

## Pro/Contra Article

# Contra: “Anti-platelet therapy is an alternative to oral anticoagulation for atrial fibrillation”

Stavros Apostolakis; Eduard Shantsila; Gregory Y. H. Lip; Deirdre A. Lane

Haemostasis Thrombosis and Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

**A**trial fibrillation (AF) is the most common sustained cardiac arrhythmia. Its prevalence increases with age, from less than 0.1% per year in those under 40 years old to 10% per year in people  $\geq 80$  years (1–3). The risk of stroke associated with AF is in the range of 1.9% to 18% per year, depending on associated stroke risk factors. Thus, prevention of thromboembolism should be considered in all patients with AF or atrial flutter (AFL). Estimating the risk of stroke for an individual patient is a crucial step for the decision to provide the correct currently available antithrombotic strategy (1–3). Certain schemes for stratification of stroke risk can be used to identify patients who will benefit more from antiplatelet or anticoagulant agents. Still, individual risk for thromboembolism or bleeding varies over time, so the need for anticoagulation must be reevaluated periodically and the antithrombotic strategy might periodically change (3).

Vitamin K antagonists (VKAs) have been recommended for high-risk patients and in current guidelines, anti-platelets are considered a reasonable option for low-risk patients (1–3). In moderate-risk patients guidelines are rather ‘loose’ as either VKAs or aspirin can be used and unfortunately this causes uncertainty for many clinicians. Assessment of the net clinical benefit between stroke prevention and bleeding risk may help (3–6). Nonetheless, all patients do not fit to the ideal trial-profile and many moderate-high-risk patients with AF can not be treated with VKAs. Thus, the need for alternative antithrombotic treatment strategies has emerged.

From the currently available oral anti-thrombotic strategies, the VKAs have been proved superior in reducing the incidence of thromboembolic complications in high-risk patients with AF, whether paroxysmal, persistent or permanent (7). This has been particularly emphasised by the ACTIVE-W study (8). The trial was prematurely stopped because of a clear benefit for stroke prevention for the warfarin arm over the combination of clopidogrel/aspirin. Indeed, the primary endpoints – rates of vascular events, defined as stroke, embolism, myocardial infarction and vascular death – were significantly higher in the clopidogrel/aspirin group than in the warfarin group. Of note, the incidence of

major bleeding was similar in the two groups. Thus, clopidogrel/aspirin was not only less efficient but also as dangerous as warfarin with regard to major bleeding events.

However, there are many concerns about the VKAs. Firstly, they have a narrow therapeutic range and require regular monitoring of the international normalised ratio (INR). Patients may not be treated with a VKA for a number of reasons, including concerns about interactions with other drugs, the increased risk of haemorrhage, inadequate compliance or monitoring, and patients’ preference to avoid VKA therapy. Thus, alternative strategies have to be developed for patients unsuitable for VKA. Common sense suggests that when the optimal therapeutic option is contraindicated or unsuitable, the second best alternative should be used. Thus, two questions arise: first, when is the optimal therapeutic option contraindicated and how is ‘unsuitable for VKA’ defined? Second, which is the next best therapeutic option after VKAs for the management of high risk patients with AF?

The ACTIVE-A study recently attempted to answer the second question (9). This trial studied clopidogrel/aspirin combination therapy for stroke prevention in moderate-high-risk patients with AF for whom VKA therapy was unsuitable. The addition of clopidogrel to aspirin reduced the risk of major vascular events (relative risk [RR] with clopidogrel, 0.89; 95% confidence interval [CI], 0.81–0.98;  $P=0.01$ ), and especially stroke (RR 0.72; 95% CI, 0.62–0.83;  $P<0.001$ ), but increased the risk of major hemorrhage (RR 1.57; 95% CI, 1.29–1.92;  $P<0.001$ ) (9). Thus, combination antiplatelet therapy seems to be the second best alternative to VKAs (and better than aspirin alone) for the prevention of thromboembolism in patients with AF.

However, ACTIVE-A fails to adequately answer the first question. The purpose of ACTIVE-A was to enroll patients who were ineligible for anticoagulation therapy with VKA. Indeed, the definition of ‘non suitable’ also included patients who did not want to take VKA and doctors who did not want to put their patients on VKA although they would have had benefitted from VKA therapy compared to dual antiplatelet therapy. Less than one quarter of participants had a clearly documented contraindi-

Correspondence to:  
Dr. Deirdre A. Lane  
Haemostasis Thrombosis and Vascular Biology Unit  
University of Birmingham Centre for Cardiovascular Sciences  
City Hospital, Birmingham, UK  
Tel.: +44 121 507 5080, Fax: +44 121 507 5907  
E-mail: deirdre.lane@swbh.nhs.uk

Received: August 14, 2009  
Accepted after minor revision: September 29, 2009

Prepublished online: October 19, 2009  
doi:10.1160/TH09-08-0563

cation to VKA therapy, whilst the preference of a patient not to take a VKA was the reason given for enrollment of a remaining 25% of participants. Yet evidence suggests that physician's judgment can be influenced by multiple factors and patient's preference can be affected by how therapeutic options are presented (10, 11).

When the trial was first presented, the legitimacy of many patients deemed not to be suitable for warfarin therapy at enrolment was questioned by discussants, given that a year later only a small proportion apparently still had the same relative contraindication to warfarin (12). Indeed, the trial discussant emphasised that it does not mean that 'once on clopidogrel/aspirin, always on clopidogrel/aspirin' as reconsidering the patient at follow-up clinical reviews might have resolved the issue that prevented initial use of VKA (12). Also, bleeding rates with clopidogrel/aspirin combination therapy were increased by >50% and are of similar magnitude to that seen with VKA use (9). Even aspirin monotherapy is not a safe option as shown in the BAFTA trial, where warfarin (INR 2–3) was clearly superior to aspirin 75 mg monotherapy in terms of stroke prevention, with similar major bleeding event rates – as has been previously debated in this journal (13, 14). Thus, the category of AF patients to whom the clopidogrel/aspirin combination therapy would be best used remains

to be determined. Until then, well-managed VKAs should remain the gold standard of antithrombotic care for all eligible patients with AF.

Indeed, VKA is even more effective if used correctly. The ACTIVE investigators themselves have shown that those patients on warfarin with INR values within the therapeutic range are those that actually benefit from anticoagulation therapy (15). A real challenge of a health care system is to create the primary care facilities that will ensure close monitoring and guidance of patients on anticoagulation (16). A revolution in thromboembolism prevention is to be expected from novel new oral anticoagulants (17). Additional developments will also have to be considered, such as the evolution of stroke risk stratification schema, to be much more inclusive of known stroke risk factors that would help identify 'truly low-risk' individuals that would not need any antithrombotic drug, whilst implying that the presence of one or more risk factors, using the recently proposed CHA<sub>2</sub>DS<sub>2</sub>-VASc [C Cardiac failure or dysfunction, H Hypertension, A Age over 75 years [Doubled], D Diabetes, S Stroke [Doubled] – Vascular disease, A Age 65–74 and S Sex category (Female)], merits the consideration of anticoagulation therapy (18), with (well-controlled) dose-adjusted VKA therapy or with new oral anticoagulants, such as the oral direct thrombin inhibitors.

## References

- 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 fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008; 99: 295–304.
- Poli D, Antonucci E, Grifoni E, et al. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost* 2009; 101: 938–942.
- Fuster V, Rydén LE, Cannom DS, et al.; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006; 8: 651–745.
- Palareti G, Cosmi B. Bleeding with anticoagulation therapy – who is at risk, and how best to identify such patients. *Thromb Haemost* 2009; 102: 268–278
- McBane RD, Hodge DO, Wysokinski WE. Clinical and echocardiographic measures governing thromboembolism destination in atrial fibrillation. *Thromb Haemost* 2008; 99: 951–955.
- Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009; 151: 297–305.
- Lip GY. Paroxysmal atrial fibrillation, stroke risk and thromboprophylaxis. *Thromb Haemost* 2008; 100: 11–13.
- The ACTIVE Writing Group on behalf of the ACTIVE Investigators: Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; 367: 1903–1912.
- The ACTIVE Investigators: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009; 360: 2066–2067.
- Man-Son-Hing M, O'Connor AM, Drake E, et al. The effect of qualitative vs. quantitative presentation of probability estimates on patient decision-making: a randomized trial. *Health Expect* 2002; 5: 246–255.
- Nieuwlaat R, Capucci A, Camm AJ, et al.; Euro Heart Survey Investigators: Atrial fibrillation management: A prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005; 26: 2422–2434.
- Jeffrey S. ACTIVE-A: Clopidogrel and aspirin reduce CV events in atrial fibrillation. [theheart.org](http://theheart.org). [Clinical Conditions > Arrhythmia/EP > Arrhythmia/EP]; Mar 31, 2009. Accessed at <http://www.theheart.org/article/955787.do> on Aug 12, 2009.
- Mant JW. Pro: 'Warfarin should be the drug of choice for thromboprophylaxis in elderly patients with atrial fibrillation'. Why warfarin should really be the drug of choice for stroke prevention in elderly patients with atrial fibrillation. *Thromb Haemost* 2008; 100: 14–15.
- Hylek EM. Contra: 'Warfarin should be the drug of choice for thromboprophylaxis in elderly patients with atrial fibrillation'. Caveats regarding use of oral anticoagulant therapy among elderly patients with atrial fibrillation. *Thromb Haemost* 2008; 100: 16–17.
- Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S, ACTIVE W Investigators: Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centres and countries as measured by time in therapeutic range. *Circulation* 2008; 118: 2029–2037.
- Tay KH, Lip GY, Lane DA. Atrial fibrillation and stroke risk prevention in real-life clinical practice. *Thromb Haemost* 2009; 101: 415–416.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al.; the RE-LY Steering Committee and Investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009; epub ahead of print.
- 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: The Euro Heart Survey on Atrial Fibrillation. *Chest* 2009; epub ahead of print.