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Childhood-onset Type 1 diabetes and cardiovascular disease



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Practice points

- Cardiovascular disease (CVD) is increased in people with Type 1 diabetes (T1D), with women losing the cardiovascular protection afforded to nondiabetic premenopausal women. Furthermore following a major cardiovascular event, mortality risk is significantly elevated, particularly in the subsequent 12 months.
- Vascular measurements such as intima-media thickness, pulse wave velocity and flow-mediated dilatation are abnormal in young people with T1D even after a short duration of diabetes.
- For traditional CVD predictors (such as smoking, obesity, family history, age), it is likely that the trajectory of CVD risk differs in people with T1D. In addition, novel predictors specific for T1D such as renal disease greatly alter risk for future CVD. Glycemic control is the major determinant of CVD, but even with HbA1c levels <6.9%, risk for CVD is elevated, indicating a multifactorial pathogenesis.
- Landmark studies such as SEARCH and the Adolescent T1D Cardio-Renal Intervention Trial (AdDIT) will continue to provide an evidence base for use of risk factor treatments in young people with T1D. The main treatments are statins primarily for use in dyslipidemia and/or angiotensin-converting enzyme inhibition for hypertension or renal disease.

SUMMARY Cardiovascular disease (CVD) is the leading cause of death in people with Type 1 diabetes (T1D), and improvements in CVD outcomes in the general population in recent decades are not mirrored in T1D populations. It is likely that CVD outcomes are worse for childhood-onset T1D due to a longer duration of disease and other important pathophysiological factors. However, repeated surveys show that screening for and treatment of CVD risk factors during adolescence is currently extremely poor. Here, we provide an overview of CVD in T1D, with a focus on aspects relevant to pediatric diabetes healthcare practitioners.

Cardiovascular disease (CVD) is the most common cause of death in people with Type 1 diabetes (T1D), and occurs more frequently, at a younger age and with greater severity compared with the general population [1] and people with Type 2 diabetes (T2D) [2]. Hyperglycemia is unequivocally a major modifiable mediator of CVD risk in T1D, and risk is reduced by achieving better glycemic control through use of intensive insulin therapy. This is now commonplace in young people; however, the pathogenesis of CVD is multifactorial and targeted assessment of cardiovascular status is often not the focus of care during a young persons diabetes clinic appointment. Moreover use of CVD risk factor, treatments (e.g., statins and angiotensin-converting enzyme inhibition [ACEI]) are low in this age group. In this article, we have attempted to provide an overview of CVD in

KEYWORDS

• angiotensin-converting enzyme inhibition
• cardiovascular disease
• glycemic control
• microalbuminuria • risk prediction • statins • Type 1 diabetes

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childhood-onset T1D mainly for a general pediatric diabetes healthcare practitioner. As there is a lack of an epidemiological evidence base for CVD specifically in childhood-onset T1D, the first part of the review will focus on the epidemiology of CVD in adult-onset T1D. Later in the review, we discuss predictors of CVD in childhood-onset T1D and the evidence base for risk factor interventions at an early age.

Definitions

CVDs are a group of disorders of both the heart and blood vessels and include coronary artery disease, cerebrovascular disease, peripheral arterial disease, coronary heart disease, deep vein thrombosis and pulmonary embolism (Table 1).

Epidemiology

• People with T1D have excess mortality

All-cause mortality in people with T1D has been difficult to quantify. This is in part due to: the chronicity of the disease processes involved, the changing patterns of mortality in the general population where there have been marked declines in mortality over recent decades particularly from CVD, and also differences in methodology between studies such as low case ascertainment, missing data and poor differentiation between T1D and T2D.

Most studies indicate that coronary artery disease is the leading cause of death in people with T1D [1,3,4,5]. Standardized mortality ratios (SMR) for T1D vary between studies but most report it to be greater for men compared with women and with increasing age, with a peak in the fourth decade of life. For example, Laing *et al.* studied 1437 deaths during follow-up of adults with T1D and observed 536 deaths from CVD and of these, 368 were from coronary artery disease. The authors reported a SMR of 11.8 and 44.8 for men and women aged 20–29 years and 8.0 and 41.6 for men and women aged 30–39 years, respectively [6]. Using different methodologies, a recent survey from Australia observed a reduced SMR in adults with T1D from 4.2 in 1997 to 3.1 in 2010 in males and from 3.9 to 3.5 in females [2]. Of these deaths, those attributed to CVD, the most cause of death, decreased from 35.6 to 31.2% and from 31.5 to 27.2% in males and females, respectively. Peak mortality was between the ages of 30 and 50 years. The novel coding methods employed in this study indicated that death related to CVD was approximately 38% underestimated when employing traditional coding methods, as many deaths

are incorrectly coded as being attributed simply to diabetes on death certificates. Importantly, the study also indicated strikingly different trends in mortality between T1D and T2D, with much greater reductions in all-cause mortality for T2D. The National Diabetes Audit [7] from England and Wales has high case ascertainment and internal quality standards which, as such, provides an authoritative contemporary resource for diabetes outcomes. Of the 198,100 people in the audit with T1D in 2012, 3300 died during the year, giving a SMR of 2.3 [7]. Importantly being diagnosed with CVD significantly increased mortality risk in the next 12 months, independent of other known risk factors. Specifically, angina, myocardial infarct, heart failure, stroke and major and minor amputation were associated with odds ratios (OR) of mortality of 1.3, 2.7, 4.5, 3.7, 2.1 and 1.8, respectively, in the subsequent 12 months. However, consistent with the Australian study, the audit found that additional deaths due to diabetes were lower in 2010–2011 compared with previous years [2].

Estimates of mortality from childhood compared with adult-onset T1D are difficult to quantify. The EURODIAB study aimed to provide a picture of mortality and causes of death in Europe following a diagnosis of T1D in childhood (<15 years), and to examine mortality trends between countries [8]. Children were followed up for an average of 7.6 years after diagnosis. From 28,887 children diagnosed since 1989, the SMR ranged from 0 to 4.7 between centers in 13 countries. One-third of deaths (47 deaths) were directly attributable to diabetes, 27 were probably from diabetic ketoacidosis and 5 deaths were directly related to hypoglycemia. This study did not, however, observe deaths from long-term complications of diabetes and longer-term follow-up of patients with childhood-onset T1D are required.

• Risk for CVD is greater in people with T1D

Large observational studies have demonstrated that risk for CVD is greater in people with T1D compared with the general population (men, HR: 3.6 [95% CI: 2.9–4.5]; women, 7.6 [95% CI: 5.5–10.7]) [9]. Within the spectrum of vascular diseases, coronary heart disease (men, 3.0 [2.2–4.1]; women, 7.6 [4.9–12.0]), stroke (women, 5.9 [4.2–8.3]) and peripheral arterial disease (85.5 [72.9–100.3]) occur with greater frequency in patients with T1D. The England and Wales National Diabetes Audit shows similar outcomes, but quantified differently; standardized ratios for angina, myocardial infarct, heart

Table 1. WHO definitions for cardiovascular events.

Cardiovascular event	Definition
Coronary heart disease	Disease of the blood vessels supplying the heart muscle
Coronary artery disease	Disease of the blood vessels supplying the heart muscle
Cerebrovascular disease	Disease of the blood vessels supplying the brain
Peripheral arterial disease	Disease of blood vessels supplying the arms and legs
Deep vein thrombosis and pulmonary embolism	Blood clots in the leg veins, which can dislodge and move to the heart and lungs

failure, stroke and a major and minor amputation were 1.8, 1.6, 1.7, 1.3, 3.2 and 4.4 [7]. Most recently analysis of the Scottish Registry Linkage Study showed that the age-adjusted incidence rate ratios were lower than those observed in previous reports: for first CVD event in the T1D versus nondiabetic Scottish population, the incidence rate ratio was 2.3 and 3.0 for men and women, respectively [10]. Therefore, although variably reported, coronary artery disease (angina, myocardial infarct, heart failure and also revascularization grouped together) is elevated and is the leading cause of death in middle-age people with T1D.

Most recently, in a registry-based observational study to determine the excess risk of death according to the level of glycemic control in a Swedish population of 33,915 patients with T1D followed from 1998 to 2011, Lind *et al.* showed an adjusted HR for death of 3.5 (3.1–4.0) [11]. The adjusted HR rates of death from cardiovascular causes was 4.6 (3.5–6.1). Death was strongly associated with HbA1c levels with no evidence of a cut-off value below which excess risk did not occur (i.e., the adjusted HR for death from cardiovascular causes was still 2.9 [2.1–4.1] for an HbA1c level <6.9%) [11].

There is also evidence that the severity of CVD is greater in T1D. Severe stenoses of coronary vessels, involvement of all three major coronary arteries and distal segment disease are all more common in adults with T1D compared with nondiabetic controls [12,13]. Important research from Norway shows a high prevalence of silent CVD in young adults with T1D. 100% of participants showed significant coronary atherosclerosis on intravascular ultrasound, 34% had stenoses of more than 50% on coronary angiography, despite a complete lack of symptoms and only 15% had pathological findings on exercise electrocardiography [14].

Vascular anatomy & function in T1D

The Bogalusa Heart study and the PDAY study provide evidence linking antemortem risk

factors and the development of atherosclerotic lesions. Bogalusa found intimal surface involvement with aorta fatty streaks was present in 32% of black and 20% of white young people aged up to 30 years [15]. Both aorta and coronary fatty streaks were strongly related to antemortem lipids levels and ponderal index [15]. PDAY found that age, non-high-density lipoprotein cholesterol concentration, smoking, hypertension, obesity and hyperglycemia are positively associated with atherosclerotic lesions, whereas female gender and high-density lipoprotein cholesterol concentration are negatively associated with lesions [16]. These studies have highlighted that risk-factor control beginning in the late teenage years will retard development of the earliest stage of atherosclerosis and its progression, and will reduce or delay occurrence of CVD.

There are excellent reviews previously published that provide more detail on the pathogenesis of CVD in T1D [5]. Here, we discuss vascular measurements such as intima-media thickness (IMT) using high-resolution ultrasound, pulse wave velocity and flow-mediated dilatation, which help in the noninvasive assessment of vascular disease processes and are emerging as predictors of future vascular events and mortality [17,18,19,20].

Both carotid IMT (cIMT) [21] and aortic IMT [17,22] are increased in young people with T1D. Blood vessel compliance is also measurable using vascular flow velocities and arterial nitrate-mediated dilatation and these have been found to be abnormal in young people with T1D, indicating increased arterial stiffness at an early age [23,24]. The SEARCH for Diabetes in Youth study is a six-center US-based study of young people with diabetes onset younger than 20 years of age and consists of 2657 with T1D. It has and continues to provide important contemporary information on young people with T1D. During SEARCH, young people, particularly males, with T1D had abnormal brachial distensibility, pulse wave velocity and augmentation index which measure autonomic function [25]. Heart rate variability was associated with peripheral and central arterial stiffness [26];

and for every 1% increase in the average HbA1c over a 6-year time period, there was a 5% decrease in the variability of measurements of early cardiac autonomic dysfunction [27]. The AddIT is also providing detailed and contemporary evidence of CVD risk in adolescents with T1D and will be discussed in detail later in this article.

Predictors of CVD in T1D

• Glycemic control

Prospective follow-up of historical observational cohorts showed no association between glycemic control and CVD risk; In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, HbA1c was not significantly associated with angina or myocardial infarction [28]. In the multicenter European study EURODIAB, HbA1c was not associated with coronary artery disease over 8 years of follow-up [29] and during the Pittsburgh Epidemiology of Diabetes Complications Study Cohort, no measure of glycemia associated with incident coronary artery disease [30].

However during clinical trials, improvements in glycemic control through use of intensive insulin regimens have unequivocally led to a reduction in coronary events and mortality in adults with T1D patients. The DCCT, and its follow-up study, the EDIC compared intensive versus conventional glycemic control in a young, healthy (no evidence of microvascular or CVDs) population of people with T1D [30]. 1441 participants were included and the mean age of the cohort was 27 years. Subjects with previous CVD were excluded. In those subjects randomized to the intensive group, three cardiovascular events were observed in three subjects, compared with 21 events in nine subjects in the conventional treatment group. The relatively short duration of diabetes and few CVD events in the DCCT study precluded any firm conclusion regarding the link between glycemic control, intensive insulin therapy and CVD outcomes. However, after 18 years of follow-up (DCCT/EDIC combined), it was found that intensive therapy decreased the risk of CVD events; reduced the risk of angina and revascularization by 42%, and myocardial infarction and stroke by 58% (Figure 1). In subcohort studies, reduced cIMT and coronary artery calcification were associated with the reduction in mean HbA1c achieved with intensive therapy [31,32]. A subsequent meta-analysis of eight randomized controlled trials of intensive diabetes therapy in T1D (1800 patients with 11,293 person-years

of follow-up), also showed a reduced incidence rate ratio for any macrovascular event of 0.4 (95% CI: 0.3–0.6) [33]. Therefore, glycemic control is a major predictor of CVD in T1D.

Early glycemic control & CVD risk: Figure 1

During the DCCT, differences in HbA1c between the two groups had a large effect on diabetes complications risk, as described above. However, during the follow-up EDIC study, mean HbA1c between the former intensive and conventional therapy groups were no longer significantly different [34]. Despite similar glycemic control, after mean follow-up of 17 years, the intensive therapy group had reduced CVD events by 42% (95% CI: 9–63) and risk for nonfatal myocardial infarction, stroke or cardiovascular death fell by 57% (95% CI: 12–79) [35]. Analysis indicated that this risk reduction was largely due to differences in mean HbA1c during the initial DCCT. Consistent with these observations, differences in cIMT [32] and coronary artery calcification [31] were also observed between the groups.

The observations from DCCT and EDIC indicate that early tight glycemic control using intensive insulin therapy may reduce future cardiovascular risk regardless of subsequent control. The mechanisms for these observations are unclear. However of note is that the DCCT, as a trial cohort, had exclusion of individuals with established CVD or hypertension or dyslipidaemia. Additionally, the mean duration of diabetes at the start of the DCCT was 6 years and the effect of poorer glycemic control prior to enrollment into the study is not known. Furthermore, the target HbA1c in order to reduce CVD risk is unclear from the data, as is the extent of added risk due to the presence of other cardiovascular risk factors. Finally, and importantly with respect to childhood-onset T1D, only a minority of DCCT individuals were adolescents. These individuals are therefore currently younger and the effect of early insulin intensification on CVD risk has not yet been fully established in this age group.

• Microalbuminuria

Historical reports show that coronary artery disease mortality is increased 37-fold in people with T1D and proteinuria and approximately fourfold without proteinuria [3,4]. Recent evidence suggests that CVD and renal disease share risk factors and develop in parallel [4], and consistent with this, landmark trials show that intensive diabetes therapy reduces both cardiovascular and renal

outcomes [32,36]. Although differences in HbA1c account for most of the benefit, multivariate analyses suggest that part of the effect on CVD risk is mediated by reduction in the incidence of renal disease [35]. During the AdDIT trial, which is discussed in more detail later, Marcovecchio and colleagues demonstrated that higher urinary albumin excretion, even within the normal range, is associated with early atherosclerosis, as evaluated by measuring carotid and aortic IMT [37]. Therefore, microalbuminuria may represent the first signs of systemic vascular damage, and can be considered an early, noninvasive marker for both diabetic nephropathy and CVD. This indicates that renal disease and renoprotective treatments may alter the trajectory of CVD risk in T1D to a greater extent than in the general population.

• Lipids

In a large cohort of Finnish adults with T1D followed for 10.2 years, strong predictors of

coronary events were ApoB (HR: 1.5 [95% CI: 1.2–1.8] per one standard deviation [SD] increase) in macroalbuminuric patients, and ApoB/ApoA-I ratio (HR: 1.4 [95% CI: 1.2–1.8] per one SD increase) in normoalbuminuric patients, whereas HDL-cholesterol, ApoA-I, total and LDL-cholesterol were poor predictors. In the SEARCH Study, 35, 27 and 12% of young people with T1D had high concentrations of total cholesterol, LDL-cholesterol and triglycerides, respectively, even after a relatively short disease duration [38]. Eleven and eight percent had elevated apoB and LDL-cholesterol levels, respectively, which increased with HbA1c levels [39]. Among those in poor glycemic control, 28% had elevated ApoB, and 18% had dense LDL. Importantly, those with optimal HbA1c had standard lipid concentrations that were similar or even less atherogenic than those observed in nondiabetic youth [40], and during prediction modeling,

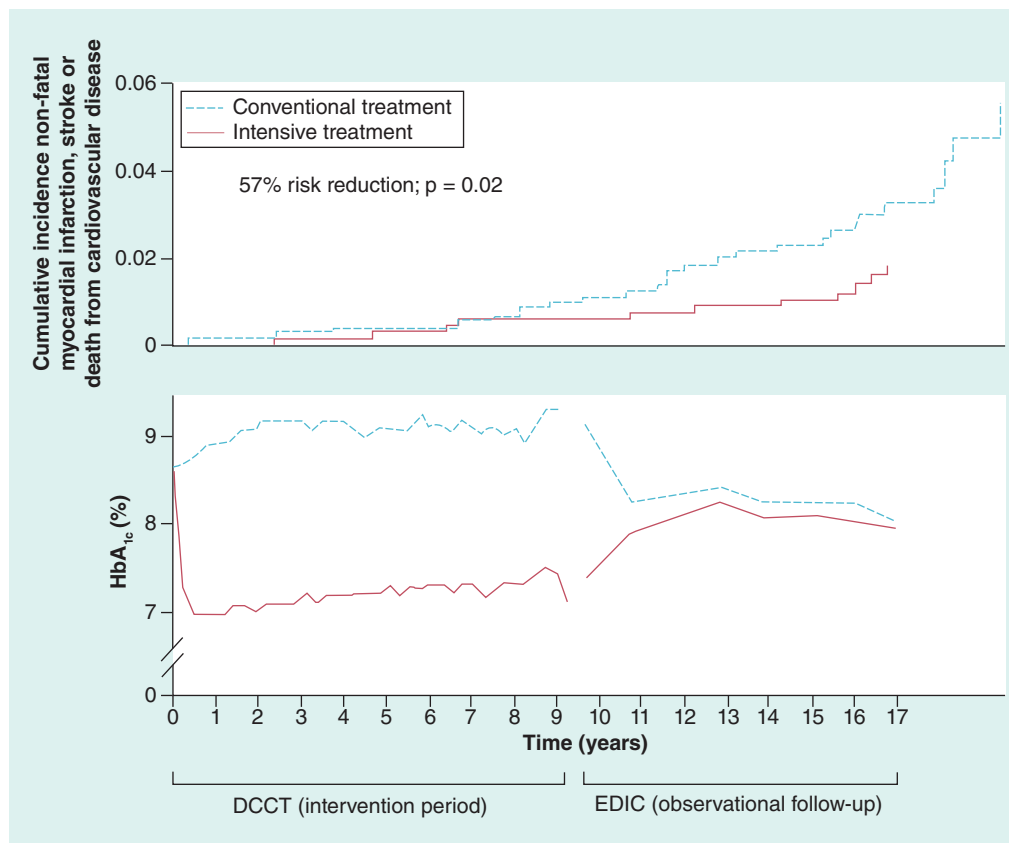


Figure 1. Differences in HbA1c and cardiovascular event rates over time between intensive and conventional diabetes treatment arms in DCCT/EDIC study cohort. These observations indicate that early tight glycemic control using intensive insulin therapy reduces future cardiovascular risk regardless of subsequent control.

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improved glycemic control over 2 years was associated with a more favorable lipid profile [41]. During the AddIT trial [37], higher non-HDL cholesterol (3.0 [0.8] vs 2.8 [0.8] mmol/l) and ApoB–ApoA-1 ratio (0.5 [0.1] vs 0.4 [0.1]; $p = 0.04$) were observed in adolescents with T1D deemed to be at higher risk of CVD and renal disease compared with those at lower risk, based on their albumin/creatinine ratios (see later text for explanation).

• Hypertension

In the Coronary Artery Calcification in T1D Study [42], hypertension was more common in adults with T1D than in matched control subjects (43 vs 15%). In the SEARCH Study, where duration of T1D is relatively short, the prevalence of elevated blood pressure was 5.9% in children aged 3–17 years [43]. Importantly in the same study, only 7.4% of those with elevated blood pressure were aware [44].

The AddIT Study

Treatment of cardiovascular risk factors in young people with T1D is inadequately studied, and large published studies of statin therapy in youth with T1D are lacking. AddIT is a multicenter multinational study involving 32 centers in the UK, Canada and Australia, that will provide important data on the efficacy of ACEIs and statins in high-risk adolescents with T1D [37]. During AddIT, 500 ‘high-risk’ T1D adolescents (defined by elevated urine albumin excretion or a high rate of rise of urine albumin excretion within the normal range) have been randomized to either Quinapril, Atorvastatin, combination therapy or placebo for 3–4 years [37]. The study also includes a parallel observational study of 400 ‘low-risk’ T1D adolescents. The primary end point is albumin excretion, but secondary end points include markers of CVD (cIMT, endothelial function, arterial stiffness, blood lipids and lipoproteins; hs-CRP and asymmetric dimethylarginine).

Data have recently been reported from the first 729 (400 from the intervention arm and 329 from the observational cohort) adolescents who underwent cardiovascular assessments, and 561 (307 trial and 254 observational) subjects where biochemical data have been processed [37]. Adolescents in the trial cohort show a significantly greater age- and sex-adjusted pulse wave velocity (a composite measure of arterial stiffness) compared with those in the observational cohort (trial: 5.00 ± 0.84 ; observational: 4.86 ± 0.70 m/s; adjusted

p -value = 0.021). This demonstrates that adolescents with T1D who have a raised albumin creatinine ratio (but still within normal range) already have increased arterial stiffening. The trial cohort had a shorter mean duration of diabetes than the observational cohort (5.9 years). This could suggest that those at higher risk of developing renal and CVDs show earlier increases in urine albumin excretion, and might reflect interaction between glycemic control, puberty a genetic predisposition in accelerating the appearance of early signs of complications [37]. Data from biochemical assessment showed that levels on non-HDL cholesterol are significantly higher in the trial compared with the observational cohort, as was the age- and sex-adjusted ApoB–ApoA-1 ratio. No differences were found between the groups in novel CVD risk markers, such as high-sensitivity C-reactive protein and asymmetric dimethylarginine. In summary, data from AddIT have shown that adolescents with T1D with a high rate of rise of albumin excretion within the normal range already have evidence of early CVD.

Further published work from the AddIT trial has evaluated carotid and aortic IMT and their relationship with cardiovascular risk factors and urinary albumin excretion in the same cohort [45]. Mean and maximal aortic but not carotid IMT was greater than in control subjects. Mean and maximal aortic IMT was also associated with urinary albumin-to-creatinine ratio (multiple regression coefficient [standard error] 0.023 [0.007]). These results indicate that aortic IMT may be a more sensitive marker of atherosclerosis than carotid IMT in adolescents with T1D.

• Retinopathy

In clinical screening studies, retinopathy has been shown to be an indicator of risk for coronary artery disease in T1D [28]. In T1D, retinopathy precedes the development of nephropathy in most cases. Nevertheless, it is an indicator of microvascular damage caused by hyperglycemia and could therefore act as a useful early predictor of CVD risk in T1D.

• Central adiposity

Overall and central adiposity is associated with insulin resistance, dyslipidemia and blood pressure [46]. Increased risk for diabetes-related complications, including CVD and mortality, has been associated with metabolic syndrome components and insulin resistance in large adult T1D cohorts [47,48]. Euglycemic clamp studies

of 40 people with T1D and matched controls showed lower whole-body-mediated glucose uptake (indicating reduced insulin sensitivity) and lower insulin-mediated nonesterified fatty acid suppression in T1D people, and both measurements correlated with coronary artery calcification as measured by computed tomography [49]. The SEARCH Study has found that prevalence of overweight was greater among young people in the USA with compared to without T1D (22.1 vs 16.1%) [50]. Importantly, for female adolescents, being overweight or obese is associated with unhealthy weight-loss practices, such as insulin omission and vomiting/laxatives and with poor glycemic control [51].

The SEARCH Study has also investigated the extent to which CVD risk factors cluster in youth with T1D using confirmatory factor analysis to determine statistical associations among CVD risk factors. The investigators found that the best-fitting model was a three-correlated-factor structure, incorporating obesity, lipids and blood pressure [52]. These outcomes highlight the importance of not only maintaining optimal glucose control but also the need to address these other CVD risk factors.

• Smoking

Smoking is associated with cIMT thickness progression, arterial stiffness and presence of coronary artery calcification in people with T1D [53,54]. Prevalence of smoking is generally high in young people with T1D, particularly males [55] and is associated with socioeconomic deprivation, dyslipidemia [9] and physical inactivity [55]. Despite these observations, levels of appropriate counseling in clinic are low [56].

• Hypoglycemia

Hypoglycemia is increased with intensive insulin therapy, which is now a standard of care in T1D [36]. In physiological investigations of vascular function, Pena *et al.* demonstrated lower flow-mediated and glyceryl trinitrate-mediated dilatation in children with T1D than controls [57]. Furthermore, hypoglycemia, but interestingly not glucose variability, was inversely related to flow-mediated dilatation [57]. Therefore, hypoglycemia may be an additional risk factor for early CVD but this requires further research.

Cardiovascular risk prediction tools for T1D

Reports consistently indicate that the effect of glycemic control on risk for CVD significantly

differs in patients with T1D compared with T2D [58]. Given that a major objective in the management of people with T1D is the prevention of cardiovascular complications, a more accurate assessment of CVD risk in people with T1D may greatly aid management decisions in clinic. Individual risk factors are poor predictors of CVD on their own. Statistical models have been calculated to estimate the future risk of CVD in the general population (Framingham and QRISK2) [59,60] and the UKPDS T2D populations [61] to enable better targeting of risk factor reduction interventions. However, their application to T1D cohorts results in a gross underestimation of CVD events [62]. Therefore, known CVD risk factors may have different trajectories of risk or there may be novel factors present specific to T1D [63], and there is currently no CVD risk score to guide intervention and support shared decision-making with people with T1D. Researchers have attempted to develop a CVD risk score unique to T1D but small cohort sizes and time lag to CVD events have been major handicaps. In the Pittsburgh Epidemiology of Diabetes Complications Cohort Study (603 subjects, 46 CVD events), predictors of CVD were only measured at a single time point and there was no relationship to HbA1c [64]. The cohort was mostly white, and may have suffered from ascertainment and survivor bias. The risk score was externally validated using data (only 53 CVD events) from the EURODIAB study. For EURODIAB, the original sample fell by 28% during follow-up, with baseline data showing that those who dropped out had worse diabetes control and greater CVD risk factors [64]. Therefore, a accurate and robust predictive model for CVD risk for individuals with T1D does not currently exist.

Interventions

The American Diabetes Association (ADA) [9,65] and the International Society for Pediatric and Adolescent Diabetes (ISPAD) [66] provide scientific statements with practical guidelines and considerations for clinicians for the treatment of CVD risk factors in individuals with T1D.

• Lipid lowering medication

A meta-analysis in adults with T1D showed that a 1.0 mmol/l (38.7 mg/dl) reduction in LDL-cholesterol was associated with a 21% reduction in major vascular events [67]. The ADA has formulated guidelines for dyslipidemia screening

and treatment in children with T1D, primarily based on expert opinions and data extrapolated from adult studies. The ADA recommends addition of a statin to glycemic control and dietary modification if the child is older than 10 years, has LDL-cholesterol levels >160 mg/dl (4.1 mmol/l) or LDL-cholesterol >130 mg/dl (3.4 mmol/l) together with one or more CVD risk factors [68]. The ISPAD Clinical Practice Consensus Guidelines 2009 recommend statin therapy for LDL-cholesterol >130 mg/dl (3.4 mmol/l) and one or more CVD risk factors, or with lower LDL-cholesterol levels if metabolic control and dietary changes fail to lower to a target of <100 mg/dl (2.6 mmol/l).

Other lipid lowering medications in the young include ezetimibe, bile acid sequestrants (resins), niacins and fibrates. Ezetimibe selectively inhibits intestinal cholesterol absorption and in adults, it has demonstrated effects in lowering LDL-cholesterol levels when combined with statin therapy [69]. At present, a trial of lipid lowering medications to reduce CVD in T1D is being conducted [70]. This trial will compare the use of simvastatin, a statin, to Vytorin® (Merck and Schering-Plough, NJ, USA) a combination of simvastatin and ezetimibe in patients aged 12–21 years with T1D.

• Angiotensin-converting enzyme inhibition

There is good evidence that treatment of hypertension with ACEI in adults with T1D decreases the rate of decline of renal function [71,72]. In addition, ACEI treatment in adults with T1D decreases progression of retinopathy [73] and CVD [74]. The ADA recommend pharmacological treatment with ACEIs in children and adolescents with T1D, when there is confirmed, persistently elevated microalbuminuria, or as soon as the diagnosis of hypertension (defined as systolic or diastolic blood pressure consistently above the 95th percentile for age, sex and height or consistently >130/80 mmHg) is confirmed [75].

Data from >9000 children enrolled in the T1D Exchange Clinic Registry [76] in 2002 showed that hypertension is likely underdiagnosed and undertreated in pediatric patients with T1D. Among those with hypertension, only 52% were receiving treatment with ACEI or Angiotensin Receptor Blocker therapy, suggesting underuse of both medications in the pediatric T1D population. Despite recommendations from the ADA in 2004, more recent data [77] from the T1D Exchange Clinic Registry (2013) showed

no improvement in these figures. 4.4% of the participants had evidence of microalbuminuria or macroalbuminuria and only 36% of these were using a ACEI or angiotensin receptor blocker.

• Lifestyle

Conflicting evidence exists regarding the benefits of physical activity for long-term blood glucose control in adults with T1D. In the EURODIAB Prospective Complications Study, participation in moderate or vigorous physical activity more than once a week was borderline inversely associated with all-cause mortality (HR: 0.7 [95% CI: 0.4–1.0]) and incident CVD (women only) (HR: 0.7 [95% CI: 0.4–1.1]) [78]. In a systematic review, six randomized trials were identified and showed that with an exercise frequency varying from twice weekly to daily, with varying intensities and session durations, four trials reported a decrease in HbA1c (mean difference: -0.8% [95% CI: -1.1 to -0.4]) compared with controls [79]. Exercise training improved cardiorespiratory fitness and one trial reported an effect on insulin dose (mean difference: -0.4 U/kg, [95% CI: -0.5 to -0.3]) compared with controls [79].

In an exploration of diet in young people with T1D, the SEARCH Study found that males had lower consumption of vegetables, fruit and fiber, and higher consumption of soda and saturated fat than females [80]. African-Americans had lower dairy and higher soda intake than non-Hispanic whites. Lifestyle and physical activity patterns were also significantly associated with dietary intake. Dietary approaches targeting CVD risk factors such as hypertension were also reported and shown to improve atherogenic lipid profiles [81]. Specifically higher adherence to these diets was significantly and inversely associated with low-density lipoprotein/high-density lipoprotein ratio, HbA1c and to hypertension, independent of demographic, clinical and behavioral characteristics [82]. High intakes of sugar-sweetened beverages and diets high in eggs, potatoes and high-fat meats was associated with not only an adverse CVD risk profile and but also increased aortic stiffness [83,84]. The authors postulate that these dietary habits may be a marker of unhealthy lifestyle which, in turn, is associated with worse metabolic control and CVD risk profile. These observations suggest that interventions to improve dietary patterns may be beneficial in the prevention and management of CVD risk in these young people.

• Metformin

Metformin has been proposed as a good candidate for early prevention of CVD in children with T1D. It has been prescribed in youth with T2D for over 10 years and reduces CVD in T2D. Although the mechanism of action of metformin has been very difficult to elucidate, one recent study by Madiraju *et al.* [85,86] has added to our understanding. Their results indicate that metformin selectively inhibits glycerophosphate dehydrogenase, an enzyme that catalyzes the conversion of glycerophosphate to dihydroxy acetone phosphate. This inhibition causes a decrease in dihydroxy acetone phosphate, and a rise in the NADH–NAD ratio in the cytosol. This in turn causes inhibition of the conversion of lactate to pyruvate. Gluconeogenesis decreases, and so hepatocytic secretion of glucose also decreases. These mechanisms result in a build-up of glycerol and lactate in the plasma.

One ongoing 12-month-randomized double-blinded controlled trial [87] aims to determine the effects of metformin on vascular health in children aged 8–18 years. Outcome measures include vascular endothelial function, vascular smooth muscle function and vascular structure. Elucidating mechanisms of metformin actions as an antihyperglycemic agent and describing its effects on cardiovascular outcomes could potentially identify an early intervention for CVD in T1D and is an important area for further study.

• Transplantation

In addition to normalizing blood glucose levels in most T1D patients and thereby reducing T1D-related co-morbidities, transplantation has been shown to have beneficial effects on lipid profile and blood pressure [87]. Simultaneous pancreas and kidney transplant is associated with a reduced cardiovascular mortality and incidence of myocardial infarction, improved left ventricular function and cardiac metabolism, reduced incidence of cerebrovascular disease, improvement of carotid atherosclerosis and of peripheral arterial disease.

Clinical challenge

We have attempted to summarize our discussions in **Figure 2**. In the context of silent CVD occurring at a younger age and with greater severity in people with T1D, early attention to modifiable cardiac risk factors is an important aim of management. The importance of the role of early glycemic control in CVD is

unequivocal; however, this needs to be balanced against excessive hypoglycemia secondary to intensive insulin therapy. Even in adults, the role of screening for coronary artery disease and composite assessment of CVD risk in T1D is unclear. The appropriate timing for initiation of risk-modifying therapies such as ACEI and statins are important, as such treatments are generally lifelong. When considering CVD risk, practical considerations are twofold: first, whether to start ACEI and at what age? The decision is straight forward in those with hypertension or microalbuminuria. The issue is more difficult in those who are normotensive and/or normoalbuminuric. Second, whether to start a statin and at what age? This would be justified not just to treat lipid abnormalities but to lower CVD risk. By age 40 years, most patients have initiated statin therapy with plans to continue for greater than 30 years, which goes well beyond experience of statin exposure duration.

For childhood-onset T1D less is known but evidence indicates that risk for CVD may be greater due to earlier pathogenesis. Pediatric diabetes healthcare practitioners need to consider how to ensure adequate assessment of cardiovascular risk factors in young people with T1D. When to intervene to reduce CVD risk is currently unclear and studies such as SEARCH and AddIT will provide a wealth of information on this subject in future years. If absolute CVD risk could be accurately predicted, it could greatly facilitate more effective preventive and treatment strategies by clinicians. Basic and more advanced screening for CVD risk that can be undertaken in young people with T1D during routine clinic appointments are summarized in **Box 1**.

Future perspective

In the next 5–10 years, our knowledge of CVD in T1D will significantly expand following further publications from landmark studies such as SEARCH and AddIT. Clinicians will be better informed on the pathogenesis of disease processes and interventions to alter CVD trajectories in T1D. The challenge for clinicians will be to better judge when to intervene, for example at what age, which parameters to use, the cut-offs (if any) for these parameters and many other factors. For researchers, in addition to developing new biomarkers and therapies, a challenge is to develop better prediction of CVD in a way that can be applied in clinic. Qualitative

Box 1. Screening for cardiovascular disease risk factors in adolescents and young people with Type 1 diabetes during clinic.

Basic

- HbA1c
- Blood pressure – ideally documented as age and sex adjusted standard deviation scores
- Lipids – nonfasting is initially sufficient
- Body mass index standard deviation scores
- Dietary and lifestyle factors

Advanced

- Urine albumin excretion including rate of rise within the normal range
- Frequency and severity of hypoglycemia
- C-peptide secretion

work would aid developing behavioral interventions to change lifestyle and attitudes to CVD by both patient and pediatric healthcare workers. Given the severity of CVD in T1D and evidence indicating that its pathogenesis starts at an early age, an evidence base to start risk factor treatments at initial presentation

with diabetes may need evaluation. Finally, given the link between endogenous insulin production and reduced vascular complications, immune-modulating therapies aimed at preserving beta cell function from diagnosis of T1D may have a beneficial effect on CVD risk in the longer term.

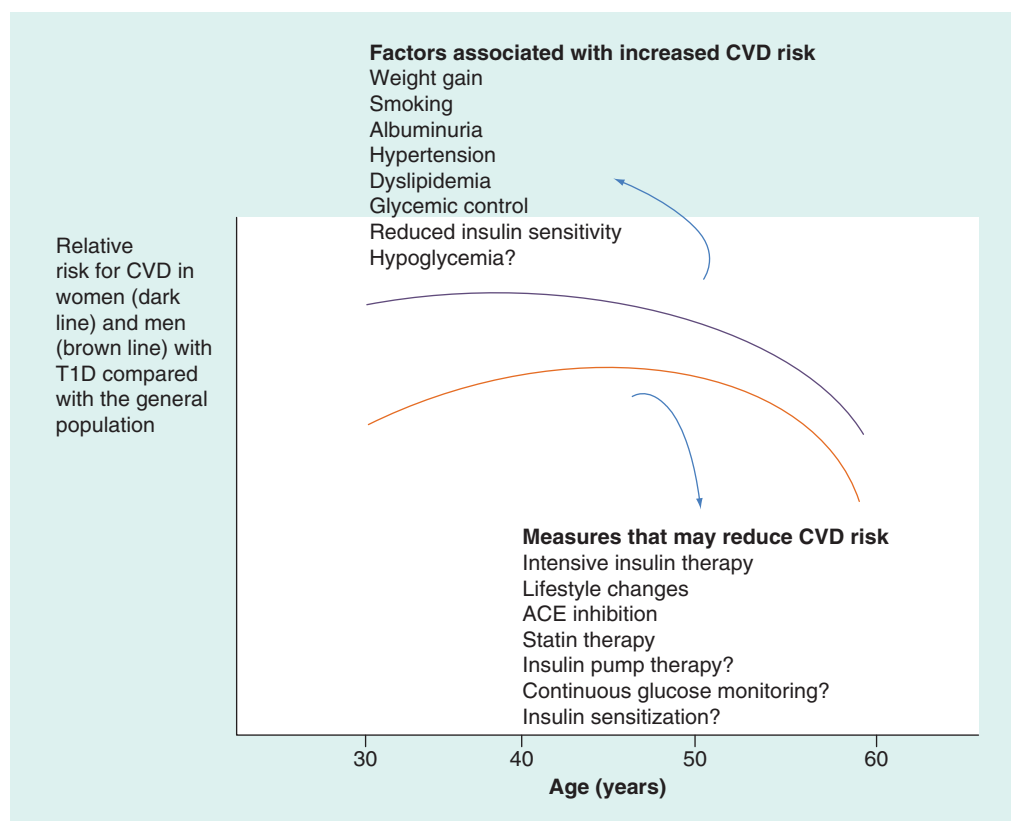


Figure 2. Relative risk for cardiovascular disease in Type 1 diabetes across age with factors associated with increased risk. Relative risk for CVD differs in women compared with men.

Interventions to reduce risk are largely unproven for childhood-onset T1D.

CVD: Cardiovascular disease; T1D: Type 1 diabetes.

For color figures, please see online at www.futuremedicine.com/doi/full/10.2217/DMT.14.61

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References

Papers of special note have been highlighted as:
• of interest

- Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with Type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. *Diabetologia* 49(4), 660–666 (2006).
- Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with Type 1 and Type 2 diabetes in Australia: 1997–2010. *Diabetes Care* 37(9), 2579–2586 (2014).
- This study provides robust epidemiological evidence of mortality and cardiovascular disease (CVD) using novel methods to interpret hospital coding.**
- Krolewski AS, Kosinski EJ, Warram JH *et al.* Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am. J. Cardiol.* 59(8), 750–755 (1987).
- Libby P, Nathan DM, Abraham K *et al.* Report of the National Heart, Lung, and Blood Institute–National Institute of Diabetes and Digestive and Kidney Diseases Working Group on cardiovascular complications of Type 1 diabetes mellitus. *Circulation* 111(25), 3489–3493 (2005).
- The landmark DCCT study describes the beneficial effect of insulin intensification on CVD.**
- Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. *Lancet* 371(9626), 1790–1799 (2008).
- Laing SP, Sverdlow AJ, Slater SD *et al.* Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 46(6), 760–765 (2003).
- National Diabetes Audit. Report 2. Mortality and Complications (2011–2012).
- Patterson CC, Dahlquist G, Harjutsalo V *et al.* Early mortality in EURODIAB population-based cohorts of Type 1 diabetes diagnosed in childhood since 1989. *Diabetologia* 50(12), 2439–2442 (2007).
- De Ferranti SD, De Boer IH, Fonseca V *et al.* Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 37(10), 2843–2863 (2014).
- Livingstone SJ, Looker HC, Hothersall EJ *et al.* Risk of cardiovascular disease and total mortality in adults with Type 1 diabetes: Scottish registry linkage study. *PLoS Med.* 9(10), e1001321 (2012).
- Lind M, Svensson AM, Kosiborod M *et al.* Glycemic control and excess mortality in Type 1 diabetes. *N. Engl. J. Med.* 371(21), 1972–1982 (2014).
- An observational study using national registry data with robust methods that describes excess mortality for CVD in relation to glycemic control.**
- Valsania P, Zarich SW, Kowalchuk GJ, Kosinski E, Warram JH, Krolewski AS. Severity of coronary artery disease in young patients with insulin-dependent diabetes mellitus. *Am. Heart J.* 122(3 Pt 1), 695–700 (1991).
- Pajunen P, Taskinen MR, Nieminen MS, Syvanne M. Angiographic severity and extent of coronary artery disease in patients with Type 1 diabetes mellitus. *Am. J. Cardiol.* 86(10), 1080–1085 (2000).
- Larsen J, Brekke M, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K. Silent coronary atheromatosis in Type 1 diabetic patients and its relation to long-term glycemic control. *Diabetes* 51(8), 2637–2641 (2002).
- Berenson GS, Wattigney WA, Tracy RE *et al.* Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am. J. Cardiol.* 70(9), 851–858 (1992).
- Mcmahan CA, Gidding SS, McGill HC, Jr. Coronary heart disease risk factors and atherosclerosis in young people. *J. Clin. Lipidol.* 2(3), 118–126 (2008).
- Jarvisalo MJ, Jartti L, Nanto-Salonen K *et al.* Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. *Circulation* 104(24), 2943–2947 (2001).
- Provides evidence of early vascular abnormalities in Type 1 diabetes (T1D).**
- Theilade S, Lajer M, Persson F, Joergensen C, Rossing P. Arterial stiffness is associated with cardiovascular, renal, retinal, and autonomic disease in Type 1 diabetes. *Diabetes Care* 36(3), 715–721 (2013).
- Amato M, Montorsi P, Ravani A *et al.* Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. *Eur. Heart J.* 28(17), 2094–2101 (2007).
- Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 115(4), 459–467 (2007).
- Urbina EM, Dabelea D, D'agostino RB, Jr. *et al.* Effect of Type 1 diabetes on carotid structure and function in adolescents and young adults: the SEARCH CVD study. *Diabetes Care* 36(9), 2597–2599 (2013).
- Carotid intima-media thickness (IMT) may be increased in youth with T1D at high risk for cardiovascular disease.**
- Harrington J, Pena AS, Gent R, Hirte C, Couper J. Aortic intima-media thickness is an early marker of atherosclerosis in children with Type 1 diabetes mellitus. *J. Pediatr.* 156(2), 237–241 (2010).
- Rabago Rodriguez R, Gomez-Diaz RA, Tanus Haj J *et al.* Carotid intima-media thickness in pediatric Type 1 diabetic patients. *Diabetes Care* 30(10), 2599–2602 (2007).
- Jarvisalo MJ, Lehtimäki T, Raitakari OT. Determinants of arterial nitrate-mediated dilatation in children: role of oxidized low-density lipoprotein, endothelial function, and carotid intima-media thickness. *Circulation* 109(23), 2885–2889 (2004).
- Urbina EM, Wadwa RP, Davis C *et al.* Prevalence of increased arterial stiffness in children with Type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. *J. Pediatr.* 156(5), 731–737 (2010).
- Jaiswal M, Urbina EM, Wadwa RP *et al.* Reduced heart rate variability is associated with increased arterial stiffness in youth with Type 1 diabetes: the SEARCH CVD study. *Diabetes Care* 36(8), 2351–2358 (2013).

- Carotid IMT may be increased in youth with T1D at high risk for cardiovascular disease.
- 27 Jaiswal M, Fingerlin TE, Urbina EM *et al.* Impact of glycemic control on heart rate variability in youth with Type 1 diabetes: the SEARCH CVD study. *Diabetes Technol. Ther.* 15(12), 977–983 (2013).
- 28 Klein BE, Klein R, McBride PE *et al.* Cardiovascular disease, mortality, and retinal microvascular characteristics in Type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Arch. Intern. Med.* 164(17), 1917–1924 (2004).
- 29 Soedamah-Muthu SS, Chaturvedi N, Toeller M *et al.* Risk factors for coronary heart disease in Type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes Care* 27(2), 530–537 (2004).
- 30 Orchard TJ, Olson JC, Erbey JR *et al.* Insulin resistance-related factors, but not glycemia, predict coronary artery disease in Type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 26(5), 1374–1379 (2003).
- 31 Cleary PA, Orchard TJ, Genuth S *et al.* The effect of intensive glycemic treatment on coronary artery calcification in Type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes* 55(12), 3556–3565 (2006).
- 32 Nathan DM, Lachin J, Cleary P *et al.* Intensive diabetes therapy and carotid intima-media thickness in Type 1 diabetes mellitus. *N. Engl. J. Med.* 348(23), 2294–2303 (2003).
- The landmark DCCT study describes the beneficial effect of insulin intensification on CVD.
- 33 Stettler C, Allemann S, Juni P *et al.* Glycemic control and macrovascular disease in Types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am. Heart J.* 152(1), 27–38 (2006).
- 34 Writing Team for the Diabetes C, Complications Trial/Epidemiology of Diabetes I, Complications Research G. Sustained effect of intensive treatment of Type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290(16), 2159–2167 (2003).
- 35 Nathan DM, Cleary PA, Backlund JY *et al.* Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. *N. Engl. J. Med.* 353(25), 2643–2653 (2005).
- The landmark DCCT study describes the beneficial effect of insulin intensification on CVD.
- 36 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 329(14), 977–986 (1993).
- 37 Marcovecchio ML, Woodside J, Jones T *et al.* Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AddIT): urinary screening and baseline biochemical and cardiovascular assessments. *Diabetes Care* 37(3), 805–813 (2014).
- The details of the AddIT study at baseline.
- 38 Petitti DB, Imperatore G, Palla SL *et al.* Serum lipids and glucose control: the SEARCH for diabetes in Youth study. *Arch. Pediatr. Adolesc. Med.* 161(2), 159–165 (2007).
- 39 Albers JJ, Marcovina SM, Imperatore G *et al.* Prevalence and determinants of elevated apolipoprotein B and dense low-density lipoprotein in youths with Type 1 and Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 93(3), 735–742 (2008).
- 40 Guy J, Ogen L, Wadwa RP *et al.* Lipid and lipoprotein profiles in youth with and without Type 1 diabetes: the SEARCH for diabetes in Youth case-control study. *Diabetes Care* 32(3), 416–420 (2009).
- 41 Maahs DM, Dabelea D, D'agostino RB, Jr. *et al.* Glucose control predicts 2-year change in lipid profile in youth with Type 1 diabetes. *J. Pediatr.* 162(1), 101–107. e101 (2013).
- 42 Rodrigues TC, Veyna AM, Haarhues MD, Kinney GL, Rewers M, Snell-Bergeon JK. Obesity and coronary artery calcium in diabetes: the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. *Diabetes Technol. Ther.* 13(10), 991–996 (2011).
- 43 Rodriguez BL, Dabelea D, Liese AD *et al.* Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: the SEARCH for diabetes in youth study. *J. Pediatr.* 157(2), e245–e251 e241 (2010).
- 44 Maftai O, Pena AS, Sullivan T *et al.* Early atherosclerosis relates to urinary albumin excretion and cardiovascular risk factors in adolescents with Type 1 diabetes: Adolescent Type 1 Diabetes cardio-renal Intervention Trial (AddIT). *Diabetes Care* 37(11), 3069–3075 (2014).
- Early results from the AddIT study showing that early atherosclerosis is associated with increased rate of urine albumin excretion, even when still in the normoalbuminuric range.
- 45 Szadkowska A, Pietrzak I, Mianowska B *et al.* Insulin sensitivity in Type 1 diabetic children and adolescents. *Diabet. Med.* 25(3), 282–288 (2008).
- 46 Pambianco G, Costacou T, Orchard TJ. The prediction of major outcomes of Type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes Care* 30(5), 1248–1254 (2007).
- 47 Makinen VP, Forsblom C, Thorn LM *et al.* Metabolic phenotypes, vascular complications, and premature deaths in a population of 4,197 patients with Type 1 diabetes. *Diabetes* 57(9), 2480–2487 (2008).
- 48 Schauer IE, Snell-Bergeon JK, Bergman BC *et al.* Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without Type 1 diabetes: the CACTI study. *Diabetes* 60(1), 306–314 (2011).
- 49 Liu LL, Lawrence JM, Davis C *et al.* Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for diabetes in Youth study. *Pediatr. Diabetes* 11(1), 4–11 (2010).
- 50 Lawrence JM, Liese AD, Liu L *et al.* Weight-loss practices and weight-related issues among youth with Type 1 or Type 2 diabetes. *Diabetes Care* 31(12), 2251–2257 (2008).
- 51 Mayer-Davis EJ, Ma B, Lawson A *et al.* Cardiovascular disease risk factors in youth with Type 1 and Type 2 diabetes: implications of a factor analysis of clustering. *Metab. Syndr. Relat. Disord.* 7(2), 89–95 (2009).
- 52 Polak JF, Backlund JY, Cleary PA *et al.* Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. *Diabetes* 60(2), 607–613 (2011).
- 53 Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers determined 18 years later in Type 1 diabetes. *Diabetes Care* 33(3), 652–657 (2010).
- 54 Mays D, Streisand R, Walker LR, Prokhorov AV, Tercyak KP. Cigarette smoking among adolescents with Type 1 diabetes: strategies for behavioral prevention and intervention. *J. Diabetes Complications* 26(2), 148–153 (2012).
- 55 Reynolds K, Liese AD, Anderson AM *et al.* Prevalence of tobacco use and association

- between cardiometabolic risk factors and cigarette smoking in youth with Type 1 or Type 2 diabetes mellitus. *J. Pediatr.* 158(4), e594–e601 e591 (2011).
- 56 Pena AS, Couper JJ, Harrington J *et al.* Hypoglycemia, but not glucose variability, relates to vascular function in children with Type 1 diabetes. *Diabetes Technol. Ther.* 14(6), 457–462 (2012).
- 57 Juutilainen A, Lehto S, Ronnema T, Pyorala K, Laakso M. Similarity of the impact of Type 1 and Type 2 diabetes on cardiovascular mortality in middle-aged subjects. *Diabetes Care* 31(4), 714–719 (2008).
- 58 Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). *Am. J. Cardiol.* 59(14), G91–G94 (1987).
- 59 Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ* 341, c6624 (2010).
- 60 Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin. Sci. (Lond.)* 101(6), 671–679 (2001).
- 61 Zgibor JC, Piatt GA, Ruppert K, Orchard TJ, Roberts MS. Deficiencies of cardiovascular risk prediction models for Type 1 diabetes. *Diabetes Care* 29(8), 1860–1865 (2006).
- 62 Ruppert K, Roberts MS, Orchard TJ, Zgibor JC. Cardiovascular disease risk prediction in Type 1 diabetes: accounting for the differences. *Diabetes Res. Clin. Pract.* 78(2), 234–237 (2007).
- 63 Zgibor JC, Ruppert K, Orchard TJ *et al.* Development of a coronary heart disease risk prediction model for Type 1 diabetes: the Pittsburgh CHD in Type 1 Diabetes Risk Model. *Diabetes Res. Clin. Pract.* 88(3), 314–321 (2010).
- 64 Chiang JL, Kirkman MS, Laffel LM, Peters AL; Type 1 Diabetes Sourcebook A. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care* 37(7), 2034–2054 (2014).
- 65 Donaghue KC, Wadwa RP, Dimeglio LA *et al.* Microvascular and macrovascular complications in children and adolescents. *Pediatr. Diabetes* 15(Suppl. 20), 257–269 (2014).
- 66 Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361(9374), 2005–2016 (2003).
- 67 American Diabetes A. Standards of medical care in diabetes 2013. *Diabetes Care* 36(Suppl. 1), S11–S66 (2013).
- 68 Bjornstad P, Wadwa RP. Risks and benefits of statin use in young people with Type 1 diabetes. *Curr. Diab. Rep.* 14(7), 499 (2014).
- 69 Bishop FK, Wadwa RP, Ellis S, Rewers M, Maahs DM. Lessons learned from a lipid lowering trial in adolescents with Type 1 diabetes. *Int. J. Pediatr. Endocrinol.* 2012(1), 24 (2012).
- 70 The Microalbuminuria Captopril Study Group. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. *Diabetologia* 39(5), 587–593 (1996).
- 71 Mathiesen ER, Hommel E, Giese J, Parving HH. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 303(6794), 81–87 (1991).
- 72 Chaturvedi N, Sjolie AK, Stephenson JM *et al.* Effect of lisinopril on progression of retinopathy in normotensive people with Type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. *Lancet* 351(9095), 28–31 (1998).
- 73 Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355(9200), 253–259 (2000).
- 74 Silverstein J, Klingensmith G, Copeland K *et al.* Care of children and adolescents with Type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 28(1), 186–212 (2005).
- 75 Nambam B, Dubose SN, Nathan BM *et al.* Therapeutic inertia: underdiagnosed and undertreated hypertension in children participating in the T1D Exchange Clinic Registry. *Pediatr. Diabetes* doi:10.1111/pedi.12231 (2014) (Epub ahead of print).
- 76 Daniels M, Dubose SN, Maahs DM *et al.* Factors associated with microalbuminuria in 7,549 children and adolescents with Type 1 diabetes in the T1D exchange clinic registry. *Diabetes Care* 36(9), 2639–2645 (2013).
- 77 Tielemans SM, Soedamah-Muthu SS, De Neve M *et al.* Association of physical activity with all-cause mortality and incident and prevalent cardiovascular disease among patients with Type 1 diabetes: the EURODIAB Prospective Complications Study. *Diabetologia* 56(1), 82–91 (2013).
- 78 Yardley JE, Hay J, Abou-Setta AM, Marks SD, Mcgavock J. A systematic review and meta-analysis of exercise interventions in adults with Type 1 diabetes. *Diabetes Res. Clin. Pract.* 106(3), 393–400 (2014).
- 79 Bortsov A, Liese AD, Bell RA *et al.* Correlates of dietary intake in youth with diabetes: results from the SEARCH for diabetes in Youth study. *J. Nutr. Educ. Behav.* 43(2), 123–129 (2011).
- 80 Liese AD, Bortsov A, Gunther AL *et al.* Association of DASH diet with cardiovascular risk factors in youth with diabetes mellitus: the SEARCH for Diabetes in Youth study. *Circulation* 123(13), 1410–1417 (2011).
- 81 Gunther AL, Liese AD, Bell RA *et al.* Association between the dietary approaches to hypertension diet and hypertension in youth with diabetes mellitus. *Hypertension* 53(1), 6–12 (2009).
- 82 Lamichhane AP, Liese AD, Urbina EM *et al.* Associations of dietary intake patterns identified using reduced rank regression with markers of arterial stiffness among youth with Type 1 diabetes. *Eur. J. Clin. Nutr.* 68(12), 1327–1333 (2014).
- **Carotid IMT may be increased in youth with T1D at high risk for cardiovascular disease.**
- 83 Bortsov AV, Liese AD, Bell RA *et al.* Sugar-sweetened and diet beverage consumption is associated with cardiovascular risk factor profile in youth with Type 1 diabetes. *Acta Diabetologica* 48(4), 275–282 (2011).
- 84 Madiraju AK, Erion DM, Rahimi Y *et al.* Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature* 510(7506), 542–546 (2014).
- 85 Ferrannini E. The target of metformin in Type 2 diabetes. *N. Engl. J. Med.* 371(16), 1547–1548 (2014).
- 86 Anderson J, Pena AS, Sullivan T *et al.* Does metformin improve vascular health in children with Type 1 diabetes? Protocol for a one year, double blind, randomised, placebo controlled trial. *BMC Pediatr.* 13, 108 (2013).
- 87 Marchetti P, Occhipinti M, Rondinini L *et al.* Metabolic and cardiovascular effects of beta cell replacement in Type 1 diabetes. *Intern. Emerg. Med.* 8(Suppl. 1), S55–S56 (2013).