ORIGINAL RESEARCH

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 m^2) 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,[9] 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.[9]

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.[10] Information on pharmacy-dispensed medications was obtained from the Swedish Dispensed Drug registry, which records all dispensations from any Swedish pharmacy (Table S2).

The index date was the day of the first warfarin dispensation after a new AF diagnosis. Demographics, comorbid 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.[11] 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,[12] 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[13] as follows: estimated glomerular filtration rate (eGFR) ≥60 mL/min per 1.73 m^2, 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%.[14] The validity of other ICD diagnoses derived from the patient register is between 85% and 95%.[15] 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.[3,16] 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

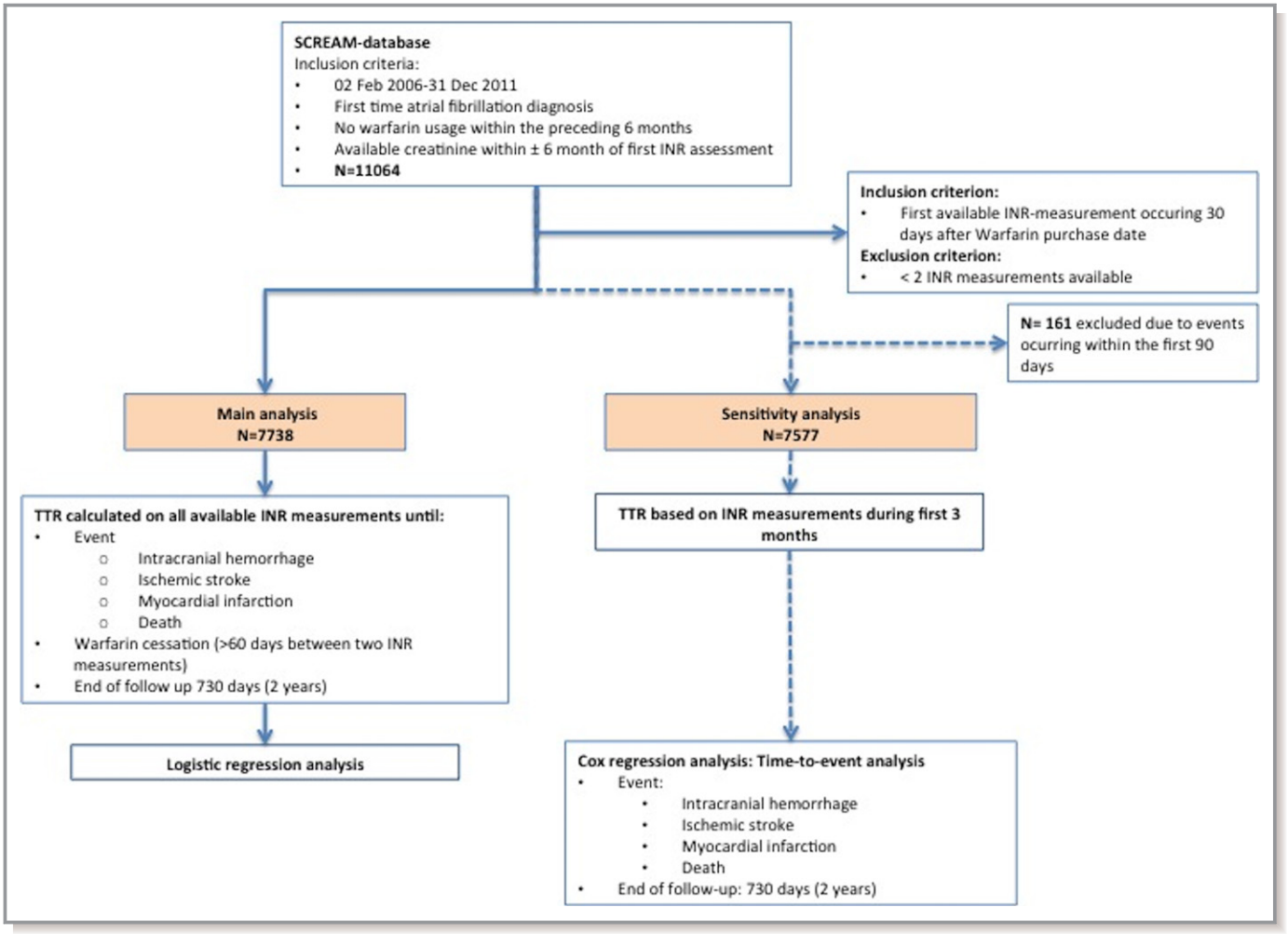

Figure 1. Flow chart. INR, international normalized ratio.

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, 7738 patients initiated warfarin treatment and had a recent creatinine measured to estimate their eGFR (Figure 1, Table 1). The median TTR (IQR) was 83% (71–92). The median eGFR was 73 (59–86) mL/min per 1.73 m^2. There were 11 patients treated with dialysis.

As compared to patients with normal renal function (eGFR ≥60 mL/min per 1.73 m^2), 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 CHA_2DS_2-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

	All	eGFR ≥60	eGFR 45 to 59	eGFR 30 to 44	eGFR <30 or Dialysis	*P* Value
N	7738	5692	1353	512	181	
eGFR, median (IQR)	73 (59–86)	80 (71–89)	54 (50–57)	39 (36–42)	23 (15–27)	
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%)	
Female	3153 (40.7%)	2112 (37.1%)	676 (50.0%)	273 (53.3%)	92 (50.8%)	<0.001
CHA_2DS_2-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%)	137 (75.7%)	<0.001
Diabetes mellitus	1153 (14.9%)	741 (13.0%)	241 (17.8%)	122 (23.8%)	49 (27.1%)	<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

Table 1. Continued

	All	eGFR ≥60	eGFR 45 to 59	eGFR 30 to 44	eGFR <30 or Dialysis	*P* Value
Statins	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.

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%.

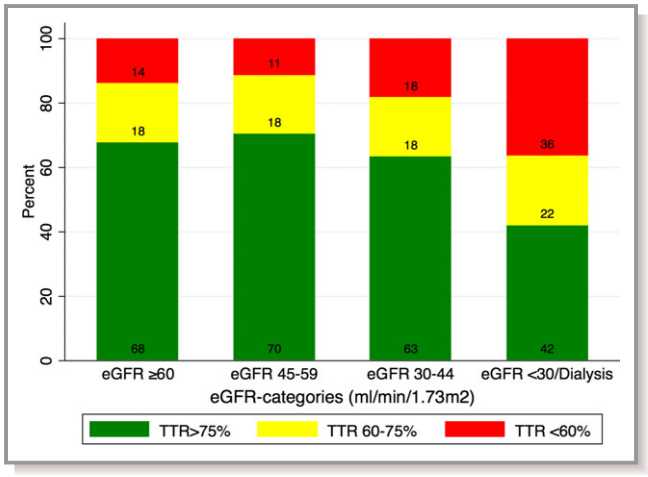

Figure 2. Proportion of patients in different time-in-therapeutic ranges (TTR) across worsening eGFR strata. eGFR indicates estimated glomerular filtration rate.

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

Table 2. TTR Across eGFR Strata

	All	eGFR ≥60	eGFR 45 to 59	eGFR 30 to 44	eGFR <30 or Dialysis	*P* Value
N	7738	5692	1353	512	181	
TTR %, median (IQR)	83 (71–92)	83 (71–92)	83 (72–91)	82 (68–90)	70 (50–82)	<0.001
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 trials[18,19]). 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.[7,21–23] The difficulty of CKD patients in keeping optimal INR was also reported by Quinn et al[24] 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

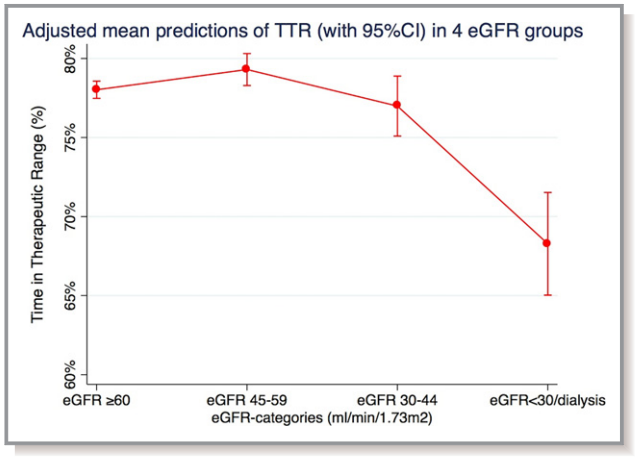

Figure 3. Adjusted mean predictions of time-in-therapeutic range (TTR) with 95% confidence intervals in 4 eGFR strata. Output from a multivariable fractional regression analysis including eGFR strata, age (in categories: <65, 65–74, 75–85, and ≥85 years), sex, diabetes mellitus, liver disease, hypertension, 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 m^2)	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.

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.

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.[25] A recent study indicated that ICH risk associated with INR ≥4.0 increased by several fold in individuals with advanced CKD.[7] 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.[26,27] 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.[28] Further, Kooiman et al[29] 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

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

	eGFR ≥60	eGFR 45 to 59	eGFR 30 to 44	eGFR <30 or Dialysis	*P* Value
N	5692	1353	512	181	
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, intractranial hemorrhage; MI, myocardial infarction.

Table 6. Multivariable Logistic Regression of Factors Associated With the Composite Endpoint of ICH, Ischemic Stroke, MI, and Death (n=7738) for All Included Patients

	OR (95% CI)	*P* Value
Renal function, mL/min per 1.73 m^2		
eGFR ≥60	1.0 (ref)	
eGFR 45 to 59	1.32 (1.01–1.72)	0.045
eGFR 30 to 44	1.54 (1.09–2.18)	0.025
eGFR <30, or dialysis	1.70 (1.06–2.72)	0.27
TTR		
TTR >75%	1.0 (ref)	
TTR 60% to 75%	1.84 (1.41–2.40)	<0.001
TTR <60%	2.09 (1.59–2.74)	<0.001
Age, y		
<65	1.0 (ref)	
65 to 74	2.03 (1.41–2.92)	<0.001
75 to 84	3.40 (2.38–4.87)	<0.001
≥85	3.14 (2.02–4.89)	<0.001
Female	0.92 (0.74–1.14)	0.427
Diabetes mellitus	1.08 (0.82–1.43)	0.574
Hypertension	0.96 (0.77–1.21)	0.740
Vascular disease (past MI, ischemic heart disease, or peripheral arterial disease)	1.40 (1.06–1.83)	0.017
Heart failure	1.78 (1.33–2.36)	<0.001
Valvular disease	1.27 (0.59–2.75)	0.542
Cancer within last 3 years	0.85 (0.62–1.15)	0.292
Coagulation/platelet defect	3.06 (1.33–7.07)	0.009
Anemia	1.10 (0.71–1.69)	0.681
Ischemic stroke	0.71 (0.43–1.20)	0.200
Past systemic emboli	1.70 (1.13–2.54)	0.010
Deep vein thrombosis/pulmonary embolism	1.51 (1.05–2.16)	0.025
Past ICH	1.12 (0.29–4.35)	0.865
Past gastrointestinal bleeding	1.37 (0.70–2.68)	0.356
Antiplatelet therapy	1.07 (0.85–1.35)	0.543
No. of INR measurements	1.03 (1.02–1.04)	<0.001
No. of days on warfarin	1.00 (0.99–1.00)	<0.001

P values for the interaction terms for the outcome is presented below the table. Interaction terms tested: age and eGFR: *P*=0.398; age and TTR, *P*=0.721; eGFR and TTR, *P*=0.169. eGFR indicates estimated glomerular filtration rate; ICH, intracranial hemorrhage; INR, international normalized ratio; MI, myocardial infarction; TTR, time-in-therapeutic range.

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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SUPPLEMENTAL MATERIAL

Table S1. Definition of co-morbidities

Co-morbidities at entry	ICD-codes (Patient registry) occurring within the last 5 years or or ATC-code (Swedish Drug Prescription registry) within the last 6 monthts 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)
Diabetes	E10-14 or purchase of antidiabetic drugs (ATC:A10)
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	I26
Deep venous thrombosis	I801-802
Composite venous thromboembolism	I26, I801-802
Myocardial infarction	I21,I252
Ischaemic heart disease	I20-25
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 Prescriptioin registry)**
Warfarin	B01AA03
Medication use at study inclusion date (first warfarin purchase-date) or within the preceding 6 months	**ATC-code**
Aspirin	B01AC06
Clopidogrel	B01AC04
Dipyridamole	B01AC07
NSAID	M01A
Paracetamol	N02BE01
Statins	C10AA
Antidepressant: Selective Serotonin Re-uptake inhibitor (SSRI)	N06AB
Proton pump inhibitor	A02BC
Amiodarone	C01BD01
Macrolide	J01FA
Quinolone	J01M
Combinations of sulfonamides and trimethoprim	J01EE

Table S3. Definition of CHA_2DS_2-VASc and HAS-BLED score

CHA_2DS_2-VASc score	**Points**	ICD-codes from Patient registry ATC-codes from Drug Prescription registry
Congestive heart failure	1 point	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Hypertension	1 point	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Age >75 years	2 points	
Diabetes	1 point	E10-14 or purchase of antidiabetic drugs (ATC:A10)
Stroke/Transient ischemic attack/ Unspecified stroke/ Systemic thromboembolism/Pumonary embolism/Deep venous thrombosis	2 point	Stroke/TIA: I63, I693, I64, I694, G45 Peripheral/sytemic embolism: I74, I63-64, G45, I74, I693, I694, I26, I801-802
Vascular disease	1 point	Previous MI/Ischemic heart disease: I21,I252, I21,I252 Vascular disease: I21, I252, I70-73 Peripheral arterial disease: I70-73
Age 65-75 years	1 point	
Sex Category: female gender	1 point	
HAS-BLED score	**Points**	
Hypertension	1 point	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Abnormal liver och renal function	1 or 2 points	Liver disease: K70-77 or procedure codes JJB, JJC Renal function: estimated glomerular filtration rate ≤ 60 ml/min/1.73 m^2/or dialysis
Stroke	1 point	Ischemic stroke: I63, I693 Unspecified stroke: I64, I694
Bleeding	1 point	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
Labile INR (TTR<60%)	1 point	Not available (all included patients were 1st time warfarin users)
Elderly (age ≥ 65 years)	1 point	
Drugs or alcohol abuse	1 or 2 points	Antiplatelet/NSAID: ATC-code: B01/M01A Alcohol abuse: E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714

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
	Population-registry
Death	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 (IQR)	8 (5-11)	8 (5-11)	8 (5-11)	7 (5-11)	8 (6-11)	0.240
Median number of days on warfarin, median (IQR)	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	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	5596	1324	495	162	
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/1.73m^2)		
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.

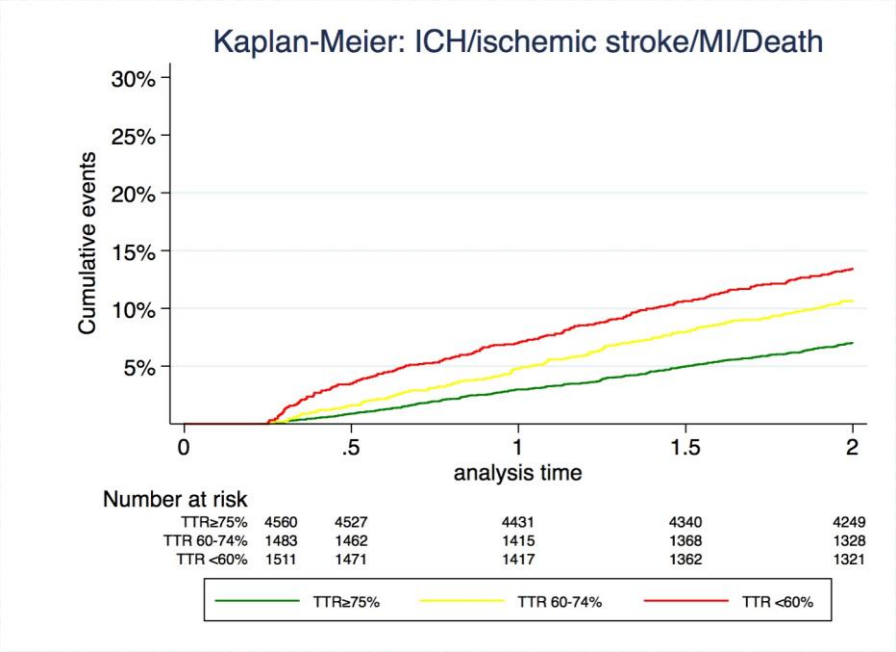
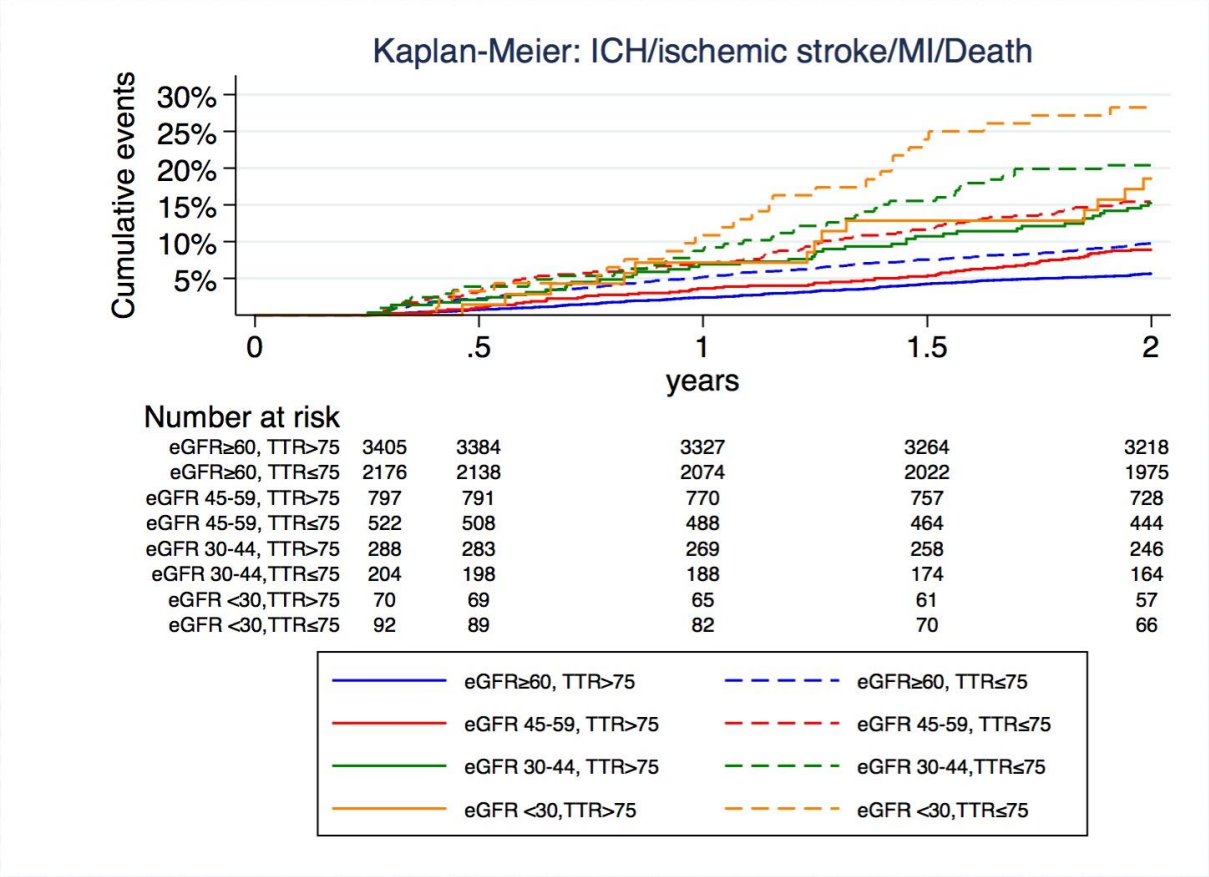
Figure S2. Kaplan-Meier curve for combined eGFR and TTR groups: