Title: Comparative Outcomes Between Direct Oral Anticoagulants, Warfarin, and Antiplatelet Monotherapy Among Chinese Patients With Atrial Fibrillation: A Population-Based Cohort Study

Running title: Use of Antithrombotic Treatments in Atrial Fibrillation

Authors: Xue Li (PhD)[1-4], Swathi Pathadka (PharmD)[1], Kenneth KC Man (PhD)[1,4,5], Vanessa WS Ng(BPharm)[1], Chung Wah Siu (MD)[6], Ian CK Wong (PhD)[1,4,5], Esther W Chan (PhD)[1,4], Wallis CY Lau (PhD)[1,4,5]

Affiliation:

1 Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, University of Hong Kong

2 Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, University of Hong Kong

3 Department of Social Work and Social Administration, Faculty of Social Science, University of Hong Kong

4 The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong, China

5 Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom

6 Department of Medicine, LKS Faculty of Medicine, University of Hong Kong

Addresses for correspondence:

Dr Wallis CY Lau, Research Department of Practice and Policy, UCL School of Pharmacy, Mezzanine Floor, BMA House, Tavistock Square, London WC1H 9JP, United Kingdom (email: wallis.lau@ucl.ac.uk; tel: +44 (0) 20 7874 1271)

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Abstract

Introduction: Outcomes associated with suboptimal use of antithrombotic treatments (antiplatelet [APT], warfarin, direct oral anticoagulants [DOACs]) are unclear in Chinese patients with atrial fibrillation (AF).

Objectives: To assess the prescription pattern, quality, effectiveness and safety of antithrombotic treatments.

Methods: A population-based cohort study using electronic health records of Hong Kong. Patients newly diagnosed with AF during 2010-2016 were followed up until 2017. Patients at high stroke risk (CHA2DS2-VASc≥2) and receiving antithrombotic treatments were matched using propensity score. Cox proportional hazards regression was used to compare the risks of ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality between groups.

Results: Of the 52,178 high-risk patients with AF, 27,614 patients (52.9%) received antithrombotic treatment and were included in the analyses. Between 2010 and 2016, APT and warfarin prescribing was declining while DOAC prescribing increased dramatically (1% to 32%). Two-thirds of warfarin users experienced poor anticoagulation control. Compared to APT, warfarin and DOACs were associated with lower risks of ischemic stroke (warfarin: hazard ratio [HR]=0.51, 95% confidence interval [CI]=0.36-0.71; DOACs: HR=0.69, 95%CI=0.51-0.94) and all-cause mortality (warfarin: HR=0.47, 95%CI=0.39-0.57; DOACs: HR=0.45, 95%CI=0.37-0.55). DOACs were associated with a lower risk of ICH compared to warfarin (HR=0.53, 95%CI=0.34-0.83). GIB risks were similar among all groups.

Conclusion: APT prescribing and suboptimal warfarin management remain common in Chinese patients with AF and high risk of stroke. DOAC use may be associated with a lower risk of ischemic stroke and all-cause mortality when compared to APT, and a lower risk of ICH when compared to warfarin.

Keypoints

- Since the introduction of the first direct oral anticoagulant (DOAC) in Hong Kong, the market share of DOAC has grown rapidly from 1% to 32% between 2010 and 2016.
- Among patients newly diagnosed with atrial fibrillation (AF) in 2016, there was still 43% of patients who had high risk of ischemic stroke and received single antiplatelet therapy (APT), against current guideline recommendations.
- Compared to APT monotherapy, DOAC use was associated with lower risk of ischemic stroke and all-cause mortality; and similar risk of intracranial hemorrhage and gastrointestinal bleeding in clinical practice.
- APT prescribing and suboptimal warfarin management remain common in Chinese patients with AF, which indicates their considerable unmet medical needs and the importance of guideline adherence from clinicians.

1 INTRODUCTION

Oral anticoagulants (OACs) are recommended for use in patients with atrial fibrillation (AF) at high risk of stroke to prevent thromboembolic events and reduce mortality [1, 2]. Vitamin K antagonists, *e.g.* warfarin, are the most commonly used OAC as the standard treatment for AF for decades. Over the past decade, direct oral anticoagulants (DOACs) have been introduced as alternatives to warfarin with the rapid growth of uptake in the Western population, given that they were non-inferior to warfarin with respect to a range of effectiveness and safety outcomes in randomised clinical trials (RCTs). However, the uptake of DOACs in Asia was only half of that of Europe or North America, at only 27.7% [3].

Antiplatelet (APT) monotherapy was generally perceived as a safer option over warfarin and has been recommended for use in some country-specific treatment guidelines in Asia [4, 5]. Although clinical practice guidelines in the United States and Europe now discourage the use of APT for stroke prevention in AF [1, 2], nearly 25% of Asian patients with AF still received APT for stroke prevention [3]. In Asia, limited data is available for the comparative effectiveness and safety outcomes of OACs versus APT outside RCT settings [6, 7]. Furthermore, the characteristics of patients receiving different antithrombotic treatments, the quality of anticoagulation control, and the prescription patterns have not been explored population-wide. Although the issue of underuse of OACs and overuse of APT were reported, the outcomes associated with suboptimal OAC treatment in Asians are largely unknown.

Using population-based territory-wide electronic medical records (EMR) in Hong Kong, we previously reported findings on the utilisation and outcomes of OAC use in patients with AF between 2010 and 2014, a short period after the first DOAC was introduced [8]. Using a similar

methodology and an extended cohort, this study aimed to provide a contemporary analysis of the prescription pattern, quality, effectiveness and safety of antithrombotic treatment among patients with AF over seven years following the introduction of DOACs.

2 METHODS

2.1 Data source

This study used the anonymised EMR of the Clinical Data Analysis and Reporting System (CDARS) developed by the Hospital Authority (HA) of Hong Kong. The HA manages all public hospitals and their ambulatory clinics, serving a population of over 7 million, and covers 80% of all hospital admissions through 43 hospitals and institutions, 49 specialist outpatient clinics, and 73 general outpatient clinics in Hong Kong. The de-identified medical records in the HA, including patient demographics, hospitalisations, consultations, emergency presentations, drug dispensing records, diagnoses, procedures, and laboratory test results are centralised in CDARS for audit purposes. The validity of the database has been demonstrated in numerous population-based studies, with a high positive predictive value for AF (95%), ischemic stroke (90%), intracranial haemorrhage (ICH: 95%), and gastrointestinal bleeding (GIB: 100%) [8-10]. Details of CDARS have been described previously [9].

2.2 Study design and cohort identification

This was a population-based cohort study. Patients with a new diagnosis of AF (International Classification of Diseases-Ninth Revision-Clinical Modification diagnosis, ICD-9-CM code: 427.3) between 2010 and 2016 were identified from CDARS. Patients with any diagnosis of valvular AF, valvular heart disease, hyperthyroidism or those who underwent valve replacement within 1 year before their first AF occurrence were excluded. Possible cases of transient AF were

excluded by identifying those with cardiac surgery, myocarditis, pericarditis, or pulmonary embolism (**Supplemental Table 1**) within 3 months before their first AF occurrence. Patients who were aged below 18 years, died during their first AF episode or had a history of study outcome(s) were also excluded from the analysis (**Figure 1**).

2.3 Treatment patterns and quality of anticoagulation control

Patients with CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age≥75 years [doubled], Diabetes mellitus, previous episodes of Stroke or transient ischemic attack or systemic embolism [doubled], Vascular disease, Age 65 to 74 years, Sex category [female]) score of ≥2 at the first occurrence of AF were considered to be at a high risk of stroke with OACs as indicated from international guidelines [1, 2]. The use of APT (aspirin and/or clopidogrel) and OACs (warfarin or DOACs available in Hong Kong during the study period - apixaban, dabigatran, edoxaban, and rivaroxaban) in the first year of AF were described based on the year when the patients were first diagnosed with AF (between 2010 and 2016).

Patients who received APT or OACs were included in subsequent analyses to study the clinical outcomes associated with suboptimal anticoagulation treatment. Warfarin users were stratified into good or poor international normalised ratio (INR) control, based on time-in-therapeutic range (TTR). TTR calculation methods are described in previous studies.[8, 11] Poor INR control was defined as TTR<60%.

2.4 Outcomes

The effectiveness outcome was defined as the occurrence of ischemic stroke. Safety outcomes included the occurrence of ICH, GIB, and all-cause mortality. Follow-up began from the date of the first treatment prescription (i.e. index date) and ended with the first occurrence of an

outcome, death, switching treatment (i.e. prescribed an OAC for the APT group; prescribed an alternative OAC for the OAC group), 90 days after treatment discontinuation (defined using >90 days of prescription refill gap [8]), or the end of the study period (December 31, 2017).

2.5 Statistical analysis

Patient characteristics were described using mean ± standard deviation (SD) for continuous variables and frequencies (percentages) for categorical variables. Incidence rates for the study outcomes were determined in all treatment groups. Propensity score derived from logistic regression was used to control for confounding factors using baseline covariates measured on or before the index date. Covariates included age, sex, year of treatment commencement, medical history, and recent use (≤90 days on or before the index date) of medications listed in **Table 1**. APT, warfarin and DOAC users were matched at 1:1:1 ratio using the nearest-neighbour matching algorithm with the sum of the Euclidean distance being 0.2 [12]. A proposed cut-off for acceptable standardised mean differences ranged from 0.1 to 0.25 [13]. Post hoc sensitivity analyses were conducted using inverse probability of treatment weighting (IPTW) to address confounding factors. Propensity score weights were derived using generalised boosted models (with a search limit of 10,000 regression trees for covariate balance) to obtain estimates representing the average treatment effects in the population [10, 14].

Cox proportional hazards regression with stratification on matching ID was applied to compare the rate of outcomes between treatment groups (warfarin vs APT, DOACs vs APT, DOACs vs warfarin) in terms of cause-specific hazard ratios (HRs). Additional post hoc analyses were conducted using the Fine-Gray Cox regression model that accounts for competing risks of death by calculating the subdistribution HRs of the outcomes. Subgroup analyses were conducted by

166 stratifying warfarin users into those with good and poor INR control. A two-sided p-value <0.05
167 was considered statistically significant.

168 **3 RESULTS**

169 **3.1 Patient characteristics and treatment patterns**

170 There were 72,373 patients newly diagnosed with AF between 2010 and 2016 (**Figure 1**).
171 Following the exclusion criteria, 52,178 patients had CHA_2DS_2-VASc score ≥2 (high-risk
172 population) and were included in the examination of treatment patterns (age [mean ± SD]: 80.0 ±
173 9.9 years; female: 55.6%; **Table 1**). There were 2,374 female patients (8.2% of the female
174 patients) with a CHA_2DS_2-VASc score of 2. In 2010, the number of high-risk patients who
175 received APT was three times more than those who received OACs (63% vs 19%, **Figure 2**).
176 From 2011 to 2015, the proportion of OACs use increased with a subsequent decrease of APT
177 use. In 2016, the two proportions became comparable (43% vs 45%). Users of DOACs first
178 outnumbered warfarin in 2014 and continued to rise in the following years, with more than 2 in 3
179 OAC users prescribed DOACs instead of warfarin in 2016 (**Figure 2**). Similar trends were
180 observed among women with CHA_2DS_2-VASc ≥3 and men with CHA_2DS_2-VASc ≥2 (i.e.
181 patients with at least two risk factors in the CHA_2DS_2-VASc score regardless of the sex
182 category) (**Supplemental Figure 1)**. Among DOACs, dabigatran was the most commonly
183 prescribed (13%), followed by rivaroxaban (11%), and apixaban (8%) (**Supplemental Figure 2**).

184 **3.2 Quality of anticoagulation control**

185 We evaluated 50,596 INR records from 3,803 eligible warfarin users in the cohort. TTR
186 evaluation indicated that 65% of the warfarin users had poor INR control. Additional analyses of

TTR by year found that the proportion of warfarin users with poor quality of INR control remained as high as ≥60% between 2010 and 2016 (**Supplemental Figure 3**).

3.3 Comparison of outcomes

A total of 27,614 high-risk patients receiving APT (n=18,878) or OAC treatments (warfarin, n=3803; DOACs, n=4933) were identified (**Figure 1**). Before propensity score matching, compared to OAC users, patients receiving APT were older (APT vs warfarin vs DOACs: 80.7 vs 74.2 vs 77.2 years) and had more comorbidities such as history of hypertension, myocardial infarction, vascular or renal diseases, and a slightly higher CHA_2DS_2-VASc score and Charlson Comorbidity Index, but were less likely to have prior transient ischemic attack/systemic embolism (**Table 2**). The patient characteristics of 7,764 propensity score-matched patients in each treatment group were balanced (**Table 2**). The median follow-up time for the matched cohort was 727 days (interquartile range=342–1268 days). While the majority of the high-risk patients received APT (64%), only a small proportion received warfarin (17%) and DOACs (19%) **(Figure 3)**. After propensity score-matching, the incidence of patients with all-cause mortality (8.0% versus 3.9%) and ischemic stroke (2.7% versus 2.5%) was nearly double in APT users compared to DOAC users. Gastrointestinal bleeding was highest in APT users, whereas intracranial bleeding was highest in warfarin users **(Figure 3)**. The crude result estimates before propensity score-matching are shown in **Supplemental Table 2**.

Compared to APT, OACs were found to be associated with lower risks of ischemic stroke [warfarin: HR = 0.51, 95% confidence interval (CI) = 0.36-0.71; DOACs: HR=0.69, 95% CI=0.51-0.94] and all-cause mortality (warfarin: HR=0.47, 95% CI=0.39-0.57; DOACs: HR=0.45, 95% CI=0.37-0.55) (**Table 3)**. There were significantly more ICH events among

warfarin users vs APT users (HR=1.69, 95% CI=1.04-2.75). No remarkable differences in the risk of GIB were observed between the treatment groups. Compared to warfarin, DOAC use was associated with similar risks of ischemic stroke, GIB, and all-cause mortality, but a significantly lower risk of ICH (HR=0.53, 95% CI=0.34-0.83). The findings were consistent with those in the IPTW analyses (**Supplemental Table 3**) and Fine-Gray Cox regression model (**Supplemental Table 4**).

3.4 Subgroup analysis

Regardless of poor or good INR control, warfarin use was associated with a lower risk of all-cause mortality compared to APT (**Table 4 & Supplemental Table 5**). There was a tendency towards a lower risk of ischemic stroke in warfarin users with good INR control vs APT users, but the result was not statistically significant (HR=0.58, 95%CI=0.33-1.04); the association of lower risk of ischemic stroke was statistically significant for poor INR control vs APT (HR=0.47, 95%CI=0.31-0.71) ($p_{interaction}$=0.57). No significant differences in bleeding outcomes were observed between warfarin and APT.

Among warfarin users, good INR control was associated with a lower risk of all-cause mortality (HR=0.67, 95% CI=0.52-0.86) compared to poor INR control. No significant differential risks in safety or effectiveness were observed between DOACs and warfarin with good INR control. When compared to warfarin with poor INR control, DOAC use was significantly associated with a lower risk of ICH (HR=0.47, 95% CI=0.25-0.87) ($p_{interaction}$=0.57).

4 DISCUSSION

To our knowledge, this is the first study that evaluated antithrombotic treatment patterns and their associated outcomes in a large group of Chinese patients with AF. We found that although the prescribing rate of APT decreased gradually, it remained as the most commonly used treatment among new patients with AF in the high-risk group. The overall utilisation of OACs has improved following the introduction of DOACs, and the uptake of DOACs has since overtaken warfarin. Of those who received warfarin, two-thirds had poor INR control, placing them at an increased risk of adverse outcomes compared to those with good INR control and DOAC users. This study also found that the use of DOACs was generally associated with better clinical outcomes in terms of ischemic stroke and all-cause mortality compared to APT.

Existing data on the use of OACs in Asians were derived from the limited number of Asian participants in the global AF registries. Only 3,071 Asian patients were enrolled in the global AF registry between 2011 and 2014, and 1 in 5 high-risk patients with CHA_2DS_2-VASc $\geq$2 did not receive OACs for stroke prevention [3]. However, it did not account for any regional differences in prescribing practice among the different Asian regions in real-world practice. Our previous population-based study of 35,551 patients with AF showed that almost 4 in 5 patients with CHA_2DS_2-VASc $\geq$2 did not receive OACs routinely in the Hong Kong clinical setting shortly after the first DOAC introduction. Our current study enlarged the number of eligible patients to 61,568 and the observational period to over seven years after the first DOAC introduction. However, we found that a significant proportion of high-risk patients still did not receive OACs (about 7 in 10 patients) and that two-thirds of warfarin users had poor INR control. These observations offer timely insight into the uptake of OACs over the period when different DOACs

gradually became available in recent years. Continuous efforts from multiple stakeholders are needed to improve the use of OACs among such high-risk patients.

The patient characteristics of this study were consistent with previous studies, which suggested that older age, multi-morbidities, and polypharmacy were the major reasons for prescribing APT instead of OACs.[15, 16] In a previous study of patients with AF and CHA_2DS_2-VASc≥2 in the United States,[17] those who received APT monotherapy were more likely to have vascular diseases, prior myocardial infarction, and hyperlipidaemia than those prescribed OACs; these results are consistent with our study. However, our study findings also suggested that among a matched group of patients with similar characteristics, the use of APT was associated with worse clinical outcomes and higher all-cause mortality compared to OACs. In addition, the limited availability of the anticoagulation services in Hong Kong and the lack of experience in using DOACs might also have contributed to the underuse of OACs. It highlights the importance to identify the barriers to prescribing OACs and develop a cost-effective intervention program to improve anticoagulation management.

It is well established that APT is inferior to dose-adjusted warfarin for stroke prevention in patients with AF, with a comparable or small increased risk of bleeding [18]. Current evidence on the effects of DOACs vs APT is only limited to an RCT of apixaban, where apixaban reduced the risk of ischemic stroke or systemic embolism and all-cause mortality, with no difference in ICH over a mean follow-up of 1.1 years [19]. Compared to APT, DOACs were found to be significantly associated with lower risks of ischemic stroke and all-cause mortality, with similar risks of ICH and GIB over a mean follow-up of 2.3 years in our study. This study also observed that patients who were at a higher risk of stroke were those who were more likely to use APT

instead of OACs, which further increases their risk of stroke. The potential clinical benefits from DOACs need to be widely recognised to reduce the current evidence-practice gap when choosing stroke preventive measures. Given the cumulative evidence on the safety of OACs vs APT in clinical practice, the common perception that APT is safer than OACs in Asian patients needs to be clarified as a priority [20].

In patients with AF on anticoagulation, sudden cardiac death and progressive heart failure have been reported to be the main cause of death, which was nearly four times that of stroke- or haemorrhage-related deaths [21]. In our warfarin cohort, we observed an association between a lower risk of all-cause mortality and good vs poor INR control, but no differences in ischemic stroke, ICH, and GIB between the two groups. It suggests that the reduction in all-cause mortality might have been driven by other cardiovascular causes, and more studies are warranted to investigate this further. Current evidence from non-Chinese populations also shows that the risk of dementia is lower in OACs users [22, 23]; these results may be applicable to Chinese populations; however, the overall risk and benefits are likely to be different. Further studies should also investigate the mortality and serious adverse events associated with antithrombotic treatments through long-term follow-up.

This study has limitations. Firstly, as inherent in population-based studies using electronic health databases, the potential of unmeasured confounding factors cannot be excluded. For example, information such as genetic factors and excessive fall risks are not available in the database. To minimise the effect of this limitation, all known confounding variables available in the database system were included in the analysis with multiple statistical models fitted and sensitivity analysis conducted. We also used propensity score modelling to control for possible prescribing

bias and confounding by assembling a cohort of patients with similar measured characteristics. Secondly, patients may purchase low-dose aspirin over-the-counter, potentially impacting evaluation of prescribing trends. However, the Hospital Authority is the only source of publicly funded primary care in Hong Kong, where medications and services are highly subsidised by the government. Drug costs alone can differ approximately 10-20-fold between the public and private sectors. Patients with chronic illness requiring long-term medications, such as oral anticoagulants and aspirin (no generic over-the-counter aspirin was available in Hong Kong at the time of the study), are more likely to utilise Hospital Authority services for ongoing management. The effect of any uncaptured prescriptions is therefore expected to be minimal. Given the significant underuse of warfarin and the small proportion of patients with good INR control, this study might have insufficient statistical power in the analyses of good INR control. Further, similar to other population-based studies that utilised routinely collected EMR, we were unable to account for patient compliance and adherence to antithrombotic treatment as such information is not available. In addition, the comparative outcomes of APT combined with different OACs were not assessed in this study. Lastly, DOACs were analysed as a group rather than an individual comparison or dosing subgroups to increase sample size and statistical power.

5 Conclusion

In this large cohort of Chinese patients with AF and a high risk of stroke, the overall utilisation of OACs increased after the introduction of DOACs. The prescribing rate of APT has declined but remain frequent, and the majority of warfarin users had poor INR control. The use of DOACs was associated with lower risks of ischemic stroke and all-cause mortality compared to APT and a lower risk of ICH compared to warfarin. The results refute the use of APT in the Chinese

population for stroke prevention in AF and support a broader uptake of OACs and better anticoagulation control among warfarin users. Future studies assessing clinical outcomes of individual DOACs at different dosages and continual assessment on the outcomes associated with antithrombotic treatments through long-term follow-up are warranted.

Declaration

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Conflict of interest

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Ethics approval

This study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW13-468).

Availability of data and material

The datasets generated during and/or analysed during the current study are not publicly available due to the nature of sensitive electronic medical data. Code will be available upon request from the corresponding author.

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