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Risk of coronary artery disease and stroke according to sex and presence of diabetic nephropathy in type 1 diabetes

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Abstract

Aims

In order to be able to distinguish patients with type 1 diabetes (T1D) with different cardiovascular risk profiles the aim of this study was to dissect the effect of different stages of diabetic nephropathy (DN) and sex on the excess and absolute morbidity of coronary artery disease (CAD) and stroke in T1D.

Materials and Methods

The study included 4,410 patients with T1D from the Finnish Diabetic Nephropathy Study (FinnDiane) divided by DN status and 12,434 non-diabetic control individuals. CVD events were identified from the Finnish nationwide health registries. Cumulative incidences for CAD and stroke were calculated and standardized incidence ratios (SIRs) were estimated between patients with T1D and non-diabetic control individuals stratified by DN status and sex.

Results

There were 487 incident CADs and 290 strokes at the end of 2014 (median follow-up 12.9 years). Cumulative incidences of CAD and stroke were similar in men and women within different nephropathy groups. SIR for CAD was 7.5 (95% CI; 6.9-8.2). It was 17.2 (14.9-19.5) in women and 5.3 (4.7-5.9) in men. The women-to-men ratio of SIR (SIRr) increased by nephropathy group; 3.3,

3.7, 5.3 and 6.8 in the normo-, micro- and macroalbuminuria and end-stage renal disease (ESRD) group, respectively. SIR for stroke was 5.0 (4.3-5.5), similar in men and women. SIRr for stroke was 0.8, 1.3, 1.6 and 1.7, in the normo-, micro- and macroalbuminuria and ESRD group, respectively. SIR in normoalbuminuric patients with eGFR ml/min/1.73 m² $\geq$ 90 was 3.5 (2.5-4.5) for CAD and 1.6 (1.0-2.3) for stroke.

Conclusions

Although the excess CVD risk is several fold increased in women compared to men, the absolute CVD risk in men and women is equal, when nephropathy is taken into account. Even normoalbuminuric patients with normal kidney function show an excess CVD risk compared to non-diabetic control individuals.

Introduction

Type 1 diabetes (T1D) is characterized by an increased risk of cardiovascular disease (CVD) [1-3]. A few years ago a Scottish study reported that the incidence rate for the first CVD event was 2.3 times higher in men and 3.0 times higher in women with T1D compared to the general population [4]. Previously the UK General Practice Research Database reported 3.6 times higher incidence rates in diabetic men and 7.7 times higher rates in diabetic women than in the general population [5]. A recent Swedish study reported, that the excess risk of coronary heart disease (CHD) varied from 2 to 15 in men and from 5 to 33 in women at different stages of diabetic nephropathy (DN) [6]. However, the magnitude of the excess risk varies depending on the characteristics of the patients being studied, including age at diagnosis, duration of diabetes, attained age, presence and

severity of other diabetic complications at enrollment, as well as the time period when the study was conducted [1, 3].

A recent meta-analysis estimated the standardized mortality ratio (SMR) due to CVD to be on average 11.3 for women and 5.7 for men with T1D [7]. This finding is in line with an early observation that there is a strong association between diabetic microangiopathy and macroangiopathy as patients with T1D and proteinuria carried a 37-times higher CVD mortality risk compared to the general population, whereas it was only 4.2 times higher in patients without proteinuria [8]. A more recent Swedish study showed an SMR of the same magnitude, namely a 39-fold increased CVD mortality risk in patients with the worst stage of kidney function [9].

The majority of the previous studies has either assessed the excess CVD mortality or analyzed the absolute risk of CVD using patients with normoalbuminuria as reference [10, 11], but studies specifically comparing the incidence of CVD between patients with T1D and non-diabetic control individuals stratified by nephropathy status are surprisingly sparse. There is thus an obvious knowledge gap, given how important the estimates of any excess risk are for the clinical practice and the individualized care that should be based on the patients' varying risk profiles. In addition, it is also important to find out whether the patients without any signs of DN (normoalbuminuria) ~~or~~ and ~~those~~ with normal kidney function (eGFR ml/min/1.73 m² $\geq$ 90) have any elevated risk of CVD at all compared to individuals without diabetes.

Therefore, our aim was to calculate the standardized incidence ratios (SIRs) for coronary artery disease (CAD) and stroke in a large Finnish population of patients with T1D thoroughly characterized for DN status and to compare with non-diabetic individuals. In addition to the

assessment of excess morbidity, we also provide absolute risk estimates by comparing sex differences within different nephropathy strata.

Methods

The Finnish Diabetic Nephropathy (FinnDiane) Study is an ongoing nationwide, prospective, comprehensive multicenter study established to identify genetic and environmental risk factors for T1D complications, with specific emphasis on DN. The FinnDiane Study has been described in detail in previous publications [12]. In brief, 4410 adult patients were recruited from university, central and district hospitals and primary health care centers across Finland. T1D was defined as permanent insulin treatment started within 1 year of diagnosis, C-peptide negativity and an age of onset of diabetes under 40 years. At baseline the patients underwent a thorough clinical examination at a regular visit to each FinnDiane center. Information about the DN status was obtained from the medical files by the attending physician using a standardized questionnaire. Furthermore, blood samples were drawn and a 24-hour urine collection was performed. Albuminuria status was determined based on measurements of urinary albumin excretion rate (UAER) from at least two overnight (g/min) or 24h urine (mg/24h) collections. Normoalbuminuria was defined when in at least two out of three urinary samples UAER was $<20 \mu\text{g}/\text{min}$ or $<30 \text{ mg}/24 \text{ h}$; microalbuminuria, when UAER ≥ 20 and $<200 \mu\text{g}/\text{min}$ or ≥ 30 and $<300 \text{ mg}/24 \text{ h}$; or macroalbuminuria, when UAER $\geq 200 \mu\text{g}/\text{min}$ or $\geq 300 \text{ mg}/24 \text{ h}$. Diabetic nephropathy (DN) was defined as microalbuminuria, macroalbuminuria or ESRD.

Patients who progressed from normo- to microalbuminuria or to even higher categories of albuminuria during follow-up were excluded from the study (n=294). Also, participants with prevalent CAD (n=174) and stroke (n=112) were excluded from the analyses, leaving 3927 patients for the analyses of incident CAD and 3997 for incident stroke. The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13].

For each FinnDiane participant, three individuals matched for sex, age and place of residence in the year of the diagnosis of T1D of the FinnDiane participant were selected from the Population Register Centre. Any individuals with entitlement to special reimbursement for the costs of diabetes drugs (n=1357) were excluded from the control group. Also control individuals with CVD established before the start of the follow-up were excluded, 55 with CAD and 66 with stroke. After exclusion of people with diabetes there were 12434 control individuals left.

CVD events were identified from the Finnish Care Register for Health Care (non-fatal CVD events) since 1970 and all deaths including fatal CVD events Cause of Death Register until the end of 2014. CVD events included cardiovascular death, nonfatal myocardial infarction (ICD-10 codes I21-I22, ICD-8/9 code 410), coronary artery bypass grafting surgery or coronary angioplasty (together denoting coronary artery disease CAD) or nonfatal stroke (ICD-10 codes I60-I64, ICD-8/9 codes 430-434).

The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District, and written informed consent was obtained prior to participation. This study was performed in accordance with the Declaration of Helsinki as revised in the year 2000.

Statistical methods

Follow-up for the FinnDiane participants started at the baseline visit. Follow-up for the controls started from the time of the baseline visit of their matched FinnDiane participant. Follow-up ended at the time of the first CVD event, any death or at the end of 2014. In order to determine the excess CVD morbidity in patients with T1D compared with that in non-diabetic individuals (relative risk) SIRs were calculated as ratios of observed and expected number of cases. The expected numbers were derived by multiplying the number of person-years at risk by sex-, age- and period-specific incidence rates observed in the non-diabetic control individuals. The SAS lexis macro was used to split the follow-up time for each individual into 1-year calendar year and 5-year age intervals [14]. The 95% confidence intervals (CI) were calculated assuming Poisson distribution. SIRs were calculated by DN status and sex. Absolute CVD risk assessed as cumulative incidences of CAD and stroke were defined by the Fine and Gray method using death from other causes than CAD or stroke as competing risk [15]. Hazard ratios (HRs) for CAD and stroke by DN and sex status were calculated with Fine and Gray competing risks regression models adjusting for traditional risk factors for CVD, namely: age at baseline visit, duration of diabetes, HbA_{1c}, history of smoking, BMI, eGFR, sex, use of lipid lowering medication and presence of hypertension [16]. In case of CAD adjusting lipid variables were triglycerides, HDL cholesterol while in case of stroke LDL cholesterol. Patients were considered to have hypertension if the mean blood pressure was $\geq 140/90$ mmHg or they were taking antihypertensive medication. The HRs for different risk factors are also presented for all DN groups together as there were no interaction between DN status and any of the risk factors. The assumption of the proportional hazards was tested by plotting Schoenfeld residuals against time and testing a non-zero slope by including time-covariate interactions.

All analyses were performed using Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics are shown in Table 1. Participants without prior CVD had a median age of 37.3 years (interquartile range [IQR], 28.8-46.4) and a median duration of diabetes of 21.0 years (IQR, 11.9-30.3).

Absolute risk

Over a median follow-up of 12.9 years (IQR, 10.1-14.9) 487 (12.4%) participants with T1D experienced an incident CAD event (82 fatal, 405 non-fatal) and 280 (7.0%) strokes (28 fatal and 252 non-fatal). The corresponding number of events in the control individuals were 274 (1.4%) CADs and 225 (1.1%) strokes. There were 355 deaths (8.5%) due to other causes than CAD of which 33 due to stroke and 477 due to other causes than stroke (11.9%) of which 125 due to CAD.

The 15-year cumulative incidence of CAD was 13.0% (95% CI, 11.9-14.1) in the entire population. It was higher in men, 14.0% (95% CI, 12.5-15.7) than in the women, 12.0% (95% CI, 10.4 to 13.6) (HR=1.25, P=0.02, Gray's test). However, after adjusting for nephropathy status, the modest sex difference was completely eliminated (P= 0.51). This is clearly seen in Figure 2A where the cumulative risk in each nephropathy group is similar in men and women. Furthermore, the interaction term between sex and nephropathy status was not significant (P=0.29) indicating that DN impacts the CAD risk regardless of the sex.

Incident CAD was strongly associated with known risk factors such as age at baseline, duration of diabetes, poor glucose and lipid control, and hypertension. In addition, incident CAD was also associated with the presence and severity of DN at baseline (Table 1, Supplemental Table 1, Figure 1A). The adjusted HRs were 1.52 (95% CI, 1.1-2.1), 2.3 (95% CI, 1.7-3.2) and 3.3 (95% CI, 2.2-4.7), respectively for the patients with microalbuminuria, macroalbuminuria or ESRD when compared to the patients with normoalbuminuria (Supplemental Table 1).

The 15-year cumulative incidence of stroke was 7.6% (95% CI, 6.7-8.5) for all patients combined. It was higher in men (9.4%; 95% CI, 8.1-10.8) than in women, (5.5%; 95% CI, 4.5-6.7, $P<0.0001$, Gray's test). Similarly to CAD, nephropathy affected the risk of stroke equally in men and women ($P=0.26$ for interaction) and there was no apparent sex difference in the risk within the nephropathy groups, apart from patients with normoalbuminuria (Figure 1B).

Incident stroke was also associated with known risk factors such as age at baseline, duration of diabetes, poor glucose control, hypertension and high LDL cholesterol. Similarly as in CAD, incident stroke was associated with the presence and severity of DN at baseline (Table 2, Figure 1B). Contrary to CAD, in the multivariable model also a decrease in eGFR and smoking status were a significant predictors, but not BMI (Supplemental Table 1). The adjusted HRs were 2.5 (95% CI, 1.6-3.7), 2.7 (95% CI, 1.8-4.2) and 3.6 (95% CI, 2.2-6.0), respectively for the patients with microalbuminuria, macroalbuminuria and ESRD compared to the patients with normoalbuminuria (Supplemental Table 1).

Relative risk

The overall SIR between participants with T1D and non-diabetic control individuals for CAD was 7.5 (95% CI, 6.9-8.2). The SIR in the participants with microalbuminuria was 6.3 (95% CI, 4.9-7.9), 13.1 (95% CI, 11.3-15.2) in the participants with macroalbuminuria, and 26.6 (95% CI, 22.0-31.9) in those with end-stage renal disease (ESRD) when compared to the non-diabetic individuals. Notably, the difference between the SIRs in women and men increased by worsening of the DN status and the women-to-men SIR ratio was thus 3.3, 3.7, 5.3 and 6.8, respectively (Figure 2A).

Figure 2B shows the SIR estimates for stroke. The overall SIR for stroke was 5.0 (95% CI, 4.4-5.6) for the sexes combined. Unlike CAD, the SIR of stroke was similar in men (5.0; 95% CI, 4.4-5.6) and women (4.7; 95% CI, 3.7-5.6). The SIR was 1.7 (95% CI, 1.3 to 2.1) in the participants with normoalbuminuria, 5.8 (95% CI, 4.3-7.4) in participants with microalbuminuria, 10.1 (95% CI, 8.1-12.1) in the participants with macroalbuminuria and 20.7 (95% CI, 15.9-25.4) in these with ESRD when compared to the matched control individuals. In contrast to CAD the difference between the SIRs in women and men increased only slightly along worsening nephropathy status and the SIR ratio was thus 0.8, 1.3, 1.6 and 1.7 in the normo-, micro, macroalbuminuria and ESRD groups, respectively.

The SIR for CAD in the participants with normoalbuminuria and normal kidney function ($\text{eGFR} \geq 90 \text{ ml/min/1.73m}^2$) at baseline was 4.0 (95% CI, 3.1-5.0) times higher than in the matched control individuals. When the patients were further divided into groups below and above the median eGFR ($108 \text{ ml/min/1.73m}^2$), the SIR tended to be higher, in those with an eGFR above the median, 5.6 (95% CI, 3.3-8.0), than in those with an eGFR below, 3.5 (95% CI, 2.5-4.5). The patients with normoalbuminuria and $\text{eGFR} > 90 \text{ ml/min/1.73m}^2$ had also a higher incidence rate of stroke than the matched controls (SIR 1.6; 95% CI, 1.0-2.3).

Discussion

In this study, we quantified the excess risk of CAD and stroke as well as the cumulative incidence of these comorbidities according to different stages of DN and sex in well characterized individuals with type 1 diabetes. A novel observation was that men and women carry a similar absolute risk of CVD, when they are stratified by DN status. Notably, the cumulative incidence of CAD was the same in men and women also in the normoalbuminuric group showing that T1D *per se* makes men and women equal with respect to their risk of CVD. Another important observation was, that the sex difference with respect to excess risk of CAD increased by worsening of DN status indicating that the relative effect of DN is even more pronounced in women. In contrast, the SIR ratio for stroke was not as striking as for CAD.

It is well established that DN increases the risk of CVD dramatically [8, 17]. The association between DN and CVD has mostly been studied in terms of mortality [1, 9, 18] or absolute morbidity [10, 11]. However, a recent Swedish study assessed the excess risk related to CHD [6] and stroke [19]. Similarly, as in our study, their HR for CHD was much higher in women than in men and was the highest in the women with ESRD (HR=32), but it was considerably lower than that in our study (SIR=113). It is notable that the overall proportion of patients with CHD was much lower 2.2% compared to 12.4% in our study, although the populations were of similar age. Likewise, the proportion of patients with stroke was 1.3% vs. 7.0% in our study. We do not know the reason for these discrepancies, but it may be due to a different distribution of patients with renal disease. However, the data on the numbers of patients at various stages of DN in men and women are not given in the Swedish study [6]. Another study that have estimated the relative risk of CVD morbidity comes from the UK [5]. Also their estimates for acute coronary events were lower than

ours, but the estimates for stroke were closer to ours. The UK study compared patients with T1D with age- and sex-matched nondiabetic individuals and reported a HR for major CVD of 3.6 for men and 7.7 for women [5].

In general, in comparison to the nondiabetic population women with T1D carry much higher CVD risk than men [3, 8, 20]. In the current study, where we compared both the absolute and the relative risks in the same T1D population, men had higher absolute risk of CAD and stroke than women in the univariable analyses. However, when adjusted for DN status, the sex difference disappeared. Thus, the generally observed higher absolute risk in males in pooled populations in which the nephropathy status has not been taken into consideration is presumably due to the fact that males in general carry a higher risk of DN. Such a higher risk in men has been observed in several studies [21-25], although also contradictory results exist [26]. In the current study the proportion of DN was 42% in men, while it was 31% in women. Because the CVD risk is increased, when DN is present, this will result in a higher absolute CVD risk in men.

Previous studies have observed that diabetes eliminates the protection against CVD afforded by being female [3, 8, 20]. In our study, after adjusting for the higher prevalence of DN in men, men and women with T1D had an equivalent cumulative incidence of CAD. This is strikingly different to what is observed in the non-diabetic population, where men develop CAD earlier and more often than women [27]. This explains why the relative increase in CAD appears to be far greater in women with T1D than in men (17.2 vs 5.3). The physiological reasons that underlie this 'loss of protection' remain to be established but may include loss of insulin sensitizing and vasoactive actions of estrogen, as well as increased pro-inflammatory and pro-thrombotic effects of estrogen, especially in the setting of underlying atheroma. For example, in women with established CAD,

administration of combined conjugated equine estrogen plus medroxyprogesterone acetate therapy increases the risk of CAD events at 1 year [28]. Notably in our study, while diabetes increased the incidence of stroke, this increase was similar in men and women, meaning that the relative gender protection against stroke was preserved. This points to a specific effect on the coronary vasculature rather than systemic atherogenesis, plaque rupture or thrombosis.

Clearly, one of the most important determinants of incident CVD in adults with T1D is the presence and severity of DN [8, 17]. Even after adjusting for known risk factors DN was strongly associated with incident CAD and incident stroke. The reasons that underlie this association are complex. Certainly, CKD and atherosclerosis may be considered tissue specific manifestations of a common process that leads to vascular damage (Steno hypothesis) [29]. Atherosclerosis and kidney disease can both be kindled or stoked by diabetes and its associated milieu. However, in addition, DN may serve to directly accelerate atherosclerosis through its effects on atherogenic pathways including augmenting oxidative stress, insulin resistance, arterial calcification, endothelial dysfunction, hypertension, dyslipidemia, inflammation, and activation of the RAAS, SNS and the AGE/RAGE axis.

Despite the important association between DN and CVD outcomes in this cohort, the risk of incident CAD and incident stroke were both elevated in participants with T1D without comorbid DN at baseline. Even in the absence of albuminuria or renal impairment, adults with T1D still had at least twice the rate of CAD and stroke when compared to non-diabetic matched individuals. This is consistent with previous data from a Scottish study that reported 2.1-fold increased risk of CVD in men and 3.7-fold increased risk in women with normal kidney function [4]. A Swedish study also showed that normoalbuminuric patients had 3.6-fold increased mortality risk from CVD [9].

The strikingly high excess CAD morbidity in women with ESRD is explained by the fact that there are only very few CAD events in women in the background population at young age [30]. However, the presence of ESRD increases the risk of CAD equally in men and women as clearly seen in the present study. Therefore, the cumulative risk is similar in women and men.

Interestingly, normoalbuminuric patients with increased eGFR had higher SIR of CAD than those with an eGFR within the normal range. These data are consistent with the results in our previous mortality study in which hyperfiltration was associated with increased all-cause mortality [31]. It is of note that hyperfiltration was recently found to increase arterial stiffness also in the non-diabetic population and given that stiffer arteries in general increase the CVD risk these data suggest that hyperfiltration is linked to CVD morbidity and mortality even in the absence of albuminuria [32].

Whether there is a direct effect of hyperglycemia on the CVD risk in T1D has been a matter of debate [9, 33, 34]. In the present study HbA_{1c} was a predictor of CAD but not of stroke in those with normoalbuminuria, and every one unit increase in HbA_{1c} increased the risk of CAD by 22% in the patients with normoalbuminuria (data not shown). Hyperglycemia is thought to increase the risk of cardiovascular events via complex and poorly-understood interactions with pro-atherogenic pathways including oxidative stress, endothelial dysfunction, dyslipidemia, shear stress, chronic inflammation and myelopoiesis and pro-thrombotic changes [34]. Optimal glycemic control early in the course of diabetes is crucial to prevent CVD events, and exposure to improved glycemic control is translated into decreased risk of complications, a phenomenon called “glycemic memory” [35].

The main strengths of this study are the large cohort of well characterized patients with T1D and the possibility to estimate the excess risk of CVD events by comparison with non-diabetic individuals. The use of administrative registers that cover every death and hospitalization event in the country

and the quality of these registers with regard to CVD has been validated and shown to be high [36]. The adjustments for eGFR and albuminuria also allows us to fully explore the link between DN and incident CVD.

There are however some limitations in the present study. The main limitation is that although this study is nationwide and considered to be a representative sample of patients with T1D in Finland the generalizability may be limited as the study is not by strict definition population-based. For example, low socio-economic position and depression predict higher CVD risk [37, 38]; reasons that usually lead to non-participation in studies. Furthermore, we did not have data for all patients regarding age at onset of proteinuria and this may have some residual effect on the results.

Conclusions

In conclusion, the presence of DN is the major contributors to the enhanced risk of CAD and stroke. Although the excess CVD risk is greatly increased in women compared to men, the absolute CVD risk in men and women is equal, when nephropathy is taken into account. It is of utmost importance to prevent the development of DN in order to prevent CVD. However, kidney disease does not explain all the excess CVD risk as the SIRs also in the patients with normoalbuminuria and normal kidney function were increased. Therefore, also the identification of specific risk factors related to T1D beyond albuminuria and impaired kidney function requires further studies. This is clinically important, since the patients with normoalbuminuria represent considerable proportion of the population with type 1 diabetes [39].

Author Contributions

V.H. designed the study, analysed the data and drafted the manuscript. M.C.T., C.F. and P-H.G. contributed by interpretation of the results and critical revision of the article. All authors contributed to the final version.

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Conflict of Interest

P-H.G. has received lecture honorariums from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, MSD, and Novartis. M.C.T. has received lecture honorariums from Astra Zeneca,

Boehringer Ingelheim, Eli Lilly, MSD, Servier, Takeda, and Novartis. P-H.G. is also an advisory board member of AbbVie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, and Novartis. All other authors declare that they have no conflicts of interest.

Figure legends

Figure 1A. Cumulative incidence of coronary artery (CAD) disease stratified by diabetic nephropathy status and sex. Death without CAD is used as competing risk (not shown). Unbroken line for men and dash line for women. HR=hazard ratio between women and men, 95% confidence interval in brackets.

Figure 1B. Cumulative incidence of stroke disease stratified by diabetic nephropathy status and sex. Death without stroke is used as competing risk (not shown). Unbroken line for men and dash line for women. HR=hazard ratio between women and men, 95% confidence interval in brackets.

Figure 2A. Standardized incidence ratios (SIRs) for coronary artery disease. * denotes the upper limit of 95% CI is 144.

Figure 2B. Standardized incidence ratios (SIRs) for coronary stroke

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Table 1. Clinical characteristics according to nephropathy status and incident coronary artery disease (CAD). Data are given as mean $\pm$ SD or median and interquartile range.

	Normoalbuminuria n=2490		Microalbuminuria n=539		Macroalbuminuria n=599		ESRD n=299	
	CAD- n=2356	CAD+ n=134	CAD- n=471	CAD+ n=68	CAD- n=427	CAD+ n=172	CAD- n=186	CAD+ n=113
Sex (male %)	47.6	48.5	58.4	60.3	57.9	63.4	59.7	54.9
Age (years) at baseline visit	34.4 (25.7-43.7)	49.9 (42.4-54.4) ****	35.8 (28.1-45.7)	46.8 (39.8-53.0) ****	37.6 (31.9-46.7)	45.4 (38.9-52.3) ****	42.5 (37.6-48.4)	45.3 (41.2-51.1) **
Age at onset of diabetes (years)	16.5 (10.7-25.2)	17.1 (10.8-25.6)	11.2 (7.0-17.8)	13.2 (8.1-23.2)	10.9 (6.9-15.2)	12.5 (8.0-19.9) *	11.4 (7.5-16.0)	12.5 (8.6-16.4)
Duration of diabetes	15.7 (8.4-24.8)	31.3 (21.8-37.5) ****	23.5 (16.1-30.5)	33.0 (27.9-37.9)****	26.6 (21.5-32.4)	31.1 (25.9-35.3) ****	30.6 (24.3-35.9)	34.1 (29.2-37.7) **
BMI (kg/m ²)	24.7 $\pm$ 3.4	25.3 $\pm$ 3.0	25.6 $\pm$ 3.6	25.6 $\pm$ 3.5	25.7 $\pm$ 4.0	26.2 $\pm$ 4.0	24.1 $\pm$ 4.0	23.9 $\pm$ 3.5
HbA _{1c} (%)	8.1 $\pm$ 1.4	8.3 $\pm$ 1.2**	8.7 $\pm$ 1.5	8.8 $\pm$ 1.6*	9.0 $\pm$ 1.6	9.2 $\pm$ 1.6 **	8.4 $\pm$ 1.5	8.5 $\pm$ 1.6
Total cholesterol (mmol/l)	4.76 $\pm$ 0.87	4.99 $\pm$ 0.93	4.99 $\pm$ 0.91	5.25 $\pm$ 0.91	5.33 $\pm$ 1.05	5.54 $\pm$ 1.31 *	5.11 $\pm$ 1.25	5.51 $\pm$ 1.29 **
HDL-cholesterol (mmol/l)	1.38 $\pm$ 0.38	1.30 $\pm$ 0.33 ****	1.33 $\pm$ 0.40	1.29 $\pm$ 0.31****	1.23 $\pm$ 0.37	1.14 $\pm$ 0.40 **	1.24 $\pm$ 0.42	1.22 $\pm$ 0.43

Triglycerides (mmol/l)	0.92 (0.70-1.26)	1.03 (0.80-1.45) **	1.06 (0.81-1.54)	1.11 (0.84-1.79)	1.36 (0.98-1.97)	1.55 (1.09-2.50) **	1.48 (0.97-1.90)	1.51 (1.07-2.23) *
LDL cholesterol (mmol/l)	2.89±0.80	3.17±0.84	3.05±0.81	3.35±0.92*	3.50±0.92	3.53±1.10	3.15±1.13	3.50±1.14***
Systolic blood pressure (mmHg)	129±15	139±17 **	136±17	143±17	142±20	152±19 **	152±25	154±24
Diastolic blood pressure (mmHg)	78±9	79±9	81±10	79±10	83±11	83±10	86±12	85±12
Antihypertensive medication (%)	15.9	41.8 **	66.2	77.9	92.3	93.6	97.9	96.5
Lipid-lowering medication (%)	5.3	23.1 **	8.5	29.4**	23.2	37.2 *	40.9	38.9
eGFR (mL/min/1.73 m ²)	99.6±19.0	88.8±18.4	93.8±21.3	82.5±19.1	60.8±30.7	49.7±27.6 **	NA	NA
Laser-treated retinopathy (%)	11.3	37.1 **	43.0	73.1 **	77.9	79.6	97.3	100
Smoking, ever smoked (%)	41.6	39.3	52.6	48.4	58.6	61.4	60.4	57.8

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin; CAD- coronary artery disease not present; CAD+ coronary artery disease is present; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate calculated by CKD-EPI equation. **** P-value <0.0001, ***P-value<0.001, ** P-value<0.01, * P-value<0.5. P-value refers to ANOVA, Kruskal-Wallis test or χ^2 -test adjusted for age at baseline when applicable. Comparisons are made within diabetic nephropathy groups.

Table 2. Clinical characteristics according to nephropathy status and incident stroke. Data are given as mean $\pm$ SD or median and interquartile range.

	Normoalbuminuria n=2511		Microalbuminuria n=555		Macroalbuminuria n=606		ESRD n=325	
	Stroke- n=2452	Stroke+ n=59	Stroke- n=502	Stroke+ n=53	Stroke- n=510	Stroke+ n=96	Stroke- n=253	Stroke+ n=72
Sex (male %)	47.3	59.3	58.2	66.0	59.2	66.7	57.7	62.5

Age (years) at baseline visit	34.9 (26.0-44.3)	48.3 (39.0-55.5) ****	37.7 (29.1-47.4)	43.7 (33.6-52.) **	39.3 (32.6-48.0)	46.5 (38.2-51.2) **	44.7 (39.6-51.0)	44.7 (39.6-51.0)
Age at onset of diabetes (years)	16.5 (10.7-25.3)	19.0 (11.6-28.2)	11.7(7.1-18.0)	10.3 (7.0-21.8)	10.9 (7.2-15.7)	13.7 (7.0-18.1)	12.0 (7.6-16.0)	10.6 (7.1-17.8)
Duration of diabetes	16.4 (8.7-25.6)	28.6 (18.9-36.2) ****	24.3 (16.5-32.1)	29.9 (23.2-36.8) **	27.6 (22.4-33.2)	30.9 (24.6-35.4) **	32.4 (26.6-37.3)	34.0 (26.6-37.4)
BMI (kg/m ²)	24.8±3.4	25.7±2.8	25.6±3.6	26.0±4.1	26.0±4.1	25.5±3.7	24.3±3.8	23.4±3.8
HbA _{1c} (%)	8.1±1.4	8.2±0.9	8.8±1.5	8.9±1.5	9.0±1.6	9.2±1.3	8.4±1.5	8.8±1.5
Total cholesterol (mmol/l)	4.76±0.87	5.08±0.82	5.00±0.92	5.11±0.89	5.36±1.12	5.45±1.11	5.16±1.23	5.43±1.42
HDL-cholesterol (mmol/l)	1.37±0.38	1.44±0.44	1.32±0.39	1.38±0.38	1.20±0.37	1.18±0.3	1.21±0.43	1.17±0.42
Triglycerides (mmol/l)	0.93 (0.71-1.27)	0.88 (0.77-1.27)	1.08 (0.83-1.55)	1.14 (0.80-1.73)	1.38 (1.00-2.06)	1.48 (1.12-2.10)	1.48 (1.03-2.12)	1.43 (0.94-1.91)
LDL cholesterol (mmol/l)	2.90±0.80	3.14±0.74	3.08±0.82	3.14±0.79	3.38±0.96	3.48±0.97	3.18±1.12	3.53±1.22*
Systolic blood pressure (mmHg)	129±15	136±15	135±17	147±19 ***	143±20	151±20 *	152±23	161±28 *
Diastolic blood pressure (mmHg)	78±9	77±9	80±10	82±10	83±11	84±10	84±12	88±13 *

Antihypertensive medication (%)	17.4	37.3	67.9	73.6	92.9	90.6	97.6	97.2
Lipid-lowering medication (%)	6.7	17.0 **	12.2	17.0	27.3	22.9	47.3	33.3 *
eGFR (mL/min/1.73 m ²)	99.2±19.1	87.9±17.8	92.4±21.0	86.3±24.4	58.7±29.9	48.8±30.6 *	NA	NA
Laser-treated retinopathy (%)	12.3	32.2	46.3	60.4	77.8	81.1	97.6	97.1
Smoking, ever smoked (%)	41.1	50.9	51.9	60.4	58.5	66.7	60.5	62.1

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin; CAD- coronary artery disease not present; CAD+ coronary artery disease is present; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate calculated by CKD-EPI equation. **** P-value <0.0001, ***P-value<0.001, ** P-value<0.01, * P-value<0.5. P-value refers to ANOVA, Kruskal-Wallis test or χ^2 -test adjusted for age at baseline when applicable. Comparisons are made within diabetic nephropathy groups.

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