Risk Factors for Atrial Fibrillation in People With Type 1 Diabetes: An Observational Cohort Study of 36,258 Patients From the Swedish National Diabetes Registry

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OBJECTIVE

This study identified variables associated with increased risk of atrial fibrillation in people with type 1 diabetes.

RESEARCH DESIGN AND METHODS

We performed a cohort study of people with type 1 diabetes from the Swedish National Diabetes Registry followed up between 1 January 2001 and 31 December 2013. Median follow-up was 9.7 years (interquartile range 5.2–13.0). The association between potential risk factors and incident atrial fibrillation was investigated using adjusted Cox regression. To compare the impact of each risk factor, the gradient of risk per 1 SD was estimated.

RESULTS

In this cohort of 36,258 patients with type 1 diabetes, 749 developed atrial fibrillation during follow-up. Older age, male sex, renal complications, increased BMI and HbA_{1c}, coronary artery disease, heart failure, and heart valve disease increased the risk of atrial fibrillation. Age, signs of renal dysfunction with macroalbuminuria, and decreasing estimated glomerular filtration rate were associated with the highest gradient of risk for atrial fibrillation. High blood pressure, severe obesity (BMI >35 kg/m^2), and elevated levels of HbA_{1c} (>9.6%) were associated with increased risk, but no associations were found with hyperlipidemia or smoking.

CONCLUSIONS

The most prominent risk factors for atrial fibrillation in people with type 1 diabetes were older age, cardiovascular comorbidities, and renal complications, while obesity, hypertension, and hyperglycemia had more modest affects.

Atrial fibrillation (AF) is a common cardiac rhythm disorder with clinical implications (1). AF is often associated with heart failure and reduced exercise capacity and is a risk factor for stroke and dementia (2,3). The global prevalence of AF is estimated to be ~0.6% in men and 0.37% in women, and the prevalence is increasing worldwide (4). A recent study reported that AF is more common in patients with type 1 diabetes, with an incidence of 2.35 per 1,000 person-years compared with 1.76 per 1,000 person-years among population-based control subjects, increasing with age and higher in men

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compared with women, but a higher risk relative to the population control subjects in women compared with men (5).

Several mechanisms could explain the increased risk of AF in patients with diabetes, and some of them are more common in persons with type 1 diabetes than in persons with type 2 diabetes. Atrial remodeling associated with diabetes and diabetic cardiac autonomic neuropathy increases risk of cardiac arrhythmia. Other underlying mechanisms explaining the increased incidence, predominantly affecting persons with type 1 diabetes, could be the arrhythmogenic effect of hypoglycemia and alterations in electrolytes associated with diabetic ketoacidosis (6,7). Hence, the risk factors of AF in persons with type 1 diabetes could differ from those seen in the general population and in persons with type 2 diabetes.

Age, chronic ischemic heart disease, valvular heart disease, smoking, obesity, and hypertension are all risk factors for AF in the general population (8). Results from prior studies in patients with type 2 diabetes or mixed groups of diabetes are in conflict regarding the association of poor glycemic control and risk of AF (9).

Few studies are focusing on the potential risk factors for AF in a population of patients with type 1 diabetes, which is important, particularly because of the increased risk of stroke associated with this disorder in a population already vulnerable to cardiovascular disease (10). Therefore, our aim was to study potential risk factors for AF in persons with type 1 diabetes, including age, sex, smoking, BMI, HbA_{1c}, blood pressure, lipids, renal complications, and cardiovascular comorbidities.

RESEARCH DESIGN AND METHODS

Study Cohort

This was a nationwide prospective observational cohort study of Swedish patients with type 1 diabetes. Every citizen in Sweden is assigned a unique personal identification number that can be used to link patient information from administrative registries. In the current study, linkages were made between the Swedish National Diabetes Registry (NDR), the Swedish National Patient Registry (NPR), the Swedish Cause of Death Registry, and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (5,11).

The NDR, which was launched in 1996 and has been described elsewhere (12,13), contains data about clinical characteristics, risk factors, diabetes-related complications, and treatments. Nearly all patients ≥18 years old and with type 1 diabetes are registered nationwide. Data are collected during visits to hospital outpatient wards or primary care clinics. Selection of patients with type 1 diabetes from the NDR was based on the epidemiological definition (diagnosis before the age of 30 years and treatment with insulin). An assessment of type of diabetes performed voluntarily by the reporting clinics, available in 75% of all participants, showed that ~97% had type 1 diabetes (14). The study cohort included all patients with at least one registration in the NDR between 1 January 2001 and 31 December 2012 and with no diagnosis of AF before the first registration and was followed up until 31 December 2013.

Education level was acquired from the Longitudinal Integration Database for Health Insurance and Labor Market Studies and stratified into three groups: *1*) low (up to 9 years), *2*) intermediate (10–12 years), and *3*) high (university or college).

Data for AF and comorbidities were retrieved from the Swedish National Patient Registry, with national coverage since 1987, which is operated by the Swedish National Board of Health and Welfare and holds information on all discharges from the hospital and, since 2001, also on outpatient care. Diagnoses were registered according to the ICD-9 and ICD-10.

Procedure

Variables analyzed from the NDR were age, sex, diabetes duration, smoking status, HbA_{1c}, systolic and diastolic blood pressure (SBP and DBP), LDL and HDL cholesterol, BMI, albuminuria, and creatinine level, which was used to calculate the estimated glomerular filtration rate (eGFR). Baseline and time-updated mean values were used for HbA_{1c}, BMI, blood pressure, and LDL and HDL cholesterol levels. Time-updated means were calculated as the mean of all values registered up to each registration (15). HbA_{1c} was reported in both International Federation of Clinical Chemistry and Laboratory Medicine mmol/mol and National Glycohemoglobin Standardization Program % according to guidelines for dual reporting of HbA_{1c} (16,17).

Microalbuminuria was defined as at least two positive results obtained within 1 year and defined as the albumin-to-creatinine ratio of 3–30 mg/mmol (~30–300 mg/g) or urinary albumin clearance of 20–200 μg/min (~20–300 mg/L). Macroalbuminuria was defined as an albumin-to-creatinine ratio >30 mg/mmol (close to 300 mg/g or more) or urinary albumin clearance >200 μg/min (>300 mg/L). eGFR was estimated from the creatinine value and calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI) equation (18). Kidney disease was defined based on the Kidney Disease: Improving Global Outcomes classification, where GFR >90 mL/min/1.73 m^2 and with diagnosed renal injury was defined as CKD 1, GFR 89–60 mL/min/1.73 m^2 was defined as CKD 2, GFR 59–30 mL/min/1.73 m^2 was defined as CKD 3, GFR 15–29 mL/min/1.73 m^2 was defined as CKD 4, and GFR <15 mL/min/1.73 m^2 or renal dialysis was classified as CKD 5 (19). Smoking was defined as current (≥1 cigarettes/day) or former (no smoking during the last 3 months).

ICD-9 and 10 codes 427D and I.48, respectively, were used to identify patients with AF as a primary or contributory diagnosis. Diagnoses of AF in the Swedish Hospital Discharge registry have been validated against clinical records, with 95% of diagnoses consistent with electrocardiogram findings and only 3% miscoded (20) The patient registry was also used to register comorbidities, including stroke, cancer, heart failure, valve disease, and coronary heart disease (ICD codes are described in the Supplementary Data). Mortality data were retrieved from the Swedish Cause of Death registry.

All patients provide informed consent to be included in the NDR. This study was approved by the regional ethics review board at the University of Gothenburg, Sweden.

Statistical Analysis

This is an etiological study, including a complete Swedish population of patients with type 1 diabetes followed up between 2001 and 2013, investigating the effect of potential risk factors on study outcome in an exploratory manner. No a priori power calculation was performed.

Baseline characteristics are described as mean and SD or median, minimum, and maximum or interquartile range as applicable for continuous variables, and with number and percentage for categorical variables. Event rates per 1,000 person-years were calculated with exact 95% Poisson limits. Time to first diagnosis of AF was analyzed using survival analysis, with Cox proportional hazards model, estimating hazard ratios (HRs) with 95% CIs separately based on baseline values and separately on time-updated means (the mean of all values registered up to each registration) for BMI, HbA_{1c}, SBP, DBP, LDL and HDL cholesterol, or time-updated values (the last of the preceding values) for age and eGFR and when considering nominal main effect variables (SAS code is presented in the Supplementary Data).

Three models were created to adjust for the different covariates. Model A was adjusted for age and sex. Model B was further adjusted for education, birth in Sweden, diabetes duration, and baseline comorbidities (chronic heart disease [CHD], heart failure, stroke, valve disease, and cancer). Model C analyzed the effect of exposure to each risk factor and, therefore, additionally adjusted for smoking, HbA_{1c}, BMI, and SBP as baseline or time-updated variables in respective analyses, as were age and diabetes duration. When DBP was the main effect variable, model C was not adjusted for SBP due to a strong correlation between the two variables.

The proportional hazard assumption was satisfied and checked by visually examining the plots of log(−log[survival]) versus log(time) for categorical variables and categories based on quintiles for continuous variables.

To enable a comparative estimate of the influence of the potential risk factors we estimated the gradient of risk per SD 95% CI (i.e., the HR per 1-SD increase) and pseudo-R^2 for each risk factor. Higher gradient of risk had a greater impact on the incidence of AF. Pseudo-R^2 was used as a complementary measure to rank the relative importance of risk factors for AF.

In addition, the potential nonlinear effect of the explanatory variables on incident AF was investigated using piecewise linear functions.

The post hoc analyses, investigating interactions for age × diabetes duration, sex × diabetes duration, and sex × age, were performed in the time-updated model C.

The Fisher exact test was used to test differences between two groups with respect to dichotomous variables, Mann-Whitney *U* test for continuous variables, and Mantel-Haenszel χ^2 test for ordered categorical variables. In the time-updated analyses, each patient contributed with the time period from the first available nonmissing value after 1 January 2001 to the last follow-up, including all available visits. The time-updated values were carried forward until the next available value used in the calculation of time-updated mean or end point, or death or end of data extraction. No data imputation was made.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). All tests were two-tailed and conducted at the 0.05 significance level.

RESULTS

Baseline Characteristics

Baseline population characteristics are presented in Table 1. Mean age was 35.6 (SD 14.6) years, and 54.7% were men. Mean diabetes duration was 20.3 (SD 14.8) years, and 3.5% had severe renal failure (CKD 4 and 5 groups combined). Over a median follow-up of 9.7 years, 749 patients were registered with a principal or contributory diagnosis of AF (incidence: 2.35 per 1,000 person-years [95% CI 2.19–2.53]). With a markedly higher mean age (55.4 [SD 13.1] years) and a higher proportion of men (61.8%), patients who developed AF had a higher burden of most cardiovascular disease risk factors at baseline, with higher BMI and blood pressure, more renal dysfunction, and a longer mean diabetes duration of 37.4 (SD 13.4) years. Mean LDL and HDL cholesterol and HbA_{1c} concentrations were similar, as was the proportion of smokers. All coexisting baseline comorbidities were more common in the group with AF.

Potential Risk Factor Effect on the Risk of AF

The proportional hazards models for time to AF using baseline variables and time-updated variables are reported in Supplementary Tables 1 and 2. Model C for time-updated variables is reported in Table 2. Increasing age was associated with an added risk of AF, with an HR of 1.10 (95% CI 1.09–1.11; $P < 0.0001$) per year. No significant interaction between age and diabetes duration was found. Men had a higher risk of AF (HR 1.60 [95% CI 1.35–1.89]; $P < 0.0001$) than women and a significantly decreasing effect for longer diabetes duration ($P = 0.0021$), with an HR of 2.83 (95% CI 1.84–4.37) for diabetes duration of 9 years (10th percentile) and 1.36 (95% CI 1.14–1.61) for 51 years (90th percentile). Similarly, the higher risk for men was decreasing with higher age ($P = 0.0009$), with an HR of 3.34 (95% CI 2.03–5.48) for 24 years old (10th percentile) and 1.41 (95% CI 1.20–1.66) for 66 years old. In analyses of patients with time-updated comorbidities, those with chronic ischemic heart disease (HR 2.61 [95% CI 2.19–3.10]; $P < 0.0001$), heart failure (HR 3.29 [95% CI 2.67–4.06]; $P < 0.0001$), and heart valve disease (HR 3.28 [95% CI 2.30–4.67]; $P < 0.0001$) had an increased risk of AF in the fully adjusted model. We found no significant association between other time-updated comorbidities, such as stroke (HR 1.27 [95% CI 0.99–1.64]; $P = 0.065$) or cancer (HR 1.12 [95% CI 0.84–1.51]; $P = 0.44$), and risk of AF.

Glycemic control measured as updated mean HbA_{1c} had a significant influence on the risk of developing AF. For every 10 mmol/mol (~1%) HbA_{1c} increase, where HbA_{1c} was analyzed as a continuous variable, the HR was 1.15 (95% CI 1.07–1.23; $P < 0.0001$). When HbA_{1c} was >82 mmol/mol (~9.6%), the HR was 1.94 (95% CI 1.38–2.73; $P = 0.0001$) compared with the reference group in the fully adjusted model (Fig. 1). The results from all three models performed using categorical variables are presented in Supplementary Table 3.

When updated mean SBP was analyzed as a continuous variable, a significant added risk of 16% (HR 1.16 [95% CI 1.10–1.22]; $P < 0.0001$) was seen with every 10-mmHg increase in the fully adjusted model. When compared with the reference category of <120 mmHg, the HR for SBP 140–149 mmHg was 1.37 (95% CI 1.08–1.75; $P = 0.010$), and the risk increased further to an HR of 1.76 (95% CI 1.37–2.27; $P < 0.0001$) among those with SBP ≥150 mmHg, as shown in Fig. 1. Updated mean DBP corresponded to an 8% (HR 1.08 [95% CI 1.03–1.15]; $P = 0.0037$) added risk for every 5-mmHg increase in the fully adjusted model, and there was a suggested protective effect of a low DBP of <75 mmHg (Fig. 1). Smoking and also baseline levels and

Table 1—Baseline characteristics of patients with type 1 diabetes free of prior AF followed up in 2001–2013 by incidence of AF

	Total (*n* = 36,258)	No AF (I48) (*n* = 35,509)	AF (I48) (*n* = 749)
Sex			
Men	19,823 (54.7)	19,360 (54.5)	463 (61.8)
Women	16,435 (45.3)	16,149 (45.5)	286 (38.2)
Age (years)	35.6 (14.6) 32.0 (17.0; 96.0) *n* = 36,258	35.2 (14.4) 32.0 (17.0; 96.0) *n* = 35,509	55.4 (13.1) 56.0 (18.0; 82.0) *n* = 749
Age categories			
18 to <35 years	19,769 (54.5)	19,714 (55.5)	55 (7.3)
35 to <50 years	9,254 (25.5)	9,093 (25.6)	161 (21.5)
50 to <65 years	5,733 (15.8)	5,397 (15.2)	336 (44.9)
≥65 years	1,502 (4.1)	1,305 (3.7)	197 (26.3)
Born in Sweden	33,730 (93.0)	33,031 (93.0)	699 (93.3)
Education category			
Low	7,985 (22.3)	7,721 (22.0)	264 (35.8)
Mid	19,223 (53.7)	18,887 (53.9)	336 (45.5)
High	8,571 (24.0)	8,433 (24.1)	138 (18.7)
Diabetes duration (years)	20.3 (14.8) 17.0 (0.0*; 88.0) *n* = 36,258	20.0 (14.6) 17.0 (0.0*; 88.0) *n* = 35,509	37.4 (13.4) 38.0 (0.0*; 75.0) *n* = 749
Smoker	4,571 (14.1)	4,471 (14.1)	100 (15.0)
BMI (kg/m^2)	25.1 (4.1) 24.5 (14.0; 70.9) *n* = 30,404	25.1 (4.1) 24.5 (14.0; 70.9) *n* = 29,776	26.0 (4.4) 25.5 (17.1; 50.0) *n* = 628
HbA_{1c} (mmol/mol, IFCC)	65.8 (15.9) 65.0 (26.0; 145.0) *n* = 33,434	65.8 (16.0) 65.0 (26.0; 145.0) *n* = 32,751	67.0 (14.5) 66.0 (33.0; 124.0) *n* = 683
HbA_{1c} (%, NGSP)	8.18 (1.46) 8.10 (4.53; 15.42) *n* = 33,434	8.17 (1.46) 8.10 (4.53; 15.42) *n* = 32,751	8.28 (1.32) 8.19 (5.17; 13.50) *n* = 683
eGFR (CKD-EPI)	104.4 (26.0) 108.6 (3.1; 246.0) *n* = 16,106	104.8 (25.7) 109.1 (3.1; 246.0) *n* = 15,879	74.1 (28.5) 77.0 (5.2; 146.7) *n* = 227
Albuminuria categories			
Normoalbuminuria	23,986 (82.3)	23,610 (82.9)	376 (58.8)
Microalbuminuria	2,921 (10.0)	2,809 (9.9)	112 (17.5)
Macroalbuminuria	2,222 (7.6)	2,070 (7.3)	152 (23.8)
LDL cholesterol (mmol/L)	2.65 (0.84) 2.56 (0.21; 8.62) *n* = 13,232	2.65 (0.83) 2.56 (0.21; 8.62) *n* = 13,041	2.73 (0.91) 2.50 (0.90; 6.26) *n* = 191
HDL cholesterol (mmol/L)	1.52 (0.45) 1.46 (0.30; 4.00) *n* = 13,485	1.52 (0.45) 1.46 (0.30; 4.00) *n* = 13,293	1.58 (0.54) 1.50 (0.50; 3.60) *n* = 192
SBP (mmHg)	126.3 (16.7) 124.0 (80.0; 220.0) *n* = 32,599	126.0 (16.5) 123.0 (80.0; 220.0) *n* = 31,925	140.7 (19.1) 140.0 (95.0; 210.0) *n* = 674
DBP (mmHg)	73.2 (9.1) 73.0 (40.0; 120.0) *n* = 32,599	73.2 (9.1) 73.0 (40.0; 120.0) *n* = 31,925	75.3 (9.7) 75.0 (40.0; 110.0) *n* = 674
CHD (I20–I25)	1,686 (4.7)	1,510 (4.3)	176 (23.5)
Heart failure (I50)	483 (1.3)	416 (1.2)	67 (8.9)
Valve disease (I05–I09, I34–I36)	120 (0.3)	107 (0.3)	13 (1.7)
Stroke (I61–I64)	559 (1.5)	518 (1.5)	41 (5.5)
Cancer (C00–C97)	524 (1.4)	499 (1.4)	25 (3.3)

Categorical variables are presented as *n* (%). For continuous variables, mean (SD), median (minimum; maximum), and *n* are presented. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program. *"Zero" for duration of diabetes indicates that diabetes was diagnosed at the time of first registration in the NDR.

Table 2—Cox proportional hazards models for association between time-updated potential risk factors and time to AF (model C)

Time-updated variable	Events, *n* (%)	Patients, *n* (%)	Value	HR (95% CI)	SD	Standardized HR per 1-SD increase (95% CI)	*P* value
Age (years)	696 (92.9)	33,971 (93.7)	Risk by 1-unit increase	1.10 (1.09–1.11)	14.43	3.91 (3.34–4.59)	<0.0001
Smoking	696 (92.9)	33,971 (93.7)		1.17 (0.92–1.48)	0.33	1.05 (0.97–1.14)	0.20
Mean BMI (kg/m^2)	696 (92.9)	33,971 (93.7)	Risk by 5-unit increase	1.16 (1.06–1.27)	3.93	1.13 (1.05–1.21)	0.0014
Mean HbA_{1c} (mmol/mol)	696 (92.9)	33,971 (93.7)	Risk by 10-unit increase	1.15 (1.07–1.23)	12.90	1.19 (1.09–1.30)	<0.0001
Mean HbA_{1c} (%)	696 (92.9)	33,971 (93.7)	Risk by 1-unit increase	1.16 (1.08–1.25)	1.18	1.19 (1.09–1.30)	<0.0001
eGFR (CKD-EPI)	609 (81.3)	32,593 (89.9)	Risk by 10-unit decrease	1.20 (1.16–1.24)	24.90	1.58 (1.46–1.72)	<0.0001
Albuminuria categories	675 (90.1)	32,933 (90.8)	Normoalbuminuria		0.60		
			Microalbuminuria	1.13 (0.92–1.38)	0.60	1.07 (0.95–1.21)	0.25
			Macroalbuminuria	2.22 (1.82–2.70)	0.60	1.61 (1.43–1.82)	<0.0001
Mean LDL (mmol/L)	586 (78.2)	31,563 (87.1)	Risk by 1-unit increase	0.90 (0.80–1.02)	0.69	0.93 (0.85–1.02)	0.11
Mean HDL (mmol/L)	585 (78.1)	31,414 (86.6)	Risk by 1-unit increase	0.99 (0.82–1.20)	0.43	1.00 (0.92–1.08)	0.93
Mean SBP (mmHg)	696 (92.9)	33,971 (93.7)	Risk by 10-unit increase	1.16 (1.10–1.22)	13.77	1.22 (1.14–1.32)	<0.0001
Mean DBP (mmHg)	696 (92.9)	33,971 (93.7)	Risk by 5-unit increase	1.08 (1.03–1.15)	7.06	1.12 (1.04–1.21)	0.0037
CHD (I20–I25)	696 (92.9)	33,971 (93.7)	No		0.26		
			Yes	2.61 (2.19–3.10)	0.26	1.29 (1.23–1.35)	<0.0001
Heart failure (I50)	696 (92.9)	33,971 (93.7)	No		0.14		
			Yes	3.29 (2.67–4.06)	0.14	1.18 (1.15–1.22)	<0.0001
Valve disease (I05–I09, I34–I36)	696 (92.9)	33,971 (93.7)	No		0.07		
			Yes	3.28 (2.30–4.67)	0.07	1.09 (1.06–1.12)	<0.0001
Stroke (I61-I64)	696 (92.9)	33,971 (93.7)	No		0.16		
			Yes	1.27 (0.99–1.64)	0.16	1.04 (1.00–1.08)	0.065
Cancer (C00-C97)	696 (92.9)	33,971 (93.7)	No		0.15		
			Yes	1.12 (0.84–1.51)	0.15	1.02 (0.97–1.06)	0.44

Model C: adjusted for time-updated age, sex, education, born in Sweden, time-updated diabetes duration and baseline comorbidities, time-updated variables of smoking, HbA_{1c}, SBP, and BMI (unless main effect variable).

updated means of LDL and HDL cholesterol as continuous variables presented no significant effects on risk of AF (data not shown).

Time-updated BMI yielded an added risk of AF, with an HR of 1.16 (95% CI 1.06–1.27; $P = 0.0014$) for every 5 kg/m^2 increase in BMI, and the HR was 1.96 (95% CI 1.35–2.84; $P = 0.0004$) when BMI >35 kg/m^2 compared with normal BMI (Fig. 1).

Time-updated eGFR was inversely related to the risk of AF with an added risk of 20% (HR 1.20 [95% CI 1.16–1.24]; $P < 0.0001$) per 10 mL/min/1.73 m^2 eGFR decrease in model C. When the risk of AF was compared with the reference group, the associated risk was significant, with increasing risk related to decreased eGFR, with an HR of 1.65 (95% CI 1.27–2.15; $P = 0.0002$) at eGFR levels 30 to <60 mL/min/1.73 m^2 and an HR of 5.38 (95% CI 4.09–7.06; $P < 0.0001$) at eGFR levels of <30 mL/min/1.73 m^2 (Fig. 1). Updated values of microalbuminuria had no effect on the risk of AF in the fully adjusted model. Time-updated presence of macroalbuminuria yielded an increased risk, with an HR of 2.22 (95% CI 1.82–2.70; $P < 0.0001$) (Table 2).

The nonlinear effects by a 1-unit increase of the continuous risk factors were also investigated and are presented in Supplementary Table 3.

Gradient of Risk Per 1 SD and Pseudo-R^2

Effects on the risk of AF for each variable with HRs per 1-SD increase are reported in Table 2. In the fully adjusted model by time-updated variables, the standardized HR per 1-SD increase or decrease was 3.91 (95% CI 3.34–4.59; $P < 0.0001$) for age, 1.61 (95% CI 1.43–1.82; $P < 0.0001$) for macroalbuminuria, 1.58 (95% CI 1.46–1.72; $P < 0.0001$) for eGFR, 1.22 (95% CI 1.14–1.32; $P < 0.0001$) for SBP, 1.19 (95% CI 1.09–1.30; $P < 0.0001$) for HbA_{1c}, 1.13 (95% CI 1.05–1.21; $P = 0.0014$) for BMI, and 1.12 (95% CI 1.04–1.21; $P = 0.0037$) for DBP. Using pseudo-R^2 as a complementary measure of relative importance showed a similar pattern, in that age, eGFR, CHD, heart failure, and albuminuria were the strongest risk factors for developing AF (Fig. 2).

Missing data at baseline were not imputed. Failure analyses were performed

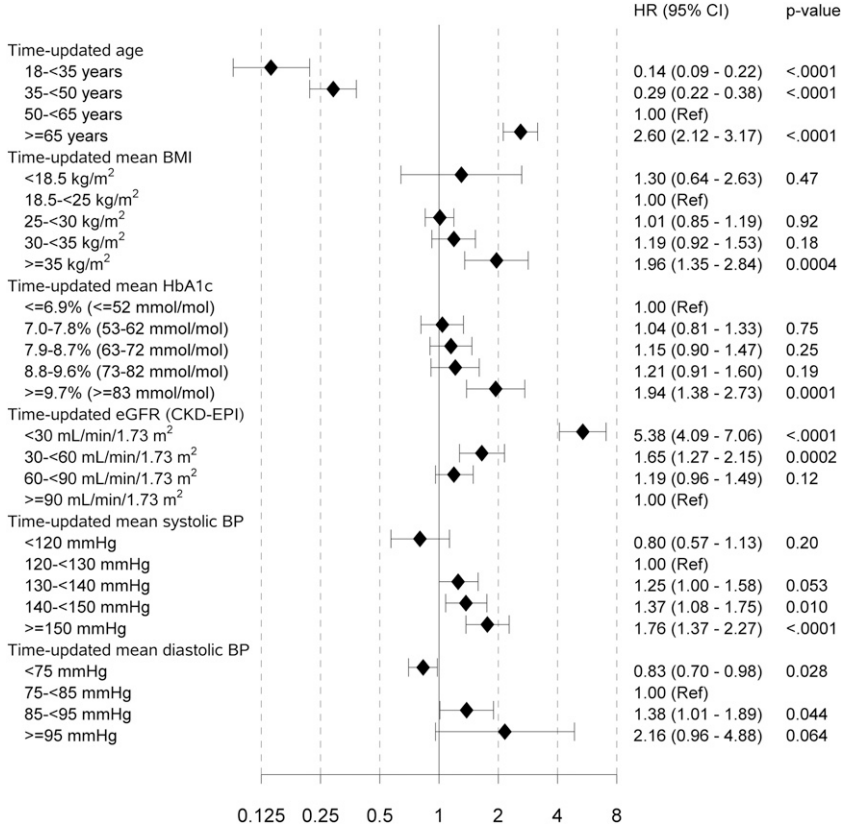

Figure 1—Cox proportional hazards model for association between categorical time-updated potential risk factors and time to AF (model C). BP, blood pressure.

for patients with and without baseline eGFR and LDL and HDL cholesterol that comprised 55.6%, 63.5%, and 62.8% missing data (Supplementary Tables 1 and 4). However, in the updated means analysis, data were used from the whole studied period, resulting in a final inclusion of 80–90% of patients with eGFR and albuminuria.

CONCLUSIONS

In this nationwide population-based study of 36,258 patients with type 1 diabetes, we found that the risk of AF increased with older age, male sex, cardiovascular comorbidities, renal dysfunction, elevated blood pressure, severe obesity, and high concentrations of glycated hemoglobin. We found no significant association between lipid concentrations or smoking and risk of AF. The variables with the strongest importance for subsequent AF were older age, low eGFR, CHD, heart failure, and albuminuria. Only very poor glycemic control showed a clear association with an increased risk of AF.

To our knowledge, the relationship between cardiovascular and other risk factors for AF among persons with type 1 diabetes has not previously been studied. A recent case-control study in patients with type 1 diabetes demonstrated an excess 13% risk of developing AF in men and 50% in women (5). The excess risk for persons with type 1 diabetes versus control subjects was more pronounced with renal dysfunction and higher levels of glycated hemoglobin (5). In the current study we wanted to evaluate a broad number of potential risk factors for AF and, accordingly, the analyzed risk factors that were adjusted for other variables affecting risk of AF.

It is noteworthy that the risk of AF was seen only at very high levels of HbA_{1c} (>82 mmol/mol [~9.6%]). The risk pattern is different from that of myocardial infarction and heart failure, where there was a monotonic increase in risk starting at comparatively low levels of HbA_{1c} (21–23). This may indicate another pathogenesis, with elevated glucose levels acting mainly via other mechanisms, for instance, renal complications. The associations for BMI and blood pressure with AF were not either as strong as for renal complications and cardiovascular comorbidities, but patients with mean SBP >150 mmHg had an ~70% increased risk, and those with severe obesity had an approximately doubled risk.

The macroangiopathy related to diabetes is explained by atherosclerosis in the arteries and depends on a combination of factors such as local inflammation, high lipid concentrations, hypertension, and hyperglycemia (24). A common effect of diabetes-related macroangiopathy is hypertension. In our study, the risk of AF related to SBP was increased at levels above current treatment targets, with an ~40% increased risk of AF at SBP >140 mmHg (25). Hypertension is an established risk factor for AF in the general population (26). Other studies have shown similar results, but the specific level of blood pressure where risk of AF begins to increase is unknown (27–30). Our findings indicate blood pressure control is needed in the prevention of AF in persons with type 1 diabetes.

Severe obesity (>BMI 35 kg/m^2), but not moderate obesity (BMI 30–35 kg/m^2) or overweight, was independently related to an increased risk of AF in our population. Overweight as a risk factor for cardiovascular disease often has a comparatively modest or no effect (31,32). A recent study of patients with type 1 diabetes did not find any significant risk of myocardial infarction or cardiovascular death associated with increased BMI (33). A previous meta-analysis in the general population showed an added risk of AF related to both overweight and obesity (34).

The risk of AF was closely related to reduced kidney function and inversely correlated to eGFR level, with an eGFR of <30 mL/min/1.73 m^2 related to a more than fivefold increase in risk. Similar results were seen in a previous study in the general population (35). We found no association between microalbuminuria and risk of AF but noted an increased risk (HR 2.22 [95% CI 1.82–2.70]; $P <$ 0.0001) related to macroalbuminuria. A comparison of our results in a population with type 1 diabetes with the Atherosclerosis Risk in Communities (ARIC) study in the general population shows that micro- and macroalbuminuria seem to be more pronounced risk factors for AF in the general population, with an increased risk related to both microalbuminuria (HR 2.0) and macroalbuminuria (HR

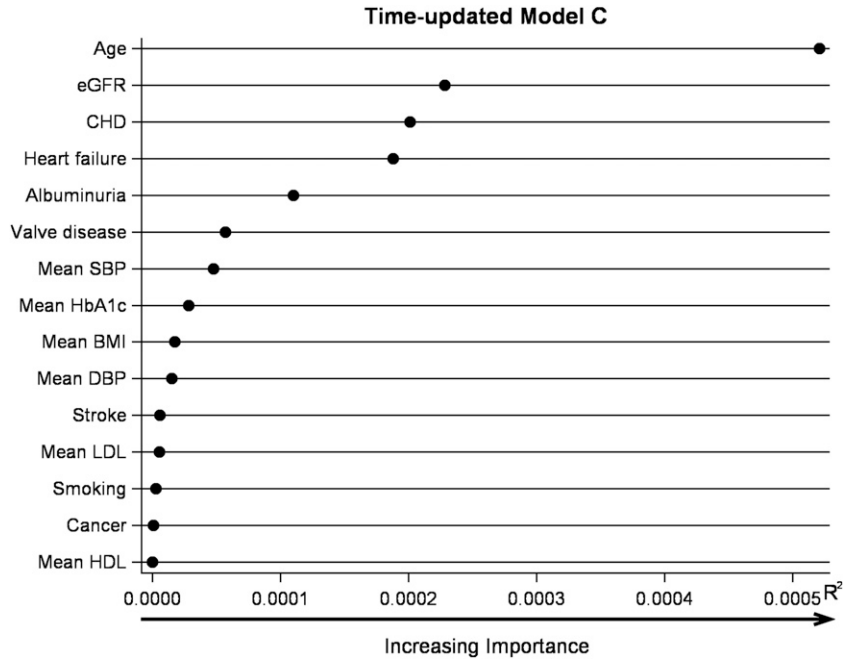

Figure 2—Relative importance of time-updated potential risk factors studied in association with atrial fibrillation (model C).

3.2) (35). This could be explained by differences in the underlying pathological process of kidney disease in patients with type 1 diabetes and kidney disease in the general population. Progress of the disease in the diabetic kidney is normally slow, developing over decades, probably leading to a longer time span between development from microalbuminuria to decreased eGFR compared with other causes of kidney disease that are more common in the general population (36,37).

The three estimates for risks of AF used give complementary information. Regular estimates describing the relative risk in relation to a certain magnitude of change in a risk factor, such as 5 mmHg or 10 mmol/mol (~1%) in HbA_{1c}, provides the clinician with a meaningful and readily understandable effect. Gradient of risk per SD has the advantage that it sets the risk of AF in relation to a certain change in the risk factor and is standardized to other risk factors but may be difficult to put into context by the clinician. Also, the gradient of risk for binary risk factors is affected by the prevalence in the cohort, which may be reasonable on the population level but less so on the individual level. The likelihood-based pseudo-R^2 measures relative importance by contribution to the log-likelihood and has the advantage of ranking both continuous and categorical variables in an order based on model fit, but does not provide information regarding the quantitative effect in relation to a numerical change in a risk factor. Comparing the numerical impact of each risk factor on developing AF, by estimating the gradient of risk and relative importance, age and variables related to heart disease and renal dysfunction were of the greatest significance. When considering modifiable risk factors only, the highest gradient of risk corresponded to increased levels of SBP and HbA_{1c}.

Our results imply that risk factors for developing AF in patients with type 1 diabetes are similar to risk factors for other forms of cardiovascular diseases. Although a direct comparison with risk factors for AF in type 2 diabetes could not be made from the data set that we obtained, Zethelius et al. (38), using data from the NDR, found older age, hypertension, and increasing BMI and albuminuria to be related to a higher risk of AF in type 2 diabetes, similar to our findings for type 1 diabetes. The difference in the impact of BMI in patients with type 2 diabetes could be explained by higher baseline BMI in the patients with type 2 and by analysis performed as continuous variables (38). Because our study is observational and the risk factors have direct effects on AF as well as the indirect effects on other risk factors, no definitive causal relationship between the analyzed variables and AF can be determined. However, our results provide additional support to the importance of prevent-ing renal damage by maintaining blood pressure and metabolic control also in order to reduce the risk of AF.

Important implications include considering screening in persons with type 1 diabetes and increased risk of AF. Of special concern are older patients, those with severe renal dysfunction (eGFR <30 mL/min/1.73 m^2), and those with cardiovascular comorbidities. Patients with very high HbA_{1c}, severe obesity, and hypertension are also at elevated risk, whereas smoking and hyperlipidemia did not indicate increased risk. Detection and treatment of AF can improve quality of life and physical capacity and also prevent stroke and heart failure.

Strengths of this study are a large number of unselected patients and nationwide coverage of patients in a country with a high prevalence of type 1 diabetes. The registries used in this study have good coverage, and the diagnoses of AF and type 1 diabetes have been validated as accurate to a high degree (14,20). Our study serves important knowledge about risk factors for incident AF among patients with type 1 diabetes, providing valuable information for future study of developing and validating an individualized prediction model for screening purposes.

Limitations include the observational nature of the study where residual confounding cannot be excluded. Although we had information on several potential risk factors for AF, these were limited to well-known cardiovascular disease risk factors and diabetes complications. Data regarding the presence of atrial remodeling, cardiac autonomic neuropathy, and recurrent severe hypoglycemia were not available but may affect the risk of AF. The more conventional definition of smoking as never, former, or current may have been preferable to use; however, only data on current smoking or nonsmoking were used in the analyses. An inevitable effect of performing an observational study on risk factors and occurrence of AF is that ~15–30% of the patients have no symptoms, but since patients with type 1 diabetes probably are more likely to undergo physical examinations than the general population, the proportion of

patients with undetected AF may be comparatively limited (2).

In conclusion, the most prominent risk factors for AF in persons with type 1 diabetes were older age, cardiovascular comorbidities, and renal complications, whereas obesity, hypertension, and hyperglycemia had more modest effects.

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