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 inflactionated 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?

Figure. Summary of the Main Changes in CABANA's Protocol & Design, & Main Findings

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

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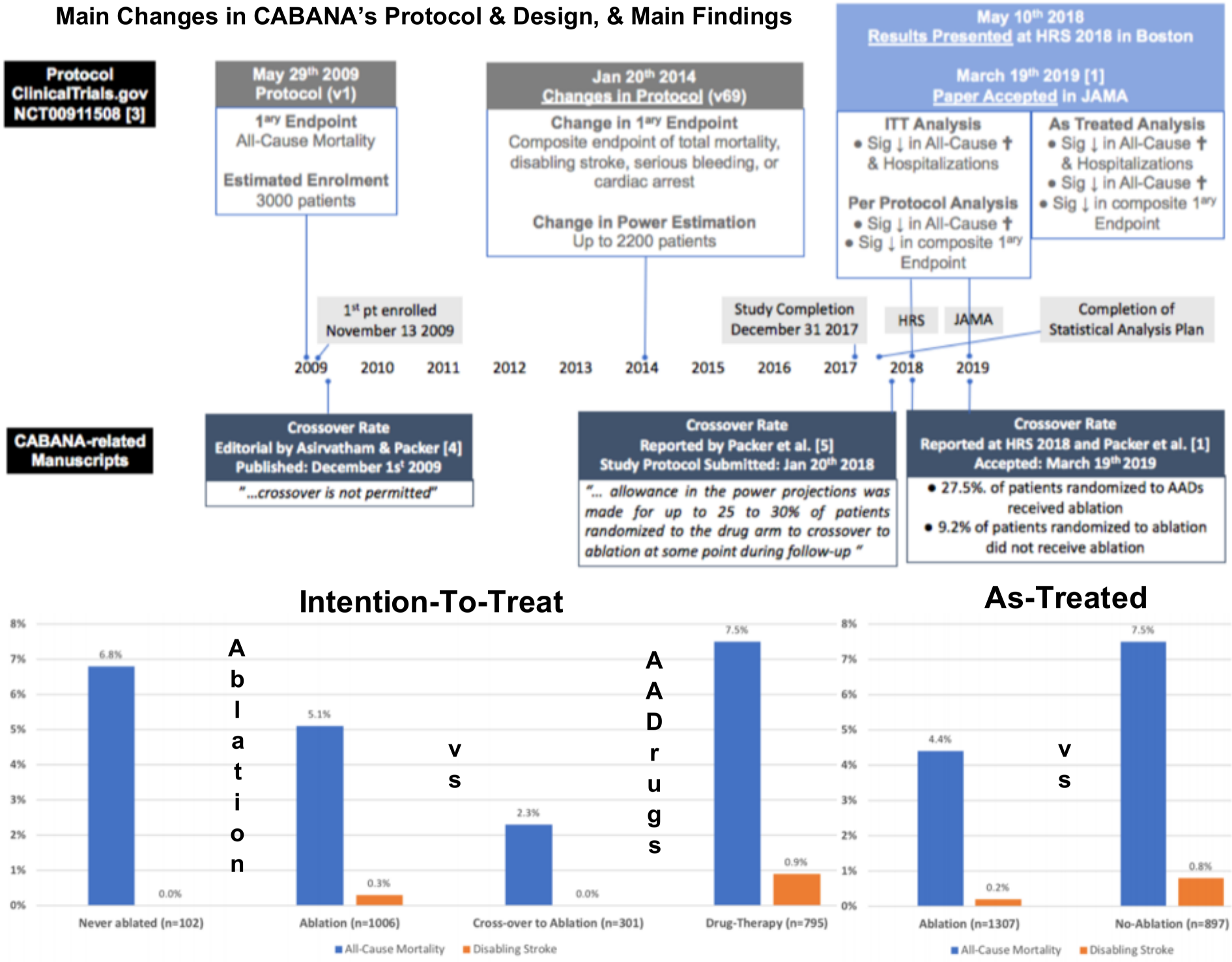
Figure


Main Changes in CABANA's Protocol & Design, & Main Findings
Protocol
ClinicalTrials.gov
NCT00911508 [3]
May 29th 2009
Protocol (v1)
1ary Endpoint
All-Cause Mortality
Estimated Enrolment
3000 patients
Jan 20th 2014
Changes in Protocol (v69)
Change in 1ary Endpoint
Composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest
Change in Power Estimation
Up to 2200 patients
May 10th 2018
Results Presented at HRS 2018 in Boston
March 19th 2019 [1]
Paper Accepted in JAMA
ITT Analysis
• Sig ↓ in All-Cause † & Hospitalizations
Per Protocol Analysis
• Sig ↓ in All-Cause †
• Sig ↓ in composite 1ary Endpoint
As Treated Analysis
• Sig ↓ in All-Cause † & Hospitalizations
• Sig ↓ in All-Cause †
• Sig ↓ in composite 1ary Endpoint
1st pt enrolled
November 13 2009
Study Completion
December 31 2017
HRS
JAMA
Completion of Statistical Analysis Plan
2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
CABANA-related Manuscripts
Crossover Rate
Editorial by Asirvatham & Packer [4]
Published: December 1st 2009
"...crossover is not permitted"
Crossover Rate
Reported by Packer et al. [5]
Study Protocol Submitted: Jan 20th 2018
"... allowance in the power projections was made for up to 25 to 30% of patients randomized to the drug arm to crossover to ablation at some point during follow-up"
Crossover Rate
Reported at HRS 2018 and Packer et al. [1]
Accepted: March 19th 2019
• 27.5%. of patients randomized to AADs received ablation
• 9.2% of patients randomized to ablation did not receive ablation
Intention-To-Treat
As-Treated
Ablation
vs
AADrugs
8%
7%
6%
5%
4%
3%
2%
1%
0%
6.8%
0.0%
5.1%
0.3%
2.3%
0.0%
7.5%
0.9%
4.4%
0.2%
7.5%
0.8%
Never ablated (n=102)
Ablation (n=1006)
Cross-over to Ablation (n=301)
Drug-Therapy (n=795)
Ablation (n=1307)
No-Ablation (n=897)
All-Cause Mortality
Disabling Stroke