New anti-arrhythmic agents

고신의대
차 태준

Table 2 New antiarrhythmic drugs

Category	Drug	Target
Atrial-selective drugs	Vernakalant (RSD-1235)	Atrial selective K inhibitor—I_{kur}, I_{to}, I_{Na}, I_{KACh}
	AVE0118	Atrial selective K inhibitor—I_{kur}, I_{to}
	AZD 7009	Atrial selective—I_{Kr}, I_{Kur}, I_{Na}
Amiodarone congeners[a]	Dronedarone	I_{Kr}, I_{Ks}, I_{Ca}, I_{to}, I_{Na}, $I_{K(Ach)}$, α, β
	SSR149744C	I_{Kr}, I_{Ks}, I_{KaCh}, $I_{Kv1.5}$, I_{Ca}, I_{to}, α, β
	ATI-2042	Atrial selective—I_{Kr}, I_{Ks}, I_{Ca}, I_{to}, I_{Na}
Others	Azimilide	I_{Kr}, I_{Ks}
	Tedisamil	I_{Kr}, I_{to}, $I_{K\text{-}ATP}$, I_{Kur}, I_{Na}
	Rotigaptide	Gap-junction-modifying drug
	Serotonin 5-HT_4 receptor antagonists	Serotonin 5-HT_4 receptor
	Muscarinic M_2-receptor blocker	Muscarinic M_2-receptor

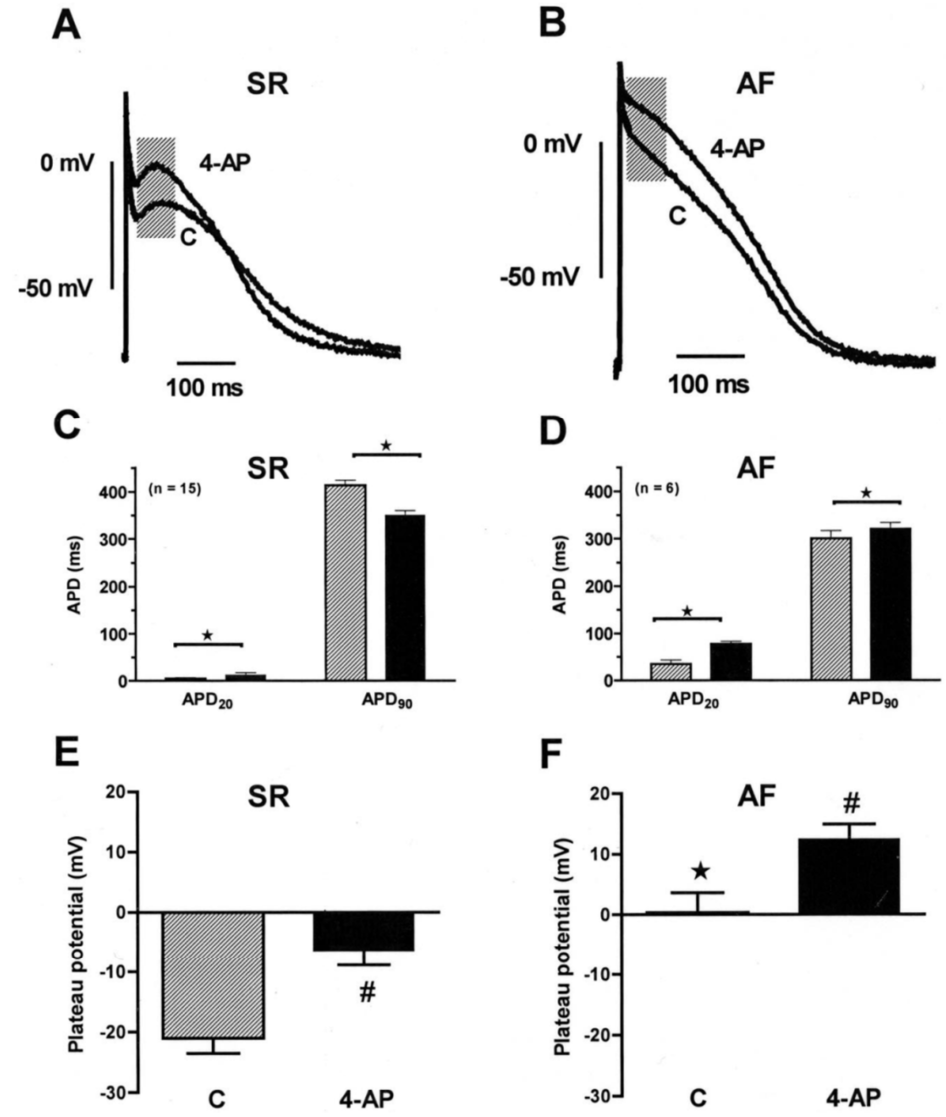
[a]Amiodarone—I_{Kr}, I_{Ks}, I_{Ca}, I_{to}, I_{Na}, α, β.

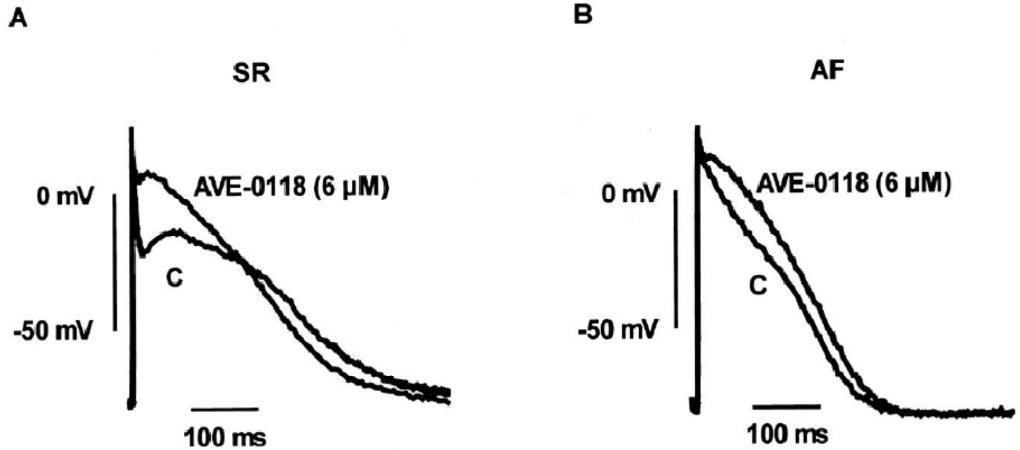
AVE0118 (Sanofi-Aventis, France) is an atrial-selective potassium channel blocker, inhibiting the ultra-rapid component of the delayed rectifier (Ikur), which is only present in the atria, and the transient outward current (Ito), which is found in much higher density in the atria.

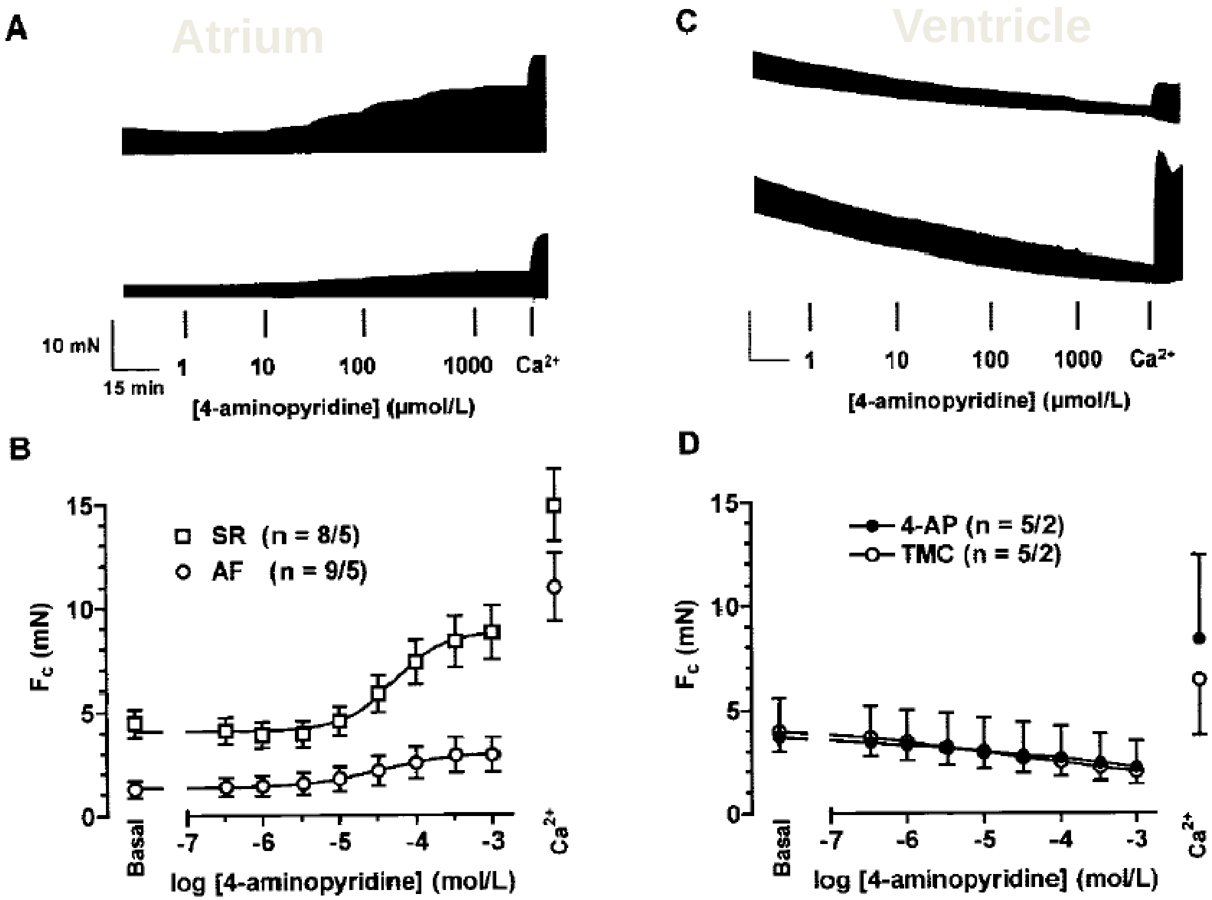
Role of IKur in Controlling Action Potential Shape and Contractility in the Human Atrium: Influence of Chronic Atrial Fibrillation

Erich Wettwer, Ottó Hála, Torsten Christ, Jürgen F. Heubach, Dobromir Dobrev, Michael Knaut, András Varró and Ursula Ravens

Circulation 2004;110;2299-2306; originally published online Oct 11, 2004;
DOI: 10.1161/01.CIR.0000145155.60288.71




A
SR
0 mV
-50 mV
AVE-0118 (6 µM)
C
100 ms
B
AF
0 mV
-50 mV
AVE-0118 (6 µM)
C
100 ms


A
Atrium
10 mN
15 min
1
10
100
1000
Ca2+
[4-aminopyridine] (µmol/L)
C
Ventricle
1
10
100
1000
Ca2+
[4-aminopyridine] (µmol/L)
B
SR (n = 8/5)
AF (n = 9/5)
Fc (mN)
Basal
log [4-aminopyridine] (mol/L)
Ca2+
D
4-AP (n = 5/2)
TMC (n = 5/2)
Fc (mN)
Basal
log [4-aminopyridine] (mol/L)
Ca2+

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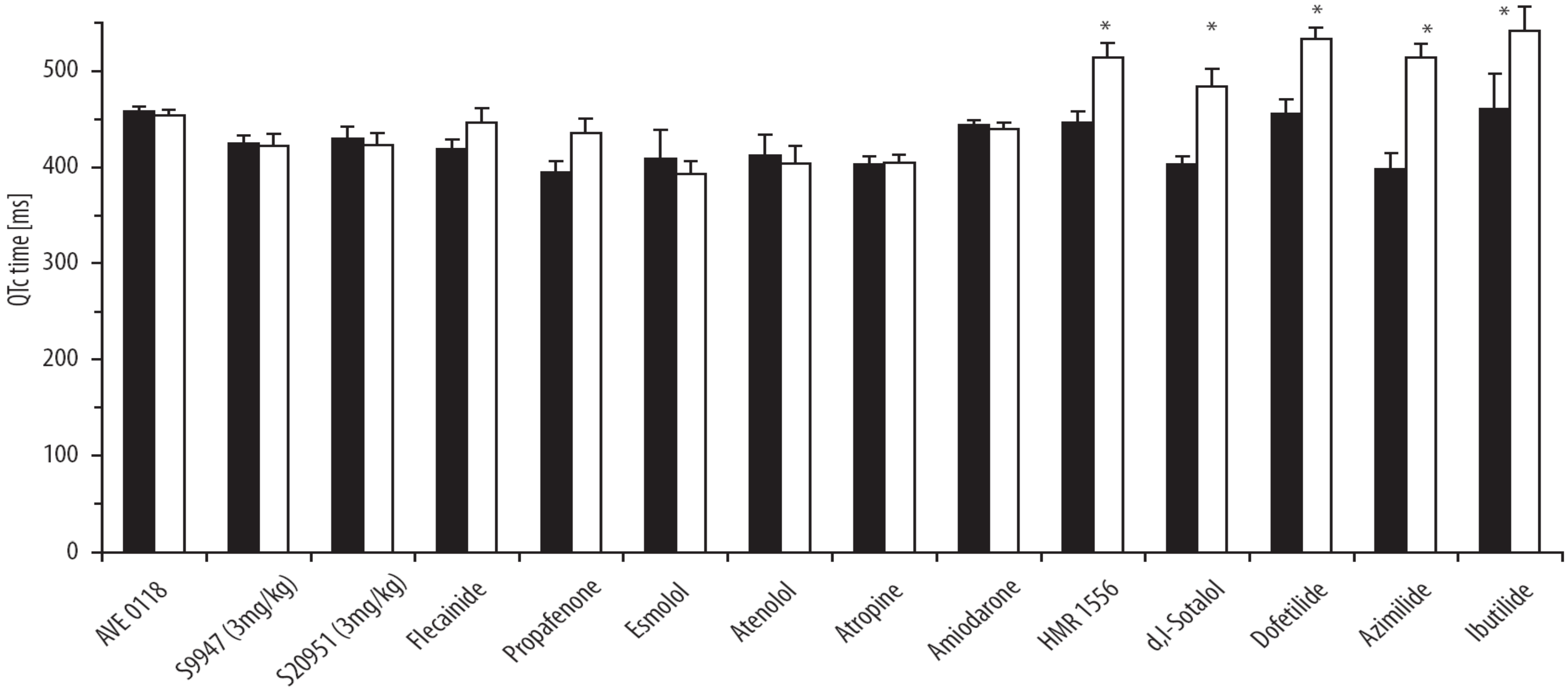
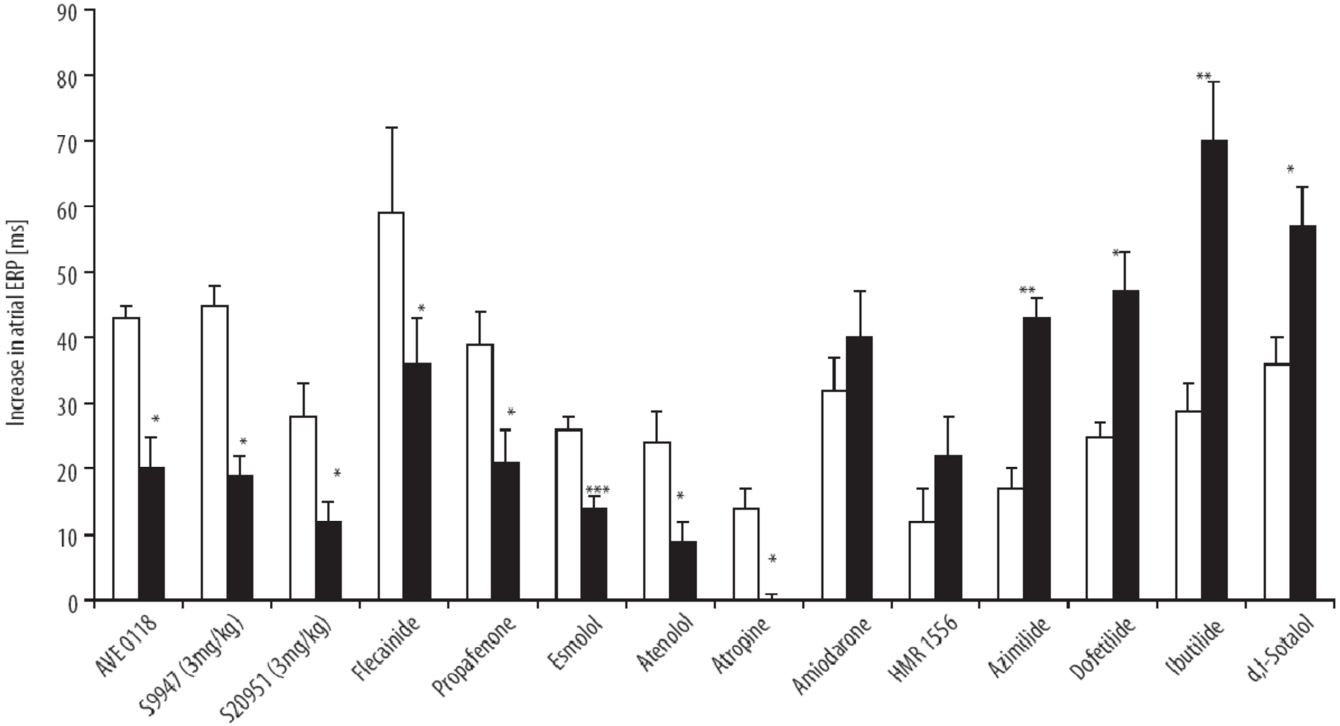
PMID: 15232496

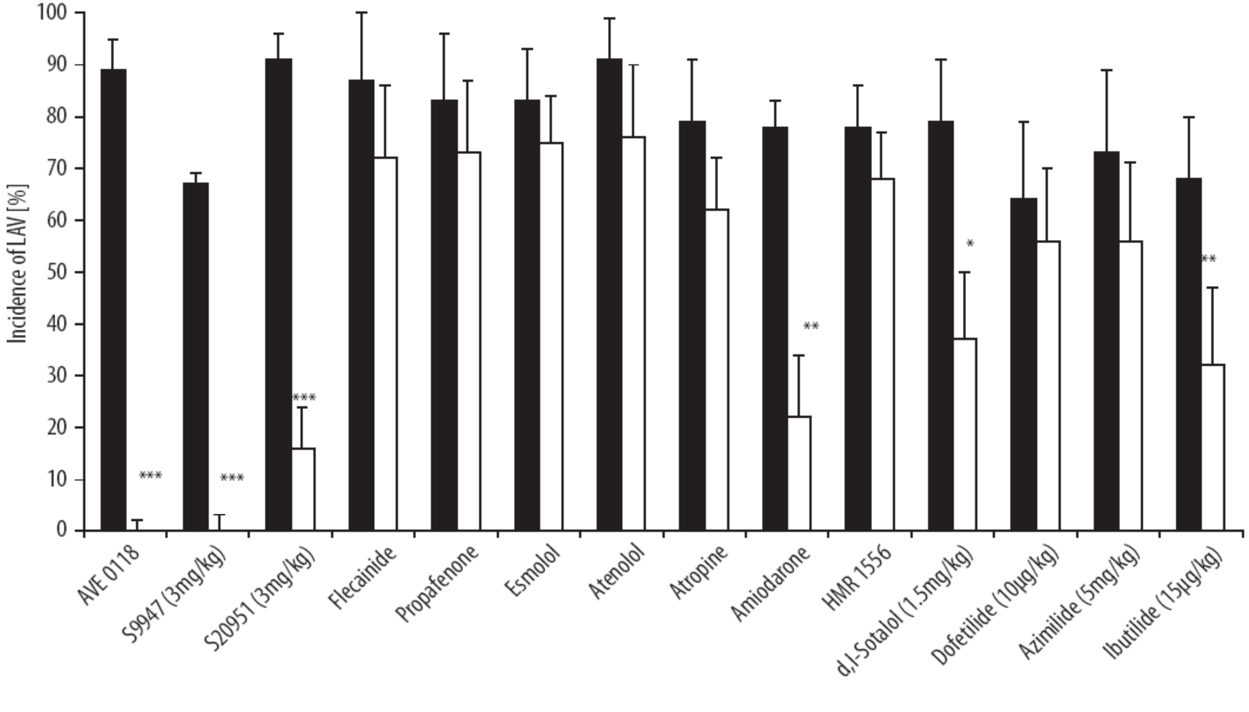
Received: 2003.09.22
Accepted: 2004.01.05
Published: 2004.07.02

Atrial-selective antiarrhythmic actions of novel I_{kur} vs. I_{kr}, I_{ks}, and I_{KAch} class Ic drugs and beta blockers in pigs



2


Increase in atrial ERP [ms]
AVE 0118
S9947 (3mg/kg)
S20951 (3mg/kg)
Flecainide
Propafenone
Esmolol
Atenolol
Atropine
Amiodarone
HMR 1556
Azimilide
Dofetilide
Ibutilide
d,l-Sotalol

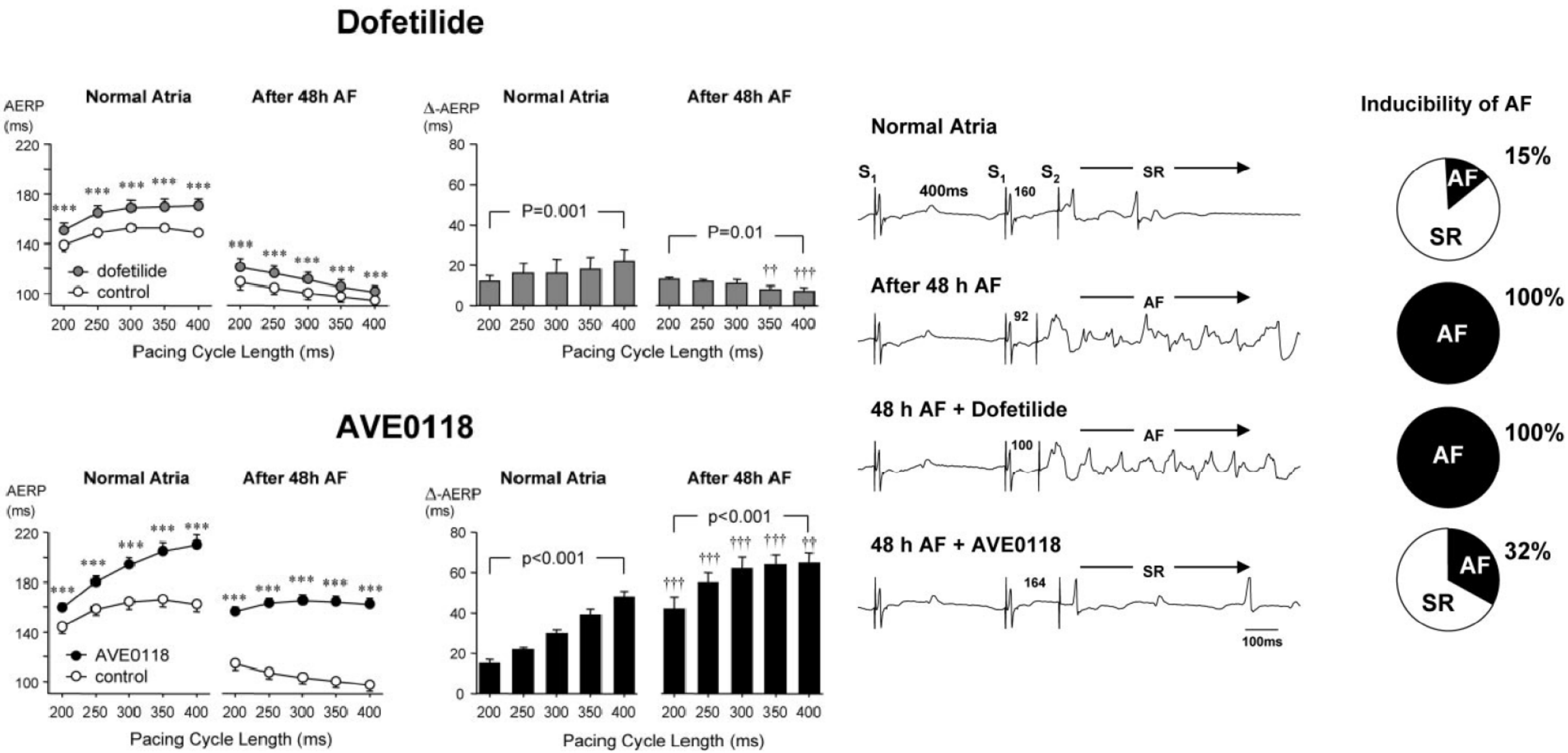

Incidence of LAV [%]
AVE 0118
S9947 (3mg/kg)
S20951 (3mg/kg)
Flecainide
Propafenone
Esmolol
Atenolol
Atropine
Amiodarone
HMR 1556
d,l-Sotalol (1.5mg/kg)
Dofetilide (10μg/kg)
Azimilide (5mg/kg)
Ibutilide (15μg/kg)

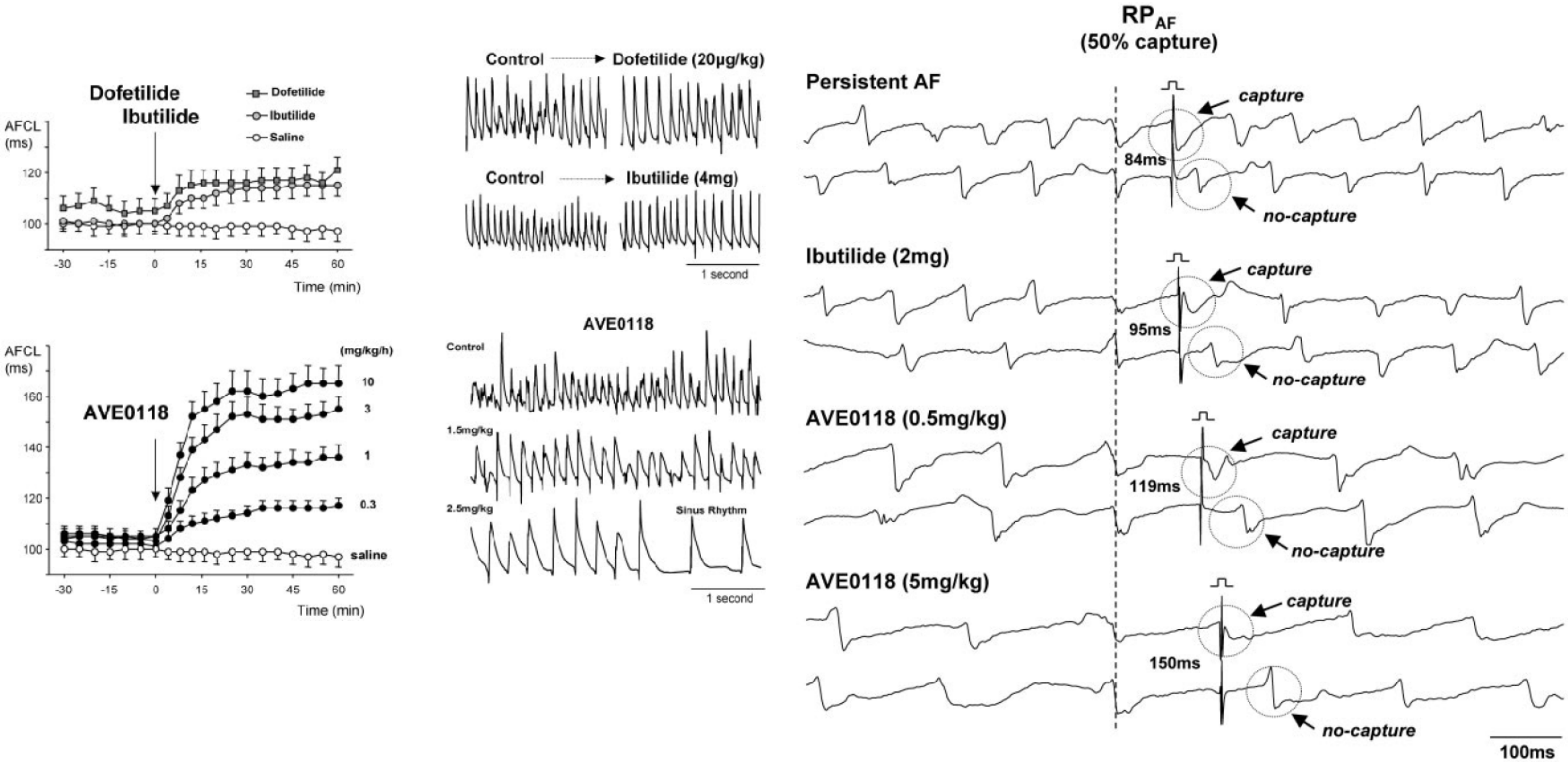
"Early" Class III Drugs for the Treatment of Atrial Fibrillation

Efficacy and Atrial Selectivity of AVE0118 in Remodeled Atria of the Goat

(*Circulation*. 2004;110:1717-1724.)

Y. Blaauw, MD; H. Gögelein, PhD; R.G. Tieleman, MD, PhD; A. van Hunnik, BS; U. Schotten, MD, PhD; M.A. Allessie, MD, PhD




Dofetilide
Ibutilide
Dofetilide
Ibutilide
Saline
AFCL (ms)
120
100
-30
-15
0
15
30
45
60
Time (min)
Control
Dofetilide (20µg/kg)
Control
Ibutilide (4mg)
1 second
AFCL (ms)
(mg/kg/h)
160
140
120
100
AVE0118
10
3
1
0.3
saline
-30
-15
0
15
30
45
60
Time (min)
AVE0118
Control
1.5mg/kg
2.5mg/kg
Sinus Rhythm
1 second
RPAF
(50% capture)
Persistent AF
capture
84ms
no-capture
Ibutilide (2mg)
capture
95ms
no-capture
AVE0118 (0.5mg/kg)
capture
119ms
no-capture
AVE0118 (5mg/kg)
capture
150ms
no-capture
100ms

- **Vernakalant** (RSD1235; Cardiom, Cananda, Astellas Pharma, USA), an investigational compound, is a relatively atrium-selective, early-activating K and frequency-dependent Na channel blocker with a half-life of 2 to 3 hours.7,8

Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation

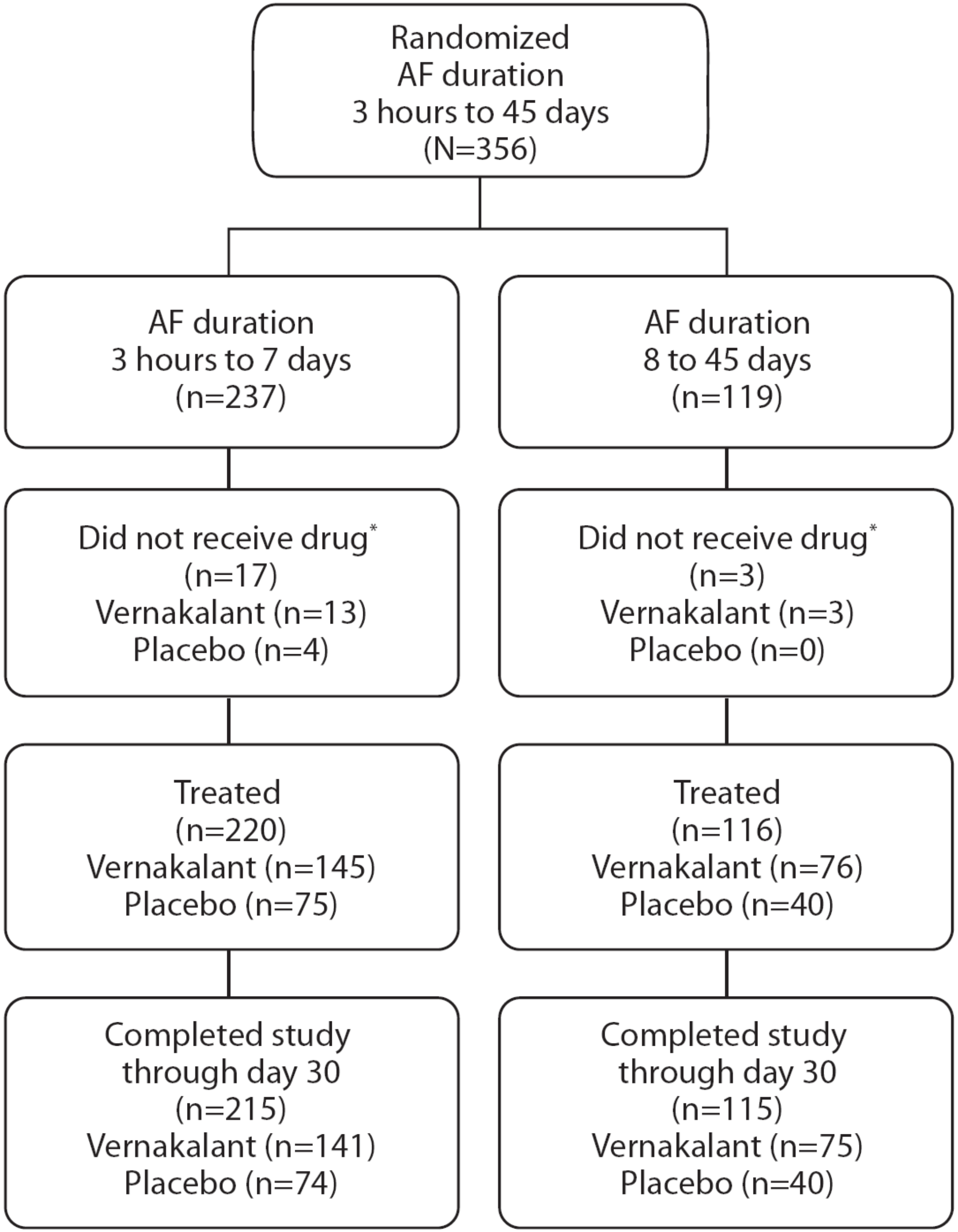
A Phase 3, Randomized, Placebo-Controlled Trial

Denis Roy, MD; Craig M. Pratt, MD; Christian Torp-Pedersen, MD; D. George Wyse, MD, PhD; Egon Toft, MD; Steen Juul-Moller, MD; Tonny Nielsen, MD; S. Lind Rasmussen, MD; Ian G. Stiell, MD; Benoit Coutu, MD; John H. Ip, MD; Edward L.C. Pritchett, MD; A. John Camm, MD; for the Atrial Arrhythmia Conversion Trial Investigators

Background—The present study assessed the efficacy and safety of vernakalant hydrochloride (RSD1235), a novel compound, for the conversion of atrial fibrillation (AF).

Methods and Results—Patients were randomized in a 2:1 ratio to receive vernakalant or placebo and were stratified by AF duration of 3 hours to 7 days (short duration) and 8 to 45 days (long duration). A first infusion of placebo or vernakalant (3 mg/kg) was given for 10 minutes, followed by a second infusion of placebo or vernakalant (2 mg/kg) 15 minutes later if AF was not terminated. The primary end point was conversion of AF to sinus rhythm for at least 1 minute within 90 minutes of the start of drug infusion in the short-duration AF group. A total of 336 patients were randomized and received treatment (short duration, n=220; long duration, n=116). Of the 145 vernakalant patients, 75 (51.7%) in the short-duration AF group converted to sinus rhythm (median time, 11 minutes) compared with 3 of the 75 placebo patients (4.0%; *P*<0.001). Overall, in the short- and long-duration AF groups, 83 of the 221 vernakalant patients (37.6%) experienced termination of AF compared with 3 of the 115 placebo patients (2.6%; *P*<0.001). Transient dysgeusia and sneezing were the most common side effects in vernakalant-treated patients. Four vernakalant-related serious adverse events (hypotension [2 events], complete atrioventricular block, and cardiogenic shock) occurred in 3 patients.

Conclusion—Vernakalant demonstrated rapid conversion of short-duration AF and was well tolerated. **(*Circulation*. 2008; 117:1518-1525.)**


Randomized
AF duration
3 hours to 45 days
(N=356)
AF duration
3 hours to 7 days
(n=237)
AF duration
8 to 45 days
(n=119)
Did not receive drug*
(n=17)
Vernakalant (n=13)
Placebo (n=4)
Did not receive drug*
(n=3)
Vernakalant (n=3)
Placebo (n=0)
Treated
(n=220)
Vernakalant (n=145)
Placebo (n=75)
Treated
(n=116)
Vernakalant (n=76)
Placebo (n=40)
Completed study
through day 30
(n=215)
Vernakalant (n=141)
Placebo (n=74)
Completed study
through day 30
(n=115)
Vernakalant (n=75)
Placebo (n=40)

Success rates in various AF populations

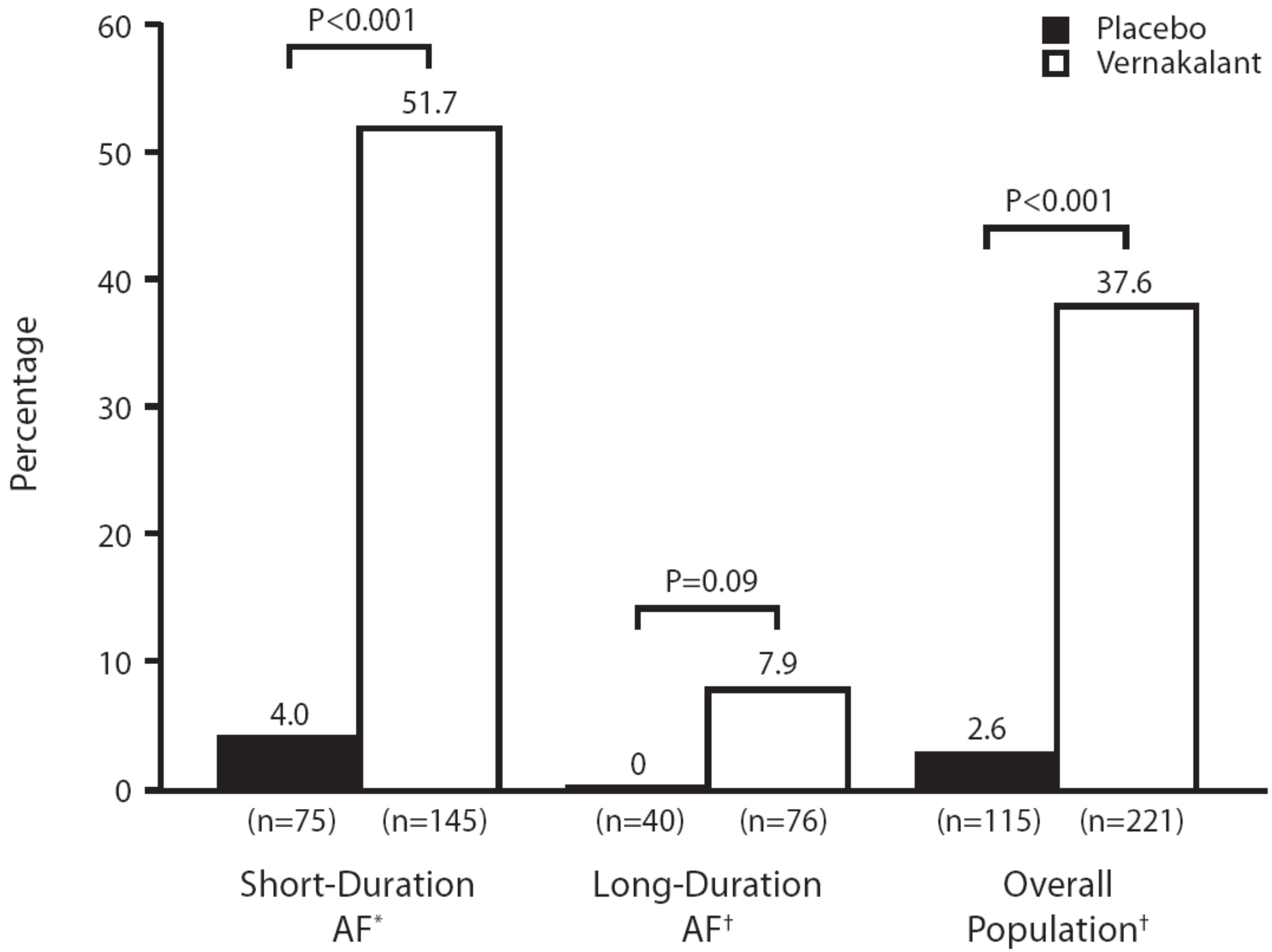
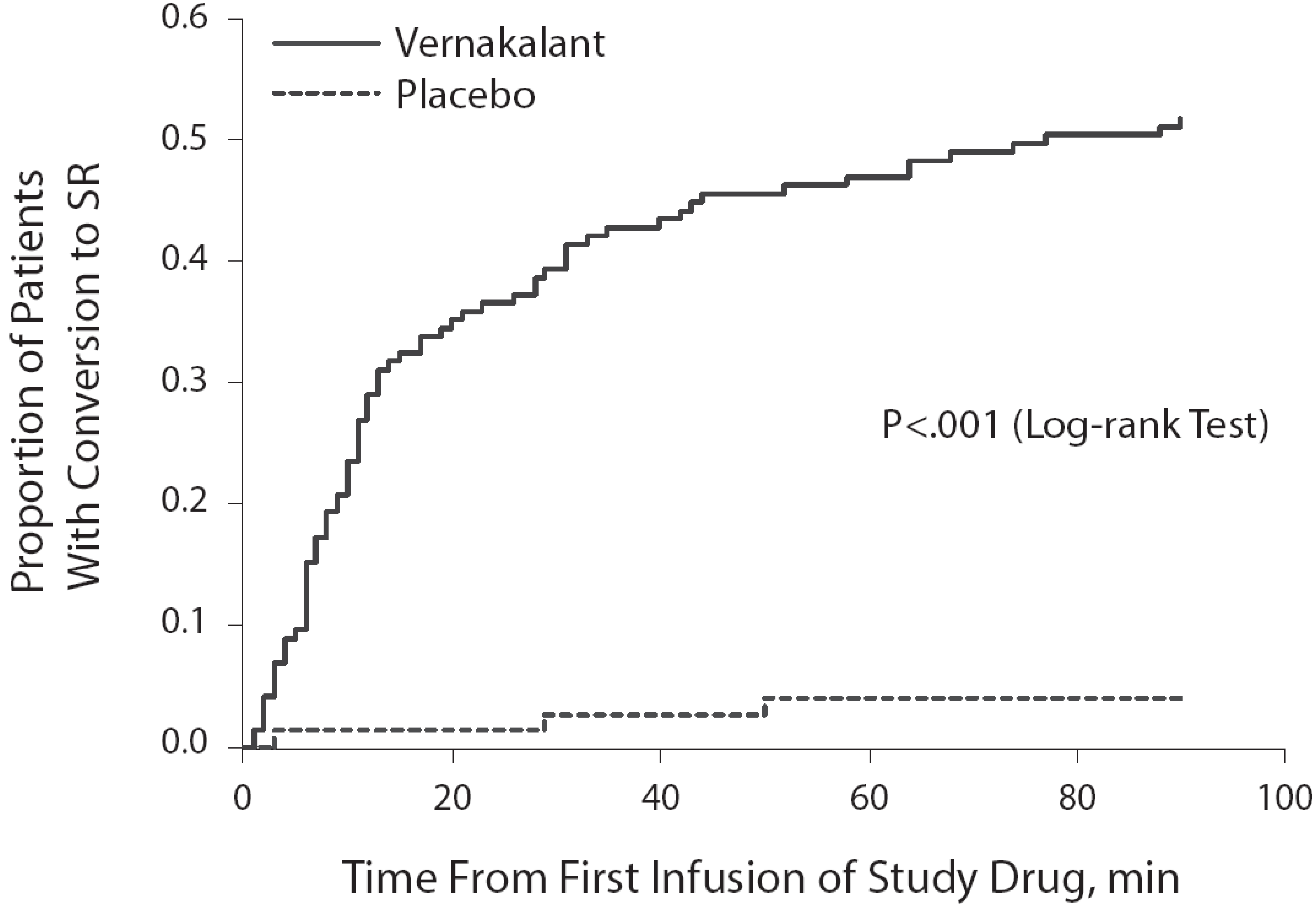
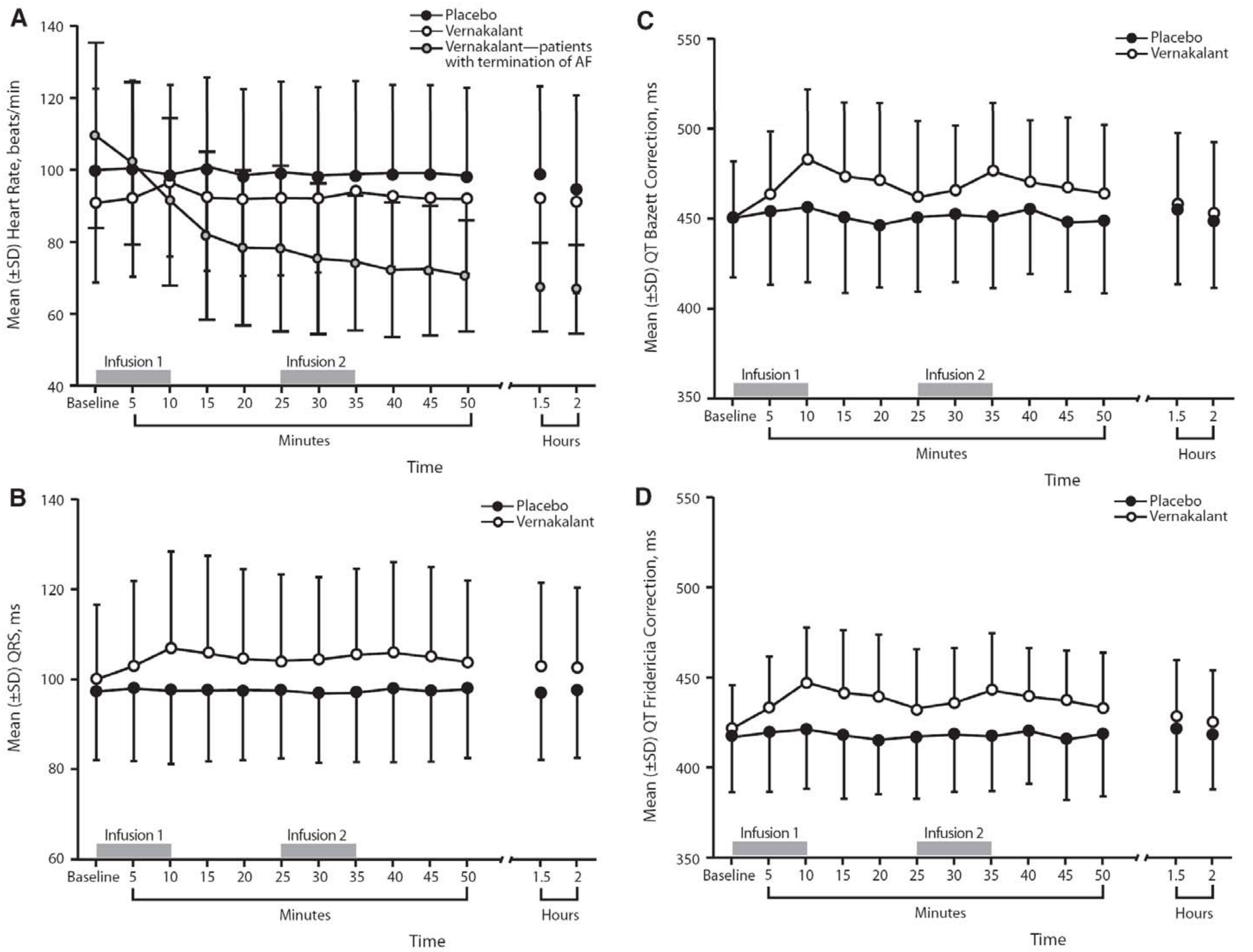


Table 2. Success Rates in Patients With AF Lasting 3 to 48 Hours and 3 to 7 Days

	Conversion to Sinus Rhythm, n (%)	Difference of Success (95% CI), %	*P*
AF lasting 3 to 48 h			
Vernakalant (n=103)	64 (62.1)	57.2 (46.4–68.0)	<0.001
Placebo (n=61)*	3 (4.9)		
AF lasting 3 to 7 d			
Vernakalant (n=42)	10 (23.8)	23.8 (10.9–36.7)	0.048
Placebo (n=16)*	0		

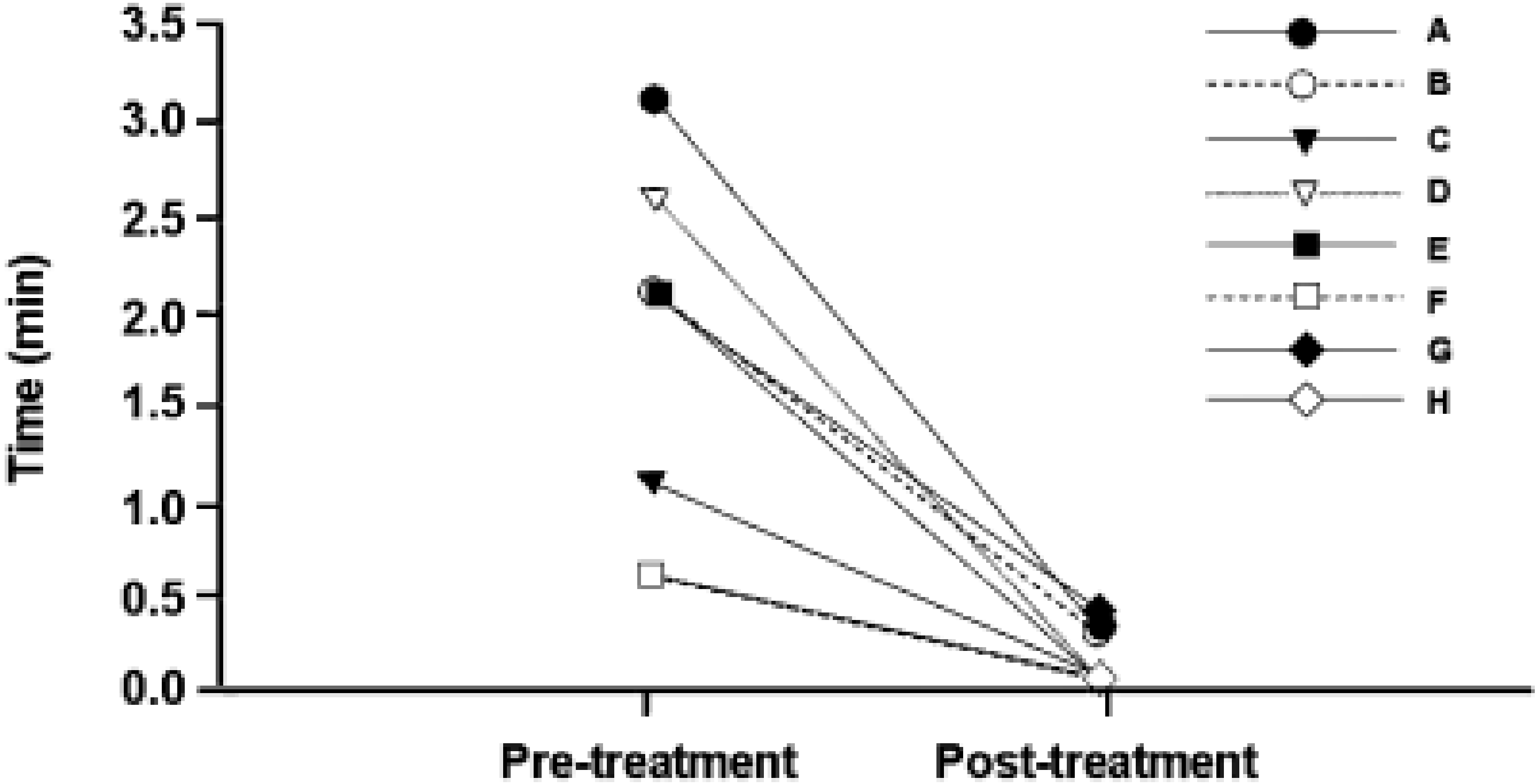
*Two patients given placebo in the long-duration AF group were reassigned after randomization for this nonprespecified analysis based on actual AF duration.


Vernakalant
Placebo
P<.001 (Log-rank Test)
Proportion of Patients With Conversion to SR
Time From First Infusion of Study Drug, min
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
20
40
60
80
100


A
Placebo
Vernakalant
Vernakalant—patients with termination of AF
Mean (±SD) Heart Rate, beats/min
140
120
100
80
60
40
Infusion 1
Infusion 2
Baseline 5 10 15 20 25 30 35 40 45 50
1.5 2
Minutes
Hours
Time
B
Placebo
Vernakalant
Mean (±SD) QRS, ms
140
120
100
80
60
Infusion 1
Infusion 2
Baseline 5 10 15 20 25 30 35 40 45 50
1.5 2
Minutes
Hours
Time
C
Placebo
Vernakalant
Mean (±SD) QT Bazett Correction, ms
550
500
450
400
350
Infusion 1
Infusion 2
Baseline 5 10 15 20 25 30 35 40 45 50
1.5 2
Minutes
Hours
Time
D
Placebo
Vernakalant
Mean (±SD) QT Fridericia Correction, ms
550
500
450
400
350
Infusion 1
Infusion 2
Baseline 5 10 15 20 25 30 35 40 45 50
1.5 2
Minutes
Hours
Time

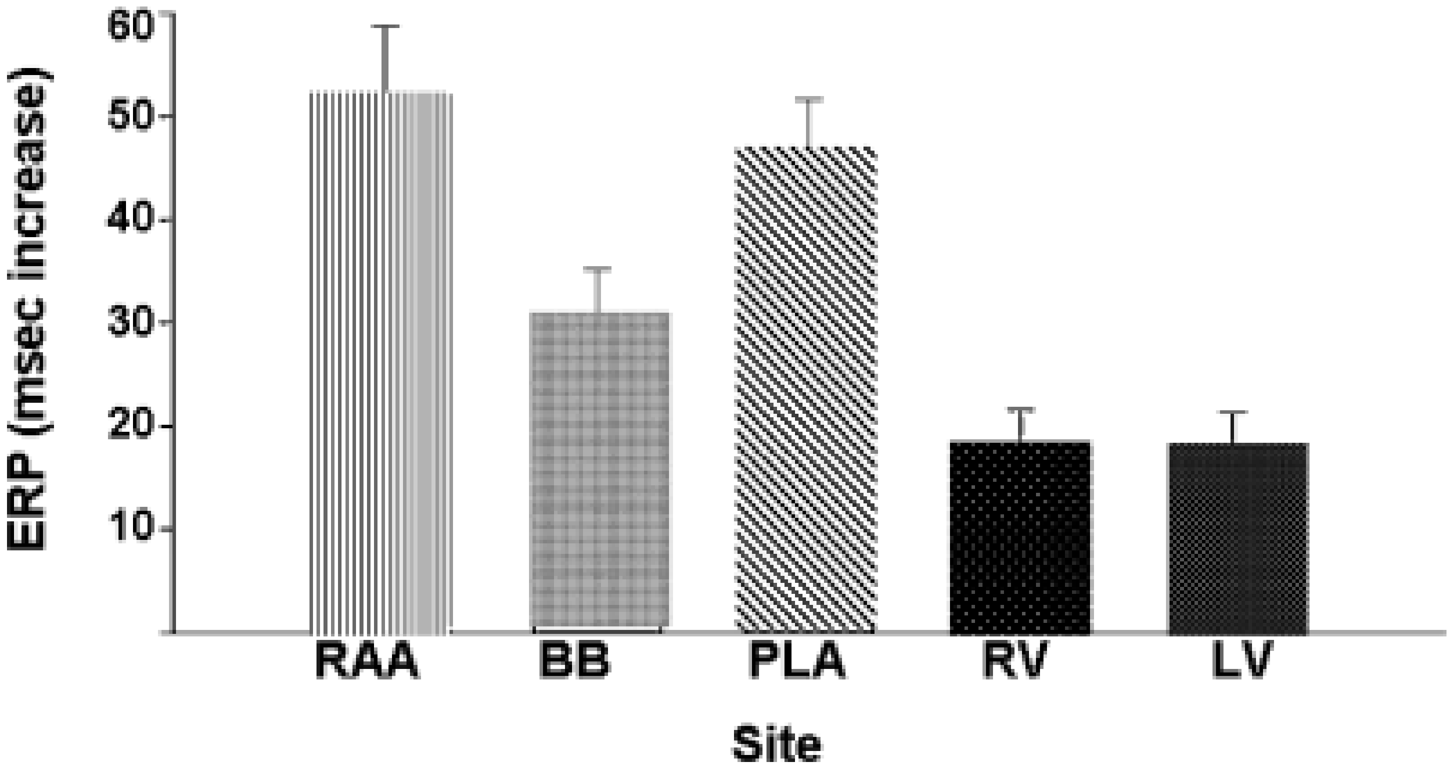
AZD7009 (AstraZeneca, UK) is a mixed ion-channel blocker blocking the delayed rectifying potassium current (IKr), the sodium current (INa), and the ultra-rapid delayed rectifying potassium current (IKur), with electrophysiological effects predominantly on atrial tissue.

Non-sustained atrial fibrillation pre- and post-AZD7009 administration

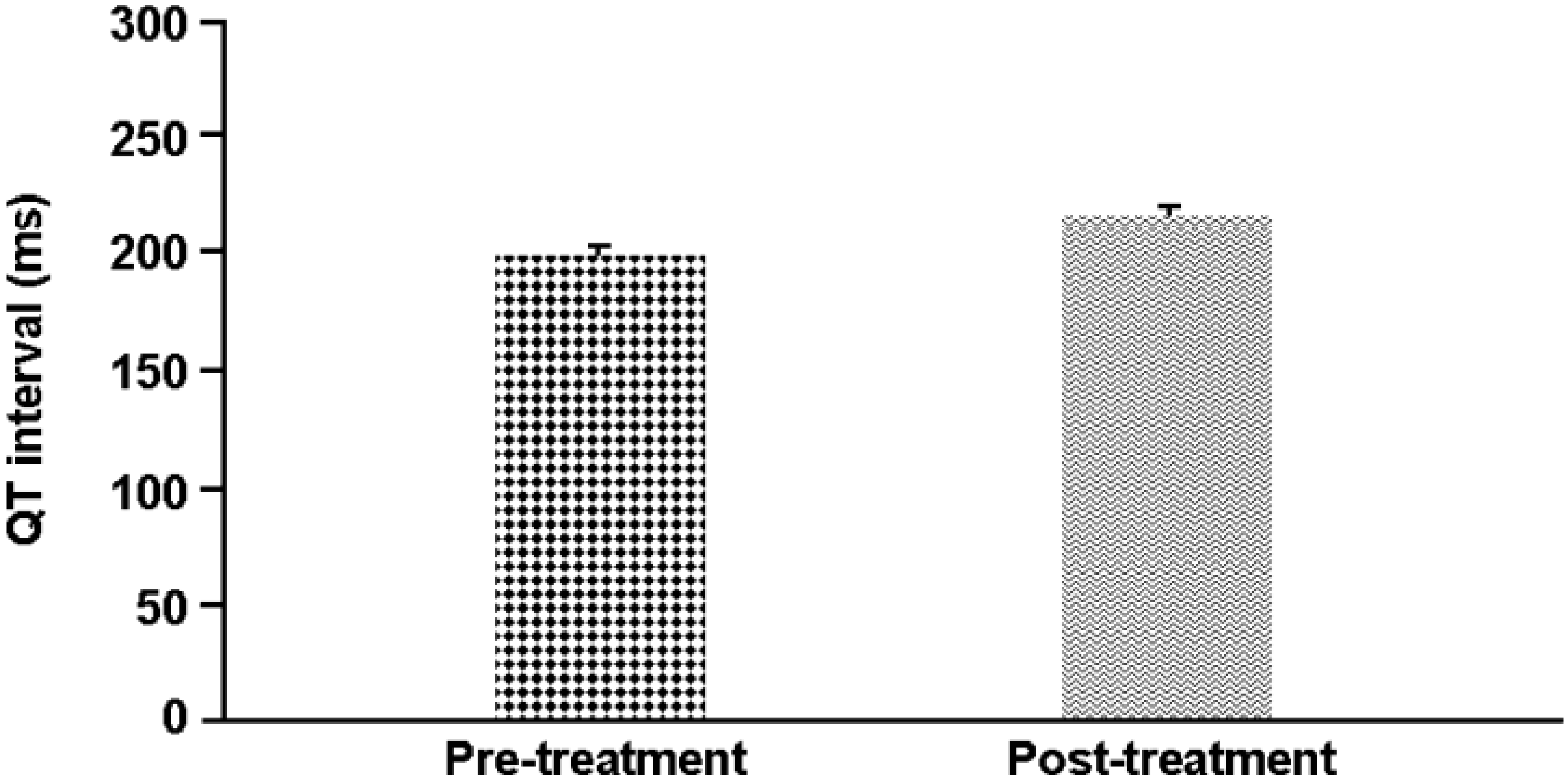


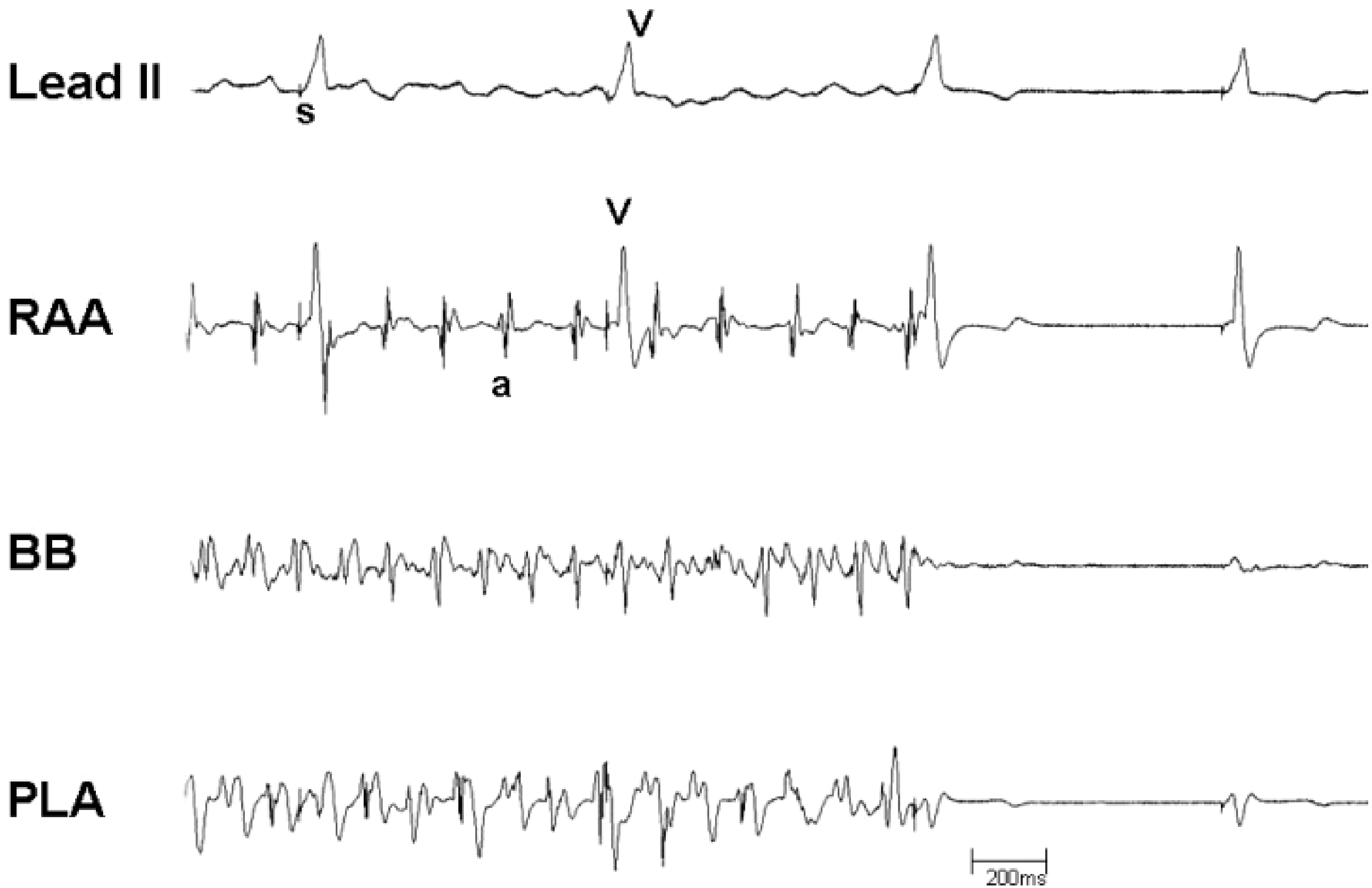
JCE 2004, 15 (12), 1444-1450

Increase in effective refractory period post-AZD7009

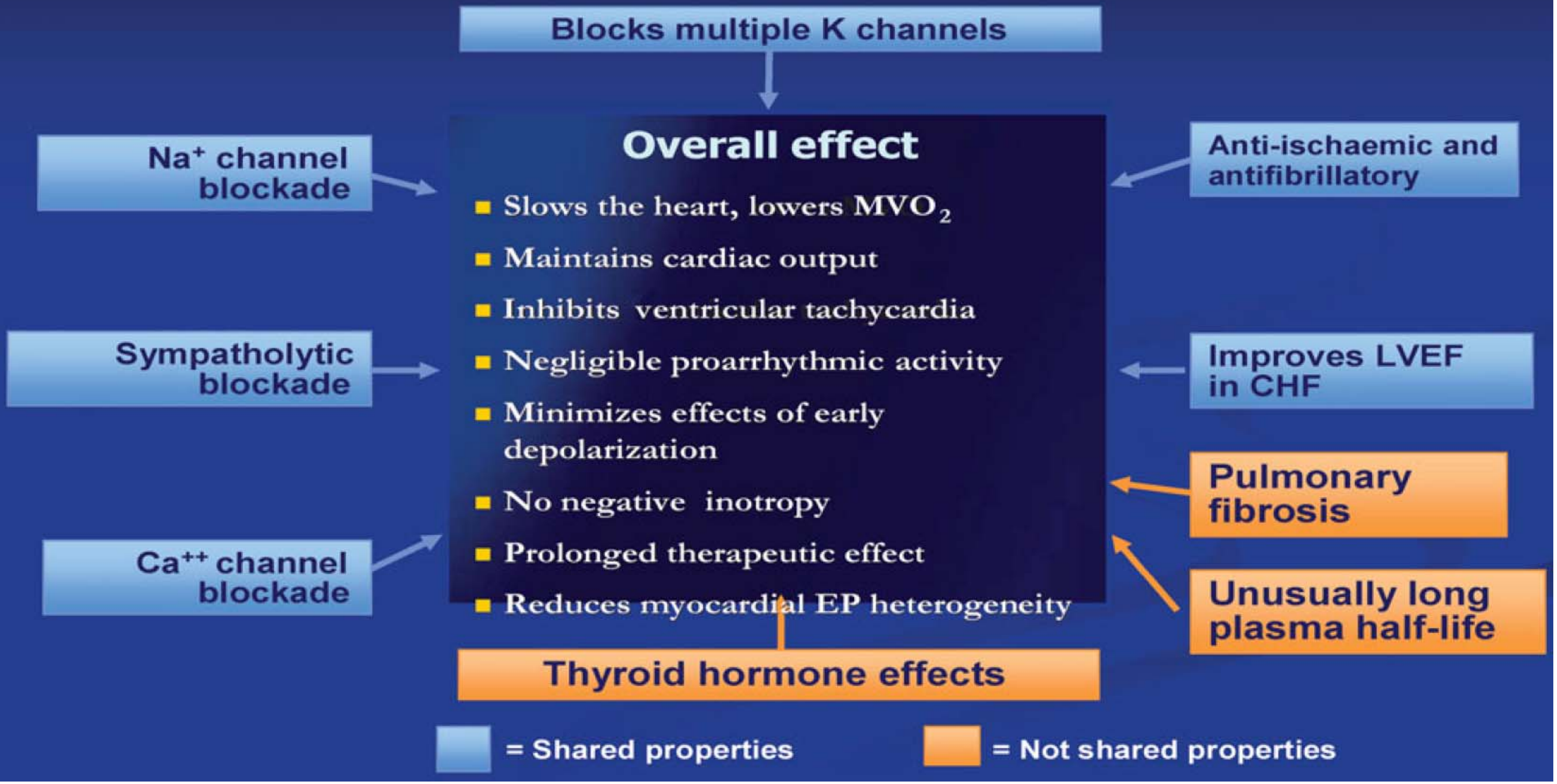


QT interval at 400 ms cycle length (QT400)




Lead II
V
s
RAA
V
a
BB
PLA
200ms

Amiodarone vs. dronedarone effects



ORIGINAL ARTICLE

Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

Bramah N. Singh, M.D., D.Sc., Stuart J. Connolly, M.D., Harry J.G.M. Crijns, M.D., Denis Roy, M.D., Peter R. Kowey, M.D., Alessandro Capucci, M.D., Ph.D., David Radzik, M.D., Etienne M. Aliot, M.D., and Stefan H. Hohnloser, M.D., for the EURIDIS and ADONIS Investigators*

ABSTRACT

BACKGROUND

Amiodarone is effective in maintaining sinus rhythm in atrial fibrillation but is associated with potentially serious toxic effects. Dronedarone is a new antiarrhythmic agent pharmacologically related to amiodarone but developed to reduce the risk of side effects.

METHODS

In two identical multicenter, double-blind, randomized trials, one conducted in Europe (ClinicalTrials.gov number, NCT00259428) and one conducted in the United States, Canada, Australia, South Africa, and Argentina (termed the non-European trial, NCT00259376), we evaluated the efficacy of dronedarone, with 828 patients receiving 400 mg of the drug twice daily and 409 patients receiving placebo. Rhythm was monitored transtelephonically on days 2, 3, and 5; at 3, 5, 7, and 10 months; during recurrence of arrhythmia; and at nine scheduled visits during a 12-month period. The primary end point was the time to the first recurrence of atrial fibrillation or flutter.

RESULTS

In the European trial, the median times to the recurrence of arrhythmia were 41 days in the placebo group and 96 days in the dronedarone group (P=0.01). The corresponding durations in the non-European trial were 59 and 158 days (P=0.002). At the recurrence of arrhythmia in the European trial, the mean (±SD) ventricular rate was 117.5±29.1 beats per minute in the placebo group and 102.3±24.7 beats per minute in the dronedarone group (P<0.001); the corresponding rates in the non-European trial were 116.6±31.9 and 104.6±27.1 beats per minute (P<0.001). Rates of pulmonary toxic effects and of thyroid and liver dysfunction were not significantly increased in the dronedarone group.

CONCLUSIONS

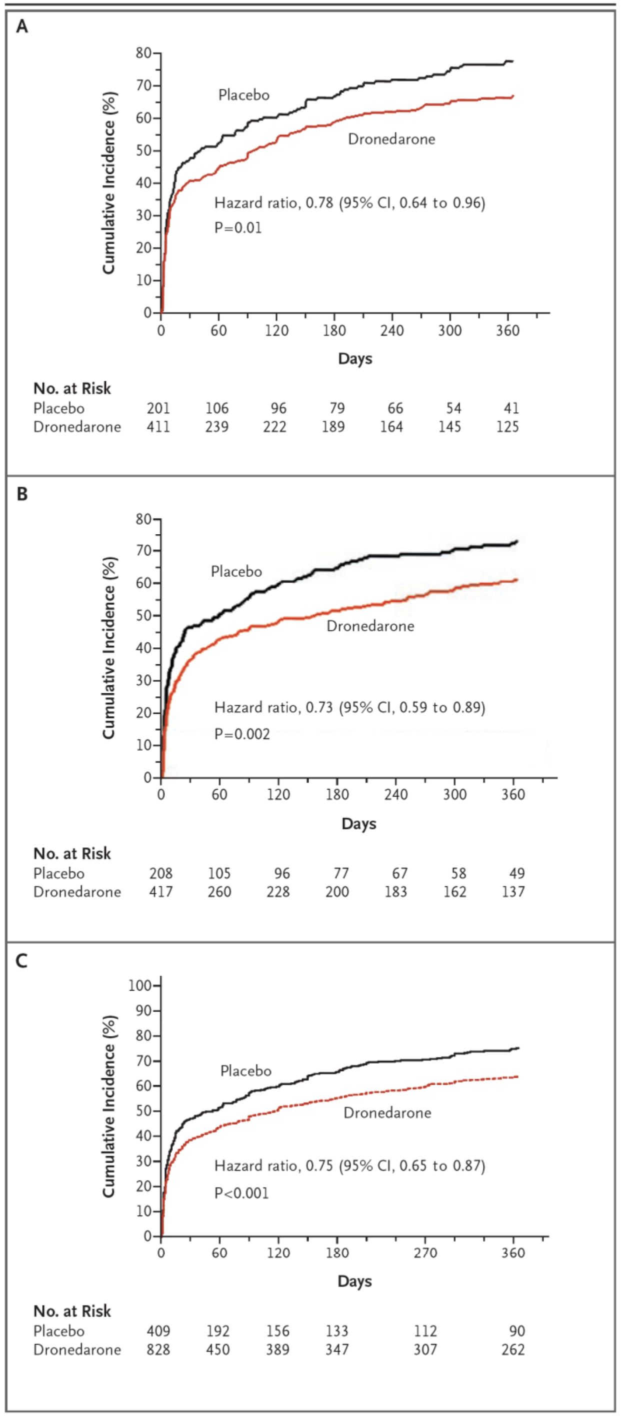
Dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia.

From the Veterans Affairs Greater Los Angeles Healthcare System and the David Geffen School of Medicine at UCLA — both in Los Angeles (B.N.S.); the University of Hamilton, Hamilton, ON, Canada (S.J.C.); the University of Maastricht, Maastricht, the Netherlands (H.J.G.M.C.); the University of Montreal, Montreal (D. Roy); Lankenau Hospital and Institute of Medical Research, Philadelphia (P.R.K.); Ospedale Clinical, Taverna, Italy (A.C.); Sanofi-Aventis, Paris (D. Radzik); Hôpital Central, Nancy, France (E.M.A.); and Goethe University, Frankfurt, Germany (S.H.H.). Address reprint requests to Dr. Singh at Veterans Affairs Greater Los Angeles Healthcare System, Cardiology Division, 11301 Wilshire Blvd., Los Angeles, CA 90073, or at bsingh@ucla.edu.

*Members of the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) are listed in the Appendix.

N Engl J Med 2007;357:987-99.

First recurrence of AF or AFL



European trial

Non-European trial

Combine

Subgroup	No. of Patients	Hazard Ratio for Event (95% CI)	P Value for Interaction
Structural heart disease			0.59
Yes	507	0.79 (0.63–0.99)	
No	714	0.74 (0.62–0.89)	
Hypertension			0.62
Yes	702	0.73 (0.60–0.89)	
No	535	0.79 (0.64–0.97)	
Left atrial diameter			0.10
≤40 mm	465	0.65 (0.51–0.82)	
>40 mm	735	0.83 (0.69–0.99)	
Heart failure criteria met			0.10
Yes	216	0.59 (0.42–0.83)	
No	946	0.81 (0.69–0.95)	
Conversion to sinus rhythm in ≤5 days			0.87
Yes	364	0.76 (0.59–0.97)	
No	873	0.76 (0.64–0.90)	
Previous use of amiodarone			0.21
Yes (stopped for trial)	223	0.60 (0.43–0.84)	
No	1014	0.79 (0.67–0.92)	
Previous use of antiarrhythmic drugs			0.11
Yes (stopped for trial)	903	0.70 (0.59–0.82)	
No	334	0.92 (0.68–1.25)	

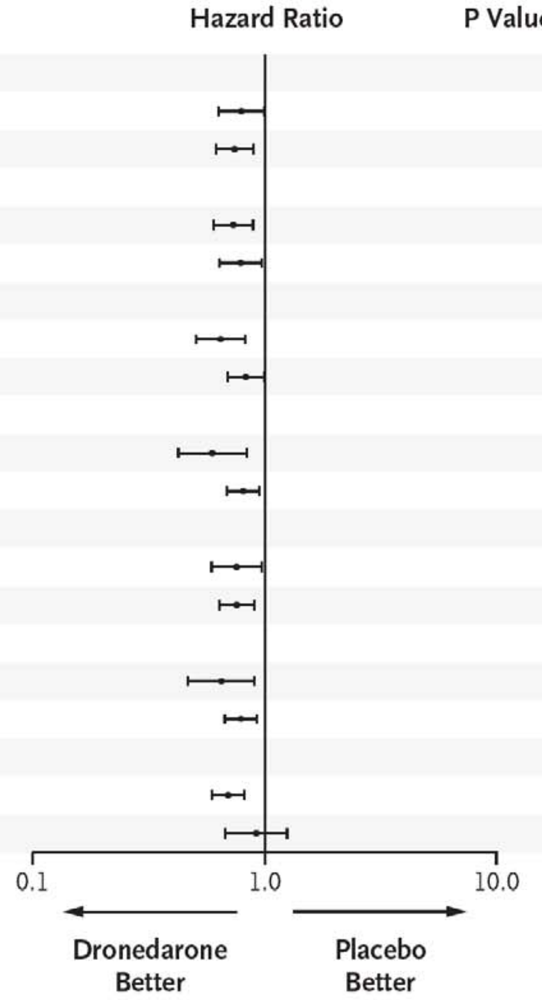


Figure 3. **Hazard Ratio for the Adjudicated First Recurrence of Atrial Fibrillation or Flutter, According to Selected Baseline Characteristics.**
The scale for the hazard ratios, which were determined from Cox models comparing the dronedarone group with the placebo group, is logarithmic. Dronedarone had a variable but consistently favorable effect, as compared with placebo, in reducing the first recurrence of atrial fibrillation or flutter.

Azimilide (Procter & Gamble, USA) is a selective class III antiarrhythmic drug that blocks both the rapid (IKr) and the slow (IKs) components of the delayed rectifier potassium channel.

Placebo-Controlled, Randomized Clinical Trial of Azimilide for Prevention of Ventricular Tachyarrhythmias in Patients With an Implantable Cardioverter Defibrillator

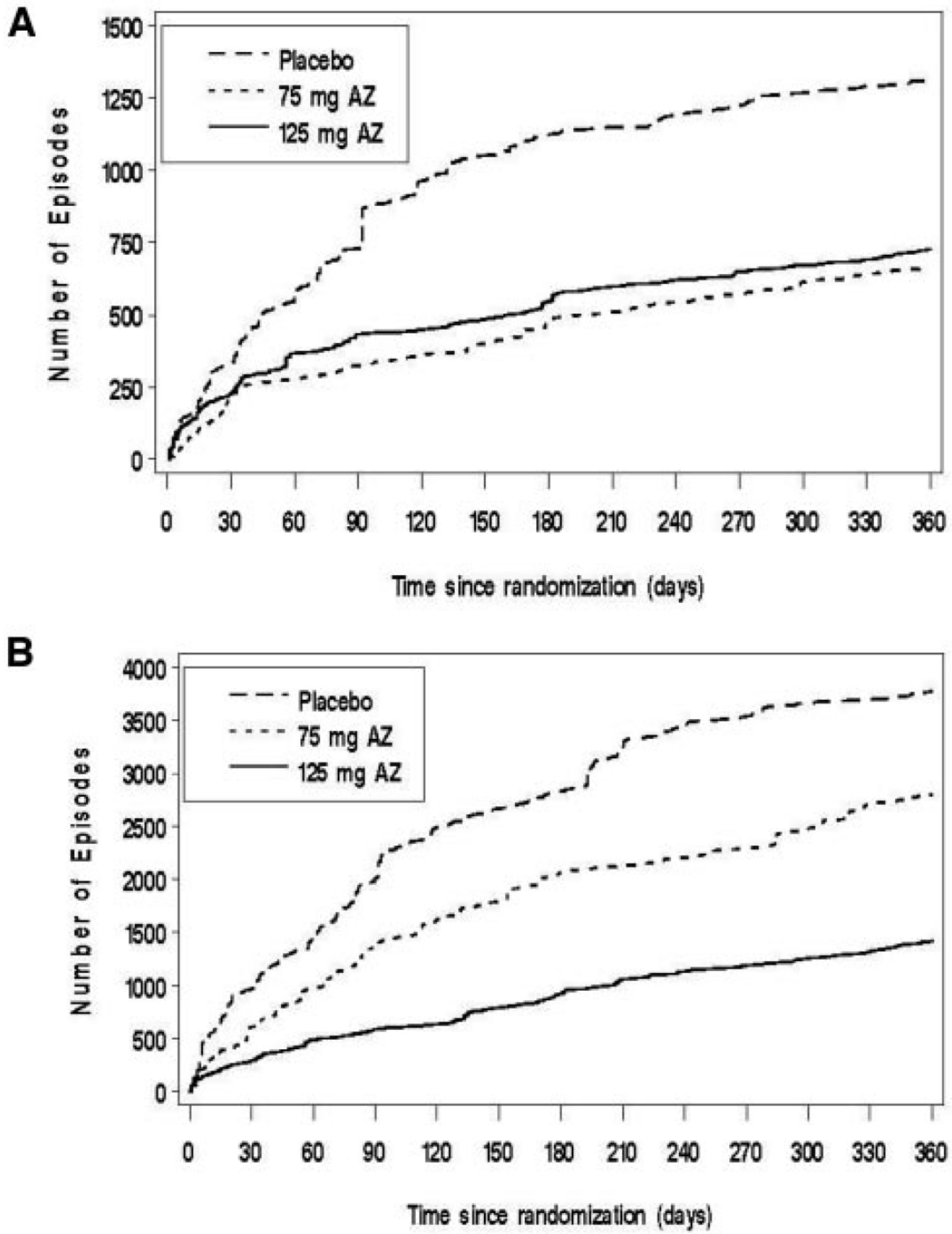
Paul Dorian, MD; Martin Borggrefe, MD; Hussein R. Al-Khalidi, PhD; Stefan H. Hohnloser, MD; Jose M. Brum, MD; Daljit S. Tatla, PhD; Johannes Brachmann, MD; Robert J. Myerburg, MD; David S. Cannom, MD; Michael van der Laan, MD; Michael J. Holroyde, PhD; Igor Singer, MD; Craig M. Pratt, MD; on Behalf of the SHock Inhibition Evaluation with azimiLiDe (SHIELD) Investigators

Background—Although implanted cardioverter defibrillators (ICDs) effectively treat sustained ventricular tachyarrhythmias, up to 50% of ICD recipients eventually require concomitant antiarrhythmic drug therapy to prevent symptomatic arrhythmia recurrences and hence reduce the number of device therapies.

Methods and Results—A total of 633 ICD recipients were enrolled in a randomized, double-blind, placebo-controlled study to evaluate the effect of daily doses of 75 or 125 mg of azimilide on recurrent symptomatic ventricular tachyarrhythmias and ICD therapies. Total all-cause shocks plus symptomatic ventricular tachycardia (VT) terminated by antitachycardia pacing (ATP) were significantly reduced by azimilide, with relative risk reductions of 57% (hazard ratio [HR]=0.43, 95% CI 0.26 to 0.69, P=0.0006) and 47% (HR=0.53, 95% CI 0.34 to 0.83, P=0.0053) at 75- and 125-mg doses, respectively. The reductions in all-cause shocks with both doses of azimilide did not achieve statistical significance. The incidence of all appropriate ICD therapies (shocks or ATP-terminated VT) was reduced significantly among patients taking 75 mg of azimilide (HR=0.52, 95% CI 0.30 to 0.89, P=0.017) and those taking 125 mg of azimilide (HR=0.38, 95% CI 0.22 to 0.65, P=0.0004). Five patients in the azimilide groups and 1 patient in the placebo group had torsade de pointes; all were successfully treated by the device. One patient taking 75 mg of azimilide had severe but reversible neutropenia.

Conclusions—Azimilide significantly reduced the recurrence of VT or ventricular fibrillation terminated by shocks or ATP in ICD patients, thereby reducing the burden of symptomatic ventricular tachyarrhythmia. (***Circulation*. 2004;110:3646-3654.**)

Key Words: drugs ■ cardioversion ■ defibrillation ■ antiarrhythmia agents ■ tachycardia


A
Placebo
75 mg AZ
125 mg AZ
Number of Episodes
Time since randomization (days)
B
Placebo
75 mg AZ
125 mg AZ
Number of Episodes
Time since randomization (days)

Tedisamil (Solvay Pharmaceuticals, Belgium), an antianginal agent, possesses multiple ion-channel effects, including blockade of the transient outward current, Ito, in addition to IKr, IKs, IKur, IK-ATP, and even INa.41–43 The drug also causes reverse, rate-dependent QT interval prolongation.

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Safety and Efficacy of Intravenously Administered Tedisamil for Rapid Conversion of Recent-Onset Atrial Fibrillation or Atrial Flutter

Stefan H. Hohnloser, MD,* Paul Dorian, MD,† Matthias Straub, MD,‡ Katrin Beckmann,‡ Peter Kowey, MD§

Frankfurt and Hannover, Germany; Toronto, Canada; and Wynnewood, Pennsylvania

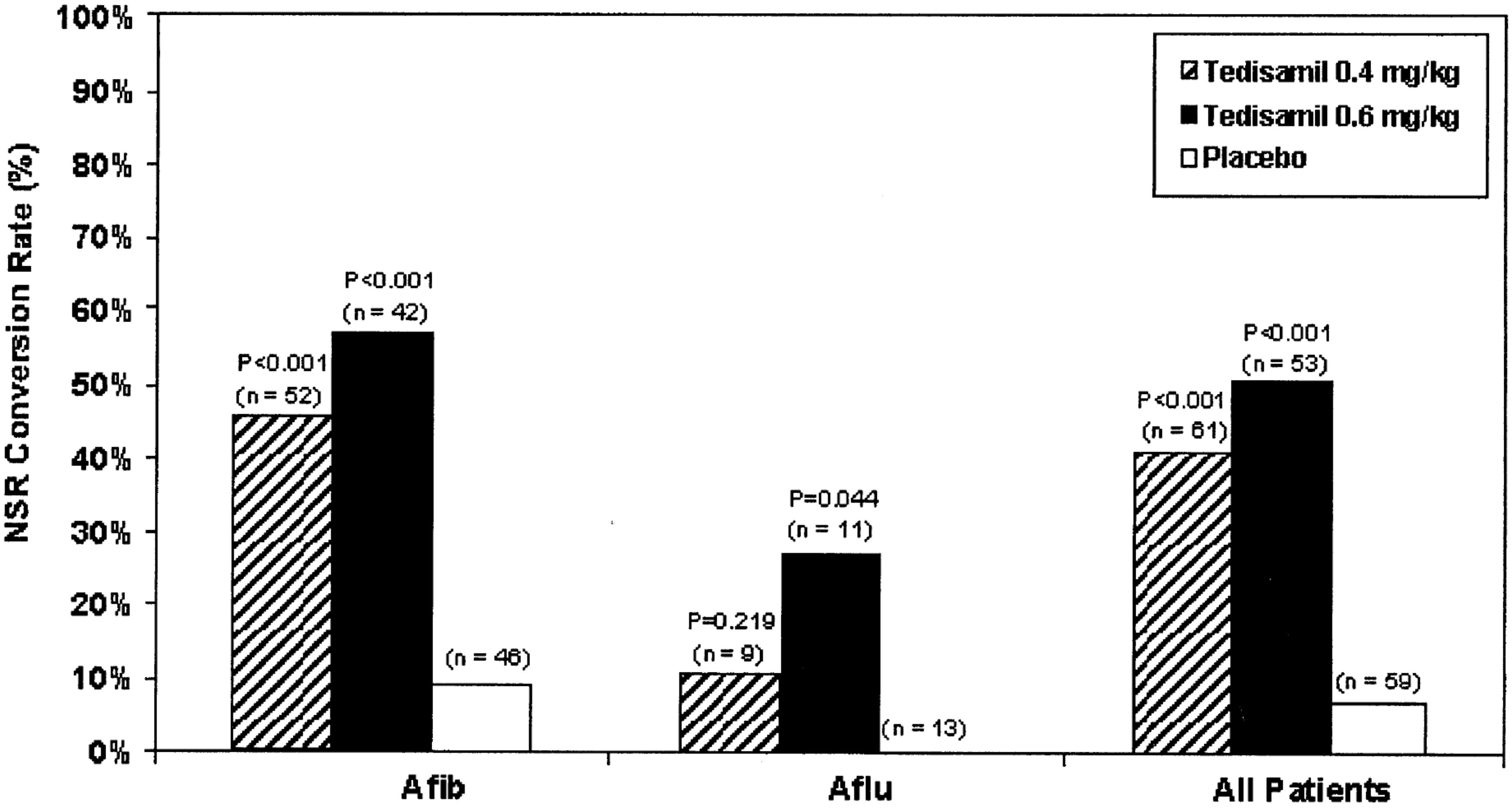
OBJECTIVES The goal of the present study was to assess the efficacy and safety of intravenous tedisamil, a new antiarrhythmic compound, for conversion of recent-onset atrial fibrillation (AF) or atrial flutter (AFL) to normal sinus rhythm (NSR).

BACKGROUND Tedisamil is a novel antiarrhythmic drug with predominantly class III activity. Its efficacy and safety for conversion of recent onset AF or AFL to NSR is not known.

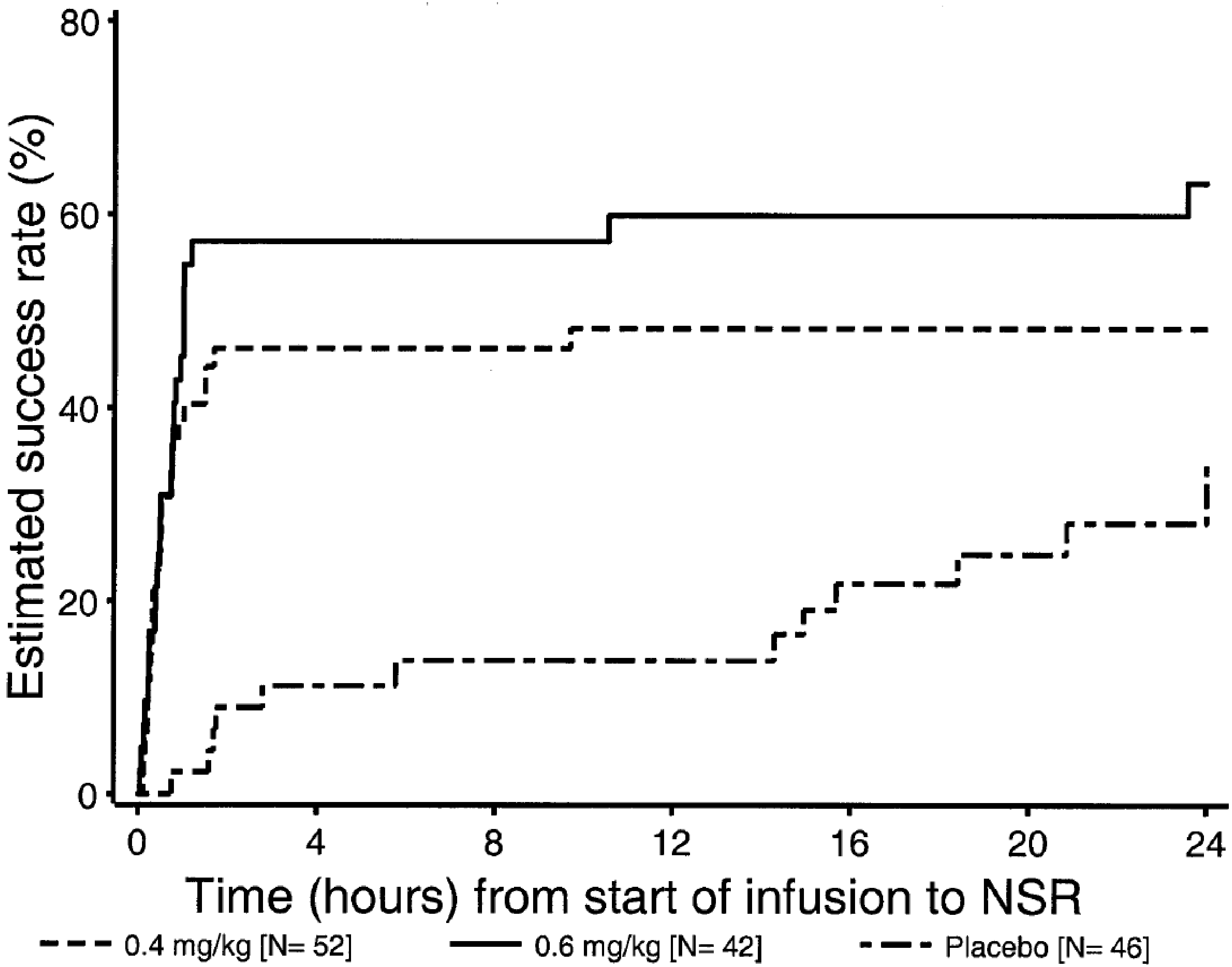
METHODS This was a multicenter, double-blind, randomized, placebo-controlled, sequential ascending dose-group trial. A total of 201 patients with symptomatic AF or AFL of 3 to 48 h duration were enrolled in a two-stage study. During stage 1, patients were randomized to receive tedisamil at 0.4 mg/kg body weight or matching placebo; during stage 2, patients received tedisamil at 0.6 mg/kg body weight or matching placebo. Treatments were given as single intravenous infusions. The primary study end point consisted of the percentage of patients converting to NSR for at least 60 s within 2.5 h.

RESULTS Of 175 patients representing the intention-to-treat sample, conversion to NSR was observed in 41% (25/61) of the tedisamil 0.4 mg/kg group, 51% (27 of 53) of the tedisamil 0.6 mg/kg group, and 7% (4/59) of the placebo group ($p < 0.001$ for both tedisamil groups vs. placebo). Average time to conversion was 35 min in patients receiving tedisamil. There were two instances of self-terminating ventricular tachycardia: one episode of torsade de pointes and one of monomorphic ventricular tachycardia, both in patients receiving 0.6 mg/kg tedisamil.

CONCLUSIONS Tedisamil at dosages of 0.4 and 0.6 mg/kg was superior to placebo in converting AF or AFL. Tedisamil has a rapid onset of action leading to conversion within 30 to 40 min in the majority of responders. (J Am Coll Cardiol 2004;44:99–104) © 2004 by the American College of Cardiology Foundation



100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
NSR Conversion Rate (%)
Tedisamil 0.4 mg/kg
Tedisamil 0.6 mg/kg
Placebo
P<0.001
(n = 52)
P<0.001
(n = 42)
(n = 46)
P=0.219
(n = 9)
P=0.044
(n = 11)
(n = 13)
P<0.001
(n = 61)
P<0.001
(n = 53)
(n = 59)
Afib
Aflu
All Patients



80
60
40
20
0
Estimated success rate (%)
0
4
8
12
16
20
24
Time (hours) from start of infusion to NSR
0.4 mg/kg [N= 52]
0.6 mg/kg [N= 42]
Placebo [N= 46]

Rotigaptide (ZP123, Zealand Pharma, Denmark) is a specific gap-junction-modifying drug. Gap junctions are specialized pores that ensure the coordinated cell-to-cell transmission of electrical impulses, essential for synchronized contraction.

Effects of the Gap Junction Modifier Rotigaptide (ZP123) on Atrial Conduction and Vulnerability to Atrial Fibrillation

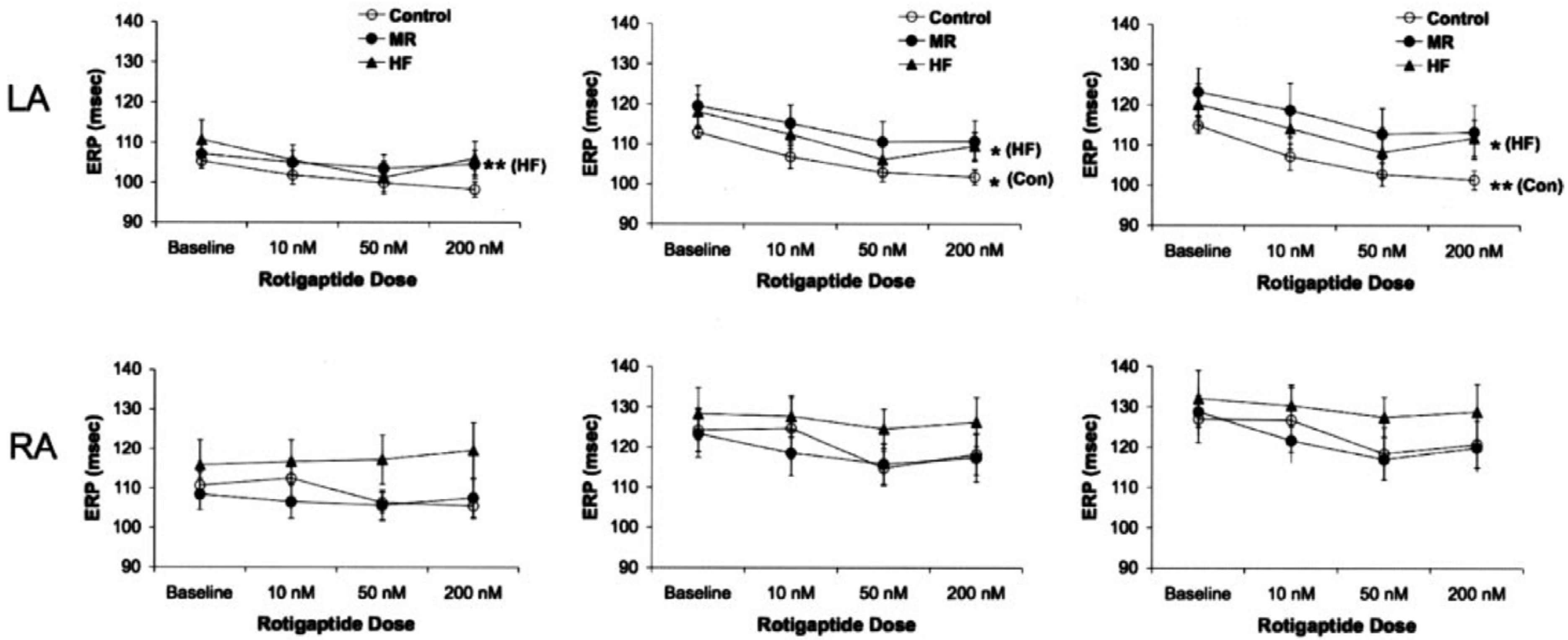
Jose M. Guerra, MD*; Thomas H. Everett IV, PhD*; Ken W. Lee, MD, MS;
Emily Wilson, BS; Jeffrey E. Olgin, MD

Background—Altered conduction is associated with increased atrial fibrillation (AF) vulnerability in canine models of chronic mitral regurgitation (MR) and heart failure (HF). Rotigaptide (ZP123) augments gap junction conductance, improving cell-to-cell coupling. We studied the effects of rotigaptide on atrial conduction and AF vulnerability in the canine MR and HF models.

Methods and Results—Twenty-one dogs in 3 groups were studied: control (n=7), chronic MR induced by mitral avulsion (n=7), and HF induced by ventricular tachypacing (n=7). Epicardial mapping of both atria was performed with a 512-electrode array at baseline and at increasing rotigaptide doses (10, 50, and 200 nmol/L). Conduction velocity increased in both atria in control animals and MR animals (maximum percentage increase: 24±5%, 38±6% [$P<0.001$, <0.001] in the left atrium and 19±9%, 18±3% [$P<0.001$, <0.001] in the right atrium). Conduction velocity did not change in the left atrium of the HF group and increased minimally in the right atrium (3±3%, 17±5% [P=NS, $P=0.001$]). AF duration was increased at baseline in MR and HF animals (control: 16±25 seconds, MR: 786±764 seconds, HF: 883±684 seconds; $P=0.013$). At 50 nmol/L of rotigaptide, duration of AF markedly decreased in the MR animals (96% reduction, $P<0.001$), reducing AF duration to that of control animals (control: 9±11 seconds, MR: 14±16 seconds, HF: 1622±355 seconds; $P=0.04$).

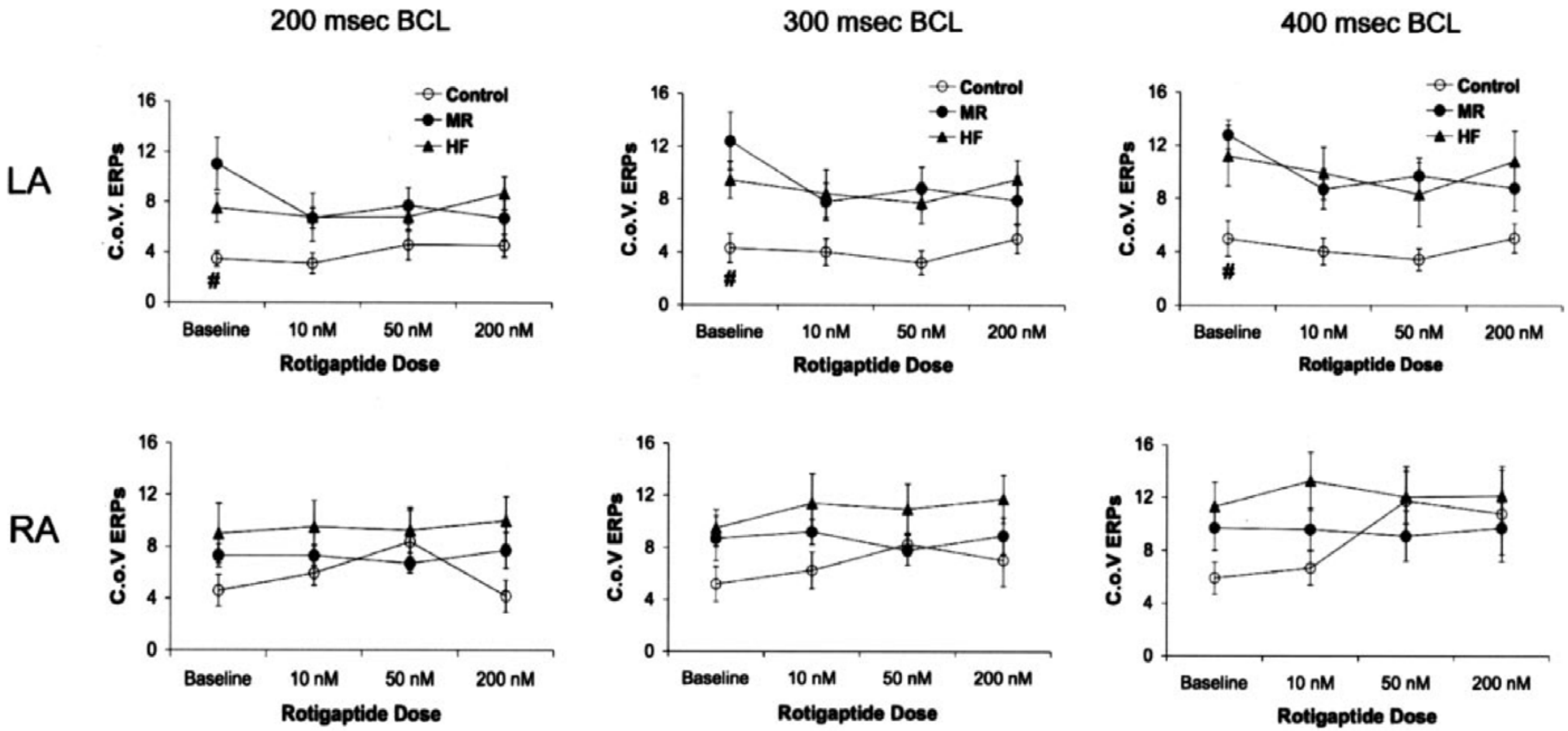
Conclusions—Gap junction modulation with rotigaptide reduces AF vulnerability in a canine MR model of AF to a level similar to control animals but does not affect AF vulnerability in the canine HF model. This may be a novel therapeutic target in some forms of AF. (***Circulation*. 2006;114:110-118.**)

Key Words: atrium ■ fibrillation ■ electrophysiology ■ conduction

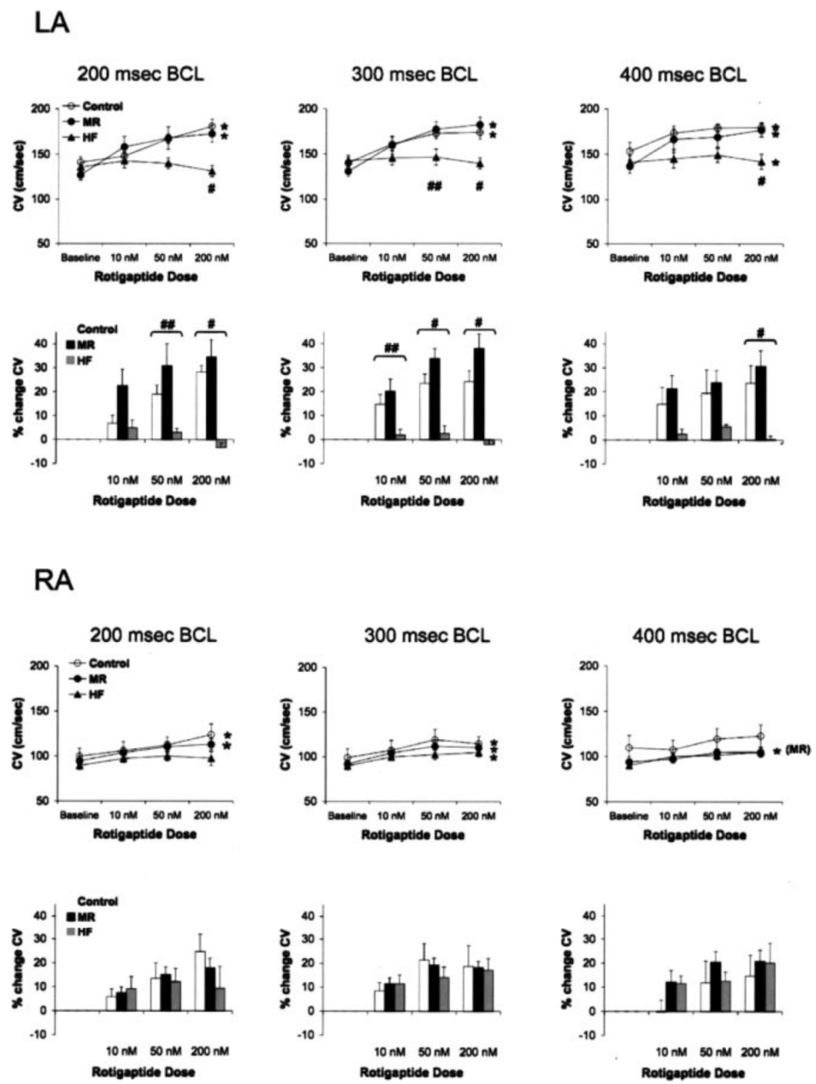


LA
RA
Control
MR
HF
ERP (msec)
140
130
120
110
100
90
Baseline
10 nM
50 nM
200 nM
Rotigaptide Dose
** (HF)
* (HF)
* (Con)
** (Con)

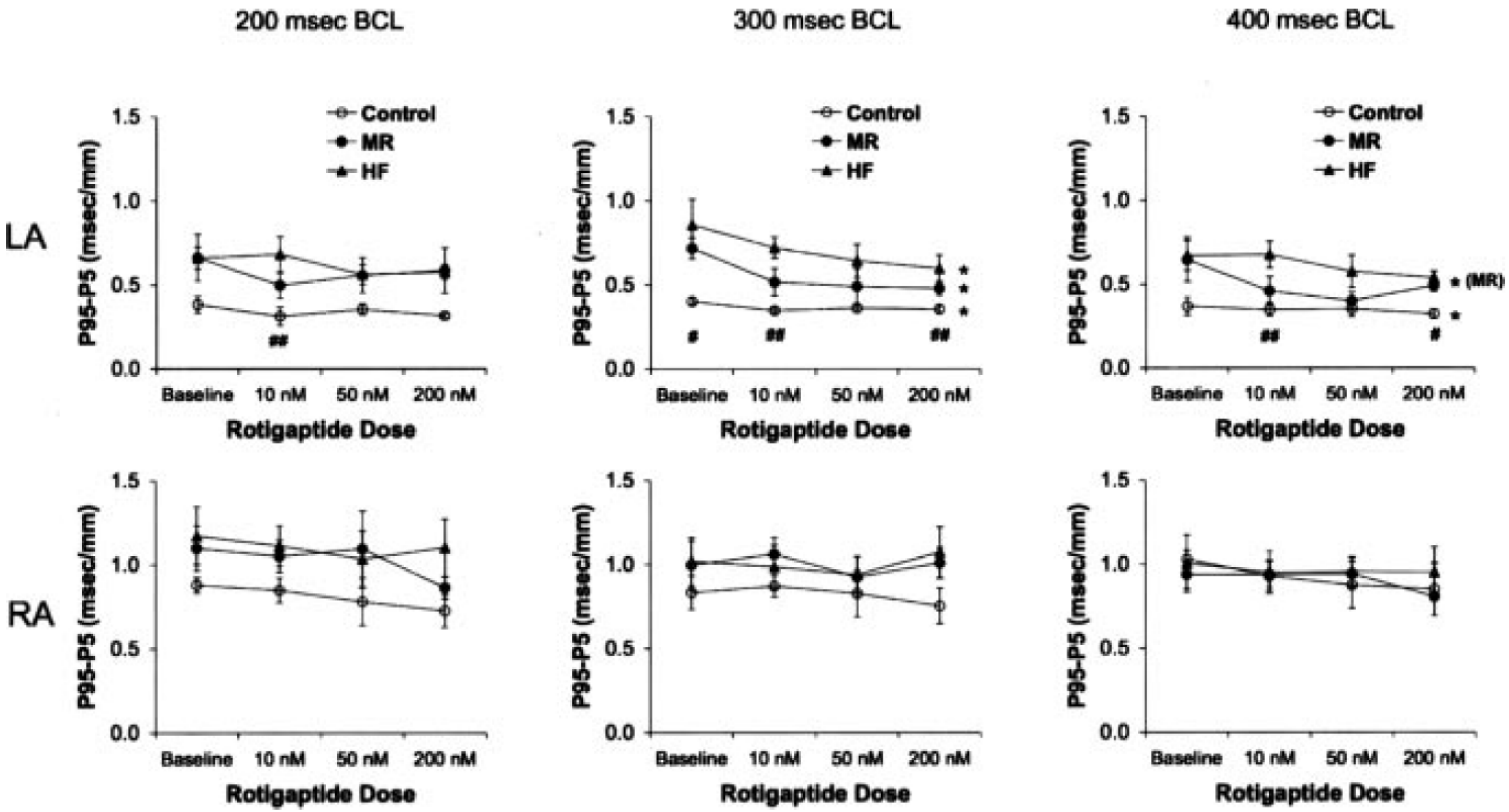
Dispersion of repolarization

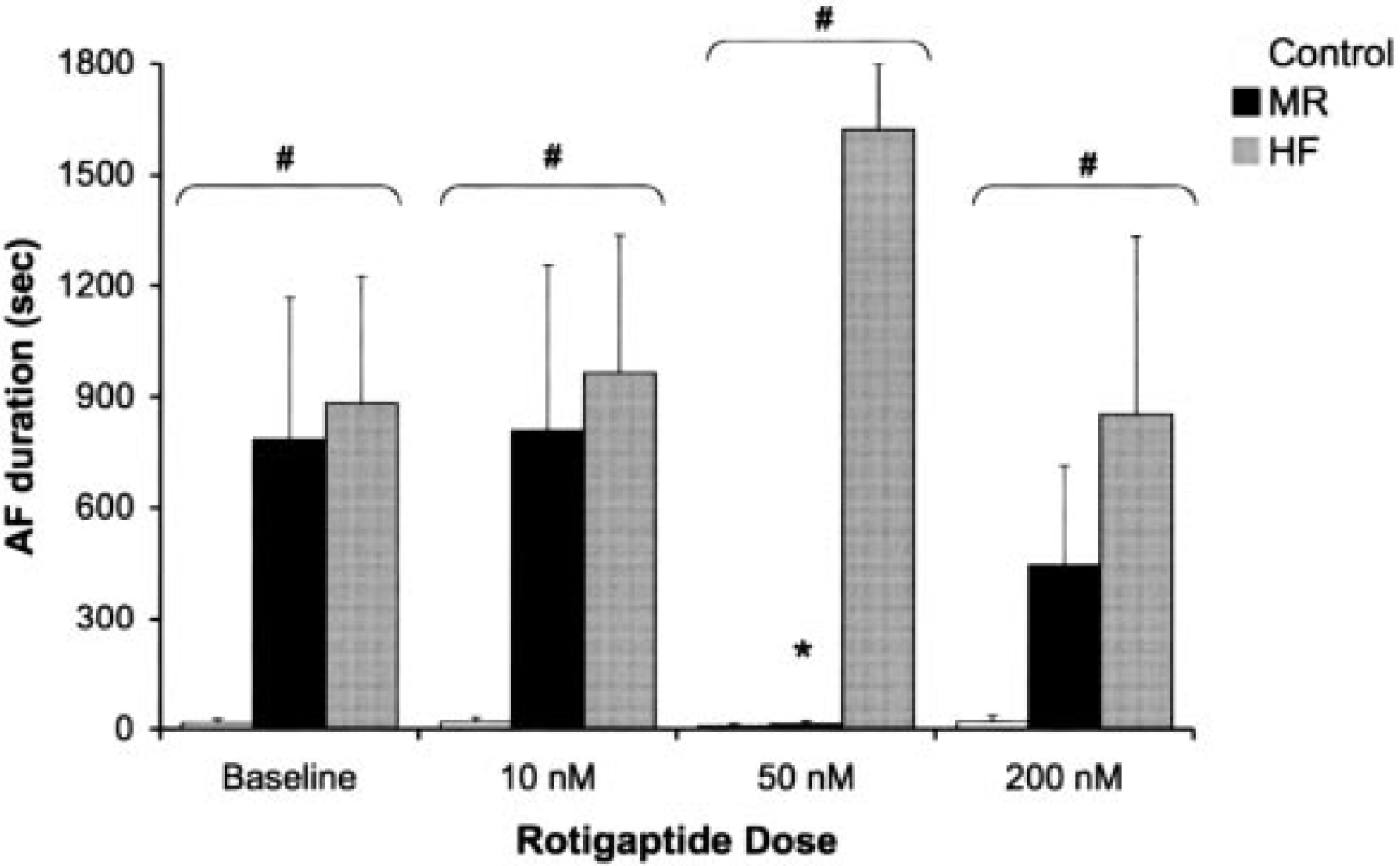


Conduction velocity

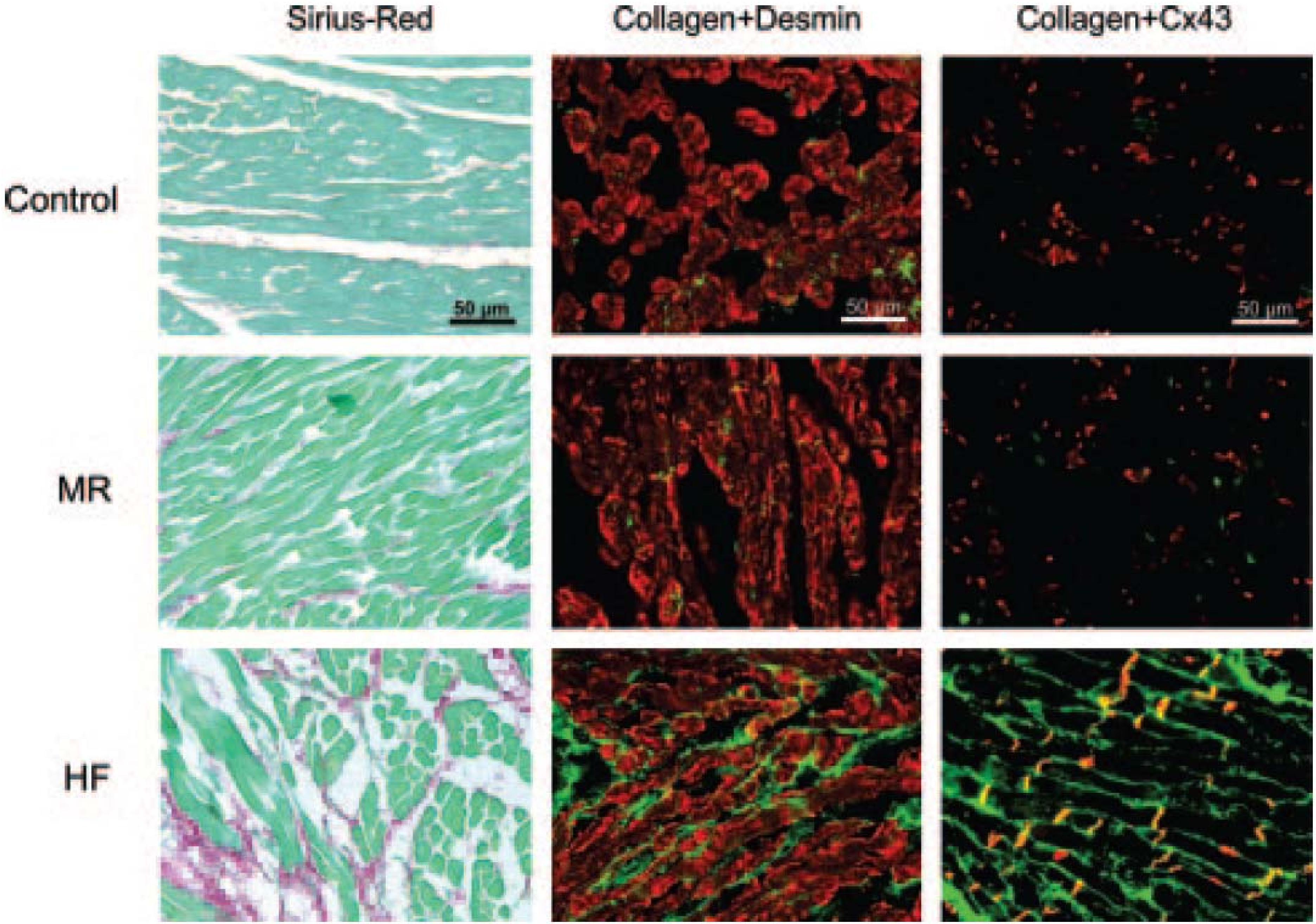


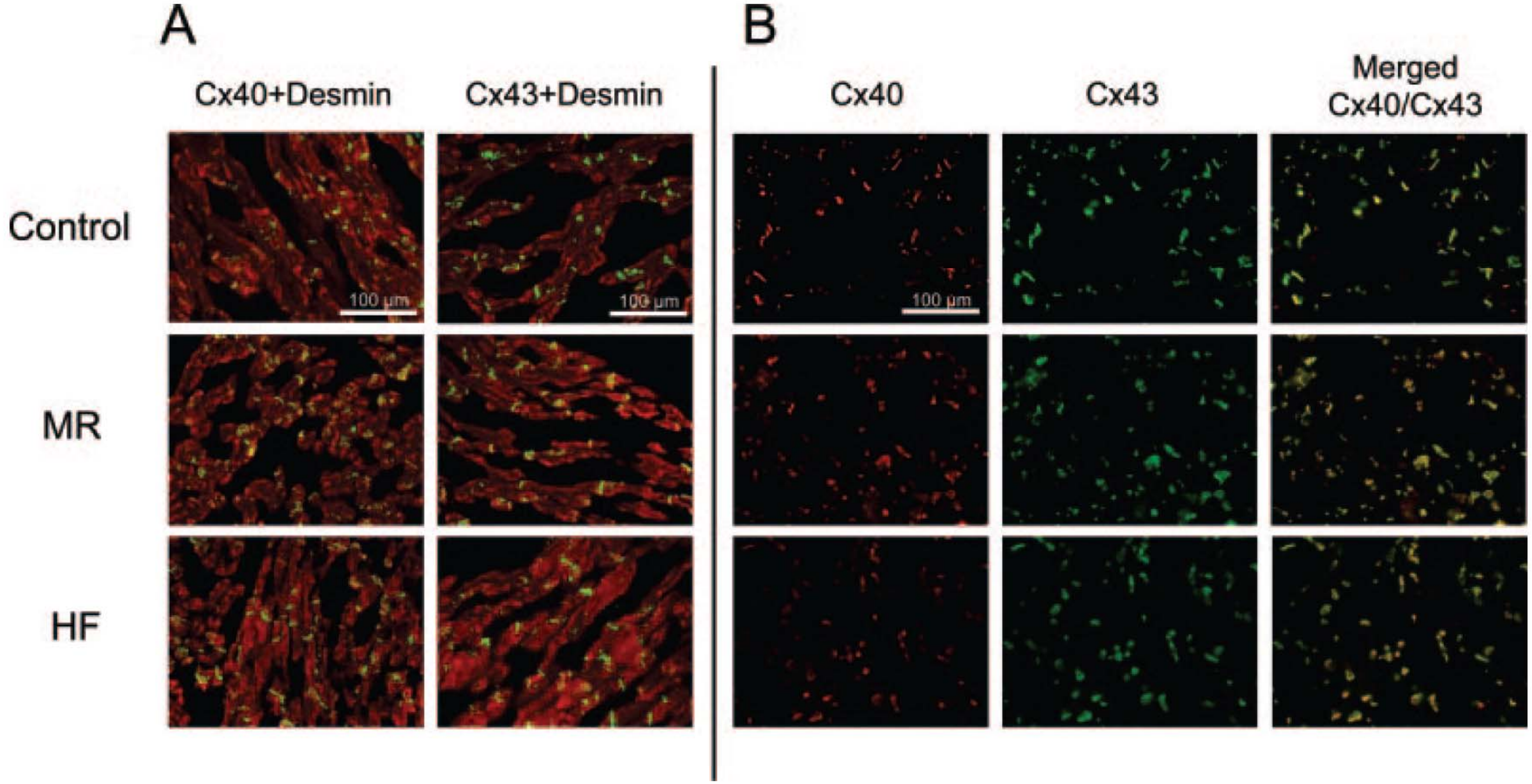
Conduction heterogeneity.





AF duration (sec)
1800
1500
1200
900
600
300
0
#
#
#
#
*
Control
MR
HF
Baseline
10 nM
50 nM
200 nM
Rotigaptide Dose


Sirius-Red
Collagen+Desmin
Collagen+Cx43
Control
MR
HF
50 μm
50 μm
50 μm

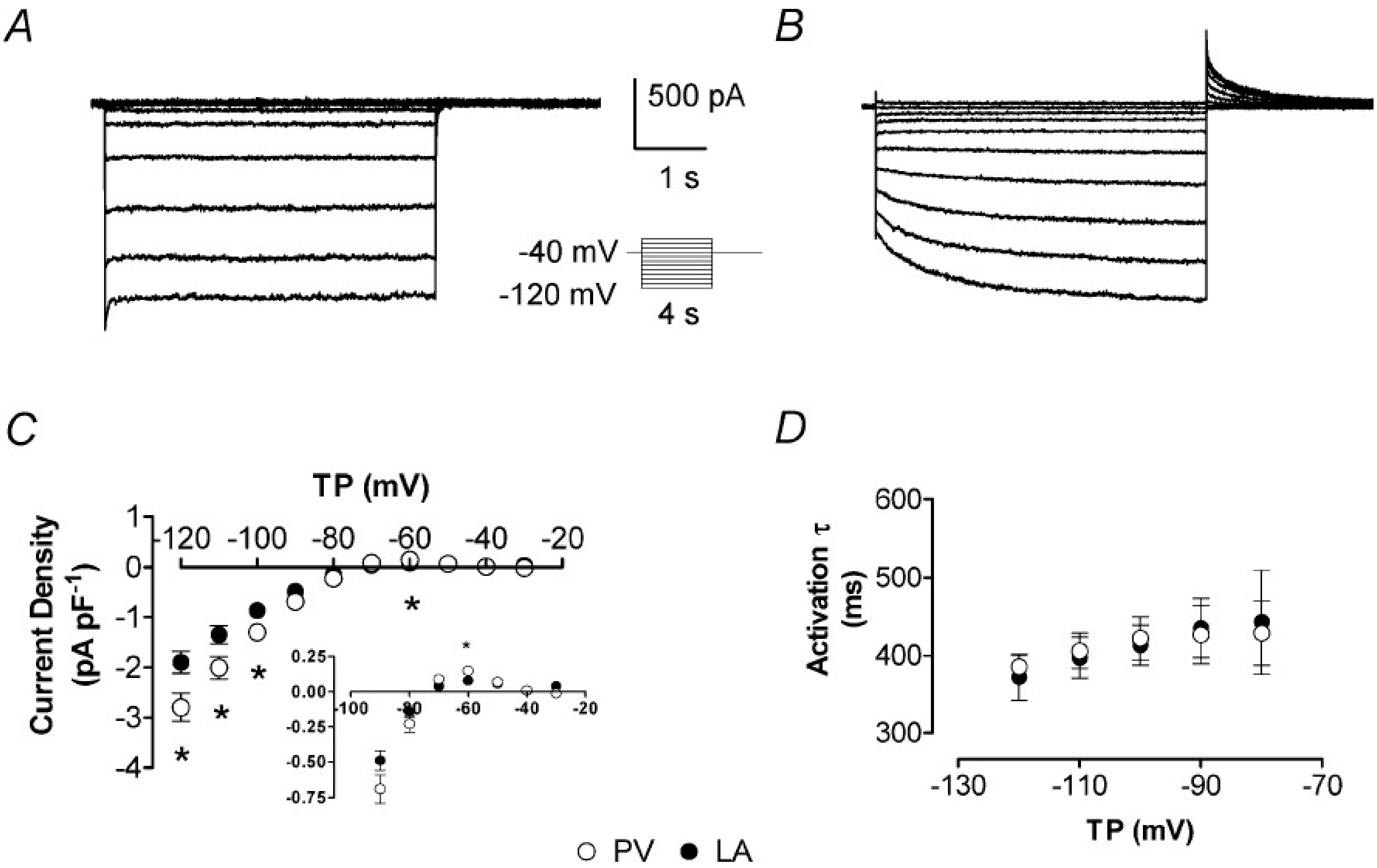

A
B
Cx40+Desmin
Cx43+Desmin
Cx40
Cx43
Merged
Cx40/Cx43
Control
MR
HF
100 µm
100 µm
100 µm

serotonin 5-HT4 receptor antagonists could be promising drugs in patients with AF, on the basis that infusion of serotonin induces sinus tachycardia and other atrial tachyarrhythmias including AF. Furthermore, the atrial-specific 5-HT4 receptor subtype is present in the atria but not in the ventricles, allowing the possibility to pharmacologically target this hormonal pathway without potentially inducing ventricular adverse effects

Characterization of a hyperpolarization-activated time-dependent potassium current in canine cardiomyocytes from pulmonary vein myocardial sleeves and left atrium

Joachim R. Ehrlich[1,2], Tae-Joon Cha[1,2], Liming Zhang[1,2], Denis Chartier[1,2], Louis Villeneuve[1],
Terence E. Hébert[2,3] and Stanley Nattel[1,2,4]

J physiol, 2004, 583-597



A
B
500 pA
1 s
-40 mV
-120 mV
4 s
C
D
TP (mV)
Current Density (pA pF-1)
-120 -100 -80 -60 -40 -20
1 0 -1 -2 -3 -4
*
0.25 0.00 -0.25 -0.50 -0.75
-100 -80 -60 -40 -20
Activation τ (ms)
600 500 400 300
-130 -110 -90 -70
TP (mV)
○ PV ● LA

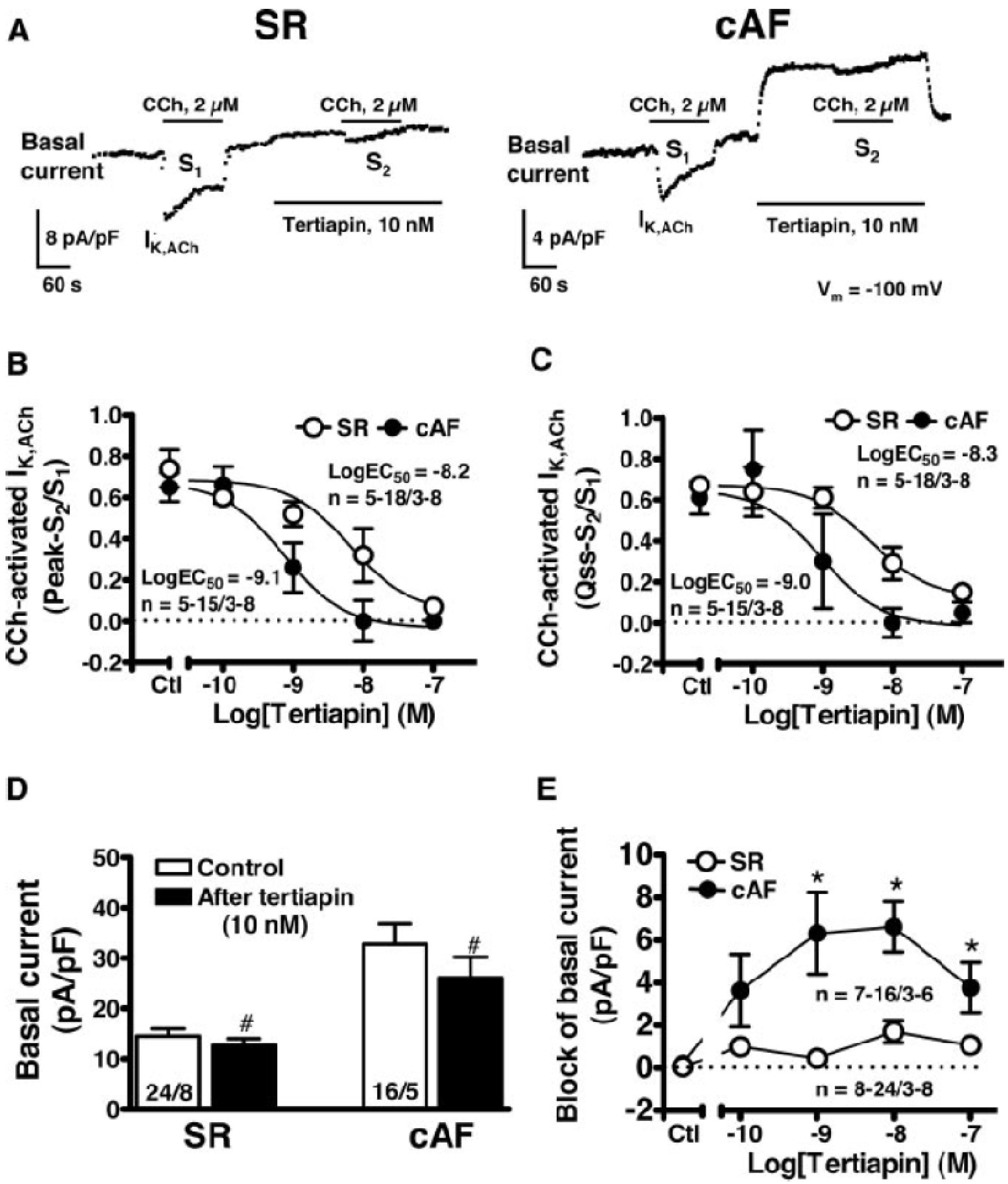
The G Protein–Gated Potassium Current $I_{K,ACh}$ Is Constitutively Active in Patients With Chronic Atrial Fibrillation

D. Dobrev, MD; A. Friedrich, CandMed; N. Voigt, CandMed; N. Jost, PhD; E. Wettwer, PhD;
T. Christ, MD; M. Knaut, MD; U. Ravens, MD

Background—The molecular mechanism of increased background inward rectifier current (I_{K1}) in atrial fibrillation (AF) is not fully understood. We tested whether constitutively active acetylcholine (ACh)-activated $I_{K,ACh}$ contributes to enhanced basal conductance in chronic AF (cAF).

Methods and Results—Whole-cell and single-channel currents were measured with standard voltage-clamp techniques in atrial myocytes from patients with sinus rhythm (SR) and cAF. The selective $I_{K,ACh}$ blocker tertiapin was used for inhibition of $I_{K,ACh}$. Whole-cell basal current was larger in cAF than in SR, whereas carbachol (CCh)-activated $I_{K,ACh}$ was lower in cAF than in SR. Tertiapin (0.1 to 100 nmol/L) reduced $I_{K,ACh}$ in a concentration-dependent manner with greater potency in cAF than in SR ($-\log IC_{50}$: 9.1 versus 8.2; $P<0.05$). Basal current contained a tertiapin-sensitive component that was larger in cAF than in SR (tertiapin [10 nmol/L]-sensitive current at −100 mV: cAF, -6.7 ± 1.2 pA/pF, n=16/5 [myocytes/patients] versus SR, -1.7 ± 0.5 pA/pF, n=24/8), suggesting contribution of constitutively active $I_{K,ACh}$ to basal current. In single-channel recordings, constitutively active $I_{K,ACh}$ was prominent in cAF but not in SR (channel open probability: cAF, $5.4\pm0.7\%$, n=19/9 versus SR, $0.1\pm0.05\%$, n=16/9; $P<0.05$). Moreover, I_{K1} channel open probability was higher in cAF than in SR ($13.4\pm0.4\%$, n=19/9 versus $11.4\pm0.7\%$, n=16/9; $P<0.05$) without changes in other channel characteristics.

Conclusions—Our results demonstrate that larger basal inward rectifier K^+ current in cAF consists of increased I_{K1} activity and constitutively active $I_{K,ACh}$. Blockade of $I_{K,ACh}$ may represent a new therapeutic target in AF.
(***Circulation*. 2005;112:3697-3706.**)


A
SR
cAF
CCh, 2 μM
CCh, 2 μM
Basal current
S1
S2
IK,ACh
Tertiapin, 10 nM
8 pA/pF
4 pA/pF
60 s
Vm = -100 mV
B
C
SR
cAF
LogEC50 = -8.2
n = 5-18/3-8
LogEC50 = -9.1
n = 5-15/3-8
LogEC50 = -8.3
LogEC50 = -9.0
CCh-activated IK,ACh (Peak-S2/S1)
CCh-activated IK,ACh (Qss-S2/S1)
Log[Tertiapin] (M)
Ctl
D
E
Control
After tertiapin (10 nM)
Basal current (pA/pF)
24/8
16/5
Block of basal current (pA/pF)
n = 7-16/3-6
n = 8-24/3-8

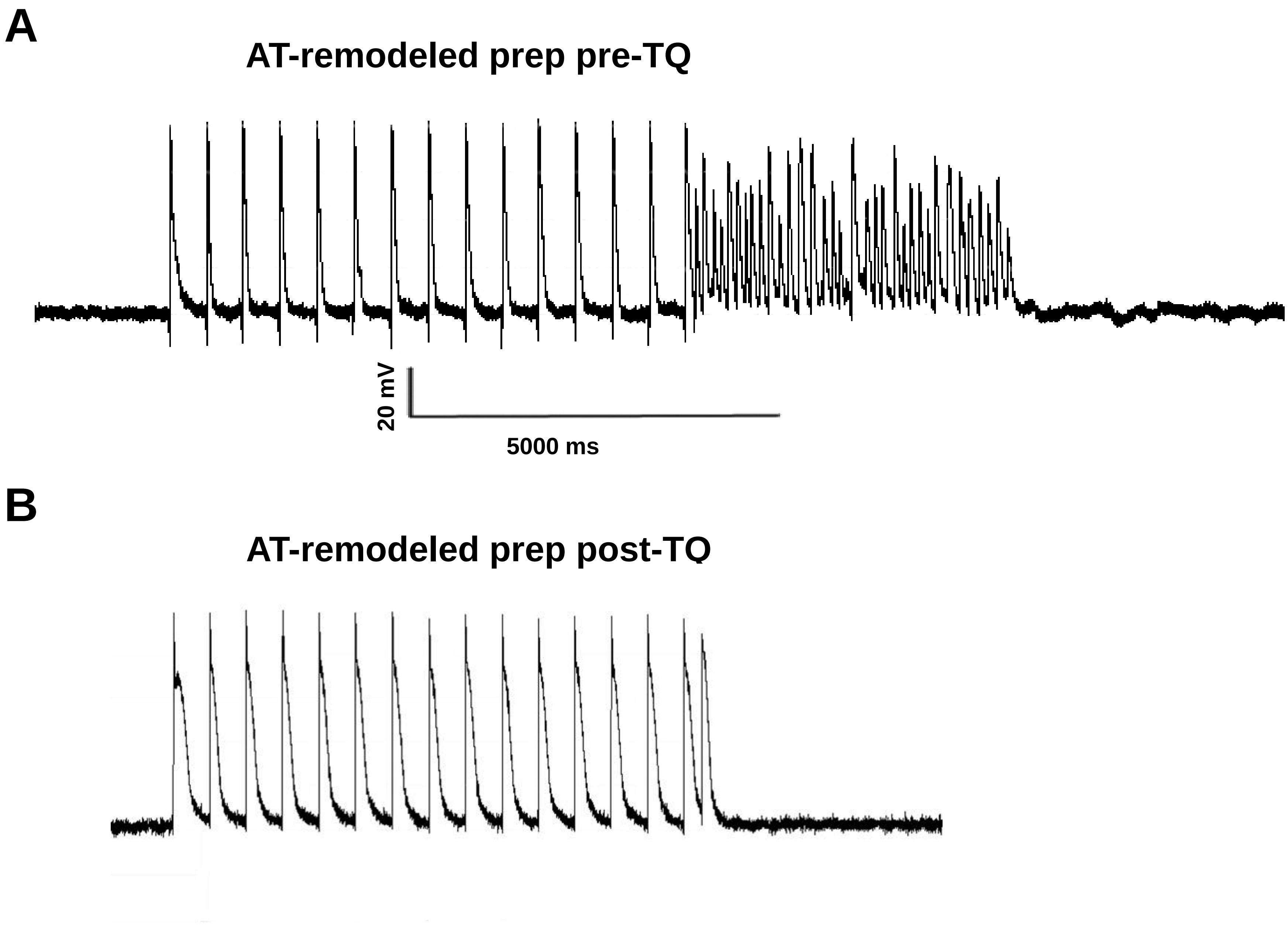
Kir3-based Inward Rectifier Potassium Current: Potential Role in Atrial Tachycardia Remodeling Effects on Atrial Repolarization and Arrhythmias

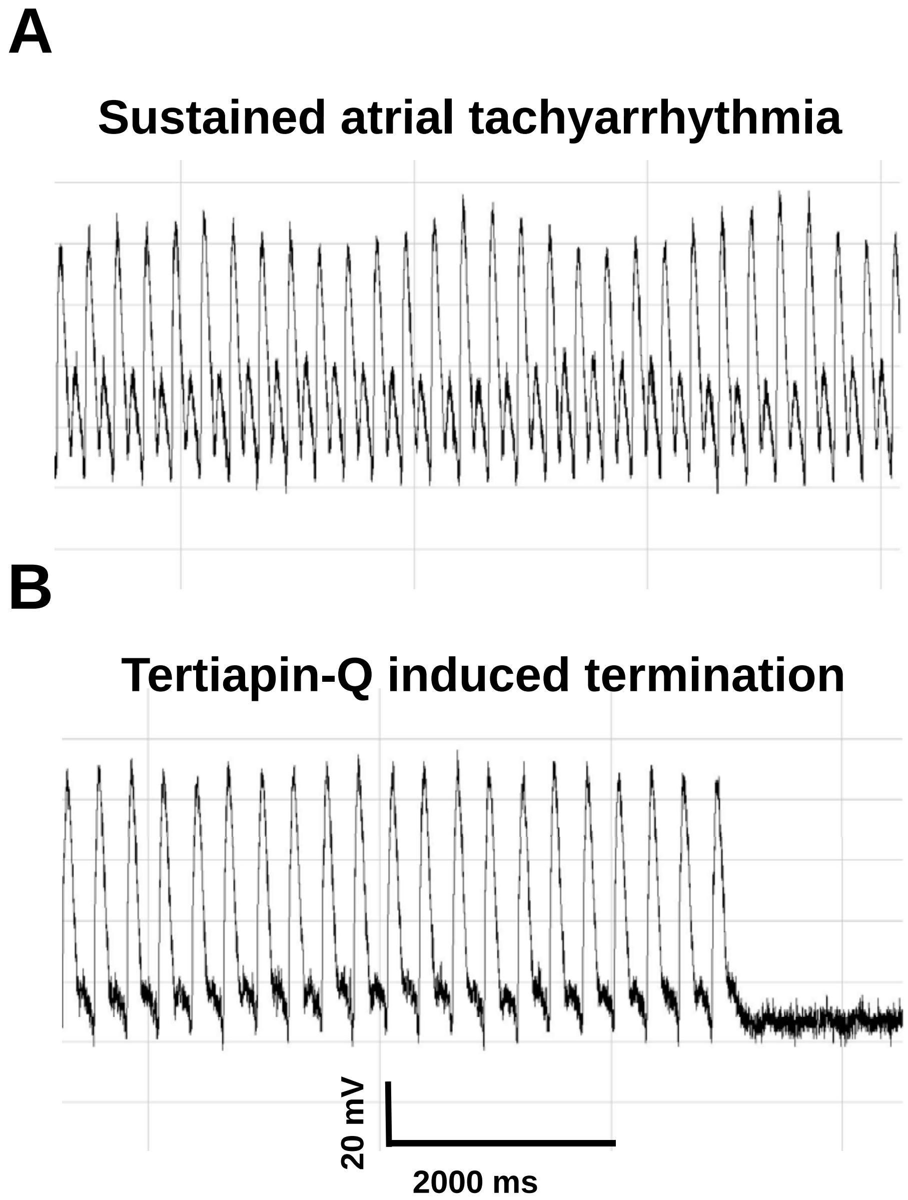
Tae-Joon Cha,* Joachim R. Ehrlich, Denis Chartier,**

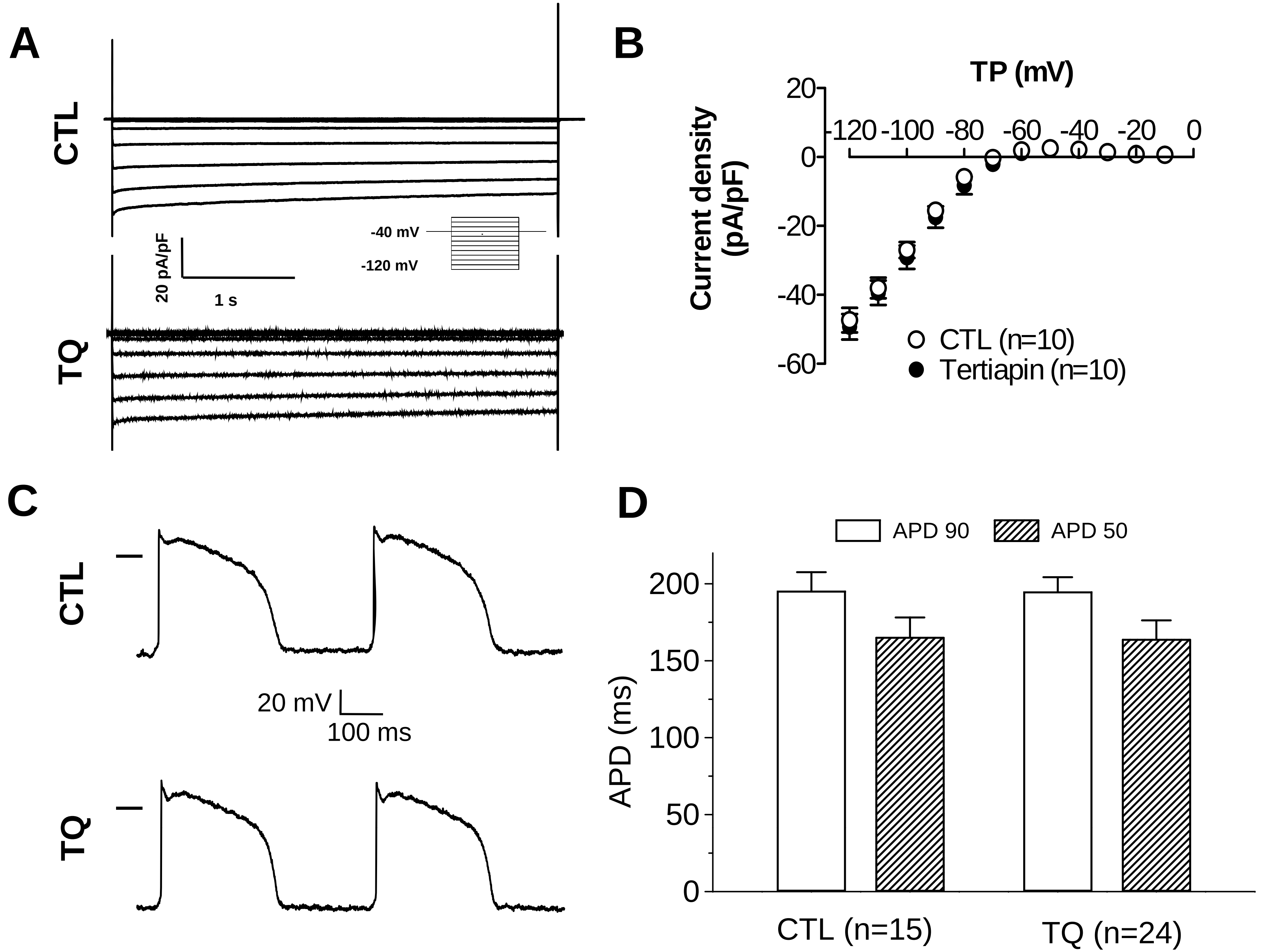
Xiaon-Yan Qi, Ling Xiao, Stanley Nattel,

***Kosin universtiy, Busan, South Korea**
**** J. W. Goethe-University, Frankfurt, Germany**
Montreal heart institute, Montreal, Canada

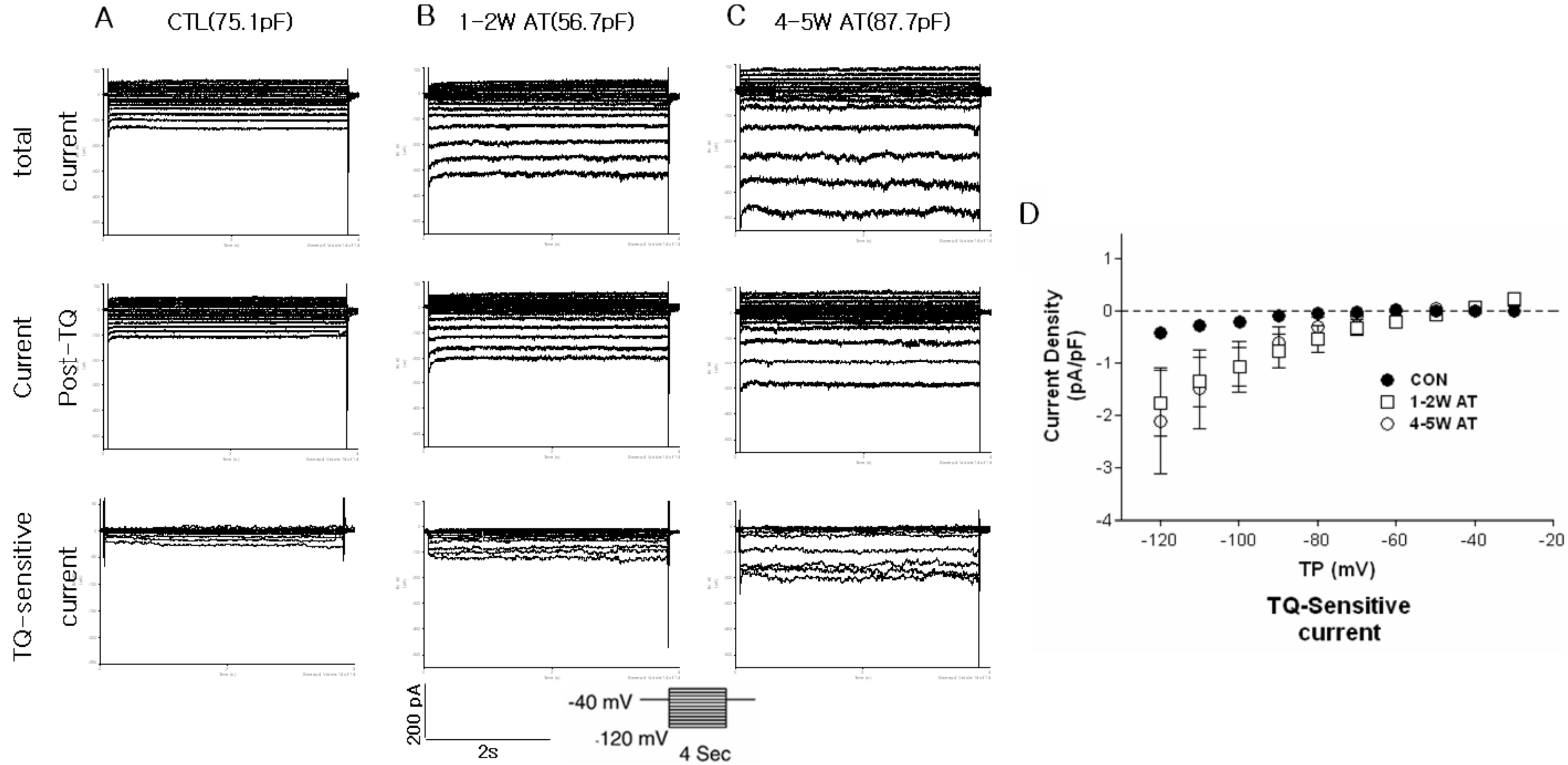
Circulation 2006, April 11


A
AT-remodeled prep pre-TQ
20 mV
5000 ms
B
AT-remodeled prep post-TQ

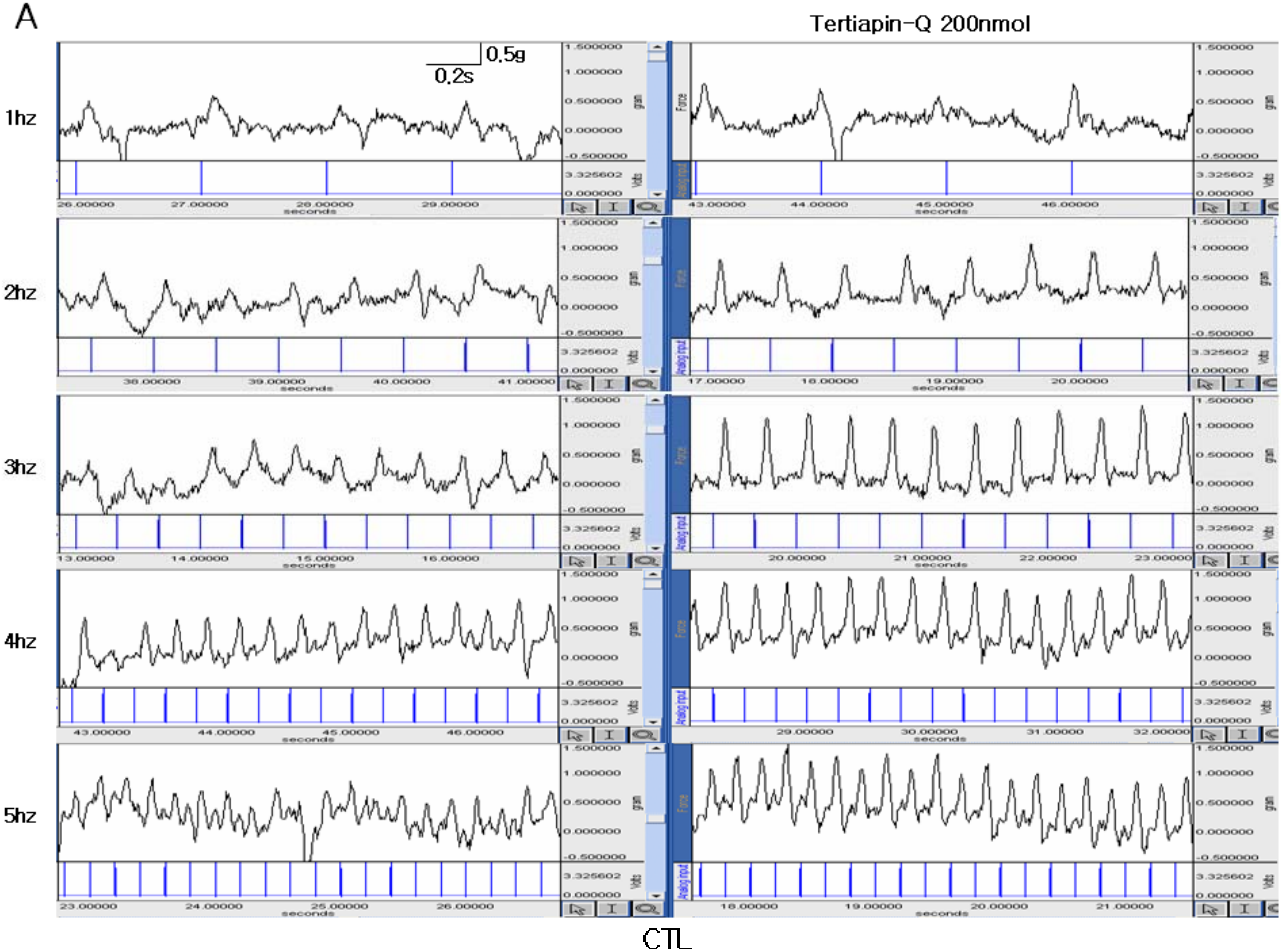

A
Sustained atrial tachyarrhythmia
B
Tertiapin-Q induced termination
20 mV
2000 ms


A
CTL
TQ
20 pA/pF
1 s
-40 mV
-120 mV
B
TP (mV)
Current density (pA/pF)
CTL (n=10)
Tertiapin (n=10)
C
CTL
TQ
20 mV
100 ms
D
APD 90
APD 50
APD (ms)
CTL (n=15)
TQ (n=24)

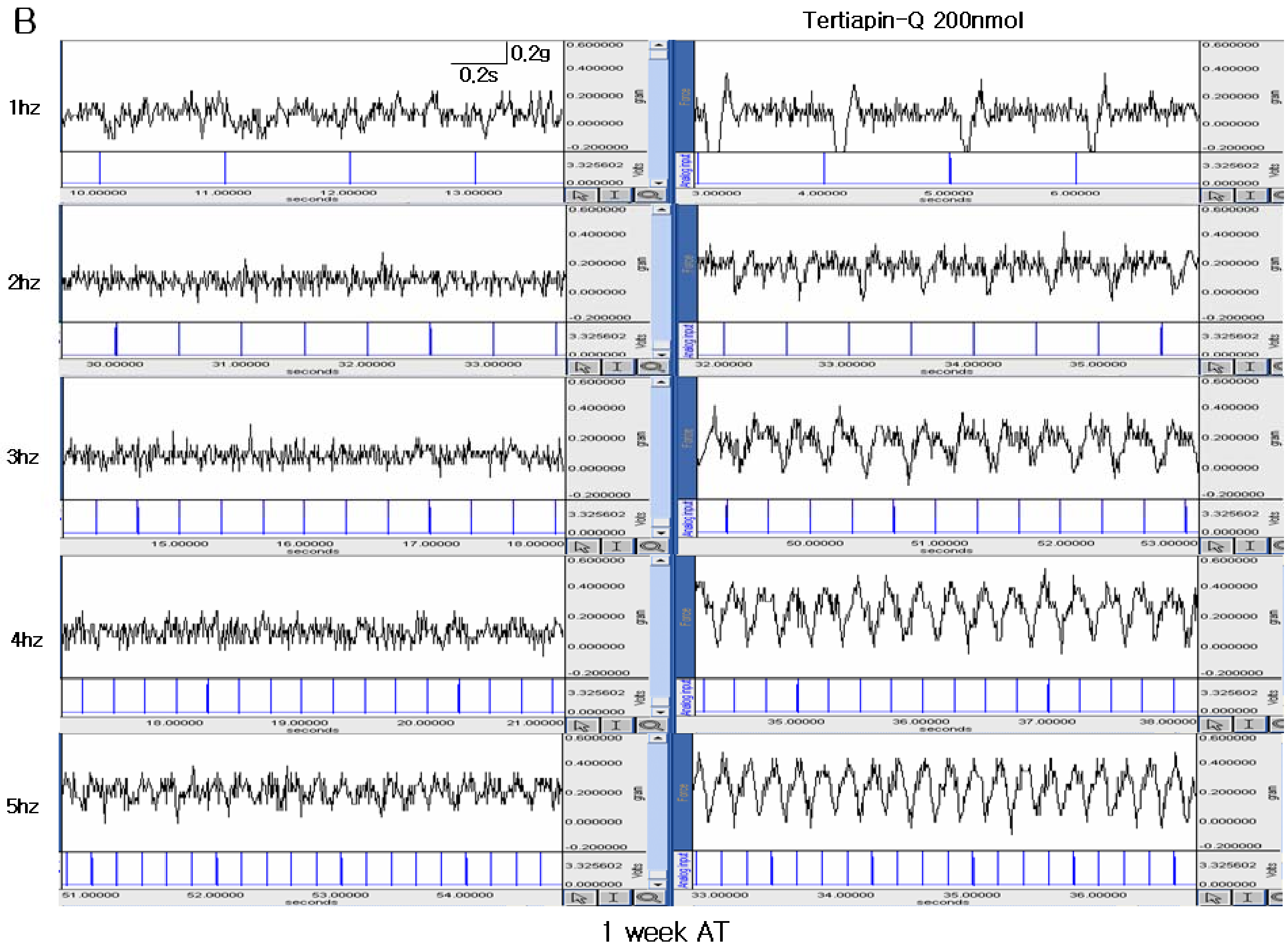
*I*KH recording in control and atrial tachycardia-remodeled myocytes



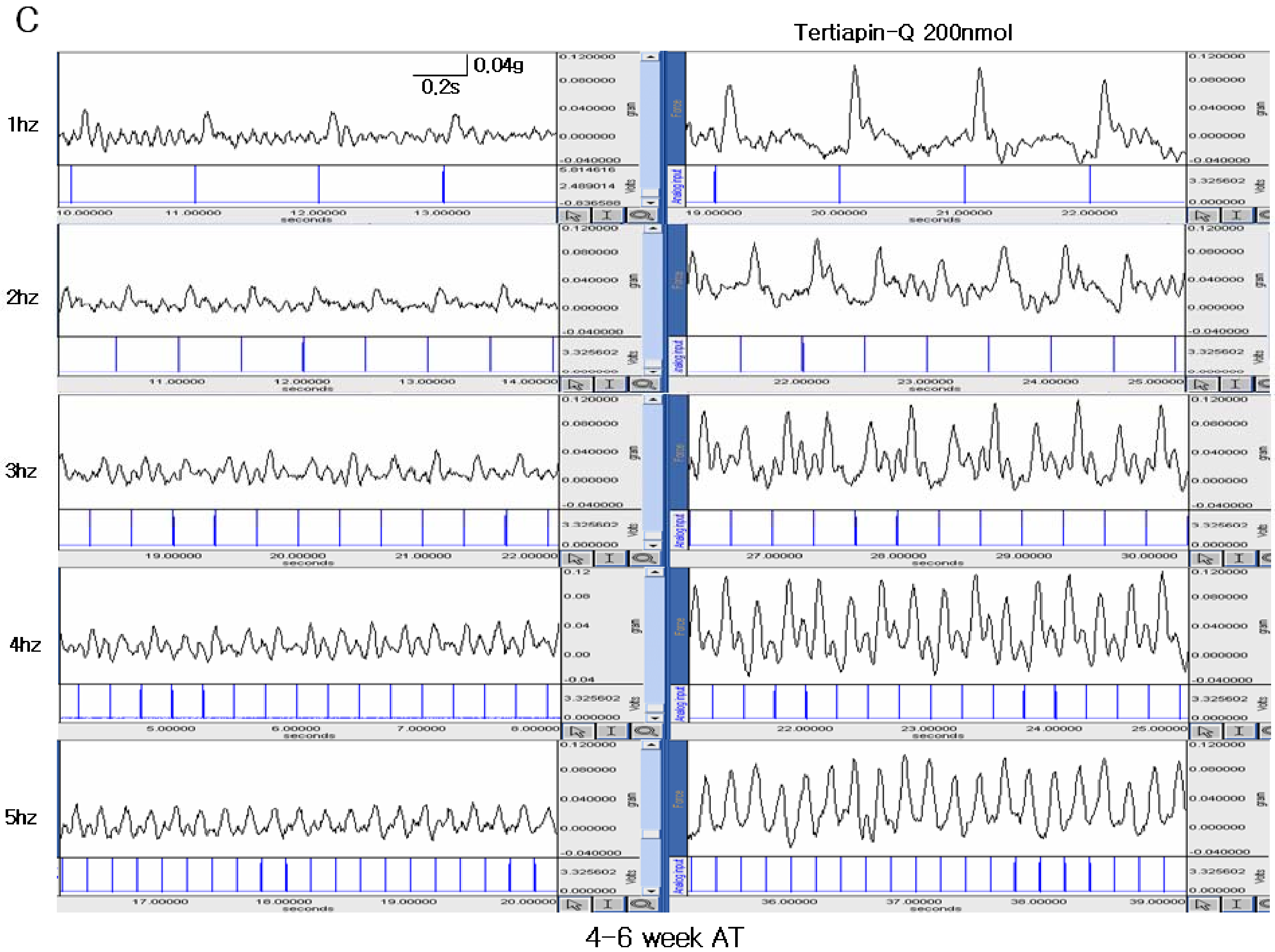
Pacing frequency dependent left atrial contractility change in control before and after tertiapin infusion



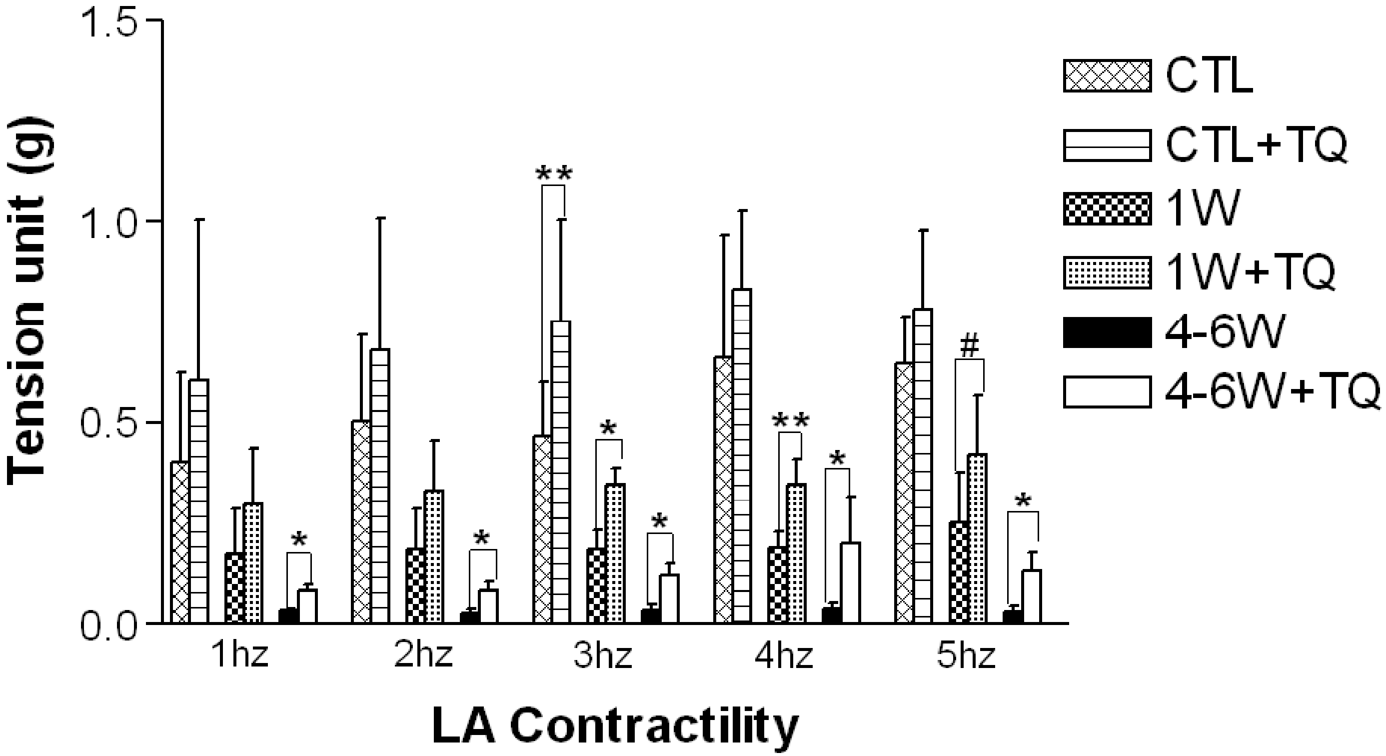
Pacing frequency dependent left atrial contractility change in 1 week tachypacing remodeled dogs before and after tertiapin infusion



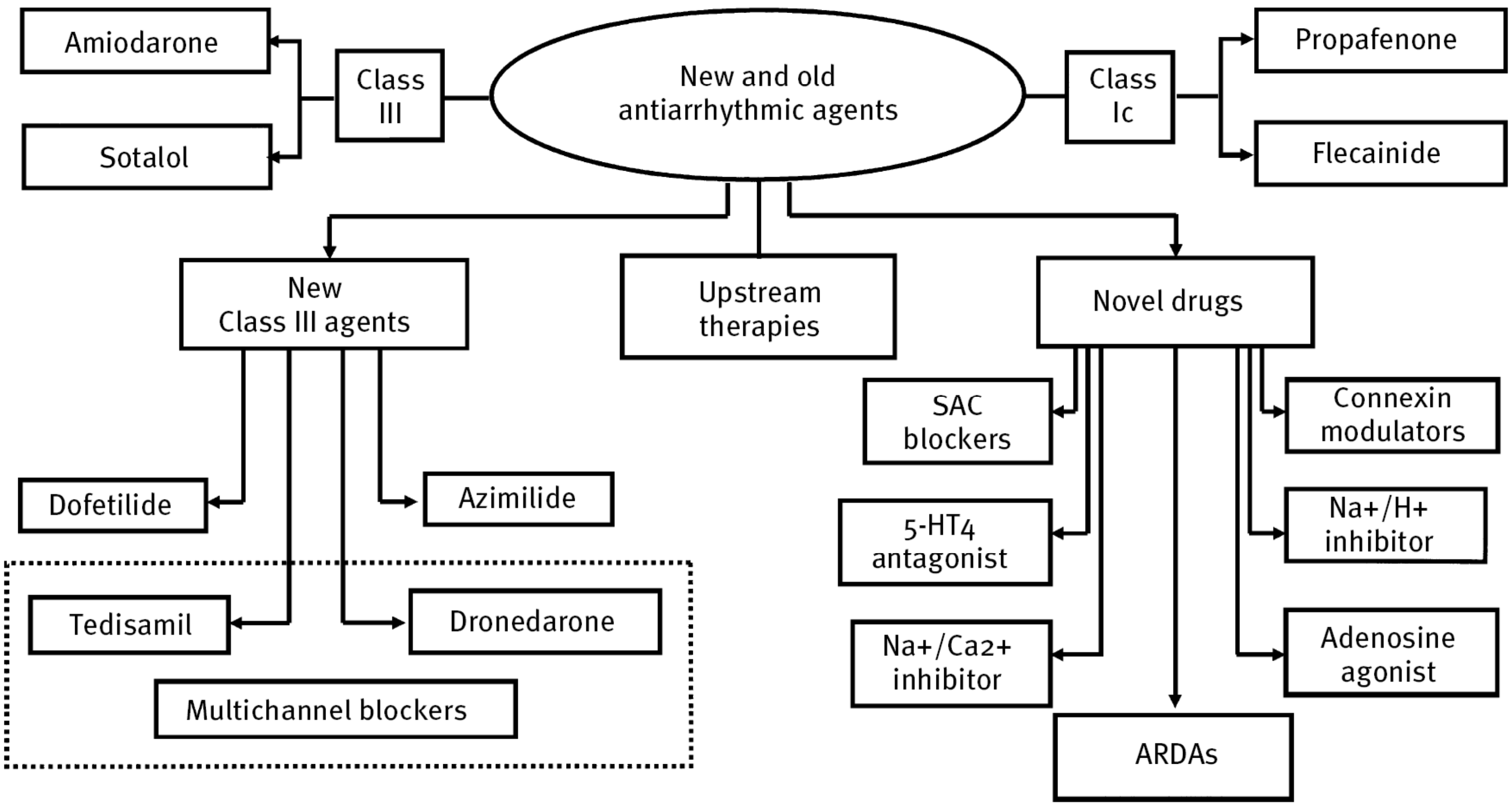
Pacing frequency dependent left atrial contractility change in 4-6 week tachypacing remodeled dogs before and after tertiapin infusion



Pacing frequency dependent left atrial contractility changes



***p<0.01, **p<0.05, #p=0.056**



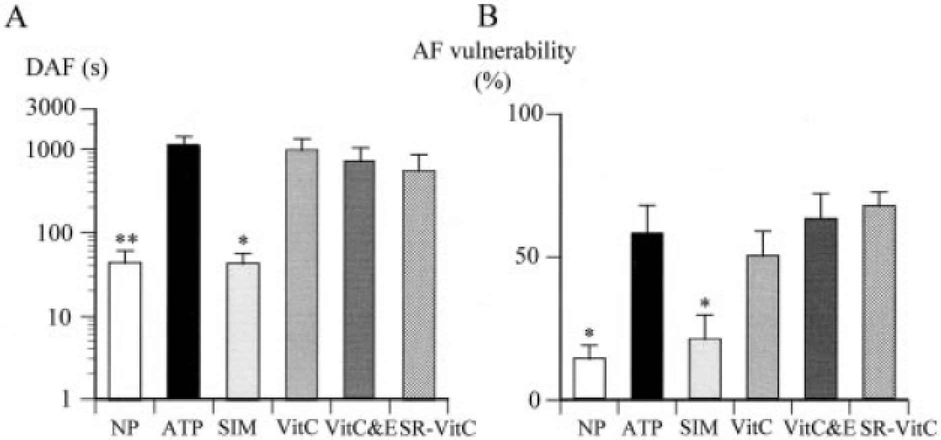
Clin. Cardiol. 31, 3, 102–108 (2008)

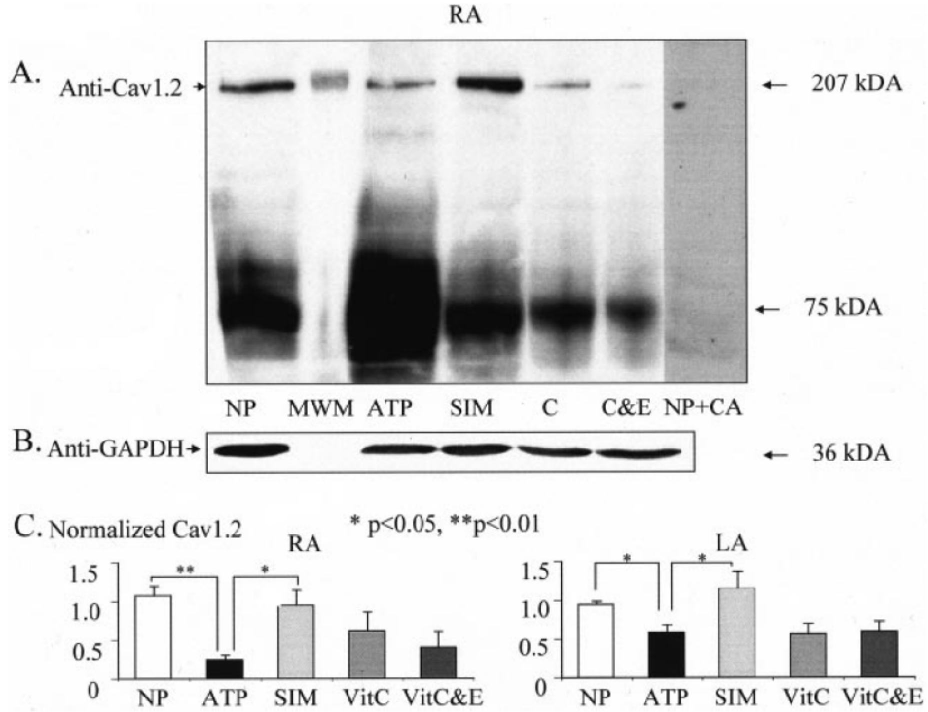
Drugs	Mode of action	Evidence base
ACE inhibitors and ARBs	Targeting underlying heart disease (e.g., hypertension, heart failure) and unloading the atria Preventing structural remodeling: antifibrotic, antiapoptotic, and anti-inflammatory effects Anti-oxidant effects via PPAR-dependent pathways Direct electrophysiological effects on ion channels (e.g., inhibition of I_{Kur}, I_{to}) Preventing gap junctional remodeling Modulating the autonomous nervous system: antisympathetic activity Modulating thrombogenesis (e.g., antiplatelet effects, P-selectin inhibition)	Good experimental data Retrospective analyses Small prospective studies 3 meta-analyses Ongoing randomized controlled trials
Aldosterone antagonists	Unloading the atria in hypertension or heart failure Preventing structural remodeling: antifibrotic effects Direct electrophysiological effects on ion channels (e.g., inhibition of I_{Kur}, I_{to})	Sparse experimental data Clinical experience: prevention of sudden cardiac death; increased AF incidence in primary aldosteronism versus essential hypertension Small observational studies
Beta-blockers	Targeting underlying heart disease and unloading the atria Atrioventricular node blockade and rate lowering effect Membrano-stabilizing effect Modulating the autonomous nervous system: antiadrenergic activity	Retrospective analyses in heart failure and hypertension Clinical experience in CABG Small prospective studies Meta-analysis
Statins	Reducing cardiovascular events and the development of underlying heart disease Preventing substrate formation: anti-inflammatory and anti-oxidant effects Protecting the atrial mycardium during ischemia via increased e-NOS activity Preventing matrix remodeling via inhibition MMPs Preventing electrical remodeling by reducing downregulation of the $I_{L\text{-}Ca}$ Modulating thrombogenesis (e.g., improved rheology, antiplatelet effects, fibrinogen reduction)	Experimental data Retrospective analyses and observational studies Prospective study in electrical cardioversion Prospective study in CABG Ongoing randomized controlled studies
Corticosteroids	Anti-inflammatory effects	Indirect evidence based on CRP reduction Small prospective studies Prospective studies in CABG and aortic valve surgery
n-3 PUFA	Preventing stretch-induced electrical remodeling Direct electrophysiological effects on ion channels (inhibition of I_{Na}, $I_{L\text{-}Ca}$) Reducing proarrhythmic eicosanoids in the myocardium Anti-inflammatory and anti-oxidant effects Preventing matrix remodeling via MMP-dependent mechanism	Experimental data Clinical experience: preventing ventricular fibrillation Analyses from the population-based studies Prospective study in CABG and after cardioversion Ongoing randomized controlled studies
PPAR antagonists (thiazolidinediones)	Anti-inflamatory, antiproliferative, and antioxidant effects Metabolic protection	Experimental data Case reports Retrospective analysis in postoperative AF (not yet completed)
pFox-inhibitors* (trimetazidine)	Altering atrial metabolism	No data

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass grafting; CRP = C reactive protein; eNOS = endothelial nitric oxide syntase; MMP = matrix metalloproteinase; PPAR = peroxisome proliferator-activated receptor; pFox = partial fatty acid oxidation; PUFA = polyunsaturated fatty acids.
**Ranolazine* is a potent inhibitor of the late sodium current and has therefore a direct antiarrhythmic effect, which significnatly outweighs any potential protective effect on atrial metabolism

Effect of Simvastatin and Antioxidant Vitamins on Atrial Fibrillation Promotion by Atrial-Tachycardia Remodeling in Dogs

Akiko Shiroshita-Takeshita, MD; Gernot Schram, MD; Joel Lavoie, PhD; Stanley Nattel, MD





(*Circulation*. 2004;110:2313-2319.)

Cardiovascular Research 62 (2004) 105–111

Cardiovascular Research

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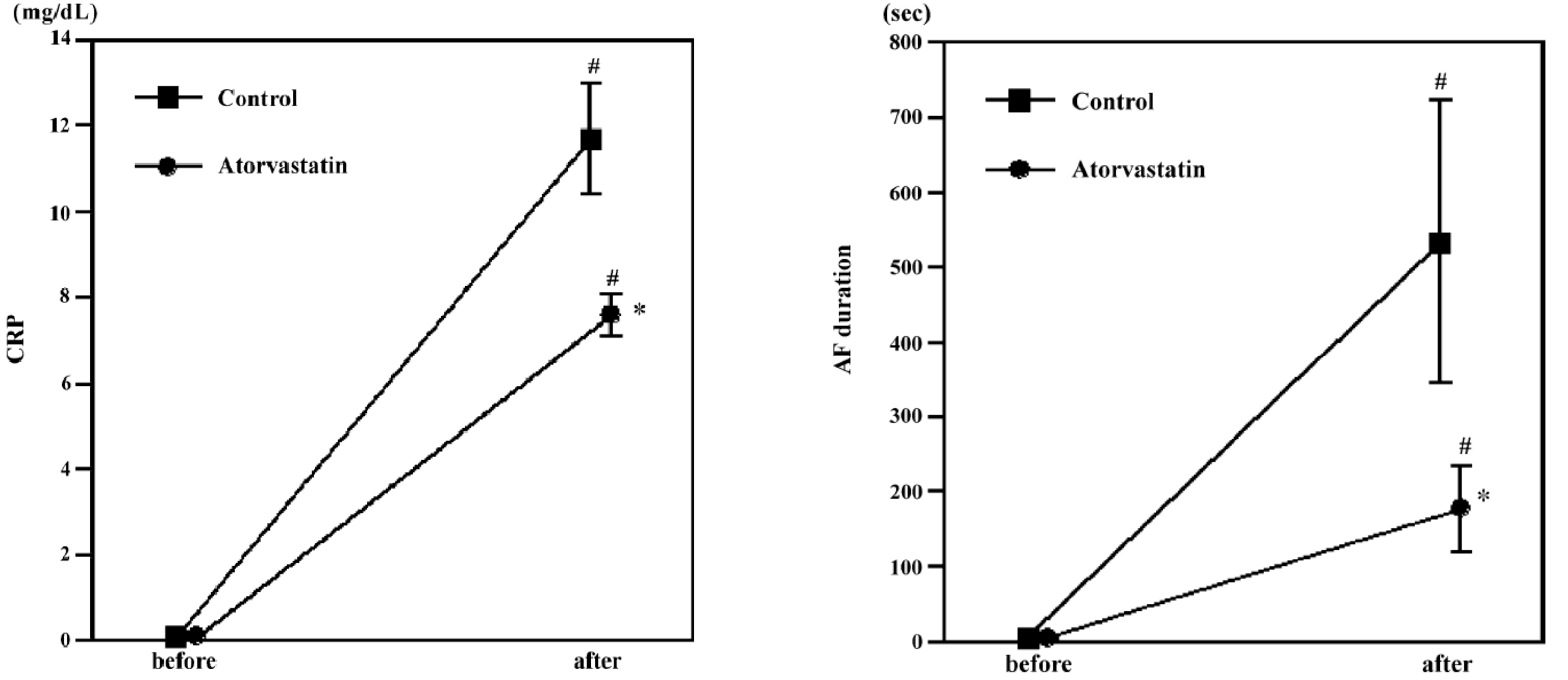
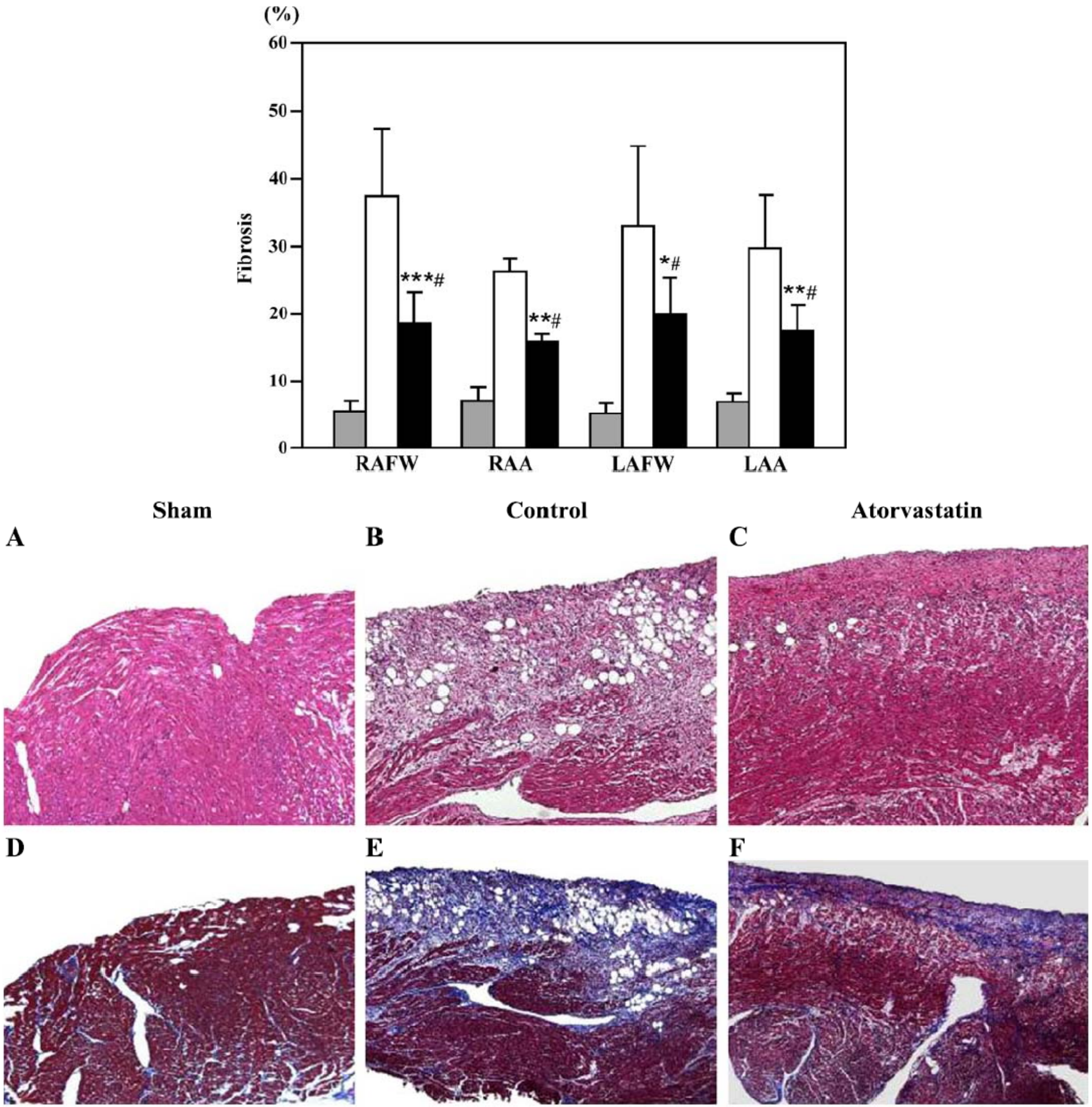
The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model☆

Koichiro Kumagai*, Hideko Nakashima, Keijiro Saku

School of Internal Medicine, Department of Cardiology, Fukuoka University Hospital, 7-45-1, Nanakuma, Jonan, Fukuoka 814-0180, Japan





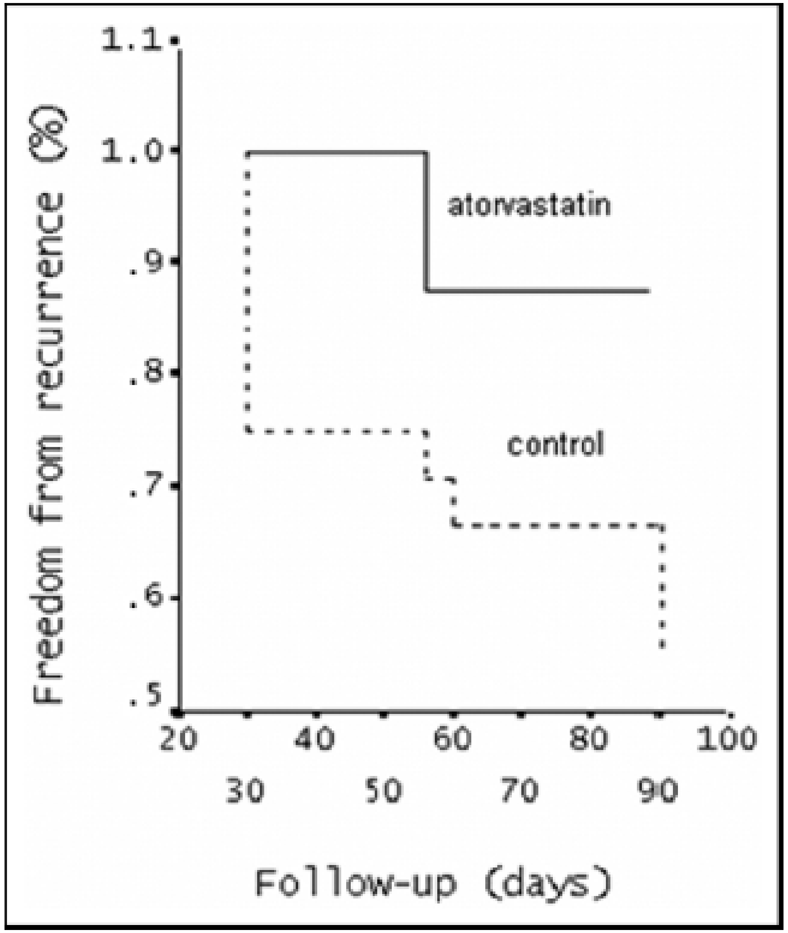
(%)
60
50
40
30
20
10
0
Fibrosis
***#
**#
*#
**#
RAFW
RAA
LAFW
LAA
Sham
Control
Atorvastatin
A
B
C
D
E
F

ARTICLE IN PRESS

Effect of *Atorvastatin* on the Recurrence Rates of Atrial Fibrillation After Electrical Cardioversion

Mehmet Ozaydin, MD[a,*], Ercan Varol, MD[c], Suleyman M. Aslan, MD[a], Zehra Kucuktepe, MD[a], Abdullah Dogan, MD[a], Mustafa Ozturk, MD[b], and Ahmet Altinbas, MD, PhD[a]

(Am J Cardiol 2006;xx:xxx)



Randomized Trial of Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery

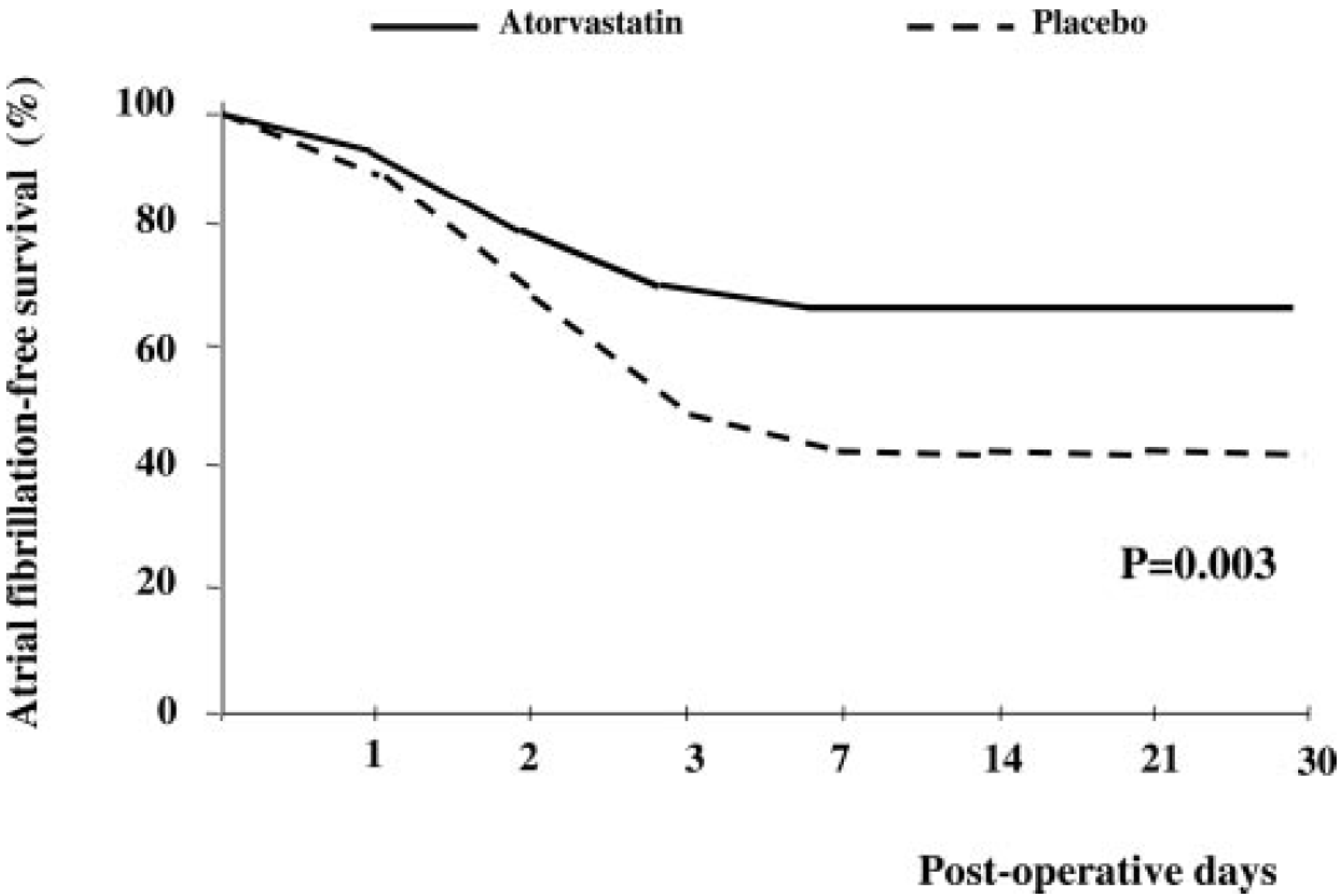
Results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) Study

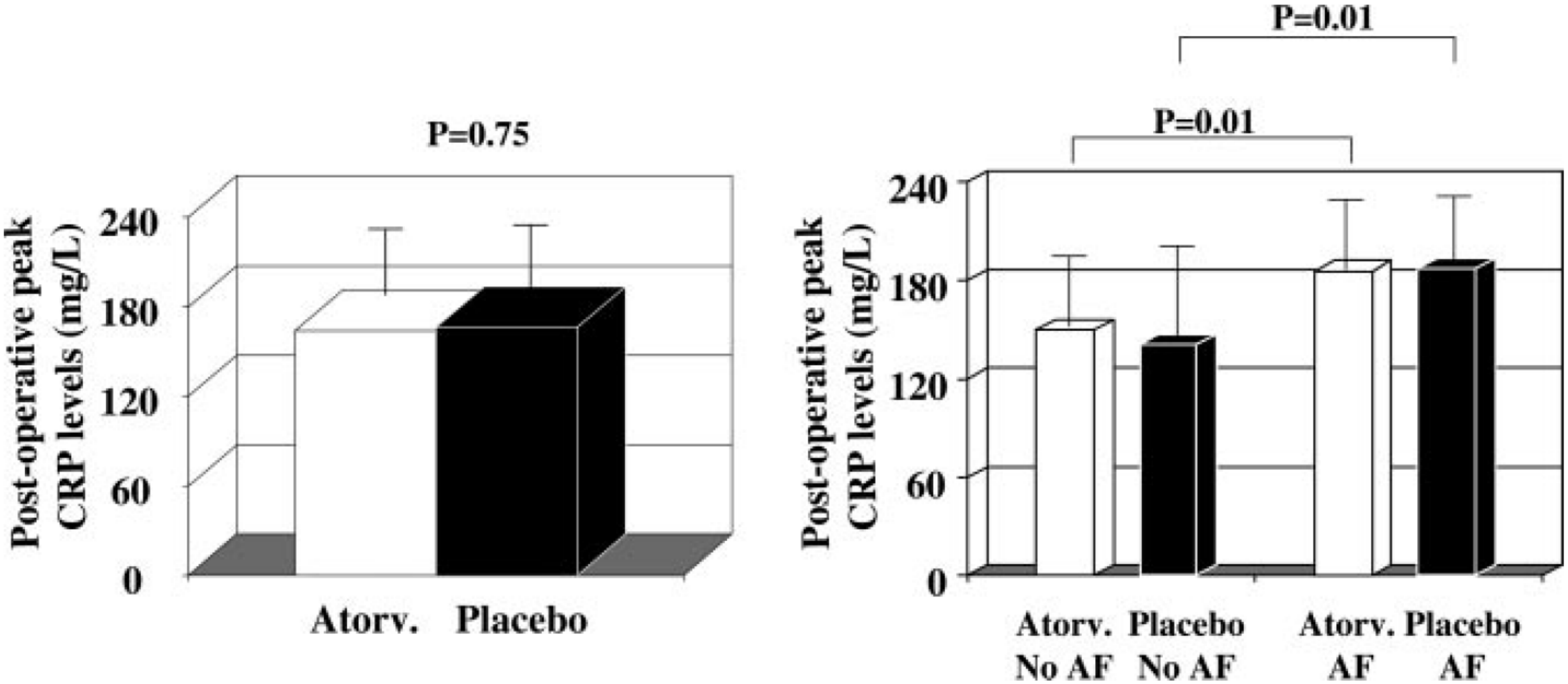
Giuseppe Patti, MD; Massimo Chello, MD; Dario Candura, MD; Vincenzo Pasceri, MD; Andrea D'Ambrosio, MD; Elvio Covino, MD; Germano Di Sciascio, MD

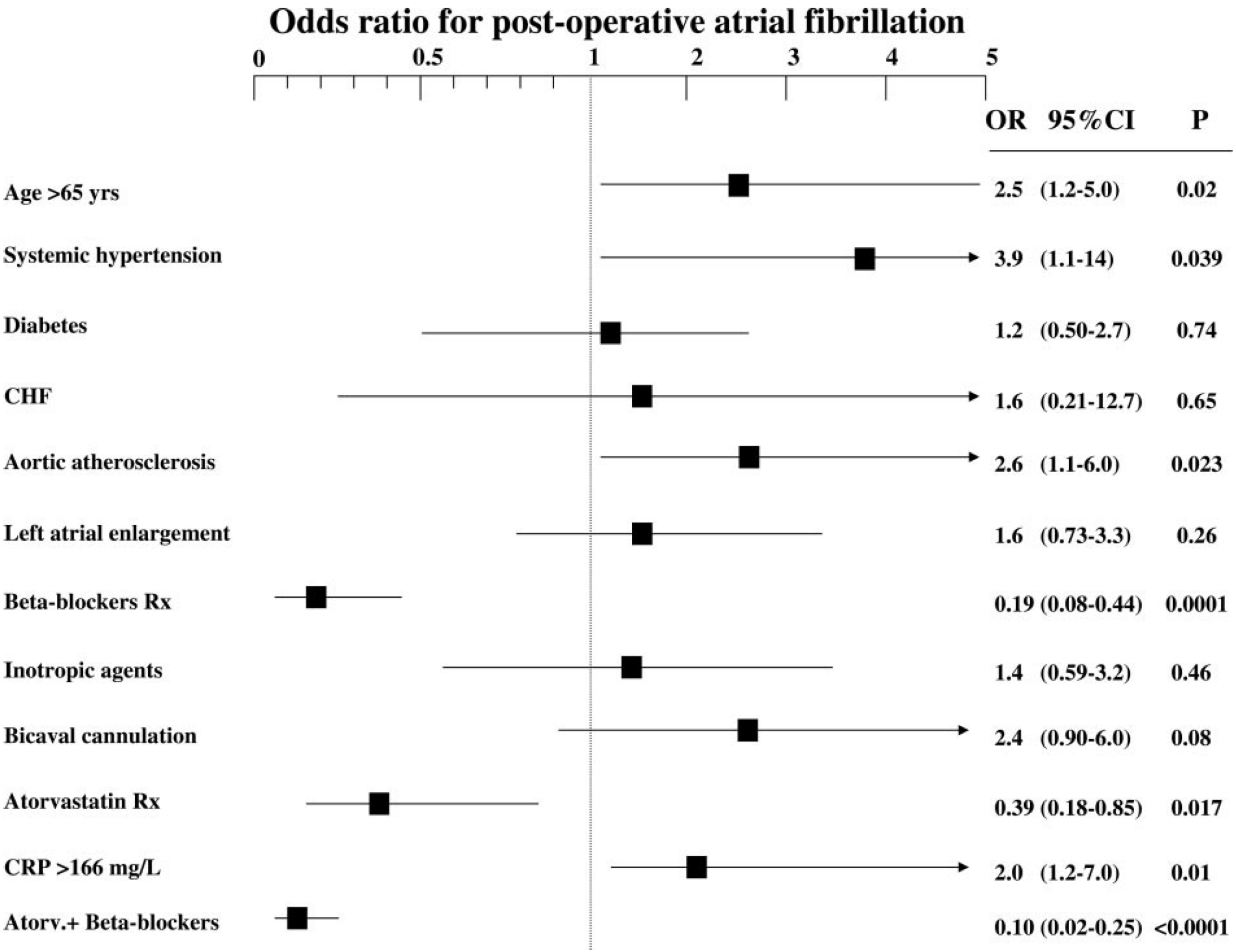
Background**—**Atrial fibrillation (AF) after cardiac surgery is associated with increased risk of complications, length of stay, and cost of care. Observational evidence suggests that patients who have undergone previous statin therapy have a lower incidence of postoperative AF. We tested this observation in a randomized, controlled trial.

Methods and Results**—**Two hundred patients undergoing elective cardiac surgery with cardiopulmonary bypass, without previous statin treatment or history of AF, were enrolled. Patients were randomized to atorvastatin (40 mg/d, n=101) or placebo (n=99) starting 7 days before operation. The primary end point was incidence of postoperative AF; secondary end points were length of stay, 30-day major adverse cardiac and cerebrovascular events, and postoperative C-reactive protein (CRP) variations. Atorvastatin significantly reduced the incidence of AF versus placebo (35% versus 57%, $P=0.003$). Accordingly, length of stay was longer in the placebo versus atorvastatin arm (6.9±1.4 versus 6.3±1.2 days, $P=0.001$). Peak CRP levels were lower in patients without AF ($P=0.01$), irrespective of randomization assignment. Multivariable analysis showed that atorvastatin treatment conferred a 61% reduction in risk of AF (odds ratio 0.39, 95% confidence interval 0.18 to 0.85, $P=0.017$), whereas high postoperative CRP levels were associated with increased risk (odds ratio 2.0, 95% confidence interval 1.2 to 7.0, $P=0.01$). The incidence of major adverse cardiac and cerebrovascular events at 30 days was similar in the 2 arms.

Conclusions**—**Treatment with atorvastatin 40 mg/d, initiated 7 days before surgery, significantly reduces the incidence of postoperative AF after elective cardiac surgery with cardiopulmonary bypass and shortens hospital stay. These results may influence practice patterns with regard to adjuvant pharmacological therapy before cardiac surgery. **(*Circulation*. 2006;114:1455-1461.)**


Atorvastatin
Placebo
Atrial fibrillation-free survival (%)
100
80
60
40
20
0
1
2
3
7
14
21
30
P=0.003
Post-operative days


P=0.75
Post-operative peak CRP levels (mg/L)
240
180
120
60
0
Atorv.
Placebo
P=0.01
P=0.01
Post-operative peak CRP levels (mg/L)
240
180
120
60
0
Atorv. No AF
Placebo No AF
Atorv. AF
Placebo AF


Odds ratio for post-operative atrial fibrillation
0
0.5
1
2
3
4
5
OR 95%CI P
Age >65 yrs
2.5 (1.2-5.0) 0.02
Systemic hypertension
3.9 (1.1-14) 0.039
Diabetes
1.2 (0.50-2.7) 0.74
CHF
1.6 (0.21-12.7) 0.65
Aortic atherosclerosis
2.6 (1.1-6.0) 0.023
Left atrial enlargement
1.6 (0.73-3.3) 0.26
Beta-blockers Rx
0.19 (0.08-0.44) 0.0001
Inotropic agents
1.4 (0.59-3.2) 0.46
Bicaval cannulation
2.4 (0.90-6.0) 0.08
Atorvastatin Rx
0.39 (0.18-0.85) 0.017
CRP >166 mg/L
2.0 (1.2-7.0) 0.01
Atorv.+ Beta-blockers
0.10 (0.02-0.25) <0.0001

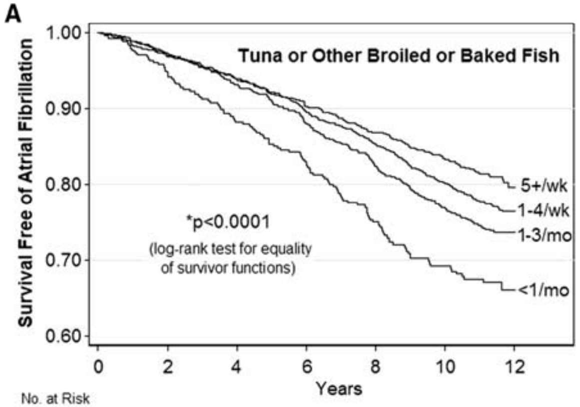
Fish Intake and Risk of Incident Atrial Fibrillation

Dariush Mozaffarian, MD, MPH; Bruce M. Psaty, MD, PhD; Eric B. Rimm, ScD; Rozenn N. Lemaitre, PhD, MPH; Gregory L. Burke, MD, MS; Mary F. Lyles, MD; David Lefkowitz, MD; David S. Siscovick, MD, MPH

Background—Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is particularly common in the elderly. Although effects of fish intake, including potential antiarrhythmic effects, may favorably influence risk of AF, relationships between fish intake and AF incidence have not been evaluated.

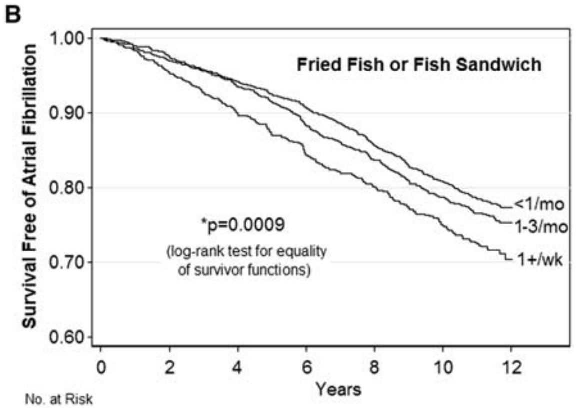
Methods and Results—In a prospective, population-based cohort of 4815 adults ≥age 65 years, usual dietary intake was assessed at baseline in 1989 and 1990. Consumption of tuna and other broiled or baked fish correlated with plasma phospholipid long-chain n-3 fatty acids, whereas consumption of fried fish or fish sandwiches (fish burgers) did not. AF incidence was prospectively ascertained on the basis of hospital discharge records and annual electrocardiograms. During 12 years' follow-up, 980 cases of incident AF were diagnosed. In multivariate analyses, consumption of tuna or other broiled or baked fish was inversely associated with incidence of AF, with 28% lower risk with intake 1 to 4 times per week (HR=0.72, 95% CI=0.58 to 0.91, P=0.005), and 31% lower risk with intake ≥5 times per week (HR=0.69, 95% CI=0.52 to 0.91, P=0.008), compared with <1 time per month (P trend=0.004). Results were not materially different after adjustment for preceding myocardial infarction or congestive heart failure. In similar analyses, fried fish/fish sandwich consumption was not associated with lower risk of AF.

Conclusions—Among elderly adults, consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, is associated with lower incidence of AF. Fish intake may influence risk of this common cardiac arrhythmia. **(*Circulation*. 2004;110:368-373.)**



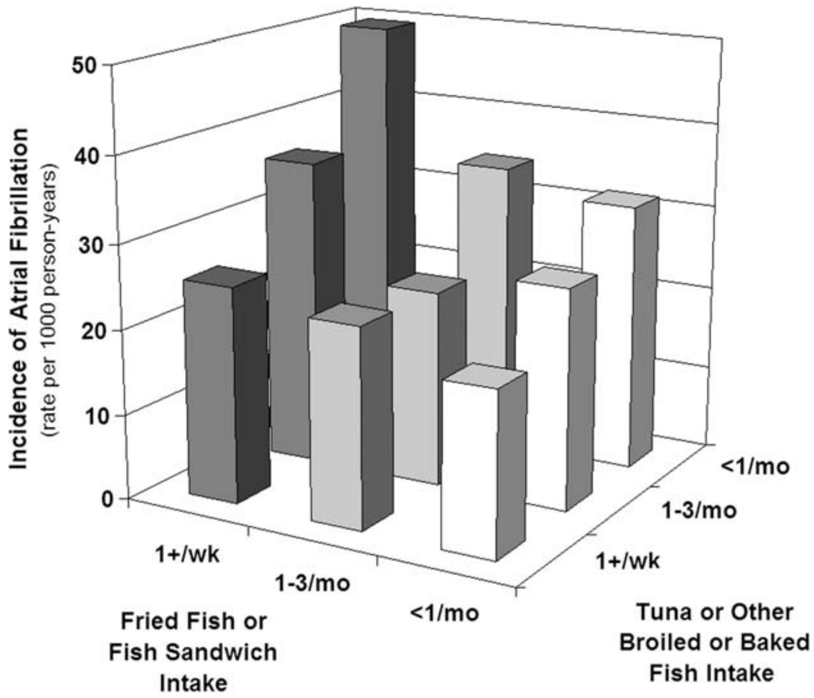
No. at Risk

<1/mo	513	454	394	342	274	210
1-3/mo	1128	1053	961	842	719	583
1-4/wk	2244	2130	1957	1745	1547	1291
5+/wk	930	879	819	750	678	579



No. at Risk

<1/mo	2309	2168	2013	1827	1595	1330
1-3/mo	1566	1485	1359	1198	1047	875
1+/wk	940	863	759	654	576	458



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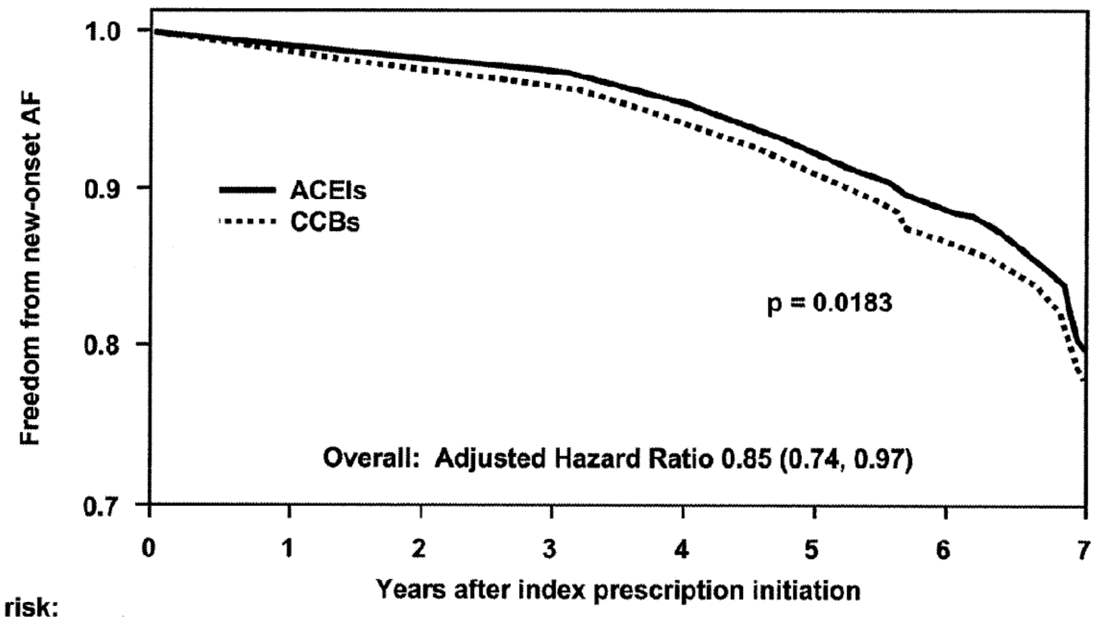
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.03.056

Angiotensin-Converting Enzyme Inhibition in Hypertensive Patients Is Associated With a Reduction in the Occurrence of Atrial Fibrillation

Philippe L. L'Allier, MD,* Anique Ducharme, MD,* Pierre-Frédéric Keller, MD,* Holly Yu, MSPH,† Marie-Claude Guertin, PHD,* Jean-Claude Tardif, MD, FACC*

Montreal, Quebec, Canada; and Bridgewater, New Jersey



No at risk:

ACEI	5463	5310	5040	4831	3381	2183	1258	205
CCB	5463	5223	4822	4570	2971	1841	888	124

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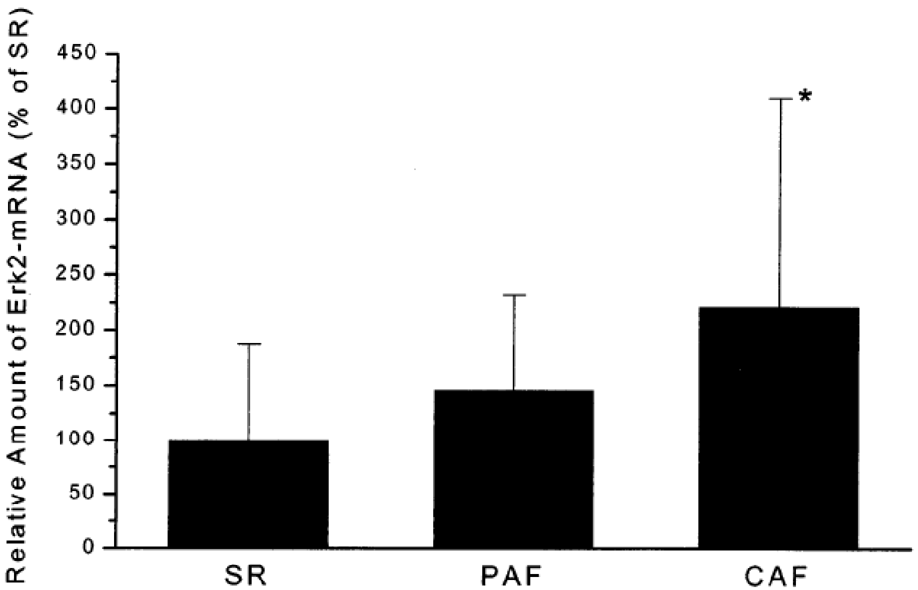
PII S0735-1097(00)00611-2

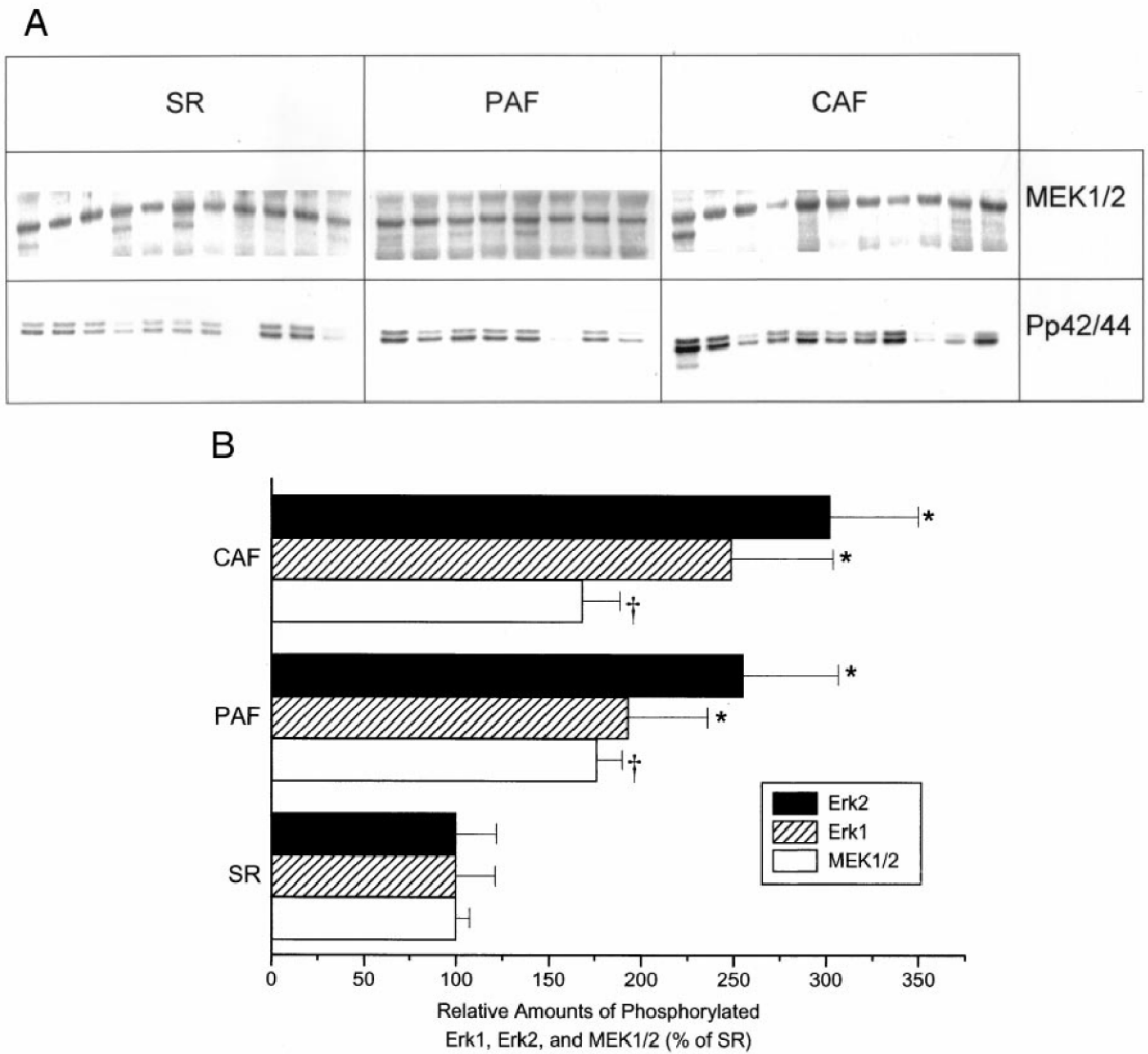
EXPERIMENTAL STUDIES

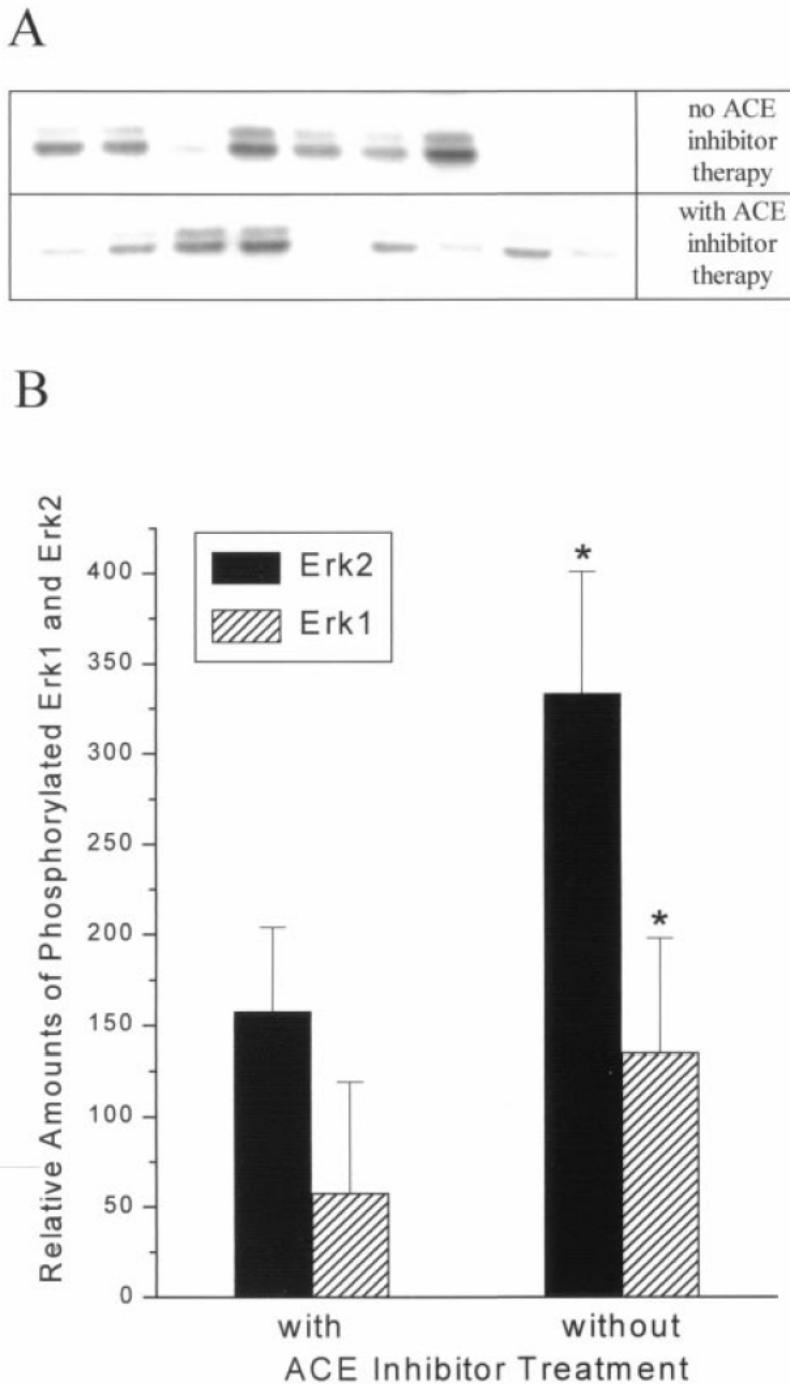
Increased Expression of Extracellular Signal-Regulated Kinase and Angiotensin-Converting Enzyme in Human Atria During Atrial Fibrillation

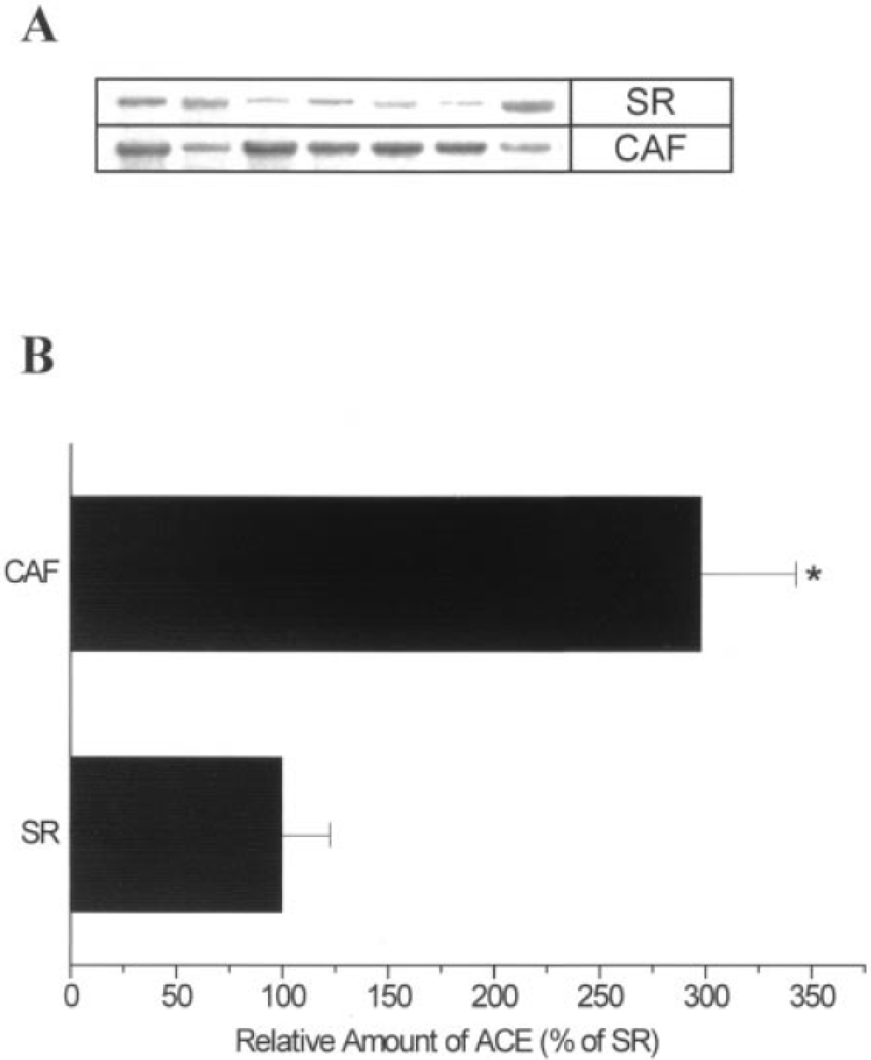
Andreas Goette, MD,* Thorsten Staack, MS,* Christoph Röcken, MD,† Marco Arndt, PHD,‡ J. Christoph Geller, MD,* Christof Huth, MD,|| Siegfried Ansorge, PHD,§ Helmut U. Klein, MD,* Uwe Lendeckel, PHD§

Magdeburg, Germany




A
SR
PAF
CAF
MEK1/2
Pp42/44
B
CAF
PAF
SR
Erk2
Erk1
MEK1/2
0
50
100
150
200
250
300
350
Relative Amounts of Phosphorylated
Erk1, Erk2, and MEK1/2 (% of SR)

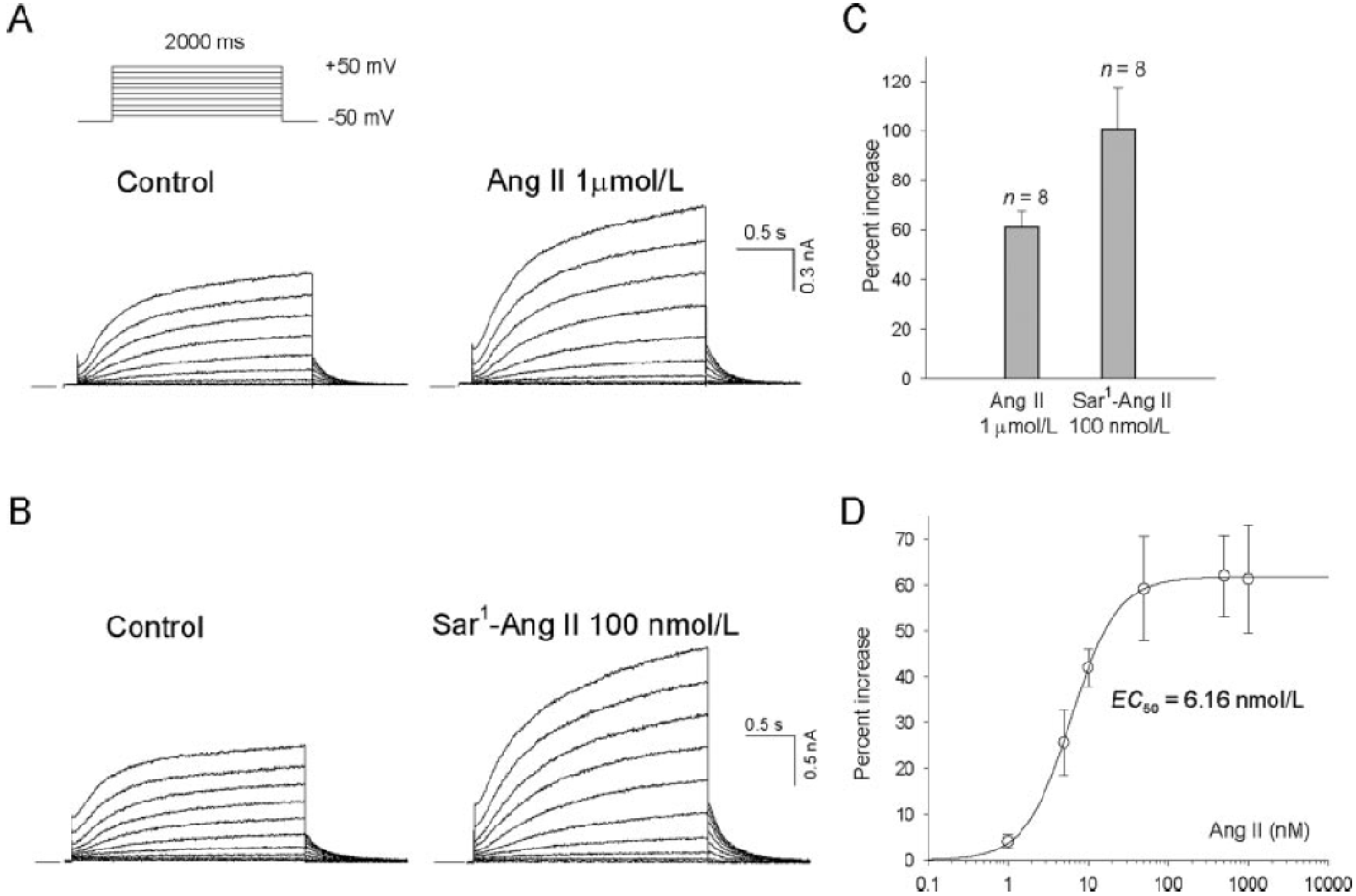

A
no ACE inhibitor therapy
with ACE inhibitor therapy
B
Relative Amounts of Phosphorylated Erk1 and Erk2
0
50
100
150
200
250
300
350
400
Erk2
Erk1
*
*
with
without
ACE Inhibitor Treatment

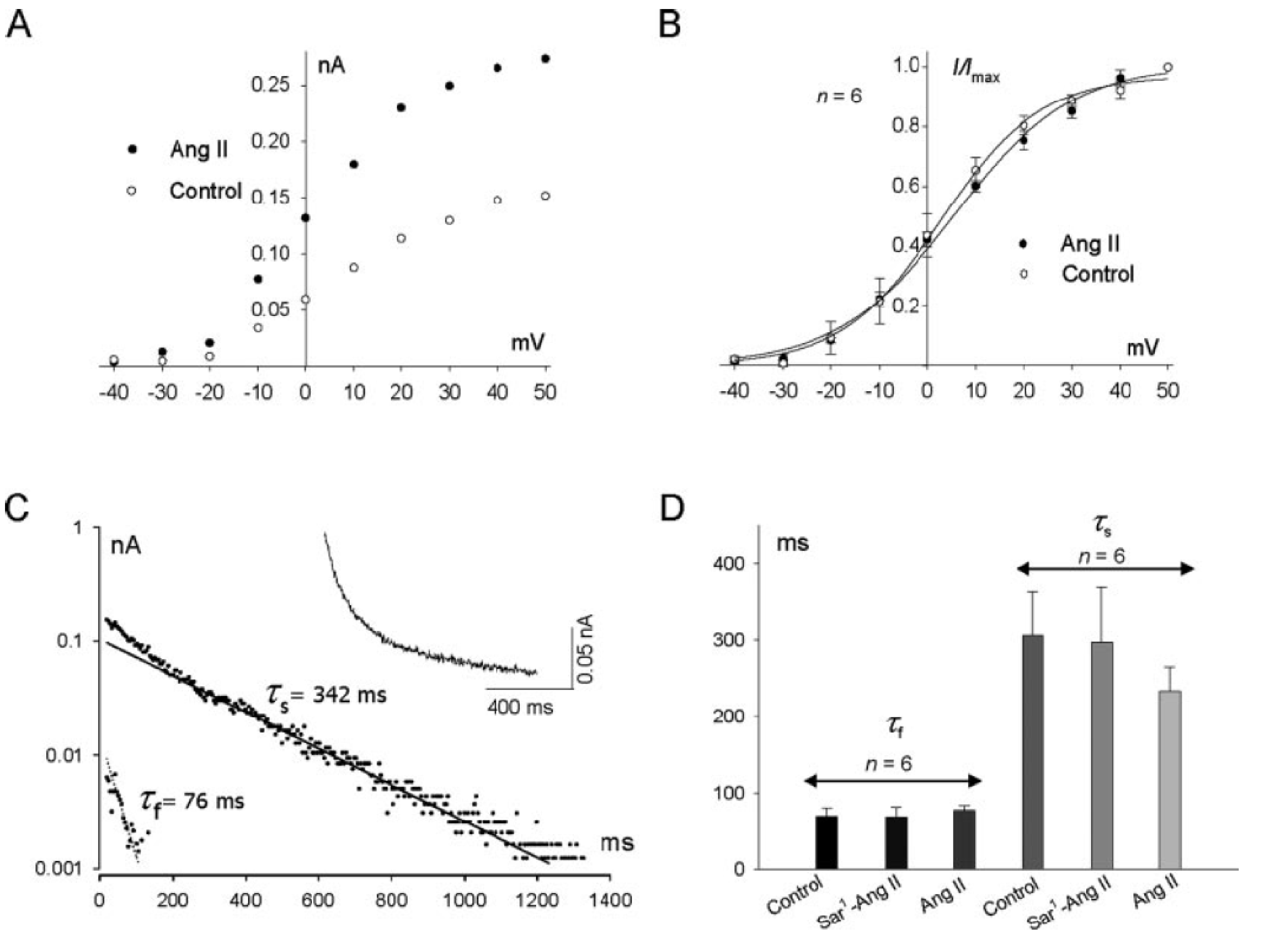

A
SR
CAF
B
CAF
SR
*
0
50
100
150
200
250
300
350
Relative Amount of ACE (% of SR)

Angiotensin II Potentiates the Slow Component of Delayed Rectifier K^+ Current via the AT_1 Receptor in Guinea Pig Atrial Myocytes

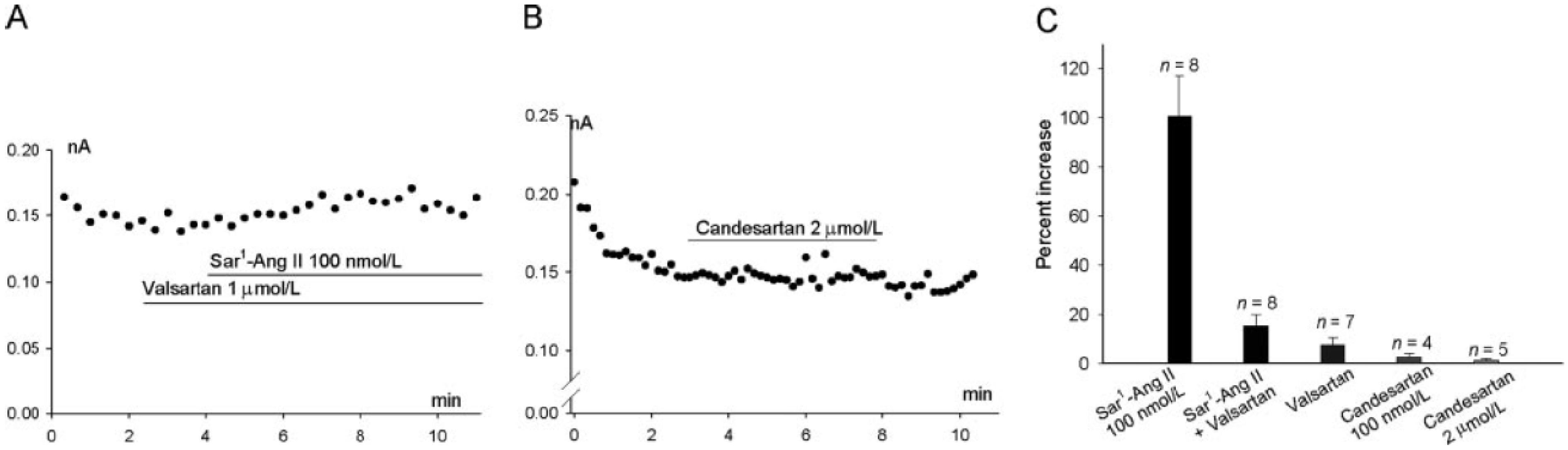
(*Circulation*. 2006;113:1278-1286.)

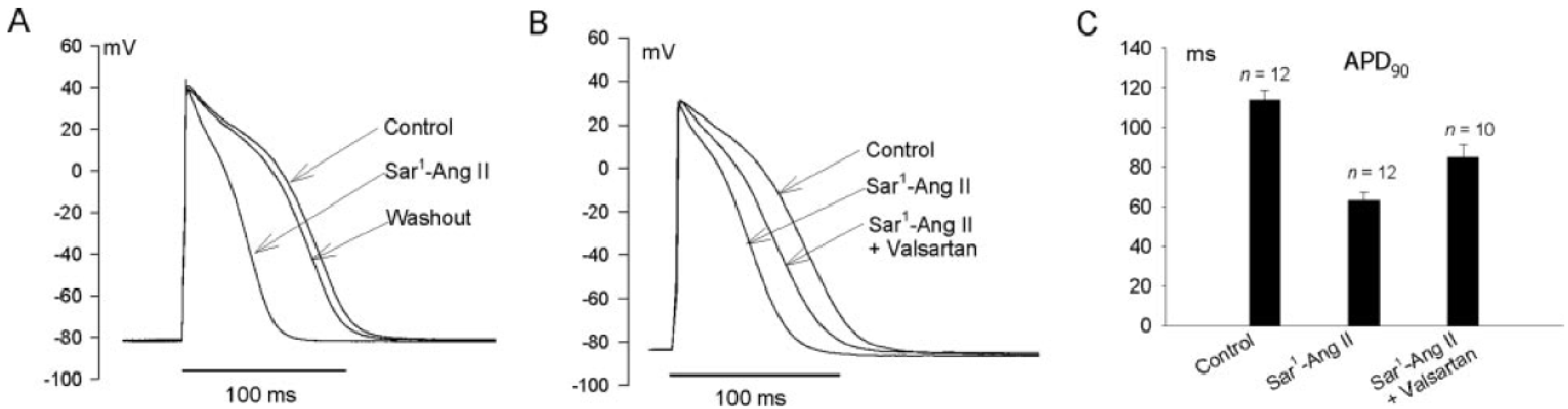
Dimitar P. Zankov, MD; Mariko Omatsu-Kanbe, PhD; Takahiro Isono, PhD; Futoshi Toyoda, PhD; Wei-Guang Ding, MD, PhD; Hiroshi Matsuura, MD, PhD; Minoru Horie, MD, PhD

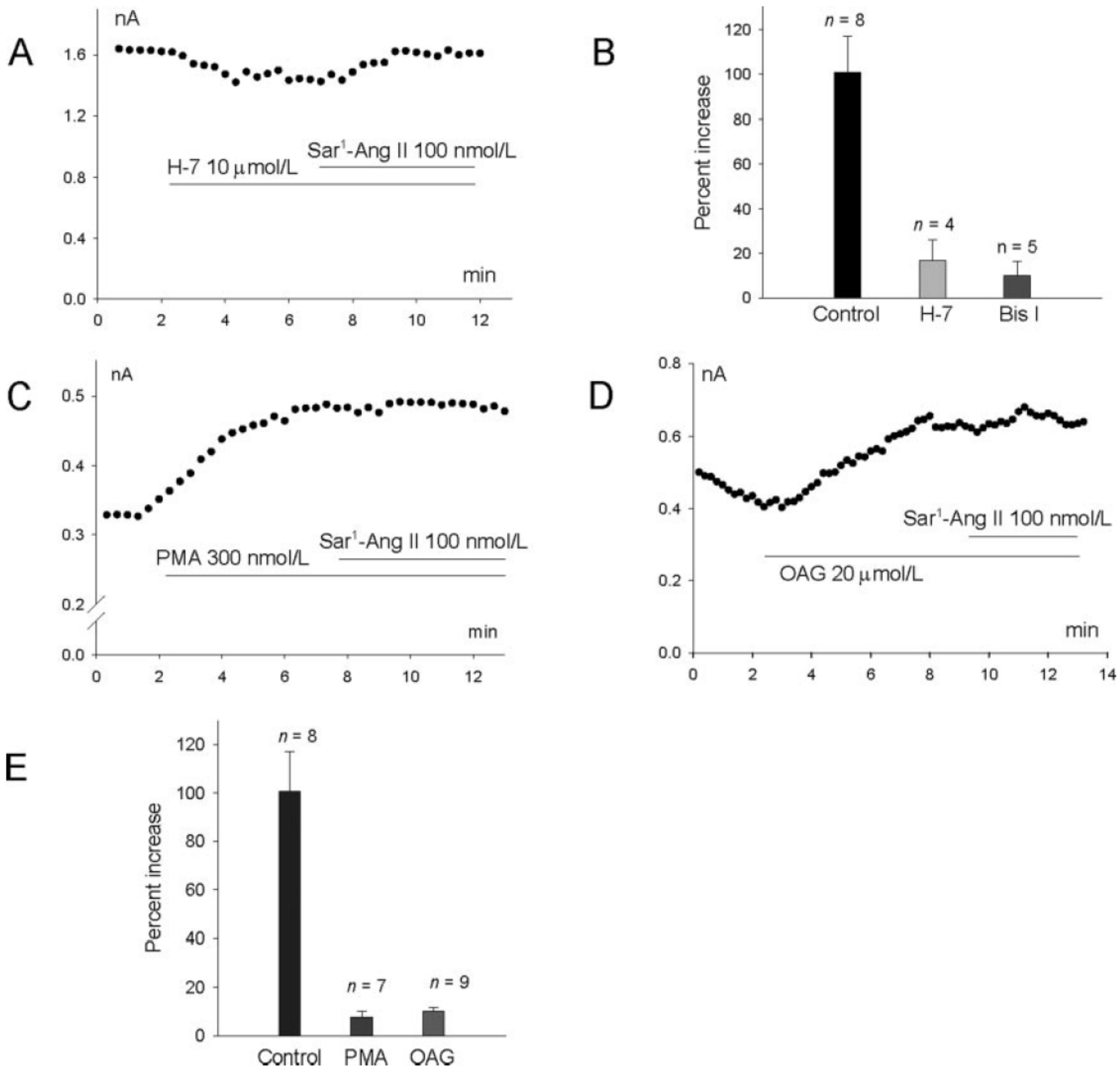




A
nA
0.25
0.20
0.15
0.10
0.05
Ang II
Control
mV
-40 -30 -20 -10 0 10 20 30 40 50
B
1.0
0.8
0.6
0.4
0.2
I/I_{max}
n = 6
Ang II
Control
mV
-40 -30 -20 -10 0 10 20 30 40 50
C
1
0.1
0.01
0.001
nA
τ_s= 342 ms
τ_f= 76 ms
0.05 nA
400 ms
ms
0 200 400 600 800 1000 1200 1400
D
ms
400
300
200
100
0
τ_s
n = 6
τ_f
n = 6
Control
Sar^1-Ang II
Ang II
Control
Sar^1-Ang II
Ang II


A
0.20
0.15
0.10
0.05
0.00
nA
Sar1-Ang II 100 nmol/L
Valsartan 1 μmol/L
min
0
2
4
6
8
10
B
0.25
0.20
0.15
0.10
0.00
nA
Candesartan 2 μmol/L
min
0
2
4
6
8
10
C
Percent increase
120
100
80
60
40
20
0
n = 8
n = 8
n = 7
n = 4
n = 5
Sar1-Ang II 100 nmol/L
Sar1-Ang II + Valsartan
Valsartan
Candesartan 100 nmol/L
Candesartan 2 μmol/L


A
60
40
20
0
-20
-40
-60
-80
-100
mV
Control
Sar1-Ang II
Washout
100 ms
B
60
40
20
0
-20
-40
-60
-80
-100
mV
Control
Sar1-Ang II
Sar1-Ang II + Valsartan
100 ms
C
140
120
100
80
60
40
20
0
ms
APD90
n = 12
n = 12
n = 10
Control
Sar1-Ang II
Sar1-Ang II + Valsartan



A
nA
1.6
1.2
0.8
0.4
0.0
H-7 10 µmol/L
Sar¹-Ang II 100 nmol/L
min
0 2 4 6 8 10 12
B
Percent increase
120
100
80
60
40
20
0
n = 8
n = 4
n = 5
Control
H-7
Bis I
C
nA
0.5
0.4
0.3
0.2
0.0
PMA 300 nmol/L
Sar¹-Ang II 100 nmol/L
min
0 2 4 6 8 10 12
D
0.8
nA
0.6
0.4
0.2
0.0
Sar¹-Ang II 100 nmol/L
OAG 20 µmol/L
min
0 2 4 6 8 10 12 14
E
Percent increase
120
100
80
60
40
20
0
n = 8
n = 7
n = 9
Control
PMA
OAG

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Cell Calcium 39 (2006) 175–186

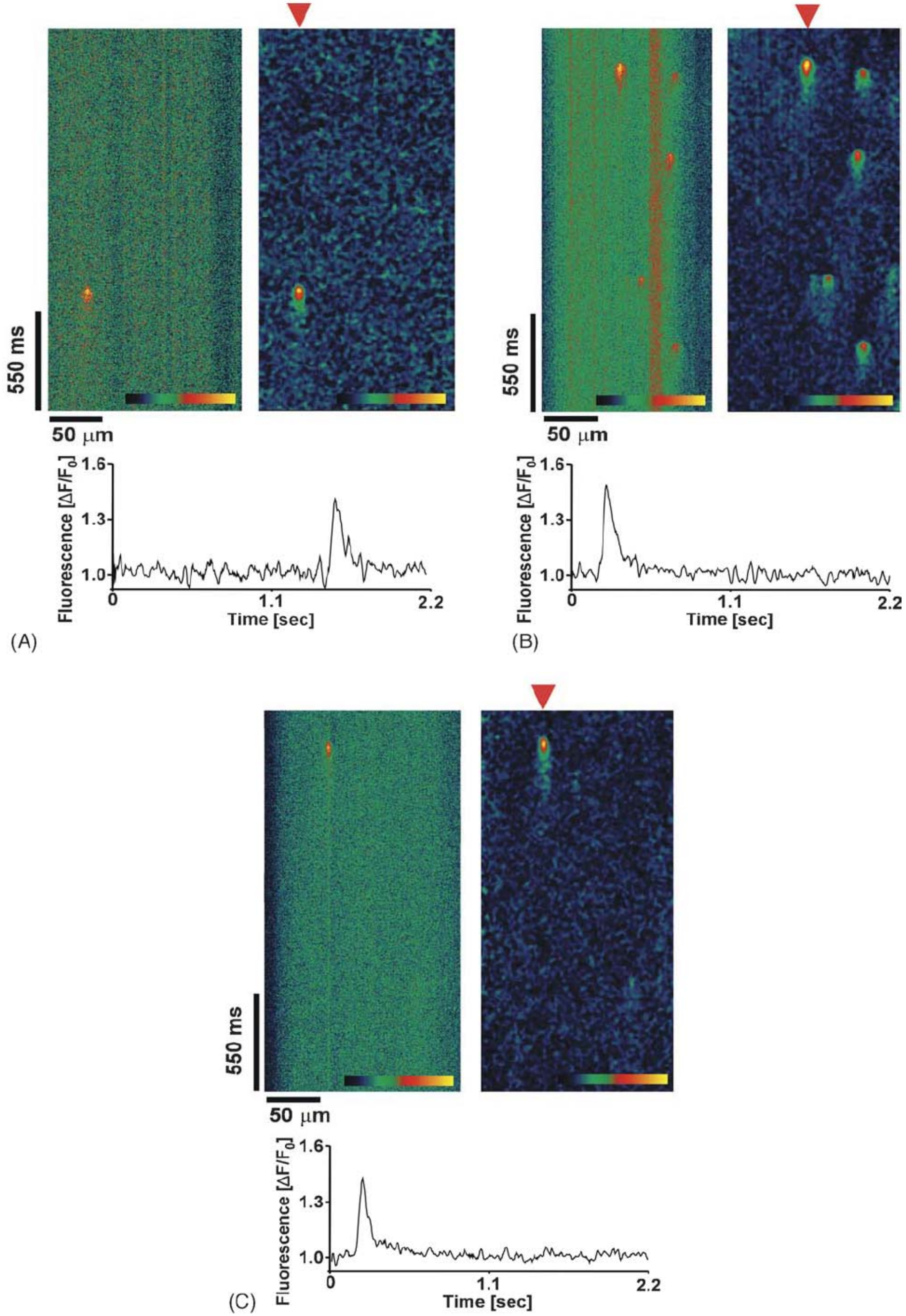
cell calcium

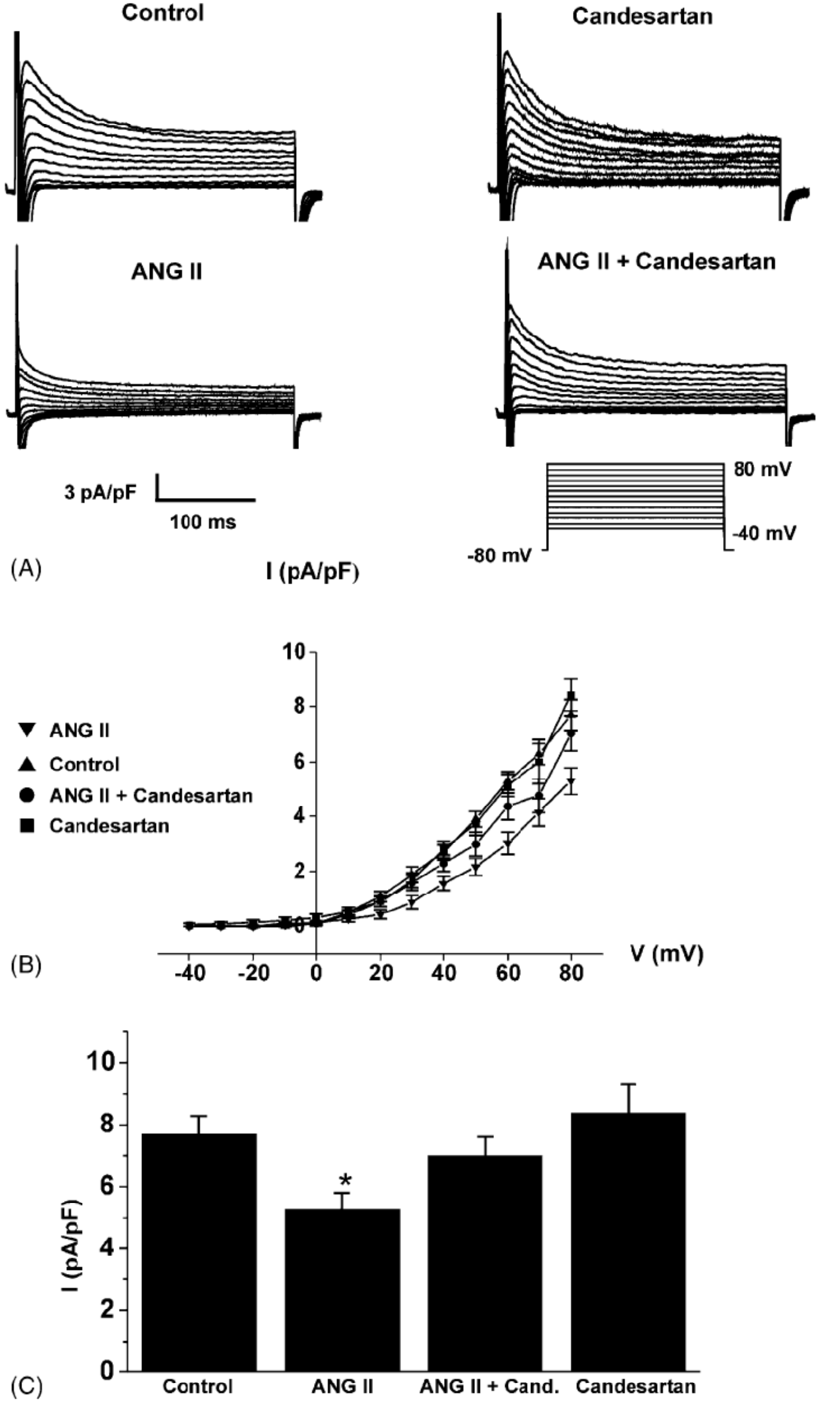
www.elsevier.com/locate/ceca

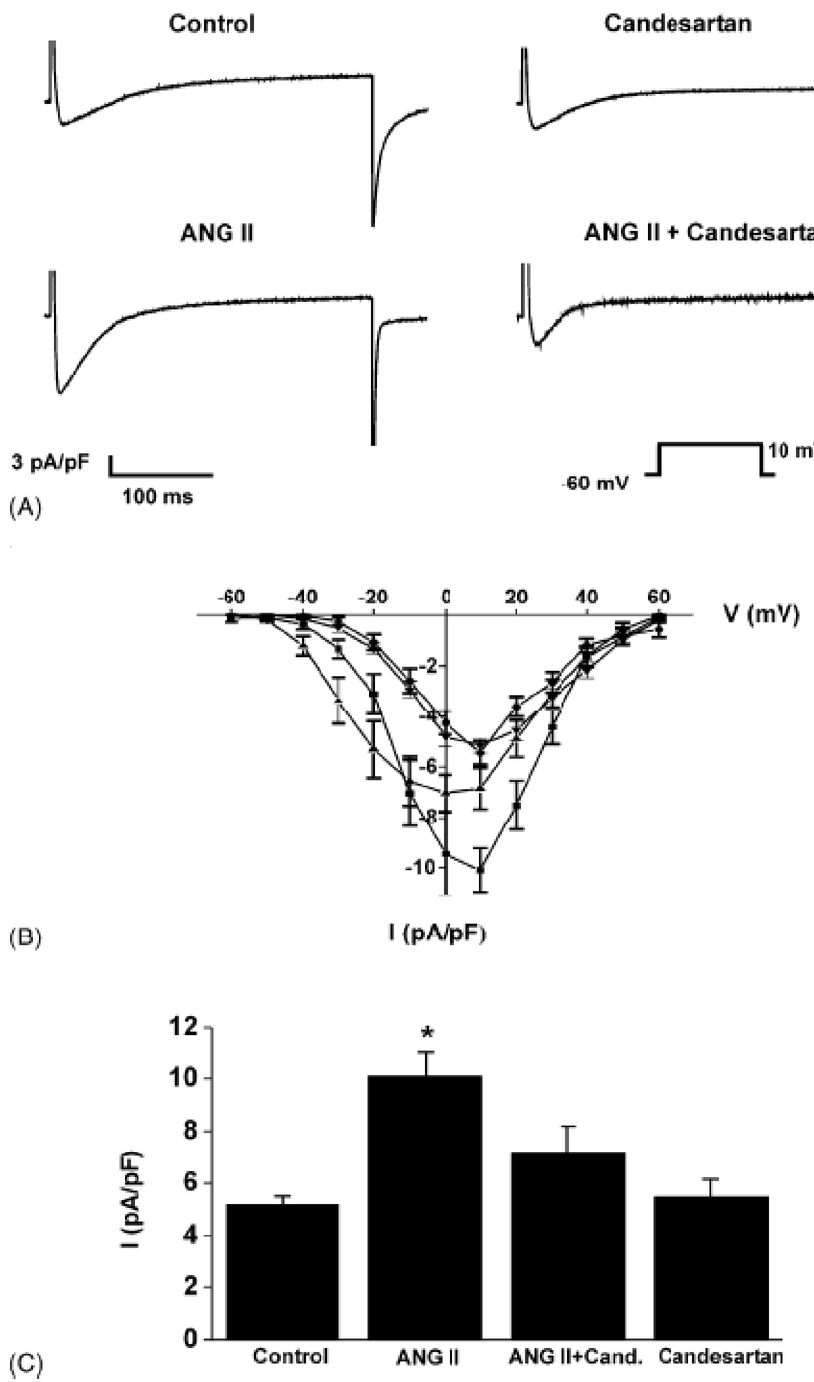
Angiotensin II-induced changes of calcium sparks and ionic currents in human atrial myocytes: Potential role for early remodeling in atrial fibrillation

Natig Gassanov [a], Mathias C. Brandt [a,b], Guido Michels [a,b], Michael Lindner [a], Fikret Er [a], Uta C. Hoppe [a,b,*]

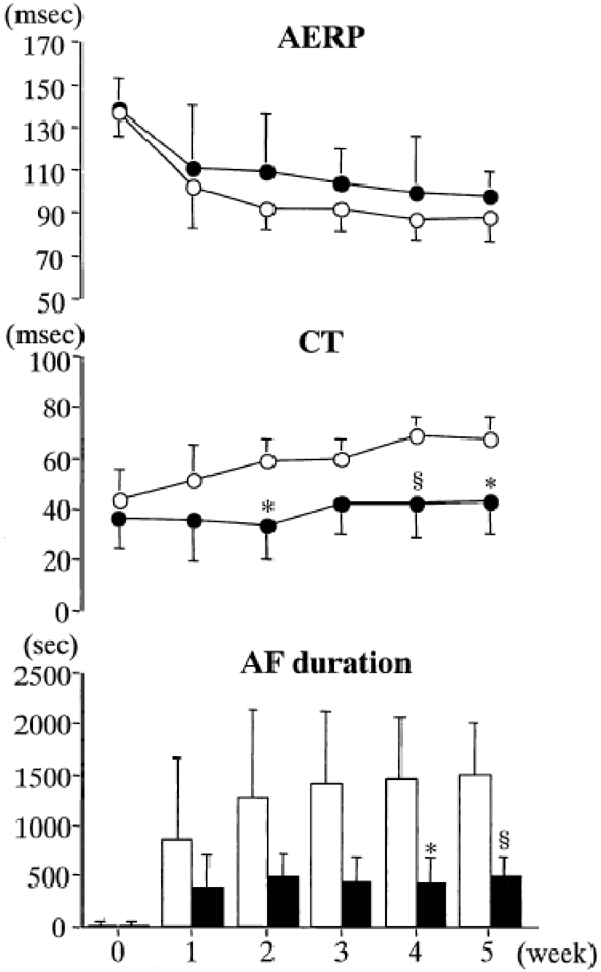
[a] *Department of Internal Medicine III, University of Cologne, Kerpener Str. 62, Cologne 50937, Germany*
[b] *Center for Molecular Medicine, University of Cologne (CMMC), University of Cologne, Germany*

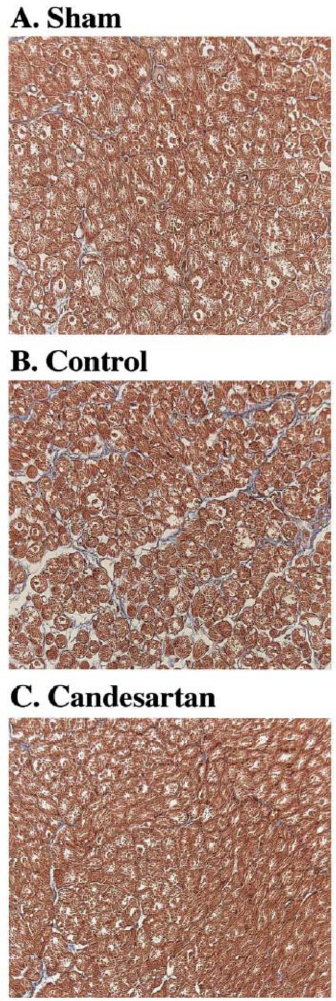

550 ms
50 μm
Fluorescence [ΔF/F0]
1.6
1.3
1.0
0
1.1
2.2
Time [sec]
(A)
(B)
(C)


Control
Candesartan
ANG II
ANG II + Candesartan
3 pA/pF
100 ms
80 mV
-40 mV
-80 mV
(A)
I (pA/pF)
ANG II
Control
ANG II + Candesartan
Candesartan
V (mV)
(B)
I (pA/pF)
*
Control
ANG II
ANG II + Cand.
Candesartan
(C)


Control
Candesartan
ANG II
ANG II + Candesartan
3 pA/pF
100 ms
10 mV
-60 mV
(A)
V (mV)
I (pA/pF)
(B)
I (pA/pF)
Control
ANG II
ANG II+Cand.
Candesartan
(C)

Effects of Angiotensin II Type 1 Receptor Antagonist on Electrical and Structural Remodeling in AF





J Am Coll Cardiol 2003;41:2197–204

Circ J 2006; **70:** 335 – 341

Blockade of Angiotensin II Type 1 Receptor Improves the Arrhythmia Morbidity in Mice With Left Ventricular Hypertrophy

Cuntai Zhang, MD*,**; Shinji Yasuno, MD#; Koichiro Kuwahara, MD#; Dimitar P. Zankov, MD##; Atsushi Kobori, MD**; Takeru Makiyama, MD**; Minoru Horie, MD##

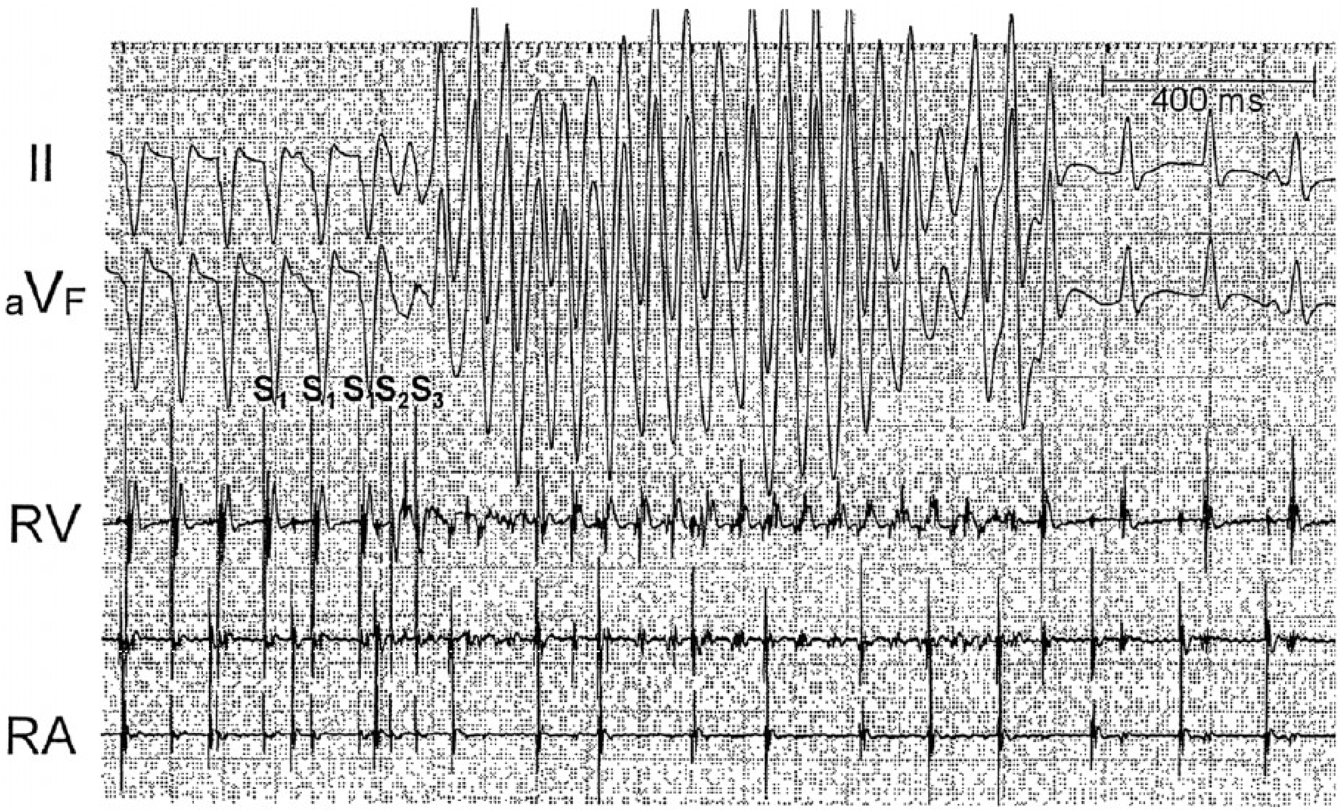
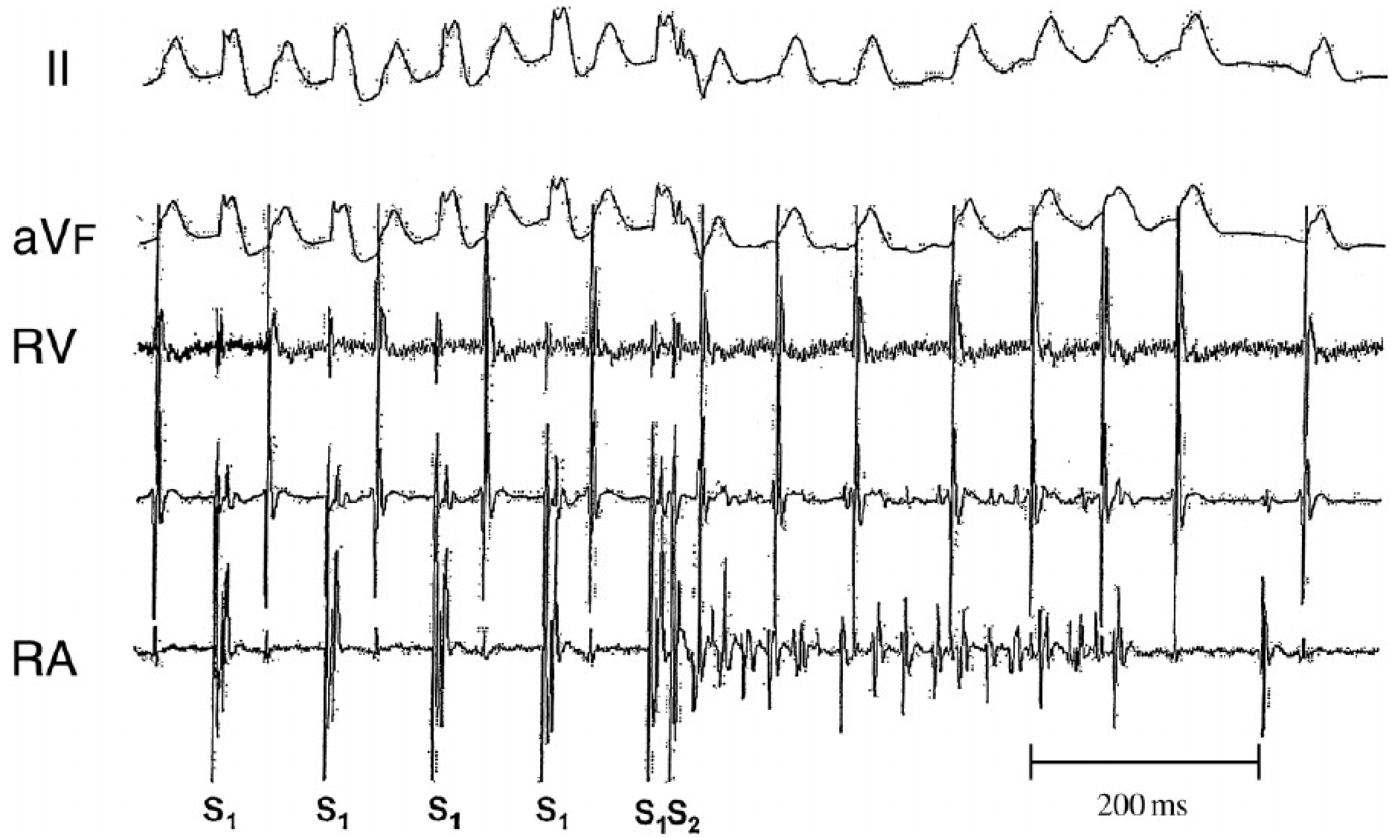


Table 4 Inducibility of Arrhythmias

	Programmed atrial pacing (n)	*Burst atrial pacing (n)*	*Programmed ventricular pacing (n)*	*Burst ventricular pacing (n)*	*Total number of arrhythmia (n)*	*Duration of arrhythmia (ms)*
VT						
Sham (n=16)	0	0	0	0	0	
TAC (n=16)	0	0	12	1	12**	714±250
Candesartan (n=16)	0	0	2	0	2##	324±10
AF						
Sham (n=16)	1	0	0	0	1	240
TAC (n=16)	6	2	0	0	8**	320±52
Candesartan (n=16)	0	0	0	0	0	

Values a ... *; Can-*
desarta ...
***p<0.0* ...



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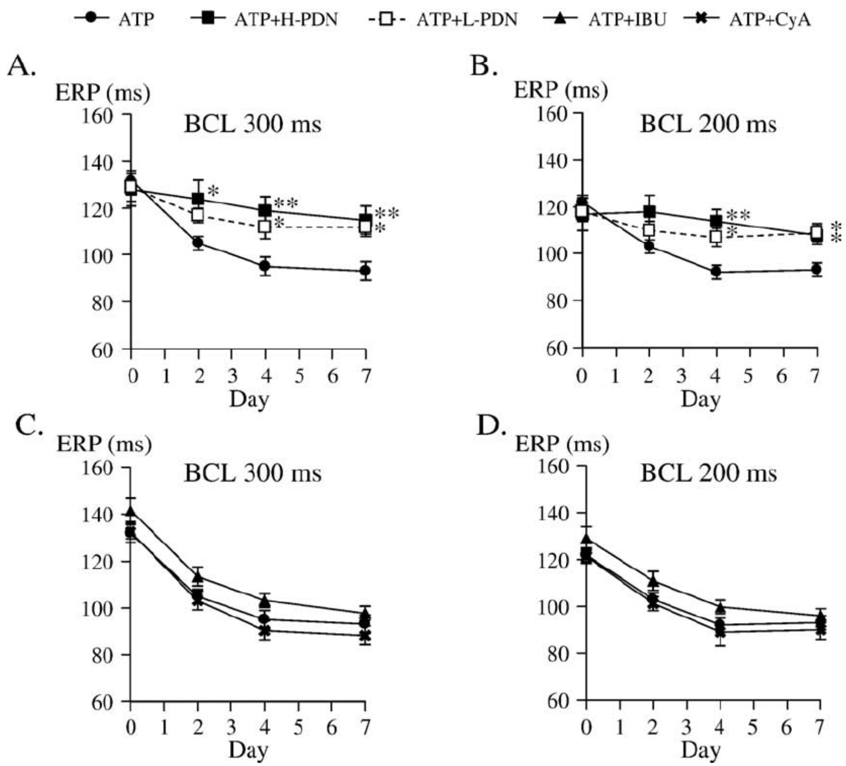
Cardiovascular Research 69 (2006) 865 – 875

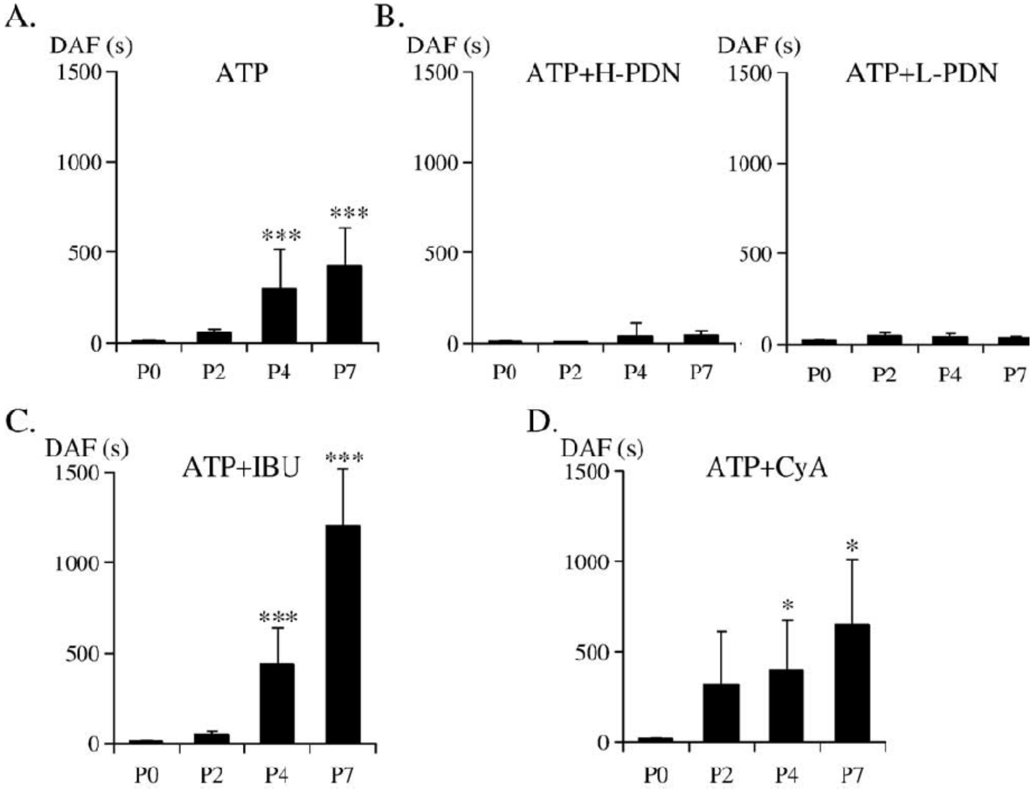
Cardiovascular Research

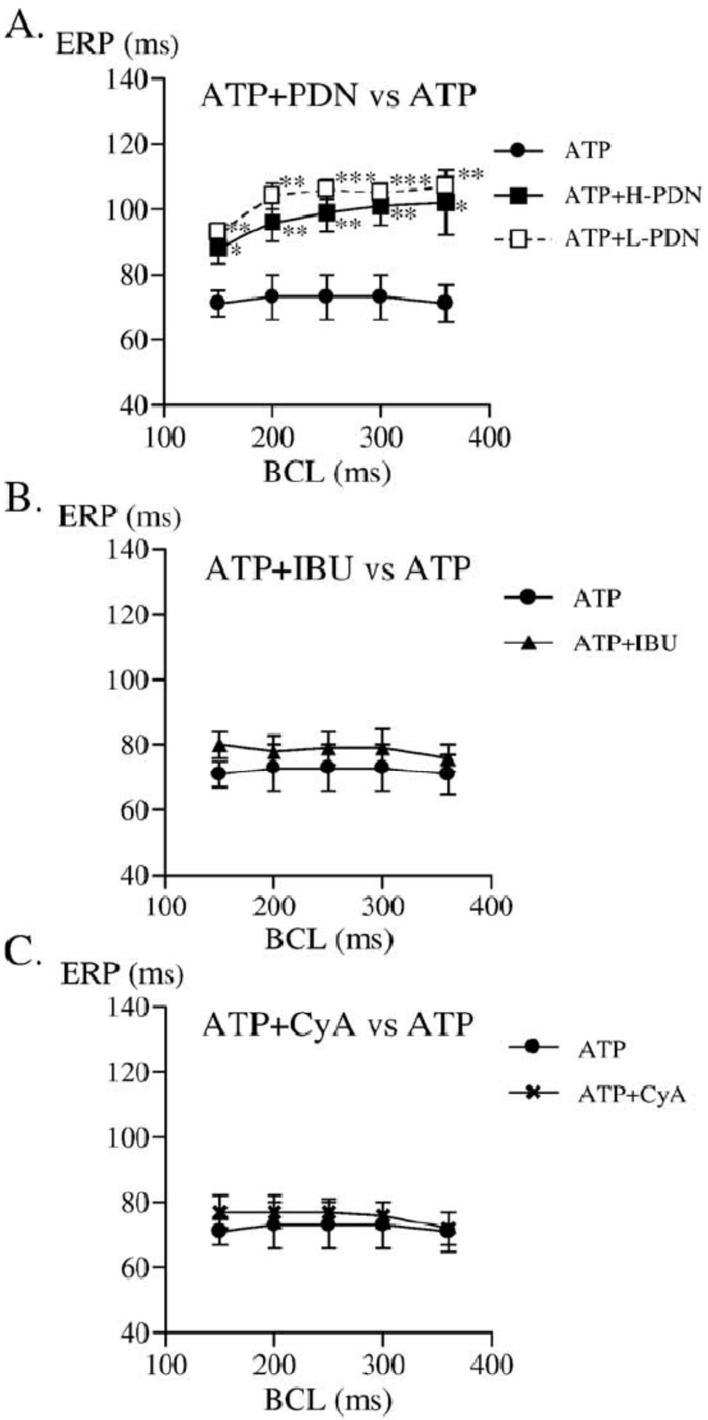
www.elsevier.com/locate/cardiores

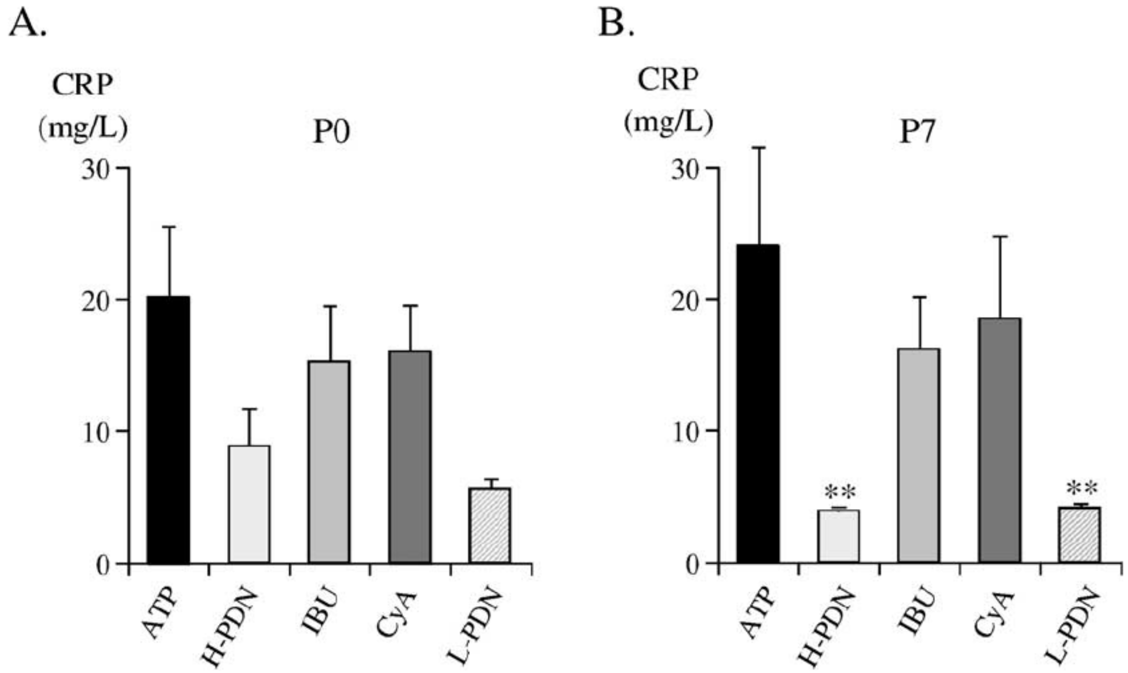
Prednisone prevents atrial fibrillation promotion by atrial tachycardia remodeling in dogs

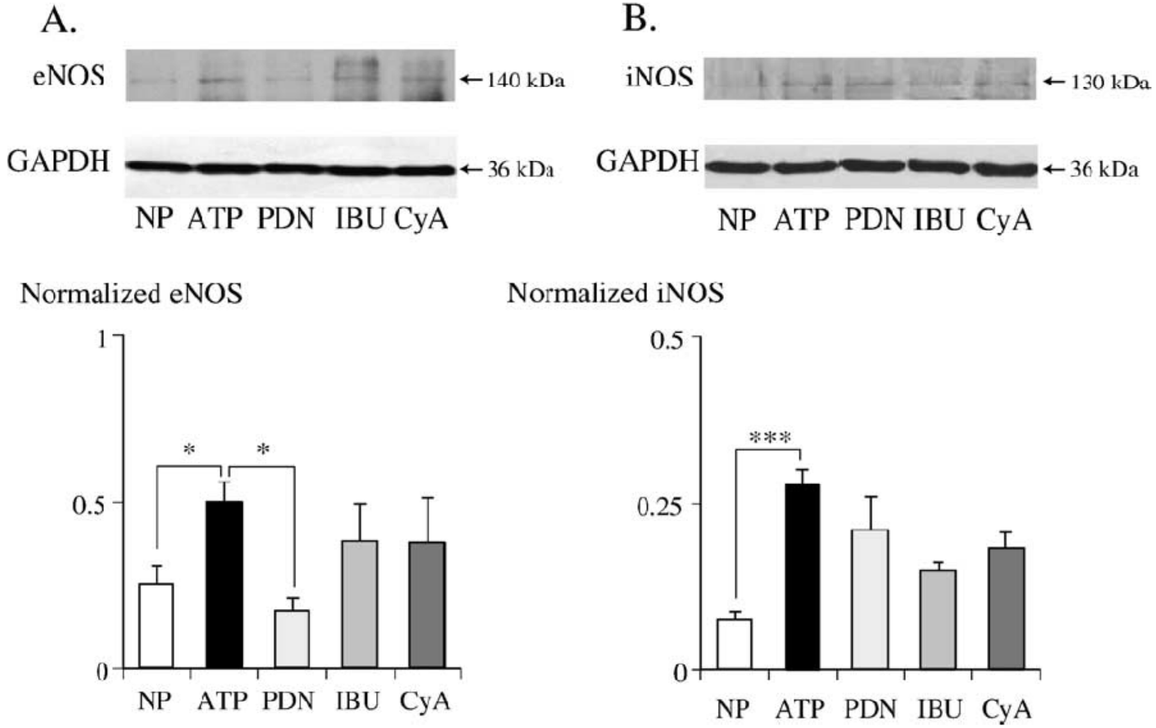
Akiko Shiroshita-Takeshita [a], Bianca J.J.M. Brundel [a,d], Joel Lavoie [b], Stanley Nattel [a,c,*]



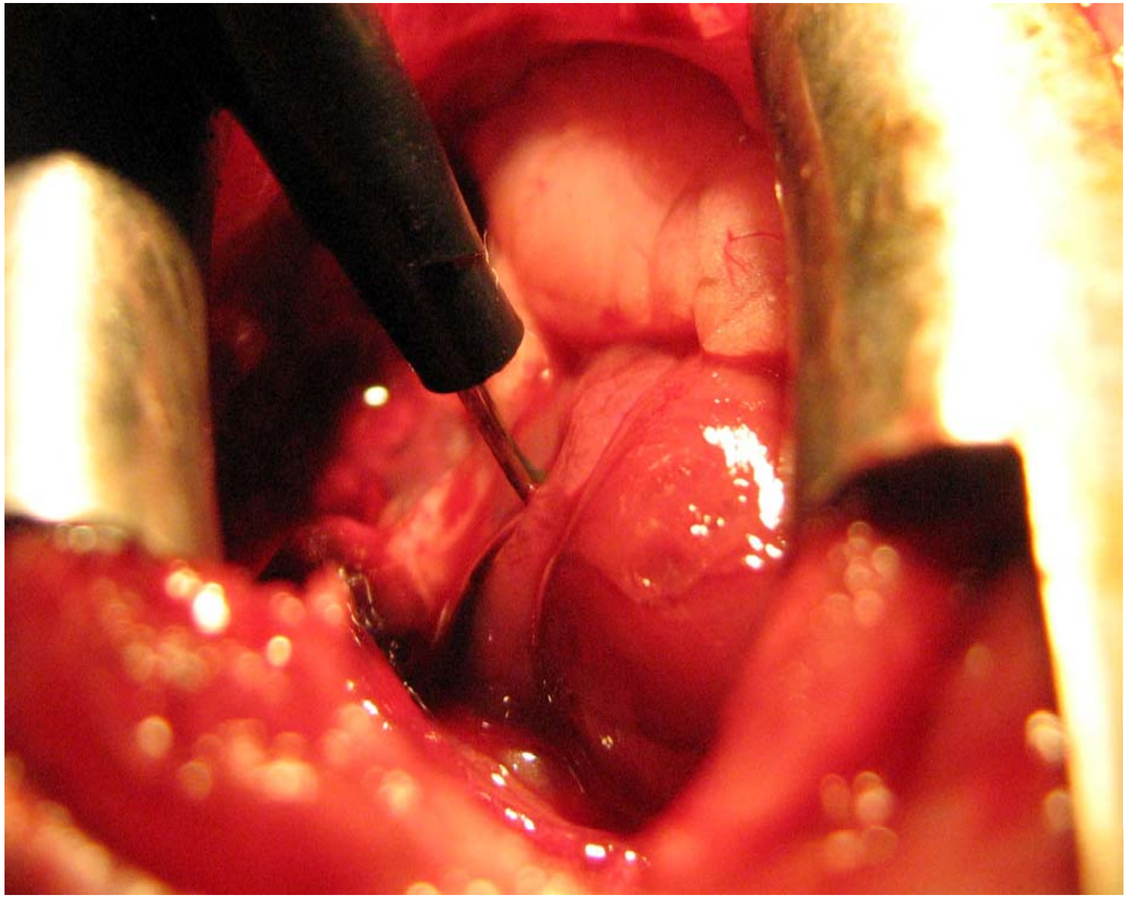



A.
ERP (ms)
ATP+PDN vs ATP
ATP
ATP+H-PDN
ATP+L-PDN
BCL (ms)
B.
ERP (ms)
ATP+IBU vs ATP
ATP
ATP+IBU
BCL (ms)
C.
ERP (ms)
ATP+CyA vs ATP
ATP
ATP+CyA
BCL (ms)


A.
CRP (mg/L)
P0
ATP
H-PDN
IBU
CyA
L-PDN
B.
CRP (mg/L)
P7
ATP
H-PDN
IBU
CyA
L-PDN

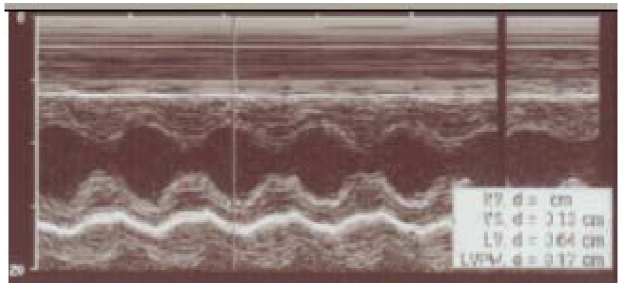

A.
eNOS
← 140 kDa
GAPDH
← 36 kDa
NP ATP PDN IBU CyA
B.
iNOS
← 130 kDa
GAPDH
← 36 kDa
NP ATP PDN IBU CyA
Normalized eNOS
NP ATP PDN IBU CyA
Normalized iNOS
NP ATP PDN IBU CyA

Rat EP study - RA pacing

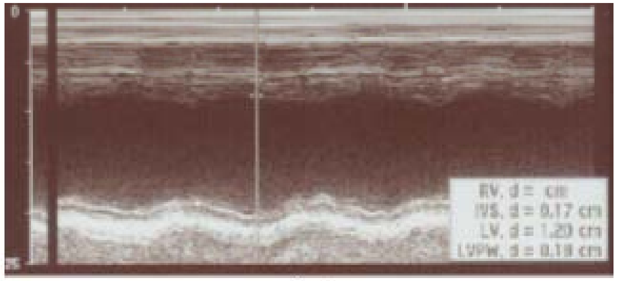


Using bipolar electrode right atrial bust pacing was performed.

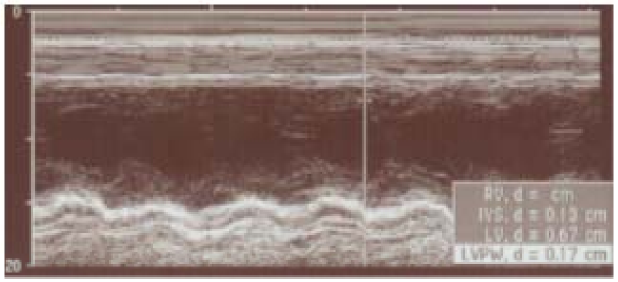
Echocardiographic indices



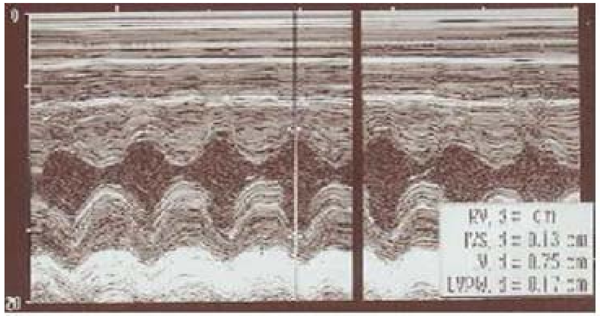
Sham



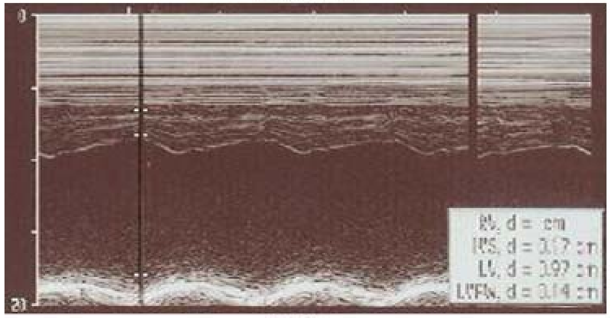
MI



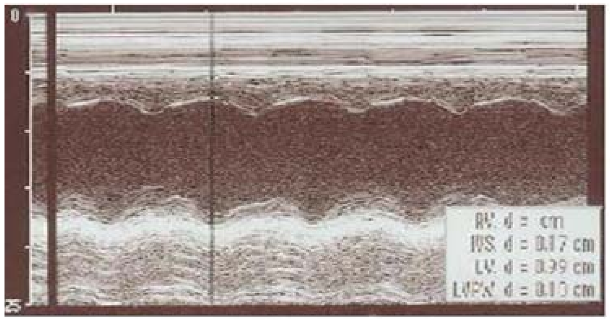
MI+Losar



Sham



MI



MI + Simvastatin

Echocardiograms showing left ventricular anteroseptal wall akinesia, dilated ventricular dimension and decreased ejection fraction in heart failure rat, and heart function slightly recovered in losartan treated rat group.

Echocardiographic parameters

	Sham	MI	MI+Losar
EF(%)	90.7±4.2	37.2±11.9 *	47.1±19.3 *
FS(%)	58.0±7.8	16.0±6.1 *	22.1±12.0 *
LVEDD(cm)	0.76±0.08	1.01±0.06 *	0.94±0.18 **
LVESD(cm)	0.32±0.07	0.85±0.10 *	0.76±0.22 *
LAD(cm)	0.33±0.08	0.50±0.13 **	0.37±0.06 **

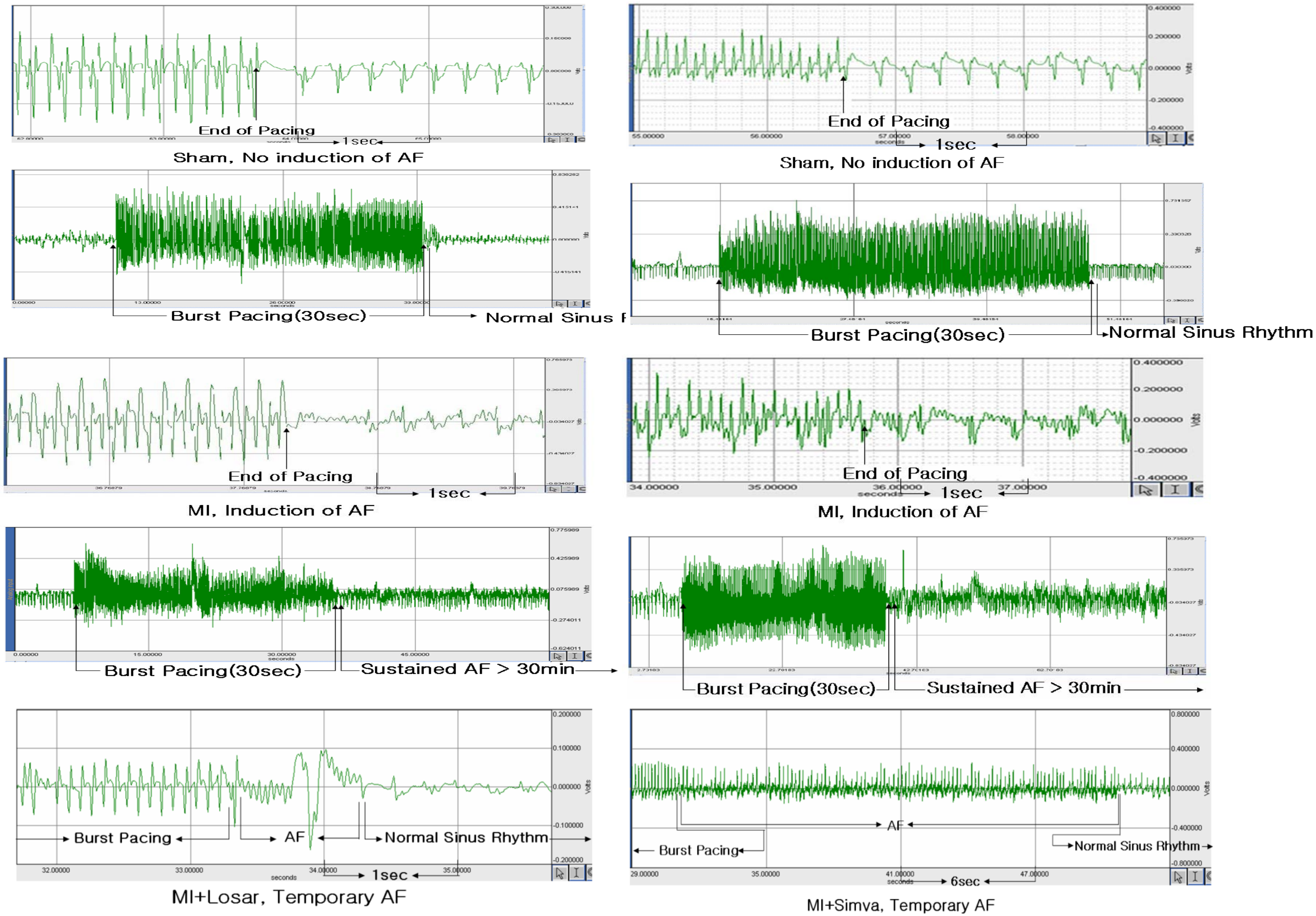
*p<0.001 versus sham, **p<0.01 versus sham, ***p<0.05 versus sham
(Sham, n=10; MI, n=10; MI+Losar, n=10)

	Sham	MI	MI+Simva
EF(%)	83.0±7.6	30.04±16.1 *	43.0±21.5 *
FS(%)	48.5±8.8	12.7±7.5 *	20.6±15.2 *
LVEDD(cm)	0.79±0.06	0.95±0.13 **	0.96±0.16 ***
LVESD(cm)	0.40±0.08	0.83±0.15 *	0.78±0.22 *
LAD(cm)	0.34±0.08	0.38±0.09	0.36±0.08

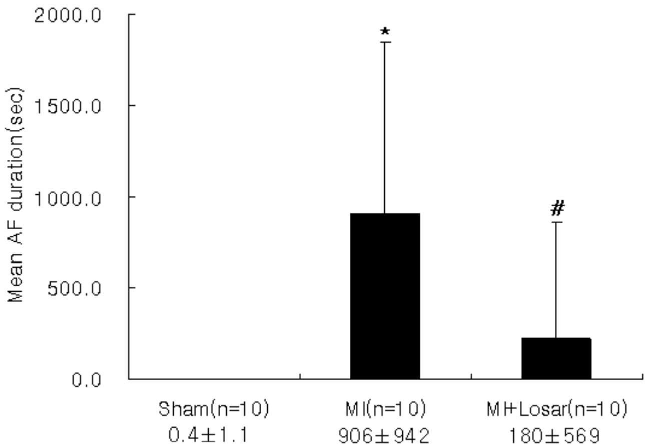
*p<0.001 versus sham, **p<0.01 versus sham, ***p<0.05 versus sham
(Sham, n=10; MI, n=10; MI+Simva, n=10)

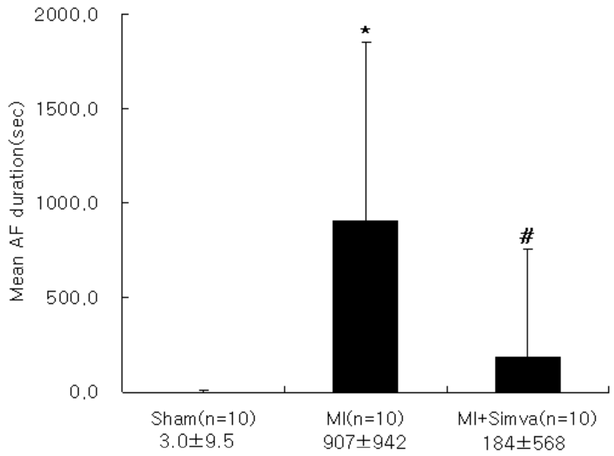
Echocardiographic parameters showing a decreased left ventricular function in heart failure group and slightly recovered in Losartan and Simvastatin treated group.

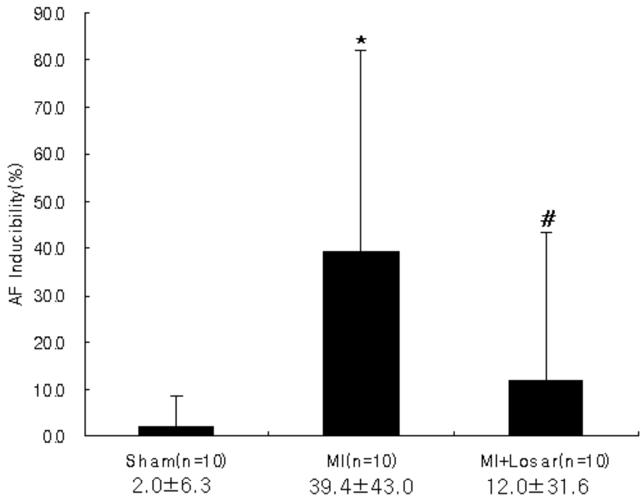
Electrophysiological study for Atrial Fibrillation duration

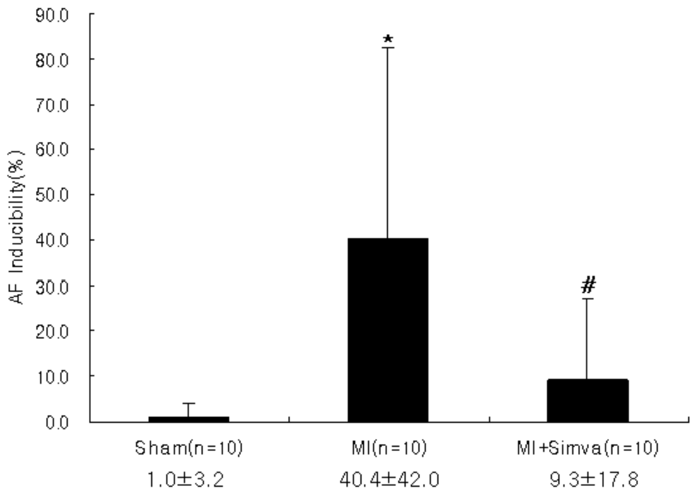


Results of AF duration and inducibility studies

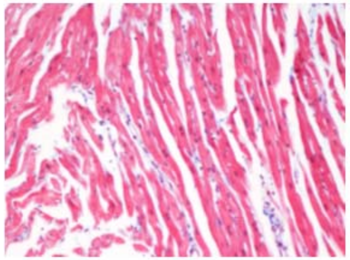


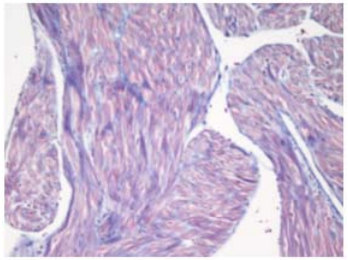


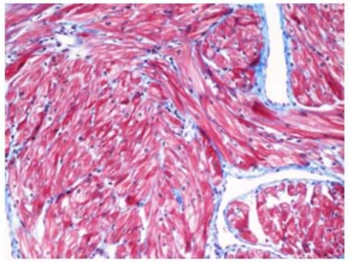


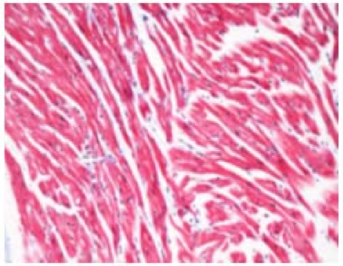


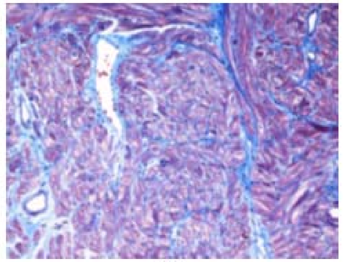
Effect of losartan and simvastatin in MI rats with regards to prevent fibrosis formation

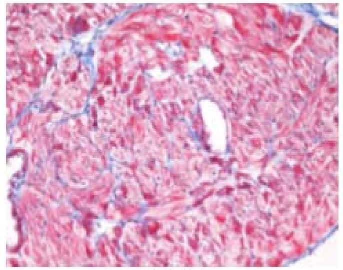

Sham

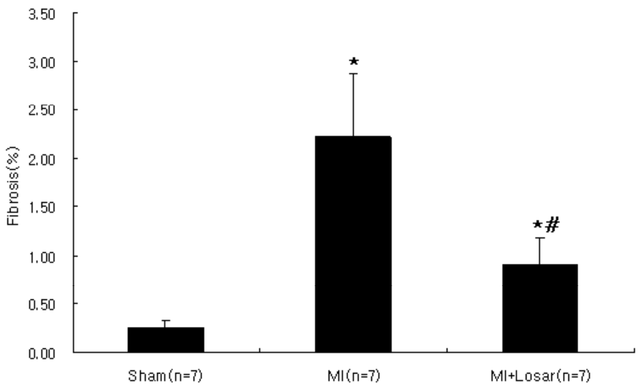

MI

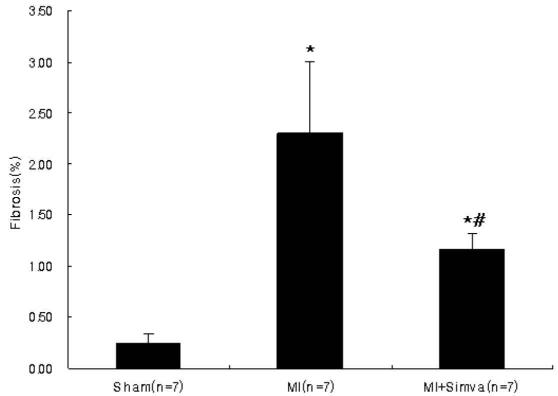

MI+Losar


Sham


MI

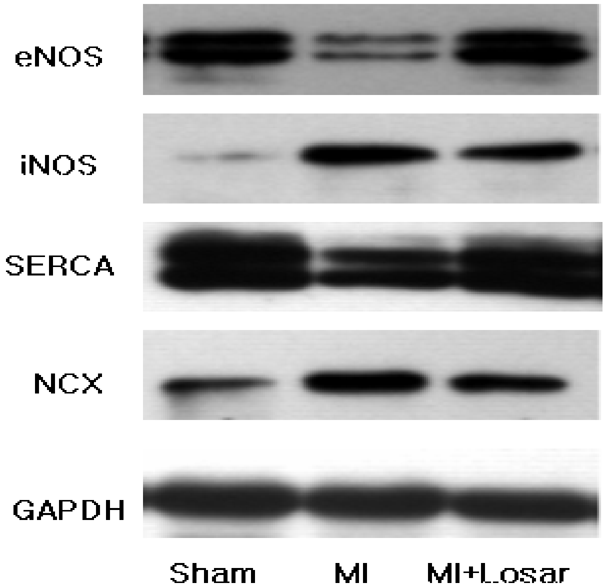

MI+Simva

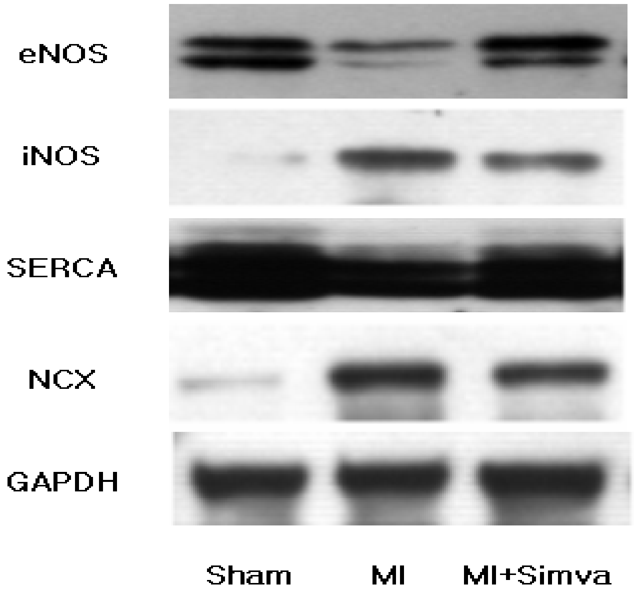




0.24±0.09 2.30±0.71 1.17±0.16

Alterations in the eNOS, iNOS, SERCA and NCX protein expression in the left atrium.





	sham	MI	MI+Losar
eNOS	12.84±2.78 (n=6)	6.56±4.08** (n=6)	11.65±3.41## (n=6)
iNOS	0.25±0.30 (n=9)	6.09±4.65* (n=10)	2.51±1.32*## (n=10)
NCX	0.78±0.44 (n=9)	15.86±12.91* (n=11)	4.73±5.20*## (n=9)
SERCA	28.59±3.28 (n=6)	19.07±3.53* (n=6)	23.32± 2.72**## (n=6)

*p<0.01 versus sham, # p<0.01 MI versus MI+Losar

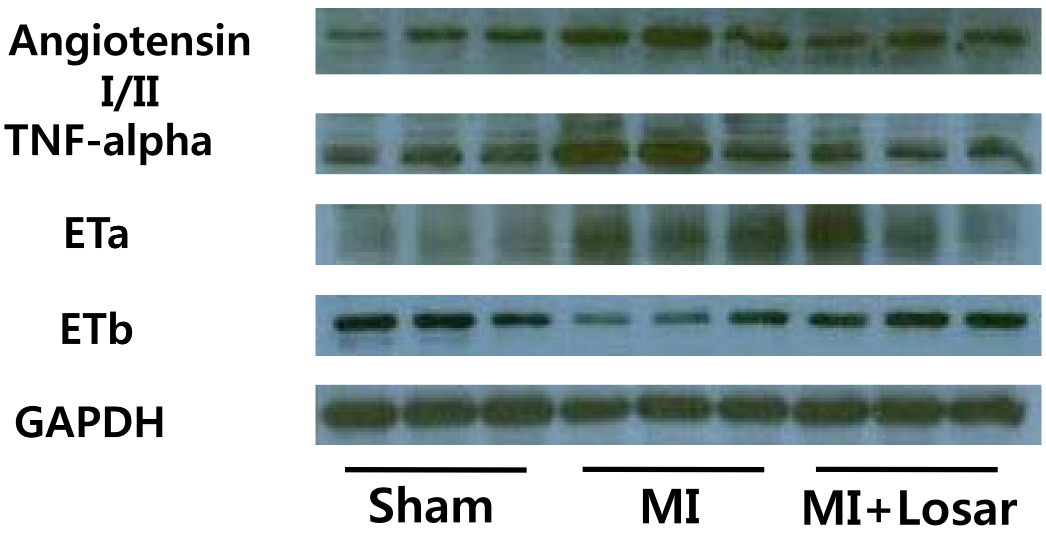
** p<0.05 versus sham, ## p<0.05 MI versus MI+Losar

	sham	MI	MI+Simva
eNOS	13.41±2.58 (n=6)	6.75±2.05 ** (n=6)	12.06±3.43 ## (n=6)
iNOS	0.28±0.30 (n=9)	7.33±5.79± * (n=10)	1.60±1.47 **# (n=12)
NCX	0.79±0.48 (n=8)	14.52±11.87 * (n=11)	4.19±11.87 *## (n=12)
SERCA	30.90±3.18 (n=6)	21.13±1.36 * (n=6)	25.43±3.27 **## (n=6)

* p<0.01 versus sham, # p<0.01 MI versus MI+simva

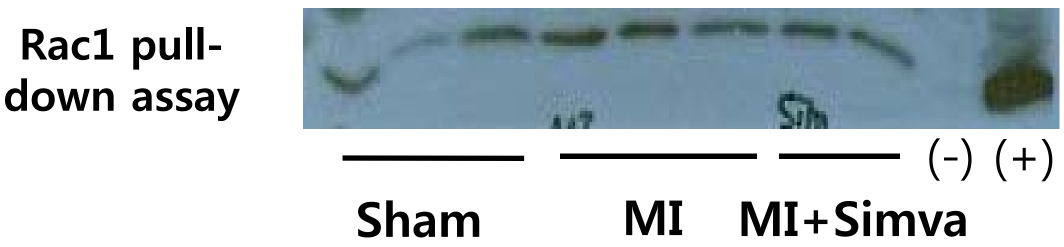
** p<0.05 versus sham, ## p<0.05 MI versus MI+simva

Other protein expression in the left atrium



	Sham	MI	MI+Losar
Angiotensin I/II	0.32±0.05 (n=6)	0.56±0.07* (n=6)	0.41±0.08# (n=6)
TNF-alpha	0.54±0.09 (n=6)	1.12±0.16* (n=6)	0.69±0.13# (n=6)
Eta	0.46±0.05 (n=6)	0.84±0.18* (n=6)	0.57±0.12# (n=6)
ETb	0.53±0.09 (n=6)	0.31±0.06* (n=6)	0.43±0.03# (n=6)

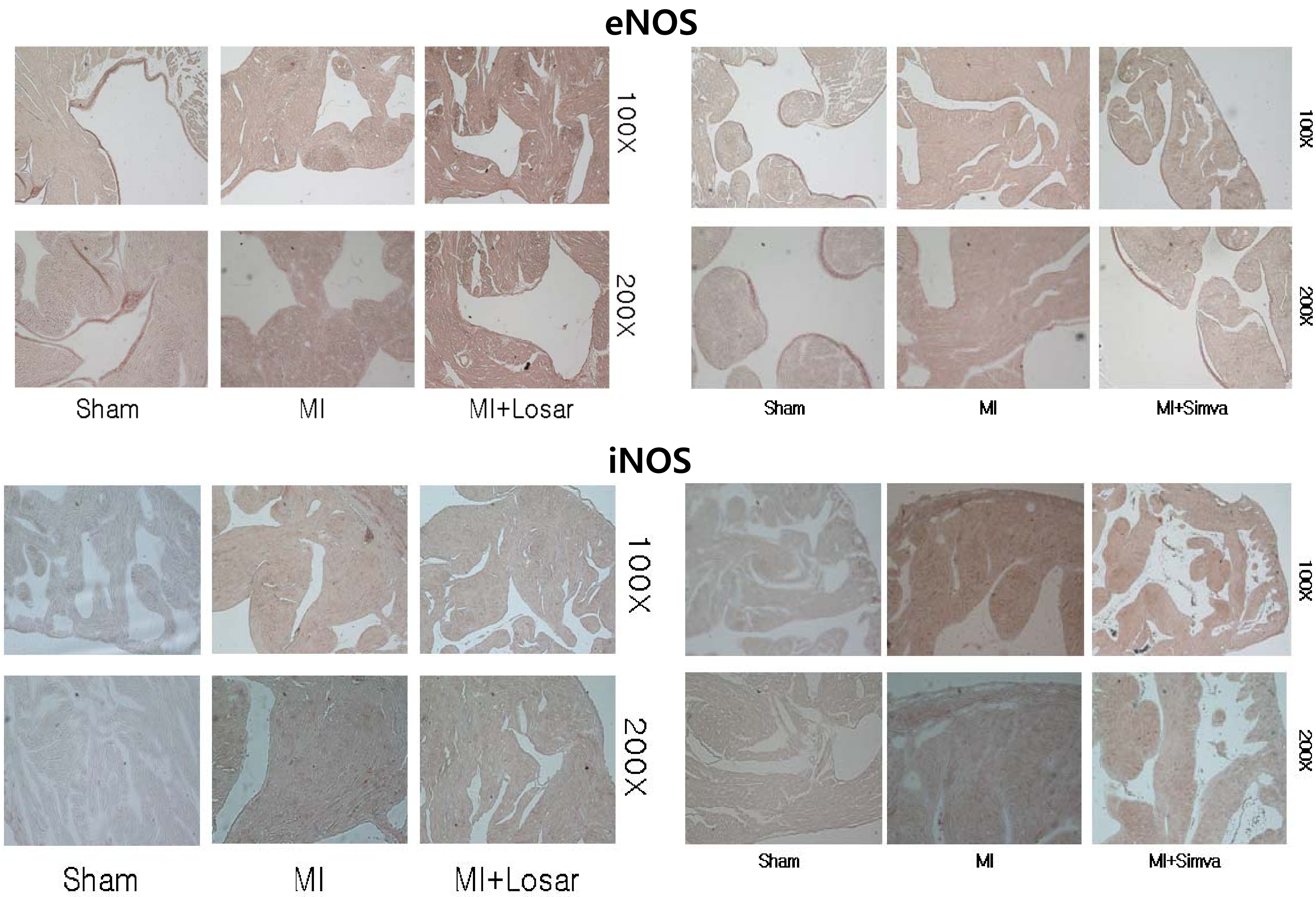
***p<0.05 sham versus MI**
#p<0.05 MI versus MI+Losar



	Sham	MI	MI+Simva
Rac1	16165±1696 (n=6)	28440±1655* (n=6)	19275±2236# (n=5)

***p<0.05 sham versus MI**
#p<0.05 MI versus MI+Simva

Imuunohistochemical staining of eNOS and iNOS



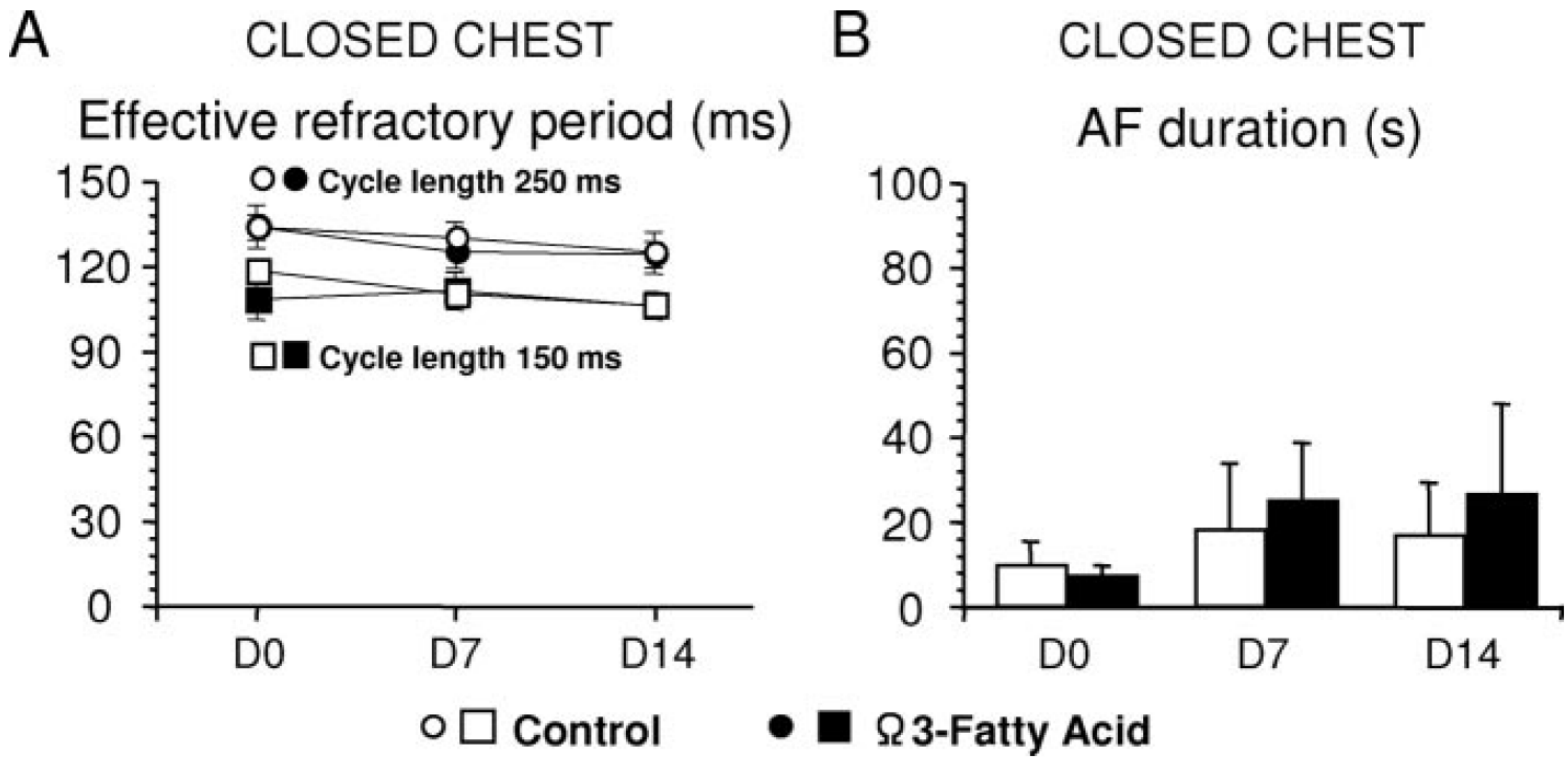
Omega-3 Polyunsaturated Fatty Acids Prevent Atrial Fibrillation Associated With Heart Failure but Not Atrial Tachycardia Remodeling

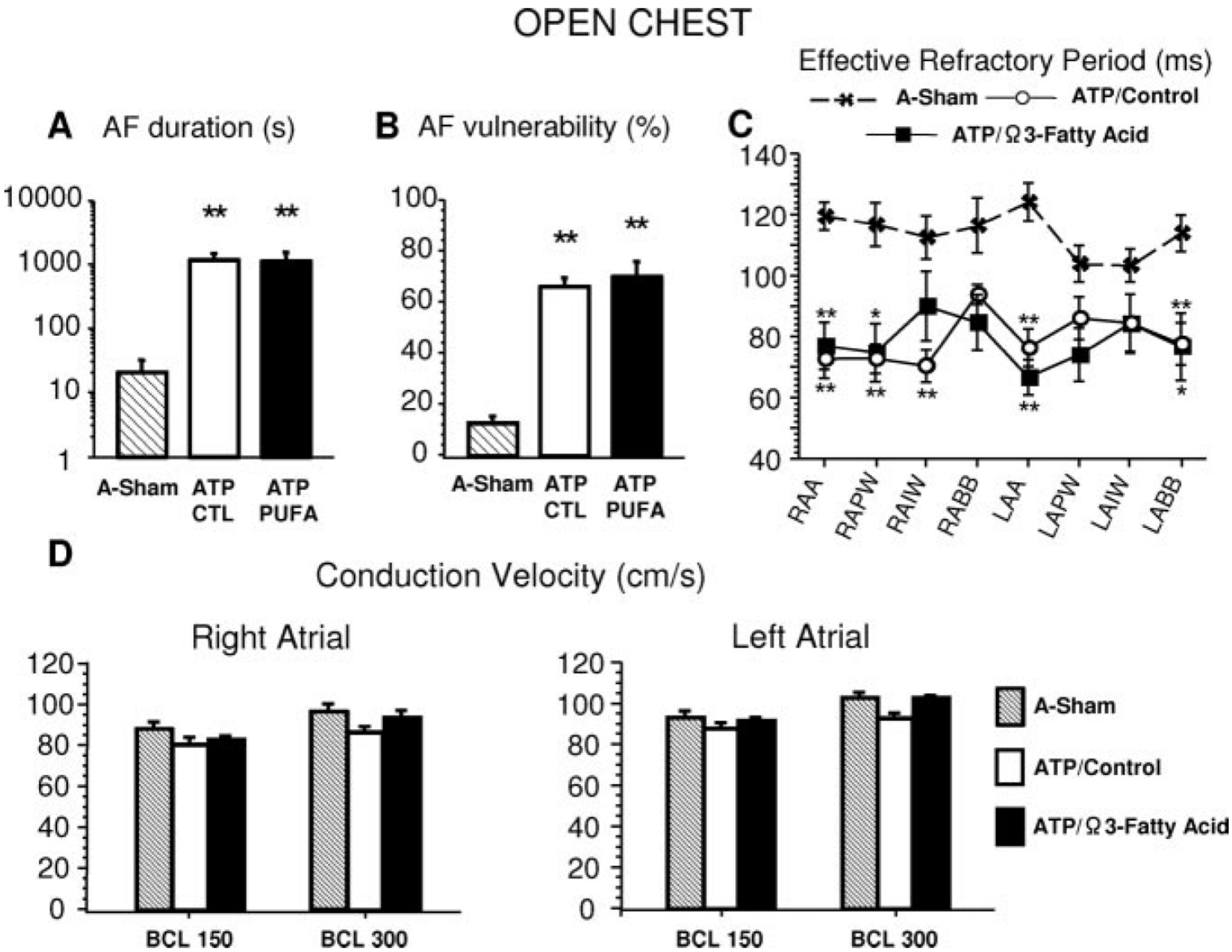
Masao Sakabe, MD, PhD; Akiko Shiroshita-Takeshita, MD, PhD; Ange Maguy, PhD; Chloe Dumesnil, BSc; Anil Nigam, MD; Tack-Ki Leung, MD; Stanley Nattel, MD

Background—There is epidemiological evidence that omega-3 polyunsaturated fatty acids (PUFAs) reduce the risk of atrial fibrillation (AF), but clinical data are conflicting. The present study assessed the effects of PUFA on AF in experimental models.

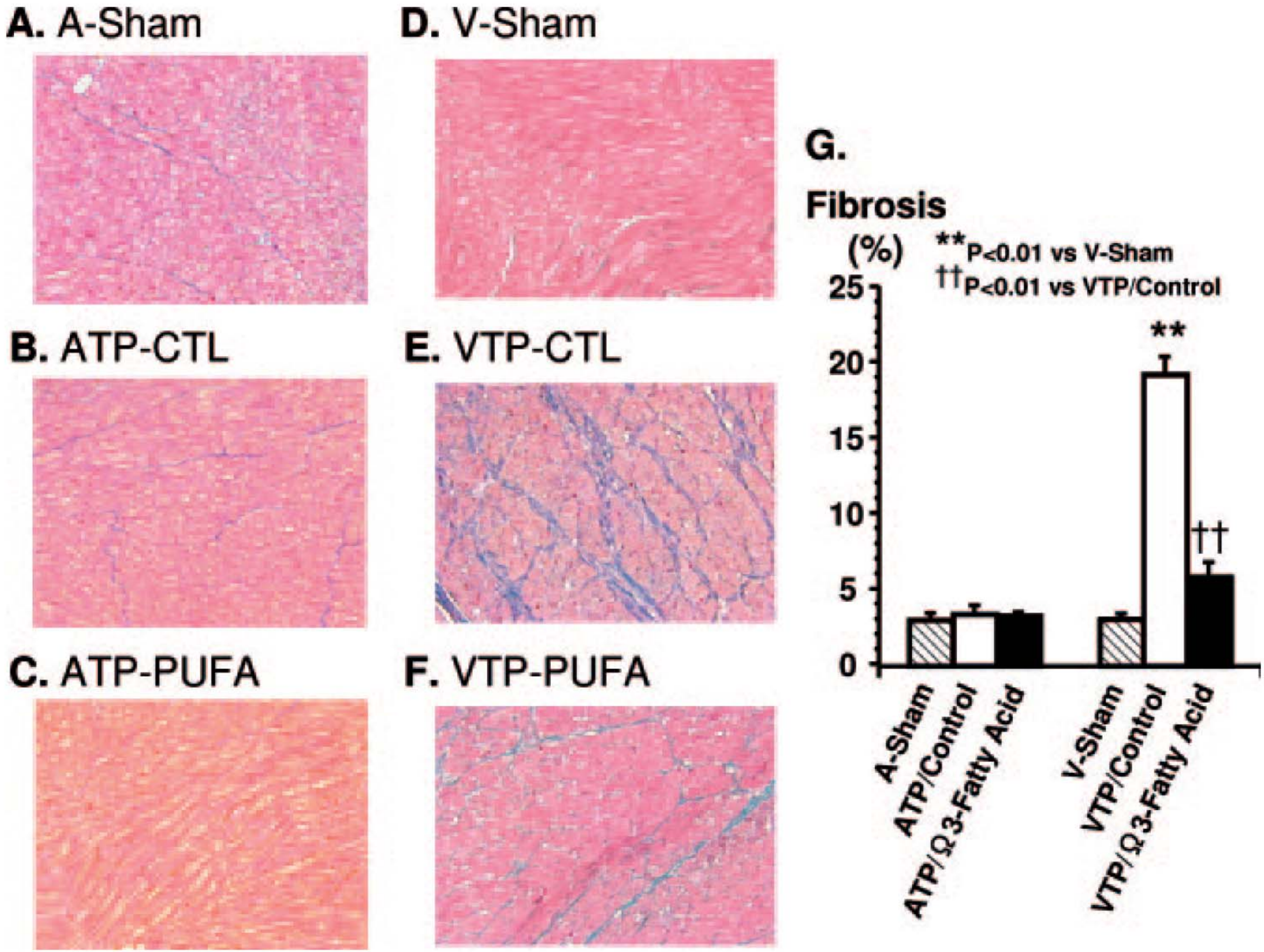
Methods and Results—We studied the effects of oral PUFA supplements in 2 experimental AF paradigms: electrical remodeling induced by atrial tachypacing (400 bpm for 1 week) and congestive heart failure–associated structural remodeling induced by ventricular tachypacing (240 bpm for 2 weeks). PUFA pretreatment did not directly change atrial effective refractory period (128±6 [mean±SEM] versus 127±2 ms; all effective refractory periods at 300-ms cycle lengths) or burst pacing–induced AF duration (5±4 versus 34±18 seconds). Atrial tachypacing dogs had shorter refractory periods (73±6 ms) and greater AF duration (1185±300 seconds) than shams (119±5 ms and 20±11 seconds; $P<0.01$ for each). PUFAs did not significantly alter atrial tachypacing effects on refractory periods (77±8 ms) or AF duration (1128±412 seconds). PUFAs suppressed ventricular tachypacing–induced increases in AF duration (952±221 versus 318±249 seconds; $P<0.05$) and attenuated congestive heart failure–related atrial fibrosis (from 19.2±1.1% to 5.8±1.0%; $P<0.001$) and conduction abnormalities. PUFAs also attenuated ventricular tachypacing–induced hemodynamic dysfunction (eg, left ventricular end-diastolic and left atrial pressure from 12.2±0.5 and 11.4±0.6 mm Hg, respectively, to 6.4±0.5 and 7.0±0.8 mm Hg; $P<0.01$) and phosphorylation of mitogen-activated protein kinases (extracellular-signal related and P38 kinase).

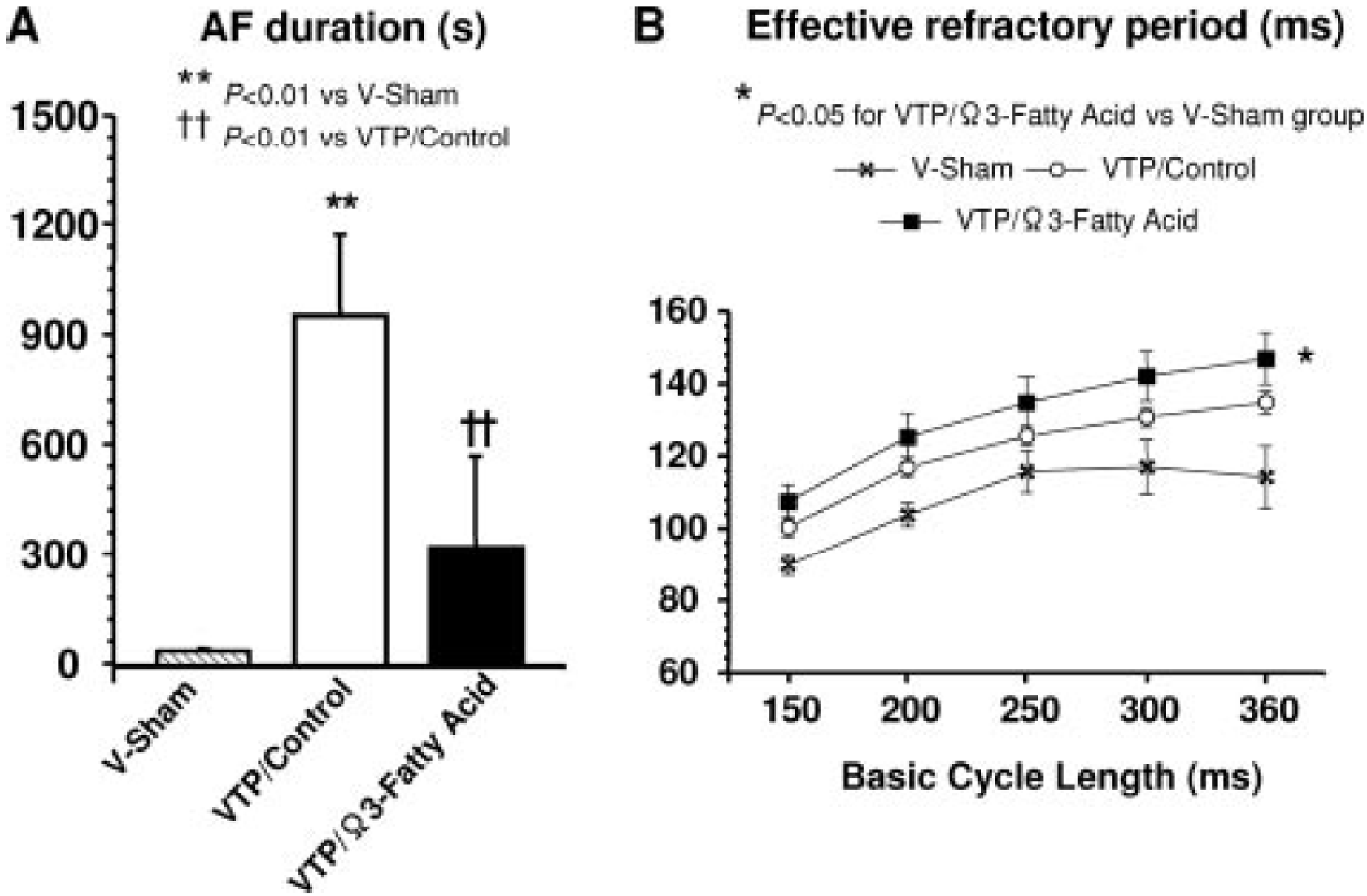
Conclusions—PUFAs suppress congestive heart failure–induced atrial structural remodeling and AF promotion but do not affect atrial tachycardia–induced electrical remodeling. The beneficial effects of PUFAs on structural remodeling, possibly related to prevention of mitogen-activated protein kinase activation, may contribute to their clinical anti-AF potential. (***Circulation*. 2007;116:2101-2109.**)

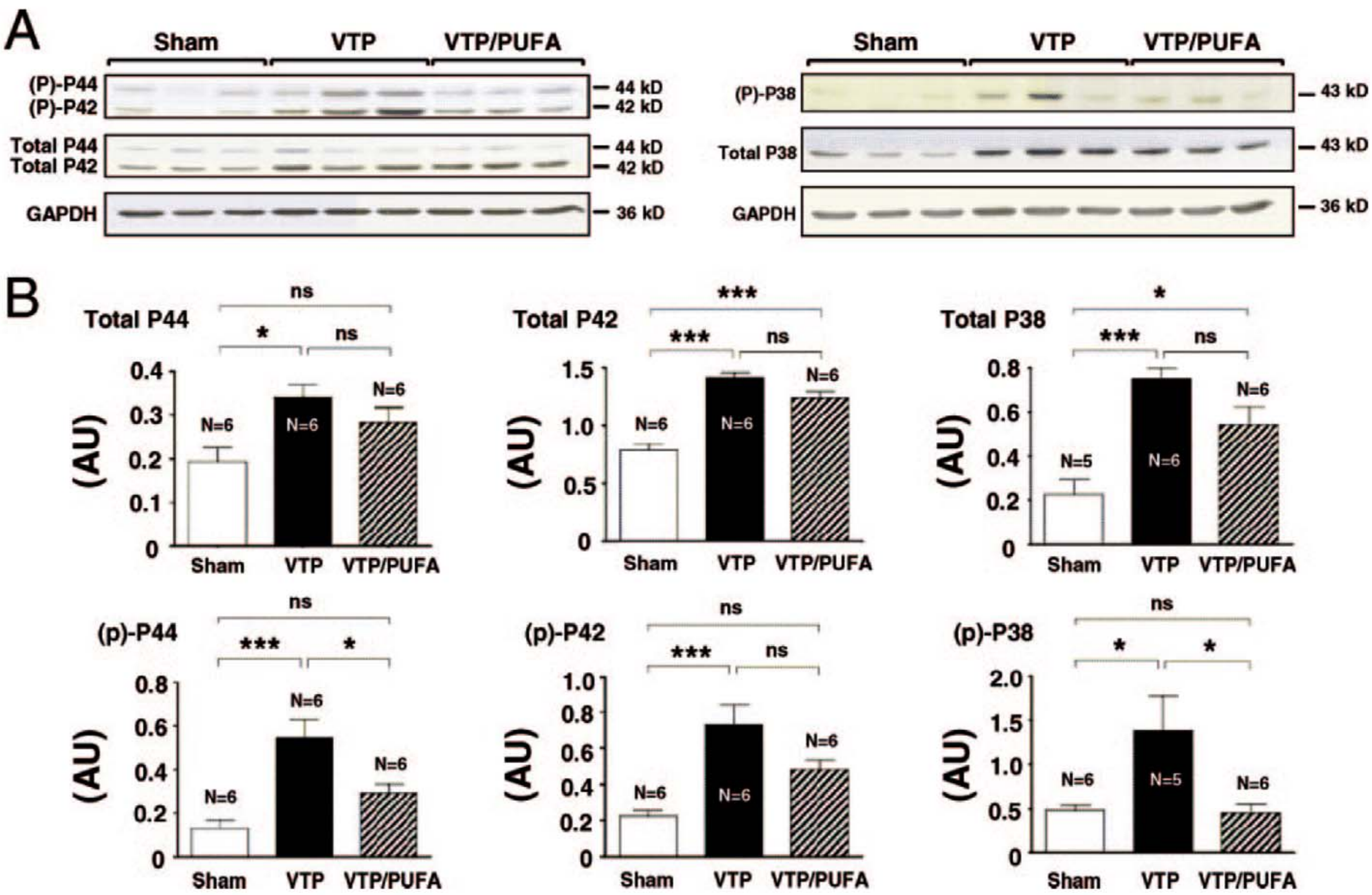

A
CLOSED CHEST
Effective refractory period (ms)
Cycle length 250 ms
Cycle length 150 ms
150
120
90
60
30
0
D0
D7
D14
B
CLOSED CHEST
AF duration (s)
100
80
60
40
20
0
D0
D7
D14
Control
Ω3-Fatty Acid



OPEN CHEST
A AF duration (s)
10000
1000
100
10
1
**
**
A-Sham
ATP CTL
ATP PUFA
B AF vulnerability (%)
100
80
60
40
20
0
**
**
A-Sham
ATP CTL
ATP PUFA
C
Effective Refractory Period (ms)
A-Sham
ATP/Control
ATP/Ω3-Fatty Acid
140
120
100
80
60
40
RAA
RAPW
RAIW
RABB
LAA
LAPW
LAIW
LABB
D
Conduction Velocity (cm/s)
Right Atrial
Left Atrial
120
100
80
60
40
20
0
BCL 150
BCL 300
A-Sham
ATP/Control
ATP/Ω3-Fatty Acid


A. A-Sham
B. ATP-CTL
C. ATP-PUFA
D. V-Sham
E. VTP-CTL
F. VTP-PUFA
G.
Fibrosis
(%)
**P<0.01 vs V-Sham
††P<0.01 vs VTP/Control
25
20
15
10
5
0
**
††
A-Sham
ATP/Control
ATP/Ω3-Fatty Acid
V-Sham
VTP/Control
VTP/Ω3-Fatty Acid


A
AF duration (s)
** P<0.01 vs V-Sham
†† P<0.01 vs VTP/Control
1500
1200
900
600
300
0
**
††
V-Sham
VTP/Control
VTP/Ω3-Fatty Acid
B
Effective refractory period (ms)
* P<0.05 for VTP/Ω3-Fatty Acid vs V-Sham group
V-Sham
VTP/Control
VTP/Ω3-Fatty Acid
160
140
120
100
80
60
*
150
200
250
300
360
Basic Cycle Length (ms)


A
Sham
VTP
VTP/PUFA
(P)-P44
(P)-P42
44 kD
42 kD
Total P44
Total P42
44 kD
42 kD
GAPDH
36 kD
(P)-P38
43 kD
Total P38
43 kD
GAPDH
36 kD
B
Total P44
Total P42
Total P38
(p)-P44
(p)-P42
(p)-P38
(AU)
ns
*
***
N=6
N=5
Sham
VTP
VTP/PUFA

Pioglitazone, a peroxisome proliferator-activated receptor-gamma activator, attenuates atrial fibrosis and atrial fibrillation promotion in rabbits with congestive heart failure

Masayuki Shimano, MD,* Yukiomi Tsuji, MD,† Yasuya Inden, MD,* Kazuhisa Kitamura, MD,* Tomohiro Uchikawa, MD,* Shuji Harata, MD,* Stanley Nattel, MD, FHRS,‡ Toyoaki Murohara, MD*

*From the *Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan, †Department of Cardiovascular Research, Research Institute of Environmental Medicine (RIEM), Nagoya University, Nagoya, Japan, and ‡Research Center and Department of Medicine, Montreal Heart Institute and University of Montreal and Department of Pharmacology, McGill University, Montreal, Canada.*

BACKGROUND The peroxisome proliferator-activated receptor-γ (PPAR-γ) activator pioglitazone antagonizes angiotensin II actions and possesses anti-inflammatory and antioxidant properties in vitro. There is evidence that pioglitazone improves ventricular remodeling in some experimental models.

OBJECTIVE The purpose of this study was to assess the effects of pioglitazone on arrhythmogenic atrial structural remodeling versus the effects of the angiotensin II type 1 receptor blocker candesartan in a rabbit model of congestive heart failure.

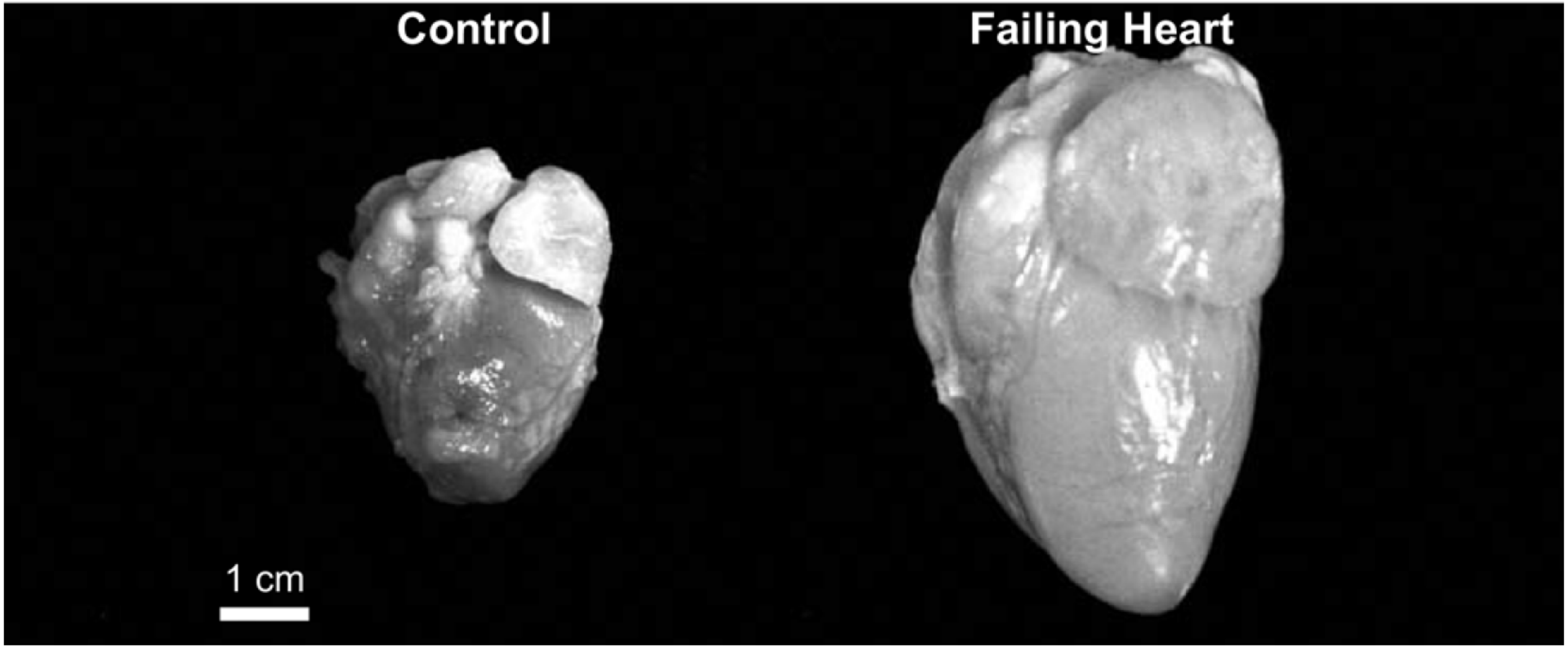
METHODS Rabbits subjected to ventricular tachypacing at 380 to 400 bpm for 4 weeks in the absence and presence of treatment with pioglitazone, candesartan, and combined pioglitazone and candesartan were assessed by electrophysiologic study, atrial fibrosis measurements, and cytokine expression analyses.

RESULTS Atrial fibrillation (AF) lasting longer than 2 seconds was induced in no nonpaced controls but in all ventricular tachypacing-only rabbits (mean duration of AF: 8.0 ± 1.4 seconds). Pioglitazone reduced the duration of AF (3.5 ± 0.2 seconds, $P < .05$) and attenuated atrial structural remodeling, with significant reductions in interatrial activation time (50 ± 2 ms vs 41 ± 2 ms, $P < .05$) and atrial fibrosis (16.8% ± 0.8% vs 10.9% ± 0.7%, $P < .05$; control 1.6% ± 0.2%), effects comparable to those of candesartan (duration of AF: 3.0 ± 0.2 seconds; activation time 44 ± 2 ms; fibrosis: 9.4% ± 0.6%). Both pioglitazone and candesartan reduced transforming growth factor-β1, tumor necrosis factor-α, and activated extracellular signal-regulated kinase expression similarly, but neither affected p38-kinase or c-Jun N-terminal kinase activation. The effects of combined pioglitazone and candesartan therapy were not significantly different from the effects of pioglitazone or candesartan alone.

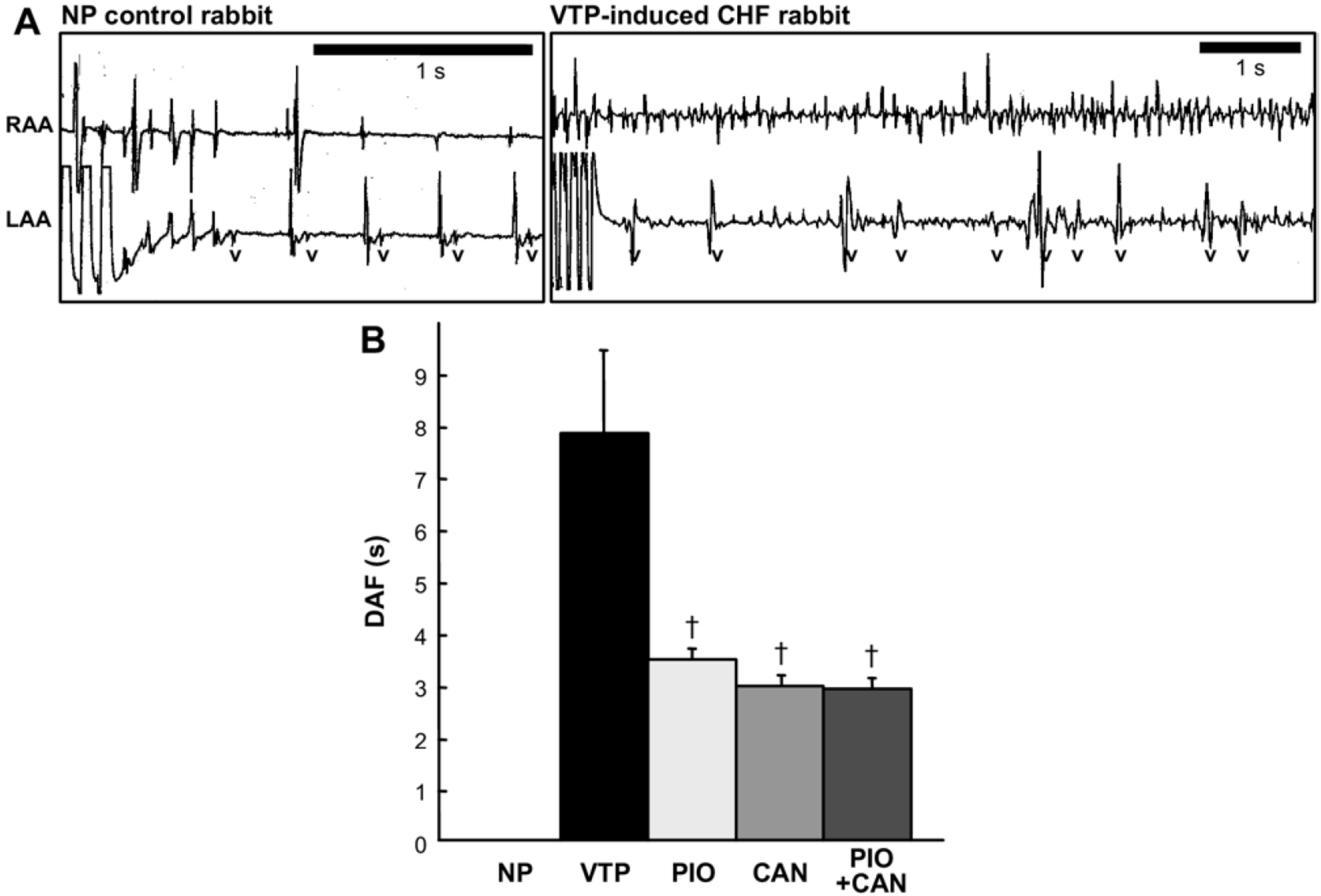
CONCLUSION Pioglitazone can attenuate congestive heart failure-induced atrial structural remodeling and AF promotion, with effects similar to those of candesartan. PPAR-γ may be a potential therapeutic target for human AF.

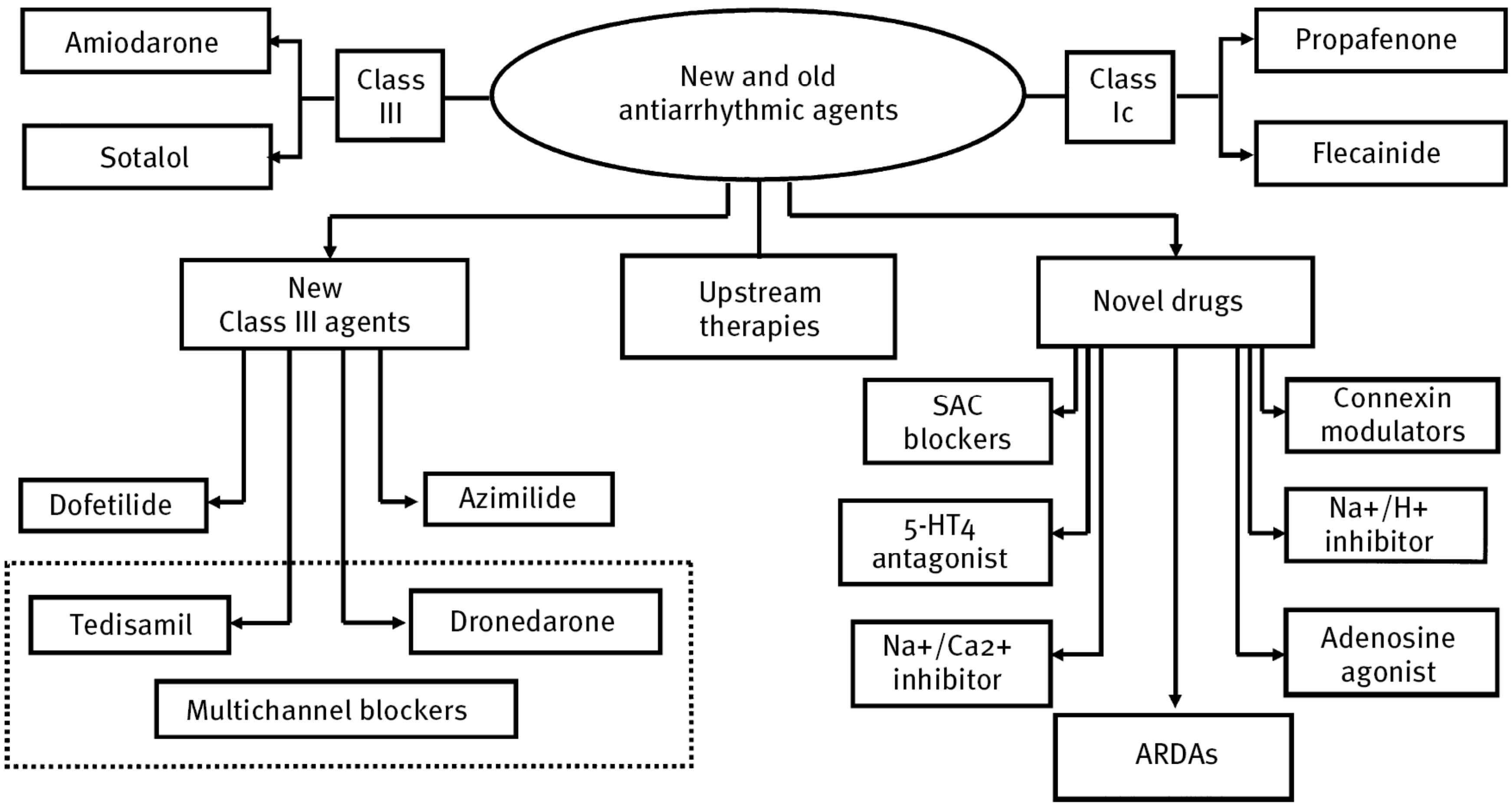
KEYWORDS Arrhythmia; Atrium; Heart failure; Remodeling; Antiarrhythmic agents

(Heart Rhythm 2008;5:451–459)



Control
Failing Heart
1 cm


A
NP control rabbit
VTP-induced CHF rabbit
1 s
1 s
RAA
LAA
B
DAF (s)
0
1
2
3
4
5
6
7
8
9
NP
VTP
PIO
CAN
PIO +CAN
†
†
†



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