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DIABETES AND CARDIOVASCULAR DISEASE (D BRUEMMER, SECTION EDITOR)

# Cardiovascular Disease in Adults with Type 1 Diabetes: Looking Beyond Glycemic Control

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## Abstract

**Purpose of Review** Despite improvements in treatment, people with type 1 diabetes continue to have increased cardiovascular disease (CVD) risk. Glycemic control does not fully explain this excess CVD risk, so a greater understanding of other risk factors is needed.

**Recent Findings** The authors review the relationship between glycemia and CVD risk in adults with type 1 diabetes and summarize evidence regarding other factors that may explain risk beyond glycemia. Insulin resistance, weight gain, sex differences, genetics, inflammation, emerging markers of risk, including lipid subclasses and epigenetic modifications, and future directions are discussed.

**Summary** As glycemic control improves, an increased focus on other CVD risk factors is warranted in type 1 diabetes. Novel markers and precision medicine approaches may improve CVD prediction, but a lack of type 1 diabetes-specific guidelines for lipids, blood pressure, and physical activity are likely impediments to optimal CVD prevention in this high-risk population.

**Keywords** Type 1 diabetes · Cardiovascular disease · Risk factors · Sex differences · Glycemic control · Clinical targets

## Introduction

Landmark findings from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study that adoption of intensive type 1 diabetes management leads to large reductions in the incidence of complications [1] had practice-changing implications. However, as of 2018 only 21% of US adults with type 1 diabetes achieve the clinical goal of HbA1c < 7% [2] and both micro- and macrovascular complications continue to exert a significant burden in terms of death and disability, quality of life, and health care costs [3]. As a result, people with type 1 diabetes continue to have a dramatically increased risk of developing premature cardiovascular disease (CVD) [4–6]. While type 1 diabetes has been shown to be associated with adverse cardiovascular risk factors starting as early as childhood [7], this review will focus on recent data on CVD risk and risk factors in adults with type 1 diabetes.

## The Burden of CVD in Type 1 Diabetes

CVD is the major cause of morbidity and mortality in type 1 diabetes [8, 9], affecting an estimated 27% of adults with this chronic disease in the USA [10]. CVD, the majority of which is coronary artery disease, is therefore one of the largest contributors to the overall health care costs associated with diabetes [11]. Indeed, people with type 1 diabetes who also have CVD are estimated to have annual health care expenses averaging > $30,000 per year compared to ~ $12,000 per year for adults with type 1 diabetes but no CVD [10].

Clinical trial evidence for a reduction in CVD complications are scarce in type 1 diabetes. However, the DCCT/EDIC study, in which microvascular complications were the primary outcomes, demonstrated a 42% decrease in CVD risk with intensive, compared to conventional, diabetes therapy [12]. Nonetheless, evidence to date suggests that the excess risk of CVD in type 1 diabetes compared to the general population remains high [4–6]. Thus, a large Norwegian registry estimated that adults with childhood-onset

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type 1 diabetes have ninefold excess risk of acute myocardial infarction (AMI) compared to age- and sex-matched adults without diabetes [5]. Similarly, recent data from the Finnish childhood-onset type 1 diabetes registry pointed to a nearly tenfold higher CVD risk in type 1 diabetes compared to the background population, despite incidence decreasing by 4% per year since 1965 [13••]. In addition to greater risk of incident CVD, type 1 diabetes is also associated with worse prognosis after an event, with 1-year case fatality rate after AMI estimated to be 1.5 times that of patients without diabetes [14•]. As demonstrated by the Pittsburgh Epidemiology of Diabetes Complications (EDC) study of childhood-onset type 1 diabetes, this excess CVD risk is particularly pronounced in younger (< 45 years) adults among whom there was over a 19-fold increased relative risk of CVD mortality, given the low CVD mortality risk in the age-matched background population [4]. Unlike the Finnish data showing a decline in CVD incidence over time [13••], CVD morbidity showed no improvement across three calendar-year diabetes diagnosis subcohorts in EDC (1965–1969, 1970–1974, and 1975–1980), although CVD mortality declined in those with more recent onset [15••]. Yet, CVD affects the vast majority of the type 1 diabetes population at long durations. In the FinnDiane cohort, cumulative incidence of CVD was 64% in those with type 1 diabetes duration of > 50 years [16]. Data from Scotland and Sweden showed slightly lower estimated CVD burden than the other studies, with 80% remaining free of CVD by age 50 and 50% by age 65 [17]. However, it is important to note the Scottish and Swedish cohorts include adult-onset type 1 diabetes cases; thus, average diabetes duration at any given age is significantly shorter than the cohorts of childhood-onset type 1 diabetes and may explain differences in observed CVD rates.

## Glycemia and CVD Risk

Despite the strong association between hyperglycemia and microvascular complications, glycemia has historically been an inconsistent predictor of CVD incidence within type 1 diabetes. In DCCT/EDIC, a reduction in HbA1c from 8 to 7.2% was associated with a significant 28% reduction in CVD risk over 20 years [12]. Additionally, HbA1c was the strongest independent risk factor for both the first [18, 19•] and subsequent [19•] CVD events in DCCT/EDIC. In contrast, HbA1c was not a strong risk factor for CVD in the observational type 1 diabetes cohorts [20]. However, more recent analyses suggest that the lack of HbA1c association in those earlier observational studies may have been due to insufficient variability in HbA1c at baseline, preventing the detection of a statistical association [21]. Indeed, in an analysis incorporating longitudinal HbA1c in the EDC study, each 1% increase in HbA1c was significantly associated with a 26% increased risk of CVD over 25 years after adjusting for traditional CVD risk factors [21].

Nevertheless, it is important to recognize that glycemia does not affect CVD risk in isolation of other pathogenic mechanisms. There is evidence that the effect of glycemia on CVD is mediated by other CVD risk factors including lipids and blood pressure, such that hyperglycemia contributes to the derangement of those factors which in turn affect CVD risk over time [22]. There is also evidence that long-term HbA1c may modify effects of other risk factors on CVD risk in type 1 diabetes, such that their effects may be increased or decreased depending on the cumulative exposure to hyperglycemia [23••]. The EDC study has recently shown that over 30 years of follow-up, kidney disease markers were stronger risk factors for CVD, especially major adverse cardiovascular events (MACE), in those with worse long-term glycemic control, but traditional risk factors including lipids, blood pressure, and smoking were stronger risk factors in those with better glycemic control [23••]. These findings support the need for a greater clinical focus on traditional CVD risk factors as glycemic control improves, which may help to reduce the remaining excess CVD risk in type 1 diabetes. Finally, from a clinical perspective, it is important to appreciate that, while HbA1c has been a valuable measure for studying epidemiologic associations between glycemic exposure and complication risk, HbA1c may not be the optimal measure of an *individual* patient's glycemic control because as an average measure of glucose exposure it does not capture glucose variability [24]. This point was demonstrated in a recent commentary by Beck et al., which clearly showed that the same HbA1c could result from very different patterns of glycemic control across individuals [24]. As continuous glucose monitoring becomes more widely adopted, utilizing more precise, individualized metrics of glycemic control, such as time in range, will be needed to optimize complication prevention.

## Insulin Resistance and Weight Gain Are Associated with CVD Risk

Insulin resistance is associated with poor glycemic control, greater insulin dose requirements, and increased risk of complications [25] and may be a stronger predictor of CVD than glycemic control itself [26]. Concern regarding insulin resistance in type 1 diabetes has increased as intensive insulin therapy has led to concomitant weight gain. In DCCT/EDIC, incidence of becoming overweight was 1.7-fold greater in intensive therapy arm participants compared to the conventional therapy arm [27]. In the EDC study, the prevalence of overweight increased by 47% and obesity sevenfold over 18 years and such weight gain was associated with initiation of intensive therapy during follow-up

[28]. Excess body weight is now commonplace in type 1 diabetes and mirrors the general population, with 29% of US adults with type 1 diabetes meeting BMI criteria for overweight and 19% for obesity [29]. Furthermore, weight gain may contribute to worsening of other CVD risk factors. For example, DCCT/EDIC participants with "excessive" weight gain (defined as BMI increase ≥ 4.39 kg/m$^2$ during the trial period) had worse CVD risk factor profiles [30], though more prevalent treatment of lipids and blood pressure in those participants seems to have protected against a concomitant increase in clinical CVD events early on [31].

Weight gain can be difficult to control in type 1 diabetes, especially via exercise, due to challenges associated with managing blood glucose during physical activity. There is also a lack of guidelines and limited data on strategies for weight management specific to type 1 diabetes [32•]. However, research is currently underway to address those gaps. One such initiative is the ongoing Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON) Consortium, which has examined mechanistic aspects of metabolism and energy requirements of people with type 1 diabetes with the goal of developing and evaluating an adaptive behavioral intervention for weight management with optimization of glycemic control [32•].

Insulin resistance has been proposed as a potential target for adjunctive therapies to insulin in type 1 diabetes [33]. The use of existing pharmacologic agents for insulin resistance and weight, such as metformin, sodium-glucose cotransporter (SGLT) inhibitors, and GLP-1 agonists, may hold promise to reduce CVD risk in type 1 diabetes. In the limited data in adults with type 1 diabetes thus far, metformin does not seem to reduce HbA1c over the long term, but does decrease body weight and insulin dose and has been shown to reduce subclinical markers of CVD risk (e.g., intima-media thickness) in high-risk individuals [33]. SGLT inhibitors have been shown to not only improve glycemic control and reduce body weight in type 1 diabetes but also increase the risk of diabetic ketoacidosis, necessitating caution [33]. Data on GLP-1 agonists in type 1 diabetes is mixed and more research is needed to identify subgroups of patients who may derive the most benefit, while reducing the risk of hypoglycemia [34].

## CVD Risk Begins to Increase Below Clinical Targets for Cholesterol and Blood Pressure

Aside from hyperglycemia, on average, people with type 1 diabetes have only minor clinical CVD risk factor differences [35], and oftentimes better risk factor profiles [36], compared to the general population. However, it has long been recognized in type 1 diabetes that CVD and other complication risk may increase at cholesterol and blood pressure levels below established clinical targets [37, 38]. In a recent analysis of long-term cumulative blood pressure levels over the 25-year follow-up of the EDC study, the risk of coronary artery disease began to increase at systolic blood pressure of 120 mmHg and diastolic blood pressure of 80 mmHg [39••]. Similar lower blood pressure targets have also been suggested by prior studies [40, 41]. Earlier data from the EDC study also suggested that CVD risk increases at LDL cholesterol > 100 mg/dl [37]; the same cut-point, which was lower than contemporary general recommendations, was also found to be optimal for CVD risk reduction in a recent report from the Swedish National Diabetes Registry [42••]. Despite such evidence, there remains a lack of type 1 diabetes-specific recommendations due to few trials focused on CVD risk reduction in this population [43]. Current guidelines are based on evidence from type 2 diabetes, despite a lack of knowledge on the appropriateness of such extrapolation.

## Loss of Female Protection Against CVD in Type 1 Diabetes

It is now well recognized that the protection against CVD observed in women compared to men in the general population is diminished in diabetes and among individuals with type 1 diabetes women have nearly equivalent absolute CVD risk as men [44, 45]. The reasons underlying this excess relative risk in women are unclear but may relate to differences in the risk factor profile [46] or disparities in risk factor treatment by sex [47]. Thus, in DCCT/EDIC, women were less likely than men to achieve HbA1c < 7% or < 8%, despite being more likely to be using insulin pumps (58% of women versus 38% of men) and as likely to monitor blood glucose ≥ 4 times per day (61% of women versus 58% of men) [47]. However, differences in glucose management and HbA1c do not seem to directly account for the greater relative risk for CVD in women with type 1 diabetes [48] and other cardiovascular risk factors may be more likely to explain their excess CVD risk. Indeed, female participants of DCCT/EDIC were less likely to be prescribed statins, even if they had elevated LDL cholesterol levels [47]. Likewise, in the EDC study, in young adults < 45 years old, women were about half as likely as men to report statin use, despite similar levels of LDL cholesterol on average [4]. This lower rate of statins, particularly in younger women, may have been due to contraindication of statin use in women who could become pregnant. As the US Food and Drug Administration has recently removed the "Pregnancy Category X" label from statins, it remains to be seen whether the disparity in statin use by sex in type 1 diabetes may be reduced in the future [49].

Differences in CVD risk factors by sex appear as early as adolescence in type 1 diabetes [46]. In the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study, women with type 1 diabetes exhibited a more adverse adiposity profile than women without diabetes while there was no difference in men by diabetes status [50]. Furthermore, in the same study, lipids and adiposity measures explained much of the excess coronary artery calcification in women with type 1 diabetes. The CACTI study also showed that type 1 diabetes is associated with greater insulin resistance in women compared to men [51], potentially explaining why women with type 1 diabetes have similar CVD rates as men, despite a greater proportion of women using intensive insulin therapy [52]. Sex hormone disturbances may contribute to that increased insulin resistance, as women with type 1 diabetes have been shown to have lower levels of estradiol and estrogen activity compared to women without diabetes [53]. The hormone disturbances may be related to the role of insulin in maintaining balance of the hypothalamus-pituitary-ovary axis; thus, both endogenous insulin deficiency [54] and exogenous hyperinsulinemia likely contribute [55].

Another reason for this excess CVD risk among women compared with men in type 1 diabetes may relate to sex differences in the association between HDL cholesterol (HDL-C) and CVD. While higher HDL-C is generally protective against CVD, HDL-C > 60 mg/dl offered no additional protection against CAD compared to 50–60 mg/dl among women in the EDC study [56]. Additionally, very high HDL-C > 80 mg/dl was associated with an increased risk of CAD in women only. That U-shaped relationship between HDL-C concentrations and CAD risk suggests that there could be differences in the composition of HDL-C in women with type 1 diabetes. In support of that hypothesis, in the Joslin Medalists study of long-duration type 1 diabetes, the HDL-C subfractions containing apolipoprotein A1 and A2 were lower in women with CVD compared to those without CVD, a difference not observed in men [57].

## Lipoprotein Subclasses

Plasma lipid levels are not necessarily elevated in type 1 diabetes, especially among individuals with good glycemic control [36]. However, poor glycemic control, diabetic kidney disease, and insulin resistance are associated with more atherogenic lipid subfractions, which may not be reflected in conventional lipid profiles [36, 58]. Therefore, lipoprotein subclasses may more accurately assess CVD risk associated with lipids in type 1 diabetes. CVD risk has been associated with lipid subclasses including greater VLDL particle number [59], greater large and medium HDL subfractions [59], and total serum ApoC3 and ApoC3 in HDL [60]. Perhaps related to the loss of female protection discussed above, type 1 diabetes may also differentially affect LDL size and particle numbers in women compared to men [61]. In a recent report from Spain, in patients with new onset type 1 diabetes, lipoprotein subclasses substantially improved after achievement of optimal glycemic control [62•]. Improvements were especially marked in the atherogenic ApoB-containing lipoproteins, including intermediate density lipoprotein (IDL), which is not detected in conventional lipid panels.

## Genetics of CVD Risk in Type 1 Diabetes

There are very limited genome-wide association studies (GWAS) for CVD in type 1 diabetes, with only two reports to date [63, 64]. The first [63] detected novel associations between three single nucleotide polymorphisms (SNP) at the *CDK18*, *FAM189A2*, and *PKD1* loci and CAD. The authors also reported that three previously identified SNPs in *ANKS1A*, *COL4A2*, and *APOE* had stronger associations with CAD in type 1 diabetes than in the general population. Apart from *CDK18* (odds ratio [OR] = 2.6), the associations were relatively weak (ORs between 1.3 and 1.9). The second, more recent GWAS [64] detected an association between a SNP near *CDKN2B-AS1* and CAD that was replicated in independent cohorts, but again the effect was relatively weak (OR = 1.3). Another variant, near *DEFB127*, had a stronger effect size (OR = 4.2) which, however, could not be replicated.

As CVD is a complex phenotype with multifaceted etiology, polygenic risk scores (PRS) may better reflect genetic risk than single variants detected in GWAS. DCCT/EDIC investigators recently applied a CAD PRS identified in individuals without diabetes based on over 6 million SNPs to type 1 diabetes and found 38% of CVD and 40% of MACE risk per PRS standard deviation [65•]. Importantly, while those associations were statistically independent of established risk factors, including age, HbA1c, lipids, and blood pressure, the PRS only modestly improved prediction of CVD over risk factor levels. Thus, PRS may help improve understanding of pathophysiologic pathways, but clinical utility remains unknown.

Haptoglobin (*HP*), a copy-number variant, is a major candidate gene for CVD risk in diabetes [66]. Haptoglobin is an acute phase plasma glycoprotein whose function is to bind free hemoglobin, inhibiting release of heme iron, resulting in reduced oxidative potential of free hemoglobin [67]. The *HP* 2 allele has been associated with an increased risk of CAD, likely via reduced anti-oxidant capacity, first in type 2 diabetes [68] and more recently in type 1 diabetes [69, 70]. *HP* may also affect CVD risk through anti-inflammatory properties associated with the *HP* 1 allele (discussed below). In the CACTI study, HP 2–2 genotype predicted progression of coronary artery calcification [71]. While the association between the *HP* 2 allele and increased CVD risk seems to be

specific to diabetes/presence of hyperglycemia, within type 1 diabetes the risk conferred by the *HP* 2 allele is stronger in individuals with lower glycemic exposure [72], suggesting that as glycemic control improves, the genetic susceptibility conferred by *HP* becomes more evident. Such an apparently non-glycemic pathway may point to new therapeutic strategies to reduce CVD risk in T1D [73]. Another promising candidate gene is fatty acid binding protein 4 (*FABP4*), a low-expression variant of which (G allele of rs77878271) was recently associated with 17% increased risk of CVD and 26% increased risk of CAD in a meta-analysis of studies focusing on type 1 diabetes [74].

## Inflammation and CVD Risk in Type 1 Diabetes

It has long been known that chronic inflammation increases the risk of vascular disease [75]. Both innate and adaptive immune responses are thought to be involved in the vascular damage underlying the development of CVD [76–78], related to endothelial injury and increased plaque instability [79]. Compared to people without diabetes, people with type 1 diabetes have increased levels of pro-inflammatory and immune response biomarkers, including cytokines, adhesion molecules, and chemokines, starting as early as childhood [80]. In type 1 diabetes, increased inflammation is correlated with worse glycemic control [81], diabetic kidney disease [82], insulin resistance [83], and hypoglycemia [79]. Thus, hyperglycemia may directly lead to increased levels of circulating inflammatory biomarkers, which may be at least partially responsible for the excess CVD risk associated with type 1 diabetes. Indeed, higher levels of candidate markers of systemic inflammation, including leukocyte count [84, 85], galectin-3 [86], high sensitivity C-reactive protein [87], Lp-PLA2 [87], and kallikrein [88], have been epidemiologically associated with increased CVD risk in type 1 diabetes. Heart failure biomarkers, high sensitivity cardiac troponin-t (hs-cTnT), and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) have recently been demonstrated to be associated with future total CVD and MACE in type 1 diabetes [89, 90]; however, they do not consistently improve prediction over traditional risk factors [90]. The candidate gene, *HP* (discussed above), is also associated with increased inflammation [91]. It has been observed that increases in isoprostanes (a measure of oxidative stress) and white blood cell count over time directly correlated with the number of *HP* 2 alleles relative to *HP* 1 alleles [92]. These findings suggest that, in addition to deficiencies in protection from oxidative stress, the *HP* 2 allele may confer inferior anti-inflammatory capacity compared to the *HP* 1 allele, a possible mechanism through which the *HP* gene influences CVD risk.

## Epigenetics

Though there is currently a lack of data on the association between epigenetic modifications and CVD outcomes in type 1 diabetes to date, epigenetics is an emerging area of research in diabetes complications. Epigenetic associations with CVD in the general population suggest that this research may help improve understanding of how environment/exposures affect gene expression to influence CVD risk [93]. There are recent epigenome-wide association studies (EWAS) examining associations between differential DNA methylation and microvascular complications in type 1 diabetes [94–96]. Of note, it has been demonstrated in DCCT/EDIC that DNA methylation of the *TXNIP* locus mediates the association between HbA1c and microvascular complication development [96]. Its relative affordability and ease of measurement, along with the potential to be pharmacologically modified [97], makes DNA methylation a particularly promising marker to elucidate pathophysiologic pathways and discover new intervention targets.

## Future Directions

As research to improve CVD risk prediction moves forward, studies in exclusively type 1 diabetes cohorts are needed to address the unique challenges of developing early interventions for this high-risk population. In particular, it is unclear whether it is appropriate to extrapolate associations detected in type 2 diabetes to type 1 diabetes. In addition to important differences in pathophysiology between type 1 and type 2 diabetes, type 1 diabetes onset occurs most commonly in children and young adults, while type 2 diabetes occurs most commonly in middle to older adulthood. Thus, on average, the length of exposure to diabetes/hyperglycemia is greater in type 1 diabetes than in type 2 diabetes at any given age [98]. Another major limitation of type 1 diabetes complication research in general is the limited data in minority groups, especially in genetic studies. The New Jersey 725 cohort has provided valuable information on black patients with type 1 diabetes but was drawn from a limited geographic region and primarily focused on eye complications [99]. Thus, there is a need for a large multi-ethnic type 1 diabetes cohort.

It is critical to understand that not only CVD risk but also its risk factors may differ by characteristics including but not limited to cumulative glycemic exposure [23••], sex and age at diabetes onset [100], and genetic factors [72]. Risk factors may also differ by the specific manifestation of CVD [101]. Thus, the CVD phenotype definition must be carefully considered to ensure the correct interpretation of the results. The decision to include coronary revascularization in the CVD definition requires careful consideration, as it indicates CVD

morbidity but is also a preventative procedure reflecting both access to care and a medical decision; thus, its inclusion or exclusion can affect detection of risk factor associations [101]. Furthermore, strength of risk factor associations for coronary artery disease and cerebrovascular disease may differ [102], so the inclusion or exclusion of stroke may also affect interpretation of results. Finally, precision medicine approaches are needed to identify subgroups of people with type 1 diabetes who may benefit from specific interventions. To that end, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have instituted a joint Precision Medicine in Diabetes Initiative to promote research and ultimately clinical implementation of precision medicine [103].

## Conclusions

This review summarized recent research on the epidemiology of CVD in adults with type 1 diabetes.

While glycemic control is the cornerstone of type 1 diabetes management, an increased focus on other CVD risk factors is needed, particularly as glycemic control improves. Genetic variants, emerging risk markers, and precision medicine approaches may improve CVD risk prediction, but a lack of type 1 diabetes-specific guidelines and clinical target levels for lipids, blood pressure, and physical activity is likely limiting progress on CVD prevention in this high-risk population.

### Compliance with Ethical Standards

**Conflict of Interest** Dr. Miller reports grants from American Diabetes Association, outside the submitted work. Dr. Costacou has nothing to disclose.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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