Αλλάζουν τα δεδομένα μετά την ανακοίνωση των αποτελεσμάτων της μελέτης CABANA;

Γ. Ανδρικόπουλος, MD, PhD, FESC
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«Ερρίκος Ντυνάν» Hospital Center, Αθήνα
Presenter Disclosure Information

The presenter has received honoraria for participation in lectures and advisory boards from the following pharmaceutical and biotechnology companies:

- AstraZeneca,
- Bard,
- Bayer Healthcare,
- Boehringer Ingelheim,
- Boston Scientific,
- Bristol-Myers Squibb,
- ELPEN,
- Galenica,
- Lilly,
- Medtronic,
- Menarini,
- MSD,
- Pfizer,
- Sanofi,
- Servier,
- StJude,
- Unifarma,
- Vianex.
Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation

Yanish Purmah\textsuperscript{1,}\textdagger, Marco Proietti\textsuperscript{1,2,}\textdagger, Cecilé Laroche\textsuperscript{3}, Michal Mazurek\textsuperscript{1,4}, Dimitrios Tahmatzidis\textsuperscript{5}, Giuseppe Boriani\textsuperscript{6,7}, Salvatore Novo\textsuperscript{8}, and Gregory Y.H. Lip\textsuperscript{1,9,*} on behalf of the EORP-AF General Pilot Registry Investigators

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Cox regression analysis for all-cause death</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.04</td>
</tr>
<tr>
<td>Rate control (vs. rhythm control)</td>
<td>2.83</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>2.14</td>
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<tr>
<td>Chronic heart failure</td>
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<td>Chronic kidney disease</td>
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<td></td>
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<tr>
<td>None (ref)</td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>0.40</td>
</tr>
<tr>
<td>Regular</td>
<td>0.29</td>
</tr>
<tr>
<td>Intense</td>
<td>0.65</td>
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</tbody>
</table>

Figure 3 Kaplan–Meier curves for all-cause death according to baseline strategy.
RACE II: strict vs. lenient rate control

CV death, heart failure, thromboembolic complications, bleeding, need for pacemaker or severe adverse effects of anti-arrhythmic drugs

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Months</th>
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<tbody>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Strict control</td>
<td>303</td>
</tr>
<tr>
<td>Lenient control</td>
<td>311</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI: 0.58–1.21) P=0.001

CV = cardiovascular; HR = hazard ratio
2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Initiation of long term rhythm control therapy in symptomatic patients with atrial fibrillation
Cardiovascular Outcomes in the AFFIRM Trial: An Assessment of Individual Antiarrhythmic Drug Therapies compared to Rate Control Using Propensity Score Matched Analyses

**Results**—729 amiodarone patients, 606 sotalol patients & 268 class 1C patients were matched. The composite outcome of mortality or CV hospitalizations (CVH) showed better outcomes with Rate compared to amiodarone (Hazard Ratio [HR] 1.18, 95% confidence intervals [CI]: 1.03–1.36, p=0.02), sotalol (HR=1.32, CI: 1.13–1.54, p<0.001) and class 1C (HR=1.22, CI: 0.97–1.56, p=0.10). There was a non-significant increase in mortality with amiodarone (HR=1.20, CI: 0.94–1.53, p=0.15) with the risk of non-CV death, being significantly higher with amiodarone versus Rate (HR=1.11, CI: 1.01–1.24, p=0.04). First CVH event rates at 3 years were 47% for amiodarone, 50% for sotalol and 44% for class 1C versus 40%, 40% and 36% respectively for Rate (amiodarone HR=1.20, CI:1.03–1.40,p=0.02, sotalol HR=1.364, CI:1.16–1.611, p<0.001, class 1C HR=1.24,CI:0.96–1.60,p=0.09). Time to CVH with intensive care unit stay (ICUH) or death was shorter with amiodarone (HR=1.22, CI: 1.02–1.46, p=0.03).

**Potential benefit of rhythm control offset by antiarrhythmic drug toxicity**

**Conclusions**—

1. In AFFIRM, composite mortality and CVH outcomes differed for Rate and AADs due to differences in CVH; CVH event rates during follow-up were high for all cohorts, but they were higher for all groups on AADs.

2. Death, ICUH and non-CV death were more frequent with amiodarone.
Catheter Ablation for Atrial Fibrillation with Heart Failure

B Death from Any Cause

No. at Risk
Ablation 179 154 130 94 71 27
Medical therapy 184 168 138 97 63 19

Hazard ratio, 0.53 (95% CI, 0.32–0.86)
P = 0.01 by Cox regression
P = 0.009 by log-rank test

AF Burden Derived from Memory of Implanted Devices

Marrouche H, et al. New Eng J Med 2018;378(5);417-427
Results CASTLE AF

Device-detected VT/VF (%)

12 months after baseline
- Ablation: 28.7%
- Medical: 39.9%

End of Study
- Ablation: 62.6%
- Medical: 66.7%

ESC Congress Munich 2018
Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) Trial

Douglas L. Packer MD, Kerry L. Lee PhD,
Daniel B. Mark MD, MPH, Richard A. Robb PhD
for the CABANA Investigators

Mayo Clinic Rochester
Duke Clinical Research Institute
National Heart, Lung, and Blood Institute
Percent AF Burden - Holter Analysis

P<0.0001

Average AF burden (%)

Subjects: 458 451 522 567 467 500 420 461 353 417 309 362 294 306 250 263 231 223 182 190 142 140

Months since randomization

AF Burden Derived from Memory of Implanted Devices

P<0.0001
"9.2% των ασθενών που τυχαιοποιήθηκαν σε ablation ΔΕΝ ΥΠΟΒΛΗΘΗΚΑΝ σε επέμβαση και 27.5% αυτών που τυχαιοποιήθηκαν σε φαρμακευτική αγωγή ΥΠΟΒΛΗΘΗΚΑΝ σε ablation εγκαταλείποντας τη μελέτη"
“9.2% των ασθενών που τυχαιοποιήθηκαν σε ablation ΔΕΝ ΥΠΟΒΛΗΘΗΚΑΝ σε επέμβαση και 27.5% αυτών που τυχαιοποιήθηκαν σε φαρμακευτική αγωγή ΥΠΟΒΛΗΘΗΚΑΝ σε ablation εγκαταλείποντας τη μελέτη”
However, Milton Packer, MD, a heart failure specialist who sharply criticized the previous CASTLE-AF trial in a blog for MedPage Today, again had strong words for electrophysiologists, noting that intent-to-treat analyses are the standard in cardiology for a reason.

"The EP community is engaging in a classic example of self-deception," he commented. "They should look at the evidence objectively without regard for self-interest. The CABANA trial missed not only on its original primary endpoint but also on its new primary endpoint.

"Therefore, the trial failed to yield any reliable evidence that ablation is better than no ablation with respect to important clinical outcomes," he continued. "If the EP community wants to violate the rules of unbiased clinical trial design and analysis, they can certainly do so. But by doing so, they will be giving up their scientific credibility"
The CABANA Trial: an honourable view

Why Was a Clear Prespecified Result Muddled by Misguided Observational Analyses?

The CABANA trial randomized 2204 patients with atrial fibrillation to catheter ablation ($n = 1108$) or drug therapy to achieve rate or rhythm control ($n = 1096$). Both groups were anticoagulated, and most patients in the non-ablation group received membrane-active antiarrhythmic drugs. Only 10% had atrial fibrillation for $>1$ year, 15% had a history of heart failure.

The original primary endpoint was all-cause mortality, which was amended to a combined endpoint of death, disabling stroke, serious bleeding, or cardiac arrest. The original trial design anticipated that 25–30% of the patients assigned to drug therapy would receive ablation later in the trial. The investigators pre-specified that success of the trial would be determined by intention-to-treat analysis on the amended primary endpoint. This was an open-label trial; event adjudication was not blinded to the patients’ rhythm. Patients were followed for $\approx5$ years.

According to the reported results, the ablation and non-ablation groups did not differ with respect to the risk of the original primary endpoint ($P = 0.377$) or the amended primary endpoint ($P = 0.303$). Ablation did not reduce the risk of any component of the primary endpoint. There was a nominally significant reduction in the combined risk of death or cardiovascular hospitalization, which was likely related to a decrease in admissions for atrial fibrillation in the ablation group. No particular benefit was seen in patients with heart failure.

Unfortunately, the investigators showed ‘per-protocol’ and ‘as-treated’ analyses, which converted the randomized trial into an observational study. In these analyses, $\approx300$ patients who had been randomized to drug therapy and who received drug therapy (as specified by the protocol) but then underwent ablation later (as anticipated by the protocol) were shifted so that they were counted only in the ablation group. In doing so, the entire period of success during drug therapy in these 300 patients was eliminated from the analysis. This ploy, which yielded a nominally significant result, was interpreted as suggesting benefit (particularly in the heart failure subgroup).

The motivation underlying these observational analyses is unclear. The investigators claimed that they were carried out because 25–30% of the drug therapy group underwent ablation later in the trial. However, this is precisely what the original protocol had anticipated, so no additional analyses were warranted. There is no evidence that these observational analyses were pre-specified on clinicaltrials.org, and it is never valid to arbitrarily exclude data in 30% of patients. Were these observational analyses adjusted for relevant confounders? We do not know.

The CABANA trial is an important study that yielded a clear result, i.e. ablation does not prevent the serious consequences of atrial fibrillation. There is little justification to perform confounded observational analyses or rely on derivative subgroup effects. If this were a trial of a new pharmaceutical agent, these questionable analyses would be uniformly rejected as ‘wishful thinking’ and would not influence guidelines. Since ablation procedures are expensive, carry risks and are available to very few, evaluation of their efficacy should not be held to a lower standard of evidence.

These thoughts on the CABANA trial are preliminary. We await publication of the full manuscript and a description of the analytical methods to fully understand how the investigators viewed their data.

Conflict of interest: M.P. has no conflicts of interest for any matter related to the commentary.
### MILTON K PACKER

**Listed Specialty:** Cardiovascular Disease

**Address:**
621 N HALL ST STE H030, DALLAS, TX, 75226

**Yearly Payment Breakdown:**

<table>
<thead>
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<th>Year</th>
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<td>$98,424</td>
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<tr>
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<td>24</td>
<td>$38,452</td>
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</table>
The CABANA Trial: an honourable view

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**Primary Endpoint**
- All-cause mortality, disabling stroke, serious bleeding, or cardiac arrest

**Major Secondary Endpoints**
- All-cause mortality
- Death (all-cause) or cardiovascular hospitalization
The CABANA Trial: an honourable view

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Conflict of interest: M.P. has no conflicts of interest for any matter related to the commentary.
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessei, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Table 2. Primary End Point of Stroke or Systemic Embolism.*

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
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</thead>
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<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>Event Rate</td>
<td>No. of Patients</td>
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<td>Per-protocol, as-treated population;‡</td>
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<td>188</td>
<td>1.7</td>
<td>7004</td>
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<tr>
<td>Safety, as-treated population</td>
<td>7061</td>
<td>189</td>
<td>1.7</td>
<td>7082</td>
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<tr>
<td>Intention-to-treat population</td>
<td>7081</td>
<td>269</td>
<td>2.1</td>
<td>7090</td>
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<tr>
<td>During treatment</td>
<td>188</td>
<td>1.7</td>
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<td>240</td>
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<tr>
<td>After discontinuation</td>
<td>81</td>
<td>4.7</td>
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Δυναμική Καταγραφή της Αντίστασης ως Ένδειξη Αποτελεσματικής Χορήγησης Βλαβών (Direct Sense catheter – Rhythmia Platform)
One Shot Multi-electrode Irrigated RF

Designed to improve procedural efficiency

Built-in Cameras
Validation of electrode contact via real-time visualization

Integrated Mapping and Pacing
Eliminates need for mapping catheter
Arctic Front Advance® ST

40% Shorter Tip than Arctic Front Advance
Balloons, balloons, balloons

(A) The second and third-generation cryoballoon
(B) The inflated balloon with a thermocouple and radiofrequency electrode
(C) The laser balloon with an endoscope and arc generator

Laser balloon efficacy

Based on data from nine studies including 1021 patients, the efficacy of the HeartLight balloon procedure ranged between 58 and 88% at 1–1.5 year follow-up (off AAD). A more compliant laser balloon is currently being developed (HeartLight Excalibur Balloon™, Cardiofocus Inc.).

3D modeling before AF ablation

LSPV
3D modeling before AF ablation
3D modeling of the heart before ablation
High-density electroanatomic mapping

Atrial Flutter
Atrial Tachycardias

Atrial Tachycardia / Flutter may appear during PV isolation
Mobile Health Advances in Physical Activity, Fitness, and Atrial Fibrillation
Moving Hearts

5ο WORKSHOP
Αρρυθμιών & Βηματοδότησης
29-31 Μαρτίου
2019
Συνέδριο
Divani Caravel
Αθήνα