (52) does not lower CV events independently of its glucose lowering effects, with no CV benefits of glucose lowering with sulfonylureas (53) or insulin (54). These findings are understandable if one considers such drugs have little evidence of meaningful gains in other risk factors. In totality, epidemiological (11, 55) and trial evidence suggests greater hyperglycemic exposure in type 2 diabetes likely exerts an aggregated 'slow burn' effect on CV disease. Of course, targeting glucose and preventing significant elevations does lower microvascular risks (56). However, newer classes of diabetes medications that favorably affect lipids, BP and/or other elements of diabetes pathogenesis, and perhaps most importantly, with associated weight loss, now have considerable evidence for CV protection (57, 58).

Newer classes of antihyperglycemic medications for type 2 diabetes.

Several new classes of medications are now licensed for the treatment of patients with diabetes, some with product-labeled indications for CV risk mitigation. From a CV perspective, the largest advances have occurred with SGLT2 inhibitors and the GLP-1 receptor agonists, and newer understanding of their outcome benefits, we suggest, can be

linked in some way to the excess ectopic fat that drives type 2 diabetes in the first place, and related pathophysiological disturbances.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i's)

SGLT2i increase urinary glucose and sodium excretion via inhibition of SGLT2 in the proximal convoluted tubule of the kidney (59). The results from the series of completed CV outcomes trials of these medications have had a profound effect on clinical practice. Results from a meta-analysis of five SGLT2i CV outcome trials in patients with type 2 diabetes reported this class lowers major adverse cardiovascular event (MACE) rates modestly (10% relative risk reduction) (Table 1), significant in those with prior ASCVD disease (at 11%) (57). More importantly, the meta-analysis results showed a far greater SGLT2i-induced reduction in the risk of incident HF hospitalization in those with (by 30%) and without (by 37%) prior ASCVD (57). They also reduce the primary outcomes of HF or CV death in people living with HF with HFrEF (60, 61) and HFpEF (62, 63). In addition, SGLT2i also favorably affect kidney-related outcomes across the spectrum of CKD and independent of diabetes status. (64–67).

Based on these results, and the fact SGLT2i are given orally once a day, and lower weight (modestly), BP and glucose levels (unless poor kidney function), and do not cause hypoglycemia in the absence of insulin therapy, they are being progressively used earlier in the life course of type 2 diabetes, even as first line treatment in some countries. In the UK, the National Institute for Health and Care Excellence (NICE) suggests starting SGLT2i soon after metformin if 10-year CV risk is >10% (68). SGLT2i do, however, increase risks of mycotic genital infections (potentially serious but commonly easily treated and preventable

by good urinary hygiene) and mildly hyperglycemic diabetic ketoacidosis (DKA) by around 2- to 3-fold (69).

SGLT2i trial findings forced a look at potential 'hidden' mechanisms linking type 2 diabetes to HF and CKD complications

The benefits of SGLT2i on HF and kidney outcomes were not widely anticipated but have been consistently demonstrated across the class (57) and extended to those with or without type 2 diabetes, as well as lower CV death risk among persons for some but not all SGLT2i. Such findings drove many mechanistic studies. Much evidence suggests an early hemodynamic effect perhaps linked to loss of fluid from interstitial and/or extracellular compartments and restoration of tubuloglomerular feedback contributing to lower BP, lower intraglomerular pressure and favorable cardiac remodeling (70–74). SGLT2i's also appear to exert a multitude of other tissue effects including improving metabolic perturbations in proximal tubular cells and dampening inflammatory pathways (75, 76). Randomized trials with MRI imaging have shown SGLT2i-induced reductions in extracellular fluid volume in myocardium (77) and kidneys (78), as well as surrogate evidence of reduced kidney perfusion (78). While none of these studies are definitive, and other mechanisms are likely at play, they are broadly consistent.

SGLT2i - mimicking starvation (and hypoxia) to effect positive cellular health?

More recently, cellular changes arising from SGLT2i actions on nutrient fluxes have also been proposed to play a key role in their CV benefits (79) (**Figure 6**). The SGLT2i's may, in part via their enhancement of glucose loss even in persons without diabetes, stimulate a nutrient deprivation signal that leads to upregulation of energy deprivation sensors (sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK)). These two molecular changes, in turn,

drive multiple downstream effects, the net effect promoting cellular repair mechanisms, including autophagy and proteostasis (79). Cardiac and kidney disease each appear to evoke a state of perceived nutrient overabundance, contributing to disease progression (80, 81). It follows that SGLT2i may lower HF and CKD risks in part by correcting some of these 'nutrient overabundance' signals. Such adverse signals will be more common in people with type 2 diabetes and/or those living with obesity, states associated with net excess calories.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

GLP-1 receptor agonists (GLP-1RAs) imitate the actions of the incretin hormone GLP-1. They enhance glucose-dependent insulin secretion from pancreatic beta cells and inhibit glucagon release from pancreatic alpha-cells. They also initially slow gastric emptying and, by stimulating GLP-1 receptors in the brain, induce satiety. The net effect is a reduction in both fasting and post prandial glucose, and for most individuals, reduction in body weight. They also lower BP and improve lipids and have direct favorable effects on the vasculature. Their effects on major adverse CV outcomes in type 2 diabetes have been summarized in a meta-analysis (58). When only longer acting GLP-1RAs (so excluding ELIXA: short acting lixisenatide) were considered, GLP-1 RAs reduced major adverse CV events (MACE) by 15%, CV death by 15%, fatal or non-fatal myocardial infarction by 12% and fatal or non-fatal stroke by 19%. There were likewise modest improvements in risk for all-cause mortality and hospitalization for heart failure (58).

Other key observations from this meta-analysis and relevant trial data include:

- The absolute and lifetime benefits of GLP-1RA are greater in those with existing ASCVD or CKD (82). Consequently, most guidelines (31, 83) prioritize GLP-1RA in secondary prevention patients, restricting GLP-1RA for the primary prevention to those at

elevated ASCVD risk *i.e.*, multiple risk factors, evidence of atherosclerotic disease on imaging (84) or elevated calculated ASCVD risk (85).

- GLP-1RA benefits appear independent of SGLT2i use, as suggested by post hoc analyses of the AMPLITUDE-O trial (86).
- The most consistent observed CV benefit of GLP-1RA is on reducing stroke, an outcome not reduced by SGLT2i's (57)
- GLP-1RAs reduce albuminuria and the rate of eGFR decline, with greatest effects in those with baseline low eGFR (87, 88).
- It remains uncertain whether incretin therapies that lower weight more in persons with type 2 diabetes (typically >5-10%), such as higher dose semaglutide, or the dual agonist, tirzepatide, or other medications targeting incretin/appetite pathways, will lower ASCVD to greater extents than previously tested GLP-1RAs (58) and/or exert more meaningful, potentially more rapid, benefits on HF and CKD outcomes. Notably, recent trial data suggest significant reductions in HF symptoms with higher dose semaglutide in people with HFpEF (89). Multiple ongoing trials in persons with diabetes and obesity will enrich these areas including providing longer term safety data over the next few years, with particular interest in SURPASS CVOT which is testing the impact of tirzepatide (dual agonist with >10% average weight loss) (90) versus dulaglutide (minimal weight loss) in people with type 2 diabetes (91).

Diabetes guidelines now recommend both SGLT2i and GLP-1RAs for cardioprotection

Given the quality of the trial evidence, SGLT2i and GLP-1RAs are now recommended in patients with type 2 diabetes and established ASCVD disease irrespective of HbA1c levels. The most recent 2022 American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) recommendations (84) suggest either SGLT2i or GLP-1RAs in

patients with existing ASCVD and type 2 diabetes without requirement for background metformin use or with regard to HbA1c status or target, whereas the 2023 European Society of Cardiology Guidelines for persons with diabetes recommend both, an SGLT2i and a GLP-1 RA among those with proven CV benefits (31). Diabetes and cardiology Guidelines and recommendations are harmonized with recommendations to prioritize SGLT2i in those with prevalent HF or CKD, in line with the abundant trial evidence summarized above.

***Perspective on recent trials and new knowledge on obesity-driven cardiovascular disease, and future* prospects**

Based on the accumulated data regarding SGLT2i effects on CKD and HF, scientific humility suggests pathways that link diabetes to HF and CKD outcomes were far from well understood. One perspective is that SGLT2i partially attenuate some of the adverse (yet hidden) pathways – e.g., hemodynamic/ cellular overnutrition/ inflammatory / other – that link the harmful effects of aggregated obesity/ectopic fat and type 2 diabetes to HF and kidney outcomes. So far, GLP-1RA benefits look complementary to SGLT2i with more consistent ASCVD benefits (i.e., strong stroke reductions), and with added weight loss benefits and more modest HF and CKD benefits (58), the latter soon to be meaningfully expanded by results of the FLOW trial (NCT03819153) with press release having announced the trial was stopped early for efficacy (https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166327). The results of ongoing trials such as SELECT (NCT03574597) and SURPASS CVOT (NCT04255433) plus several other trials will expand our understanding of the impact and safety of incretin-based or related therapies that yield greater weight loss on CV outcomes in people with and without diabetes.

Where and when affordable, GLP-1RA's and SGLT2i are likely to be used much earlier in the diabetes life course in many high-income countries than in middle- to low-income countries where access and affordability may be more challenging. The consequences of earlier SGLT2i and incretin-based therapies (particularly those that affect greater weight loss) could be a lower need for antihypertensive medications with notable reductions in BP in recent SURMOUNT 2, STEP 2 and SURPASS 1-5 trials (90, 92, 93), though not lower statins, as LDL-c levels are not meaningfully lowered by these medications. At the same time, while evidence in primary prevention is limited, it is possible that reductions in ASCVD and HF and CKD outcomes, and improved QOL will occur from their earlier use. This is because these medications appear to better address the upstream pathways (driven by excess adiposity) that lead to type 2 diabetes in the first place, or that link ectopic fat to pathways (e.g., hemodynamic, nutrient stressors, inflammatory etc.) that partially drive HF and CKD. Notably, larger weight loss should also lower risks of many other comorbidities linked to obesity that are common amongst people with diabetes (e.g., fatty liver, osteoarthritis etc.). Ongoing trials will help address these possibilities.

However, as noted above, such medications (i.e., GLP-1RAs and related medicines) will be unaffordable in LMICs, and perhaps many high-income countries, for many years and so for the time being, diagnosing diabetes earlier, followed by generic statin, BP medications and metformin are key targets and can do much to lower vascular risks. Also, even if longer term SGLT2i and GLP-1RAs can help further reduce adverse CV outcomes in persons with type 2 diabetes, they cannot address adverse impacts including on muscle mass of low activity levels, or smoking or other adverse lifestyle behaviours and so continued efforts to help people lead healthier lives will always matter to the CV health and the happiness of patients at risk of or living with type 2 diabetes.

In conclusion, considerable evidence from multiple angles and study types – clinical, epidemiological, trends in complications, genetic and treatment effects – all suggest the need to aggressively target excess weight (in addition to other established CV risk factors) to more robustly treat and prevent many type 2 diabetes-associated complications.

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Author Contributions

NS and CP wrote the first draft. MKR and DKM critically reviewed and edited the manuscript. All authors approved the final version of the manuscript. NS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Summary of the top line results of meta-analyses of the effects of SGLT2i and GLP-1RA on ASCVD and cardio-renal outcomes in patients with diabetes.

	SGLT2i	GLP-1RA (- ELIXA)
MACE	**-10% (-5 to -15%)**	**-15% (-10 to -20%)**
CV Death	**-15% (-7 to -22%)**	**-15% (-7 to -22%)**
MI	**↓9% (-1 to -16%)**	**-12% (-4 to -19%)**
Stroke	-4% (-13 to +7%)	**-19% (-10 to -26%)**
HFH	**-32% (-26 to -39%)**	**- 12% (-2 to -21%)**
CKD	**-38% (-30 to -44%)**	**- 22% (-2 to -31%)**

Data taken from refs (58) and (57). NS=non-significant. For GLP-1RA, data from the sensitivity analysis removing ELIXA were used as most investigators accept Lixisenatide was too short acting to be given once daily in this trial.

Figure Legends

Figure 1 – *From ectopic fat to ASCVD risk gain before and after development of type 2 diabetes*

A conceptual illustration depicting the development and location of ectopic fat in individuals once they have `overwhelmed' their ability to store excess fat subcutaneously, and /or have accumulated too much fat in ectopic tissues including liver, myocardium and potentially pancreas. Certain factors such as sex (females have greater storage capacity), genetics (family history of type 2 diabetes as a broad proxy measure), race (for example, South Asians) and ageing have relevance to how fast ectopic fat levels rise with increasing weight gain. With ectopic fat comes a typical lipid pattern of higher triglyceride and lower HDL-cholesterol and more atherogenic (apo-B carrying) particles, nicely captured by non-HDL-c. There is also a rise in blood pressure with weight gain, which may be partially hemodynamic (excess salt intake likely a part of this) but could also relate to gains in perivascular fat, plus other hormonal mechanisms. Some recent evidence indicates that excess fat may also accumulate in the pancreas, potentially contributing to β-cell dysfunction, and thus development of type 2 diabetes. Notably, excess ectopic fat appears reversible in many, contributing to diabetes resolution even in some patients with type 2 diabetes who were on insulin. The key point here is that many ASCVD risk factors are often elevated well in advance of development of frank hyperglycemia and type 2 diabetes such that absolute ASCVD and indeed HF and kidney risk is already elevated in persons with impaired glucose metabolism, as also shown in Figure 2. Finally, in most individuals, at a given age, correlation between elevations in BMI and HbA1c will be broadly linear up to and across the pre-diabetes range into early diabetes. The slope of this association most commonly depends on the rate at which ectopic fat accumulates.

Figure 2 – *Impaired glucose metabolism, type 2 diabetes and CHD risks over time*

(1) In line with Figure 1, as ectopic fat levels increase, several ASCVD risk factors start to increase so that absolute risk is already elevated in people with impaired glucose tolerance. Such risks appear only minimally added to glucose levels in this range.

(2) Delayed diagnosis of diabetes would mean exposure to higher glucose levels for prolonged periods leading to accelerated atherosclerosis risks.

(3) Fortunately, at least in high-income countries, more people are now diagnosed earlier after true diabetes onset, minimizing exposure to much higher glucose levels and then rapid use of statins, BP lowering medications and oral antihyperglycemic medications are further meaningfully lowering CHD risk.

(4) Development of type 2 diabetes at younger age means more rapid accumulation of ectopic fat so that ASCVD and HF /CKD risks elevate faster, and glucose levels often rise faster after diagnosis than if diagnosed with diabetes in later life due presumably to a trajectory of more rapid ectopic fat gain at younger ages. This notion is in keeping with the need to put on more weight on average to develop type 2 diabetes at younger ages (see text and Figure 5)

(5) Finally, on average, type 2 diabetes at diagnosis is not a CHD risk equivalent but approaches this level roughly after a decade or more duration of diabetes.

ASCVD = atherosclerotic cardiovascular disease; BP= blood pressure; CHD =coronary heart disease; HF = heart failure CKD = Chronic kidney disease

Figure 3a *an epidemiological look at how BMI and LDL-c compare as risk factors for acute myocardial infarction and heart failure in the Swedish Diabetes Registry.*

Notably, body mass index has much stronger associations with incident HF whereas low-density lipoprotein cholesterol for acute myocardial infarction. These are of course observational associations and, as such, these data do not mean BMI is not relevant to AMI risk. It is and genetic (MR) suggests BMI is less strongly linked to AMI than incident HF whereas we know from meta-analysis of randomized trials that lowering LDL-c does lower incident HF but only modestly, whereas it lowers AMI much more strongly. Dark lines indicate the hazard function; shaded areas show the 95% CIs. Continuous variables were modeled with restricted cubic splines. The following cut-off levels were used for risk factors: body mass index, ≥27.5 kg/m2; low-density lipoprotein cholesterol, ≥96 mg/dL. Taken from ref (2).

Figure 3b *Diabetes, excess adiposity and ASCVD vs cardiorenal complications*
(1) This figure illustrates whilst ASCVD risk in type 2 diabetes is linked to traditional risk factors, where hitherto most of intervention focus has been placed, (2) new understanding is beginning to reveal less well understood pathways linking upstream excess adiposity to heart failure and kidney complications. (3) At the same time, there is a need to tackle upstream continued calorie surplus that has majorly contributed excess adiposity in the first place.

Figure 4. *Standardized incidence rates for all cardiovascular outcomes among individuals with type 2 diabetes and matched control subjects***. A** through **D**, Age- and sex-standardized incidence rates for all outcomes compared with control subjects from the general population. Note plateauing of gains in HF in people with type 2 diabetes in recent years Taken from ref (2).

Figure 5 *The risk factor patterns at differential age of diabetes diagnosis*

(a–d) Adjusted age-specific mean (95% CI) differences in BMI (a), weight (b), systolic BP (c) and triacylglycerol level (d) in men and women recently diagnosed with type 2 diabetes compared with men and women without diabetes. (e) Age-specific mean HbA1c levels in men and women recently diagnosed with type 2 diabetes. Note much higher weight, blood pressure, lipid and HbA1c differentials at younger age with weight and BP differentials to controls without diabetes being even more marked in women (compared with men) who are diagnosed with diabetes at younger age. Taken from (42)

Figure 6 *How do SGLT2i and GLP-1RAs address cardiovascular risks in diabetes*

This illustration attempts to bring some of the prior threads together. It suggests that while a traditional focus on targeting glycemia, lipids and blood pressure has been very helpful in lowering cardiovascular risks, such a narrow focus cannot explain the profound and rapid HF and kidney benefits of SGLT2i, nor their benefits in people without diabetes. There are now suggestions that SGLT2i in part interfere with some of the pathways that link excess adiposity and related factors (e.g., excess sodium intake) to HF and kidney complications, with perhaps most interest on their hemodynamic and cellular over nutrition effects, which are currently best studied in the context of patients with heart failure. GLP-1RA have direct ASCVD benefits by lowering atherosclerosis, but they also lower weight, and the newer formulations (including the dual and triple agonists), or higher doses now licensed for weight loss, could have meaningful benefits to offset HF and kidney risks by their lowering of exposure to aggregated obesity. In other words, their effects may in part derive from lowering of ectopic fat in various tissues and by their extension “upstream” reductions in cellular over nutrition and hemodynamic stressors. That noted, there may be direct effects of incretins on the pathways to HF and CKD (*). Even so, by reducing weight, GLP-1RA may lower risks

for many other complications linked to obesity, and there is also some evidence that SGLT2i also lower risks from differential complications.