



Mediation of the Effect of Glycemia on the Risk of CVD Outcomes in Type 1 Diabetes: The DCCT/EDIC Study

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OBJECTIVE

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has demonstrated the major role of hyperglycemia as a risk factor for clinical cardiovascular outcomes in type 1 diabetes (T1D). We assessed whether and to what extent the effect of glycemia is mediated by other established cardiovascular disease (CVD) risk factors.

RESEARCH DESIGN AND METHODS

In the DCCT, 1,441 participants were randomized to receive either intensive or conventional diabetes therapy. The EDIC observational follow-up study enrolled 96% of the surviving DCCT cohort with 94% of the survivors still actively participating after more than 27 years of follow-up. Mediation of the effect of glycemia, as captured by HbA_{1c}, on the subsequent CVD risk was quantified using the relative change in the CVD risk associated with HbA_{1c} between models without and with the potential mediator.

RESULTS

Adjusted for age, only a few factors (e.g., pulse, triglycerides, albumin excretion rate) explained more than 10% of the effect of glycemia on CVD risk when considered individually. In multivariable models, these traditional risk factors together mediated up to ~50% of the effect of glycemia on the risk of CVD. However, the association between HbA_{1c} and the risk of CVD remained highly significant even after adjustment for these risk factors.

CONCLUSIONS

While HbA_{1c} is associated with many traditional CVD risk factors, its association with these factors alone cannot explain its effects on risk of CVD. Consequently, aggressive management of traditional nonglycemic CVD risk factors, coupled with aggressive glycemic management, is indicated for individuals with type 1 diabetes.

Individuals with type 1 diabetes (T1D) are at higher risk of cardiovascular disease (CVD) relative to the general population (1,2). Mechanisms explaining this increased risk are still unclear. While hyperglycemia is a well-established risk factor for microvascular complications in both type 1 (3) and type 2 (4) diabetes, its role in the pathogenesis of macrovascular disease is still under investigation.

In type 2 diabetes (T2D), the association between HbA_{1c} as a marker of long-term glycemia and CVD is weaker than it is for microvascular complications (5), with clinical

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trials designed to improve glycemic control yielding mixed results (6–8). However, such associations are more apparent with longer follow-up (9) and in meta-analyses (10,11).

In T1D, the HbA_{1c} association with CVD was weak and inconsistent in several early observational studies (12,13), but more recent registry data (2,14) have shown a clearer association. The Diabetes Control and Complications Trial and its follow-up study, Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), demonstrated that 6.5 years of intensive diabetes therapy (INT) versus conventional therapy (CON) markedly reduced the risk of CVD over a mean follow-up of 17 years (15). This long-term benefit of initial INT was still apparent, although attenuated, after 30 years of follow-up (16). Furthermore, extensive risk factor models have demonstrated that the mean DCCT/EDIC HbA_{1c} was the second strongest risk factor for CVD (i.e., it had the second-lowest *P* value) after age, even after adjustment for other traditional CVD risk factors (17).

Additional analyses have shown that poor glycemic control is associated with traditional CVD risk factors such as systolic (SBP) and diastolic (DBP) blood pressure, pulse pressure and pulse rate, triglycerides, LDL cholesterol, and HDL cholesterol (18). Therefore, it is important to investigate the potential mediation pathways that might explain the mechanisms relating glycemia and the risk of CVD. More specifically, the goal is to identify risk factors in the causal pathway linking hyperglycemia and the risk of CVD. With >30 years of follow-up and a systematic assessment of potential risk factors for CVD, DCCT/EDIC offers the opportunity to investigate such mediation analyses. Herein, we explore the extent to which the effect of glycemia, as captured by HbA_{1c}, on the risk of CVD is potentially mediated by other traditional CVD risk factors. These analyses build on and expand our recent work, which examined the impact of mediating factors for the effect of glycemia on the risk of subsequent CVD events with increasing diabetes duration (19).

RESEARCH DESIGN AND METHODS

The methods of DCCT and EDIC have previously been described in detail

(17,20,21). Briefly, 1,441 participants with T1D were randomized to receive either INT (*n* = 711), aimed at lowering glycemic levels as close to nondiabetes levels as safely possible, or CON (*n* = 730), aimed at maintaining clinical well-being with no prespecified glucose targets. The DCCT ended in 1993 after an average of 6.5 years of follow-up, and all participants were trained in INT. In 1994, 96% of the surviving DCCT cohort enrolled in the EDIC observational study, and 94% of the survivors are still actively participating in annual visits after >20 years of additional follow-up.

Cardiovascular Risk Factors

The results reported herein are based on data obtained during both DCCT and EDIC, which included detailed physical examinations (e.g., blood pressure and pulse) and the collection of bio-specimens (e.g., blood and urine samples). HbA_{1c} was measured using high-performance liquid chromatography quarterly during DCCT and annually during EDIC. Fasting lipids (triglycerides and total and HDL cholesterol) were measured in the central laboratory using standard methods (20,21,22) annually during DCCT and every other year during EDIC, and LDL cholesterol was calculated using the Friedewald equation.

Cardiovascular Outcomes

Annual medical histories and electrocardiograms were used to ascertain CVD events. All CVD events were adjudicated based on documentation in external medical records by a committee masked to DCCT treatment group and HbA_{1c} levels. The composite CVD outcome was defined as time to the first occurrence of CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, subclinical MI on electrocardiogram, angina confirmed by ischemic changes with exercise tolerance testing, or clinically significant obstruction on coronary angiography, revascularization (with angioplasty or coronary artery bypass), or congestive heart failure (paroxysmal nocturnal dyspnea, orthopnea, or marked limitation of physical activity caused by heart disease) (23). Major atherosclerotic cardiovascular events (MACE) were a secondary CVD outcome, and included CVD death, nonfatal MI, or nonfatal stroke. All CVD events that occurred prior to 31 December 2013 were included in these analyses.

Statistical Analysis

In these analyses, the main exposures of interest were the updated mean HbA_{1c} and the DCCT treatment group (CON vs. INT). The approach is described in terms of HbA_{1c} and similar analyses subsequently were performed comparing DCCT CON vs. INT groups. Cox proportional hazards (PH) models were used to assess the effect of covariates on the risk of developing a CVD event. The PH assumption was tested using weighted residuals (24). As designated in the tables, a risk factor was included in the model as a fixed or baseline covariate, as a time-dependent covariate using the current (most recent) measurement, or as the updated mean of all follow-up values since DCCT randomization up to that particular time point. The updated mean accounts for the different measurement frequencies during DCCT and EDIC by weighting each value by the time interval between measurements. Since age is a strong predictor of CVD events, all models were adjusted for age at DCCT baseline.

The effect of glycemia, as captured by HbA_{1c}, on the risk of CVD was assessed in a Cox PH model with the updated mean HbA_{1c} as a time-dependent covariate. Then, the model was fit with the addition of a potential mediator (e.g., SBP), also as a time-dependent covariate. Mediation through a particular risk factor (e.g., SBP) was concluded if the statistically significant test of the effect of HbA_{1c} on CVD risk in the first model became nonsignificant after adjustment for the potential mediator (e.g., SBP). Partial mediation was assessed using the percent mediation calculated as the relative change in the CVD risk associated with a 1-unit change in HbA_{1c} (e.g., from 7 to 8%) between the unadjusted model and the adjusted model (also called percent change [PC]) (25). Several multivariable models were also considered based on the findings in the univariate models, clinical relevance, and prior literature (1,12–19,26). Similar models assessed mediation of the effect of treatment group on CVD and MACE risk.

RESULTS

The characteristics of the DCCT/EDIC participants have previously been described in detail (16,17). Briefly, at DCCT baseline, the participants had a

median age of 27 years, 53% were male, and 19% were smokers. The median duration of diabetes was ~4 years, and the median HbA_{1c} value was 8.8%.

As of 31 December 2013, after a median follow-up of 27 years, there were 184 subjects who had experienced a CVD event (any-CVD case subjects) and 88 participants who had experienced a MACE event (MACE case subjects).

Supplementary Table 1 presents the mediation effect of each individual covariate on the association of treatment group with any-CVD, and HbA_{1c} with any-CVD, with adjustment only for age at baseline; similar covariate effects on the association for MACE are shown in Supplementary Table 2. Table 1 presents a summary of the salient results for the subset of factors with at least 10% mediation of the HbA_{1c} association with either any-CVD or MACE.

With adjustment only for the effects of age, a 1-unit increase in mean HbA_{1c} was associated with a 50% increased risk of any-CVD (hazard ratio [HR] 1.50 [95% CI 1.327–1.685]; $P < 0.0001$). The HR for mean HbA_{1c} was attenuated (i.e., mediated) by up to ~28% with adjustment for other potential mediating risk factors

one at a time but remained highly significant after separate adjustments for each of the factors ($P < 0.0001$). Adjustment for mean pulse led to a 27% risk reduction, albumin excretion rate (AER) a 23% reduction, mean total cholesterol a 20% reduction, mean LDL cholesterol a 16% reduction, triglycerides a 15% reduction, and SBP a 10% reduction in the HR for mean HbA_{1c} (Table 1 and Fig. 1).

Similarly, mean HbA_{1c} was significantly associated with a 68% increased risk of MACE after adjustment for age alone (HR 1.6774 [95% CI 1.419–1.982]; $P < 0.0001$). Further adjustment for each of the potential mediators attenuated the association between mean HbA_{1c} and MACE, but the association remained highly significant ($P < 0.0001$). Adjustment for the mean pulse reduced the association of glycemia with the risk of MACE by 29%, AER by 24%, triglycerides by 13%, mean total cholesterol by 13%, mean LDL cholesterol by 11%, estimated glomerular filtration rate [eGFR] by 11%, pulse pressure by 10%, and SBP by 10% (Table 1 and Fig. 1).

Table 2 reports the association between the mean HbA_{1c} and the risk of any-CVD and MACE in multivariable

models, which were based on clinical judgment. The mean HbA_{1c} remained significantly associated with the risk of any-CVD and MACE in these multivariable models (Table 2) ($P \leq 0.0035$). The percent reduction of the effect of glycemia, as captured by HbA_{1c}, in these multivariable models compared with a model adjusted only for age ranged from 22% for any-CVD and 16% for MACE with further adjustment for age, family history of MI, mean SBP, triglycerides, mean LDL cholesterol, any use of ACE inhibitors, and duration of T1D ($P < 0.0001$) to 54% reduction for any-CVD and 51% reduction for MACE with further adjustment for age, mean pulse, AER, and mean total cholesterol ($P = 0.0031$). Additional analyses using multivariable models including risk factors showing strong mediation of the effect of glycemia (mean HbA_{1c}) on the risk of any-CVD when considered individually (Table 1) showed similar results (Supplementary Table 3). The percent reduction of the effect of glycemia (HbA_{1c}) in these multivariable models compared with a model adjusted only for age ranged from a 29% reduction for any-CVD and 30% reduction for MACE after adjustment for age, mean pulse,

Table 1—HRs and 95% lower and upper confidence limits for the age-adjusted effect of the mean HbA_{1c} on the risk of any-CVD and MACE

Mediator	Any-CVD					MACE				
	HR	PC	LL	UL	P	HR	PC	LL	UL	P
No mediators	1.495	NA	1.327	1.685	<0.0001	1.677	NA	1.419	1.982	<0.0001
SBP (mmHg)	1.445	-10.07	1.280	1.632	<0.0001	1.608	-10.11	1.359	1.904	<0.0001
Pulse (bpm)	1.434	-12.39	1.267	1.623	<0.0001	1.582	-14.02	1.331	1.881	<0.0001
Mean pulse (bpm)	1.359	-27.54	1.198	1.541	<0.0001	1.482	-28.77	1.243	1.767	<0.0001
Pulse pressure (mmHg)						1.608	-10.22	1.358	1.904	<0.0001
Total cholesterol (mg/dL)	1.430	-13.17	1.265	1.616	<0.0001	1.609	-10.10	1.356	1.908	<0.0001
Mean total cholesterol (mg/dL)	1.395	-20.15	1.232	1.581	<0.0001	1.588	-13.12	1.334	1.890	<0.0001
Triglycerides (mg/dL)*	1.425	-14.26	1.260	1.611	<0.0001	1.591	-12.68	1.339	1.891	<0.0001
Mean triglycerides (mg/dL)*	1.417	-15.86	1.251	1.604	<0.0001	1.584	-13.68	1.331	1.885	<0.0001
Mean LDLc (mg/dL)	1.414	-16.46	1.249	1.600	<0.0001	1.603	-10.91	1.348	1.906	<0.0001
AER (mg/24 h)*	1.383	-22.57	1.216	1.574	<0.0001	1.519	-23.38	1.267	1.820	<0.0001
AER >300 mg/24 h (Y vs. N)	1.446	-10.01	1.277	1.636	<0.0001	1.591	-12.64	1.337	1.894	<0.0001
Any AER >300 mg/24 h (Y vs. N)						1.551	-18.62	1.302	1.847	<0.0001
AER >40 mg/24 h (Y vs. N)	1.432	-12.67	1.262	1.626	<0.0001	1.594	-12.19	1.333	1.906	<0.0001
Any AER >40 mg/24 h (Y vs. N)	1.405	-18.26	1.240	1.591	<0.0001	1.595	-12.12	1.337	1.902	<0.0001
Sustained AER >30 mg/24 h (Y vs. N)	1.445	-10.07	1.272	1.642	<0.0001	1.628	-7.20	1.361	1.948	<0.0001
eGFR (mL/min per 1.73 m ²)						1.604	-10.81	1.353	1.901	<0.0001
eGFR <60 mL/min per 1.73 m ² (Y vs. N)						1.604	-10.78	1.352	1.902	<0.0001

Data are shown first unadjusted (no mediators) and then adjusted for potential mediators one at a time, with the PC (% mediation) of the HbA_{1c} effect. All results are based on Cox models further adjusted for age. A "mean" covariate refers to a time-dependent covariate with value equal to the updated weighted mean of the covariate preceding the time of a CVD or MACE event. Other values are the current or most recent value for the covariate preceding the time of an event. Only factors with a PC (mediation) of at least 10% (in absolute value) for either any-CVD or MACE are shown. Complete results are reported in Supplementary Data. LDLc, LDL cholesterol; LL, lower limit; N, no; UL, upper limit; Y, yes. *Computed on the log scale.

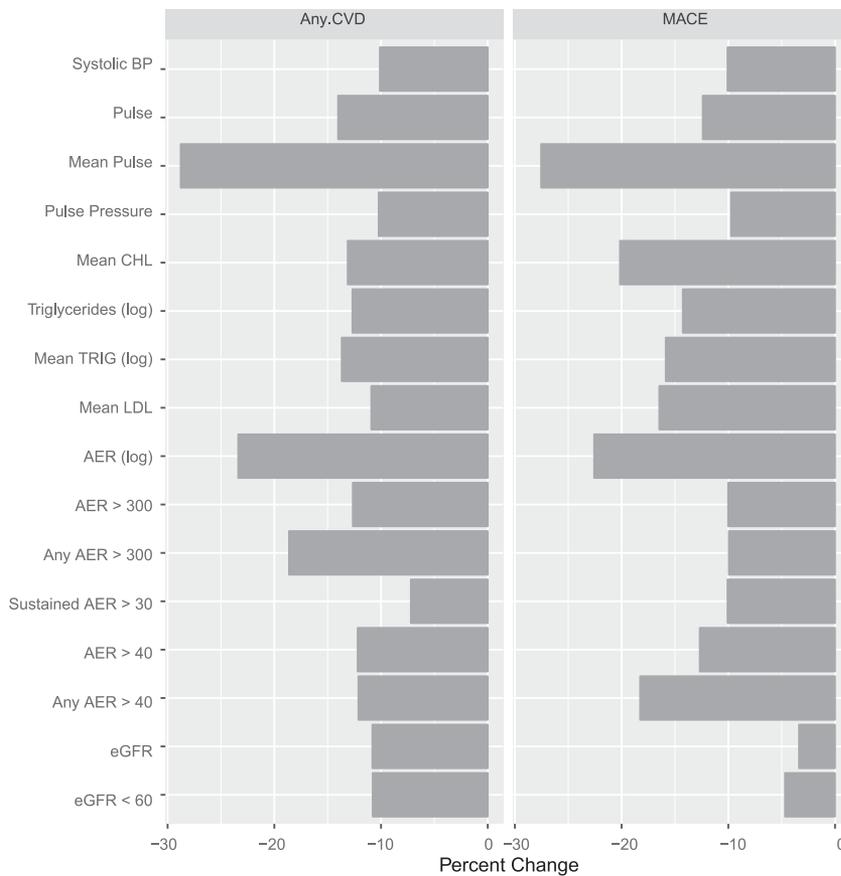


Figure 1—The PC in the risk of any-CVD and MACE associated with a 1% higher mean updated HbA_{1c} after adjustment for each risk factor individually (results based on Cox PH models further adjusted for age). AER presented as mg/24 h. eGFR presented as mL/min per 1.73 m². BP, blood pressure; CHL, total cholesterol; TRIG, triglycerides.

and mean SBP to a 47% and 43% reduction for any-CVD and for MACE, respectively, after adjustment for age, mean pulse, mean SBP, mean total cholesterol, mean LDL cholesterol, (log) mean triglycerides, and (log) AER.

Similar analyses were then conducted to investigate potential mediation pathways for the effect of the initial DCCT treatment group (CON vs. INT) on the risk of any-CVD and MACE (Supplementary Tables 1, 2, and 4). Briefly, the mean updated HbA_{1c}

completely mediated the effect of treatment group, followed by AER with a 36% and 48% reduction in the effect of treatment group on any-CVD and on MACE, respectively.

CONCLUSIONS

Despite progress in diabetes management, individuals with T1D remain at higher risk of CVD compared with the age-matched general population. A comprehensive assessment of the role of long-term hyperglycemia and of the mechanisms relating hyperglycemia to CVD risk is needed to maximize prevention efforts and reduce excess CVD morbidity and early mortality in T1D (27).

We performed a thorough evaluation of potential mediators of the effect of glycemia, as captured by HbA_{1c}, on the risk of CVD in the DCCT/EDIC cohort. With adjustment for age alone, only a few factors (such as pulse, SBP, total cholesterol, LDL cholesterol, triglycerides, and AER) explained >10% of the effect of glycemia on CVD risk when considered individually. In multivariable models, these traditional risk factors together mediated up to ~50% of the effect of glycemia on the risk of CVD. However, it is important to note that the association between HbA_{1c} and the risk of CVD remained highly significant even after adjustment for these risk factors.

Our analyses confirmed well-known CVD risk factors, such as blood pressure, lipids, and AER. For example, it is well documented that hyperglycemia contributes to kidney disease, as manifested by elevated AER values and impaired eGFR

Table 2—HRs and 95% lower and upper confidence limits for the effect of the mean HbA_{1c} on the risk of any-CVD and MACE in multivariable models

Model	Any-CVD					MACE				
	HR	PC (%)	LL	UL	P	HR	PC (%)	LL	UL	P
1: Mean HbA _{1c} and age	1.495	NA	1.327	1.685	<0.0001	1.677	NA	1.419	1.982	<0.0001
2: model 1 plus family history of MI, mean SBP, (log) Trig, mean LDL, any use of ACE inhibitors, and duration of T1D	1.385	-22.32	1.218	1.573	<0.0001	1.568	-16.15	1.311	1.874	<0.0001
3: model 2 plus hypertension, sex, lipid-lowering medication, (log) AER, eGFR, and mean LDLc	1.325	-34.29	1.152	1.524	0.0001	1.516	-23.79	1.243	1.848	<0.0001
4: model 3 plus mean pulse	1.275	-44.33	1.105	1.472	0.0009	1.413	-38.92	1.154	1.731	0.0008
5: model 4 minus hypertension	1.291	-41.24	1.087	1.533	0.0035	1.458	-32.39	1.141	1.862	0.0025
6: mean HbA _{1c} , age, mean pulse, (log) AER, and mean total cholesterol	1.229	-53.72	1.072	1.409	0.0031	1.334	-50.66	1.102	1.615	0.0031

PC data show % mediation of the HbA_{1c} effect relative to model 1. A “mean” covariate refers to a time-dependent covariate with value equal to the updated weighted mean of the covariate preceding the time of a CVD or MACE event. Other values are the current or most recent value for the covariate preceding the time of an event. LDLc, LDL cholesterol; LL, 95% lower limit; PC, percent change in the risk associated with 1% higher mean HbA_{1c} in each model relative to model 1; Trig, triglycerides; UL, 95% upper limit.

levels (28,29), which in turn are associated with left ventricular hypertrophy and arterial calcification (26,30).

In addition to such well-known CVD risk factors, our analyses also identified pulse rate and pulse pressure as potential mediators of the effect of glycemia on the risk of CVD. Higher pulse rate and higher pulse pressure were previously shown to be associated with poor glycemic control in T1D (18) and with higher risk of CVD, both in the general population (31,32) and in individuals with T1D (17). This study cannot provide the mechanisms underlying these relationships, and the exact pathways by which glycemia affects the risk of CVD remain unclear. However, it may be hypothesized that chronic hyperglycemia might induce extensive glycation of vascular mesenchymal tissues leading to arterial stiffness (33), with pulse pressure then acting as a marker of arterial and aortic stiffness and vascular aging as previously suggested in individuals with T1D (34,35). Likewise, chronic hyperglycemia might cause an imbalance between parasympathetic (cholinergic) and sympathetic (adrenergic) components of the autonomic nervous system leading to increased heart rate (cardiac autonomic neuropathy), which in turn may lead to myocardial ischemia resulting from an imbalance between myocardial oxygen demand and supply and possible ventricular arrhythmias (31).

Estimated glucose disposal rate (eGDR) is a measure of insulin sensitivity and defined based on the waist-to-hip ratio, hypertension (yes/no), and HbA_{1c} (36). Since glycemia (as captured by HbA_{1c}) is a complete mediator of the effect of the original DCCT treatment group on CVD, and HbA_{1c} is a component of eGDR, it is not surprising that eGDR is a mediator of the effect of the original DCCT treatment group on CVD. That HbA_{1c} is a component of eGDR likely also explains why eGDR was not a mediator of the effect of glycemia, as captured by HbA_{1c}, on CVD risk. Also note that hypertension, another component of eGDR, was among the DCCT baseline exclusion criteria.

The analyses herein assessed whether the association of HbA_{1c} or the DCCT treatment group assignment with CVD risk can be explained by the association of HbA_{1c} or treatment group with other potential mediating factors in this cohort. While none of the risk factors considered completely mediated the effect of hyperglycemia on the

risk of CVD, this does not mean that other factors do not play a role.

Indeed, we recently developed multivariate regression models (17), which showed that traditional risk factors such as SBP, triglycerides, LDL cholesterol, and pulse, among others, had significant associations with risk of any-CVD and MACE in addition to the associations noted with age and mean HbA_{1c}. We then conducted a detailed assessment of the changes in the mediation patterns for four traditional risk factors (SBP, triglycerides, LDL cholesterol, and pulse) with HbA_{1c} over successive 10-year intervals such as 10–20, 11–21, etc., years of EDIC (19). While the association of HbA_{1c} with CVD outcomes was stable over time, the association of these traditional risk factors increased with time, and the proportion of the effect of glycemia that was mediated by these factors increased with time. For example, the association of HbA_{1c} with CVD risk over 10–20 years of follow-up was minimally mediated by SBP (2.7%), whereas over 20–30 years, 26% of the HbA_{1c} association was mediated by SBP. Similar results were observed for the other three risk factors.

The previous and current analyses demonstrate that over time, the association of mean HbA_{1c} with CVD risk is increasingly mediated by its association with other risk factors. These results emphasize the importance of effective CVD and diabetes-related risk factor management to reduce the occurrence of CVD outcomes in T1D.

While the DCCT was a randomized trial, the follow-up EDIC is an observational study. As with any observational study, one cannot exclude the possibility of unmeasured confounding, and, therefore, the results should be interpreted with care. However, given the large number and the standardized assessment of the risk factors collected in the DCCT/EDIC cohort, and the nearly complete follow-up (with 94% of the surviving cohort still actively participating), we feel confident in our findings.

In conclusion, traditional CVD risk factors (such as SBP, triglycerides, LDL cholesterol, and pulse, among others) and diabetes-related renal risk factors (such as AER and eGFR) are strongly associated with the risk of any-CVD and MACE and are strongly associated with mean HbA_{1c} and the DCCT treatment group assignment. However, these other factors explain only a part of the effect of glycemia on

the risk of any-CVD and MACE, no more than 30% individually or 50% in combination, and the association of HbA_{1c} with CVD risk remains significant. Thus, while HbA_{1c} is associated with many of these other risk factors, its association with one or a collection of these factors alone cannot fully explain its effects on risk of CVD, and controlling the levels of these nonglycemic risk factors may only reduce the effect of glycemia on the risk of CVD by ~50%. These findings suggest that aggressive management of traditional nonglycemic CVD risk factors, coupled with aggressive glycemic management, is indicated for individuals with type 1 diabetes.

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