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Milan, 18th August 2019

To the kind attention of

Prof. Paolo G. Camici

Editor in Chief

International Journal of Cardiology

Dear Prof Camici,

RE: Managing Thromboembolic Risk in Patients with Subclinical Atrial Fibrillation: A New Challenge for the Clinical Cardiologist

It is a pleasure to me to send to your kind attention the Editorial Commentary you kindly invited me to provide, about the article entitled “Oral anticoagulation for subclinical atrial tachyarrhythmias detected by implantable cardiac devices: an international survey of the AF-SCREEN Group” recently accepted to your Journal.

I declare that I am the sole author and that the paper is not submitted elsewhere. As you will find I reproduced a figure from another published article, for which I attached in the submission the Permission released from the original publisher.

Kind Regards

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Managing Thromboembolic Risk in Patients with Subclinical Atrial Fibrillation: A New Challenge for the Clinical Cardiologist

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In 1958 Senning and Elmqvist implanted the first permanent cardiac pacemaker (PM) to Arne Larsson, that lived for more than 40 years and died from different causes. Since then, the use of cardiac implanted electronic devices (CIEDs) largely increased, secondarily to the technological advances, with more patients being indicated for implant and a progressively increasing use[1], leading to the identification of a new entity, the CIED-detected 'Atrial High Rate Episodes' (AHREs)[2]. AHREs are episodes of asymptomatic fast atrial tachyarrhythmias that cannot be identified through traditional ECG. Usually, AHRE is also referenced as 'Subclinical Atrial Fibrillation' (SCAF)[2].

After being identified, has been hypothesized that SCAF could have been associated with a higher risk of developing clinical AF and with a higher thromboembolic risk. Since then, several studies reported a significant association between SCAF and these two clinical events, up to the pivotal ASSERT study[2,3]. In this study, data on 2451 patients implanted with a CIED showed that SCAF is associated with more than 5-fold risk of developing clinical AF and with more than 2-fold risk of having an ischemic stroke/systemic embolism, in particular in those patients with a higher thromboembolic risk ($CHADS_2$ ≥3)[3].

Moreover, a differential risk of stroke was hypothesized according to the AHRE burden. In a sub-analysis of the ASSERT trial, was reported that risk of stroke was substantially higher in those patients having a SCAF burden ≥24 hours than those with a SCAF burden within 5 minutes and 24 hours[4]. Conversely, in a paper by Boriani et al., from the SOS AF project (merging data from 3 different studies), it was shown that stroke/transient ischemic attack risk was similar irrespective of the SCAF

burden[5]. Recently, a meta-analysis showed that risk of stroke progressively increased with increasing SCAF duration[6]. On this background, the benefit/risk ratio of prescribing oral anticoagulant (OAC) is still unclear[2].

Currently, while some international guidelines do not consider the issue of SCAF patients, other ones suggest that on the basis of the evidence available only patients with a high risk of stroke or having a high burden of SCAF (≥24 hours) should be considered for OAC treatment. Notwithstanding, more data have been advocated to clarify if SCAF patients treated with OAC would have a consistent clinical benefit[2,7].

In this issue of *International Journal of Cardiology*, Boriani and colleagues presented the results of an international survey organized by the AF-SCREEN International Collaboration on diagnosis and management of AHRE[8]. In this study 310 physicians from Europe (76%), Asia/Oceania (15%) and North America (8%) answered to questions designed to understand the knowledge of physicians about AHRE, its diagnostic process and the clinical decision-making about OAC prescription.

In this interesting survey emerged that while most of the physicians understand that the presence of AHRE requires medical attention (96%), a large proportion of physicians believed that in patients with very short AHRE duration (between 30 seconds and 5 minutes) a surface ECG confirmation diagnostic is needed (41% of the answers), while 49% would decide to wait for a longer episode detected through the device and 63% would check the electrograms (EGMs) stored in the device.

Conversely, in patients with AHRE lasting from 5 minutes to 24 hours the majority of physicians would check the EGMs for further confirmation (74% of the answers).

Regarding the prescription of OAC, a large heterogeneity was found about the burden of AHRE in patients with a CHA_2DS_2-VASc 1 in males or 2 in females needed to justify the treatment, with 16% to 27% of physicians that would prescribe OAC according to the various burden measurements. In patients with a higher thromboembolic risk (CHA_2DS_2-VASc ≥2 in males or ≥3 in females) 30% of the physicians would start OAC irrespective of the AHRE burden, while 34% would start OAC only if AHRE lasted ≥5 minutes. Only few physicians (1.9%) wouldn't start OAC. Less uncertainty was found about patients that experienced prior stroke, in particular those patients with prior cardioembolic stroke. In these cases, the majority of physicians would prescribe OAC irrespective of the AHRE burden. In general, most of the physicians considered that in patients with AHRE lasting ≥24 hours duration the risk of stroke is similar than in patients with clinical AF[8]. At last, while 32% of physicians reported that in their opinion there is still insufficient evidence of a substantial risk of stroke in patients with AHRE, the large majority stated that while there is evidence of a substantial risk of stroke associated with AHRE, there is still a lack of evidence on the benefit of OAC[8].

This survey allows us to make some important considerations. On one side, while most of physicians consider AHRE a relevant issue, there is large heterogeneity in the knowledge related to the diagnostic process. On the other, there is a lot of indecision regarding the evaluation of stroke risk in patients with AHRE and the overall burden to be considered sufficient to justify the prescription of OAC. The only

clinical scenario for which most of physicians agreed regarding the need of OAC prescription, was related to those patients with a previous episode of stroke, consistently with the few guidelines recommendations[7]. In general, the survey underlined how most of physicians still need to have more evidence about the risk of stroke in patients with AHRE and in particular about the clinical benefit of prescribing OAC.

While appears clear how more educational initiatives are needed to better inform the physicians about the general features of AHRE and the associated risk of stroke, evidence coming from two on-going trials, ARTESiA[9] and NOAH–AFNET 6[10], will elucidate the impact of OAC in patients with AHRE. In particular, the ARTESiA study will provide data about patients with AHRE lasting from 5 minutes to 24 hours, for which evidence about a substantial stroke risk is still unclear.

Results of these studies will provide important evidence and clarify what is the most appropriate clinical approach for these patients, likely radically changing the management of AHRE patients and assisting the clinical cardiologist in taking the best decision.

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

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