Safety and efficacy of well managed warfarin
A report from the Swedish quality register Auricula

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Summary
The safety and efficacy of warfarin in a large, unselected cohort of warfarin-treated patients with high quality of care is comparable to that reported for non-vitamin K antagonists. Warfarin is commonly used for stroke prevention in atrial fibrillation, as well as for treatment and prevention of venous thromboembolism. While reducing risk of thrombotic/embolic incidents, warfarin increases the risk of bleeding. The aim of this study was to elucidate risks of bleeding and thromboembolism for patients on warfarin treatment in a large, unselected cohort with rigorously controlled treatment. This was a retrospective, registry-based study, covering all patients treated with warfarin in the Swedish national anticoagulation register Auricula, which records both primary and specialised care. The study included 77,423 unselected patients with 100,952 treatment periods of warfarin, constituting 217,804 treatment years. Study period was January 1, 2006 to December 31, 2011. Atrial fibrillation was the most common indication (68%). The mean time in therapeutic range of the international normalised ratio (INR) 2.0–3.0 was 76.5%. The annual incidence of severe bleeding was 2.24% and of thromboembolism 2.65%. The incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation. In conclusion, warfarin treatment where patients spend a high proportion of time in the therapeutic range is safe and effective, and will continue to be a valid treatment option in the era of newer oral anticoagulants.

Introduction
Oral anticoagulation (OAC) is commonly used for stroke prevention in atrial fibrillation (AF), as well as the treatment and prevention of venous thromboembolism (VTE) (1). OAC increases the risk of bleeding, the most feared of which is intracranial bleeding (1, 2). Thus, decisions on thromboprophylaxis often have to balance the reduction in thromboembolism against the potential risk of serious haemorrhage.

Warfarin has a narrow therapeutic window, leading to an increased risk of complications with overzealous anticoagulation goals or when the treatment is poorly managed (3–6). In patients with AF, the use of warfarin reduces the risks of stroke/systemic embolism (by 64%) and all-cause mortality (by 26%), compared to control/placebo (7). Nonetheless, for warfarin to offer efficacy and safety, the quality of anticoagulation control is important, as poor control (as reflected by low proportion of time in therapeutic range, TTR) is associated with more stroke and bleeding (8–10).

The therapeutic range is defined by prothrombin time expressed as international normalised ratio (INR) between 2.0 and 3.0. The ESC Working Group on Thrombosis Anticoagulation Task Force recommends that a TTR of >70% is needed, whenever a vitamin K antagonist (VKA) such as warfarin is used.

Three non-VKA oral anticoagulants (NOACs, previously referred to as new or novel OACs [11]) that do not require monitoring have been licensed. These drugs have been shown to be more effective than warfarin in preventing stroke and systemic embolism in patients with AF (12, 13). The NOACs also showed a significantly reduced risk of intracranial haemorrhage compared to warfarin. One issue that can be raised against all pivotal NOAC studies is the varying quality of warfarin treatment in the control groups, resulting in a mean TTR of 55–64% (14–16). This TTR range is low by Swedish standards, where a mean TTR of 76% is usually evident in clinical practice (17). Of note, sub-group analyses of two studies comparing NOAC vs warfarin have shown reductions in stroke and systemic embolism, as well as reduced risk
of bleeding and death, at centres with higher levels of predicted TTR for warfarin. In these centres with high TTR, the same was also true for NOACs (4, 5). These results indicate that there could be potential benefits with NOACs regardless of quality of warfarin treatment, but that the absolute benefit may be smaller at higher levels of TTR. However, these analyses are retrospective, with centre-based modelling of TTR level, and with too few end-points in the high-TTR subgroups for statistically significant differences. Indeed, the benefits from NOACs in countries and centres with high TTR levels, as well as for individual patients who are well-controlled on warfarin are uncertain. Under these circumstances, added benefit in relation to increased costs of NOACs remains unproven.

Until recently, OAC in Sweden has almost exclusively been administered as warfarin (18).

In the present study, we aimed to determine the risk of bleeding or thrombotic/embolic events for patients on warfarin in a large, unselected cohort in a high TTR setting. Our goal was to see how well warfarin therapy can perform, and whether warfarin in the era of the NOACs can offer a competitive net clinical benefit balancing the reduction in thromboembolism against serious bleeding.

Materials and methods

Auricula, the Swedish national quality register for atrial fibrillation, was founded in 2006. Well over 100,000 patients are managed in Auricula, increasing by about 1,000 per month, corresponding to approximately half of the Swedish warfarin population. There are currently 224 active centres (19). Auricula records patients’ characteristics such as indication for anticoagulation, and concurrent illnesses.

The Auricula register is web-based and includes decision-making support for dosing of warfarin, not only for AF patients but for any patient on warfarin treatment. When using the dosing system, quality parameters are automatically registered. Records of major bleeding and thromboembolic events are requested annually, as well as at the end of each treatment period. Patients who do not want to be a part of the quality improvement system can choose to only be included in the dosing system.

The Swedish Patient register is the source of data on complications covering all diagnoses recorded in patients’ records within hospitals throughout Sweden, for outpatient as well as inpatient care. It does not cover primary care. The present study cohort was created by merging data from Auricula with data from the Patient register, creating a large dataset with 77,423 patients and 217,804 years of treatment.

Methods

The study period was from January 1, 2006 until December 31, 2011. Every treatment period registered in Auricula was given an individual identification number. Within the study period, patients could have any number of treatment periods. For treatment ongoing before or after the study period, start and end dates were set to the study’s start and end dates.

Complications in this study covers both true complications and non-prevented events. We defined ICD-10 codes that constituted a complication (see Appendix).

Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH), except the criterion haemoglobin (Hb) reduction of 20 g/l or transfusion of at least 2 units of blood, for which data was not possible to obtain from the Patient register (3, 20). Major bleedings were divided into intracranial, gastrointestinal and other bleeds. Thromboembolic events were defined as clinically verified venous or arterial thrombosis and/or embolism. They were grouped into stroke/thromboembolism/transient ischaemic attack (TIA), venous thromboembolism or myocardial infarction (see Appendix).

We then calculated time (number of days) until first complication of every specified type for every treatment period. Patients could have any and all types of complications during a treatment period. Primary and secondary diagnoses were extracted from the Patient register, but to reduce the risk of over-registering we allowed only one complication of every subtype per treatment period. We used only primary diagnoses of cerebral haemorrhage or infarction, and VTE, for the same reason, because it is not possible to distinguish between actual incidents and repeated use of an ICD-10 code at subsequent contacts. Within every treatment period, time until complication was calculated for every defined type of complication.

For cerebral infarction, as well as for VTE, it is not possible to differentiate between new events and follow-up contacts soon after the index incident. Therefore, a blanking period of two weeks was applied to these codes to reduce the risk of double-reporting in case of visits and/or admissions soon after index diagnosis. This means that patients with VTE or cerebral infarction cannot have a complication that is identical to the indication for the two weeks following start of treatment.

Age was always the patient’s age at the time an event actually occurred. We counted patient time contributed to a yearly partition of the age span 0 to 110 years (Figure 1). If a patient started a treatment period at age 62.5 that went on for two years, he or she contributed 0.5 years to age group 62–63, one year to age group 63–64 and 0.5 years to age group 64–65 (Figure 1).

Statistical methods

Data were analysed using simple descriptive analyses with SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, Armonk, NY, USA), and R version 3.0.0, R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. Confidence intervals (CI) are 95%.

Results

We studied 77,423 unselected patients on warfarin (40.6% women, mean age 70.2 years). Mean age among women was higher than...
among men (71.2 vs 68.4 years). The most common indication for treatment was AF (n=51299, 66.3 %), followed by VTE (n=17219, 22.2 %), heart valve disease (n=6997, 9.0 %) and “other” (n=6226, 8.0 %) (Table 2). The indication “other” is a mix of stroke with or without known source of emboli, thrombophilia, nephrotic syndrome and other diagnoses used as indications for OAC in clinical practice. The largest group of patients included in “other” were patients with dissections or peripheral embolism. A patient could have one or more indications for OAC at the same time.

Patients starting a treatment period with AF as cause of treatment were generally older than other patients treated with warfarin (mean age 72.1 years) (Table 1 and Figure 2), had more often hypertension (56.8 %) and were, second to the indication “other”, more likely to previously have suffered a stroke or TIA (25.0 %). In the indication “other”, a large proportion of the patients had just previous stroke as their recorded indication, leading to a very high proportion of previous stroke (41.7 %) (Table 1).

In total, 77,423 patients had all together 217,804 patient years on warfarin treatment. TTR defined as time in INR range 2.0–3.0 was consistently high in all indications, with a mean TTR in all patients of 76.5 % (Table 2). The lowest mean TTR of 74.5 % was found in patients with heart valve disease and the best in AF.

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics according to indication for warfarin.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of treatment periods on warfarin</strong></td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>n=100,952</td>
</tr>
<tr>
<td>Mean age (SD)</td>
</tr>
<tr>
<td>Female sex n (%)</td>
</tr>
<tr>
<td>Treatment periods in patients with at least one diagnosis in the Patient register before warfarin start</td>
</tr>
<tr>
<td>n=72,343</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
</tr>
<tr>
<td>Previous stroke/TIA n (%)</td>
</tr>
<tr>
<td>Liver disease n (%)</td>
</tr>
<tr>
<td>Kidney disease n (%)</td>
</tr>
<tr>
<td>COPD n (%)</td>
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</tbody>
</table>

Given as number and proportion of treatment periods, n (%). A patient could have one or several indications for OAC treatment. VTE, venous thromboembolism.
patients (77.4%). However, only 78.4% of the patients with heart valve disease had a prescribed target INR range of 2.0–3.0. Many of them had higher target ranges, most commonly INR 2.5–3.5. Of those with an actual target INR of 2.0–3.0, TTR was 77.5% in the whole population and 78.4% in patients with heart valve disease.

Mean TTR was higher among men (76.9%) than among women (75.9%). Annual incidences of major bleedings or thromboembolic events were 2.24% [CI 2.21–2.27] and 2.65% [CI 2.62–2.69] (Table 2). The yearly risk of bleeding was significantly higher in patients with heart valve disease (3.37%, [CI 3.25–3.48]) while the thromboembolic risk was higher in the indication “other” (3.53%, [CI 3.39–3.67]).

The annual incidence of intracranial bleeding was 0.37% [CI 0.36–0.38] in the whole population, and 0.38% [CI 0.37–0.40] among patients with AF (Table 3). Of note, the incidence of intracranial bleeding was higher for patients with heart valve disease (0.51%, [CI 0.46–0.55]) (Table 3). These patients also had a higher risk of gastrointestinal (GI) bleedings (1.11%, [CI 1.04–1.18]) and other bleedings (1.83%, [CI 1.74–1.91]) than patients with all other indications for warfarin treatment.

Patients with the indication “other” more often suffered ischaemic stroke/thromboembolism/TIA despite warfarin treatment compared to patients with other indications (1.76%, [CI 1.66–1.86%]). Patients with the indication “other” for warfarin treatment also had more myocardial infarctions than other patients (1.61%, [CI 1.52–1.70]) while the risk of VTE was highest among those with warfarin due to a previous VTE (1.15%, [CI 1.09–1.20]). Patients with the indication heart valve disease had lower risk of VTE than patients using warfarin for other reasons (0.03%, [CI 0.02–0.05]), although VTE was also uncommon in patients with AF (0.10%, [CI 0.09–0.11]). Patients with the VTE indication had fewer myocardial infarctions than other patients (0.79%, [CI 0.74–0.83]).

Female sex was associated with higher annual rates of major bleeding (2.38%, [CI 2.33–2.44]) vs men 2.16%, [CI 2.12–2.20]) but paradoxically with lower rates of intracranial bleedings; women 0.34% [CI 0.32–0.36]), men 0.39% [CI 0.38–0.41]) (Table 3). Women had more VTE than men (0.31%, [CI 0.29–0.33]) vs 0.25%, [CI 0.24–0.27]), but had less myocardial infarctions than men (0.94% [CI 0.91–0.97]) vs 1.09% [CI 1.06–1.12]).

Both bleedings and thromboembolism (except VTE) showed a strong positive correlation with age (Table 4). The risk of bleeding was highest at ages over 90 years, where the annual bleeding rate was over 4%. Younger patients, on the other hand, had a low risk of bleeding. At ages 50 years or younger, the annual rate of intracranial bleeding was only 0.12% [CI 0.04–0.21]. In Figure 3 the relationship is shown between age and intracranial bleedings among patients with AF and an accumulated time on treatment of 142,626 years.

### Table 2: Annual event rates in relation to gender and indication for warfarin treatment. TTR for INR 2.0–3.0 given for all patients regardless of target range, as well as for those with actual target INR of 2.0–3.0.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment periods</th>
<th>Bleeding rate</th>
<th>Thromboembolic rate</th>
<th>Mean TTR</th>
<th>Proportion with target INR 2–3</th>
<th>Mean TTR of INR 2.0–3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>45680</td>
<td>60582</td>
<td>2.16 (2.12–2.20)</td>
<td>2.69 (2.64–2.73)</td>
<td>76.9</td>
<td>88.7</td>
</tr>
<tr>
<td>Women</td>
<td>31465</td>
<td>40067</td>
<td>2.38 (2.33–2.44)</td>
<td>2.62 (2.56–2.67)</td>
<td>75.9</td>
<td>89.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>51299</td>
<td>68797</td>
<td>2.18 (2.14–2.22)</td>
<td>2.65 (2.61–2.69)</td>
<td>77.4</td>
<td>91.1</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>6997</td>
<td>8723</td>
<td>3.37 (3.25–3.48)</td>
<td>2.57 (2.47–2.67)</td>
<td>74.5</td>
<td>71.5</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>17219</td>
<td>20496</td>
<td>2.00 (1.93–2.07)</td>
<td>2.69 (2.60–2.77)</td>
<td>75.9</td>
<td>93.2</td>
</tr>
<tr>
<td>Other</td>
<td>6226</td>
<td>7359</td>
<td>2.18 (2.07–2.29)</td>
<td>3.53 (3.39–3.67)</td>
<td>76.0</td>
<td>87.1</td>
</tr>
</tbody>
</table>

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Limiting our analysis to patients with atrial fibrillation as indication for warfarin treatment, and not including the other types of patients, did not change our conclusions [data not shown].

Discussion

The main finding of our study is that it is possible to achieve efficient warfarin therapy with a mean TTR of 76.5% in routine clinical care, without exclusion of any patient groups and with very few serious bleeding complications.

Bleeding complications were fewer than what was reported in the large randomised trials where warfarin was used as comparator to NOACs. In our study, major bleedings from any cause in the AF population occurred at an annual rate of 2.18%, which is to be compared to 3.57% in the RE-LY trial (14), 3.4% in the ROCKET trial (15) and 3.09% in the ARISTOTLE trial (16).

Admittedly, the reporting of less severe major bleedings may have been more thorough in the prospective clinical trials than in our study, which may explain some of the difference in bleeding.

Sensitivity analysis

Limiting our analysis to patients with atrial fibrillation as indication for warfarin treatment, and not including the other types of patients, did not change our conclusions [data not shown].
rate. On the other hand, the TTR in our study (76.5%) was far higher than the mean TTR levels of 55–64% in the pivotal NOAC trials (14–16). Moreover, in our study all warfarin treated patients were included, which signifies that there were more elderly patients and patients with multiple concomitant diseases than in randomised clinical trials with inclusion and exclusion criteria.

Intracranial bleeding occurred at an annual rate of 0.37% per treatment year in the whole group, and of 0.38% among 51,299 patients with AF in our study. This is far lower than in the NOAC trials where the warfarin-treated control patients had intracranial bleeds at a rate of 0.70 to 0.80% annually (4, 14–16). In fact, it was even lower than with rivaroxaban (0.5%), and not much higher than with apixaban (0.33%), dabigatran 150 mg (0.30%) and dabigatran 110 mg (0.23%). Intracranial bleedings are severe events associated with high mortality. It is therefore unlikely that there was any significant underreporting of intracranial bleeds in the all-inclusive national Swedish Patient register that could have accounted for the low bleeding rate. As for thromboembolic events, the rates differ according to indication for treatment. As for the most extensively studied treatment indication, atrial fibrillation, our findings of 1.54% stroke, TIA or systemic emboli per year is considerably lower than the 1.74% and 2.42% found in the warfarin arms in the pivotal studies for dabigatran and rivaroxaban, respectively (14, 15). This despite of an unselected patient population with no inclusion or exclusion criteria.

In AF, the net clinical benefit from anticoagulant treatment depends on the span in incidence rates of thromboembolic and bleeding events of comparable severity. In this study, all patients were on anticoagulant treatment and we therefore have no way of telling what the thromboembolic rate would have been if patients had not had treatment. In a previous study of 90,706 AF patients without anticoagulant treatment utilising the same Swedish registers as this study, the overall rate of strictly defined ischaemic stroke was 4.5%/year, of thromboembolism (including unspecified stroke, TIA and systemic emboli) 6.3%/year and of intracranial haemorrhage 0.6%/year (21). If structured and optimised care of warfarin patients can reduce bleeding rates to levels similar to that of untreated patients, few AF patients will not benefit from treatment. The lower the bleeding rates are, the higher the net benefit from treatment will be, if everything else remains unchanged. It has however to be kept in mind that the majority of those without anticoagulant treatment are elderly with high risk both of bleeding and thromboembolism (21). The risk of confounding by indication therefore makes it necessary to regard such comparisons with great care.

Patients with heart valve disease had more bleeding complications than other patients. Many of these patients had treatment with a higher therapeutic range of INR 2.5–3.5 instead of the more common of INR 2.0–3.0, which could account for some of those bleedings. We believe that it is important to report the actual risks these patients have of serious bleedings or thromboembolic events, not the least since the INR goals in many cases are founded on vague scientific evidence. The bias of including patients with higher INR goals than 2–3 means that, if anything, we show a larger risk of bleeding than for the patients with lower goals, and could therefore better reflect clinical reality. Women had an overall higher incidence of bleeding events, while they paradoxically had fewer intracranial bleeds than men, despite their higher mean age and lower TTR. The absolute bleeding risks of women were, however, low. Female sex should therefore not be an argument against warfarin treatment.

Limitations
Since this is a retrospective registry-based study, we cannot exclude bias. However, the mere size of the cohort, and the fact that the Auralica data represent a nationwide Swedish cohort, both from anticoagulation clinics and primary health care settings, suggests that these results represent ‘real world’ clinical practice in Sweden. The positive predictive values for diagnoses in the Patient Register vary between diagnoses, but are generally in the range of 85–99% (22), and although little is known about the negative predictive value for most diagnoses because this requires knowledge about true prevalence of diseases in the population, including subjects who have not yet received a diagnosis. Thus, registry studies are more prone to underestimating than overestimating comorbidity.

What is known about this topic?
- Warfarin has a narrow therapeutic window, leading to an increased risk of complications when the treatment is poorly managed.
- NOACs have been shown to be safer than relatively poorly performed warfarin treatment, with TTR well under a recommended level of 70%.

What does this paper add?
- Efficient warfarin therapy with a mean TTR of 76.5% is possible to achieve in routine clinical care with unselected patients.
- Warfarin treatment with a high TTR performs well, and should not be ruled out in favour of NOACs.
We have not been able to validate the sensitivity of the detection of endpoint events. It is for example conceivable that some less severe bleeding events, which would have been recorded in a prospective trial, could have been taken care of in primary care and thus would not have been recorded. It is also likely that some endpoint events were recorded as secondary diagnoses, and therefore were not properly counted. Moreover, patients who died outside of hospital were not counted which also may have led to some under-reporting of end-point events.

It also has to be recognised that patients who did not succeed in achieving stable INRs with warfarin, for whatever reason, were taken off treatment. The true extent of premature termination of warfarin treatment in this study is not known. This constitutes a selection bias. The analyses should therefore be regarded as made according to the "on treatment", not as "intention to treat" principle. The number of patients who were changed during the study period from warfarin to NOACs because of "unstable INRs" are not known but should be virtually none. This because the first NOAC to be licensed in Sweden was not available until in the last month of the study period. Furthermore, the uptake of NOACs in Sweden has been relatively slow, corresponding to only a few percent of all anticoagulated patients now three years after the introduction.

Unfortunately, we do not have complete data on antiplatelet co-medication and therefore we could not take them under consideration in this study.

## Conclusion

Well-managed warfarin treatment with TTR ≥ 75% is safe and effective, and will continue to be a valid treatment option in the era of NOACs.

## Ethical approval

This study was approved by the regional ethical review board in Umeå, Sweden (EPN nr 2011–349-31M and 2012–277-32M) and conformed to the declaration of Helsinki.

## Author contributions

AS and PS designed the study. AS, BG-L, HR and VS extracted and analysed data. AS, VS and BG-L drafted the manuscript. All authors critically reviewed the manuscript, contributed to its revision, and approved the final version submitted.

## Conflicts of interest

AS and PS have received lecture fees from Bayer, Boehringer-Ingelheim, BMS/Pfizer and Takeda. LF has received research grants or lecture fees for Bayer, Boehringer-Ingelheim, BMS/Pfizer, Sanofi and St Jude Medical. GYHL has served as consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer-Ingelheim and Sanofi Aventis. VS has received lecture fees from Boehringer-Ingelheim. All other authors have nothing to disclose.

## References