ΠΕΜΠΤΗ 18 ΦΕΒΡΟΥΑΡΙΟΥ 2010

ΟΜΑΔΑ ΕΡΓΑΣΙΑΣ ΑΡΤΗΡΙΑΚΗΣ ΥΠΕΡΤΑΣΗΣ

Α΄ Στρογγυλό Τραπέζι: Υπέρταση και Καρδιά

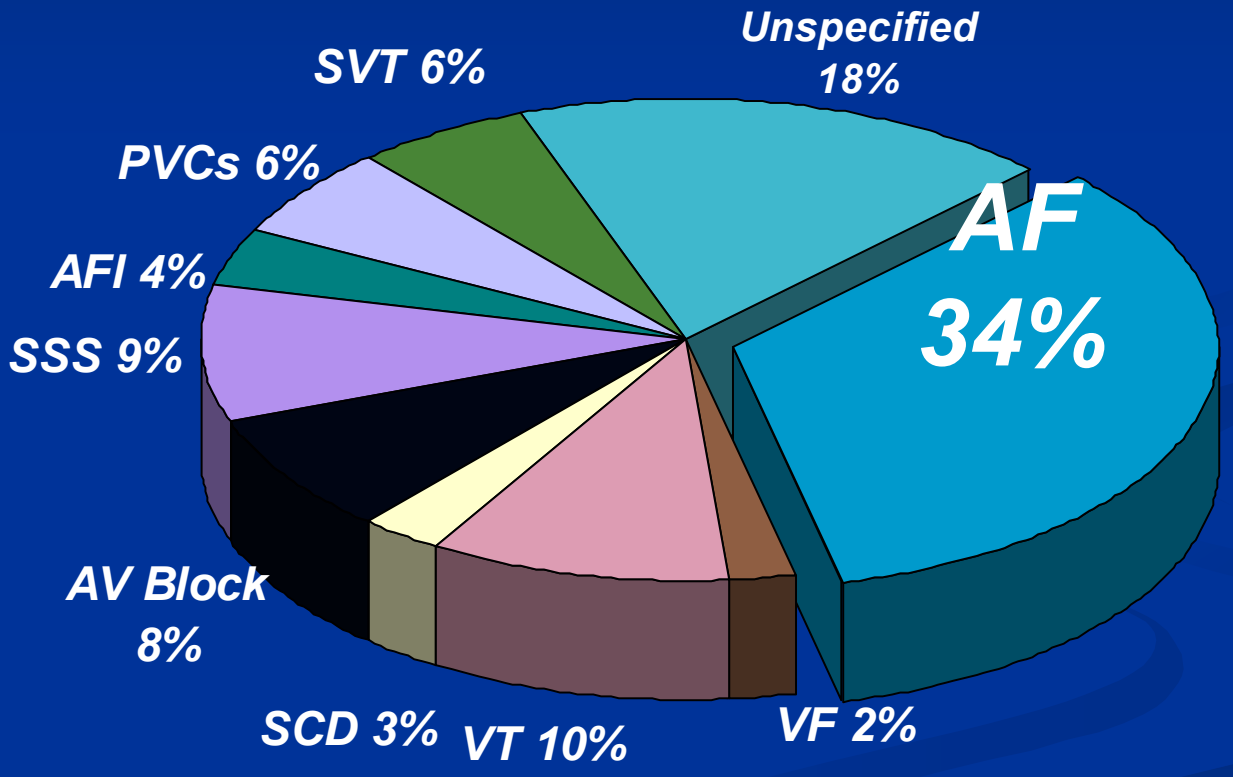
Αρτηριακή υπέρταση και κολπική μαρμαρυγή

Κακκάβας Απόστολος, Επιμελητής Β' Καρδιολογίας

ΓΝΑ ' Η Ελπίς'

Atrial Fibrillation: a common disease

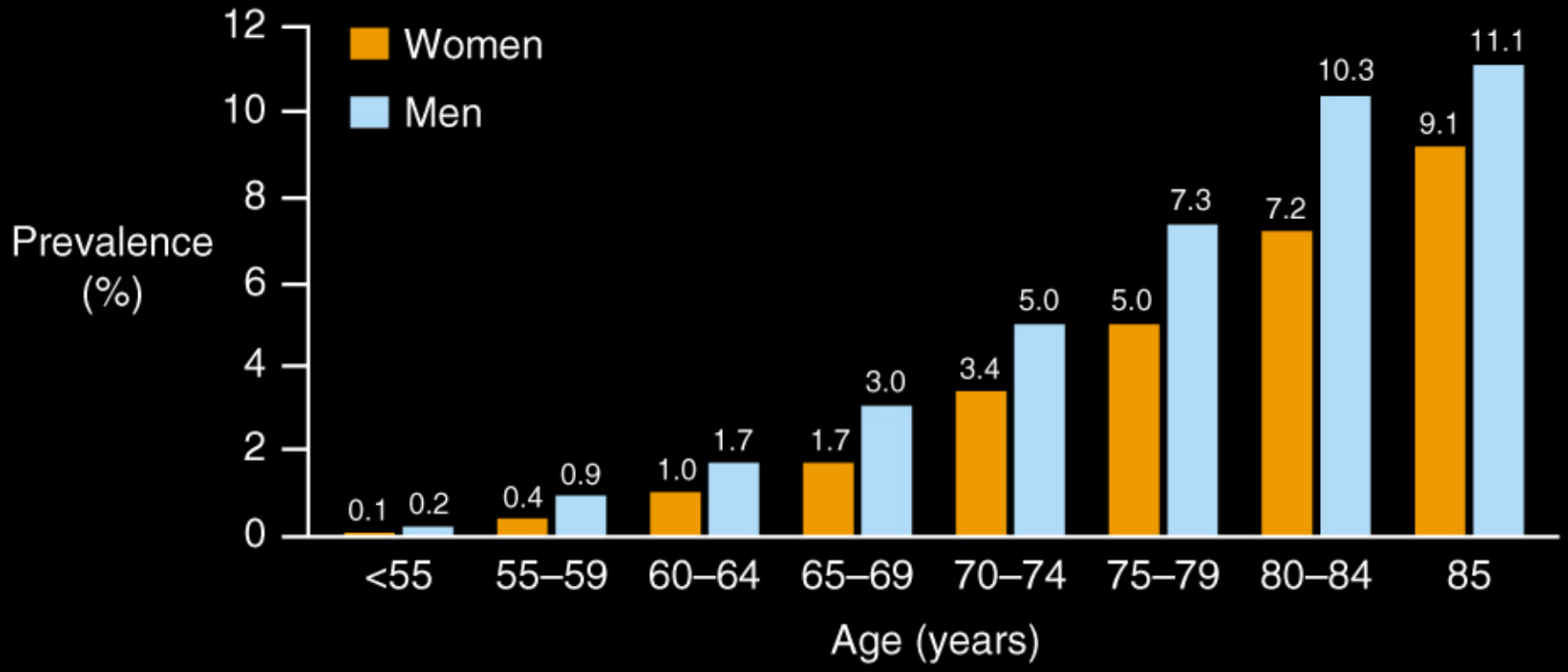
AF accounts for 1/3 of all patient discharges with arrhythmia as the principal diagnosis



Baily D. J Am Coll Cardiol 1992;19(3):41A

ATRIA: Prevalence of AF by age and sex

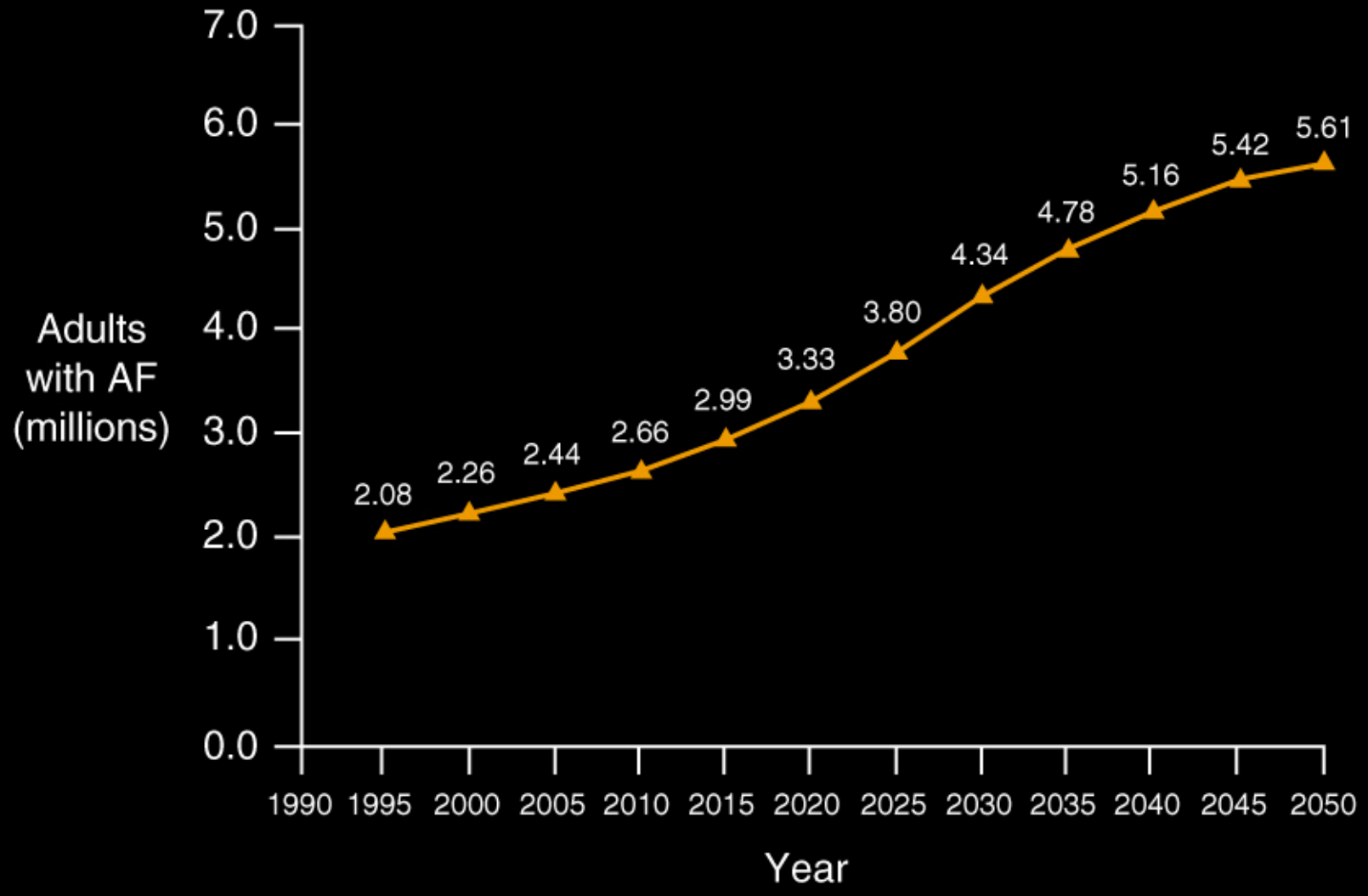
17,974 adults with AF between 1996–1997; study population 1.89 million



Anticoagulation and Risk Factors in Atrial Fibrillation

Go AS, et al. *JAMA*. 2001;285:2370-2375.

ATRIA: Projected number of patients with AF



Anticoagulation and Risk Factors in Atrial Fibrillation

Go AS, et al. *JAMA*. 2001;285:2370-2375.

Stroke risk is increased in AF

Framingham Heart Study, 30-year follow-up, N = 5184

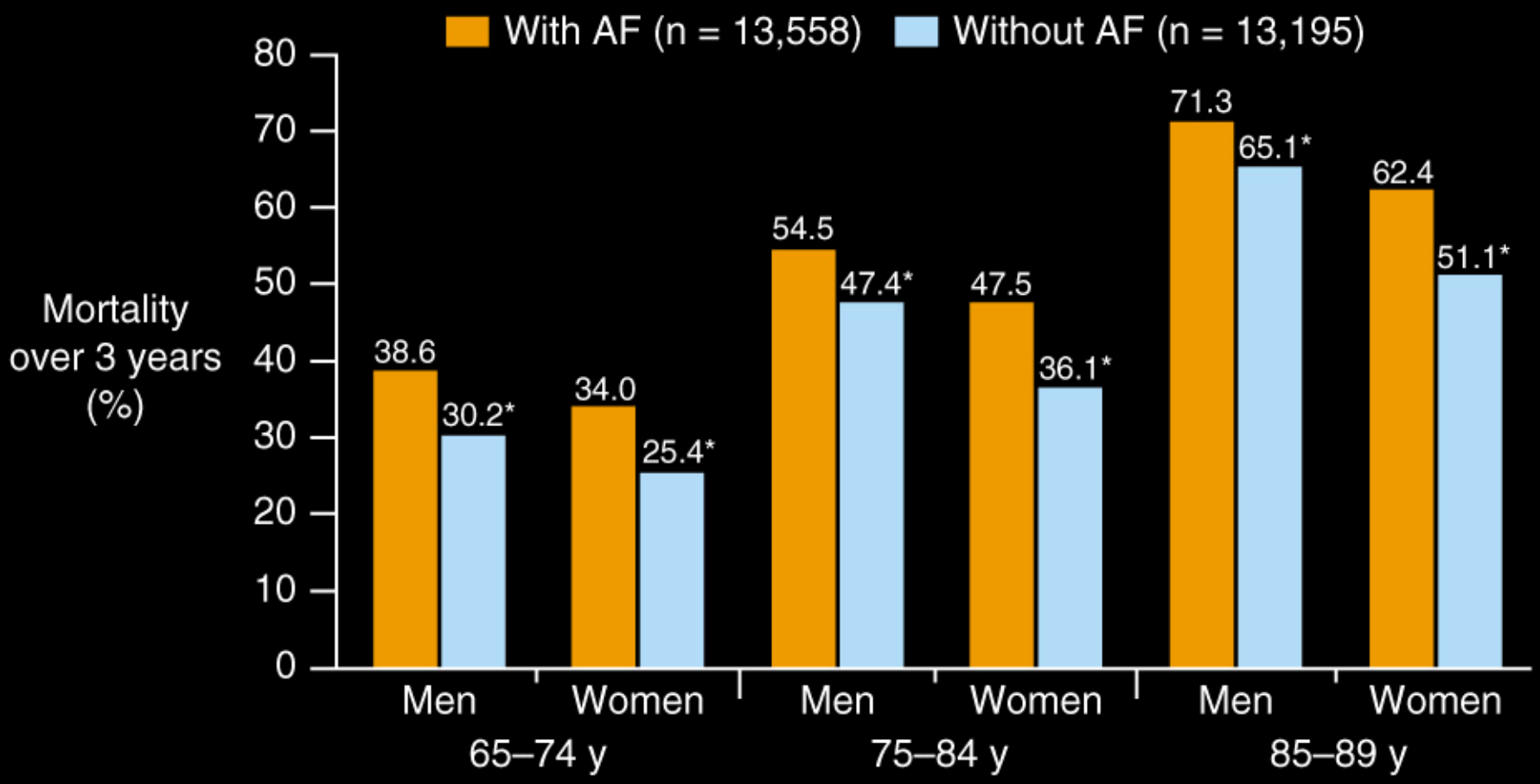
Age group	Prevalence AF	Stroke rate (per 1000 patient-years)		Population attributable risk (%)*
		AF–	AF+	
60–69	1.8%	4.5	21.2	7.3
70–79	4.7%	9.0	48.9	16.5
80–89	10.2%	14.3	71.4	30.8

*Adjusted for BP

Adapted from Wolf PA, et al. *Arch Intern Med.* 1987;147:1561-1564.

Mortality and AF

Hospitalized patients with CV disease



*Significantly different from patients with AF at $P < 0.05$

Wolf PA, et al. *Arch Intern Med.* 1998;158:229-234.

Atrial Fibrillation and Isolated Systolic Hypertension

The Systolic Hypertension in the Elderly Program and Systolic Hypertension in the Elderly Program-Extension Study

Tudor D. Vagaonescu, Alan C. Wilson, John B. Kostis

Abstract—We performed a post hoc analysis of the Systolic Hypertension in the Elderly Program database to assess the incidence of atrial fibrillation in the elderly hypertensive population, its influence on cardiovascular events, and whether antihypertensive treatment can prevent its onset. The Systolic Hypertension in the Elderly Program was a double-blind placebo-controlled trial in 4736 subjects with isolated systolic hypertension aged ≥60 years. Atrial fibrillation was an exclusion criterion from the trial. Participants were randomly assigned to stepped care treatment with chlorthalidone and atenolol (n=2365) or placebo (n=2371). The occurrence of atrial fibrillation and cardiovascular events over 4.7 years as well as the determination of cause of death at 4.7 and 14.3 years were followed. Ninety-eight subjects (2.06%) developed atrial fibrillation over 4.7 years mean follow-up, without significant difference between treated and placebo groups. Atrial fibrillation increased the risk for: total cardiovascular events (RR 1.69; 95% CI 1.21 to 2.36), rapid death (RR 3.29; 95% CI 1.08 to 10.00), total (RR 5.10; 95% CI 3.12 to 8.37) and nonfatal left ventricular failure (RR 5.31; 95% CI 3.09 to 9.13). All-cause and total cardiovascular death were significantly increased in the atrial fibrillation group at 4.7 years (HR 3.44; 95% CI 2.18 to 5.42; HR 2.39; 95% CI 1.05 to 5.43) and 14.3 years follow-up (HR 2.33; 95% CI 1.83 to 2.98; HR 2.21; 95% CI 1.54 to 3.17). Atrial fibrillation increased the risk for total cardiovascular events, rapid death, and left ventricular failure. All-cause mortality and total cardiovascular mortality were significantly increased in hypertensives with atrial fibrillation at 4.7 and 14.3 years follow-up. (*Hypertension*. 2008;51:1552-1556.)

Αρτηριακή Υπέρταση → Κολπική Μαρμαρυγή

Benjamin E et al, Framingham Heart Study, JAMA 1994:

- DM (OR, 1.4 for men and 1.6 for women), HTN (OR, 1.5 for men and 1.4 for women), CHF (OR, 4.5 for men and 5.9 for women), and valve disease (OR, 1.8 for men and 3.4 for women) were significantly associated with risk for AFib in both sexes.
- Modification of risk factors for CVD may have the added benefit of diminishing the incidence of AF

Psaty BM et al, Circulation 1997:

The use of diuretics, a history of valvular HD, CHD, advancing age, higher levels of SBP, height, glucose and left atrial size were all associated with an increased risk of AF

Kannel WB et al, Am J Cardiol. 1998:

Because of its high prevalence in the population, HTN was responsible for more AF in the population (14%) than any other risk factor

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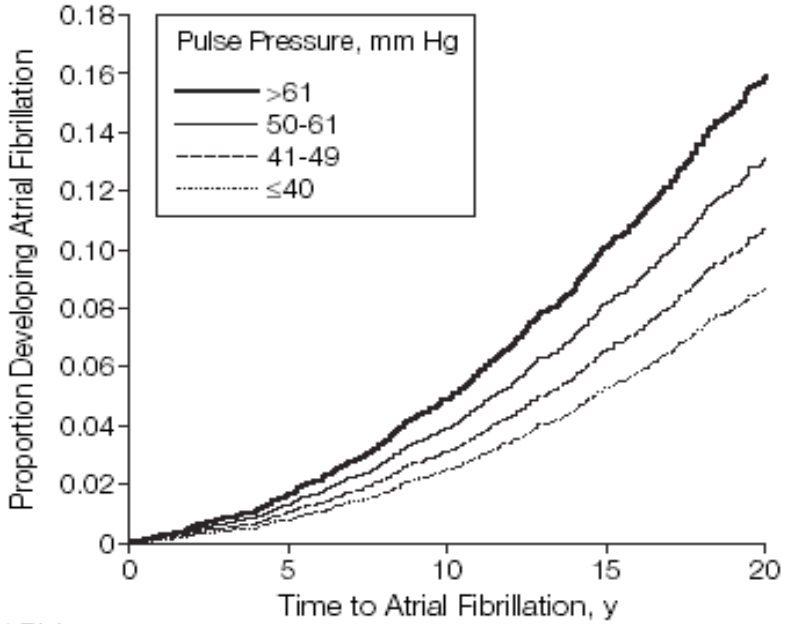
Pulse Pressure and Risk of New-Onset Atrial Fibrillation

Gary F. Mitchell; Ramachandran S. Vasan; Michelle J. Keyes; et al.

JAMA. 2007;297(7):709-715 (doi:10.1001/jama.297.7.709)

Figure. Incidence of Atrial Fibrillation According to Quartiles of Pulse Pressure



No. at Risk

Pulse Pressure, mm Hg					
>61	1293	1074	793	535	333
50-61	1341	1227	1065	872	666
41-49	1358	1300	1210	1096	947
≤40	1339	1307	1253	1187	1067

Estimates of cumulative incidence of atrial fibrillation according to quartile of pulse pressure. Cut points denoting approximate quartiles of pulse pressure were at 40, 49, and 61 mm Hg. Estimates are adjusted for age, sex, and competing risk of mortality.

Influence of Systolic and Diastolic Blood Pressure on the Risk of Incident Atrial Fibrillation in Women

David Conen, MD, MPH; Usha B. Tedrow, MD, MSc; Bruce A. Koplan, MD, MPH; Robert J. Glynn, ScD; Julie E. Buring, ScD; Christine M. Albert, MD, MPH

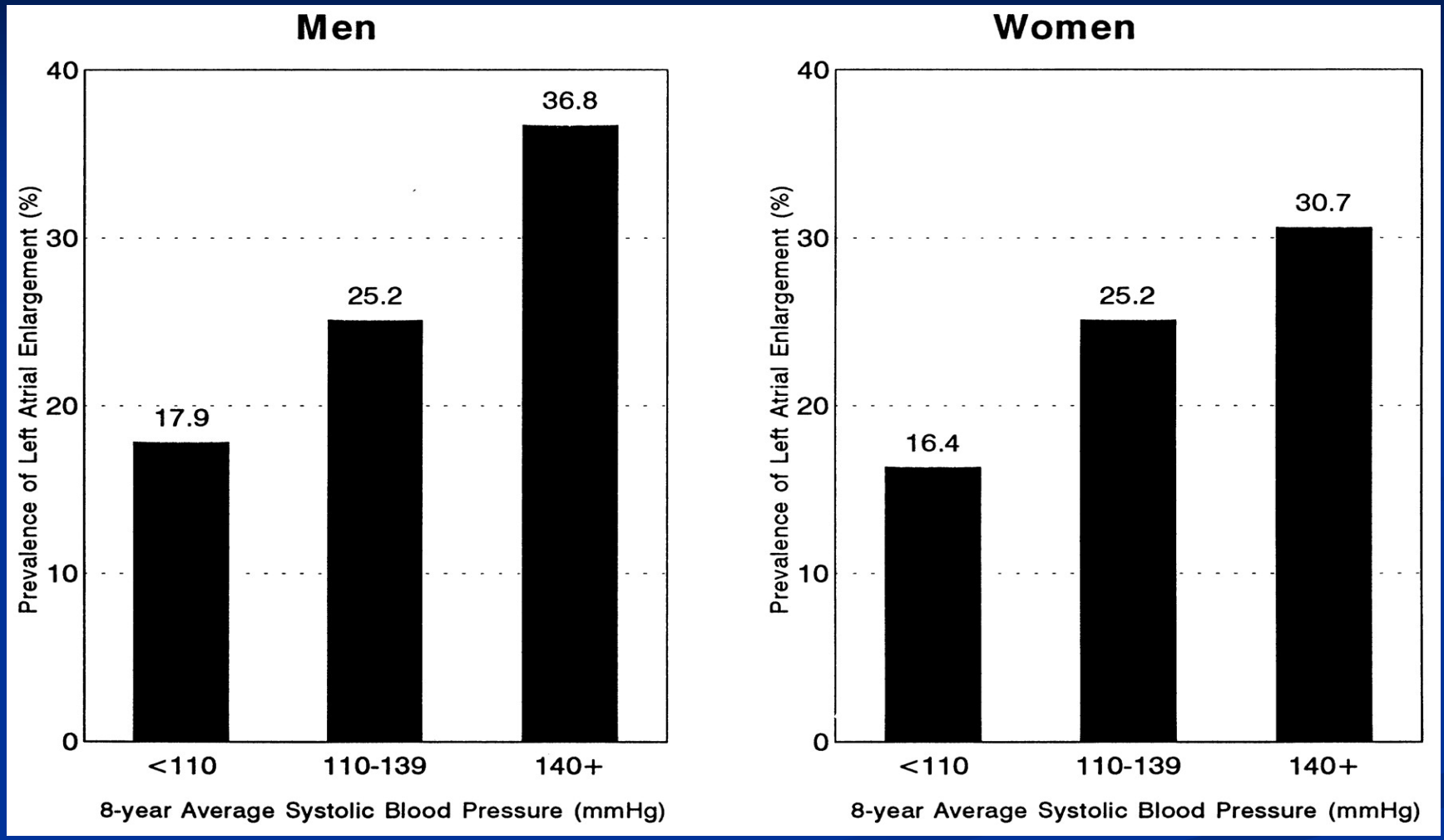
Background—The influence of systolic and diastolic blood pressure (BP) on incident atrial fibrillation (AF) is not well studied among initially healthy, middle-aged women.

Methods and Results—A total of 34 221 women participating in the Women's Health Study were prospectively followed up for incident AF. The risk of AF across categories of systolic and diastolic BP was compared by use of Cox proportional-hazards models. During 12.4 years of follow-up, 644 incident AF events occurred. Using BP measurements at baseline, we discovered that the long-term risk of AF was significantly increased across categories of systolic and diastolic BP. Multivariable-adjusted hazard ratios for systolic BP categories (<120, 120 to 129, 130 to 139, 140 to 159, and ≥160 mm Hg) were 1.0, 1.00 (95% CI, 0.78 to 1.28), 1.28 (95% CI, 1.00 to 1.63), 1.56 (95% CI, 1.22 to 2.01), and 2.74 (95% CI, 1.77 to 4.22) (*P* for trend <0.0001). Adjusted hazard ratios across baseline diastolic BP categories (<65, 65 to 74, 75 to 84, 85 to 89, 90 to 94, and ≥95 mm Hg) were 1.0, 1.17 (95% CI, 0.81 to 1.69), 1.18 (95% CI, 0.84 to 1.65), 1.53 (95% CI, 1.05 to 2.23), 1.35 (95% CI, 0.82 to 2.22), and 2.15 (95% CI, 1.21 to 3.84) (*P* for trend=0.004). When BP changes over time were accounted for in updated models, multivariable-adjusted hazard ratios were 1.0, 1.14 (95% CI, 0.89 to 1.46), 1.37 (95% CI, 1.07 to 1.76), 1.71 (95% CI, 1.33 to 2.21), and 2.21 (95% CI, 1.45 to 3.36) (*P* for trend <0.0001) for systolic BP categories and 1.0, 1.12 (95% CI, 0.82 to 1.52), 1.13 (95% CI, 0.83 to 1.52), 1.30 (95% CI, 0.89 to 1.88), 1.50 (95% CI, 1.01 to 1.88), and 1.54 (95% CI, 0.75 to 3.14) (*P* for trend=0.026) for diastolic BP categories.

Conclusions—In this large cohort of initially healthy women, BP was strongly associated with incident AF, and systolic BP was a better predictor than diastolic BP. Systolic BP levels within the nonhypertensive range were independently associated with incident AF even after BP changes over time were taken into account. (***Circulation*. 2009;119:2146-2152.**)

Key Words: blood pressure ■ cardiovascular diseases ■ atrial fibrillation ■ epidemiology ■ hypertension ■ women

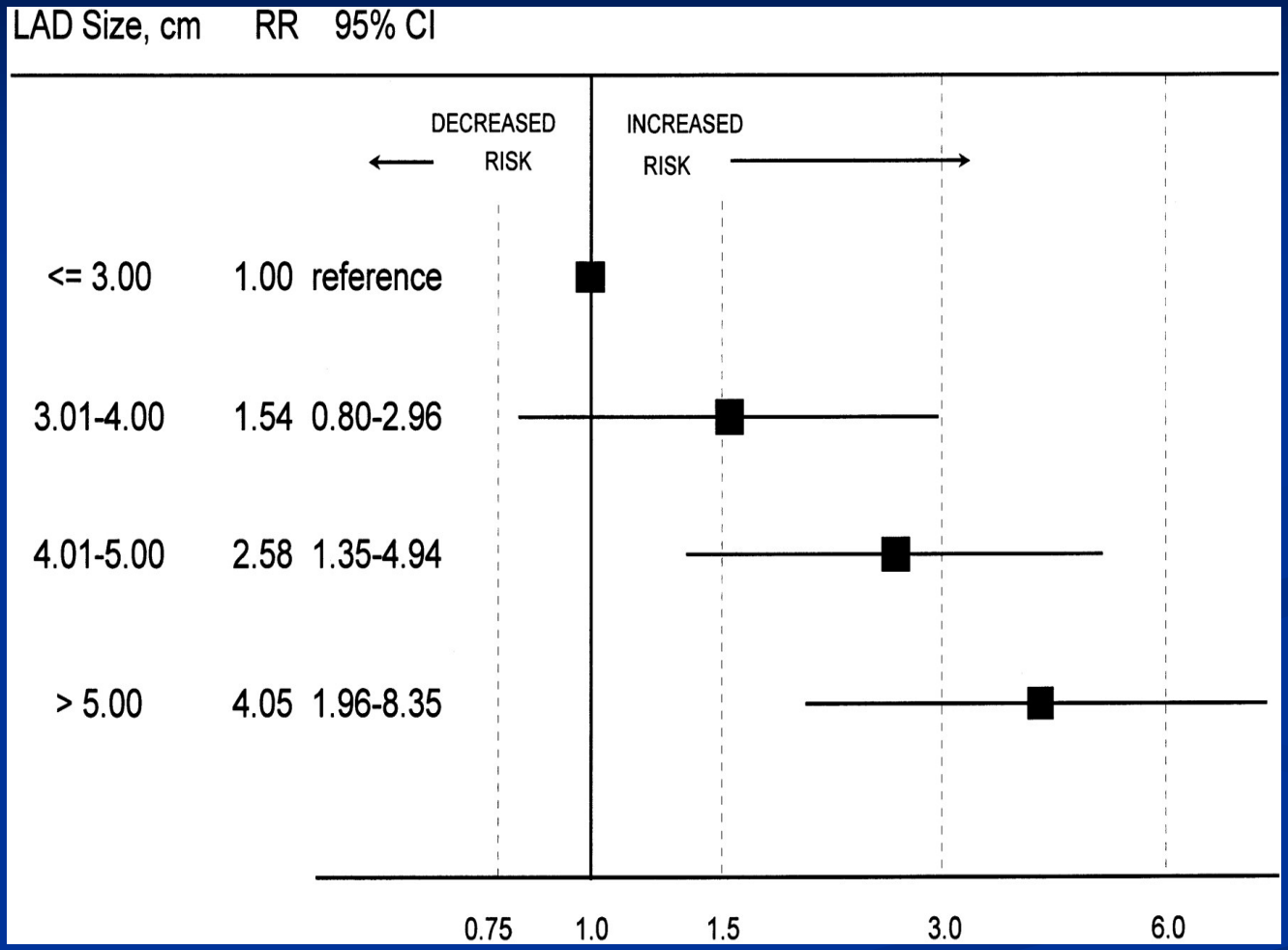
Age-adjusted prevalence of LA enlargement according to 8-year average SBP in men and women



Framingham Heart Study

Vaziri S.M. et al. Hypertension 1995;25:1155-1160

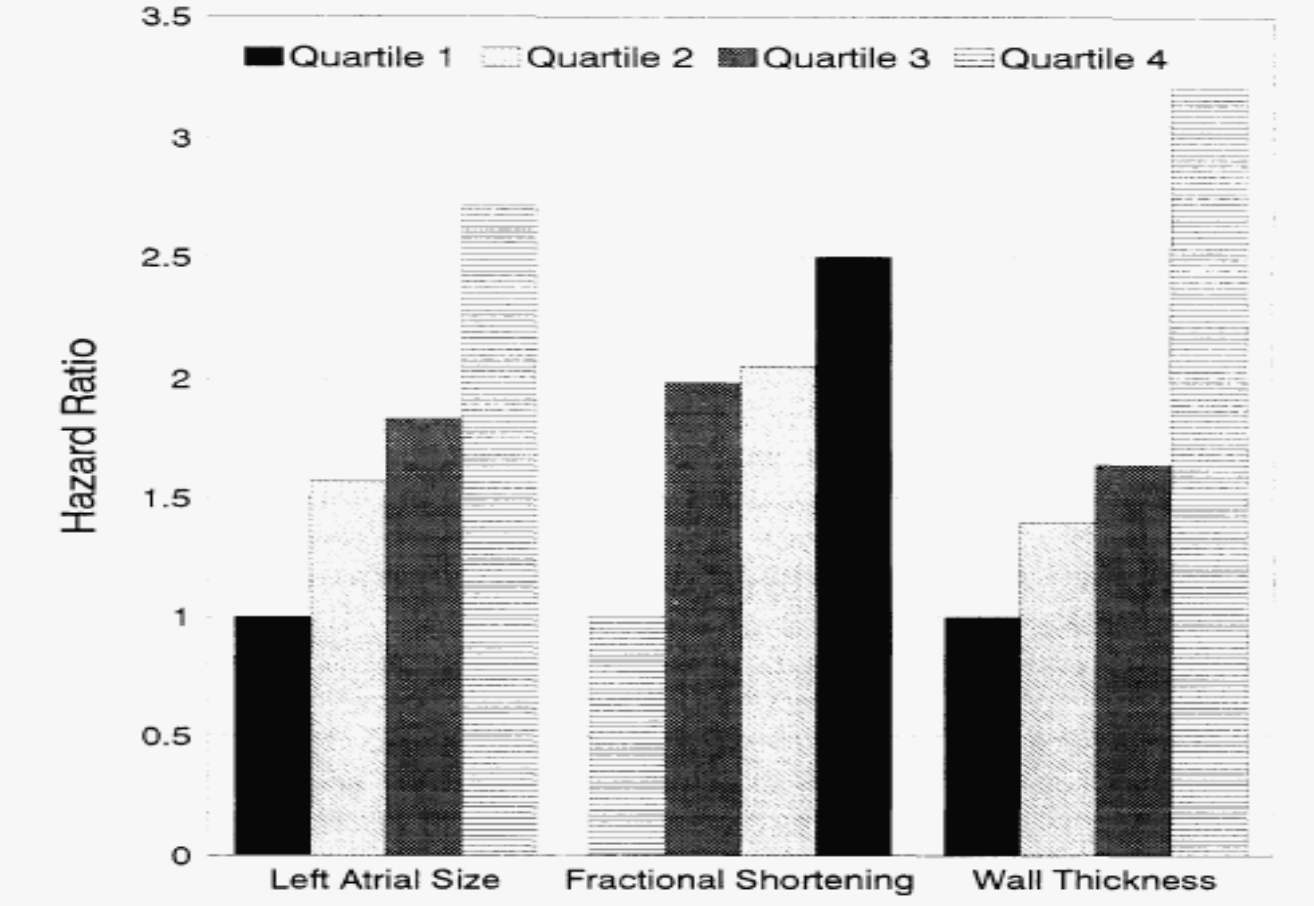
Association between LA size and the incidence of AF in the Cardiovascular Health Study



Psaty, B. M. et al. Circulation 1997;96:2455-2461

Echocardiographic Predictors of Nonrheumatic Atrial Fibrillation

The Framingham Heart Study



Varizi et al, Circulation 1994

Blood pressure control and risk of incident atrial fibrillation

Thomas et al. Am J Hypertens. 2008 October ; 21(10): 1111–1116

Background—Atrial fibrillation (AF) is a common arrhythmia that affects over 2 million people in the United States. We sought to determine whether the risk of incident AF among patients treated for hypertension differs by the degree of blood pressure control.

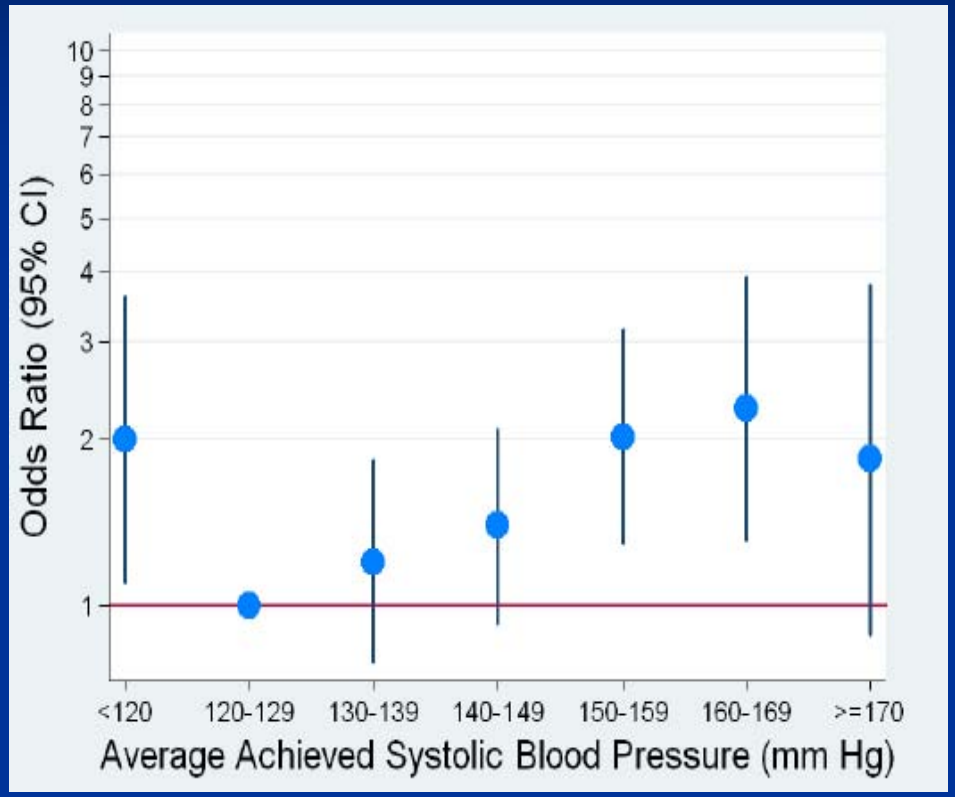
Methods—A population based, case-control study of 433 patients with verified incident AF and 899 controls was conducted to investigate the relationship between average achieved systolic (SBP) and diastolic (DBP) blood pressure and risk of AF. All patients were members of an integrated health care delivery system and were pharmacologically treated for hypertension. Medical records were reviewed to confirm the diagnosis of new onset AF and to collect information on medical conditions, health behaviors, and measured blood pressures. Average achieved SBP and DBP were calculated from the three most recent outpatient blood pressure measurements.

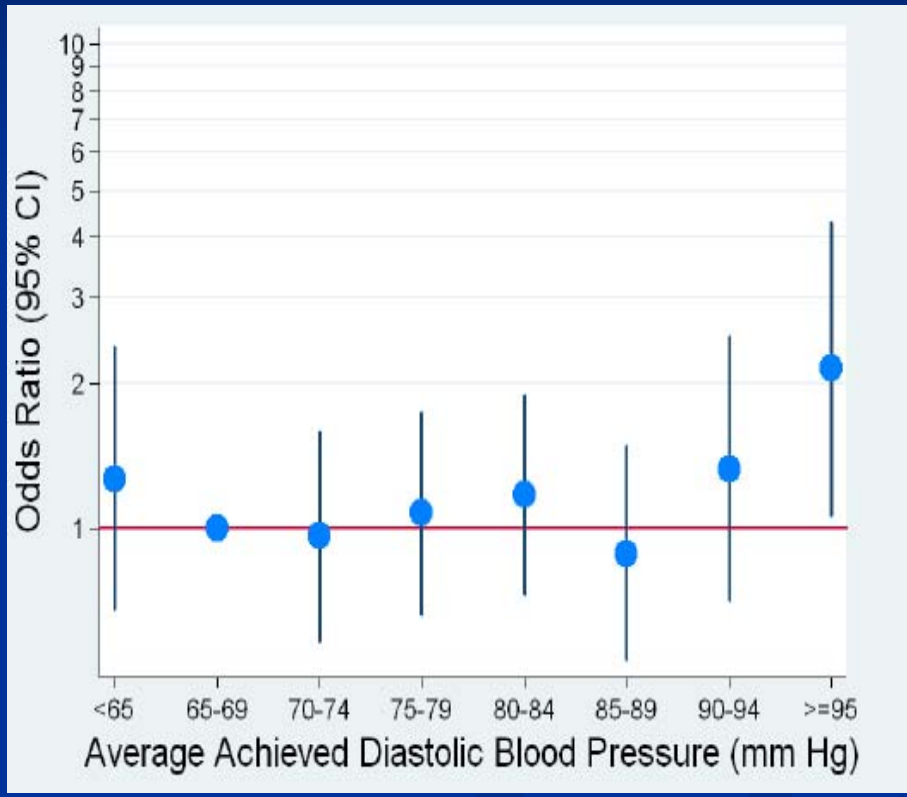
Results—Compared with the reference level of 120-129 mm Hg, for categories of average achieved SBP of <120, 130-139, 140-149, 150-159, 160-169 and ≥170 mm Hg, the odds ratios (95% confidence interval) for incident AF were 1.99 (1.10, 3.62), 1.19 (0.78, 1.81), 1.40 (0.93, 2.09), 2.02 (1.30, 3.15), 2.27 (1.31, 3.93) and 1.84 (0.89, 3.80), respectively. Based on the population attributable fraction (PAF), we estimated that, among patients with treated hypertension, 17.2% (95% CI 4.3%, 28.3%) of incident AF was attributable to an average achieved SBP ≥140 mmHg.

Conclusion—Among patients treated for hypertension, uncontrolled elevated SBP and SBP <120 mm Hg were associated with an increased risk of incident AF.

Blood pressure control and risk of incident atrial fibrillation

M.C. Thomas et al. Am J Hypertens. 2008 October ; 21(10): 1111–1116





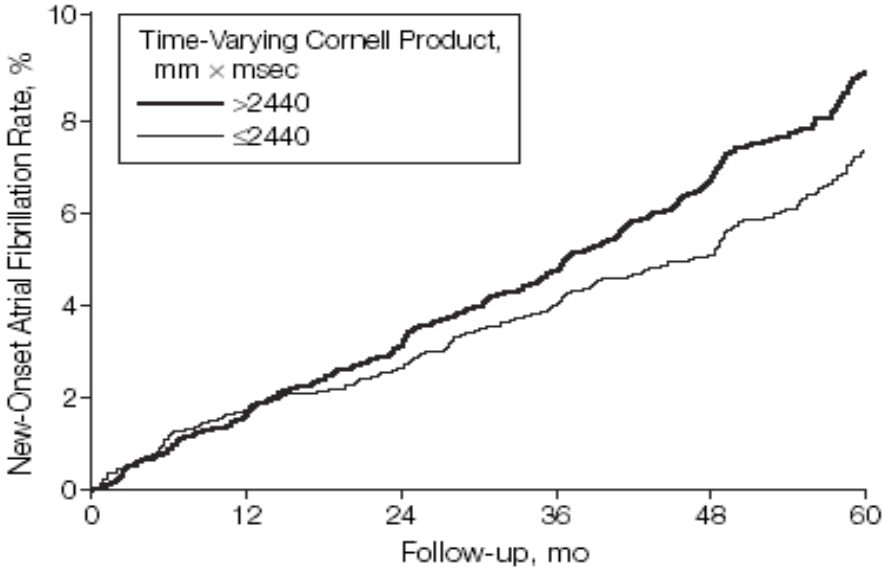
Odds ratios of incident Afib associated with average achieved SBP and DBP

Regression of Electrocardiographic Left Ventricular Hypertrophy and Decreased Incidence of New-Onset Atrial Fibrillation in Patients With Hypertension

Peter M. Okin; Kristian Wachtell; Richard B. Devereux; et al.

JAMA. 2006;296(10):1242-1248 (doi:10.1001/jama.296.10.1242)

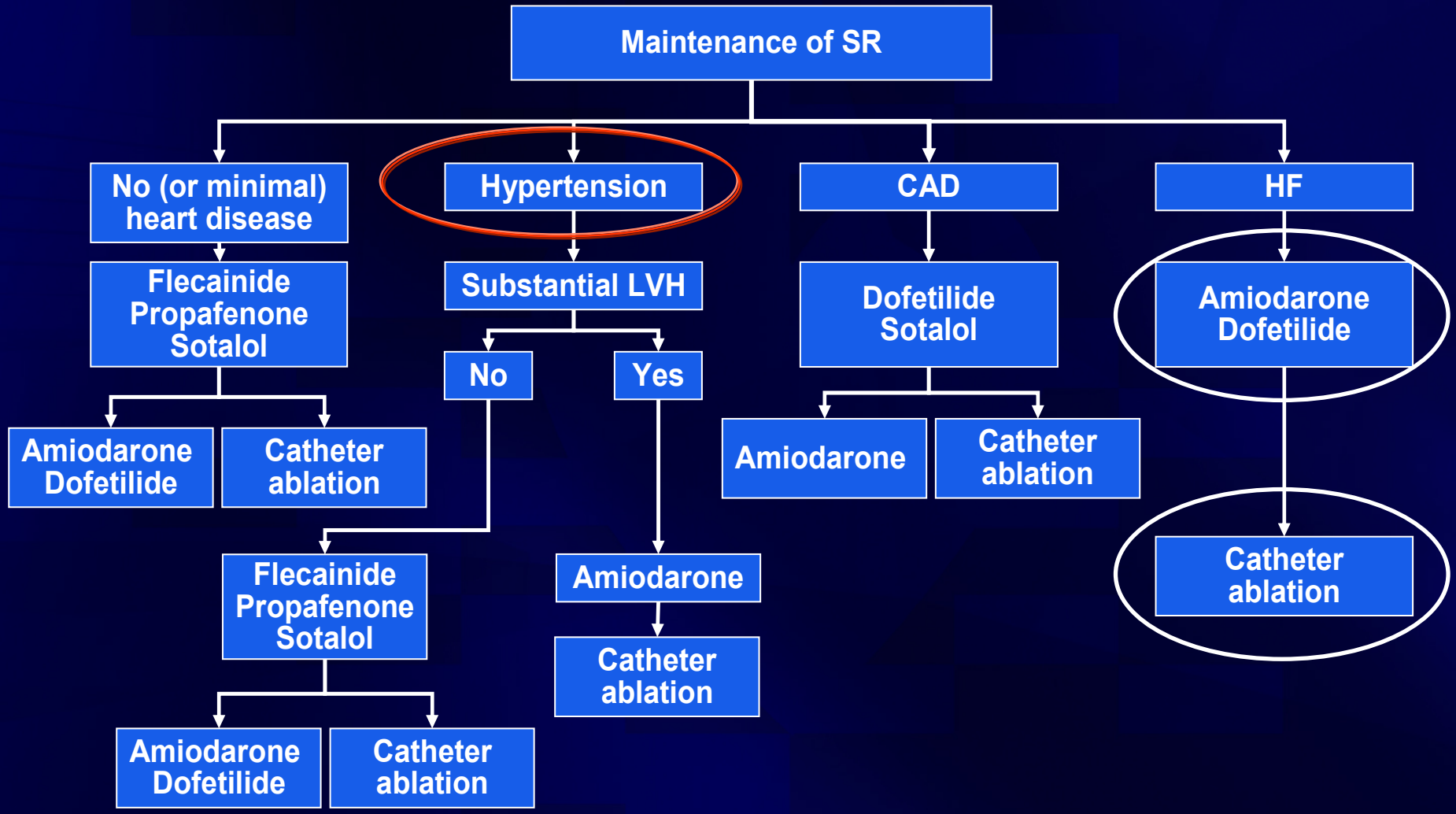
Figure. Rate of New-Onset Atrial Fibrillation



Time-Varying Cornell Product >2440 mm × msec						
Cumulative No. of Events	0	98	168	238	320	383
No. at Risk	5924	4169	3630	3321	3206	1378
Time-Varying Cornell Product ≤2440 mm × msec						
Cumulative No. of Events	0	57	91	150	198	262
No. at Risk	2907	3742	3833	3714	3525	1431

Rate is according to time-varying presence or absence of electrocardiographic left ventricular hypertrophy according to sex-specific Cornell voltage-duration product criteria partitioned at 2440 mm × msec. Patient group assignment is adjusted at the time of each electrocardiogram based on the value of Cornell product at each time point.

ACC/AHA/ESC 2006 AF rhythm-control guidelines



Fuster V et al. *Circulation*. 2006;114:e257-e354.

AF – Antithrombotic Therapy

TABLE 11. Risk Factors for Ischemic Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation

Risk Factors	Relative Risk
Previous stroke or TIA	2.5
Diabetes mellitus	1.7
History of hypertension	1.6
Heart failure	1.4
Advanced age (continuous, per decade)	1.4

TABLE 13. Antithrombotic Therapy for Patients With Atrial Fibrillation

Risk Category		Recommended Therapy
No risk factors		Aspirin, 81 to 325 mg daily
One moderate-risk factor		Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor		Warfarin (INR 2.0 to 3.0, target 2.5)*
Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

*If mechanical valve, target international normalized ratio (INR) greater than 2.5.
INR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.

ACC/AHA/ESC 2006

2007 Guidelines for the Management of Arterial Hypertension ESH / ESC

Journal of Hypertension 2007;25:1105-1187

- Increased LV mass and LA enlargement: independent predictors of the new-onset AF
- Hypertensive pts with these alterations appear to require intensive therapy

- BP control appears to be strictly required, when anticoagulant treatment is given, because stroke and bleeding episodes are more frequent when SBP is ≥140mmHg

- ACEIs - ARBs: less incidence of new AF - may be preferable antihypertensive agents
  Also in pts with previous episodes of AFib
- Conformation of large ongoing trials is desirable

- In permanent AFib: BBs and non-dihydropiridine Ca antagonists
  (in order to control ventricular rate)

Table 6 Conditions favouring use of some antihypertensive drugs versus others

Thiazide diuretics	Beta-blockers	Calcium antagonists (dihydropyridines)	Calcium antagonists (verapamil/diltiazem)
• Isolated systolic hypertension (elderly) • Heart failure • Hypertension in blacks	• Angina pectoris • Post-myocardial infarction • Heart failure • Tachyarrhythmias • Glaucoma • Pregnancy	• Isolated systolic hypertension (elderly) • Angina pectoris • LV hypertrophy • Carotid/Coronary Atherosclerosis • Pregnancy • Hypertension in blacks	• Angina pectoris • Carotid atherosclerosis • Supraventricular tachycardia

ACE inhibitors	Angiotensin receptor antagonists	Diuretics (antialdosterone)	Loop diuretics
• Heart failure • LV dysfunction • Post-myocardial infarction • Diabetic nephropathy • Non-diabetic nephropathy • LV hypertrophy • Carotid atherosclerosis • Proteinuria/ Microalbuminuria • Atrial fibrillation • Metabolic syndrome	• Heart failure • Post-myocardial infarction • Diabetic nephropathy • Proteinuria/Microalbuminuria • LV hypertrophy • Atrial fibrillation • Metabolic syndrome • ACEI-induced cough	• Heart failure • Post-myocardial infarction	• End stage renal disease • Heart failure

ACEI: ACE inhibitors; LV: Left Ventricle.

Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease

A Boldt, U Wetzel, J Lauschke, J Weigl, J Gummert, G Hindricks, H Kottkamp, S Dhein

Heart 2004;**90**:400–405. doi: 10.1136/hrt.2003.015347

See end of article for authors' affiliations

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Accepted 4 July 2003

Objective: To examine the hypothesis that major extracellular matrix (ECM) proteins are expressed differently in the left atrial tissue of patients in sinus rhythm (SR), lone atrial fibrillation (AF), and AF with underlying mitral valve disease (MVD).

Design: Case-control study.

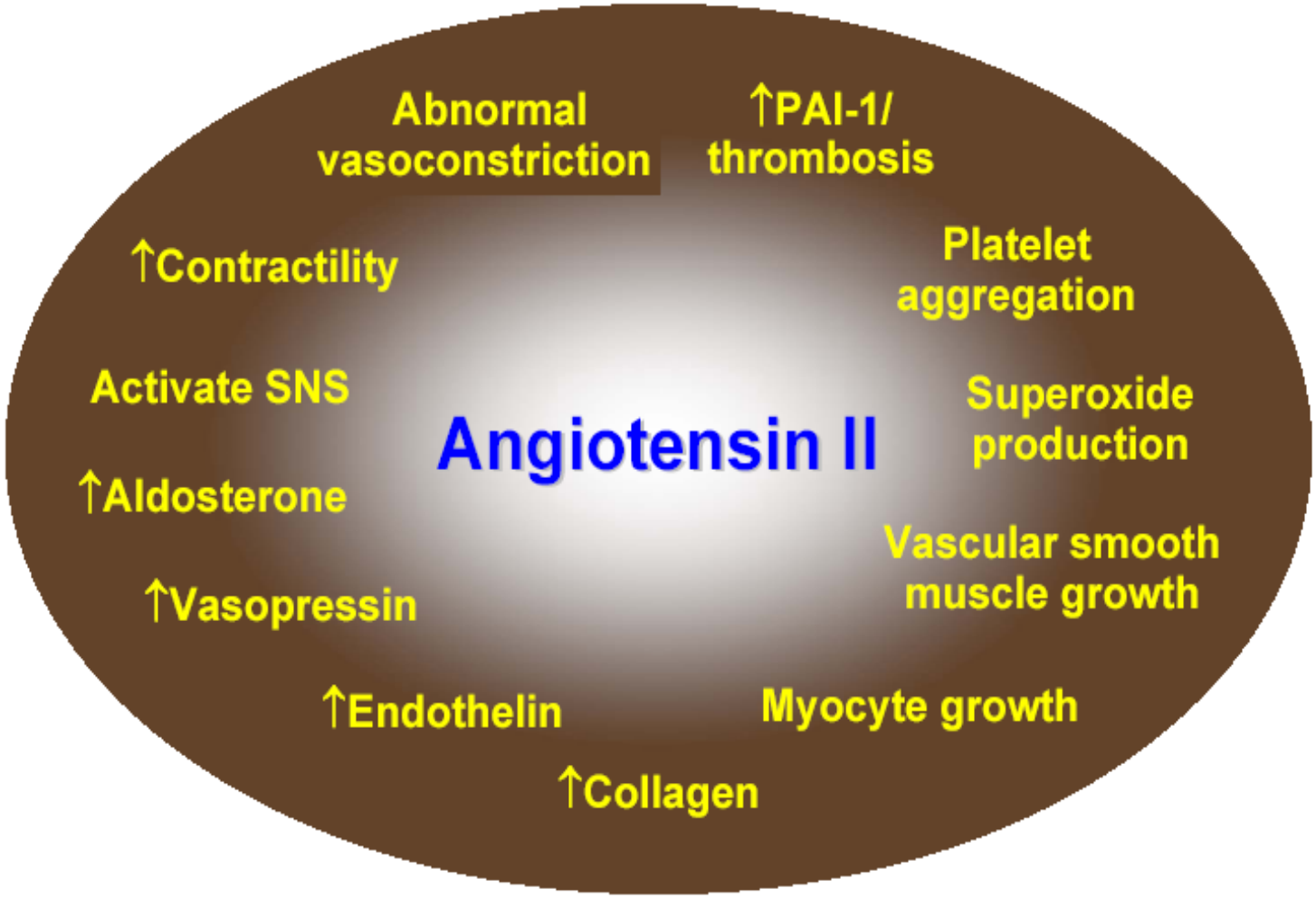
Patients: 118 patients with lone AF, MVD+AF, and SR.

Main outcome measures: Collagen I, collagen III, and fibronectin protein expression measured by quantitative western blotting techniques and immunohistochemical methods.

Results: Protein concentrations increased in patients with AF (all forms) compared with those in SR (all forms): collagen I (1.15 (0.11) *v* 0.45 (0.28), respectively; p = 0.002), collagen III (0.74 (0.05) *v* 0.46 (0.11); p = 0.002, and fibronectin (0.88 (0.06) *v* 0.62 (0.13); p = 0.08). Especially, collagen I was similarly enhanced in both lone AF (1.49 (0.15) and MVD+AF (1.53 (0.16) compared with SR (0.56 (0.28); both p = 0.01). Collagen III was not significantly increased in lone AF but was significantly increased in AF combined with MVD (0.84 (0.07) both compared with SR (0.46 (0.11); p = 0.01). The concentration of fibronectin was not significantly increased in lone AF and MVD+AF (both compared with SR). Furthermore, there was a similar degree of enhanced collagen expression in paroxysmal AF and chronic AF.

Conclusions: AF is associated with fibrosis. Forms of AF differ from each other in collagen III expression. However, there was no systematic difference in ECM expression between paroxysmal AF and chronic AF. Enhanced concentrations of ECM proteins may have a role in structural remodelling and the pathogenesis of AF as a result of separation of the cells by fibrotic depositions.

Pathophysiologic Effects of Angiotensin II



Burnier M, Brunner HR. *Lancet*. 2000;355:637–645.

Effects of Angiotensin-Converting Enzyme Inhibition on the Development of the Atrial Fibrillation Substrate in Dogs With Ventricular Tachypacing–Induced Congestive Heart Failure

Danshi Li, MD, PhD; Kaori Shinagawa, MD; Li Pang, MD; Tack Ki Leung, MD; Sophie Cardin, BSc; Zhiguo Wang, PhD; Stanley Nattel, MD

Background—Atrial structural remodeling creates a substrate for atrial fibrillation (AF), but the underlying signal transduction mechanisms are unknown. This study assessed the effects of ACE inhibition on arrhythmogenic atrial remodeling and associated mitogen-activated protein kinase (MAPK) changes in a dog model of congestive heart failure (CHF).

Methods and Results—Dogs were subjected to various durations of ventricular tachypacing (VTP, 220 to 240 bpm) in the presence or absence of oral enalapril 2 mg · kg^{-1} · d^{-1}. VTP for 5 weeks induced CHF, local atrial conduction slowing, and interstitial fibrosis and prolonged atrial burst pacing–induced AF. Atrial angiotensin II concentrations and MAPK expression were increased by tachypacing, with substantial changes in phosphorylated forms of c-Jun N-terminal kinase (JNK), extracellular signal–regulated kinase (ERK), and p38-kinase. Enalapril significantly reduced tachypacing-induced changes in atrial angiotensin II concentrations and ERK expression. Enalapril also attenuated the effects of CHF on atrial conduction (conduction heterogeneity index reduced from 3.1±0.4 to 1.9±0.2 ms/mm, $P<0.05$), atrial fibrosis (from 11.9±1.1% to 7.5±0.4%, $P<0.01$), and mean AF duration (from 651±164 to 218±75 seconds, $P<0.05$). Vasodilator therapy of a separate group of VTP dogs with hydralazine and isosorbide mononitrate did not alter CHF-induced fibrosis or AF promotion.

Conclusions—CHF-induced increases in angiotensin II content and MAPK activation contribute to arrhythmogenic atrial structural remodeling. ACE inhibition interferes with signal transduction leading to the AF substrate in CHF and may represent a useful new component to AF therapy. **(*Circulation*. 2001;104:2608-2614.)**

Enalapril Decreases the Incidence of Atrial Fibrillation in Patients With Left Ventricular Dysfunction

Insight From the Studies Of Left Ventricular Dysfunction (SOLVD) Trials

Emmanuelle Vermes, MD; Jean-Claude Tardif, MD; Martial G. Bourassa, MD; Normand Racine, MD; Sylvie Levesque, MSc; Michel White, MD; Peter G. Guerra, MD; Anique Ducharme, MD, MSc

Background—Atrial fibrillation (AF) is frequently encountered in patients with heart failure (HF) and is also a predictor of morbidity and mortality in this population. Recent experimental studies have shown electrical and structural atrial remodeling with increased fibrosis in animals with HF and have suggested a preventive effect of ACE inhibitors (ACEi) on the development of AF. To verify the hypothesis that ACEi prevent the development of AF in patients with HF, we conducted a retrospective analysis of the patients from the Montreal Heart Institute (MHI) included in the Studies Of Left Ventricular Dysfunction (SOLVD).

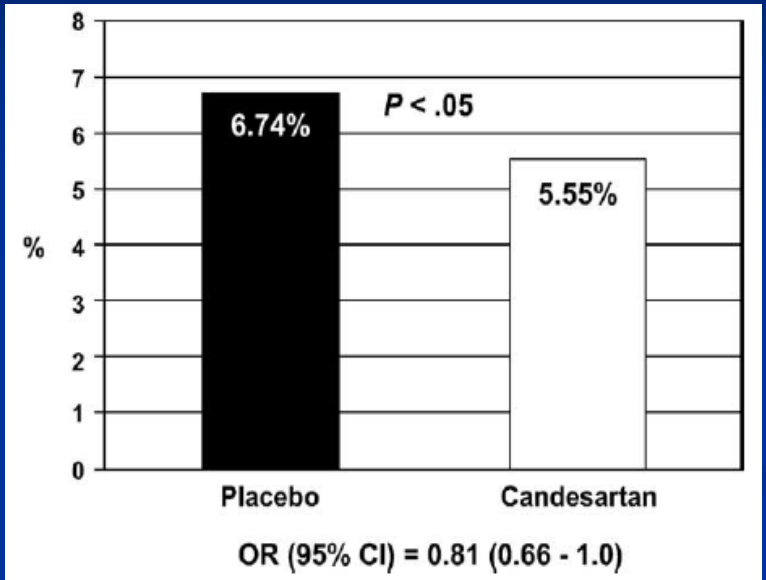
Methods and Results—Clinical charts were reviewed and serial ECGs interpreted by a single cardiologist blinded to drug allocation. Patients with AF or flutter on the baseline ECG were excluded. Baseline characteristics were obtained from the SOLVD databases. The mean follow-up was 2.9±1.0 years. Of the 391 patients randomly assigned at MHI, 374 were in sinus rhythm at the time of random assignment, with 186 taking enalapril and 188 taking placebo. Baseline characteristics were similar in the two groups except for a higher incidence of previous myocardial infarction in the enalapril group. Fifty-five patients had AF during the follow-up: 10 (5.4%) in the enalapril group and 45 (24%) in the placebo group ($P<0.0001$). By Cox multivariate analysis, enalapril was the most powerful predictor for risk reduction of AF (hazard ratio, 0.22; 95% CI, 0.11 to 0.44; $P<0.0001$).

Conclusions—Treatment with the ACEi enalapril markedly reduces the risk of development of atrial fibrillation in patients with left ventricular dysfunction. **(*Circulation*. 2003;107:2926-2931.)**

Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure:

Assessment of Reduction in Mortality and morbidity (CHARM) program

- 7601 pts with symptomatic CHF and reduced or preserved LV systolic function were randomized to Candesartan or placebo
- Treatment with the ARB candesartan reduced the incidence of AF
- There was no heterogeneity of the effects of candesartan in preventing AF between the 3 component trials

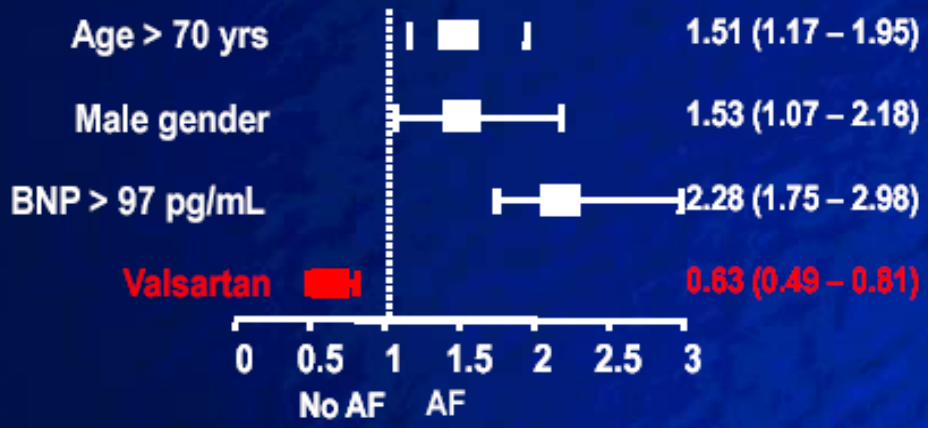


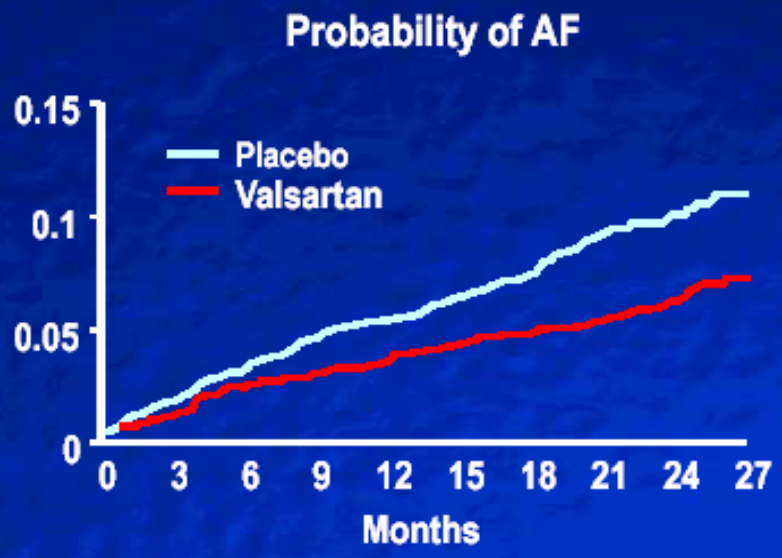
Number of patients who developed AF during the course of the study by treatment group: candesartan (white box) or placebo (black box). 6379 patients (83.9%) did not have AF on the baseline ECG. Of these, 392 patients (6.15%) developed AF during follow-up, 177 (5.55%) in the candesartan group and 215 (6.74%) in the placebo group (OR 0.812, 95% CI 0.662-0.998, $P = .048$). After adjustment for the prespecified baseline covariates, the OR was 0.802 (95% CI 0.650-0.990, $P = .039$).

Am Heart J 2006

Valsartan reduces AF in CHF: the Val-HeFT study

Patients with HF were randomised, single-blind, to valsartan (40–160 mg/bid) or placebo, in addition to their medication for HF





Variable	Valsartan	Placebo	p
Sample	2205	2190	-
New AF	113	174	0.0002
	5.12%	7.95%	

Maggioni AP *et al. Am Heart J* 2005;149:548-557.

Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study

6614 patients aged 70–84 years with HTN

(BP >180 mm Hg systolic, >105 mm Hg diastolic, or both)

	Conventional drugs group	ACE inhibitors group	Calcium antagonists group
Total mortality	33·1 (369)	34·4 (380)	32·8 (362)
Cardiovascular mortality	19·8 (221)	20·5 (226)	19·2 (212)
Fatal myocardial infarction	4·9 (55)	4·3 (48)	5·3 (59)
Fatal stroke	4·6 (51)	4·5 (50)	4·2 (46)
Sudden death	4·8 (53)	5·3 (59)	4·7 (52)
Other cardiovascular mortality	5·6 (62)	6·2 (69)	5·0 (55)
Other mortality and morbidity			
All myocardial infarction	14·1 (154)	12·8 (139)	16·7 (179)
All stroke	22·2 (237)	20·2 (215)	19·5 (207)
All major cardiovascular events	44·1 (460)	41·9 (437)	43·6 (450)
Frequency of diabetes mellitus	10·0 (97)	9·6 (93)	9·9 (95)
Frequency of atrial fibrillation	16·4 (176)	19·0 (200)	17·1 (181)
Frequency of congestive heart failure	16·4 (177)	13·9 (149)	17·5 (186)

Table 5: **Frequency of events per 1000 patient-years**

STOP-Hypertension 2 study
Hansson L et al, Lancet 1999

Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial

10 985 pts 25–66 yrs with a measured DBP≥ 100 mm Hg on two occasions were randomly assigned captopril or conventional antihypertensive treatment (diuretics, BBs)

Event (n)	Captopril group	Conventional group
Fatal myocardial infarction	27	35
Fatal stroke	20	22
Other cardiovascular deaths	23	24
Sudden death	6	14
Non-fatal myocardial infarction	137	128
Non-fatal stroke	173	127
Ischaemic heart disease	258	251
Atrial fibrillation	117	135
Congestive heart failure	75	66
Diabetes mellitus	337	380
Transient ischaemic attacks	31	25

Lancet 1999; 353: 611–16

Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol

The Losartan Intervention for End Point Reduction in Hypertension (LIFE) Study

OBJECTIVES This study was designed to evaluate whether different antihypertensive treatment regimens with similar blood pressure reduction have different effects on new-onset atrial fibrillation (AF).

BACKGROUND It is unknown whether angiotensin II receptor blockade is better than beta-blockade in preventing new-onset AF.

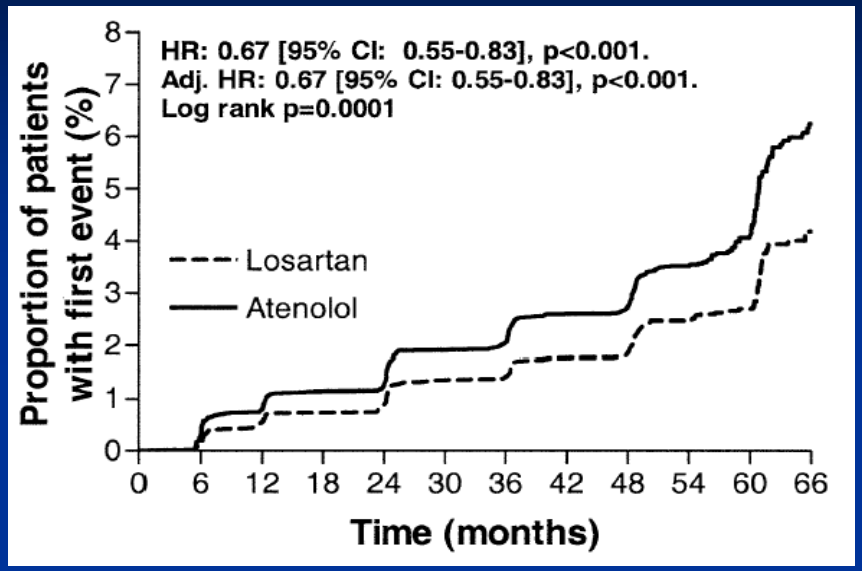
METHODS In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study 9,193 hypertensive patients and patients with electrocardiogram-documented left ventricular hypertrophy were randomized to once-daily losartan- or atenolol-based antihypertensive therapy. Electrocardiograms were Minnesota coded centrally, and 8,851 patients without AF by electrocardiogram or history, who were thus at risk of developing AF, were followed for 4.8 ± 1.0 years.

RESULTS New-onset AF occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, 95% confidence interval [CI] 0.55 to 0.83, $p < 0.001$) despite similar blood pressure reduction. Patients receiving losartan tended to stay in sinus rhythm longer (1,809 ± 225 vs. 1,709 ± 254 days from baseline, $p = 0.057$) than those receiving atenolol. Moreover, patients with new-onset AF had two-, three- and fivefold increased rates, respectively, of cardiovascular events, stroke, and hospitalization for heart failure. There were fewer composite end points (n = 31 vs. 51, hazard ratio = 0.60, 95% CI 0.38 to 0.94, $p = 0.03$) and strokes (n = 19 vs. 38, hazard ratio = 0.49, 95% CI 0.29 to 0.86, $p = 0.01$) in patients who developed new-onset AF in the losartan compared to the atenolol treatment arm of the study. Furthermore, Cox regression analysis showed that losartan (21% risk reduction) and new-onset AF both independently predicted stroke even when adjusting for traditional risk factors.

CONCLUSIONS Our novel finding is that new-onset AF and associated stroke were significantly reduced by losartan- compared to atenolol-based antihypertensive treatment with similar blood pressure reduction. (J Am Coll Cardiol 2005;45:712–9) © 2005 by the American College of Cardiology Foundation

Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol

The Losartan Intervention for End Point Reduction in Hypertension (LIFE) Study



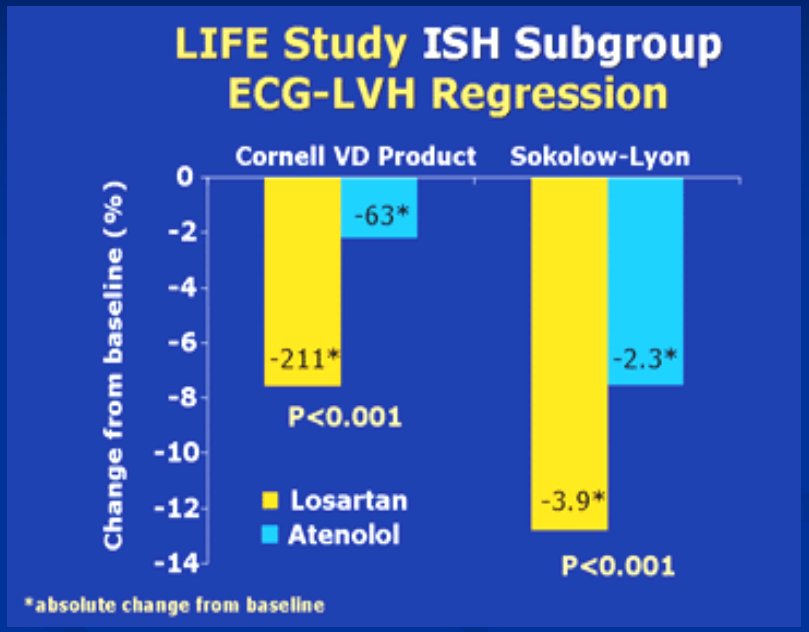


Table 4. Univariate Predictors of New-Onset Atrial Fibrillation

Variable	Hazard Ratio (95% CI)	p Value
Age (yrs)	1.09 (1.07–1.10)	<0.001
Male gender	1.3 (1.06–1.60)	0.011
Systolic blood pressure (mm Hg)	1.02 (1.01–1.02)	<0.001
Diastolic blood pressure (mm Hg)	0.99 (0.98–1.00)	0.046
Cornell voltage-duration (mV·ms/100)	1.013 (1.004–1.022)	0.006
Sokolow-Lyon voltage (mV)	1.01 (0.997–1.02)	0.170
Framingham risk score (%)	1.02 (1.01–1.03)	<0.001
Coronary disease (yes/no)	1.28 (0.99–1.67)	0.062
Total cholesterol (mmol/l)	0.89 (0.80–0.98)	0.014
Potassium (mmol/l)	0.78 (0.58–1.04)	0.091
Log UACR (mg/mmol)	1.44 (1.23–1.67)	<0.001
Treatment with losartan	0.67 (0.54–0.82)	<0.001

Heart rate, body mass index, diabetes, cerebral and peripheral vascular disease, high-density lipoprotein cholesterol, plasma glucose, and creatinine were not significant predictors ($p > 0.20$).

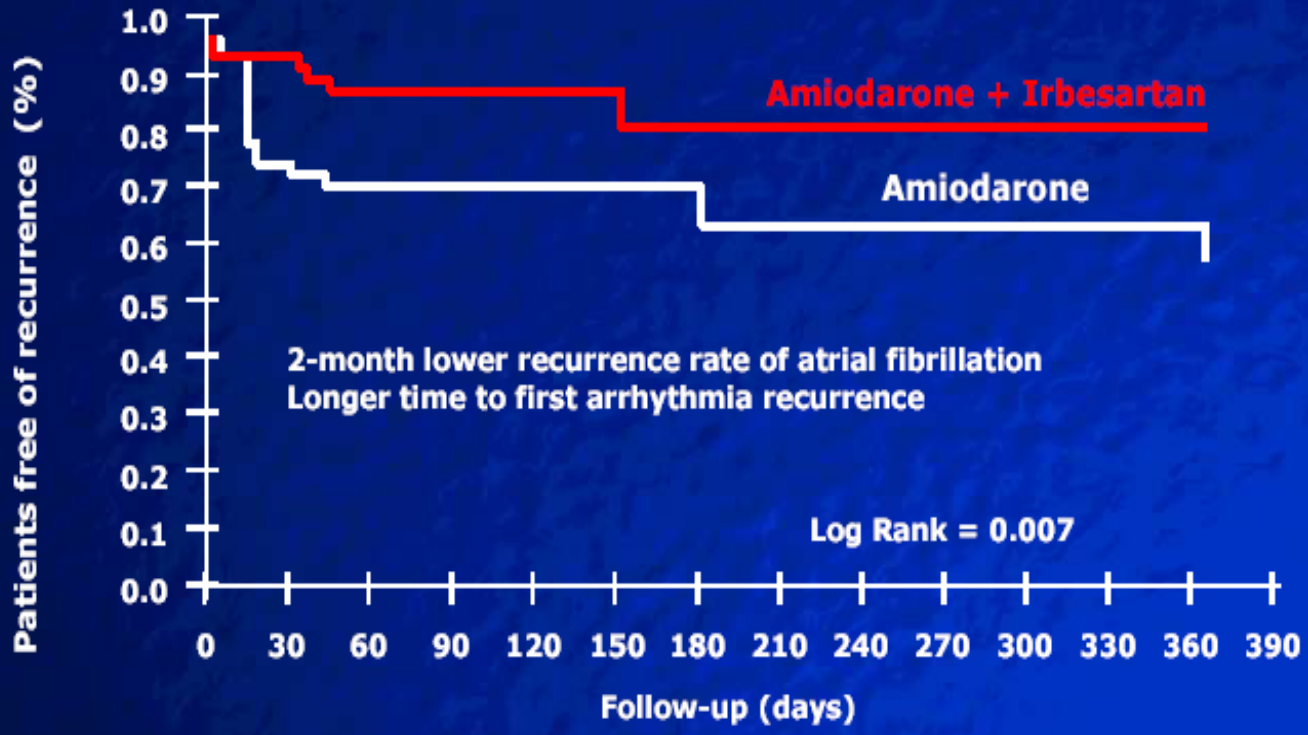
CI = confidence interval; UACR = urine albumin/creatinine ratio.

Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial

- BACKGROUND: Atrial fibrillation (AF) is the most common arrhythmia and increases cardiovascular risk in hypertensive patients. Therefore, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) a prespecified objective was to compare the effects of valsartan and amlodipine on new-onset AF.
- METHODS: A total of 15 245 hypertensive patients at high cardiovascular risk received valsartan 80-160 mg/day or amlodipine 5-10 mg/day combined with additional antihypertensive agents. Electrocardiograms were obtained every year and analyzed centrally for evidence of left ventricular hypertrophy and new-onset AF.
- RESULTS: At baseline, AF was diagnosed in 2.6% of 7649 valsartan recipients and 2.6% of 7596 amlodipine recipients. During antihypertensive treatment the incidence of at least one documented occurrence of new-onset AF was 3.67% with valsartan and 4.34% with amlodipine [unadjusted hazard ratio 0.843, [95% confidence interval (CI): 0.713, 0.997], P = 0.0455]. The incidence of persistent AF was 1.35% with valsartan and 1.97% with amlodipine [unadjusted hazard ratio 0.683 (95% CI: 0.525, 0.889), P = 0.0046].
- CONCLUSIONS: Valsartan-based treatment reduced the development of new-onset AF, particularly sustained AF in hypertensive patients, compared with amlodipine-based therapy. These findings suggest that angiotensin II receptor blockers may result in greater benefits than calcium antagonists in hypertensive patients at risk of new-onset AF

Schmieder RE et al, J Hypertens. 2008

Maintenance of Sinus Rhythm After Conversion From Persistent AF



Madrid AH *et al. Circulation* 2002; 106: 331-6.

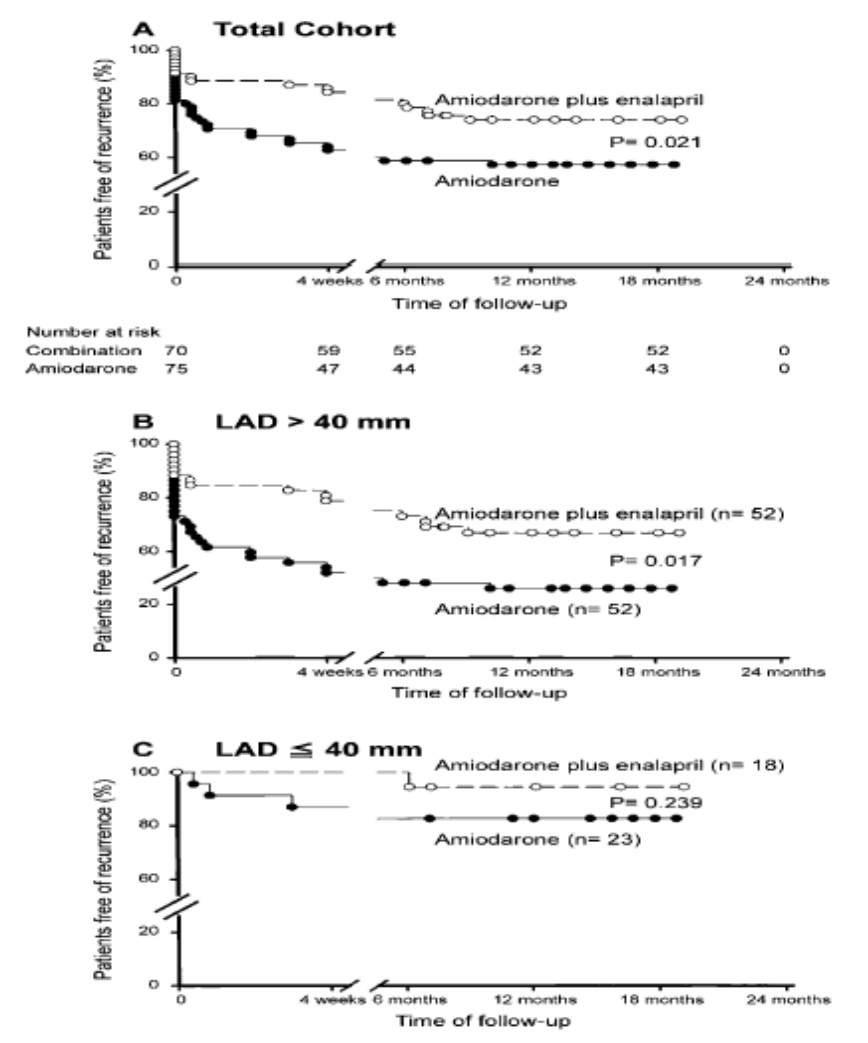
Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation

Results of a prospective and controlled study

Aims This study aimed to assess whether enalapril could improve cardioversion outcome and facilitate sinus rhythm maintenance after conversion of chronic atrial fibrillation (AF).

Methods and results Patients with chronic AF for more than 3 months were assigned to receive either amiodarone (200 mg orally 3 times a day; group I: *n*=75) or the same dosage of amiodarone plus enalapril (10 mg twice a day; group II: *n*=70) 4 weeks before scheduled external cardioversion. The end-point was the time to first recurrence of AF. In 125 patients (86.2%), AF was converted to sinus rhythm. Group II had a trend to a trend to a lower rate of immediate recurrence of AF than group I did (4.3% vs 14.7%, *P*=0.067). Kaplan–Meier analysis demonstrated a higher probability of group II remaining in sinus rhythm at 4 weeks (84.3% vs 61.3%, *P*=0.002) and at the median follow-up period of 270 days (74.3% vs 57.3%, *P*=0.021) than in group II.

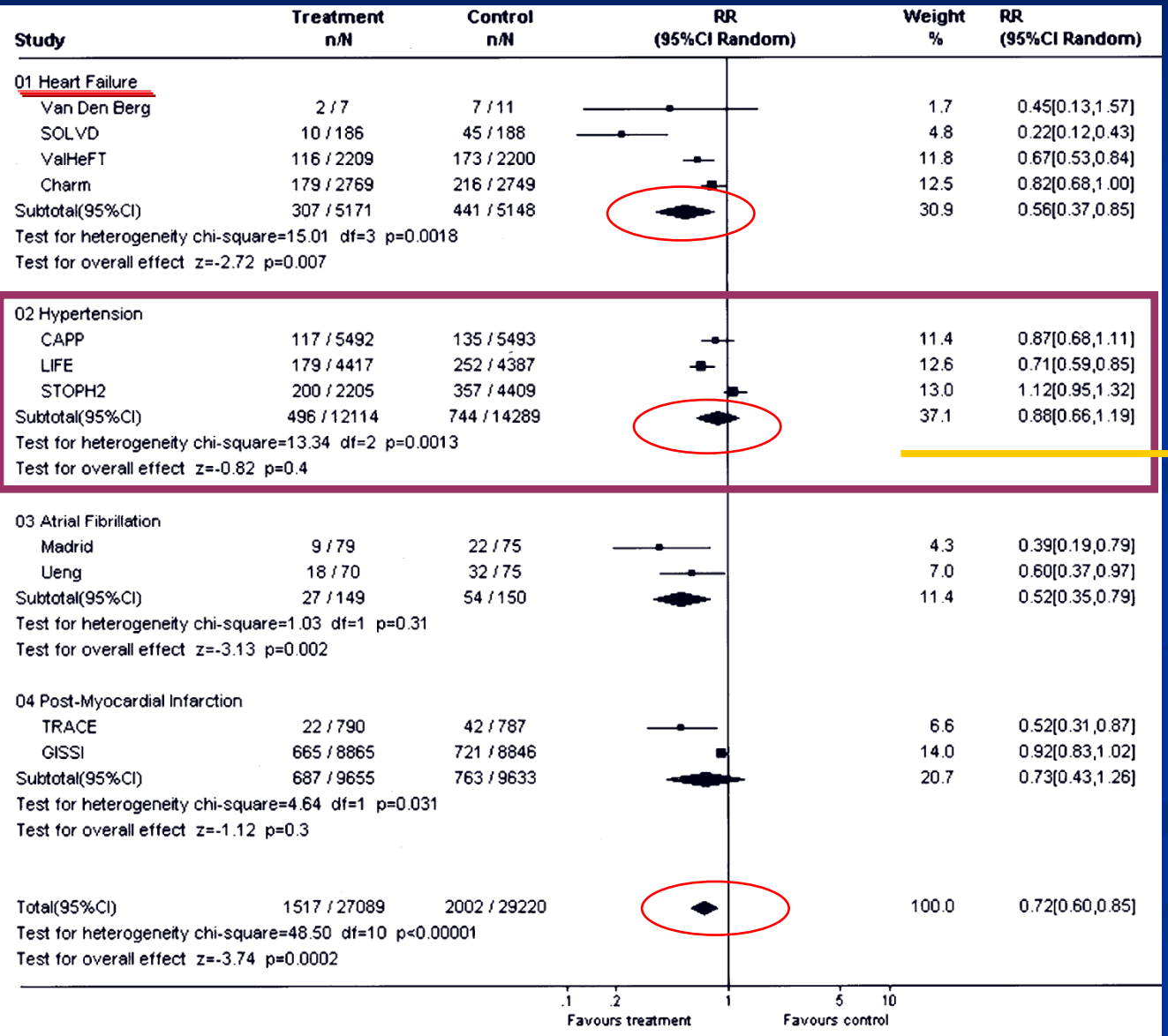
Conclusion The addition of enalapril to amiodarone decreased the rate of immediate and subacute arrhythmia recurrences and facilitated subsequent long-term maintenance of sinus rhythm after cardioversion of persistent AF.



European Heart Journal (2003) 24, 2090–2098

Prevention of AF by ACE-I and ARBs

Meta-analysis of 11 studies, 56308 pts



ACE-I =28%
ARBs =29%

Pts with HF benefited the most (RRR= 43%)

In pts with HTN overall, there was no significant reduction in AF (RRR=12%, p=0.4)

Healey, et al JACC 2005;45:1832

Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation

- BACKGROUND: Epidemiologic studies suggest that inhibition of RAAS with ACEIs and ARBs may prevent development of atrial fibrillation
- OBJECTIVE: The objective of the study was to assess if there is significant indication for using ACEIs and ARBs in the prevention of new-onset AF and to identify the target patient population
- METHODS: PubMed and Cochrane clinical trials database were searched from 1980 through March 2005 together with the review of citations. Nine randomized controlled human trials reporting the prevention of new-onset AF by inhibition of RAAS were identified. Information about study design, follow-up, intervention, population, outcomes, and methodology quality was extracted
- RESULTS: The mean follow-up of the studies ranged from 6 months to 6.1 year. The pooled estimate using random effects model was 0.82 (95% CI 0.70-0.97) for prevention of new-onset AF and 0.61 (95% CI 0.46-0.83) for primary prevention of AF. The angiotensin-converting enzyme inhibitors (0.75, 95% CI 0.57-0.99) had greater protective effect than angiotensin receptor blockers (0.81, 95% CI 0.62-1.06). Patients with heart failure benefited the most (0.57, 95% CI 0.37-0.89). The test for heterogeneity between studies was significant. There was no consistent visual or statistical evidence of publication bias
- CONCLUSION: The use of ACEIs and ARBs had an overall effect of 18% risk reduction in new-onset AF across the trials and 43% risk reduction in patients with heart failure

Anand K, Am Heart J. 2006

Inefficiency of renin-angiotensin inhibitors in preventing atrial fibrillation in patients with a normal heart

- AIM: Recent scientific evidence has emphasized the possible role of inhibitors of the RAAS in preventing arrhythmic relapses in patients with paroxysmal or persistent AFib and co-existing LVH or LV dysfunction

- METHODS: In order to verify the effects of these drugs on patients with a normal heart, we collected a series of 187 pts admitted to our division of cardiology for paroxysmal or persistent AFib
  All pts underwent cardioversion (with antiarrhythmic drugs and/or by electrical cardioversion) and were discharged in SR. Episodes of recurrent arrhythmia were recorded during a mean follow-up period was 2 yrs. Pts were subdivided into 2 groups according to Tx: group 1 comprised pts receiving RAAS inhibitors, group 2 comprised those not receiving Tx with these agents. All 91 pts in group 1 and 76 of those in group 2 had HTN. Among the 91 pts in the group 1, 55 were treated with ACEIs and 36 with ARBs. There were no statistically significant differences in CV risk factors or antiarrhythmic drug use between the 2 groups

- RESULTS: In group 1, 83% of pts experienced <2 recurrences of AFib during the follow-up period, while 17% had >2 episodes. In group 2, 86% of pts experienced <2 relapses during the follow-up period, while the remaining 14% had >2 relapses. There was no statistically significant difference between the 2 groups (P=0.85). A subgroup analysis showed that treatment with angiotensin receptor blockers, BBs, diuretics, and Ca-blockers brought no advantage in SR maintenance

- CONCLUSION: In our sample of hypertensive patients with a healthy heart, treatment with ACE inhibitors showed no statistically significant advantage in the prevention of atrial fibrillation relapses

Fagio G et al, Minerva Cardioangiol. 2007

Valsartan for Prevention of Recurrent Atrial Fibrillation

*The GISSI-AF Investigators**

BACKGROUND

Atrial fibrillation is the most common cardiac arrhythmia, and no current therapy is ideal for control of this condition. Experimental studies suggest that angiotensin II–receptor blockers (ARBs) can influence atrial remodeling, and some clinical studies suggest that they may prevent atrial fibrillation.

METHODS

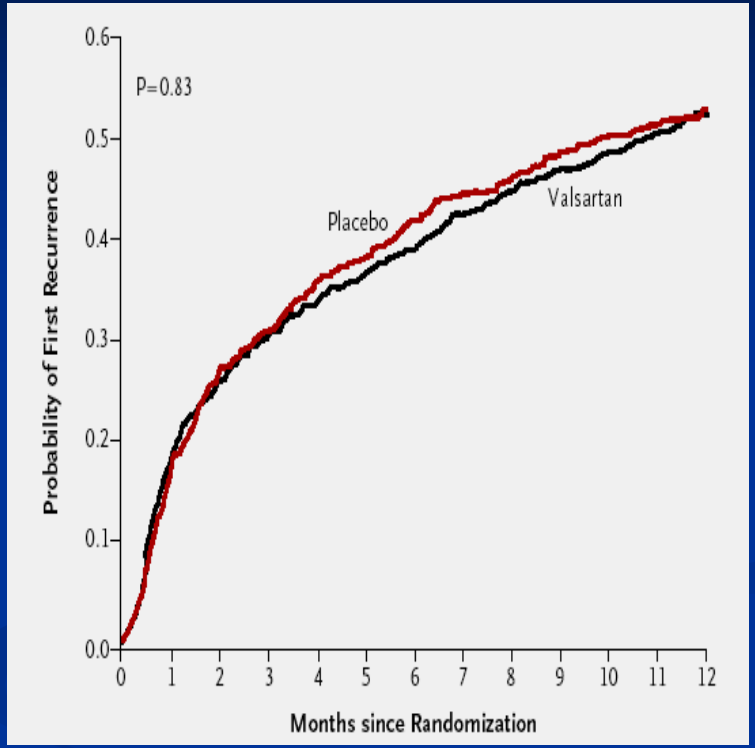
We conducted a large, randomized, prospective, placebo-controlled, multicenter trial to test whether the ARB valsartan could reduce the recurrence of atrial fibrillation. We enrolled patients who were in sinus rhythm but had had either two or more documented episodes of atrial fibrillation in the previous 6 months or successful cardioversion for atrial fibrillation in the previous 2 weeks. To be eligible, patients also had to have underlying cardiovascular disease, diabetes, or left atrial enlargement. Patients were randomly assigned to receive valsartan or placebo. The two primary end points were the time to a first recurrence of atrial fibrillation and the proportion of patients who had more than one recurrence of atrial fibrillation over the course of 1 year.

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.)



N Engl J Med 2009;360:1606-17

Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

Giuseppe Mancia[a], Stéphane Laurent[b], Enrico Agabiti-Rosei[c], Ettore Ambrosioni[d], Michel Burnier[e], Mark J. Caulfield[f], Renata Cifkova[g], Denis Clément[h], Antonio Coca[i], Anna Dominiczak[j], Serap Erdine[k], Robert Fagard[l], Csaba Farsang[m], Guido Grassi[n], Hermann Haller[o], Anthony Heagerty[p], Sverre E. Kjeldsen[q], Wolfgang Kiowski[r], Jean Michel Mallion[s], Athanasios Manolis[t], Krzysztof Narkiewicz[u], Peter Nilsson[v], Michael H. Olsen[w], Karl Heinz Rahn[x], Josep Redon[y], José Rodicio[z], Luis Ruilope[a1], Roland E. Schmieder[a2], Harry A.J. Struijker-Boudier[a3], Pieter A. van Zwieten[a4], Margus Viigimaa[a5] and Alberto Zanchetti[a6]

Journal of Hypertension 2009, 27:2121–2158

Συνοψίζοντας…

- Η κολπική μαρμαρυγή αποτελεί συχνή νοσολογική οντότητα, ιδιαίτερα στους ηλικιωμένους και προκαλεί σημαντική νοσηρότητα και θνητότητα

- Η αρτηριακή υπέρταση μέσω των δομικών και λειτουργικών μεταβολών που προκαλεί στην καρδιά και ιδιαίτερα στον αριστερό κόλπο είναι ο συχνότερος παράγοντας κινδύνου για την εμφάνιση AFib

- Η αυστηρή ρύθμιση της ΑΠ μειώνει τον κίνδυνο εμφάνισης AFib και πρέπει να προηγείται της χορήγησης αντιπηκτικής αγωγής για την αποφυγή αιμορραγικών επιπλοκών

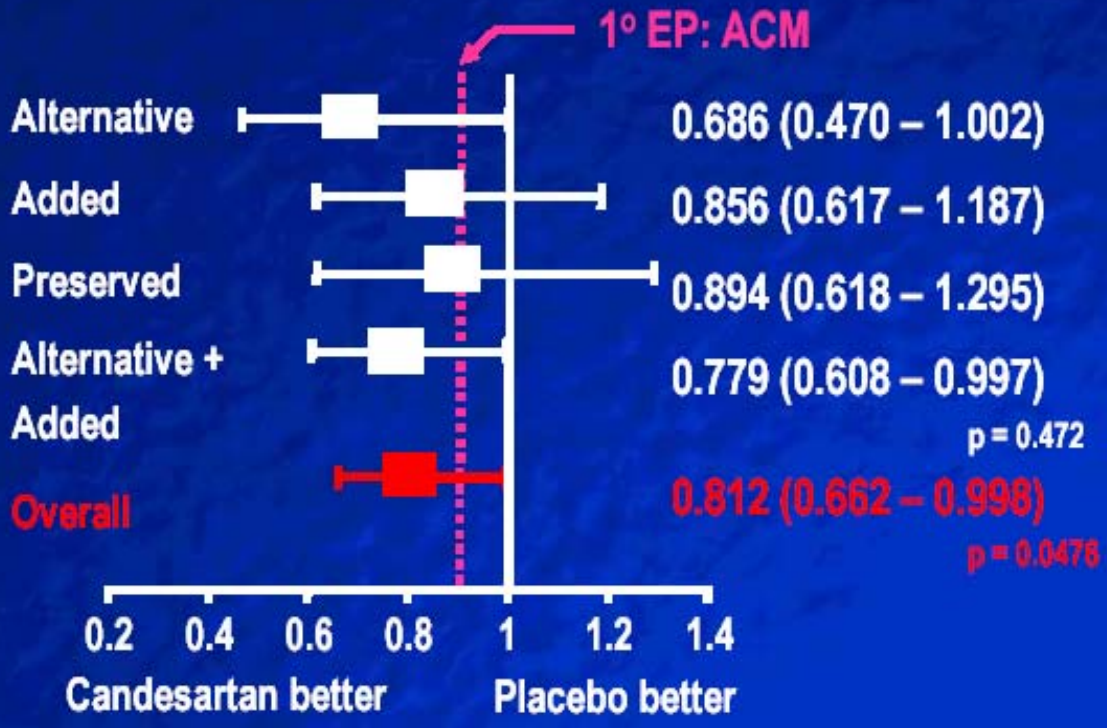
- Η υπεροχή των ανταγωνιστών του RAAS ως αντιυπερτασικά φάρμακα για τη μείωση της εμφάνισης AF έχει φανεί σε ασθενείς με HF ή LVH, αλλά δεν έχει επιβεβαιωθεί στο γενικό πληθυσμό των υπερτασικών ασθενών

- Σας ευχαριστώ !

AF prevention by candesartan

The CHARM Program

- 7601 patients with CHF
- Randomised to candesartan (target dose 32 mg/day, mean dose 24 mg/day) or placebo
- > 95% NYHA II-III heart failure
- Follow-up 37.7 months
- AF pre-specified endpoint
- No AF on baseline ECG 83.9%



Ducharme A *et al. Am Heart J* 2006;152:86-92.

Prevention of Atrial Fibrillation

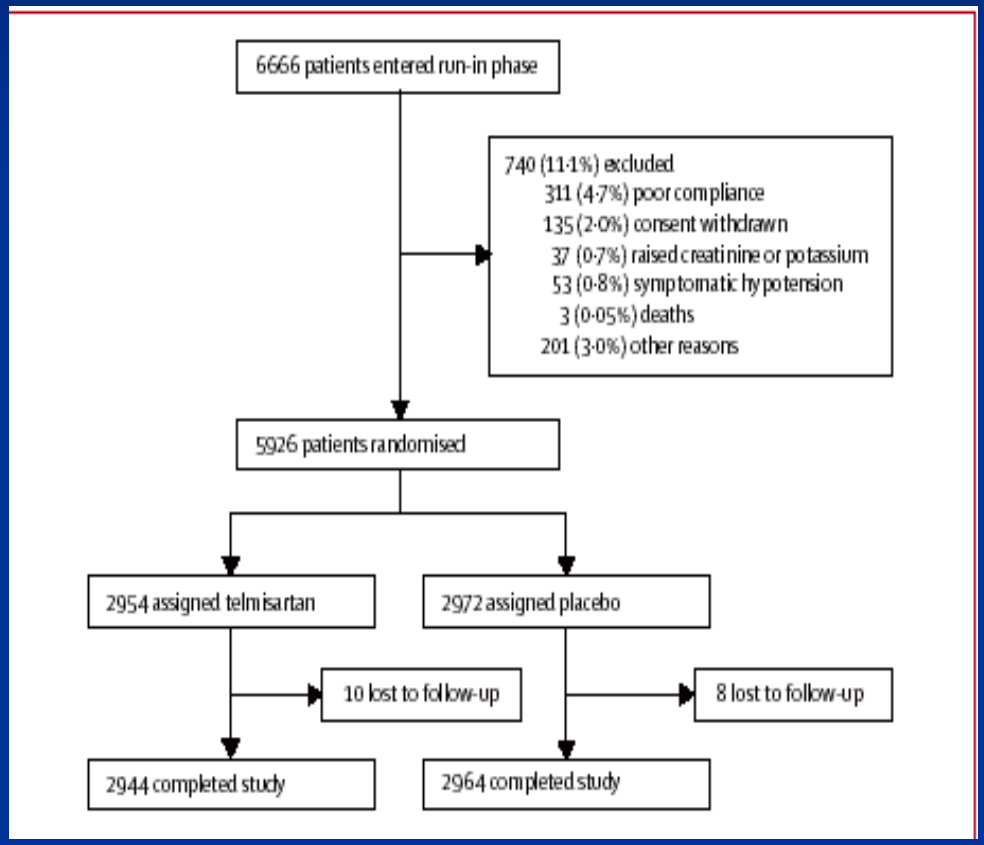
Report From a National Heart, Lung, and Blood Institute Workshop

- Atrial fibrillation (AF) is the most common arrhythmia in the United States and other developed countries
- AF is associated with significant morbidity and mortality, including :
- a 4- to 5-fold increased risk for stroke,1,2
- A doubling of risk for dementia,3,4
- a tripling of risk for heart failure,2 and
- a 40% to 90% increased risk for overall mortality.2,5

- Growth in the size of the AF population and increased recognition of the morbidity, mortality, diminished quality of life, and high healthcare costs associated with AF have spurred numerous investigations to developmore effective treatments for AF and its complications.Many risk factors for AF have been described, and some promising preventive strategies have been identified. However, although AF treatment has been studied extensively, AF prevention has received relatively little attention.

Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial

*The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators**



	Telmisartan (N=2954)	Placebo (N=2972)	Hazard ratio (95% CI)	p value
Any heart failure	191 (6·5%)	197 (6·6%)	0·98 (0·80–1·19)	0·828
Revascularisation procedures	349 (11·8%)	390 (13·1%)	0·90 (0·77–1·03)	0·133
New diabetes or fasting glucose ≥7 mmol/L	359 (20·1%)	393 (21·6%)	0·91 (0·79–1·05)	0·203
New clinical diagnosis of diabetes	209 (11·0%)	245 (12·8%)	0·85 (0·71–1·02)	0·081
New atrial fibrillation	182 (6·4%)	180 (6·3%)	1·02 (0·83–1·26)	0·829
New left ventricular hypertrophy	128 (5·0%)	202 (7·9%)	0·62 (0·50–0·78)	<0·001
Cancers	236 (8·0%)	204 (6·9%)	1·17 (0·97–1·42)	0·094
Angina with hospitalisation and ECG changes	253 (8·6%)	287 (9·7%)	0·88 (0·74–1·04)	0·135
Any cardiovascular hospitalisation	894 (30·3%)	980 (33·0%)	0·92* (0·85–0·99)	0·025
Number of patients hospitalised	1477 (50·0%)	1526 (51·4%)	0·97*(0·93–1·02)	0·300
Total mortality	364 (12·3%)	349 (11·7%)	1·05 (0·91–1·22)	0·491

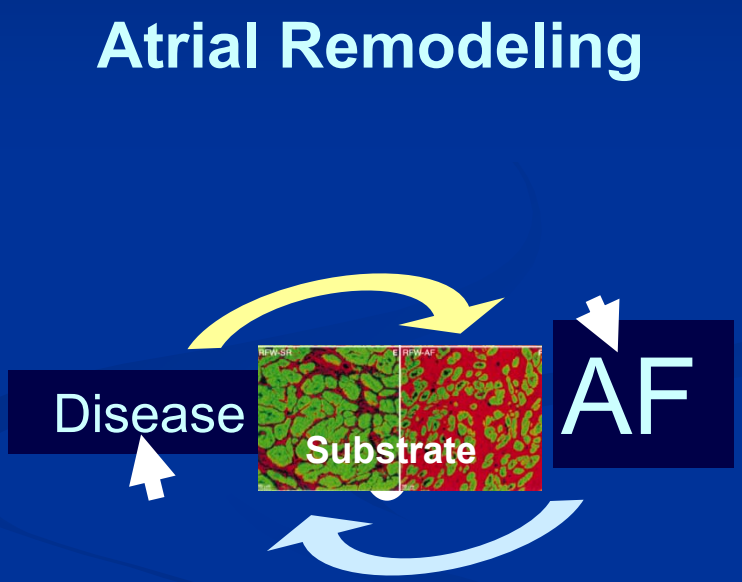
*Relative risk, rather than hazard ratio.

Table 4: Other secondary events and hospitalisations

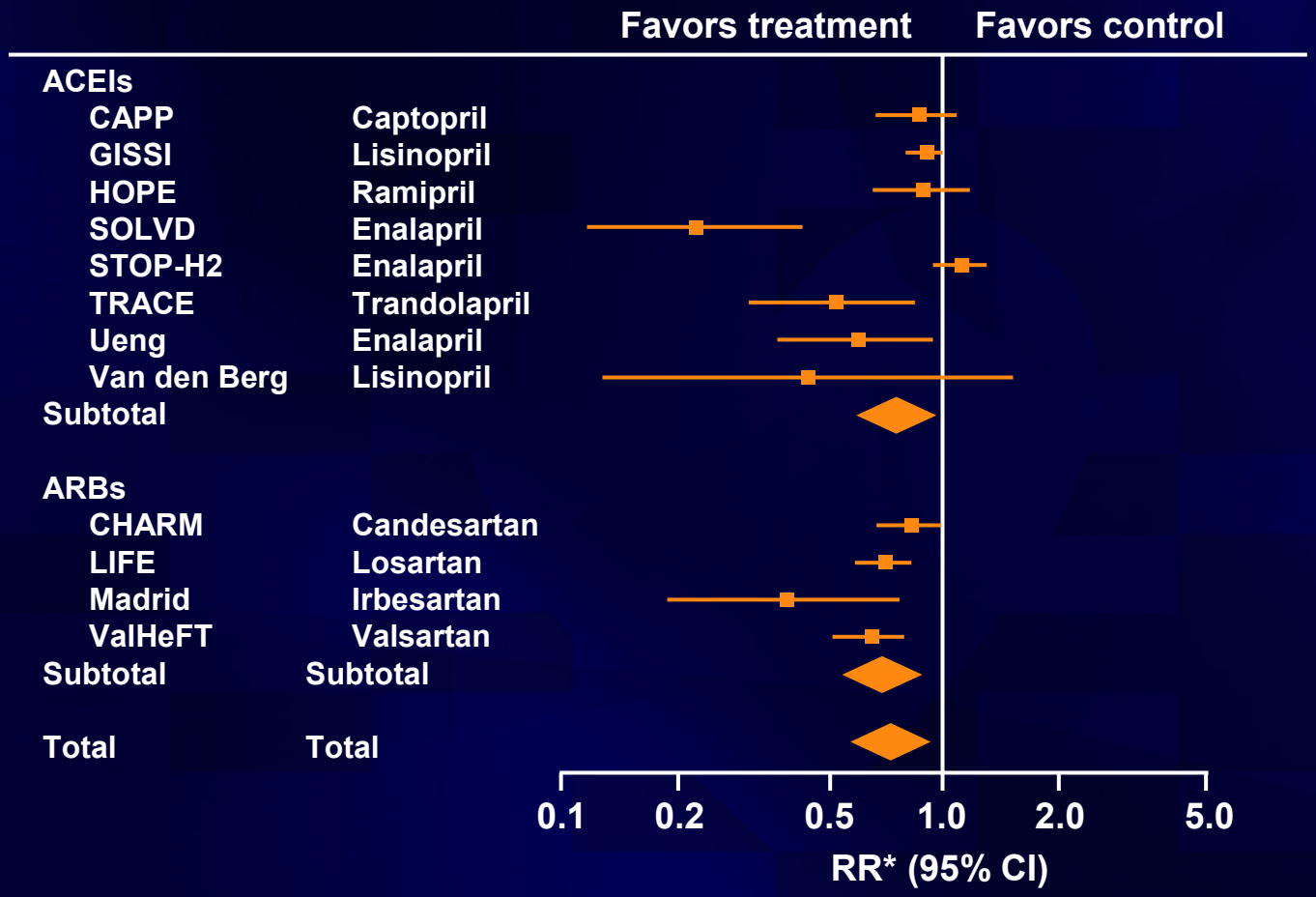
Lancet 2008; 372: 1174–83

“Upstream” Therapies in AF

Therapies	Possible Target
ACE inhibitors and ARBs	Hypertension Heart failure Direct effects (anti-fibrotic, antiarrhythmic)
Aldosterone antagonists	Hypertension, heart failure Direct effects (anti-fibrotic, antiarrhythmic?)
Statins	Coronary artery disease Systemic atherosclerosis Direct effects (anti-inflammatory, antioxidant)
Corticosteroids	Anti-inflammatory effects
n-3 PUFA (fish oil)	Lipid-lowering effects Direct antiarrhythmic effects



Trials of RAAS inhibition in AF prevention



*Random-effects model

Salehian O et al. *Am Heart J*. 2007;154:448-53.
Healey JS et al. *J Am Coll Cardiol*. 2005;45:1832-9.