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Research Paper

Impact of pharmacist-led anticoagulation clinic on anticoagulation control and clinical outcomes of warfarin-treated patients with atrial fibrillation: A retrospective study in Hong Kong

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ABSTRACT

Kwong Wah Hospital (KWH), a Hong Kong public hospital has introduced pharmacist-led anticoagulation clinic (PAC) for warfarin management. We aimed to evaluate the PAC impact on anticoagulation control and clinical outcome in patients with atrial fibrillation (AF). This was a single-centered observational retrospective study including 148 warfarin-treated AF patients over 2-year period. Time-in-therapeutic range (TTR) improved from 61.4 ± 29.4% (1-year prior to PAC) to 71.3 ± 18.9% (1-year after joining PAC) ($p < 0.001$; paired Student's t-test). There were 17 bleeding and 2 stroke events during study period. No significant difference in event incidence was observed between the two periods. Patients were divided into good (TTR ≥60%) and poor anticoagulation control (TTR <60%) group to determine possible predictors for poor anticoagulation control. Hypertension (OR = 0.37, 95%CI = 0.168–0.814, p = 0.013) and older age ≥75 (OR = 0.286, 95%CI = 0.112–0.732, p = 0.009) showed inversely association as predictor of poor anticoagulation in multivariate regression. In conclusion, PAC demonstrated improved warfarin anticoagulation quality in AF patients at KWH in Hong Kong.

Key words: pharmacist, anticoagulation clinic, warfarin, Hong Kong

1. Background

Warfarin is a common anticoagulant used for prevention of stroke in patients with atrial fibrillation (AF) in Hong Kong. However, it is a high risk medication with narrow therapeutic range. A patient has to maintain within targeted international normalized ratio (INR) range to achieve warfarin efficacy and safety. Majority of patients had INR therapeutic target range of 2–3 for stroke prophylaxis in AF and 2.5–3.5 for patients with mechanical heart valves. INR levels are easily affected by many factors such as age, comorbidities, concurrent medication, genetic variation and diet (Chan et al., 2016; Dlott et al., 2014; Singer et al., 2013; Yimer et al., 2021). Individual INR reading could not truly reflect the actual time that patient is within therapeutic INR range. Quality of anticoagulation control is usually assessed clinically using percentage time-in-therapeutic range (TTR) (Rosendaal et al., 1993).

TTR varies among ethnicity in different countries. With Asian ethnicity, the mean TTR showed variation of 66% in Hong Kong, 64% in Singapore, 47% in China and 51% in Taiwan (Lin et al., 2021; Singer et al., 2013). Pharmacist intervention in patient warfarin management significantly improved TTR with higher quality anticoagulation control (Aidit et al., 2017; Chan et al., 2006; Mwita et al., 2018; Viboonchaicheep et al., 2019; Young et al., 2011). The first Hong Kong pharmacist-led anticoagulation ambulatory care service was established in 2004 and it was shown in a Hong Kong randomized controlled trial to improve TTR, save medical cost and enhance patient satisfaction (Chan et al., 2006). Based upon the clinical trial findings (Chan et al., 2006), increasing number of pharmacist-anticoagulation clinics (PACs) have been established in the Hong Kong public healthcare system. Despite the reported efficacy of PAC in the randomized clinical trial, the effectiveness of PACs in the real-world clinical setting in Hong Kong is lacking. A PAC was implemented in October 2019 at Kwong Wah Hospital (KWH), a Hong Kong public hospital. The

present study aimed to evaluate the real-world impact of this PAC service in improving patient anticoagulation control (TTR control) and clinical outcome (bleeding and thromboembolic event).

2. Methods

2.1. Study design

This was a retrospective single-centered observational study design to analyze patient anticoagulation control who had AF and were treated with warfarin and enrolled under PAC in KWH. Patient anticoagulation control was compared before and after the start of PAC clinic service. The observation time period was September 2018–September 2019 for pre-PAC, and October 2019–October 2020 for post-PAC. Patient were identified retrospectively using Hospital Authority's Clinical Data Analysis Reporting System (CDARS). Patient demographics, clinical condition, INR results were used to analyze patient percentage of time in TTR and their clinical outcome using their INR results. This study protocol was approved by Kowloon-Center-Cluster's Clinical Research Ethics Committee/Institutional Review Board.

Inclusion criteria were 1) patients ≥18 years old; 2) diagnosed AF and treated with warfarin; 3) on warfarin therapy for ≥12 weeks; 4) started on warfarin for more than 30 days; 5) referred to PAC service during study period and 6) had follow-up at PAC clinic for more than 1 time. Exclusion criteria included 1) indication of warfarin was other than AF; 2) discontinued warfarin or deferred warfarin during study period; 3) no patients' INR result and related patient clinical outcome during hospital admission and 4) patient who was followed by a limited scope old local service of pharmacist-physician collaborated warfarin clinic that constituted of few selected doctors and one pharmacist.

Informed consent from patient were waived by the ethics committee as this was an observational retrospective study in which data were collected anonymously and did not involve any invasive intervention to human beings.

2.2. Warfarin care under physician-managed clinic

Before initiation of PAC service, all patients started warfarin were managed by physician with regular medical follow up during the period September 2018 to September 2019. INR measurements were taken before medical appointment. During consultation, physician adjusted warfarin dosage according to protocol based on their INR result. Physician also monitored patient signs and symptoms of bleeding and thromboembolism, drug interaction and patient adherence as their usual practice without any checklist.

2.3. Warfarin care under PAC

PAC service in KWH was started in October 2019. Patient would be automatically enrolled into the PAC service if doctors prescribed warfarin for more than 12 weeks. Patients would be informed about the PAC service during medication dispensing at the pharmacy counter and their medication would be spilt up to the PAC clinic appointment date, with blood test and pharmacist clinic date booked for eligible patients. Remaining medication would be issued to patients when they attend the pharmacist clinic. Prior to starting up of PAC, an in-house clinic-specific recommendation protocol was developed based on evidence-based study (Chan et al., 2006) and was approved by doctors. Pharmacists of the PAC would assess patient warfarin dose according to INR results and give clinical advice and adjustment, as indicated by the protocol.

PAC pharmacists are responsible to screen patients' INR test prior to the PAC appointment in the coming week. During the PAC consultation, pharmacists would assess patient compliance, diet, recent medication changes, any illness and ask if patient had any signs and symptoms of bleeding or stroke based on a standard checklist. Intense patient education and medical knowledge were provided, and anticoagulation booklet with contact were issued to patients and their caregiver during their first PAC follow-up. Medical assistance was readily accessible to patients if they have any inquires regarding warfarin. The intense patient education (15–20 minutes) was provided in every PAC visit, and the education covered the medical indications and benefits of warfarin therapy, missing dose management, symptoms of bleeding and thromboembolic event, dietary concerns (avoid dramatic change in intake of high vitamin K-containing food), potential drug and herb interaction with warfarin. Pharmacists would use their specialized clinical knowledge to develop a tailored-made patient care plan if any warfarin dose amendment or more frequent INR testing are required. Then the consultation record would be recorded in EPR (accessible to all healthcare professional including doctors).

Pharmacists are mandatory required to contact a doctor if there was any critical lab value or bleeding risk that required medical checkup. Prompt referral and acknowledgement of critical INR results may be related to low incidence of bleeding events. Patient knowledge may be improved under pharmacist care where study have showed an overall patient satisfaction of pharmacist service (Chan et al., 2006).

2.4. Outcome measures

The primary outcome was TTR measured by the proportion of time that INR was within therapeutic range based on clinical indication. Basal TTR before PAC service started would be evaluated, then measured TTR after patients started follow-up by PAC pharmacist for 1 years using Rosendaal's method of linear interpolation (Rosendaal et al., 1993). TTR of each patient was assessed and calculated the mean TTR. Expanded therapeutic range of INR were also assessed. Expanded therapeutic range was defined as ±0.2 unit according to their therapeutic target which led to insignificant clinical impact and would not require dosage

amendment (Chan et al., 2006). Number of INR tests were also recorded in two groups respectively.

Number of thromboembolic and bleeding events occurred during the study period was part of the secondary outcome. Bleeding event included any type of bleeding that require blood transfusion, hematoma in body cavity e.g. gross hematuria, or minor bleeding such as nose bleed, gum bleeding or rectal bleeding. Thromboembolic complication was defined as any obstruction of blood vessel e.g. occurrence of stroke, transient ischemic attack, valve thrombosis, systemic embolic etc.

Another secondary outcome was the association of patients factors with poor anticoagulation control in related to TTR based on demographic and clinical comorbidities variables. This study selected the key factors associated with poor anticoagulation control, as shown in previous studies (Björck et al., 2019; Lin et al., 2017; Macedo et al., 2015; Nelson et al., 2015; Pignatelli et al., 2015; Rose et al., 2008, Rose et al., 2010), including age, gender, hypertension, heart failure, diabetes, renal failure, and smoker status. TTR <60% was showed to associate with increased risk for all-cause mortality and major bleeding and thromboembolic complication (Björck et al., 2019; Hong et al., 2017; Morgan et al., 2009). Patients were divided into two groups based on their TTR: ≥60% as good anticoagulation or <60% of poor anticoagulation control. Regression model were used to determine the association of selected patients' factors in related to poor anticoagulation control.

2.5. Data source and sample size

There were 227 patients identified from CDARS under specialty code of PAC profile during the study period (September 2018–October 2020). All identified patients were screened by patient selection criteria.

Demographics data (including age, gender, smoking status), and clinical data (underlying comorbidities, bleeding/thrombemobolic events, CHA_2DS_2-VASc score, INR values with dates, warfarin interruption and reason were recorded) were collected. Data was retrieved by drawing list of PAC patients and their INR result using CDARS and EPR during pre-PAC and post-PAC study period. Then analyze patient % of time in TTR and their clinical outcome using their INR results.

2.6. Statistical analysis

TTR was calculated using Rosendaal's linear Interpolation, which assumes a linear progression of change in INR between 2 consecutive INR values and assumes INR changes the same amount each day using linear interpolation (Rosendaal et al., 1993). Paired student T-test was used to determine the differences of TTR before and after starting PAC service in same patient. Univariate and Multivariate regression analysis were used to determine potential factors associated with poor anticoagulation control (TTR <60%) on warfarin. Factor with a p-value <0.1 in univariate analysis were included in multivariate analysis and presented with Adjusted odd ratio and 95% CI using backward stepwise logistic regression model.

TTR for each patient were calculated, and we compared TTR before and after PAC service to determine any statistically significant changes in their TTR and anticoagulation control in terms of INR results. Patients were further categorized into two groups according to TTR (TTR <60% and TTR ≥60%) to analyze the association of baseline characteristics and comorbidities variables with anticoagulation control.

All analyses were performed by IBM SPSS Statistics 28.0.0.0 for Windows and Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA). TTR was calculated using software INR PRO®. Continuous variables were presented as mean ± SD and categorical variables as number and percentages. Student's t-test or Mann-Whitney U test were used to compare continuous variables when appropriate. Categorical variables were compared using Chi-square or Fischer's exact test as appropriate. A p-value <0.05 was considered to be statistically significant.

3. Results

3.1. Patient data source

Data of 227 patients were retrieved from CDARS data bank, and 79 patients were excluded due to joining old local service of pharmacist-physician collaborated warfarin clinic, inability to access patient EPR and dropped out from PAC clinic. Patient newly started on direct oral anticoagulants (DOACS) or warfarin after 2019, with changing INR therapeutic goal, or those who passed away during study period would also be excluded from our study. After exclusion, only 148 patients were eligible for this study. Any INR results taken during emergency department visit or hospital admission were also excluded.

This study included 148 patients throughout 2-year study period. The total number of INR measurements were 2270. Mean TTR of all 148 patients were 66.3 ± 19.6%. The mean age of patient was 69.5 ± 9.55 years and 62.8% were female.

3.2. Patients' Anticoagulation control before and after PAC

Patients TTR, INR results and their proportion of time with subtherapeutic (INR <1.5) and supratherapeutic INR (INR >5) results in pre-PAC and post-PAC were shown in Table 1. It was shown that after enrolling to PAC service, patient showed a better TTR of 71.3 ± 18.9% ($p < 0.001$) when compared pre-PAC with 61.4 ± 29.4%. Expanded TTR also showed significant increase from 79.7 ± 22.5% up to 91.9 ± 63.5% ($p = 0.012$), showing overall better performance of patient anticoagulation control under PAC service. More INR testing were performed in post-PAC ($p < 0.001$) with a higher mean of 8.83 tests per patient compared to 6.5 INR

Table 1. Patient's International normalized ratio (INR) and time in therapeutic range (TTR) before (pre) and after (post) Pharmacist-led anticoagulation clinic (PAC).

Primary Outcome	Pre-PAC (n = 148)	Post-PAC (n = 148)	p-value
TTR	61.4 ± 29.4	71.3 ± 18.9	<0.001
Expanded TTR	79.7 ± 22.5	91.9 ± 63.5	0.012
Number of INR Testing	Total = 963 (mean = 6.50 per patient)	1307 (mean = 8.83 per patient)	<0.001
Low INR <1.5 [N(%)]	45 (4.67)	25 (1.91)	
High INR >5 [N(%)]	1 (0.1)	0	
% of time INR <1.5	1.80	0.39	0.003
% of time INR >5	0.05	0	0.158

Table 2. Reported Bleeding and thromboembolism complication before (pre) and after (post) Pharmacist-led anticoagulation clinic (PAC).

Secondary Outcome	Pre-PAC (n = 148)	Post-PAC (n = 148)	p-value
Total follow up years (mean follow-up days)	125.3 years (308.9 ± 49.2 days)	135.2 years (333.3 ± 36.4 days)	<0.001
Bleeding event	9 (7.18 per 100 patient years)	8 (5.92 per 100 patient years)	0.459
Thromboembolism	1 (0.798 per 100 patient years)	1 (0.740 per 100 patient years)	0.934

tests per patient in pre-PAC. Patient proportion of time outside therapeutic range were significantly less, proportion of time in suboptimal therapeutic with INR <1.5 decreased from 1.8% to 0.39% (p = 0.003).

3.3. Bleeding and thromboembolism risk

Bleeding and thromboembolism events were listed in Table 2. A total of 17 bleeding events during study period, 9 bleeding events occurred pre-PAC and 8 events occurred in post-PAC. Among the 17 patients who experienced bleeding, 6 of them experience major bleeding (3 cases of haematuria and 3 cases of haematoma that required blood transfusion). The post-PAC group did not show a significant reduction in incidence of bleeding and thromboembolic events.

3.4. Demographics of patients with good and poor anticoagulation control

Of the 148 patients, 92 (62.2%) achieved good anticoagulation control (TTR ≥60%) and 56 (37.8%) had poor anticoagulation control group (TTR <60%). Comparing patient demographics in the two groups of anticoagulation performance (TTR ≥60% and TTR <60%), there was no significant difference in gender, comorbidities of diabetes, renal failure, heart failure and smoker status (Table 3). There was significant difference in mean TTR, INR measurements, age and hypertension. Mean TTR were much higher in good anticoagulation control group TTR ≥60% of 79.1 ± 10.5% versus 45.4 ± 11.0% in TTR <60% (p < 0.001). The baseline characteristic found that patients who spent <60% below therapeutic range were monitored more frequently with more INR tests done shown by a higher mean number of 16.9 ± 4.43 INR tests done throughout study period than those with good anticoagulation control performed 14.4 ± 3.15 INR tests (p < 0.001).

Mean age in good anticoagulation control group were significantly older 71.4 ± 9.40 years compared to 66.4 ± 9.05 years (p = 0.002) in poorly controlled group. There was significantly higher proportion of younger patient age <65 years (41.1% vs 25%) with poor warfarin performance of TTR <60% than good performance TTR ≥60% (p = 0.04), and higher prevalence of patient age ≥75 years (34.8% vs 12.5% p = 0.003) with good anticoagulation performance (TTR ≥60%) compared to poor control (TTR <60%). No significant difference was detected in incidence of bleeding and thromboembolic event when comparing across good and poor anticoagulation performance group.

Hypertension was the most common comorbidities among our included patient (42.6%), followed by heart failure (31.8%), Diabetes (27.7%) and renal failure (8.11%). Differences in hypertension prevalence were observed between good and poor anticoagulation group but not statistically significant (p = 0.007), no difference for other comorbidities such as renal failure, heart failure, diabetes and smoker status. In order to evaluate the independent variable as predictor of poor anticoagulation control, multivariate regression model was performed.

3.5. Predictors of poor TTR on warfarin

The listed predictors of AF patient with poor anticoagulation are showed in Table 4. Using univariate regression analysis, age <65 (OR = 2.091, 95% CI = 1.027–4.259, p = 0.042) was a significant predictor of poor anticoagulation control with increased risk. While age ≥75 (OR = 0.268, 95%CI = 0.109–0.659, p = 0.004) and hyper-

Table 3. Demographics and baseline characteristics of patients of poor (TTR <60%) and good (TTR ≥60%) anticoagulation control.

Patient demographic (n = 148)	All Patient (n = 148) N(%) Mean ± SD	TTR <60% (n = 56) N(%) Mean ± SD	TTR ≥60% (n = 92) N(%) Mean ± SD	p-value
Mean TTR	66.3 ± 19.6	45.4 ± 11.0	79.1 ± 10.5	<0.001
CHA_2DS_2-VASc mean score	3.2	3.02 ± 1.57	3.18 ± 1.70	0.276
Total INR measurement	2270	949 (mean: 16.9 ± 4.43)	1321 (mean: 14.4 ± 3.15)	<0.001
Mean Age	69.5 ± 9.55	66.4 ± 9.05	71.4 ± 9.40	0.002
Age <65	46 (31.1)	23 (41.1)	23 (25.0)	0.040
Age ≥75	39 (26.4)	7 (12.5)	32 (34.8)	0.003
Female gender	93 (62.8)	40 (71.4)	53 (57.6)	0.092
Hypertension	63 (42.6)	16 (28.6)	47 (51.1)	0.007
Diabetes	41 (27.7)	18 (32.1)	23 (25)	0.346
Renal Failure (GFR <30ml/min)	12 (8.11)	3 (5.36)	9 (9.78)	0.339
Heart Failure	47 (31.8)	20 (35.7)	27 (29.3)	0.420
Smoker	13 (8.78)	5 (8.93)	8 (8.70)	0.961
Bleeding event	17 (11.5)	7 (12.5)	10 (10.9)	0.763
Stroke event	2 (1.35)	0	2 (2.17)	0.267

Table 4. Predictors of Poor Anticoagulation Control among AF patients on warfarin at KWH PAC clinic with TTR <60%.

Characteristic	Poor Anticoagulation control					
	Crude OR	95% CI	p-value	Adjusted OR	95%CI	p-value
Gender (female)	1.840	0.903–3.750	0.093	2.019	0.942–4.326	0.071
Age <65	2.091	1.027–4.259	0.042	Not included in the final model		
Age ≥75	0.268	0.109–0.659	0.004	0.286	0.112–0.732	0.009
Hypertension (yes)	0.383	0.188–0.778	0.008	0.370	0.168–0.814	0.013
Diabetes (yes)	1.421	0.683–2.957	0.347	2.287	0.973–5.378	0.058
Heart Failure (yes)	1.337	0.659–2.713	0.420	Not included in the final model		
Renal Failure (yes)	0.522	0.135–2.016	0.346	Not included in the final model		
Smoking (yes)	1.029	0.319–3.318	0.961	Not included in the final model		

Abbreviations: OR, odds ratio; CI, confidence interval.

tension (OR = 0.383, 95%CI = 0.188–0.778, p = 0.008) were reversely associated with better anticoagulation control that lowered risk of poor anticoagulation control using warfarin. In multivariate regression analysis, hypertension and age ≥75 were associated with better anticoagulation with adjusted OR of 0.37 (p = 0.013) and OR 0.286 (p = 0.009) respectively.

4. Discussion

In present study, it indicated that patients enrolled in pharmacist-led anticoagulation service had a statistically significant improvement of TTR by 10% (from 61% in pre-PAC to 71% in post-PAC; p < 0.001). There were also significant improvement (p = 0.012) in expanded TTR ±0.2 unit (from 79.7% to 91.9%). These results were consistent with many prior studies showing beneficial effect of pharmacist-managed clinic in improving patient anticoagulation control (Aidit et al., 2017; Chan et al., 2006; Mwita et al., 2018; Viboonchaicheep et al., 2019; Young et al., 2011). A prospective randomized clinical trial conducted in Hong Kong showed that pharmacists achieved a significantly higher TTR (64%) than physician (59%) (p < 0.001) in 137 patients recruited (Chan et al., 2006). Our present study retrospectively compared same patient anticoagulation control before and after attending pharmacist anticoagulation clinic and showed the effect of pharmacist role on the same task.

The superiority of PAC can be explained by frequent INR testing. The mean number of INR testing during pre-PAC period was 6.5 times compared to 8.9 times in post-PAC, showing a higher number of consistent INR-monitoring testing per patient per year. Young et al. reported that the

number of INR test was higher in pharmacist-managed clinic when compared to physician standard care (Young et al., 2011), showing a beneficial effect of doing frequent INR testing with pharmacist care to maintain patient within therapeutic range. Studies also showed that pharmacist has positive influence to improve patient compliance, diet-control and advice on drug-drug interaction and early recognition of over-anticoagulation (and alerting physicians) (Chan et al., 2006; Razouki et al., 2014; Young et al., 2011).

In terms of supratherapeutic anticoagulation with INR >5, there were only one episode in pre-PAC period among all patients within study period. With such small number of event, it was not statistically significant when comparing between two groups. Also, patients would be notified by doctor or pharmacist when they received critically high INR results, and it was likely that the patient was admitted for examination of bleeding. Therefore, the INR result would be excluded in this study based on the exclusion criteria. Whereas for subtherapeutic anticoagulation, there were a statistically significant decrease in our study patient. The proportion of time with INR <1.5 dropped from 1.80% to 0.39% ($p = 0.003$) under pharmacist follow-up, showing an overall improvement in achieving therapeutic level. For patients who were under-anticoagulated, pharmacist would arrange the patients to return in earlier follow-up date for dosage adjustment in order to bring the INR up to therapeutic level (Poon et al., 2007; Samuel et al., 2021; Young et al., 2011). This result was also demonstrated in a study in which patient under pharmacist-managed group reduced percentage of time INR <1.5 compared to traditional monitoring ($p < 0.0001$) (Young et al., 2011).

Present findings indicated that patient with poor anticoagulation control were monitored more often than those with good anticoagulation control with statistically more INR tests done ($p < 0.001$). A prior study also showed patients with subtherapeutic or supratherapeutic values had INR tested more frequently (Pokorney et al., 2015). Both findings showed that patient with poor anticoagulation had higher frequency of INR monitoring. Therefore, frequent INR testing may not necessarily be correlated with better anticoagulation control as clinical inertia may present in patients (Razouki et al., 2014).

The present findings were similar to prior study that failed to demonstrate pharmacist effect to reduce bleeding risk and thromboembolic complication (Viboonchaicheep et al., 2019). This may be due to small sample size in our study and low occurrence of bleeding and thromboembolic event. A prospective, randomized clinical trial that recruited 137 patients in Hong Kong also showed no significant difference in event occurrence between physician-managed group and pharmacist-managed group (Chan et al., 2006).

In our study, patient categorized as good anticoagulation were significantly older compared to those with poor anticoagulation, with a mean age of 71.4 ± 9.40 years versus 66.4 ± 9.05 years ($p = 0.002$), respectively. There were more patients aged ≥75 years among those with good anticoagulation (34.8%) than those with poor anticoagulation (12.5%). A prior multivariate logistic regression model showed that age ≥65 years was a positive significant predictor of higher TTR, and better drug adherence in older people may have influenced TTR (Marcatto et al., 2016). Another study illustrated older people with greater severity of disease could lead to a better compliance behavior due to medication given by caregiver (Cohen et al., 2012). A Japanese study recruited 501 Japanese patients showed that patients ≥70 years had higher TTR of 77 ± 17% compared to those <70 years with TTR of 46 ± 23% ($p < 0.0001$) (Okumura et al., 2011). A cohort study of 347 patients concluded that age <65 years were predictive of warfarin non-adherence (Waterman et al., 2004). In a population-based study of 29717 patients with AF demonstrated poor anticoagulation control in younger patients age <45 years with subtherapeutic INRs and significantly higher time spent under INR range due to their lower compliance (Macedo et al., 2015).

In our predictor model using univariate and multivariate regression analysis, comorbidities such as diabetes, renal failure and heart failure did not show strong association with poor anticoagulation control. Another study previously concluded that diabetes did not increase risk associated with overall poor anticoagulation but showed higher tendency for time-under-therapeutic range (OR = 1.22, 95%CI = 1.02–1.47) (Macedo et al., 2015) in patients with AF. Diabetes and heart failure also did not influence median TTR in Marcatto et al. study (Marcatto et al., 2016). Hypertension on the other hand demonstrated a negative correlation with poor anticoagulation (OR 0.37, 95%CI = 0.168–0.814; $p = 0.013$) in our study, showing hypertensive patients having higher TTR compared to those without hypertension. It was supported in several studies (Lin et al., 2017; Rose et al., 2010) and a retrospective study of 9,433 patients showed that hypertension was associated with better INR control (Nelson et al., 2015). A longitudinal study of 23,425 patients showed a lower likelihood for hypertensive patients (OR = 0.86, 95%CI 0.80–0.93, $p < 0.001$) to have lower TTR (defined as TTR <55%) (Nelson et al., 2013). However, the reason of positive correlation of hypertension with likelihood of higher TTR was not elaborated in those mentioned studies. Nevertheless, hypertension was reported as a negative predictor of anticoagulation control and associated with lower TTR in patients (Apostolakis et al., 2013). Further study is warranted to determine association of hypertension and TTR.

This study was a single-centered retrospective study at the KWH. The small sample size over the 2-year study period from a single center therefore might limit the generalizability to other hospitals, and could not provide adequate power to detect the difference in bleeding/thromboembolic events between pre-PAC and post-PAC periods. Retrospective

studies rely heavily on medical record documentation. Multiple doctors and pharmacists have different style of recording and there may be inconsistencies and missing field in data collection in terms of patient baseline characteristics, comorbidity or social history. Pharmacists and doctors time spent with patients in each group, the format or content of education provided were also not assessed that may affect patient understanding and medical knowledge and hence overall anticoagulation control using warfarin. TTR can be affected by many factors besides comorbidities and clinical conditions, such as diet, compliance, patient genotype (VKORC1 and CYP2C9) and other concurrent medications. Chinese herbal medicine use is common among Asian population. This information may not be always available and recorded in medical records that may limit validity of this study. Larger sample population and multicenter studies may be needed to generate significant results and detect differences for potential variables of poor anticoagulation control.

In conclusion, PAC at KWH was showed to significantly improve warfarin anticoagulation control with higher time in therapeutic range (TTR). No significant difference in incidence of bleeding and thromboembolic events between PAC and usual care was observed. Patients with older age and hypertension were positive predictors for better INR control.

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Conflict of Interest

The authors have no conflicts to disclose.

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