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ORIGINAL RESEARCH

Association Between Onset of Type 2 Diabetes and Risk of Atrial Fibrillation in New Zealanders With Impaired Glucose Tolerance Over 25 Years

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BACKGROUND: The association between the onset of type 2 diabetes (T2D) and atrial fibrillation (AF) risk in individuals with impaired glucose tolerance (IGT) remains unclear. This study aimed to investigate the relationship between the incident onset of T2D and 5- and 10-year (after the landmark period) risks of AF in people with IGT identified in South and West Auckland primary care settings between 1994 and 2019.

METHODS AND RESULTS: We compared AF risk in patients with IGT with and without newly diagnosed T2D within a 1- to 5-year exposure window. Tapered matching and landmark analysis (to address immortal bias) were used to control for confounding variables. The cohorts incorporated 785 patients who had T2D newly diagnosed within 5 years from enrollment (landmark date) and 15 079 patients without a T2D diagnosis. Patients progressing to T2D exhibited significantly higher 5-year (after the landmark period) AF risk (hazard ratio [HR], 1.34 [95% CI, 1.10–1.63]) and 10-year (after the landmark period) AF risk (HR, 1.28 [95% CI, 1.02–1.62]) compared with those without incident T2D. The association was more pronounced among men, older patients, socioeconomically deprived individuals, current smokers, those with higher metabolic measures, and lower renal function. New Zealand European ethnicity was associated with a lower 5- and 10-year risk of AF.

CONCLUSIONS: This study found a mediating effect of T2D on the risk of AF in a population with IGT in New Zealand. The development of risk scores and future replication studies can help identify and guide management of individuals with IGT at the highest risk of AF following incident T2D.

Key Words: atrial fibrillation ■ impaired glucose tolerance ■ New Zealand ■ type 2 diabetes

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia worldwide. In 2010, there were ≈5 million reported cases of AF,[1] and it is predicted to double over the next 50 years due to the aging population and an increased incidence of the disease.[2] Patients with AF are at a higher risk of various health issues, including ischemic heart disease, heart failure, stroke, and all-cause death.[1] These health issues also incur higher medical costs and reduce the quality of life compared with those without AF.[3]

The risk factors for AF are well established and include age, hypertension, smoking, obesity, and high

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CLINICAL PERSPECTIVE

What Is New?

- This study used linked primary and national registration data sets in New Zealand and applied landmark analysis to minimize immortal bias, along with tapered matching methods to control confounders.
- The findings demonstrate that the development of type 2 diabetes among patients with impaired glucose tolerance is associated with an increased risk of atrial fibrillation over the 5 and 10 years after the landmark period.

What Are the Clinical Implications?

- The study highlights the need for the development of risk scores to identify and guide the management of individuals with impaired glucose tolerance who are at the highest risk of developing atrial fibrillation following incident type 2 diabetes.

Nonstandard Abbreviations and Acronyms

DCSS	Diabetes Care Support Service
IMD	Index of Multiple Deprivation
IGT	Impaired glucose tolerance
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research
T2D	type 2 diabetes

heart rate.[4–6] Type 2 diabetes (T2D) has also been identified as a risk factor for AF,[4,7,8] with a meta-analysis showing a 28% higher risk of AF in individuals with T2D compared with those without T2D.[9] Several cohort studies have investigated the association between prediabetes (impaired fasting glucose or impaired glucose tolerance [IGT]) and AF, with mixed results.[10–12] Similarly, studies of the association between blood glucose and AF have also produced inconsistent results.[13–15] This inconsistency may be due to low statistical power, differences in adjustments for covariates, and differences in participant age. In addition, no previous studies reported an association between the progression to T2D and the risk of AF in the population with IGT.

To address this gap in knowledge, the current study was conducted using matched cohorts derived from a large longitudinal primary care database with linkage to national registration databases. The study aimed to investigate the association between the onset of T2D and the 5- and 10-year risk of AF in patients with IGT. A 1- to 5-year landmark analysis was used to rule out immortal bias, and an innovative tapered matching method was used to control confounders.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

The Diabetes Care Support Service (DCSS), established in 1991, carried out an audit of diabetes management in general practice across South, East, and West Auckland with the aim of elevating the standard of care.[16] The DCSS database was linked to data from multiple sources, including the national cancer registry, death registry, hospitalization, pharmaceutical claim, and socioeconomic status databases. A cohort was identified of individuals aged ≥18 years with IGT, based on the 2-hour glucose between 7.8 and 11 mmol/L during an oral glucose tolerance test.[17]

Data available included demographic and clinical information, smoking status, body mass index, blood pressure, HbA_{1c}, lipids, and treatment information for antihypertensive, statin, antiplatelet, and anticoagulant therapy. The data were thoroughly validated through internal quality control measures, such as enumeration assessments, regular cross checking by auditors, random and routine data entry sampling, and active data management techniques (eg, queries, checking unusual numbers, ranking of columns, duplicate checking).[16,18,19]

The pharmaceutical claims data included all prescription records for the patients and were used to cross validate the prescription information in the DCSS database. However, only the claims data after 2006 were available for data linkage due to unavailability of National Health Index numbers before 2006. The data for all patients were included starting from their first DCSS enrollment date, with the last enrollment taking place on July 31, 2018.

The DCSS was approved by the North Health Ethics Committee for research purposes in 1992 and as an ongoing audit in 1996 (92/006). Ethics review was waived by the New Zealand Health and Disability Ethics Committees on March 25, 2019. Anonymized data were used for this analysis. Signed consent to participate was provided by an authorized signatory for each general practice. This study was written in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Exposure

We categorized patients with IGT on the basis of their exposure to T2D. Newly diagnosed cases with T2D recorded in any linked data sets were considered as the

exposure. We applied a landmark analysis method to assess the impact of the onset of T2D on the risk of AF. The landmark analysis involved selecting a fixed time point after cohort entry for conducting a survival analysis.[20] Only patients with IGT who were alive at the landmark date were included in the analysis, and the onset of T2D was based on exposure before the landmark date. The exposure was evaluated only within a predetermined exposure window, which was the interval between the index date and the landmark time point. The outcome was then evaluated from the landmark time point.[21] Five landmark time points were determined a priori in this study, specifically at 1, 2, 3, 4, and 5 years after the cohort enrollment date. The exposure status was assigned to patients with IGT who were still alive at each of the landmark dates. The method of landmark analysis was illustrated in Figure S1. The numbers of ineligible patients excluded during the period between the index date and the landmark time point are presented in Figures S2 through S6.

Outcomes

The outcome of the present study was incident AF, defined as the first recorded case of AF in any of the linked data during the follow-up period from the end of the landmark period. Patients with IGT were followed up from the end of landmark period until the occurrence of the outcome of interest, or until December 31, 2019, for those without any outcome of interest. Immortal person-time over the landmark period was not included in the denominator for the risk estimation. AF was identified using the primary *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Classification of Diseases*, *Tenth Revision* (*ICD-10*) codes.

Covariates

Patient demographics, clinical measurements, antihypertensive medications, anticoagulants, and lipid-lowering drugs by the time of enrollment were taken into consideration as covariates. Socioeconomic status was determined using the NZDep2013 Index of Deprivation, which measures the level of deprivation in a given area.[22] The NZDep2013 assigns an Index of Multiple Deprivation (IMD) score for each New Zealand meshblock (geographic unit containing a median of 81 people).[22] Scores on the NZDep2013 scale of deprivation range from 1 to 10, with lower scores indicating less deprivation; the scale divides New Zealand into tenths of the distribution of the first principal component scores and was consistent with prior deprivation measures.[23] To maintain statistical power, the IMD was recategorized into 5 groups: IMD-1 (least deprived: NZDep2013 scores of 1–2); IMD-2, IMD-3, and IMD-4 (NZDep2013 scores of 3–4, 5–6, and 7–8, respectively); and IMD-5 (most deprived: NZDep2013 scores of 9–10).

Statistical Analysis

We used tapered matching framework from Silber et al[24] to mitigate confounding by indication and establish comparative cohorts. This approach was employed to examine the effect of the onset of T2D on AF risks between the focal group (individuals with IGT and the onset of T2D during the exposure time window) and control (individuals with IGT and no onset of T2D during the exposure time window) groups via entropy balancing. This involved gradually matching the control and focal cohorts using additional covariates and directly observing how the matched cohort altered with respect to hazard ratios (HRs) and unmatched covariates.

To minimize model dependence and prevent irresolvable imbalances between the comparison groups, we used coarsened exact matching before tapered matching to restrict the comparison of patients in comparative groups to areas of common support.[25] For each of the 1- to 5-year landmark analyses, 10 matching steps were processed, and patients with IGT in comparative groups matched on the 10th step were retained (Figures S2 through S6).

After removing participants with no areas of common support, we used entropy balancing to reduce differences in the distribution of matching variables between comparison groups. Entropy balancing involves maximum entropy reweighting of the unexposed group (in this study, the group without the onset of T2D) by directly incorporating covariable balance into the weight function. The matched sample is reweighted in each matching step to key target moments (mean, variance, and skewness).[26] The final matching aimed to achieve similar distributions of each matched variable between the 2 comparison groups in terms of their mean, variance, and skewness, while also balancing other matched variables to ensure no significant differences. All preprocessing (both coarsened exact matching and entropy balancing) was carried out without reference to outcomes.

Weighted Cox proportional hazards regression was applied in each matching step incorporating matching weights estimated through entropy matching and taking into account the competing risk of all deaths (except deaths due to incident AF events). The relative risk of outcomes between comparison groups was estimated from this model. The rates of incident outcomes between the comparative groups were estimated using the incidence density method. This involved dividing the overall outcome counts by the overall person-time from all eligible patients during the follow-up period since the landmark time. The number of imputed data sets was determined by the percentage of incomplete

cases (<6% in the current study), 6 imputed data sets were created for multiple imputation with chained equations, and estimations were made by Robin's rule.[27] The estimations from the complete case analysis were also conducted for comparison with the primary estimations obtained from the imputed analysis. Subgroup analysis was also processed by sex, age group, New Zealand European, deprivation status, smoking status, obesity, levels of clinical measurements (systolic blood pressure, total cholesterol, low-density lipoprotein, and estimated glomerular filtration rate). Subgroup analyses employed a test of interaction to investigate whether there was evidence indicating a differential impact of T2D onset on the risk of AF across subgroups. The analyses were conducted using Stata/MP, version 17.0 (StataCorp LLC). Statistical significance was set at 2-tailed $P<0.05$.

RESULTS

Overall, 26 794 patients with IGT were enrolled between 1994 and 2018. Patients were omitted from the landmark analysis due to death, loss of follow-up, or the occurrence of a relevant outcome between the enrollment date and the landmark time point. Exclusions included 2054 patients from the 1-year analysis, 2097 from the 2-year analysis, 3872 from the 3-year analysis, 6867 from the 4-year analysis, and 10 930 from the 5-year analysis. For the 1-year landmark analysis, a total of 24 740 patients with IGT who were alive 1 year after enrollment were considered, out of whom 174 developed T2D within the 1-year window. Among these patients, incident T2D in each landmark year were 361 for the 2-year analysis, 553 for the 3-year analysis, 702 for the 4-year analysis, and 785 for the 5-year analysis.

Matching

The unmatched cohort underwent 10 matching steps to create matched pairs of individuals with IGT who did not develop T2D and those who did: 150 cases and 1957 controls for the 1-year period (Figure S2), 313 cases and 3838 controls for the 2-year period (Figure S3), 478 cases and 4961 controls for the 3-year period (Figure S4), 597 cases and 5051 controls for the 4-year period (Figure S5), and 650 cases and 4352 controls for the 5-year landmark analysis (Figure S6).

The characteristics of individuals with IGT who did and did not develop T2D before and after matching are displayed in Table 1 and Table S1 for each of the 1- to 5-year landmark analyses. After applying the tapered matching methods (especially entropy matching), no significant differences were observed in the variables included in the matching process between the 2 groups, indicating the effectiveness of the matching process (Table 1).

Outcomes After Matching

Table 2 shows the 5- and 10-year rates of AF in individuals with and without the onset of T2D after coarsened and exact matching for 1- to 5-year landmark analysis in the population with IGT. For the 1-year landmark analysis, the 5-year (after the landmark period) risk for those with the onset of T2D is 35.90 per 1000 person-years (95% CI, 14.43–73.96), and the 10-year (after the landmark period) risk is 15.21 per 1000 person-years (95% CI, 6.57–29.97). The corresponding figures for controls without the onset of T2D are 14.14 (95% CI, 10.27–18.98) and 6.56 (95% CI, 4.97–8.50) per 1000 person-years, respectively.

Similar trends are observed for the 2-, 3-, 4-, and 5-year landmark analysis. Generally, the incidence of AF is higher among individuals with the onset of T2D compared with those without T2D, as shown by both 5-year (after the landmark period) and 10-year (after the landmark period) risk estimates. The difference in risk is particularly pronounced at the 5-year landmark analysis, where the rate of AF among individuals with T2D is 66.88 (95% CI, 51.39–85.57) per 1000 person-years, compared with 19.89 (95% CI, 16.80–23.40) per 1000 person-years for those without T2D for 5-year risk of AF. The 10-year risk of AF among individuals with IGT and T2D is 49.54 (95% CI, 39.62–61.18), while it is 19.05 (95% CI, 16.53–21.84) for those without T2D. The rates increased sharply between the 4- and 5-year landmark window for both the group with and the group without T2D, and this increase was due to a lack of change in the numerator and a decrease in the denominator. Specifically, the population size of censoring and early outcomes reached 10 030 (Figure S6).

Association Between the Onset of T2D and AF

The final (by step-10 matching) adjusted HRs of 5-year (after the landmark period) risk of AF comparing those people with and without the new onset of T2D in the landmark analyses were 1.57 (95% CI, 1.09–2.25) at 1 year, 1.60 (95% CI, 1.14–2.24) at 2 years, 1.26 (95% CI, 1.02–1.56) at 3 years, 1.28 (95% CI, 1.01–1.63) at 4 years, and 1.34 (95% CI, 1.10–1.63) at 5 years (Figure 1 and Figure S7).

The final adjusted HRs of 10-year (after the landmark period) risk of AF comparing those people with and without the new onset of T2D in the landmark analyses were 1.44 (95% CI, 1.06–1.96) at 1 year, 1.31 (95% CI, 1.02–1.69) at 2 years, 1.24 (95% CI, 1.00–1.54) at 3 years, 1.22 (95% CI, 1.01–1.48) at 4 years, and 1.28 (95% CI, 1.02–1.62) at 5 years (Figure 1 and Figure S8).

After step-10 matching, the final adjusted HRs of the 5-year (after the landmark period) risk of AF in comparison of those with and without the onset of T2D in the landmark analyses were 1.57 (95% CI, 1.09–2.25)

Table 1. Comparison of Patients With and Without Onset of T2D in Patients With Impaired Glucose Tolerance in the Final Matched Cohorts

	1-year Landmark			2-year Landmark			3-year Landmark			4-year Landmark			5-year Landmark		
	Without T2D onset	With T2D onset		Without T2D onset	With T2D onset		Without T2D onset	With T2D onset		Without T2D onset	With T2D onset		Without T2D onset	With T2D onset	
	N=1957	N=150	*P* value	N=3838	N=313	*P* value	N=4961	N=478	*P* value	N=5051	N=597	*P* value	N=4352	N=650	*P* value
Age, y	57.1 (13.2)	58.1 (12.8)	0.644	56.8 (12.6)	58.2 (11.4)	0.144	56.4 (12.4)	57.7 (12.2)	0.110	55.9 (12.3)	57.1 (12.1)	0.077	56.1 (11.9)	56.7 (12.2)	0.393
Female sex, % (SE)	61.9 (0.03)	61.9 (0.05)	0.962	55.2 (0.2)	55.4 (0.4)	0.973	52.2 (0.02)	52.3 (0.03)	0.978	53.6 (0.01)	53.7 (0.03)	0.980	53.5 (0.01)	53.5 (0.02)	0.982
New Zealand European, % (SE)	47.7 (0.03)	47.7 (0.05)	0.989	46.2 (0.2)	46.2 (0.4)	0.992	43.8 (0.02)	43.8 (0.03)	0.994	43.3 (0.01)	43.3 (0.03)	0.994	43.8 (0.02)	43.8 (0.02)	0.995
Enrolled cohort, % (SE)															
1994–1998	1.7 (0.02)	2.2 (0.02)	0.935	0.7 (0.01)	1.1 (0.01)	0.939	0.8 (0.004)	0.7 (0.005)	0.999	1.0 (0.01)	0.5 (0.004)	0.643	1.0 (0.01)	0.5 (0.003)	0.493
1999–2003	6.6 (0.02)	4.4 (0.02)		7.3 (0.2)	5.9 (0.02)		6.5 (0.01)	6.7 (0.01)		5.8 (0.01)	7.4 (0.01)		6.3 (0.01)	8.3 (0.01)	
2004–2008	17.3 (0.03)	20.0 (0.04)		16.0 (0.2)	17.7 (0.03)		15.3 (0.01)	14.8 (0.02)		15.8 (0.01)	13.2 (0.02)		18.7 (0.01)	15.6 (0.02)	
2009–2013	44.8 (0.03)	43.3 (0.05)		45.1 (0.2)	44.1 (0.04)		47.0 (0.02)	47.3 (0.03)		52.5 (0.01)	54.2 (0.03)		61.1 (0.02)	63.3 (0.02)	
2014–2018	29.5 (0.02)	30.0 (0.05)		30.8 (0.1)	31.1 (0.03)		30.4 (0.01)	30.4 (0.03)		25.0 (0.01)	24.7 (0.02)		12.9 (0.01)	12.4 (0.02)	
IMD group (NZDep13 scale), % (SE)															
Least deprivation: IMD-1 (1 or 2)	5.1 (0.01)	5.6 (0.02)	0.967	6.1 (0.01)	5.9 (0.01)	0.970	7.7 (0.01)	7.8 (0.02)	0.999	9.1 (0.01)	9.3 (0.02)	0.923	8.6 (0.01)	8.5 (0.01)	0.998
IMD-2 (3 or 4)	14.2 (0.02)	12.2 (0.03)		16.3 (0.01)	17.2 (0.03)		16.2 (0.01)	15.9 (0.02)		15.9 (0.01)	14.8 (0.02)		15.6 (0.01)	15.8 (0.02)	
IMD-3 (5 or 6)	13.1 (0.02)	15.6 (0.04)		14.5 (0.01)	12.9 (0.02)		11.0 (0.01)	11.3 (0.02)		10.3 (0.01)	11.8 (0.02)		11.2 (0.01)	10.7 (0.02)	
IMD-4 (7 or 8)	21.2 (0.03)	20.0 (0.04)		15.9 (0.02)	17.2 (0.03)		15.9 (0.01)	15.9 (0.02)		15.4 (0.01)	14.5 (0.02)		15.9 (0.01)	16.3 (0.02)	
Most deprivation: IMD-5 (9 or 10)	46.3 (0.03)	46.7 (0.05)		47.1 (0.02)	46.8 (0.04)		49.1 (0.02)	49.1 (0.03)		49.4 (0.01)	49.6 (0.03)		48.8 (0.02)	48.7 (0.02)	
Smoking status, % (SE)															
Never smoker	55.9 (0.03)	55.6 (0.05)	0.994	52.3 (0.02)	52.2 (0.04)	0.998	54.9 (0.02)	54.8 (0.03)	0.998	54.6 (0.01)	54.5 (0.03)	0.999	54.3 (0.01)	54.3 (0.02)	0.999
Ex-smoker	26.1 (0.03)	26.7 (0.05)		32.5 (0.02)	32.8 (0.03)		30.2 (0.01)	30.4 (0.03)		29.5 (0.01)	29.6 (0.02)		28.8 (0.01)	29.0 (0.02)	
Current smoker	18.0 (0.02)	17.8 (0.04)		15.1 (0.01)	15.1 (0.03)		14.9 (0.01)	14.8 (0.02)		15.9 (0.01)	15.9 (0.02)		16.8 (0.01)	16.8 (0.01)	
Body mass index, kg/m^2	32.9 (7.1)	32.9 (7.1)	0.958	33.1 (6.9)	33.1 (6.9)	0.959	33.4 (7.0)	33.4 (7.0)	0.965	33.3 (6.7)	33.4 (6.7)	0.968	33.8 (6.8)	33.8 (6.8)	0.972

(*Continued*)

Table 1. Continued

	1-year Landmark			2-year Landmark			3-year Landmark			4-year Landmark			5-year Landmark		
	Without T2D onset	With T2D onset		Without T2D onset	With T2D onset		Without T2D onset	With T2D onset		Without T2D onset	With T2D onset		Without T2D onset	With T2D onset	
	N=1957	N=150	*P* value	N=3838	N=313	*P* value	N=4961	N=478	*P* value	N=5051	N=597	*P* value	N=4352	N=650	*P* value
Systolic blood pressure, mm Hg	134 (16)	134 (16)	1.000	134 (17)	133 (17)	0.417	133 (17)	132 (17)	0.488	133 (17)	132 (16)	0.291	133 (17)	132 (16)	0.179
Diastolic blood pressure, mm Hg	79 (10)	79 (10)	1.000	80 (10)	80 (10)	0.856	80 (10)	80 (10)	0.742	80 (10)	80 (10)	0.738	81 (10)	81 (10)	0.753
HbA_{1c}, mmol per mol/%	42.9 (4.1)/6.1 (2.5)%	42.9 (4.1)/6.1 (2.5)%	1.000	43.5 (4.0)/6.1 (2.5)%	43.5 (4.0)/6.1 (2.5)%	0.916	44.2 (4.3)/6.2 (2.5)%	44.2 (4.3)/6.2 (2.5)%	0.932	44.5 (4.1)/6.2 (2.5)%	44.5 (4.1)/6.2 (2.5)%	0.938	44.7 (3.9)/6.2 (2.5)%	44.7 (3.9)/6.2 (2.5)%	0.940
Total cholesterol, mmol/L	4.8 (0.8)	4.8 (0.8)	0.936	4.8 (0.9)	4.8 (0.9)	0.955	4.8 (0.9)	4.8 (0.9)	0.962	4.8 (0.9)	4.8 (0.9)	0.968	4.8 (0.9)	4.8 (0.9)	0.971
Triglyceride, mmol/L	1.7 (0.8)	1.7 (0.8)	0.353	1.8 (0.8)	1.7 (0.7)	0.449	1.7 (0.8)	1.8 (0.8)	0.800	1.8 (0.8)	1.8 (0.8)	0.588	1.8 (0.8)	1.8 (0.8)	0.884
Low-density lipoprotein cholesterol, mmol/L	2.7 (0.7)	2.7 (0.7)	0.958	2.7 (0.7)	2.7 (0.7)	0.970	2.7 (0.8)	2.7 (0.8)	0.974	2.7 (0.8)	2.7 (0.8)	0.978	2.7 (0.8)	2.7 (0.8)	0.980
High-density lipoprotein cholesterol, mmol/L	1.3 (0.4)	1.3 (0.4)	0.744	1.3 (0.4)	1.3 (0.4)	0.762	1.3 (0.4)	1.3 (0.4)	0.999	1.2 (0.4)	1.2 (0.4)	0.910	1.2 (0.4)	1.2 (0.3)	0.400
Estimated glomerular filtration rate <90 mL/min per 1.73 m^2	38.4 (0.03)	37.8 (0.05)	0.908	35.3 (0.02)	35.5 (0.04)	0.998	35.5 (0.01)	35.7 (0.03)	0.999	39.9 (0.01)	40.0 (0.03)	0.999	37.1 (0.02)	37.0 (0.02)	0.999
Antihypertensive treatment, n (%)	29.9 (0.03)	30.0 (0.05)	0.993	28.5 (0.02)	28.5 (0.03)	0.994	31.1 (0.02)	31.1 (0.03)	0.995	31.2 (0.02)	31.2 (0.02)	0.996	36.2 (0.02)	36.2 (0.02)	0.996
Statin treatment, % (SE)	28.8 (0.03)	28.9 (0.05)	0.993	26.9 (0.02)	26.9 (0.03)	0.995	27.9 (0.02)	27.9 (0.03)	0.996	28.8 (0.02)	28.8 (0.02)	0.996	34.3 (0.02)	34.3 (0.02)	0.996
Antiplatelet or anticoagulant treatment, % (SE)	3.3 (0.2)	3.3 (0.02)	0.998	1.6 (0.01)	1.6 (0.01)	0.999	1.1 (0.004)	1.1 (0.007)	0.999	0.8 (0.003)	0.8 (0.005)	0.999	1.0 (0.004)	0.9 (0.005)	0.999

The continuous variables have been presented as weighted means (SE), and the categorical variables have been presented as weighted percentage (SE) with weights applied from the entropy matching. The landmark indicates a fixed time point after cohort entry, and those who were alive at the landmark date have been included. IMD indicates Index of Multiple Deprivation; SE, standard error; and T2D, type 2 diabetes.

Table 2. 5-Year and 10-Year (After the Landmark Period) Rates of Atrial Fibrillation Among Cases With and Without Onset of T2D After Coarsened and Exact Matching for 1- to 5-Year Landmark Analysis in Population With Impaired Glucose Tolerance

	5-year Risk		10-year Risk	
	Exposure: with onset of T2D	Nonexposure: without onset of T2D	Exposure: with onset of T2D	Nonexposure: without onset of T2D
	Rate (95% CI), per 1000 person-years	Rate (95% CI), per 1000 person-years	Rate (95% CI), per 1000 person-years	Rate (95% CI), per 1000 person-years
1-y Landmark analysis	35.90 (14.43–73.96)	14.14 (10.27–18.98)	15.21 (6.57–29.97)	6.56 (4.97–8.50)
2-y Landmark analysis	18.52 (9.24–33.13)	8.68 (6.75–10.99)	14.58 (7.97–24.47)	6.58 (5.29–8.09)
3-y Landmark analysis	11.99 (5.75–22.05)	6.94 (5.43–8.74)	10.87 (5.79–18.59)	6.44 (5.20–7.89)
4-y Landmark analysis	10.47 (5.02–19.26)	7.04 (5.47–8.90)	12.20 (7.11–19.54)	6.69 (5.36–8.24)
5-y Landmark analysis	66.88 (51.39–85.57)	19.89 (16.80–23.40)	49.54 (39.62–61.18)	19.05 (16.53–21.84)

T2D indicates type 2 diabetes.

at 1 year, 1.60 (95% CI, 1.14–2.24) at 2 years, 1.26 (95% CI, 1.02–1.56) at 3 years, 1.28 (95% CI, 1.01–1.63) at 4 years, and 1.34 (95% CI, 1.10–1.63) at 5 years (Figure 1 and Figure S7).

Regarding the 10-year (after the landmark period) risk of AF, the final adjusted HRs in the landmark analyses were 1.44 (95% CI, 1.06–1.96) at 1 year, 1.31 (95% CI, 1.02–1.69) at 2 years, 1.24 (95% CI, 1.00–1.54) at 3 years, 1.22 (95% CI, 1.01–1.48) at 4 years, and 1.28 (95% CI, 1.02–1.62) at 5 years (Figure 1 and Figure S8).

Significant interactions were observed across subgroups (Figure 2). The results of the stratified 5-year landmark analysis indicate that there were significant differences in the HRs for the 5- and 10-year (after the landmark period) risk of AF between IGT patients with and without the onset of T2D among various subgroups. The risk was found to be higher among men and individuals who were older, non–New Zealand European, from the most deprived populations; those who were current or former smokers; those who were obese; and those with elevated levels of systolic blood pressure, HbA_{1c}, total cholesterol, low-density lipoprotein, and lower estimated glomerular filtration rate. These findings are presented in Figure 2. Similar overall estimations were observed in the complete case analysis (Figure S9).

DISCUSSION

Derived from a large longitudinal primary care database linked with national registration databases in New Zealand, the current cohort study investigated the association between the onset of T2D and 5- and 10-year (after the landmark period) risk of AF among patients with IGT, using landmark analysis and an innovative tapered matching methodology. A significant association between the onset of T2D and both risks of 5- and 10-year (after the landmark period) risk of AF were identified among patients with IGT, especially in men and those who were older, were of non–New Zealand European ethnicity, were more deprived, were current smokers, and were obese, with higher HbA_{1c}, blood pressure, lipids, or reduced renal function. These findings have significant clinical implications for the prevention and management of AF in patients with IGT and highlight the importance of screening and managing those with IGT to reduce their long-term risk of AF.

Previous studies have found a significant association between T2D and AF[9,28]; for example, a meta-analysis reported a 28% higher risk of AF in patients with T2D compared with those without.[9] However, few studies have investigated the association between prediabetes and AF, and the results have been inconsistent.[29,30] In the post hoc analysis of the NAVIGATOR (Nateglinide and Valsartan in Impaired

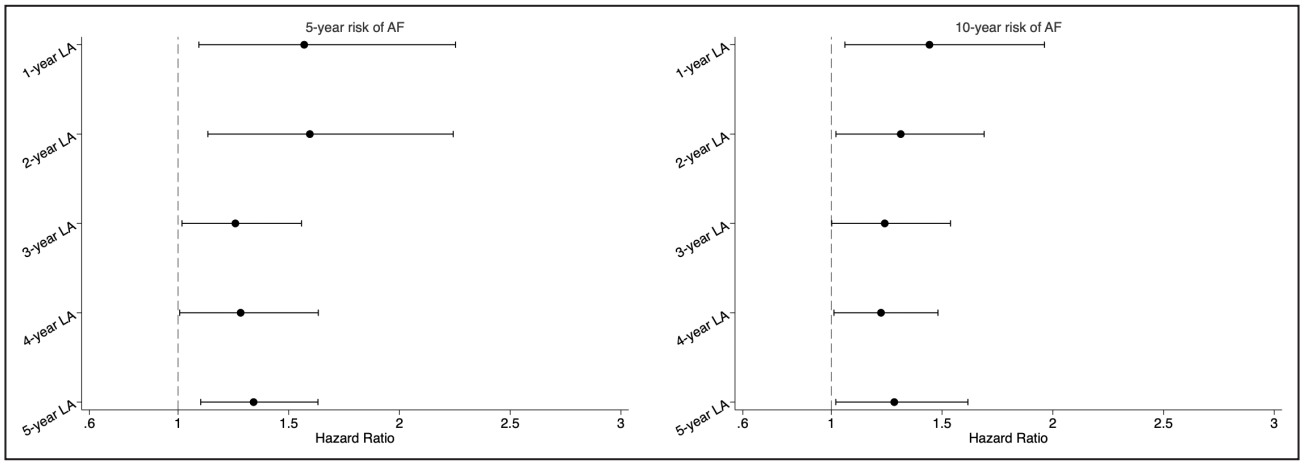

Figure 1. Association between the onset of type 2 diabetes and the 5-year and 10-year (after the landmark period) risk of AF in patients with impaired glucose tolerance estimated by landmark models.
AF indicates atrial fibrillation; and LA, landmark analysis.

Glucose Tolerance Outcomes Research) trial, among older people with hypertension and IGT, the progression to T2D was not significantly associated with a risk of AF within 5 years (HR, 0.98 [95% CI, 0.80–1.20]).[31] Besides the population structure (younger and not a population defined by hypertension in the current study), the competing risk of death and the long-term (10-year) risk of AF were not addressed. The current study provides new evidence of the association between the onset of T2D and the risk of AF in patients with IGT, demonstrating that the onset of T2D is associated with an increased risk of AF in both the short (5 years after the landmark period) and long term (10 years after the landmark period).

The association between the onset of T2D and increased risk of AF in patients with IGT has important clinical implications. General practitioners and internists should be aware of the increased risk of AF in patients with IGT and should prioritize early detection and lifestyle management like diet/nutrition, smoking cessation, and physical activities to prevent the development of T2D and then be better placed to detect the onset of AF.[32–34] The study findings also highlight the importance of increased awareness and screening of patients with IGT for AF, as the 5- and 10-year risk of AF was 19 per 1000 person-years in the patients with IGT without progression to T2D, higher than the 1.7 per 1000 person-years in the general population globally estimated by a systematic review.[9] Such awareness should emphasize that those most at risk of AF with IGT are men who have a deprived socioeconomic status, smoke, are obese, have abnormal metabolic measurements, and are of non–New Zealand European ethnicity (mainly Māori and Pacific ethnicity).

Our research has a number of strengths. It is the largest multiethnic matched cohort study of participants with IGT in New Zealand and one of the largest globally to analyze the correlation between the onset of T2D and 5- and 10-year (after the landmark period) risk of AF. The study cohorts encompassed all patients from participating general practices and used large, nationally representative databases to follow patients prospectively and track all incident AF. Moreover, the accuracy of clinical recording and diagnoses has been validated for outcomes defined by *ICD* codes with high precision. The immortal person-time was effectively excluded from the risk estimation by using a robust methodology known as landmark analysis within the 1- to 5-year time windows, with follow-up time starting from the end of the landmark period.[35] Furthermore, we used an innovative, tapered matching method to form quasi-trial comparison cohorts to transparently examine how differences in specific sets of confounders contributed to the risks of AF. Limitations include the national representativeness of the sample and participating general practices in New Zealand. Although a strict validation process was applied in the current study using electronic health record data, residual validity issues such as misclassification may still exist and could potentially affect the study findings. Additionally, although we adjusted for covariates that are commonly shared by noncommunicable diseases and are available in routine primary care settings, such as age, sex, smoking status, socioeconomic status, blood pressure, lipid profiles, and estimated glomerular filtration rate; certain risk factors for AF, such as alcohol consumption, sleep apnea, family history, comorbidities like lung disease and thyroid disease; and certain medications, were not accounted for in our study. This may result in potential residual confounding effects and should be addressed in future investigations.

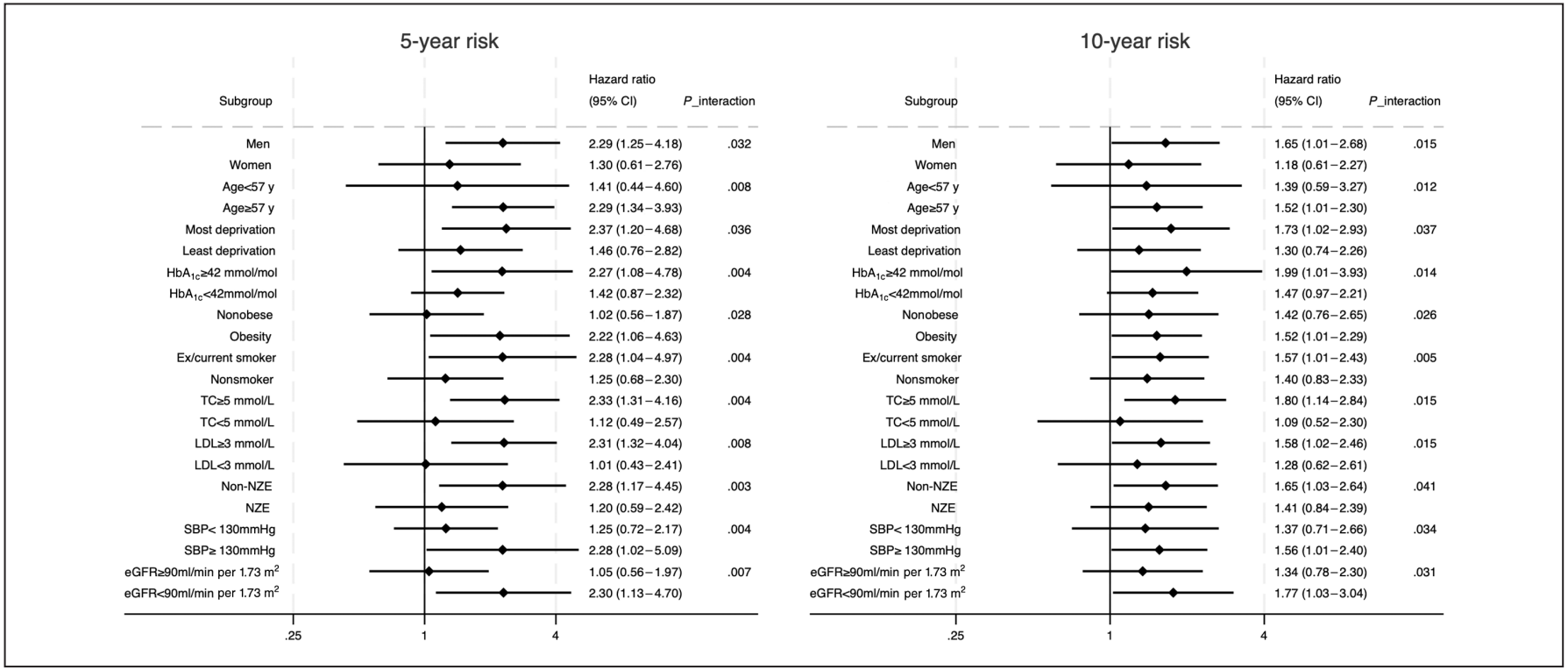

Figure 2. Stratified adjusted hazard ratio for 5- and 10-year (after the landmark period) risk of AF at the 5-year landmark (final tapered matched models).
AF indicates atrial fibrillation; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NZE, New Zealand European; SBP, systolic blood pressure; and TC, total cholesterol.

In conclusion, our study suggests that patients with IGT who develop T2D are at increased risk of developing AF, and this risk is evident in both the short term and long term. Our findings highlight the importance of screening and managing IGT to prevent its progression to T2D and the need to be aware of the increased risk of AF, a common and serious arrhythmia, in the population with IGT. Future studies should explore the underlying mechanisms of this association and investigate the potential benefits of interventions targeting IGT, potentially including the use of risk prediction models for T2D, in preventing the long-term risks of AF.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S9

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