Patients With Type 2 Diabetes Have an Increased Demand for Pacemaker Treatment: A Comparison With Age- and Sex-Matched Control Subjects From the General Population

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OBJECTIVE

Patients with type 2 diabetes have an increased risk for cardiovascular disease, including arrhythmias. The prevalence of bradyarrhythmia and the subsequent need for treatment with pacemakers (PMs) is less well explored in a contemporary patient population. The current study explores *1*) whether patients with type 2 diabetes have an increased demand for PM implantation compared with an age- and sex-matched control population without diabetes and *2*) patient characteristics associated with an increased demand for receiving a PM.

RESEARCH DESIGN AND METHODS

In this population-matched registry study, a total of 416,247 patients with type 2 diabetes from the Swedish National Diabetes Registry and 2,081,235 age- and sex-matched control subjects selected from the general population were included between 1 January 1998 and 31 December 2012 and followed until 31 December 2013. Mean follow-up time was 7 years. Cox proportional hazards regression analyses were performed to estimate the demand of PM treatment and the factors identifying patients with such demand.

RESULTS

Type 2 diabetes was associated with an increased need of PM treatment (hazard ratio 1.65 [95% CI 1.60–1.69]; $P < 0.0001$), which remained (1.56 [1.51–1.60]; $P < 0.0001$) after adjustments for age, sex, educational level, marital status, country of birth, and coronary heart disease. Risk factors for receiving a PM included increasing age, HbA_{1c}, BMI, diabetes duration, and lipid- and blood pressure–lowering medication.

CONCLUSIONS

The need for PM treatment is higher in patients with type 2 diabetes than in matched population-based control subjects. Age, diabetes duration, and HbA_{1c} seem to be risk factors for PM treatment.

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Patients with diabetes have an increased risk of cardiovascular disease, such as coronary artery disease and heart failure (HF). Moreover, arrhythmias have attracted increasing attention in this context (1). The most commonly described arrhythmias in the setting of diabetes are atrial fibrillation and an increased risk of sudden death, presumably caused by ventricular fibrillation (2). There are also indications that bradyarrhythmias are common in this context. For example, in a registry study of Veterans Health Administration hospitals, third-degree atrioventricular (AV) block was significantly more common in 293,124 male patients with diabetes (1.1% vs. 0.6%) compared with a control group of 552,623 patients with hypertension but without diabetes (3). Furthermore, an association between diabetes and disturbances of the sinus node has been reported (4,5).

If patients with diabetes are at an increased risk for severe bradyarrhythmia, they should also have an increased demand for pacemaker (PM) treatment. The prevalence of diabetes in patients with PMs or planned PM insertion were higher than among control subjects in studies performed in the 1960s–1990s; however, these studies were done before the institution of contemporary background therapy and are few in number (6,7). In a more recent report, 49% of 258 patients with PM had diabetes compared with 38% in a control group consisting of 258 age- and sex-matched patients from the same hospital with sinus rhythm. However, the high overall prevalence of diabetes in this study raise concerns about the representativeness, and, furthermore, the authors did not distinguish between type 1 and type 2 diabetes (8).

Bradyarrhythmias in need of PM treatment may, if not detected and managed in time, cause serious symptoms and sometimes exposure to injuries as a result of a sudden loss of consciousness. Thus, it is clinically important to ascertain whether the observations that such arrhythmias may be more common in patients with than without diabetes and to identify potential risk factors for such arrhythmias in order to monitor and, if needed, treat exposed patients in time.

The present aim was to investigate whether contemporary patients with type 2 diabetes included in the Swedish National Diabetes Registry (NDR) have an increased demand for a newly implanted PM compared with age- and sex-matched subjects from the general population without diabetes. A secondary aim was to identify characteristics that increase the risk for the need of PM treatment in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Cohort

This population-matched cohort study is based on five different registries: the Swedish NDR, the Swedish population registry, the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) registry, the National Patient Registry (NPR), and the Swedish Registry for Cause-Specific Mortality.

The NDR comprises nearly all patients in Sweden with type 2 diabetes aged ≥18 years (coverage 92–98%). Information about clinical characteristics, risk factors, diabetes-related complications, and treatments is registered annually or more often in cases of change of medication. Data are collected by trained nurses and physicians and include information obtained in primary care and at hospital outpatient clinics (9).

The current study cohort is based on patients with type 2 diabetes ($n = 416,247$) registered in the NDR between 1 January 1998 and 31 December 2012. Entry point for the study was at the first time of registration in the NDR (10), and patients were followed until 31 December 2013 or until time of death. Date of death during follow-up was obtained from the Swedish Registry for Cause-Specific Mortality. Exclusion criteria were a diagnosis of type 1 diabetes, a PM implantation performed before the time for the baseline registrations, or implantation of cardiac resynchronization therapy.

For each registered patient with type 2 diabetes, five control subjects ($n = 2,081,235$) from the same living area, of the same age and sex, and without previous PM and/or type 1 diabetes were randomly selected from the Swedish population registry, and the mean follow-up time was 7 years. The Swedish population registry includes all Swedish citizens since 1968 and comprises information on year and date of birth and sex. The control subjects had to be free from any registration of diabetes in the NDR throughout the whole study period to be eligible.

Information on educational level, marital status, and country of birth were retrieved from the LISA registry. The LISA registry is updated annually with information on all who are living in Sweden and combines data from the labor market and educational and social sectors.

Information on previous medical history was obtained from the NPR. ICD-10 and ICD-9 codes (Supplementary Table 1) were used for atrial fibrillation (AF), acute myocardial infarction (AMI), coronary heart disease (CHD), stroke, HF, end-stage renal disease, AV block I–III, sick sinus syndrome, and ventricular tachycardia.

The primary end point was a de novo PM implantation. Information on PM treatment, including date of implantation and type of device, was obtained from the NPR applying the diagnostic codes FPE00, FPE10, and FPE20 (11).

Definitions

Type 2 diabetes was defined as treatment with diet with or without oral glucose-lowering agents or a prescription of insulin with or without concomitant oral glucose-lowering agents; the latter category applied only to patients who were ≥40 years of age at the time of the diabetes diagnosis (10,12). Glycated hemoglobin (HbA_{1c}) was expressed both in mmol/mol and % according to the International Federation of Clinical Chemistry and Laboratory Medicine and Diabetes Control and Complications Trial (DCCT), respectively.

Microalbuminuria was defined as at least two positive results obtained within 1 year and defined as an 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 urinary albumin clearance >200 μg/min (>300 mg/L). Estimated glomerular filtration rate (eGFR) was estimated from the creatinine value and calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (13). End-stage renal disease was defined as the need for renal dialysis, renal transplantation, or an eGFR of <15 mL/min/1.73 m^2.

A smoker was defined as a person who smoked one or more cigarettes per day or a pipe daily or who had stopped smoking within the past 3 months. BMI was calculated using data on weight and height collected by primary care units and hospital outpatient clinics. Blood pressure

(BP) was recorded as the mean of two readings (Korotkoff phases 1–5) with the patient sitting or lying down and using a cuff of appropriate size. Educational level was categorized as low (<9 years), intermediate (10–12 years), or high (college/university). Marital status was defined as single, divorced, married, or widowed.

Glucose-lowering medication (lifestyle, oral, insulin, or a combination) was defined as only lifestyle, oral medication, insulin, or oral medication plus insulin. Antihypertensive medication was defined as all medication prescribed for hypertension indication. Prescription of lipid-lowering drugs was defined as all medication prescribed for lipid-lowering indication, but almost exclusively statins. HDL and LDL were measured in millimoles per liter.

Statistical Analysis

Baseline characteristics for patients are those collected at their first registration in NDR, while baseline data for control subjects are those recorded in the NPR at the same date as their respective patient. Continuous variables are presented as mean and SDs and categorical data as numbers and percentages. PM implantations performed during follow-up are presented as numbers and percentages, while the incidence of PM implantations during the time of observation is expressed as number of events per 10,000 person-years. The risk for a first PM implantation in individuals with or without type 2 diabetes was assessed by means of unadjusted Cox proportional hazards regression and presented as hazard ratios (HRs) and 95% CIs. Adjustments for relevant confounders, selected on the basis of predictive confounders in the NDR and predictors for diabetes, were performed in two steps: model 1 included age, sex, marital status, educational level, and country of birth (Sweden, Europe, outside Europe), and model 2 additionally included coronary artery disease.

The registration date in NDR served as the baseline for patients with diabetes and the respective control subjects, with the time for PM implantation as the end point. Individuals who died were censored at the time of death.

The cumulative incidence of PM implantations is presented in unadjusted Kaplan-Meier curves and assessed by log-rank test for individuals with and without diabetes. Only de novo implantations were included in incidence analysis.

To establish a risk factor profile related to the need for PM, several baseline characteristics (age, diabetes duration, HbA_{1c}, systolic BP [SBP], diastolic BP [DBP], BMI, HDL, LDL, eGFR, female sex, micro- and microalbuminuria, lipid- and BP-lowering drugs, and smoking) were included in Cox regression hazard multivariate analyses (per 1-unit increase or decrease for the respective variable). This analysis was only performed in patients with type 2 diabetes ($n = 97,844$) who had these risk factors registered in the NDR.

For all analyses, a two-sided $P < 0.05$ was considered statistically significant. The analyses were performed using SAS 9.4 statistical software.

Ethical Considerations

Each patient in NDR gave informed consent before inclusion in the registry, which included information on the use of the registry for research. For the purpose of this registry-based study, all patients and control subjects were assigned individual codes. The analyses were carried out with coded data. The study, which was conducted in agreement with the Declaration of Helsinki, was approved by the Central Ethical Review Board in Gothenburg, Sweden (DNR: 776-14, 2014-11-24).

RESULTS

Baseline Characteristics

A total of 416,247 patients with type 2 diabetes and 2,081,235 control subjects were included. Baseline characteristics of patients and control subjects are presented in Table 1. In brief, the mean age at baseline was 64.1 years, and 45.7% of the studied population was female. Patients with type 2 diabetes had a mean duration of diabetes of 5.5 ± 7.0 years at entry to the registry and an HbA_{1c} of 7.1 ± 3.5% (54.6 ± 15.0 mmol/mol). Compared with the control population, patients with type 2 diabetes had a more frequent history of AMI, AF, CHD, and HF. The frequency of a bradyarrhythmia diagnosis, defined as the presence of AV block II or III or sick sinus syndrome, was higher in patients with type 2 diabetes (Table 1).

Demand for PM Treatment

The incidence expressed as implanted PMs/10,000 person-years during follow-up (mean 6.4 years) was higher in patients than in control subjects (242.2 [range 236.1–248.4] vs. 152.5 [150.3–154.6]; $P < 0.0001$), and this difference increased over time (Fig. 1). Patients with type 2 diabetes had an increased demand for receiving a PM during follow-up both in unadjusted Cox regression hazard analyses (HR 1.65 [95% CI 1.60–1.69]; $P < 0.0001$) and after adjustments according to the two models: model 1 (age, sex, marital status, educational level, income, and country of birth) (1.69 [1.64–1.74]; $P < 0.0001$) and model 2 (adding CHD) (1.56 [1.51–1.60]; $P < 0.0001$).

Factors Predicting the Demand for PM Treatment

The profile in the 97,844 patients with type 2 diabetes with complete information on potential risk factors is presented in Fig. 2. The HRs described are per 1-unit change for the respective potential risk factor. An increasing age (HR 1.08 [95% CI 1.07–1.09]; $P < 0.0001$) and duration of type 2 diabetes (1.01 [1.01–1.02]; $P < 0.0001$), together with a higher HbA_{1c} (1.01 [1.00–1.01]; $P < 0.0001$), BMI (1.03 [1.01–1.04]; $P < 0.0001$), and the use of lipid-lowering (1.20 [1.07–1.35]; $P < 0.0001$) and BP-lowering drugs (1.43 [1.23–1.65]; $P < 0.0001$), were associated with the need for PM treatment, while female sex (0.52 [0.46–0.59]; $P < 0.0001$), increasing eGFR (0.99 [0.99–1.00]; $P < 0.0001$), and DBP (0.98 [0.97–0.99]; $P < 0.0001$) were related to a decreased risk. The risk was increased both in patients with a history of ischemic heart disease (1.31 [1.24–1.39]; $P < 0.0001$) and in those without such history (1.60 [1.54–1.65]; $P < 0.0001$). A comparison of pertinent clinical characteristics between included ($n = 97,844$) and excluded patients ($n = 318,403$) revealed that the two groups were quite similar other than that excluded patients somewhat more frequently had been prescribed antihypertensive and lipid-lowering treatment (Supplementary Table 2).

CONCLUSIONS

The main findings in this nationwide, observational study of patients with type 2 diabetes with prospective follow-up were that *1*) bradyarrhythmias were more frequent among patients with type 2 diabetes already at baseline, and the incidence of bradyarrhythmia in demand of PM treatment was higher compared with a matched control group; *2*) patients with type 2 diabetes had a significantly higher demand for PM

Table 1—Baseline characteristics for patients with type 2 diabetes and control subjects

Clinical characteristic	Patients with type 2 diabetes (n = 416,247)	Control subjects (n = 2,081,235)	P value
Age (years)	64.1 (12.3)	64.1 (12.3)	
Female sex	190,304 (45.7)	951,520 (45.7)	
Age at diagnosis (years)	58.5 (12.7)	—	
Duration of diabetes at entry into registry (years)	5.5 (7.0)	—	
BMI (kg/m^2)	29.9 (5.4)	—	
Medical history			
Smoking	54,583 (16.3)	—	
BP (mmHg)			
SBP	140.0 (18.2)	—	
DBP	78.9 (9.9)	—	
AF	27,524 (6.6)	83,053 (4.0)	<0.0001
AMI	35,418 (8.5)	79,054 (3.8)	<0.0001
CHD	67,181 (16.1)	160,997 (7.7)	<0.0001
Stroke	25,295 (6.1)	74,291 (3.6)	<0.0001
HF	24,217 (5.8)	51,788 (2.5)	<0.0001
Amputation	1,444 (0.4)	1,573 (0.1)	<0.0001
End-stage renal disease	954 (0.2)	2,433 (0.1)	<0.0001
AV block			
I	503 (0.1)	1,703 (0.1)	<0.0001
II	277 (0.1)	855 (0.04)	<0.0001
III	721 (0.2)	2,229 (0.1)	<0.0001
Sick sinus syndrome	1,124 (0.3)	4,194 (0.2)	<0.0001
Ventricular tachycardia	984 (0.2)	2,963 (0.1)	<0.0001
Laboratory findings			
HbA_{1c}			
mmol/mol	54.6 (15.0)	—	
%	7.1 (3.5)	—	
Cholesterol (mmol/L)			
LDL	3.0 (1.0)	—	
HDL	1.3 (0.4)	—	
Triglycerides	1.9 (1.2)	—	
Albuminuria			
Microalbuminuria	35,411 (15.1)	—	
Macroalbuminuria	19,280 (6.63)	—	
eGFR (mL/min/1.73 m^2)	81.7 (25.2)	—	
Treatments			
Statins	155,462 (39.9)	—	
Antihypertensive medication	246,983 (63.3)	—	
Diabetes treatment			
Diet only	156,393 (37.6)	—	
Oral drugs	178,672 (42.9)	—	
Insulin	42,645 (10.3)	—	
Oral drugs and insulin	38,537 (9.3)	—	

Data are n (%) or mean (SD). Data are from the first inclusion day in the NDR for patients and the same date for control subjects. eGFR was calculated with the CKD-EPI equation.

treatment during follow-up; and *3*) a higher age, the use of BP- and lipid-lowering drugs as well as increasing BMI, HbA_{1c}, and a longer diabetes duration were associated with PM implantations, while female sex, increasing DBP, and eGFR seemed to be protective. This investigation confirms that contemporary patients with type 2 diabetes, as seen in everyday practice, are at an increased risk for developing bradyarrhythmias and, consequently, have greater need for PM treatment. This risk needs to be taken into consideration when following such patients. Potential risk factors of importance for the development of such arrhythmias has so far not been studied to any extent. The results from this study indicate what potential factors should be taken into consideration in patients with diabetes when assessing the risk for arrhythmias.

The higher prevalence of bradyarrhythmias (AV block II and III and sick sinus syndrome) at baseline, as outlined in Table 1, in patients with type 2 diabetes compared with the control group is in line with what is reported in the few previous studies in this field (i.e., there is an association between type 2 diabetes and bradyarrhythmia) (3,4,14,15). Interestingly, the earlier studies reported on a substantially higher proportion of AV block in patients with diabetes than the present findings (3,15). This may partly be explained by differences in the study populations. For example, in the study by Malmberg and Rydén (15), a high degree AV block was present in 19% of the patients with diabetes and 7% in the remaining study population without diabetes ($P < 0.001$). In this study, all patients had a myocardial infarction

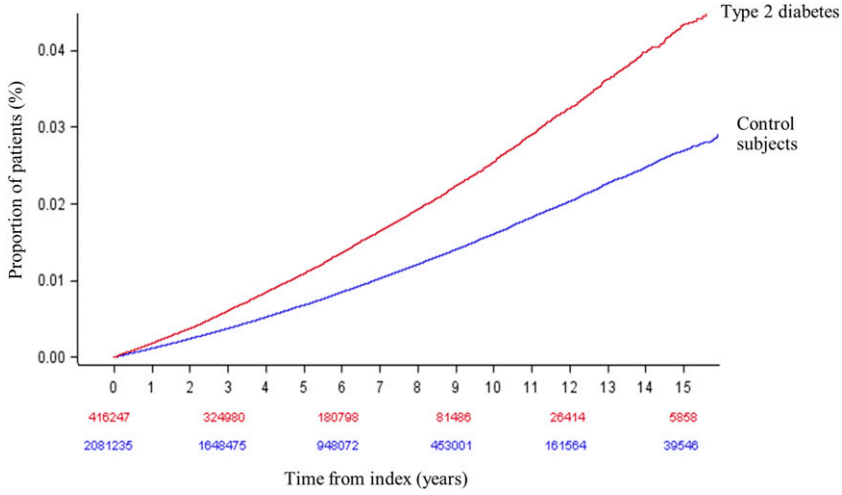

Figure 1—The cumulative risk of receiving a PM in patients with type 2 diabetes compared with control subjects. Numbers below the figure represent individuals at risk.

(15). The notion that bradyarrhythmias are more common among patients with type 2 diabetes is supported by the higher incidence of PM implantations in these patients during follow-up compared with control subjects. This supports previous reports of a higher prevalence of diabetes in patients with PM or planned PM implantations than among control groups (7,8,14). For example, in the 1975 study by Fairfax and Leatham (14), who studied 100 patients with chronic heart block admitted to the hospital for a PM implantation, 9% had diabetes. This proportion was higher than the expected (3–6%) number in the control population consisting of 100 healthy residents from retirement homes or friends of patients in the same hospital who were matched for age and sex. However, there has been a concern about representativeness in these studies, since the control groups were not well defined and sometimes consisted of patients in other studies (14) or were matched only for age and with incomplete data coding for diabetes (7,8). This is in contrast with the present study, which recruited five control subjects for each patient and had a large and well-characterized study group. Furthermore, new knowledge is contributed by demonstrating that type 2 diabetes is a predictor for a future need of PM treatment. This significantly increased risk remained after adjustment for a whole range of potential confounders.

The current study cannot provide detailed information on the etiology behind the increased risk for bradyarrhythmia and the subsequent need for a PM, even if it gives several indications. The risk factor profile shows that older patients with comorbidities, such as renal insufficiency and hypertension and use of drugs reflecting comorbidities, are at a higher risk. The risk for bradyarrhythmias may also be due to factors specific for type 2 diabetes. This disease may cause structural changes in the myocardium and the conduction system, increasing the susceptibility for not in the least bradyarrhythmias (16). Indeed, factors related to the dysglycemic condition per se, such as diabetes duration and a higher HbA_{1c}, were predictors of PM implantation. Furthermore, patients with type 2 diabetes often develop CHD, which may

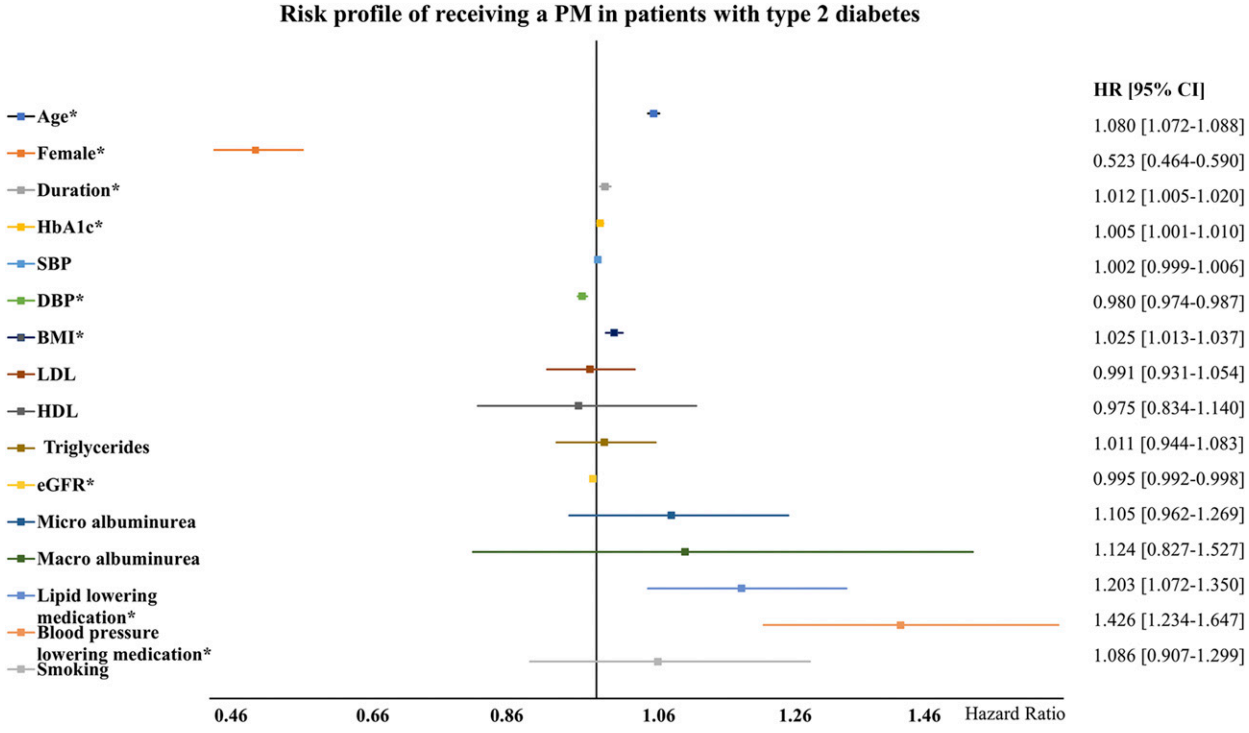

Figure 2—Risk profile of receiving a PM in patients with type 2 diabetes presented as HR (95% CI) per 1-unit change for the variable. *Significant.

increase the risk for arrhythmias directly for structural reasons or through the use of drugs that lower heart rate (e.g., β-blockers) (16). Although the risk for PM implantation decreased after adjustments for CHD, it did not disappear, indicating that other factors contribute as well. This is further underlined by the higher HR for patients without (1.60) compared with those with (1.31) a history of CHD. Moreover, diabetes-related conditions such as cardiac autonomic neuropathy and glycemic variability, in particular hypoglycemia, may contribute to arrhythmias (17–19). To further outline these possibilities, more studies are warranted.

A strength with the current study is the large number of well-defined patients with type 2 diabetes from everyday clinical practice and the likewise huge age- and sex-matched control group, five to each patient. Furthermore, the report is based on high-quality nationwide registries with practically complete coverage (9,11). Finally, the time of follow-up was long.

The study also has some limitations, including the observational nature of the study together with a possible selection bias in the control population (subjects with diabetes excluded as control subjects). This is at least partly counteracted by the prospective follow-up, but it still has to be taken into account when the results are interpreted. The lack of information on cardiovascular risk factors in the control group limits the ability to adjust for the impact of the potential differences in such characteristics between the groups. This is important to take into consideration, since people with type 2 diabetes are expected to have a higher impaired cardiovascular risk profile (e.g., higher BMI). The lack of information on some variables in the control group also limits the possibility to analyze their risk factor profiles.

In conclusion, patients with type 2 diabetes are at an increased risk of bradyarrhythmias and have a higher demand for PM treatment than control subjects from the general population. The risk was increased particularly in patients with older age and on treatment with lipid- and BP-lowering medication and seemed also to be associated with increasing BMI, long diabetes duration, and higher HbA_{1c}. The medical community should therefore recognize that patients with type 2 diabetes comprise a high-risk group for developing bradyarrhythmias with a subsequent need for PM treatment.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. E.R., L.R., and L.G.M. drafted the manuscript. E.R. and L.G.M. performed the literature search. F.G., S.G., S.F., and A.-M.S. acquired the data. S.F. performed the statistical analyses. All authors conceived, designed, and made revisions of the research/manuscript. L.G.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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References

1. Cosentino F, Grant PJ, Aboyans V, et al.; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255–323
2. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int J Cardiol 2005;105:315–318
3. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of third-degree atrioventricular block in patients with type II diabetes mellitus. Chest 2005;128:2611–2614
4. Wasada T, Katsumori K, Hasumi S, et al. Association of sick sinus syndrome with hyperinsulinemia and insulin resistance in patients with non-insulin-dependent diabetes mellitus: report of four cases. Intern Med 1995;34:1174–1177
5. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747
6. Edhag O. Long-term cardiac pacing. Experience of fixed-rate pacing with an endocardial electrode in 260 patients. Acta Med Scand Suppl 1969;502:9–110
7. Lear JT, Lawrence IG, Burden AC. Prevalence of diabetes in elderly patients with pacemakers. Postgrad Med J 1995;71:765
8. Podlaha R, Falk A. The prevalence of diabetes mellitus and other risk factors of atherosclerosis in bradycardia requiring pacemaker treatment. Horm Metab Res Suppl 1992;26:84–87
9. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B; Steering Committee of the Swedish National Diabetes Register. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care 2003;26:1270–1276
10. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732
11. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450
12. Rawshani A, Rawshani A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;377:300–301
13. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
14. Fairfax AJ, Leatham A. Idiopathic heart block: association with vitiligo, thyroid disease, pernicious anaemia, and diabetes mellitus. BMJ 1975;4:322–324
15. Malmberg K, Rydén L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988;9:259–264
16. Rydén L, Grant PJ, Anker SD, et al.; Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); Document Reviewers. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013;34:3035–3087
17. Bolognesi R, Tsialtas D, Bolognesi MG, Giumelli C. Marked sinus bradycardia and QT prolongation in a diabetic patient with severe hypoglycemia. J Diabetes Complications 2011;25:349–351
18. Imam MH, Karmakar CK, Khandoker AH, Jelinek HF, Palaniswami M. Heart rate independent QT variability component can detect subclinical cardiac autonomic neuropathy in diabetes. Conf Proc IEEE Eng Med Biol Soc 2016;2016:928–931
19. Pollock G, Brady WJ Jr., Hargarten S, DeSilvey D, Carner CT. Hypoglycemia manifested by sinus bradycardia: a report of three cases. Acad Emerg Med 1996;3:700–707