Renal Function, Time in Therapeutic Range and Outcomes in Warfarin-Treated Atrial Fibrillation Patients: A Retrospective Analysis of Nationwide Registries

Anders Nissen Bonde1  Gregory Y. H. Lip2  Anne-Lise Kamper3  Laila Staerk1  Christian Torp-Pedersen4  Gunnar Gislason1,5,6  Jonas Bjerring Olesen1

1 Department of Cardiology, Copenhagen University Hospital Gentofte, Gentofte, Denmark
2 Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom
3 Department of Nephrology, Copenhagen University Hospital Rigshospitalet, Righshospitalet, Denmark
4 Institute of Health, Science and Technology, Aalborg University, Aalborg, Denmark
5 The Danish Heart Foundation, Copenhagen, Denmark
6 The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

Address for correspondence  Anders Nissen Bonde, MD, Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte, Kildegaardsvej 28, Post 635, 2900 Hellerup, Denmark (e-mail: andersnissenbonde@gmail.com).


Abstract

Patients with severely reduced renal function have been excluded from randomized controlled trials of oral anticoagulation in atrial fibrillation (AF). Warfarin treatment in this population is controversial and data on anticoagulation control and the impact on adverse outcomes are needed. By individual-level linkage of nationwide registries, we identified all patients discharged from hospitals with AF in Denmark between 1997 and 2011. Patients with available serum creatinine tests were categorized according to the estimated glomerular filtration rate (eGFR). Time in therapeutic range (TTR) was calculated using the Rosendaal method. The risk of stroke and bleeding was estimated using multivariable Cox regression analyses with eGFR and TTR estimated time dependently throughout follow-up. We identified 10,423 warfarin-treated AF patients with available international normalized ratio and creatinine tests; 5,527 with eGFR > 60 mL/min/1.73 m², 4,524 with eGFR 30–60 mL/min/1.73 m² and 372 with eGFR < 30 mL/min/1.73 m². Median TTR was 66.7, 61.2 and 49.7% in patients with eGFR > 60, 30–59 and < 30 mL/min/1.73 m², respectively. A TTR < 70% was associated with a higher risk of stroke/thromboembolism (hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 1.20–1.60) and bleeding (HR: 1.22; 95% CI: 1.05–1.42) among patients with eGFR of 30 to 59 and a trend towards higher risk of stroke/thromboembolism (HR: 1.24; 95% CI: 0.86–1.80) and bleeding (HR: 1.17; 95% CI: 0.83–1.65) among patients with eGFR < 30 mL/min/1.73 m². In conclusion, warfarin-treated AF patients with reduced renal function have suboptimal anticoagulation control which was related to the risk of adverse outcomes.

Keywords
► atrial fibrillation
► chronic kidney disease
► warfarin
► time in therapeutic range

The review process for this paper was fully handled by Christian Weber, Editor in Chief.

received March 21, 2017
accepted after revision August 20, 2017

Copyright © 2017 Schattauer  DOI https://doi.org/10.1160/TH17-03-0198.  ISSN 0340-6245.
Introduction

Up to one-third of patients with atrial fibrillation (AF) have some degree of chronic kidney disease (CKD). Oral anticoagulation for stroke prevention is required for most patients with AF, but oral anticoagulation puts patients at increased risk of bleeding. CKD in AF is associated with increased risk of stroke, death and bleeding, and thromboprophylaxis for patients with concomitant AF and CKD is a complex clinical dilemma.

Patients with a creatinine clearance below 25 or 30 mL/min have been excluded from randomized controlled trials of non-vitamin K antagonist anticoagulants (NOAC), and the efficacy of warfarin in this specific population has never been established from randomized trials. Since all approved NOAC are partly renally excreted, vitamin K antagonists (VKA) are the only real option for thromboprophylaxis among AF patients with severely reduced renal function, but observational studies have had conflicting results regarding the efficacy and safety of warfarin in this population.

Time in therapeutic range (TTR) is a measure of quality of warfarin control, and has been linked directly to adverse outcomes, including stroke, bleeding, myocardial infarction and death, in the general warfarin-treated AF population. Little is known about TTR among AF patients with severely reduced renal function, and data are needed to answer the question of whether warfarin can be used with acceptable effectiveness and safety in this population.

Methods

Study Setting

All residents in Denmark are provided with a unique and permanent civil registration number that allows linkage of data from several nationwide registries on an individual level. All patients discharged from a Danish hospital are coded according to the International Classification of Disease (ICD) system by the discharging physician with one primary diagnosis and, if appropriate, one or more secondary diagnoses. All invasive therapeutic procedures are coded according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures. All prescriptions dispensed from Danish pharmacies are registered in the Danish Register of Medicinal Product Statistics according to the international Anatomical Therapeutic Chemical (ATC) system.

The Danish Civil Registration System holds information on vital status and cause of death for every citizen. The Danish Registry on Regular Dialysis and Transplantation keeps complete information on all Danish citizens treated with chronic renal replacement therapy.

Study Population

We included 10,423 anticoagulated AF patients discharged from a Danish hospital between 1997 and 2011 with available international normalized ratio (INR) measurements. We excluded patients with valvular AF, patients who received dabigatran, patients on renal replacement therapy, patients older than 100 years and younger than 30 years and patients without available creatinine measurements. Follow-up began on the day of their first INR test. Patients were followed until 31 December 2011, emigration, death or event. All ICD codes and ATC codes that were used to define the study population, comorbidities, medication and outcomes are shown in Supplementary Table S1 (online only).

Time in Therapeutic Range

We had access to all INR tests analysed in laboratories of hospitals in Copenhagen and in laboratories of general practitioners in Copenhagen during our study period. We only included INR tests taken during anticoagulation, determined by prescription data as is done in previous studies. INR tests taken during hospitalization were excluded. TTR for each patient was calculated using the Rosendaal method, which by interpolation assigns an INR value to each day between two successive INR measurements. TTR is then defined as the percentage of days with an INR value between 2.00 and 3.00. TTR was recalculated and updated for each patient each time a new INR test was registered. Periods with more than 100 days between INR readings were not used in the final TTR calculation, and final TTR was only reported for patients with at least three INR tests during follow-up, because TTR is only meaningful when at least three INR measurements are available. A TTR above 70%, as recommended with a VKA by European Society of Cardiology AF guidelines, was considered appropriate anticoagulation control.

Pharmacotherapy, Comorbidities and Renal Function

Baseline pharmacotherapy was defined using redeemed prescriptions from 180 days before inclusion in the study. The risk of stroke/TE was assessed for each patient using the CHA2DS2-VASc (congestive heart failure, hypertension, age 75 years [double weight], diabetes mellitus, stroke/TE [double weight], vascular disease, age 65–74, sex category) score and the risk of bleeding was assessed using the HAS-BLED (hypertension, abnormal renal/liver function, previous stroke/TE, previous bleeding, labile INR, elderly [age > 75 years], drug/alcohol abuse) score. The estimated glomerular filtration rate (eGFR) was calculated for each patient according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula using the latest available serum creatinine value. The CKD-EPI formula is recommended by Kidney Disease: Improving Global Outcomes guidelines, and is likely to be more precise than the Cockcroft–Gault equation, which was developed before the introduction of modern creatinine assays. eGFR was calculated time dependently throughout follow-up, that is, each time a new creatinine test was made, patients could switch the eGFR category.

Study Outcomes

The outcomes of interest were (1) a TTR > 70% at the end of follow-up, (2) death/hospitalization from stroke/TE and (3)
death/hospitalization from bleeding. Stroke/TE was defined using diagnosis codes for ischemic stroke, transient ischemic attack or systemic TE. Bleeding was defined using diagnosis codes for severe gastrointestinal, intracranial, urinary tract and airway bleeding.

Statistics
We analysed the effect of reduced eGFR on the chance of achieving a TTR > 70% in a multiple adjusted logistic regression model. Only patients with at least three INR tests were included in the logistic regression model. The goodness of fit was checked with the Hosmer–Lemeshow test after stepwise selection of the variables included. Incidence rates of stroke/TE and bleeding were estimated time dependently according to eGFR and TTR. Time-dependent TTR was used to avoid conditioning on the future; that is, TTR was always recorded before event. Relative risk of stroke/TE and bleeding associated with TTR was estimated for patients with eGFR > 60 mL/min/1.73 m², eGFR of 30 to 59 mL/min/1.73 m² and eGFR < 30 mL/min/1.73 m², using time-dependent Cox proportional hazards models with adjustments for eGFR and TTR during follow-up. Patients with TTR > 70% were used as reference. As sensitivity, similar analyses were repeated using latest recorded INR.

Relative risk of stroke/TE and bleeding associated with reduced eGFR was estimated in patients with INR of 2.00 to 3.00 and in patients with INR < 2.00 and >3.00, respectively, using time-dependent Cox proportional hazards models. The INR value was updated each time a patient had a new INR test. Patients with eGFR > 60 mL/min/1.73 m² were used as reference. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed with SAS statistical software version 9.4 (SAS Institute INC., Cary, North Carolina, United States) and R version 2.15.2 (R Development Core Team).

Ethics
Ethical approval is not required for retrospective registry-based studies in Denmark. The study was approved by the Danish Data Protection Agency (ref. no: 2007–58–0015/GEH-2014–012 I-Suite no: 02720).

Results
Characteristics of the Study Population
A flowchart of the selection of the study population is illustrated in Fig. 1. We identified 88,769 anticoagulated AF patients. We excluded 2,831 patients due to valvular disease, use of dabigatran, kidney transplant or age over 100 or under 30 years. Of the remaining patients, 10,423 had available creatinine and INR tests at baseline. Median age at baseline was 73 (interquartile range [IQR]: 65–79) years and 4,711 (45.2%) were females. Table 1 shows baseline characteristics according to renal function. Patients with reduced renal function were older, had more comorbidity and received more medication. Supplementary Table S2 (online only) shows baseline characteristics among patients excluded due to missing data on INR. The excluded patients had comparable age distribution and comorbidity, although included patients with available INR measurements were more likely to have prior stroke.

Follow-up
Median follow-up with warfarin was 3.2 (IQR: 1.2–6.1), 3.0 (IQR: 1.2–5.4) and 1.5 years (IQR: 0.6–3.0) for patients with eGFR > 60, 30 to 59 and <30 mL/min/1.73 m² at baseline, respectively.

Oral Anticoagulation Control
Median TTR was 64.2% (IQR: 25.8–86.2) in our study, and 3,842 patients (44.3%) had a TTR > 70%. The median number of

![Fig. 1](image-url) The selection of the study population. eGFR, estimated glomerular filtration rate; INR, international normalized ratio.
available INR tests was 21 (IQR: 9–42). Table 2 shows TTR and odds ratio for TTR > 70% according to eGFR. Patients with an eGFR > 60 mL/min/1.73 m² had a median TTR of 66.7 (IQR: 31.5–86.5) compared with median TTR of 61.2 (IQR: 21.3–86.0) and 49.7 (IQR: 11.7–89.5) for patients with eGFR of 30 to 59 and <30 mL/min/1.73 m², respectively, (p < 0.001). Patients with reduced renal function were less likely to have a TTR > 70% and had a lower number of available INR tests. An eGFR of 30 to 59 mL/min/1.73 m² (odds ratio 0.92, 95% confidence interval [CI]: 0.84–1.00) was associated with lower odds of a TTR > 70% at the end of follow-up in a multi-adjusted logistic regression model. There was a non-significant trend towards a similar association among patients with an eGFR < 30 mL/min/1.73 m² (odds ratio: 0.89; 95% CI: 0.70–1.14), compared with patients with eGFR > 60 mL/min/1.73 m² who were used as reference.

Fig. 2 shows the percentage of INR tests in therapeutic range (2.00–3.00), below therapeutic range (<2.00) or above therapeutic range (>3.00) stratified by the number of measurements for patients with baseline eGFR ≥ 60, 30 to 59 and <30 mL/min/1.73 m², respectively. Patients with eGFR < 30 mL/min/1.73 m² had the lowest percentage of

Table 1 Baseline characteristics according to eGFR

<table>
<thead>
<tr>
<th></th>
<th>eGFR ≥ 60 mL/min/1.73 m²</th>
<th>eGFR = 30–59 mL/min/1.73 m²</th>
<th>eGFR &lt; 30 mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>5,527</td>
<td>4,524</td>
<td>372</td>
</tr>
<tr>
<td>Age (median [IQR])</td>
<td>68.0 (61.00–76.00)</td>
<td>77.0 (71.00–82.00)</td>
<td>80.0 (75.00–85.00)</td>
</tr>
<tr>
<td>eGFR (median [IQR])</td>
<td>73.2 (66.1–83.4)</td>
<td>49.7 (42.9–55.1)</td>
<td>25.0 (20.4–28.1)</td>
</tr>
<tr>
<td>Stroke comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc (median [IQR])</td>
<td>2.00 (1.00–4.00)</td>
<td>4.00 (3.00–5.00)</td>
<td>4.00 (3.00–5.00)</td>
</tr>
<tr>
<td>Congestive heart failure, no. (%)</td>
<td>689 (12.5)</td>
<td>1,056 (23.3)</td>
<td>170 (45.7)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>2,910 (52.7)</td>
<td>2,730 (60.3)</td>
<td>240 (64.5)</td>
</tr>
<tr>
<td>Age ≥ 75 y, no. (%)</td>
<td>1,603 (29.0)</td>
<td>2,758 (61.0)</td>
<td>283 (76.1)</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>585 (10.6)</td>
<td>513 (11.3)</td>
<td>55 (14.8)</td>
</tr>
<tr>
<td>Previous stroke, no. (%)</td>
<td>1,065 (19.3)</td>
<td>1,075 (23.8)</td>
<td>107 (28.8)</td>
</tr>
<tr>
<td>Vascular disease, no. (%)</td>
<td>814 (14.7)</td>
<td>974 (21.5)</td>
<td>111 (29.8)</td>
</tr>
<tr>
<td>Age 65–74 y, no. (%)</td>
<td>1,899 (34.4)</td>
<td>1,309 (28.9)</td>
<td>72 (19.4)</td>
</tr>
<tr>
<td>Female gender, no. (%)</td>
<td>1,973 (35.7)</td>
<td>2,524 (55.8)</td>
<td>214 (57.5)</td>
</tr>
<tr>
<td>Bleeding comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED (median [IQR])</td>
<td>2.00 (1.00–2.00)</td>
<td>2.00 (1.00–2.00)</td>
<td>2.00 (2.00–3.00)</td>
</tr>
<tr>
<td>Previous stroke, no. (%)</td>
<td>1,065 (19.3)</td>
<td>1,075 (23.8)</td>
<td>107 (28.8)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>2,910 (52.7)</td>
<td>2,730 (60.3)</td>
<td>240 (64.5)</td>
</tr>
<tr>
<td>Alcohol abuse, no. (%)</td>
<td>277 (5.0)</td>
<td>95 (2.1)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>Liver disease, no. (%)</td>
<td>101 (1.8)</td>
<td>62 (1.4)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Previous bleeding, no. (%)</td>
<td>306 (5.5)</td>
<td>353 (7.8)</td>
<td>49 (13.2)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel, no. (%)</td>
<td>166 (3.0)</td>
<td>122 (2.7)</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>NSAID, no. (%)</td>
<td>921 (16.7)</td>
<td>788 (17.4)</td>
<td>91 (24.5)</td>
</tr>
<tr>
<td>Beta blocker, no. (%)</td>
<td>3,159 (57.2)</td>
<td>2,442 (54.0)</td>
<td>203 (54.6)</td>
</tr>
<tr>
<td>Calcium channel blocker, no. (%)</td>
<td>1,876 (33.9)</td>
<td>1,548 (34.2)</td>
<td>137 (36.8)</td>
</tr>
<tr>
<td>Loop diuretics, no. (%)</td>
<td>1,506 (27.2)</td>
<td>2,144 (47.4)</td>
<td>293 (78.8)</td>
</tr>
<tr>
<td>Statin, no. (%)</td>
<td>1,582 (28.6)</td>
<td>1,349 (29.8)</td>
<td>122 (32.8)</td>
</tr>
<tr>
<td>Digoxin, no. (%)</td>
<td>2,768 (50.1)</td>
<td>2,564 (56.7)</td>
<td>210 (56.5)</td>
</tr>
<tr>
<td>Aspirin, no. (%)</td>
<td>1,628 (29.5)</td>
<td>1,542 (34.1)</td>
<td>150 (40.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CHA2DS2-VASc, congestive heart failure, hypertension, age 75 years (double weight), diabetes mellitus, stroke/thromboembolism (double weight), vascular disease, age 65–74, sex category; eGFR, estimated glomerular filtration rate; HAS-BLED, hypertension, abnormal renal/liver function, previous stroke/thromboembolism, previous bleeding, labile international normalized ratio, elderly (age > 75 years), drug/alcohol abuse; NSAID, nonsteroidal anti-inflammatory drugs.
INR measurements within therapeutic level at the start of the study period, and the lowest number of patients with stable INR during the first 20 measurements.

**eGFR during Follow-Up**

- **Supplementary Fig. S1** (online only) shows median eGFR before death for patients included in our study.

  eGFR fell steadily with approximately 1 mL/min/1.73 m² a year. One thousand and forty-eight (17.3%) patients deteriorated from the eGFR > 60 to the eGFR of 30 to 60 mL/min/1.73 m² group, 99 (1.6%) deteriorated from the eGFR > 60 to the eGFR < 30 mL/min/1.73 m² group, and 416 (8.4%) deteriorated from the eGFR of 30 to 60 to the eGFR < 30 mL/min/1.73 m² group.

**Risk of Stroke/TE and Bleeding**

- **Table 3** shows adjusted hazard ratio [HR] of stroke/TE and bleeding according to eGFR, when INR was in therapeutic range (2.00–3.00). Reduced eGFR was associated with increased risk of stroke/TE; HR of 1.07 (95% CI: 0.92–1.24) and 2.29 (95% CI: 1.76–2.97) for patients with eGFR of 30 to 59 mL/min/1.73 m².

### Table 2 TTR at the end of follow up and adjusted odds ratio for TTR > 70% according to eGFR

<table>
<thead>
<tr>
<th>eGFR &gt;60 mL/min/1.73 m²</th>
<th>eGFR = 30–59 mL/min/1.73 m²</th>
<th>eGFR &lt;30 mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least three INR tests at the end of follow-up</td>
<td>4,537</td>
<td>3,838</td>
</tr>
<tr>
<td>TTR (median [IQR])</td>
<td>66.7 (31.5–86.5)</td>
<td>61.2 (21.3–86.0)</td>
</tr>
<tr>
<td>Days in therapeutic range (median [IQR])</td>
<td>1,210 (374–2,241)</td>
<td>1,125 (371–2,180)</td>
</tr>
<tr>
<td>Days not in therapeutic range (median [IQR])</td>
<td>600 (184–1,455)</td>
<td>746 (247–1,784)</td>
</tr>
<tr>
<td>TTR &gt;70%, no. (%)</td>
<td>2,114 (46.6)</td>
<td>1,612 (42.0)</td>
</tr>
<tr>
<td>Number of INR measurements (median [IQR])</td>
<td>21 (9–43)</td>
<td>22 (9–43)</td>
</tr>
<tr>
<td>Multi-adjusted odds ratio for TTR &gt;70% (95% CI)*</td>
<td>1.0 (reference)</td>
<td>0.92 (0.84–1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; TTR, time in therapeutic range.

*Model adjusted for sex, old age, depression, diabetes mellitus, congestive heart failure, hypertension, alcohol abuse, use of amiodarone, beta-blocker, and co-treatment with five or more drugs.

**Fig. 2** Percentage of INR measurements within (2.00–3.00), below (<2.00) or above (>3.00) therapeutic range stratified by the number of measurements. eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); INR, international normalized ratio.

**Table 3** Hazard ratio of stroke/thromboembolism and bleeding according to eGFR when INR was in level (2.00–3.00)

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Stroke/thromboembolism</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>30–59</td>
<td>1.07 (0.92–1.24)</td>
<td>1.25 (1.09–1.47)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>2.29 (1.76–2.98)</td>
<td>4.08 (3.29–5.15)</td>
</tr>
</tbody>
</table>

*Model adjusted for congestive heart failure, hypertension, diabetes mellitus, previous stroke, sex, age, vascular disease, and use of aspirin and adenosine diphosphate-receptor antagonists. eGFR and TTR were estimated time dependently throughout follow-up.*

### Notes
- The model with stroke/thromboembolism as outcome was adjusted for congestive heart failure, hypertension, diabetes mellitus, previous stroke, sex, age, vascular disease, and use of aspirin and adenosine diphosphate-receptor antagonists. eGFR and TTR were estimated time dependently throughout follow-up.
- The model with bleeding as outcome was adjusted for hypertension, age, previous bleeding, previous stroke, liver disease, alcohol use, age, and use of aspirin and adenosine diphosphate-receptor antagonists. eGFR and TTR were estimated time dependently throughout follow-up.

Abbreviations: eGFR, estimated glomerular filtration rate; INR, international normalized ratio.
and patients with eGFR < 30 mL/min/1.73 m², respectively, and reduced eGFR was associated with increased risk of bleeding; HR of 1.25 (95% CI: 1.09–1.47) and 4.08 (95% CI: 3.29–5.15) for patients with eGFR of 30 to 59 and eGFR < 30 mL/min/1.73 m², respectively.

Fig. 3 illustrates incidence rates per 100 person-years of stroke/TE and bleeding according to eGFR and TTR. In patients with eGFR of 30 to 59 mL/min/1.73 m², rates of stroke/TE (2.93 per 100 person-years) and bleeding (2.71 per 100 person-years) were lower among patients with a TTR above 70% than among patients with TTR below 70% (rates of stroke/TE: 4.19 per 100 person-years; bleeding: 3.62 per 100 person-years). In patients with eGFR < 30 mL/min/1.73 m², rates of stroke/TE (6.83 per 100 person-years) and bleeding (7.58 per 100 person-years) were not significantly lower among patients with TTR above 70% compared with rates of stroke/TE (8.24 per 100 person years) and bleeding (7.98 per 100 person years) among patients with a TTR below 70%.

Table 4 shows multi-adjusted HR of stroke/TE and bleeding according to eGFR and TTR. Among patients with eGFR of 30 to 59, a TTR < 70% was associated with a higher risk of stroke/TE (HR: 1.31; 95% CI: 1.22–1.42) and bleeding (HR: 1.06; 95% CI: 1.02–1.11). Among patients with eGFR < 30 mL/min/1.73 m², patients with TTR < 70% had a non-significant trend towards higher risk of stroke/TE (HR: 1.17; 95% CI: 0.83–1.65). Supplementary Table S3 (online only) shows HR of stroke and bleeding according to eGFR and latest INR before event. A high INR was associated with increased risk of stroke/TE and bleeding and a low INR was associated with increased risk of stroke/TE.

Discussion
This large registry-based real-world study of AF patients has the following principal findings: (1) reduced renal function was associated with poor anticoagulation control; (2) reduced eGFR was associated with increased risk of stroke/TE.
and bleeding, even when INR was in level; and (3) poor anticoagulation control was associated with an increased risk of both stroke/TE and bleeding. Very few studies have assessed TTR according to eGFR in warfarin-treated AF patients, and the present study is the largest one addressing this issue.

Risk of Stroke/TE and Bleeding According eGFR
Reduced eGFR has been linked to stroke/TE and bleeding in warfarin-treated AF patients, and poor anticoagulation control has been proposed as one of the mechanisms for this association. In the present study, we examined the risks associated with reduced eGFR in periods where INR was within therapeutic level (2.00–3.00), and found both moderately and severely reduced renal function to be associated with increased risk of stroke/TE and bleeding, even after controlling for relevant risk factors. These results suggest that poor INR control is not solely responsible for the increased risk in these patients. Of note, a low TTR was not associated with increased risk of bleeding in patients with eGFR > 60 mL/min/1.73 m². It is possible that increased bleeding risk with high INR could have been levelled out by low INR in this analysis.

Anticoagulation Control in AF Patients with Reduced eGFR
Patients with eGFR < 30 mL/min/1.73 m² had a median age of 80 years, a median CHA2DS2-VASc score of 4 and for this reason only 1.5 years of follow-up time with warfarin. The reasons that AF patients with reduced renal function have lower TTR than patients with normal renal function might be several. Warfarin is secreted mainly by the liver, but CKD influences both the metabolism and bioavailability of warfarin. CKD downregulates cytochrome p450 2C9, which is responsible for the metabolism of warfarin, by 40 to 60% of pharmacogenetics or development of NOAC not excreted by the kidneys.

Strengths and Limitations
The main strength of this study is the large number of unselected real-world patients with information available on pharmacotherapy, hospital diagnoses, eGFR and INR available from both general practitioners and from hospitals. The Danish registries are of high quality, and health care is free of charge for all inhabitants independent of labour market participation. The AF diagnosis and the stroke/TE diagnosis in our population have both previously been validated, and the CHA2DS2-VASc and HAS-BLED scores have been shown to accurately predict risk of stroke/TE and bleeding in our population. Indeed, poor anticoagulation control could be the reason for the conflicting results between Scandinavian and American studies on the subject. The present study shows that AF patients with reduced renal function have lower TTR than AF patients in general and that poor TTR in this population was associated with higher risk of stroke/TE and bleeding. In everyday clinical settings, these findings suggest that warfarin should be used with more caution and under tighter anticoagulation control among AF patients with reduced renal function than in the general population. The poor TTR in the group of patients with AF and low eGFR calls for improved management of thromboprophylaxis in this group; possibilities include the use of computer-assisted dosage programs, use of pharmacogenetics or development of NOAC not excreted by the kidneys.

Conclusion
Warfarin-treated AF patients with impaired renal function have suboptimal anticoagulation control, which was related to risk of adverse outcomes.
What is known on this topic?

- The majority of patients with atrial fibrillation require oral anticoagulation for stroke prevention; however, warfarin is controversial among patients with atrial fibrillation and reduced renal function.
- Patients with a creatinine clearance below 25 or 30 mL/min have been excluded from randomized controlled trials of non-vitamin K antagonist anticoagulants (NOAC).

What this paper adds?

- Patients with reduced renal function have suboptimal anticoagulation control, and suboptimal anticoagulation control was linked directly to adverse outcomes.
- Good anticoagulation control is essential when managing atrial fibrillation patients with reduced renal function, and warfarin should be used with more caution and under tighter anticoagulation control in this population than in the general population.

Conflict of Interest

Dr. Bonde (none); Dr. Lip (Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo; Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo, outside the submitted work); Kamper (personal fees from Boehringer Ingelheim outside the submitted work); Stærk (grants from Boehringer Ingelheim, outside the submitted work); Torp-Pedersen (grants and personal fees from Cardiome Merck, Sanofi, Daiichi, and grants from BMS, outside the submitted work); Gislason (grants from Bayer, Boehringer Ingelheim, Pfizer, AstraZeneca, Bristol-Myers Squibb, during the conduct of the study); Olesen (grants from the Capital Region of Denmark, Foundation for Health Research, during the conduct of the study; grants and other from Bristol-Myers Squibb, and other from Boehringer Ingelheim, outside the submitted work).

Funding

This study was funded by an unrestricted grant from the Capital Region of Denmark, Foundation for Health Research.

References

24 Hommel K, Rasmussen S, Madsen M, Kamper AL. The Danish Registry on Regular Dialysis and Transplantation: completeness

Thrombosis and Haemostasis

Vo. 117 No. 12/2017
Renal Function and Time in Therapeutic Range in Atrial Fibrillation  
Bonde et al.


