Atrial Fibrillation: Upstream Therapies

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Research support: Boston-Scientific, Sanofi-Aventis, Boehringer-Ingelheim, Glaxo-Smith-Kline

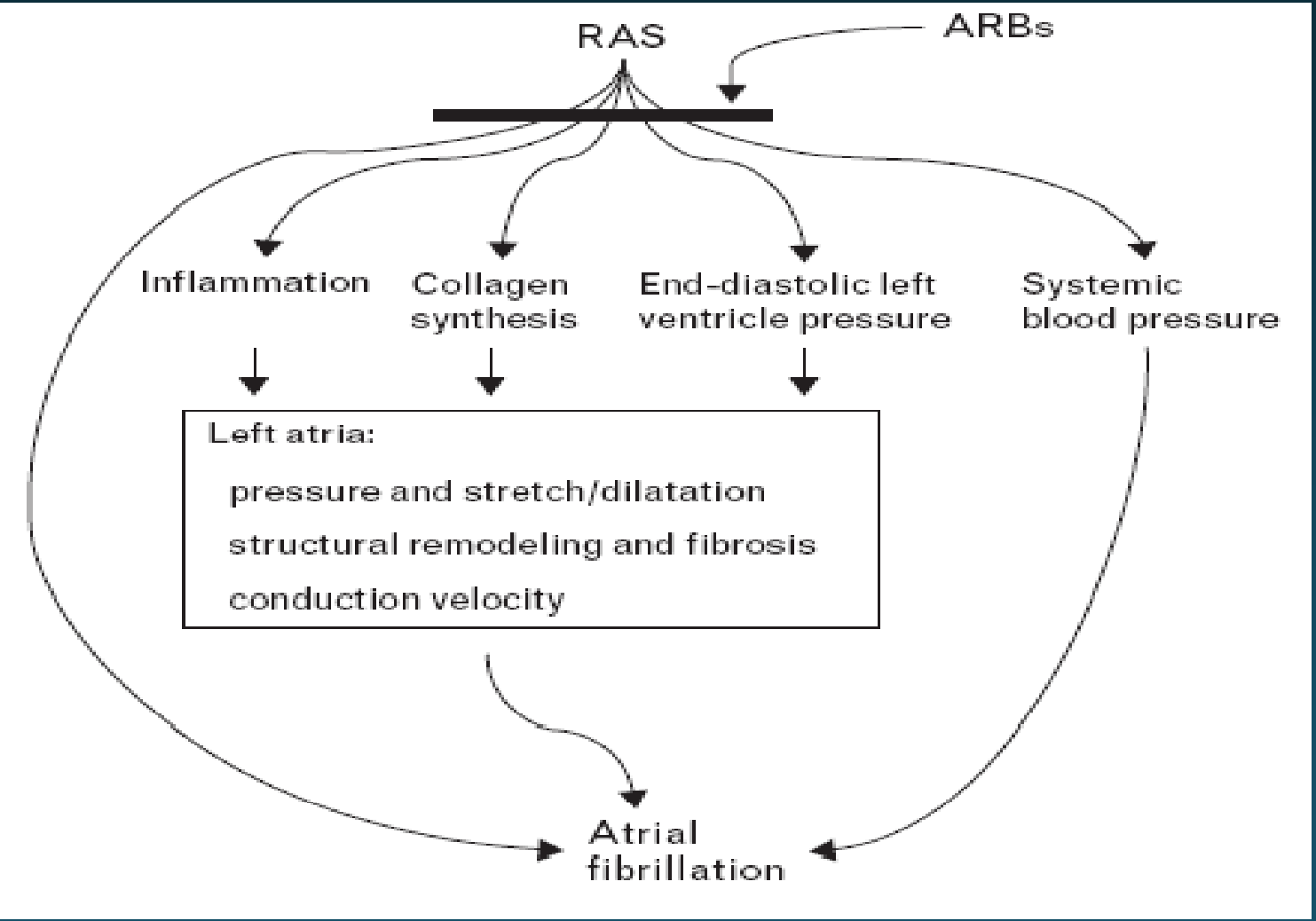
Consultant: Glaxo-Smith-Kline, Medtronic, Boston-Scientific, Pfizer, Xention, Sanofi-Aventis, Biocritique, Novartis, Astellas, Cardiome, Paracor, Gilead, Astra-Zeneca, Boehringer-Ingelheim

Effects of the RAAS on AF

- In human AF, tissue ACE is up-regulated correlating with increased atrial angiotensin II production[1]
- ACE inhibition has been shown to attenuate atrial structural remodeling (interstitial fibrosis) in a canine rapid ventricular pacing model[2] and reduce AF in post-MI LVD patients[3]
- There is an association of RAAS gene polymorphisms in patients with non-familial structural AF[4]
  - Are such patients more likely to benefit from ACEI and ARBs?

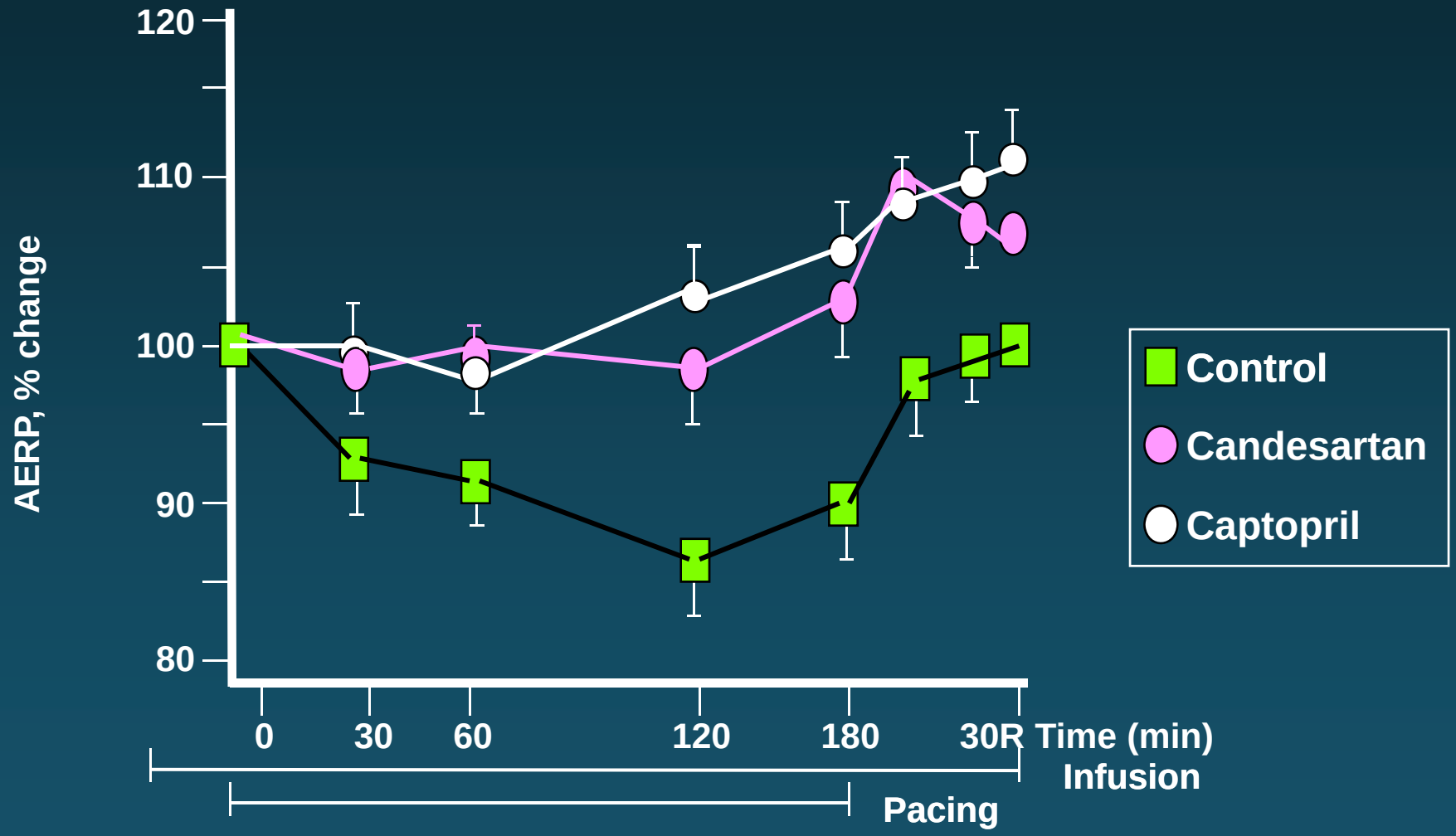
1. *Goette A, et al. J Am Coll Cardiol 2000;35:1669-1677*
2. *Li D, et al. Circulation 1999;100:87-95*
3. *Pedersen et al. Circulation 1999:100:376-380*
4. *Tsai CT, et al. Circulation 2004;109:1640-1646*

Possible Mechanisms of ARBs in Preventing AF



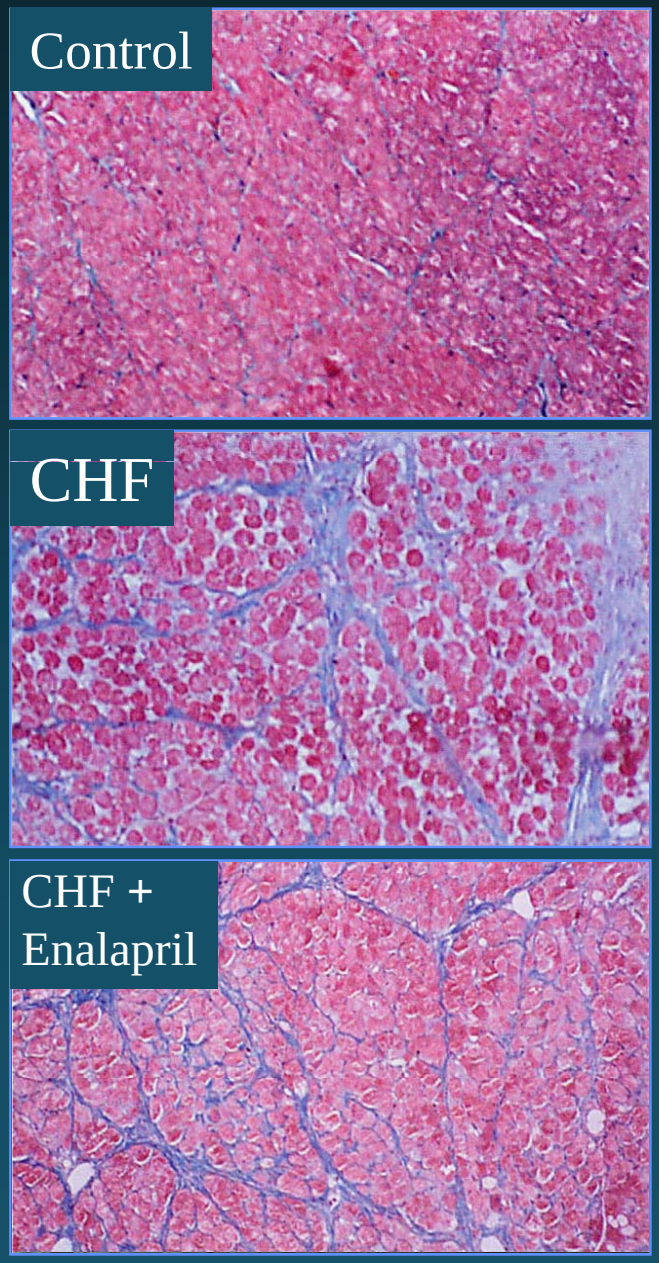
Aksnes TA, et al J Hyperten 2007;25:15-23

Angiotensin II Antagonists Attenuate Electrical Remodeling in AF

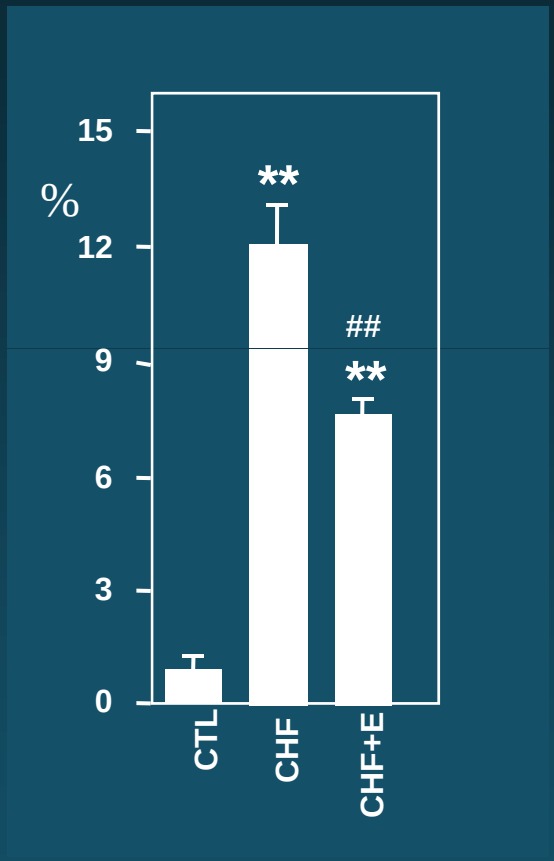


Nakashima H, et al. Circulation. 2000;101:2612-2617

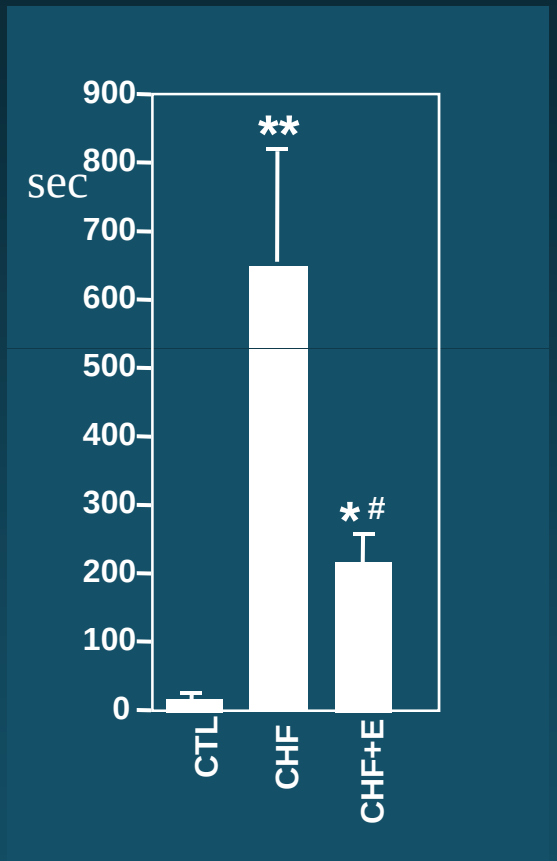
ACEI: Prevention of Structural Remodeling



Fibrosis



AF Duration



In another study, candesartan decreased duration of AF (4-5 weeks) ($p<.05$) and % atrial fibrosis in atrial paced dog model ($p<.001$)

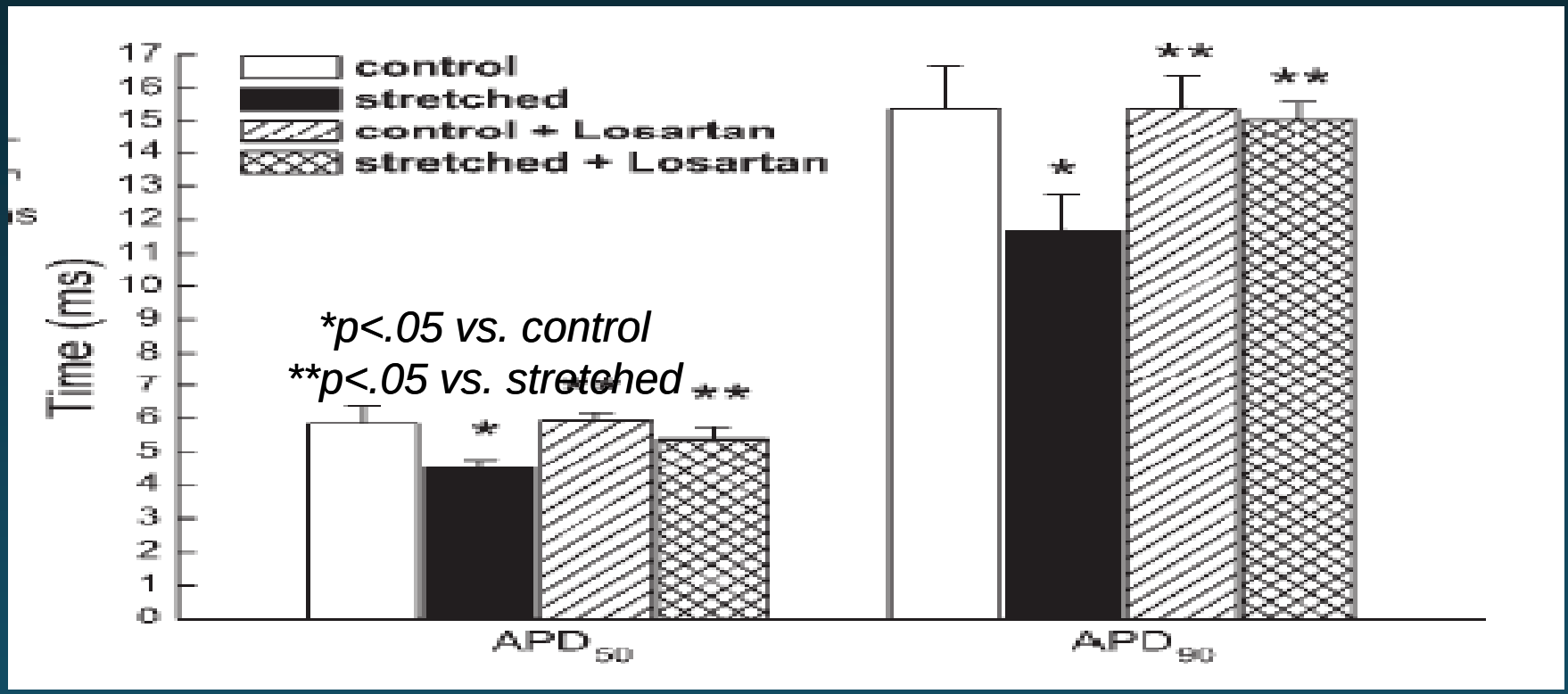
Li D, et al. Circulation 1999;100:87-95
Kumagai K, et al. JACC 2003;41:2197-2204

Does the RAAS Have Direct Electrophysiologic Effects?

- In a canine RVP model, AF duration increases compared to controls both before and following recovery of pacing-induced atrial electrical remodeling
  - Tissue fibrosis creates a substrate for increased arrhythmia persistence independent of action potential duration
- Although enalapril attenuated the development of interstitial fibrosis, it had no impact on the AERP, conduction velocity or wavelength of conduction
- Angiotensin II may contribute to the development of atrial fibrosis, but with minimal electrophysiologic effects

Shi Y, et al. Cardiovasc Res 2002;54:456-461
Ram R, Van Wagoner D. JCVEP 2006;17:42-543

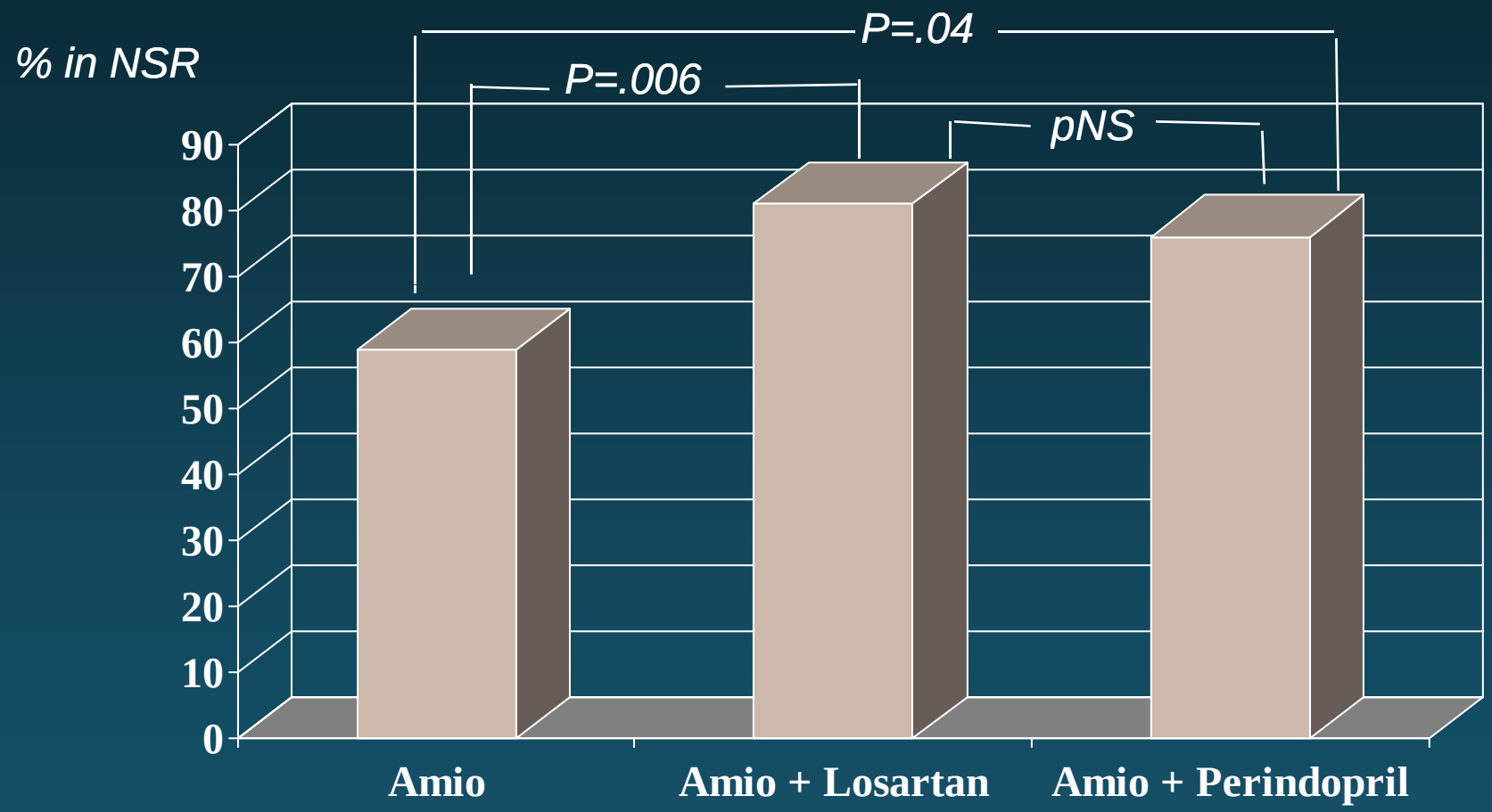
Losartan Prevents Stretch-Induced Atrial Remodeling *In Cultured Atrial Neonatal Myocytes*



- *Losartan prevented stretch -induced increases in the protein to DNA ratio, ANP mRNA expression*
- *Attenuated stretch-induced expression of IK1,IKur and Ito*
- *Thus preventing the stretch-induced abbreviation of atrial APD*

Saygili E, et al. Am J Physiol Heart Circ Physiol 2007;292:H2898-H2995

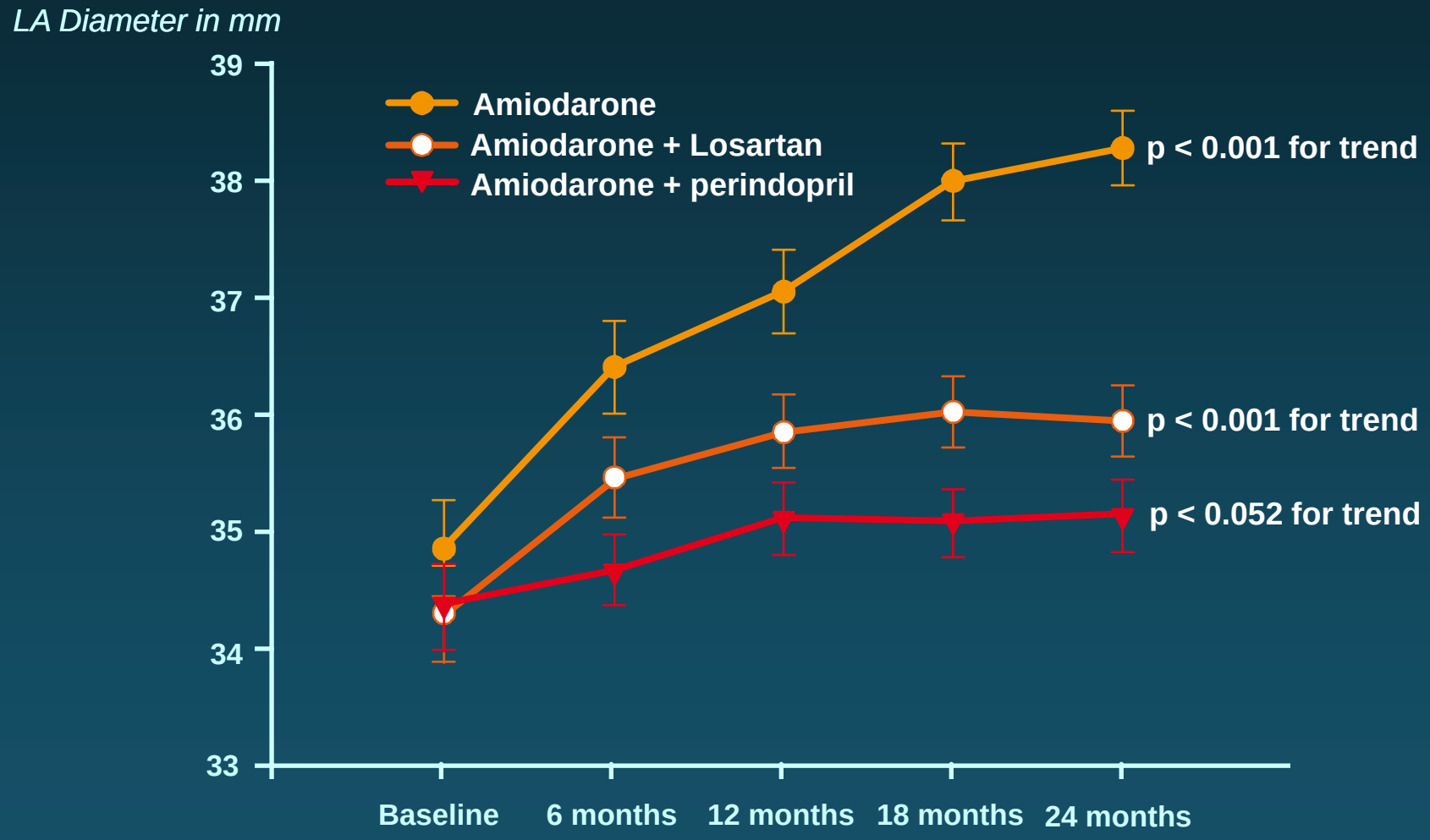
Amiodarone + Losartan or Perindopril Maintains NSR Post-CV Better Than Amiodarone Alone



59 pts in each group

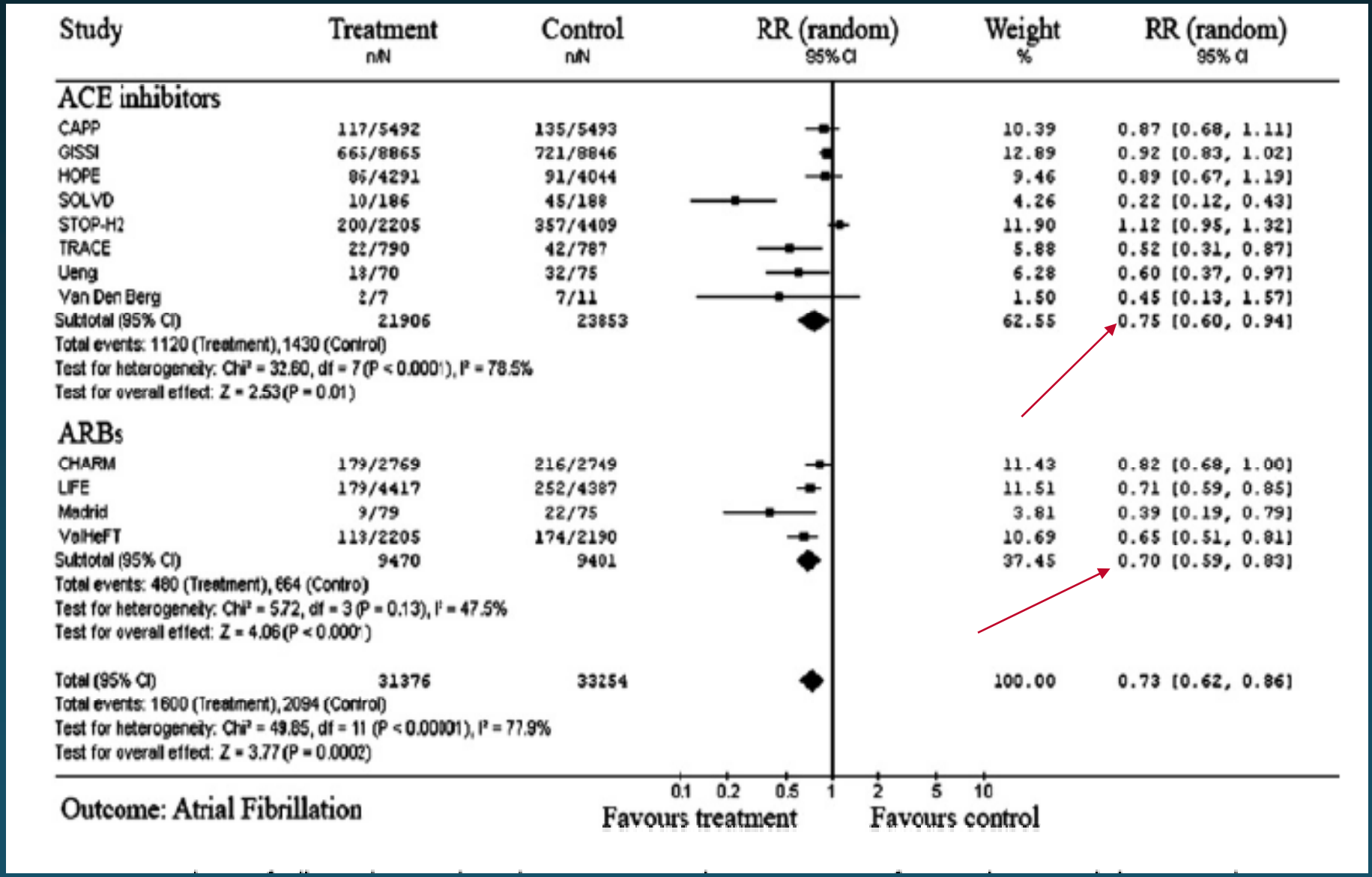
Yin Y, et al. Eur Heart J 2006;27:1841-1846

ACEI and ARB Attenuate Time Dependent Increase in LA Diameter In AF



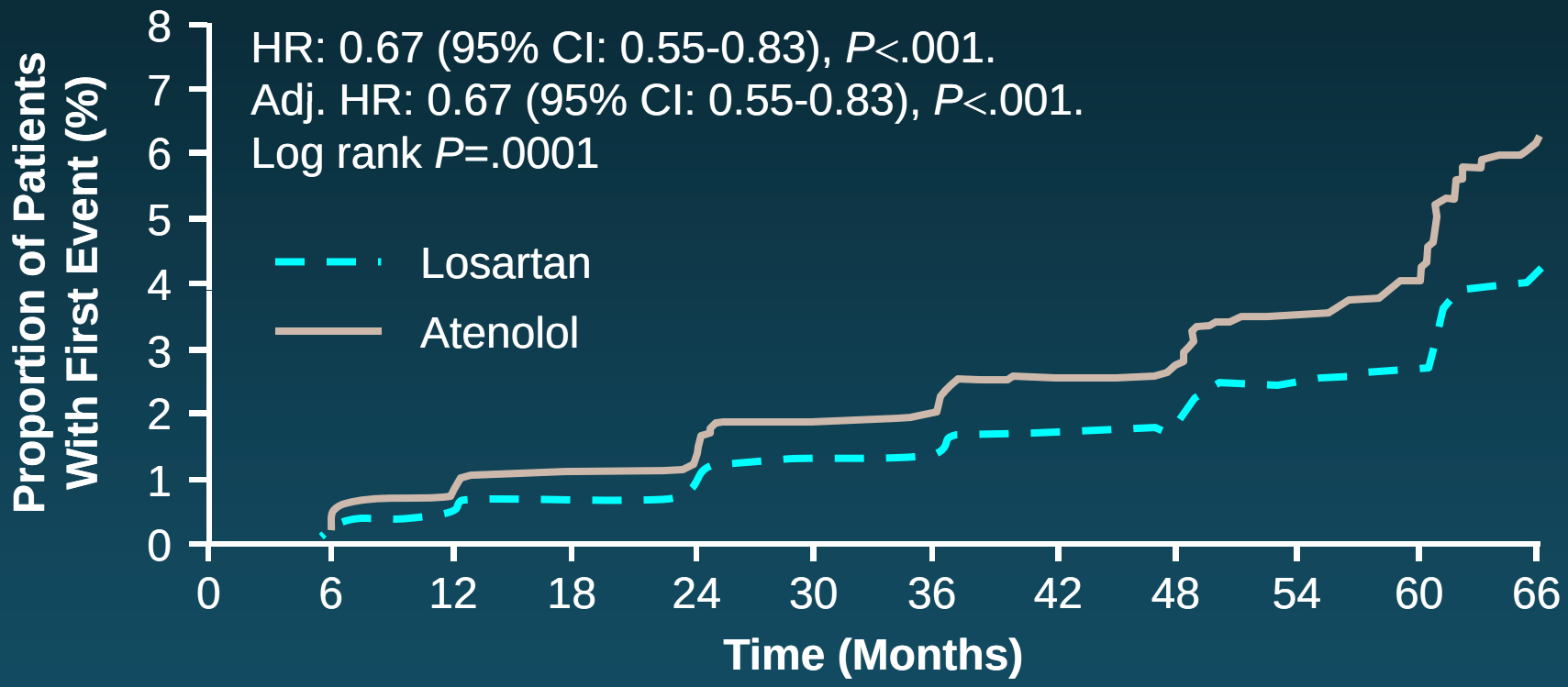
Yin Y, et al. Eur Heart J 2006;27:1841.

AF Prevention: ARBs Vs. ACEI?



Salehian et al. Am Heart J 2007;154:448-453

Losartan Is Superior to Atenolol in Suppressing AF in the LIFE Study



- Losartan reduced AF compared to atenolol (HR 0.67; *P*<.001) in 342 hypertensive patients with LVH and AF
- Losartan also reduced stroke (HR 0.49; CI 0.29-0.86; *P*=.01)

Wachtell et al. J Am Coll Cardiol. 2005;45:712-719

Which Patient Groups Does RAAS Blockade Prevent AF?

- Hypertension ± LVH
  - In LIFE, losartan reduced AF compared to atenolol (HR 0.67; *P*<.001) in 342 hypertensive patients with LVH and AF *(Wachtell et al. J Am Coll Cardiol. 2005;45: 712-719)*
- Diastolic Dysfunction
  - In CHARM, HR =0.894 (0.618-1.295) *(Ducharme et al. Am Heart J. 2006;152:86-92)*
- Systolic Dysfunction
  - In TRACE, 5.3% of placebo vs. 2.8% of trandolopril group developed AF (p<.05) *(Pedersen et al. Circulation 1999:100:376-380)*
  - In SOLVD, 5.4% enalapril vs. 24 placebo developed AF (p<.0001) *(Vermes et al. Circ 2003; 107:2926-2931)*
  - In VAL-HeFT, Valsartan added to ACEI (93%) reduced AF by 35% (7.86% to 5.27%) *(Maggioni AP, et al. Circ 2003;24:504)*
- Diabetes
  - In hypertensive/diabetic patients, valsartan-amlodipine lowered 1 year AF to 14% from 41% with atenolol-amlodipine *(Fogari R, et al. Circulation 2006;114: II)-789)*
- Post-AF ablation
  - No benefit *(Richter et al. Am Heart J 2007;153:113-119)*
- All patients
  - No benefit in HOPE if LVEF ≥ 40% with only a 2% development of AF overall (HR 0.92, pNS) (Salehian et al. Am Heart J 2007;154:448-453)

Ongoing Trials to Assess ARBs in AF

- **ACTIVE-I** (Irbesartan vs. placebo) - 9018 patients
  - Primary outcome: stroke, MI, vascular death + CHF hospitalization
- **ANTIPAF** (Olmesartan vs. placebo in PAF)
- **CAPRAF** (Candesartan vs. placebo)
- **DRAFT** (Diovan to Reduce post-CV recurrence of AF Trial)
- **GISSI-AF** (Valsartan vs. placebo) – 1442 patients
  - Primary endpoint: Time to 1st AF; total # AF episodes
- **I-PACE** (Irbesartan vs. placebo)
- **ON TARGET/TRANSCEND** (Telmisartan vs. ramipril vs telmisartan + ramipril vs. placebo)

Some of the above studies will tell us if ARBs will prevent AF on top of ACEI

Connolly S, et al. Am Heart J 2006;151:1187-1193
Disertori m, et al. J Cardiovasc Med 2006;7:29-38
Teo K, et al. Am Heart j 2004;148:52-61
Aksnes TA, et al J Hyperten 2007;25:15-23

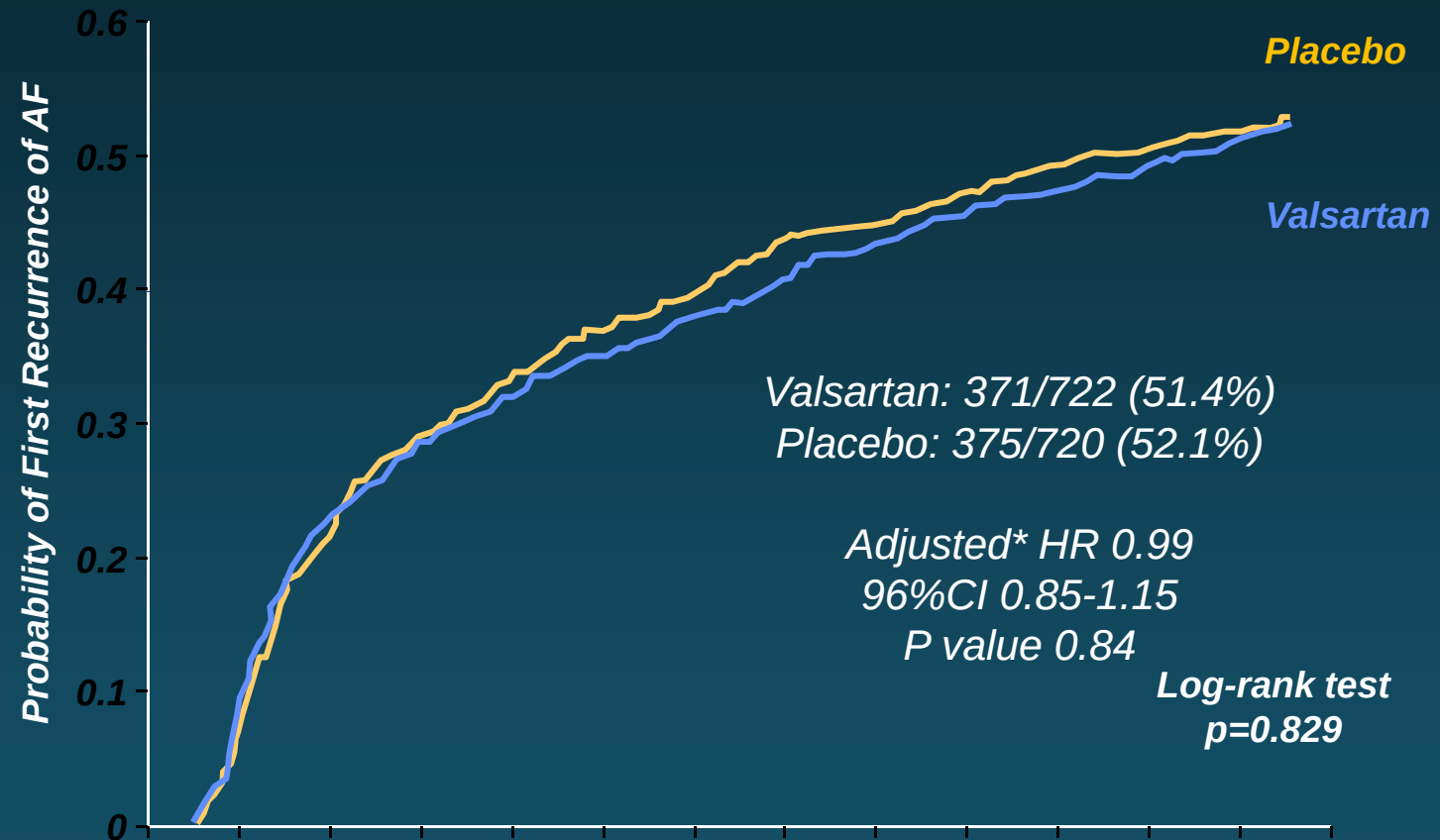
Preliminary Data ACTIVE-I

- 9018 patients (Irbesartan vs. placebo)
- Primary outcome: stroke, MI, vascular death + CHF hospitalization
- 65.2% permanent AF, 20.1 % PAF, 14.5% persistent AF
- 60.4% already on ACEI
- Largest trial of BP lowering in AF
  - 88.7% hypertensive
  - 4-7 mm Hg decrease in SBP over course of study
- Follow-up complete 5/08
  - Mean follow-up 3 years

Connolly S. Venice 10/07

GISSI AF

Study Results: Probability of First Recurrence of AF



Patients at Risk													
Valsartan	722	586	524	491	465	445	423	398	383	368	356	343	260
Placebo	720	589	520	484	454	435	407	387	377	359	344	334	254

Maggioni A. AHA 2008 Scientific Sessions, Abstract Oral Session 4096, Nov. 11, 2008

Effects of Aldosterone Antagonists on AF

- Serum aldosterone levels have been reported to be elevated in AF patients with levels returning to normal with restoration of sinus rhythm[1]
- In a rat model of heart failure following MI, spironolactone decreased atrial fibrosis and atrial P-wave duration but ACEI and beta-blockers did not[2]
- In the RVP heart model, eplerenone further prolonged right atrial appendage and left posterior AERP but no effect in Bachmann's bundle
  - No effect of Angiotensin II blockade[3]

1. *Goette A et al. Am J Cardiol 2001;88:906-909*
2. *Milliez P, et al. Eur Heart J 2005;26:2193-2199*
3. *Schroff SC, et al. JCVEP 2006;17:534-541*

Statins and AF

- In a tachycardia induced AF dog model,simvastatin suppressed RAP remodeling effects (shortening of atrial ERP) and induced AF duration (>1000 sec with placebo vs 40 sec with statin)*
- Tachy-pacing downregulated L-type calcium channel alpha subunit expression was greatly attenuated by simvastatin.
- Retrospective meta-analysis have suggested a beneficial effect in AF in man
- Statin therapy has also been found to reduce the risk for first ventricular arrhythmia in pts with CAD and an ICD.**

* *Shiroshita-Takeshita et al. Circulation 2004; 110:2313-19*

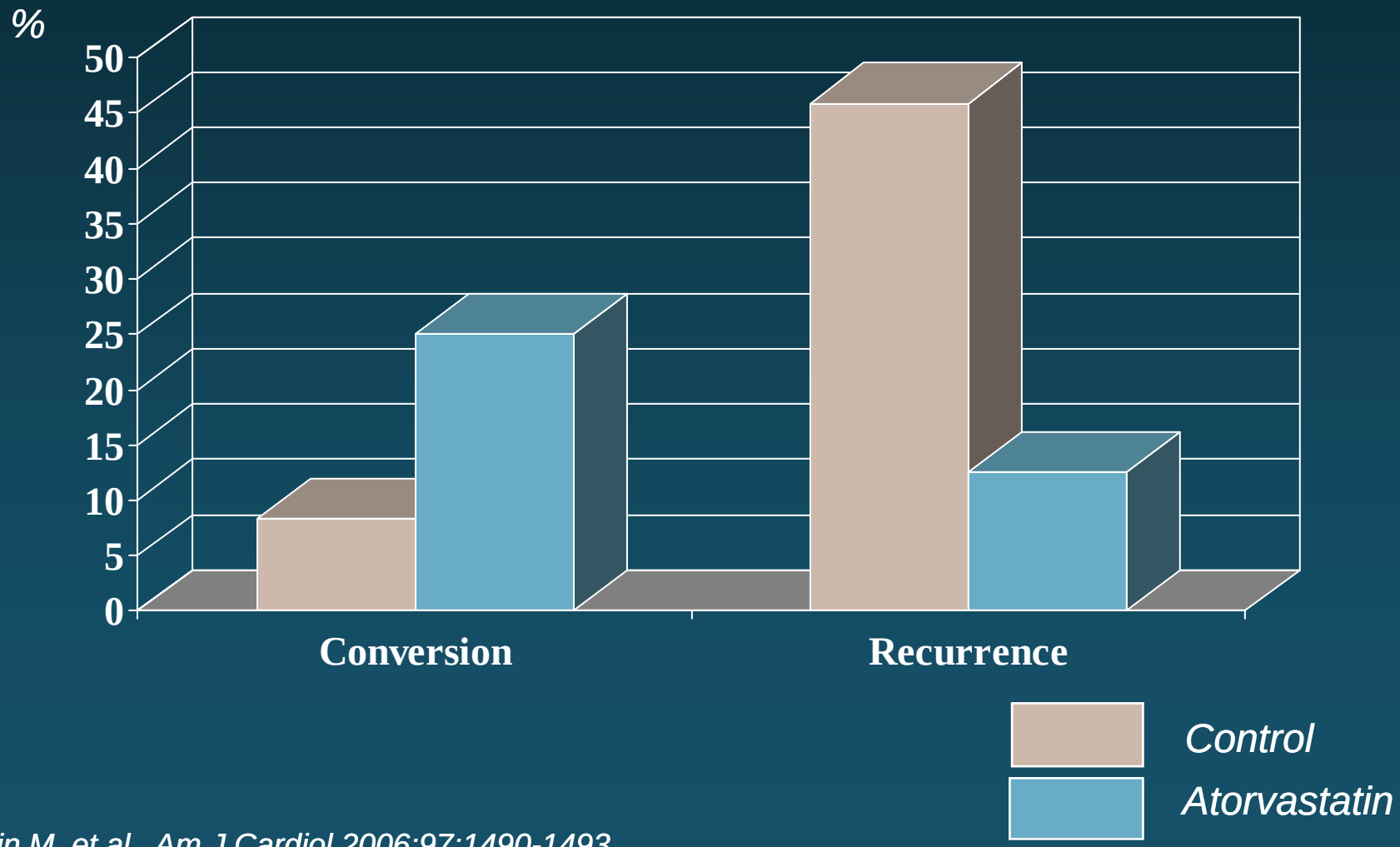
** *Chiu et al. Am J Cardiol 2005; 95:490-91*

Statins May Reduce AF in CAD

- 449 pts (age 40-87 yrs) with chronic stable CAD without AF were followed prospectively for an average of 5 yrs in a large out-patient cardiology practice
- The association between statin use and the development of AF was evaluated
- 52 pts (12%) developed AF
- Statins, used by 59% of the subjects, reduced the probability of developing AF (HR 0.49; CI 0.28-0.83; $p<0.05$)
- This remained significant after adjustment for age, HTN, LVEF, CHF, ACU, baseline TC, change in TC (HR 0.37; CI 0.18-0.76)

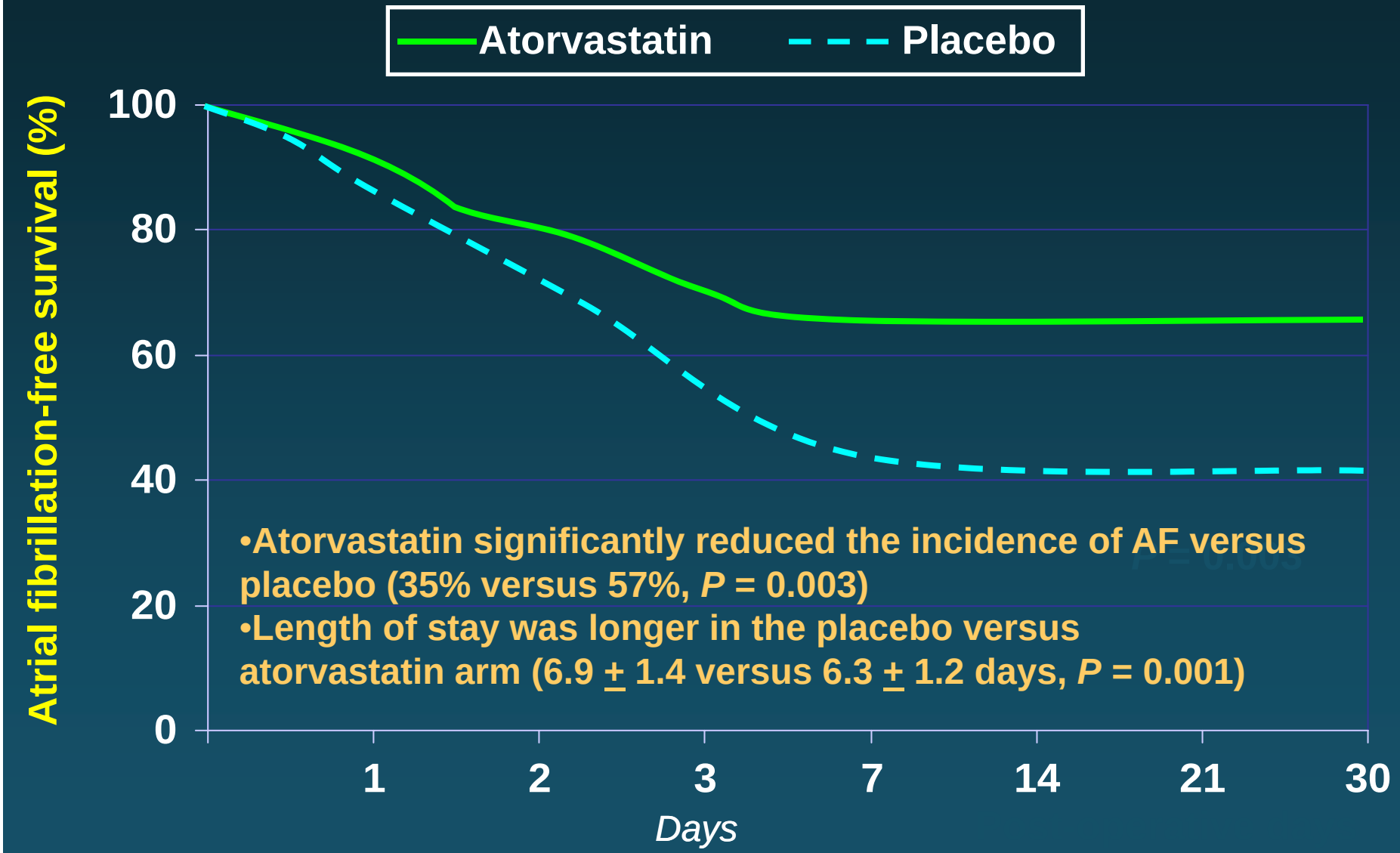
Young-Xu et al. Am J Cardiol 2003; 92:1379-1383

Effect of Atorvastatin 10 mg/day in Persistent AF



Ozaydin M, et al. Am J Cardiol 2006:97:1490-1493

ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After Cardiac Surgery): AF Free Survival



Patti, G. et al., Circulation 2006;114:1455-1461

Statins: AF Recurrence After Cardioversion

- 62 patients with lone, persistent AF underwent successful DC cardioversion.
- 10/62 were on statin therapy for hyperlipidemia (starting pre-CV). They were also older but had no difference in SHD or AF therapy.
- In a follow up of 44 months on average the use of statins in a retrospective analysis was found to significantly decrease the number with recurrent AF:
  - 40% vs 82%, p=0.007

Siu et al. Am J Cardiol 2003; 92:1343

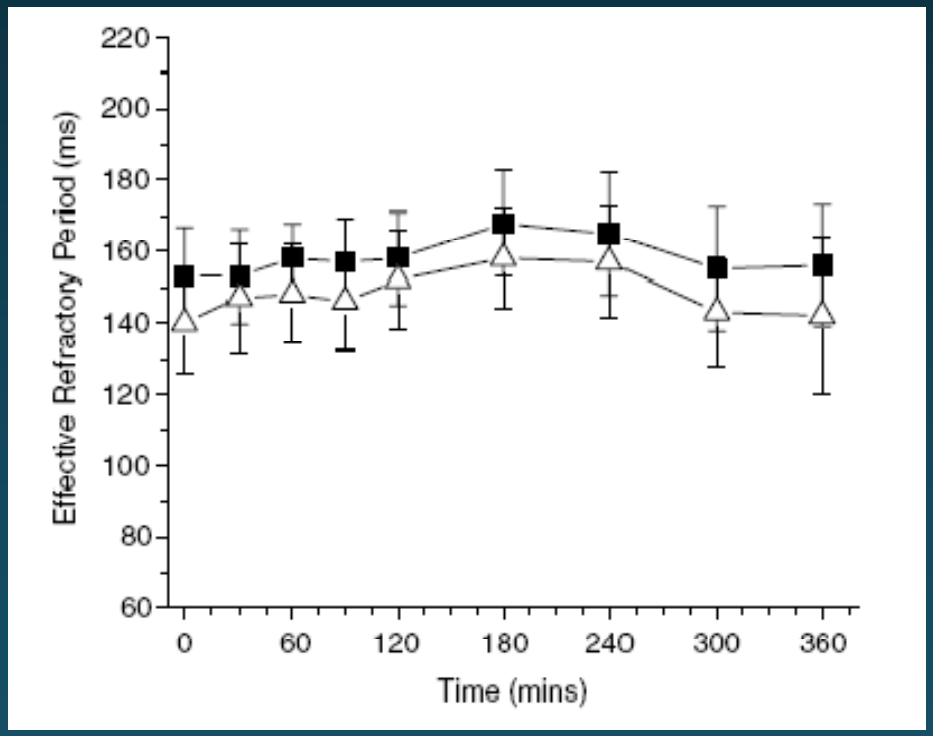
Summary of Basic EP Effects of Fish Oil

- EPA prolongs the QTc in the Langendorff rabbit model
- Fish oils block L-type calcium channels
- EPA and DHA suppress Na channels in cardiomyocytes and DHA slows Na channel dependent longitudinal conduction in the perfused heart model
- DHA and EPA raise the threshold to elicit an extrasystole
- In humans, fish oils slow heart rate, increase the PR and decrease the likelihood of a prolonged QTc
- Ninio et al noted that feeding rabbits 5% tuna oil for 12 weeks significantly increased the atrial pressure necessary to induce sustained AF compared to controls
  - The decline in AERP produced by increasing atrial pressure was less attenuated in the tuna oil group
- Mozzaferian et al showed that consumption of tuna or other broiled/baked fish lowered AF by 31% if intake was $\geq$ 5 times per week compared to < 1 per month (p=.004)

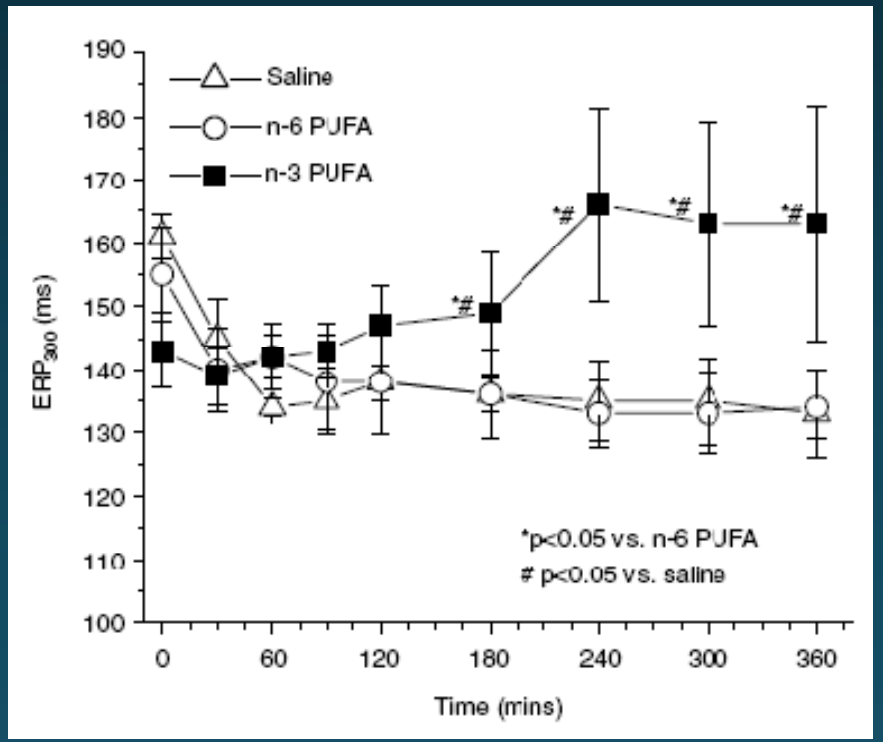
Dhein, et. al. Arch Phamacol 2005;371:202-211
Ninio DM, et al. JCVEP 2005;16:1189-1194
Xiao, et. al. Proc Natl Acad Sci 1997;94:4182-4187
Mozzaferian D, et al. Circulation 2004;110:368-373

N-3 PUFAs Prevent Acute Electrical Remodeling in Acute Atrial Tachypacing Canine Model

NSR

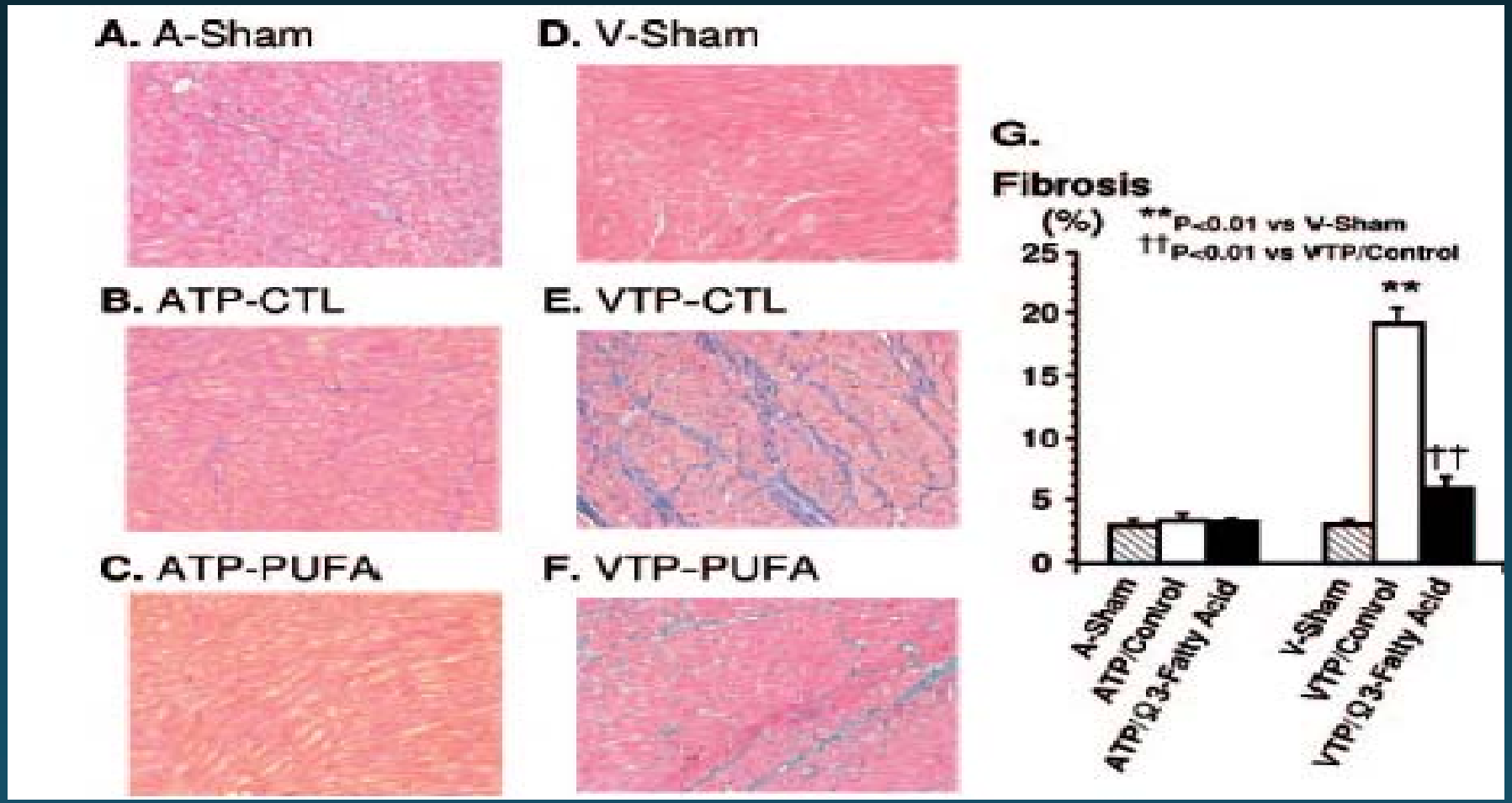


Atrial Pacing



Da Cunha DNQ, et al. Br J Pharmacol 2007;150:281-285

Omega 3-PUFA Prevent AF Associated with Heart Failure But Not Atrial Tachycardia 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."

Sakabe M, et al. Circulation 2007;116:2101-2109

Reduced Incidence of Vagally Induced AF and Expression of Connexins by n-3-PUFAs in Dogs

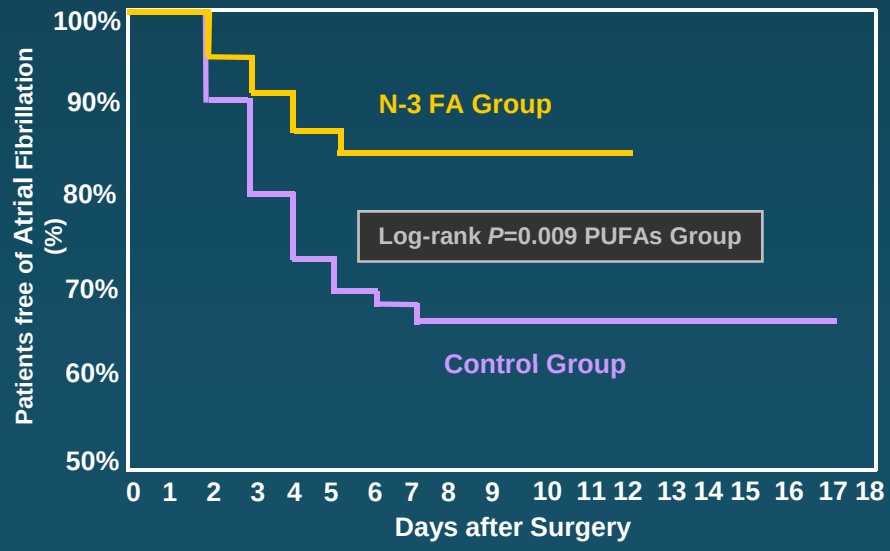
- Atrial tissue n-3 PUFA levels increased in oral treatment dogs ($p<.0001$)
- Incidence of AF inducibility decreased from 48.9% in controls to 10.5% in treated dogs using the extrastimulus technique ($p<.003$)
- Both Cx40 and Cx43 levels (primary components of the atrial GAP junctions) were lower in treated dogs ($p=.02$)
- Conclusion: Oral Rx with fish oils increased atrial n-3 PUFA levels and reduced vulnerability to AF induction. Modulation of cardiac connexin expression by n-3 PUFAs may contribute to the antiarrhythmic effect of fish oils

Sarrazin JF, et al. J Am Coll Cardiol 2007;50:1505-1512

Omega-3 for Prevention of Atrial Fibrillation Post-CABG

- 160 patients awaiting CABG
- Randomized to usual care or EPA+DHA (1.7 g/d)
- From 5 days pre-surgery through hospitalization
- Endpoint was AF detected by ECG during hospitalization. AF >5 min or requiring intervention

	Control (n=81)	N-3 FA (n=79)	*P*
Post CABG AF	33%	15%	0.013
Hours of AF	24	16	0.12
Length of Stay	8.2 days	7.3 days	0.017



Calo L et al. J Am Coll Cardiol. 2005;45:1723-1728

Omega-3 for Prevention of Atrial Fibrillation Post-CABG

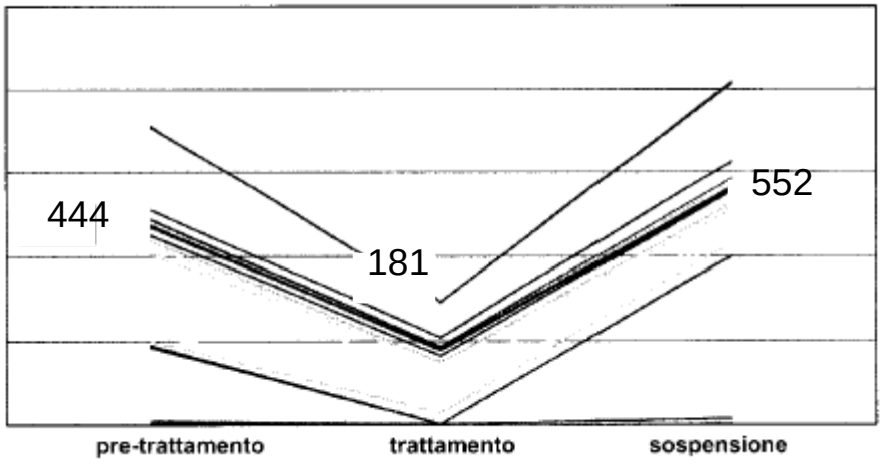
In this trial, the use of PUFAs during hospitalization in patients undergoing coronary artery bypass graft surgery (CABG) significantly reduced the incidence of postoperative AF (18.1% absolute risk reduction, 54.4% relative risk reduction) and was associated with a shorter hospital stay. Except for a single case of allergic response, no significant adverse reactions were observed. A possible role of inflammation in the pathophysiology of postoperative AF is suggested, as the anti-inflammatory activity of PUFAs is well-documented.

The graph represents the Kaplan-Meier actuarial estimates of occurrence of postoperative atrial fibrillation in the study group. Atrial fibrillation occurred a mean of 3.2 to 1.1 days after surgery in patients assigned to PUFAs and 3.4 to 1.3 days after surgery in controls (P=0.645); AF was diagnosed during continuous electocardiographic monitoring in the intensive or intermediate care units in 11 of 12 (91.6%) patients in the PUFA group and in 25 of 27 (92.5%) patients in the control group (P=0.919 by chi-square). The remaining cases of AF (one in the PUFA group and two in the control group) were detected by electrocardiography after the occurrence of symptoms. The mean duration of AF was of 15.5 to 15.8 h in patients assigned to PUFA and 23.9 to 15.3 h in controls (P=0.125). Symptoms attributable to AF were reported by 10 of 12 patients (83.3%) in the PUFA group and by 24 of 27 (88.8%) controls (P=0.634 by chi-square); AF was initially treated by amiodarone in 9 of 12 patients assigned to PUFA and in 22 of 27 controls (P=0.643 by chi-square). Spontaneous conversion to sinus rhythm without any intervention occurred in two patients receiving PUFAs and in three controls (P=0.631 by Fisher exact test). Electrical cardioversion was performed on one patient in the PUFA group and in two controls (P =0.920 by Fisher exact test). Two of 12 (16.6%) patients in the PUFA group had more than one episode of AF during hospitalization (two episodes and three episodes, respectively), while 5 of 27 (18.5%) patients in the control group had more than one episode of AF (three patients had two episodes and two patients had three episodes) (P=0.889 by Fisher exact test).

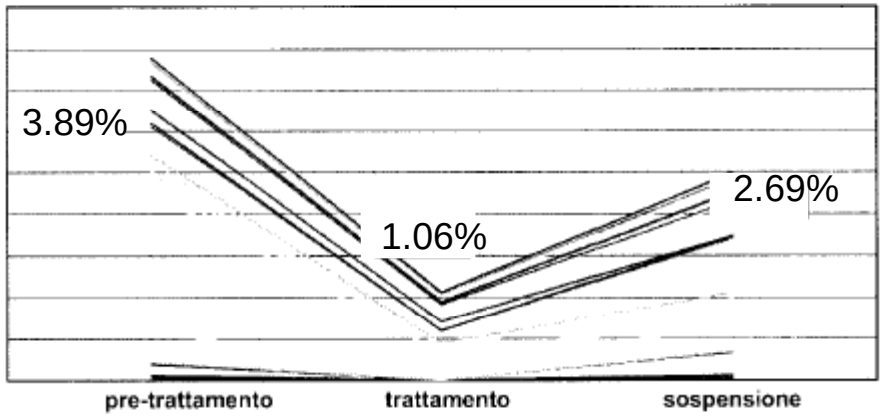
Reference:

Calo L et al. J Am Coll Cardiol. 2005;45:1723-1728.

Reduction in AF in Patients with Dual Chamber Pacemakers I



Number of atrial tachyarrhythmia episodes



Atrial tachyarrhythmia burdern

- N=46 (6 not analyzed) with dual chamber PM
- Design—OLX, received 1gm N-3 or nothing for treatment periods of 4 months
- Results
  - 59% reduction in AFib episodes (P=0.037); 67% reduction in AFib burden (P=0.029)
  - P=0.065 and 0.003 for increase in AFib episodes and AFib burden following cessation of therapy
  - For patients with sustained AFib there were similar significant reductions in AFib episodes and AFib burden.

Biscione, et. al, Ital Heart J Suppl Vol 6 Gennaio 2005 (53-59)

Benefit of Fish Oils in Suppressing Atrial Fibrillation: Possible Mechanisms

- Direct electrophysiologic effects
- Anti-inflammatory effects
- Slow progression of CAD
- Structural
- Metabolic
- Autonomic

Reiffel JA, McDonald A. Am J Cardiol 2006;98:50i-60i

OM8

- Randomized, double blind, placebo controlled, parallel-group trial to assess the efficacy and safety of Lovaza for the prevention of recurrent, symptomatic AF
- Primary Objective: assess the effect of Lovaza® on time to the first symptomatic recurrence of AF
  - Time will be measured as event-free days from the end of the loading period (Week 1)
- Inclusion criteria: ≥18 years old, electrocardiographic evidence of symptomatic paroxysmal AF, no current anti-arrhythmic therapy.
  - Rate control and/or anticoagulation therapy or no therapy is permitted.
  - Approximately 550 subjects (275 per treatment group) will be recruited

What Is The Mechanism Of Down Stream Therapies in Preventing AF?

- **ACEI, ARB** – Angiotensin II blockade; decreasing stretch activated channels; slowing progression of atrial remodeling
- **Statins** – Anti-inflammatory; decrease lipids
- **PUFA** – Anti-inflammatory; decreasing triglycerides; direct channel EP effects

Conclusion: Upstream Drugs For AF

- Encouraging data for a number of new concepts
- Proof of efficacy/safety will come from well-done, adequately powered, controlled, randomized trials
  - Which patient groups will benefit?
- Added benefits of beta-blockers, ACEI, ARB, statins, Omega-3 fish oil will have to be considered as part of any new drug's efficacy in specific patient populations
- Future possibility of drug combinations with antiarrhythmic agents