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Associations of anaemia with bleeding and thrombotic complications in patients with atrial fibrillation treated with warfarin: a registry-based nested case–control study

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ABSTRACT

Objectives We studied association of laboratory testing beyond the international normalised ratio (INR) with bleeding and stroke/transient ischaemic attack (TIA) outcomes in patients with atrial fibrillation treated with warfarin.

Design This was a retrospective nested case–control study from the Finnish Warfarin in Atrial Fibrillation (FinWAF) registry (n=54 568), reporting the management and outcome in warfarin-anticoagulated patients. Associations of blood count test frequency and results were assessed together with risk of bleeding or stroke/TIA during 5-year follow-up.

Setting National FinWAF registry, with data from all six hospital districts. Follow-up period for complications was 1 January 2007–31 December 2011.

Participants A total of 54 568 warfarin-anticoagulated patients.

Results The number of patients with bleeding was 4681 (9%) and stroke/TIA episodes, 4692 (9%). In patients with bleeds, lower haemoglobin (within 3 months) preceded the event compared with the controls (median 126 vs 135 g/L; IQR 111–141 g/L vs 123–147 g/L, p<0.001), while patients with stroke/TIA had only modestly lower INR (median 2.2 vs 2.3; 1.8–2.6 vs 2.1–2.7, p<0.001). When the last measured haemoglobin was below the reference value (130 g/L for men, 120 g/L for women), the OR for a bleeding complication was 2.9 and stroke/TIA, 1.5. If the haemoglobin level was below 100 g/L, the complication risk increased further by 10-fold. If haemoglobin values were repeatedly (more than five times) low during the preceding 3 months, future OR was for bleeds 2.3 and for stroke/TIA 2.4.

Conclusions The deeper the anaemia, the higher the risk of bleeding and stroke/TIA. However, INR remained mainly at its target and only occasionally deviated, failing to detect the complication risk. Repeated low haemoglobin results, compatible with persistent anaemia, refer to suboptimal management and increased the complication risk in anticoagulated patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The strength of the study was the inclusion of a large number of patients (n=54 568), enabling a nested case–control design with three age-matched and gender-matched controls.
⇒ The large number of patients enabled assessment of bleeding and stroke/transient ischaemic attack outcomes as separate cohorts.
⇒ The retrospective nature of the study limits the opportunity to assess the effects of interventions (eg, increasing blood count measurements).

INTRODUCTION

Since atrial fibrillation (AF) predisposes to stroke, oral anticoagulation (OAC) is recommended in most patients with AF. In clinical practice, the decision to start anticoagulation is based on the CHA_2DS_2-VASc risk score (**C**ongestive heart failure; **H**ypertension, **A**ge ≥75 years (2 points); **D**iabetes mellitus; Prior **S**troke or transient ischaemic attack (TIA) (2 points); **V**ascular disease; **A**ge 65–74 years; Female **S**ex **c**ategory), the score >1 indicating anticoagulation in men and >2 in women.[1] According to the current guidelines, the use of direct oral anticoagulants (DOACs) rather than vitamin K antagonists is recommended to prevent thromboembolic complications in patients with non-valvular AF.[1] The benefits of the DOACs include, for example, less interactions with food and other drugs and no need for routine coagulation monitoring with international normalised ratio (INR). Nevertheless, warfarin is still the only oral anticoagulant for patients with mechanical heart valve or severe mitral stenosis and patients with antiphospholipid antibody syndrome.[2]

It is well-known that anaemia, as well as other risk factors, such as increased blood pressure, decreased renal function, previous bleeds, smoking, sleep apnoea and concomitant use of antiplatelet agents, increase the risk of bleeding in patients using OAC.[3]

Low haemoglobin (Hgb) count is associated with many illnesses and increased mortality.[4] Moreover, it has also been shown that periodical checks of Hgb and total blood count can be used to screen for occult malignancy.[5] Anaemia also predisposes anticoagulated patients with AF to thromboembolic complications.[3] Hence, Hgb, blood cell counts, including red blood cells and platelets, as well as liver and kidney function, need regular follow-up to safely manage anticoagulated patients.[2]

Current AF management guidelines recommend assessment of the bleeding risk using the HAS-BLED score.[1] A potential problem with the HAS-BLED score is that unlike in some other risk scores, anaemia is not included in the risk stratification scheme.[6] The incidence of anaemia among elderly people is 4–11%,[7] and approximately 15% of patients using warfarin have low Hgb.[7 8] Despite the clear correlation with Hgb and mortality, Hgb levels are only occasionally and infrequently measured or followed up during OAC therapy. Moreover, often no attempt to explore the aetiology of anaemia is performed, if Hgb level is above 100 g/L.[7–9]

We aimed to study the frequency of anaemia, kidney and liver function assessment, their results and impact on complication risks among unselected warfarin-anticoagulated patients. We assessed the frequency of Hgb and kidney and liver function measurements and their results preceding bleeding and thromboembolic complications (stroke or TIA) in patients with AF using warfarin for stroke prevention in a large nationwide cohort in Finland. The patients with and without (controls) these complications were compared. The impact of laboratory testing and abnormal values and the adverse outcome are reported.

PATIENTS AND METHODS

This study was based on the nationwide Finnish Warfarin in Atrial Fibrillation (FinWAF) registry, which incorporated data from the Finnish Care Registry, Finnish Institutional Care Registry, Finnish Cancer Registry, Finnish National Prescription Register, laboratory databases from six Finnish hospital districts, the Finnish National Cause of Death Registry and Finnish Population Registry. Diagnosis of bleeding episodes or stroke was based on imaging, laboratory and clinical assessments, i.e International Classification of Diseases (ICD) diagnoses . The FinWAF registry has been described in more detail in previous publications.[10–13] The total number of patients included in our study was 54 568.

The current study was a retrospective nested case–control study. Cases were defined according to the first event of stroke/TIA or bleeding event in the follow-up period (1 January 2007–31 December 2011). We selected the controls without the index event from the entire cohort, and three control patients for each affected case were matched according to sex and birth year. The ICD-10 codes for bleeding included D68.3, I60–I62, J942, K221, K223, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K274, K276, K280, K282, K284, K286, K290, K631, K633, K920–K922, R04, R31, S064–S066 and S068. The ICD-10 codes for stroke/TIA included I63, I64 and G45.[10] We assessed the number of laboratory tests within the 3 months prior to the index event and provided the values of the last available test results for a given patient prior to the event, or in the controls, the end of follow-up. If a laboratory test was not obtained within 3 months prior to the event, the value was recorded as not available.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this study.

RESULTS

The number of patients with bleeding outcomes was 4681 (9%), and the number of matched controls without bleeding events was 14 042. The bleeding events were more common among men (60%, p<0.001). The number of patients with stroke/TIA was 4692 (9%), and the number of matched controls without stoke/TIA was 14 063. In contrast to the bleeding events, the stroke/TIA events were more common among women (54%, p<0.001). A summary table with laboratory test results in the whole cohort, and bleeder and stroke/TIA cases is shown in table 1.

The Hgb measurement within 3 months prior to the event was associated with later increased risk of bleeding and stroke/TIA, and the risk was higher if more than five measurements were performed in the preceding months (figures 1 and 2). Also, when examining leucocytes, alanine aminotransferase and creatinine, more frequent blood sampling preceded the risk of later bleeding and stroke/TIA (figures 1 and 2). The incidence of bleeding complication or stroke/TIA was higher if the Hgb had been measured during weekend days of Saturday or Sunday, that is, on-call hours, compared with an Hgb testing on weekdays.

A comparison of laboratory test results between cases and controls for both bleeding and stroke/TIA is shown in figure 3 and online supplemental table 1. Among cases with a bleeding complication, the preceding Hgb level was lower, and the creatinine level was higher than in the controls. These results did not differ when the stroke/TIA was analysed (figure 3 and online supplemental tables 2 and 3). On the other hand, the patients with stroke/TIA had lower INR than controls (figure 3), although the median INR remained in the therapeutic range (INR 2.0–3.0). The proportion of patients with any laboratory tests measured within 3 months prior to the outcome was between 48% and 61% in the bleeding cases, but 30–33% in the controls. In contrast, among patients with later stroke/TIA, only 55–56% had INR measured within the 3 months preceding the event (online supplemental table 1).

The frequency of Hgb measurements exceeding five time points within the 3-month period prior to the event was associated with an adverse event in the near future

Table 1 Summary data of the laboratory assessments of the entire cohort (n=54 568), for patients with bleeding complication (n=4681) and patients with stroke/TIA complication (n=4692)

	All	Bleeding cases	Bleeding controls	Stroke/TIA cases	Stroke/TIA controls
Patients, n	54 568	4681	14 042	4692	14 063
Women, n (%)	25 846 (47)	1893 (40)**	5679 (40)**	2557 (54)**	7665 (54)
Age, years, median (IQR)	77 (66–84)	78 (67–85)	78 (68–83)	77 (66–85)	77 (67–84)
INR, number of valid results (%)	32 553 (60)	2886 (62)*	7962 (57)**	2680 (57)**	7889 (56)**
INR, median (IQR)	2.3 (2.0–2.7)	2.4 (1.9–2.8)	2.4 (2.1–2.7)	2.2 (1.8–2.6)**	2.4 (2.1–2.7)
Blood count, number of valid results (%)	22 159 (41)	2336 (50)**	5055 (36)**	2115 (45)**	5035 (36)**
Haemoglobin, median (IQR) (g/L)	133 (121–145)	126 (111–141)**	135 (123–147)	132 (118–144)	133 (122–145)
Platelet count, median (IQR) ($\times 10^9$/L)	227 (175–263)	209 (169–264)	210 (172–256)	216 (177–271)	215 (175–261)
Leucocyte count, median (IQR) ($\times 10^9$/L)	6.5 (5.3–8.0)	6.8 (5.4–8.5)	6.3 (5.2–7.8)	6.8 (5.5–8.3)	6.3 (5.2–7.8)
Creatinine, number of valid results (%)	21 757 (40)	2252 (48)**	4900 (35)**	2087 (44)**	4809 (34)**
Creatinine, median (IQR) (µmol/L)	85 (71–105)	88 (72–118)**	86 (72–104)	84 (69–104)	84 (70–103)
ALT, number of valid results (%)	13 401 (25)	1308 (28)**	2766 (20)**	1116 (24)	2644 (19)**
ALT, median (IQR) (U/L)	22 (16–31)	20 (15–31)	22 (16–31)	21 (15–29)	21 (16–30)

*P<0.05, **p<0.001 (Mann-Whitney U test for medians, exact binomial test for frequencies between the entire cohort and patients with bleeding or stroke/TIA and controls).
ALT, alanine aminotransferase; INR, international normalised ratio; TIA, transient ischaemic attack.

(figures 1 and 2). The OR of frequent measures (over 5) was 2.3 (95% CI 2.2 to 2.5) for bleeding events and 2.4 (95% CI 2.1 to 2.4) for stroke/TIA compared with maximum 5 (0–5) measurements.

When the last measured Hgb level was below the low reference value (130 g/L for men, 120 g/L for women) before the time of the adverse outcome, the OR for bleeding event was 2.9 (95% CI 2.8 to 3.0), while for stroke/TIA, the OR was 1.7 (95% CI 1.6 to 1.8). Strikingly, the Hgb level below 100 g/L further emphasised the complication risk, with the risk increase of 10-fold (95% CI 7.8 to 12.3) for both bleeding and 3-fold for stroke/TIA (95% CI 2.3 to 4.0). Similarly, the last measured leucocyte level of over 10.0×10^9/L was associated with a fourfold increase (95% CI 3.0 to 4.3) in the risk of a bleed and threefold (95% CI 2.3 to 3.4) risk of stroke/TIA (figures 1 and 2). Platelet count did not associate with the future complication risk.

During the previous year of the event, in patients with stroke outcome, the number of routine Hgb measurements did not differ, median 2.0 in both patients who had a stroke and controls, with corresponding IQRs of 0–6 and 0–5, respectively. During the year prior to the event, patients with bleeding outcome had a median of 3.0 Hgb measurements (IQR 0–7), while the median was 2.0 measurements (IQR 0–5) in the controls (p<0.001).

DISCUSSION

In our large retrospective case–control study of over 54 000 patients with AF, we found that Hgb levels during the 3-month period prior to bleeding outcome were significantly lower in bleeders than in controls. In addition, the lowering of the Hgb occurred during the period of repeated observations, compatible with persisting anaemia. Anaemia predisposes to bleeds due to impaired primary haemostasis and may diminish physiological red blood cell-mediated thrombin generation.[14–16] Most people with anaemia do not bleed overtly, even while on OAC, but continued occult bleeding consumes iron and haemoglobin. However, the reserve of the red cells is unavailable upon an emergent bleeding event, and anaemia in anticoagulated patients exposes them not only to bleeding events, but also to stroke and mortality.[17] In our study, preceding anaemia was also associated with future stroke/TIA. Therefore, active resolution of diagnosing iron deficiency or a possible other cause of anaemia is critical in anticoagulated patients, especially the vulnerable elderly population with AF, who also carry renal and cardiac impairment and multiple drug interactions.

Risk scores provide a practical tool for assessing bleeding risk in patients with AF. Lifetime risk of bleeding in anticoagulated patients with AF is 50% among those with HAS-BLED or HEMORR$_2$HAGES score of 2 or more.[18] In a previous study from our dataset, male gender was associated with higher risk of bleeding.[12] It is clearly prudent to assess the bleeding risk with laboratory studies, including blood cell count and creatinine for all anticoagulated patients. Indeed, the increased risk for both low Hgb and high creatinine values for bleeding, as observed in our study, is a relevant addition to the established risk scores, paralleling the previous reports on DOACs,[3 19] and was associated with intracranial haemorrhage in our previous study.[13] Detection and management of the commonly occurring iron deficiency due to dietary and absorption defects, and ruling out continued bleeding and malignancy particularly in the gastrointestinal tract, are clinically important and preventive approaches among these vulnerable elderly patients. Higher creatinine levels and

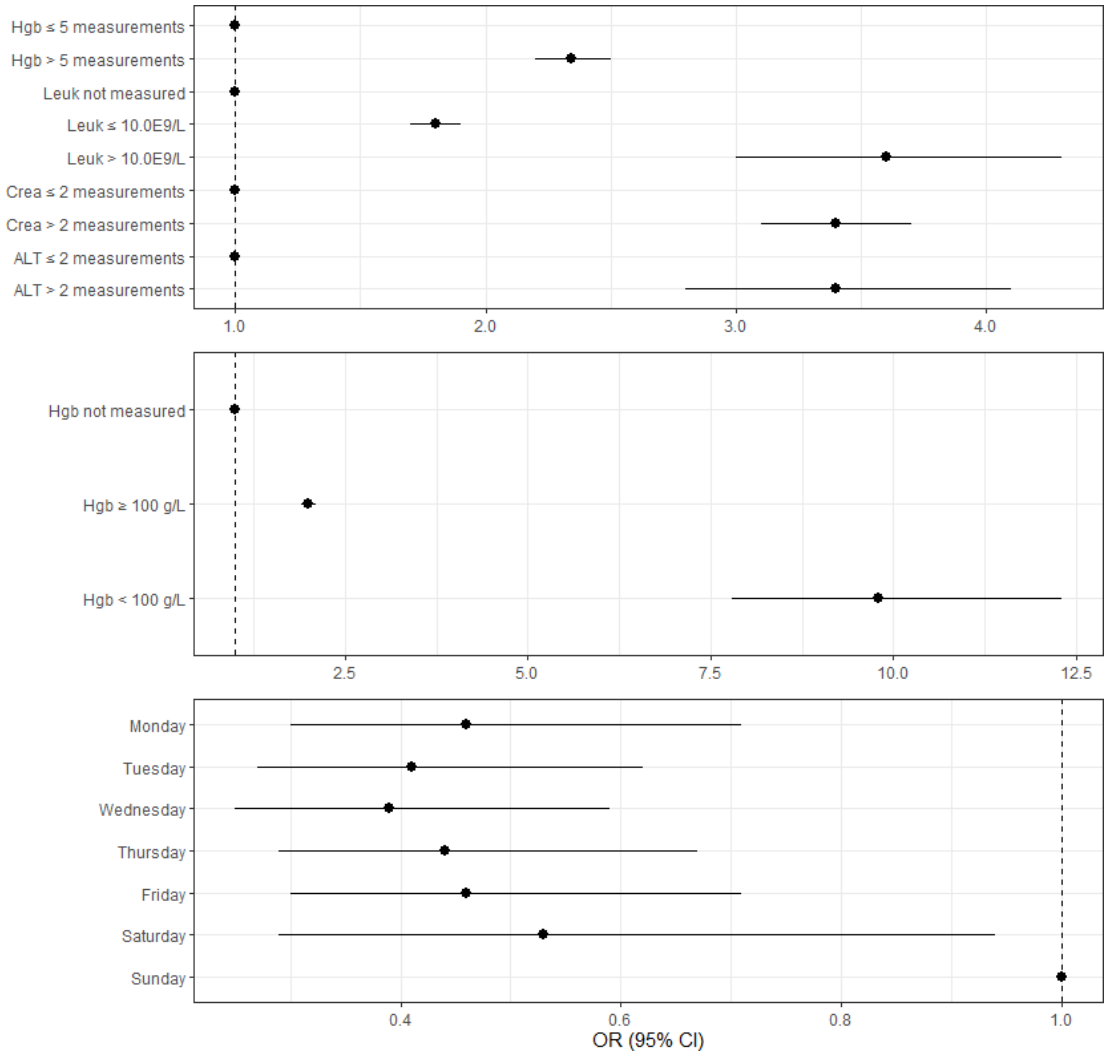

Figure 1 Laboratory measurements and the OR for bleeding events, with 95% CIs. Only statistically significant results are shown. The OR 1.0 of reference group is depicted with a dashed line. The number of cases and controls, and more detailed results in each group are provided in the online supplemental table 1. ALT, alanine aminotransferase; Crea, creatinine; Hgb, haemoglobin; Leuk, leucocytes.

lower creatinine clearance (below 30 mL/min), concordant with lowered erythropoietin levels, have also been shown to independently associate with anaemia in the elderly (over the age of 65 years).[20] In our study, higher creatinine values and lower Hgb values were observed among the patients who developed a major bleed when compared with controls. Yet, in bleeders, Hgb, when measured frequently, often during an emergency visit at on-call hours or weekends, suggests that management of anaemia had not succeeded.

For stroke/TIA risk, CHA_2DS_2-VASc score is recommended as the screening tool on whether to start anticoagulation on a given patient (European Society of Cardiology 2021). The score also predicts thrombotic events in patients while anticoagulated with warfarin.[21] However, many of these same variables are also common alerting for a bleeding risk. In our study, the incidence of stroke/TIA was as high as the incidence of major bleeding, and both enhanced up to 3-fold to 10-fold if Hgb values maintained at a level of 100 g/L or less.

Both bleeding and stroke/TIA risks were associated with low time in therapeutic range in this cohort.[10] In the present study, notably, INR had not been monitored in up to 44% of both stroke/TIA cases during the 3-month period leading to the event. This is critical as INR taken on the day of the stroke/TIA was also included in these analyses. This management defect differs markedly from, for example, the carefully controlled dabigatran RE-LY trial, where INR was measured on average 1.5 times monthly in Northern European countries, with a maximum of 4 weeks allowed between INR measurements in the study protocol.[22] Adequate INR and Hgb controls are crucial, as low Hgb also increased risk of stroke/TIA. Our cohort is consistent with previous reports, where 15–29% of patients who had a stroke had anaemia.[23] This may be related to iron deficiency and its potentially thrombogenic effects, which have been well described even in children.[24] Iron deficiency may align with concomitant thrombocytosis, and anaemia-induced hypoxia causes endothelial dysfunction and von Willebrand factor

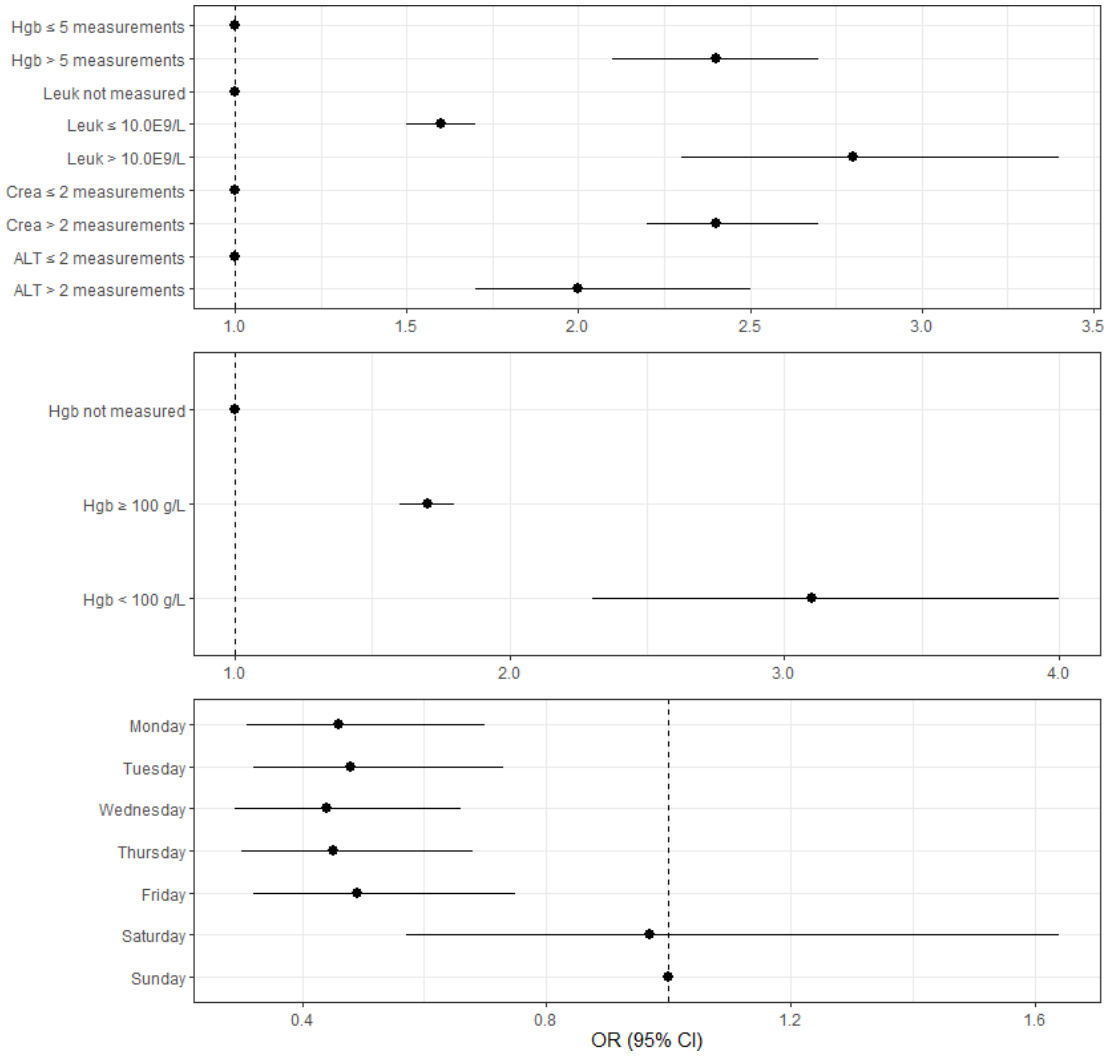

Figure 2 Laboratory measurements and the OR for stroke/TIA events, with 95% CIs. Only statistically significant results are shown. The OR 1.0 of reference group is depicted with a dashed line. The number of cases and controls, and more detailed results in each group are provided in the online supplemental table 2. ALT, alanine aminotransferase; Crea, creatinine; Hgb, haemoglobin; Leuk, leucocytes; TIA, transient ischaemic attack.

release, contributing to organ dysfunction and thrombosis.[25 26] Concordantly, pre-existing anaemia also worsens the outcome after ischaemic stroke.[27]

A bleeding event during anticoagulation therapy is a major risk factor for further bleeds and morbidity. In a study including 17 000 consecutive patients with venous thromboembolism, 2% experienced a major bleed.[28] Of these patients, 38% died within 30 days, 7% had major rebleeding and 19% fatal bleeding. Anaemia had a clear association with major bleeding, and 40–65% of the bleeders had preceding anaemia, compared with 33% of non-bleeders.[28] Bleeding risk-prone persons include patients with AF, and age above 80 years, of whom up to 40% have prevalent anaemia and iron deficiency.[29] Among warfarin-anticoagulated patients, 3% experienced a clinically relevant bleed, but only 0.3% had a major bleed during 47-month observation.[9] In our study, when Hgb was measured and resided below normal range, the risk of bleeding tripled. The bleeding risk further increased 10-fold if Hgb was below 100 g/L. It is evident that with these Hgb levels, corrective action is needed to manage this significant risk factor. The risk was highest when testing was done during the weekend, reflecting the emergency room visits of these patients, coinciding with a vulnerable clinical period in the following weeks.

Both bleeding and stroke/TIA had strong association with sample collection frequency, reflecting the quality of follow-up procedures (figures 1 and 2). Proactive laboratory testing is targeted to timely manage interventions and diminish risks of anticoagulation-associated complications. Testing itself is not sufficient; in a recent study, patients who had a laboratory test done had decreased 3-year survival, reflecting lack of appropriate interventions.[30] Selection bias may also play a role, since sicker patients frequently have tests ordered at unconventional hours or days in acutely ill patients. In our study, the weekends seem to reflect this scenario.

The limitations of our study include the retrospective observational nature and lack of data on the possible interventions after abnormal laboratory results. Due

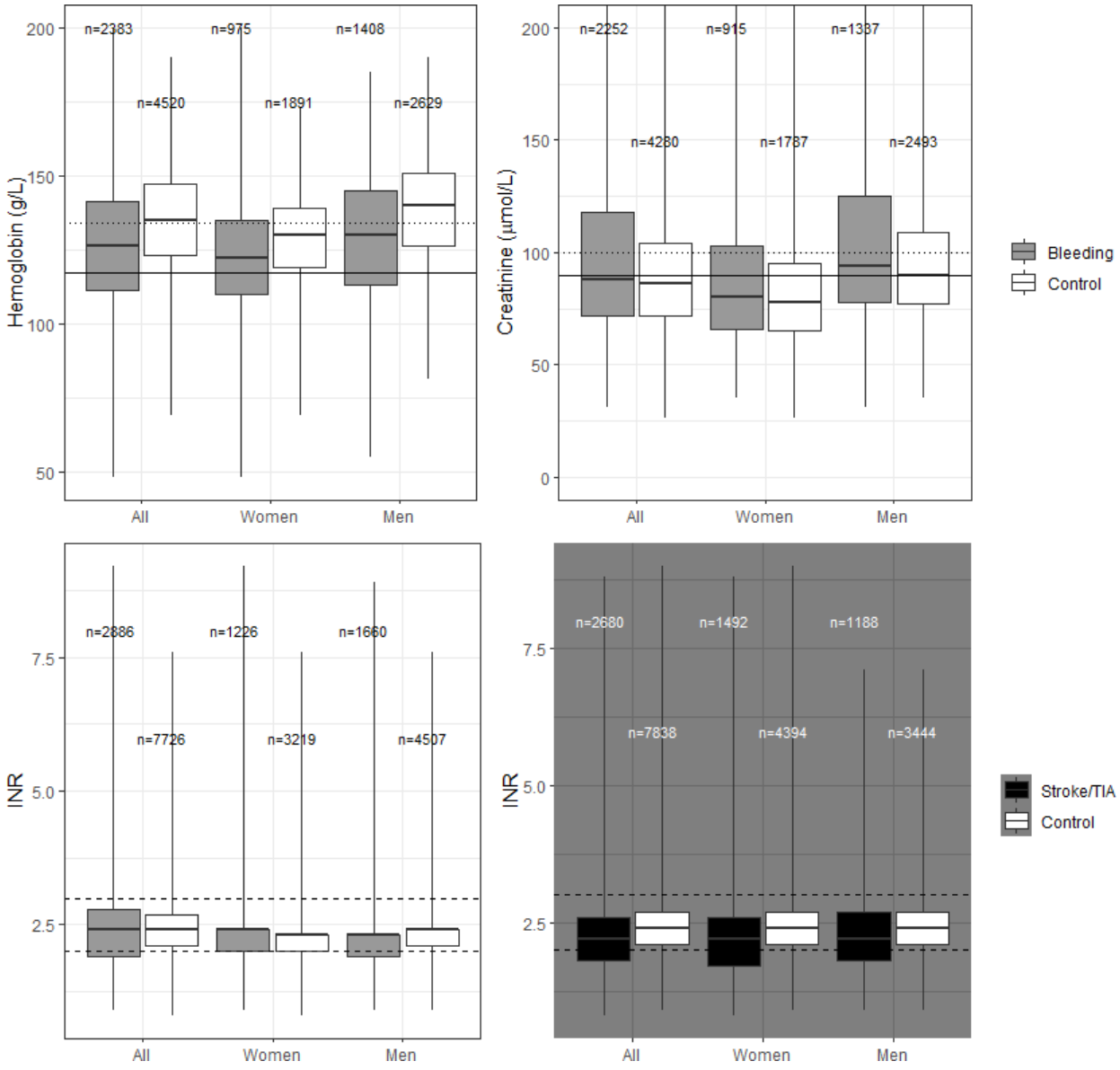

Figure 3 Significantly different laboratory test results among the controls (n=14 042) and the patient cases (n=4681) having a bleeding event (white background plots). For the patients with stroke/TIA, the box plots of the controls (n=14 063) and the stroke/TIA cases (n=4692) are shown (grey background plot). The INR levels (p for difference=0.98 for bleeding cases and p<0.001 for stroke cases) and clinically significant changes in haemoglobin and creatinine (p<0.001) laboratory values are shown. For INR, the treatment range 2.0–3.0 is shown with the dashed line. For haemoglobin, the reference interval lower limit and for creatinine, reference interval upper limit are shown with continuous and dotted lines for women and men, respectively. Box plots depict ranges (whiskers), quartiles 1 and 3 (box limits) and medians (horizontal line). The n-values in the figure represent the number of patients who had a laboratory result. For the data with corresponding p values, please see online supplemental table 3, and for the entire dataset, online supplemental tables 4 and 5. INR, international normalised ratio; TIA, transient ischaemic attack.

to the study setting, the laboratory testing appeared to increase risk of complications, as the patients whose laboratory tests were ordered had a timely clinical suspicion of deterioration, thus reflecting the complication risks. We have no data on the possible pauses in warfarin treatment before the complications occurred, if the patient, for example, has had low Hgb. We did not either exclude patients with haematological disease or active cancer from the analyses, diseases which contribute to anaemia. However, since anaemia predisposing to bleeding and stroke/TIA is evident in these patients as well, we found it important to include them also. Moreover, due to the retrospective nature of the study, we only matched the patients based on age and sex. Even though lower glomerular filtration rate and liver dysfunction are known risk factors for bleeding, we did not match based on these, as we would have had significantly less cases—only 30–50% had, for example, creatinine levels measured. Instead, we explored the above-mentioned risks by looking at the laboratory test results in cases versus controls.

In conclusion, the severity-dependent anaemia and low Hgb levels emerged as strong risk factors for both bleeding and stroke/TIA among patients with AF using warfarin. Prior to the complication, it is noteworthy that patients with bleed had no clear change in INR levels, but rather Hgb was significantly lowered. The higher number of laboratory measurements was associated with increased risk of bleeding as well as stroke/TIA events, especially when measured during on-call hours or weekends, suggesting acute exacerbation of the patient's condition. Our study highlights the need for earlier, routine testing for blood cell counts to ensure timely diagnosis and treatment of anaemia. Our observations are generalisable to the management of warfarin therapy in AF and beyond.

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Contributors TAH, PR, ML, JH and RL contributed to the planning and design of the study. TAH and JH did the statistical analyses. TAH, PR, ML, JH and RL contributed to the reporting of the results and preparation of the manuscript. TAH, PR, ML, JH and RL have all read and approved the final manuscript. RL was responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was a registry-based study with no patient-identifiable information. This study was performed in accordance with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance Code of Conduct and was registered to the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance e-register (ER12-9441). The study received approval by the Ethics Review Board of the Hospital District of Helsinki and Uusimaa, and data permits were obtained from each of the registry holders, based on the study protocol and ethics approval.

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