

Commentary on risk factors for first and subsequent cardiovascular disease events in type 1 diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study

Type 1 diabetes patients are well known to have a higher cardiovascular disease (CVD) morbidity and mortality. Livingstone *et al.*¹ analyzed the data of 26,026 type 1 diabetes patients in the Scottish nationwide diabetes register during 2005–2007, and found that the contemporary relative risk of coronary heart disease and stroke among type 1 diabetes patients remains exceptionally high when compared with the general population, although the absolute incidence of CVD was lower than previously reported. In East Asia, Lee *et al.*² analyzed the Korean health insurance data, and reported that the incidence of myocardial infarction and the rate of hospitalization for heart failure were even higher than those of type 2 diabetes patients. In the Diabetes Epidemiology Research International Mortality Study, Morimoto *et al.*³ followed 1,324 patients who developed type 1 diabetes before the age of 18 years for 35 years, and found that with increasing age, cardiovascular events became the leading cause of death in type 1 diabetes patients. All these results highlight the importance of reducing the impact of CVD in the management of type 1 diabetes patients.

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study provide

strong evidence for the relationship between blood glucose level and micro- and macrovascular complications in type 1 diabetes patients (Table 1). The DCCT study was a multicenter randomized controlled trial carried out from 1983 to 1989⁴. A total of 1,441 type 1 diabetes patients aged 13–40 years, who were free from hypertension, hypercholesterolemia and severe diabetes-related complications, were randomly assigned to an intensive treatment group (received insulin ≥ 3 times a day, with a blood glucose target as close to the normal range as possible) and a conventional treatment group (only 1 or 2 insulin injections a day to avoid hyperglycemia or hypoglycemia symptoms). The average glycated hemoglobin (A1C) of the intensive treatment group during the trial period was 7.4%, whereas the average A1C of the conventional treatment group was 9.1%.

The trial ended in 1993. Over the 6.5-year follow-up period, intensive treatment significantly reduced the incidence of microvascular complications by 39–76%, as compared with conventional treatment. Because the study had excluded patients with high cardiovascular risks, no significant difference in cardiovascular events incidence was observed between the two treatment groups at study end. Since 1994, 96% of the surviving participants have participated in the EDIC follow-up study. All participants are recommended to receive intensive blood glucose treatment. During the additional follow-up period of 11 years, the average A1C of the two originally assigned

groups was 8.0 and 8.2%, respectively. Besides the urinary albumin : creatinine ratio being higher in the original conventional treatment group, the distribution of other cardiovascular risk factors only slightly differed between the two groups. However, the incidence of all CVD was reduced by 42%, and major adverse cardiovascular events was reduced by 57% in the intensive treatment group compared with the conventional treatment group⁵. Most of the cardiovascular protective effects in the intensive treatment group could be attributed to A1C decline during the DCCT trial. These results suggest that type 1 diabetes patients should receive intensive glycemic control as early as possible, and it might take 10–20 years for cardiovascular protective effects to be manifested.

In a subsequent study that followed these patients for 27 years, the authors reported that as participants age, the number of people who develop hypertension and hyperlipidemia also increases⁶. However, in addition to age, the mean A1C is still the most important cardiovascular risk factor. In a recently published study, Bebu *et al.*⁷ found that blood glucose level is an important risk factor for various individual cardiovascular events other than silent myocardial infarction. The mean A1C is the most significant modifiable risk factor for first cardiovascular events, as well as subsequent cardiovascular events. To summarize, the aforementioned evidence shows that optimal glucose level not only reduces the risk of the first cardiovascular event, but also lowers the risk of

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Table 1 | Comparing three major prospective studies about the relationship between A1c and cardiovascular risk among type 1 diabetes patients

	DCCT/EDIC	Pittsburg EDC	Swedish NDR	
Study design	RCT + post-trial follow up	Prospective cohort study	Prospective cohort study	
Setting	Multicenters	Single center	Swedish population	
<i>n</i>	1,441	658	7,454	33,915
Study period	Trial: 1982–1993 Observational: 1993–2017	Study participants enrollment since 1986–1988	2002–2007	1998–2011
Follow-up duration	Trial: 6.5 years Total follow up: 29 years	25 years	5 years	8 years
Baseline characteristics				
Mean age (years)	27	27	37	36
Women (%)	47	50	44	45
Duration of diabetes (years)	6	19	20	20
Childhood/adolescent onset (%)	13	100	NA	32
Mean BMI	23	24	25	25
Current smoker (%)	19	22	14	14
Mean systolic BP (mmHg)	114	113	125	127
Hypertension or receiving antihypertensives (%)	0	14	24	NA
Hyperlipidemia or receiving lipid-lowering therapy	0	NA	17	NA
Mean HDL-C (mg/dL)	51	534	NA	NA
Mean LDL-C (mg/dL)	110	115	106	103
Mean total cholesterol (mg/dL)	177	190	186	NA
Mean triglycerides (mg/dL)	82	106	97	NA
Mean A1C (%)	9.1	10.4	8.0	8.2
CVD risk factor exclusion at baseline	Yes	No	No	No
Mean urinary albumin excretion rate ($\mu\text{g}/\text{min}$)	16	252	NA	NA
Microalbuminuria (%)	5	22	12	NA
Macroalbuminuria (%)	0	23	7	NA
Cardiovascular mortality rate per 1,000 person-year	0.87	NA	1.07	3.42
Findings	In the earlier report, after an additional 11 years of post-trial observational follow up, intensive treatment reduced the risk of any CVD by 42% and the risk of MACE by 57%. After a median follow up of 29 years, mean A1C was the strongest modifiable risk factor for a first CVD event (adjusted HR 1.38 per 1% higher A1C; MACE: adjusted HR 1.54), and	In the earlier reports, change in A1C had a stronger association with CAD than baseline A1C. After a median follow up of 29 years, most recent A1C was significantly associated with total CVD (adjusted HR 1.10 per 1% higher in A1C) and mean A1C was significantly associated with MACE (adjusted HR 1.18). Compared with findings in DCCT/EDIC, AER predominates in EDC and A1C in DCCT/EDIC. The	Adjusted HRs for fatal/non-fatal CHD per 1% increase in baseline or updated mean A1C were 1.31 and 1.34 and 1.26 and 1.32, respectively, for fatal/non-fatal CVD. HRs were only slightly attenuated after also adjusting for albuminuria. Patients with A1C 5–7.9% (mean 7.2) at baseline showed risk reductions of 41% for fatal/non-fatal CHD and 37% for CVD, compared with patients with A1C 8–11.9% (mean	Adjusted HRs for CV death as compared with patients with A1C $\leq 6.9\%$ were 1.13 for A1C 7.0–7.8%, 1.45 for A1C 7.9–8.7%, 1.68 for A1C 8.8–9.6% and 3.68 for A1C $\geq 9.7\%$. HRs attenuated but remained significant after the adjustment of albuminuria and stage 5 chronic kidney disease. In a separate report, the authors also found that those with younger age at onset of type 1

Table 1 (Continued)

DCCT/EDIC	Pittsburg EDC	Swedish NDR	
for subsequent CVD events (adjusted IR 1.28; MACE: adjusted IR 1.89).	relative impact of A1C and kidney disease varies according to diabetic duration.	9.0%), fully adjusted also for albuminuria.	diabetes had worse survival and poor cardiovascular outcomes, particularly for women.

A1C, glycated hemoglobin; AER, albumin excretion rate; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DCCT/EDIC, The Diabetes Control and Complications Trial/The Epidemiology of Diabetes Interventions and Complications study; EDC, The Epidemiology of Diabetes Complications; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IR incidence ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NDR, National Diabetes Register; RCT, randomized controlled trial.

subsequent cardiovascular events in patients with type 1 diabetes.

In addition to DCCT/EDIC, two other major prospective studies have consistently shown that blood glucose plays an important role in the cardiovascular risk of type 1 diabetes patients (Table 1). The Pittsburgh Epidemiology of Diabetes Complications is a single-center prospective study including type 1 diabetes patients aged <18 years at the Children's Hospital of Pittsburgh during 1950–1980⁸. Patient follow up started in 1986–1988. Although Pittsburgh Epidemiology of Diabetes Complications participants' characteristics (such as the average age, sex, body mass index and A1C) were similar to those of the DCCT/EDIC participants, due to the longer duration of diabetes, some patients had already developed significant proteinuria at the study beginning. The study also did not exclude patients with hypertension and hypercholesterolemia. In the early reports, no significant association was found between baseline A1C and the risk of cardiovascular events. However, in the subsequent study with 16 years of follow up, an increase in A1C was found to be significantly related to the risk of coronary heart diseases. Miller *et al.*⁹ analyzed the data of these patients after 27 years of follow-up, and found that after adjusting for albumin excretion rate, most recent A1C was significantly associated with the incidence of CVD, whereas the mean A1C was significantly associated with major adverse cardiovascular events. A slightly different result from DCCT/EDIC is that Pittsburgh

Epidemiology of Diabetes Complications showed that the albumin excretion rate is more important than A1C, whereas DCCT/EDIC observed A1C is more important than the albumin excretion rate. Taken together, A1C and nephropathy have important yet chronologically different degrees of influence on the incidence of cardiovascular events throughout the disease course of type 1 diabetes.

Another large prospective follow-up study was carried out by analyzing the data from the Swedish National Diabetes Register, which enrolled type 1 diabetes patients aged ≥ 20 years with age of onset <30 years from hospitals and clinics across Sweden. This study included patients with hypertension, hyperlipidemia, and heart and kidney diseases, which were more representative of the patient population in daily clinical care. Eeg-Olofsson *et al.*¹⁰ examined the data from 7,454 type 1 diabetes patients aged 20–65 years (mean 37 years), with a disease duration of 1–35 years (mean 20 years). During the 5-year follow-up period, baseline A1C and mean A1C were significantly associated with both fatal/non-fatal coronary heart disease and fatal/non-fatal CVD. Lind *et al.*¹¹ followed 33,915 type 1 diabetes patients over a period of 8 years, and found a trend of increasing all-cause and cardiovascular mortality with an increase in mean A1C. The risks of death due to all causes and from cardiovascular cause were nearly quadrupled when comparing patients with A1C $\geq 9.7\%$ with $\leq 6.9\%$. The risk estimate is only slightly attenuated after adjusting for proteinuria and

chronic kidney disease, indicating that A1C is an independent risk factor for CVD in type 1 diabetes patients.

Possible explanations for the association between elevated A1C and increased cardiovascular risk include: (i) hyperglycemia itself increases oxidative stress and directly affects vascular endothelial function; (ii) hyperglycemia accelerates atherosclerosis by mediating through other risk factors, such as high blood pressure and high blood cholesterol levels; (iii) hyperglycemia triggers an autoimmune response against myocardial tissue, causing deterioration of cardiac function¹². Meanwhile, although elevated A1C might also be a marker of poor self-care, it is likely that other unhealthy behaviors could also contribute to higher cardiovascular morbidity and mortality.

The following research questions need to be clarified in future studies:

1. In addition to mean A1C, does A1C long-term variability and trajectory have any effect on cardiovascular risk? In the FinnDiane study, Waden *et al.*¹³ found that the standard deviation of serial A1C was independently associated with CVD events, even after adjusting for mean A1C and other risk factors.
2. Does the onset age and sex of type 1 diabetes patients affect the relationship between hyperglycemia and cardiovascular risk? Rawshani *et al.*¹⁴ analyzed data from the Swedish National Diabetes Register, and suggested that early-onset type 1 diabetes patients, especially women, have a

higher risk of mortality and all cardiovascular adverse outcomes, as compared with late-onset type 1 diabetes. In contrast, Costacou *et al.*¹⁵ found that the incidence and mortality of end-stage renal disease in type 1 diabetes patients increases with onset age.

3. Prior studies have shown a linear rather than U-shaped relation between A1C and cardiovascular risk among type 1 diabetes patients, suggesting that the lower the A1C level, the lower the risk. However, strict blood glucose control will increase the risk of hypoglycemia. In fact, hypoglycemia is also a risk factor for cardiovascular-related mortality. How to use cutting-edge technology to assist type 1 diabetes patients to reduce cardiovascular mortality while avoiding hypoglycemia in the real-world setting will become an important task.

In summary, the findings of these studies provide solid evidence to support that type 1 diabetes patients should receive intensive glycemic control to reduce their cardiovascular morbidity and mortality. Healthcare professionals could help individual type 1 diabetes patients strictly control blood glucose while preventing hypoglycemia to improve their quality-of-life and prognoses.

DISCLOSURE

The authors declare no conflict of interest.

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