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TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: AN OBSERVATIONAL STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA

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ABSTRACT

Objectives: As there is debate whether warfarin-treated patients with non-valvular atrial fibrillation (NVAF) who exhibit good control will experience deterioration in control over time, we designed this study to examine the time in therapeutic range (TTR) in a population-based cohort of patients with NVAF recently initiated on warfarin.

Design: Retrospective cohort study using routinely collected health data from 2008 to 2015.

Setting: The entire Canadian province of Alberta.

Participants: All adult Albertans with NVAF who were taking warfarin for more than one month.

Main Outcome Measures: We examined frequency of INR monitoring and TTR using the Rosendaal method with time zero set at 31 days after the first warfarin dispensation.

Results: Of 81,775 patients with NVAF dispensed warfarin, 34,818 (42.6%) had less than 3 INRs measured in months 1-6. Of the 46,957 that went for regular INR monitoring in months 1-6 (median number of INRs 10, IQR 6-15), 38,888 (82.8%) met the definition of good control (TTR ≥65%); good control continued to be exhibited by 28,501 (88.9% of those who remained on warfarin) during months 7-12 and 24,447 (89.8% of continuing warfarin users) in months 13-18. Good control in the first 6 months predicted good control over the subsequent year: c index 0.785 [95% CI 0.778-0.792] for months 7-12 and c index 0.756 [95% CI 0.749-0.763] for months 13-18.

Conclusions: Two fifths of warfarin-treated patients had insufficient INR monitoring - this should be considered in the initial choice of anticoagulant and identifies a target for future quality improvement efforts. However, of those warfarin-treated patients who went for regular INR monitoring, nearly 90% exhibited levels of control similar to that in randomized trials and this remained constant over time. Thus, in patients who have already exhibited adherence with regular monitoring and good TTR, warfarin can still be a reliable anticoagulation option.

ARTICLE SUMMARY

Strengths of this Study:

-Addresses the question of whether NVAF patients who are well controlled on warfarin could continue to be reliably anticoagulated with warfarin

-Population based study of all adults with NVAF in an entire Canadian province, with complete capture of all interactions with the health care system, prescribing data, and INR results

Limitations of this Study:

-we assumed the target INR ranges were 2-3 for all patients, but recognize that for a small proportion of NVAF patients a higher (or lower) range may be targeted clinically

-we focused solely on INR control and didn't examine clinical endpoints

Although warfarin has been shown to be efficacious in preventing stroke in non-valvular atrial fibrillation (NVAF), it's effectiveness is dependent on being in therapeutic range (INR between 2 and 3).[1-6] However, some practice based studies suggest that only a minority of patients anticoagulated in the community have an average INR between 2 and 3, with wide variability from 29% to 75%.[1,3] The time in therapeutic range (TTR) is a standard measure of warfarin control which incorporates both the frequency of INR measurement and the actual values to interpolate daily INR values and define the percentage of time in range for each patient.[7] A TTR of at least two thirds is often used as the cutpoint for defining "good INR control" since patients randomized to warfarin in the clinical trials proving the efficacy of anticoagulation had their INRs within target range 65% of the time,[2,5] a large cohort with 63% of INRs in the 2-3 range reported warfarin benefits similar to those in the randomized trials,[3] and a post-hoc analysis of the ACTIVE-W Trial demonstrated that warfarin-treated patients with ≤65% of their INRs between 2 and 3 had higher rates of embolic and bleeding events than antiplatelet-treated patients.[4]

One of the key arguments in favour of the direct oral anticoagulants for NVAF is that the TTR for warfarin-treated patients is unpredictable and may well be markedly lower in clinical practice than in the randomized trials proving the efficacy of warfarin. While this is certainly a rationale for choosing a direct oral anticoagulant as the first agent for a patient newly diagnosed with NVAF, as clinicians we are often faced with the issue of what to do with patients who have been well-controlled on warfarin – can such patients be left on warfarin or should we be switching them to direct oral anticoagulants?

A recent report from ORBIT-AF raised concern that even when patients initially exhibit good INR control, this may fluctuate substantially over time: they reported that only 34% of their patients with outstanding INR control (TTR 80% or more) in the first 6 months of observation continued to exhibit that degree of control over the subsequent year.[8] However, as care varies widely across regions[1,9,10] and almost 80% of ORBIT-AF patients were enrolled from specialist offices, we designed this study to examine the adequacy of anticoagulation in an entire population more closely reflecting usual clinical practice where most NVAF patients are managed by primary care physicians. We examined the TTR and stability of INR control over time in a population-based cohort of adults with NVAF in a universal access health care system similar to the British National Health Service (the entire Canadian province of Alberta). As a secondary goal, we evaluated whether TTR and INR stability varied by kidney function.

METHODS

Design:

Retrospective cohort study using routinely collected health data.

Data Sources:

As described in full elsewhere,[11] we used de-identified but linked (using unique health number identifiers) Alberta Health administrative and laboratory databases including all residents of Alberta (population 4.3 million people). This project was approved by Alberta Health and the Health Research Ethics Boards at the University of Alberta and the University of Calgary with a waiver of individual signed patient consent (since data was de-identified).

Study Sample:

The cohort consisted of all adult Albertans (aged 18 years or older) with a diagnosis of AF (ICD-9 CM 427.3 or ICD-10 I48) between January 1, 2008 and March 31, 2015 in any fields of either the discharge abstract database (which captures most responsible diagnosis and up to 24 secondary diagnoses for all acute care hospitalizations), the national ambulatory care reporting system (which captures all visits to emergency rooms or hospital-based specialist clinics in Alberta), or the physician billing claims databases (see eAppendix for case definitions for NVAF and all covariates/outcomes listed below). Patients with a history of mitral or aortic valvular disease, valve surgery (see eAppendix) or end-stage kidney disease (defined as documented chronic dialysis or prior kidney transplant before onset of NVAF) were excluded (Figure 1). These NVAF case definitions have been evaluated in multiple studies, with sensitivity approaching 95% and specificity 99% in those that use both inpatient and outpatient data (as we did).[12] We restricted this study to patients dispensed at least one warfarin prescription of 30 days or longer (we linked to the Pharmacy Information Network and Alberta Blue Cross to obtain all prescription dispensations for cohort patients of any age). In the secondary analysis by kidney function, we restricted our analysis to only those with an outpatient serum creatinine measured at least once in the 6 months after the index date.

Covariates:

As described fully elsewhere,[11,13,14] we identified co-morbidities using the ICD-9-CM or ICD-10-CA codes validated in administrative databases (with look-back beginning in April 1994) and we used eGFR (calculated using the CKD-EPI equation) to categorize patients by kidney function at baseline.

Definition of INR Control:

To examine adequacy of anticoagulation, we examined the frequency of INR monitoring and results over subsequent timeframes. We excluded INRs done during the initialization phase for warfarin (defined as first 30 days after the first warfarin prescription after diagnosis of NVAF) and after setting time zero as day 31, we used the outpatient INR values in months 1-6 after the initial prescription to classify patients as having "good control" (TTR ≥65%) or suboptimal control (TTR <65%). We calculated TTR using the method of Rosendaal, which incorporates both the frequency of INR measurement and the actual values to interpolate daily INR values and define the percentage of time in range for each patient.[7] We also examined the frequency of extreme INR values (<1.5 or >4.0 as previously defined in the literature[8]) – in order to not falsely attribute periods during which warfarin was deliberately held for surgical or diagnostic procedures or acute illnesses, we excluded all values drawn within one week before or after a hospital visit (in Alberta virtually all biopsy procedures or surgeries are done in publically funded hospital settings and thus captured in the discharge abstract database or the national ambulatory care reporting system).

Follow-up:

We followed all study participants for 18 months from the time they met the warfarin-treated NVAF case definition or until they stopped warfarin, they left the province, died, or March 31 2015 – whichever came first.

Statistical Analysis:

All analyses were completed in Stata/MP 13.1 (www.stata.com). Descriptive statistics were reported as counts and percentages, or medians and inter-quartile

ranges, as appropriate. TTR is reported at 1-6, 7-12, and 13-18 months. In order to examine the association between TTR at 1-6 months with TTR at 7-12 months and 13-18 months, we used logistic regression. Outcomes were regressed on age (categorized as 65-74, 75-84, and ≥85 years), sex, rural or urban residence, eGFR (≥60, 45-59, 30-44, <30 mL/min*1.73m^2) and comorbidities (prior myocardial infarction, prior stroke or transient ischemic attack, alcohol misuse, metastatic cancers, non-metastatic cancers, chronic heart failure, chronic pulmonary disease, cirrhosis, dementia, diabetes mellitus, epilepsy, hypertension, peptic ulcer disease, peripheral vascular disease). McFadden's pseudo R^2 (http://stats.idre.ucla.edu/other/mult-pkg/faq/general/faq-what-are-pseudo-r-squareds/) and the likelihood ratio test were used to compare models with and without adjustment for good control in the first 6 months. P <0.05 was considered statistically significant.

RESULTS:

Of 81,775 patients with NVAF dispensed warfarin (Figure 1), 34,818 (42.6%) did not have at least 3 INRs measured in months 1-6. Of the 46,957 who did have at least 3 INRs measured in months 1-6 (median number of INRs 10, IQR 6-16), 38,888 (82.8%) demonstrated good control (TTR ≥ 65%), and 8069 (17.2%) had suboptimal control (at least 3 INRs drawn but TTR <65%). Longer term, of the 38,888 patients who demonstrated good control in the first 6 months, 28,501 (88.9% of those who remained on warfarin) exhibited TTR ≥ 65% in months 7-12 and 24,447 (89.8% of continuing warfarin users) had TTR ≥ 65% in months 13-18. Of the 34,818 patients having less than 3 INRs measured in months 1-6 after starting warfarin, 17,756 had refills for warfarin extending beyond 7 months – as warfarin may be ingested differently than

prescribed, we cannot tell exactly when the other 17,062 patients actually stopped taking warfarin.

Patients were more likely to have good INR control in months 1-6 if they lived in a rural area, had a higher CHADS score (with a higher frequency of heart failure and hypertension but not diabetes or prior stroke), or were older – Tables 1 and 2. Predisposing factors to suboptimal INR control were cirrhosis, cancer, alcohol misuse, dementia, and atherosclerotic vascular disease (prior MI or peripheral vascular disease). It is worth noting that renal function had minimal if any impact on TTR in any time period as the proportion of patients with TTR of 65% or greater did not differ substantially across eGFR strata (Figure 2) in the 1-6 month (ranging from 50.2% to 56.6%), 7-12 month (ranging from 61.2% to 63.8%), or 13-18 month (from 64.2% to 67.2% range) timeframes. It is also noteworthy that patients with CHADS scores of 2 or more had a higher frequency of INR measurements (median 13 [IQR 7-23] during months 1-6 and median 9 [IQR 5-15] in months 7-18) than patients with CHADS scores of 1 or 0 (median 10 [IQR 6-14] during months 1-6 and median 7 [IQR4-11] in months 7-18).

Of the 38,888 patients exhibiting good INR control during months 1-6, 28,501 (88.9% of those who remained on warfarin) continued to meet the definition of good INR control over months 7-12 (median number of INR measurements 10, IQR 6,15) and 24,447 (89.8% of those who remained on warfarin in that timeframe) met the definition for months 13-18 – Table 3. Good control in the first 6 months explained a significant amount of the variation in subsequent achievement of good control (Pseudo R^2 0.280, Likelihood Ratio Test $p<0.001$ for months 7-12 and Pseudo R^2 0.216, Likelihood Ratio

Test p<0.001 for months 13-18) and exhibited reasonable discrimination for good control over the subsequent year (c index 0.785 [95% CI 0.778-0.792] for months 7-12 and c index 0.756 [95% CI 0.749-0.763] for months 13-18). Of the 32,074 patients exhibiting good INR control in 1-6 months and who continued on warfarin past 6 months, 12,238 (38.2%) had at least one extreme INR value (<1.5 or >4.0) in the subsequent year. After exclusion of values drawn within one week before or after a hospital visit, this proportion was 31.8%.

Of the 42,887 patients who either had insufficient INR monitoring or exhibited suboptimal INR control during the first 6 months, 3025 (15.5% of those who remained on warfarin) met the definition of good INR control for months 7-12 and 3810 (22.9% of those who remained on warfarin during that timeframe) for months 13-18 – Table 3.

DISCUSSION

We found that although over 40% of NVAF patients dispensed warfarin had less than 3 INRs measured in months 1-6 (with approximately half of these patients stopping warfarin at some point in that first 6 months), 83% of those that had regular INR measurements exhibited TTR of 65% or better. Moreover, nearly 90% of those patients with good control in their first 6 months of warfarin therapy continued to exhibit good control over the subsequent 6 and 12 months. It is reassuring that patients with higher CHADS scores were more likely to have INRs measured and more likely to be in target range, suggesting that clinicians (and patients) were appropriately more rigorous in their approach with higher risk patients. Our finding that patients with cirrhosis, cancer, alcohol misuse, and dementia were less likely to have INRs in target range is not surprising as all are factors known to negatively impact medication adherence (as are

other factors such as malnutrition, fluctuating liver function, etc which are not captured by administrative databases). Finally, our finding that INR control and stability differed little across eGFR strata provides some reassurance for those concerned that it is more difficult to achieve good INR control in patients with reduced kidney function.

Although there is a published prediction score for identifying patients who are more likely to have poor INR control[15], this includes factors (such as ethnicity or tobacco use) which cannot be derived from administrative data and thus it has limited utility for comparative effectiveness research. Practitioner and health care system factors are also predictors of suboptimal TTR ratios in the literature.[9,10]

While our TTR and INR stability results are much higher than reported from ORBIT-AF in the US,[8] our findings are close to the levels of control reported in the Veterans Health Administration[10] and a recent Swedish nationwide study.[16] Although we suspect that the higher degree of INR control and better maintenance of that control over time in our cohort and the Swedish and VA studies reflects better integration and continuity of primary care in those 3 settings, this cannot be definitively answered in observational studies such as these. However, results from a recent audit of 474 primary care physicians in Canada would support this contention as the median TTR for warfarin-treated AF patients who had regular primary care physician follow-up was 75%.[17]

Although we were able to link inpatient and outpatient administrative data, prescribing data, and outpatient laboratory data to examine INR control for NVAF patients in an entire Canadian province whether they were treated by primary care physicians or specialists, thus avoiding the potential selection biases that many AF

registries are prone to, there are some limitations to our analysis. First, as we focused on patients newly initiated on warfarin, some may argue that this would artificially inflate their INR variability; however, we excluded inpatient and outpatient INRs drawn within the first 30 days of warfarin dispensation. Second, we assumed the target INR ranges were 2-3 for all patients, but recognize that for a small proportion of NVAF patients a higher (or lower) range may be targeted clinically if patients have had thromboembolic (or bleeding) events when INR was between 2 and 3. Third, we focused solely on INR control and didn't examine clinical endpoints and any association with out of range values, although other studies have demonstrated a clear relation between out of range INRs and bleeding or thromboembolic events.[4-6,16] It is important to acknowledge that some patients may still have events even if well anticoagulated, which may merely reflect the expected rate of noncardioembolic strokes in patients of the same age, sex, and comorbidity profile without NVAF rather than failure of anticoagulant treatment.[18]

While many of the early quality improvement studies in NVAF focused on warfarin dosing algorithms,[19,20] more recent studies[21] have highlighted the contribution of gaps in laboratory monitoring to suboptimal warfarin management – indeed we also found that a large subset of patients did not have sufficient INR values measured to calculate TTR. Our findings support the emphasis in current quality improvement efforts[22] to not only increase the use of dosing algorithms but to also encourage regular monitoring of INRs. Our findings also support those who argue for choosing a direct oral anticoagulant as the first agent for patients with NVAF given that future adherence with monitoring cannot accurately be predicted. However, our findings challenge the assumption that patients who have been well controlled on warfarin in

clinical practice will exhibit deteriorating control over time - one of the key arguments advanced in favour of switching from warfarin to the direct oral anticoagulants in chronically treated patients. We would agree with the authors of a recent nationwide audit from Sweden that “well-managed warfarin therapy…is still a valid alternative for prophylaxis of AF-associated stroke.”[16]

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All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no relevant conflicts of interest; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work. This work was supported by a peer-reviewed operating grant from the Heart and Stroke Foundation of Canada, GIA-15-0008887. FM is supported by a career salary award from Alberta Innovates-Health Solutions and holds the University of Alberta Chair in Cardiovascular Outcomes Research. The funders had no role in the design or analysis of this study, nor in the drafting or approval of this manuscript.

CONTRIBUTORS: FM conceived the study concept and design; NW and BH were involved in acquisition of the data; NW did the analyses; FM wrote the first draft of the manuscript; all authors reviewed and revised the manuscript for intellectual content. FM

and NW have access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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TRANSPARENCY DECLARATION: Dr. McAlister affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING: no additional data available.

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Figure Legends:

Figure 1: Participant flow

Figure 2. Proportion of patients with Time in Therapeutic Range ≥ 65% in different timeframes, broken down by estimated glomerular filtration rate

Table 1. Baseline characteristics by time in therapeutic range in months 1-6 of warfarin use

	Overall (n=81,775)	Time in Therapeutic Range <65% or infrequent INRs (n=42,887)	Time in Therapeutic Range ≥65% (n=38,888)	P value
Age, yrs	76 (66,82)	75 (64,82)	76 (66,82)	<0.001
Female	36,764 (45.0)	18,267 (44.1)	18,497 (45.9)	<0.001
Rural residence	10,545 (12.9)	4,423 (10.7)	6,122 (15.2)	<0.001
$CHADS_2$ score	2 (1,4)	2 (1,4)	3 (2,4)	<0.001
Prior myocardial infarction	13,134 (16.1)	7,479 (18.0)	5,655 (14.0)	<0.001
Prior stroke/TIA	22,712 (27.8)	11,628 (28.0)	11,084 (27.5)	0.08
Alcohol use disorder	5,332 (6.5)	3,410 (8.2)	1,922 (4.8)	<0.001
Cancer, metastatic	3,415 (4.2)	2,192 (5.3)	1,223 (3.0)	<0.001
Cancer, non-metastatic[1]	8,543 (10.5)	4,847 (11.7)	3,696 (9.2)	<0.001
Chronic heart failure	33,139 (40.5)	16,076 (38.8)	17,063 (42.3)	<0.001
Chronic pulmonary disease	28,036 (34.3)	14,672 (35.4)	13,364 (33.2)	<0.001
Cirrhosis	807 (1.0)	533 (1.3)	274 (0.7)	<0.001
Dementia	10,111 (12.4)	5,438 (13.1)	4,673 (11.6)	<0.001
Diabetes mellitus	24,643 (30.1)	12,545 (30.3)	12,098 (30.0)	0.45
eGFR, mL/min*1.73m^2	65 (48,81)	66 (48,82)	64 (48,79)	<0.001
Epilepsy	2,666 (3.3)	1,644 (4.0)	1,022 (2.5)	<0.001
Hypertension	66,290 (81.1)	33,420 (80.6)	32,870 (81.5)	0.001
Peptic ulcer disease	1,007 (1.2)	606 (1.5)	401 (1.0)	<0.001
Peripheral vascular disease	5,260 (6.4)	2,905 (7.0)	2,355 (5.8)	<0.001

N (%) or median (IQR) as appropriate
[1]Specifically breast, cervical, colorectal, lung, and prostate
$CHADS_2$ Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; eGFR estimated glomerular filtration rate; TIA transient ischemic attack

Table 2. Adjusted odds ratios associated with time in therapeutic range

	7-12 months (n=24,030) aOR (95% CI)	13-18 months (n=21,556) aOR (95% CI)
TTR during months 1-6	48.50 (42.58,55.24)	27.81 (24.51,31.57)
Age, yrs		
65-74	1.00	1.00
75-84	1.48 (1.35,1.63)	1.73 (1.58,1.90)
≥85	1.79 (1.63,1.97)	2.06 (1.88,2.25)
Female	0.97 (0.90,1.04)	0.99 (0.93,1.06)
Rural residence	1.04 (0.95,1.15)	1.09 (1.00,1.20)
Prior myocardial infarction	0.63 (0.57,0.69)	0.65 (0.60,0.72)
Prior stroke/TIA	1.18 (1.09,1.28)	1.15 (1.07,1.25)
Alcohol misuse	0.68 (0.59,0.79)	0.72 (0.62,0.84)
Cancer, metastatic	0.62 (0.51,0.74)	0.80 (0.65,0.98)
Cancer, non-metastatic[1]	0.87 (0.78,0.98)	0.79 (0.71,0.89)
Chronic heart failure	1.29 (1.20,1.38)	1.34 (1.25,1.43)
Chronic pulmonary disease	1.03 (0.96,1.11)	1.02 (0.95,1.10)
Cirrhosis	0.72 (0.53,1.00)	0.72 (0.52,1.01)
Dementia	0.86 (0.76,0.97)	0.79 (0.70,0.88)
Diabetes mellitus	0.96 (0.90,1.04)	0.99 (0.92,1.06)
eGFR, mL/min*1.73m^2		
≥60	1.00	1.00
45-59	1.11 (1.01,1.21)	1.13 (1.04,1.23)
30-44	1.08 (0.97,1.21)	1.10 (0.99,1.22)
<30	1.02 (0.87,1.18)	1.00 (0.85,1.16)
Epilepsy	0.95 (0.77,1.18)	0.96 (0.78,1.19)
Hypertension	1.37 (1.24,1.50)	1.29 (1.17,1.41)
Peptic ulcer disease	0.62 (0.46,0.82)	0.67 (0.49,0.90)
Peripheral vascular disease	0.96 (0.84,1.11)	0.98 (0.85,1.13)

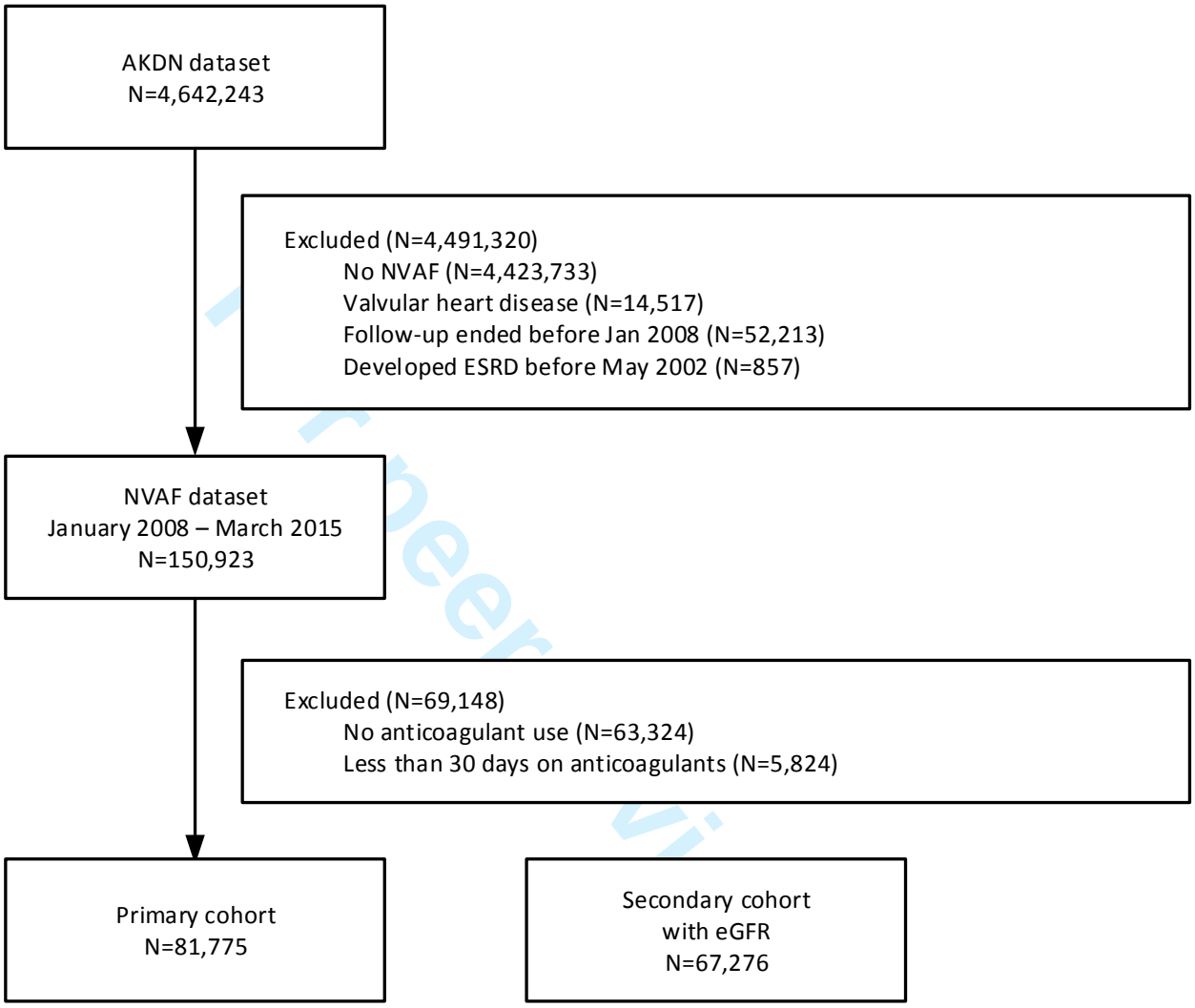
[1]Specifically breast, cervical, colorectal, lung, and prostate

CI confidence interval, eGFR estimated glomerular filtration rate, TIA transient ischemic attack, TTR time in therapeutic range

Table 3. INR control (N=81,775)

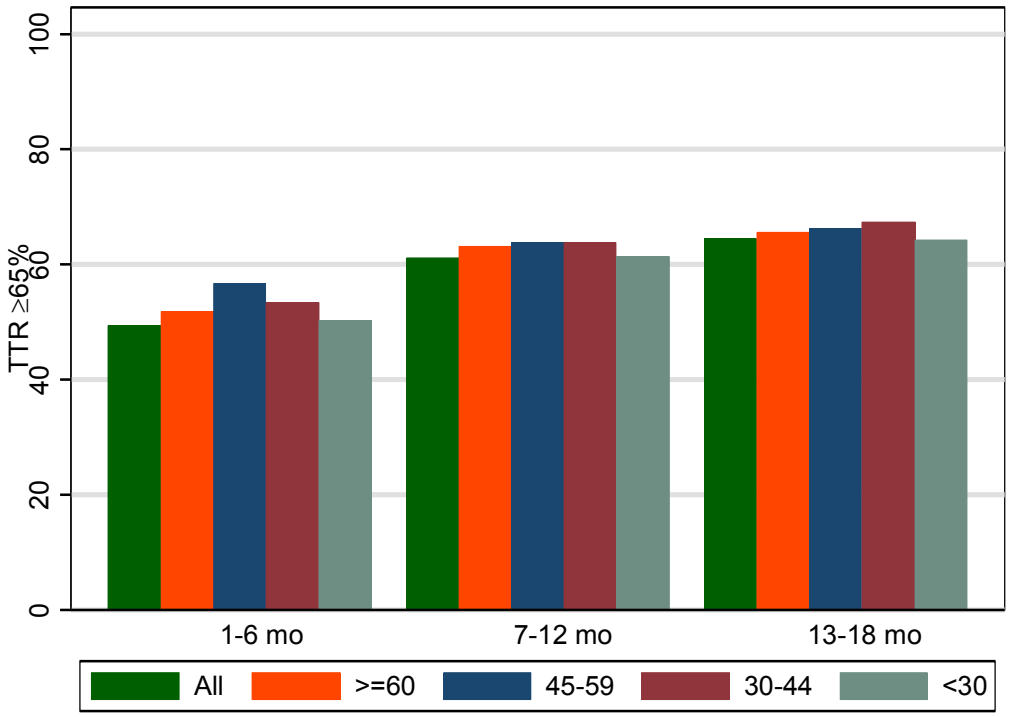
	<3 INRs in months 1-6 (n=34,818)	TTR <65% in months 1-6 (n=8,069)	TTR ≥65% in months 1-6 (n=38,888)
7-12 months:			
-still on warfarin	17,756 (51.0)	1,801 (22.3)	32,074 (82.5)
-TTR ≥65%	2,508 (14.1)	517 (28.7)	28,501 (88.9)
13-18 months:			
-still on warfarin	15,289 (43.9)	1,353 (16.8)	27,228 (70.0)
-TTR ≥65%	3,264 (21.4)	546 (40.4)	24,447 (89.8)

Figure 1. Participant flow



AKDN Alberta Kidney Disease Network (dataset containing administrative records for all 4.6 million Albertans), eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, NVAF non-valvular atrial fibrillation

Figure 2. Proportion of patients with Time in Therapeutic Range ≥ 65% in different timeframes, broken down by estimated glomerular filtration rate



INR international normalized ratio, GFR glomerular filtration rate, TTR time in therapeutic range

The height of the bars shows the percentage of participants that meet target in each 6-month interval of follow-up. The green bars represent all participants (followed and on anticoagulants) including those without estimated GFR in the first 6 months. The remaining four colors represents participants with varying levels of estimated GFR (mL/min*1.73m^2) in the first 6 months.

STROBE 2007 (v4) Statement— for McAlister et al. TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: AN OBSERVATIONAL STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	2, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2, 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9

		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 and figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-11, Tables 2 and 3, Figure 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11, Tables 2 and 3, Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	9-11, Tables 2 and 3, Figure 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11, Tables 2 and 3, Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12, 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12, 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

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TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: A RETROSPECTIVE COHORT STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA IN ALBERTA, CANADA

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TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: A RETROSPECTIVE COHORT STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA IN ALBERTA, CANADA

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Running Title: **Stability of TTR over time**

Keywords: atrial fibrillation; warfarin; quality of care

Word Count: **5310 Total, 300 Abstract, 2659 Text, 4 Tables, 3 Figures, 24 References, 1 eAppendix**

ABSTRACT

Objectives: Whether warfarin-treated patients with non-valvular atrial fibrillation (NVAF) who exhibit good control will experience deterioration in control over time is uncertain. We designed this study to examine the time in therapeutic range (TTR) in a population-based cohort of patients with NVAF recently initiated on warfarin.

Design: Retrospective cohort study using routinely collected health data from 2008 to 2015.

Setting: The Canadian province of Alberta.

Participants: All adults with NVAF who were taking warfarin for more than one month.

Main Outcome Measures: Frequency of INR monitoring and the Rosendaal TTR with time zero set at 31 days after the first warfarin dispensation.

Results: Of 57,669 patients with NVAF dispensed warfarin for more than one month, 17,099 (29.7%) had less than 3 INRs measured in months 1-6. Of the 40,570 that went for regular INR monitoring in months 1-6 (median number of INRs 11, IQR 7-16), 16,639 (41.0%) met the definition of good control (TTR ≥65%); good control continued to be exhibited by 8,177 (57.1% of those who remained on warfarin) during months 7-12 and 6,804 (56.8% of continuing warfarin users) in months 13-18. Good control in the first 6 months predicted good control over the subsequent year: aOR 4.0 [95%CI 3.8-4.2], c index 0.685 [95%CI 0.679-0.691] for months 7-12 and aOR 3.2 [95%CI 3.1-3.3], c index 0.665 [95%CI 0.659-0.671] for months 13-18.

Conclusions: Nearly one third of warfarin-treated patients had insufficient INR monitoring - this could influence the initial choice of anticoagulant and identifies a target for future quality improvement efforts. Of those warfarin-treated patients who went for regular INR monitoring, 41% exhibited levels of control similar to that in randomized trials and this deteriorated by half over time. However, in patients who have already exhibited adherence with regular monitoring and good TTR, warfarin may still be a reliable anticoagulation option.

ARTICLE SUMMARY

Strengths of this Study:

-Addresses the question of whether NVAF patients who are well controlled on warfarin could continue to be reliably anticoagulated with warfarin

-Population based study of all adults with NVAF in an entire Canadian province, with complete capture of all interactions with the health care system, prescribing data, and INR results

Limitations of this Study:

-we assumed the target INR ranges were 2-3 for all patients, but recognize that for a small proportion of NVAF patients a higher (or lower) range may be targeted clinically

-we focused solely on INR control and didn't examine clinical endpoints

Although warfarin has been shown to be efficacious in preventing stroke in non-valvular atrial fibrillation (NVAF), it's effectiveness is dependent on being in therapeutic range (INR between 2 and 3).[1-6] However, some practice based studies suggest that only a minority of patients anticoagulated in the community have an average INR between 2 and 3, with wide variability from 29% to 75%.[1,3] The time in therapeutic range (TTR) is a standard measure of warfarin control which incorporates both the frequency of INR measurement and the actual values to interpolate daily INR values and define the percentage of time in range for each patient.[7] A TTR of at least two thirds is often used as the cutpoint for defining "good INR control" since patients randomized to warfarin in the clinical trials proving the efficacy of anticoagulation had their INRs within target range 65% of the time,[2,5] a large cohort with 63% of INRs in the 2-3 range reported warfarin benefits similar to those in the randomized trials,[3] and a post-hoc analysis of the ACTIVE-W Trial demonstrated that warfarin-treated patients with ≤65% of their INRs between 2 and 3 had higher rates of embolic and bleeding events than antiplatelet-treated patients.[4]

One of the key arguments in favour of the direct oral anticoagulants for NVAF is that the TTR for warfarin-treated patients is unpredictable and may well be markedly lower in clinical practice than in the randomized trials proving the efficacy of warfarin. While this is certainly a rationale for choosing a direct oral anticoagulant as the first agent for a patient newly diagnosed with NVAF, as clinicians we are often faced with the issue of what to do with patients who have been well-controlled on warfarin – can such patients be left on warfarin or should we be switching them to direct oral anticoagulants?

A recent report from ORBIT-AF raised concern that even when patients initially exhibit good INR control, this may fluctuate substantially over time: they reported that only 34% of their patients with outstanding INR control (TTR 80% or more) in the first 6 months of observation continued to exhibit that degree of control over the subsequent year.[8] However, as care varies widely across regions[1,9,10] and almost 80% of ORBIT-AF patients were enrolled from specialist offices, we designed this study to examine the adequacy of anticoagulation in an entire population more closely reflecting usual clinical practice where most NVAF patients are managed by primary care physicians. We examined the TTR and stability of INR control over time in a population-based cohort of adults with NVAF in a universal access health care system similar to the British National Health Service (the entire Canadian province of Alberta). As a secondary goal, we evaluated whether TTR and INR stability varied by kidney function.

METHODS

Design:

Retrospective cohort study using routinely collected health data.

Data Sources:

As described in full elsewhere,[11] we used de-identified but linked (using unique health number identifiers) Alberta Health administrative and laboratory databases including all residents of Alberta (population 4.3 million people). This project was approved by Alberta Health and the Health Research Ethics Boards at the University of Alberta and the University of Calgary with a waiver of individual signed patient consent (since data was de-identified).

Study Sample:

The cohort consisted of all adult Albertans (aged 18 years or older) with a diagnosis of AF (ICD-9 CM 427.3 or ICD-10 I48) between January 1, 2008 and March 31, 2015 in any fields of either the discharge abstract database (which captures most responsible diagnosis and up to 24 secondary diagnoses for all acute care hospitalizations), the national ambulatory care reporting system (which captures all visits to emergency rooms or hospital-based specialist clinics in Alberta), or the physician billing claims databases (see eAppendix for case definitions for NVAF and all covariates listed below). Patients with a history of mitral or aortic valvular disease, valve surgery (see eAppendix) or end-stage kidney disease (defined as documented chronic dialysis or prior kidney transplant before onset of NVAF) were excluded (Figure 1). These NVAF case definitions have been evaluated in multiple studies, with sensitivity approaching 95% and specificity 99% in those that use both inpatient and outpatient data (as we did).[12] We restricted this study to patients dispensed warfarin prescriptions of 30 days or longer (we linked to the Pharmacy Information Network and Alberta Blue Cross to obtain all prescription dispensations for cohort patients of any age). In the secondary analysis by kidney function, we restricted our analysis to only those with an outpatient serum creatinine measured at least once in the 18 months after the index date.

Covariates:

As described fully elsewhere,[11,13,14] we identified co-morbidities using the ICD-9-CM or ICD-10-CA codes validated in administrative databases (with look-back beginning in April 1994) and we used eGFR (calculated using the CKD-EPI equation) to categorize patients by kidney function at baseline.

Definition of INR Control:

To examine adequacy of anticoagulation, we examined the frequency of INR monitoring and results over subsequent timeframes. We excluded INRs done during the initialization phase for warfarin (defined as within 30 days of the first warfarin prescription) and, after setting time zero as day 31, we used the outpatient INR values in months 1-6 after the initial prescription to classify patients as having "good control" (TTR ≥65%) or suboptimal control (TTR <65%). We calculated TTR using the method of Rosendaal, which incorporates both the frequency of INR measurement and the actual values to interpolate daily INR values and define the percentage of time in range for each patient.[7] We also examined the frequency of extreme INR values (<1.5 or >4.0 as previously defined in the literature[8]) – in order to not falsely attribute periods during which warfarin was deliberately held for surgical or diagnostic procedures or acute illnesses, we excluded all values drawn within one week before or after a hospitalization (in Alberta all biopsy procedures or surgeries are done in publically funded hospital settings and thus captured in the discharge abstract database or the national ambulatory care reporting system).

Follow-up:

We followed all study participants for 18 months from the time they met the warfarin-treated NVAF case definition (ie. had been on warfarin for at least 30 days) or until they stopped warfarin, they left the province, died, or March 31 2015 – whichever came first.

Statistical Analysis:

All analyses were completed in Stata/MP 13.1 (www.stata.com). Descriptive

statistics were reported as counts and percentages, or medians and inter-quartile ranges, as appropriate. TTR is reported at 1-6, 7-12, and 13-18 months. In order to examine the association between TTR at 1-6 months with TTR at 7-12 months and 13-18 months, we used logistic regression. Outcomes were regressed on age (categorized as 65-74, 75-84, and ≥85 years), sex, rural or urban residence, eGFR (≥60, 45-59, 30-44, <30 mL/min*1.73m^2) and comorbidities (prior myocardial infarction, prior stroke or transient ischemic attack, alcohol misuse, metastatic cancers, non-metastatic cancers, chronic heart failure, chronic pulmonary disease, cirrhosis, dementia, diabetes mellitus, epilepsy, hypertension, peptic ulcer disease, peripheral vascular disease). McFadden's pseudo R^2 (http://stats.idre.ucla.edu/other/mult-pkg/faq/general/faq-what-are-pseudo-r-squareds/) and the likelihood ratio test were used to compare models with and without adjustment for good control in the first 6 months. P <0.05 was considered statistically significant.

RESULTS:

Of 57,669 patients with NVAF dispensed warfarin (Figure 1), 17,099 (29.7%) did not have at least 3 INRs measured in months 1-6. Of the 40,570 who did have at least 3 INRs measured in months 1-6 (median number of INRs 11, IQR 7-16), 16,639 (41.0%) demonstrated good control (TTR ≥ 65%), and 23,931 (59.0%) had suboptimal control (at least 3 INRs drawn but TTR <65%) – Figure 1. Longer term, of the 16,639 patients who demonstrated good control in the first 6 months, 8,177 (57.1% of those who remained on warfarin) exhibited TTR ≥ 65% in months 7-12 and 6,804 (56.8% of continuing warfarin users) had TTR ≥ 65% in months 13-18 (Figure 1). Of the 17,099 patients having less than 3 INRs measured in months 1-6 after starting warfarin, 11,653

had refills for warfarin extending beyond 7 months – as warfarin may be ingested differently than prescribed, we cannot tell exactly when (or if) the other 5,446 patients with infrequent INR monitoring actually stopped taking warfarin.

Patients were more likely to have good INR control in months 1-6 if they lived in a rural area, were older, or had a lower CHADS score (with lower frequencies of heart failure, stroke, and diabetes but not hypertension) – Tables 1 and 2. In fact, all comorbidities (except hypertension), including worsening degrees of kidney dysfunction, were associated with less likelihood of good INR control (Table 2, Figure 2). Despite being less likely to have TTR $\geq$ 65%, patients with CHADS scores of 2 or more had a higher frequency of INR measurements (median 11 [IQR 7-17] during months 1-6 and median 8 [IQR 6-13] in months 7-18) than patients with CHADS scores of 1 or 0 (median 9 [IQR 6-14] during months 1-6 and median 7 [IQR 4-11] in months 7-18).

Of the 16,639 patients exhibiting good INR control in the first 6 months, 8,177 (57.1% of those who remained on warfarin) exhibited TTR $\geq$ 65% in months 7-12 (median number of INR measurements 7, IQR 5,11) and 6,804 (56.8% of continuing warfarin users) had TTR $\geq$ 65% in months 13-18 – Table 3. Details on the frequency of INR measurements, the proportion of out-of-range INRs, and the median TTRs in each time frame are provided in Table 4. We further stratify INR control by TTR 65-80% vs. >80% in Figure 3 – this demonstrates that the proportion of patients with excellent control (TTR>80%) actually increased over time ($p<0.001$ for trend). Good control in the first 6 months explained a significant amount of the variation in subsequent achievement of good control (Pseudo R^2 0.084, Likelihood Ratio Test $p<0.001$ for months 7-12 and Pseudo R^2 0.064, Likelihood Ratio Test $p<0.001$ for months 13-18)

and exhibited reasonable discrimination for good control over the subsequent year (c index 0.685 [95% CI 0.679-0.691] for months 7-12 and c index 0.665 [95% CI 0.659-0.671] for months 13-18). Of the 14,330 patients exhibiting good INR control in 1-6 months and who continued on warfarin past 6 months, 6,355 (44.3%) had at least one extreme INR value (<1.5 or >4.0) in the subsequent year. After exclusion of values drawn within one week of a hospitalization, this proportion was 41.1%.

Of the 41,030 patients who either had insufficient INR monitoring or exhibited suboptimal INR control during the first 6 months, 7,856 (25.9% of those who remained on warfarin) met the definition of good INR control for months 7-12 and 7,292 (29.8% of those who remained on warfarin during that timeframe) for months 13-18 – Table 3.

DISCUSSION

We found that 30% of NVAF patients dispensed warfarin had less than 3 INRs measured in months 1-6 (with approximately one third of these patients having apparently stopped warfarin at some point in that first 6 months), and 41% of those that had regular INR measurements exhibited TTR of 65% or better. Just over half of those patients with good control in their first 6 months of warfarin therapy continued to exhibit good control over the subsequent 6 and 12 months. It is concerning that patients with higher CHADS scores or comorbidities were less likely to have INRs measured in the first 6 months and less likely to be in target range, suggesting a risk-treatment paradox in atrial fibrillation management in that higher risk patients appear to receive less optimal care.[15] A similar pattern was seen in the ORBIT-AF registry.[16] This may not necessarily reflect physician intent and may result from the fact that comorbidities such as heart failure, cirrhosis, cancer, alcohol misuse, kidney dysfunction, and

dementia can negatively impact TTR either through poorer medication adherence or biological variation in clotting factors (as are other factors such as malnutrition, fluctuating liver function, etc which are not captured by administrative databases).

Although there is a published prediction score for identifying patients who are more likely to have poor INR control[17], this includes factors (such as ethnicity or tobacco use) which cannot be derived from administrative data and thus it has limited utility for comparative effectiveness research. Practitioner and health care system factors are also predictors of suboptimal TTR ratios in the literature.[9,10]

Our TTR and INR stability results are similar to those reported from ORBIT-AF in the US,[8] but much lower than the levels of control reported in the Veterans Health Administration[10] and a recent Swedish nationwide study.[18] Although we suspect that the higher degree of INR control and better maintenance of that control over time in the Swedish and VA studies reflects better integration and continuity of primary care in those settings, this cannot be definitively answered in observational studies such as these. However, results from a recent audit of 474 primary care physicians in Canada would support this contention as the median TTR for warfarin-treated AF patients who had regular primary care physician follow-up was 75%.[19]

As we were able to link inpatient and outpatient administrative data, prescribing data, and outpatient laboratory data to examine INR control for NVAF patients in an entire Canadian province whether they were treated by primary care physicians or specialists, our results are generalizable to the broader population of patients with NVAF treated in a single-payer universal access healthcare system such as Alberta. Indeed, our study design avoids the potential selection biases that most AF registries

are prone to. However, there are some limitations to our analysis. First, as we focused on patients newly initiated on warfarin, some may argue that this would artificially inflate their INR variability; however, we excluded inpatient and outpatient INRs drawn within the first 30 days of warfarin dispensation to limit this impact. Second, it could be argued that excluding patients who were prescribed warfarin for less than 30 days may have introduced a selection bias but our interest was on patients chronically using warfarin. We have no information on why some patients stopped warfarin after less than 30 days of therapy (in later years some may have in fact been switched to a novel direct oral anticoagulant which in the years studied was not covered publically in Alberta except with special authorization). Third, we relied on pharmacy dispensation records to determine which patients were taking warfarin and acknowledge that warfarin may be ingested differently than prescribed or patients may be non-adherent even if filling prescriptions. Fourth, we assumed the target INR ranges were 2-3 for all patients, but recognize that for a small proportion of NVAF patients a higher (or lower) range may be targeted clinically if patients have had thromboembolic (or bleeding) events when INR was between 2 and 3. Fifth, we focused solely on INR control and didn't examine clinical endpoints and any association with out of range values, although other studies have demonstrated a clear relation between out of range INRs and bleeding or thromboembolic events.[4-6,18] It is important to acknowledge that some patients may still have events even if well anticoagulated, which may merely reflect the expected rate of non-cardioembolic strokes in patients of the same age, sex, and comorbidity profile without NVAF rather than failure of anticoagulant treatment.[20]

While many of the early quality improvement studies in NVAF focused on warfarin dosing algorithms,[21,22] more recent studies[23] have highlighted the contribution of gaps in laboratory monitoring to suboptimal warfarin management – indeed we also found that a large subset of patients did not have sufficient INR values measured to calculate TTR. Our findings support the emphasis in current quality improvement efforts[24] to not only increase the use of dosing algorithms but to also encourage regular monitoring of INRs. Our findings also support those who argue for choosing a direct oral anticoagulant as the first agent for patients with NVAF given that future adherence with monitoring cannot accurately be predicted. However, our findings challenge the assumption that patients who have been well controlled on warfarin in clinical practice will invariably exhibit deteriorating control over time - one of the key arguments advanced in favour of switching from warfarin to the direct oral anticoagulants in chronically treated patients. We would agree with the authors of a recent nationwide audit from Sweden that "well-managed warfarin therapy…is still a valid alternative for prophylaxis of AF-associated stroke."[18]

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FUNDING AND COMPETING INTEREST STATEMENT*:*

All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no relevant conflicts of interest; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work. This work was supported by a peer-reviewed operating grant from the Heart and Stroke Foundation of Canada, GIA-15-0008887. FM is supported by a career salary award from Alberta Innovates-Health Solutions and holds the University of Alberta Chair in Cardiovascular Outcomes Research. The funders had no role in the design or analysis of this study, nor in the drafting or approval of this manuscript.

CONTRIBUTORS: FM conceived the study concept and design; NW and BH were involved in acquisition of the data; NW did the analyses; FM wrote the first draft of the manuscript; all authors reviewed and revised the manuscript for intellectual content. FM

and NW have access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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TRANSPARENCY DECLARATION: Dr. McAlister affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING: no additional data available.

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Figure Legends:

Figure 1. Participant flow

AKDN Alberta Kidney Disease Network (dataset containing administrative records for all 4.6 million Albertans), NVAF non-valvular atrial fibrillation. Note that percentages in the last row of boxes reflect the proportions among patients still prescribed warfarin in that timeframe.

Figure 2. Proportion of patients with with at least 3 INRs in months 1-6 and Time in Therapeutic Range ≥ 65% in different timeframes, broken down by estimated glomerular filtration rate

INR international normalized ratio, GFR glomerular filtration rate, TTR time in therapeutic range

The height of the bars shows the percentage of participants that meet target in each 6-month interval of follow-up. The green bars represent all participants (followed and on anticoagulants) including those without estimated GFR in the first 6 months. The remaining four colors represents participants with varying levels of estimated GFR (mL/min*1.73m^2) in the first 6 months.

Figure 3. Proportion of patients with Time in Therapeutic Range in various strata over time

The height of the bars shows the percentage of all participants (followed and on anticoagulants) that fall into each 'time in TTR' interval by each 6-month interval of follow-up. The black bars show the percentage of patients that met target <65% of the time, the medium gray bars show the percentage of patients that met target between 65% and 80% of the time, and the light gray bars show the percentage of patients that met target at least 80% of the time.

Table 1. Baseline characteristics by time in therapeutic range in months 1-6 of warfarin use

	Overall (n=57,669)	Time in Therapeutic Range <65% or infrequent INRs (n=41,030)	Time in Therapeutic Range ≥65% (n=16,639)	P value
Age, yrs				<0.001
65-74	13,112 (22.7)	9,538 (23.2)	3,574 (21.5)	
75-84	15,265 (26.5)	10,663 (26)	4,602 (27.7)	
≥85	29,292 (50.8)	20,829 (50.8)	8,463 (50.9)	
Female	25,655 (44.5)	18,334 (44.7)	7,321 (44.0)	0.13
Rural residence	7,670 (13.3)	5,325 (13.0)	2,345 (14.1)	<0.001
$CHADS_2$ score	2 (2,4)	3 (2,4)	2 (1,3)	<0.001
Prior myocardial infarction	8,304 (14.4)	6,108 (14.9)	2,196 (13.2)	<0.001
Prior stroke/TIA	15,786 (27.4)	11,350 (27.7)	4,436 (26.7)	0.01
Alcohol use disorder	2,736 (4.7)	2,268 (5.5)	468 (2.8)	<0.001
Cancer, metastatic	1,639 (2.8)	1,327 (3.2)	312 (1.9)	<0.001
Cancer, non-metastatic[1]	5,201 (9.0)	3,865 (9.4)	1,336 (8.0)	<0.001
Chronic heart failure	24,216 (42.0)	18,096 (44.1)	6,120 (36.8)	<0.001
Chronic pulmonary disease	18,615 (32.3)	13,841 (33.7)	4,774 (28.7)	<0.001
Cirrhosis	286 (0.5)	232 (0.6)	54 (0.3)	<0.001
Dementia	5,418 (9.4)	4,228 (10.3)	1,190 (7.2)	<0.001
Diabetes mellitus	16,951 (29.4)	12,396 (30.2)	4,555 (27.4)	<0.001
eGFR, mL/min*1.73m^2				<0.001
≥60	19,031 (55.9)	13,390 (32.6)	5,641 (33.9)	
45-59	7,830 (23.0)	5,548 (13.5)	2,282 (13.7)	
30-44	5,035 (14.8)	3,740 (9.1)	1,295 (7.8)	
<30	2,135 (6.3)	1,661 (4.0)	474 (2.8)	
Epilepsy	1,455 (2.5)	1,137 (2.8)	318 (1.9)	<0.001
Hypertension	47,534 (82.4)	33,862 (82.5)	13,672 (82.2)	0.30
Peptic ulcer disease	549 (1.0)	445 (1.1)	104 (0.6)	<0.001
Peripheral vascular disease	3,482 (6.0)	2,666 (6.5)	816 (4.9)	<0.001

N (%) or median (IQR) as appropriate

[1]Specifically breast, cervical, colorectal, lung, and prostate

$CHADS_2$ Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; eGFR estimated glomerular filtration rate; TIA transient ischemic attack

Table 2. Adjusted odds ratios associated with time in therapeutic range

	1-6 months (n=34,023) aOR (95% CI)	7-12 months (n=42,011) aOR (95% CI)	13-18 months (n=42,959) aOR (95% CI)
TTR ≥65%[1] during months 1-6	-	3.99 (3.81,4.17)	3.19 (3.05,3.34)
Age, yrs			
65-74	1.00	1.00	1.00
75-84	1.10 (1.02,1.18)	1.36 (1.27,1.47)	1.41 (1.31,1.52)
≥85	1.10 (1.03,1.18)	1.49 (1.38,1.59)	1.57 (1.46,1.68)
Female	0.91 (0.86,0.95)	0.95 (0.91,1.00)	0.94 (0.90,0.99)
Rural residence	1.13 (1.05,1.21)	1.09 (1.02,1.16)	1.15 (1.08,1.23)
Prior myocardial infarction	0.95 (0.88,1.01)	0.93 (0.87,0.99)	0.88 (0.82,0.94)
Prior stroke/TIA	1.03 (0.97,1.08)	1.03 (0.98,1.08)	1.02 (0.98,1.08)
Alcohol misuse	0.59 (0.51,0.67)	0.67 (0.59,0.76)	0.69 (0.61,0.78)
Cancer, metastatic	0.61 (0.53,0.72)	0.59 (0.50,0.69)	0.60 (0.51,0.71)
Cancer, non-metastatic[2]	0.89 (0.81,0.97)	0.90 (0.82,0.97)	0.88 (0.81,0.95)
Chronic heart failure	0.81 (0.77,0.85)	0.95 (0.90,0.99)	0.96 (0.92,1.01)
Chronic pulmonary disease	0.85 (0.81,0.90)	0.91 (0.86,0.95)	0.96 (0.91,1.01)
Cirrhosis	0.86 (0.62,1.21)	0.86 (0.61,1.21)	0.60 (0.41,0.87)
Dementia	0.72 (0.65,0.78)	0.83 (0.77,0.90)	0.75 (0.69,0.81)
Diabetes mellitus	0.93 (0.89,0.98)	0.95 (0.91,1.00)	0.94 (0.90,0.99)
eGFR, mL/min*1.73m^2			
≥60	1.00	1.00	1.00
45-59	1.00 (0.94,1.06)	1.01 (0.95,1.06)	0.99 (0.94,1.05)
30-44	0.89 (0.82,0.95)	0.97 (0.90,1.04)	0.92 (0.86,0.99)
<30	0.77 (0.69,0.86)	0.78 (0.70,0.88)	0.85 (0.76,0.95)
Epilepsy	0.68 (0.57,0.80)	0.95 (0.82,1.10)	0.88 (0.76,1.01)
Hypertension	1.06 (0.99,1.14)	1.15 (1.07,1.23)	1.15 (1.07,1.23)
Peptic ulcer disease	0.69 (0.53,0.90)	0.64 (0.49,0.84)	0.82 (0.64,1.04)
Peripheral vascular disease	0.82 (0.74,0.91)	0.88 (0.80,0.96)	0.86 (0.79,0.95)

[1]with at least 3 INRs in months 1-6
[2]specifically breast, cervical, colorectal, lung, and prostate

CI confidence interval, eGFR estimated glomerular filtration rate, TIA transient ischemic attack, TTR time in therapeutic range

Table 3. INR control (N=57,669)

	<3 INRs in months 1-6 (n=17,099)	TTR <65% in months 1-6 (n=23,931)	TTR ≥65% in months 1-6 (n=16,639)
7-12 months:			
-still on warfarin	11,653 (68.2)	18,641 (77.9)	14,330 (86.1)
-TTR ≥65%	1,157 (9.9)	6,699 (35.9)	8,177 (57.1)
13-18 months:			
-still on warfarin	9,893 (57.9)	14,558 (60.8)	11,987 (72.0)
-TTR ≥65%	1,413 (14.3)	5,879 (40.4)	6,804 (56.8)

Table 4. INR control in those with at least 3 INRs and TTR ≥65% in months 1-6 (N=16,639)

	Months 1-6	Months 7-12	Months 13-18
INR counts	9 (3,80)	7 (0,70)	7 (0,84)
>3.0, %	0.0 (0.0,35.0)	5.9 (0.0,100.0)	0.0 (0.0,100.0)
<2.0, %	12.5 (0.0,35.0)	13.0 (0.0,100.0)	12.5 (0.0,100.0)
INR SD	0.41 (0.00,3.26)	0.46 (0.00,5.70)	0.45 (0.00,5.66)
Median TTR, % (Range)	77.8 (65.0,100.0)	66.7 (0,100.0)	62.5 (0.0,100.0)

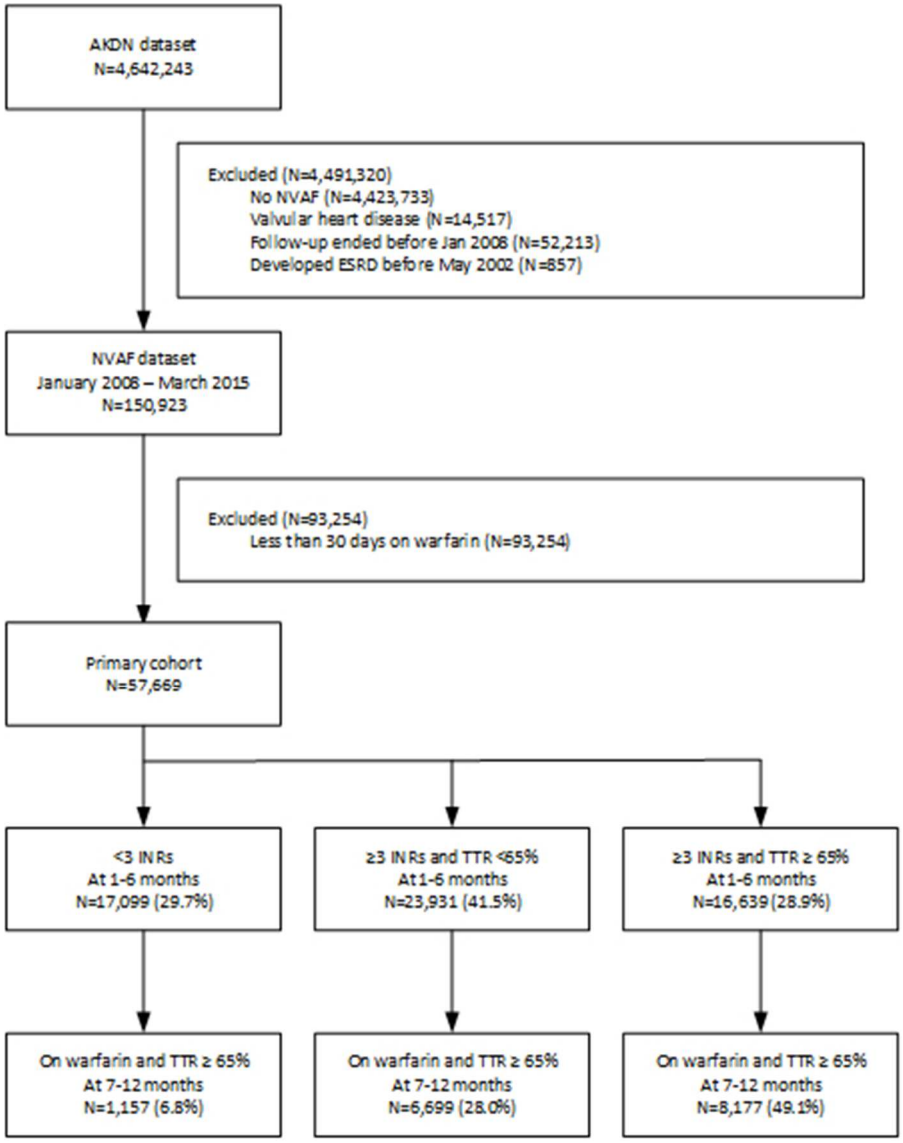

Figure 1

37x48mm (300 x 300 DPI)

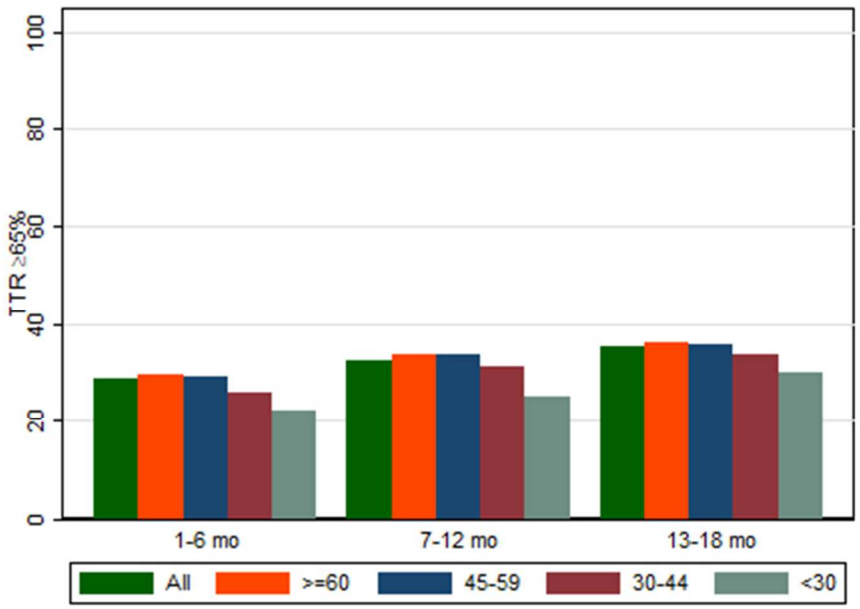

Figure 2

37x27mm (300 x 300 DPI)

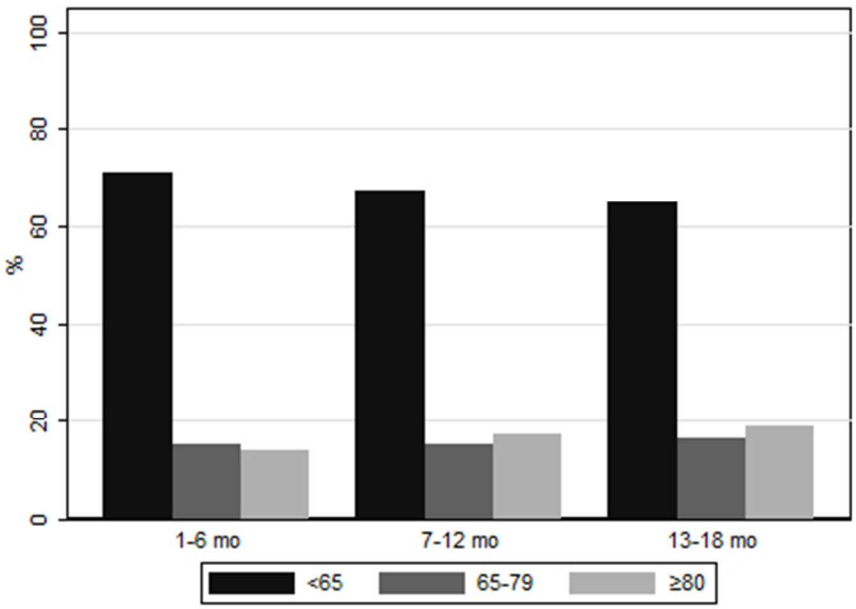

Figure 3

37x27mm (300 x 300 DPI)

eAppendix: ICD9 and ICD10 diagnosis codes. The character "x" in code listings represents any character.

	ICD-9-CM	ICD-10-CM
Diagnosis		
Atrial fibrillation and flutter	427.3x (note: the entire tree of codes)	I48.x (note: the entire tree of codes)
Mitral or aortic valvular disease	394, 396	I05, I08.0, I08.1, I08.2, I08.3
valve surgery & procedures	Procedure codes 35.0x, 35.1x, 35.2x, 35.96, 35.97, 35.99	Procedure codes 02RJ, 02RF, 02RG, 02RH, 02QF, 02QG, 02QH, 02QJ CCI Procedure Codes: 1.HT.89, 1.HV.80, 1.HU.80, 1.HT.80, 1.HS.80, 1.HV.90 1.HU.90, 1.HT.90, 1.HS.90
Co-morbidities		
Ischemic Heart Disease	410, 411, 412, 413, 414, 429.2, V45.81, procedure codes 36.xx	I20-I25, procedure codes 0210, 0211, 0212, 0213 CCI Procedure codes: 1.IJ.76, 1.IJ.50, 1.IJ.57
MI	410, 412	I21, I22, I25.2
Angina	411.1, 413	I20
Peripheral vascular diseases (PAD, aneurysm, dissection, etc.)	440, 441, 442, 443, 447.1, 557.1, 557.9, procedure codes 39.22, 39.25, 39.26, 39.29, 39.50	I70, I71, I72, I73, I77.1, I79.0, K55.1, K55.8, K55.9, Z95.82x, Z95.9, procedure codes 031, 03Q, 041, 04Q CCI Procedure Codes: 1.KE.76, 1.KA.76, 1.ID.76, 1.IB.76, 1.IA.76, 1.ID.76, 1.IC.76, 1.JM.76, 1.JJ.76, 1.KT.76, 1.KR.76, 1.KE.76, 1.KG.76, 1.JM.76, 1.JK.76, 1.JX.76, 1.JY .76, 1.KA.50, 1.IB.50, 1.IA.50, 1.ID.50, 1.IC.50, 1.KE.50, 1.JJ.50, 1.JL.50, 1.KG.50, 1.KA.57, 1.IB.57, 1.ID.57, 1.IC.57, 1.KE.57, 1.KT.57, 1.KG.57, 1.JM.57
PAD	440, 443.9	I70, I73.9
Cerebrovascular disease	430-438, 362.3, procedure codes 38.12, 39.74	I60-64, I65-69, G45, G46, H34.x (x = 0, 1, 8, 9), procedure codes 031y, where y is any of [G, S, T, H, J, K, M, L, N], and

		03Qy, where y is any of [G, H, J, K, L, M, N, P, Q, R, S, T] CCI Procedure Codes: 1.ID.76, 1.JE.76, 1.JX.76, 1.JE.50, 1.JX.50, 1.JE.57, 1.JX.57, 1.JW.57, 1.JW.76, 1.JW.50
Ischemic Stroke	434	I63
TIA	435	G45
Intracranial Hemorrhage	430, 431, 432.x (x = 0, 1, 9)	I60, I61.x, I62.x (x = 0, 1, 9)
Systemic Embolism	444	I74
Heart Failure	428	I50
Hypertension	401-405	I10-I15
Diabetes	250	E10-E13
Chronic pulmonary disease	490 - 496, 500-505, 506.4, 508.1, 508.8	I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3
Cancer	140-209, 230-234	C00 –C26, C30-41, C43-C58, C60 – C80, C81-96, D00-09
Dementia	290, 294.1, 294.2, 331.xx	F01, F02, F03, G30, G31
Peptic ulcer disease	530.2, 531, 532, 533, 534	K22.1, K25, K26, K27, K28
Chronic Kidney Disease	583, 584, 585, 586, 592, 593.9	N00-N23
Abnormal liver function tests	570-573, 574.x1	K70-K77

STROBE 2007 (v4) Statement— for McAlister et al. TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: AN OBSERVATIONAL STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	2, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2, 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9

		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 and figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-11, Tables 2 and 3, Figure 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11, Tables 2 and 3, Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	9-11, Tables 2 and 3, Figure 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11, Tables 2 and 3, Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12, 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12, 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15