DECLARATION OF CONFLICT OF INTEREST
Warfarin and the risk of major bleeding events in patients with atrial fibrillation: a population-based study

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Declaration of interests

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All other co-authors have no conflicts of interest to declare.

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Patients with atrial fibrillation (AF) are at an increased risk of arterial thromboembolism and ischemic stroke

Warfarin therapy has been shown to significantly reduce the risk of such events

However, this therapy is associated with an increased risk of bleeding

The fear of such complications is one reason why warfarin is underutilized in the AF population
While a number of studies have investigated the risk of major bleeding events with warfarin, relatively few “real world” studies have been conducted.

Warfarin does its best in RCTs and closed health care system settings where most patients spend time in therapeutic range (INR 2-3).

In such settings, the risk of major bleeding events is likely underestimated.

Furthermore, few data exists on the relationship between therapeutic range and the incidence of major bleeding events.
OBJECTIVE

To quantify the association between warfarin anticoagulation, as determined by therapeutic range, and the risk of major bleeding events in patients newly diagnosed with chronic AF, in the natural setting of clinical practice
METHODS

DATA SOURCE: GENERAL PRACTICE RESEARCH DATABASE (GPRD)

- GPRD is a large primary care database from the UK
- Medical records for more than 9.9 million people enrolled in more than 545 general practices; representative of the UK population
- Prescriptions written by GPRD physicians are automatically transcribed into the computer record

STUDY POPULATION

- All patients, at least 18 years of age, diagnosed with a first ever diagnosis of AF between January 1, 1993 and December 31, 2008
- Cohort entry was defined as the date of the first AF diagnosis
METHODS

Exclusion criteria
- < 1 year of ‘up-to-standard’ medical history in the GPRD prior to diagnosis
- History of mitral or aortic valve repair or replacement prior to diagnosis
- Hyperthyroidism (either a diagnosis or treatment) prior to diagnosis

Follow-up
From date of AF diagnosis (cohort entry) until the first of the following events:
1. First diagnosis of ICH/GI bleeding event
2. Death from any cause
3. End of registration with the general practice
4. End of the study period (December 31, 2008)
METHODS

Study design: Cohort study using a nested-case control analysis

Case-control selection

- All patients diagnosed with an intracranial haemorrhage (ICH) or gastrointestinal bleed (GI) during follow-up (date of bleeding event = index date)

- Up to 10 controls were randomly selected from the case's risk set, after matching on year of birth, sex, date of cohort entry, and duration of follow-up

- By definition, all controls were still alive, never experienced an ICH/GI bleed during follow-up, and registered with their general practice when matched to a case
METHODS

Warfarin exposure definition

- A novel algorithm was created using elements from the Rosendaal et al (1993) and Go et al (2003) methodologies
- Incorporates both international normalized ratios (INR) and warfarin prescription information
- Simultaneously classifies each person-day of follow-up as either exposed or unexposed to warfarin, as well as in different levels of anticoagulation (below, within, above, and unknown therapeutic range)
METHODS

Exposure classifications at index date

Currently exposed to:

1) Warfarin monotherapy
2) Aspirin monotherapy
3) Other antiplatelet monotherapy (such as clopidogrel)
4) Combination therapies
5) Past use of any therapy (not current, but evidence of use in the year prior to index date)
6) No use of any antithrombotic therapy in the year prior to index date (reference category)

Warfarin monotherapy further classified according to therapeutic range at index date (below: INR < 2, within: 2 – 3, above: > 3, and unknown)
STATISTICAL ANALYSIS

- Descriptive statistics were used to summarize the characteristics of the cohort, cases and matched controls.

- Conditional logistic regression to estimate rate ratios (RR), along with 95% confidence intervals (CI).

- Models were conditioned on the matching variables and adjusted for relevant confounding factors:
  - Excessive alcohol use
  - Smoking status
  - Obesity
  - Peripheral artery disease
  - Myocardial infarction
  - Previous cancer
  - Prior bleeds
  - Thromboembolic disorders
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptor blockers
  - Antidepressants
  - Antipsychotics
  - NSAIDs
  - Statins
  - Congestive heart failure
  - Hypertension
  - Diabetes mellitus
  - History of stroke
RESULTS

Patients at least 18 years of age with at least one AF diagnosis during study period (January 1, 1993 to December 31, 2008) (n = 116,288)

Exclusions:
- AF diagnosis before cohort entry (n = 41,970)
- No follow-up data (n = 510)
- Date problems (n = 716)

Patients with incident AF (n = 73,092)

Exclusions:
- Indication of mitral or aortic valve repair/replacement (n = 1258)
- Hyperthyroidism (treatment or diagnosis) (n = 1068)

Study cohort (n = 70,766)
RESULTS

COHORT CHARACTERISTICS (n=70,766)

- Mean (SD) age: 74.1 (11.8) years
- Mean (SD) duration of follow-up: 3.9 (3.3) years
- 4101 patients had an ICH or GI bleed during 260,784 person-years of follow-up (overall rate: 15.7/1000 persons per year)
- 49% of the cohort members were exposed to warfarin at least once during follow-up
## RESULTS

Table 1. Selected characteristics of cases and controls at index date

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=4101)</th>
<th>Controls (40,791)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at index date, mean (SD)</td>
<td>76.4 (10.4)</td>
<td>76.4 (10.1)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>2179 (53.1)</td>
<td>21,672 (53.1)</td>
</tr>
<tr>
<td>Excessive alcohol use , n (%)</td>
<td>104 (2.5)</td>
<td>687 (1.7)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1980 (48.3)</td>
<td>19,160 (47.0)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1903 (46.4)</td>
<td>19,197 (47.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>218 (5.3)</td>
<td>2434 (6.0)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>1087 (26.5)</td>
<td>9569 (23.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2289 (55.8)</td>
<td>21,370 (52.4)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>386 (9.4)</td>
<td>3800 (9.3)</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>261 (6.4)</td>
<td>1846 (4.5)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>557 (13.6)</td>
<td>4949 (12.1)</td>
</tr>
<tr>
<td>Previous cancer, n (%)</td>
<td>997 (24.3)</td>
<td>7649 (18.8)</td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>558 (13.6)</td>
<td>4030 (9.9)</td>
</tr>
<tr>
<td>Antipsychotics, n (%)</td>
<td>275 (6.7)</td>
<td>2292 (5.6)</td>
</tr>
<tr>
<td>NSAIDs, n (%)</td>
<td>751 (18.3)</td>
<td>6075 (14.9)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>1347 (32.8)</td>
<td>12,747 (31.2)</td>
</tr>
</tbody>
</table>
# RESULTS

Table 2. Adjusted rate ratios of ICH and all GI bleeding events with warfarin and aspirin use

<table>
<thead>
<tr>
<th>No use of any antithrombotic therapy</th>
<th>Cases/Controls (4101/40,791)</th>
<th>Crude RR</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of warfarin monotherapy</td>
<td>1615/14,338</td>
<td>1.44</td>
<td>1.38 (1.24 - 1.54)</td>
</tr>
<tr>
<td>Below therapeutic range (INR: &lt; 2)</td>
<td>107/784</td>
<td>1.75</td>
<td>1.65 (1.32 - 2.06)</td>
</tr>
<tr>
<td>Within therapeutic range (INR: 2 – 3)</td>
<td>262/2339</td>
<td>1.45</td>
<td>1.39 (1.19 - 1.63)</td>
</tr>
<tr>
<td>Above therapeutic range (INR: &gt; 3)</td>
<td>97/410</td>
<td>3.06</td>
<td>2.96 (2.32 - 3.78)</td>
</tr>
<tr>
<td>Unknown anti-coagulation level</td>
<td>1149/10,805</td>
<td>1.36</td>
<td>1.31 (1.17 - 1.46)</td>
</tr>
<tr>
<td>Current use of aspirin monotherapy</td>
<td>743/8459</td>
<td>1.09</td>
<td>1.03 (0.92 - 1.16)</td>
</tr>
</tbody>
</table>

Abbreviations: RR: Rate ratio; CI: Confidence interval; INR: International normalized ratio.

*All models were adjusted for the following variables at index date: excessive alcohol use, smoking status, obesity, peripheral artery disease, myocardial infarction, previous cancer, prior bleeds, thromboembolic disorders, congestive heart failure, hypertension, diabetes, previous stroke/TIA, ACE inhibitor use, angiotensin II receptor blocker use, antidepressant use, antipsychotic use, NSAID use, and statin use.

Note: Current users of other antiplatelet therapies, combinations of treatments, as well as past users are not displayed in the Table, but were considered in the regression model.
# RESULTS

## Table 3. Adjusted rate ratios of ICH and upper GI bleeding events with warfarin and aspirin use

<table>
<thead>
<tr>
<th></th>
<th>Cases/Controls (1696/16,640)</th>
<th>Crude RR</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use of any antithrombotic therapy</td>
<td>223/2394</td>
<td>1.00</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Current use of warfarin monotherapy</td>
<td>422/3971</td>
<td>1.19</td>
<td>1.14 (0.94, 1.37)</td>
</tr>
<tr>
<td>Below therapeutic range (INR: &lt; 2)</td>
<td>32/194</td>
<td>1.86</td>
<td>1.75 (1.16, 2.64)</td>
</tr>
<tr>
<td>Within therapeutic range (INR: 2 – 3)</td>
<td>60/632</td>
<td>1.06</td>
<td>1.03 (0.75, 1.40)</td>
</tr>
<tr>
<td>Above therapeutic range (INR: &gt; 3)</td>
<td>33/101</td>
<td>3.67</td>
<td>3.45 (2.24, 5.31)</td>
</tr>
<tr>
<td>Unknown anti-coagulation level</td>
<td>297/3044</td>
<td>1.09</td>
<td>1.04 (0.86, 1.28)</td>
</tr>
<tr>
<td>Current use of aspirin monotherapy</td>
<td>345/4162</td>
<td>0.91</td>
<td>0.88 (0.73, 1.05)</td>
</tr>
</tbody>
</table>

Abbreviations: RR: Rate ratio; CI: Confidence interval; INR: International normalized ratio.

*All models were adjusted for the following variables at index date: excessive alcohol use, smoking status, obesity, peripheral artery disease, myocardial infarction, previous cancer, prior bleeds, thromboembolic disorders, congestive heart failure, hypertension, diabetes, previous stroke/TIA, ACE inhibitor use, angiotensin II receptor blocker use, antidepressant use, antipsychotic use, NSAID use, and statin use.

Note: Current users of other antiplatelet therapies, combinations of treatments, as well as past users are not displayed in the Table, but were considered in the regression model.
LIMITATIONS

- Not able to ascertain that all bleeding events were major

- Prescriptions in the GPRD represent those written by GPs, not those filled or used by patients

- GPRD does not capture prescriptions from specialists; misclassification biasing estimates towards the null

- Aspirin is available over-the-counter, misclassifying exposed patients as unexposed
Overall, warfarin was associated with an increased risk of ICH and GI bleeding events

No increased risk was observed with aspirin

Patients below and above therapeutic range were observed as having an increased risk of such major bleeding events

Additional analyses are ongoing to understand the increased risk in the low therapeutic population. It may be a reflection of patients who discontinued treatment and this is the post event INR

These results emphasize the importance and need to maintain patients with therapeutic range