RANOLAZINE ADDED TO AMIODARONE FACILITATES EARLIER CONVERSION OF ATRIAL FIBRILLATION COMPARED TO AMIODARONE-ONLY THERAPY

University Hospital of Larissa, Cardiology Department
University of Thessaly

NO CONFLICT OF INTEREST DISCLOSURE

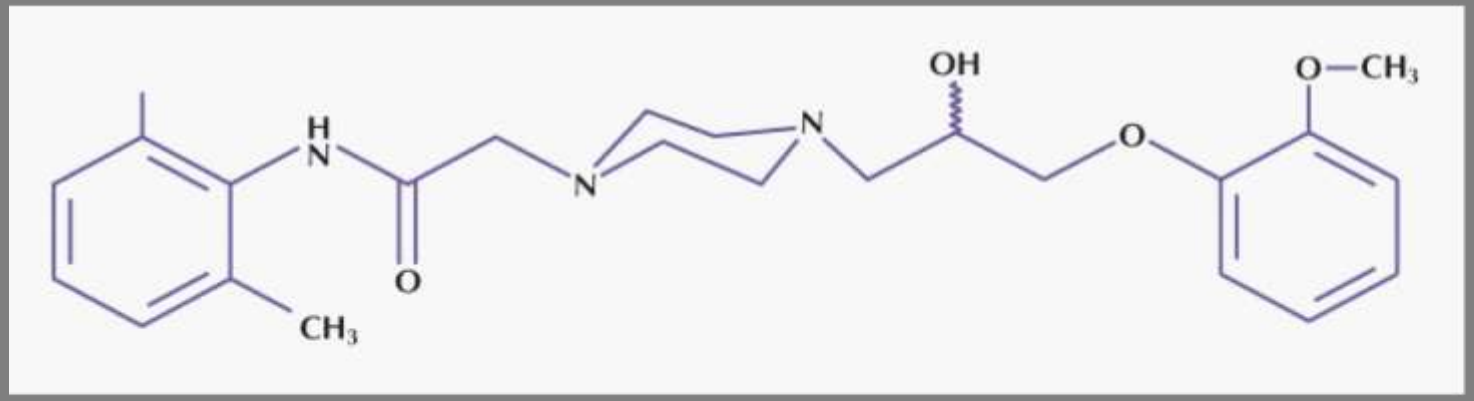
AMIODARONE

- Frequently used and effective to convert AF in patients with or without heart failure.
- Needs several hours or days for converting AF into sinus rhythm[1]
- Requires surveillance for liver, lung and thyroid toxicity[2]

1. Europace (2014) 16, 162 – 173 doi:10.1093/europace/eut274
2. Zimetbaum P. Amiodarone for AF. N Engl J Med. 2007; 935 - 941

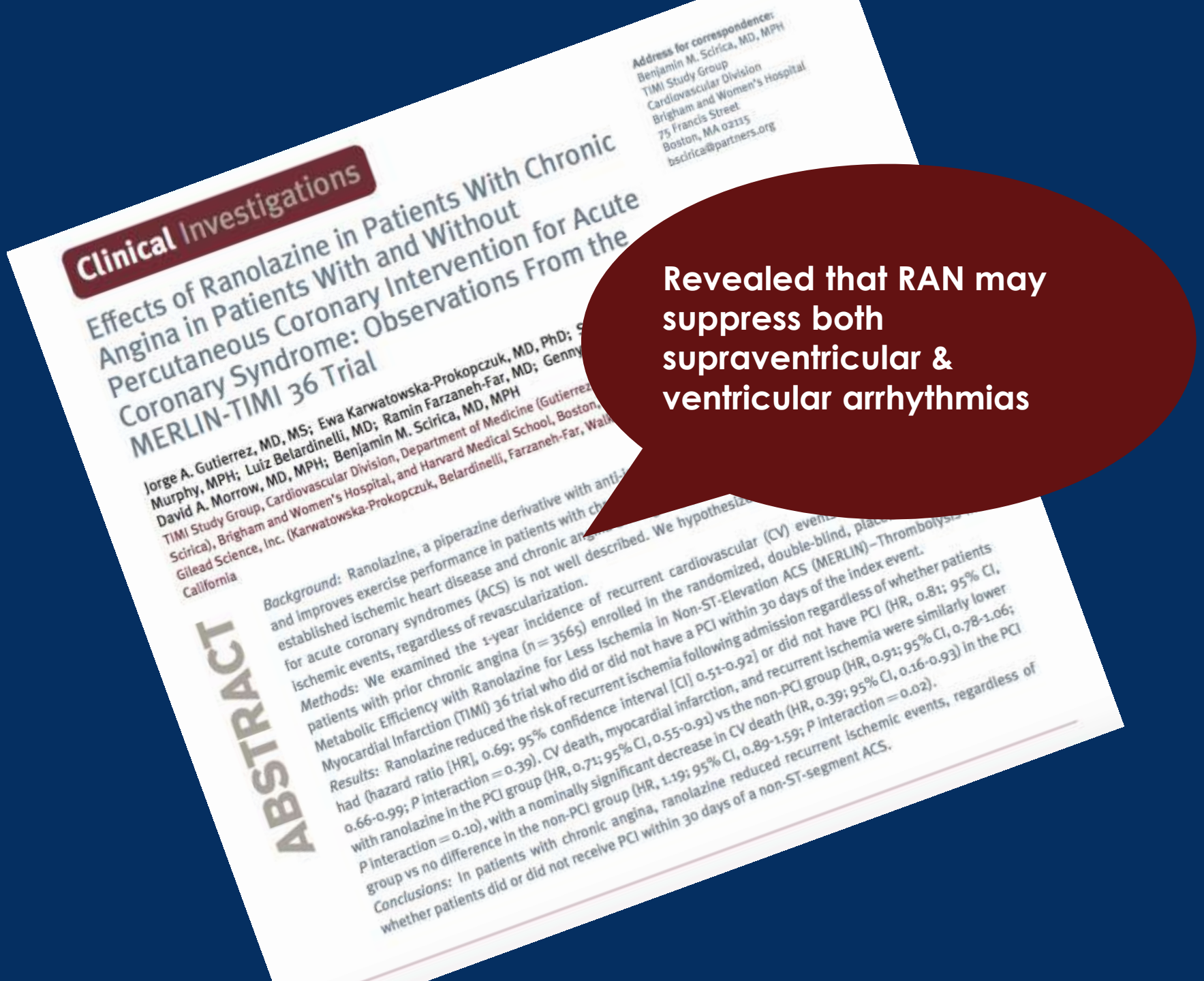
Ranolazine

NEW CLASS
"Late Cardiac Sodium Current Inhibitor"

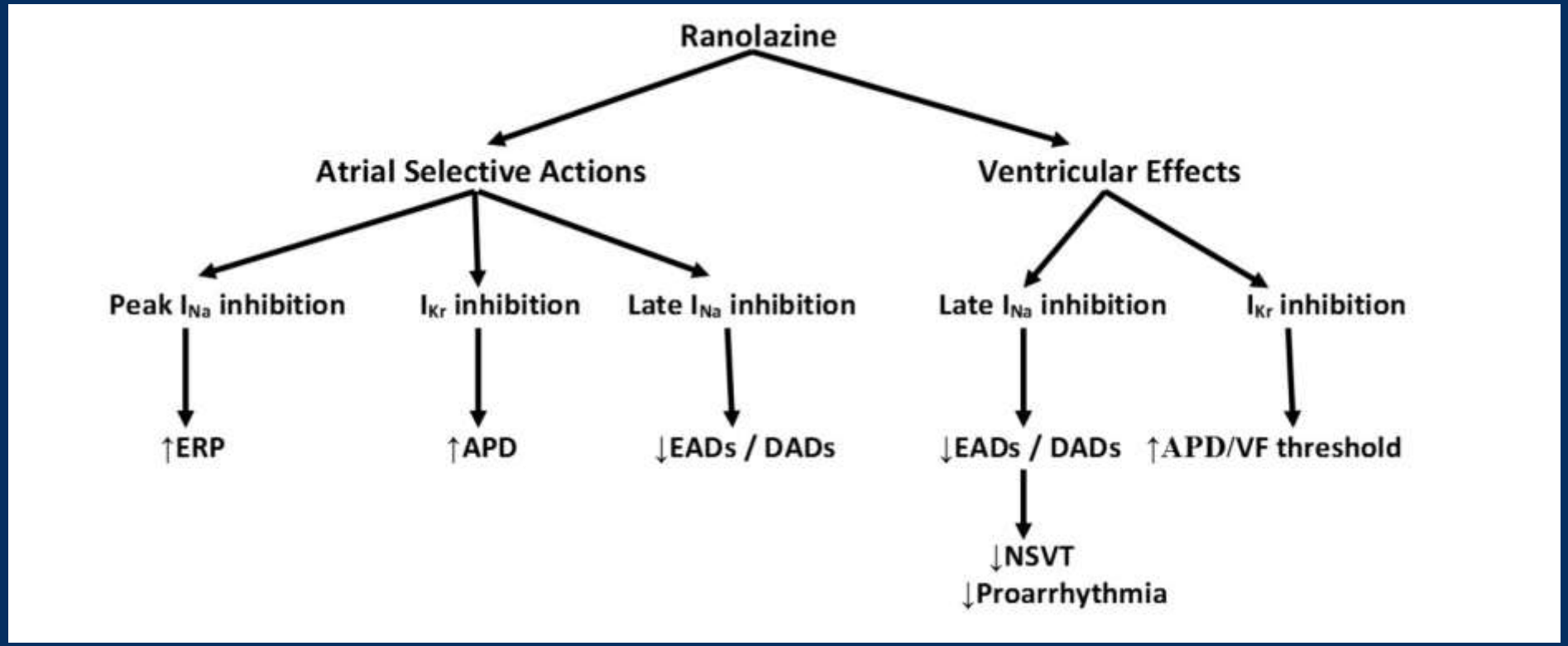


Film-coated prolonged-release tablets containing
375 mg, 500 mg or 750 mg of ranolazine

2006 - FDA approval for Chronic Stable Angina


Clinical Investigations
Effects of Ranolazine in Patients With Chronic Angina in Patients With and Without Percutaneous Coronary Intervention for Acute Coronary Syndrome: Observations From the MERLIN-TIMI 36 Trial
Address for correspondence:
Benjamin M. Scirica, MD, MPH
TIMI Study Group
Cardiovascular Division
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
bscirica@partners.org
ABSTRACT
Revealed that RAN may suppress both supraventricular & ventricular arrhythmias

Ranolazine and its Antiarrhythmic Actions



Current data of Ranolazine effect on AF

- Effectively supressed AF in experimental studies
- Demonstrated efficacy superior to AMIO alone when used synergisically w/ AMIO+RAN (1500mg single oral dose) in pts with LA>46mm
- Demonstrated to reduce the incidence of post-operative AF following CABG or valve surgeries when it was or administered in coombination with AMIO

1. JACC 2010, Vol.56, N.15
2. JAFIB 2014/Vol-6/Issue-5
3. Europace doi:10.1093/europace/eut407
4. AM J Cardiol 2011; 108: 673-676

OBJECTIVE

- Effectively restore SR in pts with recent-onset AF
- Fast and effective
- Minimal side effects and no proarrhytmia

HYPOTHESIS

Compare the antiarrhytmic effectiveness of AMIO+RAN vs AMIO alone irrespective of LA size

THE STUDY

- **PROBE design**
  - Prospective
  - Open-blinded
  - Randomized

METHODS

- Recent onset AF (< 48 hrs duration)
  - Time onset range (2 – 26 hrs)

- Eligible for pharmacologic cardioversion

DOSE SCHEME

- **Group 1 (n=81)**

  Amiodarone infusion (standard scheme)

  (loading dose 5mg/kg in 100ml D/W 5% 30’
  followed by maintenance infusion of 50mg/h)

- **Group 2 (n=92)**

  Amiodarone infusion (standard scheme) plus
  Ranolazine 1g per os as a single dose

Primary Endpoint

Time to conversion of AF after treatment initiation in the AMIO versus AMIO + RAN group

Secondary endpoint

The conversion rate of both treatments within 24 hours

Exlusion Criteria

pulmonary disease

cardiogenic shock

sick sinus syndrome

QTc > 440 ms

thyroid dysfunction

hypokalemia

renal failure (eGFR <30 mL/min/1.73 m^2)

hepatic insufficiency

patients receiving CYP3A4 inhibitors

RESULTS

Demographic and baseline clinical characteristics*

Variable	Amiodarone (n = 81)	Amiodarone Plus Ranolazine (n = 92)	P-Value
Male/Female	41/40	38/54	0.20
Age (years)	67 ± 11	70 ± 10	0.05
HTN	53 (65%)	65 (71%)	0.46
IHD	13 (16%)	29 (31%)	0.02
Obesity	32 (39%)	27 (29%)	0.16
T2DM	9 (11%)	7 (8%)	0.31
Previous AF	33 (41%)	34 (37%)	NS
New-onset AF	48 (59%)	58 (63%)	NS
Medications			
β-Blockers	32 (39%)	36 (39%)	0.96
ACEi/ARBs	55 (68%)	56 (61%)	0.59
Digoxin	0 (0%)	2 (2%)	0.18
Class III or Ia/Ic antiarrhythmics	10 (12%)	12 (13%)	0.89

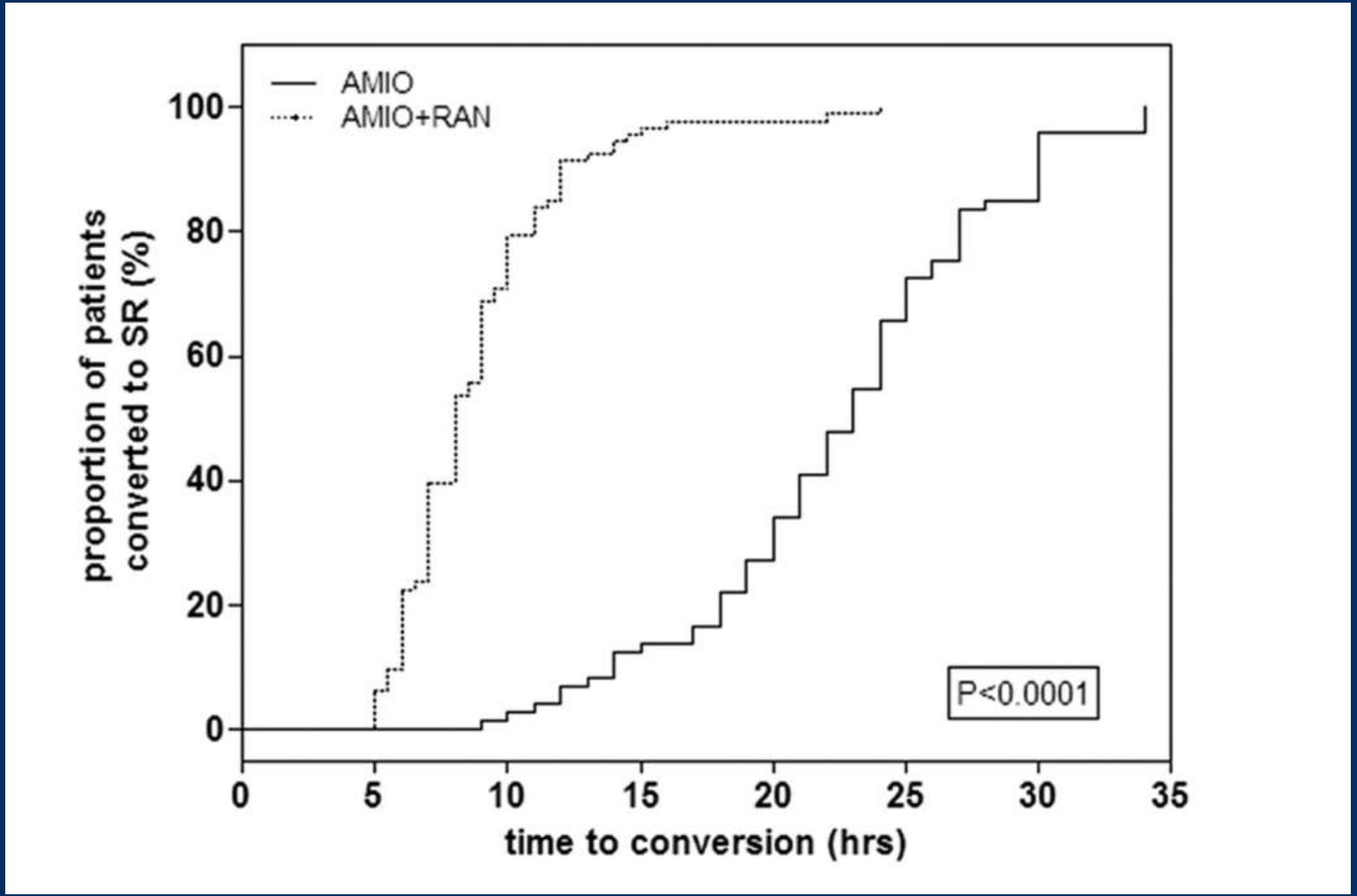
Data are expressed as mean SD or number (percentage).
*No statistically significant differences btw the Groups

ECHO and ECG characteristics after conversion of AF to SR*

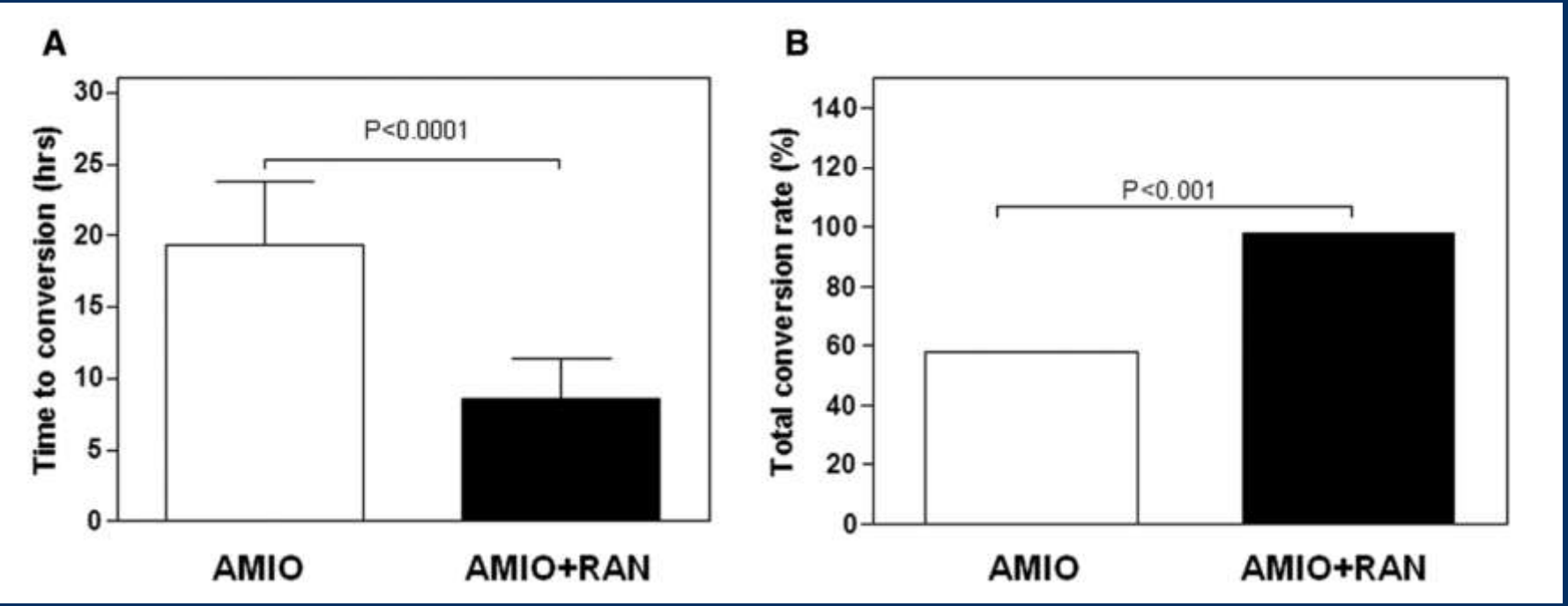
ECHO Parameters	AMIO	AMIO plus RAN	P-Value
LAd (cm)	4.2 ± 0.5	4.1 ± 0.4	0.18
LVEF (%)	53 ± 8	52 ± 10	0.58
LVEF <50%	7 (8%)	13 (14%)	0.26
ECG variables			
HR (beats/min)	74 ± 8	60 ± 7	0.00
PWD (ms)	88 ± 34	91 ± 26	0.63
PQ (ms)	182 ± 42	183 ± 42	0.70
QRS (ms)	96 ± 15	96 ± 22	0.47
QTc (ms)	433 ± 27	418 ± 33	0.04

*No statistically significant differences btw the Groups

Cumulative progression of AFconversion into SR



Effect of AMIO and AMIO+RAN treatment on AF conversion rate (A) and time to conversion (B)



POST CONVERSION OF AF TO SR IN AMIO+RAN GROUP

- No bradycardia
- No significant QTc prolongation

SIDE EFFECTS

- Overall well tolerated (both agents)
- 6 pts w/ Dizziness and mild transient hypotension (Ranolazine)
- Major side effects were not observed

CONCLUSIONS

- Our data demonstrate faster sinus rhythm restoration and enhanced conversion rate of AF after AMIO plus RAN in patients with preserved ejection fraction and left atrial size, implicating a synergistic effect of the two agents

- This is explained by the ability of ranolazine to selectively depress atrial conduction and increase post-repolarization refractoriness more than amiodarone, thereby potentially enhancing the antiarrhythmic effect of amiodarone

Ranolazine Added to Amiodarone Facilitates Earlier Conversion of Atrial Fibrillation Compared to Amiodarone-Only Therapy

NIKOS TSANAXIDIS, M.D.,* ISAAC AIDONIDIS, M.D.,†
APOSTOLIA HATZIEFTHIMIOU, M.D.,† STELLA S. PASKALOPOULOU, M.D.,‡
GRIGORIOS GIAMOU
and IOANNIS SKOU

From the *Department o ment of Physiology, Medical School of Larissa dicine and Experimental Medicine, I

Pacing and Clinical Electrophysiology
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Background: *Amiodar ventricular rate during atrial fibrillation (AF) and to convert it into sinus rhythm. However, due to its delayed onset of action, ranolazine (RAN), a new antianginal agent with atrial-selective electrophysiologic properties, has recently been attempted as add-on therapy with AMIO to facilitate AF conversion.*

Methods: *To establish the role of this combination therapy, we enrolled 173 consecutive patients (68 ± 10 years, 54% male) with recent-onset (<48-hour duration) AF who were eligible for pharmacologic cardioversion. Patients were randomized to intravenous AMIO (loading dose 5 mg/kg in 1 hour followed by 50 mg/h; n = 81), or AMIO plus a single oral dose of RAN 1 g (n = 92).*

Results: *Mean left atrial diameter did not significantly differ between groups, AMIO and AMIO + RAN (4.2 ± 0.5 cm vs 4.1 ± 0.4 cm, P = 0.18). Patients were randomized to intravenous AMIO (loading dose 5 mg/kg in 1 hour followed by 50 mg/h; n = 81), or AMIO plus a single oral dose of RAN 1 g (n = 92). The AMIO + RAN group compared with the AMIO-only group showed significantly shorter time to conversion (8.6 ± 2.8 hours vs 19.4 ± 4.4 hours, P < 0.0001) and higher conversion rate at 24 hours (98% vs 58%, P < 0.001). Left ventricular ejection fraction did not markedly vary between the two groups and ranged within moderately reduced values. No serious clinically evident adverse effects were observed in any of the patients receiving either AMIO or the combination treatment.*

Conclusions: *Our data demonstrate faster sinus rhythm restoration and enhanced conversion rate of AF after AMIO plus RAN in patients with preserved ejection fraction and left atrial size, implicating a synergistic effect of the two agents. (PACE 2017; 00:1–7)*

THANK YOU!