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# Trends and burden of diabetes in patients with atrial fibrillation during 2007–2018: A Finnish nationwide cohort study

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ABSTRACT

*Aims:* We assessed the temporal trends in the prevalence of diabetes and in its associations with outcomes among patients with atrial fibrillation (AF).
*Methods:* The registry-based FinACAF study covered all patients with incident AF in Finland between 2007 and 2018. Ischemic stroke (IS) and mortality rates were computed using Poisson regression model.
*Results:* We identified 229 565 patients (50.0% female; mean age 72.7 years; mean follow-up 4.0 years) patients with incident AF. The prevalence of diabetes increased steadily from 15.5% in 2007 to 26.3% in 2018. A decrease in IS and mortality rates was observed during the study period both in patients with and without diabetes. Diabetes was associated with IS and mortality (adjusted incidence rate ratios with 95% confidence intervals 1.22 (1.17–1.26) and 1.32 (1.29–1.34), respectively). The impact of diabetes on IS risk remained stable, while its effect on mortality increased slightly during the observation period.
*Conclusions:* The prevalence of diabetes has increased considerably among patients with AF between 2007 and 2018. There have been substantial improvements in the prognosis of AF patients with diabetes. However, diabetes remains a significant risk factor for IS and mortality in this patient population.

## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 5.2% of the adult population.[1] It is a major cause of ischemic stroke (IS), with the risk of stroke varying considerably among individuals based on their specific comorbidities and other characteristics.[2,3] Accurate stratification of stroke risk and identification of individuals who would benefit from oral anticoagulant (OAC) therapy for stroke prevention are essential in managing patients with AF.

Diabetes mellitus, in turn, is one of the most common chronic medical conditions, and its prevalence has been continuously rising.[4] It is a multifaceted metabolic disorder, marked by dysregulated glucose metabolism with elevated blood glucose levels, often leading to a myriad of vascular complications.[5] In the presence of AF, diabetes is a well-established risk factor for IS. Indeed, diabetes is a component of the $CHA_2DS_2$-VASc score, a widely employed tool for evaluating the risk of stroke and determining the need for OAC therapy.[2]

Over the past decades, progress in medical research has resulted in substantial advancements in the management of both diabetes and AF, also reflecting in improved prognosis of these conditions. [4,6–8] While the interplay between diabetes and AF has been extensively explored in prior literature, there is a paucity of information regarding the temporal

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trends in their coexistence and how advancements in the treatment of both conditions have modified the impact of diabetes on outcomes in patients with AF. These data are needed to guide treatment in the vulnerable patient group with both AF and diabetes, as well as to project trends in the burden of these prevalent conditions.[9] Therefore, we conducted a nationwide retrospective cohort study to examine the temporal trends in the prevalence of diabetes and in its association with IS and mortality among patients with AF.

## 2. Methods

### 2.1. Study population

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study that includes all patients documented with AF in Finland from 2004 to 2018. [10] Patients were identified using all available national healthcare registers, including hospitalizations and outpatient specialist visits (HILMO), primary healthcare (AvoHILMO), and the National Reimbursement Register maintained by the Social Insurance Institute (KELA). The cohort inclusion criterion was an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code of I48, encompassing atrial fibrillation and atrial flutter, collectively referred to as AF, recorded between 2004 and 2018. Exclusion criteria encompassed permanent emigration abroad before December 31, 2018, and age below 20 years at AF diagnosis. The present sub-study was conducted within a cohort of patients with incident AF from 2007 to 2018, established in previous studies of the FinACAF cohort. [6,11,12] Follow-up started from the initial AF diagnosis, and in the analysis of IS, follow-up continued until the occurrence of IS, death, or December 31, 2018, whichever came first. For mortality analyses, follow-up continued until death or December 31, 2018. Data on baseline comorbidities were obtained from the aforementioned healthcare registers. The process of cohort construction is summarized in Supplementary Fig. 1, and the definitions of baseline comorbidities are presented in Supplementary Table 1.

### 2.2. Definition of diabetes

Patients were classified as having diabetes if they had recorded diabetes mellitus diagnosis codes (ICD-10: E10-E14) in the hospital or primary care registers or diabetes medication reimbursement codes in the National Reimbursement Register, or had redeemed diabetes medications before their AF diagnosis. Patients with diabetes were further categorized based on the redeemed diabetes medications within the year before their AF diagnosis into the following categories: (1) only insulin, (2) only non-insulin medication (including oral medication and injectable non-insulin medications, i.e. glucagon-like peptide-1 receptor agonists), (3) combination of insulin and non-insulin diabetes medications, and (4) no antidiabetic medication.

### 2.3. Outcomes

In patients without prior IS before to the first AF diagnosis, IS event was considered to occur on the first date of a recorded I63 or I64 ICD-10 diagnosis code in the hospital care register after the cohort entry. In patients with prior IS, the event was considered to occur on the date of the first new hospitalization with I63 or I64 ICD-10 code as the main diagnosis with at least a 90-day gap from the prior event, which had occurred before AF diagnosis. Dates and causes of death were retrieved from the National Death Register upheld by Statistics Finland.

### 2.4. Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017), and received research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019–3; Statistics Finland TK-53–1713-18 / u1281; and Tax Register VH/874/07.01.03/2019). Patients' personal identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2013.

### 2.5. Statistical analyses

We calculated incidence rates and incidence rate ratios (IRRs) for IS and death using the Poisson regression model. The model employed a Lexis-type data structure, incorporating three time scales: follow-up time from AF diagnosis, calendar year, and age. [13] This statistical approach was selected to address age progression over the relatively long observation period (2007–2018) and to assess outcomes during calendar year periods. Age and calendar year were treated as categorical variables. The 12-year observation period was divided into two-year intervals. Adjusted IRRs accounted for the following variables: age, calendar year period, sex, heart failure, hypertension, prior IS, vascular disease, dyslipidemia, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, cancer, dementia, psychiatric disorders, income level (divided into tertiles) and OAC use. OAC use was treated as a time-varying variable, with treatment initiation marked by the first OAC purchase and continuation until 120 days after the last drug purchase. The 120-day interval was chosen since in Finland it is possible to purchase drugs with reimbursement for a maximum of 90 days and an additional 30-day grace period was allowed to cover possible stockpiling and differences in warfarin dosing. Subsequently, the models were fitted with an interaction term between calendar year period and diabetes to assess changes in the impact of diabetes on outcomes over time. Baseline variables were compared using the Chi-square test, Student's *t*-test and analysis of variance. Statistical analyses were conducted using IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, Illinois, USA) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.org).

## 3. Results

We identified 229 565 patients with new-onset AF (50.0% female; mean age 72.7 years; mean follow-up time 4.0 years). Patients with diabetes had a higher overall prevalence of comorbidities than patients without diabetes, which was also reflected in their higher stroke and bleeding risk scores. Among patients with diabetes, those receiving only insulin treatment were the youngest, while those using both insulin and non-insulin medications had the highest prevalence of comorbidities, and those without any diabetes medication had the lowest prevalence of comorbidities (Table 1). The recorded diabetes ICD-10 codes showed significant overlap across the treatment categories, with the majority of patients in each category having a recorded code for type 2 diabetes (E11) (Supplementary Table 2). Patients in all diabetes categories, except those receiving only insulin treatment, were more likely to initiate OAC therapy during the follow-up period, compared to patients without diabetes (OAC use: no diabetes 69.3%, only insulin 63.0%, insulin and non-insulin medication 73.3%, only non-insulin medication 76.8%, and no diabetes medication 73.9%; all $p < 0.001$).

The prevalence of diabetes at cohort entry exhibited a steady increase from 15.5% in 2007 to 26.3% in 2018 (Fig. 1). This increase was observed consistently across all age categories, with the most significant rise among patients receiving only non-insulin diabetes medications. In contrast, the prevalence of patients receiving only insulin treatment remained relatively stable.

A total of 16 296 (7.1%) patients suffered an IS and 76 372 (33.3%)

**Table 1**
Baseline characteristics of the study cohort according to the presence of diabetes and diabetes treatment categories.

| | No diabetes n = 180 018 | Diabetes n = 49 542 | P-value | Only insulin n = 2 573 | Insulin and non-insulin medication n = 10 647 | Only non-insulin medication n = 27 911 | No medication n = 8 416 | P-value |
|---|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | | |
| Mean age, years | 72.2 (13.8) | 74.8 (10.6) | <0.001 | 70.5 (12.9) | 74.9 (10.0) | 75.3 (10.2) | 74.4 (11.4) | <0.001 |
| Female sex | 49.4 | 52.0 | <0.001 | 58.3 | 55.3 | 50.5 | 51.0 | <0.001 |
| **Income quartiles** | | | <0.001 | | | | | <0.001 |
| 1st (lowest) | 32.8 | 38.8 | | 39.7 | 42.8 | 37.4 | 38.1 | |
| 2nd | 31.9 | 34.9 | | 32.7 | 34.9 | 34.9 | 35.4 | |
| 3rd (highest) | 35.4 | 26.3 | | 27.6 | 22.3 | 27.6 | 26.5 | |
| **Comorbidities** | | | | | | | | |
| Any vascular disease | 24.7 | 40.3 | <0.001 | 49.9 | 50.8 | 36.5 | 36.5 | <0.001 |
| Dyslipidemia | 41.1 | 71.9 | <0.001 | 69.1 | 80.6 | 72.7 | 59.1 | <0.001 |
| Heart failure | 15.4 | 24.7 | <0.001 | 29.5 | 34.0 | 21.7 | 21.6 | <0.001 |
| Hypertension | 69.7 | 90.3 | <0.001 | 85.7 | 93.4 | 91.1 | 84.4 | <0.001 |
| Prior IS | 9.6 | 13.0 | <0.001 | 13.4 | 15.4 | 11.9 | 13.1 | <0.001 |
| Abnormal liver function | 0.4 | 0.9 | <0.001 | 1.7 | 1.4 | 0.7 | 0.8 | <0.001 |
| Abnormal renal function | 2.9 | 7.9 | <0.001 | 15.7 | 14.3 | 5.1 | 6.4 | <0.001 |
| Alcohol use disorder | 3.8 | 4.5 | <0.001 | 7.0 | 4.2 | 4.3 | 4.7 | <0.001 |
| Cancer | 20.1 | 22.4 | <0.001 | 20.9 | 23.3 | 22.3 | 21.8 | <0.001 |
| Dementia | 4.9 | 6.1 | <0.001 | 4.6 | 7.1 | 5.9 | 6.1 | <0.001 |
| Prior bleeding | 9.9 | 13.4 | <0.001 | 13.5 | 15.6 | 12.7 | 13.2 | <0.001 |
| Psychiatric disorder | 12.9 | 15.8 | <0.001 | 18.2 | 16.5 | 15.4 | 15.8 | <0.001 |
| **Risk scores** | | | | | | | | |
| Mean modified HAS-BLED score | 2.4 (1.1) | 2.9 (1.0) | <0.001 | 2.8 (1.1) | 3.1 (1.0) | 2.9 (0.9) | 2.8 (1.0) | <0.001 |
| Mean $CHA_2DS_2$-VASc score | 3.1 (1.8) | 4.7 (1.6) | <0.001 | 4.6 (1.9) | 5.0 (1.7) | 4.7 (1.6) | 4.6 (1.7) | <0.001 |

Values denote proportions (%) or mean (standard deviation). Abbreviations: $CHA_2DS_2$-VASc score, congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes (1 point), history of stroke or TIA (2 points), vascular disease (1 point), age 65–74 years (1 point), sex category (female) (1 point); IS, ischemic stroke; modified HAS-BLED score, hypertension (1 point), abnormal renal or liver function (1 point each), prior stroke (1 point), bleeding history (1 point), age > 65 years (1 point), alcohol abuse (1 point), concomitant antiplatelet/NSAIDs (1 point) (no labile INR, max score 8).

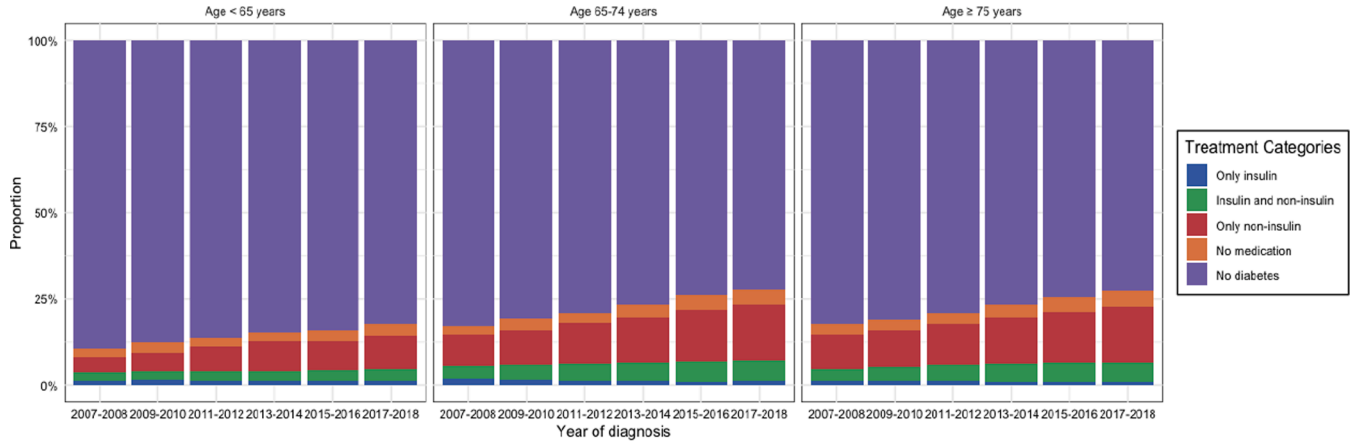


**Fig. 1.** Trends in the prevalence of diabetes in patients with incident atrial fibrillation.

patients died during the follow-up period. Diabetes was associated with elevated IS and mortality rates both in the unadjusted and adjusted analyses. Similar associations were observed across all diabetes treatment categories, with the most pronounced associations seen in patients treated with only insulin or a combination of insulin and non-insulin medications. Conversely, the category without diabetes medication exhibited the lowest rate ratios for both outcomes, and no significant association was observed with IS in the adjusted analyses (Table 2). These findings were comparable in all age categories, although the independent associations of diabetes with outcomes attenuated in older patients (Supplementary Table 3).

A continuous decrease in crude IS and mortality rates was observed during the study period in both patients with and without diabetes, with the rates remaining consistently higher in patients with diabetes (Fig. 2). This improvement in prognosis was observed across all age groups, most evidently among patients over 75 years of age (Supplementary Figs. 2 and 3). No significant interaction between calendar year period and diabetes was observed in the analyses on IS, indicating that the independent impact of diabetes on the risk of IS remained stable. On the other hand, the association between diabetes and mortality became stronger over the course of the study period (Fig. 3 and Supplementary Table 4).

## 4. Discussion

This nationwide retrospective cohort study revealed a consistent rise in the prevalence of diabetes among patients with incident AF between 2007 and 2018. However, despite this increasing diabetes burden, considerable advancements were observed in the prognosis of individuals with diabetes in parallel with those without diabetes. Diabetes

**Table 2**
Ischemic stroke and mortality rates in patients with and without diabetes.

| | P-years (1000 years) | Events, n | Incidence (per 1000p-years) | Unadjusted IRR | Adjusted IRR |
|---|---|---|---|---|---|
| **Ischemic stroke** | | | | | |
| No diabetes | 748 | 12,532 | 16.7 (16.5–17.0) | (Reference) | (Reference) |
| Diabetes | 162 | 3764 | 23.2 (22.5–23.9) | 1.39 (1.34–1.44) | 1.22 (1.17–1.26) |
| **Treatment categories** | | | | | |
| Only insulin | 9 | 236 | 27.3 (23.9–30.1) | 1.62 (1.43–1.85) | 1.45 (1.27–1.65) |
| Insulin and non-insulin | 32 | 929 | 29.1 (27.3–31.1) | 1.74 (1.63–1.86) | 1.46 (1.37–1.57) |
| Only non-insulin | 93 | 2017 | 21.7 (20.8–22.7) | 1.30 (1.24–1.36) | 1.16 (1.10–1.21) |
| No medication | 29 | 582 | 20.1 (18.5–21.8) | 1.20 (1.11–1.31) | 1.08 (0.99–1.17) |
| **Mortality** | | | | | |
| No diabetes | 780 | 56,932 | 73.0 (72.4–73.6) | (Reference) | (Reference) |
| Diabetes | 170 | 19,232 | 112.9 (111.3–114.5) | 1.55 (1.52–1.57) | 1.32 (1.29–1.34) |
| **Treatment categories** | | | | | |
| Only insulin | 9 | 1336 | 145.7 (138.0–153.7) | 2.00 (1.89–2.11) | 1.76 (1.66–1.86) |
| Insulin and non-insulin | 34 | 4946 | 146.3 (142.3–150.5) | 2.01 (1.95–2.06) | 1.55 (1.50–1.60) |
| Only non-insulin | 97 | 10,028 | 103.3 (101.3–105.4) | 1.42 (1.39–1.45) | 1.25 (1.22–1.28) |
| No medication | 30 | 2922 | 96.3 (92.8–99.8) | 1.32 (1.27–1.37) | 1.14 (1.10–1.18) |

Abbreviations: IRR, incidence rate ratio; P-year, patient-year. IRRs estimated with Poisson regression and adjusted for age, sex, calendar year, heart failure, hypertension, prior ischemic stroke, vascular disease, dyslipidemia, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, cancer, dementia, psychiatric disorders, income level and anticoagulant use.

was associated with a higher risk of IS and mortality, with the strongest associations observed in patients receiving insulin therapy or a combination of insulin and non-insulin medications. Although the overall prognosis improved, the independent impact of diabetes on IS risk remained unchanged.

The existing literature lacks previous studies investigating the temporal trends in the burden of diabetes among patients with AF. While there are reports on the rising prevalence of AF and diabetes separately, limited data exist regarding the trends in their coexistence.[1,14] Importantly, although the risks associated with diabetes in the presence of AF are well established, there has been a paucity of information regarding the evolvement of these risks during this period marked by significant advancements in the management of both AF and diabetes.[2,15]

The prevalence of diabetes increased substantially during the study period, with as many one in four patients with incident AF being comorbid with diabetes by 2018. Although we were unable to definitively distinguish patients with type 1 diabetes, it appears that the proportion of patients solely treated with insulin remained relatively consistent throughout the study period. Indeed, the increase in the burden of diabetes within this aging patient group seems to be primarily driven by type 2 diabetes, i.e., those not receiving only insulin therapy. These results are in concordance with reports of overall rising prevalence of type 2 diabetes.[14] Moreover, considering the multimorbidity associated with diabetes, our findings further emphasize the importance of cardiovascular and comorbidity risk optimization in the treatment of AF, aligning with the “C” component of the ABC pathway in the current clinical practice guidelines.[16]

The observed decrease in the IS and mortality rates among patients with coexisting AF and diabetes aligns with previous findings of improving prognosis in these patient groups separately.[6,8,17,18] However, despite advancements in the management of diabetes over the past decades, we did not observe a significant decrease in its independent impact on AF outcomes. In fact, diabetes appeared to have a slightly stronger association with mortality by the end of the study period. These findings support sustaining diabetes as a factor in the clinically used AF outcome risk scores. Notably, the patient groups requiring insulin treatment, either as a sole therapy or in combination with non-insulin diabetes medication, exhibited the highest risks of both IS and mortality in comparison to patients without diabetes. In contrast, the presence of diabetes in patients who did not require medication was not significantly associated with the risk of IS and demonstrated only a modest association with higher mortality. The group with no diabetes medication and a diabetes diagnosis is evidently a heterogeneous group, limiting the interpretation of our findings. Indeed, most patients with clinical diabetes are treated with glucose-lowering drugs. Since lifestyle interventions are difficult to implement and may unnecessarily delay the initiation of drug treatment, the Finnish Current Care guidelines (first published 2007) recommend initiating drug treatment with metformin, if not contraindicated, along with lifestyle interventions, and these guidelines have shown good adherence in primary care.[19] However, part of the patients without any medication may have had screen-detected diabetes reversible with lifestyle modifications. There could be also other factors at play, such as poor medication adherence, diabetes reversal after gastric bypass surgery, the honeymoon phase of late-onset type 1 diabetes, or the presence of concomitant severe diseases like cancer. Nonetheless, our findings raise the question of whether the benefits of OAC therapy are similar across diabetes patients with varying phenotypes and disease severity, highlighting the need for further studies to explore this aspect.

The observed trends in the prevalence and prognosis of diabetes are likely multifactorial. Similarly to the overall population, the rising prevalence of obesity and other diabetes risk factors have likely contributed to the increasing trends of diabetes in this patient population.[20]. The Development Programme for the Prevention and Care of Diabetes (DEHKO) was conducted within the Finnish primary healthcare settings between 2003 and 2008 with the aim of enhancing activities in the prevention and treatment of type 2 diabetes.[21] Subsequently, the incidence of drug-treated diabetes in Finland was reported to increase until 2010, followed by a decrease from 2010 to 2020.[22] The observed increase in diabetes prevalence in our study could thus be in parts attributed to more active diabetes screening practices and consequently the earlier detection of milder forms of type 2 diabetes. Similarly, intensified AF screening may have facilitated earlier detection of the arrhythmia, enabling timely implementation of stroke prevention and other treatment interventions. Moreover, the improved prognosis can be attributed to the broader utilization of OAC therapy and the introduction of direct oral anticoagulants, as well as the implementation of new guidelines advocating for more intensive management of diabetes, hypertension, and dyslipidemia.[5–7,23,24] Importantly, the outcome trend curves in patients with and without diabetes showed a similar pattern, suggesting shared factors underlying the improved prognosis, and thus that the improvements are not solely related to diabetes *per se.*

The retrospective registry-based design of our study has some limitations that need to be considered. Due to the overlap in recorded diabetes diagnosis codes, reflecting also the real-life complexity of the disease’s phenotypes, we were unable to reliably distinguish between different types of diabetes based solely on these codes (Supplementary

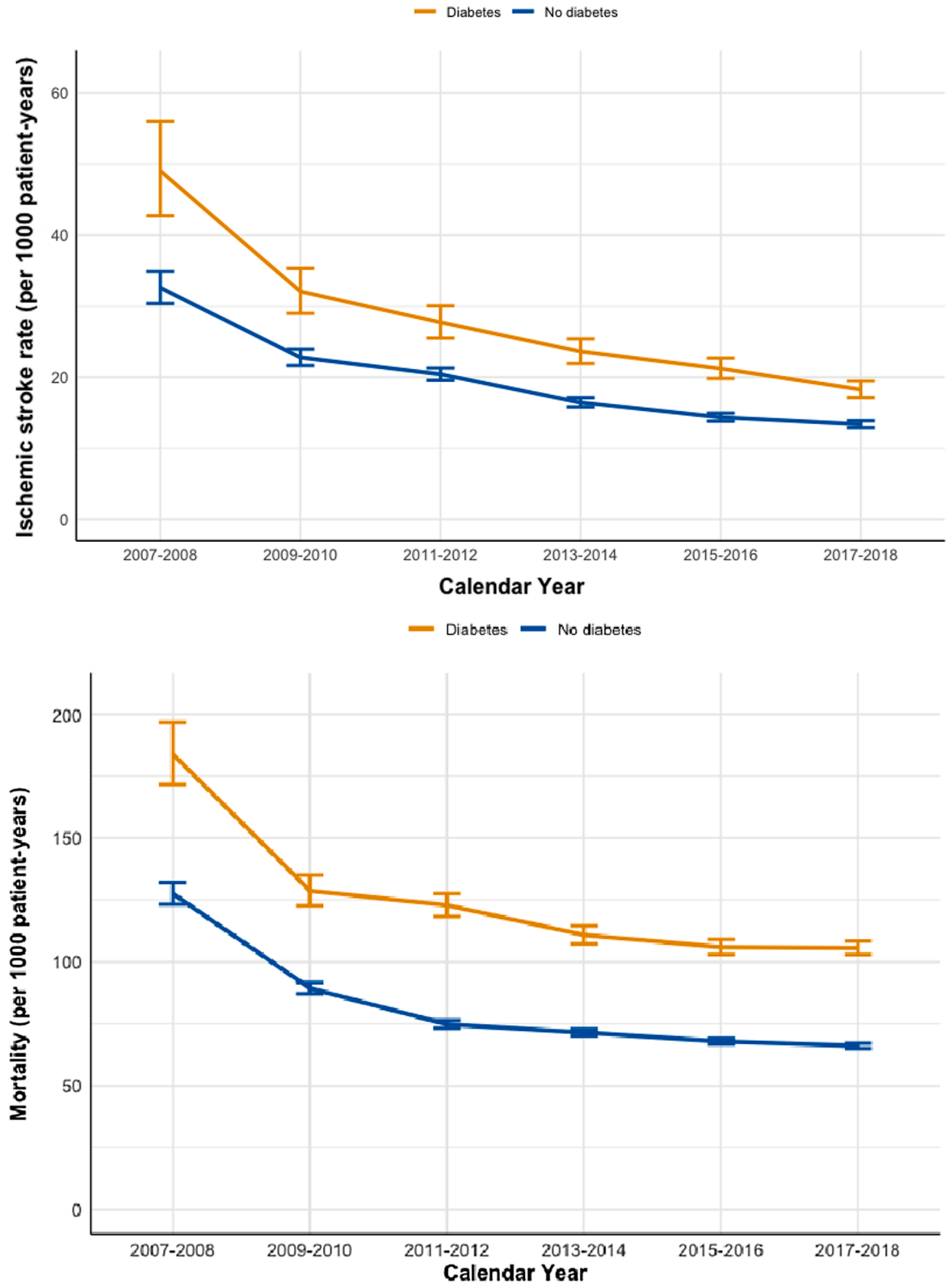


**Fig. 2.** Trends in the crude rates of ischemic stroke (above panel) and mortality (below panel) in patients with and without diabetes.

Table 2). Therefore, instead, we relied on medication usage to categorize patients with diabetes. Our results may be affected by information bias due to possible inaccuracies in the registry data. Additionally, we lacked specific data on the subtypes of AF, including atrial flutter. Indeed, a small portion of the patients have likely had atrial flutter, which could influence the interpretation of our findings. However, it is worth noting that the treatment and prognosis of atrial flutter are largely similar to those of AF.[16] Despite adjusting for a broad set of variables, residual confounding cannot be excluded. Moreover, the findings of our study represent associations and not necessarily causal relationships between diabetes, calendar years and outcomes. The primary focus in the current study was on examining temporal trends rather than investigating the

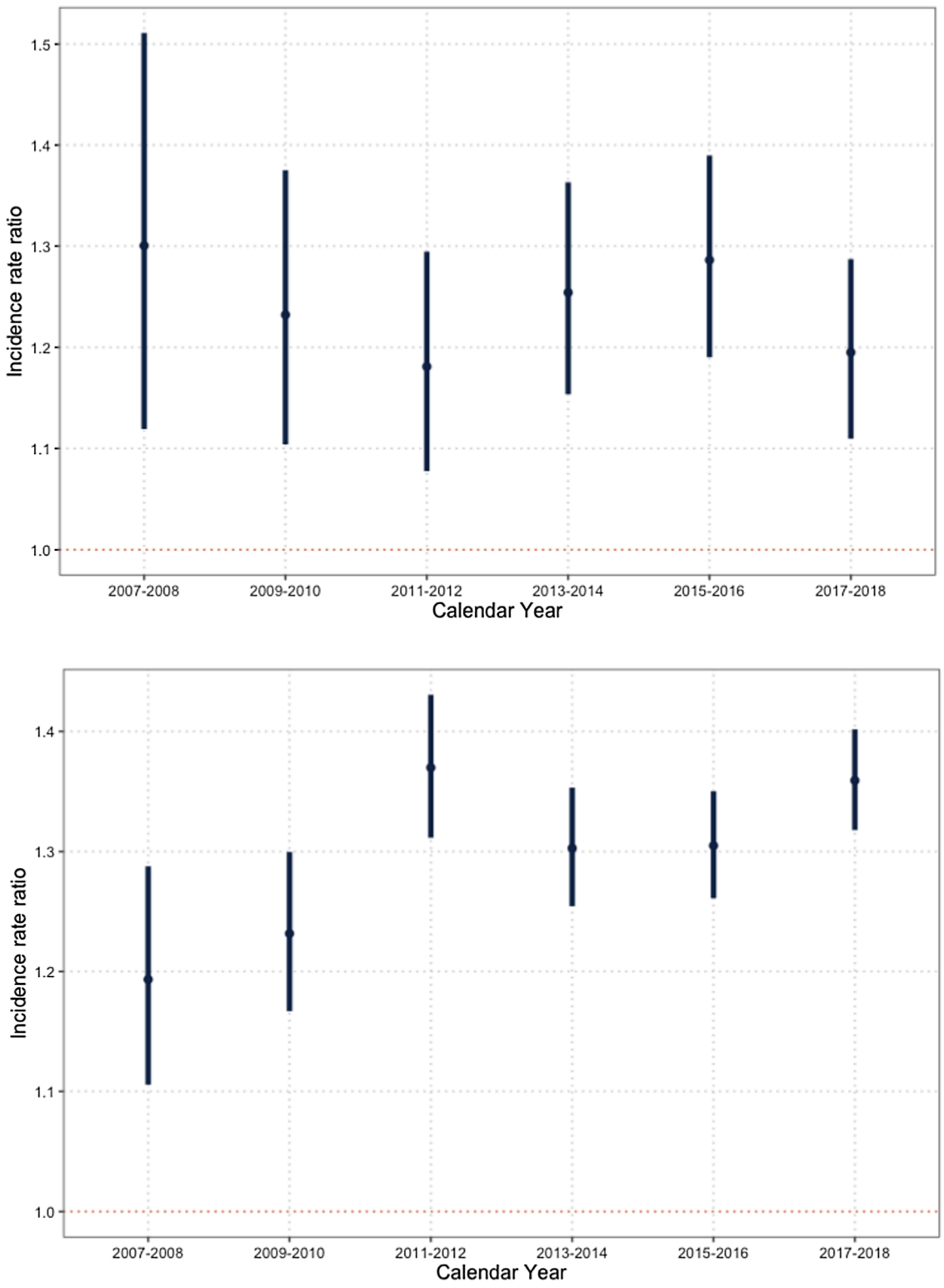


**Fig. 3.** Adjusted incidence rate ratios with 95% confidence intervals of ischemic stroke (above panel) and death (below panel) comparing patients with diabetes to those without diabetes in each calendar year period.

specific mechanisms underlying the changes in prognosis. Lastly, the observation period predates the widespread use of sodium-glucose cotransporter 2 inhibitors, so their impact on prognosis is not captured in our study. Nevertheless, our study has the advantage of a long observation period and a comprehensive nationwide coverage through linked national registries, encompassing uniquely all patients with incident AF in Finland from all levels of care. The utilization of the well-validated hospital care register further enhances the reliability of the observed IS outcomes, and the medication information is derived from complete nationwide pharmacy data on redeemed prescriptions. [25]

## 5. Conclusions

This nationwide cohort study revealed a considerable increase in the

prevalence of diabetes among patients with incident AF between 2007 and 2018. While there has been a substantial improvement in the prognosis of AF patients with diabetes, diabetes remains a significant risk factor for IS and mortality in this patient population, with diabetic patients experiencing a poorer prognosis compared to patients without diabetes. The escalating prevalence of diabetes should be recognized in the comprehensive care of patients with AF.

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## Data Availability Statement

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (KELA, Finnish Institute for Health and Welfare, Population Register Center and Tax Register) through Findata (https://findata.fi/en/).

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Konsta Teppo: Research Grants: The Finnish Foundation for Cardiovascular Research, Aarne and Aili Turunen Foundation. Jussi Jaakkola: none. Olli Halminen: none. Janne Kinnunen: none. Jukka Putaala: Speaker: Bayer, Boehringer-Ingelheim, BMS-Pfizer, Abbott; Advisory board: Portola, Novo Nordisk, Herantis Pharma; Visiting editor: Terve Media; Stock ownership: Vital Signum. Pirjo Mustonen: Consultant: Roche, BMS-Pfizer-alliance, Novartis Finland, Boehringer Ingelheim, MSD Finland. Jari Haukka: Consultant: Research Janssen R&D; Speaker: Bayer Finland. Birgitta Salmela: Speaker (BMS, Boehringer Ingelheim, Pfizer); Advisory board (Pfizer) Miika Linna: Speaker: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim. Juha Hartikainen: Research grants: The Finnish Foundation for Cardiovascular Research, EU Horizon 2020, EU FP7. Advisory Board Member: BMS-Pfizer-alliance, Novo Nordisk, Amgen. Speaker: Cardiome, Bayer. K.E. Juhani Airaksinen: Research grants: The Finnish Foundation for Cardiovascular Research; Speaker: Bayer, Pfizer and Boehringer-Ingelheim. Member in the advisory boards: Bayer, Pfizer and AstraZeneca. Mika Lehto: Consultant: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim, and MSD; Speaker: BMS-Pfizer- alliance, Bayer, Boehringer Ingelheim, MSD, Terve Media and Orion Pharma. Research grants: Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund, Boehringer-Ingelheim. Leo Niskanen: has received speaker honoraria from Amgen, Boehringer Ingelheim, Novo Nordisk, Sanofi, MSD, Astra Zeneca, Eli Lilly; research support from Novo Nordisk to the hospital; and has participated in the scientific advisory boards of Eli Lilly, Amgen, Boehringer Ingelheim, Zeneca, MSD and Novo Nordisk, received fees for educational material and books from publishing company of Duodecim.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110875.

## References

[1] Lehto M, Haukka J, Aro A, Halminen O, Putaala J, Linna M, et al. Comprehensive nationwide incidence and prevalence trends of atrial fibrillation in Finland. Open Heart 2022;9:e002140.
[2] Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM, Andresen D, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. Chest 2010:137. https://doi.org/10.1378/chest.09-1584.
[3] Björck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: A population-based study. Stroke 2013:44. https://doi.org/10.1161/STROKEAHA.113.002329.
[4] Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 1990;2023. https://doi.org/10.1016/S0140-6736(23)01301-6.
[5] Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - Summary 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). Diab Vasc Dis Res 2014:11. https://doi.org/10.1177/1479164114525548.
[6] Teppo K, Airaksinen KEJ, Jaakkola J, Halminen O, Linna M, Haukka J, et al. Trends in treatment and outcomes of atrial fibrillation during 2007–17 in Finland. Eur Heart J Qual Care Clin Outcomes 2022::qcac086. https://doi.org/10.1093/ehjqcco/qcac086.
[7] Haddad JA, Haddad AN. The past decade in type 2 diabetes and future challenges. Hormones 2018:17. https://doi.org/10.1007/s42000-018-0080-y.
[8] Gyldenkerne C, Kahlert J, Olesen KKW, Thrane PG, Sørensen HT, Thomsen RW, et al. Twenty-Year Temporal Trends in Risk of Ischemic Stroke in Incident Type 2 Diabetes: A Danish Population-Based Cohort Study. Diabetes Care 2022:45. https://doi.org/10.2337/dc22-0440.
[9] Wang A, Green JB, Halperin JL, Piccini JP. Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. J Am Coll Cardiol 2019:74. https://doi.org/10.1016/j.jacc.2019.07.020.
[10] Lehto M, Halminen O, Mustonen P, Putaala J, Linna M, Kinnunen J, et al. The nationwide Finnish anticoagulation in atrial fibrillation (FinACAF): study rationale, design, and patient characteristics. Eur J Epidemiol 2022;37:95–102. https://doi.org/10.1007/s10654-021-00812-x.
[11] Teppo K, Jaakkola J, Langén VL, Biancari F, Halminen O, Linna M, et al. Rural-urban differences in the initiation of oral anticoagulant therapy in patients with incident atrial fibrillation: A Finnish nationwide cohort study. PLoS One 2022;17:e0276612 -.
[12] Teppo K, Jaakkola J, Biancari F, Halminen O, Linna M, Haukka J, et al. Socioeconomic disparities in use of rhythm control therapies in patients with incident atrial fibrillation: A Finnish nationwide cohort study. IJC Heart Vasc 2022;41:101070. https://doi.org/10.1016/j.ijcha.2022.101070.
[13] Plummer M, Carstensen B. Lexis: An R class for epidemiological studies with Long-term follow-up. J Stat Softw 2011:38. https://doi.org/10.18637/jss.v038.i05.
[14] Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep 2020;10. https://doi.org/10.1038/s41598-020-71908-9.
[15] Klem I, Wehinger C, Schneider B, Hartl E, Finsterer J, Stöllberger C. Diabetic atrial fibrillation patients: Mortality and risk for stroke or embolism during a 10-year follow-up. Diabetes Metab Res Rev 2003:19. https://doi.org/10.1002/dmrr.386.
[16] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2020;2021:42. https://doi.org/10.1093/eurheartj/ehaa612.
[17] Forslund T, Komen JJ, Andersen M, Wettermark B, Von Euler M, Mantel-Teeuwisse AK, et al. Improved stroke prevention in atrial fibrillation after the introduction of non-Vitamin K antagonist oral anticoagulants: The Stockholm experience. Stroke 2018:49. https://doi.org/10.1161/STROKEAHA.118.021990.
[18] Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016. BMJ Open Diabetes Res Care 2020:8. https://doi.org/10.1136/bmjdrc-2019-001071.
[19] Niskanen L, Hahl J, Haukka J, Leppä E, Miettinen T, Mushnikov V, et al. Type 2 diabetes and treatment intensification in primary care in Finland. Acta Diabetol 2018:55. https://doi.org/10.1007/s00592-018-1199-7.
[20] Klonoff DC. The increasing incidence of diabetes in the 21st century. J Diabetes Sci Technol 2009:3. https://doi.org/10.1177/193229680900300101.
[21] Tuomilehto J, Uusitupa M, Gregg EW, Lindström J. Type 2 Diabetes Prevention Programs—From Proof-of-Concept Trials to National Intervention and Beyond. J Clin Med 2023:12. https://doi.org/10.3390/jcm12051876.
[22] Saaristo T, Moilanen L, Korpi-HYÖVÄLTI E, Vanhala M, Saltevo J, Niskanen L, et al. Lifestyle intervention for prevention of type 2 diabetes in primary health care: One-year follow-up of the finnish national diabetes prevention program (FIN-D2D). Diabetes Care 2010:33. https://doi.org/10.2337/dc10-0410.
[23] Lyu B, Sang Y, Selvin E, Chang AR, Alexander GC, Cohen CM, et al. Pharmacologic Treatment of Type 2 Diabetes in the U.S., Sweden, and Israel. Diabetes Care 2022:45. https://doi.org/10.2337/dc22-1253.
[24] Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease: The Task Force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J 2004;25. https://doi.org/10.1016/j.ehj.2004.06.003.
[25] Sund R. Quality of the Finnish Hospital Discharge Register: A systematic review. Scand J Public Health 2012:40. https://doi.org/10.1177/1403494812456637.