Author's response to reviews

Title: Surface ECG interatrial block-guided treatment for stroke prevention: Rationale for an attractive hypothesis

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Cristina Balla, M.D. Ph.D (Reviewer 1):

We would like to thank Reviewer 1 for the comments that have helped us to improve our manuscript.

The authors describes an interesting hypothesis about the correlation of interatrial block and stroke prevention.

Thank you for this comment.

They suggest the possibility to use the P wave duration and morphology as a markers of atrial fibrillation and the need of anticoagulation to prevent stroke. I would expand more in depth the discussion to support this interesting hypothesis.

We have expanded more in depth the discussion to support our hypothesis.

Aamir Hameed (Reviewer 2):

We would like to thank Reviewer 2 for the comments that have helped us to improve our manuscript.
Dear Authors, Thank you for this very interesting debate about Interatrial block and AF and stroke. You have very lucidly presented the evidence and I agree with the recommendation that anticoagulation should be considered over and above the "documented atrial fibrillation" because it limits the population prone to having strokes being appropriately treated due to our lack of proper and cost effective surveillance systems.

Thank you for this comment.

The recent device based data suggest that AF of duration exceeding a few minutes may put patients at risk. Although this brings more insight into the clinical condition of anticoagulation without the classical clinical documentation of AF. As stated we also know that AF is a risk marker and not a clear causal factor for the strokes seen.

We are glad that Reviewer 2 agrees with our view.

We are also grappling with the double edged sword of anticoagulation with patients at higher risk of annual bleed. Whereas you have recommended anticoagulation for patients with a higher CHADS VASC score you have not mentioned the HASBLED risk. In patients in the 80's and 100's with polypharmacy and multiple risk factors confounding the clinical condition, a HASBLED score would be of paramount importance.

We have added an explanation regarding bleeding risk and HAS-BLED score: “Also, the bleeding risk of elderly patients that receive anticoagulation should be taken into account. HAS-BLED score for major bleeding is very useful for this risk assessment, although, in the case of AF the net clinical benefit of anticoagulation seems to exist in almost all patients, as the risk of ischemic stroke without anticoagulant treatment is higher than the risk of intracranial bleeding with anticoagulant treatment. [21]”

The point of variable fibrosis and expression of spectrum of AF, would make one think as to the role IAB both absolute and partial would play. We know that AF begets more AF. We also know that with more fibrosis the chances of AF go higher as seen in rheumatic heart disease. We also know that stroke even embolic and that in the presence of AF is multifactorial. Do we have enough evidence to show that there is a congruent relationship between IAB to fibrosis to AF to stroke. So is there evidence to suggest that patients with IAB may never go to AF or stroke or the contrary. If there are data to suggest that IAB is a milestone in the journey to stroke with a higher CHADS VASC score with a balanced HASBLED score then surely as you have suggested randomised clinical trials may be planned to answer this important question. However, if data does not support this causality then we should recommend that a study to show direct causality of IAB and AF/stroke be conducted. Importantly, if IAB is just a transient effect without AF in a normal non fibrotic atrium with a CHADS VASC risk of 1 would we again be considering oral anticoagulation. So the moot point is, have we placed IAB as an independent marker of stroke or do we need more data to substantiate that and once we have done that would we be positioned for more clinical data.

We have included new data regarding the association of atrial fibrosis assessed by late gadolinium enhancement cardiovascular magnetic resonance and advanced IAB: “Moreover,
extensive atrial fibrosis assessed by late gadolinium enhancement CMR has been associated with advanced IAB. [REF] Benito EM, De Luna AB, Baranchuk A, Mont L. Extensive atrial fibrosis assessed by late gadolinium enhancement cardiovascular magnetic resonance associated with advanced interatrial block electrocardiogram pattern. Europace. 2017;19:377.”

I assume that all of this is for non rheumatic AF. What about IAB and mild rheumatic disease (disease sparing the valve and causing more atrial fibrosis). Rheumatic disease, AF and stroke forms a large piece of the pie globally or more so in the developing world.

We have included a comment regarding patients with rheumatic disease: “Finally, we would like to clarify that our hypothesis is based on data of patients without rheumatic heart disease. However, patients with IAB and rheumatic disease probably have an even higher risk of stroke as the burden of atrial fibrosis is noteworthy in patients with AF and rheumatic heart disease. [REF]”.

The thought of reversing or remodelling IAB with ACE inhibitors, ARBs and statin would be worthwhile. The role of beta blockers and catecholamine block and surveillance of the P wave.

We have included the following sentence “Our hypothesis also opens the door to other drugs, for instance as the renin-angiotensin-aldosterone system inhibition might have a role in the reduction of the risk of developing new onset AF, [REF] these medications might improve prognosis of patients with advanced IAB.”

Would you recommend a standard ECG process paper speed and amplitude enhancement to study the P wave in detail?

We think that in most patients this is not necessary so we prefer not to mention it. A detailed description on how we recommend to measure the p wave can be found in “Martínez-Sellés M, Robledo LA, Baranchuk A. Interatrial Block and the Risk of Ischemic Stroke. J Atheroscler Thromb. 2017 Feb 1;24(2):185-186”