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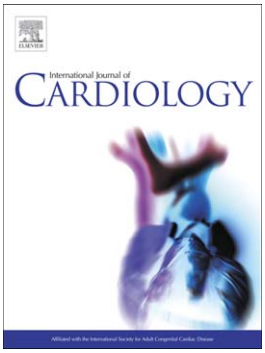

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Stroke risk reduction with oral anticoagulation using CHA_2DS_2-VASc in a Japanese AF population: a modeling analysis

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Abstract

Background Current clinical guidelines recommend that risk stratification for ischaemic stroke in patients with nonvalvular AF (NVAF) should be performed using the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years [double], Diabetes mellitus, previous thromboembolism [double], Vascular disease, Age 65-74 years, and female gender) to aid decision making for antithrombotic treatment, with a preference for Non-Vitamin K Oral Anticoagulants (NOACs) in those with CHA_2DS_2-VASc score ≥1. However, CHA_2DS_2-VASc score is not recommended in the 2014 Japanese Circulation Society (JCS) guidelines for patients with NVAF.

Methods To assess the impact of the JCS approach to stroke prevention in AF, and model the impact of using a CHA_2DS_2-VASc based 2-step decision making strategy, we calculated the incidence of ischaemic stroke in NVAF patients without OAC on basis of the $CHADS_2$ and CHA_2DS_2-VASc scores using published Japanese data, and estimated the preventable number of stroke events.

Results Using a CHA_2DS_2-VASc-based approach, the potential annual stroke events based on the estimated total number of NVAF patients in Japan was 889000, as follows: 4369 for dabigatran 150mg, 6049 for dabigatran 110mg, 5918 for rivaroxaban (intention-to-treat; ITT), 5302 for apixaban, 5843 for edoxaban 60mg (ITT), 7598 for edoxaban 30mg (ITT), respectively. Using a $CHADS_2$ score-based approach, the number of potential stroke events was much greater for each agent.

Conclusion Our modelling analysis has shown that when considering antithrombotic treatment for Japanese NVAF patients, using a CHA_2DS_2-VASc-based approach would allow greater opportunities for stroke prevention.

Keywords Dabigatran, rivaroxaban, apixaban, edoxaban, atrial fibrillation, stroke prevention

Introduction

The vitamin K antagonists (VKA, e.g. warfarin) were traditionally the only available oral anticoagulants (OAC) for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF), but more recently three non-VKA oral anticoagulants (NOACs), dabigatran, rivaroxaban and apixaban have become licensed for stroke prevention in AF, with a fourth, edoxaban, on the horizon, subject to regulatory approval. [1 2 3 4]

Treatment guidelines have evolved to reflect the availability of NOACs. The European Society of Cardiology (ESC) [5] and National Institute for Health and Care Excellence guidelines (NICE) [6] recommend a simple 2-step approach: first, to initially focus on the identification of low risk patients (essentially CHA_2DS_2-VASc score [Congestive heart failure, Hypertension, Age ≥ 75 years {double}, Diabetes mellitus, previous thromboembolism {double}, Vascular disease, Age 65–74 years, and female gender] =0 if male, 1 if female) who do not need any antithrombotic therapy; step 2 is to offer OAC to all other AF patients with ≥1 additional stroke risk factors, whether as a NOAC or well controlled VKA.

In Japan, the Japanese Circulation Society (JCS) guidelines have focused on using the older $CHADS_2$ score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack [double]), and do not operationalize a stepwise approach to OAC management decisions. The JCS guidelines recommend OAC in high-risk patients with a $CHADS_2$ score ≥2; 'prefer' the use of dabigatran or apixaban for those at intermediate-risk ($CHADS_2$ score=1); and for 'other risk factors' (age 65-74, cardiomyopathy, vascular disease)' OAC may be considered [7] .

The net clinical benefit (NCB) of OACs has been studied in 'real world' populations in Western countries, where a positive net clinical benefit, balancing stroke against serious bleeding, is evident for patients with a CHA_2DS_2-VASc score of ≥1. [8,9] Modelling NOAC data use provides evidence of even greater NCB. [10] There are currently no data on the potential impact on stroke reduction in Japan by using a CHA_2DS_2-VASc score management approach (as opposed to the $CHADS_2$ score used within the JCS guidelines) to aid OAC-decision making.

Given the benefit of OACs even in patients with ≥ 1 stroke risk factors, we performed a modeling analysis to investigate stroke events associated with the different OACs and compared the approach to stroke risk stratification based on the 2014 JCS guidelines approach (based on the $CHADS_2$ score) and the ESC guidelines approach (based on CHA_2DS_2-VASc score), using event rates from a previously published cohort of non-anticoagulated Japanese patients with NVAF [11]. The focus of the modeling analysis is to highlight the missed opportunities for stroke prevention with OACs by using the $CHADS_2$ score instead of the CHA_2DS_2-VASc score, with reference to the 2014 JCS guideline as an illustrative example.

Methods

Our modeling approach is summarized in Figure 1. The 'base case' study population used for our model was published data[11] regarding all patients with NVAF who did not receive OAC therapy during the study period from 1995 to 2008. Detailed medical history, including pharmacotherapy, and baseline risk stratification scores for ischaemic stroke/thromboembolism (IS/TE) based on the $CHADS_2$ [12,13] and CHA_2DS_2-VASc [14] scores, were available for all patients.

Model assumptions

The event rates per 100 person years for IS/TE (Table 1) were calculated using data from the published paper by Komatsu et al.[11] for patients on no treatment, stratified by stroke risk as predicted by the $CHADS_2$ [13] and CHA_2DS_2-VASc scores. [14] These data were compared with the studies of Siu et al. [15], Guo et al. [16] and Lip et al. [14]

In the study by Siu et al. [15], a total of 10,195 Chinese patients with a diagnosis of AF were identified from a computer- based hospital clinical management system. Patients were excluded if they had significant valvular heart disease including previous valvular surgery, valvular disease with planned surgical correction, and any degree of mitral stenosis, or incomplete clinical and/or follow-up data.

In the study by Guo et al. [16], patients with AF admitted to the PLA General Hospital were eligible for this study. Inclusion criteria were a pre-existing diagnosis of permanent, persistent, or paroxysmal AF, development of new-onset AF during their current admission (defined on having an ECG or Holter recording).

In the study by Lip et al. [14], detailed survey methods, center participation, patient characteristics, management and definitions of the baseline and follow-up survey of the Euro Heart Survey on AF have previously been described. [17] [18] In summary, 5,333 ambulant and hospitalized patients with AF were enrolled from the cardiology practices of 182 hospitals in 35 European countries. Patients were enrolled if they were ≥ 18 years old and if they had an ECG or Holter recording showing AF during the qualifying admission/consultation or in the preceding 12 months.

By using data from Komatsu et al.[11], the estimated event rates and the number of IS/TE events were estimated for a hypothetical Japanese AF population of n=100,000 (Table 2). Using data from recent trials of the NOACs, the potentially preventable stroke events were calculated in this population (Table 3).

For this model, the relative risks of IS/TE with the NOACs compared to warfarin were assumed to be 0.65 for dabigatran 150 mg bid [1], 0.90 for dabigatran 110 mg bid [1], 0.88 for rivaroxaban (intention-to-treat [ITT] analysis) [2], 0.79 for apixaban [3], 0.87 for edoxaban 60mg (ITT analysis) [4] and 1.13 for edoxaban 30mg (ITT analysis). [4]

The relative risks of IS/TE were assumed to be constant across all categories of stroke risk. On the basis of the general prevalence of AF in the Japanese (0.56%) in 2003 [19], we estimated that a population prevalence of AF in Japan for 2014 to be 0.7% (n=889,000), given that the prevalence of AF in Japan might be increased in its ageing society. The total population of Japan was assumed about 127,000,000 based on the recent world population review. [20] In the paper of Komatsu et al.[9], the overall observed stroke rate was 2.1%/year. Using these estimated figures, we modeled the potential stroke events in the total AF population for the whole of Japan, and we compared the impact of the JCS approach to stroke prevention in AF, with the simple CHA_2DS_2-VASc based 2-step decision making strategy advocated by the ESC and NICE guidelines.

Results

Table 1 shows the event rates for IS in Siu et al. [15] and Guo et al. [16], and IS/TE in Komatsu et al. [11] and Lip et al. [14] per 100 person years based on CHA_2DS_2-VASc and $CHADS_2$ scores, which show broad comparability between these different populations for a given risk score value. Assuming that the Japanese AF population numbers 100,000, the estimated number of IS/TE events on no treatment was calculated by using the event rates of IS/TE based on Komatsu study (Table 2).

Whilst on warfarin, the risk reduction (RR) of overall event rates is 0.36 (95% confidential interval [CI]; 0.26-0.51) from no treatment, saving 64% of IS/TE events (1320.5/2063.3) by using CHA_2DS_2-VASc score, while saving 53.2% (1236.3/2321.5) by using the $CHADS_2$ score (Table 3).

In our model, the risk reduction of IS/TE events in all of the NOACs are compared with warfarin, with dabigatran 150 mg bid (twice daily) having the highest reduction of 76.6% (1580.5/2063.3) compared to no treatment, and 74.2% (1721.9/2321.5) by using $CHADS_2$ score.

Application of treatment guidelines based on the CHA_2DS_2-VASc score and the ESC/NICE management decision approach, stroke reductions would be 67.6% (1394.8/2063.3) on dabigatran 110mg bid, 68.3% (1409.6/2063.3) on rivaroxaban (ITT), 71.6% (1476.5/2063.3) on apixaban, 68.7% (1471.1/2063.3) on edoxaban 60mg od (once daily) (ITT) and 59.3% (1223.9/2063.3) on edoxaban 30mg od (ITT) compared to no treatment.

Using treatment based on the $CHADS_2$ score and JCS guideline approach, the reductions would be 65.5% (1519.7/2321.5) on dabigatran 110mg bid, 56.9% (1319.8/2321.5) on rivaroxaban, 69.3% (1608.6/2321.5) on apixaban, 57.2% (1326.7/2321.5) on edoxaban 60mg od and 49.4% (1145.9/2321.5) on edoxaban 30mg od from no treatment, respectively.

We modeled these figures to potential stroke events among total AF population in Japan (n=889000) by using CHA_2DS_2-VASc score and $CHADS_2$ scores as follows: 4369 and 4817 for dabigatran 150mg bid, 6049 and 6448 for dabigatran 110mg bid, 5918 and 8056 for rivaroxaban (intention-to-treat; ITT), 5302 and 5731 for apixaban, 5843 and 8000 for edoxaban 60mg od (ITT), 7598 and 9454 for edoxaban 30mg od (ITT), respectively.

In every case, whether using warfarin or NOACs, prescribing OAC treatment based on the CHA_2DS_2-VASc score and the ESC/NICE management decision approach was modelled to have a numerically greater benefit for stroke prevention, as shown in Figure 2.

Discussion

In this analysis, we present a modelling analysis showing that when consider antithrombotic treatment for Japanese AF patients, using a CHA_2DS_2-VASc-based approach advocated by the European and NICE guidelines would allow greater opportunities for stroke prevention (especially with the NOACs). Many international guidelines (eg ACCP, Canadian, etc) are still based the older $CHADS_2$ score, and our paper – whilst focused on the 2014 JCS guidelines - provides important learning points on missed opportunities for stroke prevention that would be generalizable to clinical practice outwith Japan.

In the 2014 JCS guidelines[7], the $CHADS_2$ score is recommended to evaluate whether patients with nonvalvular AF have stroke risk, and all NOACs and warfarin are recommended for patients with at least 2 risk factors (if the same indication, NOACs are preferable). Dabigatran and apixaban are recommended for patients with one risk factor (ie $CHADS_2$ score=1), given the evidence in their respective trials; indeed, Banerjee et al [10] concluded that NOACs (dabigatran, apixaban) have a positive net clinical benefits in patients with a CHA_2DS_2-VASc score=1 at high risk of bleeding and stroke, and these drugs were shown to be superior (150mg bid dabigatran, apixaban) to warfarin in the prevention of stroke and have a lower risk of intracranial haemorrhage (ICH) than warfarin. On the other hand, rivaroxaban and edoxaban can be considered for those patients since the effect and safety of rivaroxaban and edoxaban were evaluated in those trials only in patients with $CHADS_2$ score of ≥ 2. In patients with a $CHADS_2$ score of 0, no treatment is recommended in the JCS guidelines, but all OACs may be considered when patients have at least one of other risk factors (cardiomyopathy, 65 to 74 years of age, vascular disease).

Why does the JCS guideline use the $CHADS_2$ score for risk stratification in AF patients, and not use CHA_2DS_2-VASc score? In a recent Editorial, the CHA_2DS_2-VASc score was considered 'more complicated' than $CHADS_2$ score for Japanese clinicians [21]. Nonetheless, risk stratification based on $CHADS_2$ score itself might not be even widespread in clinical practice in Japan. Also, all clinical trials of NOACs were based on the $CHADS_2$ score. In the JCS guideline [7], the non-$CHADS_2$ risk factors of 'Cardiomyopathy', 'Age of 65 to 74 years' and 'vascular disease' are defined as 'other risk factors'. These risk factors are essentially the 'A' and 'V' criteria of the CHA_2DS_2-VASc score, and cardiomyopathy is included within the 'C' criteria of CHA_2DS_2-VASc. However, OAC is only 'treatment to be considered' rather than being fully recommended.

Therefore, this modeling analysis could provide us with more useful information on the optimal approach to stroke in Japanese AF patients. Indeed, CHA_2DS_2-VASc score may be more simpler for clinicians in stroke prevention for Japanese AF patients, and this score is already currently recommended in the other guidelines, ESC [5], Asia Pacific Heart Rhythm Society (APHRS) guidelines [22], American Heart Association/American College of Cardiology (AHA/ACC) [23] and National Institute for Health and Care Excellence (NICE) [6].

What do current international guidelines say? Table 4 summarises several guidelines for antithrombotic therapy in NVAF, that is, the ESC 2012 [5], APHRS 2013 [22], AHA/ACC/HRS 2014 [23], NICE 2014 [6], JCS 2014 [7] and Canadian Cardiovascular Society [CCS] 2014 [24]. The ESC guidelines[5] recommend the use of the CHA_2DS_2-VASc score in the assessment of all patients. In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with adjusted-dose VKA (INR 2-3), dabigatran, rivaroxaban or apixaban is recommended. In male patients with a CHA_2DS_2-VASc score of 1, OAC therapy with adjusted-dose VKA (INR 2-3), dabigatran, rivaroxaban or apixaban should be considered based on an assessment of the risk of bleeding complications and patient preferences. However, this guideline recommends no antithrombotic therapy for 'low risk' patients <65 years and without any risk factors (including females ie. CHA_2DS_2-VASc score of 0 (males) or 1 (females) since the absolute risk of stroke is low in this population. [25]

In the APHRS 2013 statement [22], patients are classified into 3 groups (patients with a CHA_2DS_2-VASc score of ≥2, 1, and 0). Patients with a CHA_2DS_2-VASc score of ≥2 should receive OAC (dabigatran, rivaroxaban, apixaban or warfarin), those with a score of 1 should preferentially receive NOACs (dabigatran or apixaban), and those with a score of 0 should receive no treatment. Rivaroxaban can be considered an alternative in patients with a score of 1 since the effect and safety of rivaroxaban were evaluated in the ROCKET AF trial only in patients with $CHADS_2$ score of ≥2. Similar to the ESC 2012 guideline, female patients with sex alone as a single risk factor (still a CHA_2DS_2-VASc score of 1) are low risk should be regarded as those with a score of 0.

In the 2014 AHA/ACC/HRS guidelines [23], the CHA_2DS_2-VASc score is recommended for assessment of stroke risk. For patients with prior stroke/TIA or CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants, warfarin (INR 2.0-3.0), dabigatran, rivaroxaban, or apixaban, are recommended. For patients with a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered. For patients with a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy.

The 2014 NICE guidelines [6] have also shifted towards initially identifying truly low risk patients who will not benefit from antithrombotic therapy (that is CHA_2DS_2-VASc score=0 for men or score= 1 for females), as the first decision step. Subsequent to this step, oral anticoagulation can be offered to patients with ≥1 additional stroke risk factors, taking bleeding into account. In contrast to other expert-consensus guidelines, the NICE guidelines are based on systematic reviews, evidence appraisal and cost effectiveness, with a multidisciplinary guideline development group that includes patient representatives.

The CCS Guidelines 2014 [24] recommends that OAC therapy be prescribed for most patients aged ≥ 65 years or $CHADS_2$ score ≥ 1. ASA (81 mg/d) can be prescribed for patients with age<65 years and no $CHADS_2$ risk factors who have arterial disease (coronary, aortic, or peripheral). No antithrombotic therapy should be recommended for patients with age < 65 and no $CHADS_2$ risk factors and free of arterial vascular disease. Similar to the JCS guideline, the CCS guideline 2014 also recommended use of the $CHADS_2$ score for stroke risk stratification. However, a recent analysis[26] shows that the 'OAC not recommended' subgroup based on the 2014 CCS guideline, can still have a high 1 year stroke rate overall (>4%/year) if untreated, showing that such patients are not 'low risk'.

In the present modeling analysis using the 2014 JCS guideline as an illustrative example, we report the current situation of using the $CHADS_2$ score and highlight the missed opportunities for stroke prevention by using the $CHADS_2$ score instead of the CHA_2DS_2-VASc score.

In the JCS guidelines, warfarin can be considered for stroke prevention in patients with $CHADS_2$ score=1, or '$CHADS_2$ score =0 and other risk factors', because it is unclear whether the benefit of stroke prevention overweighs the risk of bleeding in such these patients. Also, when warfarin is administered, it is recommended that a target internationalized normalized ratio (INR) of 2.0 to 3.0 be set in patients <70 years, whilst patients age >70 years should be maintained with an INR 1.6 to 2.6, since some Japanese data suggest that an INR less than 1.6 increases the incidence of serious cerebral infarction and an INR above 2.6 increases serious bleeding complications. [27] [28] An INR of 2.6-2.99 is also effective, but associated with a slightly increased risk in major haemorrhage. [29]

This target INR range in elderly Japanese is different to other non-Japanese studies, where bleeding risk starts to rise only from INRs >3.0 and at INRs <3.0, the risk is low and constant, rather than declining further. Indeed, many presentations of bleed events occur even when patients are within a therapeutic range of 2.0-3.0, and we recognize that it is the quality of INR control, as reflected by the average individual time in therapeutic range (TTR) is the more important parameter[30] [31]. Published studies from Asian population generally indicate a low TTR in these studies [32] [33] [34] [35].

When Asian and non-Asian patients receiving warfarin are compared, the risks of ischemic stroke, hemorrhagic stroke and major bleeding were twice higher in Asian than in non-Asian patients[36]. It is possible that a racial or genetic factor is involved in this difference, which has been pointed out for years, but we should also consider other factors because no such differences were observed in a comparison between Asian and non-Asian patients receiving dabigatran. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RELY) substudy, the low average INR value and the low TTR in Asian patients may be the biggest reasons for the higher risks of ischemic stroke and hemorrhagic stroke. The sub-analysis of the RE-LY trial [1] revealed that the percentage of patients with a mean INR of 2 to 3 was 68.9% and 56.5% in non-Asian and Asian patients, respectively. In the

same way, the percentage of patients with a mean INR of 2 to 3 was 55.2% and 52.4% in overall patients and Asian patients in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET) trial [2], 67% and 60% in non-Asian and Asian patients in Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [3], respectively.

Thus, these results suggest that Asian patients are not receiving optimally managed warfarin therapy. Additionally, TTR was generally lower in Asian countries compared to non-Asians [36]. Physicians in Japan should be encouraged to maintain TTR at an appropriate level (≥70%) even when elderly patients receive warfarin therapy. If so, warfarin can be prescribed for patients with a CHA_2DS_2-VASc score of ≥1 in Japanese population as described in the guidelines [22]. Indeed, guideline-adherent therapy is associated with much better outcomes in AF patients [37] [38].

Limitations

Whilst Komatsu et al paper[11] does reflect an everyday clinical practice observational cohort setting, this does not hold true for the randomised trials, and therefore, modeling the expected benefit of NOACs on the basis of trial outcomes may not be the same as if derived from a clinical registry of these. All the NOACs are powerful anticoagulants, and would work well if used correctly, and when used in the appropriate patients. We have also made no assumptions on quality of anticoagulation control with warfarin (as measured by the time in therapeutic range), which may be fairly variable in the cohorts and related to prognosis [39] [40]. Residual confounding may also be possible given the current comprehensive approach to stroke risk reduction in AF populations [41]. Second, although the numbers of patients were relatively small, the study period was long (mean 53 months), and the distribution of study patients showed broad comparability between these different populations for a given risk score value as described in Table 2. Therefore, in the absence of better published data, we decided that the study

by Komatsu et al. was reasonable enough to use for this modeling analysis. Moreover, according to a report from the J-RHYTHM registry, anticoagulant therapy is administered in more than 80% of patients with nonvalvular AF. [42] Therefore, it would be very difficult to find other contemporary data to model the natural incidence of ischemic stroke/systemic embolism in untreated Japanese patients with AF based on current clinical practice.

Third, the JCS guidelines recommends physician to prevent stroke by combination of $CHADS_2$ score and some consideration of 'other risk factors' (ie. cardiomyopathy, age 65-74 and vascular disease), and not soley on the $CHADS_2$ score per se. Therefore, stroke prophylaxis by using only $CHADS_2$ score, which is calculated in this modeling study, does not fully reflect the JCS guidelines. Fourth, female gender is not considered as independent risk factor for the incidence of stroke in Japanese NVAF patients, although the analysis was based in a largely anticoagulated registry cohort[43]. In contrast, female gender is an independent predictor for stroke in Chinese patients with nonvalvular AF and CHA_2DS_2-VASc score of ≤1 (HR: 2.3, 95% CI: 1.1–4.8) [44] . Moreover, Ogawa et al. recommended use of CHA_2DS_2-VASc score in stroke prevention in the 2013 APHRS statement[22]. Hence, further research is needed to explore the influence of female gender on the incidence of stroke, amongst Japanese patients.

Whilst the debate on whether using $CHADS_2$ score and other risk factors or simply using CHA_2DS_2-VASc score continues, both scoring systems have advantages and disadvantages[45]. However, we believe that the use of CHA_2DS_2-VASc score could make stroke prevention simple and consequently lead to the intial identification of "truly" low risk patients as a first step, following which effective stroke prevention can be offered to those with ≥1 additional stroke risk factors. Finally, we did not analyze the bleeding risk on antithrombotic therapy because there are no published Japanese papers regarding bleeding rates based on CHA_2DS_2-VASc score and HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly)[46]. Indeed, modeling the expected net clinical benefit of OACs would be informative in further studies of Japanese AF patients.

In conclusion, our modelling analysis has shown that when considering antithrombotic treatment for Japanese AF patients, using a CHA_2DS_2-VASc-based approach would allow greater opportunities for stroke prevention.

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KS analyzed data, and wrote the paper. DAL reviewed it critically for important intellectual content. GL provided the idea for the article and contributed to drafting and subsequent revisions. All authors approved final version to be submitted.

Figure legends

Figure 1:

Flow chart of modelling procedure

Figure 2:

Annual Estimated stroke events among all Japanese AF population (n=889,000) according to $CHADS_2$ and CHA_2DS_2-VASc scores

AF; atrial fibrillation, $CHADS_2$ score; Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double), CHA_2DS_2-VASc score; Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender, ITT; intention-to-treat

* calculated by observed annual stroke rate (2.1%/year) [11)]

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Figure 1 Flow chart of modelling procedure

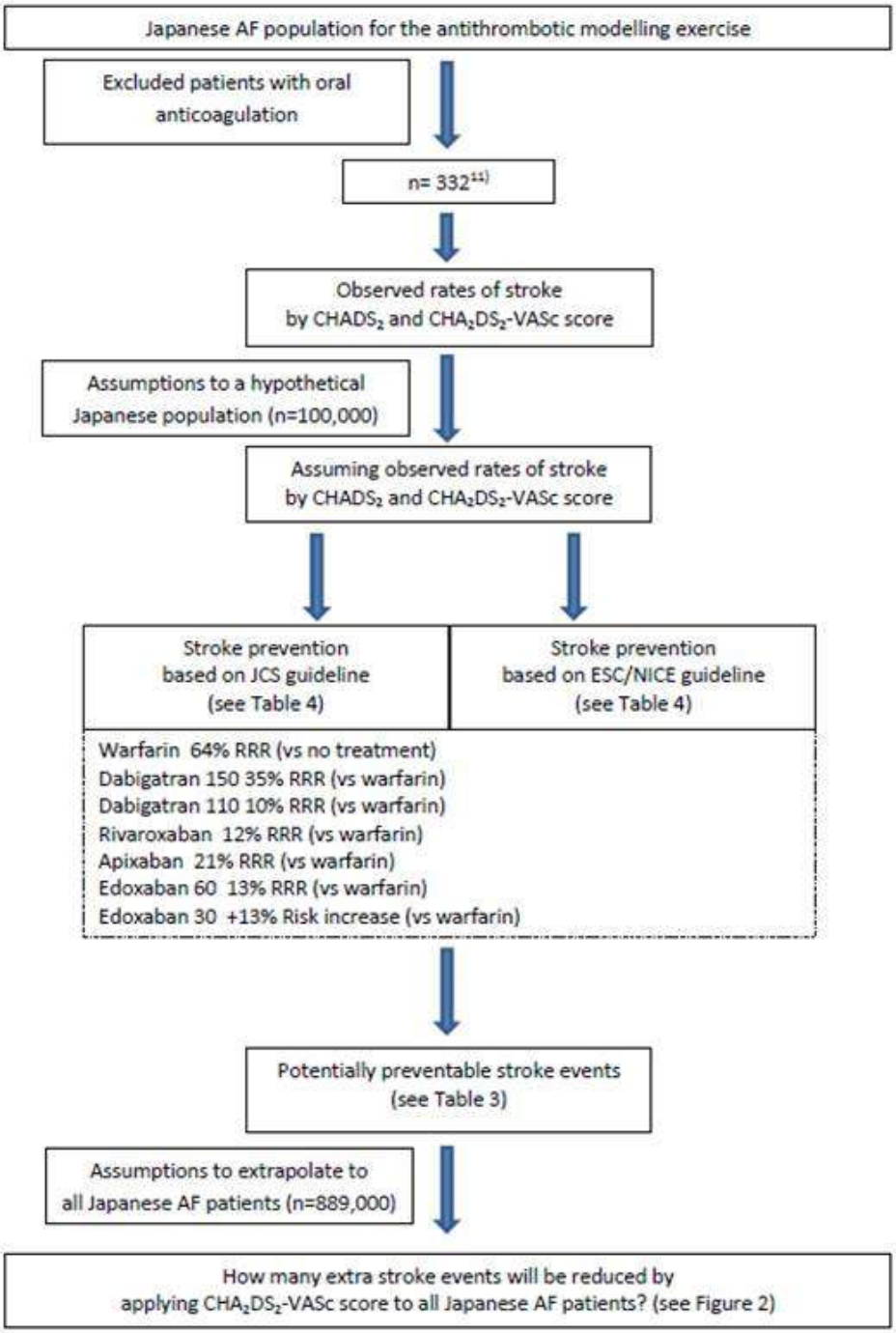
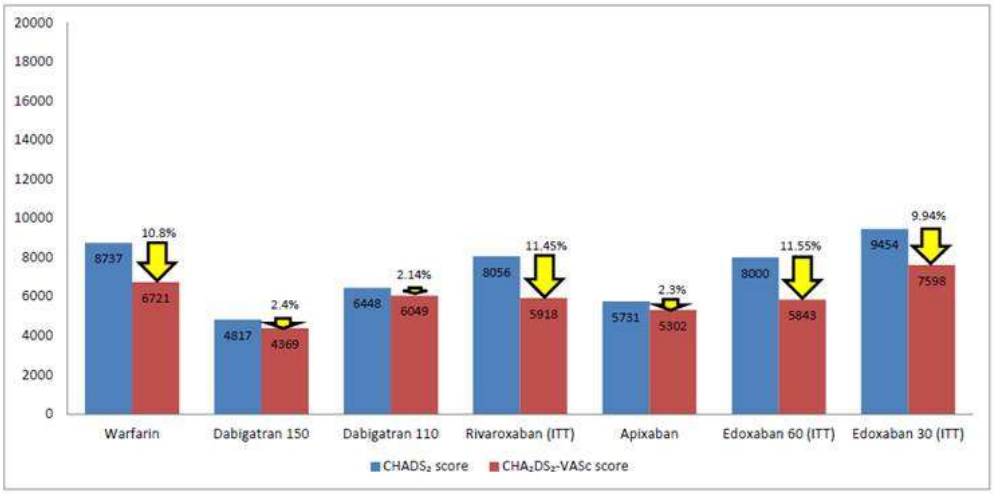


Figure 2

Annual Estimated stroke events* among all Japanese AF population (n=889,000) according to $CHADS_2$ and CHA_2DS_2-VASc scores



AF; atrial fibrillation, $CHADS_2$ score; Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double), CHA_2DS_2-VASc score; Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender, ITT; intention-to-treat

* calculated by observed annual stroke rate (2.1%/year) [11]

Table 1 Ischaemic stroke rate without oral anticoagulants based on the CHA_2DS_2-VASc and $CHADS_2$ scores

	Komatsu et al.*[11]	Siu et al.[15]		Guo et al.[16]		Lip et al.*[14]
	n=332	n=3881		n=885		n=1084
CHA_2DS_2-VASc score	Annual rates (%/year;95% CI)	Annual rates (%/year)	CHA_2DS_2-VASc score	Annual rates (%/year;95% CI)	CHA_2DS_2-VASc score	Annual rates (%/year;95% CI)
0	0	2.41	0-1		0	0
1	0.6 (0.45-0.76)	6.64	Male	0.45 (0.01-2.50)	1	0.6 (0-3.4)
2	0.95 (0.73-1.18)	7.84	Female	1.59 (0.04-8.53)	2	1.6 (0.3-4.7)
3	1.96 (1.65-2.28)	9.56	≥2		3	3.9 (1.7-7.6)
4	5.45 (5.06-5.85)	11.58	Male	2.87 (1.95-4.07)	4	1.9 (0.5-4.9)
5	9.06 (8.41-9.72)	12.69	Female	2.59 (1.35-4.48)	5	3.2 (0.7-9.0)
≥6	13.7 (11.79-15.62)	13.18			6	3.6 (0.4-12.3)
					7	8.0 (1.0-26.0)
					8	11.1 (0.3-48.3)
					9	100 (2.5-100)
$CHADS_2$ score			$CHADS_2$ score		$CHADS_2$ score†	
0	0.21 (0.10-0.33)	5.44	0-1		0	1.4
1	0.93 (0.79-1.07)	8.59	Male	1.18 (0.38-2.73)	1	1.9
2	2.78 (2.61-2.96)	11.24	Female	1.83 (0.50-4.63)	≥2	3.1
3	9.41 (8.98-9.85)	11.86	≥2			
≥4	10.92 (10.18-11.67)	14.06	Male	3.09 (2.03-4.49)		
			Female	2.91 (1.34-5.46)		

*rate of ischaemic stroke and systemic thromboembolism † no 95% CI stated in the article
CHA_2DS_2-VASc score; Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender
$CHADS_2$ score; Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double). CI; confidential interval

Table 2

Modelling event rates in a hypothetical Japanese AF population with no treatment (n=100,000)

	Komatsu et al.[11] (n=332)		Hypothetical Japanese AF population (n=100,000)	
	Number of patients (n=; %)	Annual rates (%/year; 95% CI)	Estimated Number of patients (n=)	Estimated number of stroke events (n=; 95% CI)
CHA_2DS_2-VASc score				
0	76(23)	0	23000	0
1	60(18)	0.6 (0.45-0.76)	18000	108 (81-136.8)
2	69(21)	0.95 (0.73-1.18)	21000	199.5 (153.3-247.8)
3	69(21)	1.96 (1.65-2.28)	21000	411.6 (346.5-478.8)
4	28(8)	5.45 (5.06-5.85)	8000	436 (404.8-468)
5	23(7)	9.06 (8.41-9.72)	7000	634.2 (588.7-680.4)
≥6	7(2)	13.7 (11.79-15.62)	2000	274 (235.8-312.4)
$CHADS_2$ score				
0	115(35)	0.21 (0.10-0.33)	35000	73.5 (35-115.5)
1	114(34)	0.93 (0.79-1.07)	34000	316.2 (268.6-363.8)
2	53(16)	2.78 (2.61-2.96)	16000	444.8 (417.6-473.6)
3	30(10)	9.41 (8.98-9.85)	10000	941 (898-985)
≥4	20(5)	10.92 (10.18-11.67)	5000	546 (509-583.5)

AF; Atrial fibrillation, CI; confidential interval, CHA_2DS_2-VASc score; Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender, $CHADS_2$ score; Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double)

Table 3

Estimated strokes on no treatment, warfarin and NOACs in a hypothetical Japanese AF population (n=100,000)

	Assuming Number of patients (n)	No treatment (n)	Warfarin (n)	Dabigatran 150 (n)	Dabigatran 110 (n)	Rivaroxaban (ITT) (n)	Apixaban (n)	Edoxaban 60 (ITT) (n)	Edoxaban 30 (ITT) (n)
			RR*0.36 (CI;0.26-0.51)	RR†0.65 (CI;0.52-0.81)	RR† 0.90 (CI;0.74-1.1)	RR† 0.88 (CI;0.74-1.03)	RR† 0.79 (CI;0.66-0.95)	RR† 0.87 (CI;0.73-1.04)	RR† 1.13 (CI;0.96-1.34)
Based on ESC/NICE guidelines									
CHA_2DS_2-VASc score									
Score =0	23000	0	‡	‡	‡	‡	‡	‡	‡
Score =1	18000	108 (81-136.8)	38.9§ (28.1-55.1)	25.3 (20.2-31.5)	35.0 (28.8-42.8)	34.2 (28.8-40.1)	30.7 (25.7-37.0)	33.8 (28.4-40.5)	44.0 (37.3-52.1)
Score =2	21000	199.5 (153.3-247.8)	71.8 (51.9-101.7)	46.7 (37.3-58.2)	64.6 (53.1-79)	63.2 (53.1-74)	56.7 (47.4-68.2)	62.5 (52.4-74.7)	81.1 (68.9-96.2)
Score =3	21000	411.6 (346.5-478.8)	148.2 (107-209.9)	96.3 (77.1-120.0)	133.4 (109.7-163)	130.4 (109.7-152.6)	117.1 (97.8-140.8)	128.9 (108.2-154.1)	167.5 (142.3-198.6)
Score =4	8000	436 (404.8-468)	157 (113.4-222.4)	102.1 (81.6-127.2)	141.3 (116.2-172.7)	138.2 (116.2-161.7)	124 (103.6-149.2)	136.6 (114.6-163.3)	177.4 (150.7-210.4)
Score =5	7000	634.2 (588.7-680.4)	228.3 (164.9-323.4)	148.4 (118.7-184.9)	205.5 (168.9-251.1)	200.9 (168.9-235.1)	180.4 (150.7-216.9)	198.6 (166.7-237.4)	258.0 (219.2-305.9)
Score ≥6	2000	274 (235.8-312.4)	98.6 (71.2-139.7)	64.1 (51.3-79.9)	88.7 (73.0-108.5)	86.8 (73.0-101.6)	77.9 (65.1-93.7)	85.8 (72-102.5)	111.4 (94.7-132.1)
	100000	2063.3 (1810-2324.2)	742.8 (536.5-1052.3)	482.8 (386.3-601.7)	668.5 (549.7-817.1)	653.7 (549.7-765.1)	586.8 (490.2-705.7)	646.2 (542.2-772.5)	839.4 (713.1-995.4)
Potentially preventable stroke events			-1320.5	-1580.5	-1394.8	-1409.6	-1476.5	-1417.1	-1223.9
Additional strokes prevented vs warfarin				-260	-74.3	-89.1	-156	-96.6	+96.6
Based on JCS guideline ¶									
$CHADS_2$ score									
Score =0	35000	73.5	‡	‡	‡	‡	‡	‡	‡

		(35-115.5)							
Score =1	34000	316.2 (268.6-363.8)	| |	74 (59.2-92.2)	102.4 (84.2-125.2)	| |	89.9 (75.1-108.1)	| |	| |
Score =2	16000	444.8 (417.6-473.6)	160.1 (116.7-226.8)	104.1 (83.3-129.7)	144.1 (118.5-176.1)	140.9 (118.5-164.9)	126.5 (105.7-152.1)	139.3 (116.9-166.5)	180.9 (153.7-214.5)
Score =3	10000	941 (898-985)	338.8 (244.7-479.9)	220.2 (176.2-274.4)	304.9 (250.7-372.7)	298.1 (250.7-349.0)	267.7 (223.6-321.9)	294.8 (247.3-352.4)	382.8 (325.2-454.0)
Score ≥4	5000	546 (509-583.5)	196.6 (142.0-278.5)	127.8 (102.2-159.2)	176.9 (145.5-216.3)	173.0 (145.5-202.5)	155.3 (129.8-186.8)	171.0 (143.5-204.5)	222.2 (188.7-263.4)
	100000	2321.5 (2128-2521.4)	1085.2 (807-1464.5)	599.6 (455.9-771)	801.8 (633.9-1005.8)	1001.7 (818.3-1195.6)	712.9 (569.2-884.4)	994.8 (811.3-1202.7)	1175.6 (971.2-1411.2)
Potentially preventable stroke events			-1236.3	-1721.9	-1519.7	-1319.8	-1608.6	-1326.7	-1145.9
Additional strokes prevented vs warfarin				-485.6	-283.4	-83.5	-372.3	-90.4	+90.4

NOAC; Non-VKA oral anticoagulants
AF; atrial fibrillation
ITT; Intention-to-treat analysis
CHA_2DS_2-VASc score; Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender
$CHADS_2$ score; Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double)
RR; risk ratio
*versus No treatment
†versus Warfarin
‡not recommended
§ warfarin can be alternative option
| | can be considered
¶ no consideration in regards to other risk factors (Cardiomyopathy, 65 to 74 years of age, or vascular disease

Table 4: Summary of recommendations proposed by several guidelines

<table>
<tr><td colspan="6">Based on CHADS2 score</td></tr>
<tr><td></td><td>CHADS2≥2</td><td>CHADS2=1</td><td colspan="3">CHADS2=0</td></tr>
<tr><td rowspan="2">JCS 2014 [7]</td><td></td><td></td><td>Other risk factors[a]</td><td colspan="2">No risk factor</td></tr>
<tr><td>D/R/A/E/ W[b]</td><td>D/A (R/E/W[b] can be considered)</td><td>(D/R/A/E/W[b] can be considered)</td><td colspan="2">No Tx</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td rowspan="2">CCS 2014 [24]</td><td colspan="2" rowspan="2">OAC[c]</td><td>Age 65-74</td><td>Vascular disease</td><td>No risk factor</td></tr>
<tr><td>OAC[c]</td><td>Aspirin</td><td>No Tx</td></tr>
<tr><td colspan="6">Based on CHAD2DS2-VASc</td></tr>
<tr><td></td><td>CHAD2DS2-VASc≥2</td><td>CHAD2DS2-VASc=1</td><td colspan="3">CHAD2DS2-VASc=0</td></tr>
<tr><td rowspan="2">ESC 2012 [5]</td><td colspan="2">NOAC</td><td colspan="3" rowspan="2">No TX</td></tr>
<tr><td colspan="2">Wafarin (alternative)</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td>APHRS2013 [22]</td><td>OAC (D/R/A/W)</td><td>NOAC (D/A)
W/R (alternative)</td><td colspan="3">No Tx</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td>ACC/AHA/HRS 2014 [23]</td><td>OAC (D/R/A/W) (class I)</td><td>OAC (D/R/A/W) or No Tx or Aspirin (can be considered) (class IIb)</td><td colspan="3">No Tx (class IIa)</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td rowspan="2">NICE 2014 [6]</td><td rowspan="2">OAC (D/R/A/W)</td><td>Women: No Tx</td><td colspan="3" rowspan="2">No Tx</td></tr>
<tr><td>Men: OAC (D/R/A/W) (can be considered)</td></tr>
</table>

JCS, Japanese Circulation Society; CCS, Canadian Cardiovascular Society; ESC, European Society of Cardiology; APHRS, Asia Pacific Heart Rhythm Society; ACC/AHA/HRS, American Heart Association/American College of Cardiology/ Heart Rhythm Society; NICE, National Institute for Health and Care Excellence; CHA_2DS_2-VASc score, Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender; $CHADS_2$ score, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double); OAC, oral anticoagulation; NOAC, non-VKA oral anticoagulants;
D, dabigatran; R, rivaroxaban; A, apixaban; E, edoxaban; W, warfarin
a; Cardiomyopathy, 65 to 74 years of age, or vascular disease.
b; age<70 INR 2.0-3.0, age≥70 INR 1.6-2.6
c: NOACs (D, R, A) > warfarin