

Letters to the Editor

Circulating Microparticles From Patients With Coronary Artery Disease Cause Endothelial Dysfunction

Micropartículas circulantes de pacientes con enfermedad coronaria causan disfunción endotelial

To the Editor,

In a recent article in *Revista Española de Cardiología*,¹ the author considered the debate about the impact of microparticles (MP), specially ultrafine ones, on the onset of acute coronary syndrome (ACS). However, in order to determine what the exact role of these particles is in the genesis of ACS, as well as to quantify the added risk and its effect on risk stratification of patients with ACS, the authors did not discuss the markers currently available. These are based on demonstrating the presence of endothelial dysfunction associated with this condition. Both experimental and clinical studies have indicated that endothelial dysfunction can be considered as a biomarker, as such dysfunction has been analyzed in different studies as an independent predictor of adverse events occurring in patients diagnosed with ACS.^{2,3} To this end, plasma levels of CD31+/annexin V+ microparticles have been quantified as a marker of endothelial dysfunction.^{4,5} This same marker has been assessed recently.⁶ An increase in plasma levels has been considered a risk factor for cardiovascular disease with worse endothelial function, itself considered an independent risk factor for adverse cardiovascular events in patients diagnosed with stable ACS. Similarly, Nozaki et al.⁷ studied concentrations of CD144+ as a marker of endothelial dysfunction in a strategy using different biomarkers, such as B natriuretic peptide, highly sensitive C reactive protein, and the quantity of circulating microparticles. These give an indication of endothelial dysfunction in a population at high risk of experiencing ACS. The authors found that high MP levels are an independent predictor of cardiovascular death and ACS. This biomarker also provides better stratification of cardiovascular risk and allows patients to benefit from more aggressive therapy that might improve their prognosis. Endothelial dysfunction caused by circulating MP is a risk factor for

cardiovascular disease and can be added to the risk factors considered as "traditional." Different biomarkers can be measured, and confirm the importance of these MP in the genesis of ACS.

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Circulating Microparticles From Patients With Coronary Artery Disease Cause Endothelial Dysfunction. Response

Micropartículas circulantes de pacientes con enfermedad coronaria causan disfunción endotelial. Respuesta

To the Editor,

I would like to thank the interesting comments of Bueno Jiménez et al. published in *Revista Española de Cardiología* in relation to the Editorial article¹ where I discussed the plausibility of the exposure to ambient ultrafine particles (UFP) as a risk factor for cardiovascular diseases. Numerous epidemiological studies support the association of exposure to ambient particulate matter (PM) with cardiovascular ischemic endpoints² and substantial experimental animal work support the feasibility for causality in

the case of atherosclerosis.³ While it is likely that PM with a smaller particle size such as UFP carry greater cardiovascular toxicity than particles with larger size, the possibility that inhaled UFP could translocate and access the systemic circulation still awaits more definite confirmation.³ Ambient PM can lead to systemic vascular effects by several hypothetical mechanisms that still remain to be elucidated.¹ The author's comment about the need to employ novel biomarkers for endothelial dysfunction, such as circulating endothelium-derived microparticles (EMP), that can better capture the cardiovascular risk potentially attributable to ambient PM and UFP is very appropriate as they could also aid in the identification of pathogenic mechanisms. EMPs, characterized by different phenotypes such as CD31⁺/CD41⁻, CD31⁺/annexin V⁺, CD144⁺ and/or CD62e⁺ appear not only to reflect endothelial dysfunction and serve as an stratifying biomarker⁴ but also to exert pathogenic actions such as procoagulant

effects.⁵ 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_{<2.5} μm) induced reversible vascular injury, reflected by depletion of circulating EPC levels, both in humans and mice.⁶ 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.⁷ 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.

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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.¹ 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 AF². Females have a disproportionate risk of stroke when AF develops, and various studies support the inclusion of female gender as a stroke risk factor². 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 CHA₂DS₂-VASc score. Since the original validation study, other independent validation studies have been published for CHA₂DS₂-VASc². The advantage of CHA₂DS₂-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, CHA₂DS₂-VASc is as good as—and possibly better—than scores such as CHADS₂ 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 CHA₂DS₂-VASc score=1 on that basis) would not need anticoagulation, if they fulfil the criteria of 'age <65 and lone AF'.

Anguita et al.¹ 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.¹ 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