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Cardiovascular and Kidney Risks in Individuals With Type 2 Diabetes: Contemporary Understanding With Greater Emphasis on Excess Adiposity

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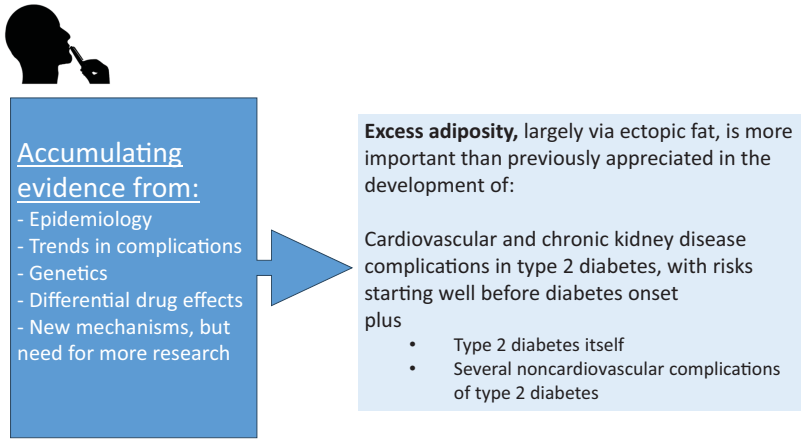

ARTICLE HIGHLIGHTS

- **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 individuals with type 2 diabetes?
- **What did we find?**
  Changes in the prevalence of complications over time (including rising heart failure rates in younger individuals with newly diagnosed type 2 diabetes) and 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 or its multiple cardiovascular-kidney-metabolic complications as well as multiple other common co-occurring conditions.

Cardiovascular and Kidney Risks in Individuals With Type 2 Diabetes: Contemporary Understanding With Greater Emphasis on Excess Adiposity

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REVIEW

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 glycemia levels. Population-wide reductions in smoking have also helped lower atherosclerotic complications and so reduce premature mortality in type 2 diabetes. However, as excess adiposity is a stronger driver for heart failure (HF), and obesity levels have remained largely unchanged, HF 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 underrecognized risk factor for chronic kidney disease (CKD). 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 HF and CKD 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 sodium–glucose cotransporter 2 inhibitors 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, the aggregated exposure to which has now increased in type 2 diabetes. All such observations suggest a greater need to tackle excess adiposity earlier in type 2 diabetes.

CARDIOVASCULAR RISK IN PEOPLE WITH TYPE 2 DIABETES

Type 2 diabetes is associated with an approximate doubling in cardiovascular (CV) risk compared with the risk for people without type 2 diabetes after adjustment for traditional risk factors (1,2). This twofold 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 associated with excess adiposity, with >10- to 20-fold higher risk for incident diabetes for those with BMI >35 kg/m^2 vs. those with BMI <23 kg/m^2 (3), and is associated with a two- to threefold higher risk for coronary artery disease, peripheral arterial disease, and heart failure (HF) (4) compared with the risk for people without diabetes, and

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increases risk for chronic kidney disease (CKD) (5) that, in turn, further increases CV risk (6,7).

PATHWAYS FOR EXCESS CV/KIDNEY RISKS IN PEOPLE WITH TYPE 2 DIABETES: EXPLORING DIABETES PATHOPHYSIOLOGY

Excess fat deposited ectopically—albeit accumulated with differing BMIs and at 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 people with excess weight, ectopic fat distributes throughout the peritoneum (reflected by higher waist circumference, a better predictor of CV outcomes than BMI) (10) and into liver, pancreas, heart, and skeletal muscle; around blood vessels; and into the circulation in the form of triglycerides and free fatty acids (Fig. 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 prediabetes according to HbA_{1c} criteria were on average 3 years older, had a 3-units-higher BMI, 6 mmHg higher systolic blood pressure (BP), and a higher total cholesterol–to–HDL cholesterol ratio in comparisons with those with normoglycemia (11). Prediabetes often progresses to type 2 diabetes with further weight gain and/or loss of muscle mass with age, with addition of the CV risk factor of diabetes-range hyperglycemia (11) (Fig. 2).

Type 2 diabetes was previously considered a CV risk equivalent (12), but such risk in people 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 ~10–15 years' duration (13) (Fig. 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 ~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

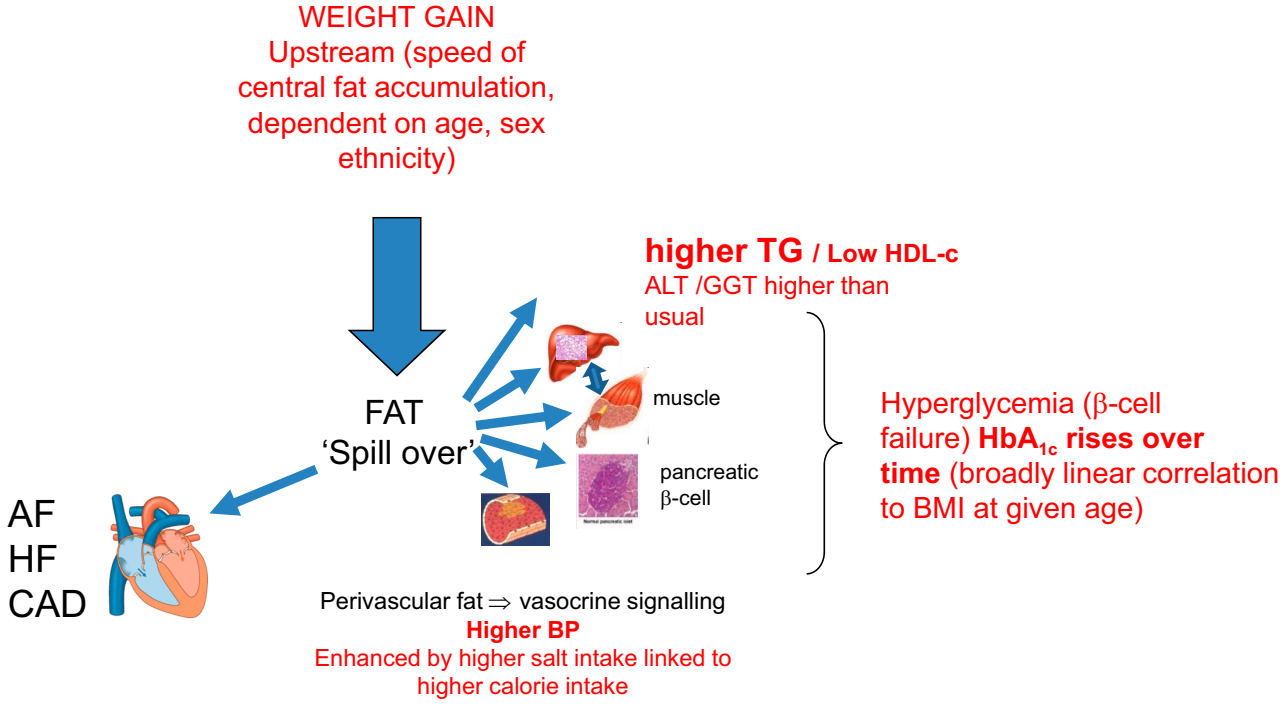

Figure 1—From ectopic fat to ASCVD risk gain before and after development of type 2 diabetes: a conceptual illustration depicting the development and location of ectopic fat in individuals once they have "overwhelmed" their ability to store excess fat subcutaneously and/or have accumulated too much fat in ectopic tissues including liver, myocardium, and potentially pancreas. Certain factors such as sex (females have greater subcutaneous storage capacity), genetics (family history of type 2 diabetes as a broad proxy measure), race (for example, South Asians) and aging are relevant 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 (HDL-c) and more atherogenic (apoB carrying) particles, nicely captured by non-HDL cholesterol levels. There is also a rise in BP 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 people with impaired glucose metabolism, as also shown in Fig. 2. Finally, in most individuals, at a given age, correlation between elevations in BMI and HbA_{1c} will be broadly linear up to and across the prediabetes range into early diabetes. The slope of this association most commonly depends on the rate at which ectopic fat accumulates. AF, atrial fibrillation; CAD, coronary artery disease; GGT, γ-glutamyl transferase; TG, triglycerides.

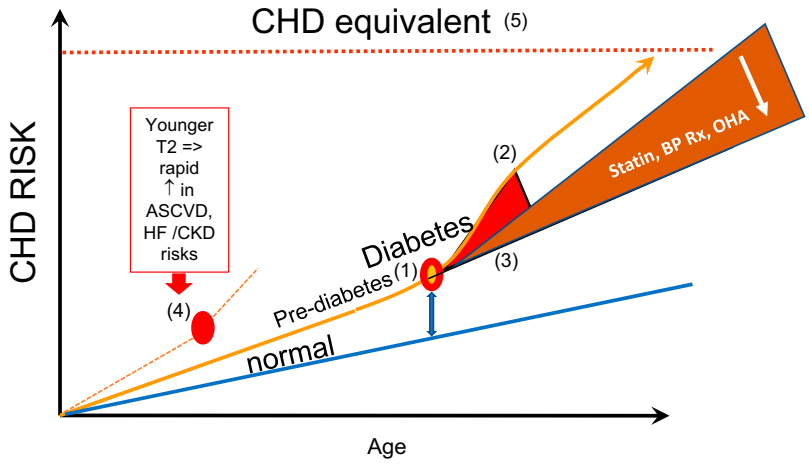

Figure 2—Impaired glucose metabolism, type 2 diabetes, and CHD risks over time. (1) In line with Fig. 1, as ectopic fat levels increase, several ASCVD risk factors start to increase so that absolute risk is already elevated in people with impaired glucose tolerance. Such risks appear only minimally added to by 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 commencement of statins, BP-lowering medications and oral antihyperglycemic medications further meaningfully lowers CHD risk. (4) Development of type 2 diabetes at younger age (Younger T2) 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 with diabetes diagnosis 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 Fig. 5). (5) Finally, on average, type 2 diabetes at diagnosis does not represent a CHD risk equivalent but approaches this level roughly after a decade or more of diabetes duration. Rx, prescription; OHA, oral hypoglycemic agents.

in lipids, most notably triglycerides, liver steatosis, and 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 that CV risk should be lowered, but the extent likely depends on the magnitude and sustainability of weight loss and whether the remission is into prediabetes or normal HbA_{1c} range. Support for a possible CV benefit from intentional weight loss comes from results of post hoc epidemiological analyses of Look AHEAD (Action for Health in Diabetes) (17), observational studies of bariatric surgery in individuals with type 2 diabetes (18), and 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 PEOPLE WITH AND WITHOUT TYPE 2 DIABETES

In a series of Mendelian randomization analyses, investigators 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 that 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 individuals 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 showed that despite a median duration of 48.6 years of modest hyperglycemia (median HbA_{1c} 6.9%), the prevalence of microvascular and macrovascular complications among individuals with a GCK mutation was not different from that of control subjects. However, those who developed type 2 diabetes at the same age were heavier, had higher BP and worsening HbA_{1c} over time, and suffered substantial kidney and vascular complications (21).

Among individuals with type 2 diabetes, polymorphisms associated with BMI and systolic BP 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 HF, CKD, AND CHD IN PEOPLE WITH TYPE 2 DIABETES

Excess adiposity is associated with HF and CKD in people with type 2 diabetes, more so than for atherosclerotic CV disease (ASCVD). In results from analyses evaluating 20-year trends in CV complications among people with type 2 diabetes in Sweden, higher BMI was almost linearly associated with substantially higher risk for incident hospitalization for HF, whereas its association with incident MI was modest (2). By contrast, LDL cholesterol (LDL-c) levels were linearly associated with incident acute MI, whereas they were flat for incident HF (Fig. 3*A*), and higher HbA_{1c} 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 individuals with type 2 diabetes who already had 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 via deragements in 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 (Fig. 3*B*). The key "hidden" pathways that link excess adiposity to HF and CKD risks are far from established but speculatively also

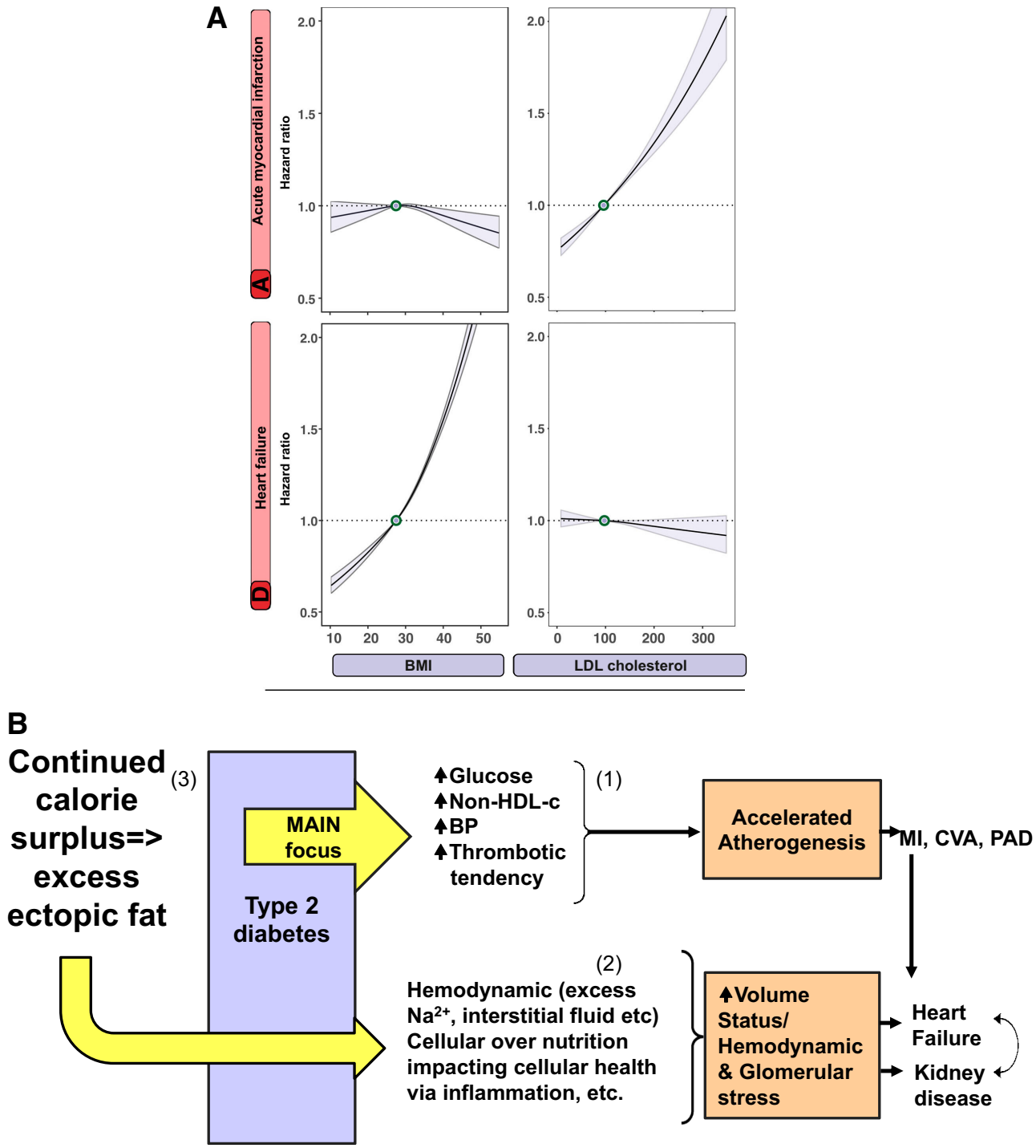

Figure 3—*A*: An epidemiological look at how BMI and LDL-c compare as risk factors for acute MI and HF in the Swedish National Diabetes Register. Notably, BMI has much stronger associations with incident HF whereas LDL-c is more strongly associated with acute MI. These are of course observational associations and, as such, these data do not mean that BMI is not relevant to acute MI risk. It is, and genetic (Mendelian randomization) studies suggest that BMI is less strongly linked to acute MI 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 acute MI 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 cutoff levels were used for risk factors: BMI ≥27.5 kg/m^2; LDL-c ≥96 mg/dL. Reprinted from Sattar et al. (2). *B*: Diabetes, excess adiposity, and ASCVD vs. cardiorenal complications. (1) ASCVD risk in type 2 diabetes is linked to traditional risk factors, where hitherto most of the intervention focus has been placed. (2) Less well-understood pathways have been revealed linking upstream excess adiposity to HF 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. CVA, cerebrovascular accident; PAD, peripheral arterial disease.

include hemodynamic and cellular "overnutrition" stressors that adversely influence myocardial and nephron health.

Whatever the mechanisms, while considerable efforts have been directed at targeting established CV risk factors of BP, LDL-c, and glucose levels in people with type 2 diabetes, far less attention has been paid to targeting excess weight

(or nontraditional 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 cogently suggested in recent reviews (24,25).

CHANGING TRENDS IN CV RISKS IN PEOPLE WITH DIABETES: IMPACT OF ADDRESSING TRADITIONAL RISK FACTORS

The progressive increase in statin and antihypertensive therapy in people with type 2 diabetes from the late 1990s onward, combined with progressively earlier diagnosis of diabetes, and reductions in smoking, has markedly driven down CV event rates in the cohort with diabetes and in the general population (26,27). Data from the U.S. 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.

Data from the Swedish National Diabetes Register investigated CV disease trends between 2001 to 2019 in a study comparing individuals with type 2 diabetes and matched control subjects (Fig. 4). Results suggested that the incidence of ASCVD and HF had generally decreased over time among individuals 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 individuals with type 2 diabetes relative to control subjects, particularly more recently (2). Other data from the U.K. published in 2015 showed HF (14.1%) and peripheral arterial disease (16.2%) to be the two most common first "vascular" outcomes in people with type 2 diabetes, with MI and stroke now less frequent (29); the latter observations suggest that fewer 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.

HF in People With Type 2 Diabetes: Time to Up Our Game

HF with preserved ejection fraction (HFpEF) or reduced ejection fraction is more common in people with than in people without type 2 diabetes, with risks approximately two- to threefold higher than in the general population (30). Given recent trends in HF incidence and prevalence, guidelines now recommend that 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 people with type 2 diabetes, however, is unaffordable in most health care systems. Yet, on the plus side, discussed in greater detail below, progressively greater use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in people with type 2 diabetes may offset rises in HF going forward.

CHANGING PATTERNS IN THE CAUSES OF DEATH IN TYPE 2 DIABETES

The reductions in CV events and CV deaths in people with type 2 diabetes have been so marked over recent decades that cancer may soon be the leading cause of deaths among people with diabetes in the U.K. (33,34) and Sweden (35). Similarly, U.S. data from 1988 to 2015 show that the percentage of total deaths due to CV causes declined from approximately 48% to 34% for people with diabetes and from 45% to 31% for those without (36). The percentage of deaths due to cancer was stable in both groups so that proportionately more deaths were due to nonvascular and noncancer 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., nonalcoholic steatohepatitis, 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 CV 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 and 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 people with type 2 diabetes will develop multiple long-term conditions, in part as premature CV deaths decline, leading to greater aggregated exposure to obesity 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

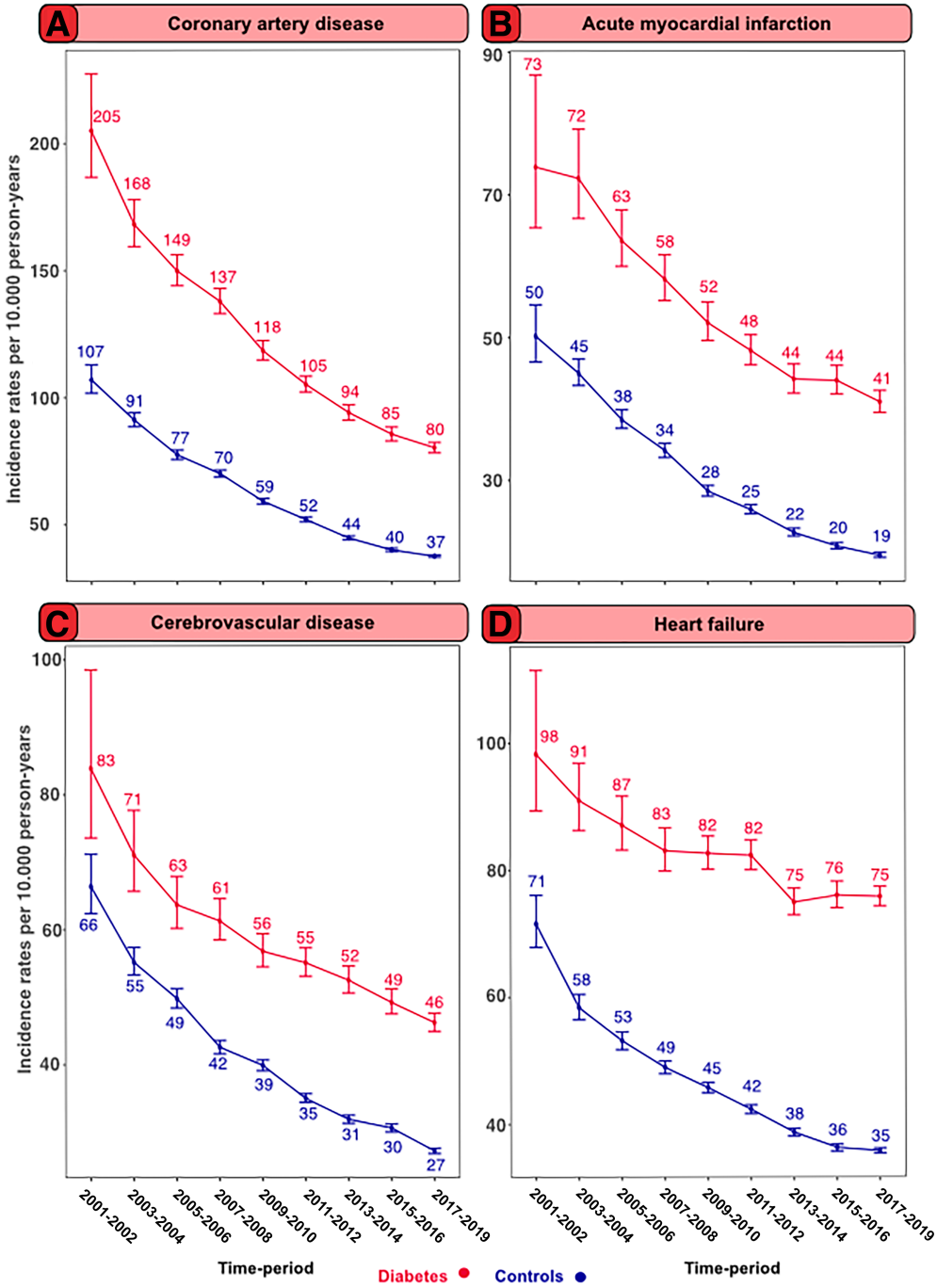

Figure 4—Standardized incidence rates for all CV outcomes among individuals with type 2 diabetes and matched control subjects. *A–D*: Age- and sex-standardized incidence rates for all outcomes in comparison with control subjects from the general population. Note plateauing of gains in HF in individuals with type 2 diabetes in recent years. Reprinted from Sattar et al. (2).

under the age of 40 years has increased globally; in the U.K., <1,000 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 with use of two large data sources showed that at age 50 years, 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 ∼3 to 4 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 β-cell reserve or their higher muscle mass compared with older people to develop type 2 diabetes. In a U.K. study of individuals diagnosed with type 2 diabetes between the ages of 20 and 39 years, men were approximately 33 pounds (15 kg) and women 53 pounds (24 kg) heavier than their age- and sex-similar counterparts without diabetes (42). In both sexes, such weight differentials narrowed as the age of diagnosis increased (Fig. 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 HbA_{1c} levels at diagnosis in comparisons with people diagnosed later in life [Fig. 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 that people developing diabetes earlier in life will have a greater and longer aggregated exposure to *1*) hyperglycemia, *2*) excess adiposity, and *3*) associated risk factors than if diabetes develops later in life.

The accelerated CV risk 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 for 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 individuals with type 2 diabetes also contribute to the greater relative risks for HF in comparison with older individuals developing type 2 diabetes (40), given excess weight is a stronger risk factor for HF than for MI (46). Collectively, inferior cardiometabolic risk factor management plus greater obesity likely explains 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 CV RISKS IN PEOPLE 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 exist for non-White populations. Of note, many races develop type 2 diabetes at lower average BMIs in comparison with White individuals, 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 β-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 toward more nonfatal MI and CKD risks in some races (49). That noted, South Asian and Black individuals with type 2 diabetes in the U.K. 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 people with type 2 diabetes were metformin, sulfonylureas, and insulin. Intensive glucose lowering does lower CV risk but only very modestly in the short-term, as suggested in a meta-analysis of intensive glucose-lowering trials (51). In this meta-analysis, major CV events were lowered by 9% (hazard ratio 0.91, 95% CI 0.84–0.99) in the more intensive arm, primarily because of a 15% reduced risk of MI (hazard ratio 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 that such drugs have little evidence of meaningful gains in other risk factors. In totality, epidemiological (11,55) and trial evidence suggests that 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, there is now considerable evidence for CV protection for newer classes of diabetes medications that favorably affect lipids, BP, and/or other elements of diabetes pathogenesis, and, perhaps most importantly, with associated intentional weight loss (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 SGLT2i and the glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RA), 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.

SGLT2i

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 reported from a meta-analysis of five SGLT2i CV outcome trials in patients with type 2 diabetes showed that this class lowers major adverse CV event (MACE) rates modestly (10% relative risk reduction) (Table 1), significant in those with prior ASCVD (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). SGLT2i also reduce the primary outcomes of HF or CV death in people living with HF with reduced ejection fraction (60,61) and HFpEF (62,63). In addition, SGLT2i also favorably affect kidney-related outcomes across the spectrum of

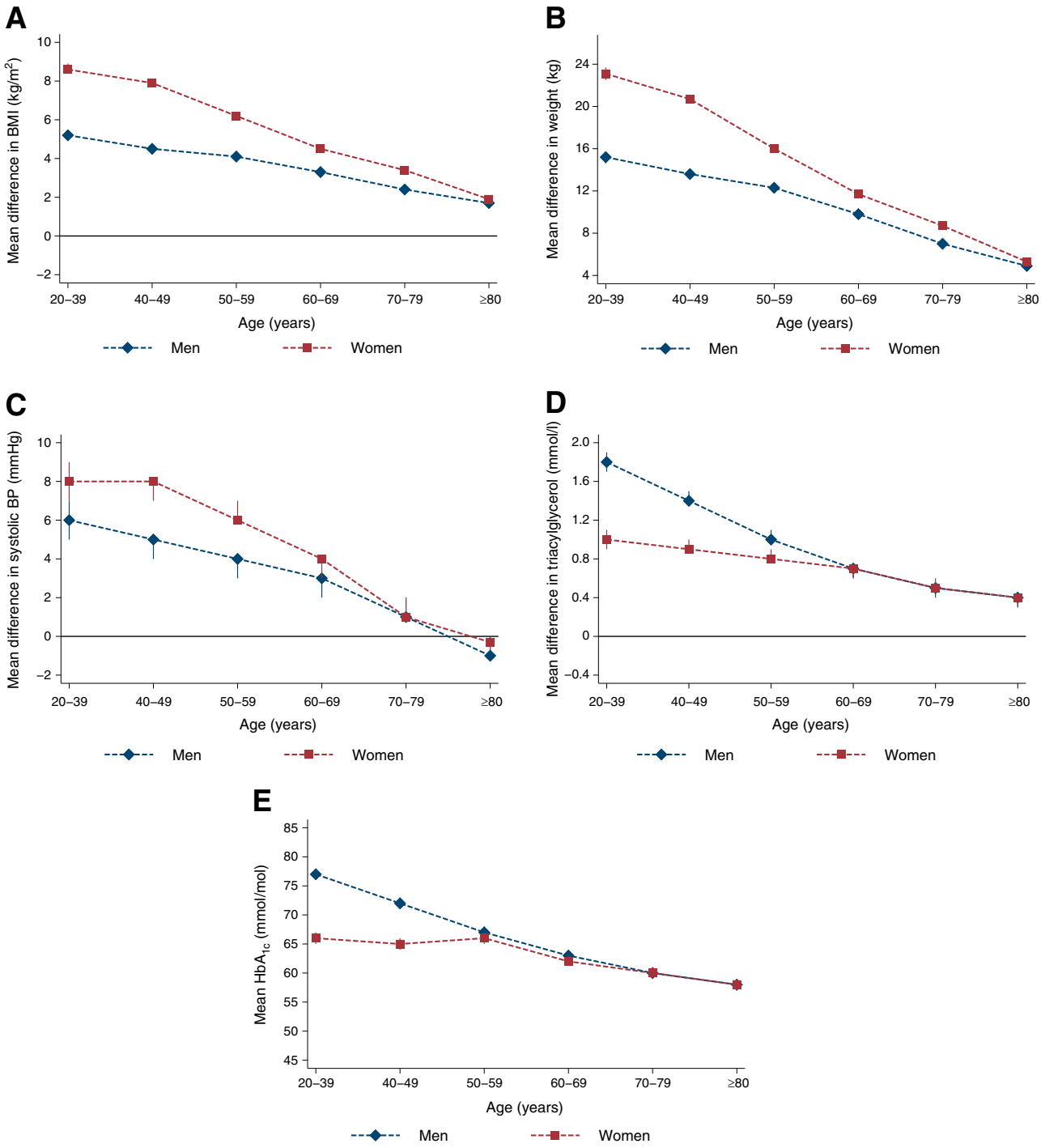

Figure 5—Risk factor patterns for differential age of diabetes diagnosis. *A–D*: Adjusted age-specific mean (95% CI) differences in BMI (*A*), weight (*B*), systolic BP (*C*), and triglyceride level (*D*) in men and women recently diagnosed with type 2 diabetes in comparison with men and women without diabetes. *E*: Age-specific mean HbA_{1c} levels in men and women recently diagnosed with type 2 diabetes. Note much higher weight, BP, lipid, and HbA_{1c} differentials at younger age, with weight and BP differentials versus control subjects without diabetes being even more marked in women (compared with men) who are diagnosed with diabetes at younger age. Reprinted from Wright et al. (42).

CKD and independent of diabetes status (64–67).

Based on these results, and the fact that SGLT2i are given orally once a day, and lower weight (modestly), BP, and glucose levels (except in the case of poor kidney function), and do not cause hypoglycemia in the absence of insulin therapy, SGLT2i are being progressively used earlier in the life course of type 2 diabetes—even as first-line treatment in some countries. In the U.K., 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 by approximately two- to threefold (69).

Table 1—Top-line results of meta-analyses of the effects of SGLT2i and GLP-1RA on ASCVD and cardiorenal outcomes in patients with diabetes

	SGLT2i	GLP-1RA (excluding 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, which are given as HR (95% CI), are taken from McGuire et al. (57) and Sattar et al. (58). For GLP-1RA, data from the sensitivity analysis with removal of ELIXA were used because most investigators consider lixisenatide to be too short acting to be given once daily in this trial. HFH, hospitalization for HF.

SGLT2i Trial Findings Forced a Look at Potential "Hidden" Mechanisms Linking Type 2 Diabetes to HF and CKD Complications

The observed 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 individuals 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 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 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, findings 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 the CV benefits of SGLT2i (79) (Fig. 6). The SGLT2i may, in part via their enhancement of glucose loss even in people without diabetes, stimulate a nutrient deprivation signal that leads to upregulation of energy deprivation sensors (sirtuin 1 [SIRT1] and 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 appears 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.

GLP-1RA

GLP-1RA imitate the actions of the incretin hormone GLP-1. They enhance glucose-dependent insulin secretion from pancreatic β-cells and inhibit glucagon release from pancreatic α-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 postprandial 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-1RA (so, excluding ELIXA: short-acting lixisenatide) were considered, GLP-1RA reduced MACE by 15%, CV death by 15%, fatal or nonfatal MI by 12%, and fatal or nonfatal stroke by 19%. There were likewise modest improvements in risk for all-cause mortality and hospitalization for HF (58).

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

- 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., with 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 results of post hoc analyses of the AMPLITUDE-O trial (Effect of Efpeglenatide on Cardiovascular Outcomes) trial (86).
- The most consistent observed CV benefit of GLP-1RA is reducing stroke, an outcome not reduced by SGLT2i (57).
- GLP-1RA reduce albuminuria and the rate of estimated glomerular filtration rate decline, with greatest effects in those with baseline low estimated glomerular filtration rate (87,88).
- It remains uncertain whether incretin therapies that lower weight more in people 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 a greater extent than did previously tested GLP-1RA (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 individuals with HFpEF (89). Multiple ongoing trials in individuals with diabetes and obesity will enrich knowledge including providing longer-term safety data over the next few years; of particular interest, SURPASS-CVOT [A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes] is testing the impact of tirzepatide (dual agonist with >10% average weight loss) (90) versus dulaglutide (minimal weight loss) in individuals with type 2 diabetes (91).

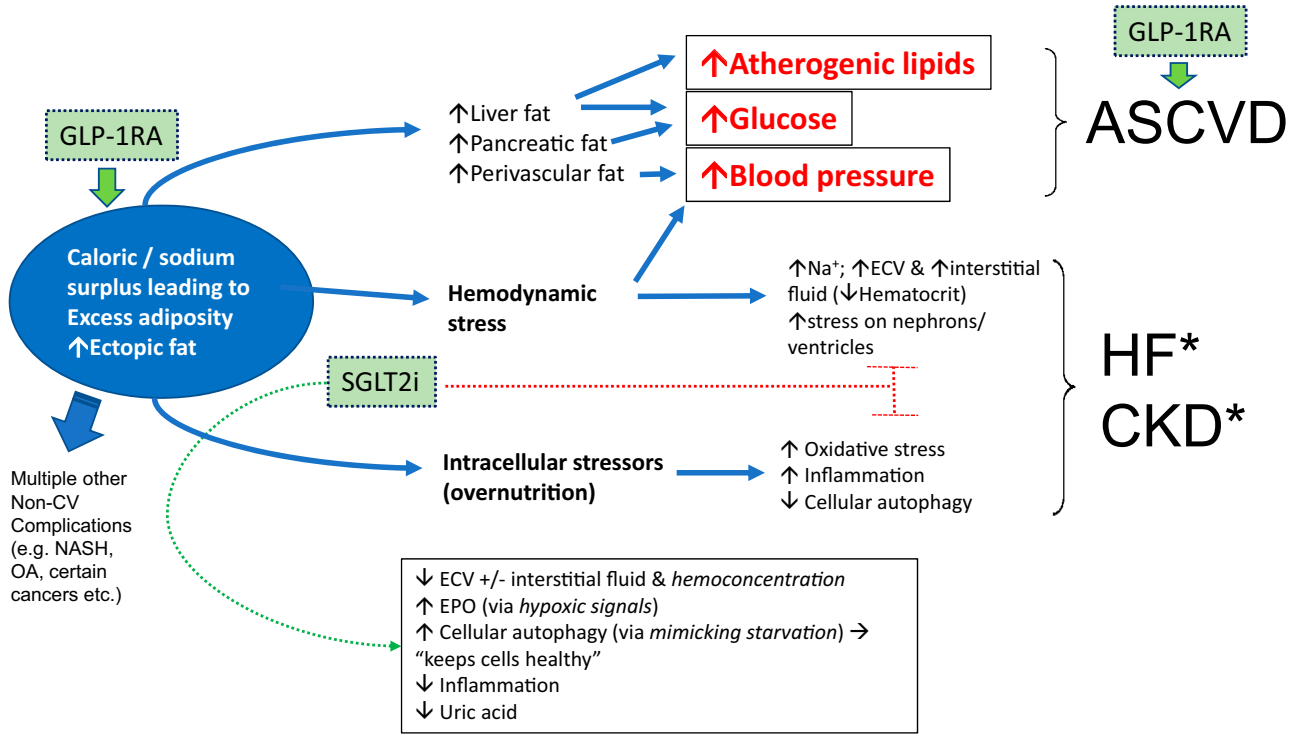

Figure 6—How do SGLT2i and GLP-1RA address CV risks in diabetes? This illustration attempts to bring some of the prior threads together; while a traditional focus on targeting glycemia, lipids, and BP has been very helpful in lowering CV risks, such a narrow focus cannot explain the profound and rapid HF and kidney benefits of SGLT2i or observed benefits of their use 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 in their hemodynamic and cellular overnutrition effects, which are currently best studied in the context of patients with HF. GLP-1RA have direct ASCVD benefits in 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 through their lowering of exposure to aggregated obesity; i.e., their effects may in part derive from lowering of ectopic fat in various tissues and, by extension, their "upstream" reductions in caloric intake, thereby lowering cellular overnutrition 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 of differential complications. ECV, extracellular volume; EPO, erythropoietin; NASH, nonalcoholic steatohepatitis; OA, osteoarthritis.

DIABETES GUIDELINES NOW RECOMMEND BOTH SGLT2I AND GLP-1RA FOR CARDIOPROTECTION

Given the quality of the trial evidence, SGLT2i and GLP-1RA are now recommended in patients with type 2 diabetes and established ASCVD irrespective of HbA_{1c} levels. The most recent 2022 American Diabetes Association/European Association for the Study of Diabetes recommendations (84) suggest either SGLT2i or GLP-1RA in patients with existing ASCVD and type 2 diabetes without requirement for background metformin use or with regard to HbA_{1c} status or target, whereas the 2023 European Society of Cardiology guidelines for people with diabetes recommend both an SGLT2i and a GLP-1RA for this patient group (31). Diabetes and cardiology guidelines and recommendations are thus harmonized with additional 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 CV DISEASE, AND FUTURE PROSPECTS

Based on the accumulated data regarding SGLT2i effects on CKD and HF, scientific humility suggests that 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. Thus 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), with the latter findings soon to be meaningfully expanded by results of the FLOW trial (clinical trial reg. no. NCT03819153, clinicaltrials.gov); a press release announced the trial was stopped early for efficacy (92). The results of ongoing trials such as 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 diabetes.

Where and when affordable, GLP-1RA 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 effect greater weight loss) could be less need for antihypertensive medications,

with notable reductions in BP in recent trials such as SURMOUNT-2, Semaglutide Treatment Effect in People with obesity (STEP) 2, and SURPASS-1 to -5 (90,93,94), though not lower statin use, 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 quality of life, will occur from their earlier use. This is because these medications appear to better target 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, greater weight loss should also lower risks of many other comorbidities linked to obesity that are common among people with type 2 diabetes (e.g., fatty liver, osteoarthritis etc.). Ongoing trials will help address these possibilities.

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