This Letter to the Editor refers to article “Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial” by Packer et al. (Published in JAMA. 2019;321:1261-1274): https://jamanetwork.com/journals/jama/fullarticle/2728676

A response to this letter is available: EUPC-D-21-00928, “Response to “CABANA: underpowered and with detrimental protocol changes. Is “ablation salvation”?” by Packer et al. [typesetter please add in hyperlinked DOI]

**Title: CABANA: underpowered and with detrimental protocol changes. Is “ablation salvation”?**

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The recently published CABANA trial demonstrated that catheter ablation was significantly more effective than anti-arrhythmic drugs for the reduction of hospitalizations and mortality (Intention-to-Treat, ITT, Analysis HR=0.83, 95%CI 0.74-0.93, p=0.001) [1], corresponding to a Number Needed to Treat (i.e. ablate) of 12.8 patients to obtain this benefit. This number is lower (and better) than what can be observed for some of the landmark device and drug-trials in the field of heart failure or coronary artery disease [2].

In 2009, when the study started enrolment, all-cause mortality was the primary endpoint [3], and the estimated number of enrolled patients was 3000 (randomized 1:1 to ablation or medical therapy). However, an update in the power calculation based on an estimated 10% mortality at 3.5 years follow-up allowed reduction of the sample to 2200 atrial fibrillation (AF) patients (v69 of the Protocol) [3]. Unfortunately, this calculation was wrong as the observed mortality in the trial was only 5 to 6% after 4.1 years of median follow-up [1]. Hence, the sample was insufficiently powered for the ITT analysis on the impact of ablation on mortality.

Back in 2009, immediately after the publication of CABANA-Pilot, in an Editorial published in Circulation Arrhythmia & Electrophysiology, the Principal Investigator stated that in CABANA no crossovers would be allowed (“Patients will be randomly assigned to catheter ablation or rate or rhythm control pharmacological therapy as first-line treatment. All patients will be anticoagulated accordingly, and crossover is not permitted”) [4]. However, nine years later, the protocol was published and mentioned a 25 to 30% expected crossover rate in patients randomized to the drug arm [5].

The unequal and extremely high crossover rate, not originally planned by the Principal Investigator when enrolment started [2], seriously affected the validity of the ITT analysis. The first reference to cross-over was only available after study completion [5] (Figure). It would be important to the general public to understand why and when there was a change in plans regarding crossover, and why the Statistical Analysis Plan took nearly eight years to be finalized.

A closer look to the group of patients initially on medical therapy and later crossing-over and receiving ablation shows there was something unique about these patients and their response to ablation, as they experienced the lower mortality. Did the apparent survival benefit occur as a result of the slightly different risk profile, follow-up duration, or were these patient-super-responders to ablation therapy? It would be
interesting to see these results presented as incidence per 100 patient-years, as no information is given regarding follow-up duration in the four treatment groups.

In sum, we believe that after the (i) wrong power calculation using a highly inflated and unrealistic event rate, the (ii) extremely high crossover rate in the control group, the (iii) unexpected crossover rate in the ablation arm, the ITT analysis in CABANA should have been reported as inconclusive to assess its primary endpoint. On the other hand, more emphasis should be given to the crucial secondary endpoint of all-cause mortality and hospitalizations which showed a highly significant reduction with ablation.

We can only wonder how the results of CABANA would look, had the protocol not been changed (preserving the projected 3000 patient sample, the all-cause mortality primary endpoint, and not allowing cross-over).

We cannot change the past, but an analysis (i) preserving the initial all-cause mortality endpoint (and also including “all-cause mortality and hospitalizations”, and “all-cause mortality and stroke”, the primary endpoints of the ongoing EAST [6] and RAAFT-AF [7] trials, as secondary endpoints), and (ii) censoring patients who crossed over should be conducted. Furthermore, (iii) sub-group analyses of the three aforementioned endpoints would be of utmost importance to identify the groups of patients with more pronounced benefit of catheter ablation. Publishing those data would certainly be a service to patients, to the cardiovascular community and science. However, part of the answer is present as Supplementary Material [1]. Had the investigators kept the original plan of “crossover not being permitted” [5] (a main analysis more similar to the per-protocol analysis), a 31-34% relative risk reduction for all-cause mortality would have been observed. Wasn’t this the original study objective and design? Had that been the reality could anyone still question the study results and the life-saving benefit of ablation?
Note: a) In one of the supplementary material sections of CABANA [1], it is also mentioned that "the Statistical Analysis Plan was finalized after the end of the follow-up period" (even though "it was completed prior to database lock and prior to any knowledge of the results of the trial by Dr. Packer and the study leadership"). b) We can observe that in the ITT analysis, patients who were not ablated did negatively affect the results of the ablation arm, and crossovers to ablation made a clear contribution to the improvement of drug therapy arm’s results. Data extracted from eTable7 of the Supplementary material 3 file of CABANA [1].
References

Main Changes in CABANA’s Protocol & Design, & Main Findings

Intention-to-Treat

As-Treated

Figure