CONTEMPORARY REVIEW

Patients with atrial fibrillation and CHA_2DS_2-VASc score 1: "To anticoagulate or not to anticoagulate? That is the question!"

Giuseppe Patti, MD, FACC, Ilaria Cavallari, MD

From the Campus Bio-Medico University of Rome, Rome, Italy.

There is uncertainty regarding the optimal therapy for preventing thromboembolic stroke in patients with atrial fibrillation and CHA_2DS_2-VASc score 1. In fact, no extensive data on this topic are available, and the latest guidelines provide different recommendations. In this article, we examine current results on the use of various antithrombotic agents, including the newer oral anticoagulant agents, in those patients. Several factors must be considered and weighted in this setting and may influence the choice of the antithrombotic approach: the expected incidence of both thromboembolic stroke and bleeding complications as well as their impact in terms of morbidity and mortality, the patient's bleeding risk profile, an accurate, further stratification of the thromboembolic risk beyond the CHA_2DS_2-VASc score, and socioeconomic issues.

KEYWORDS Atrial fibrillation; Warfarin; Novel oral anticoagulant; Bleeding risk: Thromboembolic risk

ABBREVIATIONS ACC = American College of Cardiology; **ACTIVE-W** = Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; **AF** = atrial fibrillation; **AHA** = American Heart Association; **ARISTOTLE** = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; **AVERROES** = Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin k Antagonist Treatment; **CHA_2DS_2-VASc** = Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category; **$CHADS_2$** = Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; **ENGAGE** = Effective Anticoagulation with Factor Xa Next Generation; **ESC** = European Society of Cardiology; **HAS-BLED** = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly ($\geq$65 years), Drugs/alcohol concomitantly; **RE-LY** = Randomized Evaluation of Long-term Anticoagulation Therapy; **ROCKET-AF** = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

(Heart Rhythm 2015;12:2515–2520)

Stratification of patients with atrial fibrillation (AF) according to the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category) rather than the $CHADS_2$ score (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke) allows better discrimination of those at low thromboembolic risk. Although the 2 scores have some risk factors in common, our unpublished data show that among AF patients with $CHADS_2$ score 0, 27% have CHA_2DS_2-VASc score 0, 32% CHA_2DS_2-VASc score 1, and approximately 40% CHA_2DS_2-VASc score >1. However, clinical management of AF patients with CHA_2DS_2-VASc 1 is not infrequent. Results from the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) indicated a prevalence of 10% among those patients,[1] and this percentage was more recently confirmed in a large real-world registry.[2] There is uncertainty regarding the optimal antithrombotic therapy in low thromboembolic risk patients with CHA_2DS_2-VASc score 1 because this score has only recently been introduced, and there is no close correlation in the thromboembolic risk of the $CHADS_2$ and CHA_2DS_2-VASc scores. Therefore, no firm conclusion can be derived from historical investigations that compared different antithrombotic approaches according to the $CHADS_2$ score, and only few, albeit increasing, data on the topic are available from more recent studies. This uncertainty remains in light of current guidelines. European Society of Cardiology (ESC) Guidelines indicate that use of warfarin or novel oral anticoagulants in patients with CHA_2DS_2-VASc score 1 should be based on assessment of the risk of bleeding complications and patient preference (class of recommendation IIa, level of evidence A).[3] American College of Cardiology/American Heart Association (ACC/AHA) Guidelines[4] state that no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (IIb, C).

Address reprint requests and correspondence: Dr. Giuseppe Patti, Campus Bio-Medico University of Rome, Via Alvaro del Portillo, 200, 00128 Rome, Italy. E-mail address: g.patti@unicampus.it.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2015.07.017

Historical data on thromboembolic risk in AF patients with $CHADS_2$ score 0–1

The $CHADS_2$ score, first published in 2001, was derived by combining risk factors from historical studies and tested in a cohort of 1773 patients.[5–7] However, fewer than 10% of patients screened in those investigations were included, and the majority of stroke risk factors were inconsistently defined or not systematically recorded.[8] Current guidelines based on the $CHADS_2$ score recommend initiation of anticoagulant therapy in patients with a score ≥ 1.[9,10] In the first validation cohort, the adjusted stroke rate was 1.9% per year in patients with $CHADS_2$ 0 and 2.8% per year in those with score 1, whereas in the Euro Heart Survey the incidence of stroke was lower (1.4% per year in patients with $CHADS_2$ 0 and 1.9% per year in those with score 1).[5,11] Similar discrepancies were observed in 2 different Japanese cohorts in which ischemic stroke rates ranged from 0.5% to 0.6% per year in patients with $CHADS_2$ 0 and from 0.9% to 2.8% per year in those with score 1.[12,13] The reasons for these apparent differences in the occurrence of stroke remain unclear, but the decade-long differences in the management of coexisting diseases might have a role. Moreover, the risk of patients with $CHADS_2$ 1 could vary depending on the specific conditions (risk factors) composing the score. However, although the $CHADS_2$ score is simple and easy to calculate, its limitations in stroke risk stratification are evident. In fact, many patients classified as "low risk" using the $CHADS_2$ score have stroke rates $>1.0\%$ per year, and a $CHADS_2$ score 0 does not reliably identify AF patients who are "truly at low risk."

Thromboembolic and bleeding risk in AF patients with CHA_2DS_2-VASc score 1

In clinical practice, it is not infrequent that, borrowing the famous monologue of the Shakespeare's tragedy, doctors have this hamletic doubt: "to anticoagulate or not to anticoagulate AF patients with CHA_2DS_2-VASc score 1"? When choosing the appropriate therapeutic approach, it is relevant to balance the degree of ischemic protection provided by antithrombotic therapy with the "iatrogenic" bleeding risk; thus, it appears crucial to first establish the untreated thromboembolic risk in this setting.

A wide range in the incidence of thromboembolic complications without anticoagulant therapy has been reported among AF patients with CHA_2DS_2-VASc 1 (0.2% to 6.6% per year; Table 1).[11,14–25] This variability may be due in part to differences in the design of the various studies: (1) use of a "stricter" vs a "wider" definition of thromboembolic outcome measure (ie, ischemic stroke vs a combined end-point of stroke and systemic embolism vs a composite end-point including stroke, transient ischemic attack, systemic embolism, and pulmonary embolism; (2) different prevalence of female patients without any additional risk factors, who have a low risk of thromboembolic events; (3) variable penetration of concomitant antiplatelet therapy; (4) inclusion or no inclusion of a quarantine period and different durations of quarantine periods; (5) enrollment of patients receiving anticoagulant therapy in some investigations in which the authors subsequently extrapolated the estimated untreated stroke risk; and (6) retrospective validation of the CHA_2DS_2-VASc score in different patient populations (community vs hospitalized). Of note, European registries indicated very low yearly rates of ischemic stroke in AF patients with CHA_2DS_2-VASc 1 without anticoagulant therapy ($\leq 0.7\%$), which led to further concerns regarding indiscriminate unselected use of oral anticoagulation in those patients.[16,21] The latest European registry reported a 1-year stroke rate of 1.55% for CHA_2DS_2-VASc score 1 [male] and score 2 [female], but this incidence was reduced to 0.96% per year when only primary discharge diagnoses of ischemic stroke and full follow-up were used.[17] Conversely, large studies of Asian populations showed that the incidence of this complication may be significantly higher ($\geq 2\%$/year).[19,20,23,24] Similar racial differences were noted in the recent randomized phase III trials on non–vitamin K antagonists oral anticoagulants.[3,4] To date, the reasons for such racial discrepancies are unclear. However, we can speculate that genetic factors in Asian populations may account for the pronounced thromboembolic risk, and the higher prevalence of undiagnosed risk factors (ie, more vascular disease) in the related studies might be hypothesized. Moreover, the power of vascular disease in predicting the risk of stroke in AF patients has been reported to be higher in Asian than European populations (hazard ratio 1.96 vs 1.12–1.22).[16,18,24] Finally, penetration of concomitant antiplatelet therapy was higher in the European investigations, which may have attenuated in part the occurrence of ischemic stroke.

With regard to "on-treatment" bleeding risk in patients with CHA_2DS_2-VASc score 1, randomized data indicated an incidence of major bleeding of 1.2% per year with warfarin and 0.8% per year with apixaban, with annual rates of intracranial bleeding of 0.35% and 0.2%, respectively.[1]

We next examine the available results on different antithrombotic strategies in AF patients with CHA_2DS_2-VASc score 1.

Oral anticoagulant and aspirin therapy

Data from the ARISTOTLE trial showed a 0.53% per year incidence of stroke with warfarin in the patients studied.[1] If we hypothesize that warfarin can reduce the risk of stroke by 64%, the estimated untreated stroke risk should be 1.47% per year.[26] Of note, use of warfarin vs no treatment in patients with CHA_2DS_2-VASc 1 was associated with higher risk of intracranial bleeding but very low rates of the complication (0.14% vs 0.10%) and high number needed to harm (2500).[27]

There is a paucity of data on the comparison of warfarin vs aspirin. In the Stockholm region registry, the rates of ischemic stroke were reduced with warfarin compared to aspirin in AF patients with CHA_2DS_2-VASc 1 (0.3% vs 1.2% per year), with no difference in bleeding risk.[28]

Table 1 Main features of the studies evaluating thromboembolic risk in untreated patients with atrial fibrillation and CHA_2DS_2-VASc score 1

Study	Type of study	No. of pts with CHA_2DS_2-VASc 1	Type of population	Females	Pts receiving antiplatelet agents	Length of follow-up	Definition of thromboembolic events	Yearly incidence of thromboembolic events in pts with CHA_2DS_2-VASc 1	Definition of ischemic stroke	Yearly incidence of ischemic stroke in pts with CHA_2DS_2-VASc 1
Lip GY Chest 2010 (11)	Cohort study (Euro Heart Survey)	162	European	41%	74%	1 year	Ischemic stroke, peripheral embolism, or pulmonary embolism	0.6%	Focal neurologic deficit of sudden onset as diagnosed by a neurologist lasting $>$ 24h and caused by ischemia	NA
Olesen JB BMJ 2011 (14)	Cohort study	8203	Danish	51%	35%	10 years	Ischemic stroke, peripheral embolism, or pulmonary embolism	1.5%	NA	NA
Friberg L Eur Heart J 2012 (16)	Cohort study	6770	Swedish	NA	NA	1.5 years	Ischemic stroke, unspecified stroke, TIA, and systemic embolism	0.9%	Ischemic stroke at hospital discharge (definition not specified)	0.6%
Olesen JB Thromb Haemost 2012 (18)	Cohort study	10,062	Danish	46%	29%	12 years	Peripheral artery embolism, TIA, and ischemic stroke	1.4%	NA	NA
Friberg L J Am Coll Cardiol 2015 (21)	Retrospective	12,298	Swedish	50%	NA	5 years	TIA, pulmonary embolism, arterial embolism, ischemic or hemorrhagic stroke	0.9%	Registration of admitting patients with acute stroke (definition not specified)	0.5% (0.2% F, 0.7% M)
Apostolakis S Int J Cardiol 2013 (17)	Prospective registry (Gulf SAFE)	147	Middle Eastern Gulf Countries	43%	NA	1 year	Stroke, TIA, or non–central nervous system thromboembolism	2%	NA	NA
Komatsu T J Cardiol 2012 (22)	Retrospective	60	Japanese	22%	27%	53 $\pm$ 35 months	NA	NA	Clinical symptoms and presence of a $\geq$3-mm infarct area obtained by brain CT or MRI	0.6%
Guo Y Int J Cardiol 2013 (15)	Single-center retrospective	114	Chinese	27%	79%	1.9 years	Ischemic stroke, peripheral embolism, or pulmonary embolism	0.9%	Focal neurologic deficit of sudden onset diagnosed clinically by a neurologist and confirmed by brain CT or MRI	NA
Chao TF J Am Coll Cardiol 2015 (24)	Cohort study	19,325	Taiwanese	46%	0	3.4 $\pm$ 3.7 years	NA	NA	Ischemic stroke with concomitant imaging studies of the brain including CT or MRI	2.1%
Huang D Pacing Clin Electrophysiol 2014 (19)	Cohort study	358	Chinese	29%	0	1758 patient-years	NA	NA	Neurologic deficit of sudden onset that persisted $>$24 hours confirmed by brain CT or MRI	6.6%
Siu CW Heart Rhythm 2014 (20)	Observational	358	Chinese	54%	0	3.19 $\pm$ 3.43 years	NA	NA	Hospital admission with stroke (definition not specified)	6.6%
Chao TF J Am Coll Cardiol 2015 (24)	Cohort study	12,935 M 7900 F with score 2	Taiwanese	38%	0	5.2 $\pm$ 4.3 years	NA	NA	Ischemic stroke with concomitant imaging studies of the brain including CT or MRI	2.8% M 2.6% F
Lip GY J Am Coll Cardiol 2015 (25)	Cohort study	5035 M 4422 F with score 2	Danish	47%	0	5.9 years	Ischemic stroke and systemic embolism	NA	NA	1.5% overall

CT = computerized tomography; MRI = magnetic resonance imaging; TIA = transient ischemic attack; NA = not available.

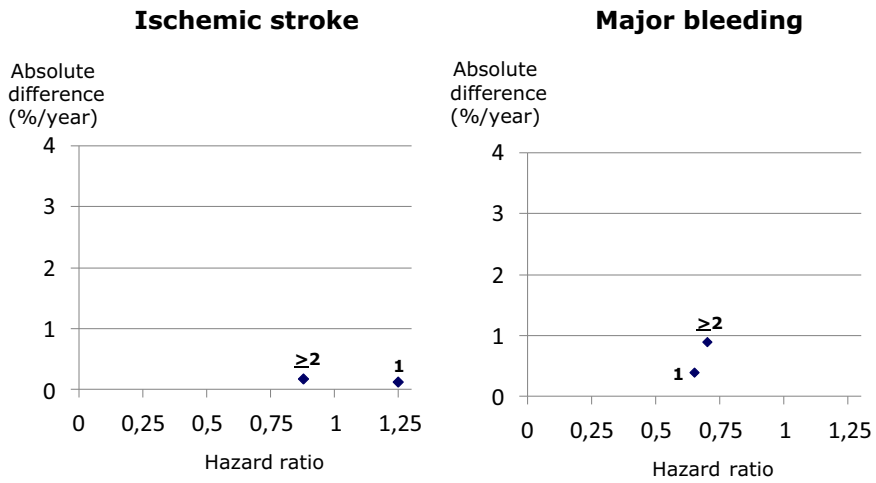

Figure 1 ARISTOTLE trial. Hazard ratio and absolute difference of ischemic stroke and major bleeding with apixaban vs warfarin according to the CHA_2DS_2-VASc score.

A subgroup analysis based on CHA_2DS_2-VASc score from the AVERROES trial (Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin k Antagonist Treatment) evaluated apixaban vs aspirin in AF patients not suitable for warfarin treatment.[29] In this study, there was a 1.44% per year stroke rate on aspirin in patients with CHA_2DS_2-VASc score 0–1. If we hypothesize that aspirin is able to decrease the risk of stroke by 22%, the estimated untreated stroke risk should be 1.76% per year.[26] However, use of apixaban instead of aspirin in patients with CHA_2DS_2-VASc 0–1 was associated with both relevant risk reduction (80%) and absolute decrease (1.1%) of ischemic stroke. Moreover, a 45% risk reduction of major bleeding with apixaban led to 0.3% per year absolute reduction of this complication.

Oral anticoagulant vs dual antiplatelet therapy

No data on this issue have been published to date. A *post hoc* analysis from the ACTIVE-W trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) showed a 3-fold higher increase in the risk of stroke with aspirin plus clopidogrel compared to warfarin, even among patients with $CHADS_2$ score 0, with no significant difference in the occurrence of major bleeding complications between the 2 arms.[30]

Warfarin vs novel oral anticoagulants

No comparison between rivaroxaban or edoxaban vs warfarin is available from randomized controlled trials. ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ENGAGE (Effective Anticoagulation with Factor Xa Next Generation) did not enroll patients with CHA_2DS_2-VASc 1.[31,32] From the ARISTOTLE data, we plotted the hazard ratios and yearly absolute difference of event rates with apixaban vs warfarin for both efficacy and safety end-points (Figure 1).[1] Use of apixaban in these patients caused a 25% relative increase of ischemic stroke vs warfarin; however, because of the low occurrence of this end-point, the absolute increase was negligible (0.12% per year). Conversely, apixaban was associated with a 35% decrease in major bleeding compared to warfarin, which translated into a 0.4% per year absolute reduction. A recent investigation extrapolated the incidence of stroke and bleeding events with dabigatran vs warfarin according to the predicted risk with different CHA_2DS_2-VASc scores,[27] and a significant net clinical benefit favoring both doses of dabigatran in patients with CHA_2DS_2-VASc score 1 was postulated.

Considerations according to thromboembolic and bleeding risk

We believe that further risk stratification is useful in AF patients with CHA_2DS_2-VASc score 1 and may influence the choice of antithrombotic therapy because thromboembolic risk can be different among these patients, for example, in (1) a 66-year-old man with lone AF, no chronic renal failure, and no left atrial enlargement at echocardiography; and (2) a 64-year-old man with insulin-dependent diabetes for >10 years, severe chronic renal failure, and left atrial enlargement.[33] Particular attention should be paid to the bleeding propensity of AF patients with low thromboembolic risk, in order to balance the ischemic protection vs the bleeding risk linked to different antithrombotic strategies. Thus, it appears crucial to also evaluate the prognostic impact of possible adverse events; in particular, hemorrhagic stroke during follow-up of AF patients has been associated with a 3-fold and 5-fold higher risk of death post event vs ischemic stroke and extracranial bleeding, respectively.[34] Moreover, in ARISTOTLE, the risk reduction of intracranial bleeding with apixaban was 45% in patients with CHA_2DS_2-VASc score 1 and was the highest in those with HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international

normalized ratio, Elderly (≥65 years), Drugs/alcohol concomitantly) ≥3 (78% reduction).[1]

A particular category is represented by patients with AF and CHA_2DS_2-VASc score 1 and are undergoing stent implantation. In this setting, thromboembolic risk due to AF is low, and the protection from thromboembolic stroke with dual antiplatelet therapy, albeit partial, might be adequate, especially in the short term, whereas the bleeding risk with triple therapy (dual antiplatelet plus anticoagulant) is elevated (up to 6% per year).[35,36] As expected, in the RE-LY trial (Randomized Evaluation of Long-term Anticoagulation Therapy), independent of the assignment arm (dabigatran 110, dabigatran 150, or warfarin), there was an incremental risk of major bleeding among patients without concomitant antiplatelet therapy, in those on single antiplatelet and in those on dual antiplatelet treatment.[37] Thus, in AF patients with CHA_2DS_2-VASc score 1, short-term dual antiplatelet therapy without anticoagulation may be considered (ie, for 1 month in patients with stable coronary artery disease receiving bare metal stents, especially if they are at high bleeding risk).[35,36]

In anticipation of future studies than will definitively clarify the optimal antithrombotic strategy for AF patients with CHA_2DS_2-VASc score 1, we note the following:

- Deep stratification of thromboembolic risk is advisable, while also considering other possible predictors of increased risk beyond the CHA_2DS_2-VASc score, such as renal failure, left atrial enlargement, low flow in the left atrial appendage, different left atrial morphologies, and spontaneous echo-contrast.
- The clinical threshold at which anticoagulant therapy is associated with net clinical benefit seems to be an expected (untreated) stroke rate ≥1% per year.[38] However, age 65 to 74 years represents a more powerful risk factor for stroke (with a >2.5-fold increase in the hazard ratio) than the other characteristics weighted as 1 point in the CHA_2DS_2-VASc score.[3] Accordingly, the yearly stroke rate without antithrombotic therapy appears surely to be >1% in AF patients with CHA_2DS_2-VASc 1 due to age 65 to 74 years, whereas the rate is generally <1% in those with CHA_2DS_2-VASc 1 due to other variables. Thus, the latter patients are unlikely to derive a net benefit from routine use of anticoagulant therapy, unless renal failure, insulin-dependent diabetes, left atrial enlargement with spontaneous echo-contrast, or very low flow velocities in the left atrial appendage coexist. Conversely, anticoagulant treatment may represent the strategy of choice over antiplatelet or no antithrombotic therapy in patients with CHA_2DS_2-VASc 1 and age between 65 and 74 years. Of note, AF patients with CHA_2DS_2-VASc 1 due to only the presence of female gender actually are considered at very low risk of ischemic stroke (<1%/year) and do not require routine oral anticoagulation.[39]
- With regard to utilization of warfarin vs novel oral anticoagulants, the patient's type of work and the patient's preferences should be considered, and the latter agents might be preferred, especially in patients with high bleeding risk. However, cost-effectiveness analyses in this context are relevant and welcome.
- Careful evaluation of bleeding risk is crucial. Of note, the HAS-BLED score may range from 0 to 5 in patients with CHA_2DS_2-VASc score 1.
- Anticoagulant therapy may be withdrawn for short, well-defined time periods after coronary stenting and resumed after interruption of an antiplatelet agent.
- CHA_2DS_2-VASc is a dynamic score, and patients must be reassessed periodically for this measurement of thromboembolic risk.
- Future research investigating the possible role of new diagnostic tools (eg, global longitudinal left atrial strain, microembolic signals by transcranial Doppler) for improvement of thromboembolic risk stratification would be welcome.

References

1. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet 2012;380:1749–1758.
2. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, Schmitt J, Zamorano JL. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events—European Registry in Atrial Fibrillation (PREFER in AF). Europace 2014;16:6–14.
3. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. ESC Committee for Practice Guidelines (CPG). 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.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;130:2071–2104.
5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–2870.
6. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449–1457.
7. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. JAMA 1998;279:1273–1277.
8. Lip GY. Stroke in atrial fibrillation: epidemiology and thromboprophylaxis. J Thromb Haemost 2011;1(Suppl). 344–251.
9. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e531S–e575S.
10. Verma A, Cairns JA, Mitchell LB, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol 2014;30:1114–1130.
11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–272.
12. Inoue H, Nozawa T, Hirai T, Iwasa A, Okumura K, Lee JD, Shimizu A, Hayano M, Yano K. Accumulation of risk factors increases risk of thromboembolic events in patients with nonvalvular atrial fibrillation. Circ J 2006;70:651–656.
13. Suzuki S, Yamashita T, Okumura K, Atarashi H, Akao M, Ogawa H, Inoue H. Incidence of ischemic stroke in Japanese patients with atrial fibrillation not receiving anticoagulation therapy—pooled analysis of the Shinken Database, J-RHYTHM Registry, and Fushimi AF Registry. Circ J 2015;79:432–438.

14. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342: d124. http://dx.doi.org/10.1136/bmj.d124.
15. Guo Y, Apostolakis S, Blann AD, Wang H, Zhao X, Zhang Y, Zhang D, Ma J, Wang Y, Lip GY. Validation of contemporary stroke and bleeding risk stratification scores in non-anticoagulated Chinese patients with atrial fibrillation. Int J Cardiol 2013;168:904–909.
16. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation Cohort Study. Eur Heart J 2012;33: 1500–1510.
17. Apostolakis S, Zubaid M, Rashed WA, Alsheikh-Ali AA, Almahmeed W, Shehab A, Sulaiman K, Alqudaimi A, Asaad N, Amin H, Lane DA, Lip GY. Gulf Survey of Atrial Fibrillation Events Investigators. Assessment of stroke risk in Middle Eastern patients with atrial fibrillation: the Gulf Safe Registry. Int J Cardiol 2013;168:1644–1646.
18. Olesen JB, Torp-Pedersen C, Hansen ML. Lip GYH. The value of the CHA_2DS_2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a $CHADS_2$ score 0–1: a nationwide cohort study. Thromb Haemost 2012;107:1172–1179.
19. Huang D, Anguo L, Yue W-S, Yin L, Tse H-F, Siu C-W. Refinement of ischemic stroke risk in patients with atrial fibrillation and CHA_2DS_2-VASc score of 1. Pacing Clin Electrophysiol 2014;37:1442–1447.
20. Siu CW, Lip GYH, Lam K-F, Tse H-F. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. Heart Rhythm 2014;11:1401–1408.
21. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA_2DS_2-VASc score of 1. J Am Coll Cardiol 2015;65:225–232.
22. Komatsu T, Tachibana H, Satoh Y, Ozawa M, Kunugita F, Ueda H, Nakamura M. Relationship between CHA(2)DS(2)-VASc scores and ischemic stroke/cardiovascular events in Japanese patients with paroxysmal atrial fibrillation not receiving anticoagulant therapy. J Cardiol 2012;59:321–328.
23. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Using the CHA_2DS_2-VASc score for refining stroke risk stratification in "low-risk" Asian patients with atrial fibrillation. J Am Coll Cardiol 2014;64:1658–1665.
24. 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 CHA_2DS_2-VASc score (beyond sex) receive oral anticoagulation? J Am Coll Cardiol 2015;65:635–642.
25. 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 CHA_2DS_2-VASc score. J Am Coll Cardiol 2015;65:1385–1394.
26. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–867.
27. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a "real world" atrial fibrillation population: a modelling analysis based on a nationwide cohort study. Thromb Haemost 2012;107:584–589.
28. Forslund T, Wettermark B, Wändell P, von Euler M, Hasselström J, Hjemdahl P. Risks for stroke and bleeding with warfarin or aspirin treatment in patients with atrial fibrillation at different CHA2DS 2VASc scores: experience from the Stockholm region. Eur J Clin Pharmacol 2014;70:1477–1485.
29. Lip GY, Connolly S, Yusuf S, Shestakovska O, Flaker G, Hart R, Lanas F, Xavier D, Eikelboom J. AVERROES Investigators. Modification of outcomes with aspirin or apixaban in relation to CHADS(2) and CHA(2)DS(2)-VASc scores in patients with atrial fibrillation: a secondary analysis of the AVERROES study. Circ Arrhythm Electrophysiol 2013;6:31–38.
30. Healey JS, Hart RG, Pogue J, Pfeffer MA, Hohnloser SH, De Caterina R, Flaker G, Yusuf S, Connolly SJ. Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). Stroke 2008;39:1482–1486.
31. Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–891.
32. Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–2104.
33. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L, Singer DE. ATRIA Study Investigators. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2009;119:1363–1369.
34. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J. de Caterina R, Hohnloser S, Hart RG; ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) Steering Committee and Investigators. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. Ann Intern Med 2011;155:579–586.
35. Patti G, Di Sciascio G. Antithrombotic strategies in patients on oral anticoagulant therapy undergoing percutaneous coronary intervention: a proposed algorithm based on individual risk stratification. Catheter Cardiovasc Interv 2010;75:128–134.
36. Holmes DR Jr, Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. J Am Coll Cardiol 2009;54: 95–109.
37. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013;127:634–640.
38. 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.
39. Chao TF, Liu CJ, Chen SJ, et al. Atrial Fibrillation and the Risk of Ischemic Stroke. Does it still matter in patients with a CHA_2DS_2-VASc score of 0 or 1? Stroke 2012;43:2551–2555.

ERRATUM

In the article titled "SCD-HeFT: Use of R-R interval statistics for long-term risk stratification for arrhythmic sudden cardiac death" by Wan-tai M. Au-yeung, MSc, Per G. Reinhall, PhD, Jeanne E. Poole, MD, Jill Anderson, RN, BSN, George Johnson, BSEE, Ross D. Fletcher, MD, Hans J. Moore, MD, FHRS, Daniel B. Mark, MD, MPh, Kerry L. Lee, PhD, Gust H. Bardy, MD that published in the October issue of **Heart**Rhythm journal (2015;12: 2058-2066), there was an error in the caption of table 4. The caption should read: Thresholds that give minimum costs and classification performance for the prediction of occurrences of VF, VFL SCD for $\gamma = 1$, $\delta = 10$.