Poor Quality of Warfarin Treatment Increases the Risk of All Types of Intracranial Hemorrhage in Atrial Fibrillation

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Background: Intracranial hemorrhage (ICH) is a devastating complication of oral anticoagulation. The aim of this study was to describe the spectrum of ICH and to evaluate the association of warfarin control with the risk of ICH in a nationwide cohort of unselected atrial fibrillation (AF) patients.

Methods and Results: The FinWAF is a retrospective registry-linkage study. Data were collected from several nationwide Finnish health-care registers and laboratory databases. The primary outcome was any ICH (traumatic or non-traumatic). The quality of warfarin therapy was assessed continuously by calculating the time in therapeutic range in a 60-day window (TTR60). Adjusted Cox proportional hazard models were used. A total of 53,953 patients were included (53% men; mean age, 73 years; mean follow-up, 2.94 years; mean TTR, 63%). In 129,684 patient-years, 1,196 patients had ICH (non-traumatic, 53.5%; traumatic, 43.6%; traumatic subdural, 38.6%); crude annual rate, 0.92%; 95% CI: 0.87–0.98). A lower TTR60 was significantly associated with higher risk of ICH (TTR60 ≤40% vs. TTR60 >80%; adjusted hazard ratio, 2.16; 95% CI: 1.83–2.54). Other variables independently associated with ICH included age >65 years, previous stroke, male sex, low hemoglobin, thrombocytopenia, elevated alanine aminotransferase, and previous bleeding other than ICH.

Conclusions: Poor control of warfarin treatment was associated with elevated risk of ICH. Approximately half of the ICH were traumatic, mainly subdural.

Key Words: Anticoagulation; Atrial fibrillation; Intracranial hemorrhage; Warfarin

Atrial fibrillation (AF) is an epidemic disease in the ageing population and a major cause of stroke. Oral anticoagulation (OAC) is the cornerstone of thrombosis prophylaxis in patients with AF. The main downside of OAC is the risk of serious bleeding complications, most devastatingly intracranial hemorrhage (ICH). Intracerebral hemorrhage has a >50% fatality rate and high morbidity, and OAC use is associated with a 7–10-fold elevated risk of intracerebral bleeding compared with those without OAC. In comparison to the incidence of ischemic stroke, however, intracerebral hemorrhage is so rare (annual incidence, 0.3–0.6) that despite the increased risk of major bleeding complications, OAC is recommended for most patients with AF. Little information is available on the incidence of different subtypes of OAC-related ICH in a real-world population. Most of the available data are related to intracerebral hemorrhage, which may account for 70% of all ICH. Subdural hematoma is the second most common OAC-related ICH, accounting for approximately 25–50% of all ICH and most of the traumatic ICH. The third common subtype of ICH is subarachnoid hemorrhage. In the case of head trauma, OAC increases the risk of ICH and makes it more difficult to manage.

The safety and efficacy of warfarin therapy is strongly associated with the quality of the regimen. The quality of warfarin treatment is commonly estimated by time in therapeutic range (TTR), in which an international normalized ratio (INR) between 2 and 3 is considered optimal for patients with non-valvular AF. High INR and labile INR increase the risk of bleeding complications. The association between patient-level TTR and the risk of ICH, however, is uncertain and poorly documented.

In the Finnish Atrial Fibrillation Cohort (FinWAF) study, several Finnish nationwide population registries and laboratory databases were linked to construct a large unselected cohort of AF patients with data on underlying diseases, individual INR, and other laboratory measurements. In the present study, we describe the incidence and
spectrum of ICH and provide novel information on the association between the quality of warfarin treatment and the risk of ICH.

Methods

The methods of the FinWAF study have been described in detail previously.28 In brief, FinWAF is a retrospective observational cohort study. Individual patient data from 7 Finnish population registries and 6 regional laboratory databases are linked by unique Finnish personal identification numbers (Supplementary Table 1). International Classification of Diseases, 10th revision (ICD-10) codes were used for defining comorbidities and ascertaining the causes of hospitalization or death (Supplementary Table 2). INR and other laboratory data were collected from the databases of the audited central laboratories that analyzed all the blood samples taken in their regions.

Subjects

Patients with AF diagnosis and warfarin purchase during 2005–2006 were defined as previous warfarin users, and those with the first warfarin purchase during 2007–2009 were defined as new warfarin users. All patients were required to have at least 1 INR measurement during 2007–2009. The cohort entry date (CED) was defined as the date of first warfarin purchase after 1 January 2007. The patients were excluded if they were <18 years of age at CED, had permanent residence outside Finland during the follow-up period, did not have valid INR measurements after the CED, or had been diagnosed with ICH prior to the CED.

Outcome, Exposure, and Other Potential Predictor Variables

The primary outcome was ICH of any kind. The ICH were divided into 3 groups: traumatic; non-traumatic; and ICH in multiple compartments with undetermined mechanisms (Supplementary Table 2). The patients were censored at the time of the first outcome event, death, or at the end of the study period (31 December 2011). Based on diagnosis codes used, hemorrhagic transformations of ischemic strokes were not included as ICH.

The main exposure was the quality of warfarin therapy measured by a continuous TTR in a 60-day window (TTR60) using the Rosendaal method (TTR60).28,29 In the new warfarin users, the first 7 days of treatment were excluded from the TTR calculations and analyses. The TTR was updated by calculation each day, based on the INR, and reported as the percentage of days the INR was in the therapeutic range (2.0–3.0) in the previous 60 days. Patients with only 1 INR measurement were included and contributed the 60 following days to analysis. If the gap between consecutive INR measurements was >60 days, the most recent INR was carried forward (Supplementary Figure). The robustness of the continuous TTR60 was verified in our previous study.28 In addition, we calculated summary TTR, that is, the TTR over the entire follow-up for patients with ≥2 INR measurements and recorded the INR closest to the ICH event for each patient.

Other potential confounding factors included well-established risk factors used to evaluate stroke risk (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke or transient ischemic attack [TIA], vascular disease, age 65–74 years, sex category; CHA2DS2-VASc). Previous bleeding diagnoses other than ICH, cancer diagnoses, and previous hospitalization for any cause were also included as potential predictors for ICH.12 Furthermore, selected laboratory data were collected from early 2007 to evaluate kidney (creatinine) and liver function (alanine aminotransferase; ALT), as well as anemia (hemoglobin; Hb) and thrombocytopenia (platelet count). The glomerular filtration rate defined by Chronic Kidney Disease Epidemiology Collaboration (GFR-EPI) was calculated according to Levey et al.30 First laboratory results during follow-up are listed in Supplementary Table 3.
Quality of Warfarin Control and Risk of ICH

Statistical Analysis

The data for baseline characteristics are presented as mean±SD for continuous variables and as percentage for categorical variables. The ICH subtypes are presented as absolute frequencies and percentages from the total. Crude event rates are given per 100 patient-years. The stratified incidence rates for the ICH subtypes were estimated in each time-dependent TTR60 category, and 95% confidence intervals (CIs) were derived by applying the Poisson assumption. Kaplan-Meier curves for the cumulative incidence of ICH were produced.

Multivariable Cox proportional hazards analysis was performed to identify the independent predictors for ICH. In this secondary analysis, time-dependent laboratory data from follow-up were also considered as potential predictors for ICH. The analysis was conducted separately for all, non-traumatic, and traumatic ICH with different TTR60. The baseline characteristics associated with excellent (summary TTR >80%) and with poor warfarin treatment quality (summary TTR ≤40%) were determined, using logistic regression. P<0.05 was considered statistically significant. R was used for data management and statistical analysis. All programs used in the analyses were validated and reviewed by a second statistician. In addition to approval by the Ethics Review Board of the Hospital District of Helsinki and Uusimaa, data permits were obtained from each of the registry holders, based on the study protocol and ethics approval.

Results

Descriptive Data

After exclusions, 53,953 patients remained eligible for the study (Figure 1). The total follow-up time was 158,541 patient-years, with a mean follow-up of 2.9±1.6 years. The baseline patient characteristics are listed in Table 1. The mean age was 73.1±10.8 years (47.5% female), and 50.7% were ≥75 years. Nearly all patients had Hb, platelet count, and creatinine plasma concentration measured at least once, whereas ALT was not measured during the follow-up in 14.0% of the patients. The mean number of INR measurements per patient was 49 (IQR, 17–79), and 2,489 patients had only 1 measurement. The mean number of INR measurements per follow-up year was 21.±26. Mean summary TTR was 63.±23% (median, 68%; IQR, 52–79). Continuous TTR60 analyses included 129,684 patient-years. Of these, 46% was spent on TTR60 >80%, while 20% of the follow-up time TTR60 was ≤40%. During patient years spent in TTR ≤40%, the INR was <2.0 for 53% of time, whereas in 22% of time the INR was >3.0.

Occurrence and Spectrum of ICH During Warfarin Therapy

During the follow-up, 1,196 patients had an ICH. Of these, 43.6% were traumatic, 53.5% non-traumatic, and 2.8% included multiple compartments with undetermined mechanism (Table 2). Traumatic subdural hematoma accounted for 38.6% of all ICH. The crude annual rate of all ICH was 0.92% (95% CI: 0.87–0.98).

Of the patients with an ICH, in 26% their last measured INR was <2.0, in 59% it was 2.0–3.0, and in 15% it was >3.0. The median for INR measured closest to the ICH occurrence was 2.3 (IQR, 1.9–2.8).

Risk Factors for ICH During Warfarin Therapy

The rate of ICH was highest in patients with TTR60 ≤40% and lowest in those with TTR60 >80%. This included the crude annual incidence per 100 patient-years of all ICH (1.35 vs. 0.62), as well as of non-traumatic (0.66 vs. 0.36) and traumatic (0.64 vs. 0.24), respectively (Table 3). Of

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Table 1. Baseline Subject Characteristics vs. Summary TTR in AF Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>&lt;40%</th>
<th>&gt;40–50%</th>
<th>&gt;50–60%</th>
<th>&gt;60–70%</th>
<th>&gt;70–80%</th>
<th>&gt;80%</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>53,953</td>
<td>7,812 (14.5)</td>
<td>4,111 (7.6)</td>
<td>6,289 (11.7)</td>
<td>9,689 (18.0)</td>
<td>11,685 (21.7)</td>
<td>11,530 (21.4)</td>
<td>2,837 (5.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean±SD</td>
<td>73±10.8</td>
<td>71.3±12.5</td>
<td>72.5±11.7</td>
<td>73.7±11.0</td>
<td>74.4±10.6</td>
<td>74.2±9.8</td>
<td>72.8±9.7</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>75 (66–81)</td>
<td>73 (63–81)</td>
<td>74 (64–81)</td>
<td>76 (66–82)</td>
<td>76 (68–82)</td>
<td>75 (68–81)</td>
<td>74 (67–80)</td>
<td>72 (62–79)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>11,465</td>
<td>2,245 (28.7)</td>
<td>1,059 (25.8)</td>
<td>1,358 (21.6)</td>
<td>1,746 (18.0)</td>
<td>1,940 (18.6)</td>
<td>2,263 (19.6)</td>
<td>854 (30.1)</td>
</tr>
<tr>
<td>65–74</td>
<td>15,146</td>
<td>1,973 (25.3)</td>
<td>1,000 (24.3)</td>
<td>1,557 (24.8)</td>
<td>2,522 (26.0)</td>
<td>3,463 (29.6)</td>
<td>3,851 (33.4)</td>
<td>780 (27.5)</td>
</tr>
<tr>
<td>≥75</td>
<td>27,342</td>
<td>3,594 (46.0)</td>
<td>2,052 (49.9)</td>
<td>3,374 (53.7)</td>
<td>5,421 (55.9)</td>
<td>6,282 (53.8)</td>
<td>5,416 (47.0)</td>
<td>2,103 (42.4)</td>
</tr>
<tr>
<td>Men</td>
<td>28,342</td>
<td>4,692 (60.1)</td>
<td>2,278 (55.4)</td>
<td>3,212 (51.1)</td>
<td>4,665 (48.2)</td>
<td>5,671 (48.5)</td>
<td>6,141 (53.3)</td>
<td>1,683 (59.3)</td>
</tr>
<tr>
<td>CHF</td>
<td>9,620</td>
<td>1,647 (21.1)</td>
<td>933 (22.7)</td>
<td>1,385 (22.0)</td>
<td>1,939 (20.0)</td>
<td>1,853 (15.9)</td>
<td>1,397 (12.1)</td>
<td>466 (16.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12,935</td>
<td>1,900 (24.3)</td>
<td>1,009 (24.5)</td>
<td>1,556 (24.7)</td>
<td>2,367 (24.4)</td>
<td>2,756 (23.6)</td>
<td>2,631 (22.8)</td>
<td>716 (25.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5,233</td>
<td>956 (12.2)</td>
<td>460 (11.2)</td>
<td>747 (11.9)</td>
<td>1,040 (10.7)</td>
<td>957 (8.2)</td>
<td>791 (6.9)</td>
<td>282 (9.9)</td>
</tr>
<tr>
<td>Ischemic stroke/TIA</td>
<td>6,463</td>
<td>823 (10.5)</td>
<td>444 (10.8)</td>
<td>798 (12.7)</td>
<td>1,235 (12.8)</td>
<td>1,442 (12.3)</td>
<td>1,365 (11.8)</td>
<td>356 (12.6)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>13,515</td>
<td>2,172 (27.8)</td>
<td>1,191 (29.0)</td>
<td>1,670 (26.6)</td>
<td>2,595 (26.8)</td>
<td>2,724 (23.3)</td>
<td>2,305 (20.0)</td>
<td>858 (30.2)</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>Mean±SD</td>
<td>2.8±1.7</td>
<td>2.6±1.8</td>
<td>2.78±1.8</td>
<td>2.92±1.8</td>
<td>2.97±1.7</td>
<td>2.84±1.6</td>
<td>2.60±1.6</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3 (2–4)</td>
<td>3 (1–4)</td>
<td>3 (1–4)</td>
<td>3 (1–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (1–4)</td>
<td>3 (1–4)</td>
</tr>
<tr>
<td>Bleeding diagnosis</td>
<td>2,213</td>
<td>456 (5.8)</td>
<td>227 (5.5)</td>
<td>291 (4.6)</td>
<td>399 (4.1)</td>
<td>428 (3.7)</td>
<td>300 (2.6)</td>
<td>112 (4.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>10,285</td>
<td>1,575 (20.2)</td>
<td>823 (20.0)</td>
<td>1,321 (21.0)</td>
<td>1,955 (20.2)</td>
<td>2,186 (18.7)</td>
<td>2,017 (17.5)</td>
<td>408 (14.4)</td>
</tr>
</tbody>
</table>

Data given as n (%), mean±SD or median (IQR). AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke or TIA, vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; INR, international normalized ratio; TIA, transient ischemic attack; summary TTR, time in therapeutic range calculated over whole follow-up for patients with ≥2 INR measurements.
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TTR >80% (OR, 1.42; 1.24–1.63, P<0.01) compared with those <65 years of age.

Discussion

The main finding of this nationwide population-based cohort study was that TTR measured continuously over a 60-day time window (TTR60) was inversely associated with the risk of both non-traumatic and traumatic ICH in patients with AF. This indicates that in warfarin-treated AF patients, the quality of anticoagulation treatment is critical with regards to the risk of ICH.

Quality of INR Control and Risk of ICH

Not only high INR, but also time spent out of the therapeutic range and labile INR increase the risk of bleeding complications in warfarin-treated patients. Knowledge of the incidence of ICH subtypes and of the association between the treatment quality – measured as TTR – and occurrence of major bleeding events, however, is limited. Several studies have demonstrated that time out of the therapeutic range (INR 2–3), considering both low and high values, is associated with increased risk of major bleeding events. Notably, in a recent meta-analysis of a heterogenic group of studies, 45% of the ICH occurred the non-traumatic and traumatic ICH, 37.5% and 42.0% occurred when the TTR60 was ≤50%, respectively. The cumulative incidence of ICH according to TTR60 level is shown in Figure 2.

On Cox regression analysis (Table 4), the risk of ICH was highest for TTR60 ≤40% and lowest for TTR60 >80% (reference group), adjusted hazard ratio 2.16 (95% CI: 1.83–2.54). Other factors associated with increased risk of ICH included more advanced age, male sex, previous stroke or TIA, Hb <100 g/L, platelet count <100 E9/L, and elevated ALT (>3-fold the upper reference value). In patients with non-traumatic ICH, the risk was associated with hypertension and prior bleeding episodes other than ICH, but not with male sex, Hb, or ALT. Prior bleeding was associated with a lower risk of traumatic ICH, and severe kidney dysfunction (GFR-EPI <30 mL/min/1.73 m²) was associated with an increased risk of traumatic ICH.

Factors Associated With Warfarin Treatment Quality

Poor warfarin control (TTR <40%) was associated with a history of congestive heart failure (OR, 1.50; 95% CI: 1.35–1.68, P<0.01), hypertension (OR, 1.18; 1.06–1.32, P<0.01), diabetes (OR, 1.31; 1.15–1.50, P<0.01), and prior diagnosis of cancer (OR, 1.34; 1.22–1.48, P<0.01). Patients 65–74 years of age had the highest probability of achieving TTR >80% (OR, 1.42; 1.24–1.63, P<0.01) compared with those <65 years of age.

<table>
<thead>
<tr>
<th>ICH type</th>
<th>Event rate per 100 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ICH</td>
<td>0.92 (0.87–0.98)</td>
</tr>
<tr>
<td>Non-traumatic</td>
<td>0.49 (0.46–0.53)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>0.40 (0.37–0.44)</td>
</tr>
<tr>
<td>Epidual</td>
<td>0.004 (0.002–0.009)</td>
</tr>
<tr>
<td>Subdural</td>
<td>0.36 (0.33–0.39)</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>0.03 (0.02–0.04)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0.008 (0.005–0.02)</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>0.005 (0.002–0.01)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ICH, intracranial hemorrhage.

Table 2. ICH Number and Incidence Rate vs. Type

<table>
<thead>
<tr>
<th>ICH type</th>
<th>Event, n (%)</th>
<th>Event rate per 100 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ICH</td>
<td>1,196 (100)</td>
<td>0.92 (0.87–0.98)</td>
</tr>
<tr>
<td>Non-traumatic</td>
<td>640 (53.5)</td>
<td>0.49 (0.46–0.53)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>522 (43.6)</td>
<td>0.40 (0.37–0.44)</td>
</tr>
<tr>
<td>Epidual</td>
<td>5 (0.4)</td>
<td>0.004 (0.002–0.009)</td>
</tr>
<tr>
<td>Subdural</td>
<td>462 (38.6)</td>
<td>0.36 (0.33–0.39)</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>38 (3.2)</td>
<td>0.03 (0.02–0.04)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>11 (0.9)</td>
<td>0.008 (0.005–0.02)</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>6 (0.5)</td>
<td>0.005 (0.002–0.01)</td>
</tr>
<tr>
<td>Multiple compartments, undetermined mechanism</td>
<td>34 (2.8)</td>
<td>0.03 (0.02–0.04)</td>
</tr>
</tbody>
</table>

TTR60, continuously calculated time in the therapeutic range (INR, 2.0–3.0) during the previous 60 days. Other abbreviations as in Tables 1, 2.
Quality of Warfarin Control and Risk of ICH

TTR reduced the risk of major bleeding by 1 event per 100 patient-years.\textsuperscript{21}

In the FinWAF study, we used time-dependent TTR60 as a TTR measurement. The clear consensus about the optimal length of time-window for TTR assessment is lacking. In our previous study we demonstrated that risk of stroke, cardiovascular mortality, and all-cause mortality decreased as time-dependent TTR improved, regardless of the TTR timespan definition.\textsuperscript{28} We consider TTR60 as a promising tool for clinical practice. Based on our novel results, it seems to perform well also as a marker for when the INR was <2.0.\textsuperscript{32} In the present cohort, only 15% of the last measured INR prior to the ICH were >3.

In the present study, the risk of non-traumatic and of traumatic ICH was almost 2-fold and >2.5-fold higher, respectively, when TTR60 was \leq 40\% than when it was >80\%. Accordingly, a recent study in Sweden showed that the risk of ICH was higher in patients with TTR \leq 70\% than in those with TTR \geq 70\%.\textsuperscript{27} In a study in China, the patients in the worst quartile of their warfarin control had an ICH incidence almost twice as high as those in the best quartile.\textsuperscript{26} And in a systematic review, a 7\% increase in

Figure 2. Kaplan-Meier cumulative incidence of intracranial hemorrhage (ICH) according to continuously calculated time in the therapeutic range (international normalized ratio, 2.0–3.0) during the previous 60 days (TTR60) for (A) all ICH; (B) non-traumatic ICH; and (C) traumatic ICH.
increased risk of ICH and as a signal to re-evaluate the patient’s care. External validation, however, is needed.

The Japanese guidelines for therapeutic INR range for AF patients on warfarin differ from the European guidelines. In particular, target range for patients aged >70 years is lower, 1.6–2.6, to reduce the risk of hemorrhage. Nevertheless, a recent Japanese study and the guidelines of the Japanese Circulation Society present TTR as a tool for warfarin quality control also in Japan, with both target levels 2–3 and 1.6–2.6. Lately, a meta-analysis demonstrated that the risk of major bleeding in East Asian patients increased significantly when INR was >3.0, whereas the benefit of targeting INR 1.5–2.5 instead of 2.0–3.0 was not as evident. In the light of these studies, we assume that although the target INR range varies, the TTR60 would be applicable also for the Japanese patients.

Incidence and Spectrum of ICH in Warfarin-Treated AF

In comparison with some previous studies, the present overall ICH rate seems relatively high. In many prior studies, however, only the incidence of non-traumatic ICH or intracerebral hemorrhage was reported. For example, in recent registry studies in Sweden, using the same diagnosis codes as the present study, the rates of ICH were lower than in the present study (0.37–0.44 vs. 0.92), but they did not report non-traumatic and traumatic ICH separately. The present rate of non-traumatic ICH (0.49) is in accordance with the rates of 0.3–0.6 recently reported for these events, and in the range 0.51–0.85 reported for the non-vitamin K antagonist oral anticoagulant (NOAC) trials. The present high overall incidence of ICH may have been due to the wide inclusion criteria used, including traumatic bleeding. Furthermore, the diagnosis codes and definitions of traumatic etiology used may have varied.

Clinical Variables, Laboratory Parameters and Risk of ICH

The present findings add to the existing evidence of age, previous stroke, and hypertension as risk factors for intracerebral bleeding. Interestingly, the risk of traumatic ICH was >6-fold higher in patients with elevated ALT (>3-fold the upper reference value) than in those with normal ALT. Liver disease is recognized as a major bleeding risk factor, and cirrhosis is an independent risk factor for intra-
cranial bleeding. Moreover, liver disease exacerbates coagulopathy with changes in both the prothrombotic and anti-thrombotic state, including platelet dysfunction and thrombocytopenia. Anemia is common in elderly people. It reflects underlying morbidities, but is also linked with aging itself. We observed an inverse association with decreased Hb and ICH risk in AF patients on warfarin, corresponding to previous findings. Several mechanisms (e.g., increased risk of falls) may explain the link between anemia and ICH. The current guidelines for AF encourage clinicians to monitor and treat anemia, and the present findings support this effort.

Limitations and Strengths
This study had several limitations and strengths. The data were retrospectively collected from administrative registries that were not created for research purposes. Hence, no data on smoking, alcohol consumption, dietary habits, or use of over-the-counter drugs (e.g., aspirin and other nonsteroidal anti-inflammatory drugs) were available. Some less severe diagnoses may also have been underreported. For example, only 25% of the cohort had registry-based diagnosis of hypertension. Likewise, we cannot rule out selection bias, because only patients with warfarin prescribed were included. Due to study design, we could not control factors associated with the decision to initiate or withhold warfarin treatment. Unfortunately, we could not include NOAC in the present study, because they were little used during the study period. Nevertheless, the population examined was large and the ICH diagnosis highly reliable, given that ICH virtually always leads to hospital admission and is verified on neuroimaging or autopsy, even if occurring outside the hospital. In the FinWAF study, the patient population was truly unselected, and the laboratory data reflected all levels of patient care.

Conclusions
The quality of warfarin control is associated with the risk of ICH, and poor quality of the warfarin regimen negates the benefits of OAC by increasing the risk of ICH. Patients with TTR60 >80% had lower risk of ICH than even patients with TTR60 70–80%, which emphasizes targeting of the best achievable level of warfarin therapy. The results for non-traumatic and for traumatic ICH were similar.

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Disclosures
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References


**Supplementary Files**