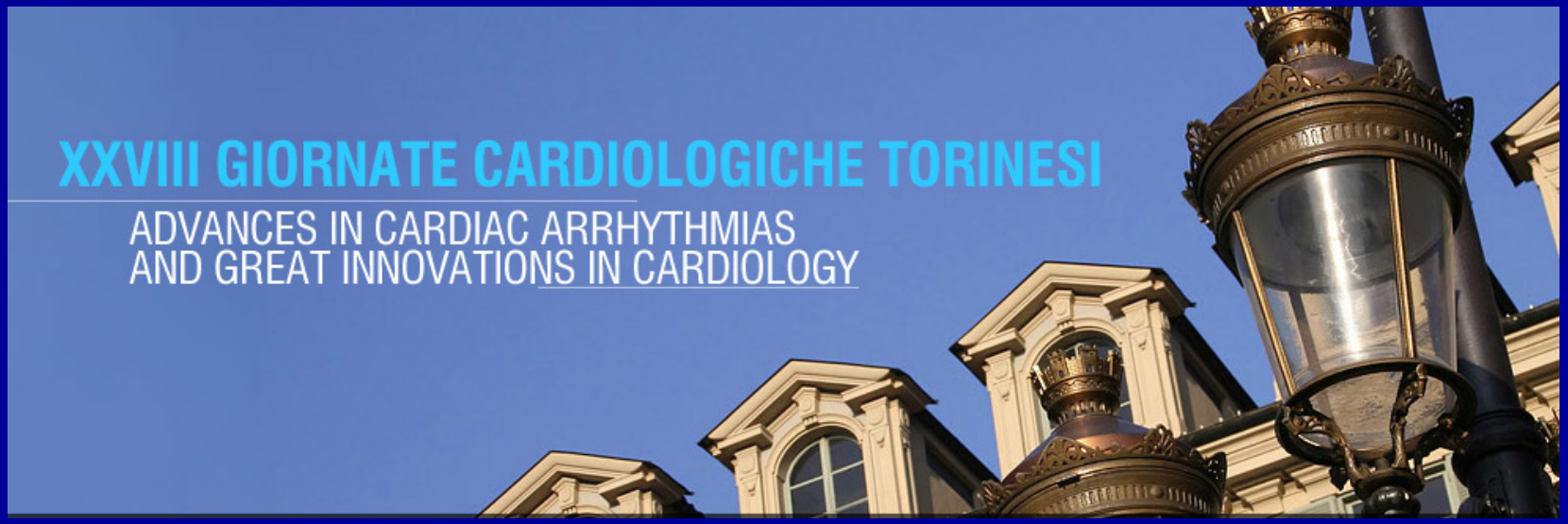

Atrial Fibrillation in Hypertension:
Mechanisns and Implications for Management and Correct Therapy

Paolo Verdecchia, F.A.C.C., F.E.S.C., F.A.H.A.
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Agenda

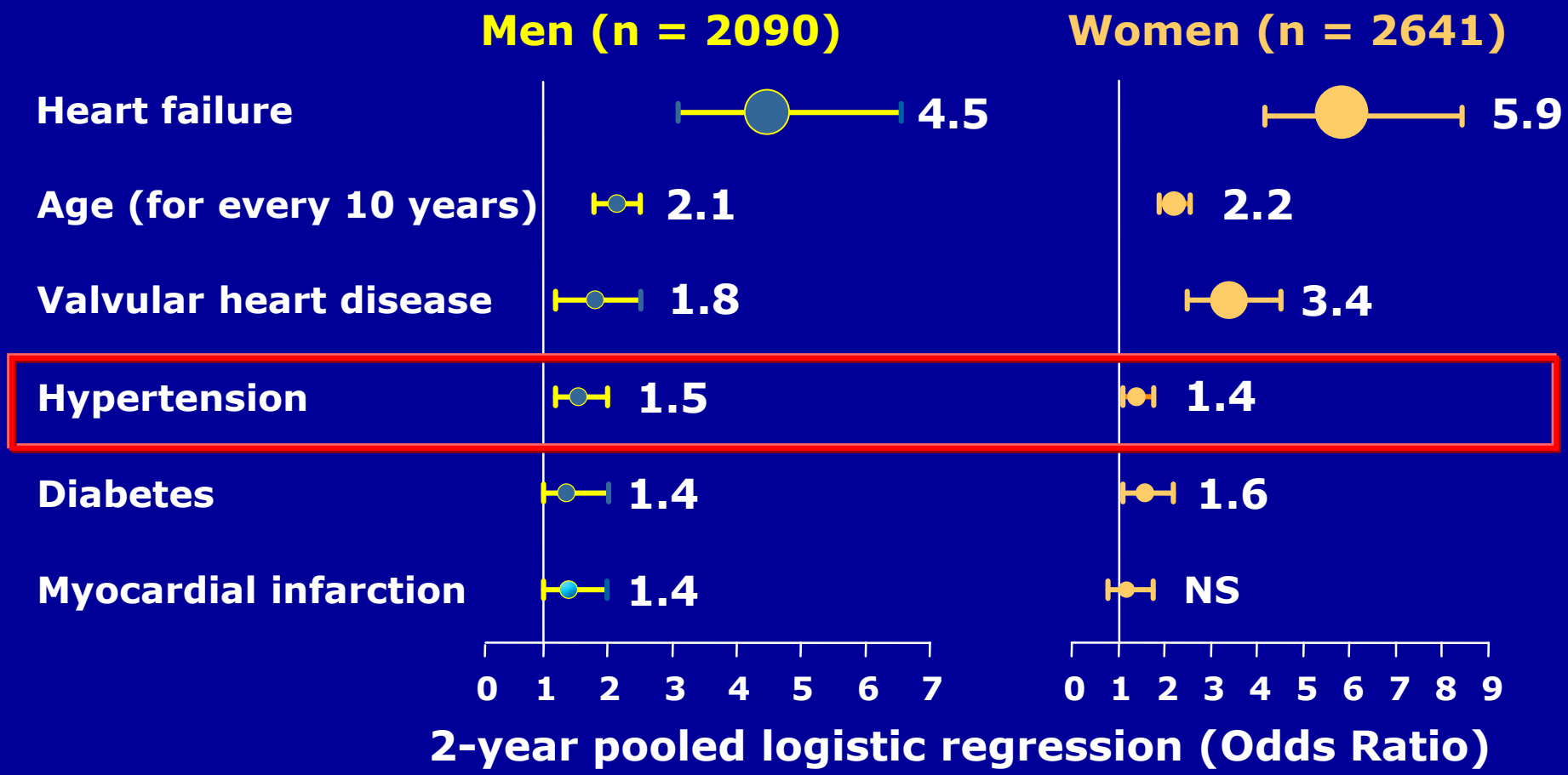
- High BP as a risk factor for AF
- Hypertensive LVH as a risk factor for AF
- Impact of AF in high-risk patients
- Inhibition of the RAS and AF
- High BP as a risk factor for stroke in patients with AF

Agenda

- High BP as a risk factor for AF

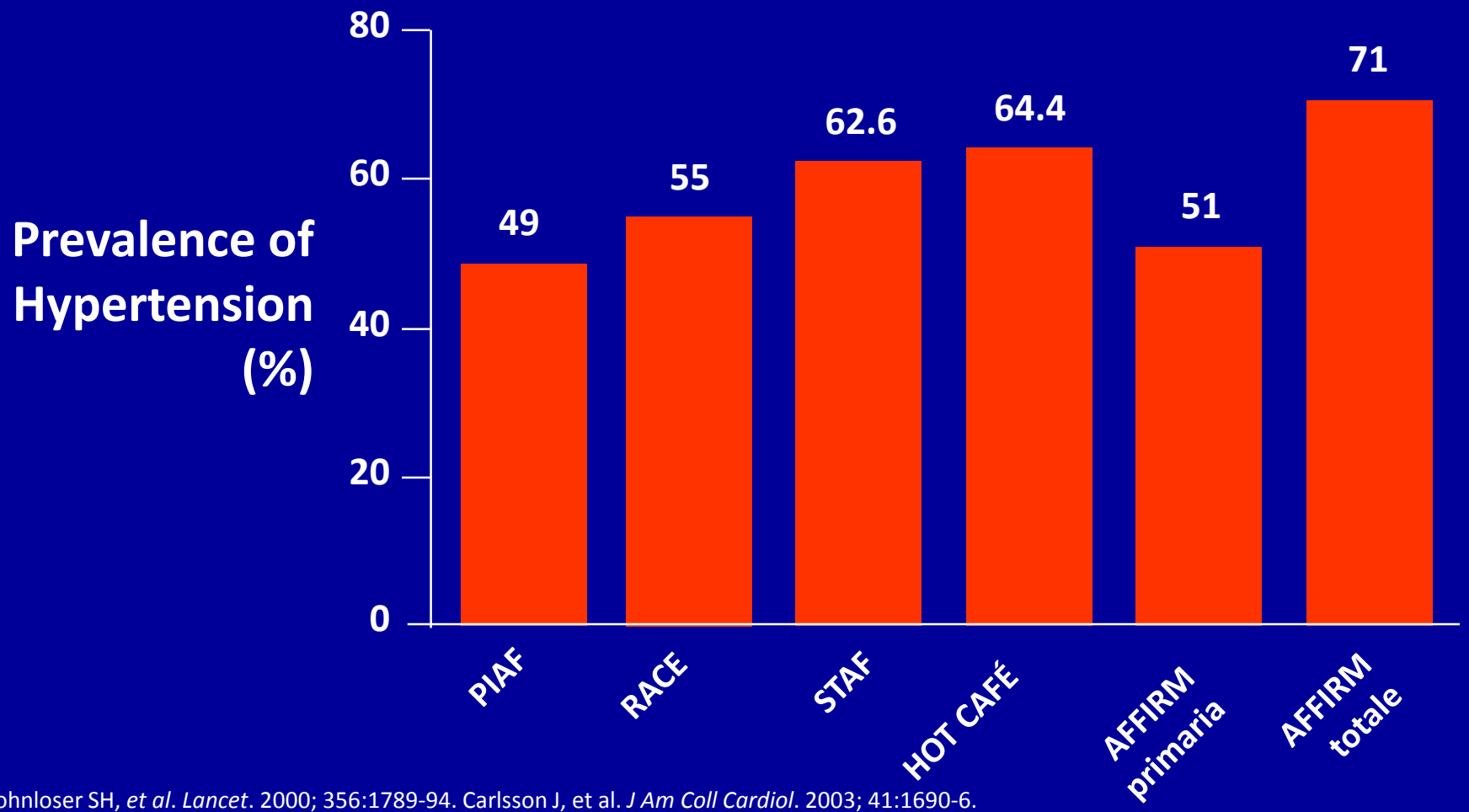
Independent risk factors for AF in subjects in sinus rhythm

The Framingham Heart Study



Benjamin EJ, et al. *JAMA*. 1994;271:840-844.

Prevalence of hypertension in patients with atrial fibrillation

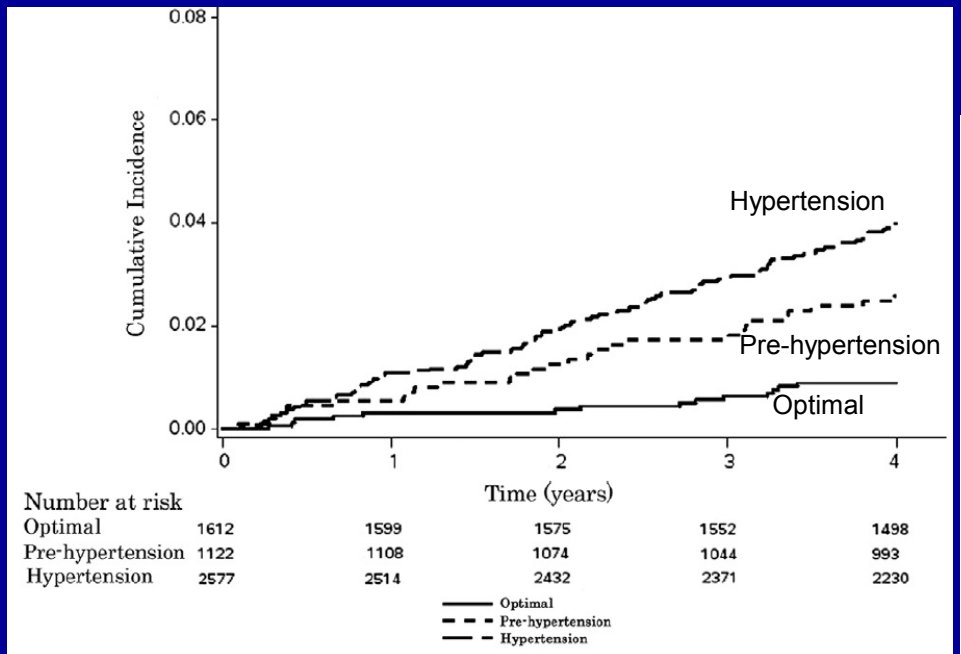


Hohnloser SH, *et al*. *Lancet*. 2000; 356:1789-94. Carlsson J, et al. *J Am Coll Cardiol*. 2003; 41:1690-6.
Wyse DG, *et al*. *N Engl J Med*. 2002; 347:1825-33. Van Gelder IC, *et al*. *Am Heart J.* 2006; 152:420-6. Opolski Chest 2004;126;476

Sustained pre–hypertensive blood pressure and incident AF

Multi–Ethnic Study of Atherosclerosis (MESA)

O'Neal et al. J Am Soc Hypertens 2015;9(3):191–196.



Reclassification of participants over time*

Visit 1 Classification	Cumulative Classification		
	Optimal	Pre–hypertension	Hypertension
Optimal	**81.5%**	15.1%	3.4%
Pre–hypertension	15.7%	**66.0%**	18.3%
Hypertension	0.0%	6.5%	**93.5%**

Bold values represent the percentage of participants who remained in the same blood pressure category between visits 1 and 3.

* Participants were reclassified using subsequent study blood pressure measurements and documentation of antihypertensive medications.

Risk of atrial fibrillation (N = 5311)

Category	Events/# at Risk	Incidence Rate per 1000 Person–years (95% CI)	Model 1* HR (95% CI)	*P*–value	Model 2† HR (95% CI)	*P*–value
Optimal	18/1612	2.2 (1.4, 3.5)	1.0	-	1.0	-
Pre–hypertension	33/1122	6.0 (4.3, 8.4)	1.9 (1.04, 3.3)	.038	1.8 (1.004, 3.2)	.048
Hypertension	131/2577	10.5 (8.8, 12.4)	2.8 (1.7, 4.6)	<.0001	2.6 (1.6, 4.4)	.0003

CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; SD, standard deviation.

* Adjusted for age, gender, race/ethnicity, income, and education.

† Adjusted for Model 1 plus smoking, diabetes, body mass index, total cholesterol, HDL–cholesterol, lipid–lowering medications, aspirin, and left ventricular hypertrophy.

ME Available

Epidemiology/Population Science

Upper Normal Blood Pressures Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men

A 35-Year Follow-Up Study

Irene Grundvold, Per Torger Skretteberg, Knut Liestøl, Gunnar Erikssen, Sverre E. Kjeldsen, Harald Arnesen, Jan Erikssen, Johan Bodegard

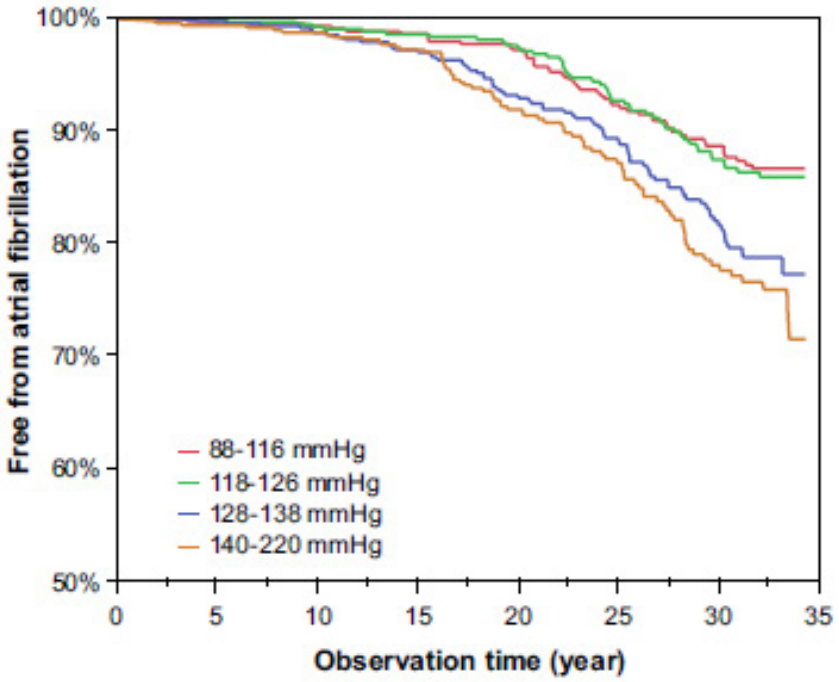


Figure 1. Kaplan-Meier curves show survival (%) free from AF among 1997 initially healthy middle-aged men according to quartiles of systolic blood pressure during 35 years of follow-up.

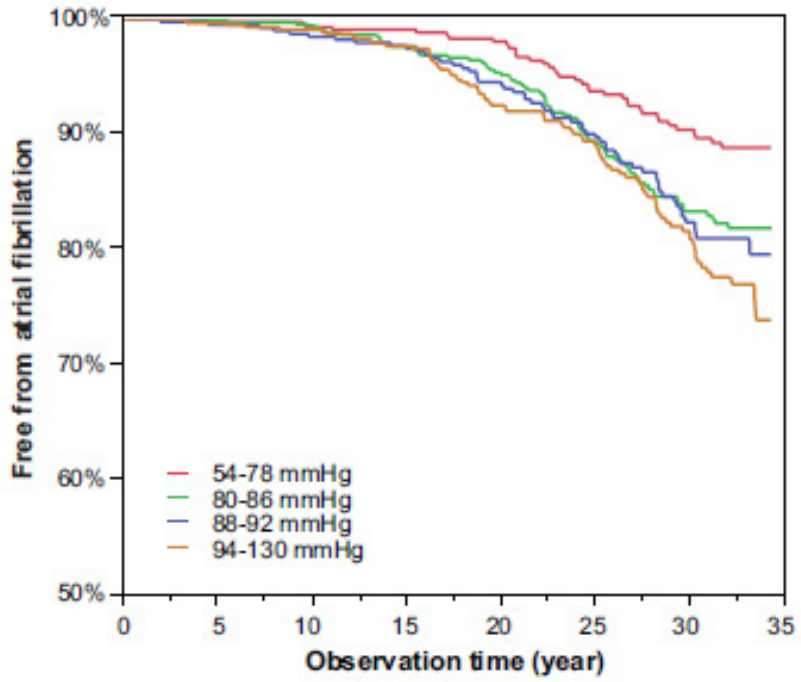


Figure 2. Kaplan-Meier curves show survival (%) free from AF among 1997 initially healthy middle-aged men according to quartiles of diastolic blood pressure during 35 years of follow-up.

Grundvold I et al. Hypertension. 2012;59:198-204

Editorial Commentary

Above Which Blood Pressure Level Does the Risk of Atrial Fibrillation Increase?

Paolo Verdecchia, Giovanni Mazzotta, Fabio Angeli, Gianpaolo Reboldi

See related article, pp 198–204

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, occurs in 1% to 2% of the general population,[1] and its incidence is growing. Mostly because of the progressive aging of the population, the prevalence of AF is expected to double over the next 50 years.[1] AF is a potentially devastating condition for several reasons. It portends a 5-fold risk of stroke,[2] and ischemic strokes that occur in people with AF are often fatal or leave surviving patients generally more disabled and at higher risk of recurrences compared with other causes of stroke. AF triples the risk of heart failure,[3] doubles the risk of dementia, and markedly

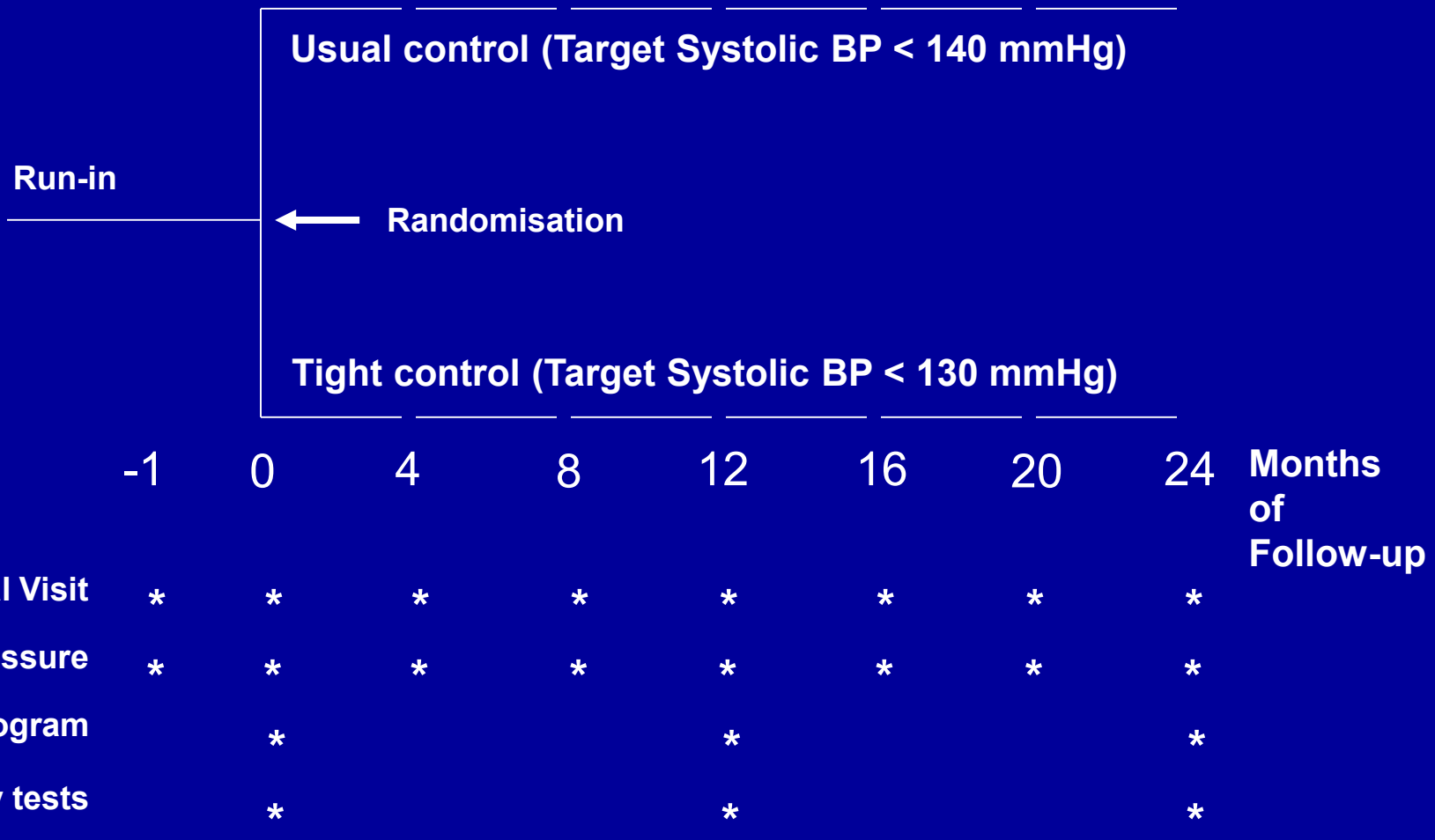
enced 28% and 53% excess risk of incident AF when compared with women with systolic BP <120 mm Hg or diastolic BP <65 mm Hg, respectively.[7]

A long-term epidemiological study featured in this issue of *Hypertension*[8] extends to men the direct relationship between BP and the risk of incident AF. Grundvold et al studied a group of 2014 healthy Norwegian men first scrutinized in the years 1972 to 1975. During a median follow-up period of 30 years, 270 men were hospitalized for various reasons, with available evidence of AF from hospital records. The risk of AF significantly increased in men with baseline systolic BP

No clear answer yet !

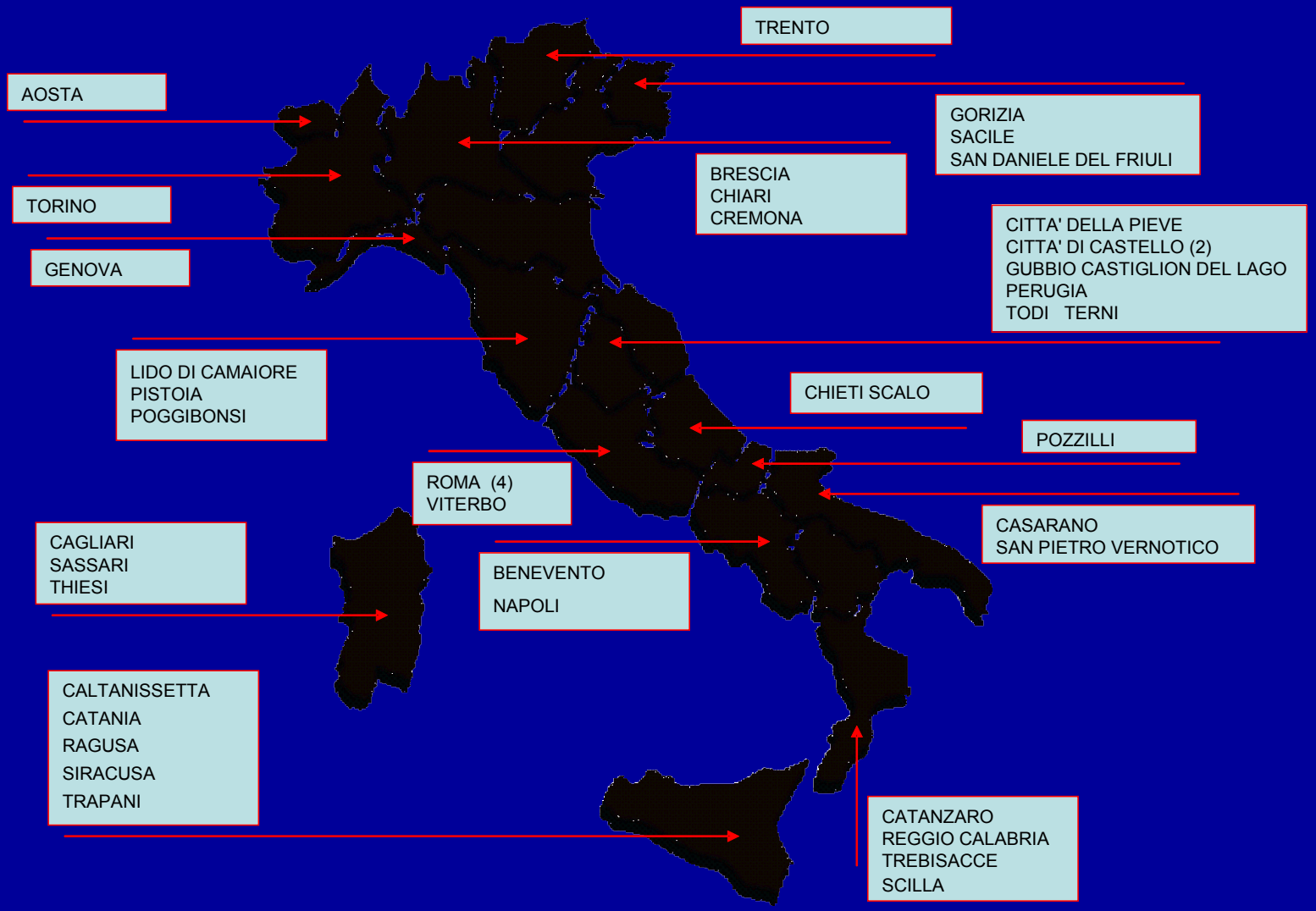
Hypertension 2012;59:184-185

Cardio-Sis



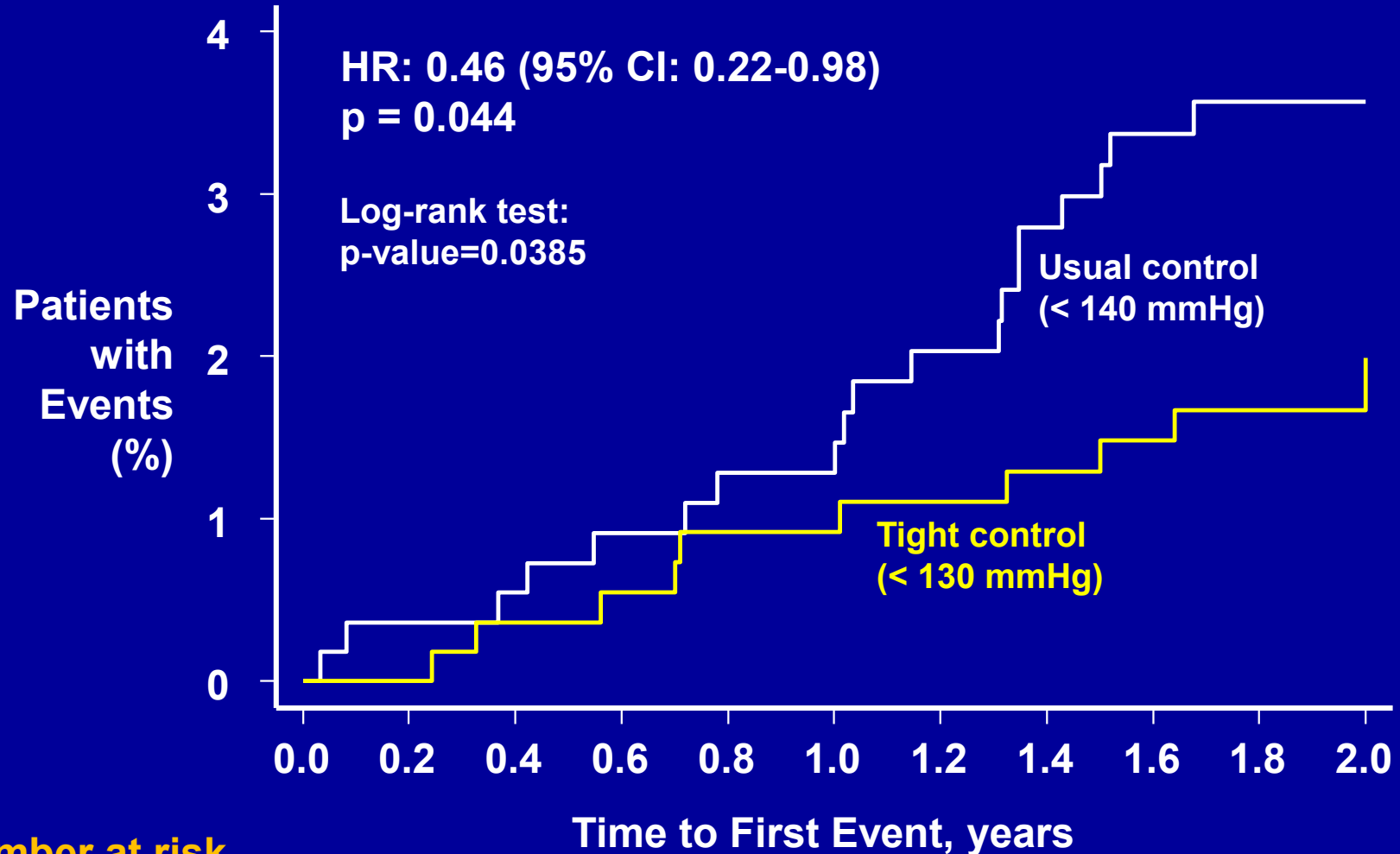
Verdecchia P et al Lancet 2009; 374: 525–33

Participating Centres (N=44)



Verdecchia P et al Lancet 2009; 374: 525–33

Atrial Fibrillation



Number at risk					
Less Intensive	553	541	529	503	266
More Intensive	557	542	530	525	296

Verdecchia P et al Lancet 2009; 374: 525–33

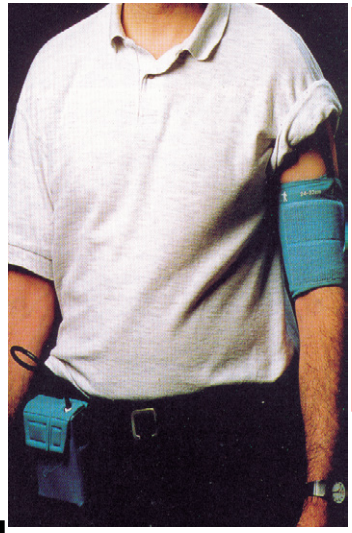
Cardio-Sis provided the first evidence, in the setting of a randomised study, that a more tight SBP target (i.e. SBP < 130 mmHg) could result in a less risk of new-onset AF when compared with a usual target (i.e., SBP < 140 mmHg).

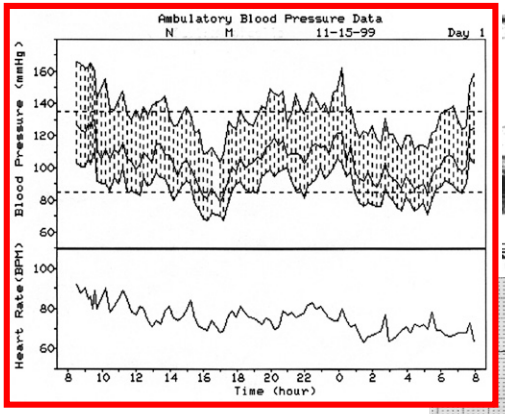
However, because of the small size of the study, these conclusions should be verified in a larger study.

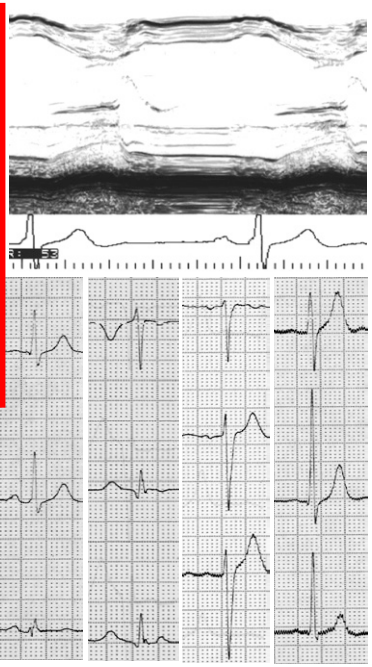
Agenda

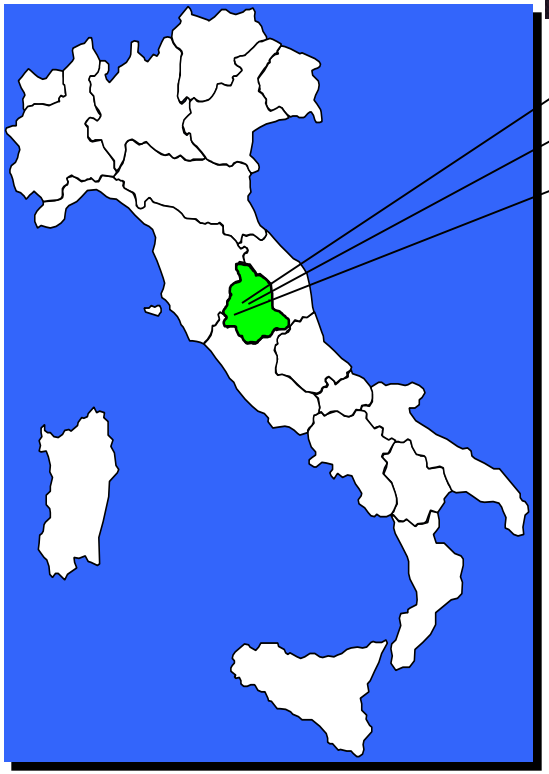
- Hypertensive LVH as a risk factor for AF

The PIUMA* Study







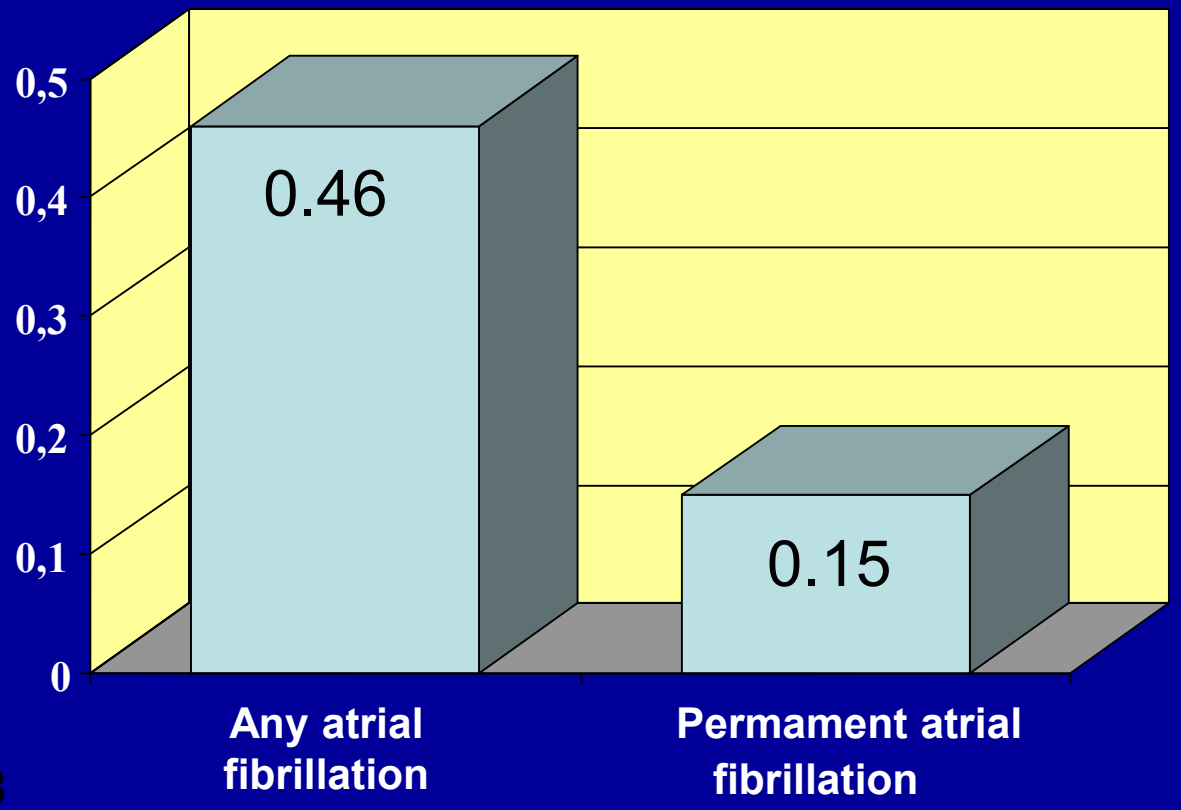


Castiglione del Lago
Perugia
Città della Pieve

* Progetto Ipertensione Umbria Monitoraggio Ambulatoriale

Observational Registry of Morbidity and Mortality in Subjects with Essential Hypertension whose Initial Off-Therapy Diagnostic Work-Up Includes 24-hour Noninvasive Ambulatory BP Monitoring According to a Standardized Protocol

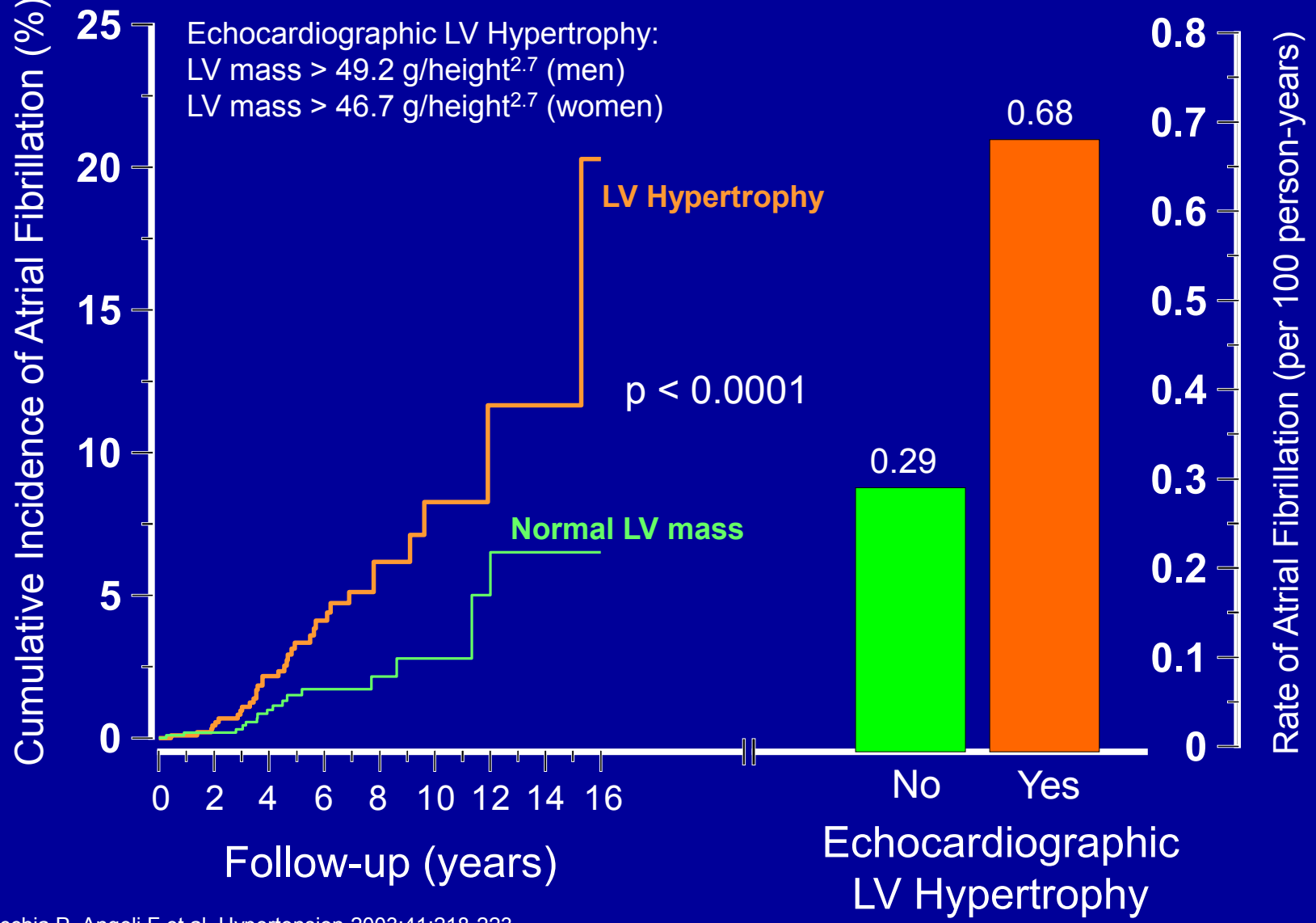
Incidence of atrial fibrillation (during follow-up) in hypertensive subjects who were in sinus rhythm at entry



FA in 61 out of 2482 subjects.
- Paroxysmal AF in 28
- Persistent AF in 13
- Permament AF in 20

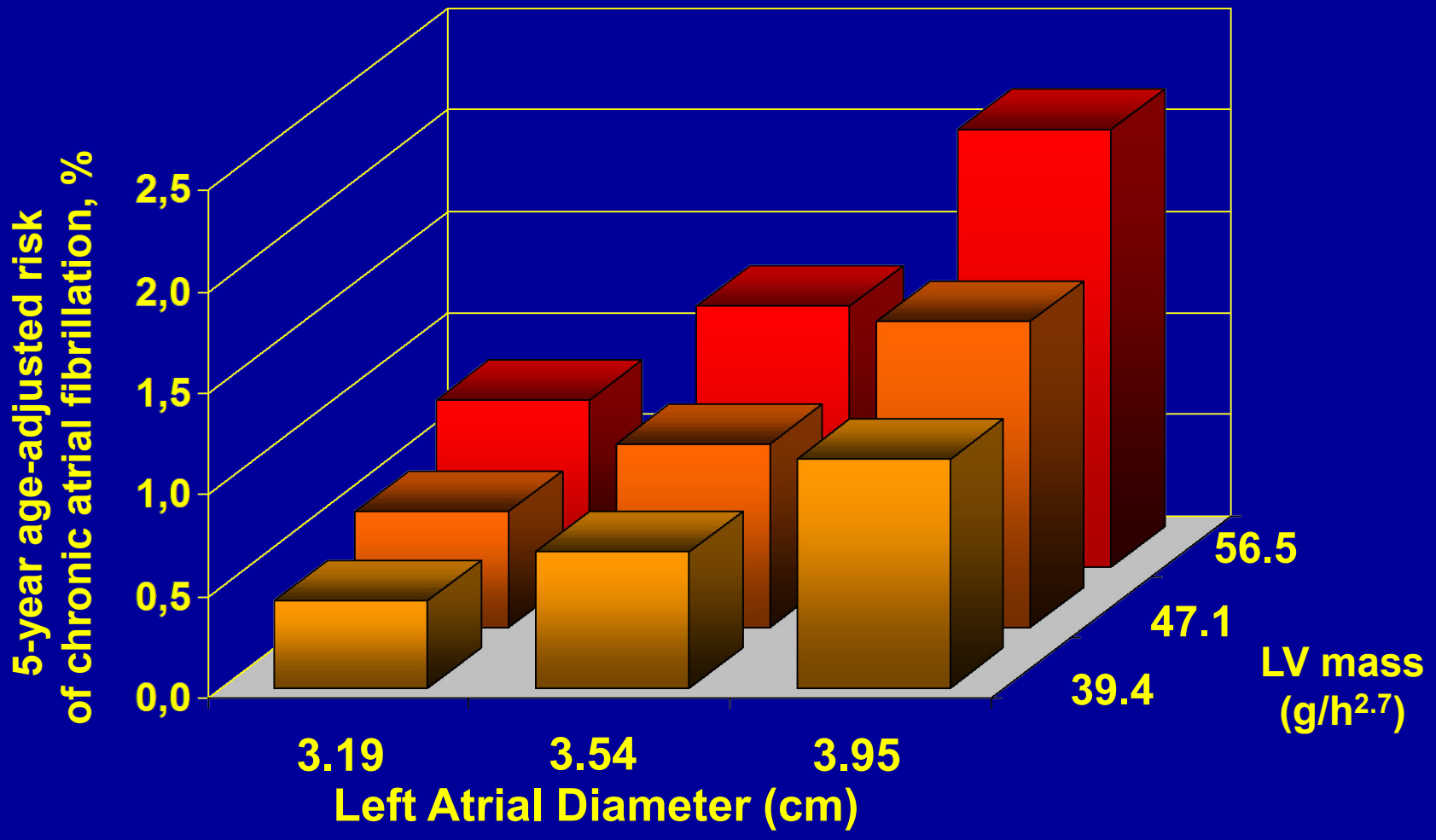
Verdecchia P, Angeli F et al. Hypertension 2003;41:218-223

Incidence of Atrial Fibrillation in relation to LVH



Verdecchia P, Angeli F et al. Hypertension 2003;41:218-223

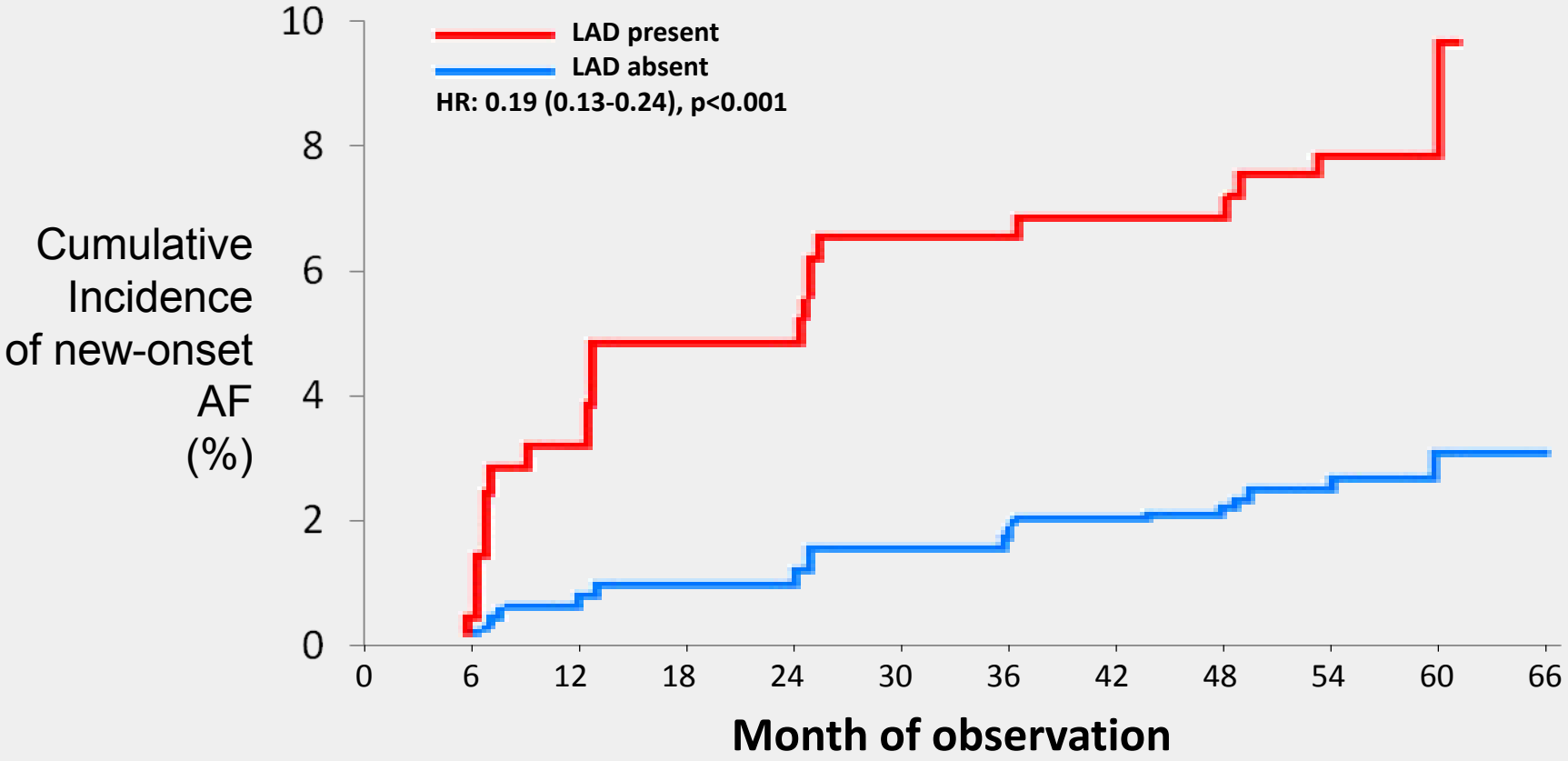
Age-adjusted 5-year risk of permanent atrial fibrillation



Verdecchia P, Angeli F et al. Hypertension 2003;41:218-223

Left atrial dilatation and atrial fibrillation

The LIFE Study



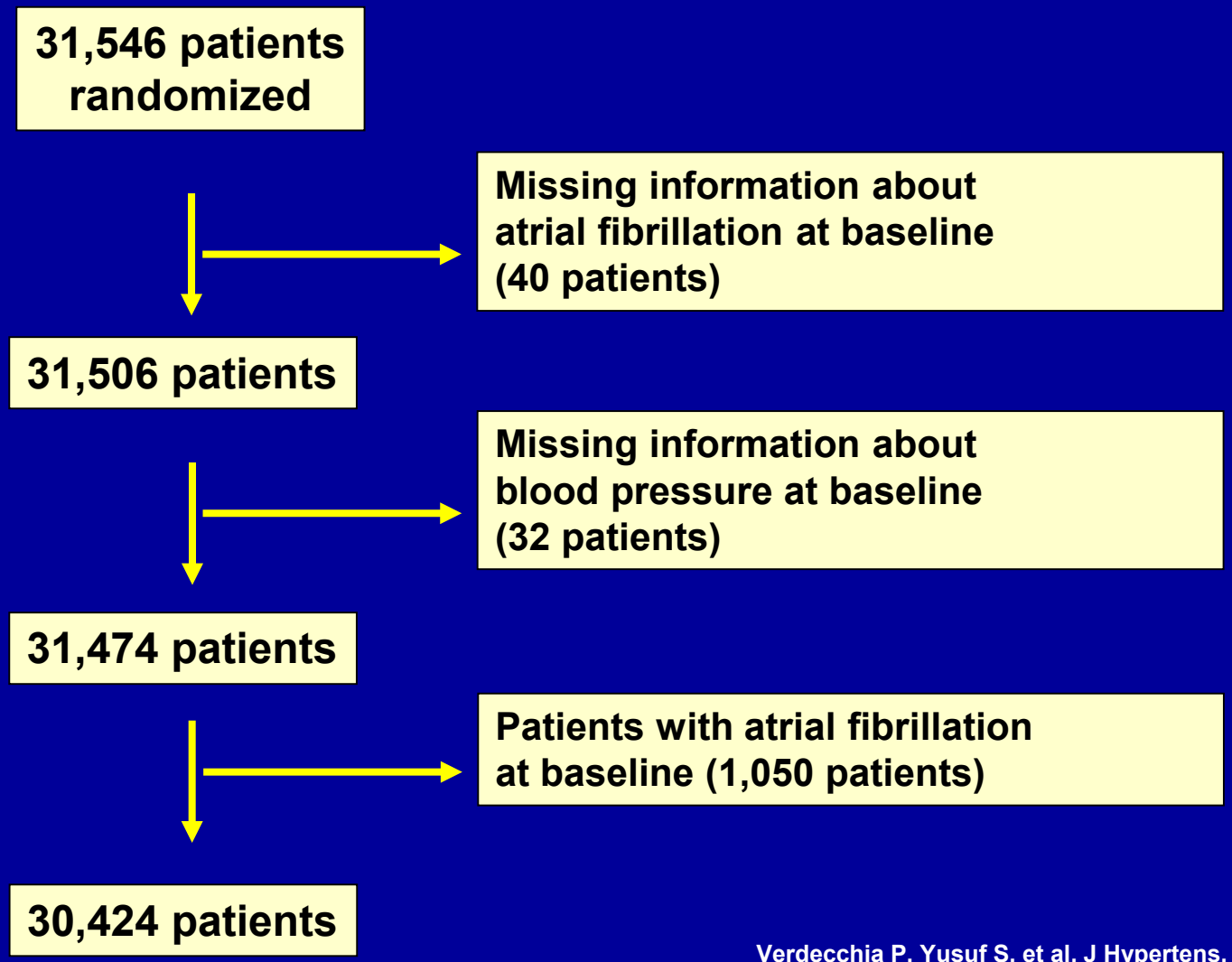
N. at risk						
LAD present	296	293	281	277	276	99
LAD absent	643	641	636	633	631	204

Wachtell et al.: J Am Coll Cardiol 2005;45 (Suppl A):374A

Agenda

- Impact of AF in high-risk patients

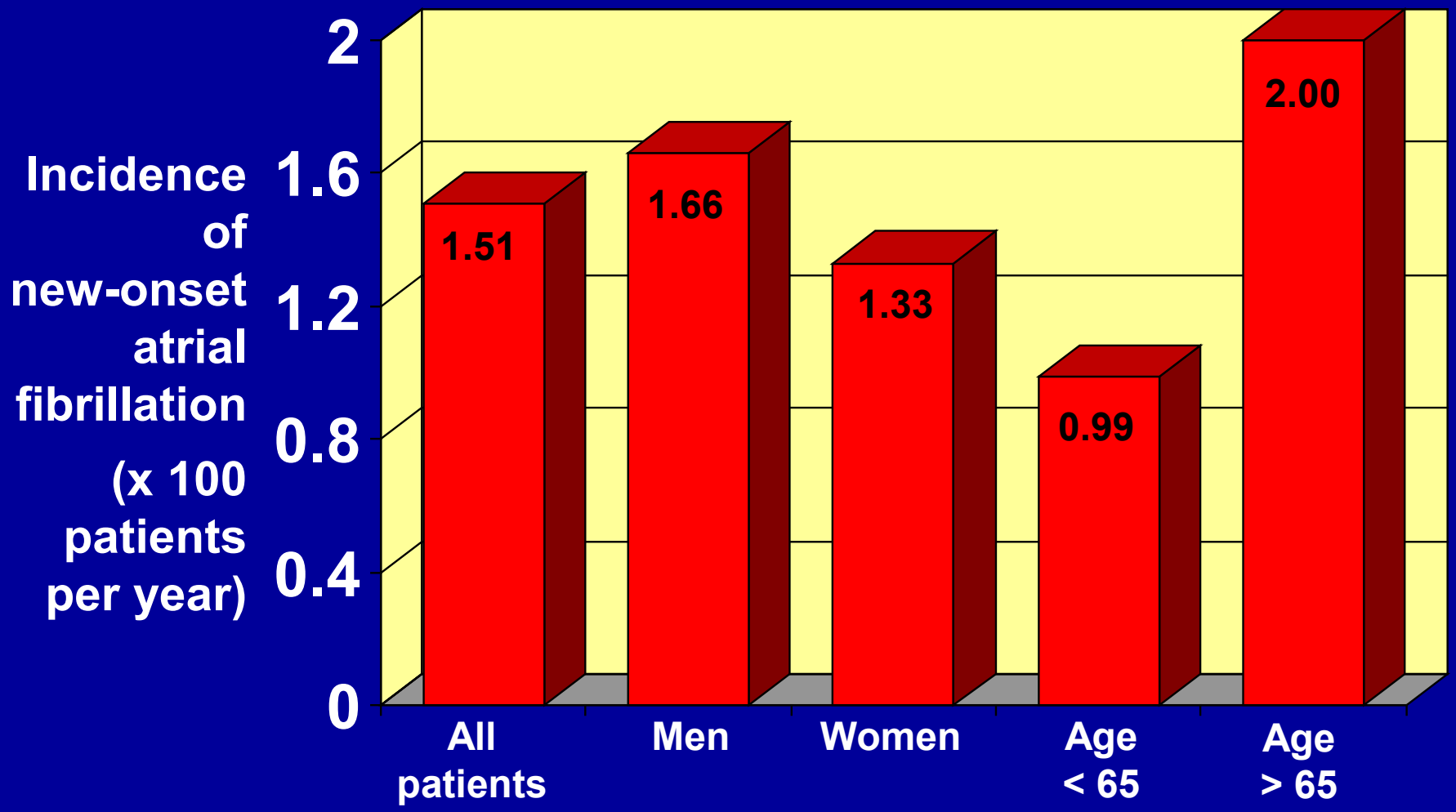
New-onset AF in high-risk patients ONTARGET/TRANSCEND study (2092/30424 pts)



Verdecchia P, Yusuf S, et al. J Hypertens. 2012;30:1004-1014

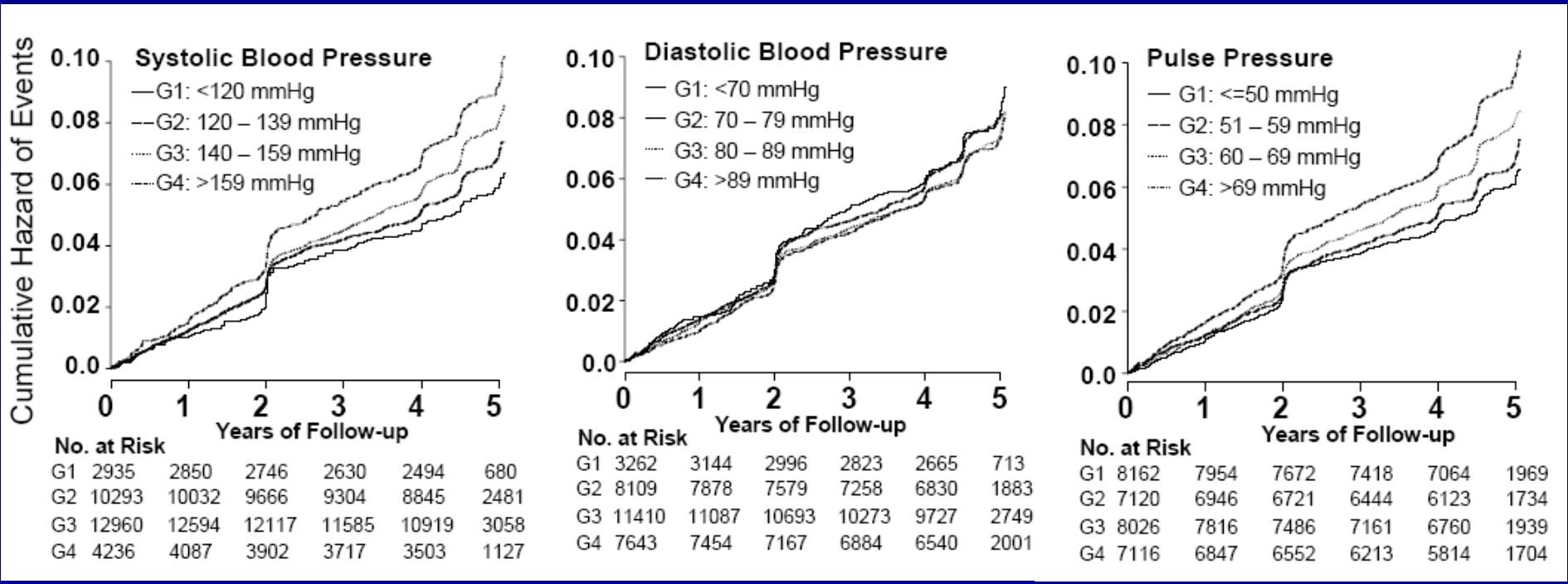
Incidence of new-onset AF in high-risk patients

ONTARGET/TRANSCEND study (2092/30424 pts)



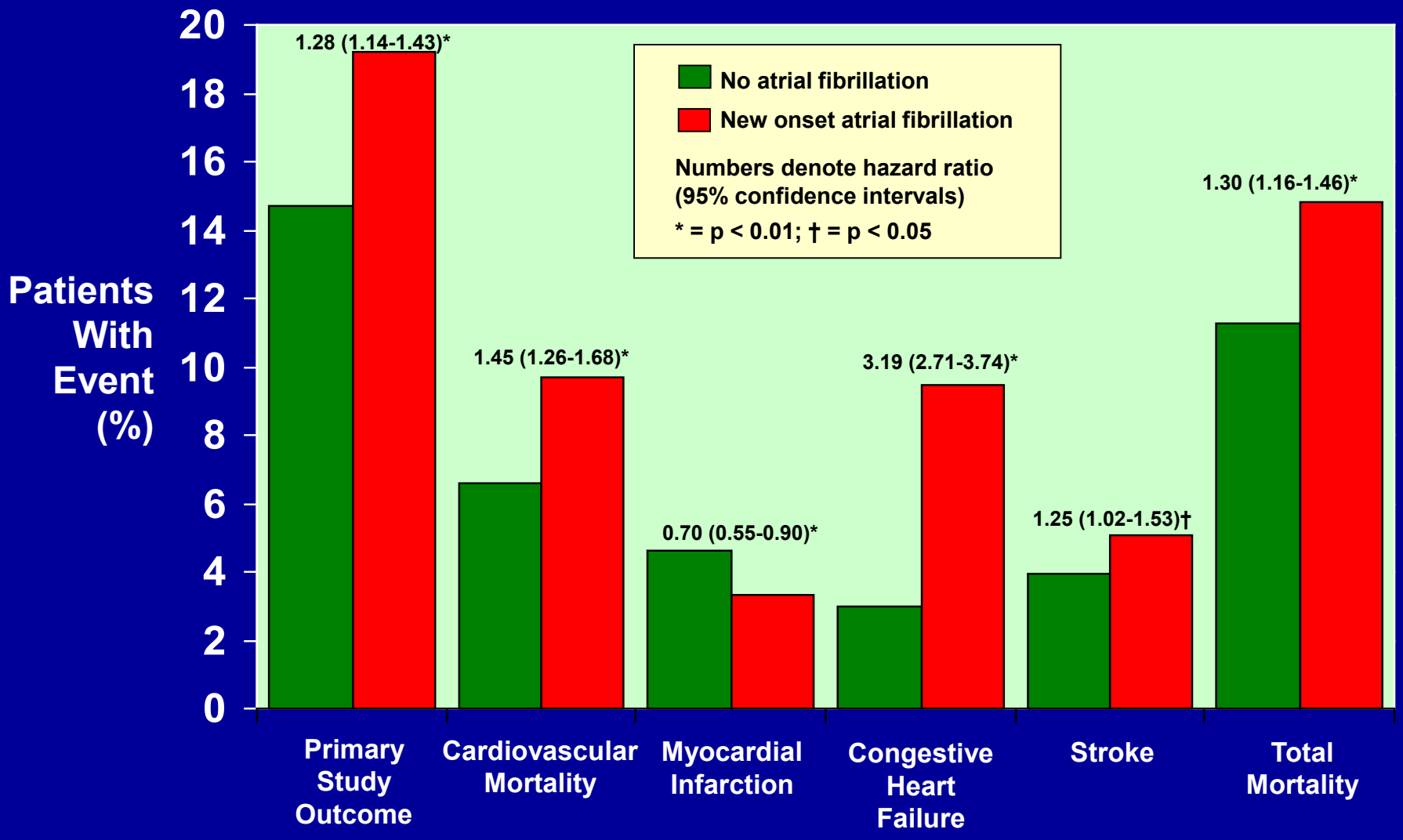
Verdecchia P, Yusuf S, et al. J Hypertens. 2012;30:1004-1014

Incidence of new-onset AF in high-risk patients ONTARGET/TRANSCEND study (2092/30424 pts)



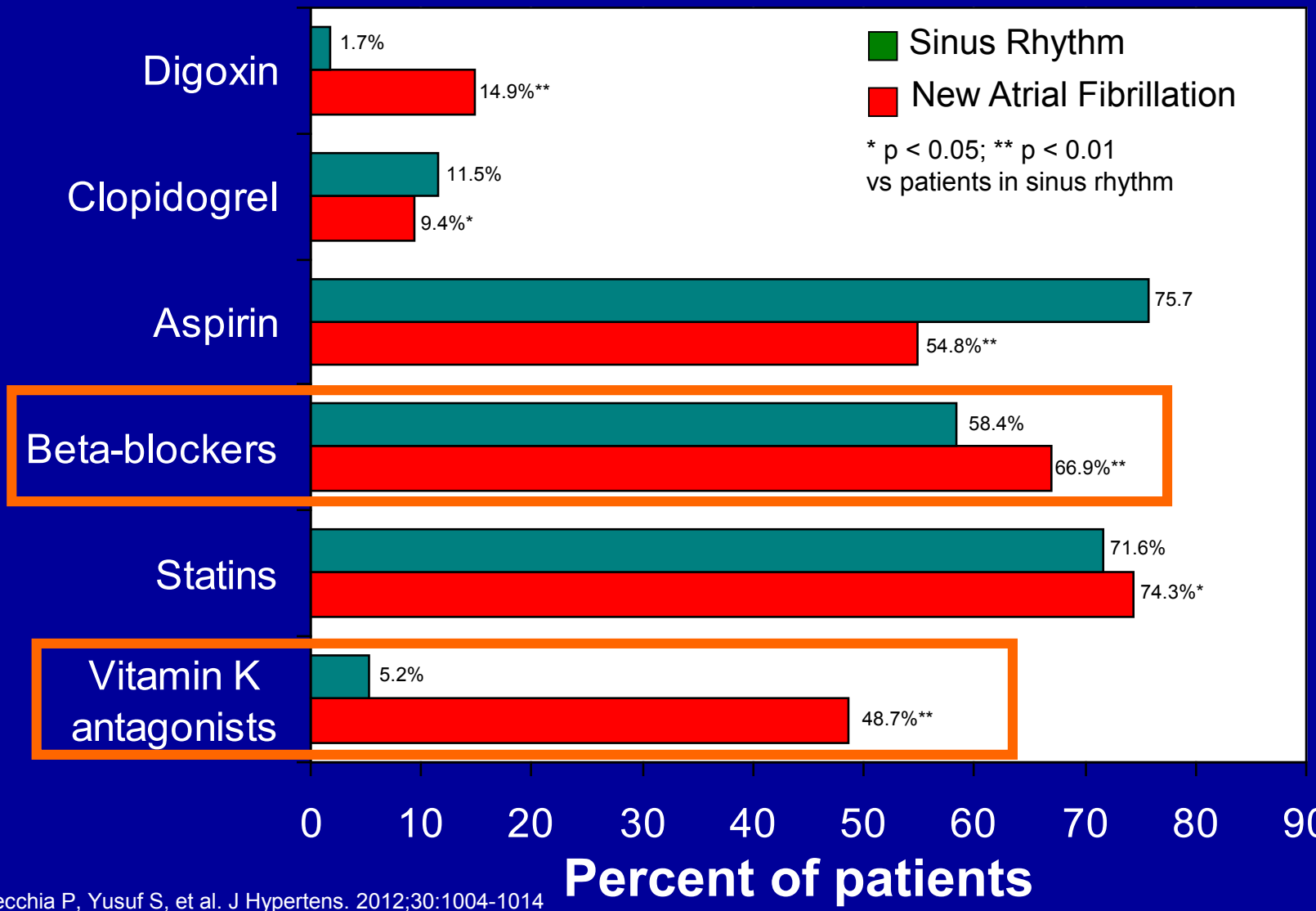
Verdecchia P, Yusuf S, et al. J Hypertens. 2012;30:1004-1014

Outcome of new-onset AF in high-risk patients ONTARGET/TRANSCEND study



Verdecchia P, Yusuf S, et al. J Hypertens. 2012;30:1004-1014

Concomitant Treatments in high-risk patients with and without new-onset AF

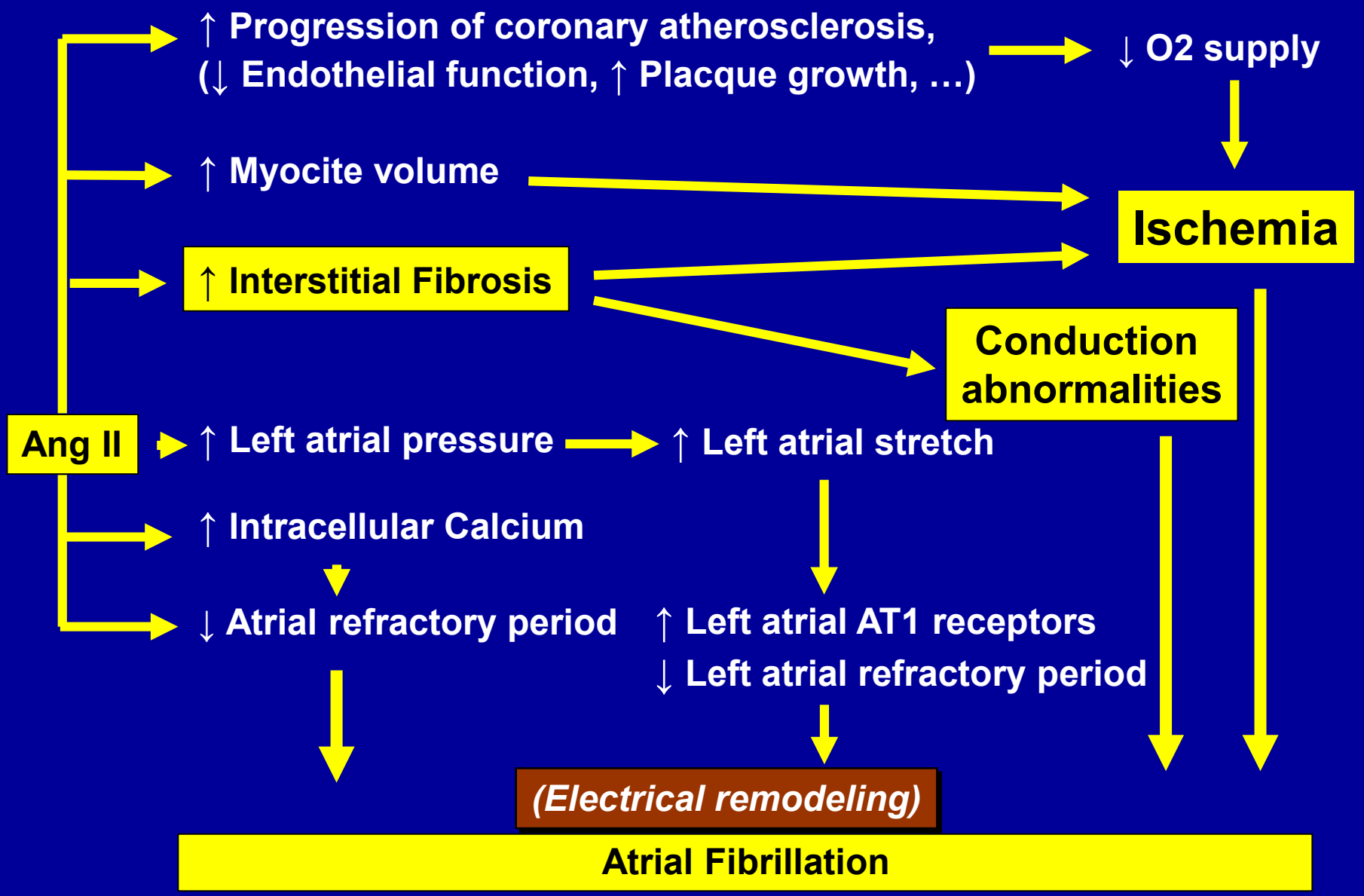


Verdecchia P, Yusuf S, et al. J Hypertens. 2012;30:1004-1014

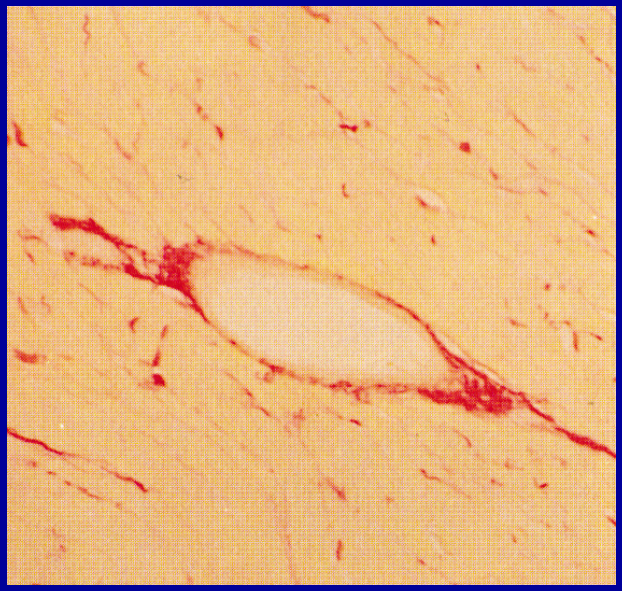
Agenda

- Inhibition of the RAS and AF

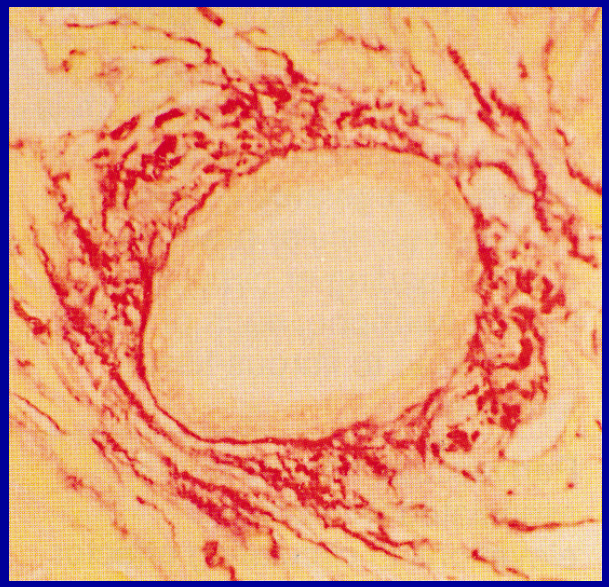
Angiotensin II and Atrial Fibrillation



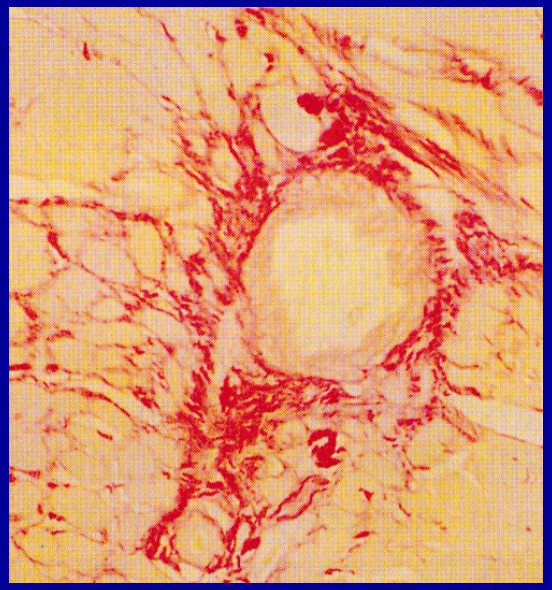
Effects of Sub-pressor Doses of Angiotensin II and Aldosterone Infused Through Implanted Minipump



Controls



Angiotensin II
(2 weeks)

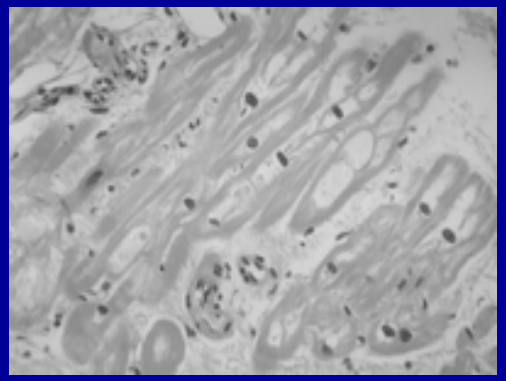


Aldosterone
(6 weeks)

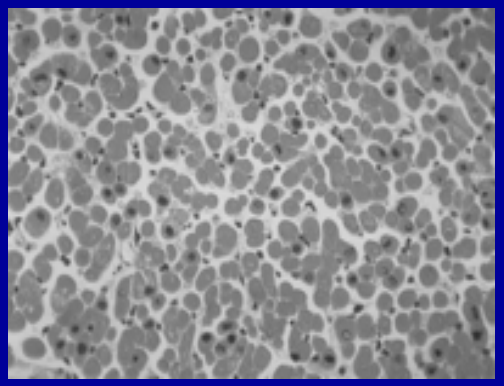
Picrosirius red indicates fibrillar collagen around intra-myocardial coronary arteries

Sun Y et al.
J Lab Clin Med 1993; 122: 395-403

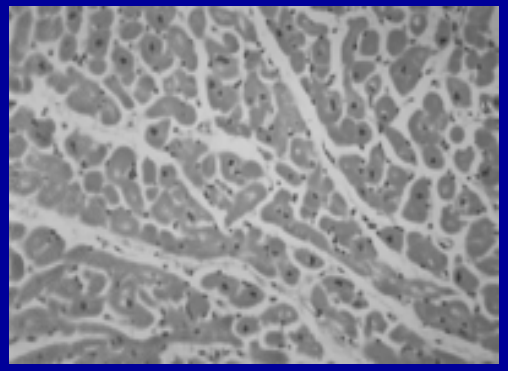
Histological Substrate of Atrial Biopsies in Patients With Lone Atrial Fibrillation



Left Atrium



Right Ventricle



Left Ventricle

Endomyocardial biopsies of the right atrial septum and of the two ventricles in 12 patients (10 men, 2 women; mean age, 32 years) with paroxysmal lone AF refractory to antiarrhythmic treatment.

Abnormal atrial histology with several alterations including fibrosis in all patients with AF.

These changes were present also in the ventricles in only 3 of these patients.

Frustaci et al. Circulation 1997; 96: 1180-1184

ACEi and ARBs reduce fibrosis and increase electrical stability in animals.

There is large and convincing experimental evidence about that…

ACEi and ARBs seem to reduce fibrosis and increase electrical stability in animals..

Does this imply a decreased risk of AF in humans?

Prevention of Atrial Fibrillation by Renin-Angiotensin System Inhibition

A Meta-Analysis

Markus P. Schneider, MD,* Tsushung A. Hua, PHD,† Michael Böhm, MD,‡
Kristian Wachtell, MD, PHD,§ Sverre E. Kjeldsen, MD, PHD,‖ Roland E. Schmieder, MD*
Erlangen and Homburg, Germany; East Hanover, New Jersey; Copenhagen, Denmark; and Ullevål, Norway

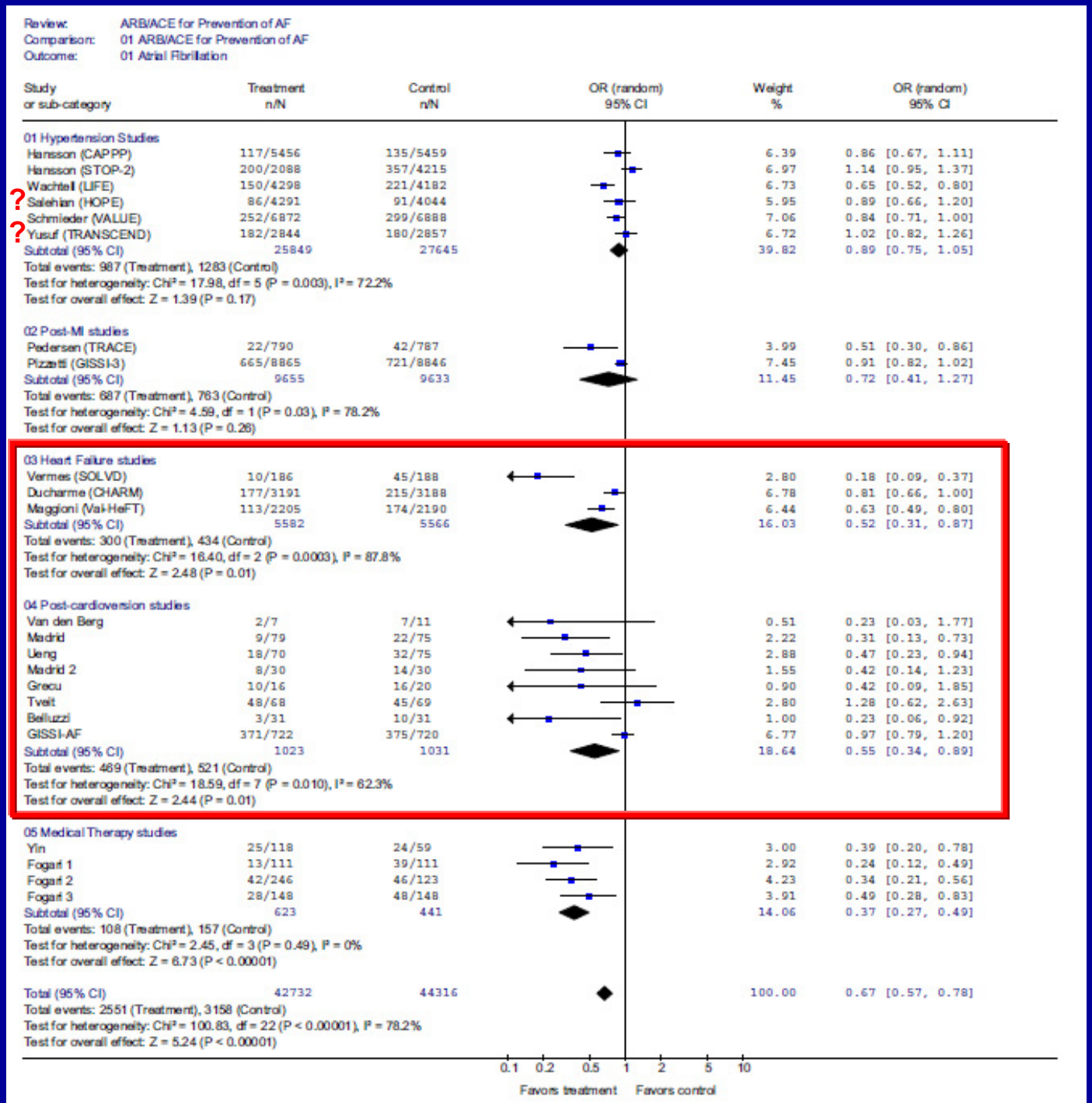
Objectives The authors reviewed published clinical trial data on the effects of renin-angiotensin system (RAS) inhibition for the prevention of atrial fibrillation (AF), aiming to define when RAS inhibition is most effective.

Background Individual studies examining the effects of RAS inhibition on AF prevention have reported controversial results.

Methods All published randomized controlled trials reporting the effects of treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the primary or secondary prevention of AF were included.

Results A total of 23 randomized controlled trials with 87,048 patients were analyzed. In primary prevention, 6 trials in hypertension, 2 trials in myocardial infarction, and 3 trials in heart failure were included (some being post-hoc analyses of randomized controlled trials). In secondary prevention, 8 trials after cardioversion and 4 trials assessing the medical prevention of recurrence were included. Overall, RAS inhibition reduced the odds ratio for AF by 33% ($p < 0.00001$), but there was substantial heterogeneity among trials. In primary prevention, RAS inhibition was effective in patients with heart failure and those with hypertension and left ventricular hypertrophy but not in post-myocardial infarction patients overall. In secondary prevention, RAS inhibition was often administered in addition to antiarrhythmic drugs, including amiodarone, further reducing the odds for AF recurrence after cardioversion by 45% ($p = 0.01$) and in patients on medical therapy by 63% ($p < 0.00001$).

Conclusions This analysis supports the concept of RAS inhibition as an emerging treatment for the primary and secondary prevention of AF but acknowledges the fact that some of the primary prevention trials were post-hoc analyses. Further areas of uncertainty include potential differences among specific RAS inhibitors and possible interactions or synergistic effects with antiarrhythmic drugs. (J Am Coll Cardiol 2010;55:2299–307)



Hypertension studies
0.89 (0.75-1.06)

Post MI studies
0.72 (0.41-1.27)

Heart Failure studies
0.52 (0.31-0.87)
p=0.01

Post cardioversion studies
0.55 (0.34-0.89)
p=0.01

Total
0.67 (0.57-0.78)

Agenda

- High BP as a risk factor for stroke in patients with AF

Independent predictors of stroke in patients with atrial fibrillation

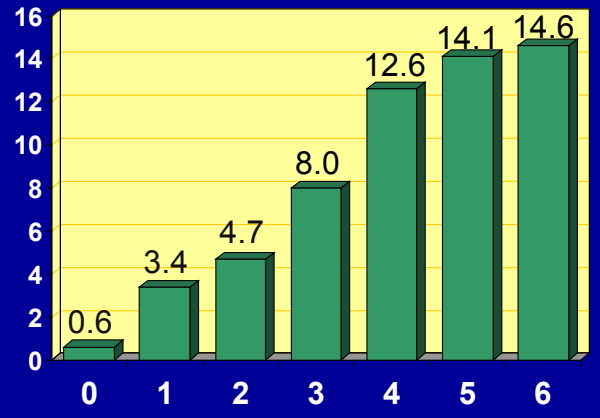
1) **Prior stroke / TIA**
   RR 2.5, 95% CI 1.8-3.5
2) **Increasing age**
   RR 1.5 per decade, 95% CI 1.3-1.7
3) **Hypertension**
   RR 2.0, 95% CI 1.6-2.5
4) **Diabetes mellitus**
   RR 1.7, 95% CI 1.4-2.0

Stroke Risk in AF Working Group. Neurology 2007;69:546-54

Ischemic Stroke in relation to $CHADS_2$ and CHA_2DS_2VASc

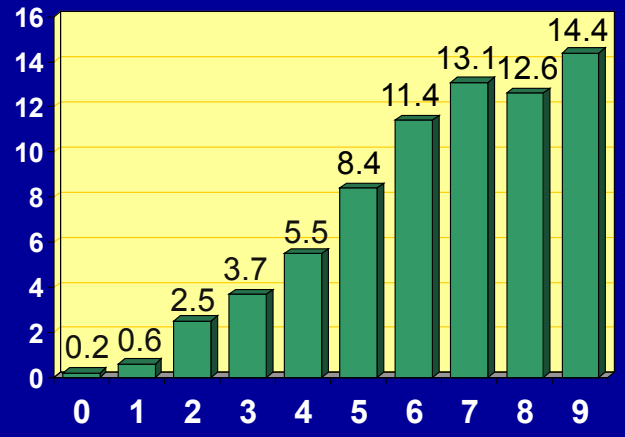
$CHADS_2$		CHA_2DS_2VASc
1	Congestive Heart Failure/LV dysfunction	1
1	Hypertension (or treated hypertension)	1
1	Age ≥ 75 years	2
1	Diabetes	1
2	Prior stroke or TIA	2
0	Vascular Disease (Prior MI, PAD, aortic plaque)	1
0	Age 65-74	1
0	Sex category (female sex)	1

Friberg L et al
Eur Heart J 2012;
33:1500-10



Annual rate* of stroke by $CHADS_2$ and CHA_2DS_2VASc scores

*** Adjusted for aspirin use**



Punteggio HAS-BLED

Caratteristiche cliniche	Punti
Hypertension (SBP >160 mmHg)	1
Abnormal renal/liver (dialisi, trapianto renale o creatinemia > 2,26 mg/sl) + (cirrosi, oppure biliribina > 2xUNL + GOT/GPT/AP > 3UNL)	1 + 1
Stroke (Anamnesi di ictus)	1
Bleeding (predisposizione o anamnesi di sanguinamento)	1
INR **L**abile (TTR < 60)	1
Elderly (età >65 anni)	1
Drugs/alcohol (farmaci* o abuso di alcool**)	1 + 1
Punteggio cumulativo	**da 0 a 9**

* FANS e/o antiaggreganti; > ** 8 U/sett (1 unità di alcool = 1/2 bicchiere medio di vino o 1 bicchiere medio di birra o 1 bicchierino [25cc] di super alcoolico)

Pisters R et al. Chest 2010;138:1093-1100

Subgroup analyses on the 1^{ry} outcome:

None of these studies showed a statistically significant interaction between treatment effect (NOA vs warfarin) and hypertension status.

N Engl J Med 2011;365:981–92

Conclusions - 1

1. **Incidence of new AF in hypertensive patients approximates 0,5% per year.** The risk of new onset AF increases with higher BP levels (even in a pre-hypertensive range), LV mass and left atrial dimension.
2. **In patients at high CV risk, new onset AF occurs at a rate of 1.5%.** It is associated with a very high risk of serious CV complications in a relatively short term.

Conclusions - 2

3. In experimental animals, inhibition of the RAAS looks effective in preventing AF.
4. In humans, results are controversial. Inhibition of RAAS seems to be effective in preventing AF essentially in patients with CHF and after cardioversion. In different clinical contexts, the benefit is unclear.

Conclusions - 3

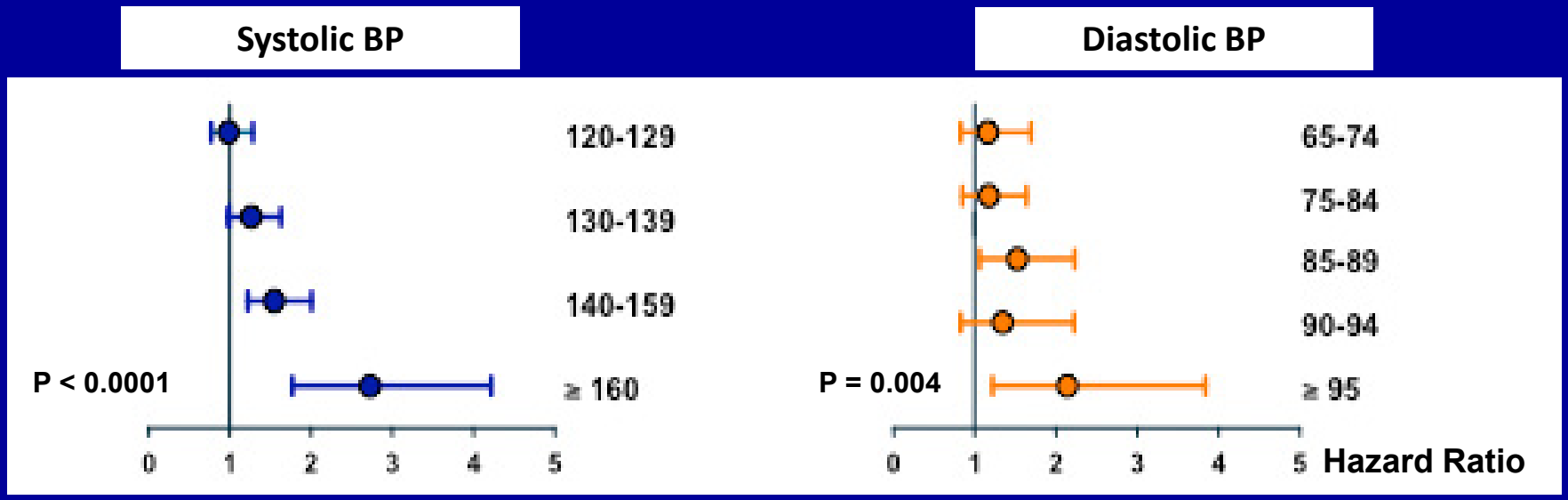
5. In patients with established AF, hypertension is an independent risk factor for stroke.
6. The efficacy of newer oral anticoagulants seems to be comparable in AF patients with and without hypertension.

Thank you for your attention

Discussion Slides

The higher the baseline BP, the greater the risk of developing atrial fibrillation

- **The Women's Health Study**: 34.221 women have been followed for a median of 12.4 years. The relation between baseline BP and subsequent occurrence of FA has been investigated



Conen D et al., Circulation 2009;119(16):2146-52.

Journal of the American Society of Hypertension 9(3) (2015) 191–196

Research Article

Sustained pre–hypertensive blood pressure and incident atrial fibrillation: the Multi–Ethnic Study of Atherosclerosis

Wesley T. O'Neal, MD, MPH[a,*], Elsayed Z. Soliman, MD, MSc, MS[b,c], Waqas Qureshi, MD[b], Alvaro Alonso, MD, PhD[d], Susan R. Heckbert, MD, PhD[e], and David Herrington, MD, MHS[b]

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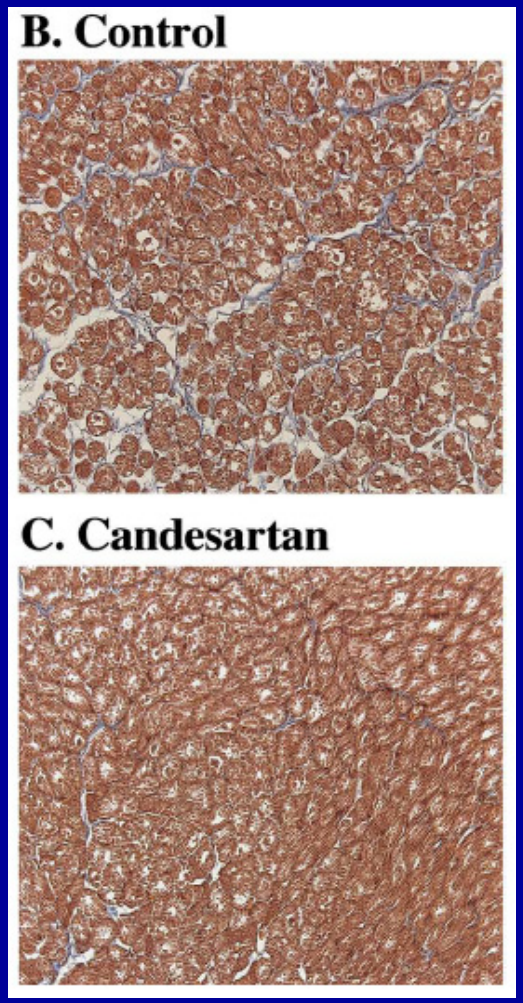
Manuscript received November 20, 2014 and accepted January 1, 2015

Effects of Angiotensin II Type 1 Receptor Blockade on Electrical and Structural Remodeling in Atrial Fibrillation



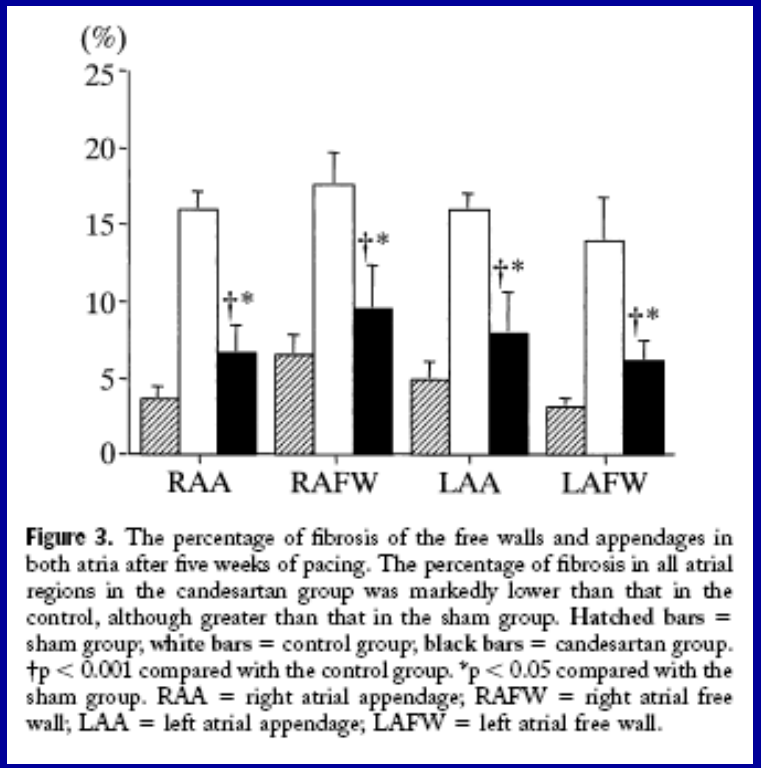
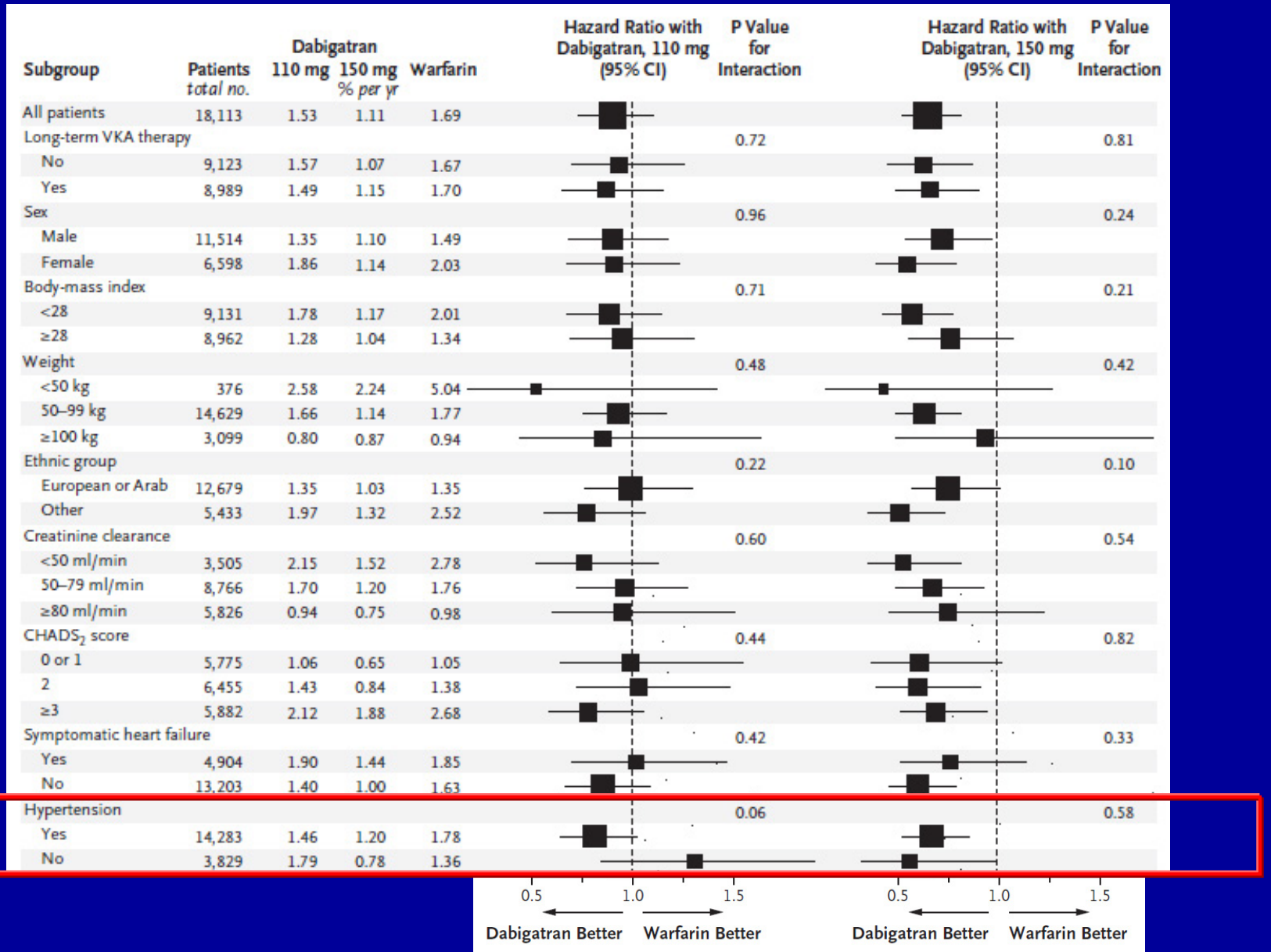


Figure 3. The percentage of fibrosis of the free walls and appendages in both atria after five weeks of pacing. The percentage of fibrosis in all atrial regions in the candesartan group was markedly lower than that in the control, although greater than that in the sham group. Hatched bars = sham group; white bars = control group; black bars = candesartan group. †$p < 0.001$ compared with the control group. *$p < 0.05$ compared with the sham group. RAA = right atrial appendage; RAFW = right atrial free wall; LAA = left atrial appendage; LAFW = left atrial free wall.

Sustained AF was induced in 20 dogs (10 in a control group and 10 in a candesartan group) by rapid pacing of the right atrium (RA) at 400 beats/min for five weeks. Candesartan was administered orally (10 mg/kg/day) for one week before rapid pacing and was continued for five weeks.

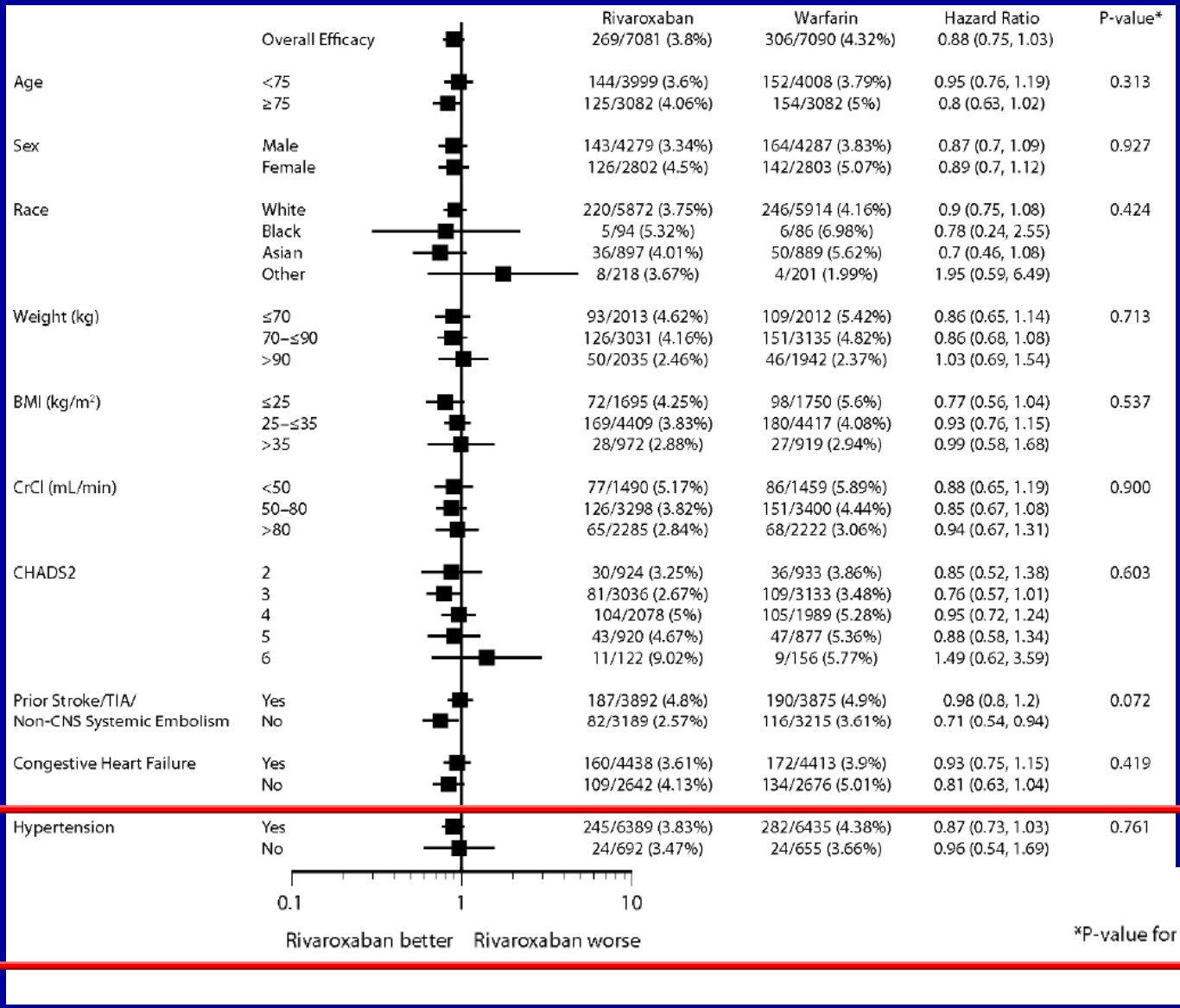
Kumagai et al. J Am Coll Cardiol 2003;41:2197–204

Dabigatran: no significant interaction with hypertension status
(Low dose: interaction with hypertension that bordered significance)



Subgroup	Patients total no.	Dabigatran 110 mg % per yr	Dabigatran 150 mg % per yr	Warfarin	Hazard Ratio with Dabigatran, 110 mg (95% CI)	P Value for Interaction	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
All patients	18,113	1.53	1.11	1.69				
Long-term VKA therapy						0.72		0.81
No	9,123	1.57	1.07	1.67				
Yes	8,989	1.49	1.15	1.70				
Sex						0.96		0.24
Male	11,514	1.35	1.10	1.49				
Female	6,598	1.86	1.14	2.03				
Body-mass index						0.71		0.21
<28	9,131	1.78	1.17	2.01				
≥28	8,962	1.28	1.04	1.34				
Weight						0.48		0.42
<50 kg	376	2.58	2.24	5.04				
50–99 kg	14,629	1.66	1.14	1.77				
≥100 kg	3,099	0.80	0.87	0.94				
Ethnic group						0.22		0.10
European or Arab	12,679	1.35	1.03	1.35				
Other	5,433	1.97	1.32	2.52				
Creatinine clearance						0.60		0.54
<50 ml/min	3,505	2.15	1.52	2.78				
50–79 ml/min	8,766	1.70	1.20	1.76				
≥80 ml/min	5,826	0.94	0.75	0.98				
$CHADS_2$ score						0.44		0.82
0 or 1	5,775	1.06	0.65	1.05				
2	6,455	1.43	0.84	1.38				
≥3	5,882	2.12	1.88	2.68				
Symptomatic heart failure						0.42		0.33
Yes	4,904	1.90	1.44	1.85				
No	13,203	1.40	1.00	1.63				
Hypertension						0.06		0.58
Yes	14,283	1.46	1.20	1.78				
No	3,829	1.79	0.78	1.36				

Rivaroxaban: no significant interaction with hypertension status

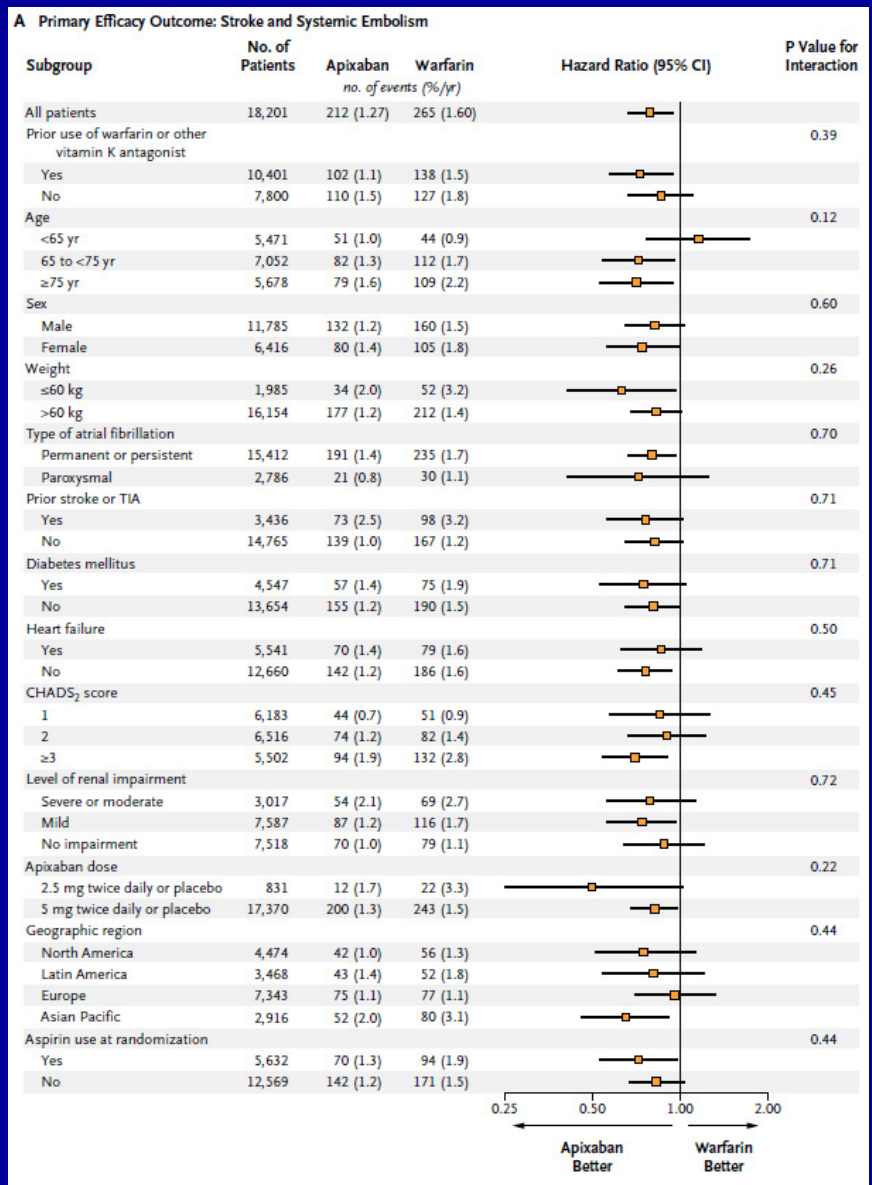


		Rivaroxaban	Warfarin	Hazard Ratio	P-value*
	Overall Efficacy	269/7081 (3.8%)	306/7090 (4.32%)	0.88 (0.75, 1.03)	
Age	<75	144/3999 (3.6%)	152/4008 (3.79%)	0.95 (0.76, 1.19)	0.313
	≥75	125/3082 (4.06%)	154/3082 (5%)	0.8 (0.63, 1.02)	
Sex	Male	143/4279 (3.34%)	164/4287 (3.83%)	0.87 (0.7, 1.09)	0.927
	Female	126/2802 (4.5%)	142/2803 (5.07%)	0.89 (0.7, 1.12)	
Race	White	220/5872 (3.75%)	246/5914 (4.16%)	0.9 (0.75, 1.08)	0.424
	Black	5/94 (5.32%)	6/86 (6.98%)	0.78 (0.24, 2.55)	
	Asian	36/897 (4.01%)	50/889 (5.62%)	0.7 (0.46, 1.08)	
	Other	8/218 (3.67%)	4/201 (1.99%)	1.95 (0.59, 6.49)	
Weight (kg)	≤70	93/2013 (4.62%)	109/2012 (5.42%)	0.86 (0.65, 1.14)	0.713
	70–≤90	126/3031 (4.16%)	151/3135 (4.82%)	0.86 (0.68, 1.08)	
	>90	50/2035 (2.46%)	46/1942 (2.37%)	1.03 (0.69, 1.54)	
BMI (kg/m^2)	≤25	72/1695 (4.25%)	98/1750 (5.6%)	0.77 (0.56, 1.04)	0.537
	25–≤35	169/4409 (3.83%)	180/4417 (4.08%)	0.93 (0.76, 1.15)	
	>35	28/972 (2.88%)	27/919 (2.94%)	0.99 (0.58, 1.68)	
CrCl (mL/min)	<50	77/1490 (5.17%)	86/1459 (5.89%)	0.88 (0.65, 1.19)	0.900
	50–80	126/3298 (3.82%)	151/3400 (4.44%)	0.85 (0.67, 1.08)	
	>80	65/2285 (2.84%)	68/2222 (3.06%)	0.94 (0.67, 1.31)	
CHADS2	2	30/924 (3.25%)	36/933 (3.86%)	0.85 (0.52, 1.38)	0.603
	3	81/3036 (2.67%)	109/3133 (3.48%)	0.76 (0.57, 1.01)	
	4	104/2078 (5%)	105/1989 (5.28%)	0.95 (0.72, 1.24)	
	5	43/920 (4.67%)	47/877 (5.36%)	0.88 (0.58, 1.34)	
	6	11/122 (9.02%)	9/156 (5.77%)	1.49 (0.62, 3.59)	
Prior Stroke/TIA/ Non-CNS Systemic Embolism	Yes	187/3892 (4.8%)	190/3875 (4.9%)	0.98 (0.8, 1.2)	0.072
	No	82/3189 (2.57%)	116/3215 (3.61%)	0.71 (0.54, 0.94)	
Congestive Heart Failure	Yes	160/4438 (3.61%)	172/4413 (3.9%)	0.93 (0.75, 1.15)	0.419
	No	109/2642 (4.13%)	134/2676 (5.01%)	0.81 (0.63, 1.04)	
Hypertension	Yes	245/6389 (3.83%)	282/6435 (4.38%)	0.87 (0.73, 1.03)	0.761
	No	24/692 (3.47%)	24/655 (3.66%)	0.96 (0.54, 1.69)	

Apixaban: no information provided about possible interactions with hypertension status, despite the high frequency of hypertensive patients

Table 1. Baseline Characteristics of the Patients.*

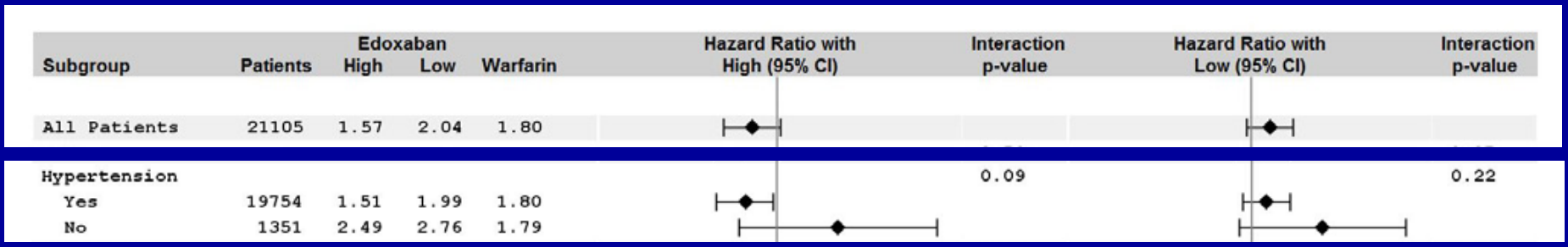
Characteristic	Apixaban (N=9120)	Warfarin (N=9081)
Age — yr		
Median	70	70
Interquartile range	63–76	63–76
Female sex — no. (%)	3234 (35.5)	3182 (35.0)
Region — no. (%)		
North America	2249 (24.7)	2225 (24.5)
Latin America	1743 (19.1)	1725 (19.0)
Europe	3672 (40.3)	3671 (40.4)
Asian Pacific	1456 (16.0)	1460 (16.1)
Systolic blood pressure — mm Hg		
Median	130	130
Interquartile range	120–140	120–140
Weight — kg		
Median	82	82
Interquartile range	70–96	70–95
Prior myocardial infarction — no. (%)	1319 (14.5)	1266 (13.9)
Prior clinically relevant or spontaneous bleeding — no. (%)	1525 (16.7)	1515 (16.7)
History of fall within previous year — no. (%)	386 (4.2)	367 (4.0)
Type of atrial fibrillation — no. (%)		
Paroxysmal	1374 (15.1)	1412 (15.5)
Persistent or permanent	7744 (84.9)	7668 (84.4)
Prior use of vitamin K antagonist for >30 consecutive days — no. (%)	5208 (57.1)	5193 (57.2)
Qualifying risk factors		
Age ≥75 yr — no. (%)	2850 (31.2)	2828 (31.1)
Prior stroke, TIA, or systemic embolism — no. (%)	1748 (19.2)	1790 (19.7)
Heart failure or reduced left ventricular ejection fraction — no. (%)	3235 (35.5)	3216 (35.4)
Diabetes — no. (%)	2284 (25.0)	2263 (24.9)
Hypertension requiring treatment — no. (%)	7962 (87.3)	7954 (87.6)
$CHADS_2$ score		
Mean	2.1±1.1	2.1±1.1
Distribution — no. (%)		
1	3100 (34.0)	3083 (34.0)
2	3262 (35.8)	3254 (35.8)
≥3	2758 (30.2)	2744 (30.2)



Edoxaban: no significant interaction with hypertension status
(Highdose: interaction with hypertension that bordered significance)

High dose Edoxanan Vs warfarin

Low dose Edoxanan Vs warfarin



Subgroup	Patients	Edoxaban High	Edoxaban Low	Warfarin	Hazard Ratio with High (95% CI)	Interaction p-value	Hazard Ratio with Low (95% CI)	Interaction p-value
All Patients	21105	1.57	2.04	1.80				
Hypertension						0.09		0.22
Yes	19754	1.51	1.99	1.80				
No	1351	2.49	2.76	1.79				

ORIGINAL CONTRIBUTION

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

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Sverker Jern, MD, PhD
Sverre E. Kjeldsen, MD, PhD
Stevo Julius, MD, ScD
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Björn Dahlöf, MD, PhD

Context Atrial fibrillation (AF) is associated with increased risk of mortality and cardiovascular events, particularly stroke, making prevention of new-onset AF a clinical priority. Although the presence and severity of electrocardiographic left ventricular hypertrophy (LVH) appear to predict development of AF, whether regression of electrocardiographic LVH is associated with a decreased incidence of AF is unclear.

Objective To test the hypothesis that in-treatment regression or continued absence of electrocardiographic LVH during antihypertensive therapy is associated with a decreased incidence of AF, independent of blood pressure and treatment modality.

Design, Setting, and Participants Double-blind, randomized, parallel-group study conducted in 1995-2001 among 8831 men and women with hypertension, aged 55-80 years (median, 67 years), with electrocardiographic LVH by Cornell voltage-duration product or Sokolow-Lyon voltage, with no history of AF, without AF on the baseline electrocardiogram, and enrolled in the Losartan Intervention for Endpoint Reduction in Hypertension Study.

Interventions Losartan- or atenolol-based treatment regimens, with follow-up assessments at 6 months and then yearly until death or study end.

Main Outcome Measure New-onset AF in relation to electrocardiographic LVH determined at baseline and subsequently. Electrocardiographic LVH was measured using sex-adjusted Cornell product criteria ($(R_{aVL} + S_{V3}$ [+ 6 mm in women]$) \times$ QRS duration).

Results After a mean (SD) follow-up of 4.7 (1.1) years, new-onset AF occurred in 290 patients with in-treatment regression or continued absence of Cornell product LVH for a rate of 14.9 per 1000 patient-years and in 411 patients with in-treatment persistence or development of LVH by Cornell product criteria for a rate of 19.0 per 1000 patient-years. In time-dependent Cox analyses adjusted for treatment effects, baseline differences in risk factors for AF, baseline and in-treatment blood pressure, and baseline severity of electrocardiographic LVH, lower in-treatment Cornell product LVH treated as a time-varying covariate was associated with a 12.4% lower rate of new-onset AF (adjusted hazard ratio [HR], 0.88; 95% CI, 0.80-0.97; $P = .007$) for every 1050 mm $\times$ msec (per 1-SD) lower Cornell product, with persistence of the benefit of losartan vs atenolol therapy on developing AF (HR, 0.83; 95% CI, 0.71-0.97; $P = .01$).

Conclusions Lower Cornell product electrocardiographic LVH during antihypertensive therapy is associated with a lower likelihood of new-onset AF, independent of blood pressure lowering and treatment modality in essential hypertension. These findings suggest that antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may reduce the incidence of new-onset AF.

JAMA. 2006;296:1242-1248 www.jama.com

ATRIAL FIBRILLATION IS THE MOST common clinically significant arrhythmia in adults[1,2] and is associated with increased risks of death,[3-5] heart failure,[5] and stroke.[3,6,7] The incidence of atrial fibrillation is increased in patients with hypertension, coronary heart disease, and heart failure.[4-6,8-10] Incidence of atrial fibrillation increases with age[1] even in the absence of these risk factors.[2] The increasing population prevalence of atrial fibrillation[2] and significant risks associated with antiarrhythmic and antithrombotic therapies aimed at preventing atrial fibrillation recurrences and decreasing the risk of embolic sequella,[11-13] coupled with the increased risks associated with the development of atrial fibrillation,[3-7] make prevention of atrial fibrillation a clinical priority.

Recent studies have found that therapies aimed at reducing blood pressure, and in particular blockade of the renin-angiotensin system by either angiotensin-converting enzyme (ACE) in-

Author Affiliations are listed at the end of this article.
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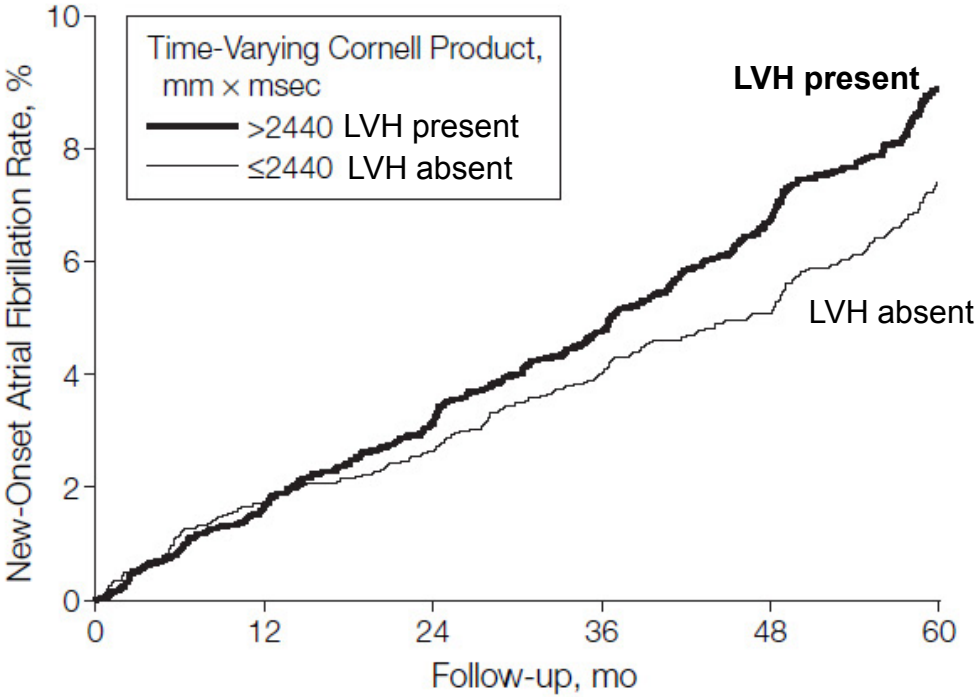
Conclusions Lower Cornell product ECG-LVH during antihypertensive therapy is associated with a lower likelihood of new-onset AF, independent of blood pressure lowering and treatment modality in essential hypertension.

These findings suggest that antihypertensive therapy targeted at regression or prevention of ECG-LVH may reduce the incidence of new-onset AF.

Okin P, et al.
JAMA. 2006;296:1242-1248

Figure. Rate of New-Onset Atrial Fibrillation

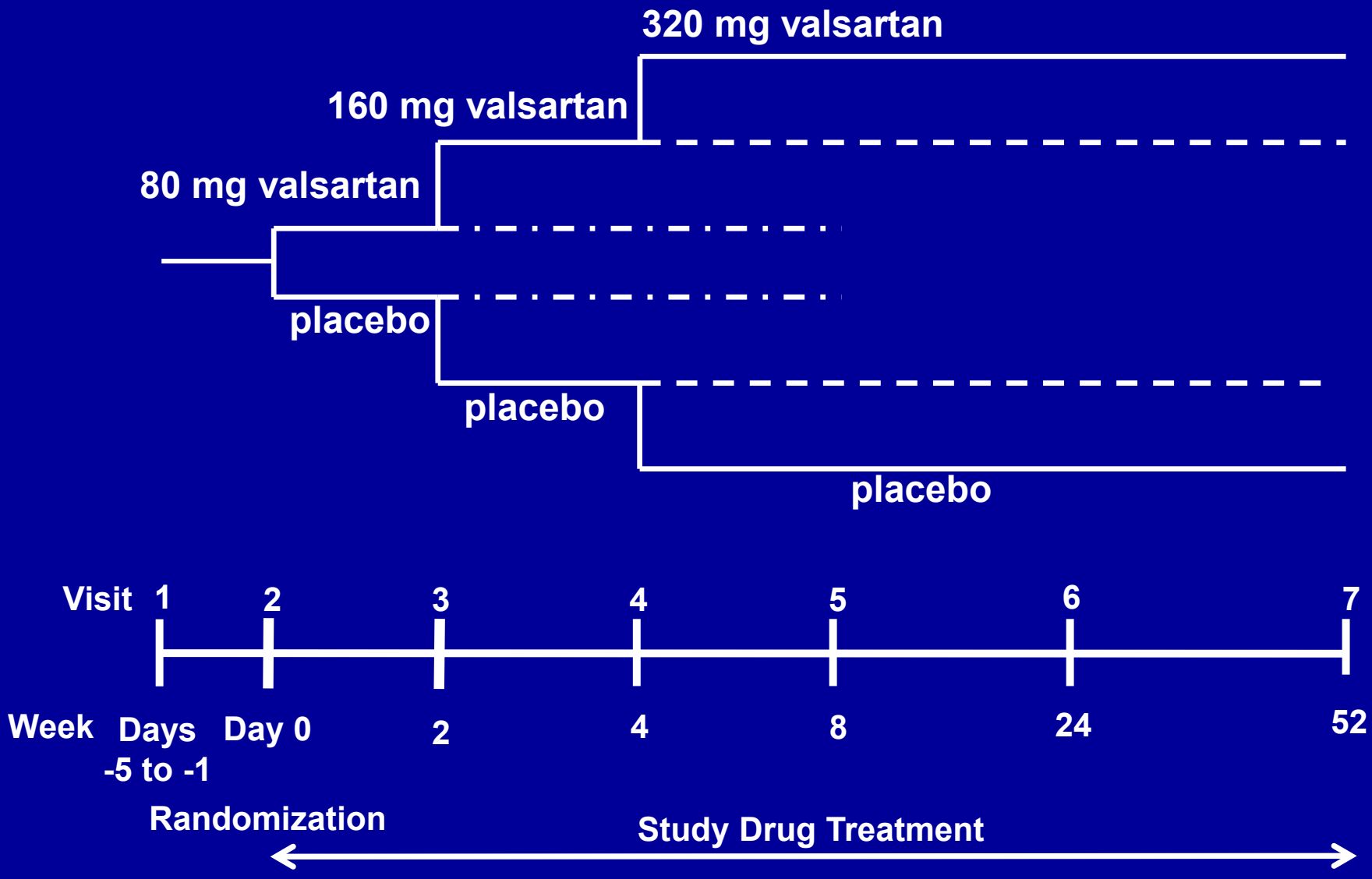


Time-Varying Cornell Product >2440 mm × msec						
Cumulative No. of Events	0	98	168	238	320	383
No. at Risk	5924	4169	3630	3321	3206	1378
Time-Varying Cornell Product ≤2440 mm × msec						
Cumulative No. of Events	0	57	91	150	198	262
No. at Risk	2907	3742	3833	3714	3525	1431

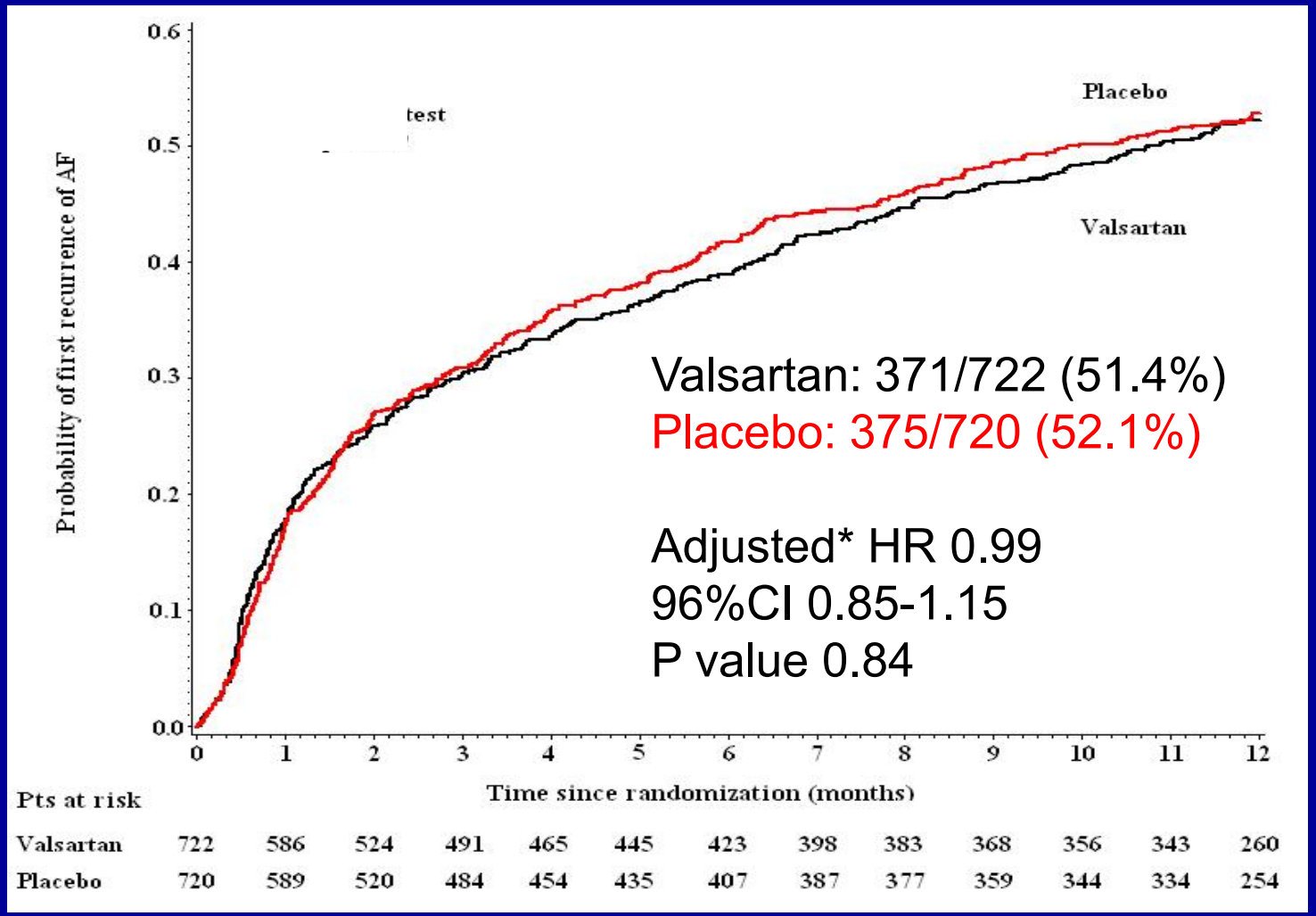
Rate is according to time-varying presence or absence of electrocardiographic left ventricular hypertrophy according to sex-specific Cornell voltage-duration product criteria partitioned at 2440 mm × msec. Patient group assignment is adjusted at the time of each electrocardiogram based on the value of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

Okin P, et al. JAMA. 2006;296:1242-1248

GISSI-AF: Study Design (2)



Time to first recurrence of Atrial Fibrillation



Valsartan: 371/722 (51.4%)
Placebo: 375/720 (52.1%)

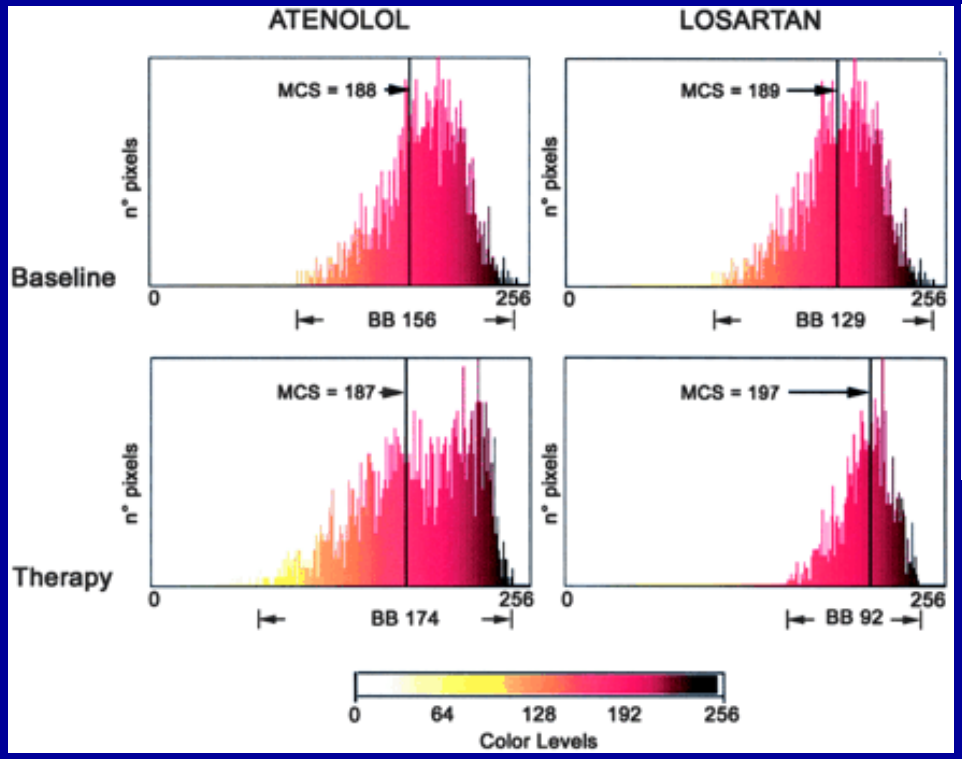
Adjusted* HR 0.99
96%CI 0.85-1.15
P value 0.84

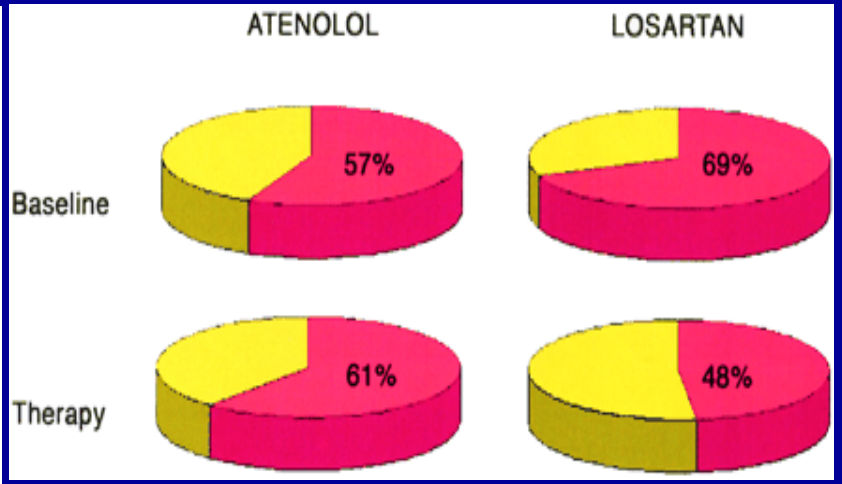
** The 96%CI was calculated by Cox proportional hazards model adjusted for ACE-I, amiodarone use, cardioversion, PAD, CAD*

Different Effects of Antihypertensive Therapies Based on Losartan or Atenolol on Ultrasound and Biochemical Markers of Myocardial Fibrosis

Results of a Randomized Trial

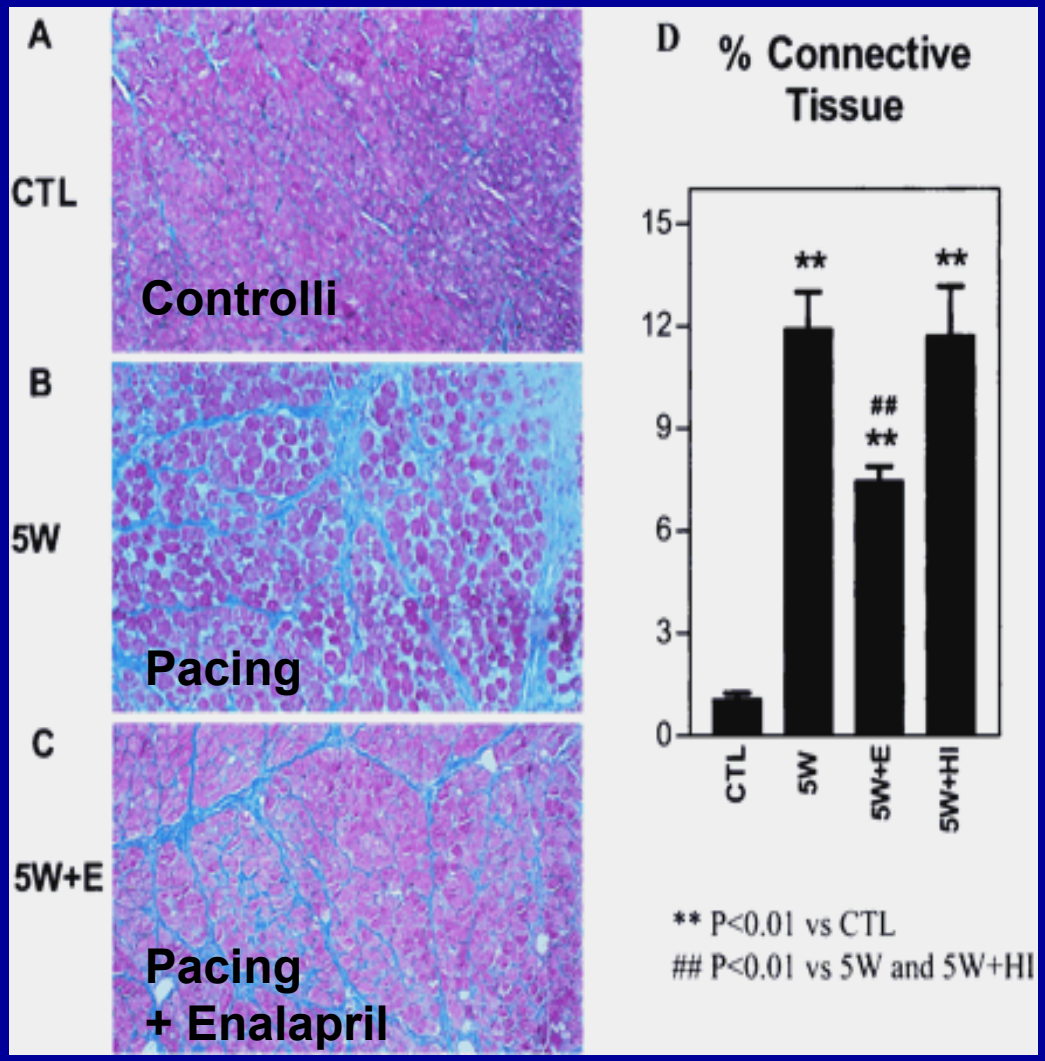
Michele M. Ciulla, MD, PhD; Roberta Paliotti, MD, PhD; Arturo Esposito, MD; Javier Diez, MD; Begoña López, BSc; Björn Dahlöf, MD; M. Gary Nicholls, MD; Ronald D. Smith, MD; Leen Gilles, PhD; Fabio Magrini, MD; Alberto Zanchetti, MD





Conclusions—In hypertensive patients with LVH, losartan decreases myocardial collagen content, whereas atenolol does not. The difference between the 2 treatments is statistically significant. (*Circulation*. 2004;110:552-557.)

Enalapril Prevent Fibrosis in Pacing-induced Congestive Heart Failure

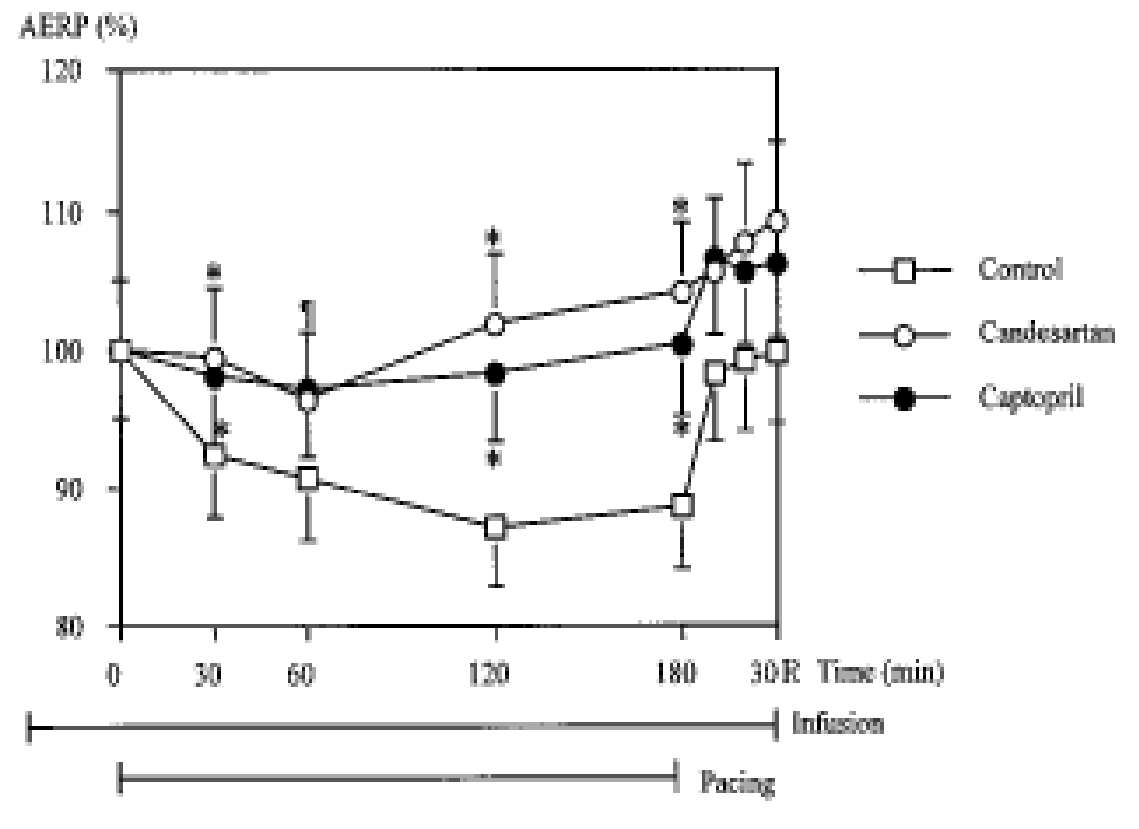


In dog models of experimental CHF due to ventricular tachi-pacing, interstitial fibrosis and atrial Ang II concentration were increased by pacing.

Enalapril significantly reduced tachypacing-induced changes in atrial angiotensin II concentrations and fibrosis.

Li D, et al. Circulation 2001;104:2608

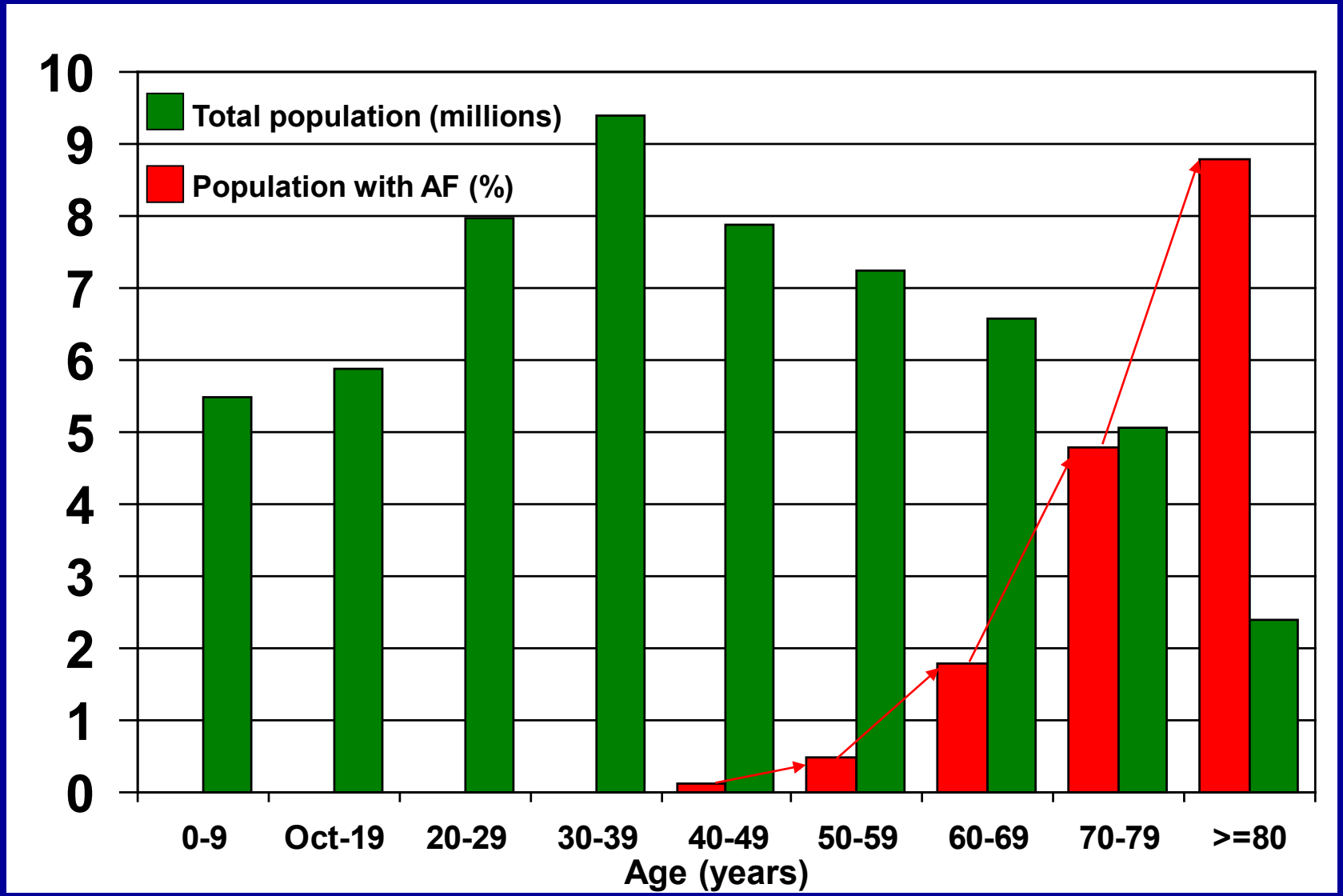
Angiotensin II Antagonists Prevents Electrical Remodeling in Atrial Fibrillation



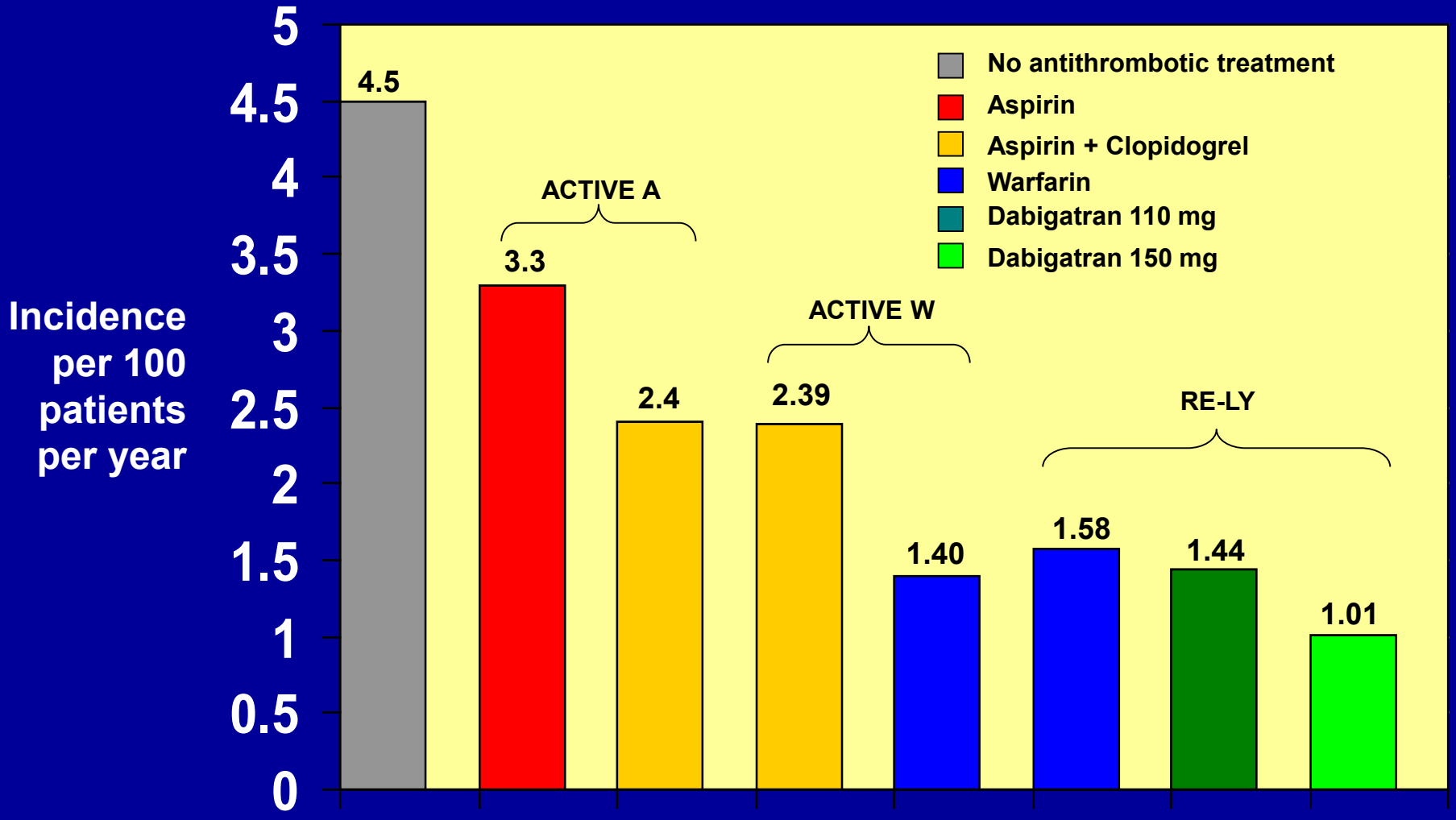
1. During rapid atrial pacing (RAP) there was a shortening in the atrial effective refractory period (AERP) in closed chest dogs.
2. Shortening of AERP during RAP was prevented by captopril or candesartan.

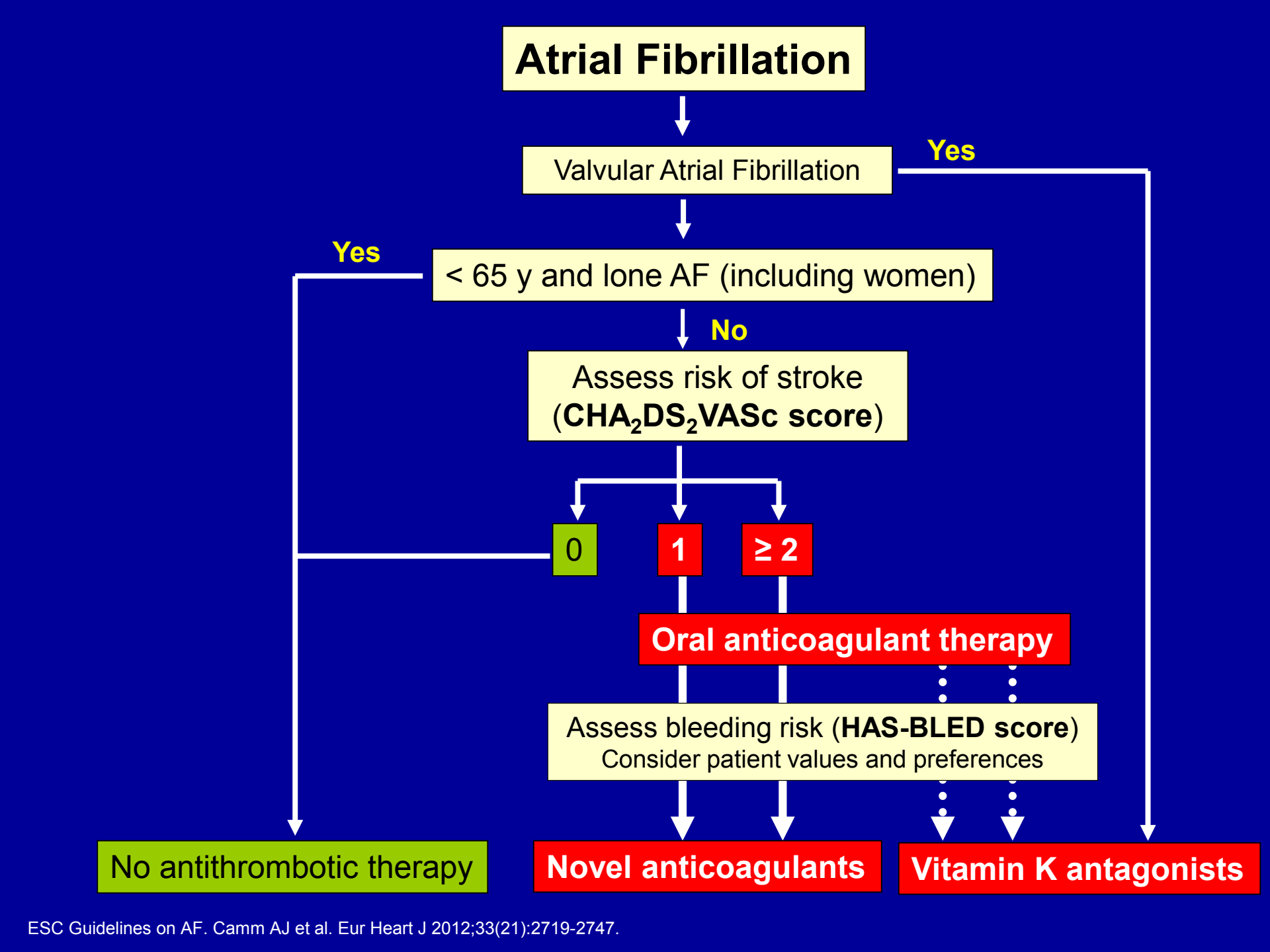
Nakashima H. Circulation 2000; 101: 2612-7

Atrial Fibrillation in Italy



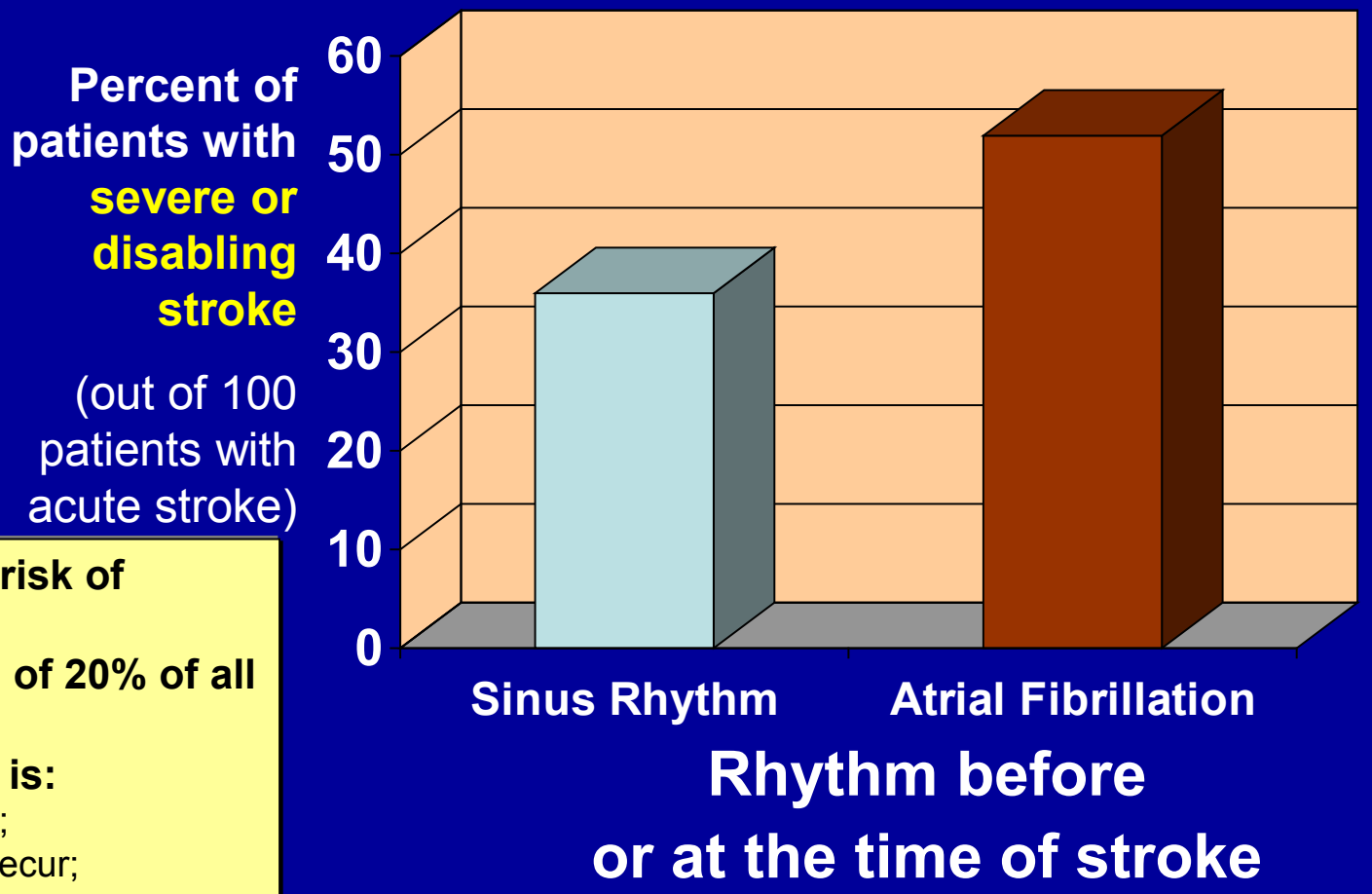
Stroke in patients with AF





ESC Guidelines on AF. Camm AJ et al. Eur Heart J 2012;33(21):2719-2747.

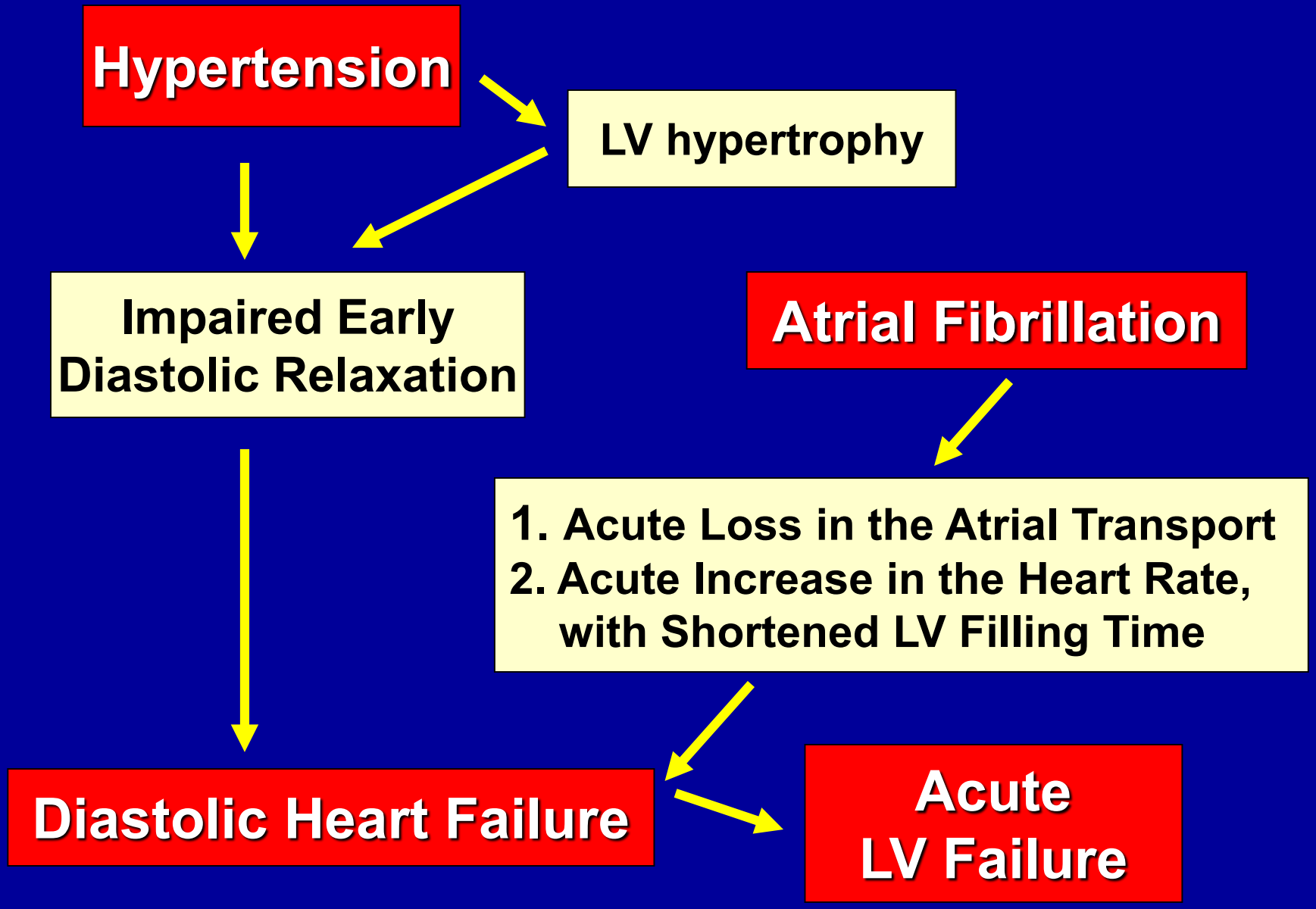
Atrial fibrillation & stroke severity



- **AF increases the risk of stroke by 5 times**
- **AF is responsible of 20% of all strokes**
- **AF-related stroke is:**
  - More disabling;
  - More likely to recur;
  - Associated with a 2-time higher risk of death;
  - Associated with a 1,5 higher cost

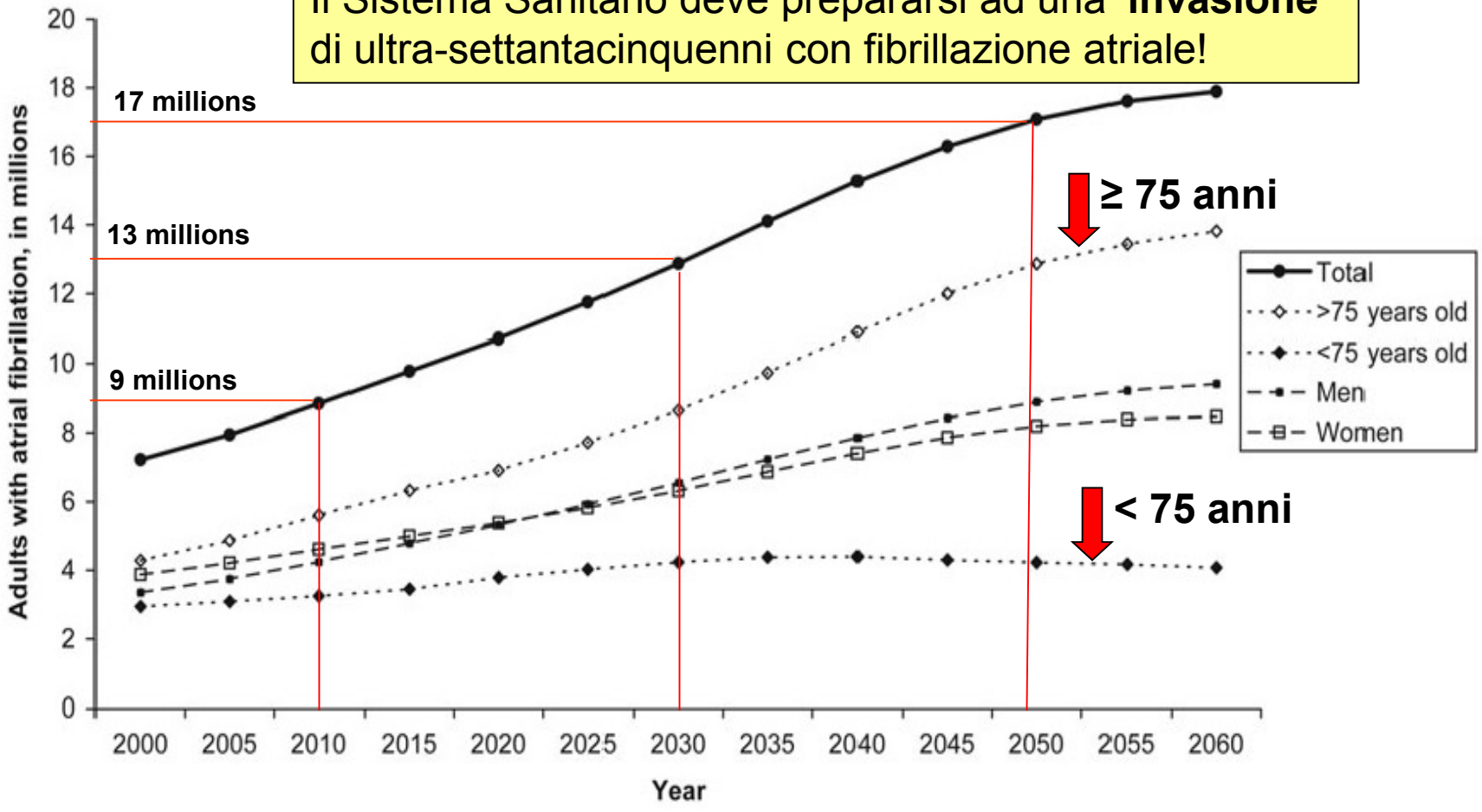
than non AF-related stroke.

AFI collaboration, Am J Med 2002


Hypertension
LV hypertrophy
Impaired Early Diastolic Relaxation
Atrial Fibrillation
1. Acute Loss in the Atrial Transport
2. Acute Increase in the Heart Rate, with Shortened LV Filling Time
Diastolic Heart Failure
Acute LV Failure

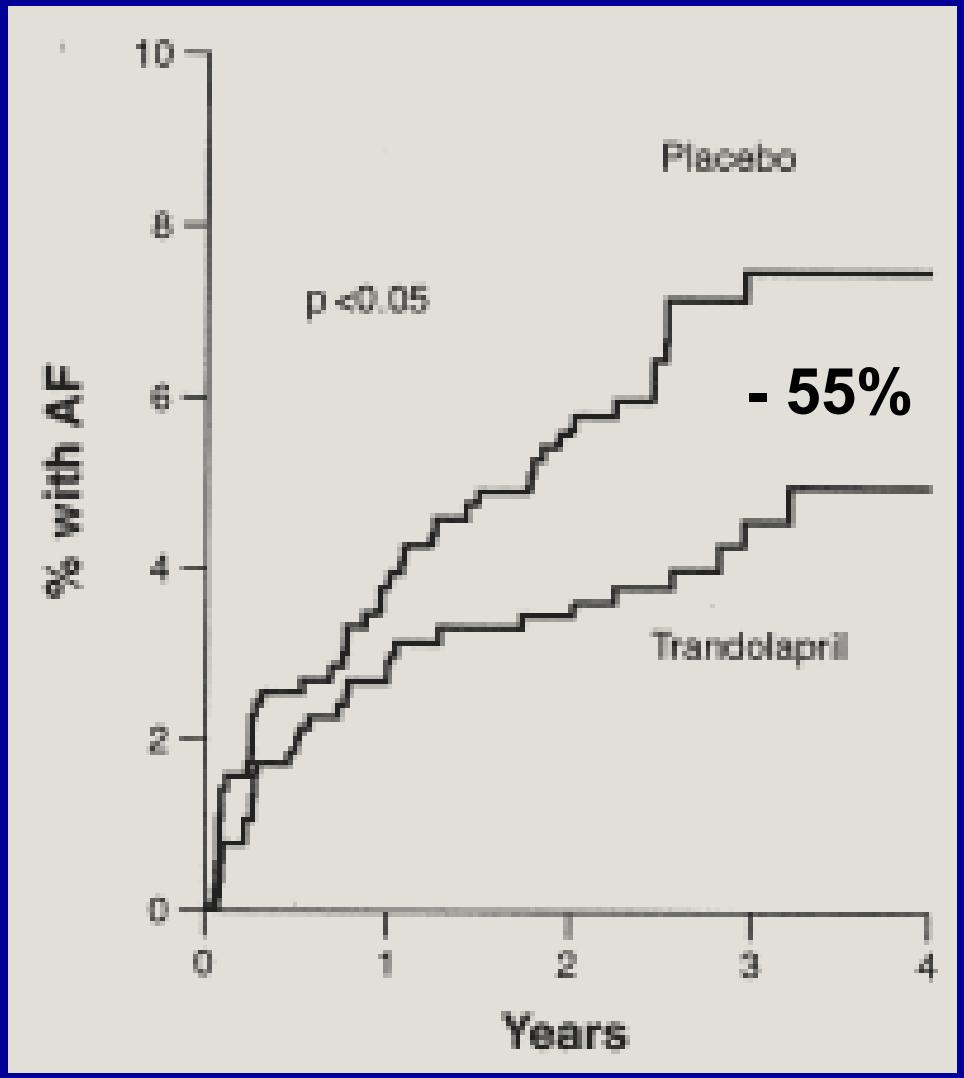
Numero stimato di soggetti adulti con fibrillazione atriale in Europa tra l'anno 2000 ed il 2060

Il Sistema Sanitario deve prepararsi ad una '**invasione**' di ultra-settantacinquenni con fibrillazione atriale!



Krijthe BP et al. Eur Heart J 2013;34:2746-2751

New-Onset Atrial Fibrillation by Treatment Group in the TRACE Study



- TRACE (1570 post-MI patients with low EF)
- Trandolapril vs Placebo
- EF 33%, HBP 22%
- 55% lesser risk of AF in the ACE-inhibitor group compared to placebo [RR: 0.45 (0.26-0.76)]

Pedersen OD, et al. Circulation 1999;100;376