**Age threshold for the use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation**

**– Insights into the optimal assessment of age and incident comorbidities**

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***Background****:* The stroke risk of patients with atrial fibrillation (AF) is not static, since AF patients get older and accumulate more comorbidities after AF is diagnosed. Therefore, the stroke risk of AF patients given certain comorbidities in different age strata should ideally be analyzed using an assessment which considers incident comorbidities and the actual age when ischemic stroke occurred. The goal of the present study is to report the age treatment thresholds for the use of NOACs for AF patients *without* or *with only 1* comorbidity of the CHA2DS2-VASc score, based on an “ideal method” of stroke risk assessments.

***Methods and Results****:* The study cohort included 31,039 and 39,020 AF patients who did not have any or had only 1 risk factor comorbidity of the CHA2DS2-VASc score except for age and sex. The risks of ischemic stroke in each age strata for each comorbidities were analyzed in 3 ways, as follows: (i) the *conventional way* (based on baseline risk factors and age), (ii) *dynamic method* (patients were censored when new-comorbidities occurred); and (iii) an *ideal method* (patients were censored when new-comorbidities occurred and the stroke risk was related to the actual age when stroke happened). The tipping point for the use of NOACs was set at a stroke risk of 0.9%/year.

The overall risk of ischemic stroke using the conventional way was overestimated compared to the dynamic or ideal assessment with the incidence rate ratio (IRR) of 1.24 for patients with hypertension, 1.22 for heart failure, 1.37 for diabetes mellitus and 1.35 for vascular diseases; all p values < 0.01. The risk of ischemic stroke for each age strata was generally higher with the conventional or dynamic methods compared to the ideal assessment. With heart failure, the tipping point (age 35 years) of NOACs was similar, irrespetive of methods used for stroke risk assessment. According to the results of ideal assessment, the age thresholds for the use of NOACs for patients with hypertension, diabetes mellitus, and vascular diseases were 50, 50 and 55 years, respectively.

***Conclusions***: Ischemic stroke risk in AF is heterogeneous, depending on different risk factors with age being as an important driver of stroke risk. Age thresholds for the use of NOACs were different for AF patients having different single risk factors beyond sex despite the same CHA2DS2-VASc score point (1 for males and 2 for females); that is, 35 years for heart failure, 50 years for hypertension or diabetes, and 55 years for vascular diseases.

**Key words**: atrial fibrillation; age, NOACs

**Introduction**

Atrial fibrillation (AF) is associated with an excess of stroke risk but this risk is not homogeneous, and depends on the presence of various stroke risk factors. Current European, American and Asian clinical guidelines recommend use of CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female) score for stroke risk stratification, and the strategy about the use of oral anticoagulants (OACs) is determined accordingly.1-3

According to the guideline recommendations, OACs should be offered or considered for every AF patients except for those at low risk, ie. males with a CHA2DS2-VASc score of 0 and females with a CHA2DS2-VASc score of 1. However, there are some debates over the use of OACs for AF patients with single 1 additional risk factor beyond sex (ie. CHA2DS2-VASc score=1 (males) or 2 (females)). Several previous studies have suggested that OACs should be prescribed for these patients,4-7 but another suggested less benefits of OACs in such patients.8 The wide variations of the reported stroke risks for AF patients with a CHA2DS2-VASc score of 1 or 2 make the decision even more difficult for this population.9 Furthermore, since the association between age and increased risk of ischemic stroke is a continuous curve,10 and whether OACs should be prescribed for young patients with a CHA2DS2-VASc score of 1 (males) or 2 (females)(e.g. a 30-year-old male/female with hypertension) whose stroke risk is probably lower than older patients is a clinical dilemma. Similarly, whether OACs should be considered for patients younger but close to the age criteria of the CHA2DS2-VASc scheme (e.g. 60-64 years old) is another difficult management scenario, especially for Asians where the age threshold for an increased risk of ischemic stroke may be lower.10

With the availability of the non-Vitamin K antagonist oral anticoagulants (NOACs) that offer relative efficacy, safety and convenience compared to warfarin, the ‘tippping point’ of offering stroke pevention has been proposed as 0.9%/year.11 This means that NOACs should be offered for patients whose stroke risk without treatment is estimated to be higher than 0.9%/year.

When assessing stroke risk of AF patients, age and associated comorbities are conventionally determined at baseline and the outcomes (stroke, thromboembolism, death, etc) are determined after a period of follow up, anything between 1 to 10 years (or more). In reality, AF patients would get older and accumulate more comorbidities after AF has been diagnosed.12 Therefore, the stroke event could happen many years later when patients are much older and had more comorbidities. Consequently, the reported stroke risk of each CHA2DS2-VASc score or age strata could be over estimated if patients were not censored when new comorbidities occur or the risk of stroke was estimated simply based on the “baseline” age.

In the present study, the risk of ischemic stroke was assessed in 3 ways, as follows: (i) the *conventional way* (based on baseline risk factors and age), (ii) *dynamic method* (patients were censored when new-comorbidities occurred); and (iii) an *ideal method* (patients were censored when new-comorbidities occurred and the stroke risk was related to the acutal age when stroke happened). We aimed to demonstrate that the stroke risk assessed using the “conventional way” would be overestimated when compared to the “dynamic” or “ideal” methods. Second, we also aimed to report the age thresholds for the use of NOACs for AF patients *without* or *with only 1* risk factor comorbidity of the CHA2DS2-VASc score based on the data analyzed using ideal method, when setting the ‘tipping point’ for treatment at a stroke risk of 0.9%/year.

**Methods**

This study used the “National Health Insurance Research Database (NHIRD)” released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan’s population. In this cohort dataset, the patients’ original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of theclaims belonging to the same patient was feasible within the NHI database and can be followed continuously.

*Study cohort*

The study protocol of the present study was similar to our previous studies.4,10,12-17 From January 1, 1996 to December 31, 2009, a total of 299,902 AF patients with age ≥ 20 years were identified from the NHIRD as the study population. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31). To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed for at least 2 times in the outpatient department. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.18 Among the study population, there were 159,999 patients without use of antiplatelet agents or OACs. The study cohort included 31,039 and 39,020 patients who did not have any or had only 1 comorbidity of the CHA2DS2-VASc scheme except for age and sex. Patients with previous history of ischemic stroke or transient ischemic attack were not included. The diagnostic accuracies of important comorbidities using the ICD-9-CM codes in NHIRD, such as hypertension, diabetes mellitus, heart failure and myocardial infarction have been validated previously.19 The flowchart of study design and patient enrollment is shown in Figure 1.

The clinical endpoint was the occurrence of ischemic stroke with concomitant imaging studies of the brain, such as computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in Taiwan’s NHIRD has been reported to be around 94%.19 Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively.20

*Assessments of annual risk of ischemic stroke in different age strata*

We assessed the risk of ischemic stroke using 3 different approaches [see Figure 1] which were different from each other regarding the definitions of the age when ischemic stroke occurred and whether patients were censored when they acquired incident comorbidities during the follow up. In all three kinds of assessments, patients were censored when OACs were prescribed before the occurrence of ischemic stroke, mortality or the end of follow up.

**Method 1 Conventional assessment** - Patients were not censored when they acquired new comorbidities before the occurrence of ischemic stroke or mortality or December 31, 2011. The occurrence of ischemic stroke was related to “baseline age” when AF was diagnosed even the stroke happened several years later (similar to an ‘intention to treat’ approach).

**Method 2 Dynamic assessment** - Patients were censored when they acquired new comorbidities before the occurrence of ischemic stroke or mortality or December 31, 2011. The occurrence of ischemic stroke was related to “baseline age” when AF was diagnosed even the stroke happened several years later.

**Method 3 Ideal assessment** - Patients were censored when they acquired new comorbidities before the occurrence of ischemic stroke or mortality or December 31, 2011. The occurrence of ischemic stroke was related to the ‘actual age’ when the ischemic stroke occurred, rather than ‘baseline age’.

*Examples of the impacts of different methods of assessments on stroke risk*

The examples of the impacts of different methods of assessments on stroke risk are shown in Figure 2. Consider a 50 year old male with newly-diagnosed AF having a CHA2DS2-VASc score of 1 due to hypertension at baseline who experienced ischemic stroke at age 62 years. There are 2 different scenarios described as follows:

**Scenario 1** - The patient did not acquire new comorbidities before the occurrence of ischemic stroke (Figure 2A): The CHA2DS2-VASc score of the patient was still 1 when he experienced ischemic stroke at age 62 years. All three kinds of assessments would correctly calculate the risk of ischemic stroke as a CHA2DS2-VASc score of 1, due to hypertension as the sole risk factor; however, only the “ideal assessment” could correctly assign the stroke risk to the correct age (62 years) and age strata (60-64 years).

**Scenario 2** - The patient acquired new comorbidities before the occurrence of ischemic stroke (Figure 2B): Since the patients developed incident diabetes mellitus when he was 56 years old and experienced ischemic stroke at age 62 years, the CHA2DS2-VASc score would be 2 when the stroke occurred. However, using the ‘conventional method’, this patient was not censored when he got diabetes, and therefore, the risk of ischemic stroke would be “incorrectly” attributed to a CHA2DS2-VASc score of 1. Besides, the occurrence of ischemic stroke would also “incorrectly” be attributed to the ‘wrong’ age (50 years) rather than 62 years. On the contrary, this patient would be censored when he developed diabetes using the dynamic or ideal assessment methods, and the incorrect attribution of the stroke risk to a CHA2DS2-VASc score of 1 could be avoided.

According to the example scenarios described above, the use of “ideal assessment” would be able to analyze the risk of ischemic stroke correctly, and would more accurately provide age thresholds for initiations of NOACs and guide clinical decision making for AF patients with one comorbidity.

*The“tipping point” of NOACs for stroke prevention*

In an analysis of the “tipping point” of NOACs for stroke prevention using a decision analytic model, Eckman et al. estimated the threshold of ischemic stroke risk below which NOACs should be withheld and above which NOACs should be prescribed.11 The results demonstrate that anticoagulation with NOACs is preferred at a stroke rate of above 0.9% per year.11 Therefore, AF patients with an annual risk of ischemic stroke higher than 0.9% in our study cohort would be assumed to be candidates for using NOACs for stroke prevention.

*Statistical analysis*

Data are presented as the mean value and standard deviation (SD) for normally distributed continuous variables and proportions for categorical variables. Incidence rates of ischemic stroke of AF patients were calculated by dividing the number of events by person-time at risk, with the 95% confidence interval (CI) estimated by exact Poisson distribution. The incidence rate ratio (IRR) was used to compare the incidence of ischemic stroke analyzed using conventional way compared to dynamic or ideal method.

**Results**

Table 1 summarizes the baseline characteristics of study cohort, where our study population (n=70,059) had a mean age of 67.7 years (SD 15.7), with 64.3% being age ≥65 years. Mean baseline CHA2DS2-VASc score was 2.01 (SD 1.19). Among the population with one comorbidity, hypertension was the most prevalent systemic disease which was noted in 53.6% of patients followed by heart failure (30.2%), diabetes mellitus (11.1%) and vascular diseases (5.3%). The clinical characteristics of patients *without any* or w*ith only 1 comorbidity* of the CHA2DS2-VASc score - except for age and sex - who were excluded from the analysis due to the treatments with antiplatelet agents or OACs at baseline are shown in Supplemental Table 1.

Among the patients without comorbidities of the CHA2DS2-VASc score except for age and gender (n = 31,039), 3,868 suffered an ischemic stroke during the total follow up of 165,015 person-years, with an incidence of 2.34%/year using the conventional assessment method (Table 2). When the dynamic or ideal assessments were performed, the number of ischemic strokes was 1,460, with an incidence of 1.45%/year; thus, 2,408 (62.3%) events occurred at the time point after patients acquired new comorbidities. Therefore, the estimated stroke risk for patients without comorbidities would be inappropriately overestimated (IRR = 1.61, 95%CI = 1.52–1.71; p<0.001) if we focused on baseline risk status only.

Table 2 and Supplemental Figure 1 summarizes the risks of ischemic stroke in different age strata using different methods of assessments for patients without comorbidities at baseline, which clearly demonstrates that the conventional or dynamic assessments could overestimate the true risk of ischemic stroke. With *conventional assessment,* the age range 50-54 is where the ischemic stroke rate was 1.29 (1.10-1.47) per 100 person-years. With a *dynamic assessment* method, the age range with ischemic stroke rate >0.9%/year was 55-59 where the ischemic stroke rate was 1.03 (0.82-1.25). For the *ideal assessment*, the age threshold for the tipping point for NOAC use is age 60-64 (Table 2).

*Impact of different stroke risk factors*

Table 3 shows the risk of ischemic stroke in different age strata using different methods of assessment for patients with *hypertension*. The incidence of ischemic stroke was 3.79% per 100 person-years using the conventional way, which is higher than that of the dynamic or ideal methods of assessments (3.07 per 100 person-years; IRR = 1.24, 95%CI = 1.17–1.31; p<0.001). For conventional, dynamic and ideal assessment approaches, the tipping point age ranges for the 3 methods were 40-44, 40-44 and 50-54, respectively.

Table 4 shows the risk of ischemic stroke in different age strata using different methods of assessment for patients with *heart failure*. The incidence of ischemic stroke was 3.98% per 100 person-years using the conventional way which was higher than using the dynamic or ideal methods of assessments (3.27 per 100 person-years; IRR = 1.22, 95%CI = 1.12–1.32; p<0.001). This shows that irrespective of method of assessment, the tipping point age strata was 35-39, where the ischemic stroke rate was >0.9 per 100 person-years.

Table 5 shows the risk of ischemic stroke in different age strata using different methods of assessment for patients with *diabetes mellitus*. The incidence of ischemic stroke was 4.20% per 100 person-years using the conventional way, which was higher than that of dynamic or ideal methods of assessments (3.07 per 100 person-years; IRR = 1.37, 95%CI = 1.19–1.57; p<0.001). The tipping point age strata using the conventional, dynamic and ideal assessment approaches were 40-44, 45-49 and 50-54 years, respectively.

Table 6 shows the risk of ischemic stroke in different age strata using different methods of assessment for patients with *vascular diseases*. The incidence of ischemic stroke was 2.35% per 100 person-years using the conventional method, which is higher than that of dynamic or ideal methods of assessments (1.73 per 100 person-years; IRR = 1.35, 95%CI = 1.08 – 1.70; p = 0.007). The tipping point age strata for conventional, dynamic and ideal assessment approaches were 45-49, 50-54 and 55-59 years, respectively.

*Age thresholds for initiating NOACs*

The age thresholds for the use of NOACs for stroke prevention in patients with or without comorbidities except for age and sex using different methods of assessment are summarized in Figure 2. According to the stroke risk analyzed using the ideal assessment, NOACs should be considered for patients age > 60 years without other comorbidities of the CHA2DS2-VASc score. Age treatment thresholds for NOACs in AF patients with heart failure, hypertension, diabetes mellitus, and vascular diseases were 35, 50, 50 and 55 years, respectively.

**Discussion**

In this nationwide cohort study, our principal findings are as follows : (i) ischemic stroke risk in AF is heterogeneous, depending on risk factor type; (ii) conventional risk assessment based on baseline risk *per se* may overestimate ischemic stroke risk, while use of the ideal method may provide better and more accurate assessment of the age threshold when NOAC use should be considered; (iii) for heart failure, the age tipping point (35 years) of NOAC was similar, irrespective of methods for stroke risk assessment; (iv) with age, hypertension, diabetes mellitus and vascular disease per se, the age thresholds for the use of NOACs were 60, 50, 50 and 55 years, respectively. The key messages of the present study are summarized in the central illustration.

Unsurprisingly, ischemic stroke risk in AF is heterogeneous, depending on particular risk factors. This is evident from previous studies examining stroke risk with one non-gender CHA2DS2-VASc risk factor.4,5 Also, recent papers have highlighted the diverse range of reported stroke rates for a given CHA2DS2-VASc score point, refelcting the different study settings, methodology, population studied, etc.9,21 The present analysis extends prior studies by reporting the tipping point threshold for offering NOACs for stroke prevention in AF.

One prior study has shown how heart failure is a powerful driver of stroke risk even in young AF patients.22 Indeed, our study shows how if heart failure is present, the tipping point threshold is the same (35 years) irrespective of methods used for stroke risk assessment. Of note, we have previously reported that recent decompensated heart failure is a risk factor for stroke, irrespective of the ejection fraction.23 Thus, the “C” in CHA2DS2-VASc includes both heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF).23 Hence the present analysis reaffirms these data, showing that the presence of heart failure confers a high stroke risk, and as Chan et al. show,22 this is evident even in young age strata.

Our study also shows how conventional assessment based on baseline risk and age per se may overestimate ischemic stroke risk, while use of the dynamic or ideal methods may provide better assessment of the tipping point of ischemic stroke where NOAC use would have a postive net clinical benefits. Indeed, baseline risk is probably a misleading assessment of subsequent stroke risk, given that risk is dynamic, and AF patients get older with age and risk increases with the accumulation of stroke risk factors.12

As an *illustrative example* is for a male AF patient who was enrolled at a baseline age of 50 years with hypertension only (CHA2DS2-VASc score 1), and he acquires diabetes when he is aged 56 years old (CHA2DS2-VASc score increased to 2) and suffers from an ischemic stroke when age 62 years. In this patient, if we rely on the conventional or dynamic assessments, the reported risk for AF males with a CHA2DS2-VASc score of 1 (due to hypertension) in the age strata of 50 years will count this patient, and the reported event rate is thus misleading and overestimated. On the contrary, a ideal approach we investigated in the present study in which patients were censored when new comorbidities developed and the stroke risk was related to the acual age when ischemic stroke occurred would represent a more precise method to ascertain the stroke risk which could be properly attributable to a given comorbidity and age strata.

In the present study, we also demonstrated that the annual risk of ischemic stroke was higher than 0.9% for patients aged >60 years without other comorbidities assessed using the ideal method. Given the better safety of NOACs compared to warfarin, further studies are necessary to investigate whether the definition of age (A) criterion of the CHA2DS2-VASc score should be reduced to 60 rather than 65 years, especially for Asian AF patients.

*Clinical Implications*

Our study clearly reaffirms the well-accepted concept that age is an important driver of ischemic stroke for AF patients. No matter which kinds of comorbidities the patients had, the risks of ischemic stroke increased in older age strata. Therefore, physicians should ideally also consider the age of patients having a single CHA2DS2-VASc risk factor [ie, score of 1 (male) or 2 (females)] when determining the use of NOACs for stroke prevention or not. Although the 2016 AF guidelines of European Society of Cardiology suggest that OACs should be considered for AF patients with a CHA2DS2-VASc score of 1 for males and 2 for females (Class IIa recommendation),2 the clinical dilemma is that should NOACs be prescribed for the young population (e.g. a 30-year-old male/female with hypertension only).

Even for physicians determined to only prescribe NOACs for “older” patients with single risk factor, the appropriate age threshold is also unclear. According to the stroke risks we reported using the “ideal assessment”, the age thresholds for the use of NOACs for AF patients having one additional risk factor beyond sex are 35, 50, 50 and 55 years for heart failure, hypertension, diabetes, and vascular disease, respectively. These findings may provide useful guidance about the optimal stroke prevention strategy for this particular AF population (with one non-sex risk factor) given the reported wide ranges of stroke risk were diverse in previous reports and where debates exist regarding the use of OAC.

*Study limitations*

There are several limitations of the present study, First, this study is based on a nationwide cohort study based on the Taiwan NHIRD, and may be limited by errors of coding. However, this is a well validated dataset, where the diagnoses of AF, stroke and other risk factors are well validated.18-20,24 Second, patients without or with only 1 comorbidity of the CHA2DS2-VASc score except for age and sex who already received antiplatelet agents or OACs at baseline (n = 41,300) were excluded from our analysis. Although some selection biases were possibly present, the CHA2DS2-VASc score of the study population was similar to that of patients excluded (2.01 versus 1.96), and therefore, the results we presented here may not be significantly confounded. Third, we did not consider the impact of lifestyle modificatons, rhythm control via catheter ablations and optimal management of comorbidities on the long-term stroke risk of our patients. Fourth, the present study only enrolled Asian patients whose stroke risk was probably higher than that of non-Asians. In two large-scale cohort studies, the annual stroke risks for patients with a CHA2DS2-VASc score of 0 were 1.15% and 2.41% in the Taiwan and Hong Kong cohorts, respectively.13,25 These reported stroke risks for Asians were higher than that of other registry studies which mainly enrolled Caucasians, with reported stroke risks ranging from 0.04% to 0.66% per year.26 The consistently higher risk of ischemic stroke in Asians compared to non-Asians was also noted in patients who received NOACs in the randomized trials (*eg.* 2.05%/year versus 1.14%/year in RE-LY (110 mg BID); 2.12%/year versus 1.59%/year in ROCKET-AF; 2.52%/year versus 1.12%/year in ARISTOTLE).27-29 Therefore, whether the results can be extrapolated to other ethnic populations remains uncertain. Fifth, we did not further separate patients with vascular disease into prior myocardial infarction or peripheral arterial diseases, since the numbers of patients and events in some age strata were small, and thus the calculated annual risk of stroke could be significantly confounded. Finally, the age thresholds we proposed for the initiations of NOACs were based on the “tipping point” reported by a single study,11 which did not consider the use of different NOACs and the increasing risk of bleeding for older patients or those with renal dysfunction. Based on these limitations, the age thresholds for the initiations of NOACs we proposed should be regarded as hypothesis generating and further studies are necessary to confirm our findgins.

**Conclusion**

Ischemic stroke risk in AF is heterogeneous, depending on different risk factors with age being as an important driver of stroke risk. Age thresholds for the use of NOACs were different for AF patients having different single risk factors beyond sex despite the same CHA2DS2-VASc score point (1 for males and 2 for females); that is, 35 years for heart failure, 50 years for hypertension and diabetes, and 55 years for vascular diseases. Further studies are necessary to confirm these findings.

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**Disclosures**

None

**References**

**1.** January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, Members AATF. 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.

**2.** Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-2962.

**3.** Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T, Saxena A, Takahashi Y, Siong Teo W. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. *Journal of arrhythmia* 2017;33:345-367.

**4.** Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol* 2015;65:635-642.

**5.** Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, Babuty D, Lip GY. Oral Anticoagulation and the Risk of Stroke or Death in Patients With Atrial Fibrillation and One Additional Stroke Risk Factor: The Loire Valley Atrial Fibrillation Project. *Chest* 2016;149:960-968.

**6.** Fauchier L, Clementy N, Bisson A, Ivanes F, Angoulvant D, Babuty D, Lip GY. Should Atrial Fibrillation Patients With Only 1 Nongender-Related CHA2DS2-VASc Risk Factor Be Anticoagulated? *Stroke* 2016;47:1831-1836.

**7.** Lip GY, Skjoth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am Coll Cardiol* 2015;65:1385-1394.

**8.** Friberg L, Skeppholm M, Terent A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J Am Coll Cardiol* 2015;65:225-232.

**9.** Quinn GR, Severdija ON, Chang Y, Singer DE. Wide Variation in Reported Rates of Stroke Across Cohorts of Patients With Atrial Fibrillation. *Circulation* 2017;135:208-219.

**10.** Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Liao JN, Chen TJ, Chiang CE, Lip GY, Chen SA. Age Threshold for Increased Stroke Risk Among Patients With Atrial Fibrillation: A Nationwide Cohort Study From Taiwan. *J Am Coll Cardiol* 2015;66:1339-1347.

**11.** Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;4:14-21.

**12.** Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2018;71:122-132.

**13.** Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. *J Am Coll Cardiol* 2014;64:1658-1665.

**14.** Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Chen SA. Rate-control treatment and mortality in atrial fibrillation. *Circulation* 2015;132:1604-1612.

**15.** Chao TF, Liu CJ, Liao JN, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Chen TJ, Lip GY, Chen SA. Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage. *Circulation* 2016;133:1540-1547.

**16.** Chao TF, Liu CJ, Tuan TC, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Hsieh MH, Lip GY, Chen SA. Impact on Outcomes of Changing Treatment Guideline Recommendations for Stroke Prevention in Atrial Fibrillation: A Nationwide Cohort Study. *Mayo Clin Proc* 2016;91:567-574.

**17.** Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, Chen SA. Lifetime Risks, Projected Numbers, and Adverse Outcomes in Asian Patients With Atrial Fibrillation: A Report From the Taiwan Nationwide AF Cohort Study. *Chest* 2018;153:453-466.

**18.** Chang CH, Lee YC, Tsai CT, Chang SN, Chung YH, Lin MS, Lin JW, Lai MS. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. *Atherosclerosis* 2014;232:224-230.

**19.** Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf* 2011;20:236-242.

**20.** Hsieh CY, Chen CH, Li CY, Lai ML. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *Journal of the Formosan Medical Association* 2015;114:254-259.

**21.** van Doorn S, Debray TPA, Kaasenbrood F, Hoes AW, Rutten FH, Moons KGM, Geersing GJ. Predictive performance of the CHA2DS2-VASc rule in atrial fibrillation: a systematic review and meta-analysis. *J Thromb Haemost* 2017;15:1065-1077.

**22.** Chan YH, Wu LS, Chang SH, Lee HF, Liu JR, See LC, Yeh YH, Kuo CT. Young Male Patients with Atrial Fibrillation and CHA2DS2-VASc Score of 1 May Not Need Anticoagulants: A Nationwide Population-Based Study. *PloS one* 2016;11:e0151485.

**23.** Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. *Eur J Heart Fail* 2012;14:295-301.

**24.** Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. *Journal of the Formosan Medical Association* 2005;104:157-163.

**25.** Siu CW, Lip GY, Lam KF, Tse HF. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm* 2014;11:1401-1408.

**26.** Nielsen PB, Chao TF. The risks of risk scores for stroke risk assessment in atrial fibrillation. *Thromb Haemost* 2015;113:1170-1173.

**27.** Hori M, Connolly SJ, Zhu J, Liu LS, Lau CP, Pais P, Xavier D, Kim SS, Omar R, Dans AL, Tan RS, Chen JH, Tanomsup S, Watanabe M, Koyanagi M, Ezekowitz MD, Reilly PA, Wallentin L, Yusuf S, Investigators R-L. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. *Stroke* 2013;44:1891-1896.

**28.** Wong KS, Hu DY, Oomman A, Tan RS, Patel MR, Singer DE, Breithardt G, Mahaffey KW, Becker RC, Califf R, Fox KA, Berkowitz SD, Hacke W, Hankey GJ, Executive Steering C, the RAFSI. Rivaroxaban for stroke prevention in East Asian patients from the ROCKET AF trial. *Stroke* 2014;45:1739-1747.

**29.** Goto S, Zhu J, Liu L, Oh BH, Wojdyla DM, Aylward P, Bahit MC, Gersh BJ, Hanna M, Horowitz J, Lopes RD, Wallentin L, Xavier D, Alexander JH, Investigators A. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: a subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *Am Heart J* 2014;168:303-309.

**Figure Legends**

**Figure 1. Flow chart of the patient enrollment.** From January 1, 1996 to December 31, 2009, a total of 299,902 AF patients with age ≥ 20 years were identified as the study population. Among the study population, there were 159,999 patients without use of antiplatelet agents or oral anticoagulants. The study cohort included 31,039 and 39,020 patients who did not have any or had only 1 comorbidity of the CHA2DS2-VASc scheme except for age and sex. Patients with previous history of ischemic stroke or transient ischemic attack were not included. The risk of ischemic stroke in each age strata for each comorbidities were analyzed using 3 different methods of assessments.

AF = atrial fibrillation; NHIRD = National Health Insurance Research Database

**Figure 2. Examples of the impacts of different methods of assessments on stroke risk.** Take a 50 y/o male with newly-diagnosed AF having a CHA2DS2-VASc score of 1 due to hypertension at baseline who experienced ischemic stroke at age 62 years for example. **Scenario 1** - The patient did not acquire new comorbidities before the occurrence of ischemic stroke (Figure 2A): The CHA2DS2-VASc score of the patient was still 1 when he experienced ischemic stroke at age 62 years. All three kinds of assessments would correctly calculate the risk of ischemic stroke as a CHA2DS2-VASc score of 1, due to hypertension as the sole risk factor; however, only the “ideal assessment” could correctly count the stroke risk to a correct age (62 years) and age strata (60-64 years). **Scenario 2** - The patient acquired new comorbidities before the occurrence of ischemic stroke (Figure 2B): Since the patients developed incident diabetes mellitus when he was 56 years old and experienced ischemic stroke at age 62 years, the CHA2DS2-VASc score would be 2 when the stroke occurred. However, using the ‘conventional method’, this patient was not censored when he got diabetes, and therefore, the risk of ischemic stroke would be “incorrectly” attributed to a CHA2DS2-VASc score of 1. Besides, the occurrence of ischemic stroke would also “incorrectly” be attributed to the ‘wrong’ age (50 years) rather than 62 years. On the contrary, this patient would be censored when he developed diabetes using the dynamic or ideal assessment methods, and the incorrect attribution of the stroke risk to a CHA2DS2-VASc score of 1 could be avoided.

\*The patient was censored when he acquired incident DM before the occurrence of ischemic stroke

AF = atrial fibrillation; DM = diabetes mellitus; HTN = hypertension; N/A = not applicable

**Figure 3. Age threshold for the initiation of NOACs according to different methods of the risk assessment.** According to the stroke risk analyzed using the ideal assessment, NOACs should be considered for patients aged > 60 years without other comorbidities of the CHA2DS2-VASc scheme. The age thresholds for patients with heart failure, hypertension, diabets, and vascular diseases are 35, 50, 50 and 55 years, respectively.

DM = diabetes mellitus; HF = heart failure; HTN = hypertension; NOACs = non-vitamin K antagonist oral anticoagulants