АНТИАРИТМИЧЕСКИЕ ЭФФЕКТЫ БЛОКАТОРОВ РЕНИН-АНГИОТЕНЗИНОВОЙ СИСТЕМЫ

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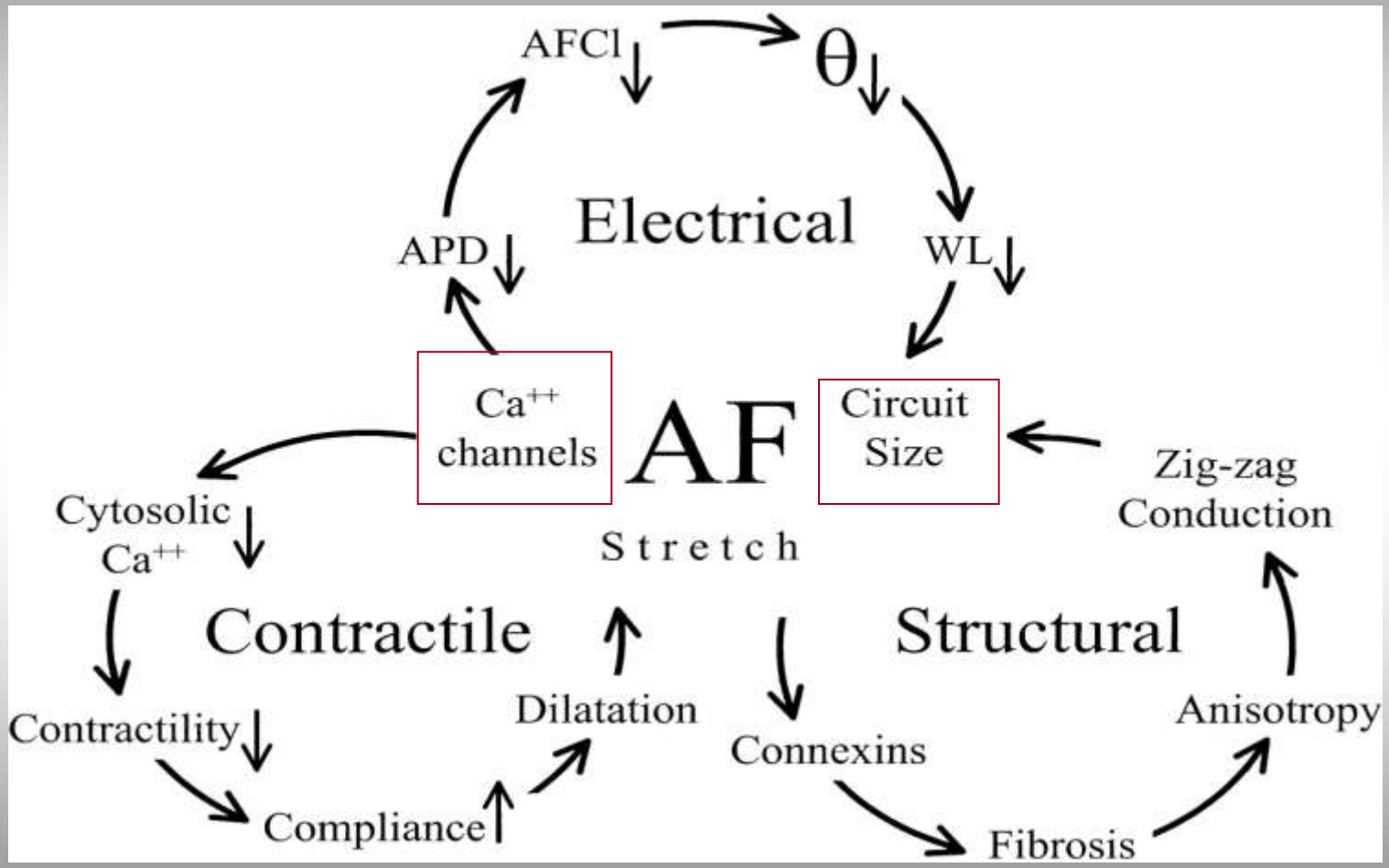
Применение бокаторов ренин-ангиотензиновой системы

ИАПФ		БРА	
1.	ХСН	1.	ХСН
2.	Дисфункция ЛЖ	2.	Перенесенный ИМ
3.	Перенесенный ИМ	3.	Диабетическая нефропатия
4.	Диабетическая нефропатия	4.	МАУ/протеинурия
5.	Недиабетическая нефропатия	5.	ГЛЖ
6.	ГЛЖ	6.	Фибрилляция предсердий ?
7.	Каротидный атеросклероз	7.	Метаболический синдром
8.	МАУ/протеинурия	8.	Кашель при приеме ИАПФ
9.	Фибрилляция предсердий ?		
10.	Метаболический синдром		

Бойцов С.А., 2008

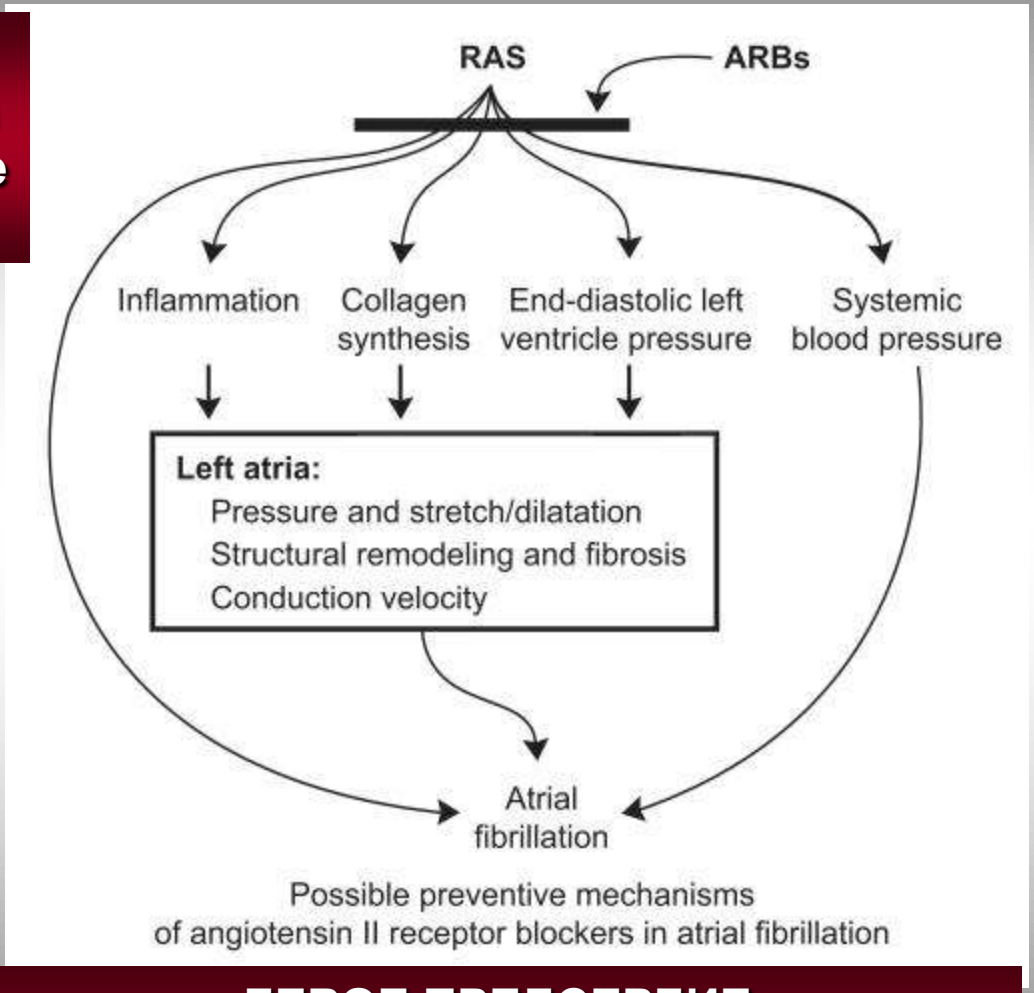
Три предполагаемых возвратных цикла, раскрывающих механизм ремоделирования предсердий при ФП .
Снижение регуляции Ca 2 +-каналов L-типа считается основной причиной ремоделирования ЛП.



Allessie M et al. Cardiovasc Res 2002;54:230-246

Механизм антиаритмического действия блокаторов РАС

Воспаление
Синтез коллагена
КДО ЛЖ давление
Системное АД



Possible preventive mechanisms of angiotensin II receptor blockers in atrial fibrillation

ЛЕВОЕ ПРЕДСЕРДИЕ:
Давление/растяжение/дилятация
Структурное ремоделирование и фиброз
Ускорение проводимости

Механизм антиаритмического действия блокаторов РАС

Бойцов С.А., 2008

ИАПФ и БРА не снижают относительный риск ФП

При АГ снижение относительного риска =1 2%, p=0,4

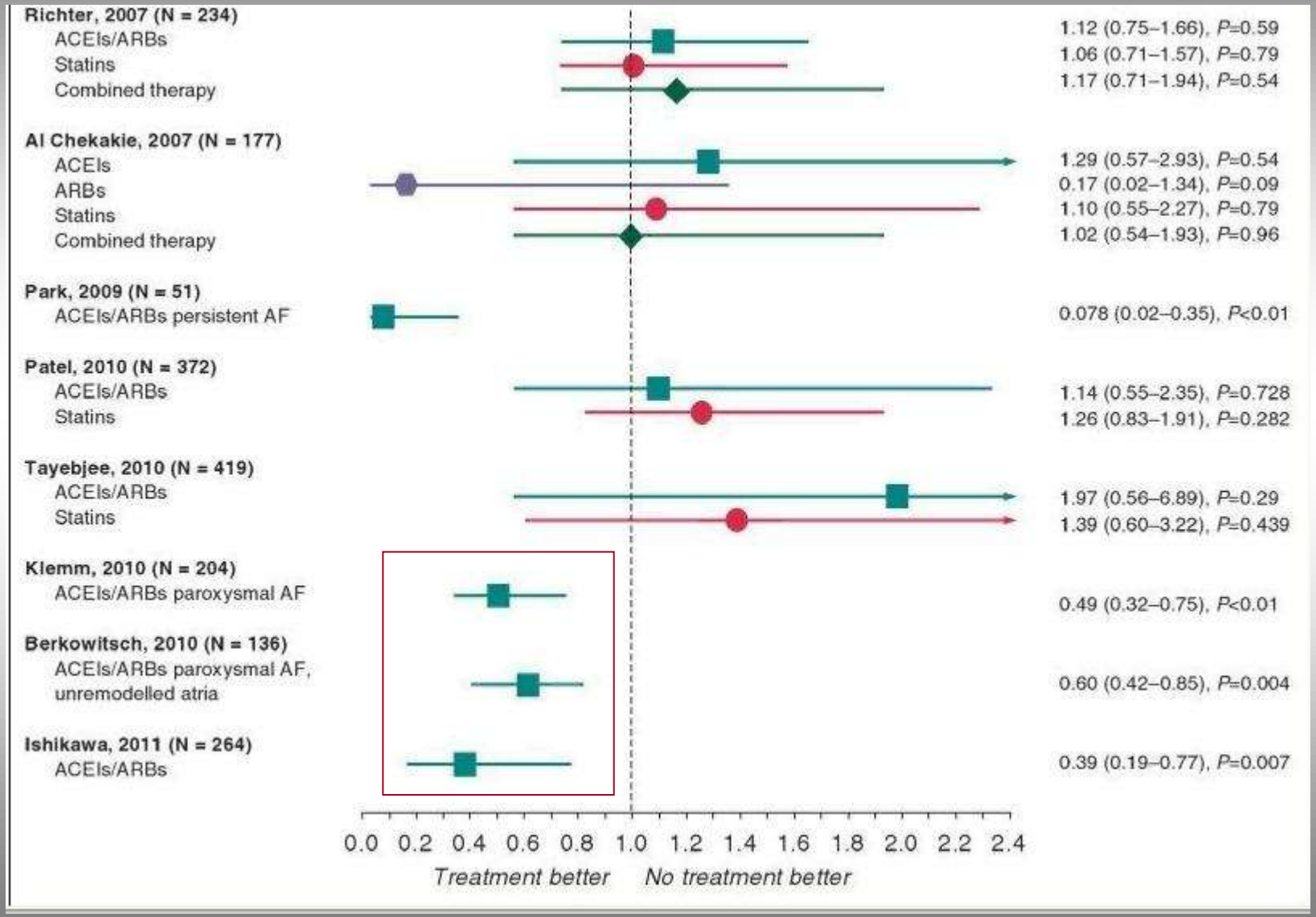
Исследование CAPPP
(каптоприл, - 13%, p>0,05)

Исследование STOP-H2
(эналаприл, - 12%, p>0,05)

HOPE и TRANSCEND

НЕ ДОСТОВЕРНО !!!

Эффект ингибиторов РАС в лечении персистирующей ФП после перевязки легочных вен при ретроспективном изучении



N Engl J Med. 2009 Apr 16;360(16):1606-17.

Valsartan for prevention of recurrent atrial fibrillation.

GISSI-AF Investigators, Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, Di Pasquale G, Tognoni G.

GISSI-AF

RESULTS: A total of 1442 patients were enrolled in the study. Atrial fibrillation recurred in 371 of the 722 patients (51.4%) in the valsartan group, as compared with 375 of 720 (52.1%) in the placebo group (adjusted hazard ratio, 0.97; 96% confidence interval [CI], 0.83 to 1.14; P=0.73). More than one episode of atrial fibrillation occurred in 194 of 722 patients (26.9%) in the valsartan group and in 201 of 720 (27.9%) in the placebo group (adjusted odds ratio, 0.89; 99% CI, 0.64 to 1.23; P=0.34). The results were similar in all predefined subgroups of patients, including those who were not receiving angiotensin-converting-enzyme inhibitors.

CONCLUSIONS: Treatment with valsartan was not associated with a reduction in the incidence of recurrent atrial fibrillation. (ClinicalTrials.gov number, NCT00376272.)

1442 пациента, включенных в исследование. Пароксизмальная ФП наблюдалась у 371 из 722 пациентов (51,4%) в группе валсартана по сравнению с 375 из 720 (52,1%) в группе плацебо (p=0,73)

ВЫВОД: Лечение валсартаном не влияло на снижение случаев ФП

Review of Clinical Evidence and Implications for European Society of Cardiology Guidelines

Irene Savelieva; Nicholaos Kakouros; Antonios Kourliouros; A. John Camm

AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management)

from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study has shown that, although in the general study population risk of AF recurrence in 421 patients treated with RAAS inhibitors in the initial 2-month follow-up did not differ from the risk observed in 732 patients not taking RAAS inhibitors [hazard ratio (HR), 0.91; 95% confidence interval (CI), 0.77–1.09], patients with congestive heart failure (CHF) treated with RAAS inhibitors had fewer AF recurrences (11.9 vs. 35.9%; $P < 0.0001$).[9]

В исследовании AFFIRM было показано, что хотя в общей популяции риск пароксизмальной ФП у 421 пациента, леченных блокаторами РАС в течение 2-х мес. не отличался от риска у 732 пациентов, которые не получали блокаторы РАС, однако у пациентов с застойной СН, которые получали блокаторы РАС было меньше случаев пароксизмальной ФП

ИАПФ снижают относительный риск ФП

SOLVD (Studies of Left Ventrcular Dysfunction)

Vermes E., Tardif J.C., Bourassa M.G. et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies of Left Ventricular Dysfunction (SOLVD) trials. // Circulation 2003;107:2926–31.

Лечение эналаприлом больных с низкой ФВ ЛЖ в течение 3-х лет привело к снижению числа новых случаев ФП в 4 раза у больных, получавших эналаприл по сравнению с группой плацебо

ИАПФ и БРА снижают относительный риск ФП

Метаанализ 11 исследований, 56 308 пациентов:

- 4 исследования ХСН
- 3 исследования АГ
- 2 - после кардиоверсии по поводу ФП
- 2 исследования ИМ

ИАПФ и БРА снижение относительный риск ФП на

28% (95% ДИ 15%-40%, p=0,0002)

ИАПФ: **28%,** p=0,01; БРА: **29%,** p=0,00002)

При кардиоверсии снижение относительного риска на

48% (95% ДИ 21 %-65%)

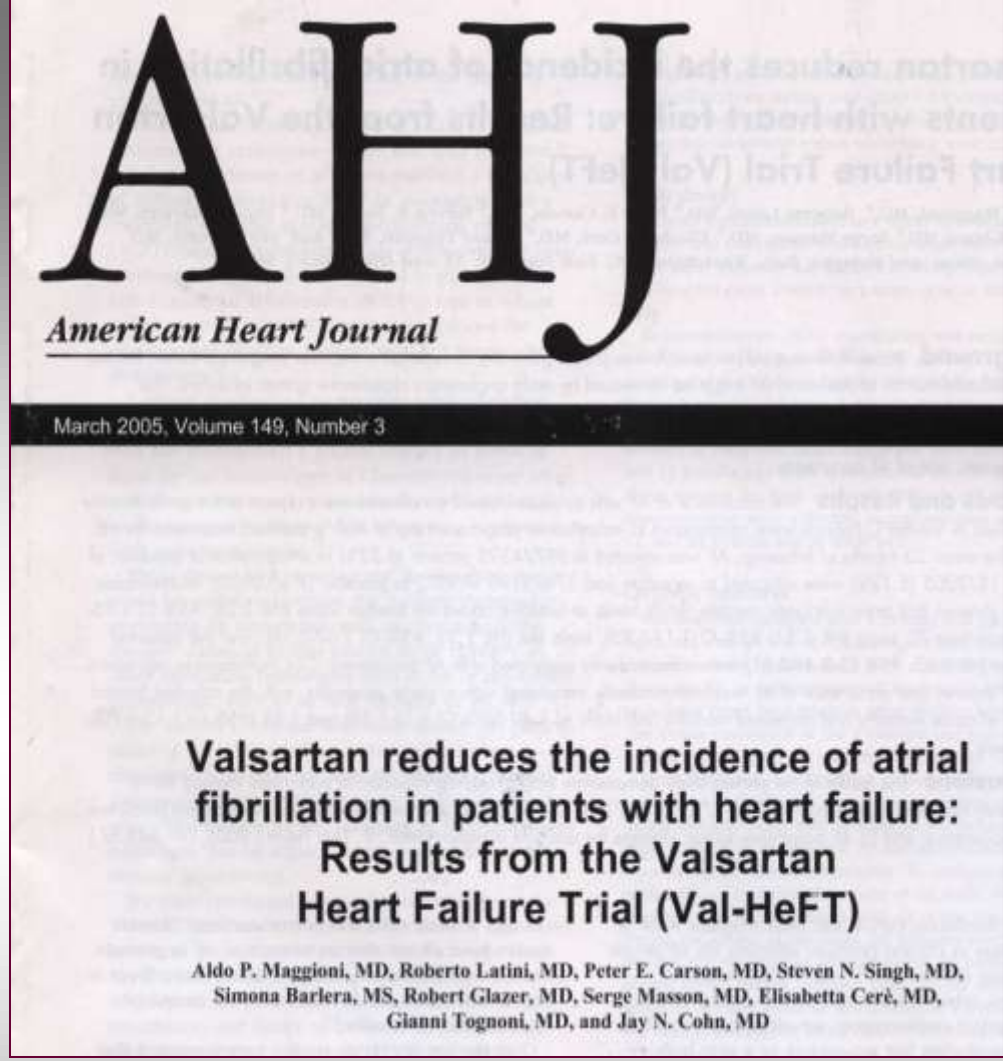
У пациентов с ХСН снижение относительного риска на

44%, p=0,007.

J Am Coll Cardiol 2005;45:1832-9.

Пароксизмальная фибрилляция предсердий

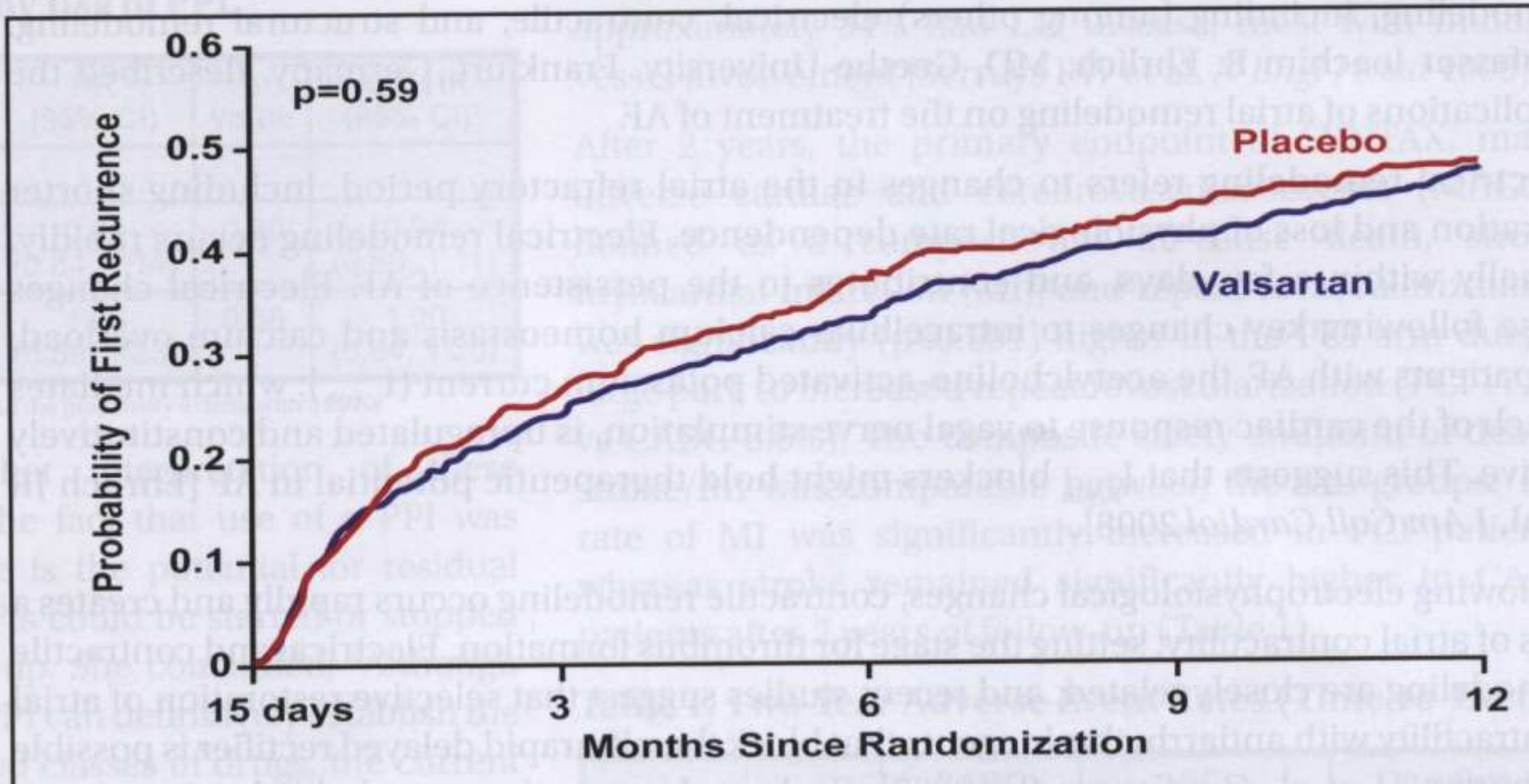
НА 37% СНИЖАЕТ РИСК ФП ПРИ ДОБАВЛЕНИИ К БАЗОВОЙ ТЕРАПИИ



Conclusions The results of the present study demonstrate that (*a*) adding valsartan to prescribed therapy for HF significantly reduces the incidence of AF by 37%; (*b*) BNP level and advanced age were the strongest independent predictors for AF occurrence; and (*c*) AF occurrence further worsens the outcome in patients with HF. (Am Heart J 2005;149:548-57.)

Пароксизмальная фибрилляция предсердий

Figure 1. Prospective Data – AF "All Comers."



Исследование CHARM

Кандесартан у больных с ХСН показал достоверное снижение вероятности ФП у больных с ХСН на 18%

Am Heart J. 2006;152(1):86-92.

Madrid AH, Bueno MG, Rebollo JM, et al.
Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study.
Circulation 2002;106:331-6.

Применение ирбесартана достоверно способствует повышению эффективности поддержания синусового ритма на 61%

Prevention of new-onset atrial fibrillation and its predictors with angiotensin II receptor blockers in the treatment of hypertension and heart failure. *J Hypertens*. 2007;25:15–23.51 Copyright © wolters Kluwer Health.

Studies of the effectiveness of ARBs in the prevention of AF (new onset and recurrent)

Study	Design/follow-up	N	Interventions	AF-related endpoints	
New-onset AF					
SCOPE71	MC, R, DB, hypertension (elderly)	4964	Candesartan (Can)	Incidence of nonfatal stroke	
			PL	Can 7.4 vs PL 10.3/1000 patient-years (risk reduction 27.8%, $P = 0.04$)	**на 27%**
	Mean, 3.7 years				
LIFE28	MC, R, DB, hypertension/LVH	8851[a]	Losartan (Los)	Incidence of AF	
	Mean, 4.8 years		Atenolol (At)	Los 6.8 vs At 10.1/1000 patient-years (RR 0.67, $P < 0.001$)	**на 33%**
				Maintenance of sinus rhythm	
				Los 1809 ±225 days vs At 1709 ± 254 days ($P = 0.057$)	
VALUE27,30	Retrospective analysis of MC, R, DB study (hypertension)	15,245	Valsartan (Val)	Incidence of new-onset AF	**37% vs 43%**
			Amlodipine (Aml)	Val 3.7% vs Aml 4.3% ($P = 0.044$)	
				Rate of persistent AF	
	Mean, 4.2 years			Val 1.4% vs Aml 2.0% ($P = 0.005$)	
ONTARGET72	MC, R, DB, patients at high risk of vascular events	25,620	Telmisartan (Tel)	Incidence of new-onset AF	
			Ramipril (Ram)	Tel 6.7% vs Ram 6.9% vs Ram ± Tel 6.5% (all P = NS between treatments; Tel vs Ram RR 0.97)	
	Median, 56 months		Ram ± Tel combination therapy		

Prevention of new-onset atrial fibrillation and its predictors with angiotensin II receptor blockers in the treatment of hypertension and heart failure. *J Hypertens*. 2007;25:15–23.51 Copyright © wolters Kluwer Health.

Recurrent AF

Fogari et al73	R, open-label, hypertension/type 2 diabetes/AF	296	Valsartan (Val)	Incidence of recurrent AF
			Atenolol (At)	Val ± Aml 20.3% vs At + Aml 34.1% ($P < 0.01$)
	1 year		(± Amlodipine [Aml])	
Fogari et al74	R, DB, hypertension/AF	369	Valsartan (Val)	Incidence of recurrent AF
	1 year		Ramipril (Ram)	Val 16.1% vs Ram 27.9% vs Aml 47.4% ($P < 0.01$ Val vs Aml and $P < 0.05$ Val vs Ram)
			Amlodipine (Aml)	
GISSI-AF75	MC, R, DB, PL, AF	1442	Valsartan (V)	Incidence of recurrent AF
	Median, 1 year		PL	Val 51.4% vs PL 52.1% (HR 0.99), but trend favored Val in patients with CHF and/or LV dysfunction (HR 0.81)
CAPRAF76,77	R, DB, PL, AF	171	Candesartan (Can)	Incidence of recurrent AF
	6 months		PL	Can 71% vs PL 65% ($P = 0.20$) in patients with persistent AF who underwent ECV

20,3% vs 34.1%

16,1% vs 27,9% vs 47,4%

51,4% vs 52,1%

71% vs 63%

J Am Coll Cardiol, 2010; 55:2299-2307

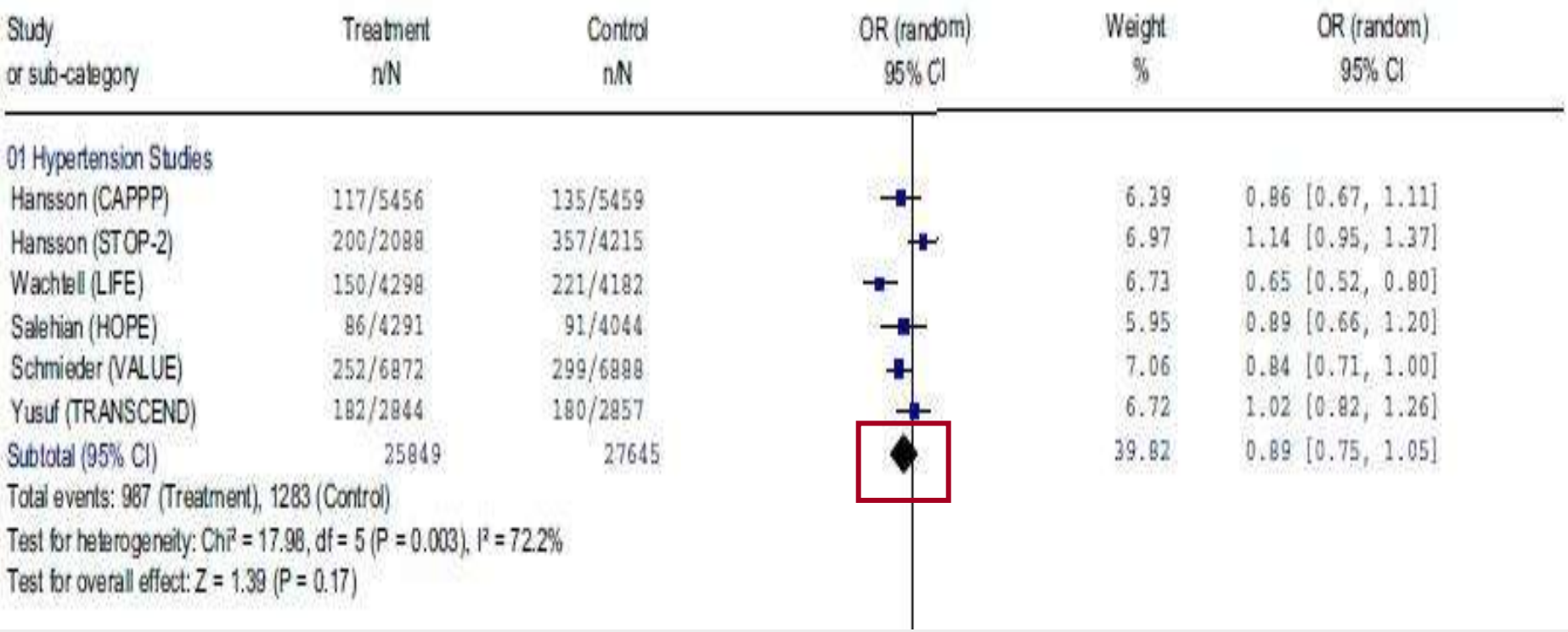
Prevention of Atrial Fibrillation by Renin-Angiotensin System Inhibition

A Meta-Analysis

Journal of the American College of Cardiology

Published by Elsevier Inc.

Первичная профилактика ФП: Блокаторы РАС при АГ

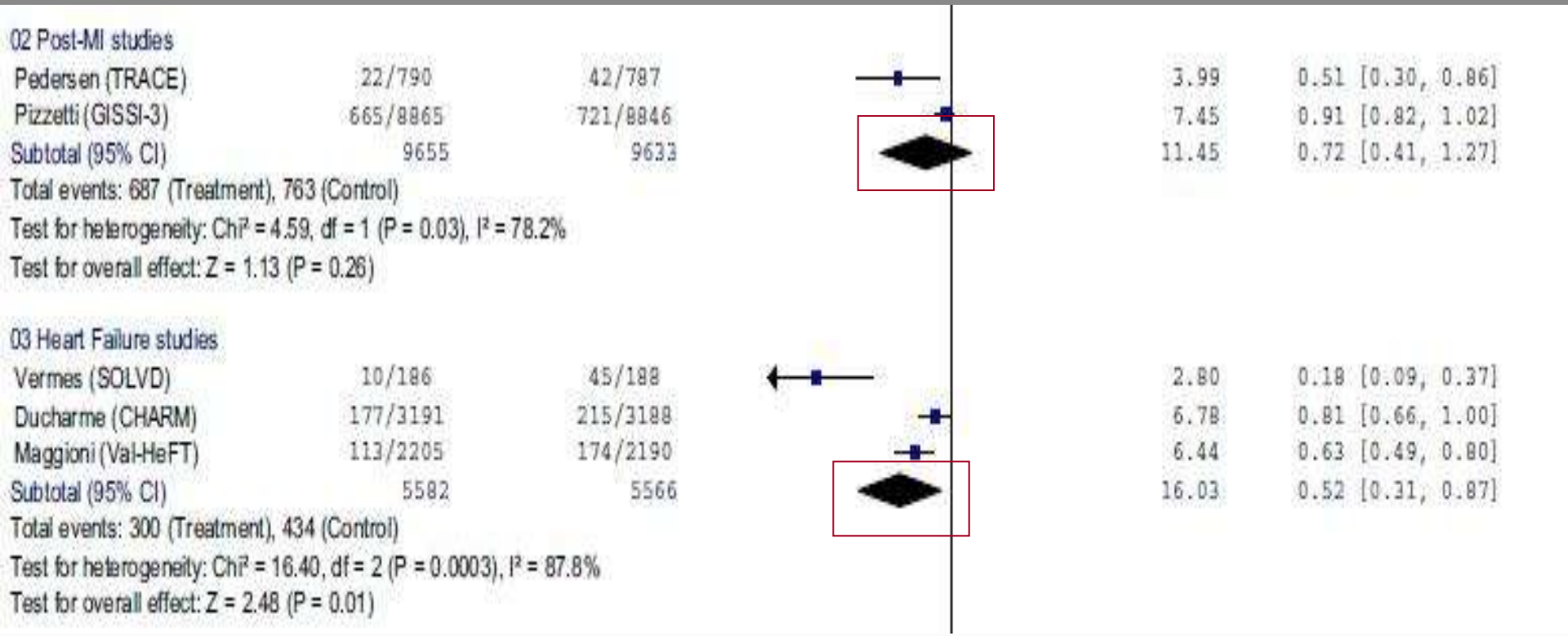


J Am Coll Cardiol, 2010; 55:2299-2307

Prevention of Atrial Fibrillation by Renin-Angiotensin System Inhibition

A Meta-Analysis

Вторичная профилактика ФП: Блокаторы РАС при постинфарктном кардиосклерозе и СН

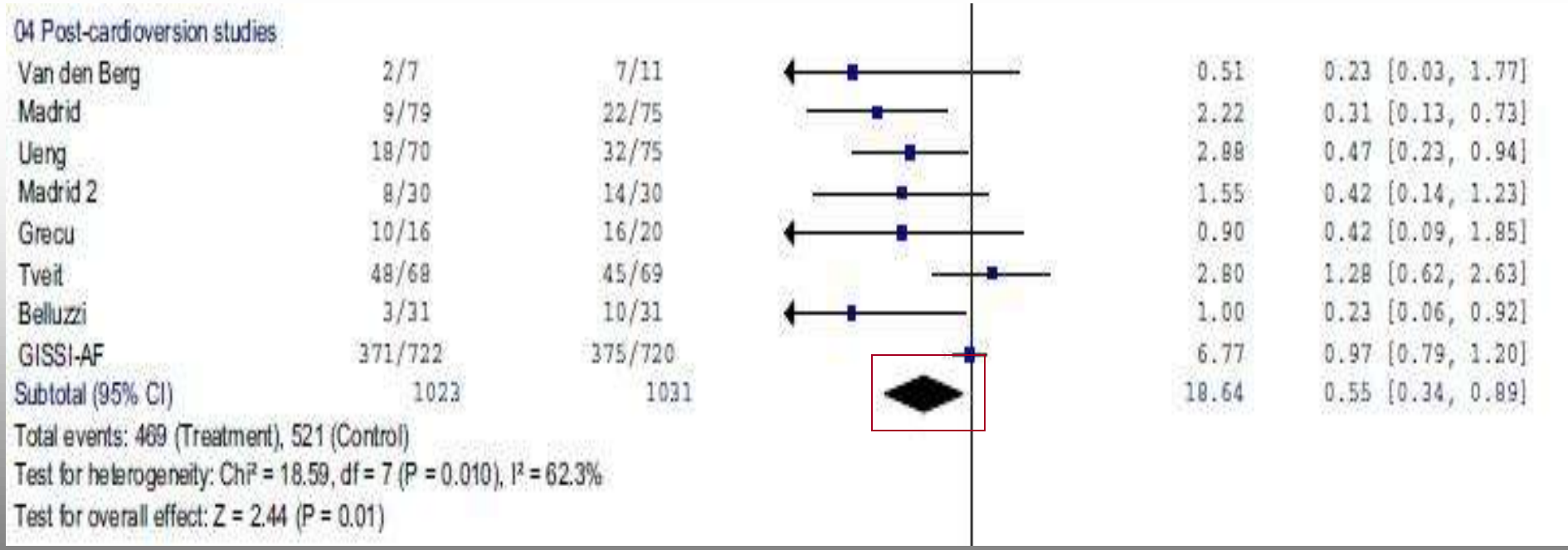


J Am Coll Cardiol, 2010; 55:2299-2307

Prevention of Atrial Fibrillation by Renin-Angiotensin System Inhibition

A Meta-Analysis

Вторичная профилактика ФП: Блокаторы РАС после кардиоверсии

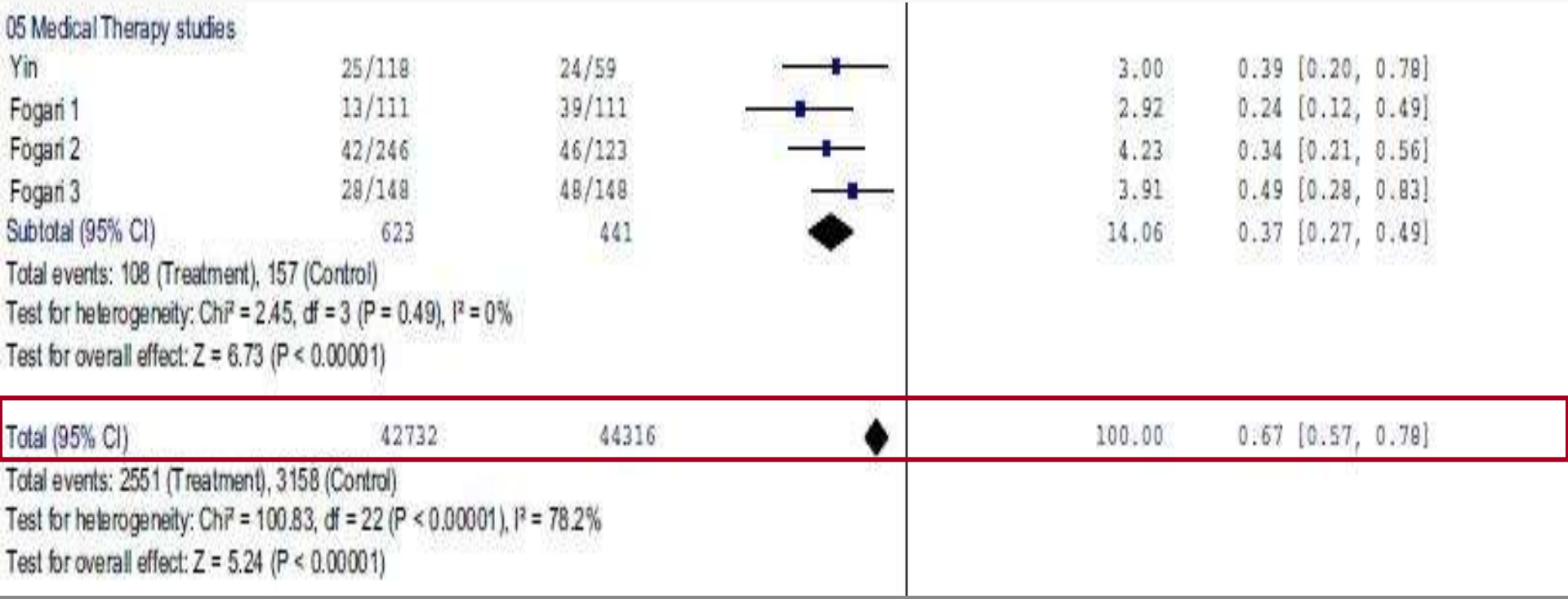


J Am Coll Cardiol, 2010; 55:2299-2307

Prevention of Atrial Fibrillation by Renin-Angiotensin System Inhibition

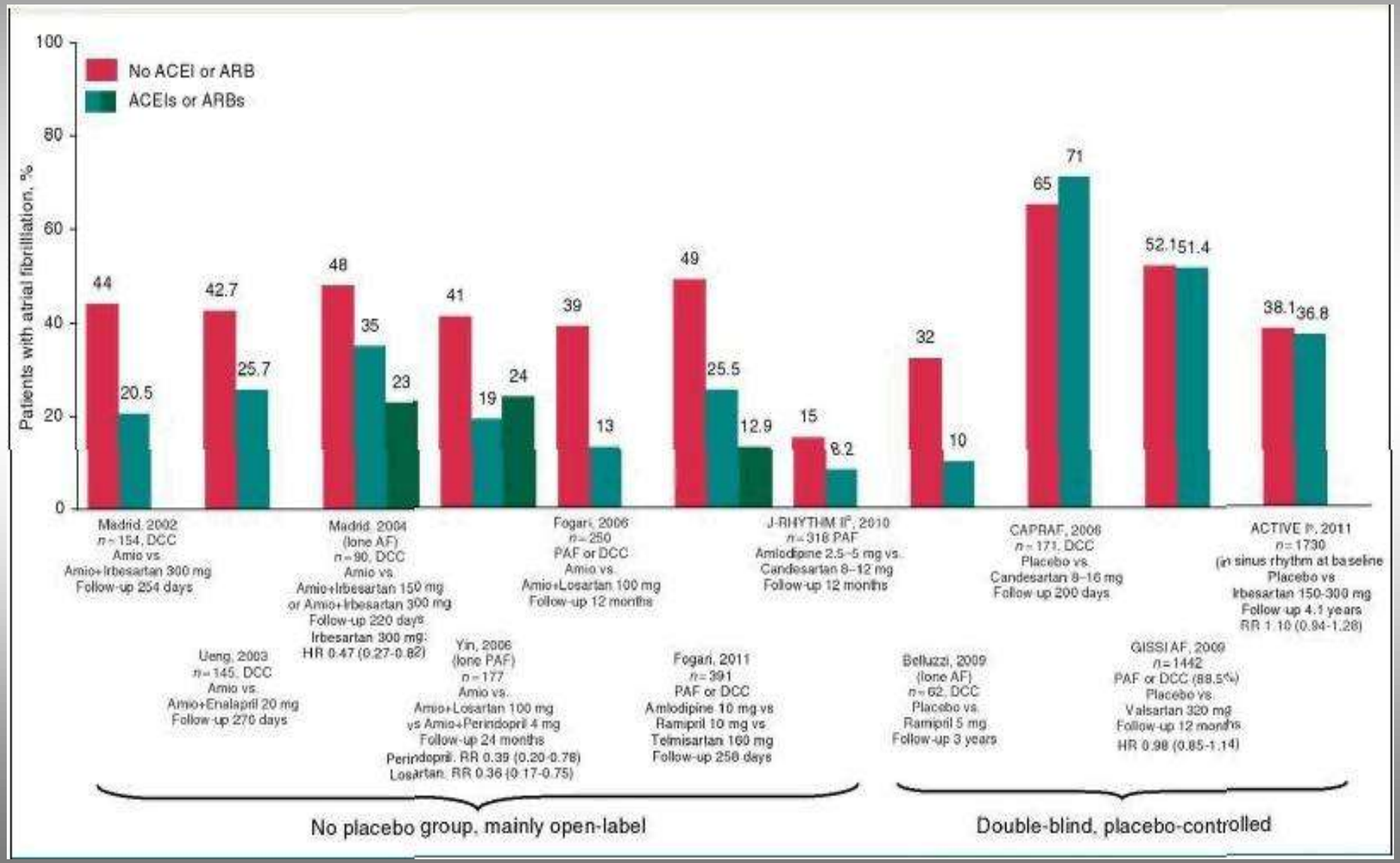
A Meta-Analysis

Вторичная профилактика ФП



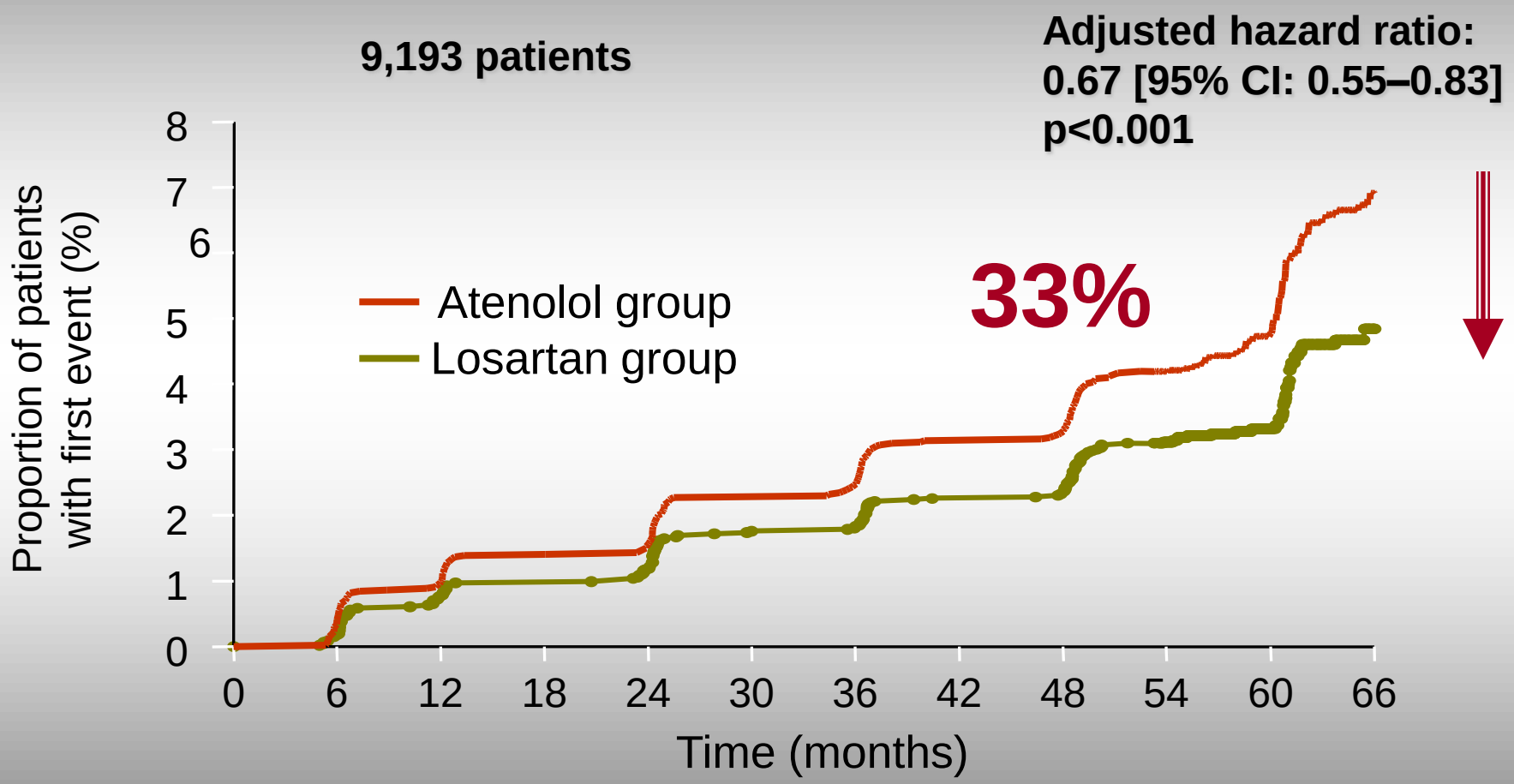
J Am Coll Cardiol, 2010; 55:2299-2307

% пациентов с ФП, которые дополнительно к амиодарону получали/не получали блокатор РАС



Фибрилляция предсердий

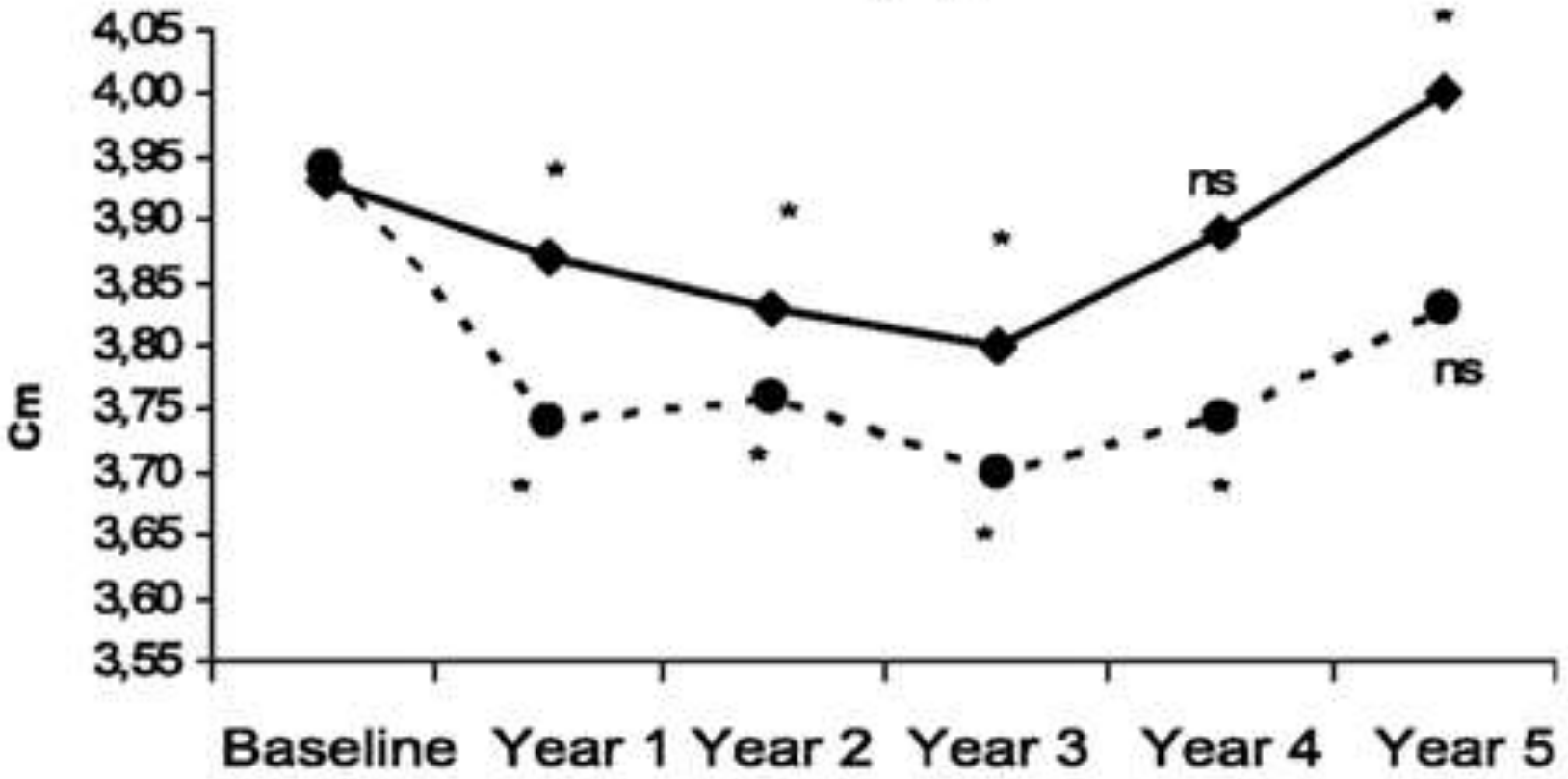
ARBs reduce risk of AF in humans (LIFE Study)



CI = confidence interval

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

Figure 1. Mean left atrial diameter at baseline and at annual echocardiograms in patients randomly assigned to atenolol- (—) or losartan- (--) based antihypertensive treatment (*P<0.01 vs baseline within group).



Losartan (n)	442	426	396	380	356	171
Atenolol (n)	439	421	394	366	362	171

Gerdts E et al. Hypertension 2007;49:311-316

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Left Atrial Size and Risk of Major Cardiovascular Events During Antihypertensive Treatment : Losartan Intervention for Endpoint Reduction in Hypertension Trial

Eva Gerdts, Kristian Wachtell, Per Omvik, Jan Erik Otterstad, Lasse Oikarinen, Kurt Boman, Björn Dahlöf and Richard B. Devereux

Hypertension 2007, 49:311-316: originally published online December 18, 2006

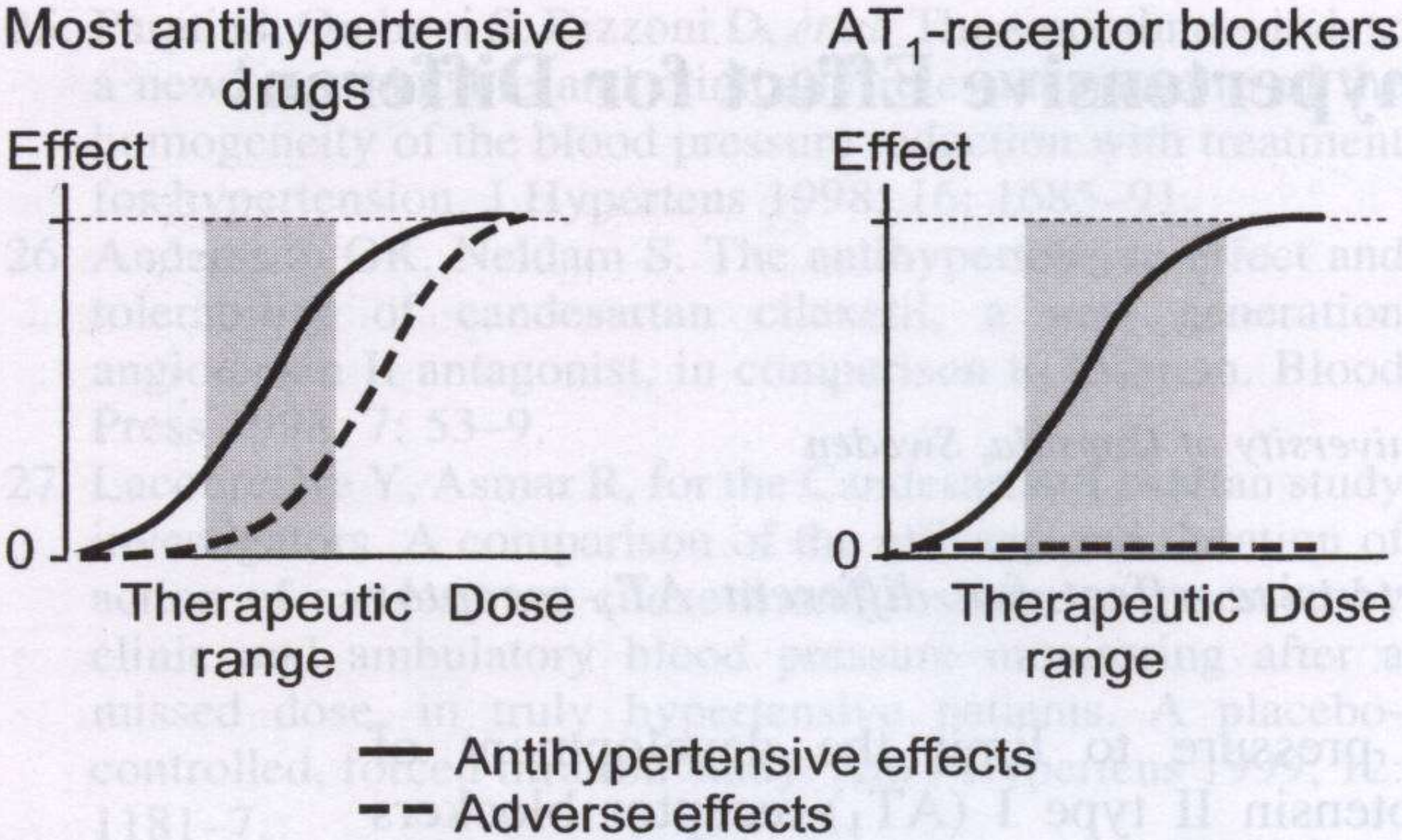
TABLE 2. Correlates of LA Diameter Reduction During 4.8 Years of Randomized Losartan– or Atenolol–Based Antihypertensive Therapy Evaluated by Multiple Linear Regression Analysis (Multiple R =0.29; *P*<0.001)

Variable	B	SE	β	*t*	*P*
Baseline LA diameter/height, cm/m	0.82	0.05	0.46	15.85	<0.001
Black	0.14	0.05	0.09	2.98	0.003
LV mass reduction, per SD (40 g)	0.04	0.02	0.07	2.30	0.023
LV ejection fraction increase, per SD (8%)	0.03	0.02	0.06	1.92	0.056
New–onset atrial fibrillation	−0.14	0.06	−0.07	−2.34	0.019
New–onset mitral regurgitation	−0.12	0.03	−0.10	−3.52	0.001
Systolic blood pressure reduction, per SD (19 mm Hg)	0.01	0.01	0.01	0.21	0.832
Heart rate reduction, per SD (12 bpm)	−0.03	0.02	−0.05	−1.64	0.102
Losartan therapy	0.15	0.03	0.14	4.63	<0.001

TABLE 3. Association Between LA Diameter/Height Measured by 2D Echocardiography at Baseline LA Diameter/Height and Subsequent Primary Combined CV Event (Combined CV Death, Myocardial Infarction, and Stroke, n=88) in Hypertensive Patients During 4.8 Years of Randomized Losartan- or Atenolol-Based Antihypertensive Therapy Evaluated by Cox Regression Analysis

Variable	Hazard Ratio	95% Confidence Intervals	*P*
Baseline LA diameter/height, cm/m	1.98	1.02 to 3.83	0.042
Framingham risk score	1.05	1.03 to 1.07	<0.001
Black	1.21	0.66 to 2.19	0.538
Echocardiographic LV hypertrophy	1.07	0.65 to 1.77	0.800
History of atrial fibrillation	3.30	1.62 to 6.72	0.001
History of congestive heart failure	1.41	0.34 to 5.83	0.634
Losartan-based therapy	0.97	0.64 to 1.48	0.898

HYPERTENSION 2007:49:311-316



those on placebo. In a thorough Cochrane meta-analysis, withdrawal rates due to adverse effects in a total of 46 studies and 13 451 patients were significantly lower on ARBs than on placebo [RR 0.68 (95% CI 0.54–0.87)].[16] In contrast, the Cochrane meta-analysis of 92 studies and 12 954 patients documented that

Трайлы по исследованию антиаритмической эффективности блокаторов ренин-ангиотензиновой системы 2010-2014

Study	Number of patients	Drug and dose	Primary or secondary prevention	Clinic setting	Primary endpoint	Follow-up	Expected completion, year
CTAF 2, NCT00461903	320	Perindopril 8 mg/day	Secondary	Paroxysmal or persistent AF in hypertension	Time to first sustained recurrence of AF	6 months	Not stated
DRAFT, NCT00343499	200	Valsartan 160–320 mg/day	Secondary	Post-cardioversion	Time to first recurrence of AF	Not stated	Terminated because of problems with recruitment
CREATIVE-AF, NCT00613496	60	Irbesartan 150–300 mg/day	Secondary	Persistent AF or permanent AF	Changes in biomarkers of oxidative stress and adhesion molecules[a]	22 weeks	2010
EPLERAF, NCT00647192	220	Eplerenone 50 mg/day	Secondary	Post-cardioversion	Recurrence of AF	8 weeks	2011
RACE 3, NCT00877643	250	Aldosterone antagonist, statin (type and dose not specified)	Secondary	Recent-onset persistent AF and mild-to-moderate CHF	Maintenance of sinus rhythm post-cardioversion	1 year	2012
Taichung study, NCT00689598	30	Spironolactone 25–50 mg/day	Secondary	Paroxysmal AF	Time to first ECG-confirmed recurrence of AF	3 months	2011
PREFACE, NCT00736294	390	Ramipril 5 mg/day	Primary	Post-atrial flutter ablation	Clinically relevant symptomatic or asymptomatic AF[a]	1 year	2014
Taiwan study, NCT00647257	220	Losartan 100 mg/day	Primary	Sinus node dysfunction treated with pacemaker	Proportion of patients with any AF and permanent AF	1 year	Not stated
Vanderbilt study, NCT00141778	777	Ramipril, spironolactone (dose not specified)	Primary	Heart surgery	ECG-documented AF or flutter	In hospital	2010
PRESAGE NCT01281787	300	Losartan 50 mg/day	Primary	Surgery for lung cancer	Incidence of postoperative AF	10 days	2013

Выводы:

1.Первичная профилактика ФП: эффект блокаторов РАС у пациентов с ГЛЖ и/или СН

2. Вторичная профилактика ФП: эффект блокаторов РАС после кардиоверсии при персистирующей ФП и медикаментозной профилактике ФП.
Если больной получает амиодарон антиаритмический эффект блокаторов РАС нивелируется

3. Необходимы новые исследования по изучению эффективности блокаторов РАС.

Эффективное СНИЖЕНИЕ АД

КОМПЛАЙЕНС

Хорошая переносимость

Надежная органопротекция

Улучшение прогноза