

effects.<sup>5</sup> Likewise, other biomarkers such as the level and function of endothelial progenitor cells (EPC) could prove to be helpful to reflect endothelial damage caused by air pollutants, as it has been recently shown that exposure to ambient fine particles (PM<sub><2.5</sub> μm) induced reversible vascular injury, reflected by depletion of circulating EPC levels, both in humans and mice.<sup>6</sup> It would be valuable to determine whether exposure to ambient PM and UFP in particular result in increased levels of EMPs as well. Interestingly, exposure to secondhand smoking, thought to mimic some of the effects associated with PM exposure and to activate similar pathogenic mechanisms, have been shown to result in increased EMP as well as EPC.<sup>7</sup> Therefore, it would be highly desirable to use these biomarkers in the assessment of vascular effects caused by the exposure to UFP, as suggested by the author.

Jesus A. Araujo

Division of Cardiology, Department of Medicine,  
David Geffen School of Medicine, University of California,  
Los Angeles, CA, United States

E-mail address: JAraujo@mednet.ucla.edu

Available online 4 February 2012

## REFERENCES

1. Araujo JA. Are ultrafine particles a risk factor for cardiovascular diseases? Rev Esp Cardiol. 2011;64:642–5.
2. Brook RD, Rajagopalan S, Pope III CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al.; on behalf of the American Heart Association Council on Epidemiology and Prevention CotKICDaCoNPAaM. Particulate Matter Air Pollution and Cardiovascular Disease. An Update to the Scientific Statement From the American Heart Association. Circulation. 2010;121:2331–78.
3. Araujo J. Particulate air pollution, systemic oxidative stress, inflammation, and atherosclerosis. Air Qual Atmos Health. 2011;4:79–93.
4. Nozaki T, Sugiyama S, Koga H, Sugamura K, Ohba K, Matsuzawa Y, et al. Significance of a multiple biomarkers strategy including endothelial dysfunction to improve risk stratification for cardiovascular events in patients at high risk for coronary heart disease. J Am Coll Cardiol. 2009;54:601–8.
5. Mallat Z, Benamer H, Hugel B, Benessiano J, Steg PG, Freyssinet JM, et al. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. Circulation. 2000;101:841–3.
6. O'Toole TE, Hellmann J, Wheat L, Haberzettl P, Lee J, Conklin DJ, et al. Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. Circ Res. 2010;107:200–3.
7. Heiss C, Amabile N, Lee AC, Real WM, Schick SF, Lao D, et al. Brief secondhand smoke exposure depresses endothelial progenitor cells activity and endothelial function: sustained vascular injury and blunted nitric oxide production. J Am Coll Cardiol. 2008;51:1760–71.

SEE RELATED ARTICLE:

DOI: 10.1016/j.rec.2011.10.026

doi:10.1016/j.rec.2011.12.006

## 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,

The critique by Anguita et al.<sup>1</sup> perpetuates many misconceptions. Many reported risk factors for stroke in atrial fibrillation (AF) were derived from the non-warfarin arms of trial cohorts but in the historical trials, females were under-represented, many risk factors were not systematically recorded or not uniformly defined and <10% of those screened were ultimately randomised. Thus, additional data are needed from epidemiological and cohort studies. Numerous studies have now shown how the risk of stroke rises from age >65 and that vascular disease also increases the risk of stroke and/or death in AF<sup>2</sup>. Females have a disproportionate risk of stroke when AF develops, and various studies support the inclusion of female gender as a stroke risk factor<sup>2</sup>. More contemporary studies do suggest that uncontrolled hypertension is more of a risk, rather than well-controlled blood pressure. After all, any (single) stroke risk factor will confer a risk of stroke when present with AF.

The previous artificial division into low/moderate/high stroke 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 (OAC), 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 CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Since the original validation study, other independent validation studies have been published for CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>2</sup>. The advantage of CHA<sub>2</sub>DS<sub>2</sub>-VASc, which is more inclusive of common stroke risk factors, is that it consistently identifies '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 OAC with either (very) well controlled warfarin or one of the new agents. Certainly, CHA<sub>2</sub>DS<sub>2</sub>-VASc is as good as—and possibly better—than scores such as CHADS<sub>2</sub> in identifying patients who develop stroke.

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 (i.e. lone AF) would fall into this category. As a consequence, patients with 'female gender' only as a single risk factor (but still a CHA<sub>2</sub>DS<sub>2</sub>-VASc score=1 on that basis) would not need anticoagulation, if they fulfil the criteria of 'age <65 and lone AF'.

Anguita et al.<sup>1</sup> take issue with the recommendation that AF patients with stable vascular disease can be managed with 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 (multifactorial) risk of late stent thrombosis.

Anguita et al.<sup>1</sup> suggest the dronedarone was recommended for use in permanent AF, which is incorrect. Both the ESC and the American guidelines provide near identical recommendations relating to the use of dronedarone for reduction of hospitalizations (Class IIa, LoE B) and it directly follows from its regulatory

approval. Dronedronarone was also given a recommendation as an antiarrhythmic agent for patients with AF on the basis of consistent although modest antiarrhythmic effects. The alphabetically-arranged positioning of dronedronarone in ESC guideline flowcharts does not imply that it is superior to other antiarrhythmics within the same category.

Anguita et al.<sup>1</sup> also argue 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 which chose a range of left ventricular ejection fractions to guide antiarrhythmic drug choice.

Post approval pharmacovigilance data suggested that dronedronarone may be associated with hepatotoxicity. One trial found an increase in all-cause mortality, stroke rate and cardiovascular hospitalizations, particularly for heart failure, associated with dronedronarone treatment in permanent AF. The ESC has kept in close touch with developments and would re-consider its AF guidelines with a focussed update as soon as feasible.

The full text of this article is available only as supplementary material.

### CONFLICT 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.

### SUPPLEMENTARY MATERIAL



Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.rec.2011.12.008](https://doi.org/10.1016/j.rec.2011.12.008).

Gregory Y.H. Lip<sup>a,\*</sup> and A. John Camm<sup>b</sup>

<sup>a</sup>Centre for Cardiovascular Sciences, University of Birmingham, City Hospital, Birmingham, United Kingdom

<sup>b</sup>Centre for Cardiovascular Sciences, St. George's University of London, London, United Kingdom

\* Corresponding author:

E-mail address: [g.y.h.lip@bham.ac.uk](mailto:g.y.h.lip@bham.ac.uk) (Gregory Y.H. Lip).

Available online 18 February 2012

### REFERENCES

1. Anguita M, Worner F, Domenech P, Marín F, Ortigosa J, Pérez-Villacastín J, et al. Nuevas evidencias, nuevas controversias: análisis crítico de la guía de práctica clínica sobre fibrilación auricular 2010 de la Sociedad Europea de Cardiología. *Rev Esp Cardiol.* 2012;65:7–13.
2. Lip GY. Stroke in atrial fibrillation: epidemiology and thromboprophylaxis. *J Thromb Haemost.* 2011;9 Suppl 1:344–51.

#### SEE RELATED ARTICLES:

DOI: [10.1016/j.rec.2011.10.005](https://doi.org/10.1016/j.rec.2011.10.005)

DOI: [10.1016/j.rec.2012.01.004](https://doi.org/10.1016/j.rec.2012.01.004)

[doi:10.1016/j.rec.2011.12.008](https://doi.org/10.1016/j.rec.2011.12.008)

### Comments on the Spanish Society of Cardiology Critical Review of the ESC 2010 Clinical Practice Guidelines on Atrial Fibrillation. Response

#### *Comentarios al análisis crítico de la Sociedad Española de Cardiología de la guía de práctica clínica de fibrilación auricular 2010 de la ESC. Respuesta*

#### To the Editor,

We have read with great interest the comments given by professors Lip and Camm regarding our recent critical review of the 2010 atrial fibrillation (AF) guidelines from the ESC,<sup>1</sup> and we would like to thank them for their contributions to our article, which may clarify certain aspects of this subject that were left unresolved, in our opinion, by the guidelines. First of all, we would like to say that we do not refute that female sex, arterial hypertension, heart failure, and vascular disease can all increase the risk of embolism in patients with AF, but it is not clear whether this is the case only in certain situations or as a general rule. As the authors themselves and the guidelines of the ESC recognize, heart failure in the absence of left ventricular systolic dysfunction, controlled hypertension with no ventri-

cular hypertrophy, a diagnosis of angina (with no other evidence of vascular disease), and female sex with no other risk factors for embolism and age <65 years may not constitute significant risk. In fact, in their letter Lip and Camm state that female sex as a lone risk factor, and therefore a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, may not require anticoagulant therapy. However, although the text of the ESC guidelines contains this same idea, the tables of recommendations (Tables 8 and 9) include anticoagulation for a score of 1 as a general rule, without specifying any details. We believe that this might confuse doctors reading the guidelines and we assume that it will be clarified in the updated version of the ESC guidelines on AF coming out in 2012. We can agree “in general terms” that the CHA<sub>2</sub>DS<sub>2</sub>-VASc scale can identify additional subgroups not covered by the CHADS<sub>2</sub> scale and better categorizes patients with a low (0) and high (2 or more) embolic risk score. However, in addition to the fact that not all studies agree that a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 reflects a greater risk of embolism,<sup>2</sup> the greatest caution against applying this standard is the total lack of evidence that anticoagulation therapy in patients with a CHADS<sub>2</sub> ≤2 and a low CHA<sub>2</sub>DS<sub>2</sub>-VASc (1-2) score provides a significant net clinical benefit if we assess the hypothetical decrease in embolic events versus the possible