Editor's key points

- This study examined the quality of warfarin management in primary care, as measured by the proportion of time that patients' international normalized ratio (INR) values remained within the therapeutic range. This study found that patients with good INR control at baseline were likely to stay well controlled; the authors believe that clinicians should consider this when deciding which established warfarin-treated patients to switch to newer agents such as direct-acting oral anticoagulants.
- While primary care warfarin management appears to be at least as good as that provided in head-to-head randomized controlled trials against direct-acting oral anticoagulants, data in this study indicate a systematic tendency for providers to err on the side of underdosing (ie, an INR of <2.0 is 3 times more common than an INR of >3.5), which potentially opens up opportunities for improvement.

Quality of warfarin management in primary care

Determining the stability of international normalized ratios using a nationally representative prospective cohort

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Abstract

Objective To determine the stability of warfarin anticoagulation using a nationally representative sample of Canadian primary care patients and providers.

Design Prospective cohort study.

Setting Primary care practices associated with the Canadian Primary Care Sentinel Surveillance Network.

Participants Adult warfarin users with 7 or more evaluable international normalized ratio (INR) readings.

Main outcomes measures International normalized ratio time in therapeutic range (TTR) determined using the Rosendaal method; TTR above 75% was considered good INR control and TTR below 60% was considered poor INR control. The primary outcome was the proportion of all warfarin users (using an INR target range of 2.0 to 3.5) with good INR control during their first year taking warfarin who have poor INR control the following year. Secondary outcomes included the TTR using an INR target of 2.0 to 3.0 when restricted to patients with known atrial fibrillation (AF) or venous thromboembolism (VTE); and the proportion of INR values below the target of 2.0 and above the targets of 3.0 and 3.5 in the year before the availability of other oral anticoagulants.

Results Among 18 303 adult warfarin users (mean age of 71.0 years, 46.6% female), the median TTR (INR target range of 2.0 to 3.5) was 77.4% (interquartile range of 64.6% to 86.4%). The TTR was above 75% in 56.0% of patients and below 60% in 19.3% of patients. Of those exhibiting good INR control in year 1 of anticoagulation therapy, only 10.2% had poor control the following year. When restricted to patients with known AF or VTE (89.7% with AF and 13.5% with VTE), and assuming an INR target range of 2.0 to 3.0, the TTR was 67.8% (interquartile range of 54.8% to 77.9%). Of these patients, 27.9% had INR values below 2.0, and 19.4% and 8.6% had values above 3.0 and 3.5, respectively.

Conclusion Primary care warfarin management produces a TTR comparable to that in randomized trials, with out-of-range INR values 3 times more likely to predispose to thrombosis (INR of <2.0) than to hemorrhage (INR of >3.5). A history of good INR control does predict future INR stability and meaningfully informs decisions to switch established warfarin users onto newer agents.

Qualité de la prise en charge du traitement par warfarine dans les soins primaires

Déterminer la stabilité des rapports internationaux normalisés à l'aide d'une cohorte prospective représentative de la situation à l'échelle nationale

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Résumé

Objectif Déterminer la stabilité de l'anticoagulation obtenue avec la warfarine à l'aide d'un échantillon de patients et de soignants canadiens représentatifs de la situation à l'échelle nationale.

Type d'étude Une étude de cohorte prospective.

Contexte Des cliniques de soins primaires faisant partie du Réseau canadien de surveillance sentinelle en soins primaires.

Participants Des patients adultes recevant de la warfarine qui avaient au moins 7 résultats de rapports internationaux normalisés (RIN) évaluables.

Principaux paramètres à l'étude Le temps durant lequel le RIN est resté dans la marge thérapeutique (TMT), tel que mesuré au moyen de la méthode de Rosendaal; un TMT supérieur à 75 % était considéré comme indiquant un bon contrôle du RIN et un TMT inférieur à 60 %, comme un mauvais contrôle. L'issue primaire était la proportion des utilisateurs de warfarine (avec comme cible un RIN entre 2,0 et 3,5) qui avaient un bon contrôle du RIN durant la première année du traitement, mais pas l'année suivante. Les issues secondaires comprenaient le TMT, avec comme cible un RIN entre 2,0 et 3,0, pour les patients présentant une fibrillation auriculaire (FA) ou une thromboembolie veineuse (TEV) connue; et la proportion de valeurs inférieures à la cible de 2,0, et de valeurs supérieures aux cibles de 3,0 et 3,5, durant l'année précédant l'arrivée d'autres anticoagulants oraux.

Résultats Chez 18 303 utilisateurs de warfarine (âge moyen de 71,0 ans dont 46,6 % de femmes), la valeur médiane du TMT (avec un RIN cible entre 2,0 et 3,5) était de 77,4 % (écart interquartile entre 64,6 % et 86,4 %). Le TMT était supérieur à 75 % chez 56 % des patients et inférieur à 60 % chez 19,3 % d'entre eux. Parmi ceux qui avaient eu un bon contrôle durant la première année du traitement, seulement 10,2 % avaient eu un mauvais contrôle l'année suivante. En se limitant aux patients présentant une FA ou une TEV connues (89,7 % une FA et 13,5 % une TEV) et en prenant pour acquis un RNI cible entre 2,0 et 3,0, le TMT était de 67,8 % (écart interquartile entre 54,8 % et 77,9 %). Enfin, 27,9 % de ces patients avaient une valeur de RIN inférieure à 2,0, tandis que 19,4 % et 8,6 % d'entre eux avaient respectivement des valeurs supérieures à 3,0 et 3,5.

Conclusion La façon de gérer la warfarine dans un contexte de soins primaires permet d'obtenir un TMT comparable à celui qu'on observe dans des essais randomisés, avec des valeurs de RIN en-dehors des valeurs normales qui sont 3 fois plus susceptibles d'entraîner une thrombose (RNI < 2,0) plutôt qu'une hémorragie (RNI > 3,5). Un historique indiquant un bon contrôle du RIN permet de prévoir une stabilité des RIN futurs et constitue une information particulièrement utile lorsqu'on envisage de prescrire des nouveaux agents à des utilisateurs réguliers de warfarine.

Points de repère du rédacteur

- Cette étude portait sur la qualité de la prise en charge du traitement par warfarine dans les soins primaires, en mesurant chez les patients le pourcentage de temps où le rapport international normalisé (RIN) demeurait à l'intérieur des valeurs thérapeutiques. L'étude a observé que les patients dont le RIN était initialement bien contrôlé étaient susceptibles de continuer d'avoir un bon contrôle; les auteurs croient que les médecins devraient tenir compte de cela lorsqu'ils doivent choisir, parmi les patients déjà sous traitement par warfarine, ceux qui devront utiliser de nouveaux agents, tels que les anticoagulants oraux à action directe.
- Bien que la gestion de la warfarine par les soins primaires semble être au moins aussi bonne que celle observée avec les anticoagulants oraux à action directe dans des essais randomisés contrôlés, les résultats de notre étude indiquent que chez les soignants, il existe une tendance systématique à sous-traiter (c.-à-d. une fréquence 3 fois plus élevée de RIN < 2,0 que de RIN > 3,5), ce qui donne à penser qu'une amélioration est possible.

Pulmonary embolism (PE) and stroke have devastating and potentially lifelong health consequences, and conditions that predispose to these events (eg, atrial fibrillation [AF], mechanical heart valves, and deep vein thrombosis [DVT]) are common in primary care. Warfarin, and the newer direct oral anticoagulants (DOACs), substantially reduce the risk of such thromboembolic events.[1,2] However, the safety and effectiveness of warfarin, as well as its use relative to DOACs, depends greatly on the proportion of time patients spend within the international normalized ratio (INR) therapeutic range.[3-7]

Although randomized controlled trials (RCTs) have consistently demonstrated no clinically important difference in time in therapeutic range (TTR) when warfarin is managed by "usual care" community primary care providers (as compared with an anticoagulation service, a specialty clinic, a pharmacist, or a primary care provider using an algorithm),[8-11] there remain substantial differences in TTR across geographic boundaries and clinical settings, with TTR often being lower in the community than in randomized trials.[12,13] It has also been suggested that a history of good control does not predict good control in the future.[14] Whether TTR can predictably remain stable among seemingly well controlled or established warfarin users, and whether community TTR is comparable to TTR reported in RCTs that compare warfarin with DOACs,[15-17] has great relevance for clinical guideline recommendations.

In this study, we accessed (via database review) the medical records of a nationally representative sample of warfarin users managed in Canadian primary care to determine both the quality of community warfarin management and the stability of seemingly well controlled patients. Specifically, our main objectives were to determine whether patients who appear well controlled in the first year of available data stay well controlled in the following year (using an INR target range of 2.0 to 3.5, and analyzing all warfarin users for maximum generalizability), and whether TTR in Canadian primary care is comparable to the TTR achieved in clinical trials comparing warfarin with DOACs (using the INR target range of 2.0 to 3.0 that is employed in DOAC trials and restricting analysis to patients with AF or VTE for whom that target range can be assumed). Our secondary (exploratory) objectives included determining if population TTR is changing over time (which might occur as selected patients are switched to DOACs), and if there is seasonality to extreme INR values (which we speculated might occur based on previous work that demonstrated some seasonality to human physiology[18,19]).

Methods

Data sources

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) extracts and processes the electronic medical records (EMRs) of more than 1200 primary care providers (primarily family physicians) widely distributed across 7 Canadian provinces (British Columbia, Alberta, Manitoba, Ontario, Quebec, Nova Scotia, and Newfoundland and Labrador). As of April 2016 the CPCSSN repository held primary care EMR data that tracked the health of more than 1.2 million Canadians, including demographic characteristics (eg, age, sex), ICD-9 diagnoses (available from both medical history and individual visit diagnoses), prescriptions written by the primary care provider (both provider initiated and renewals of specialist prescriptions), selected clinical measurements (eg, blood pressure, body mass index), and selected laboratory results (including INR and creatinine values).[20,21] Our data set for this study comprised all such data from January 1, 2008, to December 31, 2016, for all 1031 CPCSSN practices (with the date of earliest available data varying between practices according to the date each practice transitioned to electronic records).

Approval for this study came from the University of Alberta Research Ethics Board, the University of Manitoba Research Ethics Board, and the CPCSSN Standing Committee on Research and Surveillance.

Study population

The study population comprised community primary care–managed warfarin users. Inclusion criteria were as follows:

- 19 years of age and older;
- patient had at least 1 warfarin prescription written by the primary care provider (1 prescription was deemed sufficient given the following: concurrent serial INR testing confirmed use of warfarin; renewals can be obtained from other prescribers and might be missed in the EMR; and we wanted to ensure the inclusion of patients who might have struggled and not gone on to long-term warfarin use); and
- patient had 7 or more eligible INR blood tests over the duration of available data. Eligible INR tests are within 8 weeks of another INR test, and the first 5 readings are excluded (so as not to include the initial period of warfarin titration). Some patients have INR measured repeatedly for reasons other than warfarin anticoagulation (eg, those receiving potentially hepatotoxic drugs). We chose a minimum of 7 INR readings, as this was the smallest threshold that appeared to remove a notable subset of patients with serial INR values that never deviated meaningfully from 1.0. We assumed such patients were not receiving therapeutic anticoagulation.

Population for main analysis. This included all eligible warfarin users regardless of indication.

Population for subgroup analysis. This included all patients for whom a tighter INR target range of 2.0 to 3.0 could be assumed, including those with AF, DVT, and PE.

Measurements

Warfarin indications and comorbidities. Diagnostic ICD-9 codes were used to detect the likely indications for anticoagulation including AF and atrial flutter (427.3, 427.31, 427.32), DVT (453.40, 453.41, 453.42), and PE (415.1). We did not separately identify patients with mechanical heart valves, as ICD-9 codes do not distinguish between mechanical valves and other forms of valvular heart disease. Validated CPCSSN case-detection algorithms were used to identify individuals with selected common comorbidities (including diabetes, hypertension, chronic obstructive pulmonary disease, dementia, osteoarthritis, and depression).[22]

International normalized ratio TTR. Time in therapeutic range was determined using the Rosendaal method,[23] which conceptually draws a line between the values of consecutive INR tests (maximum 8 weeks apart) and assigns an interpolated INR value to every day of the week in this time period. Multiple INR tests reported on the same day were averaged and considered as 1 reading. Any INR values that were less than or equal to 0.0 or greater than or equal to 30.0 were considered erroneous and excluded. When analyzing whether apparently well controlled patients continue to stay well controlled, a 2.0 to 3.5 therapeutic range was assumed because 1) this is the range of lowest overall risk from observational studies[3,4]; 2) this range spans all indications; 3) this range has been used to describe population TTR in the past[24]; and 4) this range allowed us to analyze all warfarin users. When determining population TTR we additionally used a 2.0 to 3.0 INR range and restricted analysis to patients for whom this range could be assumed (those with known AF, DVT, or PE) in order to match the TTR definition used in clinical trials comparing DOACs with warfarin.

Prescriptions, clinical measures, and laboratory results. Only 1 warfarin prescription was required for eligibility. When determining other medications in use at the same time as warfarin, we required 2 prescriptions for that medication's ATC[25] code (indicating renewal) in the interval between the first and last INR test (the "period of warfarin use"). Age, body mass index, and estimated glomerular filtration rate were reported as the average during this period.

Statistical analysis

The population distributions of both TTR and INR were displayed as histograms. For TTR, each patient contributed only once to the histogram and all of their eligible INR values were used to determine a single TTR. In contrast, each patient contributed multiple INR values to the INR histogram (as many as were available); however, the period of evaluation was limited to the year before the availability of DOACs (October 1, 2009, to September 30, 2010). We used this shorter (immediately pre-DOAC) period to examine how INR was distributed in the event that case selection pressure, from patients switching to DOACs, influenced the stability of INR in the population as a whole. That is, in the last year before DOACs became available, all anticoagulant users were taking warfarin, whether they had high or low economic status and had good or poor INR control; this provided a better picture of the range of INRs that might be achieved if warfarin is offered to all patients with an indication.

As distributions were not Gaussian, summary statistics were reported as median and interquartile range (IQR). Time in therapeutic range was further broken down (using previously published ranges[6]) into the proportion of patients with good control (TTR of >75%), intermediate control (TTR of 60% to 75%), and poor control (TTR of <60%).

To assess whether good control at baseline predicts future INR stability, we reported the proportion of patients with good control in the first 365 days of eligible INR readings who would go on to have poor control the following year. In creating the cohort for this analysis, we required a minimum of 6 eligible INR tests be present in both of the 365-day periods being examined. Six eligible INR tests per year was the smallest number of INR tests that guaranteed at least 3 interpolated INR segments in each time period. In the event that using the first 2 years might introduce bias from a training effect, we also made the same comparison using the fixed 2-year period from October 1, 2008, to September 30, 2010.

For our 2 exploratory analyses we assessed the following: whether the quality of warfarin management was changing over time by examining, as a time series, the proportion of INR readings in range each month; and whether there is seasonality to extreme highs and lows of INR values by examining, as a time series, the proportion of INR values that were below 1.7 and above 7.0 each month.

Results

Of the eligible warfarin users (13 481 individuals attached to 1043 primary care providers [**Figure 1**]), 53.4% were male and the mean age was 71.0 (range of 19 to 105 years of age). Of these, 5556 individuals could be identified as having AF, DVT, or PE. **Table 1** presents patient characteristics.

Time in therapeutic range

All warfarin users (INR target range of 2.0 to 3.5). Among this group (13 481 individuals), TTR was non-Gaussian, with a median TTR of 77.4% (IQR of 64.6% to 86.4%). Fifty-six percent of patients had good INR control (TTR of >75%), 24.7% had intermediate INR control (TTR of 60% to 75%), and 19.3% had poor INR control (TTR of <60%) (**Figure 2**).

Patients taking warfarin with known AF, DVT, or PE (INR target of 2.0 to 3.0). Among this group, the median TTR was 67.8% (IQR 54.8% to 77.9%). Good INR control was present in 32.5% of patients, intermediate control in 33.4%, and poor control in 34.1% (**Figure 2**).

Durability of good control

Of all warfarin users, 8054 had at least 6 eligible INR readings per year over a 2-year span. In year 1, 63.1% had good INR control and 15.1% had poor INR control. In year 2, 62.6% had good INR control and 17.5% had poor INR control. The median TTR was 81.0% for both years. Of the group with good INR control in year 1, 72.5% maintained good INR control while 10.2% developed poor INR control (**Figure 3**). Assessing change over time using a fixed 2-year period (October 1, 2008, to September 30, 2010) provided similar results. **Figure 4** presents this analysis and is available at **CFPlus**.*

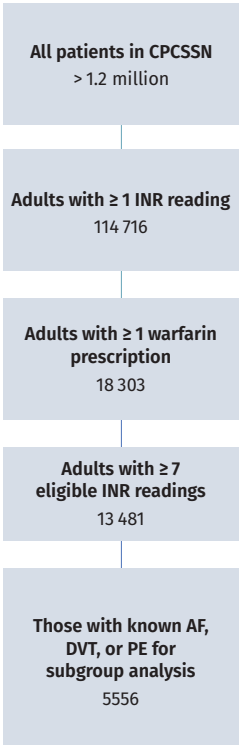
Distribution of INR

Of all patients with AF, DVT, or PE contributing to the TTR analysis, 2184 had INR data in the October 1, 2009, to September 30, 2010, window of observation. The distribution of INR values was non-Gaussian, with a median of 2.4 (IQR of 2.0 to 2.8) (**Figure 5**). Of these INR values, 52.7% were within the assumed 2.0 to 3.0 target range, 27.9% were below 2.0, 19.4% were above 3.0, and 8.6% were above 3.5.

Exploratory analysis

No clear seasonal pattern emerged from plotting, as a time series, the average monthly proportion of INR values within range, nor the average monthly proportion of extreme INR results (separately evaluating INR values <1.7 and INR values >7.0). This suggests there is no substantial seasonality to INR control. There was, however, a trend to a lower proportion of INR readings in target range over time (driven by the last 3 years of available data) with the line of best-fit for January 2008 to December 2016 falling from 0.480 to 0.444. Over the same period, the proportion of readings below 1.7 rose from 0.293 to 0.358 while the proportion of readings above 7.0 was unchanged (**Figures 6A** to **6C** available at **CFPlus**).*

Figure 1. Flowchart of cohort creation



AF—atrial fibrillation, CPCSSN—Canadian Primary Care Sentinel Surveillance Network, DVT—deep vein thrombosis, INR—international normalized ratio, PE—pulmonary embolism.

Discussion

We have found that Canadian primary care–managed warfarin users have a median TTR (77.4% for an INR target range of 2.0 to 3.5, and 67.8% for an INR target range of 2.0 to 3.0) similar to that observed for warfarin-treated patients in clinical trials comparing DOACs with warfarin (ie, median TTR of 58% in the ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation] trial, 66% in the ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation] trial, and 67% in the RELY [Randomized Evaluation of Long-term Anticoagulation Therapy] trial, in which each trial employed an INR target range of 2.0 to 3.0).[7,15-17] We have further shown that good INR control in the past year predicts good control in the year to come and that when the INR is out of range, it is 3 times more likely patients will be at increased risk of thrombosis (ie, INR <2.0) than increased risk of hemorrhage (INR >3.5).

The TTR in a primary care setting varies widely, being as high as 80.3% in a large Swedish registry and as low as 51.0% in a meta-analysis of US studies.[26,27] Our results are certainly within this wide range and similar to those of a population-based Danish study, where TTR was 71.0% using an INR range of 2.0 to 3.5.[24] Given that RCTs

*__Figure 4,__ which presents the international normalized ratio changes over time using a fixed 2-year period (October 1, 2008, to September 30, 2010), and **Figures 6A** to **6C,** which present the proportion of international normalized ratio values in range per month over time, as well as the monthly proportion of values above 7.0 and below 1.7 (January 2008 to December 2016), are available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Table 1. Patient characteristics

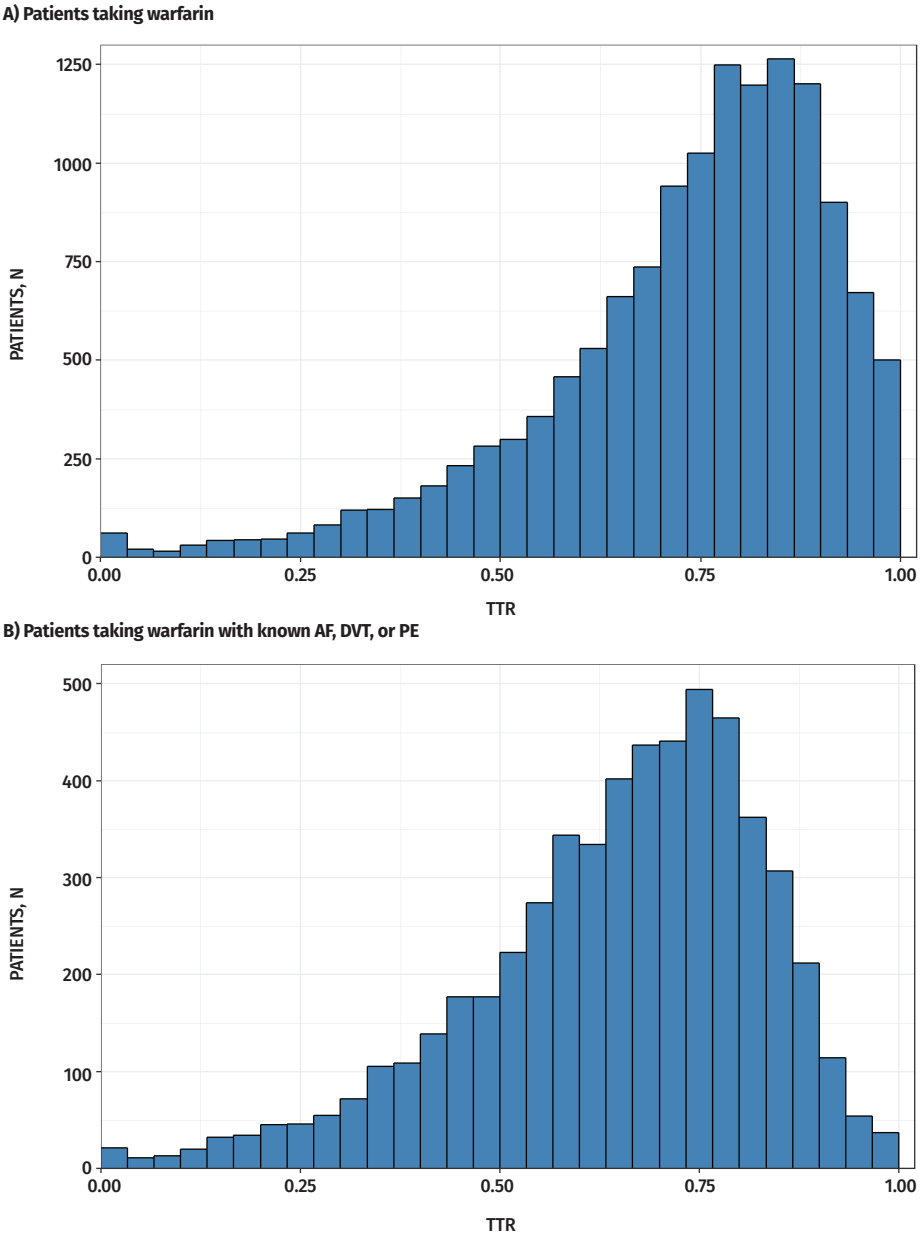
PATIENT CHARACTERISTICS	ALL WARFARIN USERS (N = 13 481)	THOSE WITH AF (N = 5010)	THOSE WITH VTE (N = 730)
Female sex, n (%)	6285 (46.6)	2221 (44.3)	379 (51.9)
Mean (SD) age, y	71.9 (14.0)	75.1 (11.3)	63.1 (15.9)
Mean (SD) BMI, kg/m^2	30.1 (6.8)	30.2 (6.5)	31.8 (7.3)
Mean (SD) GFR, mL/min	64.7 (19.9)	58.2 (16.7)	56.3 (17.7)
Comorbidities, n (%)			
• Hypertension	8103 (60.1)	3349 (66.9)	370 (50.7)
• Osteoarthritis	4852 (36.0)	2149 (42.9)	288 (39.5)
• Diabetes	4144 (30.7)	1670 (33.3)	178 (24.4)
• Depression	3075 (22.8)	1061 (21.2)	233 (31.9)
• COPD	2747 (20.4)	1146 (22.9)	125 (17.1)
• Dementia	1770 (13.1)	731 (14.6)	62 (8.5)
Warfarin-related condition, n (%)			
• AF	5010 (37.2)	5010 (100.0)	184 (25.2)
• DVT	621 (4.6)	160 (3.2)	621 (85.1)
• PE	131 (1.0)	33 (0.7)	131 (18.0)
Medications, n (%)			
• ≥ 4 medications (including warfarin)	7120 (52.8)	2807 (56.0)	292 (40.0)
• Cardiovascular drugs	9973 (74.0)	4179 (83.4)	340 (46.6)
• Lipid-modifying drugs	5779 (42.9)	2187 (43.7)	179 (24.5)
• Drugs for acid disorders	4323 (32.1)	1707 (34.1)	202 (27.7)
• Drugs for COPD or asthma	3085 (22.9)	1213 (24.2)	134 (18.4)
• Antidepressants	2961 (22.0)	1029 (20.5)	186 (25.5)
• Thyroid-related drugs	1975 (14.7)	799 (16.0)	73 (10.0)
• Antiepileptics	1743 (12.9)	660 (13.2)	125 (17.1)
• Anxiolytics	1510 (11.2)	510 (10.2)	62 (8.5)
• ASA	967 (7.2)	499 (10.0)	39 (5.3)
• Other antiplatelets	457 (3.4)	165 (3.3)	10 (1.4)
• Psycholeptics	576 (4.3)	196 (3.9)	46 (6.3)
• Anti-dementia drugs	381 (2.8)	132 (2.6)	5 (0.7)

AF—atrial fibrillation, ASA—acetylsalicylic acid, BMI—body mass index, COPD—chronic obstructive pulmonary disease, DVT—deep vein thrombosis, GFR—glomerular filtration rate, PE—pulmonary embolism, VTE—venous thromboembolism.

have consistently demonstrated no clinically important difference in TTR when warfarin is managed by "usual care" community primary care providers (as compared with more specialized or algorithm-driven care),[8-11,28] observed differences in TTR might stem less from provider abilities and more from the health care systems and patient populations under study. The patients in this study all had family physicians and, similar to many countries attaining high population TTR, universal coverage for health care services. Conceivably, this might offer an advantage over countries such as the United States where cost and access to care might be a barrier. If real, the trend over the past few years to a lower proportion of INR readings in range could conceivably result from selection bias, given that patients with higher socioeconomic status (who traditionally have better overall health) are better able to afford the more expensive DOACs and might represent a gradually diminishing proportion of warfarin users.

Contradicting our finding that good baseline control predicts good control in future is a single study suggesting the opposite.[14] Pokorney and colleagues' study of patients with AF (968 of whom had a "stable" INR at baseline) differed from our analysis in several ways that

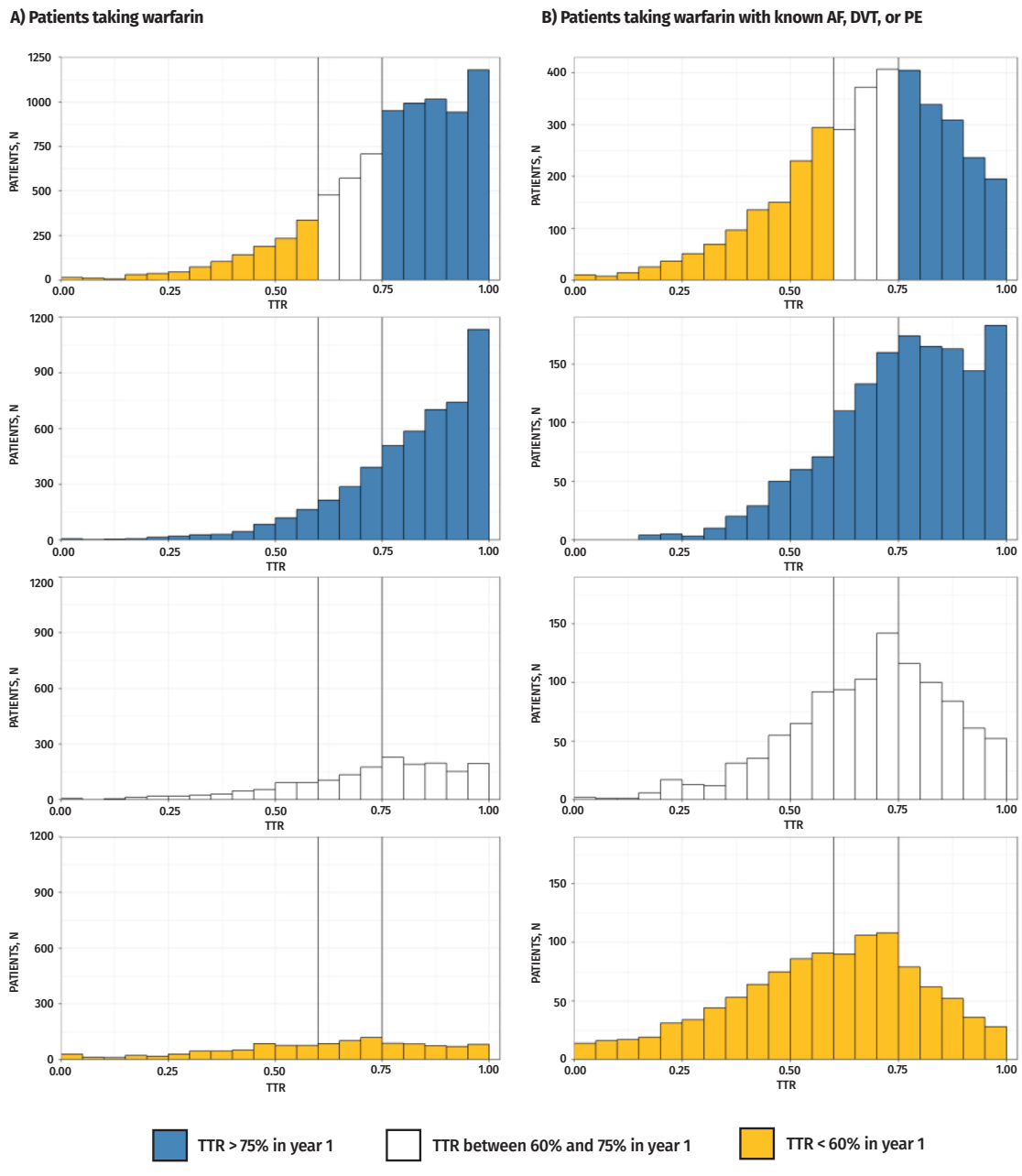
Figure 2. Proportion of TTR for A) the 13 481 patients taking warfarin (with an INR target range of 2.0 to 3.5) and B) the 5556 patients taking warfarin with known AF, DVT, or PE (with an INR target range of 2.0 to 3.0): *Both were determined over the 2008 to 2016 study period.*



AF—atrial fibrillation, DVT—deep vein thrombosis, INR—international normalized ratio, PE—pulmonary embolism, TTR—time in therapeutic range.

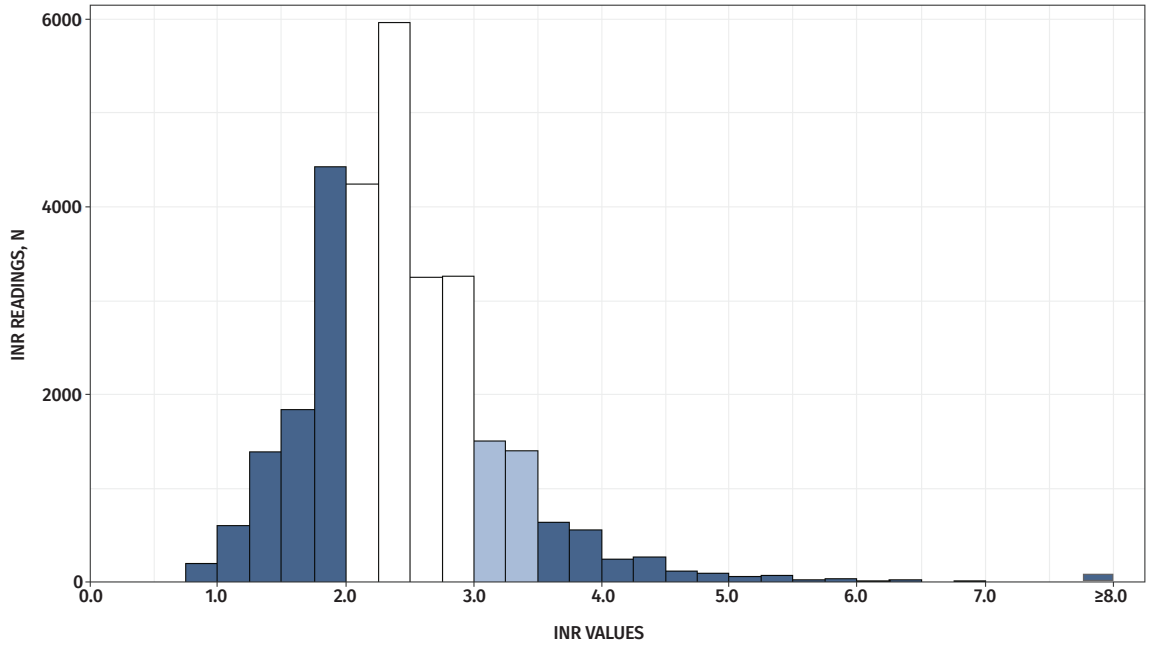
might explain this discrepancy: 1) their definition of stability required greater control (≥80% of readings in range), and many patients initially meeting this high bar would have uncharacteristically high TTR that can be expected to regress to the mean on follow-up; 2) becoming unstable was defined as falling below the 80% threshold, hence a change of only a few percentage points could potentially change a patient from stable to unstable; and 3) the baseline TTR calculation in this study required 3 or more INR tests over 6 months, while the authors' follow-up period looked over a full year and required 6 or more readings. Using a small number of baseline readings will push baseline TTR to uncharacteristic extremes (many patients appearing to have 100% of such a small number of readings in range). The TTR would be expected to fall for patients initially classified as stable based on only a few readings once a subsequent (longer) observation period produces a more accurate (lower) TTR.

Figure 3. Predictive value of baseline TTR: *The top histograms are year 1 of warfarin use, with blue indicating good INR control, white intermediate INR control, and yellow poor INR control. The bottom histograms show the distribution of the same patients in year 2 with the same colour coding (eg, the second all-blue histograms show the TTR distribution in year 2 for all patients whose TTR was > 75% in year 1). N = 8054.*



AF—atrial fibrillation, DVT—deep vein thrombosis, INR—international normalized ratio, PE—pulmonary embolism, TTR—time in therapeutic range.

Figure 5. Distribution of INR readings and all recorded INR values from October 2009 to October 2010 in patients with AF, DVT, or PE taking warfarin: *Dark blue indicates INR values out of the low-risk range. Light blue is above the presumed 2.0 to 3.0 target for patients with these indications but within the low-risk range. N = 2184.*



AF—atrial fibrillation, DVT—deep vein thrombosis, INR—international normalized ratio, PE—pulmonary embolism.

Limitations

Usual care data are not designed for research and their use is a limitation of this study. We believe the risk of misclassification is low given our reliance on the presence of multiple INR tests, a prescription for warfarin, and (for our subgroup analysis) selected ICD-9 diagnoses, but missing data are common in such data sets. In particular, while laboratory data are automatically populated into CPCSSN EMRs, detecting diagnoses relies on providers inputting these diagnoses in discrete fields where they can be searched. If a diagnosis is instead discussed in the body of an encounter note it cannot be detected, as CPCSSN does not process free text. This limitation comes into play in identifying patients with AF, DVT, or PE for our subgroup analysis, many of whom could be missed. If there was unmeasured confounding that systematically affected our ability to detect the indication for anticoagulation, and if TTR was materially different among detectable patients, our results could have been affected.

Because ICD-9 codes do not distinguish mechanical heart valves from other forms of valvular heart disease, we were also unable to detect patients with this indication for anticoagulation. To address this, rather than analyzing subgroups based on differing indications and target ranges, our main analysis exploring the predictive value of good baseline control made use of all warfarin patients (regardless of indication) and used an INR target range that spanned all indications.

Although we excluded the first 5 INRs to avoid the period of initial warfarin titration, we were unable to detect patients advised to transiently stop and restart warfarin (eg, for elective surgery). As a result, our TTR estimate might be somewhat conservative, including subtherapeutic INRs in the analysis during a period in which the patient was not actively receiving anticoagulation. However, as this reflects real life, we believe it is appropriate for these INRs to be included.

Although the wide disbursement and large number of patients and providers in this study is a strength, it is also possible that physicians contributing EMR data to CPCSSN are not representative of providers more generally. However, our median TTR findings are consistent with that observed in other Western countries with universal health care.

Conclusion

Patients with good INR control at baseline are likely to stay well controlled, and clinicians should consider this when deciding which established warfarin-treated patients to switch to newer agents such as DOACs. In addition, while warfarin management in primary care appears to be at least as good as that provided in

head-to-head RCTs against DOACs, our data indicate a systematic tendency for providers to err on the side of underdosing (ie, an INR of <2.0 is 3 times more common than an INR of >3.5), which potentially opens up opportunities for improvement.

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Contributors

All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests

None declared

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This article has been peer reviewed.
Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2019;65:416-25