3rd Atrial Fibrillation Worldwide Internet Symposium

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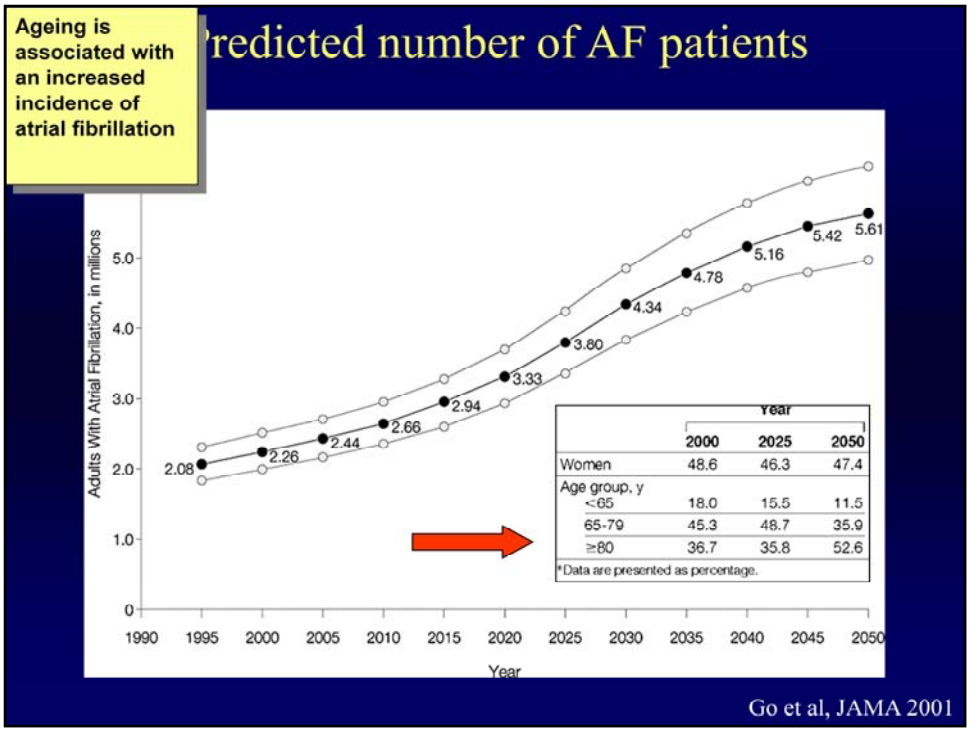
ACE inhibitors and AF

F. Lombardi.

Cardiologia, Dipartimento di Medicina, Chirurgia e Odontoiatria, Osp. San Paolo, University of Milan, Italy.

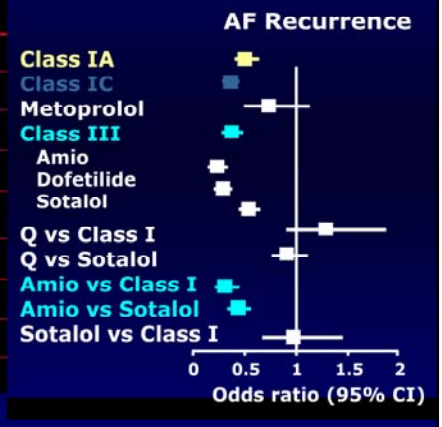


Ageing is associated

The limited effects of traditional anti-arrhythmic drugs is illustrated

for Prevention of AF after DCC
Systematic Review of RCTs

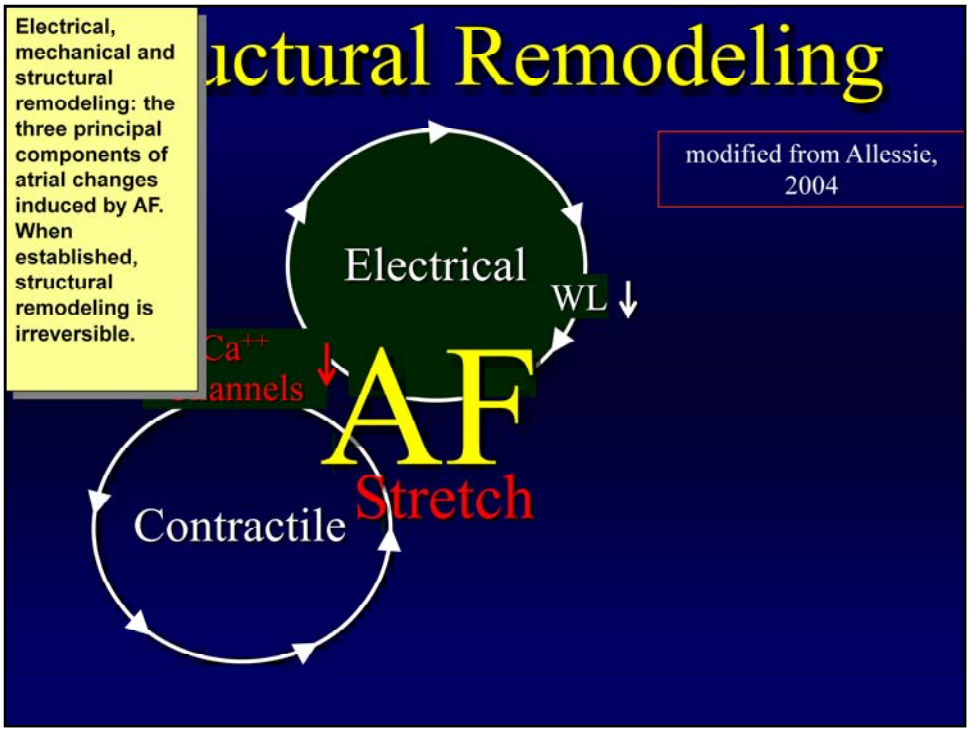
ded into analysis	
Total	44
No. of patients	11,322
Placebo controlled	25
Active comparator	14
Persistent AF	38 (60% pts)
PAF/recent onset	6
EF > 50%	41
Lone AF	1
Follow-up	1 year

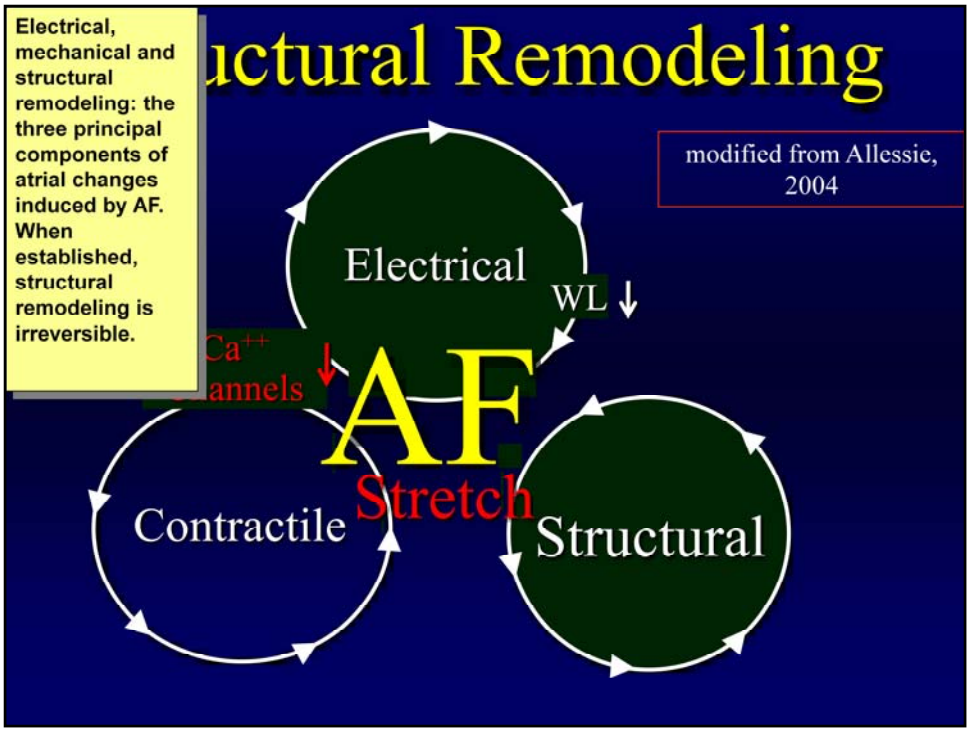


Lafuente-Lafuente C, et al. *Arch Intern Med.* 2006;166:719-728.

The limited efficacy of anti-arrhythmic drugs and a better knowledge of the mechanisms responsible for atrial remodeling have determined a new interest for the pro-arrhythmic role of renin-angiotensin-aldosteron system ad for a possible anti-arrhythmic efficacy of ACE inhibitors.

In the following slides experimental and clinical evidence supporting this hypothesis will be presented.


Electrical, mechanical and structural remodeling: the three principal components of atrial changes induced by AF. When established, structural remodeling is irreversible.
uctural Remodeling
modified from Allessie, 2004
Electrical
WL
Ca++
annels
AF
Stretch
Contractile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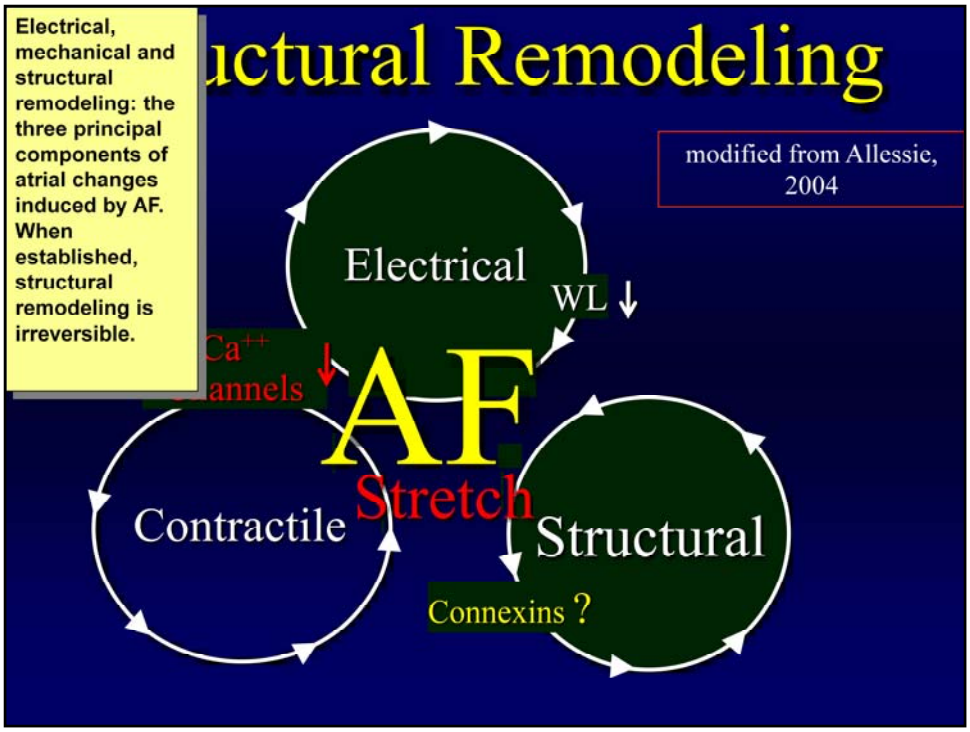
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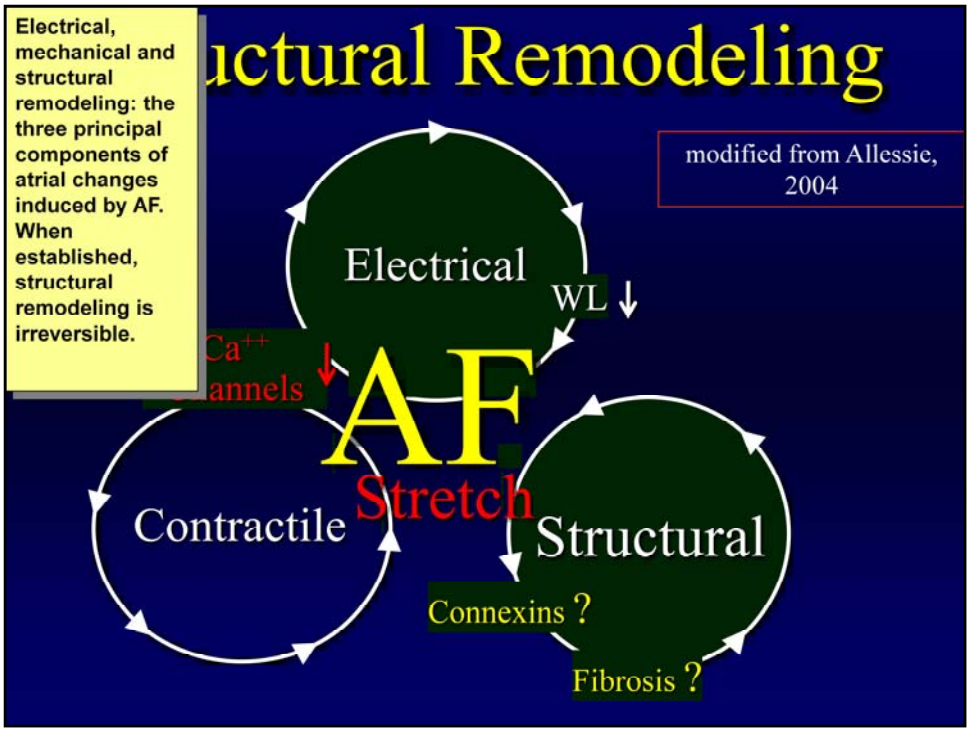
Structural
Connexins ?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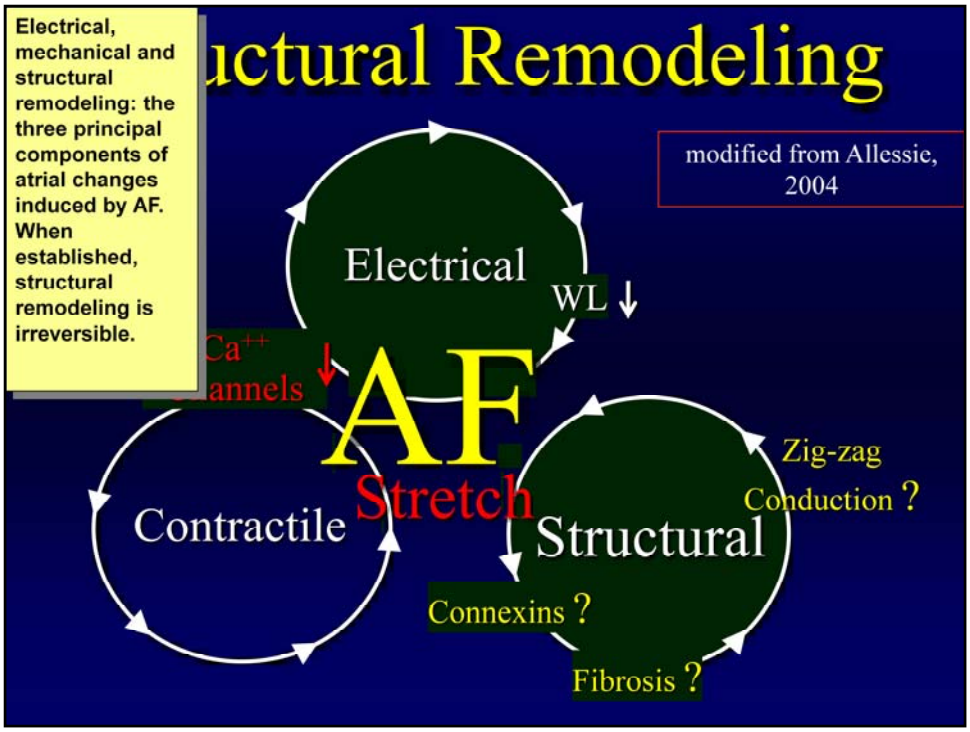
Fibrosis ?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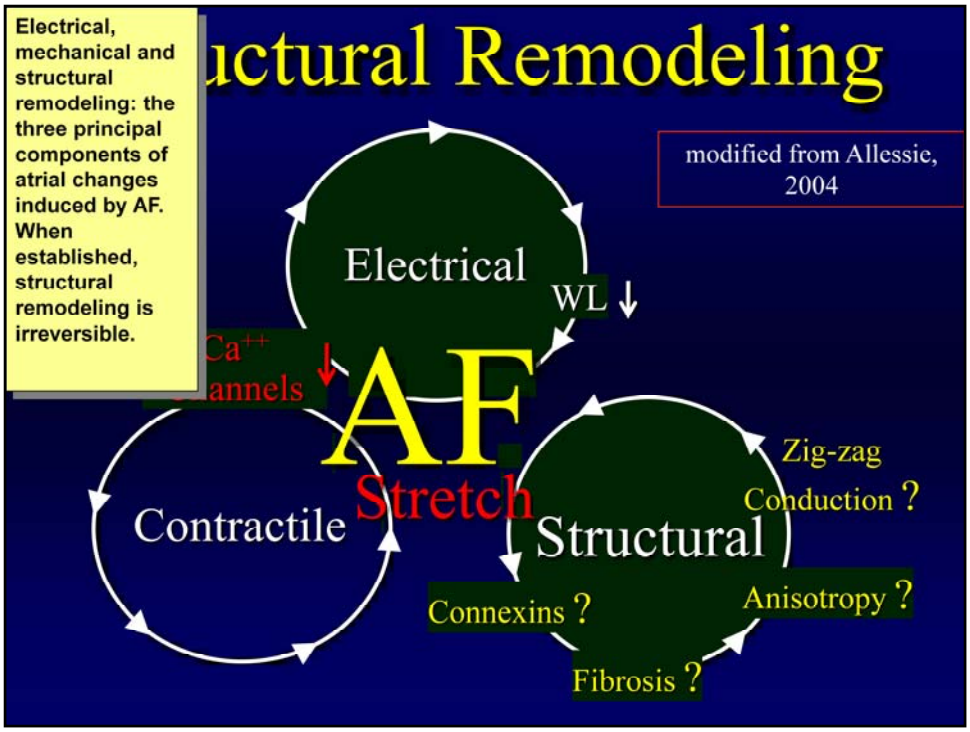
Electrical, mechanical and structural remodeling: the three principal components of atrial changes induced by AF. When established, structural remodeling is irreversible.
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Stretch
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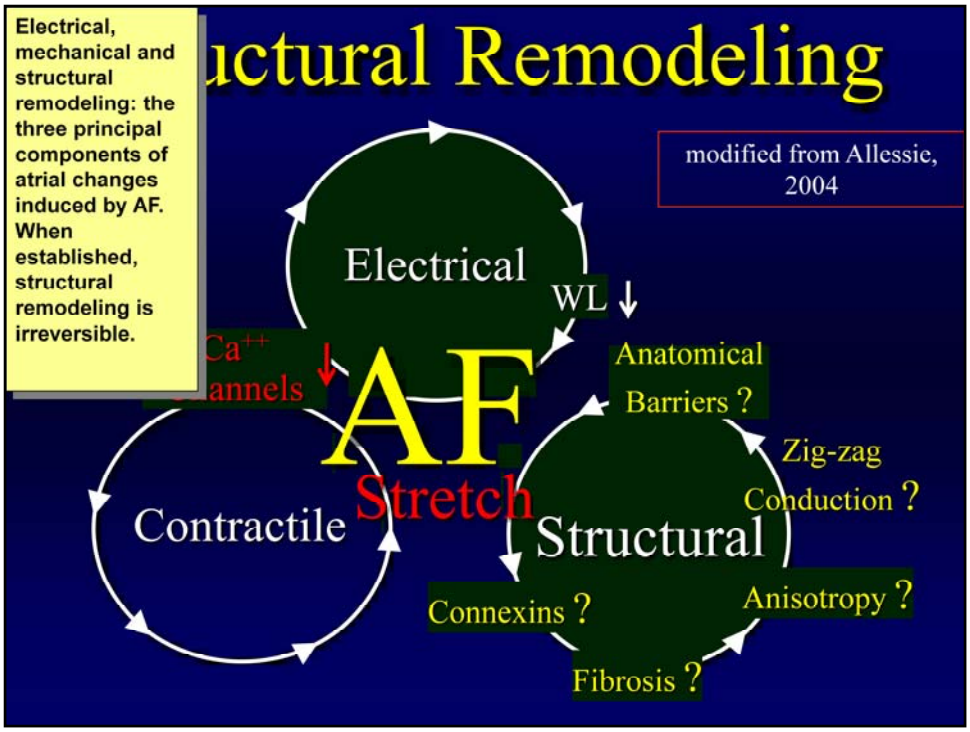
Structural
Zig-zag
Conduction ?
Connexins ?
Anisotropy ?
Fibrosis ?


Electrical, mechanical and structural remodeling: the three principal components of atrial changes induced by AF. When established, structural remodeling is irreversible.
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Ca++
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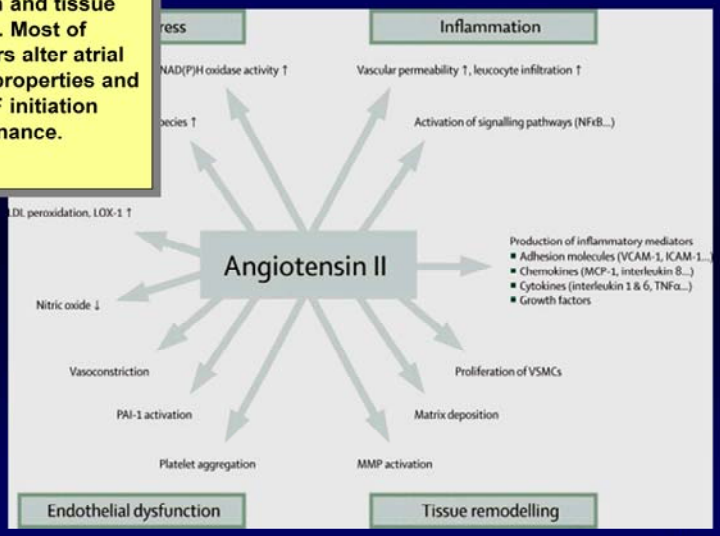
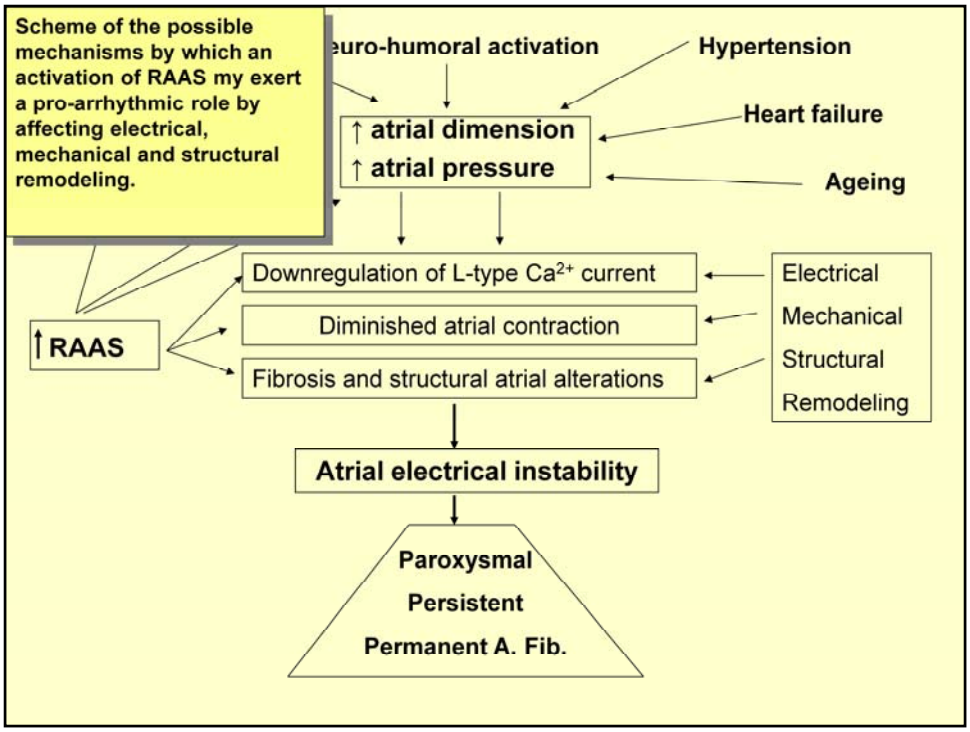
AF
Anatomical
Barriers ?
Zig-zag
Conduction ?
Stretch
Contractile
Structural
Connexins ?
Anisotropy ?
Fibrosis ?

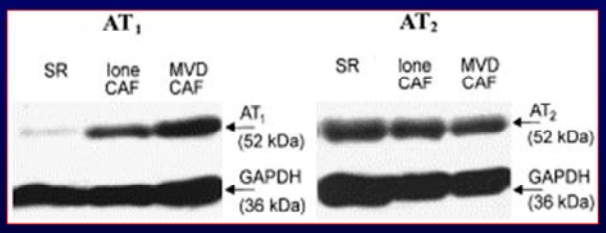
The critical role of Angiotensin II in relation to oxidative stress, inflammation, endothelial dysfunction and tissue remodeling. Most of these factors alter atrial functional properties and facilitate AF initiation and maintenance.



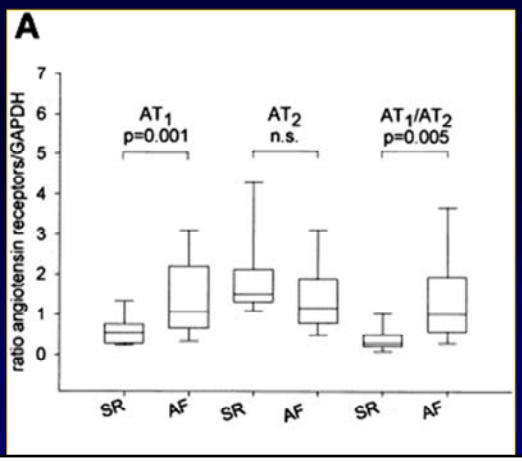
Schmieder et al, 2007


Scheme of the possible mechanisms by which an activation of RAAS my exert a pro-arrhythmic role by affecting electrical, mechanical and structural remodeling.
euro-humoral activation
Hypertension
↑ atrial dimension
↑ atrial pressure
Heart failure
Ageing
↑ RAAS
Downregulation of L-type Ca2+ current
Diminished atrial contraction
Fibrosis and structural atrial alterations
Electrical
Mechanical
Structural
Remodeling
Atrial electrical instability
Paroxysmal
Persistent
Permanent A. Fib.

Experimental evidence of a greater AT1 expression in the atria of AF patients in comparison to controls in sinus rhythm.



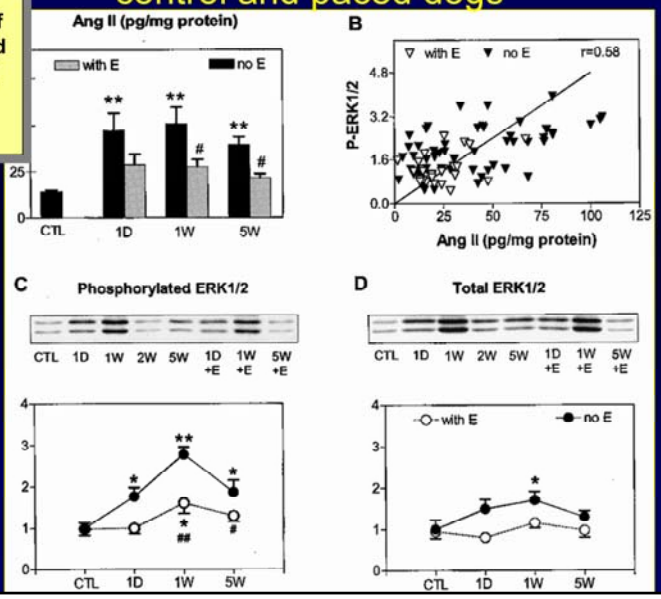
Basic differences in AT_1 and AT_2 expression and ratio



Boldt et al. 2004

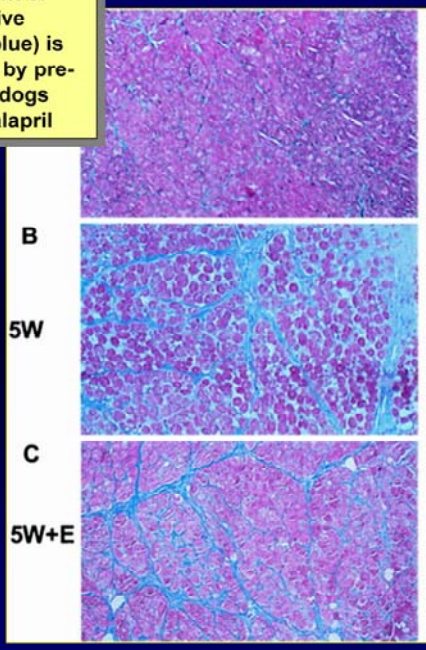
Correlation between Angiotensin II and P-ERK in an experimental animal model of heart failure and increased atrail distension.

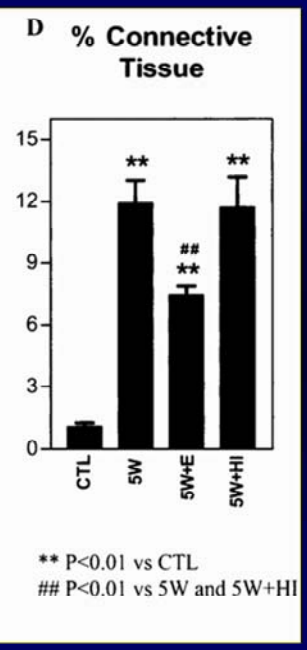
# of Enalapril on Ang II and phosphorilated lar signal-regulated protein kinase (ERK) in control and paced dogs



Li et al, Circulation 2001

The extent of connective tissue (blue) is reduced by pre-treating dogs with Enalapril





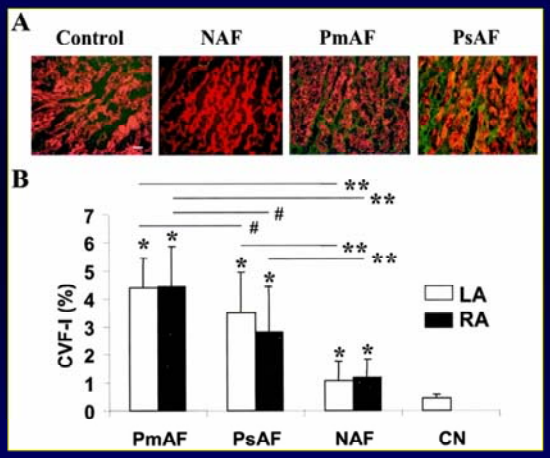
Li et al, Circulation 2001

Evidence for an increased collagen I content in patients with dilated cardiomyopathy in relation to presence or absence of AF

xtra-cellular matrix remodelling and aintenance of atrial fibrillation

from
s of
DCM pts.

Representative images of immunofluoresecnt staining of LA collagen I (green). Bars indicate % of Collagen I volume fraction



Xu et al, Circulation 2004

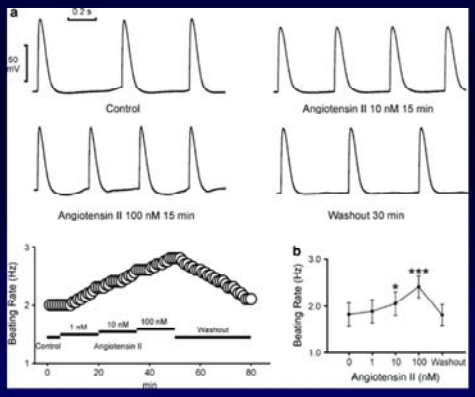
Angiotensin II may exert its pro-arrhythmic effect by increasing the firing rate of pulmonary vein foci.

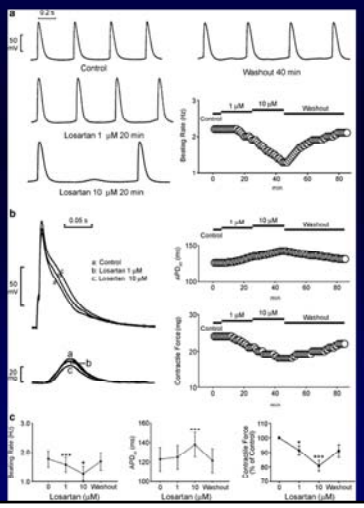
2006) 147, 12-22

www.nature.com/bjp

and angiotensin II receptor blocker modulate enic activity of pulmonary veins

Thang Chen, [3]Ching-Tai Tai, [4]Hung-I Yeh, [5]Cheng-I Lin & [3]Shih-Ann Chen



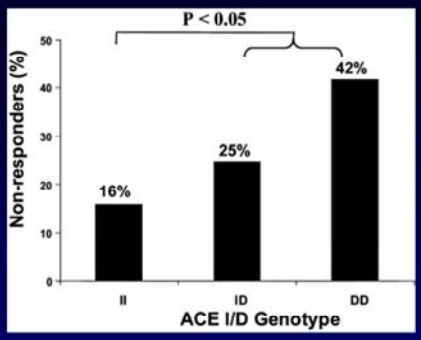


ACE I/D genotype modulates response to anti-arrhythmic therapy in patients with lone AF: another potential mechanism by which Angiotesin II may affect AF.

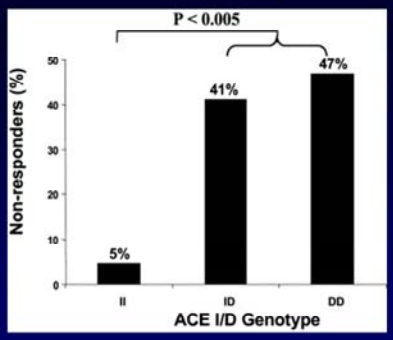
ulates symptomatic response to
g therapy in patients with lone

. Motsinger, MS,† Marylyn D. Ritchie, PhD,† James V. Gainer, MD,*,‡

All AFib pts



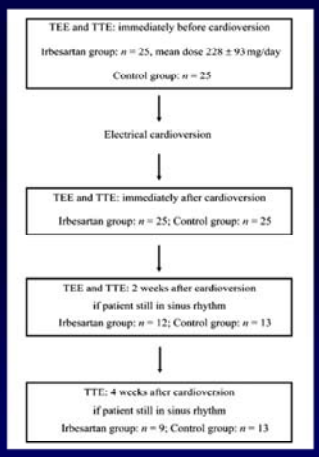
Lone AFib pts

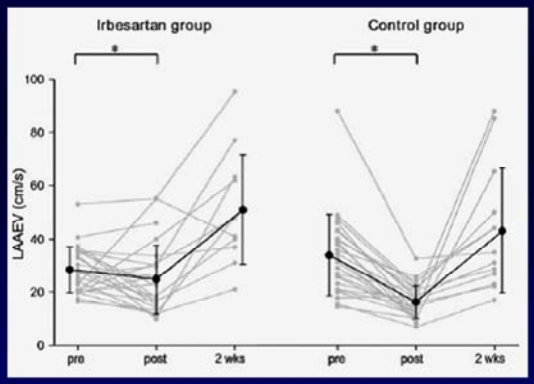


Heart Rhythm, 2007

Irbesartan positively affect atrial mechanical properties after DC cardioversion in pats with persistent AF.

with Irbesartan attenuates left
after electrical cardioversion
tion





Dagres et al, EHJ 2006

Clinical data on RAAS blockade and atrial fibrillation

- Development of new onset atrial fibrillation (it is important to remember that most results derive from post-hoc analysis)
- Recurrence of atrial fibrillation after DC cardioversion.

This is the first study that showed that ACE inhibitors could reduce the incidence of new AF episodes in post-MI pts with reduced LVEF.

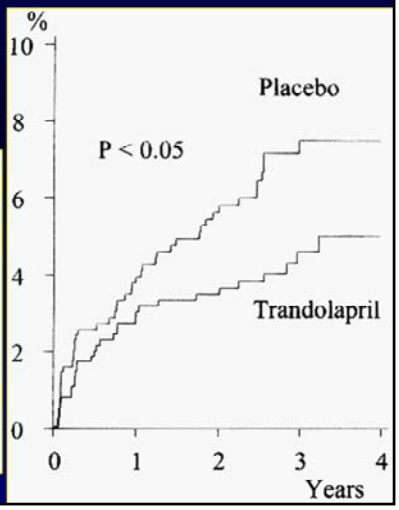
...educes the incidence of AF ...s with left ventricular

...edersen et al, Circulation 1999).

TRACE: 1577 post-MI pts with EF <36% randomised to Trandolapril or placebo. During f-up, AF occurred in 42 P and 22 T pts.

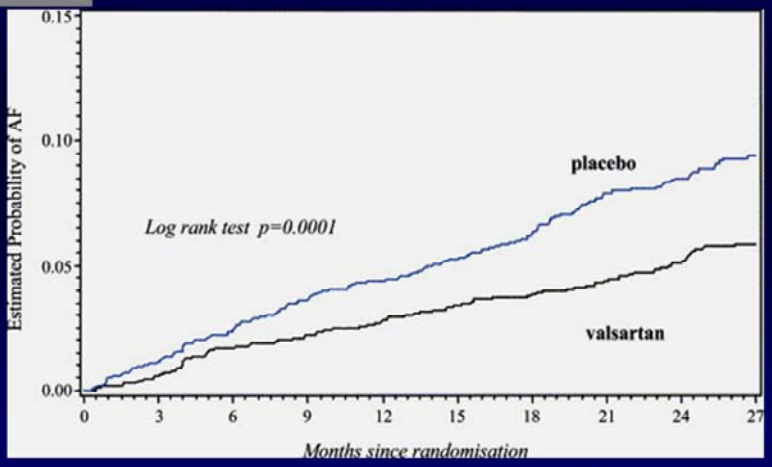
	LVEF, %			
	Trandolapril		Placebo	
	AF	No AF	AF	No AF
Baseline	30 (18–36)	33 (21–36)	30 (18–36)	33 (21–36)
Month 3	30 (24–39)	35 (24–45)	33 (18–45)	33 (21–42)
Month 6	33 (21–42)	36 (24–48)	33 (18–48)	36 (21–48)
Month 12	33 (27–42)	36 (24–48)	35 (18–42)	36 (24–51)

The treatment groups are separated into those who did (AF) or did not (no AF) develop atrial fibrillation during the 2- to 4-year follow-up period. Median values and 5th and 95th percentiles are indicated.



In the Val-Heft study, valsartan administration was associated with a reduced incidence of AF.

tan reduces the incidence of atrial ation in patients with heart failure (Val-Heft Study)

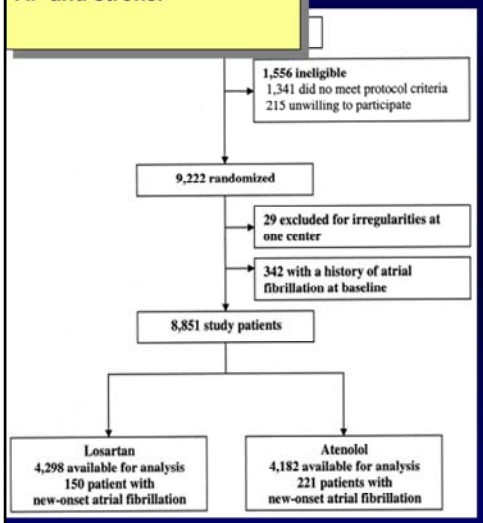


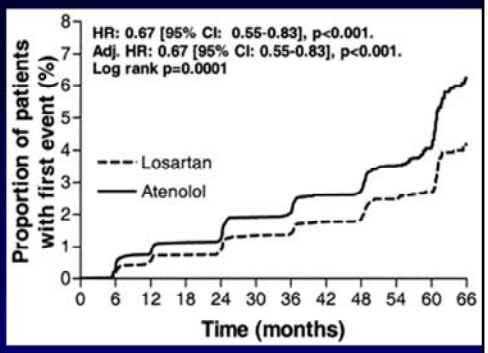
Maggioni et al, 2005

In the LIFE study carried out in hypertensive patients, Losartan was associated with a reduction in new cases of AF and stroke.

receptor blockade reduces new- nd stroke compared to Atenolol

LIFE Study



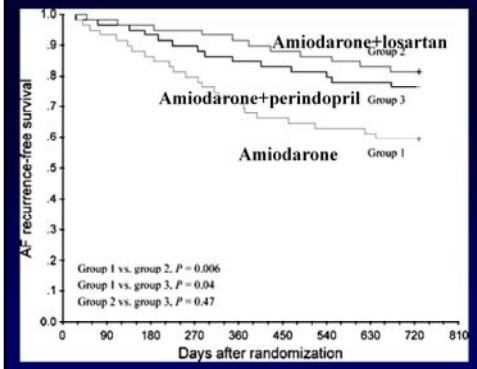


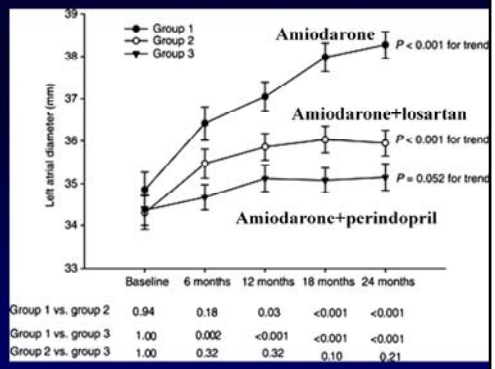
Wachtell et al, 2005

In this study, the association of Losartan or Perindopril with Amiodarone determined a reduction in AF recurrence and in left atrial dimension.

randomized study comparing amiodarone one plus losartan vs. amiodarone plus or the prevention of atrial fibrillation n patients with lone paroxysmal tion

Methods and results One hundred and seventy-seven patients with lone paroxysmal AF were randomly assigned to three treatment groups: group 1 received low-dose amiodarone alone, group 2 received low-dose amiodarone plus losartan, and group 3 received low-dose amiodarone plus perindopril. Left





Yin et al, EHJ 2006

This is the first randomised prospective study that showed that Irbesartan in adjunction with Amiodarone determined a significant reduction of AF recurrences after DC cardioversion.

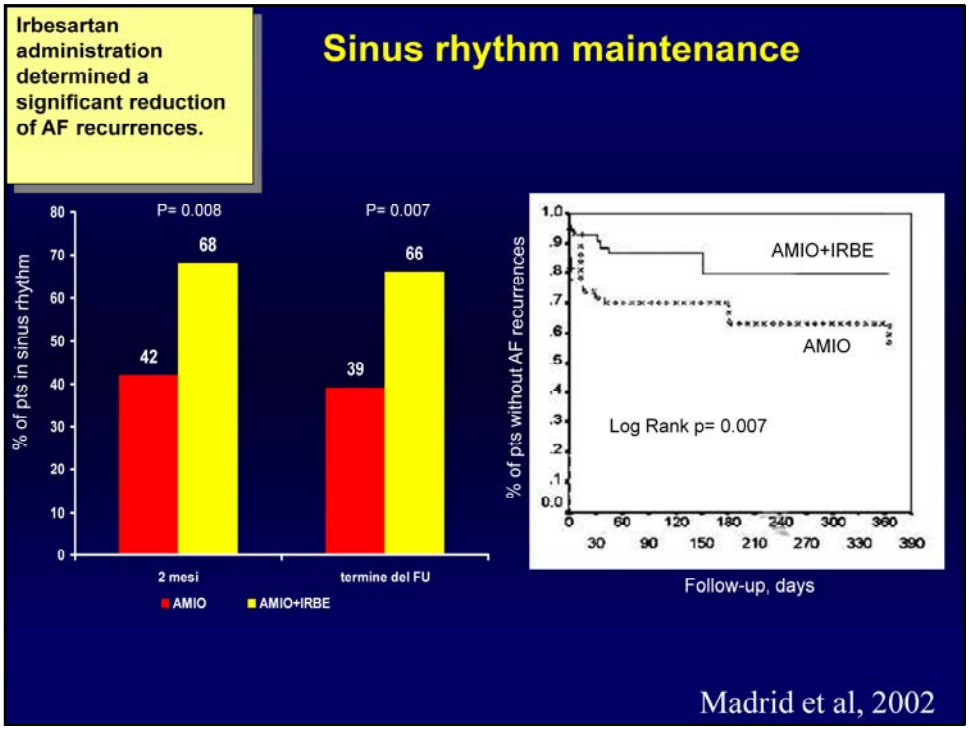
artan to maintain sinus tients with long-lasting nt atrial fibrillation.

	75	79	...
Pharmacological conversion after randomization, n	29	33	0.693
Successful electrical cardioversion, n	37	41	0.270
Ineffective electrical cardioversion, n	6	3	0.270
Complete shock failure	2	3	...
Immediate recurrence	4	0	...
Joules, mean±SD	267±79	258±77	0.280
Number of shocks, n	1.7±1.5	1.4±1.6	0.314
Sinus rhythm at 2 months, n	42	68	0.008
Sinus rhythm at the end of follow-up, n	39	66	0.007

Madrid et al, 2002

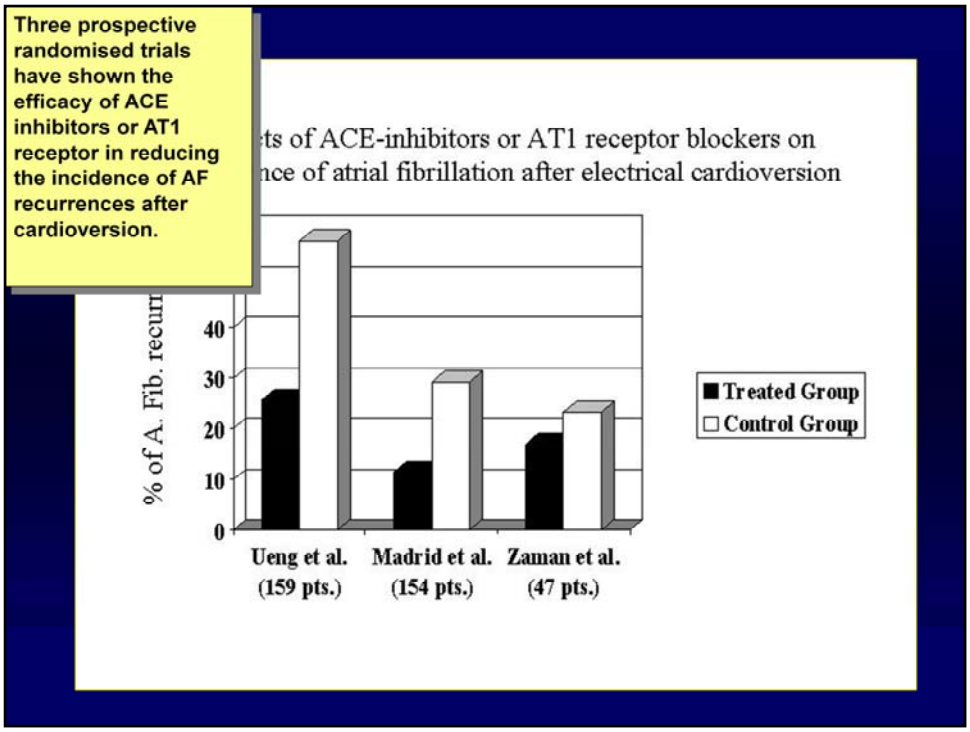
Randomization, follow-up and endpoints

The patients were randomized to treatment with amiodarone (400 mg daily) or with the combination (amiodarone + irbesartan 150 mg daily or 300 mg daily in hypertensive patients) 3 weeks before the ECV. For those who were not on anticoagulant therapy, anticoagulant treatment was started 3 weeks before initiating therapy with amiodarone. The maintenance dose of amiodarone (200 mg daily) was set in the visit at 2 months, no special adjustments were provided for irbesartan, but for any increase in dosage in case of occurrence of hypertension. The primary study end-point was the time to onset of first relapse of AF /AFl lasting> 10 min documented with ECG.Results There were no statistically significant differences in the two treatment groups of clinical features of the patient at baseline, except for the highest percentage of patients with bundle branch block in the group of those in combination (9% amio vs 30% amio+Irbe; p = 0.001). The concomitant therapy did not differ between the two treatment groups, although we observed a higher percentage of patients with beta-blockers in the combination group (15% vs 7%, p = 0.086) and a higher percentage of patients in ACE-inhibitors in the amio group (22% vs 16%, p = 0.191). A 39% of patients in the amio group and a 42% of the group in amio + Irbe were in SR in the visit planned for conducting the ECV. The patients that were not in SR had a history of AF of longer duration (median 10 months vs 5 months). The ECV was therefore performed in 92 patients with a success of 90% (82 patients): The ECV failed in 6 patients treated with amio and in 3 with the association. No significant differences were observed with systolic blood pressure and diastolic blood pressure at the end of follow-up in the two treatment groups.



Efficacy and tolerability/lRecurrence of AF and maintenance of sinus rhythm/lThe recurrence rate of AF is significantly lower compared with the association of AMIO alone or after 2 months of the end of follow-up. The Kaplan-Meier analysis shows a probability of maintaining SR at 2 months of 85% in the amio + Irbe compared with 63% of the group with amio. Multivariate analysis showed that the use of IRBE was the only variable significantly correlated with the maintenance of SR after ECV. The hazard ratio (similar to Odds Ratio) for the recurrence of AF in patients treated with the combination was 0.35, reflecting a reduction in the risk of recurrence by 65% (RR 0.35; 95% CI 0.12-0.46, P = 0.018). The use of the mathematical model of Cox, adjusting for other variables that may influence the outcome (diabetes, bundle branch block, duration of AF), suggests a risk reduction of 81% (RR 0.19; 95% CI 0.04-0.86 P = 0.031)./lAt the end of the follow-up, Kaplan-Meier analysis shows a probability of remaining in SR by 56% in the amio arm compared to 79% of the amio + Irbe arm. The most important factor that is able to predict the recurrence of AF was the length of AF prior to randomization./lThere was a trend of superiority of the association amio + Irbe observed in patients with hypertension (RR 0:49; 95% CI 0.11-2.06, ns), with structural heart disease (RR 0:37; 95% CI 0.09-1.5, NS) and AF lasting> 12 months (RR 0.20; 95% CI 0.024-1.76; ns)./lTolerability/lOne patient in the combination group died of sudden death 21 days after favorable ECV. There were 11 adverse events that required treatment (6 amio and amio + Irbe).

Three prospective randomised trials have shown the efficacy of ACE inhibitors or AT1 receptor in reducing the incidence of AF recurrences after cardioversion.



A meta-analysis of published studies on prevention of AF with ACE inhibitors (upper part) or AT1 receptor blockers (lower part).

Heart Rhythm Disorders

of Atrial Fibrillation
otensin-Converting Enzyme
nd Angiotensin Receptor Blockers
s

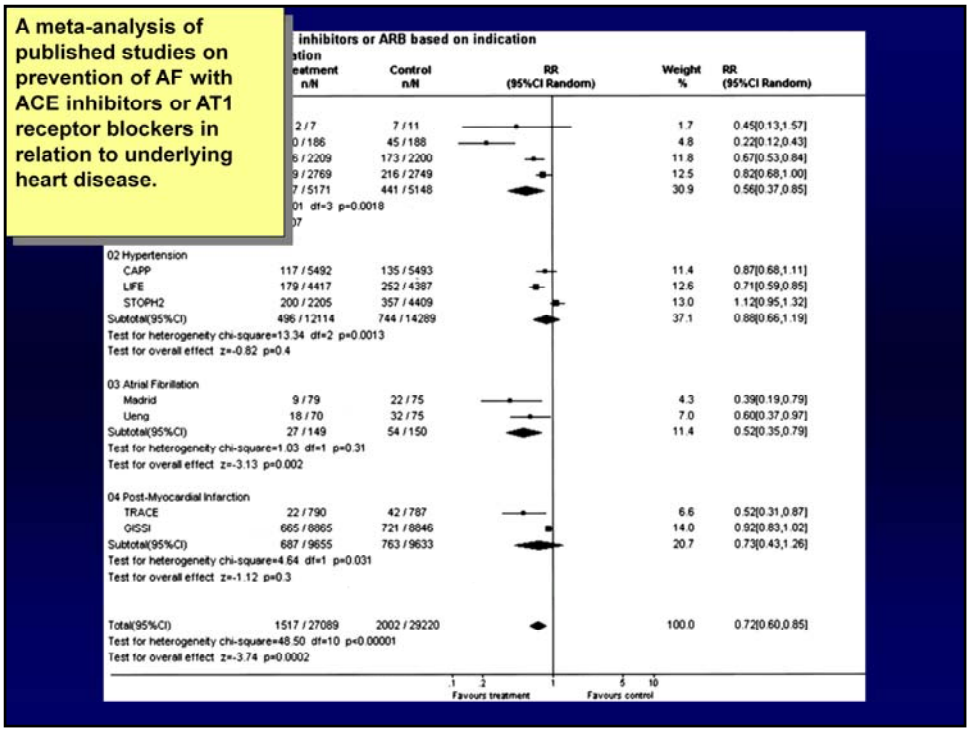
Adnan Baranchuk, MD,* Eugene Crystal, MD,† Carlos A. Morillo, MD,*
BA,† Salim Yusuf, MD, PHD,* Stuart J. Connolly, MD*
Hamilton and Toronto, Ontario, Canada

Comparison: 04 Effect of treatment based on class of drug
Outcome: 01 Atrial Fibrillation

Study	Treatment n/N	Control n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
01 ACE inhibitor					
Van Den Berg	2 / 7	7 / 11		1.7	0.45[0.13,1.57]
SOLVD	10 / 186	45 / 188		4.8	0.22[0.12,0.43]
TRACE	22 / 790	42 / 787		6.6	0.52[0.31,0.87]
Ueng	18 / 70	32 / 75		7.0	0.60[0.37,0.97]
CAPP	117 / 5492	135 / 5493		11.4	0.87[0.68,1.11]
STOPH2	200 / 2205	357 / 4409		13.0	1.12[0.95,1.32]
GISSI	665 / 8865	721 / 8846		14.0	0.92[0.83,1.02]
Subtotal(95%CI)	1034 / 17615	1339 / 19809		58.7	0.72[0.56,0.93]
Test for heterogeneity chi-square=32.58 df=6 p<0.00001					
Test for overall effect z=-2.53 p=0.01					
02 ARB					
Madrid	9 / 79	22 / 75		4.3	0.39[0.19,0.79]
ValHeFT	116 / 2209	173 / 2200		11.8	0.67[0.53,0.84]
Charm	179 / 2769	216 / 2749		12.5	0.82[0.68,1.00]
LIFE	179 / 4417	252 / 4387		12.6	0.71[0.59,0.85]
Subtotal(95%CI)	483 / 9474	663 / 9411		41.3	0.71[0.60,0.84]
Test for heterogeneity chi-square=5.25 df=3 p=0.15					
Test for overall effect z=-4.12 p=0.00004					
Total(95%CI)	1517 / 27089	2002 / 29220		100.0	0.72[0.60,0.85]
Test for heterogeneity chi-square=48.50 df=10 p<0.00001					
Test for overall effect z=-3.74 p=0.0002					

.1 .2 1 5 10
Favours treatment Favours control

A meta-analysis of published studies on prevention of AF with ACE inhibitors or AT1 receptor blockers in relation to underlying heart disease.



The rationale of GISSI-AF study.

...nd design of the GISSI-Atrial Fibrillation trial: a ...d, prospective, multicentre study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence

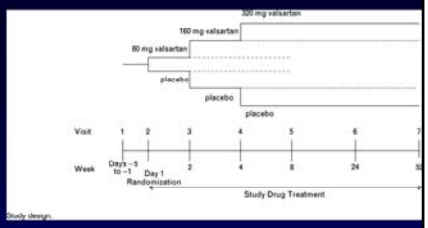
Criteria

1. Male and female patients with at least 40 years of age
2. In sinus rhythm at randomization (for at least 48 h in case of electric or pharmacological cardioversion)
3. At least two ECG documented episodes of symptomatic atrial fibrillation in the previous 6 months or successful cardioversion for atrial fibrillation between 14 days and 48 h before
4. At least one of the following:

Heart failure or documented history of left ventricular dysfunction (defined as an ejection fraction < 40%)
History of hypertension ≥ 6 months with or without left ventricular hypertrophy
Type II diabetes mellitus
Documented history of stroke or peripheral vascular disease
Documented history of coronary artery disease
Lone atrial fibrillation with documented left atrium dilation (left atrium diameter ≥ 45 mm for men and ≥ 40 mm for women)

5. The patient has provided informed consent

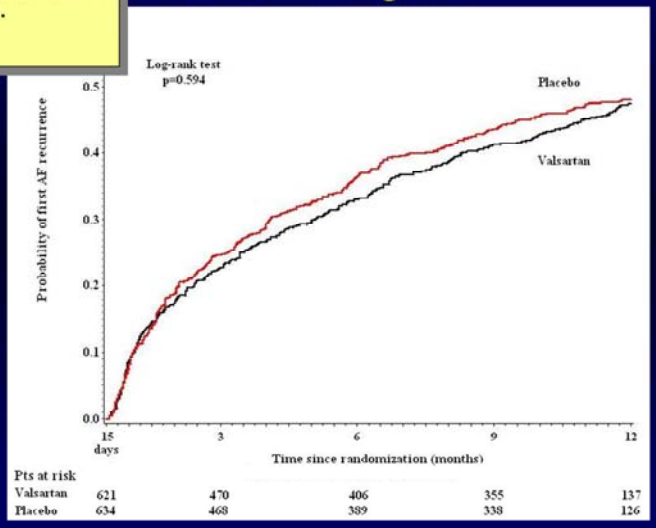
N= 1402 pts



Disertori et al, JCM 2006

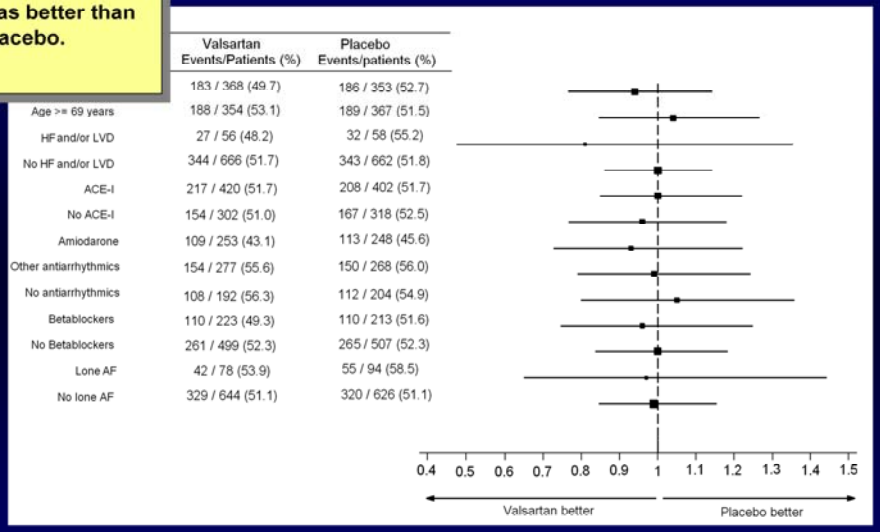
The results of GISSI-AF trial did not show a beneficial effect of Valsartan on AF recurrences during 1 year follow-up period.

rial on the Angiotensin Receptor Blocker
evention of Atrial Fibrillation Recurrence
GISSI-AF Investigators*



Disertori et al. NEJM 2009

There were no subgroups in which Valsartan was better than placebo.



Disertori et al. NEJM 2009

Conclusions:

- There are controversial data regarding the anti-arrhythmic effects of ACE inhibitors or AT1 receptor blockers on AF.
- This is partially due to the heterogeneity of studies regarding primary endpoint definitions, modality of assessment of AF recurrence and patient's characteristics in relation to arrhythmic history and underlying cardiomyopathy.
- Experimental evidence indicates, however, that blocking of RAAS may positively affect structural remodeling by limiting atrial fibrosis. A possible explanation for the recent negative findings is that structural remodeling once established is almost irreversible thus making ineffective our attempts to modify the arrhythmogenic substrate with ACE inhibitors or AT1 receptor blockers.