Dedicated warfarin care program results in superior warfarin control in Queensland, Australia

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ABSTRACT

BACKGROUND

Warfarin is used to prevent stroke in patients with atrial fibrillation (AF). Ongoing monitoring of International Normalised Ratio (INR) is required and time in therapeutic range (TTR) commonly used to assess the quality of warfarin management. Anticoagulant clinics have demonstrated improved TTRs, particularly in countries with poorer control in primary care settings. Reported TTR in Australia has been relatively high so it is unknown if benefit would be seen from dedicated warfarin clinics in Australia. The aim of this study was to compare the level of warfarin control in patients managed by their general practitioner (GP) and a warfarin care program (WCP) by Sullivan Nicolaides Pathology.

METHOD

Retrospective data was collected for AF patients enrolled in the warfarin care program at WCP, and included patients with INR tests available whilst managed by their GP. INR tests were used to calculate TTR and frequency of testing for the time managed by GP and WCP, with mean data used for analysis and comparison.

RESULTS

The eligible 200 warfarin patients had a TTR of 69% with GP management and 82% with WCP management (<0.0001). Significant differences were also found between GP and WCP management in the percentage of tests in range, total number of tests, and frequency of testing. WCP had a reduced time to repeat test at extremes of INR results.

CONCLUSION

Australian warfarin control was good when managed by either GP or WCP, but WCP management increased TTR by 13%. Dedicated warfarin programs can improve warfarin control and optimise therapy for patients.

WHAT'S KNOWN

Anticoagulant options for patients with atrial fibrillation have recently expanded but warfarin remains widely prescribed. Warfarin outcomes may be optimised by good control, as measured by time in therapeutic range (TTR), but this varies according to geographical areas and management practices. Dedicated anticoagulant clinics can improve TTR, but there is conflicting data on improvements in warfarin TTR in areas where the overall control is high.

WHAT'S NEW

This is the first study comparing warfarin management options in Australia. This study found a high level of warfarin control when managed by general practitioners (69% TTR) and a warfarin care program (82% TTR). Both management options achieved warfarin control above TTR targets of 65%, but the increased control by the dedicated warfarin program can further improve outcomes and optimise therapy for patients placed on warfarin.

KEYWORDS

Warfarin, anticoagulants, atrial fibrillation, quality improvement

INTRODUCTION

Warfarin is an oral anticoagulant used for both the prevention and treatment of thromboembolism, including stroke due to atrial fibrillation (AF).(1) Patient variability in warfarin response and a narrow therapeutic index necessitates monitoring of the international normalised ratio (INR) to guide therapy.(2) Tight control of INR between 2.0 to 3.0 is the strategy used to ensure optimal benefit of warfarin whilst minimising risk.(3) Time in therapeutic range (TTR) is a routinely used measure of warfarin control in clinical settings, with patients obtaining lower TTR more likely to experience negative outcomes such as haemorrhage or stroke.(4) A minimum threshold TTR of 65% is recommended (5), but wide variations of TTR have been demonstrated by different countries and clinical settings.(6)

Sub-analyses of the recent large comparative trials of warfarin and the newer oral anticoagulants (NOACs) have showed substantial variation in TTRs of 43-77% across countries.(7-9) Singer et al (9) found the highest TTRs in Canada, United States and Western European countries. Similarly, Wallentin et al (7) reported Sweden to be the country with the highest TTR of 77%, followed by Finland and Australia with 74%. Further to this, Wallentin et al (8) observed TTR variation not only between countries but also between sites within a country dependent on the processes of care at the site and country level. Van Walraven et al (10) showed time spent outside of therapeutic INR range was higher in patient groups from community based settings than anticoagulation clinics. The improvement in TTR achieved by anticoagulant clinics compared to general practitioner (GP) care has been reported to range from 8% (11) to 17% (12). However, differences have again been reported between countries. A meta-analysis of warfarin control in the United States by Baker et al (13) reported an 11% improvement in TTR for patients managed by an anticoagulation clinic. Wilson et al (14) and Young et al (15) reported a more modest improvement of warfarin control of 6-8% in Canada. However, in contrast, Lalonde et al (16) reported no difference in control for patients in Canada managed by anticoagulant services or physicians. Similarly, in Sweden, Wallvik et al (17)

found no differences in complications between anticoagulation clinics and primary care, whilst Wieloch et al (18) found no differences in terms of TTR due to a high-level of warfarin control in primary care in Sweden.

In Australia, a high level of warfarin control has been demonstrated from sub-analyses of the large comparative trials of warfarin and the NOACs with TTR values of 73-76%.(7-9) However this was in controlled clinical trial conditions with limited data on warfarin TTR in real-world clinical practice.

Bereznicki et al (19) reported an overall TTR of 64.0% in Australian veterans taking warfarin. Further Australian studies have reported regionally specific TTRs of 69.1% in southern Tasmanian patients (20), 55.4% in the top end of the Northern Territory (21), and 79-81% in Queensland (22, 23).

Australian approaches for managing patients taking warfarin include care by the GP or by laboratory care programs.(24) However, to our knowledge, there is no Australian data comparing warfarin management by the GP and dedicated warfarin programs. Therefore, the aim of this study was to determine the level of warfarin control as measured by TTR in patients managed by their GP and when managed by a pathology laboratory offering a warfarin management program in Queensland, Australia.

METHODS

Griffith University ethics was obtained PHM/09/14/HREC. A retrospective analysis was conducted for patients enrolled in the Warfarin Care program (WCP) at Sullivan Nicolaides Pathology. Warfarin Care is a service open to patients of the pathology practice's regular referring doctors and the program aims to manage the patient's warfarin in partnership with the patient, GP, and WCP staff. At enrolment, patient medical and medication history is recorded. At subsequent appointments for blood collections, patients are required to complete a questionnaire detailing any medication changes, compliance, adverse effects, and any planned surgery or holidays. Following INR testing,

results are reviewed by specialists GPs employed at Warfarin Care and instructions on dosing and time to next appointment provided to the patients via telephone, text, or e-mail depending on patient preference.

Patients with AF enrolled in the WCP at Sullivan Nicolaides Pathology as of September 2014 were identified. Patients were ineligible for inclusion if they had been with the program since commencement of the current database in Nov 2007, or had enrolled at WCP less than six months after commencing warfarin. Remaining patients were screened to determine if they had INR results available prior to enrolment in the program, i.e. whilst managed by their GP. Further patient exclusions were less than six months of continuous pathology results during GP management, and INR target ranges not recorded or documented as mixed ranges.

Patients with greater than six months of continuous data for both GP and WCP management had their INR test dates and results recorded, together with date of commencing warfarin and date of commencing at WCP. Further data collected included gender, age, medical conditions, and concurrent medications at the time of enrolment in the program. TTR was calculated using Rosendaal's linear interpolation method with software downloaded from INR Pro®. TTR for an individual patient was calculated for the entire time managed by both the GP and WCP, and for a six month period immediately prior and after enrolment with WCP. Percentage of tests in range, total number of tests, frequency of testing, and total days of testing were calculated. For the overall time of GP and WCP management, the mean time in days to next INR test was calculated for INR results in therapeutic range, i.e. 2.0 to 3.0, when INR was subtherapeutic ($\text{INR} < 2.0$), supratherapeutic ($\text{INR} 3.1\text{--}5.0$ and $\text{INR} > 5$), and at extremes of INR, i.e. ≤ 1.5 and ≥ 4.0 was calculated. Mean patient data was used for analysis and comparison between GP and WCP management, with comparisons made using ordinary analysis of variance via nonparametric methods including Kruskal-Wallis test. Statistical analysis was performed on GraphPad InStat Version 3.

RESULTS

Of the 3954 patients with AF enrolled at WCP as of September 2014, 2804 were ineligible for inclusion in the study. Of the 1150 patients screened for further pathology results, 354 had data for the time managed by their GP. There were 200 patients included in the study following exclusions for continuous data being unavailable (83 patients), less than six months of continuous INR results with their GP (52 patients), and INR target ranges either not recorded or recorded as mixed ranges (19 patients).

Of the 200 patients included in the study, there were 104 (52%) males and 96 (48%) females (Table 1). The mean age of the patients at the time of enrolment at WCP was 78.9 ± 7.5 years. The overall mean TTR was $68.5 \pm 16.2\%$ when managed by the GP and $81.5 \pm 9.1\%$ when managed at WCP, which was significantly different ($p < 0.0001$) (Table 2). The percentage of tests in range was significantly different between management by GP and WCP ($62.8 \pm 15.4\%$ vs $75.5 \pm 9.4\%$, $p < 0.0001$), as was the total days of testing (741.5 ± 462.6 days vs 1287 ± 41.6 days, $p < 0.0001$ respectively), and frequency of testing (22.5 ± 9.1 days vs 15.9 ± 7.0 days, $p < 0.0001$ respectively). For the six month period immediately prior to enrolment in the program, the mean TTR for GP management was $67.6 \pm 25.1\%$. This was significantly different ($p < 0.0001$) to the mean TTR for WCP management of $79.8 \pm 13.3\%$ for the six month period immediately after enrolment in the warfarin management program. Significant differences were also found at this time period between GP and WCP management for percentage of tests in therapeutic range, total number of tests, and frequency of testing.

<Insert Table 1 and 2>

The percentage of INR tests < 2 was 22.9% for GP and 15.3% for WCP (Figure 1). At supratherapeutic INRs of 3.1-5.0 and > 5.0 the percentage of INR tests for GPs was 15.9% and 0.9% respectively, compared to 10.3% and 0.2% respectively for WCP. The mean time interval to next INR test

following a therapeutic test (i.e. INR 2.0-3.0) was 21.5 ± 19.8 days for GP and 15.4 ± 18.5 days for WCP management, which was significantly different ($p < 0.001$) (Table 3). Significant differences were also found in time interval to next INR test when the result was subtherapeutic, supratherapeutic in the range 3.1-5.0, and for extremes of INR, i.e. ≤ 1.5 and ≥ 4.0 .

<Insert Figure 1 and Table 3>

DISCUSSION

Warfarin is an effective therapy for the prevention of stroke in patients with AF, but differences in TTR can affect outcomes.(6) Anticoagulant clinics have been suggested to improve outcomes and optimise TTR(25), however reported TTR increases have varied. Further to this, studies from countries with a high quality of warfarin control in general practice have demonstrated no significant change in TTR with dedicated warfarin clinics. Warfarin control in Australia has been reported to be relatively high, with TTRs of 73-76% in clinical trial settings(7-9) and TTRs of 55% (21) to 81%(22) in real-world practice settings. However, to date, there is no Australian data comparing warfarin management by the GP and dedicated anticoagulant clinics. Therefore, the aim of this study was to determine the level of warfarin control in AF patients when managed by their GP and by a pathology practice offering a warfarin management program in Queensland, Australia. This study found significant differences in mean TTR between GP and WCP management for the overall time period (69% and 82% respectively), and for the six month period (68% and 80% respectively) either side of enrolment in the warfarin management program. Significant differences were also found at these time periods between GP and WCP management in the percentage of tests in range, total number of tests, frequency of testing, and interval to next INR test.

The Australian TTR data from the comparative trials of warfarin and the NOACs was 73-76%.(7-9) In our study, the GP TTR of 69% was 4-7% below the mean Australian TTR, and the WCP TTR of 82%

was 9-12% above these values. In comparison, van Walraven et al (10) reported 12% lower TTRs for studies from community practices compared to randomised trials, but found no difference between anticoagulation clinics and randomised trials. Further to this, Ansell et al (26) found a TTR of 57-61% in routine medical care across US, Canada and France in comparison to TTR of 64-69% in anticoagulation clinics in Italy and Spain. Genetic differences in warfarin metabolism may account for variable responses across ethnic groups.(27) However Van Spall et al (28) found clinical skill in warfarin dose decisions accounts for the majority of variation between countries and centres and is an important determinant of TTR. The GP TTR of 69% in our study is more comparable to the TTR reported for some overseas anticoagulation clinics, whilst the WCP TTR of 82% far exceeds these reported values and shows that WCP management with specialist GPs can improve TTR by 13%. This improvement in TTR by the dedicated clinic is comparable to data from the United States showing an improvement by anticoagulant clinics of 11% TTR (13), and exceeds the improvement of 6-8% TTR in Canadian studies.(14, 15)

Mearns et al (29) in a meta-analysis of warfarin treated AF patients demonstrated 56% of INR tests to be within range. In our study, both the GP and WCP results were superior to this with 63% and 76% of INR results in range respectively. This 13% increase of INRs in range between GP and WCP management is comparable to reports by Wilson et al (14) of a 6% increase of INRs in target range when changed to anticoagulant clinic management, and slightly lower than that found by Bungard et al (12) of a 17% increase. Chiquette et al (30) reported that patients managed by anticoagulation clinics have more INR values in range with less high risk INR values of greater than 5 compared to usual care. Consistent with this, our study found a significantly higher percentage of tests in range by WCP compared to GP management, and a lower percentage of INR>5 by WCP compared to GP (0.2% versus 0.9%).

Wittkowsky et al (31) suggested the more consistent INR monitoring at anticoagulant clinics contributed to improved patient outcomes. In addition, Chamberlain et al (32) concluded that

patients managed at anticoagulant clinics had 21% more INR tests performed per patient year of therapy. Likewise, our study showed WCP management to have more frequent INR tests and subsequently a higher number of tests per patient year. Interestingly in our study the testing frequency of 16 days by WCP and 22 days by GP achieved a TTR of 82% and 69% respectively. This is similar to findings by Singer et al (9) who correlated TTRs of around 66% to an average INR testing frequency of 19-21 days. In contrast, Carrier et al (4) associated poor control (TTR<65%) with a median of 12 tests over a six month period or a testing interval of 15 days. In addition, Schaefer et al (33) identified poor control to be associated with long intervals between measurements but defined this as >14 days. Therefore, given both GP and WCP management achieved above a TTR of 65% but the average testing interval was 16 and 22 days respectively, further investigation is required to determine the association with testing frequency and overall TTR.

The time interval to next INR test was significantly lower by WCP compared to GP management across a range of INR values, including extremes of ≤ 1.5 and ≥ 4.0 . This is in accordance with findings by Witt et al (11) of significantly lower time to follow-up testing by anticoagulant services when INR values were ≤ 1.5 or ≥ 4.0 . Similar to this, Nichol et al (34) reported significantly lower number of days between out-of-range INR tests for anticoagulation clinic patients compared to usual care. Rose et al (35) concluded that better anticoagulation control is achieved with shorter follow-up intervals after out-of-range INR values. Thus decreasing the time to next INR test, particularly for out-of-range INR, could assist in further improving the TTR by GP management.

The improved outcomes from anticoagulation clinics have been associated with more consistent INR testing (32), early recognition of patient risk factors (15), and improved patient education (31). Due to the retrospective nature of our study and access only to INR results prior to enrolment at the clinic, we were unable to measure outcomes in terms of adverse events and influence of interacting medications. However, TTR has been shown to be a good surrogate marker of outcomes with warfarin therapy (36-38), and enrolment in the dedicated warfarin clinic was shown to improve TTR

even after only a six month period. This is likely to translate into improved outcomes from warfarin therapy but further investigation is required to confirm this improvement in terms of clinical efficacy and safety. Further investigation should also include other Australian States and Territories to determine if warfarin management programs could improve warfarin control on a nation-wide level and ensure optimal outcomes for patients on warfarin.

In conclusion, this study found a high level of warfarin control in Australia with a TTR of 69% when managed by the GP and 82% when managed at WCP. The TTR for both management approaches is above recommended targets of 65%, suggesting good management by Australian GPs but superior control by the dedicated WCP. These findings suggest that dedicated warfarin management programs can improve warfarin control for Australian patients and are an important approach to optimise TTR and warfarin therapy for patients.

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AUTHOR CONTRIBUTIONS

Nijole Bernaitis: Data collection; data analysis, drafting article; approval of article.

Tony Badrick: Data analysis/interpretation; statistics; critical revision of article; approval of article.

Shailendra Anoopkumar-Dukie: Concept/design; data interpretation; critical revision of article; approval of article.

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Table 1 – Demographics of 200 patients at time of enrolment at Sullivan Nicolaides Pathology. Data shown is number (percentage), mean (SD) for age, and median (IQR) for HASBLED and CHA₂DS₂-VASc scores.

	Number (%)
Male	104 (52%)
Female	96 (48%)
Age <60 years	2 (1%)
Age 60-69 years	20 (10%)
Age 70-79 years	71 (35.5%)
Age 80-89 years	96 (48%)
Age ≥90 years	11 (5.5%)
Past Medical History	
Hypertension	83 (41.5%)
Diabetes	38 (19%)
Heart Failure	27 (13.5%)
Vascular Disease (CAD or IHD)	22 (11%)
Chronic Kidney Disease	16 (8%)
History of stroke or TIA	39 (19.5%)
History of cancer	25 (12.5%)
Anaemia	7 (3.5%)
Cardiomyopathy	4 (2%)
Dyslipidaemia	25 (12.5%)
Risk Model Scores	
CHA ₂ DS ₂ -VASc median (IQR)	3 (2-4)
CHA ₂ DS ₂ -VASc score 0	2 (1%)
CHA ₂ DS ₂ -VASc score 1	21 (10.5%)
CHA ₂ DS ₂ -VASc score 2	41 (20.5%)
CHA ₂ DS ₂ -VASc score 3	50 (25%)
CHA ₂ DS ₂ -VASc score 4	42 (21%)
CHA ₂ DS ₂ -VASc score 5	24 (12%)
CHA ₂ DS ₂ -VASc score 6	16 (8%)
CHA ₂ DS ₂ -VASc score 7	3 (1.5%)
CHA ₂ DS ₂ -VASc score 8	1 (0.5%)
HAS-BLED median (IQR)	2 (1-2)
HAS-BLED score 0	4 (2%)
HAS-BLED score 1	84 (42%)
HAS-BLED score 2	77 (38.5%)
HAS-BLED score ≥3	35 (17.5%)
Concurrent treatment	
Amiodarone	10 (5%)
Beta-blocker	118 (59%)
Digoxin	65 (32.5%)
Angiotensin Converting Enzyme Inhibitor	71 (35.5%)
Angioreceptor Blocker	48 (24%)
Calcium channel blocker	43 (21.5%)
Statin	103 (51.5%)
Platelet Inhibitor	18 (9%)

Diuretic	99 (49.5%)
Proton Pump Inhibitor	73 (36.5%)

Table 2 – Data on warfarin control for the 200 patients when managed by general practitioner (GP) and warfarin care program (WCP). Data is shown for the entire time of testing and for the six month period of management prior to enrolment in program for GP and after enrolment for WCP. Data represented is mean (standard deviation).

	GP	WCP	p Value
ENTIRE TIME			
Time in Therapeutic range (%)	68.5 (16.2)	81.5 (9.1)	<0.0001
Percentage tests in therapeutic range	62.8 (15.4)	75.5 (9.4)	<0.0001
Total number of tests	36.7 (26.6)	89.5 (66.1)	<0.0001
Frequency of testing (days)	22.5 (9.1)	15.9 (7.0)	<0.0001
Total days of testing	741.5 (462.6)	1287.1 (41.6)	<0.0001
SIX MONTHS			
Time in Therapeutic range (%)	67.6 (25.1)	79.8 (13.3)	<0.0001
Percentage tests in therapeutic range	63.3 (23.8)	75.2 (13.8)	<0.0001
Total number of tests	11.1 (6.8)	15.9 (4.8)	<0.0001
Frequency of testing (days)	21.5 (10.1)	12.9 (5.7)	<0.0001
Total days of testing	185.1 (1..0)	184.6 (9.5)	0.3899

Table 3 – Time intervals in days to next International Normalised Ratio (INR) test for general practitioner (GP) and warfarin care program (WCP) when INR was subtherapeutic (INR<2.0), therapeutic (INR 2.0-3.0), and supratherapeutic (INR 3.1-5.0 and INR >5).

	FREQUENCY OF TESTING IN DAYS		
INR	GP	WCP	P Value
<2.0	18.8 (20.0)	12.6 (12.9)	<0.0001
2.0 – 3.0	21.5 (19.8)	15.4 (18.5)	<0.0001
3.1 – 5.0	20.7 (22.5)	14.4 (11.4)	<0.0001
> 5.0	18.3 (21.9)	11.9 (14.2)	0.2231
INR EXTREMES			
≤ 1.5	16.8 (21.3)	12.3 (14.9)	0.0013
≥ 4.0	18.1 (16.2)	13.5 (13.1)	0.0146

Figure 1 – Distribution of INR tests for 200 patients when managed by general practitioner (GP) and warfarin care program (WCP).