Evaluation of a pharmacist vs. Haematologist-managed anticoagulation clinic: A retrospective cohort study

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Abstract

Introduction: Warfarin is the core component in the management of various thromboembolic disorders, which requires specialized expertise to optimize outcomes. There is limited data comparing a pharmacist vs. a haematologist-managed anticoagulation clinic in our setting, and in the Middle East. We aimed to evaluate the effectiveness and safety of a pharmacist vs. a haematologist-managed anticoagulation clinic in the Ambulatory Care Center at King Abdulaziz Medical City, Jeddah, Saudi Arabia.

Methods: A retrospective cohort study was conducted from 2016 to 2018, which included adult patients who have been followed-up for at least six months and who received warfarin for an extended period. The primary outcome was the proportion of time the patients in the two arms were in the therapeutic range. The secondary outcomes were the differences in expanded time in the therapeutic range, as well as the frequency of bleeding and thromboembolic events between the two arms.

Results: We enrolled 104 and 124 patients in the pharmacist and haematologist arms respectively. The median time in the therapeutic range for the pharmacist arm was 71.4%, IQR (60.8–83.8) vs. 65%, IQR (43.5–79.1), in the haematologist arm (p = 0.0049). The median expanded time in the therapeutic range was 86.4%, IQR (77.5–95.3) vs. 81.21%, IQR (67.1–93.3) in the pharmacist vs. haematologist arm (p = 0.015) respectively. Major bleeding events occurred in 5.7% vs. 3.2% and thromboembolic events in 5.7% vs. 4%, in the pharmacist vs. haematologist arm respectively.

Conclusions: Our results demonstrated that the time in the therapeutic range was significantly higher in the pharmacist arm, with no significant difference in bleeding and thromboembolic events compared to the haematologist arm.

1. Introduction

Warfarin is the core component in the management of various clinical conditions, including venous thromboembolism, atrial fibrillation (A-Fib), mechanical prosthetic heart valves and stroke (Guyatt et al. 2012). However, there are many challenges associated with warfarin therapy to achieve the target therapeutic concentration (Levine et al. 2004). These include, 1) The narrow therapeutic range, 2) The presence of many drug-drug, disease-drug and food-drug interactions, 3) Genetic differences causing a significant variation in the dose–response, which require an individualized dosing regimen, 4) The altered sensitivity to warfarin in some clinical conditions and specific populations, and 5) The need for frequent laboratory monitoring to assess the efficacy and minimize the risk of bleeding events (Levine et al. 2004). The management of anticoagulation requires expertise and specialized training to optimize therapeutic outcomes, including the prevention of recurrent thrombosis with inadequate treatment and minimize bleeding events with a supratherapeutic International Normalized ratio (INR) (Francis 2008, Anthony et al. 2009, Moyer et al. 2009).
The time in the therapeutic range (TTR) is a measure of the percentage of time a patient's INR is within the target therapeutic range, which is used as a marker of the effectiveness of warfarin therapy and as a quality metric (Rosendaal et al. 1993). A systematic review, including 67 studies and >50,000 patients, reported that the practice setting for anticoagulation has a substantial impact on achieving therapeutic INR levels. The TTR ranged from 57% in a community setting, 66% in an anticoagulation clinic and 67% in clinical trials. The average difference in the TTR between the community setting and the anticoagulation clinics was $-8.3\%,\ 95\%\ CI\ (-4.4\ to\ -12.1)$ (Van Walraven et al., 2006).

Subsequently, several models of anticoagulation management services, provided by a physician, pharmacist, nurse and self-managed care have been developed to provide optimum care for this complex population in the outpatient setting (Zhou et al. 2016).

Many studies compared usual medical care (UMC), a mixed care provided by family medicine physicians, with a pharmacist-managed anticoagulation clinic (PMAC) and demonstrated that the PMAC was superior to the UMC (Saokaew et al. 2010, Entezari-Maleki et al. 2016, Manzoor et al. 2017, Alghadeer et al. 2020, Samuel et al. 2021). In addition, many studies reported patient and physician satisfaction with the PMAC services (Lodwick and Sahbel 2000, Bishop et al. 2015).

At King Abdulaziz Medical City (KAMC), Jeddah, a collaborative practice agreement was created to allow clinical pharmacists to manage an anticoagulation clinic with the haematologists in 2013. The collaborative practice agreement was based on the updated American College of Chest Physicians’ evidence-based clinical practice guidelines, which included clinical pharmacist training requirements, guidelines for patient referral to clinical pharmacists, authorities, privileges, responsibilities and activities in warfarin therapy management.

We have not yet assessed the quality of this service in our institution. To our knowledge, there is a paucity of data comparing PMAC, to the physician-managed anticoagulation clinic, serviced by haematologists in Arab countries and the Middle East. Therefore, we aimed to evaluate the efficacy and safety of PMAC compared to the haematology-managed anticoagulation clinic (HMAC) in our hospital for patients receiving warfarin.

2. Material and methods

2.1. Study design and setting

We conducted a retrospective cohort study, at the Ambulatory Care Center at KAMC, Jeddah, Saudi Arabia from July 2016 to June 2018.

2.2. Sampling technique

A convenience sample of eligible patients.

2.3. Study participants

The informatics technology team generated a list of ambulatory patients who received warfarin in the study period (July 2016-June 2018). Patients were screened according to the eligibility criteria, using the electronic health records (EHRs). Patients were eligible for enrolment if they met the following criteria: adult patients (≥18 years), with regular follow-up visits at the anticoagulation clinic for at least six months and receiving warfarin for an extended duration for any of the following indications: Deep venous thromboembolism, Pulmonary embolism, Afib, mechanical valve replacement, and antiphospholipid syndrome. We excluded pregnant women, and patients for whom the target therapeutic INR was increased due to the development of a new clinical condition during the study period, for example a mitral valve replacement. We also excluded INR results of patients within the first 30 days of the initiation of warfarin or post discharge in case of hospitalization. We excluded INR results during a temporary planned interruption (e.g., due to a surgical procedure), which was defined as the period from the first day warfarin was withheld to 2 weeks after resuming the warfarin.

2.4. Study arms

2.4.1. PMAC arm

PMAC is defined as the care provided by clinical pharmacists who follow-up patients, assess INRs, evaluate warfarin therapy, assess adverse drug reactions, drug-drug or drug-food interactions, counsel patients and make dosage adjustments according to the collaborative practice agreement. The clinical pharmacists document all therapeutic recommendations in the patient’s EHR and prescribe a new warfarin prescription.

2.4.2. HMAC arm

The HMAC provides the same service, with haematologists managing the clinic. They follow the same process stipulated in the collaborative practice agreement. In addition, the haematologists are following more complicated cases of benign hematology apart from the anticoagulation service.

2.4.3. Assignment of study arms

As some of the patients may alternate the PMAC and HMAC services during the follow-up visits, we used a cut-off of 75% to assign the patients to the two study arms. For example, patients were included in the PMAC group if they were followed by clinical pharmacists > 75% of their clinic visits and vice versa.

2.5. Baseline characteristics

Baseline characteristics included age, gender, and the indication for warfarin use. We used the CHA2DS2-VASc validated score to define the risk for the development of thromboembolic events in patients with A-Fib, (C: Congestive heart failure, H: Hypertension, A: age ≥ 75 years, D: Diabetes mellitus, S: Stroke or transient ischemic attack (TIA), V: Vascular disease, A: Age 65 to 74 years, S: sex category) (Lip et al. 2010). We used the HAS-BLED score to assess the one-year risk of major bleeding in a patient with A-Fib, H: Hypertension, A: Abnormal liver function, A: Abnormal renal function, S: Stroke, B: bleeding tendency or predisposition, L: Labile INRs, E: Elderly, age > 65 years, D: Drugs; concomitant antiplatelet agents or non-steroidal anti-inflammatory drugs, Drugs; alcohol abuse (Lip 2011). We recorded the comorbidities documented in the EHRs.

2.6. Outcomes

2.6.1. Primary outcome

To compare the TTR in days in the PMAC and HMAC groups. TTR is defined as the percentage of time a patient’s INR was within the target therapeutic range during the study period.

2.6.2. Secondary outcomes

Major bleeding was defined as a fatal bleeding, and/or a symptomatic bleeding which occurred in specific critical body sites or fundamental organs, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial bleeding and/or extra-surgical bleeding, resulting in a drop of the haemoglobin level of ≥ 2 g/dL, or a transfusion of ≥ 2 units of whole blood or red blood cells, within
24–48 h of the bleeding event as documented in the EHR (Schulman et al. 2010).

Thromboembolic events were defined as the development of a new onset stroke, transient ischaemic attack, arterial thrombosis, pulmonary embolism (PE) and deep venous thrombosis (DVT), while receiving oral anticoagulation therapy as diagnosed by a physician and documented in the EHR.

Expanded TTR was defined as INR levels within 0.2 variance of the target therapeutic INR range, which did not require a significant dose change (Wilson et al. 2003, Chan et al. 2006).

Extreme INR values was defined as the percentage of visits with the INR value above 5 or below 1.5 (Lalonde et al. 2008).

Clinically relevant non-major bleeding was defined as any sign or symptom of hemorrhage that does not fit the criteria of the definition of the International Society on Thrombosis and Haemostasis (ISTH) of major bleeding, but does meet at least one of the following criteria: requiring medical intervention by a healthcare professional, leading to hospitalization or increased level of care, or prompting a face to face evaluation (Kaatz et al. 2015).

2.7. Sample size

We estimated a total sample of 225 patients with a 1:1 ratio for each arm to detect at least a 10% difference based on previous studies between the PMAC and HMAC groups (expected to achieve TTR of 60% as per literature). The standard deviation was 0.25, a power of 80% and an alpha of 0.05, using a two-tailed test (Entezari-Maleki et al. 2016).

2.8. Statistical analysis

Descriptive statistics for the baseline characteristics such as the mean ± standard deviation (SD) or median, inter-quartile range (IQR) or proportions were used as deemed necessary. We compared the baseline characteristics of the two groups using Two-sample t-test or Mann-Whitney of continuous normally distributed and non-normally distributed variables respectively and Fisher ‘exact test or Chi-square test for binary variables as deemed necessary.

The primary outcome of the percentage and median days of TTR and expanded TTR was determined by two methods. The first method was the Rosendaal method, which predicts the proportion of time within the therapeutic range between clinic visits during the study period, calculated by INR Pro© (Rosendaal et al. 1993). The second method was the traditional method, which is the proportion of visits within the target INR (Tan et al. 2018). Mann-Whitney test was used to compare the median time in TTR between the two groups using the two different methods.

For the secondary outcomes, a Chi-square test to compare between the two arms for the incidence of bleeding and throm-

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**Fig. 1.** Patient Screening Flowchart.
boembolic events was used as well as for extremes of INR readings among all visits. A multiple linear regression was used to adjust for potential confounders between the two groups including age, gender, number of visits during the study period, heart failure, hypertension, diabetes, history of stroke, vascular diseases, renal and hepatic impairment, HAS-BLED risk of bleeding, and the indication for the anticoagulation.

A two-sided P-value of < 0.05 was considered to indicate statistical significance in all analyses. The data analysis was performed with the STATA 14 (StataCorp LP, College Station, TX, USA).

3. Ethics approval

The study received Institutional Review Board approval by King Abdullah International Medical Research Center on 13th March 2018. The IRB protocol number is RJ18/002/J.

4. Results

We enrolled 228 of 767 patients screened for eligibility, with 124 patients included in the HMAC arm and 104 patients in the PMAC arm. Fig. 1 demonstrates the patient screening process and indicates the reasons for the exclusion of 539 patients.

The baseline characteristics for the study participants were slightly different between the two groups. The mean age (years) was 64.7 ± 13.8 vs. 57.9 ± 19.2, hypertension 69% vs.49%, heart failure 25% vs.12.5% and diabetes mellitus 62.5% vs. 35% in the PMAC vs. HMAC arms. The most prevalent indication for the warfarin therapy was A-Fib. The other indications and details of the baseline characteristics are reported in Table 1.

The primary outcome, the median TTR, using the Rosendaal method, was 71.44%, IQR (60.82–83.87) in PMAC compared to 65.14%, IQR (43.53–79.18) in HMAC, (p = 0.0049). The findings were comparable for the median TTR, using traditional methods and demonstrated in Fig. 2 and Table 2. The findings were consistent when comparing the expanded TTR between the arms. Additional details are presented in Fig. 3 and Table 2. The TTR results demonstrated persistent significant findings after adjusting for potential confounders in the regression analysis for the Rosendaal and traditional methods, as well as the expanded TTR (Table 3).

However, the difference in major bleeding, thromboembolic events and clinically relevant non-major bleeding was not statistically significant in the PMAC vs. HMAC (Table 4). The proportion of visits with an INR above 5 was not statistically different between the two arms, but the proportion of visits with the INR below 1.5 was significantly higher in the HMAC arm compared to the PMAC arm (Fig. 4). Finally, the hospitalization rate was 9.6% vs 4%, (p = 0.09) and emergency department (ED) visits 10.5% vs. 10%, (p = 0.98) due to bleeding or thromboembolic events between PMAC and HMAC respectively.

5. Discussion

The current study demonstrated that the TTR was significantly higher in the clinical pharmacist arm vs. the haematologist arm, consistent with literature (Saokaew et al. 2010, Manzoor et al. 2017). A Saudi prospective observational study compared pharmacists vs. clinician led anticoagulation clinic, included 62 patients showed consistent findings to our study despite a smaller
samples were statistically higher among patients in pharmacist-led than the physician-led clinic (87.27%±3.82% and 52.48±5.49%, respectively; p < 0.001). For 27 patients followed retrospectively by physicians and prospectively by clinical pharmacists, TTR was statistically higher during clinical pharmacists’ care (91.70% ±2.93% versus 61.39%±5.11%, respectively; p < 0.001). (Alghadeer et al. 2020).

In addition, another local study conducted in the Saudi Aramco Medical Services Organization, reported results congruent with the current study. However, they reported a lower TTR in both arms, 59% in PMAC vs. 48% in the physician group (Dib et al. 2014).

Furthermore, a study conducted in Qatar also reported a TTR of 81.8% in the pharmacist arm vs. 69.8% in the physician arm (P < 0.001)(Elewa et al. 2016). The authors highlighted that the proportion of visits within the extreme subtherapeutic range was significantly lower in the PMAC compared to the physician-managed group. There was no significant difference between the two groups in the extreme supratherapeutic INR values, similar to the current results (Elewa et al. 2016). It should be noted that in the Qatar study, the study arms were at two different hospitals, the pharmacist arm had younger patients and the majority of the indications for anticoagulation were DVT and PE, in contrast to the current study, the PMAC arm had older patients and the majority of the patients had an indication of A-Fib (Elewa et al. 2016).

The current findings are in line with international literature. A meta-analysis of 24 studies conducted to compare the effects of PMAC with Usual Medical Care (UMC), in terms of bleeding and thromboembolic outcomes, demonstrated that the PMAC group had a statistically significant impact on the prevention of total bleeding [RR, 0.51; 95% CI, 0.28–0.94] (Saokaew et al. 2010). However, the incidence of major bleeding and thromboembolic events were not significantly different between the two groups (Saokaew et al. 2010).

In addition to, a systematic review reported that the pharmacist group achieved a higher TTR, but the proportions of the TTR in the expanded therapeutic range was similar, slightly different to our results (Zhou et al. 2016). The effect of the pharmacist group on bleeding, thrombosis and mortality events were not significant, consistent with our
Moreover, a systematic review comparing PMAC services vs. UMC demonstrated that of 20 observational studies, the TTR was 72.1% vs. 56.7%; (P = 0.013), major bleeding events 0.6% vs. 1.7%, (P < 0.001), thromboembolic events 0.6% vs. 2.9%; (P < 0.001), hospitalization 3% vs. 10%, (P < 0.001), ED visits due to thromboembolic or bleeding events 7.9% vs. 23.9%; (P < 0.0001) in the PMAC vs. UMC respectively (Entezari-Maleki et al. 2016). The results of the safety outcomes were not consistent with our study, possibly due to the small number of bleeding and thromboembolic events, hospitalization, and ED visits in our cohort.

Although there is a collaborative practice agreement for the anticoagulation clinic between the clinical pharmacists and haematology, the differences in the TTR may be explained by the following: 1) The pharmacists managing the clinic were clinical pharmacists who had special training anticoagulation courses by the American College of Clinical Pharmacists and University of Florida prior to managing the anticoagulation clinic. They also managed the anticoagulation service in the inpatient setting for at least 5 years. The pharmacy residents received a rigorous consolidated learning experience of three months before they managed the clinic independently, in comparison to the haematology fellows who may not have had similar training and had less experience in managing warfarin patients. 2) PMAC used a standardized, systematic, and a consistent approach to assess the indication, target INR, adherence, warfarin dose, drug-drug interaction, drug-food interactions and adjusted the warfarin dose after addressing all these elements. 3) The clinical pharmacists provided regular and detailed patient counselling and this approach may have been inconsistent in HMAC. In addition, our hospital is a tertiary care hospital, providing healthcare for a more acute patient population compared to primary healthcare. An on-call haematologist is available to evaluate patients with critical laboratory results, with a referral to the ED if there is a suspicion of active bleeding or thromboembolism.

The current study has the following limitations: firstly, it represents a single center experience with limited generalizability to similar populations. The study participants received warfarin for

Table 3
Results of Regression Analysis.

| Outcome                        | Unadjusted analysis | Adjusted analysis a |
|-------------------------------|---------------------|---------------------|
|                               | Mean difference and 95% CI, P-value | Mean difference and 95% CI, P-value |
| TTR (Rosendaal Method)        | 8.7%, (3–14.5), p = 0.003 | 7.31%, (1.12–13.5), p = 0.021 |
| TTR (Traditional method)      | 7.6%, (2.2–12), p = 0.005 | 6%, (0.55–11.7), p = 0.031 |
| Expanded TTR (Rosendaal Method) | 6%, (1–11.4), p = 0.027 | 5.6%, (0.29–11), p = 0.039 |
| Expanded TTR (Traditional method) | 8.4%, (3.5–13.1), p = 0.001 | 6.8%, (1.5–12), p = 0.012 |

a Adjusted for age, gender, number of visits during the study period, heart failure, hypertension, diabetes, history of stroke, vascular diseases, renal and hepatic impairment, HAS-BLED risk of bleeding and the indication for anticoagulation.

Table 4
Major bleeding and Thromboembolism.

| Secondary outcomes | Haematologist (n = 124) | Clinical Pharmacist (n = 104) | P-value |
|--------------------|-------------------------|-----------------------------|---------|
| Thromboembolism, n (%) | 5 (4) | 6 (5.7) | 0.55 |
| Major Bleeding, n (%) | 4 (3.2) | 6 (5.7) | 0.35 |
| Clinically Relevant Non-Major Bleeding, n (%) | 11 (9) | 7 (7) | 0.56 |
more than six months; the findings may not apply to patients who have been treated for a shorter period. The majority of the participants received warfarin for A-Fib, DVT and PE. Secondly, the design was retrospective, and we relied on EHRs for data collection, which could be a source of documentation bias, however, the data present a real-life practice. Thirdly, although our study was not randomized, we attempted to minimize for potential differences between the two arms by adjusting for potential confounders of baseline characteristics and the results consistently demonstrated significantly higher TTR in the PMAC arm vs. HAMC, though the PMAC arm had an older population, with higher CHA2DS2-VASc scores. Finally, as our anticoagulation service is a mixed service, we aimed to minimize the contamination of the outcome assessed by including patients who attended the clinic of a specific arm at least 75% of the time. Though the results favor the clinical pharmacist arm, we acknowledge the role of collaboration with the Haematology Department in this achievement as the overall TTR for the clinic was comparable or even better than large randomized control trials (RCTs) comparing warfarin vs. direct oral anticoagulants (Connolly et al. 2009, Granger et al. 2011, Patel et al. 2011).

The current study has several strengths. We have a dedicated anticoagulation clinic managed by pharmacists and haematologists. To our knowledge, this is the first study comparing the efficacy and safety of PMAC and HAMC in the Middle East. Other studies compared general practitioners, internal medicine physicians or nurses with pharmacists (Connolly et al. 2009, Granger et al. 2011, Patel et al. 2011). The study evaluated a service established for 5 years, representing a real-life experience and providing evidence of the quality of the established service in our setting. We conducted a multiple linear regression analysis to adjust for potential confounders of the baseline characteristics to provide a precise estimate for the comparison. The long follow-up period of 2 years demonstrated the sustainability of the outcomes of the service and minimized the short-term effects of many factors that could change the results. Finally, the results provide evidence of the efficiency of our service. The TTR in the PMAC arm was 71%, which is higher than reported in literature for a community setting (57%), anticoagulation clinic (66%) and randomized control trials such as RE-LY, ROCKET-AF, and ARISTOTLE, ranging from 55% – 68% (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Van Walraven et al., 2006). Additional research is required to assess optimal methods to standardize the practice and to develop tools to improve the effectiveness of the anticoagulation clinic on a larger scale.

6. Conclusions

Our results demonstrated that the TTR of the INR was significantly higher in the pharmacist compared to the haematologist-managed anticoagulation clinic. Major bleeding, clinically relevant non-major bleeding, thromboembolic events, hospitalization and ED visits and the proportion of an INR above 5 were not significantly different between the two groups.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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