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Published in:
European Heart Journal

DOI:
10.1093/eurheartj/ehac092

ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–2
https://doi.org/10.1093/eurheartj/ehac092

DISCUSSION FORUM

Is APAF-CRT robust enough to change clinical practice?

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This commentary refers to 'AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial', by M. Brignole *et al.*, https://doi.org/10.1093/eurheartj/ehab569 and the discussion piece 'Ablate and pace for patients with atrial fibrillation: a fragile option?', by H. Kaur *et al.*, https://doi.org/10.1093/eurheartj/ehac091.

Kaur *et al.* raise the point of the fragility of results of APAF-CRT trial due to the relatively small population and consequently the small difference in the number of patients who died in the two study groups (7 vs. 20 patients) which make results vulnerable to random error. Applying the fragility index, Kaur *et al.* stated that two additional deaths in the ablation + CRT arm and two less deaths in the Drug arm (i.e. 9 vs. 18 deaths) would have resulted in a loss of statistical significance.[1]

Indeed, the fragility index has been suggested by some to use as a measure of the robustness of randomized controlled trials, since *P*-values are often misinterpreted. However, the fragility index has also limitations, namely the appropriateness for use only with dichotomous outcomes, since it disregards potential differences in time to event in both treatment arms, and the absence of cut-off values. Applying the survival-inferred fragility index (SIFI)[2] (a modified fragility index that takes into account the survival times) to APAF-CRT, the fragility score resulted 4. Even so, the fragility index is at odds with an adequate powered randomized controlled trial, and in this case, one that is prematurely stopped because of the superiority of one treatment arm to the other. Indeed APAF-CRT[3] was advised to stop prematurely as soon a minimal, but significant and clinically relevant difference was observed by the data safety and monitoring board. Considering this, it is not surprising that the fragility index of APAF-CRT is low. Also, the fragility index is dependent of the sample size, where smaller studies have lower indexes than larger studies.

Albeit the fragility index has its limitations, the point about fragility or robustness of findings in APAF-CRT is of great importance. In the sensitivity analysis (see Supplementary material online, *Table S6*), the 'fragility' of the primary endpoint was assessed by iterative estimates of the hazard ratio. From the eighth event onwards, the estimated hazard ratio was statistically significant, suggesting the robustness of our findings. Probably the best way to indicate the fragility or robustness of randomized controlled trials results is to include the confidence intervals as these may more directly indicate the size of an effect and its associated uncertainty[4] and the interpretation of the observed differences in the context of absolute estimates and measures of clinical significance, such as minimal clinically important differences.

We agree with the authors that the relatively small population is very relevant to consider, not only for statistical reasons (fragility) but also for the generalizability of results. Also, after APAF-CRT, much larger studies are needed that conclusively determine treatments effective to reduce mortality and will allow us to upgrade current recommendations of the guidelines of the European Society of Cardiology from Class IIa to Class I. We do hope that, also thanks to the impact of APAF-CRT on the scientific community, such larger trials will be performed in the near future.

Awaiting additional supportive evidence, we believe that APAF-CRT demonstrated that within 4 years, AV junction ablation + CRT was superior to drug therapy in this patient population (hazard ratio was 0.26 with a 95% confidence interval of 0.10–0.65) and has its clinical value.[5] Indeed, APAF-CRT can help clinicians to make better informed decisions for their patients with atrial fibrillation and heart failure.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

APAF-CRT trial is an investigator-initiated independent clinical trial, sponsored by a non-profit organization named Centro Prevenzione Malattie Cardiorespiratorie 'Nuccia e Vittore Corbella', Rapallo, Italy, which received an unrestricted research grant from The Boston Scientific Investigator Sponsored Research (ISR) Committee, Boston

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Scientific, St Paul, MN, USA. Boston did not influence the trial design, data collection, analysis, or the decision to publish.

Conflict of interest: M.R. received grants from Dutch Heart Foundation: RACE V, RED-CVD, CVON-AI, DECISION studies; grant from SJM/Abbott to institution: VIP-HF study; Grant for Medtronic to institution: Cryoballoon AF registry/biobank study. The other authors declare that there is no conflict of interest.

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