

**Additional material****Letter to the Editor****Comments on the Spanish Society of Cardiology Critical Review of the ESC 2010 Clinical Practice Guidelines on Atrial Fibrillation***Comentarios al análisis crítico de la Sociedad Española de Cardiología de la guía de práctica clínica de fibrilación auricular 2010 de la ESC***To the Editor,**

We read with interest the article by Anguita et al¹, providing a critical review of the 2010 European Society of Cardiology (ESC) Clinical Practice Guidelines on Atrial Fibrillation². The writers take issue with various aspects of the 2010 ESC guidelines, and we offer the following comments. Contrary to their assumption, Anguita et al¹ should be aware that the previous 2006 ACC/AHA/ESC guidelines have only been updated with *focussed updates* on dabigatran, dronedarone and rate /rhythm control, rather than being a full guideline re-write per se.

Stroke prevention. Anguita et al¹ suggest that 'No consensus exists in the medical literature regarding whether the new criteria included, such as female sex and a history of vascular disease limited to angina, are associated with a greater embolic risk in patients with AF'¹. This point needs further discussion.

Many of the original risk factors for stroke were derived from the non-warfarin arms of trial cohorts - in the historical trials, females were under-represented, many risk factors were not systematically recorded nor uniformly defined and <10% of those screened were ultimately randomised³. Thus, additional data are needed from epidemiological and cohort studies.

As an example, the Stroke in AF Working Group systematic review (largely driven by trial data from non-warfarin treated patients) even found that history of heart failure (the 'C' in CHADS₂, which was a scoring system derived from the AF Investigators and SPAF risk schemes, part of the historical trial dataset)⁴. Contrary to the assertion by Anguita et al¹, numerous studies have now shown how vascular disease (myocardial infarction, peripheral artery disease) confers an increased risk of stroke and/or death in AF, which are the 2 endpoints significantly reduced by oral anticoagulation⁵⁻⁷. In the most recent analysis of 87,202 patients with non-valvular AF, vascular disease was even an independent predictor of stroke/thromboembolism and significantly improved the predictive ability of the CHADS₂ score⁶. Angina per se is probably not a good indicator for definite underlying vascular disease, although one early study did suggest that symptomatic angina did confer an independent risk for stroke in AF⁸. Females also seem to have a disproportionate risk of stroke when AF develops and various studies support the inclusion of female gender as a stroke risk factor^{4,9}.

We accept the uncertainty raised on hypertension - more contemporary studies do suggest that uncontrolled hypertension is more a risk, rather than well-controlled blood pressure¹⁰, but the Stroke in AF Working Group⁴ had defined this significant risk factor as a history of hypertension or uncontrolled blood pressure, given the variable definitions from the historical trials.

Most other stroke risk schemes, including CHADS₂, when used to identify 'high risk' patients only have modest predictive value (c-statistics 0.6) and the artificial division into low/moderate/high risk strata evolved so that we could pick out the 'high risk' category to subject these patients to an inconvenient drug, warfarin. With the availability of new oral anticoagulants, the 2010 ESC guideline focuses more on improving our identification of 'truly low risk' patients, de-emphasises the (artificial) low/moderate/high risk stratification approach and recommended the use of a risk factor based approach with the CHA₂DS₂-VASc score². After all, any stroke risk factor will confer a risk stroke when present with AF. Since the original validation study, other independent validation studies have been published for CHA₂DS₂-VASc, which is more inclusive of common stroke risk factors¹¹⁻¹⁵. The advantage of CHA₂DS₂-VASc is that it consistently outperforms all other published stroke risk schemes for identifying 'truly low risk' patients who do not need any antithrombotic therapy, whilst those with ≥1 stroke risk factors can be considered for effective stroke prevention therapy, which is essentially oral anticoagulation with either (very) well controlled warfarin or one of the new agents².

A recent Spanish study has even shown that the CHA₂DS₂-VASc risk stratification schema was better in discriminating between patients at a low and intermediate risk of thromboembolic complications when compared to 2006 ACC/AHA/ESC guideline, 8th ACCP, and Framingham schemes¹⁴. Also, CHA₂DS₂-VASc even seems to refine stroke risk assessment in 'low-risk' AF patients after ablation¹⁵. Certainly, CHA₂DS₂-VASc is as good as - and possibly better^{12,13} - than scores such as CHADS₂ in identifying patients who develop stroke. Whilst CHADS₂ is simple, most now agree that it does not include many common stroke risk factors¹⁶ and furthermore, its validity has even been questioned¹⁷. Indeed, most cardiologists would offer anticoagulation to a 74 year old man with AF who has peripheral artery disease, recognising that such a patient is at high risk of stroke - such a patient has a CHADS₂ score of 0 (hence, 'no anticoagulation' recommended in the older guidelines) but this hypothetical patient does have a CHA₂DS₂-VASc score=2, and thus, anticoagulation is recommended as per the 2010 ESC guidelines. In their section on 'recommendations for anticoagulant therapies' some statements by Anguita et al¹ are misleading. Guidelines should be applicable for >80% of the time, for >80% of the patients, and the ESC guideline stroke risk assessment approach would 'cover' the most of the patients we commonly seen in everyday clinical practice. The ESC guideline already clearly recommends that antithrombotic therapy is necessary in all patients with AF unless they are 'age <65 and low risk', and thus, young women who essentially have no risk factors (ie. lone AF) would fall into this category². As a consequence, patients with 'female gender' only as a single risk factor (but still a CHA₂DS₂-VASc score=1 on that basis) would not need anticoagulation, if they fulfil the criteria of 'age <65 and lone AF'. The central issue is carefully defining 'truly low risk' and the CHA₂DS₂-VASc score helps, as it performs best in identifying 'low risk' AF patients².

In the section on management of AF patients who present with an acute coronary syndrome (ACS) and/or require PCI/stenting, Anguita et al¹ take issue with the recommendation that patients with stable vascular disease (including >1 year post-stenting) can be managed

with oral anticoagulation (OAC) monotherapy. The addition of aspirin to OAC substantially increases the risk of major bleeding and results in a 2.4-fold increase in intracranial haemorrhage. Thus, long term combination therapy would probably outweigh the potential small risk of late stent thrombosis, which has a multifactorial aetiology. Whilst RCTs are awaited, this approach of OAC monotherapy is supported by European¹⁸ and North American experts^{19,20}.

Antiarrhythmic drugs. Anguita et al¹ write that they are ‘suspicious’ about the ESC recommendations relating to dronedarone. First, they seem to suggest the dronedarone was recommended in the ESC guidelines for use in patients with permanent AF, which is not correct. All recommendations in the ESC guideline relate to non-permanent (paroxysmal or persistent) AF. Both the ESC guidelines and the ACCF/AHA/HRS guidelines²¹ provide near identical recommendations relating to the use of dronedarone for reduction of hospitalizations (Class IIa, LoE B). This recommendation was based on the results of the ATHENA trial²² (a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter) and it directly follows from the basis for approval given by the USA Food and Drugs Administration (FDA) and the United Kingdom National Institute for Health and Clinical Excellence (NICE). The US guidelines do not give any specific recommendations for the use of dronedarone for the reduction or delay of AF recurrence, possibly because of the wording of the FDA approval. However, the modified flow chart in the updated guidelines suggested that its use for this purpose was anticipated. The European Medicines Agency (EMA) wording specifically approved dronedarone for the prevention of AF recurrences and the ESC guideline reflects this approval. Dronedarone was given a class 1 LoE A recommendation as an antiarrhythmic agent for patients with AF on the basis of consistent although modest antiarrhythmic effects demonstrated in the largest ever antiarrhythmic drug development programme for AF. Anguita et al¹ also make much of the ordering of antiarrhythmic drugs within the text boxes in flow charts in the ESC guideline. They point out that dronedarone is always positioned first, but the legend to the figure clearly states that the antiarrhythmic drugs are arranged alphabetically. The positioning of dronedarone does not imply that it is superior to other antiarrhythmics within the same box. This way of ordering alternative treatments is entirely conventional. It was used in the 2001 and 2006 versions of the ACC/AHA/ESC AF guidelines and in the 2011 AACC/AHA/HRS Update. It may be unfortunate and visually misleading but we fail to see what else could or should have been done. Anguita et al¹ also complain that the ESC guideline picks out hypertension with LV hypertrophy as a distinct pathology to be considered when choosing an antiarrhythmic agent. This was entirely in line with previous and current guidelines except for the Canadian guidelines on AF²³. In the latter guideline, the authors chose a range of left ventricular ejection fractions in order to guide antiarrhythmic drug choice. This was a departure from usual practice but has much to recommend it. The Canadian guideline did not consider hypertrophy (and consequent diastolic dysfunction) which might also be considered as an omission. Post approval pharmacovigilance data suggested that dronedarone may be associated with hepatotoxicity²⁴. Appropriate epidemiological and basic science studies were put in place to investigate this further and the EMA immediately proposed additional liver function tests during follow-up. Very recently, the PALLAS trial²⁵ (permanent atrial fibrillation outcome study using dronedarone on top of standard therapy) which explored a potential new indication for dronedarone recruited patients with permanent AF and randomized them to dronedarone or placebo on top of optimum medical therapy. The Data and Safety Monitoring Board halted the trial early when only 3236

patients had been recruited because of an increase in all-cause mortality, stroke rate and cardiovascular hospitalizations, particularly for heart failure, associated with dronedarone. These results have already been assessed by European regulators who continue to believe that dronedarone has a favorable benefit-risk ratio provided that it is not administered to patients with permanent AF or to patients with recurrent AF any degree of past or present heart failure. The ESC has kept in close touch with the developments relating to dronedarone and has issued two press releases to draw attention to the new findings and to reassure its members that the ESC would reconsider its “Guidelines for the Management of Atrial Fibrillation” with a focussed update as soon as practicable. The guideline committee is now at work and it appreciates all constructive comments such as many of those put forward by Anguita and colleagues. However, the innuendo of “suspicion” is not well founded and should have been more restrained.

CONFLICTS OF INTEREST

Both authors were members of the Task Force for the 2010 ESC guidelines on atrial fibrillation, and Prof Camm acted as Chair of the Task Force.

Prof Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. Prof Camm has served as a consultant and has been on the speakers bureau for various pharmaceutical companies, and was a member of the steering committee for the PALLAS trial.

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