

# Anticoagulation therapy and the risk of stroke in patients with atrial fibrillation at 'moderate risk' [CHADS<sub>2</sub> score=1]: Simplifying stroke risk assessment and thromboprophylaxis in real-life clinical practice

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Atrial fibrillation (AF) is a common and increasingly important risk factor for stroke and thromboembolism. However, this risk is not homogeneous, many recognised risk factors have been used to formulate stroke risk stratification schemas for AF (1, 2).

These schemas have been used to categorise patients into 'low', 'moderate/intermediate' and 'high' risk strata, and the majority of guidelines recommend the use of oral anticoagulation (currently, the vitamin K antagonists, VKA) for high risk subjects, whilst aspirin is recommended for low risk subjects (3). For moderate/intermediate risk subjects, the guidelines recommend 'oral anticoagulation or aspirin' given the inconvenience and limitations of VKA, and the possibility that the net clinical benefit in this category between stroke prevention and the potential harm from bleeding allows a choice between the oral anticoagulants and aspirin.

Firstly, stroke risk is a continuous variable, and the artificial categorisation into low, moderate and high risk strata based on (now) historical untreated stroke rates is probably debatable. Even on anticoagulation, stroke rates are declining (4) with improvements in cardiovascular drug prevention strategies, and greater emphasis on blood pressure control, etc – as well as improvements in delivering anticoagulation monitoring for the VKA.

Secondly, current stroke risk schemas are only of modest predictive value in predicting the subjects at high risk of a stroke or thromboembolic event (5, 6), and some categorise a large proportion of AF subjects into the 'moderate/intermediate' risk category, which causes some confusion to clinicians over whether to give anticoagulation or aspirin, or sometimes, the latter (i.e. aspirin) being prescribed as the 'guidelines allow it'. Clinicians are also poor at estimating stroke, as well as bleeding risk (7), and treatment surveys have even reported a high proportion of so-called low-risk subjects being prescribed VKA therapy (8).

However, increasing evidence points towards thrombi in AF being fibrin-rich ('red clot') where oral anticoagulation is best, in contrast to embolised thrombi and thrombi from coronary arteries which is platelet-rich ('white clot') where antiplatelet therapy is more effective (9). Also, oral anticoagulation is very effective in normalising markers of thrombogenesis in AF, whilst antiplatelet therapy is less so (10). Aspirin has been perceived to be safer than VKA in AF patients – but recent trials have shown that VKA are substantially more effective than aspirin for stroke prevention, with no difference in major bleeding event rates between VKA and aspirin treated patients (11), or a tendency to even more adverse events with aspirin compared to VKA use (12). Even the value of aspirin for 'low risk' AF subjects has been questioned following publication of the Japanese AF Trial, where aspirin was no different to control in primary endpoint rates amongst low risk AF subjects, with a trend towards more bleeding with aspirin compared to control (13).

Indeed, recent studies have also reported that VKA may be better than antiplatelet therapy in subjects with moderate/intermediate risk. In a post-hoc analysis of moderate-risk patients (defined as CHADS<sub>2</sub> score =1) from the ACTIVE-W

trial (14), stroke rates were: 1.25% per year for patients receiving aspirin-clopidogrel combination therapy, compared to 0.43% per year for patients receiving VKA (relative risk [RR] 2.96, 95% confidence interval [CI] 1.26 to 6.98, p<0.01). For patients with a CHADS<sub>2</sub> score >1, stroke rates were 3.15% per year and 2.01% per year, respectively (RR 1.58, 95% CI 1.11 to 2.24, p<0.01). Of note, the benefits of oral anticoagulation were not significantly different between these two groups, based on CHADS<sub>2</sub> score (p for interaction=0.19) (14).

In a study of 422 Korean AF patients with a CHADS<sub>2</sub> score =1 (15), the incidence of stroke over a two-year mean follow-up was significantly lower in those patients receiving warfarin compared to aspirin (4.2% vs. 12.9%; p=0.008) and no antithrombotic therapy (4.2% vs. 20.9%; p<0.001). In a Cox regression analysis, the use of VKA significantly reduced the risk of ischaemic stroke (high risk [HR] 0.28; 95% CI 0.10 to 0.79; p=0.016) compared to antiplatelet therapy (15).

In the recent RE-LY trial (16) of the oral direct thrombin inhibitor dabigatran compared to VKA in moderate- to high-risk subjects with AF, approximately one-third of subjects had a CHADS<sub>2</sub> score of 0 to 1, whilst one-third had a CHADS<sub>2</sub> score=2, and a third had a CHADS<sub>2</sub> score of ≥2. The primary endpoint annual rate on dabigatran 110 mg bid was 1.06%, compared to 0.65% with dabigatran 150 mg bid and 1.05% with VKA therapy (p=NS for heterogeneity) (16).

In the current issue of *Thrombosis and Haemostasis*, Gorin et al. (17) report on a cohort of 1,012 moderate risk subjects with AF (again, defined as a CHADS<sub>2</sub> score=1). They found that VKA use was associated with a lower rate of stroke and mortality events (8.4% vs. non-VKA users, 17.9%; RR 0.42, 95% CI 0.29 to 0.60, p<0.0001).

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On multivariate analysis (HR 0.38; 95% CI 0.25 to 0.58;  $p < 0.0001$ ) whilst the prescription of an antiplatelet agent was not significantly associated with a lower risk of events (HR 0.74; 95% CI 0.48 to 1.14;  $p = 0.17$ ). The Kaplan-Meier curves showed clear differentiation in event-free rates between the VKA-treated patients, compared to those treated with antiplatelet therapy or no anti-thrombotic therapy.

Thus, the conclusion in the paper by Gorin et al. (17) that prescription of an anticoagulant is independently associated with a decreased risk of death or stroke among patients with AF at moderate risk (that is, a CHADS<sub>2</sub> score=1), is consistent with other data on the benefits of VKA therapy in reducing stroke in subjects with a CHADS<sub>2</sub> score=1. Hence, moderate risk AF patients should be prescribed oral anticoagulation rather than aspirin. This was largely summed up in the 8<sup>th</sup> American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy in AF, where for 'moderate/intermediate' risk, the recommendation was 'prescribe antithrombotic therapy with VKA or aspirin;

we suggest a VKA rather than aspirin' (18). Nonetheless, the study by Gorin et al. (17) was not a randomised trial, but importantly, still represents a 'real life' cohort of AF patients. Residual confounding may also influence some patients who were (or were not) treated with oral anticoagulation, and various comorbidities may determine outcomes.

If the benefits of aspirin in low-risk subjects are under debate (19, 20), perhaps we need a stroke risk schema where those categorised as 'low risk' are truly low risk for stroke and thromboembolism, which is a paradigm shift in our approach, since successive risk stratification schemas (over the last two decades) have only offered modest predictive value for identifying high-risk subjects. Clearly, a schema that categorises a low proportion of subjects into the moderate/intermediate-risk category would be helpful, and many validation studies have shown that the CHADS<sub>2</sub> schema classifies >60% of subjects into the 'moderate/intermediate risk' category, and 'low risk' subjects using this schema may not necessarily be truly low risk.

Indeed, those identified as *truly low risk* patients would probably *not* need anticoagulation or even antiplatelet therapy, given the lack of benefit and potential harm with the latter. How can we progress with this concept? A refinement of the existing CHADS<sub>2</sub> scoring system, incorporating elements of the UK NICE schema and the 2006 ACC/AHA/ESC guideline risk stratification schema to incorporate other potential stroke risk factors (with greater emphasis on age, female gender and vascular disease) has recently been published (19). This schema, called CHA<sub>2</sub>DS<sub>2</sub>VASc (► Table 1), has slightly better predictive value for stroke and thromboembolism over other contemporary stroke risk stratification schemas, and it is able to clearly identify AF patients at truly low risk (0% event rates at one year), as well as categorise only a small proportion of patients (15%) into the 'moderate risk' category, hence allowing less uncertainty over whether VKA or aspirin should be prescribed. In contrast, the subjects classified as 'low risk' using the CHADS<sub>2</sub> schema (i.e. a score=0) still had an annual event rate of 1.4%/year. Thus, those at truly low risk with the new schema (CHA<sub>2</sub>DS<sub>2</sub>VASc score=0) would not need to be prescribed any antithrombotic therapy, whilst all other AF patients (CHA<sub>2</sub>DS<sub>2</sub>VASc score ≥1) can be considered for anticoagulation (22).

The paper by Gorin et al. (17) is an important one to reaffirm the value of oral anticoagulation for stroke prevention in AF (23). Once we can adequately identify truly low-risk subjects, who probably do not need antithrombotic therapy, all others can be managed with oral anticoagulation, especially with the new oral anticoagulant agents (e.g. dabigatran) that would overcome the inherent restrictions and disadvantages of the VKA. A simplification of thromboprophylaxis in AF patients is long overdue for real-life clinical practice (24), and the availability of the new oral anticoagulants may facilitate this.

## References

1. Hughes M, Lip GY, Guideline Development Group. National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care, National Institute for Health and Clinical Excellence. Stroke and thromboembolism in atrial fibril-

A	
Stroke risk factors	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior MI, PAD, or aortic plaque]	1
Aged 65–74 years	1
Sex category [i.e. female gender]	1

**Table 1: The CHA<sub>2</sub>DS<sub>2</sub>VASc schema in patients with non-valvular atrial fibrillation (A) and recommended antithrombotic therapy in relation to the CHA<sub>2</sub>DS<sub>2</sub>VASc score (B) (21).**

B	
CHA <sub>2</sub> DS <sub>2</sub> VASc score	Recommended antithrombotic therapy
>1	Oral anticoagulation therapy e.g. VKA (INR 2–3, target 2.5), ?dabigatran
1	Antithrombotic therapy, either as oral anticoagulants or aspirin 75–325 mg daily <b>We suggest oral anticoagulation therapy rather than aspirin.</b>
0	Aspirin 75–325 mg daily or no antithrombotic therapy. <b>We suggest no antithrombotic therapy.</b>

VKA, vitamin K antagonist.

- lation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008; 99: 295–304.
2. McBane RD, Hodge DO, Wysokinski WE. Clinical and echocardiographic measures governing thromboembolism destination in atrial fibrillation. *Thromb Haemost* 2008; 99: 951–955.
  3. Lip GY, Lim HS. Atrial fibrillation and stroke prevention. *Lancet Neurol* 2007; 6: 981–993.
  4. Connolly SJ, Eikelboom J, O'Donnell M, et al. Challenges of establishing new antithrombotic therapies in atrial fibrillation. *Circulation* 2007; 116: 449–455.
  5. Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2008; 51: 810–815.
  6. Poli D, Antonucci E, Grifoni E, et al. Stroke risk in atrial fibrillation patients on warfarin. Predictive ability of risk stratification schemes for primary and secondary prevention. *Thromb Haemost* 2009; 101: 367–372.
  7. Lip GY, Zarifis J, Watson RD, et al. Physician variation in the management of patients with atrial fibrillation. *Heart* 1996; 75: 200–205.
  8. Nieuwlaat R, Capucci A, Lip GY, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2006; 27: 3018–3026.
  9. Wysokinski WE, Owen WG, Fass DN, et al. 2nd. Atrial fibrillation and thrombosis: immunohistochemical differences between in situ and embolized thrombi. *J Thromb Haemost* 2004; 2: 1637–1644.
  10. Kamath S, Blann AD, Chin BS, et al. A prospective randomized trial of aspirin-clopidogrel combination therapy and dose-adjusted warfarin on indices of thrombogenesis and platelet activation in atrial fibrillation. *J Am Coll Cardiol* 2002; 40: 484–490.
  11. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged study, BAFTA): a randomized controlled trial. *Lancet* 2007; 370: 493–503.
  12. Rash A, Downes T, Portner R, et al. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007; 36: 151–156.
  13. Sato H, Ishikawa K, Kitabatake A, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. *Stroke* 2006; 37: 447–451.
  14. Healey JS, Hart RG, Pogue J, et al. 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.
  15. Lee BH, Park JS, Park JH, et al. The effect and safety of the anti-thrombotic therapies in patients with atrial fibrillation and CHADS2 score 1. *J Cardiovasc Electrophysiol* 2010; in press.
  16. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.
  17. Gorin L, Fauchier L, Nonin et al. Antithrombotic treatment and the risk of death and stroke in patients with atrial fibrillation and a CHADS2 score=1. *Thromb Haemost* 2010; 103: 833–840.
  18. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 546S–592S.
  19. Apostolakis S, Shantsila E, Lip GY, et al. Contra: „Anti-platelet therapy is an alternative to oral anticoagulation for atrial fibrillation“. *Thromb Haemost* 2009; 102: 914–915.
  20. Healey JS. Pro: „Anti-platelet therapy is an alternative to oral anticoagulation for atrial fibrillation“. *Thromb Haemost* 2009; 102: 912–913.
  21. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. *Chest* 2009; pre-published online doi:10.1378/chest.09–1584.
  22. Lip GYH, Halperin JL. Improving stroke risk stratification in atrial fibrillation. *Am J Med* 2010; in press.
  23. Rietbrock S, Plumb JM, Gallagher AM, et al. How effective are dose-adjusted warfarin and aspirin for the prevention of stroke in patients with chronic atrial fibrillation? An analysis of the UK General Practice Research Database. *Thromb Haemost* 2009; 101: 527–534.
  24. Tay KH, Lip GY, Lane DA. Atrial fibrillation and stroke risk prevention in real-life clinical practice. *Thromb Haemost* 2009; 101: 415–416.