International Journal of Cardiology 268 (2018) 137–142

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Type 1 versus type 2 diabetes and thromboembolic risk in patients with atrial fibrillation: A Danish nationwide cohort study

Mia V. Fangel [a,*,1], Peter B. Nielsen [b,c,1], Torben B. Larsen [b,c,1], Bo Christensen [d,1], Thure F. Overvad [b,1], Gregory Y.H. Lip [b,e,1], Samuel Z. Goldhaber [f,1], Martin B. Jensen [a,1]

[a] Research Unit for General Practice in Aalborg, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[b] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark
[c] Department of Cardiology, Atrial Fibrillation Study Group, Aalborg University Hospital, Aalborg, Denmark
[d] Department of Public Health, Section for General Practice, Aarhus University, Aarhus, Denmark
[e] Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom
[f] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

ARTICLE INFO

Article history:
Received 21 March 2018
Received in revised form 8 May 2018
Accepted 14 May 2018

Keywords:
Atrial fibrillation
Diabetes
Stroke
Thromboembolism
Risk stratification
Cohort study

ABSTRACT

Background: Atrial fibrillation is a common cause of stroke, and diabetes increases stroke risk. Stroke risk may vary depending on the type of diabetes. We investigated whether type 1 and type 2 diabetes are associated with different risks of thromboembolism among patients with atrial fibrillation.
Methods: We used data from Danish nationwide registries to identify patients with a prior diagnosis of diabetes and an incident nonvalvular atrial fibrillation diagnosis in the period of January 1, 2005 to December 31, 2015. Cox regression analysis was used to estimate hazard ratios (HR) for the outcome thromboembolism.
Results: The study population included 10,058 patients with a prior diagnosis of diabetes and an incident diagnosis of atrial fibrillation. At three-year follow-up, type 2 diabetes was not associated with a higher risk of thromboembolism compared to type 1 diabetes, with an adjusted HR of 1.15 (95% CI: 0.91–1.44). In an age-stratified analysis, patients aged below 65 years of age had an adjusted HR of 1.97 (95% CI: 1.07–3.61), whereas patients aged 65–74 years or ≥75 years had adjusted HRs of 0.99 (95% CI: 0.67–1.46) and 1.10 (95% CI: 0.80–1.51), respectively.
Conclusion: We found no overall credible association between the type of diabetes and risk of thromboembolism in this cohort of non-anticoagulated patients with incident atrial fibrillation. Nonetheless, the subset of patients aged below 65 years of age displayed a higher risk of thromboembolism among patients with type 2 diabetes as compared to patients with type 1 diabetes.

1. Introduction

Atrial fibrillation is a common cause of stroke [1] and stroke prevention is of upmost importance when managing these patients [2]. Diabetes is associated with a higher risk of thromboembolic events in atrial fibrillation [3,4] and is incorporated in stroke risk stratification scores, such as the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75, diabetes, prior stroke/transient ischemic attack, myocardial infarction/peripheral artery disease, age ≥65, and female sex) [5]. According to guidelines, anticoagulation therapy should be considered for patients with a CHA_2DS_2-VASc score ≥1, balancing the expected stroke reduction, bleeding risk, and patient preferences [5]. Consequently, all patients with diabetes are potential candidates for life-long anticoagulant therapy, a treatment that is effective in stroke prevention but also leads to an increased risk of bleeding.

It is generally recognized that in patients with atrial fibrillation, the presence of diabetes increases the risk of stroke [3], although the magnitude of the estimated risk has varied considerably [6–9]. This observed difference in risk could be due to the heterogeneity of the diabetes population, underlining the need to identify stroke risk prediction markers among patients with diabetes and atrial fibrillation. For example, patients may have type 1 or type 2 diabetes, diseases with different pathogeneses, leading to a different distribution of cardiovascular risk factors by the time atrial fibrillation is diagnosed. For instance, patients with type 1 diabetes could have a longer duration of disease by the time of atrial fibrillation diagnosis as compared to type 2 diabetes, an attribute that has been associated with a higher stroke risk [10,11]. In addition, physical inactivity, high body mass index, and presence of dyslipidaemia are associated with

* Corresponding author at: Fyrkildevej 7, 9220 Aalborg, Denmark.
E-mail address: fangel@dcm.aau.dk (M.V. Fangel).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2018.05.037
0167-5273/

type 2 diabetes [12–14] and these factors have been associated with an increased stroke risk [15–18].

In this nationwide cohort study, we aimed to examine whether type 1 and type 2 diabetes are associated with different risks of thromboembolism among patients with incident nonvalvular atrial fibrillation.

2. Methods

The study was an observational cohort study using data from three Danish nationwide registries. All registries were cross-linked with a unique personal identification number to obtain individual level data. The registries were: 1) The Danish National Prescription Registry, which holds information on all prescription drugs sold in Denmark. Each prescription record includes patient identifier, ATC-code, package size, and quantity [19]; 2) The Danish National Patient Register, which includes all diagnoses, procedures, and outpatient services. Since 1994, diagnoses have been classified according to the International Classification of Diseases version 10 (ICD-10) [20]; 3) The Danish Civil Registration System, which holds information on date of birth, sex, migration, and date of death for all citizens in Denmark [21].

2.1. Study population

The study population consisted of all inpatients and outpatients registered in the Danish National Patient Register [20] who were discharged with a hospital diagnosis of atrial fibrillation (ICD-10 code: I48) from January 1, 2005 through December 31, 2015. The index date (baseline) was defined as the date of an incident atrial fibrillation diagnosis. Patients with a diagnosis of mechanical heart valve (ICD-10 code: Z95.2, Z95.3, Z95.4) or valvular disease (ICD-10 code: I05, I06, I34, I35) were excluded to focus on nonvalvular atrial fibrillation. Patients with inconsistent information from the Danish Civil Registration System [21], immigration within one year before entrance in the study, and/or patients who were diagnosed with thromboembolism or died on the day of admission were excluded (Fig. 1). Moreover, patients who were baseline users of anticoagulation therapy were excluded to assess stroke risk in atrial fibrillation free from stroke prevention therapy. Baseline status of being anticoagulated was defined as claiming a prescription of an oral anticoagulant [warfarin, phenprocoumoun, dabigatran, rivaroxaban, or apixaban] six months before or seven days after index date.

Baseline comorbidities and concomitant medication were ascertained using information from the Danish National Patient Register [20] and the Danish National Prescription Registry [19] (Supplemental Table 1).

2.2. Exposure

Patients were identified as belonging to the groups of 'type 1 diabetes' or 'type 2 diabetes' based on an algorithm developed by the Danish Health Data Authority, using a combination of ICD-10 codes for diabetes and ATC codes for claimed prescriptions of glucose lowering drugs (Supplemental Text 1) [22]. Type 1 diabetes was identified as patients with a combination of at least one diagnosis of type 1 diabetes (ICD-10 code: E10) and one claimed prescription of insulin or insulin analogues (ATC code: A10A) or as patients with at least two claimed prescriptions of insulin or insulin analogues. Patients were classified as having type 2 diabetes if they had at least two diagnoses of type 2 diabetes (ICD-10 code: E11) or a minimum of two claimed prescriptions of glucose lowering drugs (ATC code: A10), one of which had to be oral glucose lowering drugs (ATC code: A10B). Finally, type 2 diabetes was also identified as patients with a combination of a type 2 diabetes diagnosis and a prescription of glucose lowering drugs (ATC code: A10).

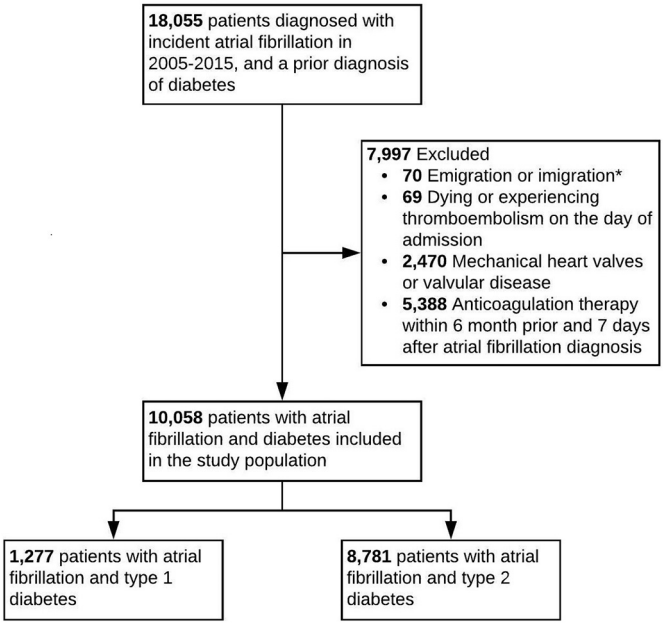

Fig. 1. Selection of the study population. *Emigrated and not back 1 year before entrance in the study or immigration within 1 year before entrance in the study.

2.3. Outcomes

Included patients were followed in the Danish National Patient Register [20] for the primary outcome of thromboembolism, which was a composite endpoint defined as a primary diagnosis of ischemic stroke (ICD-10 codes: I63, I64.9) or systemic arterial embolism (ICD-10: I74). The secondary outcome was 'time to initiation of anticoagulation therapy' defined as the time to the first claimed prescription of non-vitamin K antagonist oral anticoagulants or vitamin K antagonists. This outcome was included to unmask if prescribing physicians had behaved differently in their management of stroke risk assessment among type 1 or type 2 diabetes patients and to be able to assess the potential impact of censoring patients in the main analysis, when they initiated anticoagulation therapy.

2.4. Statistical analyses

Baseline characteristics were described separately for patients with type 1 and type 2 diabetes, using proportions for categorical measures and means for continuous measures. Incidence rates per 100 person-years for thromboembolism and 'time to initiation of anticoagulant therapy' were calculated for the groups; 'type 1 diabetes' and 'type 2 diabetes'. Specifically, the absolute number of events was divided by the number of person-years in each stratum. For the primary outcome thromboembolism, end of follow-up, death, and emigration were considered to be censoring events. Moreover, claiming a prescription of anticoagulation therapy was considered to be a censoring event in order to focus on patients who did not receive anticoagulation therapy [23]. For the secondary outcome 'time to initiation of anticoagulation therapy', end of follow-up, death, and emigration were considered to be censoring events.

Cox proportional hazards regression analyses were used to estimate the association between having type 1 or type 2 diabetes and the risk of the primary outcome thromboembolism and the secondary outcome 'time to initiation of anticoagulation therapy'. The underlying time axis was time since atrial fibrillation diagnosis. Results were reported at one- and three-year follow-up and adjusted for the individual components of the CHA_2DS_2-VASc score and baseline use of antiplatelet therapy. Age was modelled using a restricted cubic spline.

In a secondary analysis, patients were stratified by baseline age (age <65 years, 65–74 years, and ≥75 years) and previous thromboembolism status. Furthermore, we investigated a potential modification by sex on the association between the type of diabetes and the primary outcome thromboembolism.

In a sensitivity analysis, all baseline users of oral blood glucose-lowering drugs in the 'type 1 diabetes' group were relocated to the 'type 2 diabetes' group because patients using oral glucose lowering drugs are most likely to be patients with type 2 diabetes. The purpose of this sensitivity analysis was to expose whether our analysis was affected by misclassification bias, induced by the algorithm that was used to identify the two diabetes groups.

Data were analysed with Stata Statistical Software: Release 14 (College Station, TX: StataCorp LP) and R version 3.3.3 (R Foundation for statistical Computing, Vienna, Austria). Results are reported with a 95% confidence interval (CI).

3. Results

The study population included 10,058 patients with atrial fibrillation and diabetes, 12.7% with type 1 diabetes and 87.3% with type 2 diabetes. The baseline characteristics of the study population are summarized in Table 1. The mean age was 72.0 and 75.7 years for type 1 and type 2 diabetes, respectively. The distribution of sex was similar in the two groups and both groups had a mean CHA_2DS_2-VASc score of 4.6. Congestive heart failure, peripheral artery disease, and diabetic retinopathy were more prevalent among patients with type 1 diabetes. The frequency of hypertension, prior stroke, prior systemic embolism, myocardial infarction, and previous bleeding were similar in the two groups. Additionally, the prescription of antihypertensive therapy, statins, and platelet inhibitors was also similar in the two groups. Similar distribution of comorbidity was found in each of the age groups and in the group with no prior thromboembolism (Supplemental Table 2–5).

Incidence rates for thromboembolism and initiation of anticoagulation therapy, at one and three year follow-up, are shown in Table 2. During one year follow-up the total number of events of thromboembolism was 73 (5.7%) among patients with type 1 diabetes and 543 (7.6%)