Title: The Impact of Suboptimal Anticoagulation Treatment with Antiplatelet Therapy and Warfarin on Clinical Outcomes among Patients with Non-Valvular Atrial Fibrillation: A Population-Wide Cohort Study

Short title: Suboptimal Anticoagulation Treatment

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Abstract

Background: The actual consequence of suboptimal anticoagulation management in patients with non-valvular atrial fibrillation(NVAF) is unclear in the real-life practice.

Objective: To identify the prevalence of suboptimally anticoagulated patients with NVAF, and compare the effectiveness and safety of antiplatelet drugs with warfarin.

Methods: We performed a retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with NVAF during 2010-2013 were included in the analysis. Cox proportional hazards regression model with 1:1 propensity-score-matching was used to compare the risk of ischemic stroke, intracranial hemorrhage(ICH), gastrointestinal bleeding(GIB), and all-cause mortality between patients on antiplatelet drugs and warfarin stratified by level of international normalized ratio(INR) control.

Results: Among the 35,551 patients with NVAF, 30,294(85.2%) had CHA_2DS_2-VASc≥2(target group for anticoagulation). Of these, 7,029(23.2%) received oral anticoagulants and 18,508 (61.1%) received antiplatelet drugs alone. There were 67.7% of warfarin users had poor INR control (time-in-therapeutic-range[2.0-3.0]<60%). Patients on warfarin had comparable risks of ICH(hazard ratio,1.24;95%confidence interval,0.65-2.34) and GIB(1.23;0.84-1.81); lower risk of ischemic stroke(0.40;0.28-0.57) and all-cause mortality(0.45;0.36-0.57) when compared to patients on antiplatelet drugs alone. Good INR control was associated with reduced risk of ischemic stroke(0.48;0.27-0.86) compared to poor control. Modelling analyses suggested that ~40,000 stroke cases could be potentially prevented per year in the Chinese population if patients were optimally treated.

Conclusions: Over three-quarters of high-risk patients were not anticoagulated or had poor INR control in this Chinese NVAF population. There is an urgent need to improve the optimization of anticoagulation for stroke prevention in AF patients.

Keywords: Atrial fibrillation; oral anticoagulant; antiplatelet drugs; warfarin; Chinese

Introduction

Atrial Fibrillation (AF) is the commonest sustained cardiac arrhythmia which is associated with a five-fold higher risk of stroke.[1] Its prevalence has been increasing along with the aging population, and has become a significant cause of rising healthcare costs world-wide. In particular, Asia has a much higher AF burden compared to the Western countries. By 2050, it is estimated that the number of AF patients in Asia will reach 72 million, which is more than double of the combined figures from Europe and the United States.[2]

Oral anticoagulation therapy (OAC) is the standard management of stroke prevention in patients with AF. However ,with the particular concerns of bleeding, antiplatelet drugs such as aspirin and clopidogrel are often perceived to be safer alternatives to OACs among the Asians.[3] Aspirin is still recommended in the latest 2014 American Heart Association(AHA)/American College of Cardiology(ACC)/Heart Rhythm Society(HRS) guideline for stroke prevention in AF patients with CHA2DS2-VASc=1.[4] Meanwhile, the US Food and Drug Administration is requiring additional studies for further evaluation of aspirin use in prevention of cardiovascular event.[5] Indeed, the 'real-world' clinical outcome of the use of antiplatelet drugs for stroke prevention remains unclear, especially for the Asian population including Chinese.

Despite the recent development of non-vitamin K antagonist oral anticoagulants (NOACs), warfarin remains the most commonly prescribed oral anticoagulation therapy (OAC) in AF.[6] It was estimated that about 1%-2% of the world population of developed countries were taking warfarin.[7] The efficacy and safety on warfarin is associated with anticoagulation control. However, the actual quality of anticoagulation control and its impact on clinical outcomes among Asians are not well described in the real-life setting.

This study identified the suboptimally anticoagulated patients using a large population database in Hong Kong. Second, we studied the clinical consequence of the suboptimal anticoagulation of AF patients by comparing the clinical effectiveness and adverse bleeding events between patients on antiplatelet drugs and warfarin, based on different levels of anticoagulation control.

Methods

Data source

This study used the population-wide anonymized electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (HA), which is the sole public-funded healthcare provider of Hong Kong. HA is serving a population of over seven million through 42 hospitals, 47 Specialist Outpatient Clinics, and 73 General Outpatient Clinics.[8] Electronic patient records in HA, including demographics, date of registered death, date of consultation, drug dispensing records, date of hospital admission and discharge, diagnoses, procedures, and laboratory tests are centralized in CDARS and have been extensively used for epidemiological research.[9-15] The high coding accuracy in CDARS including AF and gastrointestinal bleeding has been demonstrated in previous studies.[10,11] Detailed descriptions of CDARS are available.[10,15]

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468). Informed patient consent was not required since all information used for data analysis in this study were anonymized.

Source population

Patients who received their first diagnosis of AF (International Classification of Diseases codes, Ninth-Revision, Clinical Modification [ICD-9-CM] = 427.3) between January 1, 2010 and December 31, 2013 in CDARS were defined as patients with newly diagnosed AF (Figure 1). To select for patients with non-valvular AF only, patients diagnosed with valvular AF, valvular heart disease or hyperthyroidism, or underwent valve replacement (ICD-9-CM; Supplemental Table I) within 1 year prior to their first AF occurrence were excluded. Any possible cases of transient AF, cardiac surgery, myocarditis, pericarditis, or pulmonary embolism (Supplemental Table I) within 3 months before their first AF occurrence were excluded. Patients aged<18 years, died during their first AF episode, or had history of outcome(s) were also excluded from the analysis (Figure1).

Study design

Patients were considered at high risk of stroke with the need for OAC if they had CHA_2DS_2-VASc (congestive heart failure [CHF],hypertension,aged≥75y[doubled],diabetes mellitus [DM],aged 65-74y,prior stroke/transient ischemic attack[doubled],vascular disease, and sex category[female]) score≥2[4,16] at their first AF occurrence. The use of antiplatelet drugs (aspirin and/or clopidogrel) and OACs (warfarin and NOACs available in Hong Kong during the study period: dabigatran, rivaroxaban, and apixaban) during the first year of AF was examined. Patients receiving antiplatelet drugs and warfarin were included in subsequent analyses to study the clinical outcomes associated with suboptimal use of anticoagulation treatment. The start of follow-up (i.e. index date) was commenced from the date of the first prescription of treatment. The end of follow-up was censored by the occurrence of outcome, death, switching of treatment (i.e. received OAC for the antiplatelet drugs group; received an alternative OAC including dabigatran, rivaroxaban, and apixaban for the warfarin group), the end of the study period (July 31, 2014), or 90 days after discontinuation of treatment (defined

as >90 days of interval between prescription refills), whichever came first. The 90-day period was added to detect any outcomes which might have led to discontinuation of treatment.

Time in therapeutic range (TTR)

Warfarin users were further stratified into having good and poor international normalized ratio (INR) control based on TTR during follow-up. Poor INR control was defined as TTR<60%.[17,18] The Rosendaal method[19] was used to calculate TTR where INR was aimed at 2.0-3.0 based on the current guidelines.[4,16] This method assumes a linear relationship between two consecutive INR values and is well-recognized for evaluation of anticoagulation control. Intervals between INR measurements that were ≥8 weeks were not interpolated based on the formula assumptions. We excluded the INR records measured during hospitalization since patient could receive temporary treatment that would affect the INR values. The INR records in the first 28 days of warfarin were excluded from the analysis to allow time for stabilization of anticoagulation control. As a result, patients who had ≤28 days of follow-up were excluded from the analysis. To allow for fair comparison, patients in the antiplatelet drugs group who had ≤28 days of follow-up were also excluded.

Outcomes and Data validation

The outcomes of interest were the development of ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality after the commencement of treatment (ICD-9-CM; Supplemental Table I). A high coding accuracy for GIB (positive predictive value [PPV] = 100%) and AF (PPV=95%) in CDARS has been demonstrated previously.[10] Nonetheless, we conducted further validation on the coding for ischemic stroke and ICH in a sample patient of this specific study cohort, where the corresponding PPVs for ischemic stroke and ICH were 90% and 95% respectively (Appendix I).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation whereas categorical data were reported as frequencies (percentages). The proportions of patients receiving antiplatelet drugs, OACs, and no treatment were determined. Patients on warfarin with poor INR control were identified.

Cox proportional hazards regression model was used to compare the risk of the outcomes, between patients receiving antiplatelet drugs and warfarin with good and poor INR control, in terms of hazard ratios (HR) with 95% confidence intervals (CI). Absolute rates for each outcome were determined in all treatment groups. We estimated the number of ischemic strokes that could be potentially prevented per year in the Chinese AF population in mainland China, Hong Kong and Taiwan overall[20-24] if: 1) patients on antiplatelet drugs were treated with warfarin; 2) patients with poor INR control achieved good INR control; based on the absolute risk reduction (ARR) between comparison groups (Appendix II).

A 5% level was considered statistically significant. The ARR and number needed to treat (NNT) were estimated for outcomes with statistically significant results. Statistical Analysis System® v9.3 (SAS Institute Inc., Cary, NC) was used for conducting statistical analyses. Programming and analyses were performed independently by WCYL and KKCM as quality assurance.

Propensity-score matching

Since the choice of anticoagulation treatment is likely to be confounded by patient characteristics, we calculated propensity scores (PS) using logistic regression to estimate the likelihood to receive different treatment. The variables considered in the PS model were risk factors of the outcomes including age, sex, index year, CHF, hypertension, DM, myocardial

infarction (MI), vascular disease, transient ischemic attack/systemic embolism, bleeding, renal disease, and Charlson comorbidity index; recent use (≤90 days prior to index date) of aspirin, clopidogrel, amiodarone, statin, proton-pump inhibitors, histamine type-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors. All diagnosis and medication records dated prior to individual index date were retrieved from CDARS for the assessment of PS variables. Patients receiving antiplatelet drugs and warfarin were matched at 1:1 ratio using PS-matching based on the greedy matching algorithm, which has been demonstrated to perform well in both actual and simulation studies.[25]

Sensitivity analysis

We conducted several additional analyses to test the robustness of the study results. Additional analyses were conducted using 180-day and 30-day permissible medication gaps for detecting potential discontinuation of treatment. The same duration of time was added after the date of discontinuation of treatment to capture any outcomes that might have led to treatment discontinuation. In addition, we repeated the whole analysis based on $CHADS_2$ (CHF, hypertension, aged≥75y, DM, prior stroke/transient ischemic attack[doubled]) score,[4] to allow for comparisons with previous studies. Gender-stratified analyses were conducted to test for any gender differences in the effectiveness and safety of warfarin versus antiplatelet drugs; and the incidence of the outcome events.

Results

Patient characteristics

There were 41,997 patients with newly diagnosed AF between January 1, 2010 and December 31, 2013. Of these, 6446 patients were excluded (Figure 1). The final analysis included 35,551 patients with non-valvular AF where 30,294 (85.2%) patients were at high

risk of stroke (CHA_2DS_2-VASc≥2). The mean age of the patients was 76.7 ± 12.5 years and 50.7% were female (Supplemental Table II).

Underuse of anticoagulation treatment

Among the high-risk patients with CHA_2DS_2-VASc≥2, 4,757 patients (15.7%) received no treatment, 18,508 patients (61.1%) received antiplatelet drugs alone, and 7,029 patients (23.2%) received OACs during the first year of AF (Figure2). Of the patients who received OACs, most were prescribed warfarin (n=5,048,71.8%), followed by dabigatran (n=2,078,29.6%), rivaroxaban (n=435,6.2%), and apixaban (n=19,0.3%). Similar results were found for patients with $CHADS_2$≥2 (Figure 2; Supplemental Table III).

Poor anticoagulation control

In total, 2,276 warfarin users were included in the analysis, contributing 33,935 INR records (Figure1). The mean number of INR tests performed for each patient during follow-up was 15 (standard deviation=11). There were 15,077 records (44.4%) with INR<2.0 and 3,446 records (10.2%) with INR>3.0, respectively. Evaluation of TTR found that 1,541 patients (67.7%) had poor INR control. When restricted to patients with $CHADS_2$≥2, 70.3% had poor INR control.

Propensity-score-matching analysis

There were 12,149 patients on antiplatelet drugs and 2,276 patients on warfarin identified for PS-matching (Figure 1). The mean follow-up for this cohort was 639 ± 445 days. Before PS-matching, patients on antiplatelet drugs were older (80.3 vs.73.9y), possessed more comorbidities such as history of MI and higher CHA_2DS_2-VASc-scores as compared to those on warfarin (Supplemental Table IV). Based on the 1:1 matching ratio, 4,450 patients were

matched. The patient characteristics were balanced between treatment groups after PS-matching (Supplemental Table IV; Supplemental Figure I).

After PS-matching, the mean follow-up for the PS-matched cohort was 705 ± 448 days. Patients on warfarin had significantly lower risk of ischemic stroke (HR, 0.40; 95%CI, 0.28-0.57; ARR=3.3%; NNT=31) and all-cause mortality (HR, 0.45; 95%CI, 0.36-0.57; ARR=6.2%; NNT=17) when compared to those on antiplatelet drugs (Table 1). No significant differences in the risk of ICH (HR, 1.24; 95%CI, 0.65- 2.34) and GIB (HR, 1.23; 95%CI, 0.84-1.81) were noted between two groups. The results were not significantly differed by gender (Supplemental Table V). Among the patients on warfarin, those with good INR control were associated with reduced risk of ischemic stroke (HR, 0.48; 95%CI, 0.27-0.86; ARR=1.8%; NNT=56), similar risk of ICH (HR, 0.89; 95%CI, 0.46-1.71), GIB (HR, 1.08; 95%CI, 0.71-1.63), and all-cause mortality (HR, 0.89; 95%CI, 0.65-1.22) compared to those with poor control. Similar results were obtained in all sensitivity analyses (Supplemental Table VI- IX). Extrapolating our findings to the approximately 8 million Chinese AF patients in China, Hong Kong, and Taiwan,[20-24] about 40,000 strokes could be potentially prevented per year among the high-risk patients on antiplatelet drugs if they were treated optimally with warfarin, and further about 4,000 strokes could be potentially prevented per year if the patients on warfarin achieved good INR control (Appendix II).

Discussion

This study highlights the considerable unmet needs in the management of Chinese AF patients in the 'real-world' clinical practice in Hong Kong, where only 23% of AF patients at high risk for stroke were anticoagulated in our population. Second, antiplatelet drugs were used in 61% of patients with AF, but its use was associated with a higher risk of ischemic

stroke and mortality compared to warfarin after PS-matching. Third, although warfarin was the most prescribed OAC (72%), two-thirds of warfarin users had poor INR control, placing them at higher risk of ischemic stroke than those with good INR control. The results were consistent for all sensitivity analyses, including the analyses using $CHADS_2$-score as risk stratification for stroke; and different permissible medication gaps for detecting treatment discontinuation.

Notably, we identified a much lower anticoagulation treatment level in this Chinese patient group (23%) when compared to the other areas including the United States (38.8%-71.8%), Europe (56.9%), Australia (65%), and the Middle East and Africa (67%).[26-28] This might be explained by the primary concern of bleeding in the Chinese population.[3] Importantly, we found that antiplatelet drugs, which have been commonly perceived as safer alternatives to OACs among the Chinese, were prescribed to more than twice the number of patients compared to OACs (61% vs. 23%). Indeed, higher preferences for antiplatelet drugs over OAC were also reported previously in China (58% vs.7%)[29] and Taiwan (67% vs.15%)[30]. After taking into consideration all the patient characteristics between treatment groups, we found that antiplatelet drugs use was associated with comparable risks of bleeding, but notably a 60% higher risk of ischemic stroke when compared to warfarin. Therefore, our findings support that antiplatelet drugs should not be considered first line treatment for stroke prevention in high-risk AF patients.

One of the largest RCTs that compared the use of antiplatelet drugs with warfarin in AF patients was the ACTIVE-W trial[31] (n=6706), which showed that dual antiplatelet combination was inferior to warfarin in prevention of stroke with comparable bleeding events. However, only a small number of participants from the Chinese countries were involved in

this trial. Relatively small-scale RCTs among the Chinese patients were conducted by the Liu *et al.* 2014 (n=101) and Hu *et al.* 2008 (n=828), but the results were conflicting.[21,32] While there are only few observational studies to compare antiplatelet drugs and warfarin, one retrospective cohort study of 9297 Chinese AF patients suggested that antiplatelet drugs were as effective as warfarin in stroke prevention, yet without assessment of any underlying differences in characteristics between treatment groups.[29] Therefore, our study provided important epidemiological data concerning the use of antiplatelet drugs and warfarin in Chinese AF patients, where similar data are lacking.

Strengths and limitations

A key strength of this study is the utilization of the largest territory-wide clinical database in Hong Kong, which covers 80% of all hospital admissions.[33] The inter-linkage between INR tests records, dispensing details and diagnosis records in hospitals as well as outpatient clinics facilitates comprehensive assessment of OAC use and has allowed for reliable calculations of TTR. While the use of OACs among AF patients has been investigated world-wide, the situation for Asians is inadequately explored. To our knowledge, this is the largest pharmacoepidemiological study conducted in Asia to inform the management of AF patients in a Southern Chinese population group. Importantly, we clearly identify an unmet need that has to be addressed with priority.

Several limitations are worthy of mention. Similar to other healthcare databases, CDARS does not capture all the medications available over-the-counter such as aspirin. However, HA is the only source of publicly funded primary care in Hong Kong, of which the services and medications are highly subsidized (85%-98%) by the government.[34] It is common for patients with chronic illness requiring long-term medications, such as AF, to attend outpatient clinics

of the HA for ongoing treatment care rather than obtaining full-cost medications from elsewhere.[34] Therefore, the impact of uncaptured prescriptions is anticipated to be minimal. The estimated number of potentially preventable stroke cases in the Chinese population was based on the treatment characteristics in this Chinese cohort of Hong Kong. Therefore, it may not be generalizable to the whole Chinese population. However, since considerable underuse of OACs was reported in other Chinese populations in the mainland China and Taiwan,[21,28-30] our extrapolation is likely to be conservative. Given the significant underuse of warfarin, and the small proportion of patients with good INR control, this study might have insufficient power to detect a statistical significance in the analyses for good INR control. Finally, as the volume of NOACs increases, there will be opportunities for meaningful comparison with warfarin and antiplatelet drugs as well as long-term safety surveillance of NOACs.

Conclusion

In this cohort, over three-quarters of high-risk patients with non-valvular AF were either not protected by anticoagulation or had poor INR control. Compared to patients prescribed warfarin, patients on antiplatelet drugs were not statistically associated with reduced risk of bleeding, but higher risk of ischemic stroke and all-cause mortality. It is important to study the reasons for the underutilization of anticoagulation therapy. Measures are urgently needed to raise awareness and improve the underutilization and optimization of anticoagulation in AF patients, especially in the Chinese population.

References

1. Go AS, Hylek EM, Phillips KA, Chang YC, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults - National implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA. 2001; 285:2370-2375.
2. Chiang CE, Wang KL, Lip GYH. Stroke prevention in atrial fibrillation: An Asian perspective. Thromb Haemost. 2014; 111:789-797.
3. Sabir I, Khavandi K, Brownrigg J, Camm AJ. Oral anticoagulants for Asian patients with atrial fibrillation. Nat Rev Cardiol. 2014; 11:290-303.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014; 130:e199-267.
5. The US Food and Drug Administration. Use of Aspirin for Primary Prevention of Heart Attack and Stroke. 2015. http://www.fda.gov/drugs/resourcesforyou/consumers/ucm390574.htm. Accessed May 10, 2015.
6. Kakkar AK, Mueller I, Bassand JP, et al. Risk Profiles and Antithrombotic Treatment of Patients Newly Diagnosed with Atrial Fibrillation at Risk of Stroke: Perspectives from the International, Observational, Prospective GARFIELD Registry. PLoS One. 2013; 8:e63479.
7. Ansell J. New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation. 2012; 125:165-170.
8. The Hospital Authority. Clusters, Hospitals & Institutions. Available at: http://www.ha.org.hk/visitor/ha_visitor_text_index.asp?Content_ID=10036&Lang=ENG&Dimension=100&Parent_ID=10004&Ver=TEXT. Accessed June 11, 2015.
9. Chiu SS, Lau YL, Chan KH, Wong WHS, Peiris JSM. Influenza-related hospitalizations among children in Hong Kong. N Engl J Med. 2002; 347:2097-2103.

10. Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, Wong IC. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology. 2015; 149:586-595.e583.

11. Wong AYS, Root A, Douglas IJ, Chui CSL, Chan EW, Ghebremichael-Weldeselassie Y, Siu C-W, Smeeth L, Wong ICK. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ. 2016; 352:h6926.

12. Man KK, Chan EW, Coghill D, Douglas I, Ip P, Leung LP, Tsui MS, Wong WH, Wong IC. Methylphenidate and the risk of trauma. Pediatrics. 2015; 135:40-48.

13. Chui CS, Man KK, Cheng CL, Chan EW, Lau WC, Cheng VC, Wong DS, Yang Kao YH, Wong IC. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. J Antimicrob Chemother. 2014; 69:2563-2567.

14. He Y, Chan EW, Man KK, Lau WC, Leung WK, Ho LM, Wong IC. Dosage Effects of Histamine-2 Receptor Antagonist on the Primary Prophylaxis of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Associated Peptic Ulcers: A Retrospective Cohort Study. Drug Saf. 2014; 37:711-721.

15. Man KK, Ip P, Hsia Y, Chan EW, Chui CS, Lam MP, Wong WH, Chow CB, Yung A, Wong IC. ADHD Drug Prescribing Trend Is Increasing Among Children and Adolescents in Hong Kong. J Atten Disord. 2014. doi: 10.1177/1087054714536047.

16. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Guidelines ESCCfP. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012; 33:2719-2747.

17. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S, Investigators AW. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by

centers and countries as measured by time in therapeutic range. Circulation. 2008; 118:2029-2037.

18. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control - Results from SPORTIF III and IV. Arch Intern Med. 2007; 167:239-245.

19. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69:236-239.

20. Tse HF, Wang YJ, Ai-Abdullah MA, et al. Stroke prevention in atrial fibrillation-An Asian stroke perspective. Heart Rhythm. 2013; 10:1082-1088.

21. Hu D, Sun Y. Epidemiology, risk factors for stroke, and management of atrial fibrillation in China. J Am Coll Cardiol. 2008; 52:865-868.

22. Census and Statistics Department, The Government of the Hong Kong Special Adminstrative Region. Hong Kong Statistics (Population Estimates). Available at: http://www.censtatd.gov.hk/hkstat/sub/sp150.jsp?tableID=001&ID=0&productType=8. Accessed May 21, 2015.

23. Lip GYH, Brechin CM, Lane DA. The Global Burden of Atrial Fibrillation and Stroke A Systematic Review of the Epidemiology of Atrial Fibrillation in Regions Outside North America and Europe. Chest. 2012; 142:1489-1498.

24. Ministry of the Interior, Republic of China (Taiwan). Number of Villages, Neighborhoods, Households and Resident Population. Available at: http://sowf.moi.gov.tw/stat/month/elist.htm. Accessed May 21, 2015.

25. Austin PC. Some Methods of Propensity-Score Matching had Superior Performance to Others: Results of an Empirical Investigation and Monte Carlo simulations. Biometrical J. 2009; 51:171-184.

26. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010; 123:638-645.

27. Gamra H, Murin J, Chiang CE, Naditch-Brule L, Brette S, Steg PG. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. Arch Cardiovasc Dis. 2014; 107:77-87.

28. Suarez J, Piccini JP, Liang L, Atherton JJ, Hayward CS, Krum H, Fonarow GC, Lopes RD, Hernandez AF. International variation in use of oral anticoagulation among heart failure patients with atrial fibrillation. Am Heart J. 2012; 163:804-811.

29. Wen-Hang QI. Retrospective investigation of hospitalised patients with atrial fibrillation in mainland China. Int J Cardiol. 2005; 105:283-287.

30. Guo GB, Chang HW, Chen MC, Yang CH. Underutilization of anticoagulation therapy in chronic atrial fibrillation. Jpn Heart J. 2001; 42:55-65.

31. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006; 367:1903-1912.

32. Liu XB, Huang HM, Yu JH, Cao GL, Feng LL, Xu QT, Zhang SF, Zhou MC, Li YG. Warfarin compared with aspirin for older Chinese patients with stable coronary heart diseases and atrial fibrillation complications. Int J Clin Pharm Th. 2014; 52:454-459.

33. The Hospital Authority. Hospital Authority Statistical Report 2012 - 2013. Available at: http://www.ha.org.hk/upload/publication_15/491.pdf. Accessed November 27, 2014.

34. WHO and Department of Health Hong Kong. Health Service Delivery Profile. Hong Kong (China). 2012. Available at: http://www.wpro.who.int/health_services/service_delivery_profile_hong_kong_%28china%29.pdf. Accessed January 30, 2015.

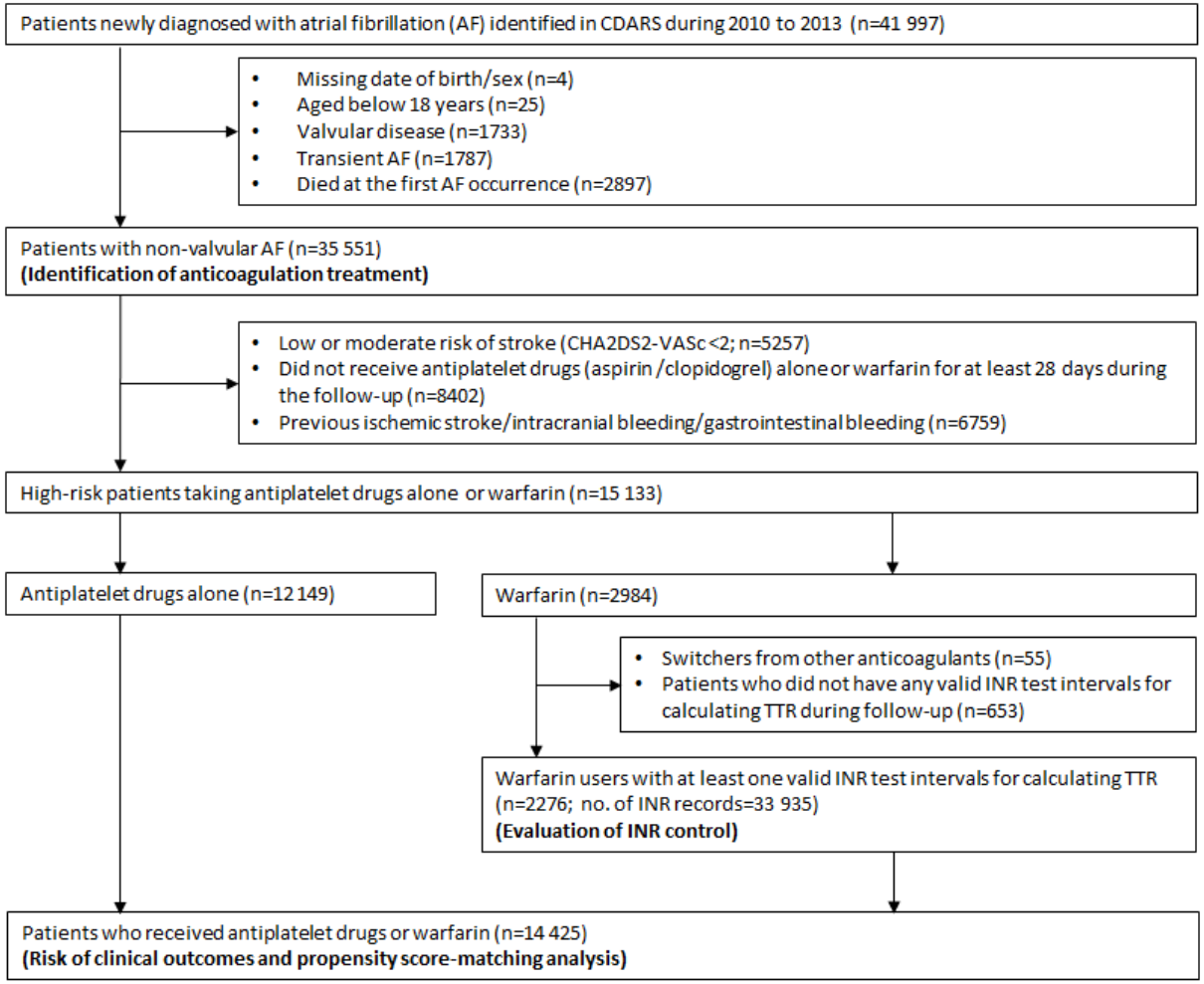

Figure 1.Flow of patients

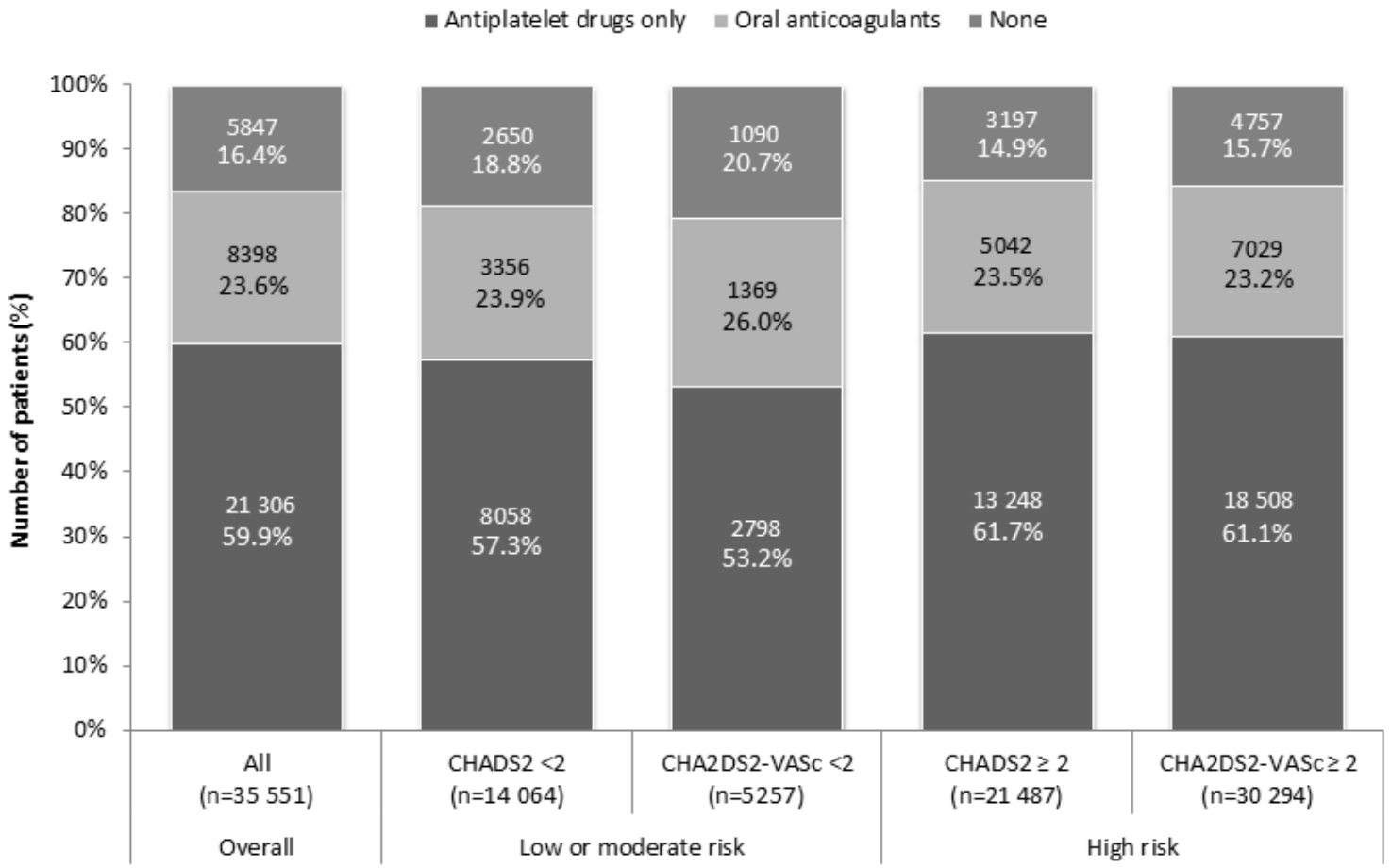

Figure 2.Distribution of the use of antithrombotic therapy stratified by risk of stroke

Table 1.Outcome events among patients receiving antiplatelet drugs and warfarin.

	Overall cohort				PS-matched cohort			
	N	No. of events/absolute risk/incidence†	Warfarin vs. Antiplatelet drugs, HR(95%CI)	Good vs. Poor INR control, HR(95%CI)	N	No. of events/absolute risk/incidence†	Warfarin vs. Antiplatelet drugs, HR(95%CI)	Good vs. Poor INR control, HR(95%CI)
Ischemic stroke								
Antiplatelet drugs	12149	761/6.3/3.7	Reference	-	2225	144/6.5/3.6	Reference	-
Warfarin	2276	73/3.2/1.6	0.42 (0.33, 0.53)*	-	2225	72/3.2/1.6	0.40 (0.28, 0.57)*	-
Poor INR control	1541	59/3.8/1.9	0.51 (0.39, 0.67)*	Reference	1510	58/3.8/1.9	0.41 (0.27, 0.62)*	Reference
Good INR control	735	14/1.9/0.9	0.24 (0.14, 0.41)*	0.47 (0.26, 0.84)*	715	14/2.0/0.9	0.37 (0.18, 0.73)*	0.48 (0.27, 0.86)*
Intracranial hemorrhage								
Antiplatelet drugs	12149	178/1.5/0.9	Reference	-	2225	24/1.1/0.6	Reference	-
Warfarin	2276	42/1.8/0.9	1.03 (0.74, 1.44)	-	2225	42/1.9/0.9	1.24 (0.65, 2.34)	-
Poor INR control	1541	29/1.9/0.9	1.07 (0.72, 1.59)	Reference	1510	29/1.9/1.0	1.07 (0.52, 2.22)	Reference
Good INR control	735	13/1.8/0.8	0.95 (0.54, 1.66)	0.88 (0.46, 1.69)	715	13/1.8/0.8	2.00 (0.50, 8.00)	0.89 (0.46, 1.71)
Gastrointestinal bleeding								
Antiplatelet drugs	12149	495/4.1/2.4	Reference	-	2225	74/3.3/1.9	Reference	-
Warfarin	2276	101/4.4/2.2	0.89 (0.72, 1.10)	-	2225	99/4.4/2.2	1.23 (0.84, 1.81)	-
Poor INR control	1541	65/4.2/2.1	0.86 (0.67, 1.12)	Reference	1510	64/4.2/2.1	1.41 (0.86, 2.31)	Reference
Good INR control	735	36/4.9/2.3	0.94 (0.67, 1.32)	1.08 (0.72, 1.63)	715	35/4.9/2.3	1.00 (0.54, 1.86)	1.08 (0.71, 1.63)
All-cause mortality								
Antiplatelet drugs	12149	2533/20.8/12.3	Reference	-	2225	315/14.2/7.9	Reference	-
Warfarin	2276	181/8.0/3.9	0.32 (0.28, 0.37)*	-	2225	177/8.0/3.9	0.45 (0.36, 0.57)*	-
Poor INR control	1541	125/8.1/4.0	0.33 (0.28, 0.40)*	Reference	1510	122/8.1/4.0	0.43 (0.32, 0.57)*	Reference
Good INR control	735	56/7.6/3.5	0.30 (0.23, 0.39)*	0.88 (0.64, 1.20)	715	55/7.7/3.6	0.49 (0.34, 0.73)*	0.89 (0.65, 1.22)

Abbreviations: PS, propensity score; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio. Poor INR control, time-in-therapeutic-range<60%; Good INR control, time-in-therapeutic-range≥60%.

**P*-value<0.05. †absolute risk per 100 patients; incidence per 100 patient-years.

ONLINE SUPPLEMENT

Appendix I. Data validation

To validate the coding accuracy for ischemic stroke and intracranial hemorrhage (ICH) in the Clinical Data Analysis and Reporting System database (CDARS), original medical records of the patients from the Hong Kong West Cluster (HKWC), which is one of the seven hospital clusters of the Hospital Authority, were extracted for data validation. The HKWC has a population of over half a million, representing 8% of the total population of Hong Kong.[1] It manages seven hospitals, one specialist rehabilitation center, and six general outpatient clinics.[1,2] The age and sex characteristics of the people in the HKWC are similar to that of the overall Hong Kong population.[3] The diagnoses of ischemic stroke and ICH were ascertained by radiology, computerized tomography or magnetic resonance imaging of the brain, or documentation of the disease in medical chart. The corresponding positive predictive values (PPV) were calculated.

In this study, 14425 patients were included in the analysis for the risk of ischemic stroke and ICH (before propensity-score matching). Of these, 1404 patients (10%) were from the HKWC. All patients who had ischemic stroke (n=71) and ICH (n=19) were selected from the HKWC for validation. The corresponding PPVs for ischemic stroke and ICH were 90% (64 out of 71) and 95% (18 out of 19) respectively.

References

1. Hospital Authority. Clinical Services Plan for the Hong Kong West Cluster. 2013; http://www.ha.org.hk/upload/publication_44/453.pdf. Accessed 23rd July 2015.

2. The Hospital Authority. Clusters, Hospitals & Institutions. http://www.ha.org.hk/visitor/ha_visitor_text_index.asp?Content_ID=10036&Lang=ENG&Dimension=100&Parent_ID=10004&Ver=TEXT. Accessed 23rd July 2015.

3. Census and Statistics Department HKSAR. Population and Household Statistics Analysed by District Council District 2013. 2013; http://www.statistics.gov.hk/pub/B11303012013AN13B0100.pdf. Accessed 23rd July 2015.

Appendix II. Modelling analysis

We extrapolated our findings to the whole Chinese population in mainland China, Hong Kong and Taiwan to estimate the number of ischemic stroke cases that could be potentially prevented per year by the optimal use of anticoagulation treatment in the high-risk patients with atrial fibrillation (AF) over the study period (1st January 2010 – 31st July 2014):

Scenario 1: if patients on antiplatelet drugs were optimally treated with warfarin.

Method: [Total number of Chinese population with AF] x [proportion of high-risk patients] x [proportion of patients on antiplatelet drugs] ÷ [number needed to treat; calculated as 1/absolute risk reduction (event rate on antiplatelet drugs – event rate on warfarin)] ÷ [length of study period];

Scenario 2: if patients with poor INR control achieved good INR control.

Method: [Total number of Chinese population with AF] x [proportion of high-risk patients] x [proportion of patients on warfarin] x [proportion of patients with poor INR control] ÷ [number needed to treat; calculated as 1/absolute risk reduction (event rate on poor INR control – event rate on good INR control)] ÷ [length of study period].

The estimated number of patients with AF in the Chinese population was 8 million.[1-5] Therefore, based on the findings in our study, there were 8 million x 85% x 61% ÷ [1/ (6.5%-3.2%)] ÷ 3.6 years = approx. 40000 ischemic stroke cases that could be potentially prevented per year among the patients on antiplatelet drugs if they were optimally treated with warfarin; and 8 million x 85% x 17% x 68% ÷ [1/(3.8%-2.0%)] ÷ 3.6 years = approx. 4000 ischemic stroke cases that could be potentially prevented per year if patients on warfarin had good INR control.

References

1. Tse HF, Wang YJ, Ai-Abdullah MA, et al. Stroke prevention in atrial fibrillation-An Asian stroke perspective. Heart rhythm: the official journal of the Heart Rhythm Society. Jul 2013;10(7):1082-1088.

2. Hu D, Sun Y. Epidemiology, risk factors for stroke, and management of atrial fibrillation in China. Journal of the American College of Cardiology. Sep 2 2008;52(10):865-868.

3. Census and Statistics Department, The Government of the Hong Kong Special Administrative Region. Hong Kong Statistics (Population Estimates). 2015; http://www.censtatd.gov.hk/hkstat/sub/sp150.jsp?tableID=001&ID=0&productType=8. Accessed May 21, 2015, 2015.

4. Lip GYH, Brechin CM, Lane DA. The Global Burden of Atrial Fibrillation and Stroke A Systematic Review of the Epidemiology of Atrial Fibrillation in Regions Outside North America and Europe. Chest. Dec 2012;142(6):1489-1498.

5. Ministry of the Interior, Republic of China (Taiwan). Number of Villages, Neighborhoods, Households and Resident Population. 2015; http://sowf.moi.gov.tw/stat/month/elist.htm. Accessed 21st May 2015.

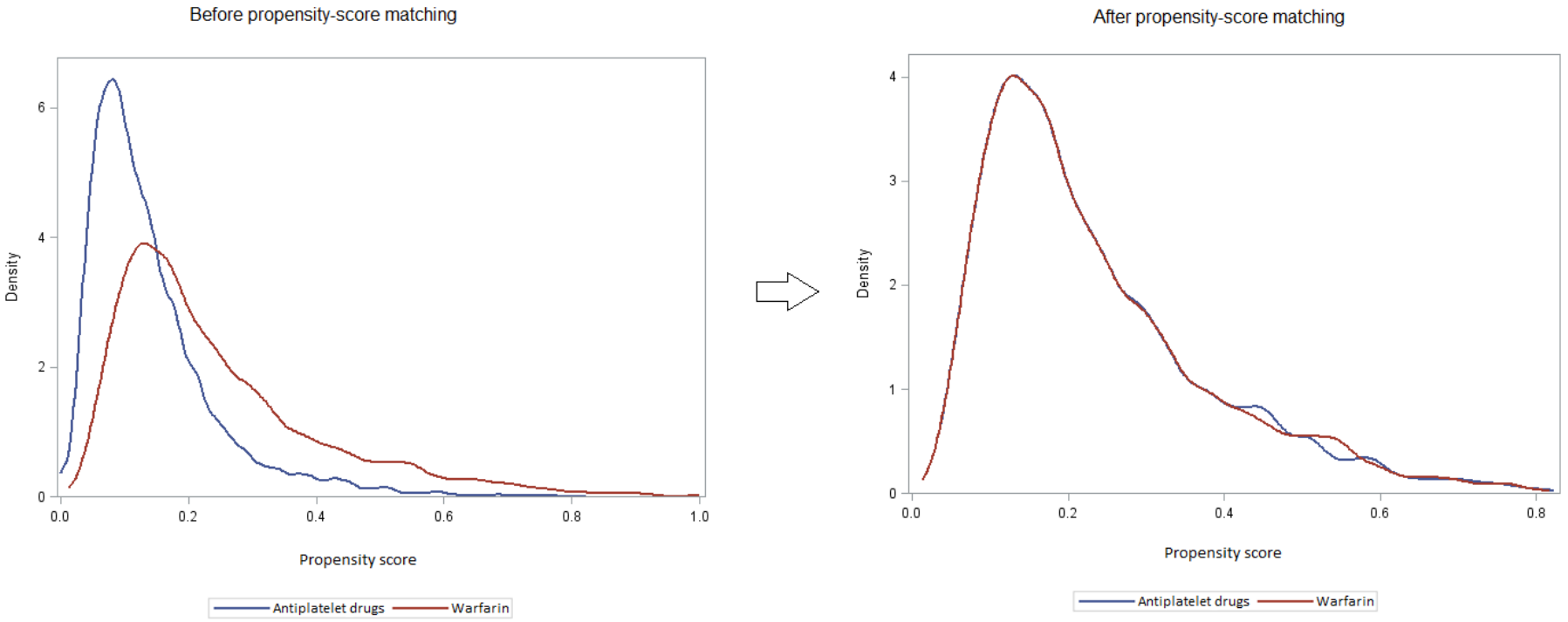

Figure I. Distribution of propensity scores between treatment groups.

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study.

ICD-9-CM codes	Descriptions
Atrial fibrillation	
427.3	Atrial fibrillation and flutter
Valvular heart diseases/replacement or hyperthyroidism	
242	Thyrotoxicosis with or without goitre
394.0	Mitral stenosis
Procedure codes	
35.20	Open and other replacement of unspecified heart valve
35.22	Open and other replacement of aortic valve
35.24	Open and other replacement of mitral valve
35.26	Open and other replacement of pulmonary valve
35.28	Open and other replacement of tricuspid valve
Transient atrial fibrillation	
Cardiac surgery (procedure codes)	
00.5	Other cardiovascular procedures
35	Operations on valves and septa of heart
36	Operations on vessels of heart
37	Other operations on heart and pericardium
Pericarditis	
391	Rheumatic fever with heart involvement
393	Chronic rheumatic pericarditis
420	Acute pericarditis
423.2	Constrictive pericarditis
036.41	Meningococcal pericarditis
074.21	Coxsackie pericarditis
093.81	Syphilitic pericarditis
098.83	Gonococcal pericarditis
Myocarditis	
130.3	
391.2	Acute rheumatic myocarditis
398.0	Rheumatic myocarditis
422	Acute myocarditis
429.0	Myocarditis, unspecified
032.82	Diphtheritic myocarditis
036.43	Meningococcal myocarditis
074.23	Coxsackie myocarditis
093.82	Syphilitic myocarditis
Pulmonary embolism	
415.1	Pulmonary embolism and infarction

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
$CHADS_2$ and CHA_2DS_2-VASc scores	
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428	Heart failure
Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
437.2	Hypertensive encephalopathy
Diabetes	
250	Diabetes mellitus
Ischaemic stroke	
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434	Occlusion of cerebral arteries
436	Acute, but ill-defined, cerebrovascular disease
437.0	Cerebral atherosclerosis
437.1	Other generalized ischemic cerebrovascular disease

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Transient ischaemic attack	
435	Transient cerebral ischemia
Systemic embolism	
444	Arterial embolism and thrombosis
445	Atheroembolism
Vascular disease	
410-414	Ischemic heart disease
443.8	Other specified peripheral vascular diseases
443.9	Peripheral vascular disease, unspecified
Myocardial infarction	
410	Acute myocardial infarction
Intracranial haemorrhage	
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other and unspecified intracranial haemorrhage
Gastrointestinal bleeding	
531.0	Acute gastric ulcer with hemorrhage
531.2	Acute gastric ulcer with hemorrhage and perforation, without mention of obstruction
531.4	Chronic or unspecified gastric ulcer with hemorrhage
531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
532.0	Acute duodenal ulcer with hemorrhage
532.2	Acute duodenal ulcer with hemorrhage and perforation
532.4	Chronic or unspecified duodenal ulcer with hemorrhage
532.6	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
533.0	Acute peptic ulcer of unspecified site with hemorrhage
533.2	Acute peptic ulcer of unspecified site with hemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
533.6	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
534.0	Acute gastrojejunal ulcer with hemorrhage
534.2	Acute gastrojejunal ulcer with hemorrhage and perforation, without mention of obstruction
534.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
534.6	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation
535.01	Acute gastritis, with hemorrhage
535.11	Atrophic gastritis, with hemorrhage
535.21	Gastric mucosal hypertrophy, with hemorrhage
535.31	Alcoholic gastritis, with hemorrhage

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Gastrointestinal bleeding [continued]	
535.41	Other specified gastritis, with hemorrhage
535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage
535.61	Duodenitis, with hemorrhage
535.71	Eosinophilic gastritis, with hemorrhage
562.02	Diverticulosis of small intestine with hemorrhage
562.03	Diverticulitis of small intestine with haemorrhage
562.12	Diverticulosis of colon with haemorrhage
562.13	Diverticulitis of colon with haemorrhage
569.3	Hemorrhage of rectum and anus
569.85	Angiodysplasia of intestine with haemorrhage
569.86	Dieulafoy lesion (hemorrhagic) of intestine
578.0	Hematemesis
578.1	Melena
578.9	Hemorrhage of gastrointestinal tract, unspecified
Other bleeding	
423.0	Hemopericardium
459.0	Haemorrhage NOS
593.81	Vascular disorders of kidney
599.7	Haematuria
623.8	Other specified noninflammatory disorders of vagina
626.2	Excessive menstruation
626.6	Metrorrhagia
719.1	Hemarthrosis
784.7	Epistaxis
784.8	Haemorrhage from throat
786.3	Haemoptysis
Renal disease	
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
580	Acute glomerulonephritis
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis and nephropathy not specified as acute or chronic
584	Acute kidney failure
585	Chronic kidney disease (ckd)
586	Renal failure unspecified
590.0	Chronic pyelonephritis
753.1	Cystic kidney disease

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Charlson comorbidity index	
Myocardial infarction	
410	Acute myocardial infarction
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428	Heart failure
Peripheral vascular disease	
441	Aortic aneurysm and dissection
443.9	Peripheral vascular disease, unspecified
785.4	Gangrene
V43.4	Blood vessel replaced by other means
Cerebrovascular disease	
430-438	Cerebrovascular disease
Chronic obstructive pulmonary disease	
490-496	Chronic Obstructive Pulmonary Disease and Allied Conditions
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to other silica or silicates
503	Pneumoconiosis due to other inorganic dust
504	Pneumonopathy due to inhalation of other dust
505	Pneumoconiosis, unspecified
506.4	Respiratory conditions due to chemical fumes and vapors
Dementia	
290	Dementias

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Charlson comorbidity index [continued]	
Paralysis	
342	Hemiplegia and hemiparesis
344.1	Paraplegia
Diabetes without chronic complication	
250.0	Diabetes mellitus without mention of complication
250.1	Diabetes with ketoacidosis
250.2	Diabetes with hyperosmolarity
250.3	Diabetes with other coma
250.7	Diabetes with peripheral circulatory disorders
Diabetes with chronic complication	
250.4	Diabetes with renal manifestations
250.5	Diabetes with ophthalmic manifestations
250.6	Diabetes with neurological manifestations
Chronic renal failure	
582	Chronic glomerulonephritis
583.0	Nephritis and nephropathy, not specified as acute or chronic, with lesion of proliferative glomerulonephritis
583.1	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
583.2	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
583.6	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal cortical necrosis
583.7	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal medullary necrosis
585	Chronic kidney disease (ckd)
586	Renal failure, unspecified
588	Disorders resulting from impaired renal function
Various cirrhodites	
571.2	Alcoholic cirrhosis of liver
571.4	Chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
Moderate-severe liver disease	
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without bleeding
456.2	Esophageal varices in diseases classified elsewhere

Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Charlson comorbidity index [continued]	
Moderate-severe liver disease [continued]	
572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
Ulcers	
531	Gastric ulcer
532	Duodenal ulcer
533	Peptic ulcer site unspecified
534	Gastrojejunal ulcer
Rheumatoid arthritis and other inflammatory polyarthropathies	
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.4	Polymyositis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.81	Rheumatoid lung
725	Polymyalgia rheumatica
Acquired Immune Deficiency Syndrome	
042	Human immunodeficiency virus [HIV] disease
Malignancy	
140-149	Malignant neoplasm of lip, oral cavity, and pharynx
150-159	Malignant neoplasm of digestive organs and peritoneum
160-165	Malignant neoplasm of respiratory and intrathoracic organs
170-172, 174-176	Malignant neoplasm of bone, connective tissue, and breast
179-189	Malignant neoplasm of genitourinary organs
190-195	Malignant neoplasm of other sites
200-208	Malignant neoplasm of lymphatic and hematopoietic tissue
Metastatic solid tumour	
196	Secondary and unspecified malignant neoplasm of lymph nodes
197	Secondary malignant neoplasm of respiratory and digestive systems
198	Secondary malignant neoplasm of other specified sites
199	Malignant neoplasm without specification of site

Table II. Baseline characteristics.

Characteristics	Overall (%)
Total	35 551
Age (years), mean ± SD	76.7 ± 12.5
Age ≥65	29 248 (82.3)
Age ≥75	22 492 (63.3)
Sex (Female)	18 015 (50.7)
Baseline medical conditions	
Congestive heart failure	9287 (26.1)
Diabetes	8067 (22.7)
Hypertension	18 633 (52.4)
Myocardial infarction	2819 (7.9)
Vascular disease	8613 (24.2)
Prior ischaemic stroke/TIA/SE	7392 (20.8)
Prior bleeding	7412 (20.8)
Intracranial bleeding	1334 (3.8)
Gastrointestinal bleeding	3836 (10.8)
Others*	3063 (8.6)
Renal disease	4577 (12.9)
CHA_2DS_2-VASc score, mean ± SD	3.6 ± 1.9
0	1901 (5.3)
1	3356 (9.4)
2	5001 (14.1)
≥3	25 293 (71.1)
$CHADS_2$ score, mean ± SD	2.1 ± 1.5
0	5462 (15.4)
1	8602 (24.2)
2	8767 (24.7)
≥3	12 720 (35.8)
Charlson comorbidity index, mean ± SD	1.8 ± 1.9
0-3	30 598 (86.1)
4-5	3138 (8.8)
6-7	913 (2.6)
≥8	902 (2.5)
Recent use of medications	
Aspirin	19018 (53.5)
Clopidogrel	1808 (5.1)
Amiodarone	4714 (13.3)
Statin	9655 (27.2)
Proton-pump inhibitor	7535 (21.2)
Histamine type-2 receptor antagonist	15918 (44.8)
NSAIDs	2374 (6.7)
SSRIs	935 (2.6)

Abbreviations: SD, standard deviation; TIA, transient ischaemic attack; SE, systemic embolism; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.
*includes epistaxis, haematuria, haemarthrosis, haemorrhage from kidney, throat, and vagina, hemopericardium, and haemoptysis.

Table III. Distribution of the use of oral anticoagulants during the first year of atrial fibrillation.

Oral anticoagulants, no. of patients (%)*	Overall	Low or moderate risk		High risk	
	All users (n=8398)	CHADS2 <2 (n=3356)	CHA2DS2-VASc <2 (n=1369)	CHADS2 ≥ 2 (n=5042)	CHA2DS2-VASc ≥ 2 (n=7029)
Warfarin	6151 (73.2)	2514 (74.9)	1103 (80.6)	3637 (72.1)	5048 (71.8)
NOACs	2789 (33.2)	1032 (30.8)	341 (24.9)	1757 (34.8)	2448 (34.8)
Apixaban	23 (0.3)	12 (0.4)	4 (0.3)	11 (0.2)	19 (0.3)
Dabigatran	2362 (28.1)	859 (25.6)	284 (20.7)	1503 (29.8)	2078 (29.6)
Rivaroxaban	493 (5.9)	197 (5.9)	58 (4.2)	296 (5.9)	435 (6.2)

Abbreviations: NOACs, non-vitamin K antagonist oral anticoagulants.
*included patients who were exposed to more than one type of oral anticoagulant during their first year of atrial fibrillation (hence figures do not add to 100%).

Table IV. Characteristics of patients before and after propensity score matching.

Characteristics	Before PS matching			After PS matching		
	Antiplatelet drugs (n=12 149)	Warfarin (n=2276)	Standardized difference*	Antiplatelet drugs (n=2225)	Warfarin (n=2225)	Standardized difference*
Age (years), mean ± SD	80.3 ± 9.2	73.9 ± 9.7	-0.67	74.0 ± 10.5	74.3 ± 9.3	0.03
Age >=65	11 418 (94.0)	1892 (83.1)	-0.35	1826 (82.1)	1881 (84.5)	0.07
Age >=75	9237 (76.0)	1217 (53.5)	-0.49	1139 (51.2)	1213 (54.5)	0.07
Sex (Female)	6875 (56.6)	1204 (52.9)	-0.07	1189 (53.4)	1185 (53.3)	-0.004
Baseline medical conditions						
Congestive heart failure	4006 (33.0)	856 (37.6)	0.10	794 (35.7)	827 (37.2)	0.03
Diabetes	2902 (23.9)	635 (27.9)	0.09	573 (25.8)	624 (28.0)	0.05
Hypertension	6875 (56.6)	1251 (55.0)	-0.03	1248 (56.1)	1230 (55.3)	-0.02
Myocardial infarction	1355 (11.2)	149 (6.5)	-0.16	140 (6.3)	148 (6.7)	0.01
Vascular disease	3818 (31.4)	607 (26.7)	-0.10	575 (25.8)	598 (26.9)	0.02
Prior transient ischemic attack or systemic embolism	253 (2.1)	174 (7.6)	0.26	120 (5.4)	142 (6.4)	0.04
Prior bleeding	998 (8.2)	184 (8.1)	-0.005	174 (7.8)	178 (8.0)	0.01
Renal disease	1704 (14.0)	221 (9.7)	-0.13	195 (8.8)	219 (9.8)	0.04
CHA_2DS_2-VASc score, mean ± SD	3.8 ± 1.3	3.5 ± 1.3	-0.18	3.4 ± 1.3	3.5 ± 1.3	0.09
2	2405 (19.8)	588 (25.8)	0.14	707 (31.8)	568 (25.5)	-0.14
3	3287 (27.1)	657 (28.9)	0.04	599 (26.9)	644 (28.9)	0.05
≥4	6457 (53.1)	1031 (45.3)	-0.16	919 (41.3)	1013 (45.5)	0.09
$CHADS_2$ score, mean ± SD	1.9 ± 1.0	1.9 ± 1.1	-0.04	1.8 ± 1.1	1.9 ± 1.0	0.08
0-1	4515 (37.2)	891 (39.1)	0.04	988 (44.4)	881 (39.6)	-0.10
2	4229 (34.8)	795 (34.9)	0.003	694 (31.2)	777 (34.9)	0.08
3	2578 (21.2)	424 (18.6)	-0.06	407 (18.3)	412 (18.5)	0.01
≥4	827 (6.8)	166 (7.3)	0.02	136 (6.1)	155 (7.0)	0.03

Table IV. Characteristics of patients before and after propensity score matching [continued].

Characteristics	Before PS matching			After PS matching		
	Antiplatelet drugs (n=12 149)	Warfarin (n=2276)	Standardized difference*	Antiplatelet drugs (n=2225)	Warfarin (n=2225)	Standardized difference*
Charlson comorbidity index, mean ± SD	1.5 ± 1.8	1.3 ± 1.4	-0.15	1.2 ± 1.3	1.3 ± 1.3	0.05
0-3	10 796 (88.9)	2116 (93.0)	0.14	2080 (93.5)	2068 (92.9)	-0.02
4-5	891 (7.3)	123 (5.4)	-0.08	117 (5.3)	122 (5.5)	0.01
6-7	263 (2.2)	28 (1.2)	-0.07	24 (1.1)	28 (1.3)	0.02
≥8	199 (1.6)	9 (0.4)	-0.12	4 (0.2)	7 (0.3)	0.03
Recent use of medications						
Aspirin	7870 (64.8)	1259 (55.3)	-0.19	1222 (54.9)	1239 (55.7)	0.02
Clopidogrel	825 (6.8)	113 (5.0)	-0.08	105 (4.7)	112 (5.0)	0.01
Amiodarone	1631 (13.4)	251 (11.0)	-0.07	229 (10.3)	245 (11.0)	0.02
Statin	3033 (25.0)	768 (33.7)	0.19	727 (32.7)	741 (33.3)	0.01
Proton-pump inhibitor	2361 (19.4)	362 (15.9)	-0.09	325 (14.6)	357 (16.0)	0.04
Histamine type-2 receptor antagonist	5817 (47.9)	1048 (46.0)	-0.04	1001 (45.0)	1027 (46.2)	0.02
NSAIDs	806 (6.6)	132 (5.8)	-0.03	145 (6.5)	128 (5.8)	-0.03
SSRIs	247 (2.0)	37 (1.6)	-0.03	36 (1.6)	37 (1.7)	0.004
Anticoagulation control (for warfarin users only)						
Total number of INR tests		33 935			33 174	
Number of INR tests performed for each patient, mean ± SD		15 ± 11			15 ± 11	
Time in therapeutic range, mean ± SD		44.6 ± 28.8%			44.4 ± 28.8%	
<30%		754 (33.1)			742 (33.3)	
30-40%		254 (11.2)			249 (11.2)	
40-50%		280 (12.3)			275 (12.4)	
50-60%		253 (11.1)			244 (11.0)	
60-70%		244 (10.7)			241 (10.8)	
≥70%		491 (21.6)			474 (21.3)	

Abbreviations: PS, propensity score; SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; INR, international normalized ratio.
*Standardized difference is the mean difference divided by the pooled standard deviation.

Table V. Gender-stratified analyses.

	Overall cohort					PS-matched cohort				
	Male		Female			Male		Female		
	N	No. of cases (incidence*)	N	No. of cases (incidence*)	p-value for gender difference†	N	No. of cases (incidence*)	N	No. of cases (incidence*)	p-value for gender difference†
Ischemic stroke										
Overall	6346	306 (2.8)	8079	528 (3.7)	<0.001	2076	96 (2.4)	2374	120 (2.6)	0.56
Antiplatelet drugs	5274	267 (3.1)	6875	494 (4.2)	<0.001	1036	58 (3.2)	1189	86 (3.9)	0.22
Warfarin	1072	39 (1.8)	1204	34 (1.4)	0.32	1040	38 (1.8)	1185	34 (1.4)	0.35
Warfarin vs. Antiplatelet drugs, HR (95% CI)	0.57 (0.41, 0.80)		0.33 (0.23, 0.47)		0.03	0.52 (0.25, 1.09)		0.29 (0.14, 0.61)		0.27
Intracranial hemorrhage										
Overall	6346	102 (0.9)	8079	118 (0.8)	0.38	2076	29 (0.7)	2374	37 (0.8)	0.69
Antiplatelet drugs	5274	83 (1.0)	6875	95 (0.8)	0.27	1036	10 (0.6)	1189	14 (0.6)	0.71
Warfarin	1072	19 (0.9)	1204	23 (0.9)	0.76	1040	19 (0.9)	1185	23 (1.0)	0.79
Warfarin vs. Antiplatelet drugs, HR (95% CI)	0.89 (0.54, 1.47)		1.16 (0.74, 1.83)		0.44	1.00 (0.20, 4.96)		1.40 (0.44, 4.41)		0.74
Gastrointestinal bleeding										
Overall	6346	255 (2.3)	8079	341 (2.4)	0.74	2076	78 (2.0)	2374	95 (2.1)	0.73
Antiplatelet drugs	5274	213 (2.4)	6875	282 (2.4)	0.82	1036	38 (2.1)	1189	36 (1.7)	0.30
Warfarin	1072	42 (1.9)	1204	59 (2.4)	0.23	1040	40 (1.8)	1185	59 (2.4)	0.17
Warfarin vs. Antiplatelet drugs, HR (95% CI)	0.77 (0.55, 1.07)		1.00 (0.76, 1.33)		0.23	1.00 (0.42, 2.40)		1.58 (0.77, 3.26)		0.43

Abbreviations: HR, hazard ratio; CI, confidence interval.

*Incidence per 100 patient years.

†Least squares means method was used to compare the incidence of outcome events by gender under Poisson distribution, whereas t-test was used to compare the hazard ratios by gender.

Table VI. Sensitivity analysis using 180-day permissible medication gap.

	Overall cohort				PS-matched cohort			
	N	No. of events /absolute risk /incidence†	Warfarin vs. Antiplatelet drugs, HR (95%CI)	Good vs. Poor INR control, HR (95%CI)	N	No. of events /absolute risk /incidence†	Warfarin vs. Antiplatelet drugs, HR (95%CI)	Good vs. Poor INR control, HR (95%CI)
Ischemic stroke								
Antiplatelet drugs	12149	789/6.5/3.7	Reference		2231	135/6.1/3.2	Reference	
Warfarin	2286	78/3.4/1.6	0.44 (0.35, 0.55)*		2231	76/3.4/1.6	0.42 (0.29, 0.59)*	
Poor INR control	1546	61/3.9/1.9	0.52 (0.40, 0.67)*	Reference	1509	59/3.9/1.9	0.50 (0.33, 0.76)*	Reference
Good INR control	740	17/2.3/1.1	0.29 (0.18, 0.46)*	0.56 (0.33, 0.95)*	722	17/2.4/1.1	0.29 (0.15, 0.54)*	0.58 (0.34, 0.99)*
Intracranial hemorrhage								
Antiplatelet drugs	12149	184/1.5/0.9	Reference		2231	31/1.4/0.7	Reference	
Warfarin	2286	42/1.8/0.9	1.01 (0.72, 1.41)		2231	42/1.9/0.9	0.96 (0.56, 1.67)	
Poor INR control	1546	29/1.9/0.9	1.05 (0.71, 1.55)	Reference	1509	29/1.9/0.9	0.94 (0.49, 1.83)	Reference
Good INR control	740	13/1.8/0.8	0.93 (0.53, 1.64)	0.89 (0.46, 1.71)	722	13/1.8/0.8	1.00 (0.38, 2.66)	0.89 (0.46, 1.71)
Gastrointestinal bleeding								
Antiplatelet drugs	12149	519/4.3/2.4	Reference		2231	81/3.6/1.9	Reference	
Warfarin	2286	102/4.5/2.1	0.87 (0.70, 1.08)		2231	100/4.5/2.1	0.98 (0.68, 1.42)	
Poor INR control	1546	66/4.3/2.1	0.85 (0.66, 1.09)	Reference	1509	64/4.2/2.0	1.19 (0.74, 1.90)	Reference
Good INR control	740	36/4.9/2.2	0.92 (0.66, 1.29)	1.08 (0.72, 1.62)	722	36/5.0/2.3	0.73 (0.40, 1.32)	1.11 (0.74, 1.68)
All-cause mortality								
Antiplatelet drugs	12149	2677/22.0/12.5	Reference		2231	347/15.6/8.3	Reference	
Warfarin	2286	194/8.5/4.0	0.33 (0.29, 0.38)*		2231	190/8.5/4.0	0.40 (0.31, 0.50)*	
Poor INR control	1546	135/8.7/4.2	0.34 (0.29, 0.41)*	Reference	1509	132/8.7/4.2	0.43 (0.32, 0.56)*	Reference
Good INR control	740	59/8.0/3.7	0.30 (0.23, 0.39)*	0.87 (0.64, 1.18)	722	58/8.0/3.7	0.33 (0.22, 0.51)*	0.87 (0.64, 1.19)

Abbreviations: PS, propensity score; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.
Poor INR control, time in therapeutic range<60%; Good INR control, time in therapeutic range≥60%.*P Value<0.05.
†absolute risk per 100 patients; incidence per 100 patient-years.

Table VII. Sensitivity analysis using 30-day permissible medication gap.

	Overall cohort				PS-matched cohort			
	N	No. of events /absolute risk /incidence†	Warfarin vs. Antiplatelet drugs, HR (95%CI)	Good INR vs. Poor INR control, HR (95%CI)	N	No. of events /absolute risk /incidence†	Warfarin vs. Antiplatelet drugs, HR (95%CI)	Good INR vs. Poor INR control, HR (95%CI)
Ischemic stroke								
Antiplatelet drugs	12149	711/5.9/3.8	Reference		2165	111/5.1/3.1	Reference	
Warfarin	2214	66/3.0/1.5	0.40 (0.31, 0.51)*		2165	63/2.9/1.5	0.48 (0.32, 0.72)*	
Poor INR control	1493	54/3.6/1.8	0.49 (0.37, 0.64)*	Reference	1466	51/3.5/1.8	0.60 (0.37, 0.95)*	Reference
Good INR control	721	12/1.7/0.8	0.21 (0.12, 0.38)*	0.44 (0.23, 0.81)*	699	12/1.7/0.8	0.27 (0.12, 0.62)*	0.47 (0.25, 0.88)*
Intracranial hemorrhage								
Antiplatelet drugs	12149	159/1.3/0.8	Reference		2165	19/0.9/0.5	Reference	
Warfarin	2214	39/1.8/0.9	1.04 (0.73, 1.48)		2165	39/1.8/0.9	1.80 (0.83, 3.90)	
Poor INR control	1493	27/1.8/0.9	1.09 (0.72, 1.63)	Reference	1466	27/1.8/0.9	1.63 (0.67, 3.92)	Reference
Good INR control	721	12/1.7/0.8	0.95 (0.53, 1.71)	0.87 (0.44, 1.72)	699	12/1.7/0.8	2.50 (0.49, 12.89)	0.88 (0.45, 1.74)
Gastrointestinal bleeding								
Antiplatelet drugs	12149	460/3.8/2.4	Reference		2165	55/2.5/1.5	Reference	
Warfarin	2214	93/4.2/2.1	0.86 (0.69, 1.07)		2165	92/4.2/2.1	1.29 (0.84, 1.97)	
Poor INR control	1493	57/3.8/2.0	0.79 (0.60, 1.05)	Reference	1466	56/3.8/1.9	1.29 (0.76, 2.20)	Reference
Good INR control	721	36/5.0/2.4	0.99 (0.70, 1.38)	1.24 (0.82, 1.88)	699	36/5.2/2.5	1.29 (0.64, 2.59)	1.27 (0.84, 1.94)
All-cause mortality								
Antiplatelet drugs	12149	2238/18.4/11.9	Reference		2165	281/13.0/7.7	Reference	
Warfarin	2214	150/6.8/3.4	0.29 (0.25, 0.35)*		2165	146/6.7/3.4	0.35 (0.27, 0.46)*	
Poor INR control	1493	101/6.8/3.5	0.30 (0.24, 0.36)*	Reference	1466	99/6.8/3.4	0.32 (0.23, 0.45)*	Reference
Good INR control	721	49/6.8/3.3	0.29 (0.22, 0.38)*	0.95 (0.68, 1.34)	699	47/6.7/3.3	0.41 (0.27, 0.63)*	0.94 (0.67, 1.33)

Abbreviations: PS, propensity score; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.
Poor INR control, time in therapeutic range<60%; Good INR control, time in therapeutic range≥60%.*P Value<0.05.
†absolute risk per 100 patients; incidence per 100 patient-years.

Table VIII. Baseline characteristics of the patients in the analysis based on CHADS2 score.

Characteristics	Before PS matching			After PS matching		
	Antiplatelet drugs (n=7568)	Warfarin (n=1342)	Standardized difference*	Antiplatelet drugs (n=1311)	Warfarin (n=1311)	Standardized difference*
Age (years), mean ± SD	82.0 ± 8.5	75.4 ± 9.7	-0.73	75.7 ± 10.4	75.9 ± 9.2	0.01
Age >=65	7223 (95.4)	1128 (84.1)	-0.38	1092 (83.3)	1123 (85.7)	0.07
Age >=75	6547 (86.5)	886 (66.0)	-0.50	861 (65.7)	884 (67.4)	0.04
Sex (Female)	4363 (57.7)	652 (48.6)	-0.18	647 (49.4)	645 (49.2)	-0.003
Baseline medical conditions						
Congestive heart failure	3702 (48.9)	634 (47.2)	-0.03	601 (45.8)	620 (47.3)	0.03
Diabetes	2731 (36.1)	566 (42.2)	0.13	579 (44.2)	556 (42.4)	-0.04
Hypertension	5963 (78.8)	1032 (76.9)	-0.05	1040 (79.3)	1018 (77.7)	-0.04
Myocardial infaraction	1028 (13.6)	101 (7.5)	-0.20	92 (7.0)	100 (7.6)	0.02
Vascular disease	2762 (36.5)	391 (29.1)	-0.16	381 (29.1)	387 (29.5)	0.01
Prior transient ischemic attack/systemic embolism	251 (3.3)	167 (12.4)	0.34	117 (8.9)	145 (11.1)	0.07
Prior bleeding	664 (8.8)	110 (8.2)	-0.02	121 (9.2)	108 (8.2)	-0.04
Renal disease	1455 (19.2)	190 (14.2)	-0.14	201 (15.3)	189 (14.4)	-0.03
CHA_2DS_2-VASc score, mean ± SD	4.5 ± 1.1	4.2 ± 1.2	-0.24	4.1 ± 1.2	4.2 ± 1.2	0.06
2	122 (1.6)	73 (5.4)	0.21	85 (6.5)	61 (4.7)	-0.08
3	1357 (17.9)	319 (23.8)	0.14	324 (24.7)	310 (23.6)	-0.02
≥4	6089 (80.5)	950 (70.8)	-0.23	902 (68.8)	940 (71.7)	0.06
$CHADS_2$ score, mean ± SD	2.6 ± 0.7	2.6 ± 0.8	0.004	2.5 ± 0.8	2.6 ± 0.8	0.05
2	4172 (55.1)	765 (57.0)	0.04	790 (60.3)	746 (56.9)	-0.07
3	2572 (34.0)	414 (30.8)	-0.07	380 (29.0)	410 (31.3)	0.05
≥4	824 (10.9)	163 (12.1)	0.04	141 (10.8)	155 (11.8)	0.03

Table VIII. Baseline characteristics of the patients in the analysis based on CHADS2 score [continued].

Characteristics	Before PS matching			After PS matching		
	Antiplatelet drugs (n=7568)	Warfarin (n=1342)	Standardized difference*	Antiplatelet drugs (n=1311)	Warfarin (n=1311)	Standardized difference*
Charlson comorbidity index, mean ± SD	2.0 ± 1.8	1.7 ± 1.5	-0.19	1.7 ± 1.4	1.7 ± 1.4	0.02
0-3	6348 (83.9)	1195 (89.0)	0.15	1169 (89.2)	1167 (89.0)	-0.005
4-5	828 (10.9)	114 (8.5)	-0.08	108 (8.2)	113 (8.6)	0.01
6-7	248 (3.3)	26 (1.9)	-0.08	28 (2.1)	26 (2.0)	-0.01
≥8	144 (1.9)	7 (0.5)	-0.13	6 (0.5)	5 (0.4)	-0.01
Recent use of medications						
Aspirin	5310 (70.2)	776 (57.8)	-0.26	751 (57.3)	763 (58.2)	0.02
Clopidogrel	565 (7.5)	72 (5.4)	-0.09	64 (4.9)	71 (5.4)	0.02
Amiodarone	1048 (13.8)	145 (10.8)	-0.09	126 (9.6)	140 (10.7)	0.04
Statin	2213 (29.2)	519 (38.7)	0.20	501 (38.2)	501 (38.2)	<.001
Proton-pump inhibitor	1686 (22.3)	239 (17.8)	-0.11	245 (18.7)	236 (18.0)	-0.02
Histamine type-2 receptor antagonist	3824 (50.5)	640 (47.7)	-0.06	616 (47.0)	626 (47.7)	0.02
NSAIDs	472 (6.2)	78 (5.8)	-0.02	66 (5.0)	75 (5.7)	0.03
SSRIs	163 (2.2)	24 (1.8)	-0.03	21 (1.6)	24 (1.8)	0.02
Anticoagulation control (for warfarin users only)						
Total number of INR tests included		19517			19013	
Number of INR tests performed for each patient, mean ± SD		15 ± 11			15 ± 11	
Time in therapeutic range, mean ± SD		42.9 ± 29.0%			42.7 ± 29.0%	
<30%		483 (36.0)			474 (36.2)	
30-40%		157 (11.7)			151 (11.5)	
40-50%		157 (11.7)			156 (11.9)	
50-60%		146 (10.9)			142 (10.8)	
60-70%		131 (9.8)			129 (9.8)	
≥70%		268 (20.0)			259 (19.8)	

Abbreviations: PS, propensity score; SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors, INR, international normalized ratio.
*Standardized difference is the mean difference divided by the pooled standard deviation.

Table IX. Sensitivity analysis among the high-risk patients taking antiplatelet drugs and warfarin based on $CHADS_2$ score.

	Overall cohort				PS-matched cohort			
	N	No. of events /absolute risk /incidence†	Warfarin vs. Antiplatelet drugs, HR (95%CI)	Good vs. Poor INR control, HR (95%CI)	N	No. of events /absolute risk /incidence†	Warfarin vs. Antiplatelet drugs, HR (95%CI)	Good vs. Poor INR control, HR (95%CI)
Ischemic stroke								
Antiplatelet drugs	7568	534/7.1/4.3	Reference	-	1311	93/7.1/3.9	Reference	-
Warfarin	1342	49/3.7/1.8	0.42 (0.32, 0.57)*	-	1311	48/3.7/1.8	0.63 (0.42, 0.95)*	-
Poor INR control	943	39/4.1/2.1	0.49 (0.35, 0.68)*	Reference	923	39/4.2/2.1	0.76 (0.47, 1.24)	Reference
Good INR control	399	10/2.5/1.2	0.28 (0.15, 0.51)*	0.57 (0.28, 1.13)	388	9/2.3/1.1	0.41 (0.19, 0.89)*	0.51 (0.25, 1.05)
Intracranial hemorrhage								-
Antiplatelet drugs	7568	117/1.5/0.9	Reference	-	1311	17/1.3/0.7	Reference	-
Warfarin	1342	31/2.3/1.1	1.21 (0.81, 1.79)	-	1311	31/2.4/1.2	1.08 (0.51, 2.29)	
Poor INR control	943	20/2.1/1.1	1.14 (0.71, 1.82)	Reference	923	20/2.2/1.1	1.00 (0.38, 2.66)	Reference
Good INR control	399	11/2.8/1.3	1.36 (0.73, 2.53)	1.18 (0.56, 2.46)	388	11/2.8/1.3	1.20 (0.37, 3.93)	1.17 (0.56, 2.44)
Gastrointestinal bleeding								
Antiplatelet drugs	7568	368/4.9/2.9	Reference	-	1311	48/3.7/2.0	Reference	-
Warfarin	1342	65/4.8/2.4	0.81 (0.62, 1.05)	-	1311	63/4.8/2.4	1.06 (0.66, 1.69)	-
Poor INR control	943	47/5.0/2.5	0.85 (0.63, 1.16)	Reference	923	46/5.0/2.5	1.22 (0.70, 2.11)	Reference
Good INR control	399	18/4.5/2.1	0.71 (0.45, 1.15)	0.83 (0.48, 1.43)	388	17/4.4/2.0	0.73 (0.29, 1.81)	0.80 (0.46, 1.39)
All-cause mortality								
Antiplatelet drugs	7568	1891/25.0/15.1	Reference	-	1311	197/15.0/8.2	Reference	-
Warfarin	1342	118/8.8/4.3	0.29 (0.24, 0.35)*	-	1311	115/8.8/4.3	0.39 (0.29, 0.53)*	-
Poor INR control	943	80/8.5/4.3	0.29 (0.23, 0.36)*	Reference	923	78/8.5/4.3	0.39 (0.28, 0.56)*	Reference
Good INR control	399	38/9.5/4.4	0.30 (0.22, 0.42)*	1.03 (0.70, 1.52)	388	37/9.5/4.4	0.39 (0.23, 0.68)*	1.02 (0.69, 1.51)

Abbreviations: PS, propensity score; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.
Poor INR control, time in therapeutic range<60%; Good INR control, time in therapeutic range≥60%. **P* Value<0.05.
†absolute risk per 100 patients; incidence per 100 patient-years.