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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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# **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.

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**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<sub>2</sub> score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (16). In 2010, CHA<sub>2</sub>DS<sub>2</sub>-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



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

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

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56 The present study is based on anonymised and unidentifiable THIN data, thus the need for informed  
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58 consent was waived by the THIN scientific review committee (SRC). This study was reviewed and  
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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 (%)
<b>Total</b>	<b>36,570 (100%)</b>
<b>Age (Mean <math>\pm</math> SD)*</b>	72 $\pm$ 10.2
<b>Gender (Male)</b>	21,586 (59.9)
<b>Social</b>	
Smoking	3,598 (10.0)
Alcohol drinking	23,879 (69.6)
<b>Comorbidities**</b>	
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)
<b>Medications</b>	
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)
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc Score<sup>a</sup></b>	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
<b>HASBLED<sup>b</sup></b>	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

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

<sup>a</sup>CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); <sup>b</sup>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

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3 101 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  
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5 102 T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08)  
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7 103 in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).

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10 104 **Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with**  
11 105 **and without T2DM**

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13 106 The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM  
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15 107 maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications  
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17 108 prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of  
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19 109 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  
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21 110 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI  
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23 111 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure  
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25 112 5).

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29 113 **DISCUSSION**

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32 114 This study investigated the drug utilisation pattern of oral anticoagulant medications in individuals with  
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34 115 T2DM, and the prevalence of AF in individuals with T2DM. The key findings are: 1) the prescribing  
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36 116 prevalence of OACs in individuals with T2DM has increased markedly between 2001 and 2015, 2) the  
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38 117 increase in the prescribing prevalence of OACs was not consistent across individuals of different gender  
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40 118 and age group, males and individuals aged 60 years and above had a higher prescribing prevalence  
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42 119 compared to females and individuals younger than 60 years, 3) the prescribing of DOACs is clearly  
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44 120 replacing the prescribing of warfarin since their introduction to the UK market in 2011.  
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46 121 Previous studies investigating the trend of OACs prescribing in individuals with T2DM are limited. A  
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48 122 previous study by Hamada *et al.* examined the trend of cardiovascular medication prescribing in  
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50 123 diabetic individuals aged 80 years or above in the UK between 1990 to 2010 (22), concluding that the  
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52 124 prescribing of OACs in individuals with T2DM had increased [from 5% in 1999 to 19% in 2010]. These  
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54 125 results showed similar trends to our study in the increase of OACs prescriptions in T2DM. However,  
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56 126 our results showed that OAC prescriptions increased less sharply, which is explicable by restriction of  
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58 127 their population to include only individuals aged 80 years and older. Despite this, age is considered a  
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3 128 risk factor of many conditions for which OACs are indicated, and our results showed an increased rate  
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5 129 of OAC prescribing among individuals aged 60 years and above. Furthermore, an increasing prescribing  
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7 130 prevalence of DOACs in the last few years have been reported in several studies that examined the trend  
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9 131 of OACs in the general population or in individuals with AF across different countries (35-38). Alalwan  
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11 132 *et al.*, using data from MarketScan Medicare, reported that DOACs increased from 1.39% (95% CI,  
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13 133 1.34–1.44%) in 2010 to 28.33% (95% CI, 28.14–28.52%) in 2014 (35). Similarly, Loo *et al.* found that  
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15 134 the rate of initiation of DOAC increased significantly, particularly from 2012 onwards, with a 17-fold  
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17 135 increase from 2012 to 2015 (RR 17.68; 95% CI 12.16, 25.71) (36). The findings presented in our study,  
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19 136 and specifically related to DOACs' prescribing trend are in line with previous findings, however, it is  
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21 137 important to highlight that those studies concerned the general population and were not specific to  
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23 138 T2DM. (35-38).  
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26 139 This study showed that since the introduction of DOACs, individuals with T2DM using OACs were  
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28 140 prescribed different classes of OAC, possibly due to individuals switching from one class to another.  
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30 141 DOACs have been reported to be non-inferior to warfarin in the prevention of major strokes and embolic  
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32 142 events in different clinical trials and observational studies (39-43). Evidence from meta-analyses  
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34 143 showing better efficacy and non-inferior safety when comparing DOACs and warfarin could be a reason  
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36 144 for the paradigm shift in favouring the prescribing of DOACs (44, 45). This led in a change in the UK  
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38 145 National Institute for Health and Care Excellence (NICE) guidance for the management of AF (15),  
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40 146 and as of 2014, DOACs have been recommended as first-line therapy for AF (46). However, it is crucial  
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42 147 to recognise that older people with comorbidities were excluded or underrepresented in the pivotal  
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44 148 clinical trials of DOACs and therefore, DOACs should be prescribed with caution and strict monitoring  
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46 149 in this population (47). Another major issue with warfarin is that it is more prone to several drug-food  
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48 150 and drug-drug interactions (24-26, 48), which could explain why DOACs are being prescribed more  
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50 151 favourably in the recent years compared to warfarin, especially accounting for elements such as ageing  
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52 152 and polypharmacy. Nonetheless, a major advantage for DOACs is their wider therapeutic index and  
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54 153 that it does not require regular monitoring during intake for international normalized ratio (INR)  
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56 154 compared to warfarin (49-51).  
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3 155 The results of this study highlighted that individuals with T2DM have a high risk profile of  
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5 156 cardiovascular comorbidities including hypertension, coronary heart disease, heart failure, peripheral  
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7 157 vascular diseases and hyperlipidaemia (Table 1), in which they are predictors for the initiation of OAC  
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9 158 prescribing (21). However, T2DM complications are also linked to these comorbidities (7, 8), and  
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11 159 therefore it is difficult to draw a causal inference and we urge for further studies to investigate this  
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14 160 association.

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16 161 As expected, our results showed that AF was the main indication for OAC prescriptions among  
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18 162 individuals with T2DM. Several international guidelines, including those from the US (52), Europe (18)  
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20 163 and the UK (15) have recommended the use of OACs in individuals with atrial fibrillation based on  
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22 164 CHADS2 (16) and CHA2DS2–VASc score (17). This was also in line with our results as it showed that  
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24 165 individuals with AF and coexisting T2DM had a higher rate of OACs prescribing compared to  
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26 166 individuals with AF without T2DM. However, our results showed a higher prescribing rate of OAC  
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28 167 among males compared to females that is similar to other studies that highlighted the higher prevalence  
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30 168 of OAC prescribing amongst males (53, 54). Given that females are associated with a higher risk of  
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33 169 stroke and thromboembolisms (55) and that major guidelines recommend OAC prescribing among  
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35 170 females, the finding of this study could potentially highlight an underuse of OAC prescribing in females.

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37 171 **Strengths and limitations**

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39 172 To the best of our knowledge, this was the first study that examined the overall and stratified trend of  
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41 173 OAC medication prescribing in individuals with T2DM over a 15-year period. This study used a clinical  
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43 174 record primary care research database which was representative of the UK general population.  
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45 175 However, this study has some limitations. Firstly, underestimation of OAC prescribing as THIN  
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47 176 database only contains information from the primary care setting, and therefore, it was not possible to  
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49 177 include individuals treated in different health care settings (secondary, tertiary, private) in the study,  
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51 178 and this can create gaps in the data recorded by THIN on the treatment of individuals. However, the  
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53 179 UK National Health Service (NHS) heavily subsidises the treatment of chronic illness and the majority  
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55 180 of individuals with chronic illness are looked after by primary care; therefore, our results should not be  
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58 181 affected significantly. Secondly, individuals were identified using relevant Read code lists and  
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60 182 algorithms. This may have led to bias in the study due to under-reporting or misreporting of T2DM

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3 183 diagnoses; however, this issue was mitigated by validating our codes with clinicians and previously  
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5 184 published studies. Furthermore, THIN is a medical record database and therefore, similar to other  
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7 185 clinical databases, it was not possible to confirm if individuals were adherent.  
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9 186 Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications  
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11 187 and oral anticoagulants medications for possible drug-drug interactions, especially when warfarin is the  
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13 188 drug of choice. However, with DOACs being relatively new to the market and rapidly replacing  
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15 189 warfarin, it is imperative to investigate the effect of concomitant use of this class of medication and the  
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17 190 risk of hypoglycaemia or bleeding. This will identify medications that are associated with higher risk,  
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19 191 and thus improve the safety of OAC use in individuals with T2DM.  
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## 23 192 **CONCLUSIONS**

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26 193 This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin  
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28 194 since its introduction to the UK market, which is consistent with UK guidelines. However, there is a  
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30 195 lack of studies examining their safety when used in individuals with T2DM. Further studies are  
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32 196 warranted to investigate the safety of the concurrent use of antidiabetic and oral anticoagulant  
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34 197 medications for possible drug-drug interactions.  
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**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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## 227 REFERENCES

- 228 1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates  
229 of diabetes prevalence for 2013 and projections for 2035. *Diabetes research and clinical practice*.  
230 2014;103(2):137-49.
- 231 2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al.  
232 IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res*  
233 *Clin Pract*. 2017;128:40-50.
- 234 3. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2  
235 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ open*.  
236 2016;6(1):e010210.
- 237 4. Pierce MB, Zaninotto P, Steel N, Mindell J. Undiagnosed diabetes-data from the English  
238 longitudinal study of ageing. *Diabetic medicine : a journal of the British Diabetic Association*.  
239 2009;26(7):679-85.
- 240 5. National Institute for Health and Care Excellence. Type 2 diabetes in adults:  
241 management.NICE guideline.[NG28]. 2015.
- 242 6. Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in  
243 type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes, obesity*  
244 *& metabolism*. 2017;19(11):1537-45.
- 245 7. Robbins JM, Webb DA, Sciamanna CN. Cardiovascular comorbidities among public health  
246 clinic patients with diabetes: the Urban Diabetics Study. *BMC Public Health*. 2005;5:15-.
- 247 8. Celis-Morales CA, Petermann F, Hui L, Lyall DM, Iliodromiti S, McLaren J, et al. Associations  
248 Between Diabetes and Both Cardiovascular Disease and All-Cause Mortality Are Modified by Grip  
249 Strength: Evidence From UK Biobank, a Prospective Population-Based Cohort Study. *Diabetes care*.  
250 2017;40(12):1710-8.
- 251 9. Pantalone KM, Hobbs TM, Wells BJ, Kong SX, Kattan MW, Bouchard J, et al. Clinical  
252 characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes  
253 mellitus in a large integrated health system. *BMJ Open Diabetes Res Care*. 2015;3(1):e000093.

1  
2  
3 254 10. Dinesh Shah A, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et  
4  
5 255 al. Type 2 diabetes and incidence of a wide range of cardiovascular diseases: a cohort study in 1.9  
6  
7 256 million people. *Lancet (London, England)*. 2015;385 Suppl 1:S86.  
8  
9 257 11. Xiong Z, Liu T, Tse G, Gong M, Gladding PA, Smaill BH, et al. A Machine Learning Aided  
10  
11 258 Systematic Review and Meta-Analysis of the Relative Risk of Atrial Fibrillation in Patients With  
12  
13 259 Diabetes Mellitus. *Front Physiol*. 2018;9:835.  
14  
15 260 12. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014:  
16  
17 261 epidemiological update. *European heart journal*. 2014;35(42):2950-9.  
18  
19 262 13. Wilkins E WL, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R,  
20  
21 263 Rayner M, Townsend N. Cardiovascular disease statistics 2017. British Heart Foundation. 2017.  
22  
23 264 14. Tse G, Lai ET, Tse V, Yeo JM. Molecular and Electrophysiological Mechanisms Underlying  
24  
25 265 Cardiac Arrhythmogenesis in Diabetes Mellitus. *J Diabetes Res*. 2016;2016:2848759.  
26  
27 266 15. Excellence NfHaC. Atrial fibrillation management. NICE guideline (CG180). 2014.  
28  
29 267 16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of  
30  
31 268 clinical classification schemes for predicting stroke: results from the National Registry of Atrial  
32  
33 269 Fibrillation. *Jama*. 2001;285(22):2864-70.  
34  
35 270 17. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for  
36  
37 271 predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach:  
38  
39 272 the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-72.  
40  
41 273 18. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines  
42  
43 274 for the management of atrial fibrillation developed in collaboration with EACTS. *European heart*  
44  
45 275 *journal*. 2016;37(38):2893-962.  
46  
47 276 19. January Craig T, Wann LS, Calkins H, Chen Lin Y, Cigarroa Joaquin E, Cleveland Joseph C,  
48  
49 277 et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the  
50  
51 278 Management of Patients With Atrial Fibrillation: A Report of the American College of  
52  
53 279 Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart  
54  
55 280 Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*.  
56  
57 281 2019;140(2):e125-e51.

- 282 20. Cheng JW, Barillari G. Non-vitamin K antagonist oral anticoagulants in cardiovascular disease  
283 management: evidence and unanswered questions. *Journal of clinical pharmacy and therapeutics*.  
284 2014;39(2):118-35.
- 285 21. Łabuz-Roszak B, Machowska-Majchrzak A, Skrzypek M, Mossakowska M, Chudek J, Więcek  
286 A, et al. Antiplatelet and anticoagulant therapy in elderly people with type 2 diabetes mellitus in Poland  
287 (based on the PolSenior Study). *Archives of medical science : AMS*. 2017;13(5):1018-24.
- 288 22. Hamada S, Gulliford MC. Antidiabetic and cardiovascular drug utilisation in patients diagnosed  
289 with type 2 diabetes mellitus over the age of 80 years: a population-based cohort study. *Age and ageing*.  
290 2015;44(4):566-73.
- 291 23. Excellence NIHaC. Warfarin | Interactions | BNF Provided by NICE 2017.
- 292 24. Ament P BJ, Liszewski J. . Clinically Significant Drug Interactions. *American Family*  
293 *Physician*. 2000;15(61):1745-54.
- 294 25. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Han X, Nam YH, et al. Gastrointestinal  
295 bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics().  
296 *International journal of cardiology*. 2017;228:761-70.
- 297 26. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use  
298 of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis.  
299 *BMJ*. 2015;351.
- 300 27. Naganuma M, Hashimoto Y, Matsuura Y, Terasaki T, Uchino M. A case of sustained  
301 hypoglycemia induced by taking glibenclamide and warfarin  
302 subtitle\_in\_Japanese. *Nosotchu*. 2003;25(3):334-7.
- 303 28. Namazi S aRG. Case Presentation of a 45 Years Old Woman with Hypoglycemia and Bleeding.  
304 *Iranian Journal of Pharmaceutical Sciences*. 2005;9(3):183-8.
- 305 29. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement  
306 Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics*  
307 *in primary care*. 2011;19(4):251-5.

1  
2  
3 308 30. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health  
4  
5 309 improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology*  
6  
7 310 and drug safety. 2007;16(4):393-401.  
8  
9 311 31. Brauer R, Lau WCY, Hayes JF, Man KKC, Osborn DPJ, Howard R, et al. Trazodone use and  
10  
11 312 risk of dementia: A population-based cohort study. *PLoS Med.* 2019;16(2):e1002728.  
12  
13 313 32. Digital N. Read Codeds. 2018.  
14  
15 314 33. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality  
16  
17 315 reporting for research using automated data from primary care. *Pharmacoepidemiology and drug safety.*  
18  
19 316 2009;18(1):76-83.  
20  
21 317 34. International Diabetes Federation. *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium.  
22  
23 318 International Diabetes Federation. 2017.  
24  
25 319 35. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral  
26  
27 320 anticoagulants in older adult patients with atrial fibrillation. *American Journal of Health-System*  
28  
29 321 *Pharmacy.* 2017;74(16):1237-44.  
30  
31 322 36. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral  
32  
33 323 anticoagulants in UK primary care. *British journal of clinical pharmacology.* 2017;83(9):2096-106.  
34  
35 324 37. Lee S-R, Choi E-K, Han K-D, Cha M-J, Oh S, Lip GYH. Temporal trends of antithrombotic  
36  
37 325 therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-  
38  
39 326 vitamin K antagonist oral anticoagulants: A nationwide population-based study. *PLoS ONE.*  
40  
41 327 2017;12(12):e0189495.  
42  
43 328 38. Gadsboll K, Staerk L, Fosbol EL, Sindet-Pedersen C, Gundlund A, Lip GYH, et al. Increased  
44  
45 329 use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in  
46  
47 330 Denmark. *European heart journal.* 2017;38(12):899-906.  
48  
49 331 39. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus  
50  
51 332 warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine.* 2011;365(10):883-  
52  
53 333 91.  
54  
55  
56  
57  
58  
59  
60

- 334 40. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban  
335 versus warfarin in patients with atrial fibrillation. The New England journal of medicine.  
336 2011;365(11):981-92.
- 337 41. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran  
338 versus warfarin in patients with atrial fibrillation. The New England journal of medicine.  
339 2009;361(12):1139-51.
- 340 42. Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, et al. Efficacy and  
341 safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective  
342 nationwide cohort study. Journal of the American College of Cardiology. 2013;61(22):2264-73.
- 343 43. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral  
344 anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362.
- 345 44. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with  
346 AF: a systematic review and meta-analysis. Open heart. 2016;3(1):e000279.
- 347 45. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al.  
348 Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial  
349 fibrillation: a meta-analysis of randomised trials. Lancet (London, England). 2014;383(9921):955-62.
- 350 46. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than  
351 the old? Open heart. 2018;5(1):e000712.
- 352 47. Fanning L, Ilomaki J, Bell JS, Darzins P. The representativeness of direct oral anticoagulant  
353 clinical trials to hospitalized patients with atrial fibrillation. Eur J Clin Pharmacol. 2017;73(11):1427-  
354 36.
- 355 48. Di Minno A, Frigerio B, Spadarella G, Ravani A, Sansaro D, Amato M, et al. Old and new oral  
356 anticoagulants: Food, herbal medicines and drug interactions. Blood reviews. 2017;31(4):193-203.
- 357 49. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and  
358 disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with  
359 thromboembolic events. Therapeutics and Clinical Risk Management. 2015;11:967-77.
- 360 50. Kimmel SE. Warfarin therapy: in need of improvement after all these years. Expert opinion on  
361 pharmacotherapy. 2008;9(5):677-86.

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60

51. Tse G, Gong M, Li G, Wong SH, Wu WKK, Wong WT, et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol*. 2018;84(9):1868-82.

52. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-104.

53. Kjerpeseth LJ, Ellekjaer H, Selmer R, Ariansen I, Furu K, Skovlund E. Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. *Eur J Clin Pharmacol*. 2017;73(11):1417-25.

54. Scowcroft ACE, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009. 2013;99(2):127-32.

55. Demel Stacie L, Kittner S, Ley Sylvia H, McDermott M, Rexrode Kathryn M. Stroke Risk Factors Unique to Women. *Stroke*. 2018;49(3):518-23.

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377 **Figure titles and legends**

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

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

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

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

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

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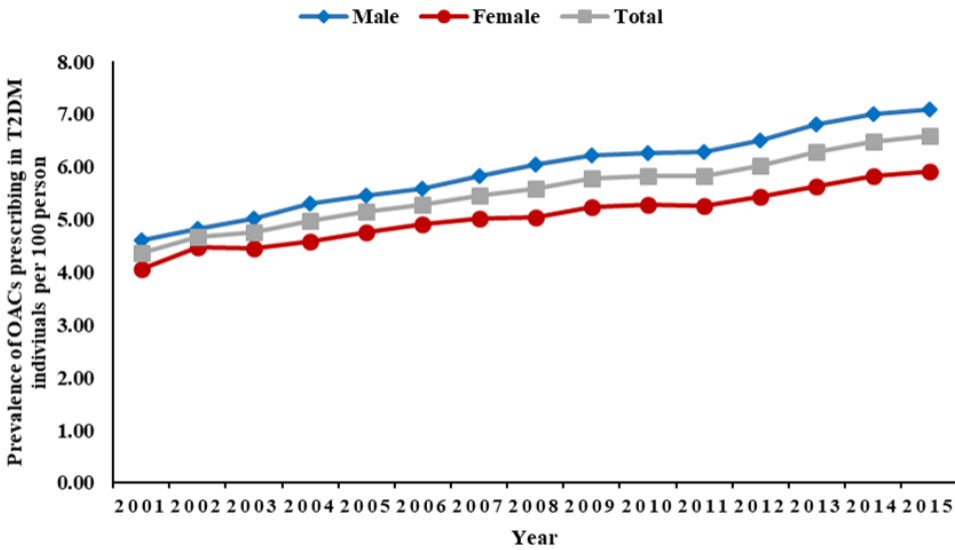


Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

73x42mm (300 x 300 DPI)

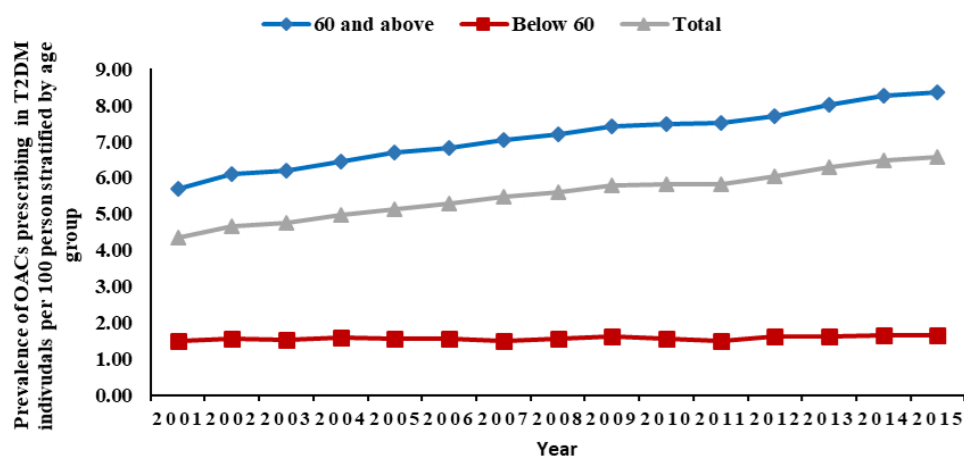


Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

74x38mm (300 x 300 DPI)

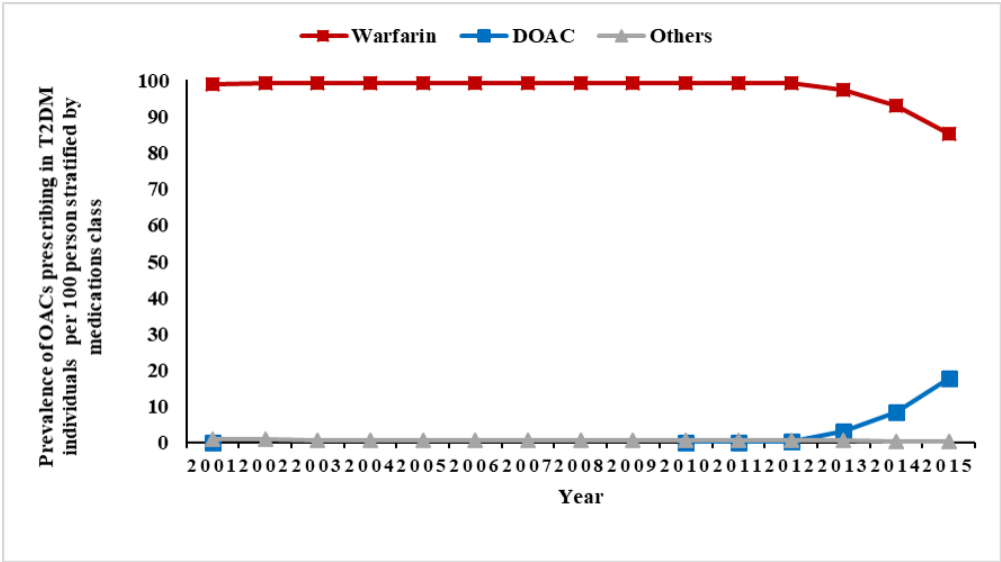


Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

75x42mm (300 x 300 DPI)

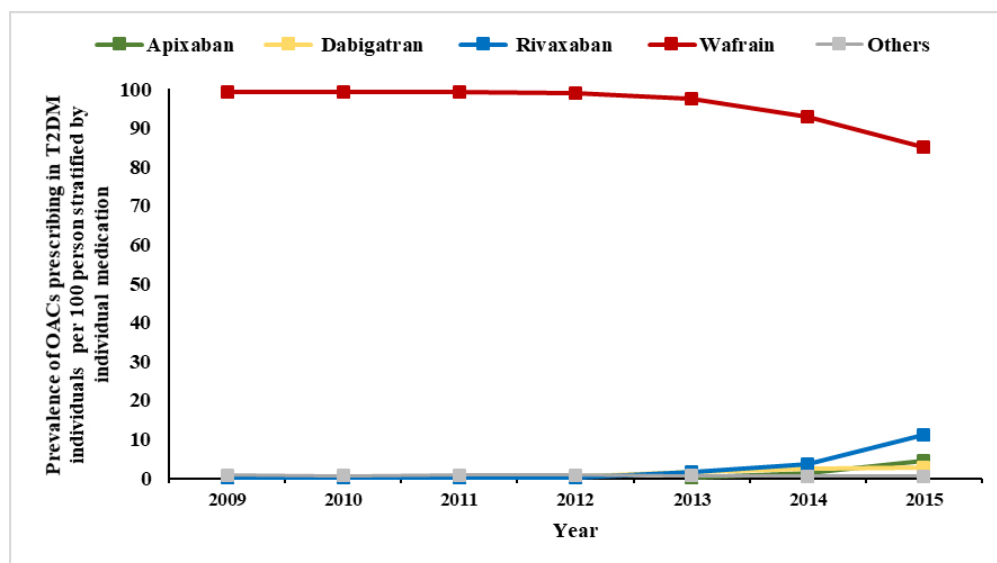


Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

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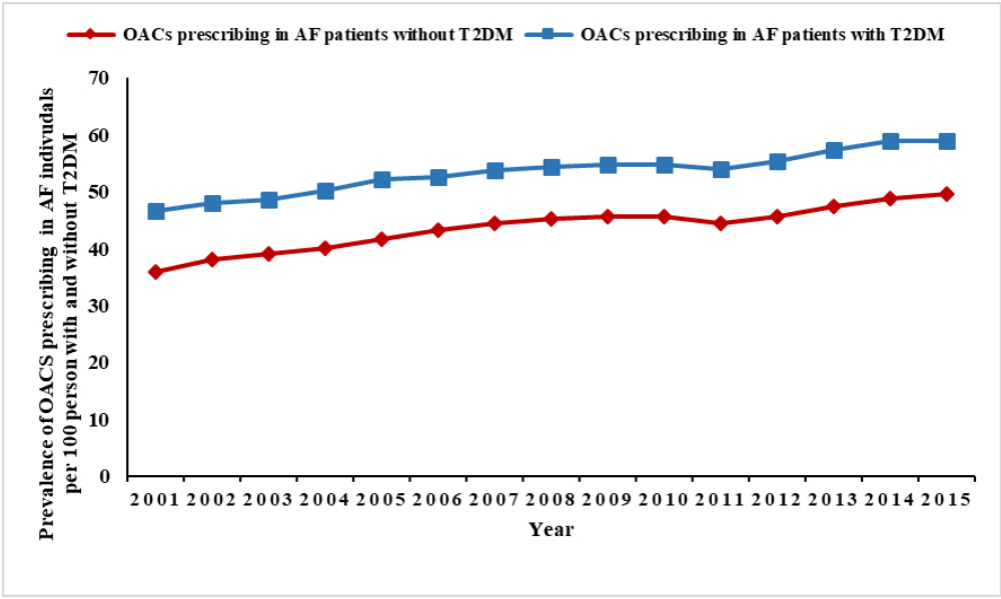


Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM.

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	4,5	Methods
		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		
		(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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		Not applicable
		(e) Describe any sensitivity analyses		Not applicable
<b>Results</b>				
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time		Not applicable
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		Not applicable
		<i>Cross-sectional study</i> —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 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
<b>Discussion</b>				
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
<b>Other information</b>				
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](http://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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# **Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom**

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1  
2  
3 43 **ABSTRACT (219 words)**

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6 44 **Objective:** To evaluate oral anticoagulant (OAC) prescribing trends in type 2 diabetes mellitus (T2DM)  
7  
8 45 in the United Kingdom (UK) from 2001 to 2015.

9  
10 46 **Design:** A cross-sectional drug utilisation study.

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12 47 **Setting:** Electronic health records from The Health Improvement Network (THIN) primary care  
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14 48 database of the UK.

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16 49 **Participants:** Individuals with T2DM who received a record of OAC prescription.

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18 50 **Outcome measures:** The prescribing trends of OAC medications in individuals with T2DM were  
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20 51 examined from 2001 to 2015, stratified by age, gender and therapeutic classifications.

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22 52 **Results:** The prevalence of OAC prescribing increased by 50.8% [from 4.4 (95% confidence intervals  
23  
24 53 (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  
25  
26 54 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  
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28 55 2015 per 100 persons]. This corresponded with increased prescribing of direct oral anticoagulants  
29  
30 56 (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]  
31  
32 57 during the same period.

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34 58 **Conclusions:** Prescribing of OACs in individuals with T2DM increased from 2001 to 2015. Since the  
35  
36 59 introduction of DOACs there has been a clear shift in prescribing towards these agents. Future studies  
37  
38 60 are needed to assess the safety of the co-administration of OAC medications and antidiabetic therapy  
39  
40 61 with T2DM.

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42 62 **Keywords:** Diabetes mellitus, Drug utilisation, Oral anticoagulants therapies, Trend, United Kingdom  
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## 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.

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**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 CHA<sub>2</sub>DS<sub>2</sub> score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (16). In 2010, CHA<sub>2</sub>DS<sub>2</sub>-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.

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**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  $\pm$  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.

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3185RESULTS

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5186Demographics and characteristics

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7187During the study period of 2001 and 2015, a total of 361,635 individuals with T2DM were identified

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9188of whom 36,570 received a prescription for OAC. Characteristics of the entire cohort included in our

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11189study are presented at the time of first OAC prescription. The average age of individuals at the time of

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13190first OAC prescription was 72 (SD, 10.2) years old, and the majority of individuals were male (59.9%).

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15191Around 64.6% of individuals were diagnosed with atrial fibrillation and 22.2% were diagnosed with

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17192venous thromboembolism diseases. Baseline demographics of the study sample are described in Table

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22194Table 1: characteristics of the study sample at the time of first OAC prescription

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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)
<b>Medications</b>	
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)
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc Score<sup>a</sup></b>	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
<b>HASBLED<sup>b</sup></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; <sup>a</sup>CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); <sup>b</sup>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).

## 239 Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with 240 and without T2DM

241 The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM  
242 maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications  
243 prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of  
244 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  
245 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI  
246 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure  
247 5).

## 248 DISCUSSION

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

256 Previous studies investigating the trend of OACs prescribing in individuals with T2DM are limited. A  
257 previous study by Hamada *et al.* examined the trend of cardiovascular medication prescribing in  
258 diabetic individuals aged 80 years or above in the UK between 1990 to 2010 (22), concluding that the  
259 prescribing of OACs in individuals with T2DM had increased [from 5% in 1999 to 19% in 2010]. These  
260 results showed similar trends to our study in the increase of OACs prescriptions in T2DM. However,  
261 our results showed that OAC prescriptions increased less sharply, which is explicable by restriction of  
262 their population to include only individuals aged 80 years and older. Despite this, age is considered a  
263 risk factor for many conditions for which OACs are indicated, and our results showed an increased rate  
264 of OACs prescribing among individuals aged 75 years and above, which was also similar to a previous  
265 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<sub>2</sub> (16) and CHA<sub>2</sub>DS<sub>2</sub>-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 subsidises 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<sub>2</sub>DS<sub>2</sub>-VASc in the comparison between the trend in OAC use in individuals with AF, with and without T2DM. However, CHA<sub>2</sub>DS<sub>2</sub>-VASc was introduced in 2010 (17),



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3 321 and was only implemented in the NICE guidelines in 2014 (15), considering that our study end date  
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5 322 was 2015, the practice will not be reflected in our study period  
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7 323 Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications  
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9 324 and OAC medications for possible drug-drug interactions, especially when warfarin is the drug of  
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11 325 choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is  
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13 326 imperative to investigate the effect of concomitant use of this class of medication and the risk of  
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15 327 hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus  
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17 328 improve the safety of OAC use in individuals with T2DM.  
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21 329 **CONCLUSIONS**  
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24 330 This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin  
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26 331 since its introduction to the UK market, which is consistent with UK guidelines. However, there is a  
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28 332 lack of studies examining their safety when used in individuals with T2DM. Further studies are  
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30 333 warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for  
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32 334 possible drug-drug interactions.  
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37 336 **Abbreviations**  
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39 337 ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs:  
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41 338 Confidence intervals; Cytochrome P450: CYP450; DOAC: Direct oral anticoagulant; IDF:  
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43 339 International Diabetes Federation; INR: International normalized level; NHS: National Health Service;  
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45 340 NICE: National Institute for Health and Care Excellence; OAC: oral anticoagulant; SD: Standard  
46  
47 341 deviation; SRC: Scientific Review Committee; STROBE: Strengthening the reporting of observational  
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49 342 studies in epidemiology; THIN: The Health Improvement Network; T1DM: Type 1 diabetes mellitus  
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51 343 T2DM: Type 2 diabetes mellitus UK: United Kingdom.  
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53 344 **Consent for publication**  
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55 345 Not applicable.  
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57 346 **Data Availability**  
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59 347 No further data are available.  
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## 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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## REFERENCES

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes research and clinical practice*. 2014;103(2):137-49.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*. 2017;128:40-50.
3. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ open*. 2016;6(1):e010210.
4. Pierce MB, Zaninotto P, Steel N, Mindell J. Undiagnosed diabetes-data from the English longitudinal study of ageing. *Diabetic medicine : a journal of the British Diabetic Association*. 2009;26(7):679-85.
5. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guideline.[NG28]. 2015.

6. Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes, obesity & metabolism*. 2017;19(11):1537-45.
7. Robbins JM, Webb DA, Sciamanna CN. Cardiovascular comorbidities among public health clinic patients with diabetes: the Urban Diabetics Study. *BMC Public Health*. 2005;5:15-.
8. Celis-Morales CA, Petermann F, Hui L, Lyall DM, Iliodromiti S, McLaren J, et al. Associations Between Diabetes and Both Cardiovascular Disease and All-Cause Mortality Are Modified by Grip Strength: Evidence From UK Biobank, a Prospective Population-Based Cohort Study. *Diabetes care*. 2017;40(12):1710-8.
9. Pantalone KM, Hobbs TM, Wells BJ, Kong SX, Kattan MW, Bouchard J, et al. Clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. *BMJ Open Diabetes Res Care*. 2015;3(1):e000093.
10. Dinesh Shah A, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of a wide range of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet (London, England)*. 2015;385 Suppl 1:S86.
11. Xiong Z, Liu T, Tse G, Gong M, Gladding PA, Smaill BH, et al. A Machine Learning Aided Systematic Review and Meta-Analysis of the Relative Risk of Atrial Fibrillation in Patients With Diabetes Mellitus. *Front Physiol*. 2018;9:835.
12. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *European heart journal*. 2014;35(42):2950-9.
13. Wilkins E WL, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. Cardiovascular disease statistics 2017. British Heart Foundation. 2017.
14. Tse G, Lai ET, Tse V, Yeo JM. Molecular and Electrophysiological Mechanisms Underlying Cardiac Arrhythmogenesis in Diabetes Mellitus. *J Diabetes Res*. 2016;2016:2848759.
15. Excellence NifHaC. Atrial fibrillation management. NICE guideline (CG180). 2014.
16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama*. 2001;285(22):2864-70.
17. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-72.
18. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European heart journal*. 2016;37(38):2893-962.
19. January Craig T, Wann LS, Calkins H, Chen Lin Y, Cigarroa Joaquin E, Cleveland Joseph C, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e51.
20. Cheng JW, Barillari G. Non-vitamin K antagonist oral anticoagulants in cardiovascular disease management: evidence and unanswered questions. *Journal of clinical pharmacy and therapeutics*. 2014;39(2):118-35.
21. Łabuz-Roszak B, Machowska-Majchrzak A, Skrzypek M, Mossakowska M, Chudek J, Więcek A, et al. Antiplatelet and anticoagulant therapy in elderly people with type 2

- diabetes mellitus in Poland (based on the PolSenior Study). *Archives of medical science : AMS*. 2017;13(5):1018-24.
22. Hamada S, Gulliford MC. Antidiabetic and cardiovascular drug utilisation in patients diagnosed with type 2 diabetes mellitus over the age of 80 years: a population-based cohort study. *Age and ageing*. 2015;44(4):566-73.
  23. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *International journal of cardiology*. 2005;105(3):315-8.
  24. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart (British Cardiac Society)*. 2007;93(5):606-12.
  25. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL, et al. Diabetes Mellitus, Glycemic Control, and Risk of Atrial Fibrillation. *Journal of General Internal Medicine*. 2010;25(8):853-8.
  26. Excellence NifHaC. Warfarin | Interactions | BNF Provided by NICE 2017.
  27. Ament P BJ, Liszewski J. . Clinically Significant Drug Interactions. *American Family Physician*. 2000;15(61):1745-54.
  28. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Han X, Nam YH, et al. Gastrointestinal bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics(). *International journal of cardiology*. 2017;228:761-70.
  29. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis. *BMJ*. 2015;351.
  30. Naganuma M, Hashimoto Y, Matsuura Y, Terasaki T, Uchino M. A case of sustained hypoglycemia induced by taking glibenclamide and warfarin  
subtitle\_in\_Japanese. *Nosotchu*. 2003;25(3):334-7.
  31. Namazi S aRG. Case Presentation of a 45 Years Old Woman with Hypoglycemia and Bleeding. *Iranian Journal of Pharmaceutical Sciences*. 2005;9(3):183-8.
  32. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in primary care*. 2011;19(4):251-5.
  33. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology and drug safety*. 2007;16(4):393-401.
  34. Brauer R, Lau WCY, Hayes JF, Man KKC, Osborn DPJ, Howard R, et al. Trazodone use and risk of dementia: A population-based cohort study. *PLoS Med*. 2019;16(2):e1002728.
  35. Alfageh BH, Man KKC, Besag FMC, Alhawassi TM, Wong ICK, Brauer R. Psychotropic Medication Prescribing for Neuropsychiatric Comorbidities in Individuals Diagnosed with Autism Spectrum Disorder (ASD) in the UK. *Journal of autism and developmental disorders*. 2019.
  36. Murray ML, Hsia Y, Glaser K, Simonoff E, Murphy DG, Asherson PJ, et al. Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology*. 2014;231(6):1011-21.
  37. McCarthy S, Wilton L, Murray M, Hodgkins P, Asherson P, Wong IC. Management of adult attention deficit hyperactivity disorder in UK primary care: a survey of general practitioners. *Health Qual Life Outcomes*. 2013;11:22.
  38. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong ICK. Persistence of pharmacological treatment into adulthood, in UK primary care, for ADHD patients who started treatment in childhood or adolescence. *BMC Psychiatry*. 2012;12:219-.

39. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. *BMC pediatrics*. 2012;12:78.
40. Digital N. Read Codeds. 2018.
41. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and drug safety*. 2009;18(1):76-83.
42. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium. International Diabetes Federation. 2017.
43. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *British journal of clinical pharmacology*. 2017;83(9):2096-106.
44. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *American Journal of Health-System Pharmacy*. 2017;74(16):1237-44.
45. Lee S-R, Choi E-K, Han K-D, Cha M-J, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: A nationwide population-based study. *PLoS ONE*. 2017;12(12):e0189495.
46. Gadsboll K, Staerk L, Fosbol EL, Sindet-Pedersen C, Gundlund A, Lip GYH, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *European heart journal*. 2017;38(12):899-906.
47. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine*. 2011;365(10):883-91.
48. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2011;365(11):981-92.
49. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2009;361(12):1139-51.
50. Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. *Journal of the American College of Cardiology*. 2013;61(22):2264-73.
51. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018;362.
52. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open heart*. 2016;3(1):e000279.
53. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London, England)*. 2014;383(9921):955-62.
54. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old? *Open heart*. 2018;5(1):e000712.
55. Fanning L, Ilomaki J, Bell JS, Darzins P. The representativeness of direct oral anticoagulant clinical trials to hospitalized patients with atrial fibrillation. *Eur J Clin Pharmacol*. 2017;73(11):1427-36.

56. Di Minno A, Frigerio B, Spadarella G, Ravani A, Sansaro D, Amato M, et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood reviews*. 2017;31(4):193-203.
57. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Therapeutics and Clinical Risk Management*. 2015;11:967-77.
58. Kimmel SE. Warfarin therapy: in need of improvement after all these years. *Expert opinion on pharmacotherapy*. 2008;9(5):677-86.
59. Tse G, Gong M, Li G, Wong SH, Wu WKK, Wong WT, et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol*. 2018;84(9):1868-82.
60. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-104.
61. Kjerpeseth LJ, Ellekjaer H, Selmer R, Ariansen I, Furu K, Skovlund E. Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. *Eur J Clin Pharmacol*. 2017;73(11):1417-25.
62. Scowcroft ACE, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009. *2013;99(2):127-32*.



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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.

view only

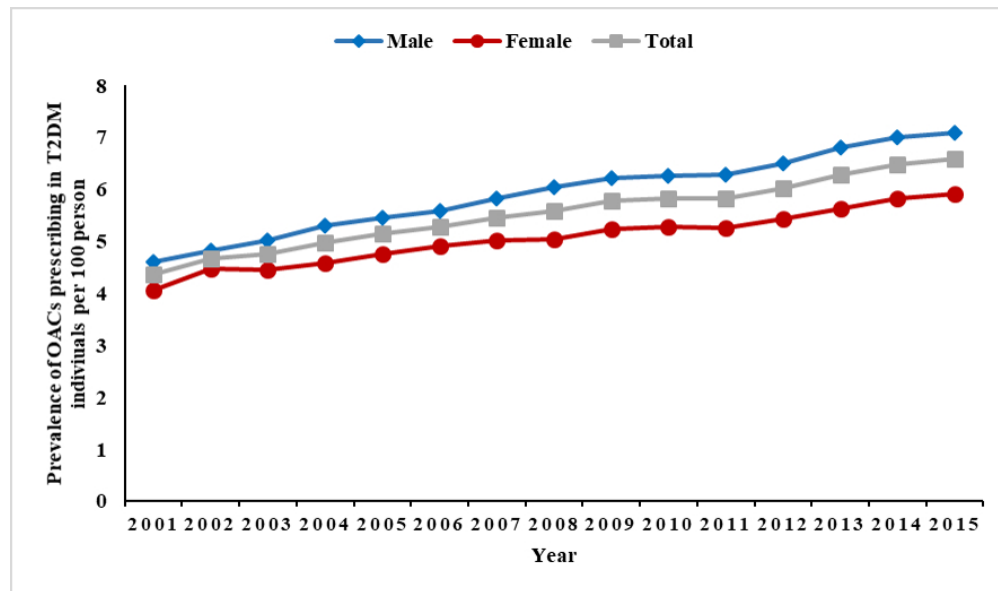


Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

75x44mm (300 x 300 DPI)

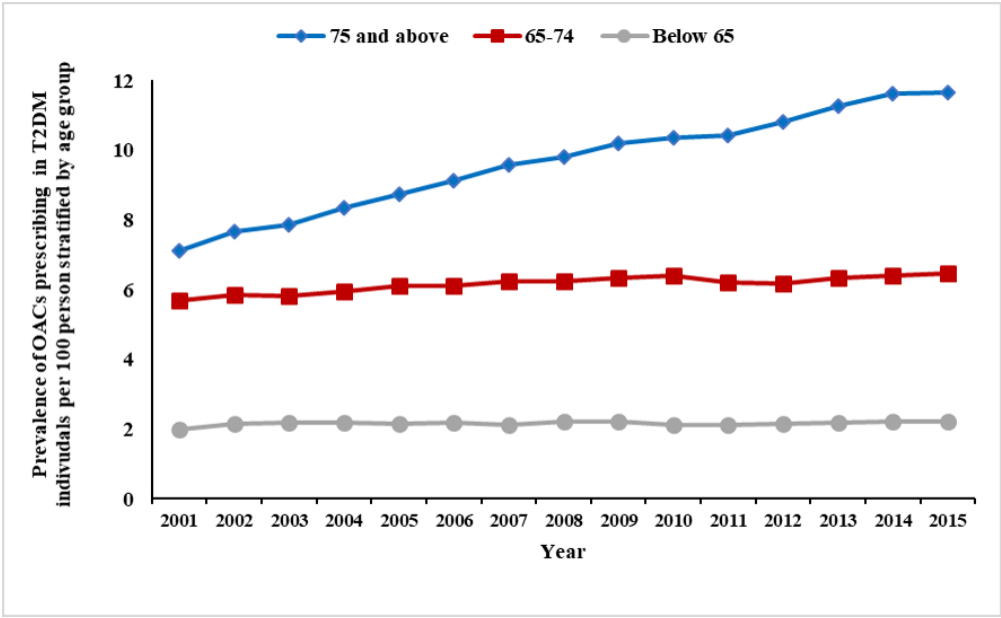


Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.  
75x46mm (300 x 300 DPI)



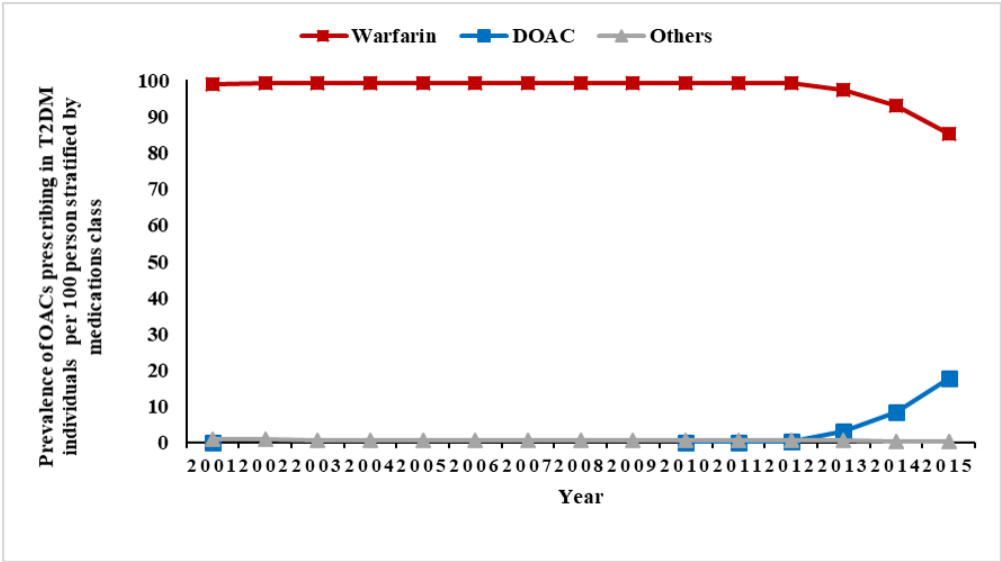


Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

75x42mm (300 x 300 DPI)

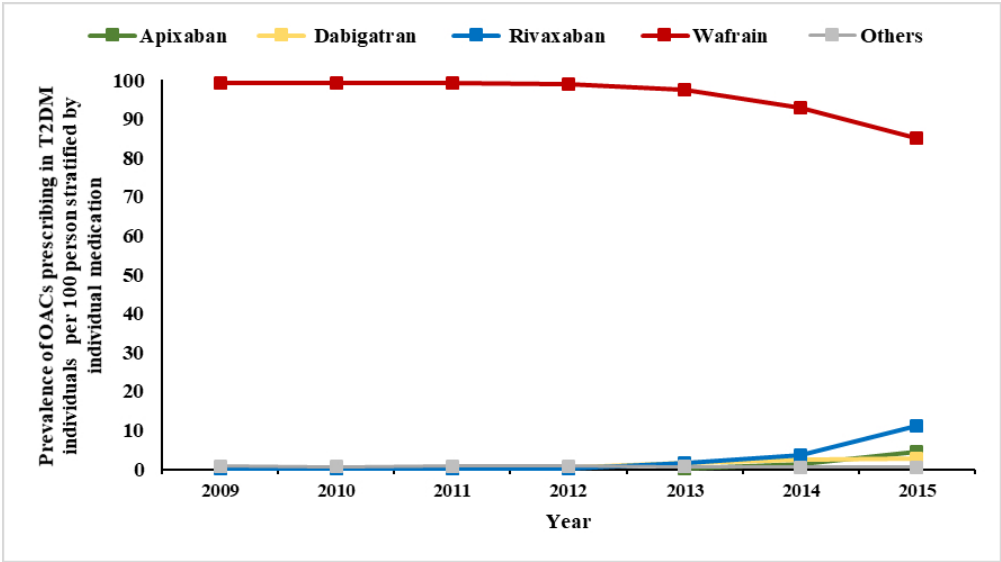


Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

75x42mm (300 x 300 DPI)

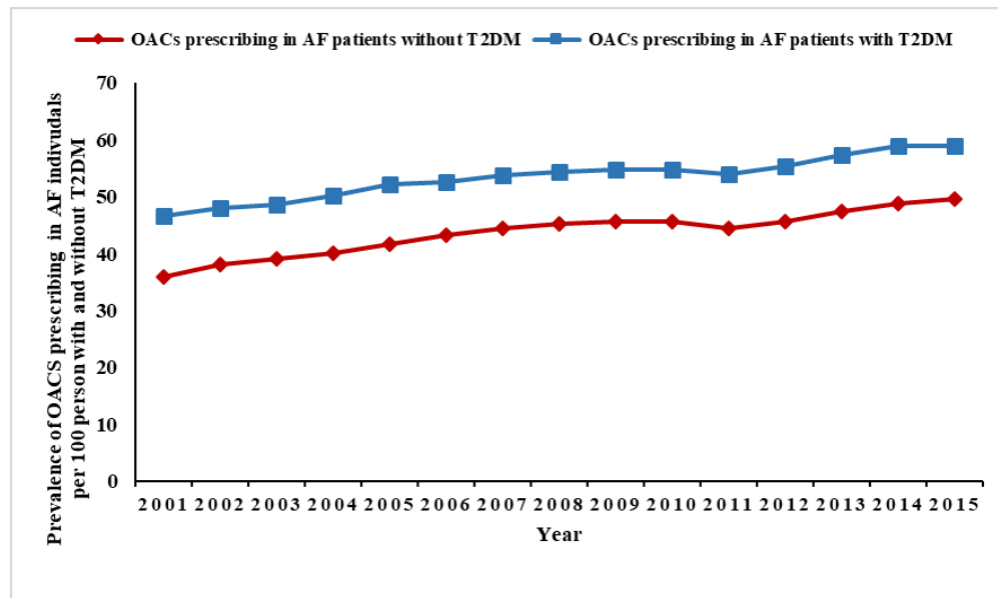


Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM

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Supplement:

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

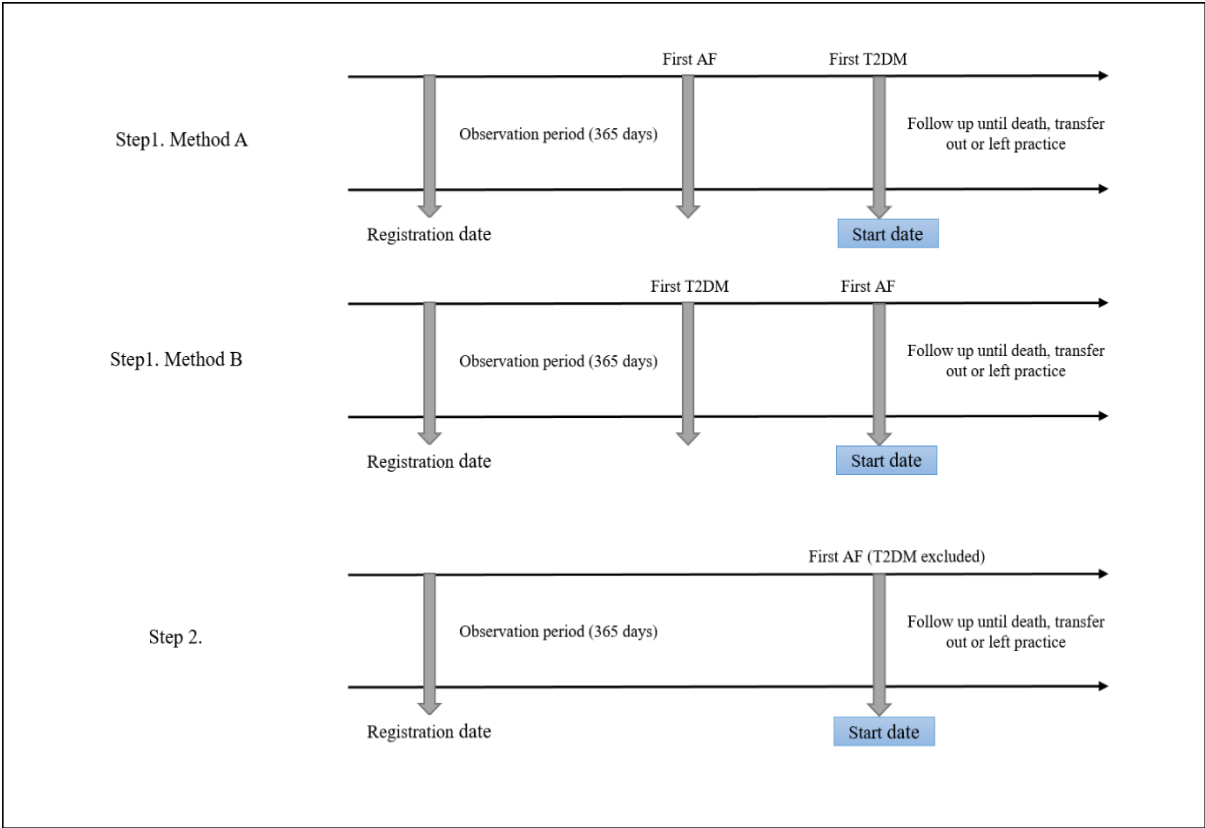


Figure S1. Methods to identify study population of AF individuals with and without T2DM

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
<b>Discussion</b>				
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
<b>Other information</b>				
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](http://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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# **Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom**

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1  
2  
3 44 **ABSTRACT (219 words)**  
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5  
6 45 **Objective:** To evaluate oral anticoagulant (OAC) prescribing trends in type 2 diabetes mellitus (T2DM)  
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8 46 in the United Kingdom (UK) from 2001 to 2015.  
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11 47 **Design:** A cross-sectional drug utilisation study.

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13 48 **Setting:** Electronic health records from The Health Improvement Network (THIN) primary care  
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15 49 database of the UK.

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17 50 **Participants:** Individuals with T2DM who received a record of OAC prescription.

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19 51 **Outcome measures:** The prescribing trends of OAC medications in individuals with T2DM were  
20  
21 52 examined from 2001 to 2015, stratified by age, gender and therapeutic classifications.

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23 53 **Results:** The prevalence of OAC prescribing increased by 50.0% [from 4.4 (95% confidence intervals  
24  
25 54 (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  
26  
27 55 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  
28  
29 56 2015 per 100 persons]. This corresponded with increased prescribing of direct oral anticoagulants  
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31 57 (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]  
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33 58 during the same period.

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35 59 **Conclusions:** Prescribing of OACs in individuals with T2DM increased from 2001 to 2015. Since the  
36  
37 60 introduction of DOACs there has been a clear shift in prescribing towards these agents. Future studies  
38  
39 61 are needed to assess the safety of the co-administration of OAC medications and antidiabetic therapy  
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41 62 with T2DM.

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43 63 **Keywords:** Diabetes mellitus, Drug utilisation, Oral anticoagulants therapies, Trend, United Kingdom  
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## 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.

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**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 CHA<sub>2</sub>DS<sub>2</sub> score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (9). In 2010, CHA<sub>2</sub>DS<sub>2</sub>-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.

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**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  $\pm$  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)
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc Score<sup>a</sup></b>	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
<b>HASBLED<sup>b</sup></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; <sup>a</sup>CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); <sup>b</sup>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%.

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3 215 Similarly, the prescribing prevalence of OAC medications varied among individuals from the different  
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5 216 age groups. The prevalence of OAC medications among individuals aged 75 years or above increased  
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7 217 [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].  
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9 218 However, it was clearly lower among younger individuals, which increased [from 5.7 (95%CI 5.2 –  
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11 219 6.1) in 2001 to 6.5 (95%CI 6.3 – 6.6) in 2015 per 100 persons with T2DM], for individuals aged between  
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13 220 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  
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15 221 with T2DM], for individuals aged below 65 years (Figure 2).

17  
18 222 **Trends in prevalence of oral anticoagulant prescribing stratified by medication**

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20 223 Although warfarin was the most common OAC prescribed during the entire study period (86.3%), its  
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22 224 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  
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24 225 persons with T2DM]. In contrast, there was a corresponding increase in the proportion of individuals  
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26 226 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  
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28 227 persons with T2DM]. Other OACs, including acenocoumarol and phenindione were less likely to be  
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30 228 prescribed during the entire study period (0.03%), their prescribing rate decreased [from 1.1 (95% CI  
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32 229 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,  
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34 230 a small percentage of individuals with T2DM using OAC were prescribed different OAC classes during  
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36 231 the same year ranging from less than 1% in 2010 to 3% in 2015.

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39 232 Further stratification by individual OAC drug treatment showed that the prescribing prevalence of  
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41 233 rivaroxaban markedly increased [from 0.1 (95% CI 0.05–0.2) in 2010 to 10.9 (95% CI 10.5–11.4) in  
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43 234 2015 per 100 persons with T2DM], while the prescribing prevalence of dabigatran increased to a lesser  
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45 235 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  
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47 236 T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08)  
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49 237 in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).

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51 238 **Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with**  
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53 239 **and without T2DM**

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55 240 The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM  
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57 241 maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications  
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59 242 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<sub>2</sub> (9) and CHA<sub>2</sub>DS<sub>2</sub>-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 subsidises 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<sub>2</sub>DS<sub>2</sub>-VASc in the comparison between the trend in OAC use in individuals with AF, with and without T2DM. However, CHA<sub>2</sub>DS<sub>2</sub>-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

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3 327 choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is  
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5 328 imperative to investigate the effect of concomitant use of this class of medication and the risk of  
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7 329 hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus  
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9 330 improve the safety of OAC use in individuals with T2DM.

11 331 **CONCLUSIONS**

12  
13 332 This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin  
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15 333 since its introduction to the UK market, which is consistent with UK guidelines. However, there is a  
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17 334 lack of studies examining their safety when used in individuals with T2DM. Further studies are  
18  
19 335 warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for  
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21 336 possible drug-drug interactions.

22 337 **Abbreviations**

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24 338 ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs:  
25  
26 339 Confidence intervals; Cytochrome P450: CYP450; DOAC: Direct oral anticoagulant; IDF:  
27  
28 340 International Diabetes Federation; INR: International normalized level; NHS: National Health Service;  
29  
30 341 NICE: National Institute for Health and Care Excellence; OAC: oral anticoagulant; SD: Standard  
31  
32 342 deviation; SRC: Scientific Review Committee; STROBE: Strengthening the reporting of observational  
33  
34 343 studies in epidemiology; THIN: The Health Improvement Network; T1DM: Type 1 diabetes mellitus  
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36 344 T2DM: Type 2 diabetes mellitus UK: United Kingdom.

37 345 **Consent for publication**

38 346 Not applicable.

39 347 **Data Availability**

40 348 No further data are available.

41 349 **Conflict of Interest Disclosures**

42 350 The authors declare that they have no competing interest.

43 351 **Funding**

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45  
46 353 collaborative research between UCL, Monash and UNC.



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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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## REFERENCES

- Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*. 2017;128:40-50.
- Pierce MB, Zaninotto P, Steel N, Mindell J. Undiagnosed diabetes-data from the English longitudinal study of ageing. *Diabetic medicine : a journal of the British Diabetic Association*. 2009;26(7):679-85.
- National Institute for Health and Care Excellence. Type 2 diabetes in adults: management.NICE guideline.[NG28] 2015 [Available from: <https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493>.
- Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes, obesity & metabolism*. 2017;19(11):1537-45.
- Celis-Morales CA, Petermann F, Hui L, Lyall DM, Iliodromiti S, McLaren J, et al. Associations Between Diabetes and Both Cardiovascular Disease and All-Cause Mortality Are Modified by Grip Strength: Evidence From UK Biobank, a Prospective Population-Based Cohort Study. *Diabetes care*. 2017;40(12):1710-8.
- Dinesh Shah A, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of a wide range of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet (London, England)*. 2015;385 Suppl 1:S86.
- Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *European heart journal*. 2014;35(42):2950-9.
- Excellence NifHaC. Atrial fibrillation management. NICE guideline (CG180). 2014.



9. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama*. 2001;285(22):2864-70.
10. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-72.
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European heart journal*. 2016;37(38):2893-962.
12. January Craig T, Wann LS, Calkins H, Chen Lin Y, Cigarroa Joaquin E, Cleveland Joseph C, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e51.
13. Cheng JW, Barillari G. Non-vitamin K antagonist oral anticoagulants in cardiovascular disease management: evidence and unanswered questions. *Journal of clinical pharmacy and therapeutics*. 2014;39(2):118-35.
14. Łabuz-Roszak B, Machowska-Majchrzak A, Skrzypek M, Mossakowska M, Chudek J, Więcek A, et al. Antiplatelet and anticoagulant therapy in elderly people with type 2 diabetes mellitus in Poland (based on the PolSenior Study). *Archives of medical science : AMS*. 2017;13(5):1018-24.
15. Hamada S, Gulliford MC. Antidiabetic and cardiovascular drug utilisation in patients diagnosed with type 2 diabetes mellitus over the age of 80 years: a population-based cohort study. *Age and ageing*. 2015;44(4):566-73.
16. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *International journal of cardiology*. 2005;105(3):315-8.
17. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart (British Cardiac Society)*. 2007;93(5):606-12.
18. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL, et al. Diabetes Mellitus, Glycemic Control, and Risk of Atrial Fibrillation. *Journal of General Internal Medicine*. 2010;25(8):853-8.
19. Excellence NifHaC. Warfarin | Interactions | BNF Provided by NICE 2017.
20. Ament P BJ, Liszewski J. . Clinically Significant Drug Interactions. *American Family Physician*. 2000;15(61):1745-54.
21. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Han X, Nam YH, et al. Gastrointestinal bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics(). *International journal of cardiology*. 2017;228:761-70.
22. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis. *BMJ*. 2015;351.
23. Naganuma M, Hashimoto Y, Matsuura Y, Terasaki T, Uchino M. A case of sustained hypoglycemia induced by taking glibenclamide and warfarin subtitle\_in\_Japanese. *Nosotchu*. 2003;25(3):334-7.
24. Namazi S aRG. Case Presentation of a 45 Years Old Woman with Hypoglycemia and Bleeding. *Iranian Journal of Pharmaceutical Sciences*. 2005;9(3):183-8.

25. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in primary care*. 2011;19(4):251-5.
26. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology and drug safety*. 2007;16(4):393-401.
27. Brauer R, Lau WCY, Hayes JF, Man KKC, Osborn DPJ, Howard R, et al. Trazodone use and risk of dementia: A population-based cohort study. *PLoS Med*. 2019;16(2):e1002728.
28. Alfageh BH, Man KKC, Besag FMC, Alhawassi TM, Wong ICK, Brauer R. Psychotropic Medication Prescribing for Neuropsychiatric Comorbidities in Individuals Diagnosed with Autism Spectrum Disorder (ASD) in the UK. *Journal of autism and developmental disorders*. 2019.
29. Murray ML, Hsia Y, Glaser K, Simonoff E, Murphy DG, Asherson PJ, et al. Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology*. 2014;231(6):1011-21.
30. McCarthy S, Wilton L, Murray M, Hodgkins P, Asherson P, Wong IC. Management of adult attention deficit hyperactivity disorder in UK primary care: a survey of general practitioners. *Health Qual Life Outcomes*. 2013;11:22.
31. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong ICK. Persistence of pharmacological treatment into adulthood, in UK primary care, for ADHD patients who started treatment in childhood or adolescence. *BMC Psychiatry*. 2012;12:219-.
32. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. *BMC pediatrics*. 2012;12:78.
33. Digital N. Read Codeds. 2018.
34. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and drug safety*. 2009;18(1):76-83.
35. International Diabetes Federation. *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium. International Diabetes Federation. 2017.
36. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *British journal of clinical pharmacology*. 2017;83(9):2096-106.
37. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *American Journal of Health-System Pharmacy*. 2017;74(16):1237-44.
38. Gadsboll K, Staerk L, Fosbol EL, Sindet-Pedersen C, Gundlund A, Lip GYH, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *European heart journal*. 2017;38(12):899-906.
39. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine*. 2011;365(10):883-91.
40. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2011;365(11):981-92.
41. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2009;361(12):1139-51.

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489 42. Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, et al.  
490 Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial  
491 fibrillation: a prospective nationwide cohort study. *Journal of the American College of*  
492 *Cardiology*. 2013;61(22):2264-73.

493 43. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct  
494 oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*.  
495 2018;362.

496 44. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in  
497 patients with AF: a systematic review and meta-analysis. *Open heart*. 2016;3(1):e000279.

498 45. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD,  
499 et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in  
500 patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London,*  
501 *England)*. 2014;383(9921):955-62.

502 46. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always  
503 better than the old? *Open heart*. 2018;5(1):e000712.

504 47. Fanning L, Ilomaki J, Bell JS, Darzins P. The representativeness of direct oral  
505 anticoagulant clinical trials to hospitalized patients with atrial fibrillation. *Eur J Clin*  
506 *Pharmacol*. 2017;73(11):1427-36.

507 48. Di Minno A, Frigerio B, Spadarella G, Ravani A, Sansaro D, Amato M, et al. Old and  
508 new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood reviews*.  
509 2017;31(4):193-203.

510 49. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their  
511 advantages and disadvantages compared with vitamin K antagonists in the prevention and  
512 treatment of patients with thromboembolic events. *Therapeutics and Clinical Risk*  
513 *Management*. 2015;11:967-77.

514 50. Kimmel SE. Warfarin therapy: in need of improvement after all these years. *Expert*  
515 *opinion on pharmacotherapy*. 2008;9(5):677-86.

516 51. Tse G, Gong M, Li G, Wong SH, Wu WKK, Wong WT, et al. Genotype-guided  
517 warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of  
518 randomized controlled trials. *Br J Clin Pharmacol*. 2018;84(9):1868-82.

519 52. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al.  
520 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation:  
521 executive summary: a report of the American College of Cardiology/American Heart  
522 Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*.  
523 2014;130(23):2071-104.

524 53. Kjerpeseth LJ, Ellekjaer H, Selmer R, Ariansen I, Furu K, Skovlund E. Trends in use  
525 of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. *Eur J*  
526 *Clin Pharmacol*. 2017;73(11):1417-25.

527 54. Scowcroft ACE, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in  
528 the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009.  
529 2013;99(2):127-32.

531 **Figure titles and legends**

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

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

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

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

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

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view only

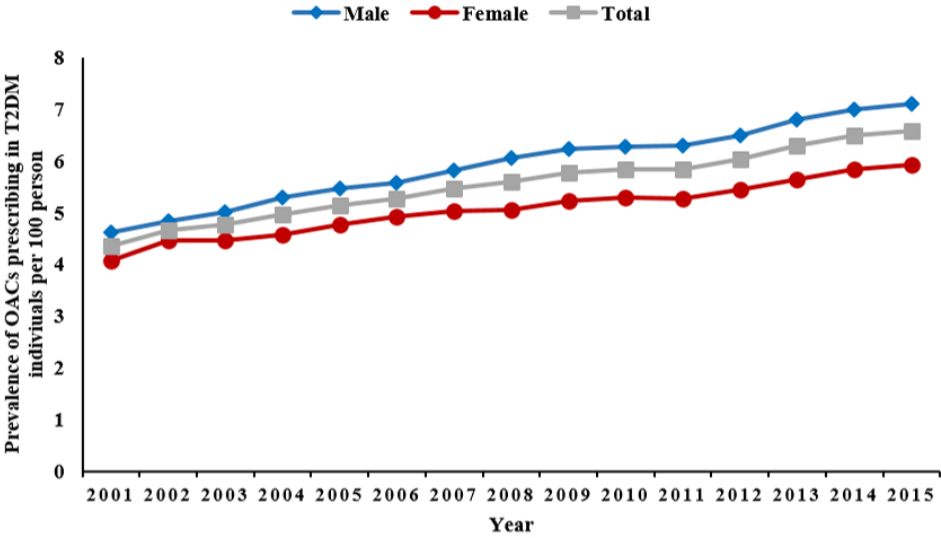


Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

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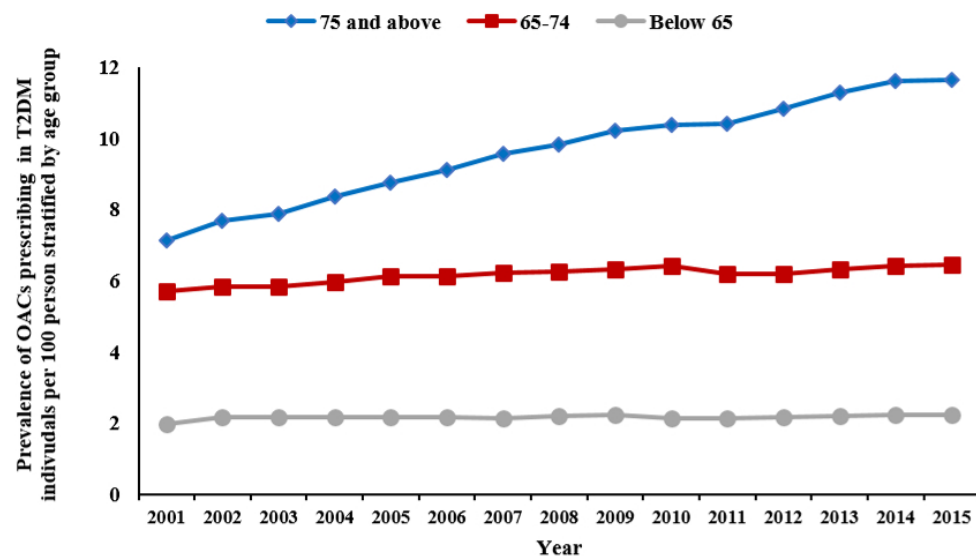


Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

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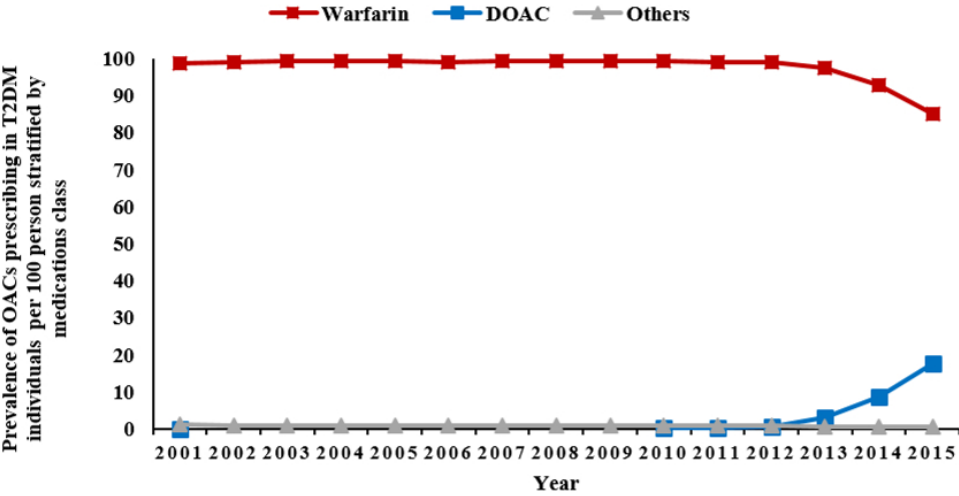


Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

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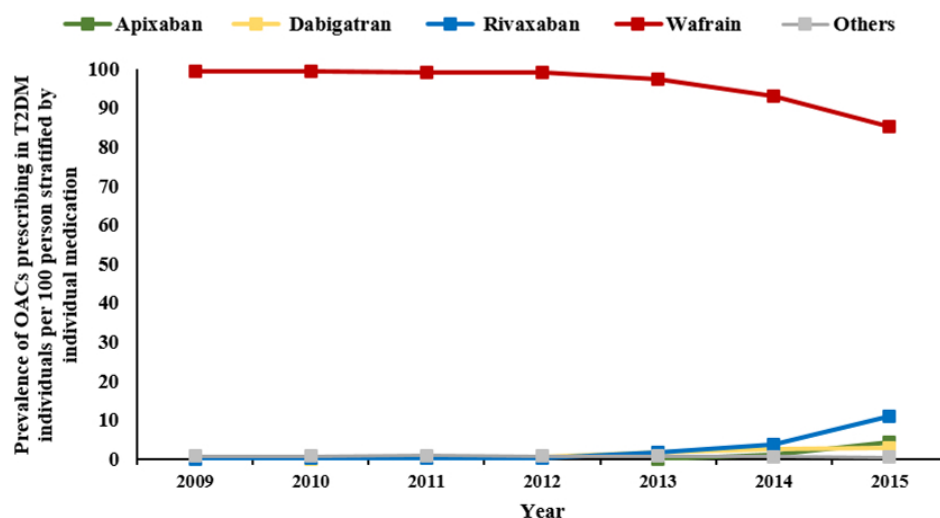


Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

75x41mm (300 x 300 DPI)



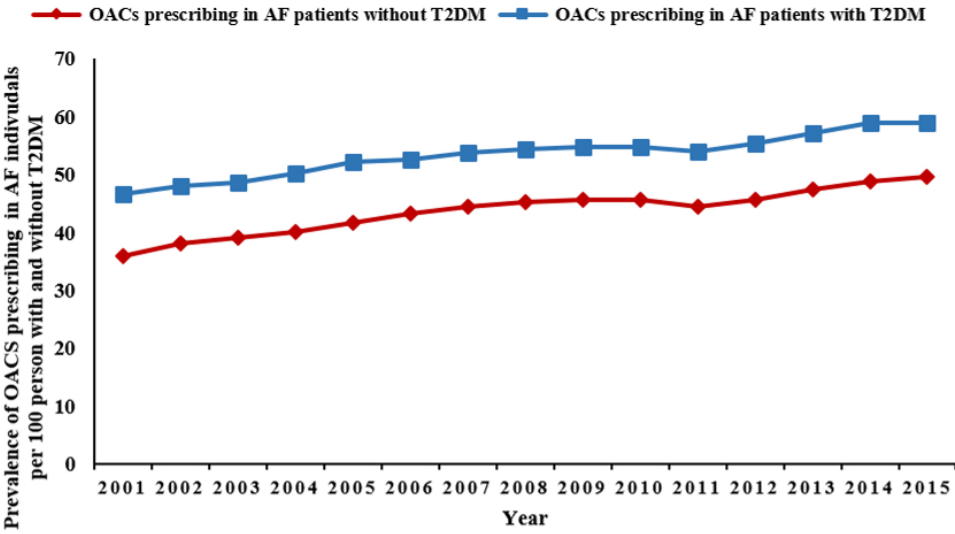
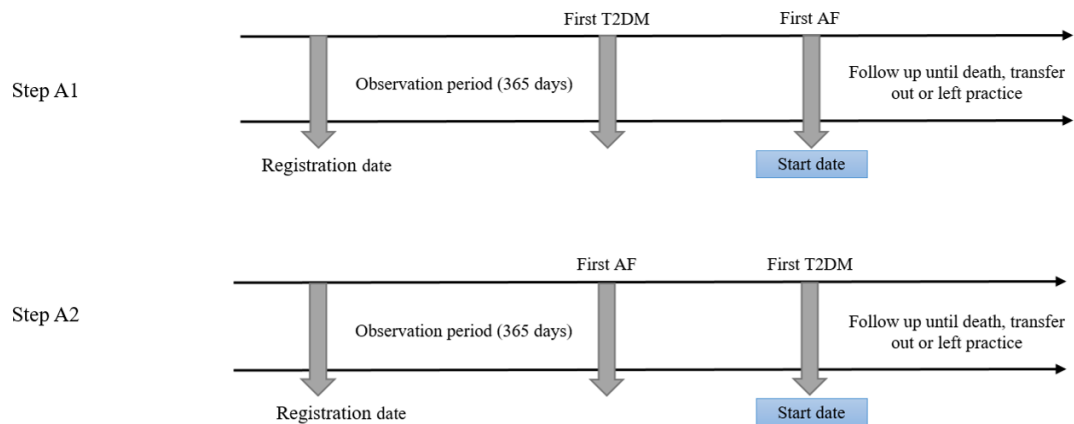


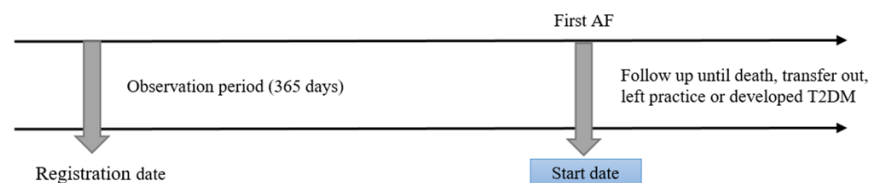
Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM  
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**Supplement:**

**Step A. The start date of individuals with AF and T2DM**



**Step B. The start date of individuals with AF and without T2DM**



**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
		<b>Results</b>		
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
<b>Discussion</b>				
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
<b>Other information</b>				
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](http://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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# **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

## 69 **Strengths and limitations of this study**

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

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**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 CHA<sub>2</sub>DS<sub>2</sub> score, which is a prediction of the risk of stroke and guides the optimisation of management in individuals with AF (9). In 2010, CHA<sub>2</sub>DS<sub>2</sub>-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.

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**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  $\pm$  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)

<b>Medications</b>	
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)
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc Score<sup>a</sup></b>	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
<b>HASBLED<sup>b</sup></b>	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

\*Standard deviation  $\pm$ ; 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; <sup>a</sup>CHA<sub>2</sub>DS<sub>2</sub>-VASc indicates individuals with congestive cardiac failure, hypertension, age  $\geq 75$  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<sub>2</sub>DS<sub>2</sub>-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); <sup>b</sup>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



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3 218 prevalence of OAC medications among females increased [from 4.0 (95%CI 3.8 – 4.4) to 5.9 (95%CI  
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5 219 5.8 – 6.1) per 100 persons with T2DM], with an overall increase of 47.5%.  
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7 220 Similarly, the prescribing prevalence of OAC medications varied among individuals from the different  
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9 221 age groups. The prevalence of OAC medications among individuals aged 75 years or above increased  
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11 222 [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].  
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13 223 However, it was clearly lower among younger individuals, which increased [from 5.7 (95%CI 5.2 –  
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15 224 6.1) in 2001 to 6.5 (95%CI 6.3 – 6.6) in 2015 per 100 persons with T2DM], for individuals aged between  
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17 225 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  
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19 226 with T2DM], for individuals aged below 65 years (Figure 2).  
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22 227 **Trends in prevalence of oral anticoagulant prescribing stratified by medication**

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24 228 Although warfarin was the most common OAC prescribed during the entire study period (86.3%), its  
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26 229 use declined by 14.0% [from 1,761 individuals receiving warfarin prescriptions (IRWP), 98.9 (95% CI  
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28 230 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,  
29  
30 231 there was a corresponding increase in the proportion of individuals who used DOACs [from 18  
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32 232 individuals receiving DOAC prescriptions (IRDOACP), 0.1 (95% CI 0.08–0.23) in 2010 to 3,016  
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34 233 (IRDOACP), 17.6 (95% CI 17.1–18.2) in 2015 per 100 persons]. Other OACs, including  
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36 234 acenocoumarol and phenindione were less likely to be prescribed during the entire study period  
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38 235 (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)  
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40 236 in 2015 per 100 persons with T2DM] (Figure 3). In addition, a small percentage of individuals with  
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42 237 T2DM using OAC were prescribed different OAC classes during the same year ranging from less than  
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46 239 Further stratification by individual OAC drug treatment showed that the prescribing prevalence of  
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48 240 rivaroxaban markedly increased [from 0.1 (95% CI 0.05–0.2) in 2010 to 10.9 (95% CI 10.5–11.4) in  
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50 241 2015 per 100 persons with T2DM], while the prescribing prevalence of dabigatran increased to a lesser  
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52 242 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  
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54 243 T2DM]. In addition, the prescribing prevalence of apixaban increased [from 0.05 (95% CI 0.01–0.08)  
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56 244 in 2010 to 4.36 (95% CI 4.1– 4.6) in 2015 per 100 persons with T2DM] (Figure 4).  
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## 245 Trends in prescribing prevalence of oral anticoagulants in individuals with atrial fibrillation with 246 and without T2DM

247 The prescribing prevalence of OACs in individuals with AF with and without coexisting T2DM  
248 maintained a parallel increase. Individuals with AF and T2DM had a higher rate of OAC medications  
249 prescribing compared to those without T2DM (38.2% vs. 26.4%, respectively). The prevalence of  
250 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  
251 100 persons] for individuals with AF and T2DM, and [from 36.0 (95% CI 35.1 – 36.7) to 49.7 (95% CI  
252 49.4 – 50.0) per 100 persons] between 2001 and 2015 for individuals with AF without T2DM (Figure  
253 5).

## 254 DISCUSSION

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

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

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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<sub>2</sub> (9) and CHA<sub>2</sub>DS<sub>2</sub>-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 subsidises 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

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3 328 secondary objective of this study we did not adjust for CHA<sub>2</sub>DS<sub>2</sub>-VASc in the comparison between the  
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5 329 trend in OAC use in individuals with AF, with and without T2DM. However, CHA<sub>2</sub>DS<sub>2</sub>-VASc was  
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7 330 introduced in 2010 (10), and was only implemented in the NICE guidelines in 2014 (8), considering  
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9 331 that our study end date was 2015, the practice will not be reflected in our study period  
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11 332 Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications  
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13 333 and OAC medications for possible drug-drug interactions, especially when warfarin is the drug of  
14  
15 334 choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is  
16  
17 335 imperative to investigate the effect of concomitant use of this class of medication and the risk of  
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19 336 hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus  
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21 337 improve the safety of OAC use in individuals with T2DM.  
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23  
24 338 **CONCLUSIONS**

25  
26 339 This study highlights a clear change in prescribing pattern towards DOAC use compared to warfarin  
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28 340 since its introduction to the UK market, which is consistent with UK guidelines. However, there is a  
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30 341 lack of studies examining their safety when used in individuals with T2DM. Further studies are  
31  
32 342 warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for  
33  
34 343 possible drug-drug interactions.  
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37 344 **Abbreviations**

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39 345 ADEs: Adverse drug events; AF: Atrial fibrillation; AMR: Acceptable mortality reporting; CIs:  
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41 346 Confidence intervals; Cytochrome P450: CYP450; DOAC: Direct oral anticoagulant; IDF:  
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43 347 International Diabetes Federation; INR: International normalized level; IRDOACP: Individuals  
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45 348 received DOAC prescription; IROACP: Individuals received OAC prescription; IRWP: Individuals  
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47 349 received warfarin prescription; NHS: National Health Service; NICE: National Institute for Health and  
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49 350 Care Excellence; OAC: oral anticoagulant; SD: Standard deviation; SRC: Scientific Review  
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51 351 Committee; STROBE: Strengthening the reporting of observational studies in epidemiology; THIN:  
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53 352 The Health Improvement Network; T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus  
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55 353 UK: United Kingdom.  
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58 354 **Consent for publication**

59  
60 355 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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## **REFERENCES**

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*. 2017;128:40-50.
2. Pierce MB, Zaninotto P, Steel N, Mindell J. Undiagnosed diabetes-data from the English longitudinal study of ageing. *Diabetic medicine : a journal of the British Diabetic Association*. 2009;26(7):679-85.
3. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management.NICE guideline.[NG28] 2015 [Available from: <https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493>].



4. Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes, obesity & metabolism*. 2017;19(11):1537-45.
5. Celis-Morales CA, Petermann F, Hui L, Lyall DM, Iliodromiti S, McLaren J, et al. Associations Between Diabetes and Both Cardiovascular Disease and All-Cause Mortality Are Modified by Grip Strength: Evidence From UK Biobank, a Prospective Population-Based Cohort Study. *Diabetes care*. 2017;40(12):1710-8.
6. Dinesh Shah A, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of a wide range of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet (London, England)*. 2015;385 Suppl 1:S86.
7. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *European heart journal*. 2014;35(42):2950-9.
8. Excellence NifHaC. Atrial fibrillation management. NICE guideline (CG180). 2014.
9. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama*. 2001;285(22):2864-70.
10. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-72.
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European heart journal*. 2016;37(38):2893-962.
12. January Craig T, Wann LS, Calkins H, Chen Lin Y, Cigarroa Joaquin E, Cleveland Joseph C, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e51.
13. Cheng JW, Barillari G. Non-vitamin K antagonist oral anticoagulants in cardiovascular disease management: evidence and unanswered questions. *Journal of clinical pharmacy and therapeutics*. 2014;39(2):118-35.
14. Łabuz-Roszak B, Machowska-Majchrzak A, Skrzypek M, Mossakowska M, Chudek J, Więcek A, et al. Antiplatelet and anticoagulant therapy in elderly people with type 2 diabetes mellitus in Poland (based on the PolSenior Study). *Archives of medical science : AMS*. 2017;13(5):1018-24.
15. Hamada S, Gulliford MC. Antidiabetic and cardiovascular drug utilisation in patients diagnosed with type 2 diabetes mellitus over the age of 80 years: a population-based cohort study. *Age and ageing*. 2015;44(4):566-73.
16. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *International journal of cardiology*. 2005;105(3):315-8.
17. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart (British Cardiac Society)*. 2007;93(5):606-12.
18. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL, et al. Diabetes Mellitus, Glycemic Control, and Risk of Atrial Fibrillation. *Journal of General Internal Medicine*. 2010;25(8):853-8.
19. Excellence NifHaC. Warfarin | Interactions | BNF Provided by NICE 2017.

20. Ament P BJ, Liszewski J. . Clinically Significant Drug Interactions. *American Family Physician*. 2000;15(61):1745-54.
21. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Han X, Nam YH, et al. Gastrointestinal bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics(). *International journal of cardiology*. 2017;228:761-70.
22. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis. *BMJ*. 2015;351.
23. Naganuma M, Hashimoto Y, Matsuura Y, Terasaki T, Uchino M. A case of sustained hypoglycemia induced by taking glibenclamide and warfarin subtitle\_in\_Japanese. *Nosotchu*. 2003;25(3):334-7.
24. Namazi S aRG. Case Presentation of a 45 Years Old Woman with Hypoglycemia and Bleeding. *Iranian Journal of Pharmaceutical Sciences*. 2005;9(3):183-8.
25. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in primary care*. 2011;19(4):251-5.
26. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology and drug safety*. 2007;16(4):393-401.
27. Brauer R, Lau WCY, Hayes JF, Man KKC, Osborn DPJ, Howard R, et al. Trazodone use and risk of dementia: A population-based cohort study. *PLoS Med*. 2019;16(2):e1002728.
28. Alfageh BH, Man KKC, Besag FMC, Alhawassi TM, Wong ICK, Brauer R. Psychotropic Medication Prescribing for Neuropsychiatric Comorbidities in Individuals Diagnosed with Autism Spectrum Disorder (ASD) in the UK. *Journal of autism and developmental disorders*. 2019.
29. Murray ML, Hsia Y, Glaser K, Simonoff E, Murphy DG, Asherson PJ, et al. Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology*. 2014;231(6):1011-21.
30. McCarthy S, Wilton L, Murray M, Hodgkins P, Asherson P, Wong IC. Management of adult attention deficit hyperactivity disorder in UK primary care: a survey of general practitioners. *Health Qual Life Outcomes*. 2013;11:22.
31. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong ICK. Persistence of pharmacological treatment into adulthood, in UK primary care, for ADHD patients who started treatment in childhood or adolescence. *BMC Psychiatry*. 2012;12:219-.
32. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. *BMC pediatrics*. 2012;12:78.
33. Digital N. Read Codeds. 2018.
34. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and drug safety*. 2009;18(1):76-83.
35. International Diabetes Federation. *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium. International Diabetes Federation. 2017.
36. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *British journal of clinical pharmacology*. 2017;83(9):2096-106.
37. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *American Journal of Health-System Pharmacy*. 2017;74(16):1237-44.



38. Gadsboll K, Staerk L, Fosbol EL, Sindet-Pedersen C, Gundlund A, Lip GYH, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *European heart journal*. 2017;38(12):899-906.
39. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine*. 2011;365(10):883-91.
40. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2011;365(11):981-92.
41. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2009;361(12):1139-51.
42. Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. *Journal of the American College of Cardiology*. 2013;61(22):2264-73.
43. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018;362.
44. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open heart*. 2016;3(1):e000279.
45. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London, England)*. 2014;383(9921):955-62.
46. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old? *Open heart*. 2018;5(1):e000712.
47. Fanning L, Ilomaki J, Bell JS, Darzins P. The representativeness of direct oral anticoagulant clinical trials to hospitalized patients with atrial fibrillation. *Eur J Clin Pharmacol*. 2017;73(11):1427-36.
48. Di Minno A, Frigerio B, Spadarella G, Ravani A, Sansaro D, Amato M, et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood reviews*. 2017;31(4):193-203.
49. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Therapeutics and Clinical Risk Management*. 2015;11:967-77.
50. Kimmel SE. Warfarin therapy: in need of improvement after all these years. *Expert opinion on pharmacotherapy*. 2008;9(5):677-86.
51. Tse G, Gong M, Li G, Wong SH, Wu WKK, Wong WT, et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol*. 2018;84(9):1868-82.
52. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-104.
53. Kjerpeseth LJ, Ellekjaer H, Selmer R, Ariansen I, Furu K, Skovlund E. Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. *Eur J Clin Pharmacol*. 2017;73(11):1417-25.

- 536 54. Scowcroft ACE, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in  
537 the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009.  
538 2013;99(2):127-32.  
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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.

view only

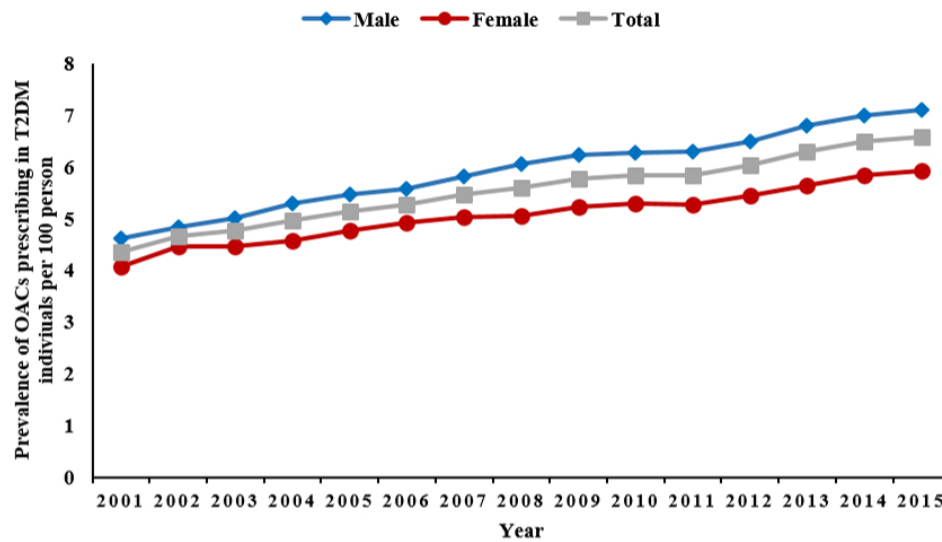


Figure 1: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by gender.

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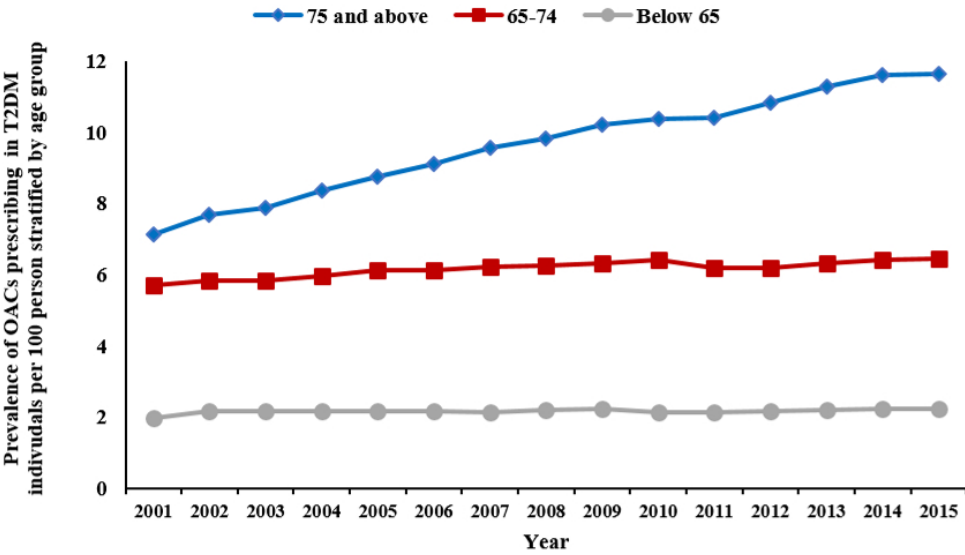


Figure 2: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by age.

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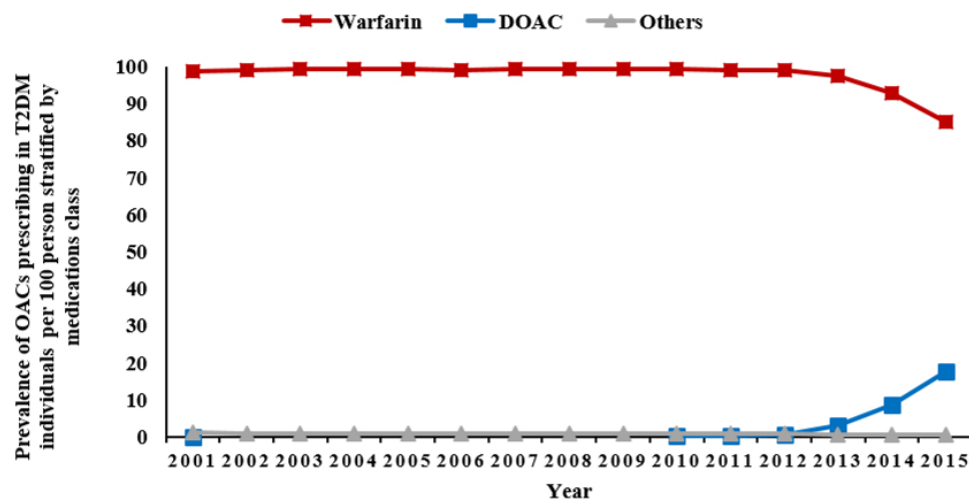


Figure 3: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by medications class.

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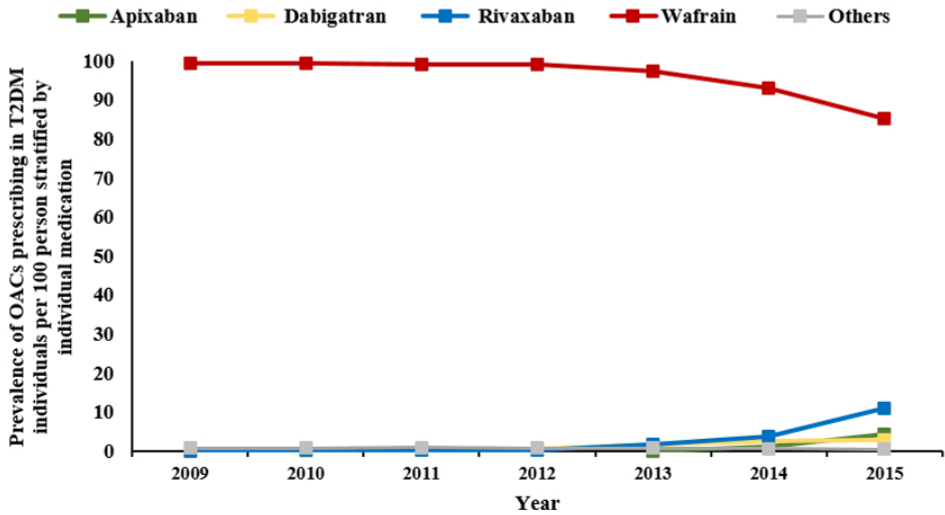


Figure 4: Prescribing prevalence of oral anticoagulant medications in individuals with T2DM stratified by individual medication.

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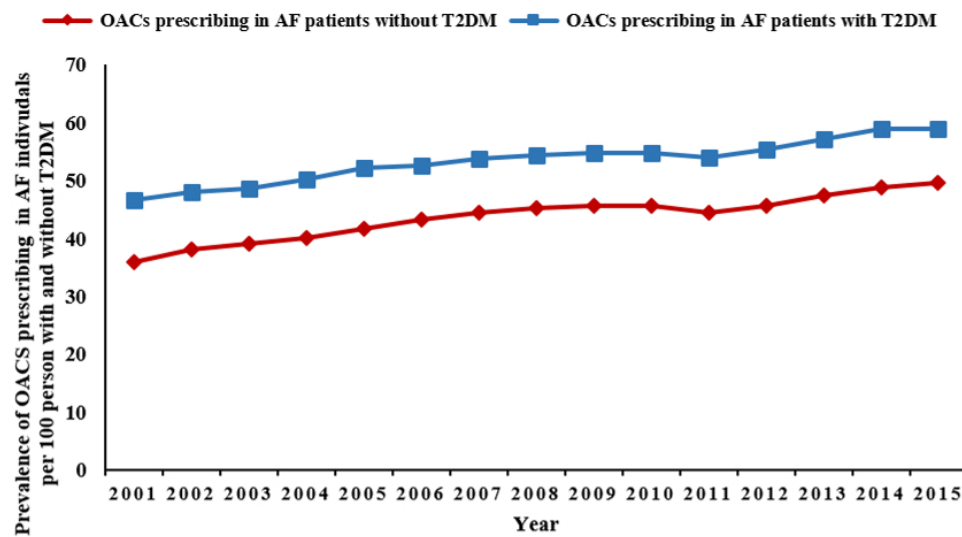


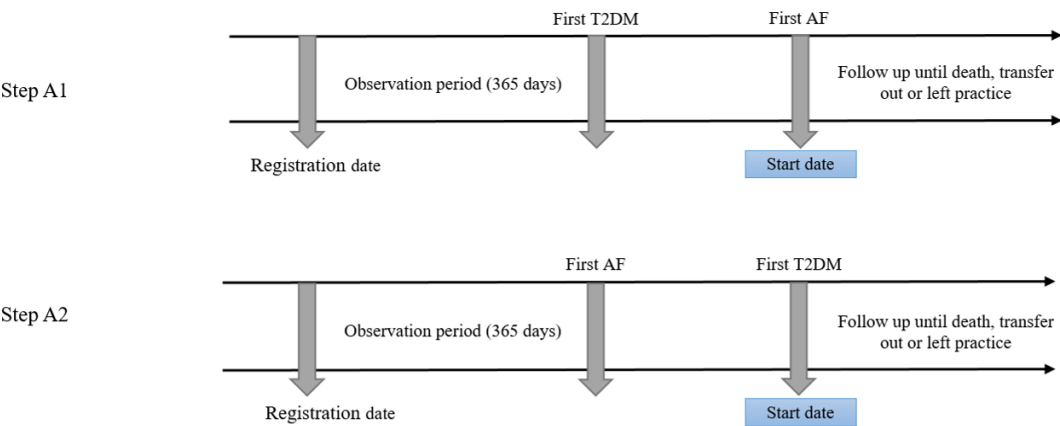
Figure 5: Prescribing prevalence of oral anticoagulant medications in AF individuals with and without T2DM

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Supplement:

Step A. The start date of individuals with AF and T2DM



Step B. The start date of individuals with AF and without T2DM

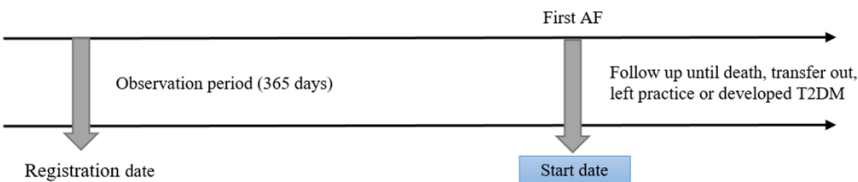


Figure S1. Methods to identify the study population of AF individuals with and without T2DM

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
<b>Discussion</b>				
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
<b>Other information</b>				
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](http://www.strobe-statement.org).