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ORIGINAL RESEARCH

Carotid-Femoral Pulse Wave Velocity as a Risk Marker for Development of Complications in Type 1 Diabetes Mellitus

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BACKGROUND: The value of carotid-femoral pulse wave velocity (cfPWV) as risk factor for development of complications in type 1 diabetes mellitus remains to be determined. We investigated associations between cfPWV and renal outcomes, cardiovascular events, and all-cause mortality in people with type 1 diabetes mellitus.

METHODS AND RESULTS: cfPWV was measured with SphygmoCor in 633 people with type 1 diabetes mellitus. Median (interquartile range) follow-up was 6.2 (5.8–6.7) years. End points included progression in albuminuria group, decline in estimated glomerular filtration rate (eGFR) ≥30%, end-stage kidney disease, cardiovascular event, mortality, and a composite renal end point. Hazard ratios (HRs) were calculated per 1-SD increase in cfPWV. Adjustments included age, sex, hemoglobin A1c, mean arterial pressure, body mass index, low-density lipoprotein cholesterol, smoking, urine albumin excretion rate, and eGFR. The cohort included 45% women, mean (SD) age was 54 (13) years, mean (SD) eGFR was 83.2 (27.9) mL/min per 1.73 m^2, and mean (SD) cfPWV was 10.4 (3.3) m/s. Median (interquartile range) albumin excretion rate was 17 (17-63) mg/24 h. After adjustment, higher cfPWV was associated with increased hazard of progression in albuminuria (HR, 1.59; 95% CI, 1.10–2.32); decline in eGFR ≥30% (HR, 1.38; 95% CI, 1.06–1.79); cardiovascular event (HR, 1.31; 95% CI, 1.01–1.70); mortality (HR, 1.36; 95% CI, 1.00–1.85); and the composite renal end point (HR, 1.30; 95% CI, 1.04–1.63), but not with end-stage kidney disease (HR, 1.18; 95% CI, 0.62–2.26). Higher cfPWV was associated with steeper yearly increase in albumin excretion and steeper yearly decline in eGFR after adjustment (P=0.002 and P=0.01, respectively).

CONCLUSIONS: cfPWV was associated with increased hazard of renal outcomes, cardiovascular event, and mortality. cfPWV may be suited for risk stratification in type 1 diabetes mellitus.

Key Words: arterial stiffness ■ carotid-femoral pulse wave velocity ■ diabetic complications ■ type 1 diabetes mellitus

Life expectancy for people with type 1 diabetes mellitus (T1D) is on average 16 years shorter than in the general population,[1] and the leading causes of death include cardiovascular disease (CVD) and end-stage kidney disease (ESKD).[2,3] Despite significant risk reductions over the past years, people with T1D are still at increased risk of death, cardiovascular events (CVEs), and renal events, compared with the general population.[4–6] This fact stresses the importance of implementing new clinical risk markers to improve risk assessment and thereby timely intervention, aiming at preventing complications, morbidity, and mortality in T1D.

Large artery stiffness is an important factor in the pathogenesis of hypertension, and increased carotid-femoral pulse wave velocity (cfPWV) is an established risk factor for mortality and CVD in various populations.[7] Cross-sectional data have demonstrated that people with T1D have higher cfPWV than healthy individuals, but the value of arterial stiffness

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CLINICAL PERSPECTIVE

What Is New?

- In this cohort study, we demonstrate an association between arterial stiffness, measured by carotid-femoral pulse wave velocity, and development of complications, including albuminuria progression, decline in estimated glomerular filtration rate, a composite renal outcome, cardiovascular events, and mortality, in a population of people with type 1 diabetes mellitus.

What Are the Clinical Implications?

- The results from our study add knowledge to the search for new markers to improve risk stratification of people with type 1 diabetes mellitus at high risk of developing diabetic complications, aiming at initiating early treatment and thus prevention of diabetic complications.
- As carotid-femoral pulse wave velocity is independently associated with complications in type 1 diabetes mellitus, reduction of arterial stiffness is a potential target for preventing adverse renal and cardiovascular events.

Nonstandard Abbreviations and Acronyms

cfPWV	Carotid-femoral pulse wave velocity
CVE	cardiovascular event
ESKD	end-stage kidney disease
HbA1c	hemoglobin A1c
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
UACR	urinary albumin-creatinine ratio
UAER	urinary albumin excretion rate

assessment in longitudinal studies is still unresolved in T1D.[8]

Assessment of arterial stiffness can be achieved by calculation of pulse wave velocity (PWV) based on transcutaneous pulse wave measurements. cfPWV is considered the gold standard[9,10] and has demonstrated predictive value of mortality and CVEs.[7,11,12] The prognostic value of cfPWV is independent of known cardiovascular risk factors, but differs between populations, with higher values in people with baseline cardiovascular risk compared with the healthy population.[7,11,13,14] As prospective data are lacking for people with T1D, we aimed to evaluate its value as a risk marker and determine the association between cfPWV and risk of all-cause mortality, CVE, progression in albuminuria status, decline in kidney function, ESKD, and a composite renal end point in a large cohort of people with T1D.

METHODS

Participants

A cohort of 633 adults with T1D were recruited between 2009 and 2011 from the outpatient clinic at Steno Diabetes Center (Copenhagen, Denmark). The cohort has been described previously.[15] ESKD was an exclusion criterion and was defined as estimated glomerular filtration rate (eGFR)/glomerular filtration rate <15 mL/min per 1.73 m^2 or receiving dialysis or previous renal transplantation. All participants gave written informed consent, and the study was approved by the regional ethics committee (ClinicalTrials.gov ID NCT01171248). The data that support the findings of this study are available from the corresponding author on reasonable request.

Baseline Measurements

Arterial stiffness was measured as cfPWV by a tonometry-based technique using the SphygmoCor device (AtCor Medical, Sydney, Australia). cfPWV was calculated as the difference in transit time of the pulse wave between the 2 recording points and the heart, divided by the travel distance. The travel distance was measured by a measuring tape between the 2 measuring points and the suprasternal notch. The distance from the carotid location to the suprasternal notch was subtracted from the distance between the suprasternal notch and the femoral site of recording. Three cfPWV measurements were recorded, and the 2 closest to each other were averaged and used in the analyses.

Data on covariables at baseline included low-density lipoprotein cholesterol, hemoglobin A1c (HbA_{1c}), eGFR, current daily smoking, mean arterial pressure, and albuminuria status. HbA_{1c} was measured by high-performance liquid chromatography (Bio-Rad Laboratories, Munich, Germany). The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[16] Brachial blood pressure was measured at the time of cfPWV measurement. Mean arterial pressure was calculated as diastolic blood pressure plus one third of pulse pressure. Current daily smoking was assessed by a standardized questionnaire and was defined as smoking ≥1 cigarettes, cigars, or pipes per day. Urinary albumin excretion rate (UAER) was determined in three 24-hour urine collections at baseline by enzyme immunoassay (Vitros, Raritan, NJ). The 2 measurements

closest to each other were averaged and used in the analyses. The baseline classification of albuminuria status is based on historical values of albumin excretion measured as UAER or urinary albumin-creatinine ratio (UACR), which were considered comparable measures and were pooled as a composite variable of albumin excretion.[17] At baseline, the participants were classified into albuminuria groups based on historical values of albumin excretion from the medical records and the 3 baseline measurements of UAER: Macroalbuminuria was defined as 2 of 3 consecutive measurements of UAER ≥300 mg/24 h or UACR ≥300 mg/g. Otherwise, if 2 of 3 consecutive measurements were 30 to 299 mg/24 h for UAER or 30 to 299 mg/g for UACR, the participant was classified as microalbuminuric. Participants who never had 2 of 3 consecutive measurements of UAER >30 mg/24 h or UACR >30 mg/g were classified as normoalbuminuric. Previous CVD included history of myocardial infarction, coronary intervention, stroke, or peripheral arterial disease based on standardized World Health Organization questionnaires and patient records.[18]

Follow-Up and Outcomes

End points were collected through national registers and patient electronic health records until December 31, 2016.[18,19] Information on cause of death was available until December 31, 2015. Outcome data were available for all participants, and the median (interquartile range [IQR]) follow-up time was 6.2 (5.8–6.7) years. The composite end point of CVE comprised cardiovascular death, nonfatal myocardial infarction (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes I21–I24), nonfatal stroke (*ICD-10* codes I61–I66), coronary interventions (procedural codes KFNA-D), or peripheral arterial interventions, including amputations, in accordance with previous studies.[20] Cardiovascular death included acute myocardial infarction, ischemic heart disease, stroke, or heart failure as primary cause of death as coded in the Danish Cause of Death register. Furthermore, deaths were classified as cardiovascular unless any other cause was determined (relevant for 3 people). This is a recognized approach.[21] The composite end point of renal events comprised decline in eGFR ≥30%, development of ESKD (definition below), and all-cause mortality, as recently suggested.[22] The other end points were as follows: (1) progression from normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria; (2) decline in eGFR of minimum 30% from baseline; (3) ESKD (defined as chronic kidney disease [CKD] stage 5 (*ICD-10* code N18.5), chronic dialysis (procedural code BJFD2), kidney transplantation (procedural code KKAS 00, 10, and 20), or eGFR <15 mL/min per 1.73 m^2; and (4) all-cause mortality. Data on eGFR and albumin excretion (UACR/UAER) during follow-up were obtained from laboratory records. Progression from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria was defined as progression in classification based on 2 of 3 consecutive urine collections. Decline in eGFR was assessed as time to the first occurrence of ≥30% decrease from baseline.[23] Yearly change in albumin excretion and eGFR was calculated on the basis of all available measurements from outpatient visits during follow-up, in participants with at least 2 measurements of eGFR and albumin excretion, respectively, and a minimum follow-up time of 3 years. Yearly change in albumin excretion and eGFR was calculated for a median of 6.0 (IQR, 5.5–6.4) and 5.6 (IQR, 5.0–6.2) years and for 489 and 491 people, respectively.

Data on hospital admissions, *ICD-10* diagnoses, cause of death, and the respective dates for the events were drawn from the Danish Register of Causes of Death and the Danish National Patient Register. As data were collected from registers, there was no adjudication of events. Cause of death was undefined for 3 participants, and we classified these as cardiovascular.

Statistical Analysis

The distribution of the albumin excretion was skewed, and the variable was log transformed for analyses and presented as median and IQR. The other continuous variables are given as mean with SD, and categorical variables are given as percentages. Baseline characteristics were compared across quartiles of cfPWV using analysis of covariance for continuous variables and χ^2 test for categorical variables. In the follow-up analyses, a Kaplan-Meier curve depicts the survival curve for all-cause mortality. The Aalen-Johansen estimator illustrates the cumulative incidence of each other end point accounting for mortality as a competing risk.[24,25] Estimated hazard ratios (HRs) with 95% CIs by Cox proportional cause-specific hazard models for all end points were calculated per 1-SD (3.3 m/s) increase in cfPWV. Censoring was made for emigration, for death in the analysis of nonmortality end points, or by end of follow-up. Cox model assumption for proportional hazards was tested using cumulative sums of martingale residuals and was fulfilled for all outcomes. Adjustment included the clinically relevant parameters sex, age, mean arterial pressure, body mass index, low-density lipoprotein cholesterol, current daily smoking, HbA_{1c}, UAER, and eGFR at baseline. In the supplementary analyses, we

performed additional adjustment for previous CVD and separate analyses where the participants with preexisting CVD were excluded. These supplementary analyses were made for outcomes that included CVE and death (all-cause mortality, CVE, and the composite renal end point). As another set of supplementary analyses, we restricted our analyses to 419 patients treated with renin-angiotensin-aldosterone system (RAAS) blockade. To illustrate the linear shape of the associations, we performed smoothing splines in the Cox models with 4 degrees of freedom, depicting log HR for cfPWV as a continuous variable with mean cfPWV (10.4 m/s) as reference. A general linear model was applied for calculation of individual UAER/UACR and eGFR slopes (yearly change). For the analyses of change in UAER/UACR and eGFR, we applied unadjusted and adjusted linear regression models and calculated the β estimates per 1-SD increase in cfPWV. A prespecified statistical analysis plan describing all the end points was made before testing, and all analyses were presented; therefore, we did not correct for multiple testing. A 2-tailed α level of <0.05 was considered statistically significant. Analyses were performed using SAS software (v.7.1; SAS Institute, Cary, NC) and R software (version 3.6.0; 2019-04-26; The R Foundation for Statistical Computing; and RStudio; version 1.2.5001; 2019 RStudio, Inc).

RESULTS

Baseline Characteristics

In the cohort of 633 participants (45% women; 66% were treated with RAAS blocking agents); mean (SD) age was 54 (13) years, mean (SD) eGFR was 83.2 (27.9) mL/min per 1.73 m^2, and mean (SD) cfPWV was 10.4 (3.3) m/s. Median (IQR) albumin excretion rate is 17 (8-63) mg/24 h. Baseline characteristics across quartiles of cfPWV are shown in Table 1. Participants in the highest quartiles of cfPWV were older, had longer diabetes mellitus duration, had more frequently known CVD, had higher UAER and mean arterial pressure, and had lower eGFR (all $P<0.001$). Highest percentage of active smokers were found in quartiles 2 and 3. The distribution of sex, HbA_{1c}, and low-density lipoprotein cholesterol was comparable across quartiles. The proportion of people receiving antihypertensive, RAAS blockade, or statin treatment increased by the quartiles.

Follow-Up

During follow-up, 34 participants (5%) progressed to a higher albuminuria status, 90 (14%) had a decline in eGFR of ≥30%, 19 (3%) developed ESKD, 81 (13%) experienced a CVE, 48 (8%) died, and 112 (18%) experienced the composite renal end point of decline in eGFR, ESKD, or mortality. Kaplan-Meier

Table 1. Baseline Characteristics Across Quartiles of cfPWV

Characteristic	cfPWV in Quartiles			
	1	2	3	4
Range, m/s	<7.8	≥7.8 to <9.8	≥9.8 to <12.3	≥12.3
No. of participants	146	170	155	162
Men, %	51	52	52	64
Age, y	42 (13)	52 (9)	58 (9)	64 (9)
Diabetes mellitus duration, y	20 (15)	29 (13)	35 (13)	44 (12)
Known cardiovascular disease, %	5	14	27	30
Body mass index, kg/m^2	25.1 (9.5)	25.3 (4.3)	25.0 (4.1)	26.0 (4.0)
Active smokers, %	18	23	26	15
HbA_{1c}, mmol/mol	62 (14)	64 (12)	66 (13)	64 (11)
HbA_{1c}, %	7.9 (1.3)	8.0 (1.1)	8.2 (1.2)	8.0 (1.0)
UAER, mg/24 h	11 (7-19)	12 (7-35)	25 (10-91)	34 (11- 129)
eGFR, mL/min per 1.73 m^2	96 (26)	87 (25)	79 (28)	72 (27)
Systolic blood pressure, mm Hg	122 (12)	126 (14)	135 (16)	144 (19)
Diastolic blood pressure, mm Hg	73 (8)	76 (10)	74 (9)	74 (9)
Mean arterial pressure, mm Hg	89 (8)	93 (10)	94 (10)	97 (11)
LDL cholesterol, mmol/L	2.5 (0.7)	2.5 (0.8)	2.4 (0.7)	2.4 (0.7)
Antihypertensive treatment, %	42	66	82	91
RAAS blockade, %	39	61	76	87
Statin treatment, %	33	59	70	73

Data are shown as percentage, mean (SD), or median (interquartile range). cfPWV indicates carotid-femoral pulse wave velocity; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A1c; LDL, low-density lipoprotein; RAAS, renin-angiotensin-blocking system; and UAER, urinary albumin excretion rate.

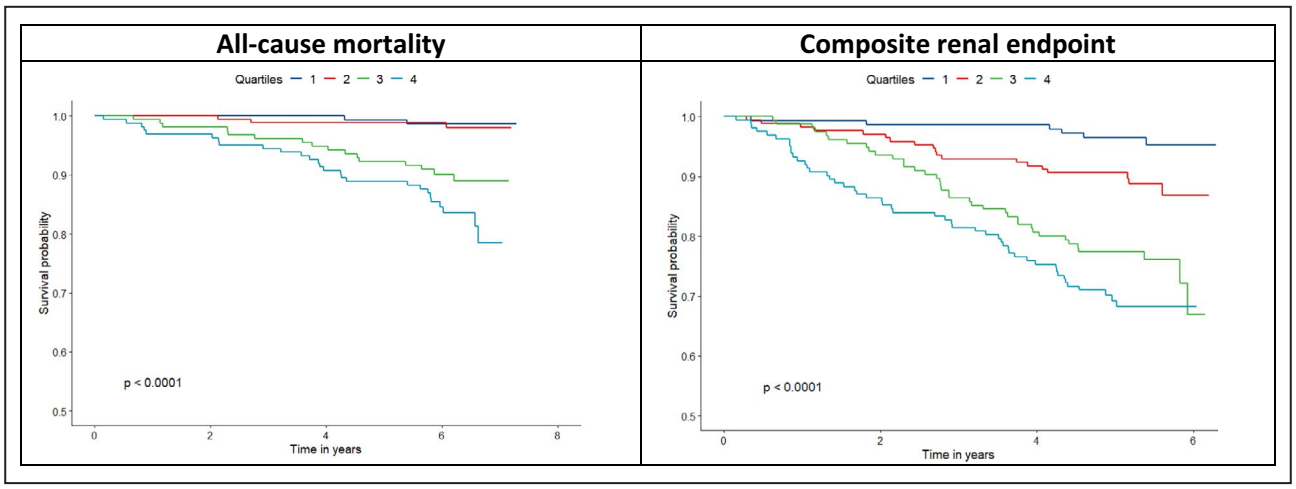

Figure 1. Kaplan-Meier survival plots for all-cause mortality and for the composite renal end point in quartiles of carotid-femoral pulse wave velocity.

plots illustrate the probability of all-cause mortality and the composite renal end point in the quartiles (Figure 1). The log-rank tests were highly significant (P<0.0001), and the graphs illustrate a trend for higher mortality and higher probability of the composite renal end point by increasing cfPWV quartile. Risks of the other end points are illustrated as cumulative incidence curves for the quartiles, and the risks in the quartiles were significantly different, tested with the Gray method (Figure 2). The plots demonstrate an increased probability of renal events and CVEs by increasing cfPWV quartile even after the

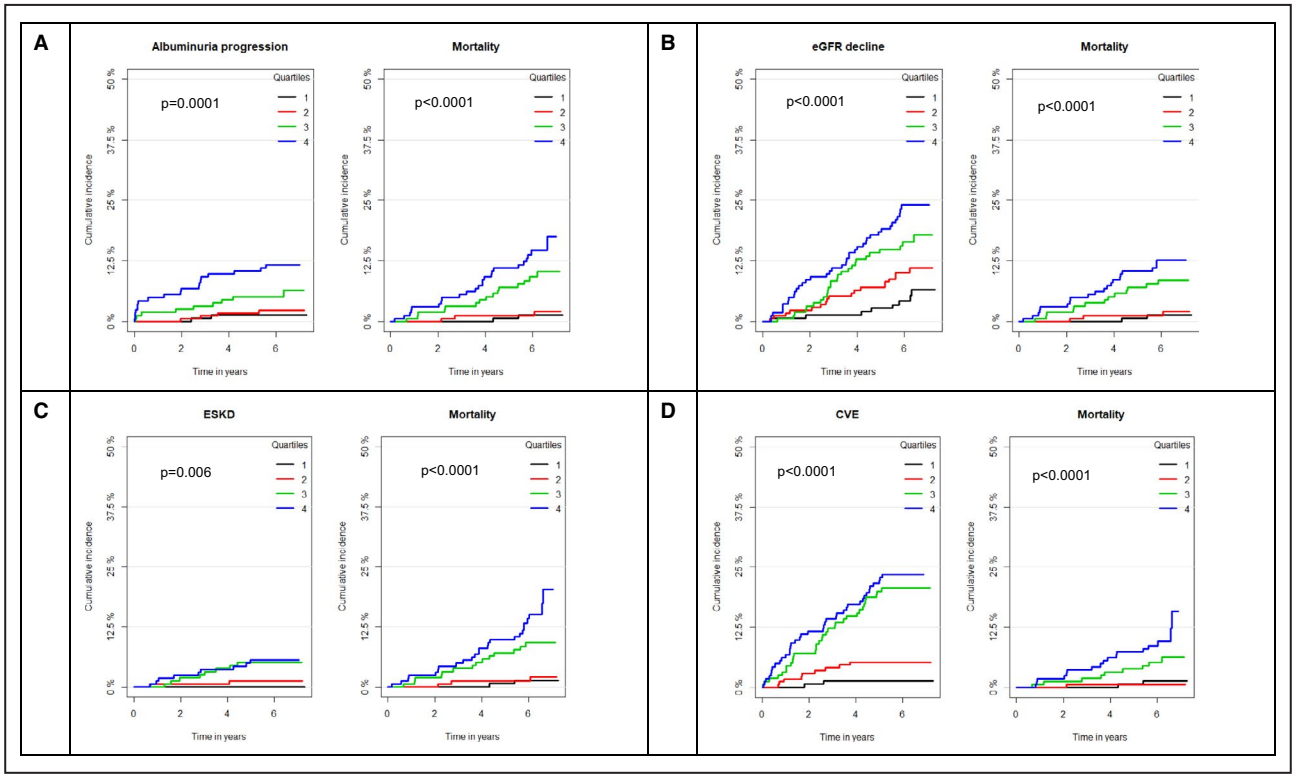

Figure 2. Cumulative incidences of cardiovascular and renal outcomes with mortality as competing risk in quartiles of carotid-femoral pulse wave velocity calculated with the Aalen-Johansen estimator.
A, Cumulative incidence of progression in albuminuria group and all-cause mortality. **B**, Cumulative incidence of estimated glomerular filtration rate (eGFR) decline and all-cause mortality. **C**, Cumulative incidence of end-stage kidney disease (ESKD) and all-cause mortality. **D**, Cumulative incidence of cardiovascular events (CVEs) and death of other causes.

competing risk of mortality is considered. After adjustment, higher cfPWV was significantly associated with progression in albuminuria (HR, 1.59; 95% CI, 1.10–2.32), decline in eGFR ≥30% (HR, 1.38; 95% CI, 1.06–1.79), CVE (HR, 1.31; 95% CI, 1.01–1.70), all-cause mortality (HR, 1.36; 95% CI, 1.00–1.85), and the composite renal end point (HR, 1.30; 95% CI, 1.04–1.63) (Table 2). cfPWV was associated with ESKD in the unadjusted model, but not after adjustment (HR, 1.18; 95% CI, 0.62–2.26). The smoothing splines confirmed that the associations could be considered linear (Figure S1). The mean (SD) yearly change in albumin excretion was −2% (20%), and the mean (SD) yearly change in eGFR was −0.9 (0.1) mL/min per 1.73 m^2. In the regression model with yearly change in UACR and eGFR during follow-up, higher cfPWV was associated with a slower yearly decrease in albumin excretion (P=0.002) or a steeper yearly increase in albumin excretion and decline in eGFR after adjustment (P=0.002 and P=0.01, respectively) (Table 3).

Supplementary Analyses

In supplementary analyses of CVE, all-cause mortality, and the composite renal end point, including additional adjustment for previous CVD, the significance of the association disappeared for CVE (HR, 1.24; 95% CI, 0.96–1.61) and mortality (HR, 1.30; 95% CI, 0.96–1.78) but not for the composite renal end point (HR, 1.27; 95% CI, 1.01–1.59). In the analyses excluding the 123 people with preexisting CVD, the estimates did not change substantially (CVE [n=35]: HR, [95% CI]: 1.47 [1.00–2.18]; mortality [n=22]: HR [95% CI]: 1.28 [0.79–2.09]; and the composite renal end point [n=64]: HR [95% CI]: 1.25 [0.91–1.72]), although the significance disappeared, probably because of loss of power. Supplementary analyses restricted to the participants prescribed RAAS-blocking treatment demonstrated only slightly changed

Table 3. Associations Between cfPWV and Yearly Change in UAER and eGFR

	Difference in Yearly Change in Albumin Excretion (Relative)		Difference in Yearly Change in eGFR (mL/min per 1.73 m^2)	
	(n=489)		(n=491)	
Variable	β (SE)	*P* Value	β (SE)	*P* Value
Unadjusted	0.04 (0.01)	<0.0001	−0.34 (0.11)	0.002
Adjusted	0.02 (0.01)	0.002	−0.37 (0.16)	0.01

The β estimates represent the effect of 1-SD increase in cfPWV (3.3 m/s) on yearly change of UAER/urine albumin creatinine ratio and eGFR. Adjustment included sex, age, mean arterial pressure, body mass index, low-density lipoprotein cholesterol, smoking, hemoglobin A1c, UAER, and eGFR at baseline. cfPWV indicates carotid-femoral pulse wave velocity; eGFR, estimated glomerular filtration rate; and UAER, urinary albumin excretion rate.

Table 2. HRs for Progression in Albuminuria Group, Decline in eGFR ≥30%, ESKD, CVEs, Mortality, and Renal Outcomes in Relation to cfPWV

	Progression in Albuminuria Group		Decline in eGFR ≥30%		ESKD		CVE		All-Cause Mortality		Composite Renal End Point	
	(n=34)		(n=90)		(n=19)		(n=81)		(n=48)		(n=112)	
Events	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted	1.88 (1.46–2.43)	<0.0001	1.56 (1.32–1.84)	<0.0001	1.57 (1.10–2.26)	0.01	1.74 (1.47–2.10)	<0.0001	1.95 (1.57–2.42)	<0.0001	1.62 (1.40–1.88)	<0.0001
Adjusted	1.59 (1.10–2.32)	0.02	1.38 (1.06–1.79)	0.02	1.18 (0.62–2.26)	0.6	1.31 (1.01–1.70)	0.04	1.36 (1.00–1.85)	0.05	1.30 (1.04–1.63)	0.02

Values are HRs (95% CIs) related to 1-SD increase in cfPWV (3.3 m/s). Adjustment included age, sex, hemoglobin A1c, mean arterial pressure, body mass index, low-density lipoprotein cholesterol, smoking, urine albumin excretion rate, and eGFR. ESKD was defined as chronic kidney disease stage 5, chronic dialysis, kidney transplantation, or eGFR <15 mL/min per 1.73 m^2. The composite cardiovascular end point comprised cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary or peripheral arterial interventions. The composite renal end point comprised a decline in eGFR ≥30%, ESKD, and all-cause mortality. cfPWV indicates carotid-femoral pulse wave velocity; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; and HR, hazard ratio.

HRs, although with wider CIs because of fewer events (CVE [n=71]: HR [95% CI]: 1.28 [0.95–1.62]; mortality [n=42]: HR [95% CI]: 1.34 [0.97–1.86]; and the composite renal end point [n=95]: HR [95% CI]: 1.28 [1.01–1.62]). In the group without RAAS blocking treatment, the associations for the other end points were difficult to interpret because of low number of events.

DISCUSSION

In this prospective study, we investigated the value of cfPWV, a measure of arterial stiffness, as a marker of mortality and renal and cardiovascular outcomes in people with T1D. We demonstrated a significant association between cfPWV and progression in albuminuria, a decline in eGFR ≥30% from baseline, CVE, all-cause mortality, and the composite renal end point of ≥30% decline in eGFR, ESKD, or mortality, but not for ESKD. The results from the slope analyses underlined the relationship between higher cfPWV and progression in albuminuria and decline in eGFR. The supplementary analyses indicated that the associations between cfPWV and CVE and all-cause mortality may be stronger in people without previous CVD.

Increasing arterial stiffness is accompanied by reduced compliance of the arterial wall followed by augmented pulse wave reflection and higher systolic blood pressure and pulse pressure.[26,27] The increased pressures damage target organs with low resistance vascular beds, including the kidney glomeruli, brain, and myocardium. Moreover, the increased pulsatility affecting the glomeruli is considered a contributing factor in the pathogenesis of proteinuria and impaired glomerular filtration.[28] The higher systolic pressure increases afterload, a situation associated with increased myocardial oxygen demand and left ventricular concentric hypertrophy.[29] cfPWV is considered the gold standard measure of arterial stiffness.[9,12,30]

Previously, using this cohort, we demonstrated that cfPWV was higher in people with T1D than in healthy controls[15] and that measures of central hemodynamics reflecting increased arterial resistance were associated with a history of CVD and albuminuria and with incident ESKD and all-cause mortality during a short follow-up for a median of 2.8 (IQR, 0.7–3.8) years.[31] To our knowledge, the associations between cfPWV and development of cardiovascular and renal outcomes in people with T1D have never been evaluated after a longer follow-up, as the published studies include people with unspecified or type 2 diabetes mellitus (T2D). Although combining T1D and T2D in a cohort may improve power by providing more events, the 2 conditions are recognized as pathophysiologically distinct and follow different trajectories for complications, including cardiovascular outcomes, and are considered non-generalizable for complication development.[32] Thus, a specific analysis for T1D is warranted. In a meta-analysis including >17 000 participants, higher cfPWV was significantly associated with CVE and mortality in the pooled cohort (1785 CVEs and 2041 deaths) and with CVE in a subanalysis of people with unspecified diabetes mellitus (326 events).[7] In a Brazilian study including 629 people with T2D, the association between cfPWV and progression of renal disease was investigated and a higher hazard rate for albuminuria progression, but no association with doubling of serum creatinine to ≥200 μmol/L or ESKD was demonstrated for an increment of 1 SD of cfPWV.[33] When observing renal end points in a T2D cohort of 461 people, progression in albuminuria group and yearly eGFR decline were associated with cfPWV above the median of 9.1 m/s compared with the group with cfPWV below the median.[34] The association between progression of kidney disease and arterial stiffness has also been investigated in CKD cohorts. In the CRIC (Chronic Renal Insufficiency Cohort) study, comprising 2795 people with a mean eGFR of 44 mL/min per 1.73 m^2 and 47% with unspecified diabetes mellitus, a significantly higher hazard rate of death (HR, 1.72) and ESKD (HR, 1.37), but an insignificantly higher hazard rate for the composite end point of ESKD and 50% decline in eGFR (HR, 1.25), was found in the highest tertile of cfPWV compared with the lowest.[35,36] In addition, higher cfPWV was cross-sectionally associated with proteinuria in the CRIC study participants with diabetes mellitus, but not in the participants without diabetes mellitus.[36,37] The results from these cohorts are in line with our findings. A study of 120 people with CKD stage 3 and 4 (23% with unspecified diabetes mellitus) showed that a more rapid decline in renal functions was associated with higher cfPWV at baseline, comparable to our findings in the eGFR slope analysis.[38]

Major strengths of our study are the large size of the cohort that includes well-characterized participants with comprehensive outcome information. No participants were lost to follow-up. Moreover, the cohort is diverse, when it comes to kidney function and included people with a large range of albuminuria and with CKD stages ranging from 2 to 5. In addition to the Cox regression, we evaluated yearly changes in eGFR and albuminuria in linear regression models. The method of eGFR slopes has recently been validated as a surrogate end point for CKD progression, and a meta-analysis of randomized, controlled trials demonstrated validity of 3-year eGFR slopes for the prediction of ESKD.[39,40]

The fact that this was a single-center study may compromise generalizability but may also be a strength, considering interobserver and interequipment variability. In this study, 4 trained biomedical laboratory scientists performed the PWV measurements. The manual

measurement of the pulse wave travel distance results in intraobserver and interobserver variability. We measured the distance of the pulse wave with measuring tape instead of a caliper, which might have compromised accuracy in case of extensive abdominal fat. We did not show an independent association between cfPWV and development of ESKD. However, this may reflect a power issue, as only 19 people developed ESKD. We did not perform a power calculation, because of the nature of the study. All CIs are reported to provide the evidence of whether power is an issue for the specific analysis. We decided to adjust for 9 clinically relevant parameters, which we consider as confounders of the relationship between aortic stiffness and development of the complications, although this number of covariates compared with the number of events leads to a risk of overfitting the model.

As a limitation of our study, cfPWV was approximated by the subtraction method, according to guidelines existing at baseline. This method might underestimate the cfPWV compared with the actual travel distance measured from magnetic resonance imaging. The newer "0.8 method" by which the distance between the common carotid artery and the femoral artery is measured and multiplied by 0.8 is considered more precise. To make the subtraction method comparable to the 0.8 method, it has been suggested to apply a correction factor of 1.1 to cfPWV.[40] When we converted our measurements of cfPWV by this method, the mean (SD) cfPWV in our cohort was 11.5 (6.7) m/s and 59% had a cfPWV >10 m/s (considered a risk factor for CVEs in middle-aged, hypertensive individuals when using the 0.8 method).[10,41] As we use quartiles and change per 1 SD to define exposure, we do not expect this possible systematic underestimation of cfPWV to bias the results of the outcome analyses.

Perspectives

Our results from this large T1D cohort indicate that measurement of cfPWV improves risk stratification in T1D and may be suited for monitoring the central hemodynamic effects of preventive treatment for renal and cardiovascular complications. Currently available prediction models for the general population have only been proved applicable for T2D populations as they underestimate the risk in T1D.[42,43] New specific tools are needed for risk stratification in this population, and cfPWV may be an important risk marker.[44] Arterial stiffness is considered both a cause and a consequence of arterial hypertension, and pharmacological approaches for reducing arterial stiffness have been evaluated.[45–47] Several antihypertensive agents, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, have been demonstrated to reduce arterial stiffness independent of blood pressure reduction.[47] In addition, intensified glycemic control with incretin-based agents decreased PWV after 12 months, adjusted for change in HbA_{1c}, but not for change in blood pressure.[48] In our cohort, antihypertensive treatment was more frequent among participants with higher PWV (Table 1). We suspected that use of antihypertensive drugs might be an intermediate variable on the causal path. A possible protective effect of antihypertensive drugs on the outcomes would result in negative confounding and possibly underestimate the association between PWV and the outcomes. The supplementary analyses indicated that the associations were still present when restricted to participants treated with RAAS blockade. Considering the associations between PWV and renal and cardiovascular outcomes and mortality demonstrated in our study, arterial stiffness is a potential target for preventing adverse renal events and CVEs. In an ESKD cohort, the lack of cfPWV reductions in response to pharmacological blood pressure reductions was independently associated with mortality.[49] It must therefore be clarified whether a reduction in cfPWV can be translated to lower risk. This question is directly addressed in the ongoing French intervention study of 3000 hypertensive people, SPARTE (Strategy for Preventing Cardiovascular and Renal Events Based on arterial Stiffness),[50] where a possible risk reduction of mortality and renal disease and CVD after pharmacological lowering of cfPWV independently of blood pressure reduction is being investigated.

In conclusion, in this T1D cohort, higher cfPWV was independently associated with increased risk of albuminuria progression, decline in eGFR, and the composite renal end point. cfPWV was also associated with CVE and all-cause mortality, but not independently of previous CVD. Measurement of cfPWV may have a future role for risk stratification in T1D.

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Supplementary Material

Figure S1

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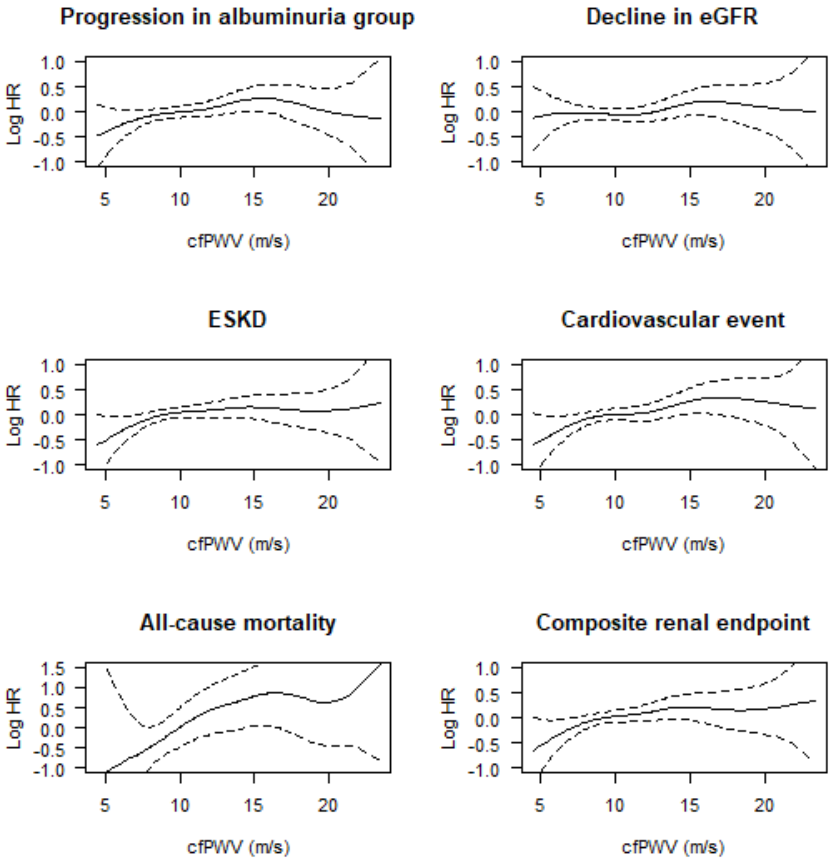
SUPPLEMENTAL MATERIAL

Figure S1. Smoothing splines of adjusted log hazard ratios for progression in albuminuria group, decline in eGFR ≥ 30%, end stage kidney disease, cardiovascular events, mortality and renal outcomes in relation to carotid-femoral pulse wave velocity with population mean of cfPWV as reference value for the ratio.



Dashed lines represent standard errors. eGFR indicates estimated glomerular filtration rate; ESKD, end stage kidney disease.