Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction

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Background—It is unknown whether renal dysfunction conveys poor anticoagulation control in warfarin-treated patients with atrial fibrillation and whether poor anticoagulation control associates with the risk of adverse outcomes in these patients.

Methods and Results—This was an observational study from the Stockholm CREatinine Measurements (SCREAM) cohort including all newly diagnosed atrial fibrillation patients initiating treatment with warfarin (n=7738) in Stockholm, Sweden, between 2006 and 2011. Estimated glomerular filtration rate (eGFR; mL/min per 1.73 m²) was calculated from serum creatinine. Time-in-therapeutic range (TTR) was assessed from international normalized ratio (INR) measurements up to warfarin cessation, adverse event, or end of follow-up (2 years). Adverse events considered a composite of intracranial hemorrhage, ischemic stroke, myocardial infarction, or death. During median 254 days, TTR was 83%, based on median 21 INR measurements per patient. TTR was 70% among patients with eGFR <30, around 10% lower than in those with normal renal function. During observation, adverse events occurred in 4.0% of patients, and those with TTR <75% were at higher adverse event risk. This was independent of patient characteristics, comorbidities, number of INR tests, days exposed to warfarin, and, notably, independent of eGFR: adjusted odds ratio (OR) 1.84 (95% CI, 1.41–2.40) for TTR 75% to 60% and adjusted OR 2.09 (1.59–2.74) for TTR <60%. No interaction was observed between eGFR and TTR in association to adverse events (P=0.2).

Conclusion—Severe chronic kidney disease (eGFR <30) patients with atrial fibrillation have worse INR control while on warfarin. An optimal TTR (>75%) is associated with lower risk of adverse events, independently of underlying renal function. (J Am Heart Assoc. 2017;6:e004925. DOI: 10.1161/JAHA.116.004925.)

Key Words: all-cause death • anticoagulant • atrial fibrillation • bleeding • ischemic stroke • renal function

Atrial fibrillation (AF) is a common cardiovascular complication associated to poor outcomes, including an increased risk of stroke. Anticoagulant therapy with warfarin can effectively reduce stroke risk by 60% at the cost, however, of an increased risk of intracranial hemorrhage (ICH) and bleeding.1 The success of preventing adverse events (both ischemic and bleeding events), with warfarin is dependent on maintaining an optimal anticoagulation management, namely, achieving international normalized ratio (INR) between 2.0 and 3.0. The time in therapeutic range (TTR) quantifies the percentage of time within this range, and optimal TTR has been associated with better outcomes.2 TTR is typically affected by patient-related factors (including comorbidities and genetic predisposition), warfarin dose, drugs known to interact with warfarin, as well as center- and country/health care–related factors.3,4

Patients with chronic kidney disease (CKD) often develop AF. At the same time, CKD confers increased risk of ischemic stroke and bleeding.5,6 Anticoagulation management in these patients is challenging, and some observational studies have raised concerns regarding the safety and effectiveness of warfarin in AF patients with CKD, particularly those with end-stage renal disease and undergoing dialysis.7,8 A limitation of those studies is, however, the lack of information on the patient’s INR control, which could explain the observed

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Accompanying Tables S1 through S7 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/6/3/e004925/DC1/embed/inline-supplementary-material-1.pdf

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increased risk of adverse outcomes in warfarin-treated patients with CKD.

In this study, we hypothesized that patients with CKD have worse anticoagulant control (poor TTR), and that it is a worse TTR that associates with poor outcomes. We tested this hypothesis in a real-world setting of newly diagnosed AF patients initiating warfarin therapy.

Methods
Study Population and Exposure
Patients were selected from the Stockholm CREatinine Measurements (SCREAM) project, a health care utilization cohort for the region of Stockholm, Sweden. SCREAM collected laboratory tests and health care use data from all individuals ≥18 years who had serum creatinine measured at least once between 2006 and 2011. SCREAM covers 98% of all cardiovascular disease cases registered in the region.

Eligible patients for this study were newly diagnosed AF patients initiating warfarin treatment (see Figure 1, flow chart). Diagnosis of AF and other comorbidities was obtained from International Classification of Diseases, Tenth Revision (ICD-10) codes (see Tables S1 through S4 for definitions). AF has been shown to have a high diagnostic validity, with 95% having AF on electrocardiogram when based on ICD codes. Information on pharmacy-dispensed medications was obtained from the Swedish Dispensed Drug registry, which records all dispensions from any Swedish pharmacy (Table S2).

The index date was the day of the first warfarin dispensation after a new AF diagnosis. Demographics, comorbidity history, and ongoing/recent medication (dispensations during the preceding 6 months) were calculated at that point. All available INR measurements from day 30 and up to 730 days (2 years) from the first warfarin purchase were used to estimate TTR. TTR was calculated as the percentage of time that INR was therapeutic (an INR between 2 and 3), assuming a linear association between 2 measurements. Patients were followed until INR measurements stopped (defined as lack of INR measurements within 60 days), occurrence of an adverse event (ICH/ischemic stroke/myocardial infarction [MI]/death), or 2 years from warfarin initiation.

The serum creatinine measured closest (within ±6 months) to index date was used to calculate eGFR by the Chronic Kidney Disease Epidemiology Collaboration formula, which is based on creatinine, age, sex, and race. All creatinines were isotope dilution mass spectrometry standardized, and renal function was categorized according to Kidney Disease: Improving Global Outcomes staging as follows: estimated glomerular filtration rate (eGFR) ≥60 mL/min per 1.73 m², 45 to 59, 30 to 44, and <30 or treated with dialysis. Patients undergoing dialysis were ascertained by linkage with the Swedish Renal Register. Given that albuminuria is less routinely measured in health care, differentiation of early CKD stages was not possible.

The requirement for informed consent was waived in this study. The study was approved by the local ethics committee in Stockholm, Sweden.

Outcome
The study outcome considered a composite of ICH, ischemic stroke, MI, or death. Events were ascertained through ICD-10 codes (Table S4) in connection with a health care consultation and by linkage with the Swedish Population registry, which records deaths and ICD-10 causes of death for all Swedish citizens with no loss to follow-up. The validity of ICH in the Swedish registry is very high at 99.4%. The validity of other ICD diagnoses derived from the patient register is between 85% and 95%. Events were included if occurring within 30 days from the last INR measurement (30-day lag phase).

Statistical Analysis
Continuous data are presented as mean (±SD) or median (interquartile interval; IQR). Categorical data are presented as number and percentage. Fractional regression analysis was used to assess whether eGFR and CKD stages associated with TTR. Analyses were adjusted for clinically relevant factors and factors reported to be associated with TTR in previous studies. These were: age (in categories: <65, 65–74, 75–85, and ≥85 years), sex, diabetes mellitus, liver disease, hypertension, vascular disease, heart failure, valvular disease, amiodarone use, aspirin use, cancer, and renal function (as 4 eGFR categories eGFR ≥60, 45–59, 30–44, and <30/dialysis).

The association between TTR, renal function, and adverse outcomes was assessed in a logistic regression model. Covariates included renal function categories (same as above), TTR (categories >75, 60–75, and <60%), age (<65, 65–74, 75–84, and ≥85 years), sex, diabetes mellitus, hypertension, vascular disease, heart failure, valvular disease, cancer, known coagulation/platelet defect, anemia, past ischemic stroke, past venous thromboembolism, past intracranial bleeding, past gastrointestinal bleeding, antiplatelet use, number of INR measurements, and number of days on warfarin. Interactions were tested between renal function and TTR, renal function and age, and age and TTR.

As a sensitivity analysis, we recomputed TTR using only INR measurements during the first 180 days (3 months) of therapy (Figure 1) and then estimated time-to-event from day 180 onward. In this setting, we followed patients for up to 2 years regardless of whether warfarin was discontinued. A Kaplan–Meier curve was used to graphically display the unadjusted association between an adverse outcome and...
TTR. A multivariable Cox regression analysis assessed the association between renal function, TTR, and the composite outcome. Covariates included the same as mentioned above. The proportional hazards assumption for the Cox model was tested with the Schoenfeld residuals, and overall fit of the Cox model was evaluated by plotting the Cox-Snell residuals. All analyses were performed using STATA software (version 14.1; StataCorp LP, College Station, TX).

Results

Study Population
Between 2006 and 2011, 11,064 new AF cases were registered in the region of Stockholm. Of those, 7,738 patients initiated warfarin treatment and had a recent creatinine measured to estimate their eGFR (Table 1). The median TTR (IQR) was 83% (71–92). The median eGFR was 73 (59–86) mL/min per 1.73 m². There were 11 patients treated with dialysis.

As compared to patients with normal renal function (eGFR ≥60 mL/min per 1.73 m²), those within CKD were older. Across lower eGFR strata, there was a higher proportion of women and a more-frequent history of hypertension and MI. Both the CHA2DS2-VASC and HAS-BLED scores were higher. Patients with lower eGFR categories more often used medications that could increase the risk of bleeding (eg, aspirin or a combined antiplatelet therapy; Table 1) or drugs known to interact with warfarin (ie, antibiotics).

eGFR Strata and TTR
TTR was poorer across lower eGFR strata (Figure 2, Table 2). This association remained after multivariable adjustment (Figure 3, Table 3). As shown in Table 3, patients with eGFR of 45 to 59 had mean predicted TTR of 79%, which, albeit significantly (P<0.05) lower than the reference category (eGFR ≥60), was only 1% higher (95% CI, 0–25). Patients with eGFR of 30 to 44 had mean predicted TTR of 77%, which was 1% lower (95% CI, −3 to −10; P=0.3) than the reference category. On the
Table 1. Baseline Characteristics of Study Participants

| N          | All  | eGFR ≥60 | eGFR 45 to 59 | eGFR 30 to 44 | eGFR <30 or Dialysis | P Value |
|------------|------|----------|---------------|---------------|----------------------|---------|
| All        | 7738 | 5692     | 1353          | 512           | 181                  |         |
| eGFR, median (IQR) | 73 (59–86) | 80 (71–89) | 54 (50–57) | 39 (36–42) | 23 (15–27) | <0.001 |
| Age, median (IQR), y | 73 (65–80) | 70 (63–78) | 78 (72–83) | 81 (76–85) | 80 (71–85) | <0.001 |
| <65        | 2006 (25.9%) | 1846 (32.4%) | 108 (8.0%) | 30 (5.9%) | 22 (12.2%) | <0.001 |
| 65 to 74   | 2461 (31.8%) | 1953 (34.3%) | 382 (28.2%) | 88 (17.2%) | 38 (21.0%) |         |
| 75 to 84   | 2565 (33.1%) | 1603 (28.2%) | 631 (46.6%) | 253 (49.4%) | 78 (43.1%) |         |
| ≥85        | 706 (9.1%) | 290 (5.1%) | 232 (17.1%) | 141 (27.5%) | 43 (23.8%) | <0.001 |
| Female     | 3153 (40.7%) | 2112 (37.1%) | 676 (50.0%) | 273 (53.3%) | 92 (50.8%) | <0.001 |
| CHA2DS2-VASc, mean (SD) | 2.9 (1.8) | 2.6 (1.8) | 3.7 (1.6) | 4.4 (1.6) | 4.2 (1.7) | <0.001 |
| HAS-BLED, mean (SD) | 2.1 (1.1) | 1.9 (1.1) | 2.4 (1.0) | 2.6 (0.9) | 3.1 (1.0) | <0.001 |

Comorbid history

| MI          | 690 (8.9%) | 402 (7.1%) | 146 (10.8%) | 105 (20.5%) | 37 (20.4%) | <0.001 |
| Ischemic heart disease | 1423 (18.4%) | 892 (15.7%) | 309 (22.8%) | 168 (32.8%) | 54 (29.8%) | <0.001 |
| Peripheral arterial disease | 382 (4.9%) | 227 (4.0%) | 83 (6.1%) | 49 (9.6%) | 23 (12.7%) | <0.001 |
| PCI         | 216 (2.8%) | 134 (2.4%) | 48 (3.5%) | 31 (6.1%) | 3 (1.7%) | <0.001 |
| CABG        | 112 (1.4%) | 73 (1.3%) | 26 (1.9%) | 12 (2.3%) | 1 (0.6%) | 0.068 |
| Hypertension | 4014 (51.9%) | 2693 (47.3%) | 820 (60.6%) | 364 (71.1%) | 92 (50.8%) | <0.001 |
| Diabetes mellitus | 1153 (14.9%) | 741 (13.0%) | 241 (17.8%) | 122 (23.8%) | 43 (23.8%) | <0.001 |
| Heart failure | 716 (9.3%) | 315 (5.5%) | 203 (15.0%) | 137 (26.8%) | 61 (33.7%) | <0.001 |
| Valvular disease | 94 (1.2%) | 60 (1.1%) | 18 (1.3%) | 11 (2.1%) | 5 (2.8%) | 0.033 |
| Biological valve prosthesis | 43 (0.6%) | 25 (0.4%) | 9 (0.7%) | 6 (1.2%) | 3 (1.7%) | 0.027 |
| Mechanical valve prosthesis | 65 (0.8%) | 38 (0.7%) | 17 (1.3%) | 7 (1.4%) | 3 (1.7%) | 0.046 |
| Pacemaker/ICD | 367 (4.7%) | 226 (4.0%) | 80 (5.9%) | 47 (9.2%) | 14 (7.7%) | <0.001 |
| Known liver disease | 31 (0.4%) | 23 (0.4%) | 2 (0.1%) | 3 (0.6%) | 3 (1.7%) | 0.021 |
| Chronic obstructive pulmonary disease | 489 (6.3%) | 332 (5.8%) | 95 (7.0%) | 46 (9.0%) | 16 (8.8%) | 0.009 |
| Cancer (within last 3 years) | 971 (12.5%) | 631 (11.1%) | 211 (15.6%) | 94 (18.4%) | 35 (19.3%) | <0.001 |
| Alcohol abuse | 151 (2.0%) | 123 (2.2%) | 16 (1.2%) | 7 (1.4%) | 5 (2.8%) | 0.071 |
| Dementia     | 33 (0.4%) | 17 (0.3%) | 10 (0.7%) | 6 (1.2%) | 0 (0.0%) | 0.005 |
| Gastrointestinal bleeding | 124 (1.6%) | 85 (1.5%) | 23 (1.7%) | 9 (1.8%) | 7 (3.9%) | 0.091 |
| Known coagulation/platelet defect | 58 (0.7%) | 37 (0.7%) | 13 (1.0%) | 6 (1.2%) | 2 (1.1%) | <0.001 |
| Known anemia | 311 (4.0%) | 178 (3.1%) | 65 (4.8%) | 41 (8.0%) | 27 (14.9%) | <0.001 |
| Ischemic stroke | 616 (8.0%) | 421 (7.4%) | 122 (9.0%) | 59 (11.5%) | 14 (7.7%) | 0.004 |
| Transient ischemic attack | 289 (3.7%) | 201 (3.5%) | 55 (4.1%) | 27 (5.3%) | 6 (3.3%) | 0.21 |
| Peripheral systemic embolism | 66 (0.9%) | 31 (0.5%) | 15 (1.1%) | 15 (2.9%) | 5 (2.8%) | <0.001 |
| Pulmonary embolism | 308 (4.0%) | 191 (3.4%) | 64 (4.7%) | 38 (7.4%) | 15 (8.3%) | <0.001 |
| Deep venous thrombosis | 191 (2.5%) | 138 (2.4%) | 30 (2.2%) | 19 (3.7%) | 4 (2.2%) | 0.29 |

Medication history (last 6 months)

| Aspirin     | 2782 (36.0%) | 1870 (32.9%) | 598 (44.2%) | 241 (47.1%) | 73 (40.3%) | <0.001 |
| Clopidogrel | 158 (2.0%) | 94 (1.7%) | 34 (2.5%) | 24 (4.7%) | 6 (3.3%) | <0.001 |
| NSAID       | 1250 (16.2%) | 908 (16.0%) | 217 (16.0%) | 94 (18.4%) | 31 (17.1%) | 0.54 |
| Acetaminophen | 971 (12.5%) | 642 (11.3%) | 185 (13.7%) | 99 (19.3%) | 45 (24.9%) | <0.001 |

Continued
other hand, patients with an eGFR <30/dialysis had a mean predicted TTR of 68% (95% CI, 65–72), which was 10% lower than the reference category. The fully adjusted multivariable model is shown in Table 4. Other covariates independently associated with worse TTR were, besides eGFR strata, female sex (weak association), higher age (weak association), presence of diabetes mellitus, vascular disease, or heart failure, and concomitant use of aspirin (Table 4).

TTR, eGFR Strata, and Risk of Adverse Outcomes

A total of 402 (5.1%) adverse events occurred during 254 days (IQR, 91–691; Table 5). The most common adverse event was death (2.6%), followed by ischemic stroke (1.7%), ICH (0.5%), and MI (0.4%). In adjusted logistic regression analyses, both renal function and TTR were independently associated with the odds of adverse events (Table 6). The association between TTR and adverse events was not modified by differing eGFR (P for interaction, 0.169). Patients with TTR 60% to 75% (odds ratio [OR], 1.84; 95% CI, 1.41–2.40) and TTR <60% (OR, 2.09; CI, 1.59–2.74) had higher odds of adverse events than patients with TTR >75%.

Sensitivity Analyses

There were 7577 (98%) event-free patients during the first 3 months of warfarin therapy (Figure 1). Survival is graphically displayed after the first 3 months according to TTR strata (Figure S1) and in relation to renal function (Figure S2). We estimated TTR from the first 3 months of INR measurement (Table S5) and modeled time to event from month 3 onward by Cox proportional models without censoring at warfarin cessation. During follow-up, 683 patients (9.0%) had an event (Table S6). In adjusted Cox regression analysis (Table S7), both a lower TTR and a lower renal function predicted adverse outcomes, with no interaction terms (P for interaction = 0.8). Patients with TTR 60% to 75% (hazard ratio [HR], 1.52; CI, 1.25–1.83) and with TTR <60% (HR, 1.89; CI, 1.58–2.25) had a 52% and 89% higher risk of adverse events, respectively, as compared with a TTR >75%.

Discussion

This study shows a clinically relevant association between renal dysfunction and poor TTR among new AF patients on warfarin. An adequate TTR was less frequently achieved in CKD patients, especially among those with severe CKD. This study also shows that fewer adverse events are observed in patients with adequate TTR, irrespective of underlying renal function.

TTR is a measure of long-term INR control, which is frequently used in clinical trials and recommended by current National Institute for Health and Care Excellence guidelines.17 However, we acknowledge that it is probably still rarely used in clinical practice. TTR gives a percentage of time of the treatment period that the INR was therapeutic, but it does not tell whether values were sub- or supratherapeutic. Adverse events are closely related to achieved TTR, with an optimal

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**Table 1. Continued**

| Statins | All       | eGFR ≥60 | eGFR 45 to 59 | eGFR 30 to 44 | eGFR <30 or Dialysis | P Value |
|---------|-----------|----------|---------------|---------------|-----------------------|---------|
|         | 1927 (24.9%) | 1299 (22.8%) | 395 (29.2%) | 176 (34.4%) | 57 (31.5%) | <0.001  |
| SSRI    | 337 (4.4%) | 233 (4.1%) | 71 (5.2%) | 25 (4.9%) | 8 (4.4%) | 0.28    |
| Proton pump inhibitor | 1023 (13.2%) | 666 (11.7%) | 212 (15.7%) | 104 (20.3%) | 41 (22.7%) | <0.001  |
| Amiodarone | 12 (0.2%) | 8 (0.1%) | 2 (0.1%) | 1 (0.2%) | 1 (0.6%) | 0.58    |
| Macrolides | 52 (0.7%) | 33 (0.6%) | 12 (0.9%) | 2 (0.4%) | 5 (2.8%) | 0.003   |
| Quinolones | 260 (3.4%) | 171 (3.0%) | 54 (4.0%) | 22 (4.3%) | 13 (7.2%) | 0.004   |
| Cotrimoxazole | 24 (0.3%) | 17 (0.3%) | 4 (0.3%) | 0 (0.0%) | 3 (1.7%) | 0.007   |

Data are presented as n (%), median (IQR) or mean (SD). CABG indicates coronary artery bypass graft; ICD, intracardiac defibrillator; IQR, interquartile range; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; SSRI, selective serotonin reuptake inhibitors.

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**Figure 2.** Proportion of patients in different time-in-therapeutic ranges (TTR) across worsening eGFR strata. eGFR indicates estimated glomerular filtration rate.

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Table 2. TTR Across eGFR Strata

| N         | All   | eGFR ≥60 | eGFR 45 to 59 | eGFR 30 to 44 | eGFR <30 or Dialysis | P Value |
|-----------|-------|----------|---------------|---------------|--------------------|---------|
| TTR %, median (IQR) | 7738  | 5692     | 1353          | 512           | 181                |         |
| TTR %, mean (SD) | 78 (20) | 78 (20) | 79 (19)       | 76 (21)       | 66 (23)            | <0.001  |
| TTR in categories |    |          |               |               |                    |         |
| TTR >75%, n (%)     | 5204 (67.3) | 3853 (67.7) | 951 (70.3)   | 324 (63.3)    | 76 (42.0)        | <0.001  |
| TTR 60% to 75%, n (%) | 1423 (18.4) | 1042 (18.3) | 248 (18.3)   | 94 (18.4)     | 39 (21.5)        |         |
| TTR <60%, n (%)     | 1111 (14.4) | 797 (14.0) | 154 (11.4)    | 94 (18.4)     | 66 (36.5)        |         |
| Number of INR measurements, median (IQR) | 21 (9–39) | 20 (9–38) | 25 (10–41)   | 24 (11–42)    | 21 (9–43)        | <0.001  |
| Median (IQR) days on warfarin | 254 (91–691) | 244 (91–671) | 329 (99–708) | 287 (96–704)  | 175 (57–589)     | <0.001  |
| Median (IQR) days between INRs | 12 (8–17) | 12 (8–17) | 13 (8–17)    | 12 (8–16)     | 9 (5–14)         | <0.001  |
| Percent (IQR) of INRs >3.0 | 11% (0–19) | 11 (0–19) | 12 (3.7–20)  | 13 (5.8–21)   | 14 (6.5–23)      | <0.001  |
| Percent (IQR) of INRs ≤2.0 | 19% (9–31) | 18 (9–30) | 19 (10–30)   | 20 (10–31)    | 29 (18–43)       | <0.001  |

IQR indicates interquartile range; INRs, international normalized ratios; TTR, time-in-therapeutic range.

threshold of TTR somewhere above 58% to 65%.²,¹⁷–²⁰ In our study, the observed TTR was exceptionally high, in accord with Sweden’s renowned good INR control (with a mean over 75% in several randomized, controlled, clinical trials¹⁶,¹⁸). Yet, our study did observe that despite extensive adjustment for confounders, those with eGFR <30/dialysis had a clinically worse TTR. The reasons behind the worse TTR in CKD patients cannot be inferred from our observational design, but may be attributed to renal function per se, as well as factors/conditions associated with CKD. It is notable that patients with severe CKD had more-frequent INR measurements, possibly attributed to difficulties in achieving optimal INR, more-frequent therapy discontinuations attributed to procedures/intervention, or by the more-frequent use of drugs known to interact with warfarin. Our study expands to a real-life North European setting the series of studies from Limdi et al, showing, in the US Warfarin Pharmacogenetics Cohort, that patients with CKD not requiring dialysis require lower warfarin doses, more often had supratherapeutic INRs (INR >4), and have a higher risk of hemorrhage, as compared to patients with normal kidney function.²,²¹–²³ The difficulty of CKD patients in keeping optimal INR was also reported by Quinn et al²⁴ in 46 US dialysis patients with weekly INR measurements and an achieved mean TTR of 49.2%.

There is strong evidence that the risk of ischemic stroke caused by AF can be substantially reduced with adequate

Figure 3. Adjusted mean predictions of time-in-therapeutic range (TTR) with 95% confidence intervals in 4 eGFR strata. Output from a multivariable fractional regression analysis including eGFR strata, age (in categories: <65, 65–74, 75–85, and ≥85 years), sex, diabetes mellitus, liver disease, hypertension, vascular disease, heart failure, valvular disease, amiodarone use, aspirin use, and cancer. eGFR indicates estimated glomerular filtration rate.

Table 3. Predictors of TTR

| CKD Stage* (mL/min per 1.73 m²) | TTR (95% CI) | P Value | Change in TTR (95% CI) | P Value |
|--------------------------------|-------------|---------|-----------------------|--------|
| ≥60                            | 78% (77–79) | <0.001  | (Ref)                 | …      |
| 45 to 59                       | 79% (78–80) | <0.001  | 1% (0–25)             | 0.033  |
| 30 to 44                       | 77% (75–79) | <0.001  | −1% (−3 to 10)        | 0.313  |
| <30 or dialysis                | 68% (65–72) | <0.001  | −10% (−13 to −60)     | <0.001 |

Simplified fractional regression analysis showing the mean predicted TTR across renal function categories and the relative change (in proportion) from the reference category. *Fractional regression analysis adjusted for: age (in categories: <65, 65–74, 75–85, ≥85 years), sex, diabetes mellitus, liver disease, hypertension, vascular disease (myocardial infarction, ischemic heart disease, peripheral arterial disease), heart failure, valvular disease, amiodarone use, aspirin use, and cancer. CKD indicates chronic kidney disease; TTR, time-in-therapeutic range.
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Table 4. Full Fractional Regression Analysis Showing the Coefficients (and 95% Confidence Intervals) of All Available Covariates Considered to Influence TTR

| Predictors of TTR                           | Coefficient (95% CI) | P Value |
|--------------------------------------------|----------------------|---------|
| Renal function categories                  |                      |         |
| eGFR ≥60                                   | Ref                  |         |
| eGFR 45 to 59                              | 7.6% (0.5–14.7)      | 0.035   |
| eGFR 30 to 44                              | –5.9% (–17.3 to 5.4) | 0.307   |
| eGFR <30 or dialysis                        | –50.1% (–65.5 to –34.6) | <0.001 |
| Age, y                                     |                      |         |
| Age <65                                    | Ref                  |         |
| Age 65 to 74                                | 7.7% (0.6–14.7)      | 0.034   |
| Age 75 to 84                                | 3.1% (–4.2 to 10.5)  | 0.404   |
| Age ≥85                                    | –2.4% (–13.3 to 8.6) | 0.671   |
| Women                                      | –5.3% (–10.8 to 1.8) | 0.058   |
| Diabetes mellitus                          | –13.2% (–20.6 to –5.8) | <0.001 |
| Liver disease                              | –21.9% (–66.0 to 22.2) | 0.330   |
| Hypertension                               | 1.5% (–4.0 to 7.0)   | 0.596   |
| Vascular disease (past MI, ischemic heart disease, peripheral arterial disease) | –10.5% (–18.5 to –2.5) | 0.010   |
| Heart failure                              | –17.1% (–26.4 to –7.7) | <0.001 |
| Valvular disease                           | 4.4% (–19.3 to 28.0) | 0.717   |
| Amiodarone                                  | –35.9% (–111 to 39.6) | 0.351   |
| Aspirin                                    | 6.3% (5.4–11.9)      | 0.032   |
| Cancer within last 3 years                 | –4.9% (–12.8 to 3.0) | 0.226   |

eGFR indicates estimated glomerular filtration rate; MI, myocardial infarction; TTR, time-in-therapeutic range.

Table 5. Proportion of Survivors as Well as Single and Composite Study Outcomes Across eGFR Strata

| N     | eGFR ≥60 | eGFR 45 to 59 | eGFR 30 to 44 | eGFR <30 or Dialysis | P Value |
|-------|----------|---------------|---------------|----------------------|---------|
| Single endpoints |         |               |               |                      |         |
| ICH   | 26 (0.5%) | 9 (0.7%)      | 2 (0.4%)      | 2 (1.1%)             | <0.001  |
| Ischemic stroke | 86 (1.5%) | 31 (2.3%)     | 11 (2.2%)     | 5 (2.8%)             |         |
| MI    | 12 (0.2%) | 10 (0.7%)     | 9 (1.8%)      | 1 (0.6%)             |         |
| Death | 102 (1.8%) | 42 (3.1%) | 33 (6.5%) | 21 (11.6%) |         |
| Combined endpoint |     |               |               |                      |         |
| ICH/ischemic stroke/MI/death | 226 (4.0%) | 92 (6.8%) | 55 (10.7%) | 29 (16.0%) | <0.001  |

Data presented as n (%). eGFR indicates estimated glomerular filtration rate; ICH, intracranial hemorrhage; MI, myocardial infarction.

Strengths of this study are the large real-life cohort with information on INR control and eGFR. In addition, the inclusion of newly diagnosed AF patients with complete information on warfarin therapy and outcomes provides more-unbiased associations. However, this study also has limitations: Our analysis is based on repeated warfarin dispensations, but we lack

In our study, subtherapeutic INRs (19% of measurements) were more common than supratherapeutic ones (11%). We speculated that poor TTR may, in part, explain the worse outcome and higher bleeding rate described in observational studies of CKD patients on warfarin, particularly among those undergoing dialysis. We observed no interaction between TTR and eGFR and outcome in our study, suggesting that both factors affect outcome independently of each other, and that adequate TTR reduces the adverse event risk also in patients with advanced CKD/dialysis. Despite being the largest study of its kind, we could only identify 11 patients on dialysis satisfying inclusion criteria, and we are therefore underpowered to report TTR-associated outcomes in this particular population. However, our findings accord with an earlier small, retrospective study indicating that no dialysis patient with adequate INR control had a stroke or a fatal bleeding event. Further, Kooiman et al observed that both less time spent within therapeutic range and high INR variability were factors associated with increased risk of stroke and bleeding in warfarin-treated CKD patients. Within our study design, we were concerned that patients who were critically ill/moribund would be taken off warfarin and died shortly after warfarin discontinuation. For that reason, our sensitivity analysis estimated TTR on the first 3 months and analyzed outcome risk emulating an “intention to treat” design. The fact that results were comparable to our main analysis provides robustness to our conclusions.

warfarin therapy. Subtherapeutic INR (below 2.0) increases the risk of ischemic stroke, and supratherapeutic INR (above 3.0 and particularly above 4.0) sharply increases the risk of intracranial bleeding. A recent study indicated that ICH risk associated with INR ≥4.0 increased by several fold in individuals with advanced CKD. In most reports, as well as in our study, subtherapeutic INRs (19% of measurements) were more common than supratherapeutic ones (11%). We speculated that poor TTR may, in part, explain the worse outcome and higher bleeding rate described in observational studies of CKD patients on warfarin, particularly among those undergoing dialysis. We observed no interaction between TTR and eGFR and outcome in our study, suggesting that both factors affect outcome independently of each other, and that adequate TTR reduces the adverse event risk also in patients with advanced CKD/dialysis. Despite being the largest study of its kind, we could only identify 11 patients on dialysis satisfying inclusion criteria, and we are therefore underpowered to report TTR-associated outcomes in this particular population. However, our findings accord with an earlier small, retrospective study indicating that no dialysis patient with adequate INR control had a stroke or a fatal bleeding event. Further, Kooiman et al observed that both less time spent within therapeutic range and high INR variability were factors associated with increased risk of stroke and bleeding in warfarin-treated CKD patients. Within our study design, we were concerned that patients who were critically ill/moribund would be taken off warfarin and died shortly after warfarin discontinuation. For that reason, our sensitivity analysis estimated TTR on the first 3 months and analyzed outcome risk emulating an “intention to treat” design. The fact that results were comparable to our main analysis provides robustness to our conclusions.

Strengths of this study are the large real-life cohort with information on INR control and eGFR. In addition, the inclusion of newly diagnosed AF patients with complete information on warfarin therapy and outcomes provides more-unbiased associations. However, this study also has limitations: Our analysis is based on repeated warfarin dispensations, but we lack
information on short-term therapy discontinuations or indications for it. This probably would have prompted the physician to order more INR measurements during that period of time, but likely in the long term would have less effect on TTR. Finally, we only accounted for comorbidities and drugs interacting with warfarin at index date, but not during follow-up. In the multivariable fractional regression analysis, we have included all available variables. However, there could still be residual confounding, given that unmeasured factors associated with a worse TTR are not accounted for. However, it is unknown whether renal function is associated with additional harmful factors.

### Conclusion

In real-life newly diagnosed AF patients on warfarin, those with eGFR <30/dialysis have a significantly worse INR control. An optimal TTR (>75%) is associated with lower risk of adverse events, independently of underlying renal function. Identifying the reasons behind, and applying more-stringent efforts to improve, the TTR of these patients is necessary to ensure warfarin’s net clinical benefit.

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### Disclosures

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| Co-morbidities at entry | ICD-codes (Patient registry) occurring within the last 5 years or or ATC-code (Swedish Drug Prescription registry) occurring within the last 6 months to study entry |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Heart failure           | I50, I110, I130, I132, I255, K761, I42-43 and purchase of diuretics (ATC: C03)                                                                                                                     |
| Valvular disease        | I342, I050, I052, Q232, Z952                                                                                                                                                                      |
| Other valvular disease  | I34-39 except I342, Z953                                                                                                                                                                          |
| Prosthetic heart valve (biological) | Z953                                                                                                                                                                                               |
| Prosthetic heart valve (mechanic) | Z952                                                                                                                                                                                               |
| Pacemaker or ICD        | Z950, Z450 or procedure code FPE                                                                                                                                                                   |
| Hypertension            | I10-15 or purchase of antihypertensive drugs (ATC: C02)                                                                                                                                          |
| Liver disease           | K70-77 or procedure codes JJB, JJC                                                                                                                                                                  |
| Chronic obstructive pulmonary disease | J43-44                                                                                                                                                                                               |
| Cancer                  | Any diagnosis in the C domain of ICD-10                                                                                                                                                              |
| Alcohol use, via the Swedish alcohol index | E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714                                                                                                    |
| Dementia                | F00-03                                                                                                                                                                                                  |
| Intracranial bleeding   | I60-62, S064-066, I690-692                                                                                                                                                                          |
| Gastrointestinal bleeding | I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922                                                                 |
| Urogenital bleeding     | N02, R319, N95                                                                                                                                                                                      |
| Other bleeding          | H431, R04, R58, D629, or procedure code DR029                                                                                                                                                        |
| Coagulation or platelet defect | D65-69                                                                                                                                                                                               |
| Anaemia                 | D50-64                                                                                                                                                                                                  |
| Ischaemic stroke        | I63, I693                                                                                                                                                                                               |
| Unspecified stroke      | I64, I694                                                                                                                                                                                               |
| Transient ischaemic attack | G45                                                                                                                                                                                                     |
| Peripheral systemic embolism | I74                                                                                                                                                                                                   |
| Composite thromboembolism | I63-64, G45, I74, I693, I694                                                                                                                                                                         |
| Pulmonary embolism      | 126                                                                                                                                                                                                 |
| Deep venous thrombosis  | I801-802                                                                                                                                                                                               |
| Composite venous thromboembolism | 126, I801-802                                                                                                                                                                                          |
| Myocardial infarction   | 121, I252                                                                                                                                                                                               |
| Ischaemic heart disease | 120-25                                                                                                                                                                                                  |
| PCI-procedure procedure code | FNG                                                                                                                                                                                                     |
| CABG-procedure procedure codes | FNA, FNB, FNC, FND, FNE, FNF, FNH                                                                                                                                                                  |
| Peripheral arterial disease | I70-73                                                                                                                                                                                                |
| Vascular disease        | I21, I252, I70-73                                                                                                                                                                                      |
Table S2. Medication collected from the pharmacy obtained from the Swedish Drug Prescription Registry

| Exposure medication                                      | ATC-code (Swedish Drug Prescription registry) |
|----------------------------------------------------------|---------------------------------------------|
| Warfarin                                                  | B01AA03                                     |
| Medication use at study inclusion date                    | ATC-code                                   |
| (first warfarin purchase-date) or within the preceding 6 months |                                            |
| Aspirin                                                   | B01AC06                                     |
| Clopidogrel                                               | B01AC04                                     |
| Dipyridamole                                              | B01AC07                                     |
| NSAID                                                     | M01A                                        |
| Paracetamol                                               | N02BE01                                     |
| Statins                                                   | C10AA                                       |
| Antidepressant: Selective Serotonin Reuptake inhibitor (SSRI) | N06AB                                       |
| Proton pump inhibitor                                     | A02BC                                       |
| Amiodarone                                                | C01BD01                                     |
| Macrolide                                                 | J01FA                                       |
| Quinolone                                                 | J01M                                        |
| Combinations of sulphonamides and trimethoprim            | J01EE                                       |
Table S3. Definition of CHA₂DS₂-VASc and HAS-BLED score

| CHA₂DS₂-VASc score                                      | Points | ICD-codes from Patient registry | ATC-codes from Drug Prescription registry |
|--------------------------------------------------------|--------|---------------------------------|------------------------------------------|
| Congestive heart failure                               | 1 point|                                |                                          |
| Hypertension                                           | 1 point|                                |                                          |
| Age >75 years                                          | 2 points|                               |                                          |
| Diabetes                                               | 1 point|                                |                                          |
| Stroke/Transient ischemic attack/Unspecified stroke/    | 2 point|                                |                                          |
| Systemic thromboembolism/Pulmonary embolism/Deep venous|        |                                |                                          |
| thrombosis                                             |        |                                |                                          |
| Vascular disease                                       | 1 point|                                |                                          |
| Age 65-75 years                                        | 1 point|                                |                                          |
| Sex Category: female gender                            | 1 point|                                |                                          |

**HAS-BLED score**

| HAS-BLED score                                      | Points | ICD-codes from Patient registry | ATC-codes from Drug Prescription registry |
|-----------------------------------------------------|--------|---------------------------------|------------------------------------------|
| Hypertension                                        | 1 point|                                |                                          |
| Abnormal liver och renal function                   | 1 or 2 points|                                |                                          |
| Stroke                                              | 1 point|                                |                                          |
| Bleeding                                             | 1 point|                                |                                          |
| Labile INR (TTR<60%)                                 | 1 point|                                |                                          |
| Elderly (age ≥ 65 years)                             | 1 point|                                |                                          |
| Drugs or alcohol abuse                               | 1 or 2 points|                                |                                          |
### Table S4. Definition of events during follow-up

| Definition of outcomes during follow-up | ICD 10-code (Patient registry) |
|----------------------------------------|--------------------------------|
| Intracranial bleeding                  | I60-62, S064-066, I690-692     |
| Ischemic stroke                        | I63, I693                       |
| Myocardial infarction                  | I21, I252                       |
| Death                                  | Population-registry             |
|                                        | Date of death                   |
Table S5. Sensitivity analysis (TTR based on first 90 days): Time-in-therapeutic range (TTR) in the different renal function categories

|                      | All     | eGFR ≥60 | eGFR 45-59 | eGFR 30-44 | eGFR ≤30 or dialysis | p-value |
|----------------------|---------|----------|------------|------------|----------------------|---------|
| N                    | 7577    | 5596     | 1324       | 495        | 162                  |         |
| TTR %, median (IQR)  | 82 (64-96) | 82 (65-96) | 81 (65-97) | 81 (61-95) | 71 (55-86)            | <0.001  |
| TTR %, mean (SD)     | 77 (23) | 77 (23)  | 77 (22)    | 75 (25)    | 68 (24)              | <0.001  |
| TTR in categories    |         |          |            |            |                      |         |
| TTR >75%, n (%)      | 4567 (60.3%) | 3409 (60.9%) | 799 (60.3%) | 289 (58.4%) | 70 (43.2%)            | <0.001  |
| TTR 60-75%, n (%)    | 1486 (19.6%) | 1085 (19.4%) | 267 (20.2%) | 93 (18.8%) | 41 (25.3%)            |         |
| TTR <60%, n (%)      | 1524 (20.1%) | 1102 (19.7%) | 258 (19.5%) | 113 (22.8%) | 51 (31.5%)            |         |
| Number of INR        |         |          |            |            |                      |         |
| measurement, median  | 8 (5-11) | 8 (5-11)  | 8 (5-11)   | 7 (5-11)   | 8 (6-11)              | 0.240   |
| Median number of days|         |          |            |            |                      |         |
| on warfarin, median  | 79 (67-88) | 80 (68-85)  | 79 (66-85) | 80 (70-85) | 77 (63-84)            | 0.279   |
| Median (IQR) number  |         |          |            |            |                      |         |
| of days passing between|         |          |            |            |                      |         |
| each INR % (IQR)     | 9 (6-12) | 8 (6-12)  | 9 (6-12)   | 9 (7-13)   | 9 (6-12)              | 0.079   |
| % (IQR) of INR        |         |          |            |            |                      |         |
| measurements above 3 | 0 (0-20) | 0 (0-19)  | 8 (0-22)   | 9 (0-25)   | 9 (0-22)              | <0.001  |
| % (IQR) of INR        |         |          |            |            |                      |         |
| measurements below 2 | 20 (0-36) | 20 (0-36)  | 20 (0-33)  | 20 (0-33)  | 29 (14-50)            | <0.001  |
Table S6. Sensitivity analysis (TTR based on first 90 days): Proportion of single and composite study outcomes across eGFR strata

| Level                      | eGFR ≥60 | eGFR 45-59 | eGFR 30-44 | eGFR <30 or dialysis | p-value |
|----------------------------|----------|------------|------------|----------------------|---------|
| **Single endpoints**       |          |            |            |                      |         |
| ICH                        | 45 (0.8%)| 16 (1.2%)  | 3 (0.6%)   | 1 (0.6%)             | <0.001  |
| Ischemic stroke            | 129 (2.3%)| 41 (3.1%)  | 13 (2.6%)  | 6 (3.7%)             |         |
| MI                         | 24 (0.4%)| 9 (0.7%)   | 10 (2.0%)  | 1 (0.6%)             |         |
| Death                      | 208 (3.7%)| 86 (6.5%)  | 60 (12.1%) | 31 (19.1%)           |         |
| **Combined endpoint**      |          |            |            |                      |         |
| ICH/Ischemic stroke/MI/Death| 406 (7.3%)| 152 (11.5%)| 86 (17.4%)| 39 (24.1%)           | <0.001  |

ICH: Intracranial hemorrhage; MI: Myocardial infarction.
Table S7. Sensitivity analysis (TTR based on first 90 days): Multivariable Cox regression analysis of factors associated with the composite endpoint of intracranial hemorrhage, ischemic stroke, myocardial infarction and death (n=7577)

|                                    | HR (95% CI) | p-value* |
|------------------------------------|-------------|----------|
| **Renal function (ml/min/1.73m²)** |             |          |
| eGFR ≥60                           | 1.0 (ref)   |          |
| eGFR 45-59                         | 1.06 (0.87-1.29) | 0.545 |
| eGFR 30-44                         | 1.26 (0.98-1.62) | 0.074 |
| eGFR <30, or dialysis              | 1.69 (1.20-2.39) | 0.003 |
| **Time in therapeutic range (TTR)**|             |          |
| TTR ≥75%                           | 1.0 (ref)   |          |
| TTR 60-75%                         | 1.52 (1.25-1.83) | <0.001 |
| TTR <60%                           | 1.88 (1.58-2.24) | <0.001 |
| **Age (years)**                    |             |          |
| < 65 years                         | 1.0 (ref)   |          |
| 65-74 years                        | 1.56 (1.19-2.06) | 0.001 |
| 75-84 years                        | 2.75 (2.11-3.57) | <0.001 |
| ≥ 85 years                         | 3.77 (2.77-5.14) | <0.001 |
| **Female**                         | 1.00 (0.85-1.16) | 0.995 |
| Diabetes                           | 1.32 (1.08-1.60) | 0.006 |
| Hypertension                       | 1.01 (0.86-1.19) | 0.890 |
| Vascular disease (prior myocardial infarction, ischemic heart disease, or peripheral arterial disease) | 1.33 (1.09-1.62) | 0.006 |
| Heart failure                      | 1.72 (1.39-2.11) | <0.001 |
| Valvular disease                   | 1.17 (0.65-2.11) | 0.595 |
| Cancer within last 3 years         | 1.22 (1.01-1.49) | 0.047 |
| Coagulation/platelet defect         | 1.19 (0.56-2.52) | 0.650 |
| Anemia                             | 1.17 (0.86-1.58) | 0.376 |
| Ischemic stroke                    | 1.04 (0.71-1.47) | 0.832 |
| Prior systemic emboli              | 1.11 (0.81-1.53) | 0.507 |
| Deep vein thrombosis/Pulmonary embolism | 1.52 (1.18-1.95) | 0.001 |
| Prior intracranial hemorrhage      | 1.78 (0.79-4.02) | 0.001 |
| Prior gastrointestinal bleeding    | 0.93 (0.51-1.69) | 0.807 |
| Antiplatelet therapy               | 1.05 (0.89-1.24) | 0.549 |

* Interaction terms tested: age and eGFR: p=0.044; age and TTR, p =0.244; eGFR and TTR, p=0.804.
Figure S1. Sensitivity analysis: Association of TTR and renal function to outcome. Kaplan-Meier curve: time-in-therapeutic range and association to outcome
Outcome is a composite of intracranial hemorrhage/ischemic stroke/myocardial infarction/death.
**Figure S2.** Kaplan-Meier curve for combined eGFR and TTR groups: