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Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom

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ABSTRACT (221 words)

Objective: To evaluate oral anticoagulant (OAC) prescribing trends in type 2 diabetes mellitus (T2DM) in the United Kingdom (UK) from 2001 to 2015.

Design: A cross-sectional drug utilisation study.

Setting: Electronic health records from The Health Improvement Network (THIN) primary care database of the UK.

Participants: Individuals with T2DM who received a record of OAC prescription.

Outcome measures: The prescribing trends of oral anticoagulant medications in individuals with T2DM were examined from 2001 to 2015, stratified by age, gender and therapeutic classifications.

Results: The prevalence of OAC prescribing increased by 50.8% [from 4.4 (95% confidence intervals (CI) 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons]. The prevalence of warfarin prescribing decreased by 13.9% [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons]. This corresponded with increased prescribing of direct oral anticoagulants (DOACs) [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons] during the same period.

Conclusions: Prescribing of OACs in individuals with T2DM increased from 2001 to 2015. Since the introduction of DOACs there has been a clear shift in prescribing towards these agents. Future studies are needed to assess the safety of the co-administration of oral anticoagulant medications and antidiabetic therapy with T2DM.

Keywords: Diabetes mellitus, Drug utilisation, Oral anticoagulants therapies, Trend, United Kingdom

Strengths and limitations of this study

- To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period.
- This study used a clinical record primary care research database which was representative of the UK general population.
- Underestimation of OAC prescribing could be a limitation of this study as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide and has become a major global public health concern (1, 2). According to the International Diabetes Federation (IDF) report in 2017 (2), it was estimated that 425 million people worldwide are living with diabetes, compared to 30 million in the year of 1985, of whom 90% were diagnosed with T2DM (1, 2). In the UK, the prevalence of diabetes has doubled over the last three decades (3-5). Using a national health database in the UK, Zghebi et al estimated that the prevalence of diabetes increased from 3.2 % in 2004 to 5.2 % in 2014 (6).

T2DM and cardiovascular diseases often coexist with many individuals with T2DM experiencing cardiovascular complications (7-11). Cardiovascular diseases including cardiac arrhythmias, venous thromboembolism, and ischaemic heart disease are among the leading causes of mortality worldwide in individuals with T2DM (12-14). Anticoagulants are widely prescribed for the prevention and treatment of atrial fibrillation, stroke, venous and arterial thrombosis. When prescribed for venous thromboembolism, OAC treatment is typically of short duration, but it can be lifelong treatment when prescribed for atrial fibrillation (AF) (15).

T2DM is one of the main risk factors contributing in $CHA2DS_2$ score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (16). In 2010, CHA_2DS_2-VASc was adapted from the previous score (17), and it is now recommended by most of the current guidelines (15, 18, 19), in which individuals with AF are likely to be prescribed OAC if they score two or more in the total score. In addition, since the introduction of direct oral anticoagulants (DOACs) in 2011, several guidelines recommended their use for indications such as atrial fibrillation (15, 18, 19). DOACs have much more predictable pharmacokinetics and pharmacodynamics, and are less prone for drug interactions when compared with warfarin (20). However, OAC use in individuals with T2DM remains unclear, with limited studies focused on their use in individuals with T2DM (21, 22).

Investigating OAC use in individuals with T2DM is important due to the high number of individuals, the possibility of drug-drug interactions, and the potential association with serious adverse events such as bleeding and hypoglycaemia (23, 24). This was highlighted in particular among individuals with

T2DM in previous large-scale epidemiological studies and in multiple case reports where warfarin was associated with an increased risk of hypoglycaemia (25-28).

Given the recent update in guidelines for OAC prescribing, and the limited research on their use in individuals with T2DM, this research aimed to describe the prescribing patterns of oral anticoagulant medications in individuals with T2DM in the UK population as an important step in investigating its safety within this high risk population.

The primary objective of this study was to examine the prescribing trends of oral anticoagulant medications in individuals with T2DM from 2001 to 2015, stratified by age, gender and therapeutic classifications. The secondary objective was to compare the trend in OAC use in individuals with AF, with and without T2DM, given that AF is the main indication for OAC use.

METHODS

Data sources

This was a retrospective drug utilisation study using primary care data in the Health Improvement Network (THIN); a UK primary care database containing anonymised administrative, clinical and prescribing data from over 587 practices with more than 12 million individuals (29, 30). THIN is one of the largest sources for primary care data in the UK, and has been validated for epidemiological research purposes (29-31). It holds data on personal information, health related behaviours, and diagnoses information which is recorded and identified using Read codes (29, 30). Read codes, which are also known as clinical terms, are clinical terminologies used to describe the care, diagnosis of diseases and treatments of individuals. It is used to manage primary care data in electronic health records (32). The database also has prescribing information that is linked with the British National Formulary.

Study population

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study. The AMR date is the year that data reporting is deemed to be complete, based on information derived from the Office for National Statistics (33). Individuals were included only if they had an observation period of at least 12 months prior to their start date and were

registered with the general practice during the study period. Individuals with T2DM aged > 18 and registered with the THIN database between 2001 and 2015 (of which data were only available up to) were identified based on the following criteria of having; 1) a diagnostic code for T2DM (using Read codes), or 2) a diagnostic code for any type of diabetes and a record of any oral hypoglycaemic agent prescription. Individuals with a non-specific code for T2DM and who only had records for insulin prescription were excluded because they may have type 1 diabetes mellitus (T1DM), although their age at first event is taken into account. T2DM is typically diagnosed over the age of 30 years, however, the rate of young onset T2DM is increasing (34). We therefore only excluded children (less than 18 years old) who were more likely to have T1DM. Individuals with T2DM receiving at least one prescription of oral anticoagulant medication were identified. Oral anticoagulant medications were consigned into three categories: warfarin, DOACs (apixaban, rivaroxaban, dabigatran and edoxaban), and other anticoagulant medications (acenocoumarol, pentosan polysulfate and phenindione). Furthermore, individuals with AF aged > 18 years and registered with THIN were identified using Read codes. The prescribing of oral anticoagulants in individuals with AF with and without T2DM involved a two-step cohort identification. The first step was designed to identify individuals with AF with coexisting T2DM. The second step involved identifying individuals with AF without a diagnosis of T2DM.

Statistical analysis

Descriptive statistics were used to describe individuals' demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data was reported as percentages (frequencies). The prevalence of oral anticoagulant medications presented per 100 persons with 95% CIs were calculated on an annual basis by dividing the number of all individuals prescribed anticoagulant medications in a particular year over the mid-year population of individuals with T2DM in the same calendar year. The prescribing trend of oral anticoagulant medications was assessed using Poisson model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The present study is based on anonymised and unidentifiable THIN data, thus the need for informed consent was waived by the THIN scientific review committee (SRC). This study was reviewed and

scientific approval was obtained by THIN SRC in 2018 (18THIN009). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement (Supplement 1).

Patient involvement

Patients were not involved in the design of the study.

RESULTS

Demographics and characteristics

During the study period of 2001 and 2015, a total of 361,635 individuals with T2DM were identified of whom 36,570 received a prescription for OAC. Characteristics of the entire cohort included in our study are presented at the time of first OAC prescription. The average age of individuals at the time of first OAC prescription was 72 (SD, 10.2) years old, and the majority of individuals were male (59.9%). Around 64.6% of individuals were diagnosed with atrial fibrillation and 22.2% were diagnosed with venous thromboembolism diseases. Baseline demographics of the study sample are described in Table 1.

Table 1: characteristics of the study sample at the time of first OAC prescription

Demographics	T2DM individuals receiving OAC (%)
Total	**36,570 (100%)**
Age (Mean ± SD)*	72 ± 10.2
Gender (Male)	21,586 (59.9)
Social	
Smoking	3,598 (10.0)
Alcohol drinking	23,879 (69.6)
Comorbidities**	
Atrial fibrillation	23,655 (64.6)
Venous thromboembolisms	8,127 (22.2)
Stroke	7,441 (20.3)
Coronary heart diseases	12,606 (34.4)
Chronic kidney diseases	10,097 (27.6)
Heart failure	8,181 (22.3)

Hypertension	25,342 (69.3)
Hyperlipidaemia	8,563 (23.4)
COPD	3,815 (10.4)
PUD	10,266 (28.0)
PVD	3,522 (9.6)
Bleeding	8,062 (22.0)
Depression	8,186 (22.8)
Mild liver disease	146 (0.4)
Moderate to severe liver disease	209 (0.5)
Medications	
Aspirin	13,940 (38.1)
Other anti-platelets	2,736 (7.4)
Statin	25,138 (68.7)
BB	18,503 (50.6)
CCB	13,597 (37.1)
ACEs/ARBs	25,490 (69.7)
Diuretics	16,796 (45.9)
Digoxin	11,867 (32.4)
CHA_2DS_2-VASc Score[a]	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
HASBLED[b]	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

*Standard deviation ±. Alcohol missing: (10.5%), Smoking missing (3.2%)

[a]CHA_2DS_2-VASc indicates individuals with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or TIA or SE (doubled), vascular disease, and gender category (women). CHA_2DS_2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); [b]HAS-BLED indicates individuals with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

Trends in prescribing prevalence of oral anticoagulant medications in T2DM

Between 2001 and 2015, the prescribing prevalence of OACs in individuals with T2DM increased by 50.8% [from 4.4 (95% CI 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons with T2DM], p<0.001, with an average increase of 3.2% per year (Figure 1).

The changes in prevalence of OAC prescribing between 2001 and 2015 stratified by gender are shown in Figure 1. The prescribing prevalence of oral anticoagulant medications among males increased by 54.3% [from 4.6 (95%CI 4.3 – 4.9) to 7.1 (95%CI 6.9 – 7.2) per 100 persons with T2DM], while the prescribing prevalence of oral anticoagulant medications among females increased [from 4.0 (95%CI 3.8 – 4.4) to 5.9 (95%CI 5.8 – 6.1) per 100 persons with T2DM], with an overall increase of 47.5%.

Similarly, the prescribing prevalence of oral anticoagulant medications varied among individuals from the different age groups. Individuals aged 60 years or above showed a higher prescribing prevalence of OACs compared to individuals aged below 60 years of 46.2% [from 5.7 (95%CI 5.4– 6.0) in 2001 to 8.4 (95%CI 8.2 – 8.5) in 2015 per 100 persons with T2DM] vs 13.3% [from 1.5 (95%CI 1.3 – 1.7) in 2001 to 1.7 (95%CI 1.6 – 1.8) in 2015 per 100 persons with T2DM] for younger individuals aged below 60 years (Figure 2).

Trends in prevalence of oral anticoagulant prescribing stratified by medication

Although warfarin was the most common medication prescribed during the entire study period (86.3%), its use declined [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons with T2DM]. In contrast, there was a corresponding increase in the proportion of individuals who used DOACs [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons with T2DM]. Other OACs, including acenocoumarol and phenindione were less likely to be prescribed during the entire study period (0.03%), their prescribing rate decreased [from 1.1 (95% CI 0.7 – 1.7) in 2001 to 0.4 (95% CI 0.3 – 0.5) in 2015 per 100 persons with T2DM] (Figure 3). In addition, a small percentage of individuals with T2DM using OAC were prescribed different OAC classes during the same year ranging from less than 1% in 2010 to 3% in 2015.

Further stratification by individual OAC drug treatment showed that the prescribing prevalence of rivaroxaban markedly increased [from 0.1 (95% CI 0.05–0.2) in 2010 to 10.9 (95% CI 10.5–11.4) in 2015 per 100 persons with T2DM], while the prescribing prevalence of dabigatran increased to a lesser

degree [from 0.03 (95% CI 0.001–0.07) in 2010 to 2.7 (95% CI 2.5–2.9) in 2015 per 100 persons with T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08) in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).

Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with and without T2DM

The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of prescribing ranged [from 46.6 (95% CI 43.5 – 49.7) in 2001 to 59.0 (95% CI 58.3 – 60.0) in 2015 per 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure 5).

DISCUSSION

This study investigated the drug utilisation pattern of oral anticoagulant medications in individuals with T2DM, and the prevalence of AF in individuals with T2DM. The key findings are: 1) the prescribing prevalence of OACs in individuals with T2DM has increased markedly between 2001 and 2015, 2) the increase in the prescribing prevalence of OACs was not consistent across individuals of different gender and age group, males and individuals aged 60 years and above had a higher prescribing prevalence compared to females and individuals younger than 60 years, 3) the prescribing of DOACs is clearly replacing the prescribing of warfarin since their introduction to the UK market in 2011.

Previous studies investigating the trend of OACs prescribing in individuals with T2DM are limited. A previous study by Hamada *et al*. examined the trend of cardiovascular medication prescribing in diabetic individuals aged 80 years or above in the UK between 1990 to 2010 (22), concluding that the prescribing of OACs in individuals with T2DM had increased [from 5% in 1999 to 19% in 2010]. These results showed similar trends to our study in the increase of OACs prescriptions in T2DM. However, our results showed that OAC prescriptions increased less sharply, which is explicable by restriction of their population to include only individuals aged 80 years and older. Despite this, age is considered a

risk factor of many conditions for which OACs are indicated, and our results showed an increased rate of OAC prescribing among individuals aged 60 years and above. Furthermore, an increasing prescribing prevalence of DOACs in the last few years have been reported in several studies that examined the trend of OACs in the general population or in individuals with AF across different countries (35-38). Alalwan *et al*., using data from MarketScan Medicare, reported that DOACs increased from 1.39% (95% CI, 1.34–1.44%) in 2010 to 28.33% (95% CI, 28.14–28.52%) in 2014 (35). Similarly, Loo *et al*. found that the rate of initiation of DOAC increased significantly, particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI 12.16, 25.71) (36). The findings presented in our study, and specifically related to DOACs' prescribing trend are in line with previous findings, however, it is important to highlight that those studies concerned the general population and were not specific to T2DM. (35-38).

This study showed that since the introduction of DOACs, individuals with T2DM using OACs were prescribed different classes of OAC, possibly due to individuals switching from one class to another. DOACs have been reported to be non-inferior to warfarin in the prevention of major strokes and embolic events in different clinical trials and observational studies (39-43). Evidence from meta-analyses showing better efficacy and non-inferior safety when comparing DOACs and warfarin could be a reason for the paradigm shift in favouring the prescribing of DOACs (44, 45). This led in a change in the UK National Institute for Health and Care Excellence (NICE) guidance for the management of AF (15), and as of 2014, DOACs have been recommended as first-line therapy for AF (46). However, it is crucial to recognise that older people with comorbidities were excluded or underrepresented in the pivotal clinical trials of DOACs and therefore, DOACs should be prescribed with caution and strict monitoring in this population (47). Another major issue with warfarin is that it is more prone to several drug-food and drug-drug interactions (24-26, 48), which could explain why DOACs are being prescribed more favourably in the recent years compared to warfarin, especially accounting for elements such as ageing and polypharmacy. Nonetheless, a major advantage for DOACs is their wider therapeutic index and that it does not require regular monitoring during intake for international normalized ratio (INR) compared to warfarin (49-51).

The results of this study highlighted that individuals with T2DM have a high risk profile of cardiovascular comorbidities including hypertension, coronary heart disease, heart failure, peripheral vascular diseases and hyperlipidaemia (Table 1), in which they are predictors for the initiation of OAC prescribing (21). However, T2DM complications are also linked to these comorbidities (7, 8), and therefore it is difficult to draw a causal inference and we urge for further studies to investigate this association.

As expected, our results showed that AF was the main indication for OAC prescriptions among individuals with T2DM. Several international guidelines, including those from the US (52), Europe (18) and the UK (15) have recommended the use of OACs in individuals with atrial fibrillation based on CHADS2 (16) and CHA2DS2–VASc score (17). This was also in line with our results as it showed that individuals with AF and coexisting T2DM had a higher rate of OACs prescribing compared to individuals with AF without T2DM. However, our results showed a higher prescribing rate of OAC among males compared to females that is similar to other studies that highlighted the higher prevalence of OAC prescribing amongst males (53, 54). Given that females are associated with a higher risk of stroke and thromboembolisms (55) and that major guidelines recommend OAC prescribing among females, the finding of this study could potentially highlight an underuse of OAC prescribing in females.

Strengths and limitations

To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period. This study used a clinical record primary care research database which was representative of the UK general population.

However, this study has some limitations. Firstly, underestimation of OAC prescribing as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals. However, the UK National Health Service (NHS) heavily subsidies the treatment of chronic illness and the majority of individuals with chronic illness are looked after by primary care; therefore, our results should not be affected significantly. Secondly, individuals were identified using relevant Read code lists and algorithms. This may have led to bias in the study due to under-reporting or misreporting of T2DM

diagnoses; however, this issue was mitigated by validating our codes with clinicians and previously published studies. Furthermore, THIN is a medical record database and therefore, similar to other clinical databases, it was not possible to confirm if individuals were adherent.

Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications and oral anticoagulants medications for possible drug-drug interactions, especially when warfarin is the drug of choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is imperative to investigate the effect of concomitant use of this class of medication and the risk of hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus improve the safety of OAC use in individuals with T2DM.

CONCLUSIONS

This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin since its introduction to the UK market, which is consistent with UK guidelines. However, there is a lack of studies examining their safety when used in individuals with T2DM. Further studies are warranted to investigate the safety of the concurrent use of antidiabetic and oral anticoagulant medications for possible drug-drug interactions.

Abbreviations

ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs: Confidence intervals; DOAC: Direct oral anticoagulant; IDF: International Diabetes Federation; INR: International normalized level; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OAC: oral anticoagulant; SD: Standard deviation; SRC: Scientific Review Committee; STROBE: Strengthening the reporting of observational studies in epidemiology; THIN: The Health Improvement Network; T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus UK: United Kingdom.

Consent for publication

Not applicable.

Data Availability

No further data are available.

Conflict of Interest Disclosures

The authors declare that they have no competing interest.

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Authors Contributions: HA, LW and IW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors who contributed to the work described in this paper are as follows: HA, LW and IW contributed to the study design. HA, LW, KM and PM contributed to the Statistical analysis. HA, LW and IW were involved in interpretation of data. HA wrote the first draft of the article. HA, LW, AN, JSB, JI, GT, GF and IW made substantial contributions to the drafts, reviewed the manuscript for important intellectual content and provided final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure titles and legends

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM.

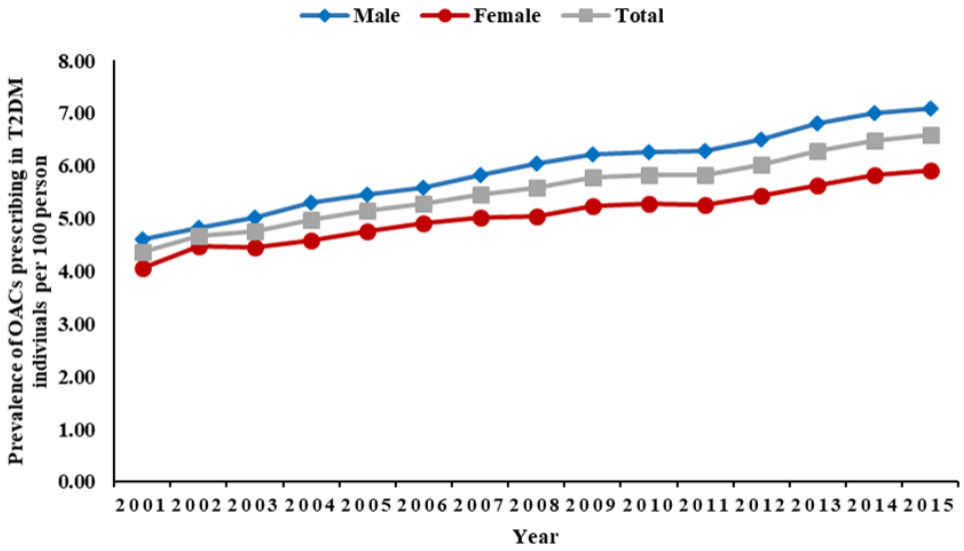

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

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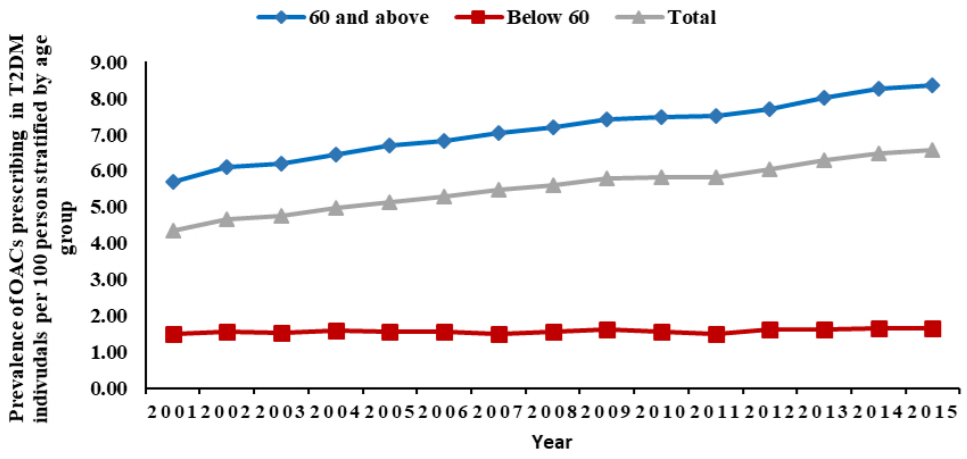

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

74x38mm (300 x 300 DPI)

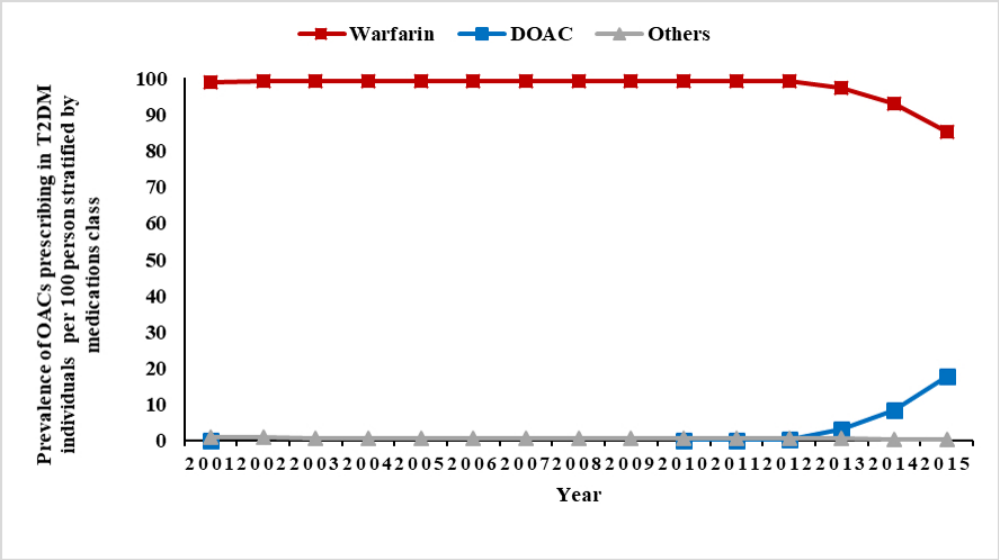

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

75x42mm (300 x 300 DPI)

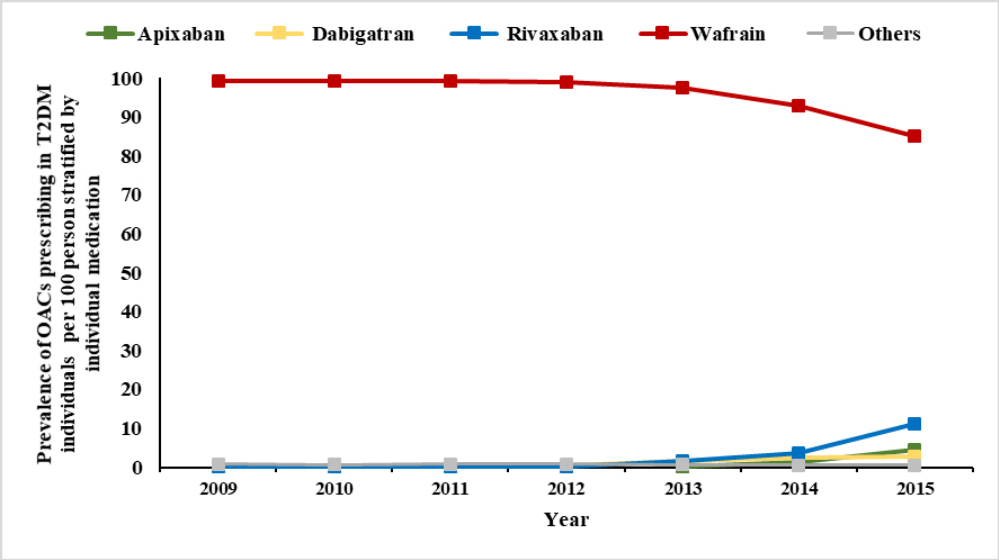

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

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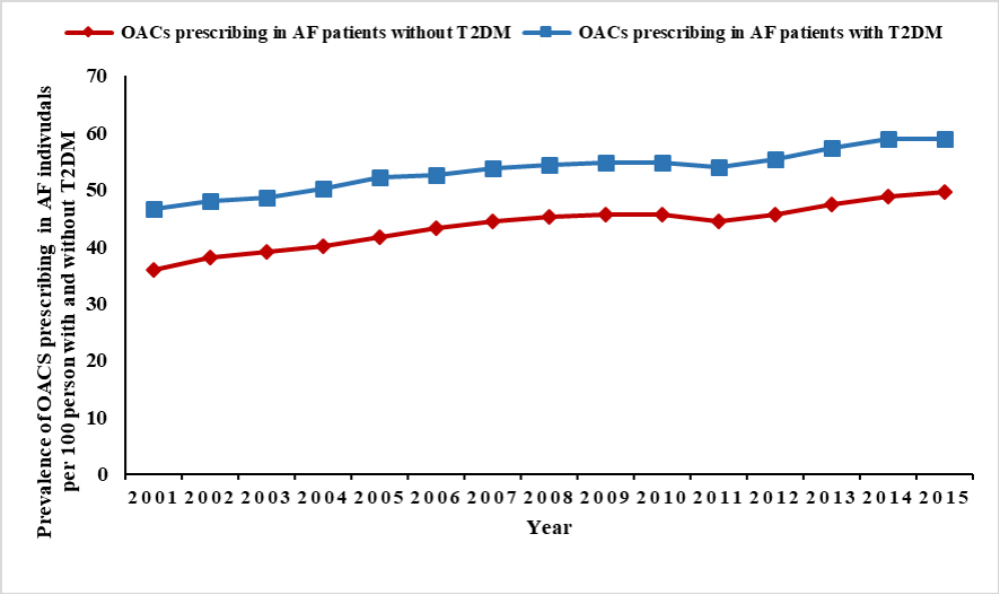

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM.

75x44mm (300 x 300 DPI)

Supplement

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Introduction
Methods				
Study design	4	Present key elements of study design early in the paper	4	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		Not applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Not applicable
Bias	9	Describe any efforts to address potential sources of bias		Not applicable
Study size	10	Explain how the study size was arrived at		Not applicable

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5	
		(*b*) Describe any methods used to examine subgroups and interactions	5	
		(*c*) Explain how missing data were addressed		Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		Not applicable
		(*e*) Describe any sensitivity analyses		Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6	Results
		(b) Give reasons for non-participation at each stage		Not applicable
		(c) Consider use of a flow diagram		Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6	Results
		(b) Indicate number of participants with missing data for each variable of interest		Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	7	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Not applicable
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7,8	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	8	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	10	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11	Declarations

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Keywords:	EPIDEMIOLOGY, DIABETES & ENDOCRINOLOGY, Anticoagulation < HAEMATOLOGY

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Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom

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ABSTRACT (219 words)

Objective: To evaluate oral anticoagulant (OAC) prescribing trends in type 2 diabetes mellitus (T2DM) in the United Kingdom (UK) from 2001 to 2015.

Design: A cross-sectional drug utilisation study.

Setting: Electronic health records from The Health Improvement Network (THIN) primary care database of the UK.

Participants: Individuals with T2DM who received a record of OAC prescription.

Outcome measures: The prescribing trends of OAC medications in individuals with T2DM were examined from 2001 to 2015, stratified by age, gender and therapeutic classifications.

Results: The prevalence of OAC prescribing increased by 50.8% [from 4.4 (95% confidence intervals (CI) 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons]. The prevalence of warfarin prescribing decreased by 13.9% [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons]. This corresponded with increased prescribing of direct oral anticoagulants (DOACs) [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons] during the same period.

Conclusions: Prescribing of OACs in individuals with T2DM increased from 2001 to 2015. Since the introduction of DOACs there has been a clear shift in prescribing towards these agents. Future studies are needed to assess the safety of the co-administration of OAC medications and antidiabetic therapy with T2DM.

Keywords: Diabetes mellitus, Drug utilisation, Oral anticoagulants therapies, Trend, United Kingdom

Strengths and limitations of this study

- To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period.
- This study used a clinical record primary care research database which was representative of the UK general population.
- Underestimation of OAC prescribing could be a limitation of this study as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide and has become a major global public health concern (1, 2). According to the International Diabetes Federation (IDF) report in 2017 (2), it was estimated that 425 million people worldwide are living with diabetes, compared to 30 million in the year of 1985, of whom 90% were diagnosed with T2DM (1, 2). In the United Kingdom (UK), the prevalence of diabetes has doubled over the last three decades (3-5). Using a national health database in the UK, Zghebi et al estimated that the prevalence of diabetes increased from 3.2 % in 2004 to 5.2 % in 2014 (6).

T2DM and cardiovascular diseases often coexist with many individuals with T2DM experiencing cardiovascular complications (7-11). Cardiovascular diseases including cardiac arrhythmias, venous thromboembolism, and ischaemic heart disease are among the leading causes of mortality worldwide in individuals with T2DM (12-14). Anticoagulants are widely prescribed for the prevention and treatment of atrial fibrillation (AF), stroke, venous and arterial thrombosis. When prescribed for venous thromboembolism, oral anticoagulant (OAC) treatment is typically of short duration, but it can be lifelong treatment when prescribed for AF (15).

T2DM is one of the main risk factors contributing in $CHA2DS_2$ score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (16). In 2010, CHA_2DS_2-VASc was adapted from the previous score (17), and it is now recommended by most of the current guidelines (15, 18, 19), in which individuals with AF are likely to be prescribed OAC if they score two or more in the total score. In addition, since the introduction of direct oral anticoagulants (DOACs) in 2011, several guidelines recommended their use for indications such as atrial fibrillation (15, 18, 19). DOACs have much more predictable pharmacokinetics and pharmacodynamics, and are less prone for drug interactions when compared with warfarin (20). However, OAC use in individuals with T2DM remains unclear, with limited studies focused on their use in individuals with T2DM (21, 22).

Previous studies have demonstrated that the prevalence of AF in individuals with T2DM ranges from 8% to 14.9% (23, 24), and that individuals with T2DM have 40% higher risk of developing AF compared to individuals without T2DM (25). Investigating OAC use in individuals with T2DM is important due to the high number of individuals, the possibility of drug-drug interactions, and the

potential association with serious adverse events such as bleeding and hypoglycaemia (26, 27). This was highlighted in particular among individuals with T2DM in previous large-scale epidemiological studies and in multiple case reports where warfarin was associated with an increased risk of hypoglycaemia. It has been suggested that displaced plasma protein and Cytochrome P450 (CYP450) hepatic metabolic pathway could be potential mechanisms for the increased risk of hypoglycaemia (28-31).

Given the recent update in guidelines for OAC prescribing, and the limited research on their use in individuals with T2DM, this research aimed to describe the prescribing patterns of OAC medications in individuals with T2DM in the UK population as an important step in investigating its safety within this high risk population.

The primary objective of this study was to examine the prescribing trends of OAC medications in individuals with T2DM from 2001 to 2015, stratified by age, gender and therapeutic classifications. The secondary objective was to compare the trend in OAC use in individuals with AF, with and without T2DM, given that AF is the main indication for OAC use.

METHODS

Data sources

This was a retrospective drug utilisation study using primary care data in The Health Improvement Network (THIN); a UK primary care database containing anonymised administrative, clinical and prescribing data from over 587 practices with more than 12 million individuals (32, 33). THIN is one of the largest sources for primary care data in the UK, and has been validated for epidemiological research purposes (32-34). In addition, it has been used by our team to study prescribing of OAC and various psychotropic medications (35-39). It holds data on personal information, health related behaviours, and diagnoses information which is recorded and identified using Read codes (32, 33). Read codes, which are also known as clinical terms, are clinical terminologies used to describe the care, diagnosis of diseases and treatments of individuals. It is used to manage primary care data in electronic health records (40). The database also has prescribing information that is linked with the British National Formulary. THIN contains records of prescriptions issued only by GPs and recorded in the individuals records.

Study population

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study. The AMR date is the year that data reporting is deemed to be complete, based on information derived from the Office for National Statistics (41). The start date was defined as the date of the first record for T2DM diagnosis. Individuals were included only if they had an observation period of at least 12 months prior to their start date and were registered with the general practice during the study period. The end date was the date were individuals left the practice, died or transferred out. Individuals with T2DM aged > 18 and registered with the THIN database between 2001 and 2015 (of which data were only available up to) were identified based on the following criteria of having; 1) a diagnostic code for T2DM (using Read codes), or 2) a diagnostic code for any type of diabetes and a record of any oral hypoglycaemic agent prescription, and the start date for these individuals was defined as the date of the first record for diabetes. Individuals with a non-specific code for T2DM and who only had records for insulin prescription were excluded because they may have type 1 diabetes mellitus (T1DM), although their age at first event is taken into account. T2DM is typically diagnosed over the age of 30 years, however, the rate of young onset T2DM is increasing (42). We therefore only excluded children (less than 18 years old) who were more likely to have T1DM. Individuals with T2DM receiving at least one prescription of OAC medication were identified. Oral anticoagulant medications were consigned into three categories: warfarin, DOACs (apixaban, rivaroxaban, dabigatran and edoxaban), and other anticoagulant medications (acenocoumarol, pentosan polysulfate and phenindione). Furthermore, individuals with AF aged > 18 years and registered with THIN were identified using Read codes. The prescribing of OAC medications in individuals with AF with and without T2DM involved a two-step cohort identification (Figure S1). The first step was designed to identify individuals with AF with coexisting T2DM, and the latest first record between AF and DM was counted as the start date (coexisting of both diseases) for this cohort. The second step involved identifying individuals with AF without a diagnosis of T2DM, and the start date for these individuals was the first recorded AF diagnosis. Individuals who developed AF first and T2DM later contributed to the AF only cohort and then to the AF and T2DM cohort. For baseline characteristics:

chronic comorbidities were measured over the 12-month period preceding the first OAC prescription. However, medication use was assessed over the 6-month period preceding the first OAC prescription.

Statistical analysis

Descriptive statistics were used to describe individuals' demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data was reported as percentages (frequencies). The prevalence of OAC medications presented per 100 persons with 95% confidence intervals (CIs) were calculated on an annual basis by dividing the number of all individuals prescribed OAC medications in a particular year over the mid-year population of individuals with T2DM in the same calendar year, stratified by age, gender and therapeutic classifications. For the secondary objective: the trend in OAC use in AF individuals with T2DM, was calculated on an annual basis by dividing the number of AF individuals with T2DM prescribed OAC medications in a particular year over the mid-year population of AF individuals with T2DM in the same calendar year. The trend in OAC use in individuals with AF and without T2DM was calculated by dividing the number of AF individuals without T2DM prescribed OAC medications in a particular year over the mid-year population of AF individuals without T2DM in the same calendar year. The prescribing trend of OAC medications was assessed using Poisson model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The present study is based on anonymised and unidentifiable THIN data, thus the need for informed consent was waived by the THIN scientific review committee (SRC). This study was reviewed and scientific approval was obtained by THIN SRC in 2018 (18THIN009). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement (Supplements Table S1).

Patient involvement

Patients were not involved in the design of the study.

RESULTS

Demographics and characteristics

During the study period of 2001 and 2015, a total of 361,635 individuals with T2DM were identified of whom 36,570 received a prescription for OAC. Characteristics of the entire cohort included in our study are presented at the time of first OAC prescription. The average age of individuals at the time of first OAC prescription was 72 (SD, 10.2) years old, and the majority of individuals were male (59.9%). Around 64.6% of individuals were diagnosed with atrial fibrillation and 22.2% were diagnosed with venous thromboembolism diseases. Baseline demographics of the study sample are described in Table 1.

Table 1: characteristics of the study sample at the time of first OAC prescription

Demographics	T2DM individuals receiving OAC (%)
Total	**36,570 (100%)**
Age (Mean ± SD)*	72 ± 10.2
Gender (Male)	21,586 (59.9)
Social	
Smoking	3,598 (10.0)
Alcohol drinking	23,879 (69.6)
Comorbidities**	
Atrial fibrillation	23,655 (64.6)
Venous thromboembolisms	8,127 (22.2)
Stroke	7,441 (20.3)
Coronary heart diseases	12,606 (34.4)
Chronic kidney diseases	10,097 (27.6)
Heart failure	8,181 (22.3)
Hypertension	25,342 (69.3)
Hyperlipidaemia	8,563 (23.4)
COPD	3,815 (10.4)
PUD	10,266 (28.0)
PVD	3,522 (9.6)
Bleeding	8,062 (22.0)
Depression	8,186 (22.8)
Mild liver disease	146 (0.4)

Moderate to severe liver disease	209 (0.5)
Medications	
Aspirin	13,940 (38.1)
Other anti-platelets	2,736 (7.4)
Statin	25,138 (68.7)
BB	18,503 (50.6)
CCB	13,597 (37.1)
ACEIs/ARBs	25,490 (69.7)
Diuretics	16,796 (45.9)
Digoxin	11,867 (32.4)
CHA_2DS_2-VASc Score[a]	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
HASBLED[b]	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

*Standard deviation ±; Alcohol missing: (10.5%), Smoking missing (3.2%); OAC: Oral anticoagulant; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; PUD: Peptic ulcer disease; PVD: Peripheral vascular disease; BB: Beta-blocker; CCB: Calcium channel blocker; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; [a]CHA_2DS_2-VASc indicates individuals with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or transient ischemic attack or systemic embolism (doubled), vascular disease, and gender category (women). CHA_2DS_2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); [b]HAS-BLED indicates individuals with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

Trends in prescribing prevalence of oral anticoagulant medications in T2DM

Between 2001 and 2015, the prescribing prevalence of OACs in individuals with T2DM increased by 50.8% [from 4.4 (95% CI 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons with T2DM], p<0.001, with an average increase of 3.2% per year (Figure 1).

The changes in prevalence of OAC prescribing between 2001 and 2015 stratified by gender are shown in Figure 1. The prescribing prevalence of OAC medications among males increased by 54.3% [from 4.6 (95%CI 4.3 – 4.9) to 7.1 (95%CI 6.9 – 7.2) per 100 persons with T2DM], while the prescribing

prevalence of OAC medications among females increased [from 4.0 (95%CI 3.8 – 4.4) to 5.9 (95%CI 5.8 – 6.1) per 100 persons with T2DM], with an overall increase of 47.5%.

Similarly, the prescribing prevalence of OAC medications varied among individuals from the different age groups. The prevalence of OAC medications among individuals aged 75 years or above increased [from 7.1 (95%CI 6.6– 7.6) in 2001 to 11.6 (95%CI 11.4 – 11.9) in 2015 per 100 persons with T2DM]. However, it was clearly lower among younger individuals, which increased [from 5.7 (95%CI 5.2 – 6.1) in 2001 to 6.5 (95%CI 6.3 – 6.6) in 2015 per 100 persons with T2DM], for individuals aged between 65-74 years, and [from 2.0 (95%CI 1.8 – 2.2) in 2001 to 2.2 (95%CI 2.1 – 2.3) in 2015 per 100 persons with T2DM], for individuals aged below 65 years (Figure 2).

Trends in prevalence of oral anticoagulant prescribing stratified by medication

Although warfarin was the most common OAC prescribed during the entire study period (86.3%), its use declined [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons with T2DM]. In contrast, there was a corresponding increase in the proportion of individuals who used DOACs [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons with T2DM]. Other OACs, including acenocoumarol and phenindione were less likely to be prescribed during the entire study period (0.03%), their prescribing rate decreased [from 1.1 (95% CI 0.7 – 1.7) in 2001 to 0.4 (95% CI 0.3 – 0.5) in 2015 per 100 persons with T2DM] (Figure 3). In addition, a small percentage of individuals with T2DM using OAC were prescribed different OAC classes during the same year ranging from less than 1% in 2010 to 3% in 2015.

Further stratification by individual OAC drug treatment showed that the prescribing prevalence of rivaroxaban markedly increased [from 0.1 (95% CI 0.05–0.2) in 2010 to 10.9 (95% CI 10.5–11.4) in 2015 per 100 persons with T2DM], while the prescribing prevalence of dabigatran increased to a lesser degree [from 0.03 (95% CI 0.001–0.07) in 2010 to 2.7 (95% CI 2.5–2.9) in 2015 per 100 persons with T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08) in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).

Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with and without T2DM

The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of prescribing ranged [from 46.6 (95% CI 43.5 – 49.7) in 2001 to 59.0 (95% CI 58.3 – 60.0) in 2015 per 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure 5).

DISCUSSION

This study investigated the drug utilisation pattern of OAC medications in individuals with T2DM, and in individuals with AF, with and without T2DM. The key findings are: 1) the prescribing prevalence of OACs in individuals with T2DM has increased markedly between 2001 and 2015, 2) the increase in the prescribing prevalence of OACs was not consistent across individuals of different gender and age group, males and individuals aged 75 years and above had a higher prescribing prevalence compared to females and individuals younger than 75 years, 3) the prescribing of DOACs is clearly replacing the prescribing of warfarin since their introduction to the UK market in 2011.

Previous studies investigating the trend of OACs prescribing in individuals with T2DM are limited. A previous study by Hamada *et al*. examined the trend of cardiovascular medication prescribing in diabetic individuals aged 80 years or above in the UK between 1990 to 2010 (22), concluding that the prescribing of OACs in individuals with T2DM had increased [from 5% in 1999 to 19% in 2010]. These results showed similar trends to our study in the increase of OACs prescriptions in T2DM. However, our results showed that OAC prescriptions increased less sharply, which is explicable by restriction of their population to include only individuals aged 80 years and older. Despite this, age is considered a risk factor for many conditions for which OACs are indicated, and our results showed an increased rate of OACs prescribing among individuals aged 75 years and above, which was also similar to a previous study that used primary care data in the UK (43). Furthermore, an increasing prescribing prevalence of

DOACs in the last few years have been reported in several studies that examined the trend of OACs in the general population or in individuals with AF across different countries (43-46). Alalwan *et al*., using data from MarketScan Medicare, reported that DOACs increased from 1.39% (95% CI, 1.34–1.44%) in 2010 to 28.33% (95% CI, 28.14–28.52%) in 2014 (44). Similarly, Loo *et al*. found that the rate of initiation of DOAC increased significantly, particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI 12.16, 25.71) (43). The findings presented in our study, and specifically related to DOACs' prescribing trend are in line with previous findings, however, it is important to highlight that those studies concerned the general population and were not specific to T2DM. (43-46).

This study showed that since the introduction of DOACs, individuals with T2DM using OACs were prescribed different classes of OAC, possibly due to individuals switching from one class to another. DOACs have been reported to be non-inferior to warfarin in the prevention of major strokes and embolic events in different clinical trials and observational studies (47-51). Evidence from meta-analyses showing better efficacy and non-inferior safety when comparing DOACs and warfarin could be a reason for the paradigm shift in favouring the prescribing of DOACs (52, 53). This led in a change in the UK National Institute for Health and Care Excellence (NICE) guidance for the management of AF (15), and as of 2014, DOACs have been recommended as first-line therapy for AF (54). However, it is crucial to recognise that older people with comorbidities were excluded or underrepresented in the pivotal clinical trials of DOACs and therefore, DOACs should be prescribed with caution and strict monitoring in this population (55). Another major issue with warfarin is that it is more prone to several drug-food and drug-drug interactions (27-29, 56), which could explain why DOACs are being prescribed more favourably in the recent years compared to warfarin, especially accounting for elements such as ageing and polypharmacy. Nonetheless, a major advantage for DOACs is their wider therapeutic index and that it does not require regular monitoring during intake for international normalized ratio (INR) compared to warfarin (57-59).

The results of this study highlighted that individuals with T2DM receiving OACs have a high risk profile of cardiovascular comorbidities including hypertension, coronary heart disease, heart failure, peripheral vascular diseases and hyperlipidaemia (Table 1), in which it could be associated with the

initiation of OAC prescribing (21). However, due to the nature of this descriptive study it is difficult to draw this conclusion and we urge for further studies to investigate this association.

As expected, our results showed that AF was the main indication for OAC prescriptions among individuals with T2DM. Several international guidelines, including those from the US (60), Europe (18) and the UK (15) have recommended the use of OACs in individuals with AF based on $CHADS_2$ (16) and CHA_2DS_2-VASc score (17). This was also in line with our results as it showed that individuals with AF and coexisting T2DM had a higher rate of OACs prescribing compared to individuals with AF without T2DM. However, our results showed a higher prescribing rate of OAC among males compared to females that is similar to other studies that highlighted the higher prevalence of OAC prescribing amongst males (61, 62).

Strengths and limitations

To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period. This study used a clinical record primary care research database which was representative of the UK general population.

However, this study has some limitations. Firstly, underestimation of OAC prescribing as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals. However, the UK National Health Service (NHS) heavily subsidies the treatment of chronic illness and the majority of individuals with chronic illness are looked after by primary care; therefore, our results should not be affected significantly. Secondly, individuals were identified using relevant Read code lists and algorithms. This may have led to bias in the study due to under-reporting or misreporting of T2DM diagnoses; however, this issue was mitigated by validating our codes with clinicians and previously published studies. THIN is a medical record database and therefore, similar to other clinical databases, it was not possible to confirm if individuals were adherent. Furthermore, in the secondary objective of this study we did not adjust for CHA_2DS_2-VASc in the comparison between the trend in OAC use in individuals with AF, with and without T2DM. However, CHA_2DS_2-VASc was introduced in 2010 (17),

and was only implemented in the NICE guidelines in 2014 (15), considering that our study end date was 2015, the practice will not be reflected in our study period

Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications and OAC medications for possible drug-drug interactions, especially when warfarin is the drug of choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is imperative to investigate the effect of concomitant use of this class of medication and the risk of hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus improve the safety of OAC use in individuals with T2DM.

CONCLUSIONS

This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin since its introduction to the UK market, which is consistent with UK guidelines. However, there is a lack of studies examining their safety when used in individuals with T2DM. Further studies are warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for possible drug-drug interactions.

Abbreviations

ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs: Confidence intervals; Cytochrome P450: CYP450; DOAC: Direct oral anticoagulant; IDF: International Diabetes Federation; INR: International normalized level; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OAC: oral anticoagulant; SD: Standard deviation; SRC: Scientific Review Committee; STROBE: Strengthening the reporting of observational studies in epidemiology; THIN: The Health Improvement Network; T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus UK: United Kingdom.

Consent for publication

Not applicable.

Data Availability

No further data are available.

Conflict of Interest Disclosures

The authors declare that they have no competing interest.

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The authors who contributed to the work described in this paper are as follows: HA, LW and IW contributed to the study design. HA, LW, KM and PM contributed to the Statistical analysis. HA, LW and IW were involved in interpretation of data. HA wrote the first draft of the article. HA, LW, AN, JSB, JI, GT, GF and IW made substantial contributions to the drafts, reviewed the manuscript for important intellectual content and provided final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure titles and legends

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM.

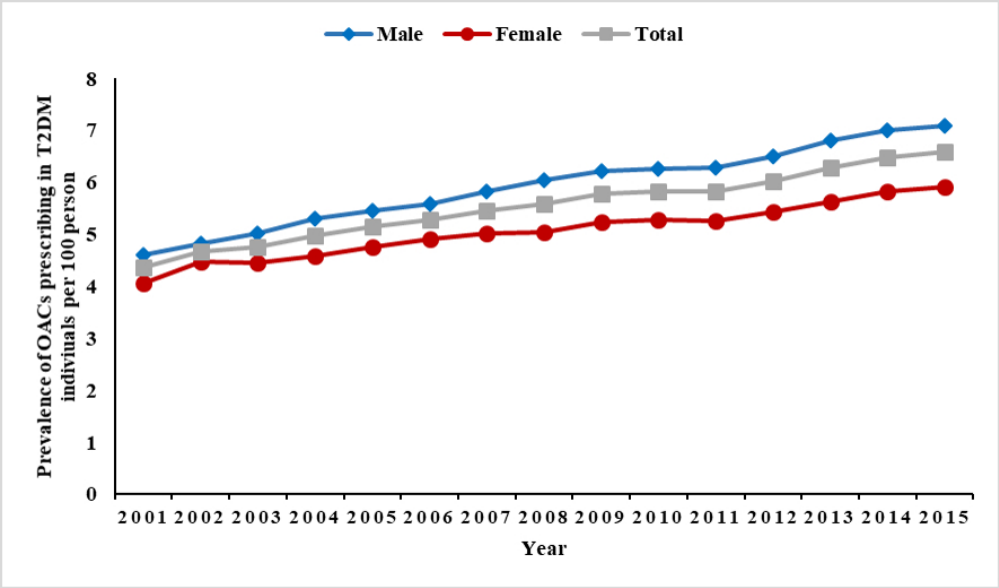

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

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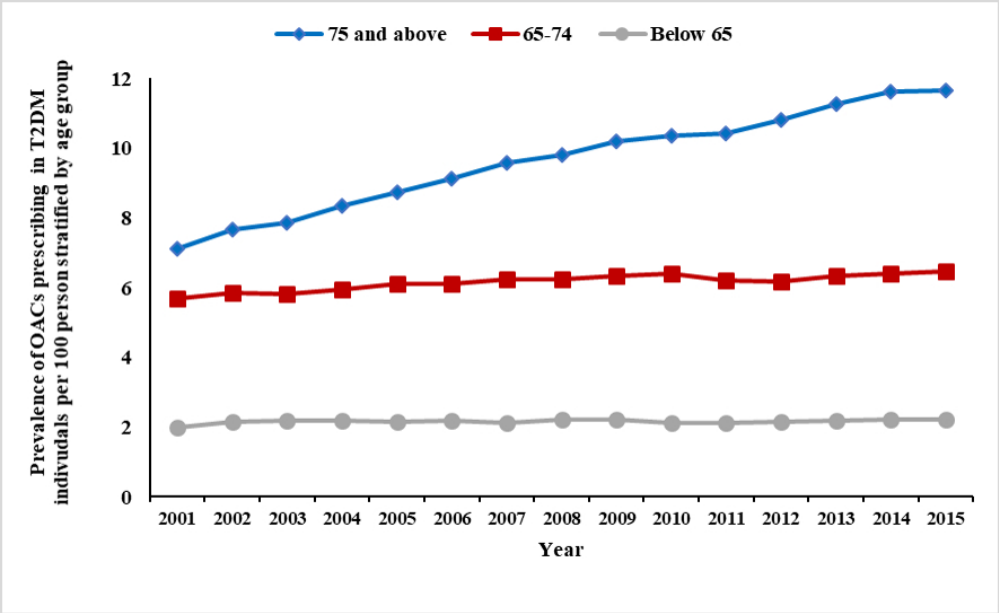

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

75x46mm (300 x 300 DPI)

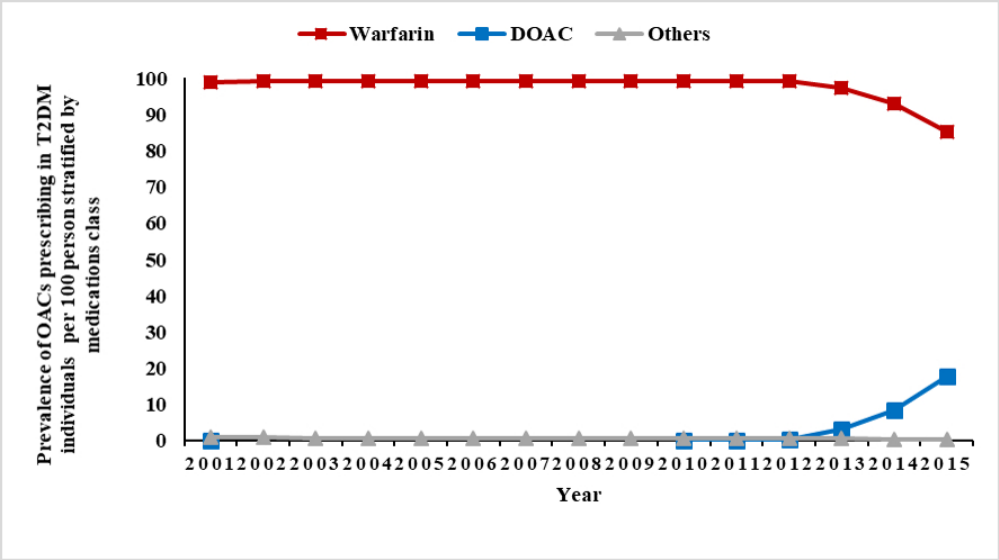

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

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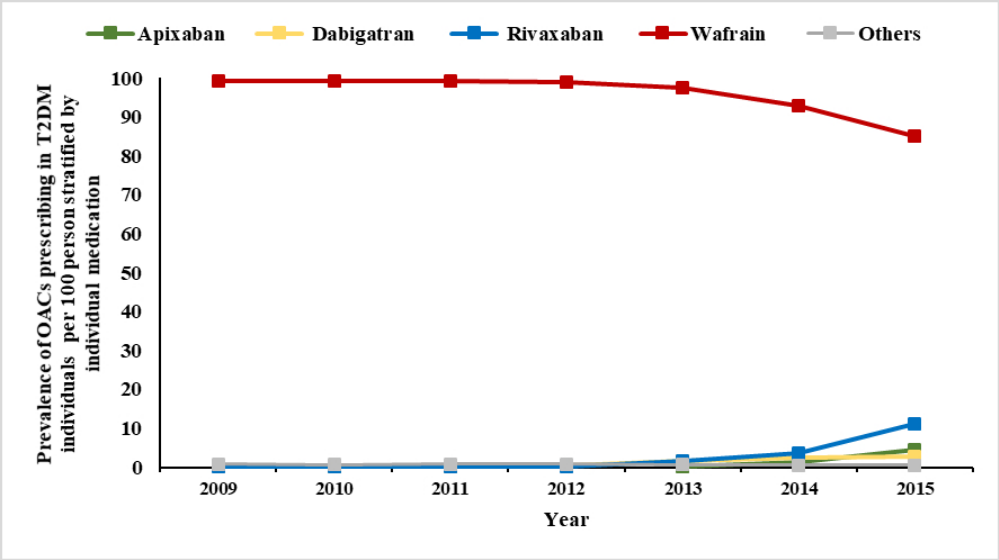

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

75x42mm (300 x 300 DPI)

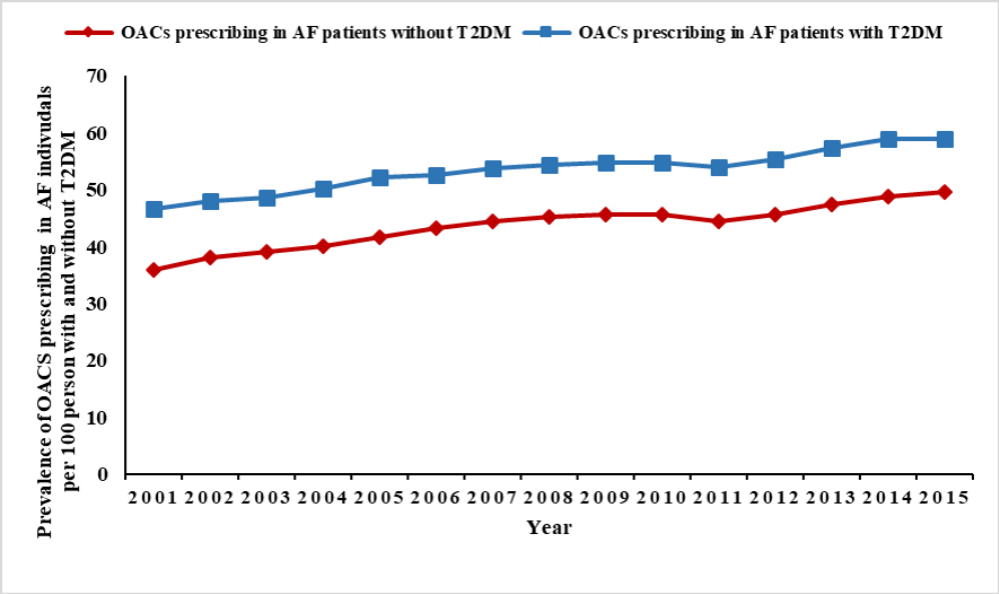

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM

75x44mm (300 x 300 DPI)

Supplement:

Figure S1: Methods to identify study population of AF individuals with and without T2DM.

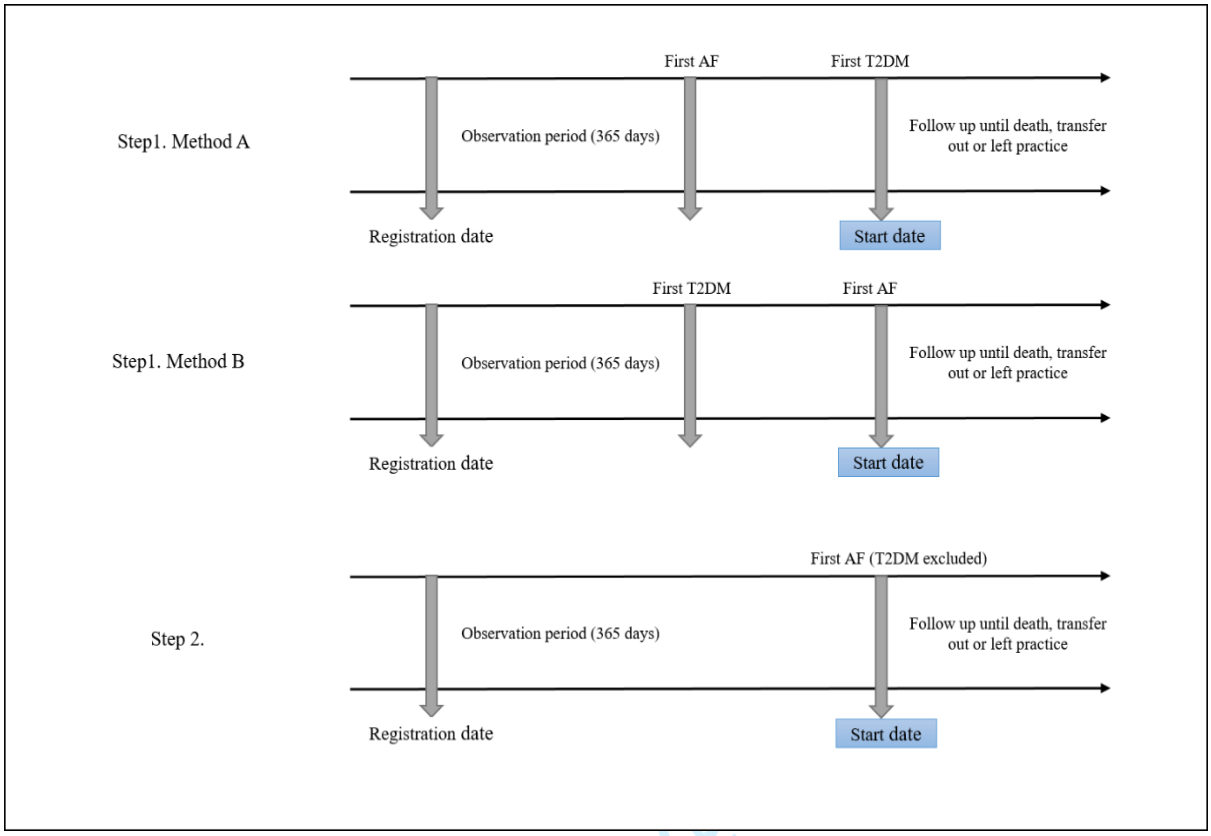

Figure S1. Methods to identify study population of AF individuals with and without T2DM

Registration date: is the date of individual's registration with the general practice

AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus

Table S1: Strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1,2	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	2	Introduction
Methods				
Study design	4	Present key elements of study design early in the paper	2	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2,3	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3,4	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		Not applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Not applicable
Bias	9	Describe any efforts to address potential sources of bias		Not applicable
Study size	10	Explain how the study size was arrived at		Not applicable

Continue on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4	
		(*b*) Describe any methods used to examine subgroups and interactions	4	
		(*c*) Explain how missing data were addressed		Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		Not applicable
		(*e*) Describe any sensitivity analyses		Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4	Results
		(b) Give reasons for non-participation at each stage		Not applicable
		(c) Consider use of a flow diagram		Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4	Results
		(b) Indicate number of participants with missing data for each variable of interest		Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	6,7	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Not applicable
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable

Continue on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7,8	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	8,9	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	10	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12	Declarations

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom

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Keywords:	EPIDEMIOLOGY, DIABETES & ENDOCRINOLOGY, Anticoagulation < HAEMATOLOGY

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Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom

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ABSTRACT (219 words)

Objective: To evaluate oral anticoagulant (OAC) prescribing trends in type 2 diabetes mellitus (T2DM) in the United Kingdom (UK) from 2001 to 2015.

Design: A cross-sectional drug utilisation study.

Setting: Electronic health records from The Health Improvement Network (THIN) primary care database of the UK.

Participants: Individuals with T2DM who received a record of OAC prescription.

Outcome measures: The prescribing trends of OAC medications in individuals with T2DM were examined from 2001 to 2015, stratified by age, gender and therapeutic classifications.

Results: The prevalence of OAC prescribing increased by 50.0% [from 4.4 (95% confidence intervals (CI) 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons]. The prevalence of warfarin prescribing decreased by 14.0% [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons]. This corresponded with increased prescribing of direct oral anticoagulants (DOACs) [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons] during the same period.

Conclusions: Prescribing of OACs in individuals with T2DM increased from 2001 to 2015. Since the introduction of DOACs there has been a clear shift in prescribing towards these agents. Future studies are needed to assess the safety of the co-administration of OAC medications and antidiabetic therapy with T2DM.

Keywords: Diabetes mellitus, Drug utilisation, Oral anticoagulants therapies, Trend, United Kingdom

Strengths and limitations of this study

- To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period.
- This study used a clinical record primary care research database which was representative of the UK general population.
- Underestimation of OAC prescribing could be a limitation of this study as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide and has become a major global public health concern (1) . According to the International Diabetes Federation (IDF) report in 2017, it was estimated that 425 million people worldwide are living with diabetes, compared to 30 million in the year of 1985, of whom 90% were diagnosed with T2DM (1). In the United Kingdom (UK), the prevalence of diabetes has doubled over the last three decades (2, 3). Using a national health database in the UK, Zghebi et al estimated that the prevalence of diabetes increased from 3.2 % in 2004 to 5.2 % in 2014 (4).

T2DM and cardiovascular diseases often coexist with many individuals with T2DM experiencing cardiovascular complications (5, 6). Cardiovascular diseases including cardiac arrhythmias, venous thromboembolism, and ischaemic heart disease are among the leading causes of mortality worldwide in individuals with T2DM (7). Anticoagulants are widely prescribed for the prevention and treatment of atrial fibrillation (AF), stroke, venous and arterial thrombosis. When prescribed for venous thromboembolism, oral anticoagulant (OAC) treatment is typically of short duration, but it can be lifelong treatment when prescribed for AF (8).

T2DM is one of the main risk factors contributing in $CHA2DS_2$ score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (9). In 2010, CHA_2DS_2-VASc was adapted from the previous score (10), and it is now recommended by most of the current guidelines (8, 11, 12), in which individuals with AF are likely to be prescribed OAC if they score two or more in the total score. In addition, since the introduction of direct oral anticoagulants (DOACs) in 2011, several guidelines recommended their use for indications such as atrial fibrillation (8, 11, 12). DOACs have much more predictable pharmacokinetics and pharmacodynamics, and are less prone for drug interactions when compared with warfarin (13). However, OAC use in individuals with T2DM remains unclear, with limited studies focused on their use in individuals with T2DM (14, 15).

Previous studies have demonstrated that the prevalence of AF in individuals with T2DM ranges from 8% to 14.9% (16, 17), and that individuals with T2DM have 40% higher risk of developing AF compared to individuals without T2DM (18). Investigating OAC use in individuals with T2DM is important due to the high number of individuals, the possibility of drug-drug interactions, and the

potential association with serious adverse events such as bleeding and hypoglycaemia (19, 20). This was highlighted in particular among individuals with T2DM in previous large-scale epidemiological studies and in multiple case reports where warfarin was associated with an increased risk of hypoglycaemia. It has been suggested that displaced plasma protein and Cytochrome P450 (CYP450) hepatic metabolic pathway could be potential mechanisms for the increased risk of hypoglycaemia (21-24).

Given the recent update in guidelines for OAC prescribing, and the limited research on their use in individuals with T2DM, this research aimed to describe the prescribing patterns of OAC medications in individuals with T2DM in the UK population as an important step in investigating its safety within this high risk population.

The primary objective of this study was to examine the prescribing trends of OAC medications in individuals with T2DM from 2001 to 2015, stratified by age, gender and therapeutic classifications. The secondary objective was to compare the trend in OAC use in individuals with AF, with and without T2DM, given that AF is the main indication for OAC use.

METHODS

Data sources

This was a retrospective drug utilisation study using primary care data in The Health Improvement Network (THIN); a UK primary care database containing anonymised administrative, clinical and prescribing data from over 587 practices with more than 13 million individuals (25, 26). THIN is one of the largest sources for primary care data in the UK, and has been validated for epidemiological research purposes (25-27). In addition, it has been used by our team to study prescribing of OAC and various psychotropic medications (28-32). It holds data on personal information, health related behaviours, and diagnoses information which is recorded and identified using Read codes (25, 26). Read codes, which are also known as clinical terms, are clinical terminologies used to describe the care, diagnosis of diseases and treatments of individuals. It is used to manage primary care data in electronic health records (33). The database also has prescribing information that is linked with the British National Formulary. THIN contains records of prescriptions issued only by GPs and recorded in the individuals records.

Study population

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study. The AMR date is the year that data reporting is deemed to be complete, based on information derived from the Office for National Statistics (34). The start date was defined as the date of the first record for T2DM diagnosis. Individuals were included only if they had an observation period of at least 12 months prior to their start date and were registered with the general practice during the study period. The end date was the date were individuals left the practice, died or transferred out. Individuals with T2DM aged > 18 and registered with the THIN database between 2001 and 2015 (of which data were only available up to) were identified based on the following criteria of having; 1) a diagnostic code for T2DM (using Read codes), or 2) a diagnostic code for any type of diabetes and a record of any oral hypoglycaemic agent prescription, and the start date for these individuals was defined as the date of the first record for diabetes. Individuals who had a diagnostic code for T2DM accounted for 92.7% of the entire cohort, while the remaining were of criteria two. Individuals with a non-specific code for T2DM and who only had records for insulin prescription were excluded because they may have type 1 diabetes mellitus (T1DM), although their age at first event is taken into account. T2DM is typically diagnosed over the age of 30 years, however, the rate of young onset T2DM is increasing (35). We therefore only excluded children (less than 18 years old) who were more likely to have T1DM. Individuals with T2DM receiving at least one prescription of OAC medication were identified. Oral anticoagulant medications were consigned into three categories: warfarin, DOACs (apixaban, rivaroxaban, dabigatran and edoxaban), and other anticoagulant medications (acenocoumarol, pentosan polysulfate and phenindione). Furthermore, individuals with AF aged > 18 years and registered with THIN were identified using Read codes. The prescribing of OAC medications in individuals with AF with and without T2DM involved a two-step cohort identification (Figure S1). The first step was designed to identify individuals with AF with coexisting T2DM, and the latest first record between AF and DM was counted as the start date (coexisting of both diseases) for this cohort. The second step involved identifying individuals with AF without a diagnosis of T2DM, and the start date for these individuals was the first recorded AF diagnosis. Individuals who developed AF first and T2DM later contributed to the AF only cohort and then to the AF and T2DM cohort. For

baseline characteristics: chronic comorbidities were measured over the 12-month period preceding the first OAC prescription. However, medication use was assessed over the 6-month period preceding the first OAC prescription.

Statistical analysis

Descriptive statistics were used to describe individuals' demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data was reported as percentages (frequencies). The prevalence of OAC medications presented per 100 persons with 95% confidence intervals (CIs) were calculated on an annual basis by dividing the number of all individuals prescribed OAC medications in a particular year over the mid-year population of individuals with T2DM in the same calendar year, stratified by age, gender and therapeutic classifications. For the secondary objective: the trend in OAC use in AF individuals with T2DM, was calculated on an annual basis by dividing the number of AF individuals with T2DM prescribed OAC medications in a particular year over the mid-year population of AF individuals with T2DM in the same calendar year. The trend in OAC use in individuals with AF and without T2DM was calculated by dividing the number of AF individuals without T2DM prescribed OAC medications in a particular year over the mid-year population of AF individuals without T2DM in the same calendar year. The prescribing trend of OAC medications was assessed using Poisson model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The present study is based on anonymised and unidentifiable THIN data, thus the need for informed consent was waived by the THIN scientific review committee (SRC). This study was reviewed and scientific approval was obtained by THIN SRC in 2018 (18THIN009). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement (Supplements Table S1).

Patient involvement

Patients were not involved in the design of the study.

RESULTS

Demographics and characteristics

During the study period of 2001 and 2015, a total of 361,635 individuals with T2DM were identified of whom 36,570 received a prescription for OAC. Characteristics of the entire cohort included in our study are presented at the time of first OAC prescription. The average age of individuals at the time of first OAC prescription was 72 (SD, 10.2) years old, and the majority of individuals were male (59.9%). Around 64.6% of individuals were diagnosed with atrial fibrillation and 22.2% were diagnosed with venous thromboembolism diseases. Baseline demographics of the study sample are described in Table 1.

Table 1: characteristics of the study sample at the time of first OAC prescription

Demographics	T2DM individuals receiving OAC (%)
Total	**36,570 (100%)**
Age (Mean ± SD)*	72 ± 10.2
Gender (Male)	21,586 (59.9)
Social	
Smoking	3,598 (10.0)
Alcohol drinking	23,879 (69.6)
Comorbidities**	
Atrial fibrillation	23,655 (64.6)
Venous thromboembolisms	8,127 (22.2)
Stroke	7,441 (20.3)
Coronary heart diseases	12,606 (34.4)
Chronic kidney diseases	10,097 (27.6)
Heart failure	8,181 (22.3)
Hypertension	25,342 (69.3)
Hyperlipidaemia	8,563 (23.4)
COPD	3,815 (10.4)
PUD	10,266 (28.0)
PVD	3,522 (9.6)
Bleeding	8,062 (22.0)
Depression	8,186 (22.8)
Mild liver disease	146 (0.4)
Moderate to severe liver disease	209 (0.5)
Medications	
Aspirin	13,940 (38.1)

Other anti-platelets	2,736 (7.4)
Statin	25,138 (68.7)
BB	18,503 (50.6)
CCB	13,597 (37.1)
ACEIs/ARBs	25,490 (69.7)
Diuretics	16,796 (45.9)
Digoxin	11,867 (32.4)
CHA_2DS_2-VASc Score[a]	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
HASBLED[b]	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

*Standard deviation ±; Alcohol missing: (10.5%), Smoking missing (3.2%); OAC: Oral anticoagulant; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; PUD: Peptic ulcer disease; PVD: Peripheral vascular disease; BB: Beta-blocker; CCB: Calcium channel blocker; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; [a]CHA_2DS_2-VASc indicates individuals with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or transient ischemic attack or systemic embolism (doubled), vascular disease, and gender category (women). CHA_2DS_2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); [b]HAS-BLED indicates individuals with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

Trends in prescribing prevalence of oral anticoagulant medications in T2DM

Between 2001 and 2015, the prescribing prevalence of OACs in individuals with T2DM increased by 50.0% [from 4.4 (95% CI 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons with T2DM], p<0.001, with an average increase of 3.2% per year (Figure 1).

The changes in prevalence of OAC prescribing between 2001 and 2015 stratified by gender are shown in Figure 1. The prescribing prevalence of OAC medications among males increased by 54.3% [from 4.6 (95%CI 4.3 – 4.9) to 7.1 (95%CI 6.9 – 7.2) per 100 persons with T2DM], while the prescribing prevalence of OAC medications among females increased [from 4.0 (95%CI 3.8 – 4.4) to 5.9 (95%CI 5.8 – 6.1) per 100 persons with T2DM], with an overall increase of 47.5%.

Similarly, the prescribing prevalence of OAC medications varied among individuals from the different age groups. The prevalence of OAC medications among individuals aged 75 years or above increased [from 7.1 (95%CI 6.6– 7.6) in 2001 to 11.6 (95%CI 11.4 – 11.9) in 2015 per 100 persons with T2DM]. However, it was clearly lower among younger individuals, which increased [from 5.7 (95%CI 5.2 – 6.1) in 2001 to 6.5 (95%CI 6.3 – 6.6) in 2015 per 100 persons with T2DM], for individuals aged between 65-74 years, and [from 2.0 (95%CI 1.8 – 2.2) in 2001 to 2.2 (95%CI 2.1 – 2.3) in 2015 per 100 persons with T2DM], for individuals aged below 65 years (Figure 2).

Trends in prevalence of oral anticoagulant prescribing stratified by medication

Although warfarin was the most common OAC prescribed during the entire study period (86.3%), its use declined [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons with T2DM]. In contrast, there was a corresponding increase in the proportion of individuals who used DOACs [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons with T2DM]. Other OACs, including acenocoumarol and phenindione were less likely to be prescribed during the entire study period (0.03%), their prescribing rate decreased [from 1.1 (95% CI 0.7 – 1.7) in 2001 to 0.4 (95% CI 0.3 – 0.5) in 2015 per 100 persons with T2DM] (Figure 3). In addition, a small percentage of individuals with T2DM using OAC were prescribed different OAC classes during the same year ranging from less than 1% in 2010 to 3% in 2015.

Further stratification by individual OAC drug treatment showed that the prescribing prevalence of rivaroxaban markedly increased [from 0.1 (95% CI 0.05–0.2) in 2010 to 10.9 (95% CI 10.5–11.4) in 2015 per 100 persons with T2DM], while the prescribing prevalence of dabigatran increased to a lesser degree [from 0.03 (95% CI 0.001–0.07) in 2010 to 2.7 (95% CI 2.5–2.9) in 2015 per 100 persons with T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08) in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).

Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with and without T2DM

The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of

prescribing ranged [from 46.6 (95% CI 43.5 – 49.7) in 2001 to 59.0 (95% CI 58.3 – 60.0) in 2015 per 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure 5).

DISCUSSION

This study investigated the drug utilisation pattern of OAC medications in individuals with T2DM, and in individuals with AF, with and without T2DM. The key findings are: 1) the prescribing prevalence of OACs in individuals with T2DM has increased markedly between 2001 and 2015, 2) the increase in the prescribing prevalence of OACs was not consistent across individuals of different gender and age group, males and individuals aged 75 years and above had a higher prescribing prevalence compared to females and individuals younger than 75 years, 3) the prescribing of DOACs is clearly replacing the prescribing of warfarin since their introduction to the UK market in 2011.

Previous studies investigating the trend of OACs prescribing in individuals with T2DM are limited. A previous study by Hamada *et al*. examined the trend of cardiovascular medication prescribing in diabetic individuals aged 80 years or above in the UK between 1990 to 2010 (15), concluding that the prescribing of OACs in individuals with T2DM had increased [from 5% in 1999 to 19% in 2010]. These results showed similar trends to our study in the increase of OACs prescriptions in T2DM. However, our results showed that OAC prescriptions increased less sharply, which is explicable by restriction of their population to include only individuals aged 80 years and older. Despite this, age is considered a risk factor for many conditions for which OACs are indicated, and our results showed an increased rate of OACs prescribing among individuals aged 75 years and above, which was also similar to a previous study that used primary care data in the UK (36). Furthermore, an increasing prescribing prevalence of DOACs in the last few years have been reported in several studies that examined the trend of OACs in the general population or in individuals with AF across different countries (36-38). Alalwan *et al*., using data from MarketScan Medicare, reported that DOACs increased from 1.39% (95% CI, 1.34–1.44%) in 2010 to 28.33% (95% CI, 28.14–28.52%) in 2014 (37). Similarly, Loo *et al*. found that the rate of initiation of DOAC increased significantly, particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI 12.16, 25.71) (36). The findings presented in our study, and

specifically related to DOACs' prescribing trend are in line with previous findings, however, it is important to highlight that those studies concerned the general population and were not specific to T2DM (36-38).

This study showed that since the introduction of DOACs, individuals with T2DM using OACs were prescribed different classes of OAC, possibly due to individuals switching from one class to another. DOACs have been reported to be non-inferior to warfarin in the prevention of major strokes and embolic events in different clinical trials and observational studies (39-43). Evidence from meta-analyses showing better efficacy and non-inferior safety when comparing DOACs and warfarin could be a reason for the paradigm shift in favouring the prescribing of DOACs (44, 45). This led in a change in the UK National Institute for Health and Care Excellence (NICE) guidance for the management of AF (8), and as of 2014, DOACs have been recommended as first-line therapy for AF (46). However, it is crucial to recognise that older people with comorbidities were excluded or underrepresented in the pivotal clinical trials of DOACs and therefore, DOACs should be prescribed with caution and strict monitoring in this population (47). Another major issue with warfarin is that it is more prone to several drug-food and drug-drug interactions (20-22, 48), which could explain why DOACs are being prescribed more favourably in the recent years compared to warfarin, especially accounting for elements such as ageing and polypharmacy. Nonetheless, a major advantage for DOACs is their wider therapeutic index and that it does not require regular monitoring during intake for international normalized ratio (INR) compared to warfarin (49-51).

The results of this study highlighted that individuals with T2DM receiving OACs have a high risk profile of cardiovascular comorbidities including hypertension, coronary heart disease, heart failure, peripheral vascular diseases and hyperlipidaemia (Table 1), in which it could be associated with the initiation of OAC prescribing (14). However, due to the nature of this descriptive study it is difficult to draw this conclusion and we urge for further studies to investigate this association.

As expected, our results showed that AF was the main indication for OAC prescriptions among individuals with T2DM. Several international guidelines, including those from the US (52), Europe (11) and the UK (8) have recommended the use of OACs in individuals with AF based on $CHADS_2$ (9) and CHA_2DS_2-VASc score (10). This was also in line with our results as it showed that individuals with AF

and coexisting T2DM had a higher rate of OACs prescribing compared to individuals with AF without T2DM. However, our results showed a higher prescribing rate of OAC among males compared to females that is similar to other studies that highlighted the higher prevalence of OAC prescribing amongst males (53, 54).

Strengths and limitations

To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period. This study used a clinical record primary care research database which was representative of the UK general population.

However, this study has some limitations. Firstly, underestimation of OAC prescribing as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals. However, the UK National Health Service (NHS) heavily subsidies the treatment of chronic illness and the majority of individuals with chronic illness are looked after by primary care; therefore, our results should not be affected significantly. Secondly, individuals were identified using relevant Read code lists and algorithms. Codes were selected with reference to clinicians' comments and previously published studies. However, as described in the methods section, there is a possibility of misclassification in identifying individuals with T2DM. This may have led to overestimation of T2DM diagnoses in the study, however, it is also important to mention that individuals who had a diagnostic code for T2DM contributed to over 92% of the study cohort. Therefore, it is reasonable to assume that this did not have a major impact on our findings. THIN is a medical record database and therefore, similar to other clinical databases, It was not possible to confirm if individuals were adherent. Furthermore, in the secondary objective of this study we did not adjust for CHA_2DS_2-VASc in the comparison between the trend in OAC use in individuals with AF, with and without T2DM. However, CHA_2DS_2-VASc was introduced in 2010 (10), and was only implemented in the NICE guidelines in 2014 (8), considering that our study end date was 2015, the practice will not be reflected in our study period

Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications and OAC medications for possible drug-drug interactions, especially when warfarin is the drug of

choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is imperative to investigate the effect of concomitant use of this class of medication and the risk of hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus improve the safety of OAC use in individuals with T2DM.

CONCLUSIONS

This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin since its introduction to the UK market, which is consistent with UK guidelines. However, there is a lack of studies examining their safety when used in individuals with T2DM. Further studies are warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for possible drug-drug interactions.

Abbreviations

ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs: Confidence intervals; Cytochrome P450: CYP450; DOAC: Direct oral anticoagulant; IDF: International Diabetes Federation; INR: International normalized level; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OAC: oral anticoagulant; SD: Standard deviation; SRC: Scientific Review Committee; STROBE: Strengthening the reporting of observational studies in epidemiology; THIN: The Health Improvement Network; T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus UK: United Kingdom.

Consent for publication

Not applicable.

Data Availability

No further data are available.

Conflict of Interest Disclosures

The authors declare that they have no competing interest.

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The authors who contributed to the work described in this paper are as follows: HA, LW and IW contributed to the study design. HA, LW, KM and PM contributed to the Statistical analysis. HA, LW and IW were involved in interpretation of data. HA wrote the first draft of the article. HA, LW, AN, JSB, JI, GT, GF and IW made substantial contributions to the drafts, reviewed the manuscript for important intellectual content and provided final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure titles and legends

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM.

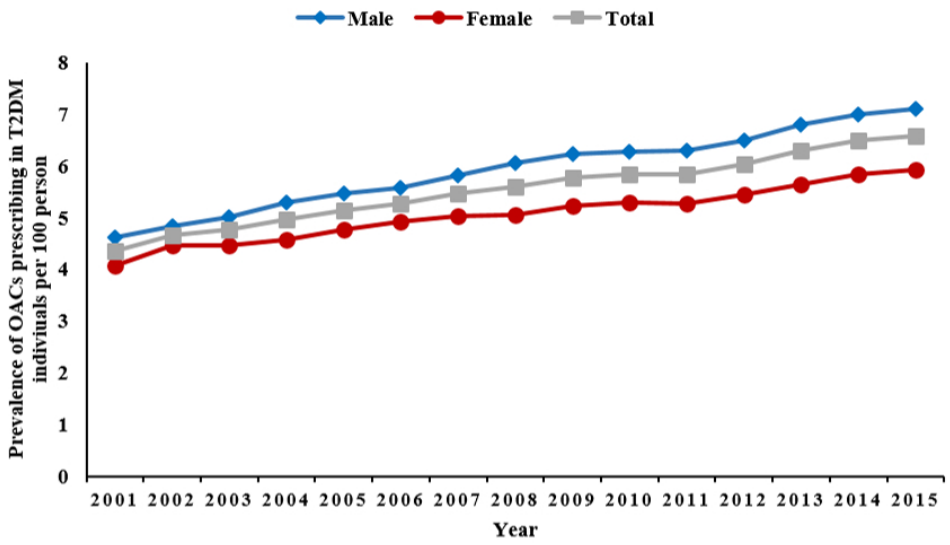

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

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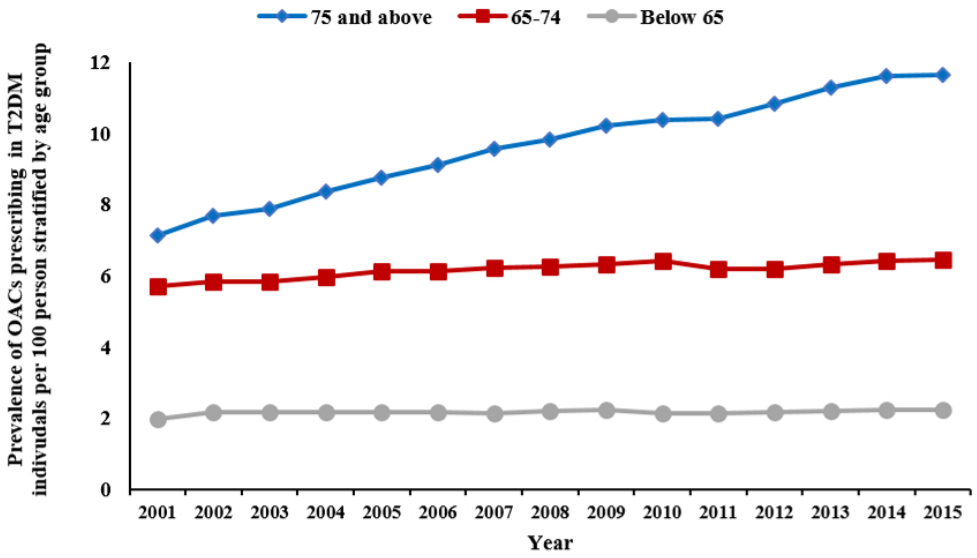

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

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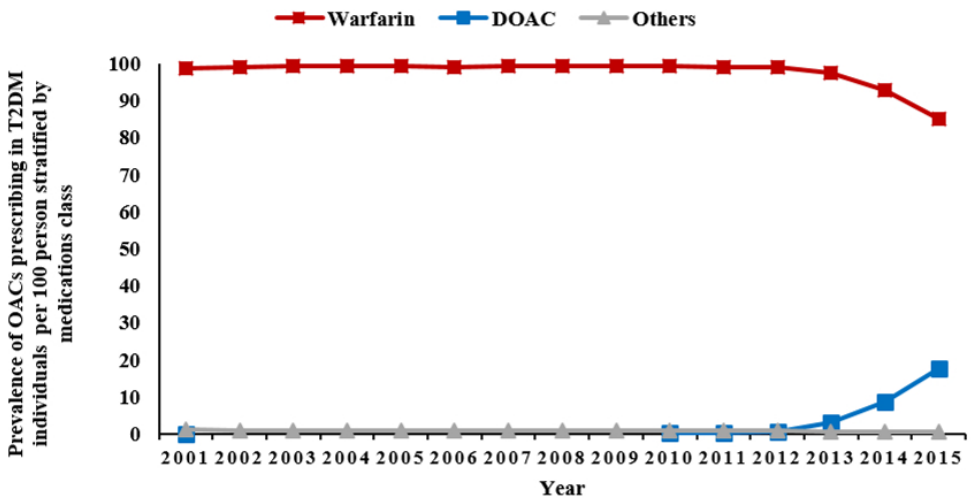

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

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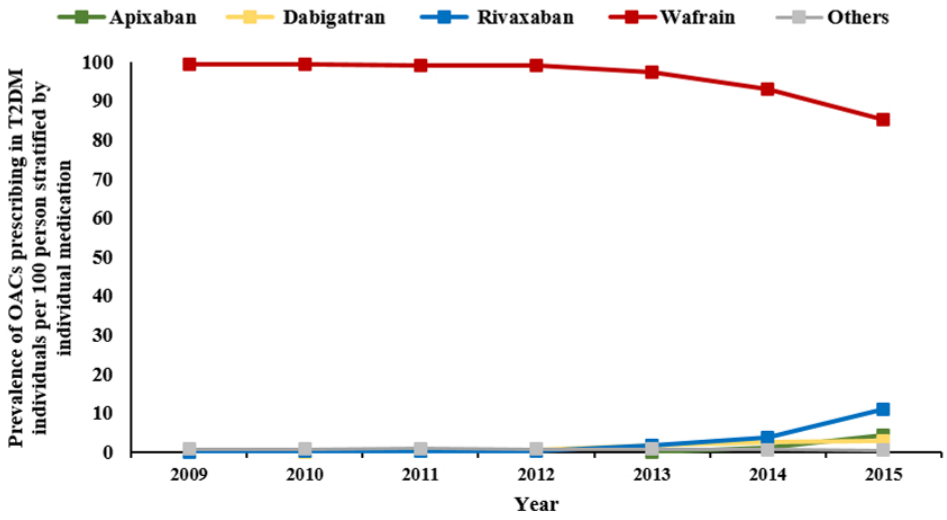

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

75x41mm (300 x 300 DPI)

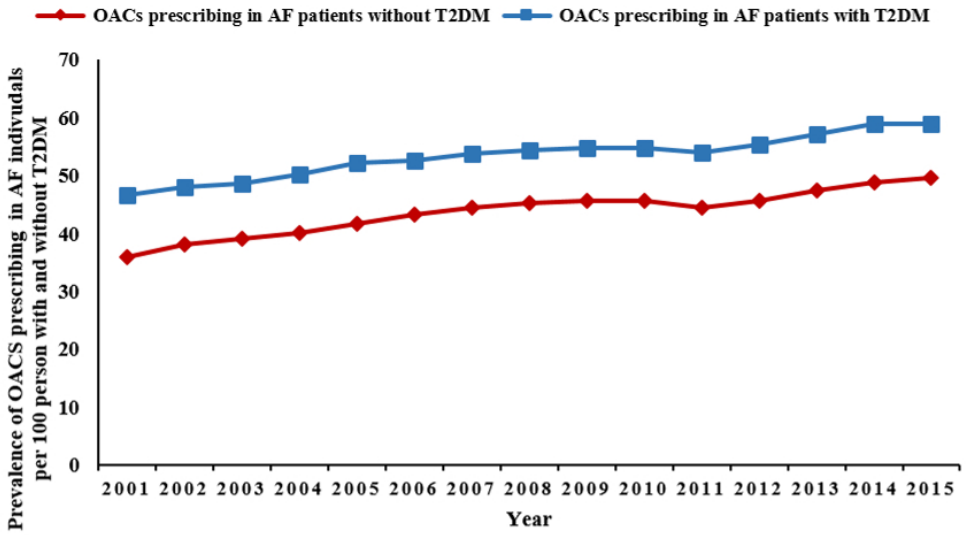

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM

73x41mm (300 x 300 DPI)

Supplement:

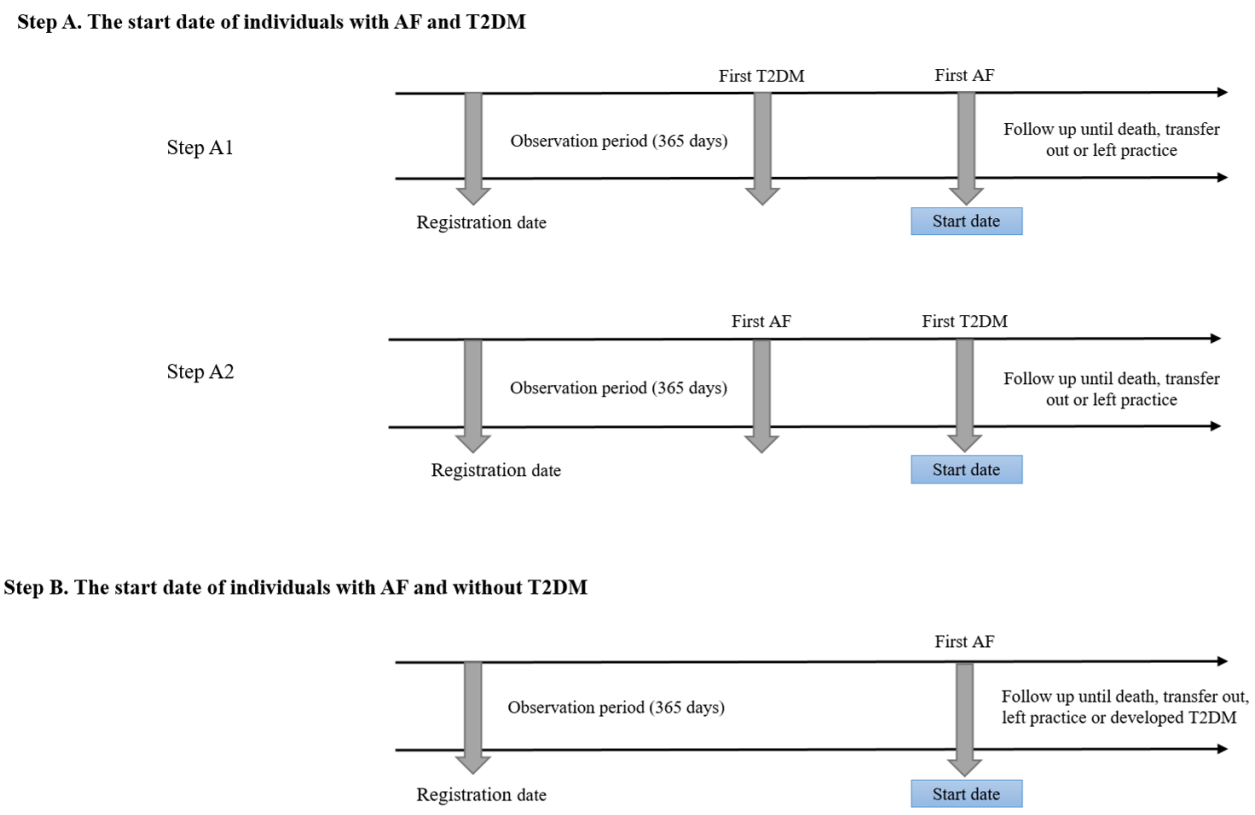

Figure S1. Methods to identify the study population of AF individuals with and without T2DM

Registration date: is the date of an individual's registration with the general practice; AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus. Individuals who developed AF first and T2DM later (Step A2) contributed to the AF only cohort (Step B) until they developed T2DM

Table S1: Strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	5	Introduction
Methods				
Study design	4	Present key elements of study design early in the paper	5	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6,7	Methods
Bias	9	Describe any efforts to address potential sources of bias		Not applicable
Study size	10	Explain how the study size was arrived at	5,6	Methods

Continue on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	7	Methods
		(*c*) Explain how missing data were addressed		Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		Not applicable
		(*e*) Describe any sensitivity analyses		Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Results
		(b) Give reasons for non-participation at each stage	6	Methods
		(c) Consider use of a flow diagram		Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Results
		(b) Indicate number of participants with missing data for each variable of interest		Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	9,10,11	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Not applicable
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable

Continue on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	11,12,13	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12,13,14	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	5,13	Methods and discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15	Declarations

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom

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ABSTRACT (262 words)

Objective: To evaluate oral anticoagulant (OAC) prescribing trends in type 2 diabetes mellitus (T2DM) in the United Kingdom (UK) from 2001 to 2015.

Design: A cross-sectional drug utilisation study.

Setting: Electronic health records from The Health Improvement Network (THIN) primary care database of the UK.

Participants: Individuals with T2DM who received a record of OAC prescription.

Outcome measures: The prescribing trends of OAC medications in individuals with T2DM were examined from 2001 to 2015, stratified by age, gender and therapeutic classifications.

Results: A total of 361,635 individuals with T2DM were identified, of which 36,570 were prescribed OAC from 2001 to 2015. The prevalence of OAC prescribing increased by 50.0% [from 1,781 individuals receiving OAC prescriptions (IROACP), 4.4 (95% confidence intervals (CI) 4.2–4.6) in 2001 to 17,070 (IROACP), 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons]. The prevalence of warfarin prescribing decreased by 14.0% [from 1,761 individuals receiving warfarin prescriptions (IRWP), 98.9 (95% CI 98.4–99.4) in 2001 to 14,533 (IRWP), 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons]. This corresponded with increased prescribing of direct oral anticoagulants (DOACs) [from 18 individuals receiving DOAC prescriptions (IRDOACP), 0.1 (95% CI 0.08–0.23) in 2010 to 3,016 (IRDOACP), 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons] during the same period.

Conclusions: Prescribing of OACs in individuals with T2DM increased from 2001 to 2015. Since the introduction of DOACs there has been a clear shift in prescribing towards these agents. Future studies are needed to assess the safety of the co-administration of OAC medications and antidiabetic therapy with T2DM.

Keywords: Diabetes mellitus, Drug utilisation, Oral anticoagulants therapies, Trend, United Kingdom

Strengths and limitations of this study

- To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period.
- This study used a clinical record primary care research database which was representative of the UK general population.
- Underestimation of OAC prescribing could be a limitation of this study as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide and has become a major global public health concern (1) . According to the International Diabetes Federation (IDF) report in 2017, it was estimated that 425 million people worldwide are living with diabetes, compared to 30 million in the year of 1985, of whom 90% were diagnosed with T2DM (1). In the United Kingdom (UK), the prevalence of diabetes has doubled over the last three decades (2, 3). Using a national health database in the UK, Zghebi et al estimated that the prevalence of diabetes increased from 3.2 % in 2004 to 5.2 % in 2014 (4).

T2DM and cardiovascular diseases often coexist with many individuals with T2DM experiencing cardiovascular complications (5, 6). Cardiovascular diseases including cardiac arrhythmias, venous thromboembolism, and ischaemic heart disease are among the leading causes of mortality worldwide in individuals with T2DM (7). Anticoagulants are widely prescribed for the prevention and treatment of atrial fibrillation (AF), stroke, venous and arterial thrombosis. When prescribed for venous thromboembolism, oral anticoagulant (OAC) treatment is typically of short duration, but it can be lifelong treatment when prescribed for AF (8).

T2DM is one of the main risk factors contributing in $CHA2DS_2$ score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (9). In 2010, CHA_2DS_2-VASc was adapted from the previous score (10), and it is now recommended by most of the current guidelines (8, 11, 12), in which individuals with AF are likely to be prescribed OAC if they score two or more in the total score. In addition, since the introduction of direct oral anticoagulants (DOACs) in 2011, several guidelines recommended their use for indications such as atrial fibrillation (8, 11, 12). DOACs have much more predictable pharmacokinetics and pharmacodynamics, and are less prone for drug interactions when compared with warfarin (13). However, OAC use in individuals with T2DM remains unclear, with limited studies focused on their use in individuals with T2DM (14, 15).

Previous studies have demonstrated that the prevalence of AF in individuals with T2DM ranges from 8% to 14.9% (16, 17), and that individuals with T2DM have 40% higher risk of developing AF compared to individuals without T2DM (18). Investigating OAC use in individuals with T2DM is important due to the high number of individuals, the possibility of drug-drug interactions, and the

potential association with serious adverse events such as bleeding and hypoglycaemia (19, 20). This was highlighted in particular among individuals with T2DM in previous large-scale epidemiological studies and in multiple case reports where warfarin was associated with an increased risk of hypoglycaemia. It has been suggested that displaced plasma protein and Cytochrome P450 (CYP450) hepatic metabolic pathway could be potential mechanisms for the increased risk of hypoglycaemia (21-24).

Given the recent update in guidelines for OAC prescribing, and the limited research on their use in individuals with T2DM, this research aimed to describe the prescribing patterns of OAC medications in individuals with T2DM in the UK population as an important step in investigating its safety within this high risk population.

The primary objective of this study was to examine the prescribing trends of OAC medications in individuals with T2DM from 2001 to 2015, stratified by age, gender and therapeutic classifications. The secondary objective was to compare the trend in OAC use in individuals with AF, with and without T2DM, given that AF is the main indication for OAC use.

METHODS

Data sources

This was a retrospective drug utilisation study using primary care data in The Health Improvement Network (THIN); a UK primary care database containing anonymised administrative, clinical and prescribing data from over 587 practices with more than 13 million individuals (25, 26). THIN is one of the largest sources for primary care data in the UK, and has been validated for epidemiological research purposes (25-27). In addition, it has been used by our team to study prescribing of OAC and various psychotropic medications (28-32). It holds data on personal information, health related behaviours, and diagnoses information which is recorded and identified using Read codes (25, 26). Read codes, which are also known as clinical terms, are clinical terminologies used to describe the care, diagnosis of diseases and treatments of individuals. It is used to manage primary care data in electronic health records (33). The database also has prescribing information that is linked with the British National Formulary. THIN contains records of prescriptions issued only by GPs and recorded in the individuals records.

Study population

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study. The AMR date is the year that data reporting is deemed to be complete, based on information derived from the Office for National Statistics (34). The start date was defined as the date of the first record for T2DM diagnosis. Individuals were included only if they had an observation period of at least 12 months prior to their start date and were registered with the general practice during the study period. The end date was the date were individuals left the practice, died or transferred out. Individuals with T2DM aged > 18 and registered with the THIN database between 2001 and 2015 (of which data were only available up to) were identified based on the following criteria of having; 1) a diagnostic code for T2DM (using Read codes), or 2) a diagnostic code for any type of diabetes and a record of any oral hypoglycaemic agent prescription, and the start date for these individuals was defined as the date of the first record for diabetes. Individuals who had a diagnostic code for T2DM accounted for 92.7% of the entire cohort, while the remaining were of criteria two. Individuals with a non-specific code for T2DM and who only had records for insulin prescription were excluded because they may have type 1 diabetes mellitus (T1DM), although their age at first event is taken into account. T2DM is typically diagnosed over the age of 30 years, however, the rate of young onset T2DM is increasing (35). We therefore only excluded children (less than 18 years old) who were more likely to have T1DM. Individuals with T2DM receiving at least one prescription of OAC medication were identified. Oral anticoagulant medications were consigned into three categories: warfarin, DOACs (apixaban, rivaroxaban, dabigatran and edoxaban), and other anticoagulant medications (acenocoumarol, pentosan polysulfate and phenindione). Furthermore, individuals with AF aged > 18 years and registered with THIN were identified using Read codes. The prescribing of OAC medications in individuals with AF with and without T2DM involved a two-step cohort identification (Figure S1). The first step was designed to identify individuals with AF with coexisting T2DM, and the latest first record between AF and DM was counted as the start date (coexisting of both diseases) for this cohort. The second step involved identifying individuals with AF without a diagnosis of T2DM, and the start date for these individuals was the first recorded AF diagnosis. Individuals who developed AF first and T2DM later contributed to the AF only cohort and then to the AF and T2DM cohort. For

baseline characteristics: chronic comorbidities were measured over the 12-month period preceding the first OAC prescription. However, medication use was assessed over the 6-month period preceding the first OAC prescription.

Statistical analysis

Descriptive statistics were used to describe individuals' demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data was reported as percentages (frequencies). The prevalence of OAC medications presented per 100 persons with 95% confidence intervals (CIs) were calculated on an annual basis by dividing the number of all individuals prescribed OAC medications in a particular year over the mid-year population of individuals with T2DM in the same calendar year, stratified by age, gender and therapeutic classifications. For the secondary objective: the trend in OAC use in AF individuals with T2DM, was calculated on an annual basis by dividing the number of AF individuals with T2DM prescribed OAC medications in a particular year over the mid-year population of AF individuals with T2DM in the same calendar year. The trend in OAC use in individuals with AF and without T2DM was calculated by dividing the number of AF individuals without T2DM prescribed OAC medications in a particular year over the mid-year population of AF individuals without T2DM in the same calendar year. The prescribing trend of OAC medications was assessed using Poisson model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The present study is based on anonymised and unidentifiable THIN data, thus the need for informed consent was waived by the THIN scientific review committee (SRC). This study was reviewed and scientific approval was obtained by THIN SRC in 2018 (18THIN009). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement (Supplements Table S1).

Patient and public involvement

We used anonymised administrative data and it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Demographics and characteristics

During the study period of 2001 and 2015, a total of 361,635 individuals with T2DM were identified of whom 36,570 received a prescription for OAC. Characteristics of the entire cohort included in our study are presented at the time of first OAC prescription. The average age of individuals at the time of first OAC prescription was 72 (SD, 10.2) years old, and the majority of individuals were male (59.9%). Around 64.6% of individuals were diagnosed with atrial fibrillation and 22.2% were diagnosed with venous thromboembolism diseases. Baseline demographics of the study sample are described in Table 1.

Table 1: characteristics of the study sample at the time of first OAC prescription

Demographics	T2DM individuals receiving OAC (%)
Total	**36,570 (100%)**
Age (Mean ± SD)*	72 ± 10.2
Gender (Male)	21,586 (59.9)
Social	
Smoking	3,598 (10.0)
Alcohol drinking	23,879 (69.6)
Comorbidities**	
Atrial fibrillation	23,655 (64.6)
Venous thromboembolisms	8,127 (22.2)
Stroke	7,441 (20.3)
Coronary heart diseases	12,606 (34.4)
Chronic kidney diseases	10,097 (27.6)
Heart failure	8,181 (22.3)
Hypertension	25,342 (69.3)
Hyperlipidaemia	8,563 (23.4)
COPD	3,815 (10.4)
PUD	10,266 (28.0)
PVD	3,522 (9.6)
Bleeding	8,062 (22.0)
Depression	8,186 (22.8)
Mild liver disease	146 (0.4)
Moderate to severe liver disease	209 (0.5)

Medications	
Aspirin	13,940 (38.1)
Other anti-platelets	2,736 (7.4)
Statin	25,138 (68.7)
BB	18,503 (50.6)
CCB	13,597 (37.1)
ACEIs/ARBs	25,490 (69.7)
Diuretics	16,796 (45.9)
Digoxin	11,867 (32.4)
CHA_2DS_2-VASc Score[a]	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
HASBLED[b]	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

*Standard deviation ±; Alcohol missing: (10.5%), Smoking missing (3.2%); OAC: Oral anticoagulant; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; PUD: Peptic ulcer disease; PVD: Peripheral vascular disease; BB: Beta-blocker; CCB: Calcium channel blocker; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; [a]CHA_2DS_2-VASc indicates individuals with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or transient ischemic attack or systemic embolism (doubled), vascular disease, and gender category (women). CHA_2DS_2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); [b]HAS-BLED indicates individuals with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

Trends in prescribing prevalence of oral anticoagulant medications in T2DM

Between 2001 and 2015, the prescribing prevalence of OACs in individuals with T2DM increased by 50.0% [from 1,781 individuals receiving OAC prescriptions (IROACP), 4.4 (95% confidence intervals (CI) 4.2–4.6) in 2001 to 17,070 (IROACP), 6.6 (95% CI 6.5–6.7) in 2015 per 100 persons], p<0.001, with an average increase of 3.2% per year (Figure 1).

The changes in prevalence of OAC prescribing between 2001 and 2015 stratified by gender are shown in Figure 1. The prescribing prevalence of OAC medications among males increased by 54.3% [from 4.6 (95%CI 4.3 – 4.9) to 7.1 (95%CI 6.9 – 7.2) per 100 persons with T2DM], while the prescribing

prevalence of OAC medications among females increased [from 4.0 (95%CI 3.8 – 4.4) to 5.9 (95%CI 5.8 – 6.1) per 100 persons with T2DM], with an overall increase of 47.5%.

Similarly, the prescribing prevalence of OAC medications varied among individuals from the different age groups. The prevalence of OAC medications among individuals aged 75 years or above increased [from 7.1 (95%CI 6.6– 7.6) in 2001 to 11.6 (95%CI 11.4 – 11.9) in 2015 per 100 persons with T2DM]. However, it was clearly lower among younger individuals, which increased [from 5.7 (95%CI 5.2 – 6.1) in 2001 to 6.5 (95%CI 6.3 – 6.6) in 2015 per 100 persons with T2DM], for individuals aged between 65-74 years, and [from 2.0 (95%CI 1.8 – 2.2) in 2001 to 2.2 (95%CI 2.1 – 2.3) in 2015 per 100 persons with T2DM], for individuals aged below 65 years (Figure 2).

Trends in prevalence of oral anticoagulant prescribing stratified by medication

Although warfarin was the most common OAC prescribed during the entire study period (86.3%), its use declined by 14.0% [from 1,761 individuals receiving warfarin prescriptions (IRWP), 98.9 (95% CI 98.4–99.4) in 2001 to 14,533 (IRWP), 85.1 (95% CI 84.6–85.7) in 2015 per 100 persons]. In contrast, there was a corresponding increase in the proportion of individuals who used DOACs [from 18 individuals receiving DOAC prescriptions (IRDOACP), 0.1 (95% CI 0.08–0.23) in 2010 to 3,016 (IRDOACP), 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons]. Other OACs, including acenocoumarol and phenindione were less likely to be prescribed during the entire study period (0.03%), their prescribing rate decreased [from 1.1 (95% CI 0.7 – 1.7) in 2001 to 0.4 (95% CI 0.3 – 0.5) in 2015 per 100 persons with T2DM] (Figure 3). In addition, a small percentage of individuals with T2DM using OAC were prescribed different OAC classes during the same year ranging from less than 1% in 2010 to 3% in 2015.

Further stratification by individual OAC drug treatment showed that the prescribing prevalence of rivaroxaban markedly increased [from 0.1 (95% CI 0.05–0.2) in 2010 to 10.9 (95% CI 10.5–11.4) in 2015 per 100 persons with T2DM], while the prescribing prevalence of dabigatran increased to a lesser degree [from 0.03 (95% CI 0.001–0.07) in 2010 to 2.7 (95% CI 2.5–2.9) in 2015 per 100 persons with T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08) in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).

Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with and without T2DM

The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of prescribing ranged [from 46.6 (95% CI 43.5 – 49.7) in 2001 to 59.0 (95% CI 58.3 – 60.0) in 2015 per 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure 5).

DISCUSSION

This study investigated the drug utilisation pattern of OAC medications in individuals with T2DM, and in individuals with AF, with and without T2DM. The key findings are: 1) the prescribing prevalence of OACs in individuals with T2DM has increased markedly between 2001 and 2015, 2) the increase in the prescribing prevalence of OACs was not consistent across individuals of different gender and age group, males and individuals aged 75 years and above had a higher prescribing prevalence compared to females and individuals younger than 75 years, 3) the prescribing of DOACs is clearly replacing the prescribing of warfarin since their introduction to the UK market in 2011.

Previous studies investigating the trend of OACs prescribing in individuals with T2DM are limited. A previous study by Hamada *et al*. examined the trend of cardiovascular medication prescribing in diabetic individuals aged 80 years or above in the UK between 1990 to 2010 (15), concluding that the prescribing of OACs in individuals with T2DM had increased [from 5% in 1999 to 19% in 2010]. These results showed similar trends to our study in the increase of OACs prescriptions in T2DM. However, our results showed that OAC prescriptions increased less sharply, which is explicable by restriction of their population to include only individuals aged 80 years and older. Despite this, age is considered a risk factor for many conditions for which OACs are indicated, and our results showed an increased rate of OACs prescribing among individuals aged 75 years and above, which was also similar to a previous study that used primary care data in the UK (36). Furthermore, an increasing prescribing prevalence of DOACs in the last few years have been reported in several studies that examined the trend of OACs in

the general population or in individuals with AF across different countries (36-38). Alalwan *et al*., using data from MarketScan Medicare, reported that DOACs increased from 1.39% (95% CI, 1.34–1.44%) in 2010 to 28.33% (95% CI, 28.14–28.52%) in 2014 (37). Similarly, Loo *et al*. found that the rate of initiation of DOAC increased significantly, particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI 12.16, 25.71) (36). The findings presented in our study, and specifically related to DOACs' prescribing trend are in line with previous findings, however, it is important to highlight that those studies concerned the general population and were not specific to T2DM (36-38).

This study showed that since the introduction of DOACs, individuals with T2DM using OACs were prescribed different classes of OAC, possibly due to individuals switching from one class to another. DOACs have been reported to be non-inferior to warfarin in the prevention of major strokes and embolic events in different clinical trials and observational studies (39-43). Evidence from meta-analyses showing better efficacy and non-inferior safety when comparing DOACs and warfarin could be a reason for the paradigm shift in favouring the prescribing of DOACs (44, 45). This led in a change in the UK National Institute for Health and Care Excellence (NICE) guidance for the management of AF (8), and as of 2014, DOACs have been recommended as first-line therapy for AF (46). However, it is crucial to recognise that older people with comorbidities were excluded or underrepresented in the pivotal clinical trials of DOACs and therefore, DOACs should be prescribed with caution and strict monitoring in this population (47). Another major issue with warfarin is that it is more prone to several drug-food and drug-drug interactions (20-22, 48), which could explain why DOACs are being prescribed more favourably in the recent years compared to warfarin, especially accounting for elements such as ageing and polypharmacy. Nonetheless, a major advantage for DOACs is their wider therapeutic index and that it does not require regular monitoring during intake for international normalized ratio (INR) compared to warfarin (49-51).

The results of this study highlighted that individuals with T2DM receiving OACs have a high risk profile of cardiovascular comorbidities including hypertension, coronary heart disease, heart failure, peripheral vascular diseases and hyperlipidaemia (Table 1), in which it could be associated with the

initiation of OAC prescribing (14). However, due to the nature of this descriptive study it is difficult to draw this conclusion and we urge for further studies to investigate this association.

As expected, our results showed that AF was the main indication for OAC prescriptions among individuals with T2DM. Several international guidelines, including those from the US (52), Europe (11) and the UK (8) have recommended the use of OACs in individuals with AF based on $CHADS_2$ (9) and CHA_2DS_2-VASc score (10). This was also in line with our results as it showed that individuals with AF and coexisting T2DM had a higher rate of OACs prescribing compared to individuals with AF without T2DM. However, our results showed a higher prescribing rate of OAC among males compared to females that is similar to other studies that highlighted the higher prevalence of OAC prescribing amongst males (53, 54).

Strengths and limitations

To the best of our knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in individuals with T2DM over a 15-year period. This study used a clinical record primary care research database which was representative of the UK general population.

However, this study has some limitations. Firstly, underestimation of OAC prescribing as THIN database only contains information from the primary care setting, and therefore, it was not possible to include individuals treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals. However, the UK National Health Service (NHS) heavily subsidies the treatment of chronic illness and the majority of individuals with chronic illness are looked after by primary care; therefore, our results should not be affected significantly. Secondly, individuals were identified using relevant Read code lists and algorithms. Codes were selected with reference to clinicians' comments and previously published studies. However, as described in the methods section, there is a possibility of misclassification in identifying individuals with T2DM. This may have led to overestimation of T2DM diagnoses in the study, however, it is also important to mention that individuals who had a diagnostic code for T2DM contributed to over 92% of the study cohort. Therefore, it is reasonable to assume that this did not have a major impact on our findings. THIN is a medical record database and therefore, similar to other clinical databases, It was not possible to confirm if individuals were adherent. Furthermore, in the

secondary objective of this study we did not adjust for CHA_2DS_2-VASc in the comparison between the trend in OAC use in individuals with AF, with and without T2DM. However, CHA_2DS_2-VASc was introduced in 2010 (10), and was only implemented in the NICE guidelines in 2014 (8), considering that our study end date was 2015, the practice will not be reflected in our study period

Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications and OAC medications for possible drug-drug interactions, especially when warfarin is the drug of choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is imperative to investigate the effect of concomitant use of this class of medication and the risk of hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus improve the safety of OAC use in individuals with T2DM.

CONCLUSIONS

This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin since its introduction to the UK market, which is consistent with UK guidelines. However, there is a lack of studies examining their safety when used in individuals with T2DM. Further studies are warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for possible drug-drug interactions.

Abbreviations

ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs: Confidence intervals; Cytochrome P450: CYP450; DOAC: Direct oral anticoagulant; IDF: International Diabetes Federation; INR: International normalized level; IRDOACP: Individuals received DOAC prescription; IROACP: Individuals received OAC prescription; IRWP: Individuals received warfarin prescription; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OAC: oral anticoagulant; SD: Standard deviation; SRC: Scientific Review Committee; STROBE: Strengthening the reporting of observational studies in epidemiology; THIN: The Health Improvement Network; T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus UK: United Kingdom.

Consent for publication

Not applicable.

Data Availability

No further data are available.

Conflict of Interest Disclosures

The authors declare that they have no competing interest.

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Authors Contributions: HA, LW and IW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors who contributed to the work described in this paper are as follows: HA, LW and IW contributed to the study design. HA, LW, KM and PM contributed to the Statistical analysis. HA, LW and IW were involved in interpretation of data. HA wrote the first draft of the article. HA, LW, AN, JSB, JI, GT, GF and IW made substantial contributions to the drafts, reviewed the manuscript for important intellectual content and provided final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure titles and legends

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM.

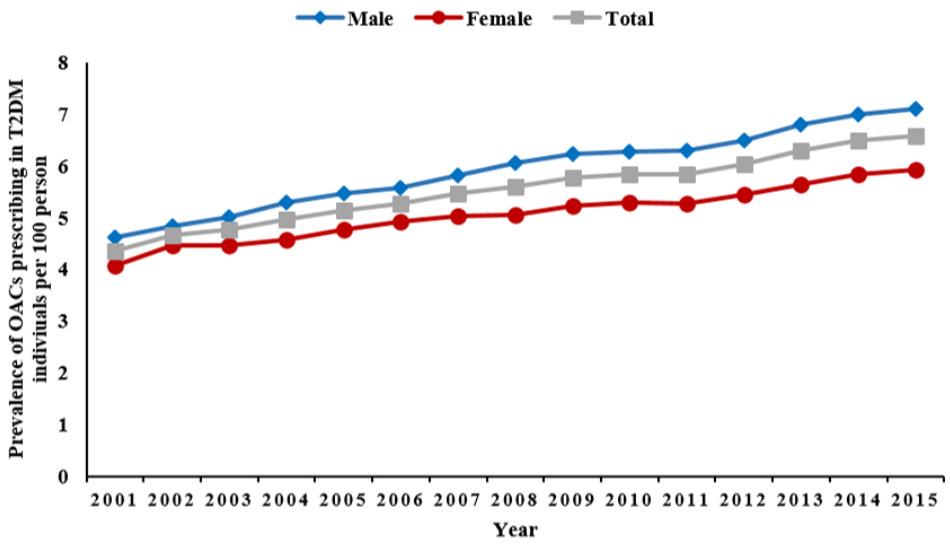

Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

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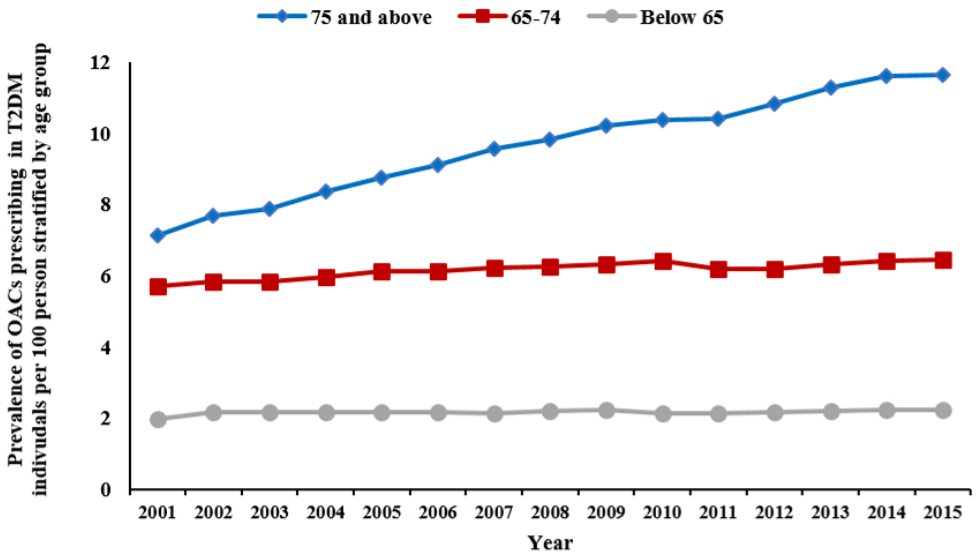

Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

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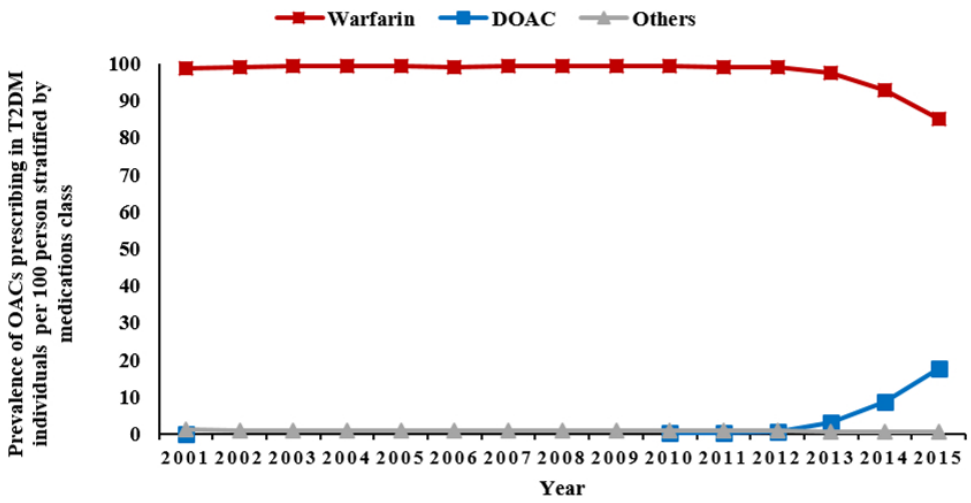

Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

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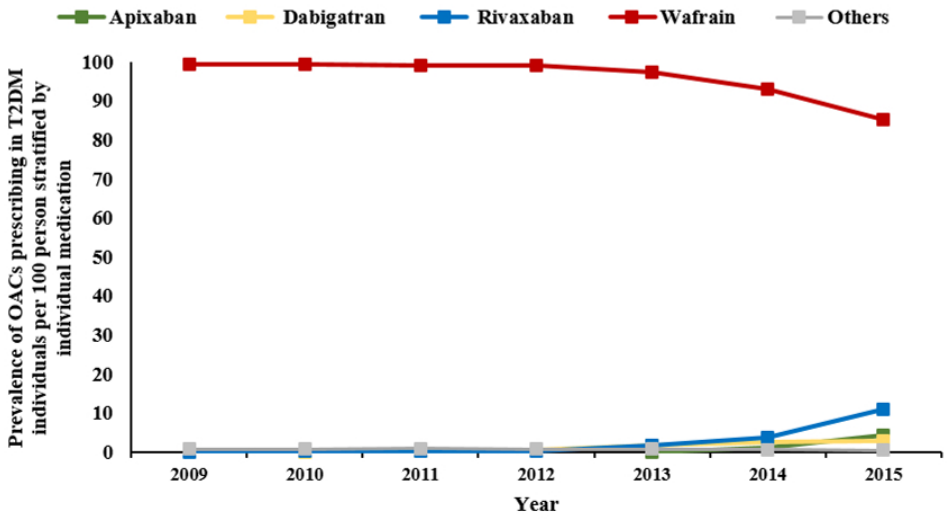

Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

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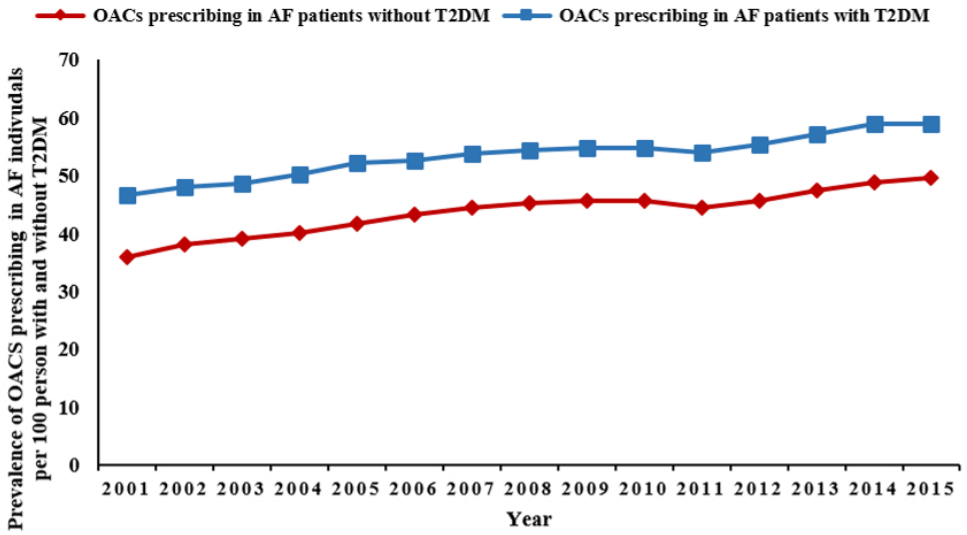

Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM

73x41mm (300 x 300 DPI)

Supplement:

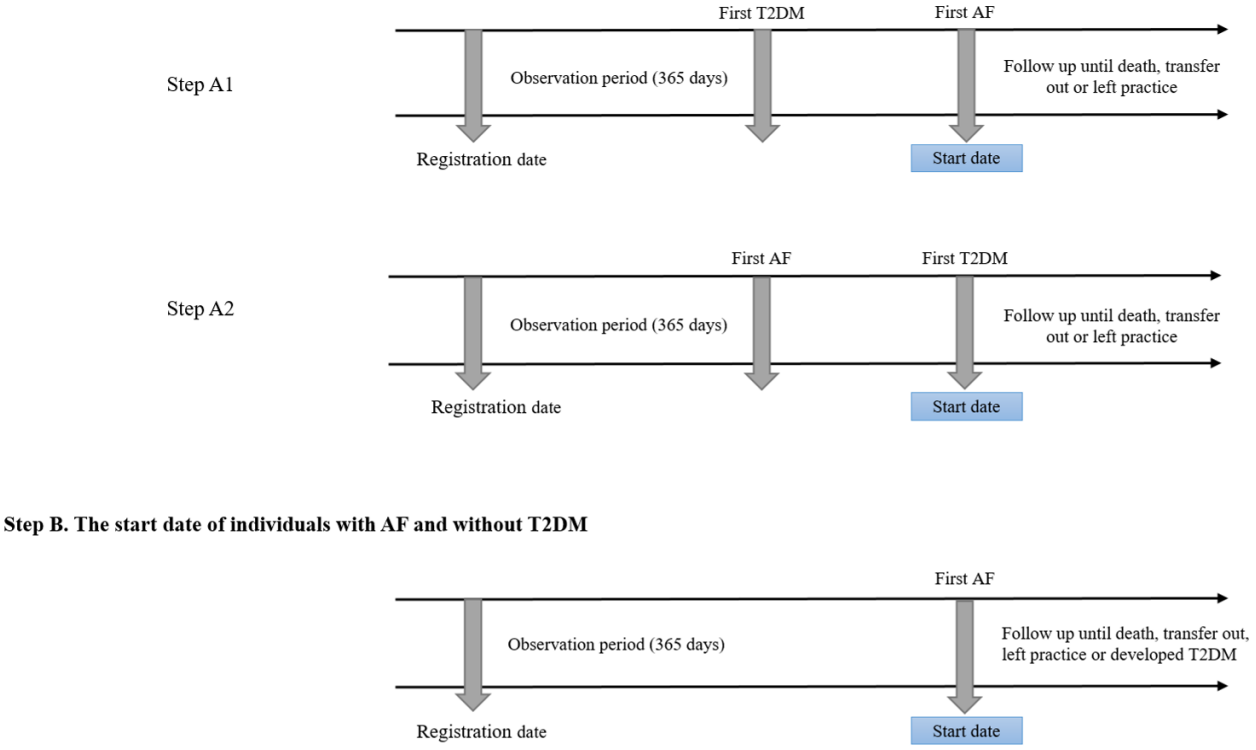

Figure S1. Methods to identify the study population of AF individuals with and without T2DM

Registration date: is the date of an individual's registration with the general practice; AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus. Individuals who developed AF first and T2DM later (Step A2) contributed to the AF only cohort (Step B) until they developed T2DM

Table S1: Strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	5	Introduction
Methods				
Study design	4	Present key elements of study design early in the paper	5	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6,7	Methods
Bias	9	Describe any efforts to address potential sources of bias		Not applicable
Study size	10	Explain how the study size was arrived at	5,6	Methods

Continue on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	7	Methods
		(*c*) Explain how missing data were addressed		Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		Not applicable
		(*e*) Describe any sensitivity analyses		Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Results
		(b) Give reasons for non-participation at each stage	6	Methods
		(c) Consider use of a flow diagram		Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Results
		(b) Indicate number of participants with missing data for each variable of interest		Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	9,10,11	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Not applicable
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable

Continue on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	11,12,13	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12,13,14	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	5,13	Methods and discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15	Declarations

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