Insulin Resistance and Risk of Major Vascular Events and All-Cause Mortality in Type 1 Diabetes: A 10-Year Follow-up Study

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In spite of being at target for glucose (1) or traditional cardiovascular (CV) risk factors (2), individuals with type 1 diabetes (T1D) still have an excess of CV mortality and morbidity implying a role for other mechanisms including insulin resistance (IR). Impaired insulin action in T1D was established by clamp technique long ago (3). Estimated glucose disposal rate (eGDR) correlates well with the clamp technique (4) and is a risk marker for microangiopathy (5,6), diabetic kidney disease (DKD) (6), CV risk, and mortality (5,7).

In this observational single-center study, we investigated to what extent eGDR is a predictor of CV events, coronary artery disease (CAD), and all-cause mortality irrespective of CV risk factors and DKD in 774 subjects with T1D over a 10-year follow-up, as previously described (8). eGDR (mg/kg/min) was calculated at baseline as follows (4): $eGDR = 21.158 - (0.09 \times WC) - (3.407 \times HTN) - (0.551 \times HbA_{1c})$, where WC is waist circumference (cm), HTN is hypertension (yes = 1, no = 0), and HbA_{1c} is in %. Follow-up data were retrieved from the national and regional health care registers (ICD-9, Clinical Modification, codes) by searching for CV outcomes (primary outcome) up to 31 December 2017 and for all-cause death up to 31 October 2018. Incidence of CV outcomes was available for 736 participants (95.1%), and vital status was available for all individuals (8). We used univariate and multivariate Cox proportional hazards models to identify key covariates, with impact of eGDR evaluated for each SD. Results are expressed as hazard ratio (HR) and 95% CI. A two-sided *P* value ≤0.05 was considered significant.

At baseline, as previously reported (8), mean ± SD age was 40.2 ± 11.7 years, diabetes duration was 19.4 ± 12.2 years, and HbA_{1c} was 7.8 ± 1.2% (62.1 ± 12.9 mmol/mol); 52.6% were male, and 10.6% had DKD. Mean eGDR was 7.52 ± 2.28 mg/kg/min (median 8.29 mg/kg/min [interquartile range 5.54–9.31]) with bimodal distribution. Overall, the lower the eGDR, the worse the CV risk profile. For proper assessment of the most reliable relationship between eGDR and outcomes, eGDR was included into Cox models as a linear or quadratic term, as both linear and quadratic terms, and as square root. Goodness of fit was evaluated by Akaike information criterion. The best fitting model, the one minimizing Akaike information criterion, was the linear model for all outcomes. The shape of these relationships is reported in Fig. 1.

Rates and incidence density of outcomes are given in the Fig. 1 legend. eGDR was an independent covariate of CV events in all regression models and remained so after adjustment for IR-related variables (models 4 or 5: HDL cholesterol, triacylglycerol, and urinary albumin-to-creatinine ratio [uACR] or DKD), yielding, in model 5, an HR 0.56 (95% CI 0.39–0.80; $P = 0.002$) with independent effects for age, prior CV events, and DKD (Table 1). An independent role of eGDR was confirmed for CAD (HR 0.63, 95% CI 0.42–0.96; $P = 0.033$), with independent effects for the same covariates (Table 1). Finally, eGDR remained independently associated with all-cause mortality after adjustment for several CV risk factors (model 3 HR 0.66, 95% CI 0.48–0.91; $P = 0.011$) but not after further correction for uACR or DKD, HDL cholesterol, and triacylglycerol.

The results of our single-center 10-year observation study show that insulin sensitivity is an independent predictor of major CV events, CAD, and all-cause mortality. Importantly, these associations were maintained after adjustment for multiple confounders including IR-related parameters. A similar association pertains to all-cause death, although it lost significance upon correction for uACR or DKD. Previous cross-sectional studies showed an association of eGDR with retinopathy, DKD, or CV disease (4). Moreover, in the

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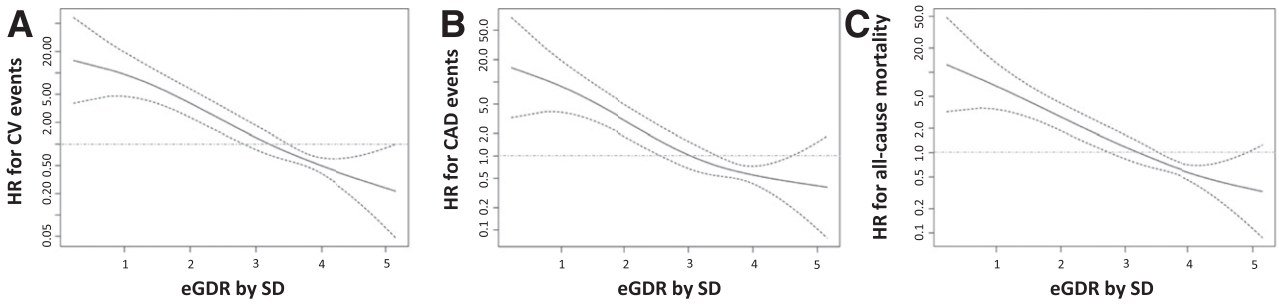

Figure 1—The spline plots display the HR (solid black lines) and 95% CIs (dashed lines) for the association between the baseline eGDR (expressed as SD) and major CV events (panel *A*: 49 events [6.7%], incidence density 6.35 × 1,000 person-years, mean ± SD 10.4 ± 2.9 years of follow-up), CAD (panel *B*: 35 events [4.8%], incidence density 4.50 × 1,000 person-years, 10.5 ± 2.6 years of follow-up), and all-cause mortality (panel *C*: 57 deaths [7.4%], incidence density 6.4 × 1,000 person-years, 11.6 ± 2.6 years of follow-up). The baseline eGDR was modeled using penalized spline in a Cox regression model. The eGDR by SD reference levels were set at their mean, i.e., 3.3 SD, for major CV events, CAD events, and all-cause mortality, respectively, for the estimation of HRs. The gray lines represent an HR of 1.0. *y*-axes were appropriately reported in a log scale.

Table 1—Outcomes analyses by unadjusted and adjusted Cox regression models according to eGDR by SD

	HR (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Model 5
Major CV events					
eGDR, 1 SD	0.36 (0.27–0.48)*	0.45 (0.32–0.62)*	0.53 (0.37–0.75)*	0.57 (0.39–0.82)†	0.56 (0.39–0.80)†
Age, 1 year		1.06 (1.04–1.09)	1.04 (1.01–1.06)	1.04 (1.01–1.06)	1.04 (1.01–1.06)
Sex, male		0.96 (0.55–1.70)	—	—	—
Prior CV disease			3.74 (1.88–7.43)	4.33 (2.16–8.69)	4.64 (2.32–9.28)
Retinopathy					—
No retinopathy			1	1	
Nonadvanced			2.11 (0.90–4.94)	2.08 (0.89–4.87)	
Advanced			3.46 (1.50–7.99)	2.84 (1.19–6.78)	
eGFR (CKD-EPI), mL/min/1.73 m^2			0.99 (0.98–1.01)	1.00 (0.98–1.02)	
uACR, mg/mmol				1.02 (1.01–1.03)	
DKD					3.03 (1.61–5.71)
CAD events					
eGDR, 1 SD	0.40 (0.28–0.56)*	0.49 (0.34–0.72)*	0.57 (0.38–0.86)‡	0.63 (0.41–0.96)§	0.63 (0.42–0.96)§
Age, 1 year		1.06 (1.02–1.09)	1.03 (1.00–1.06)	1.04 (1.01–1.07)	1.03 (1.00–1.06)
Sex, male		1.37 (0.69–2.74)	—	—	—
Prior CV disease			4.26 (1.84–9.85)	6.10 (2.61–14.24)	5.12 (2.21–11.86)
Retinopathy				—	—
No retinopathy			1		
Nonadvanced			1.26 (0.48–3.31)		
Advanced			2.54 (1.01–6.39)		
eGFR (CKD-EPI), mL/min/1.73 m^2			0.99 (0.97–1.01)	1.00 (0.98–1.02)	
uACR, mg/mmol				1.03 (1.02–1.04)	
DKD					3.25 (1.54–6.87)
All-cause mortality					
eGDR, 1 SD	0.44 (0.34–0.56)*	0.61 (0.45–0.82)†	0.66 (0.48–0.91)§	—	—
Age, 1 year		1.07 (1.05–1.10)	1.05 (1.03–1.08)	1.06 (1.04–1.09)	1.07 (1.05–1.09)
Sex, male		1.56 (0.90–2.71)	1.69 (0.96–2.96)	—	—
Active smoking			2.28 (1.22–4.26)	2.07 (1.11–3.86)	1.85 (0.99–3.45)
Retinopathy					
No retinopathy			1	1	1
Nonadvanced			2.21 (1.04–4.66)	2.74 (1.30–5.79)	2.78 (1.32–5.87)
Advanced			2.56 (1.13–5.78)	2.46 (1.07–5.68)	2.62 (1.16–5.93)
eGFR (CKD-EPI), mL/min/1.73 m^2			0.98 (0.96–0.99)	0.99 (0.97–1.00)	
uACR, mg/mmol				1.02 (1.01–1.03)	
Triacylglycerol, mmol/L				1.68 (1.28–2.22)	1.43 (1.08–1.90)
DKD					3.46 (1.86–6.43)

Data are reported only for those variables selected as significant in each model. Major CV events have been defined as first event of myocardial infarction, coronary revascularization, stroke, carotid revascularization, and ulcer, gangrene, amputation, and peripheral revascularization. Coronary artery events have been defined as first event of myocardial infarction or coronary revascularization. DKD has been defined as uACR ≥3.4 mg/mmol or eGFR <60 mL/min/1.73 m^2. Model 1, unadjusted Cox regression; model 2, adjustment for age and sex; model 3, adjustment for age and sex and further for diabetes duration, active smoking, LDL cholesterol, eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]), lipid-lowering drugs, metformin use, total daily dose of insulin, peripheral neuropathy, retinopathy, and prior CV events; model 4, model 3 adjustments plus further adjustment for HDL cholesterol, triacylglycerol, and uACR; model 5, model 4 adjustments with exclusion of uACR and eGFR (Chronic Kidney Disease Epidemiology Collaboration) as continuous variables and inclusion of DKD as categorical covariate. *$P < 0.0001$; †$P < 0.005$; ‡$P < 0.01$; §$P < 0.05$.

Diabetes Control and Complications Trial (DCCT), eGDR was associated with risk of CV disease, although uACR and estimated glomerular filtration rate (eGFR) were not accounted for (5). Similar to our results, in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study cohort, eGDR was a predictor of CAD independent of several confounders, including DKD (9). We now show this is independent of the combination of uACR and eGFR, or DKD. At variance, in the Pittsburgh EDC Study, eGDR was an independent predictor for mortality (10). Finally, in 17,050 Swedish individuals with T1D the steep increase in all-cause mortality associated with eGDR reduction persisted after adjustment for several covariates (7).

Our study relies on robust national and regional registries and on availability of survival information for the entire cohort and prospective CV data for virtually all subjects. Nonetheless, the number of events is relatively small, limiting the confidence for some estimates, and data on CV death could not be retrieved.

In conclusion, our study suggests that eGDR, estimated by handy clinical parameters, could improve risk stratification beyond traditional CV risk factors.

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Author Contributions. M.G., S.D.P., and G.P. designed the study, drafted the manuscript, approved the final version, and made the decision to submit and publish the manuscript. M.G., M.G.S., D.L., R.M., and G.P. contributed to analysis and interpretation of data, revised the article's intellectual content, and approved the final version. M.G., E.G., C.B., M.A., F.C., G.D., and P.F. acquired data, revised the article's intellectual content, and approved the final version. S.D.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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