Hypertension and Atrial Fibrillation

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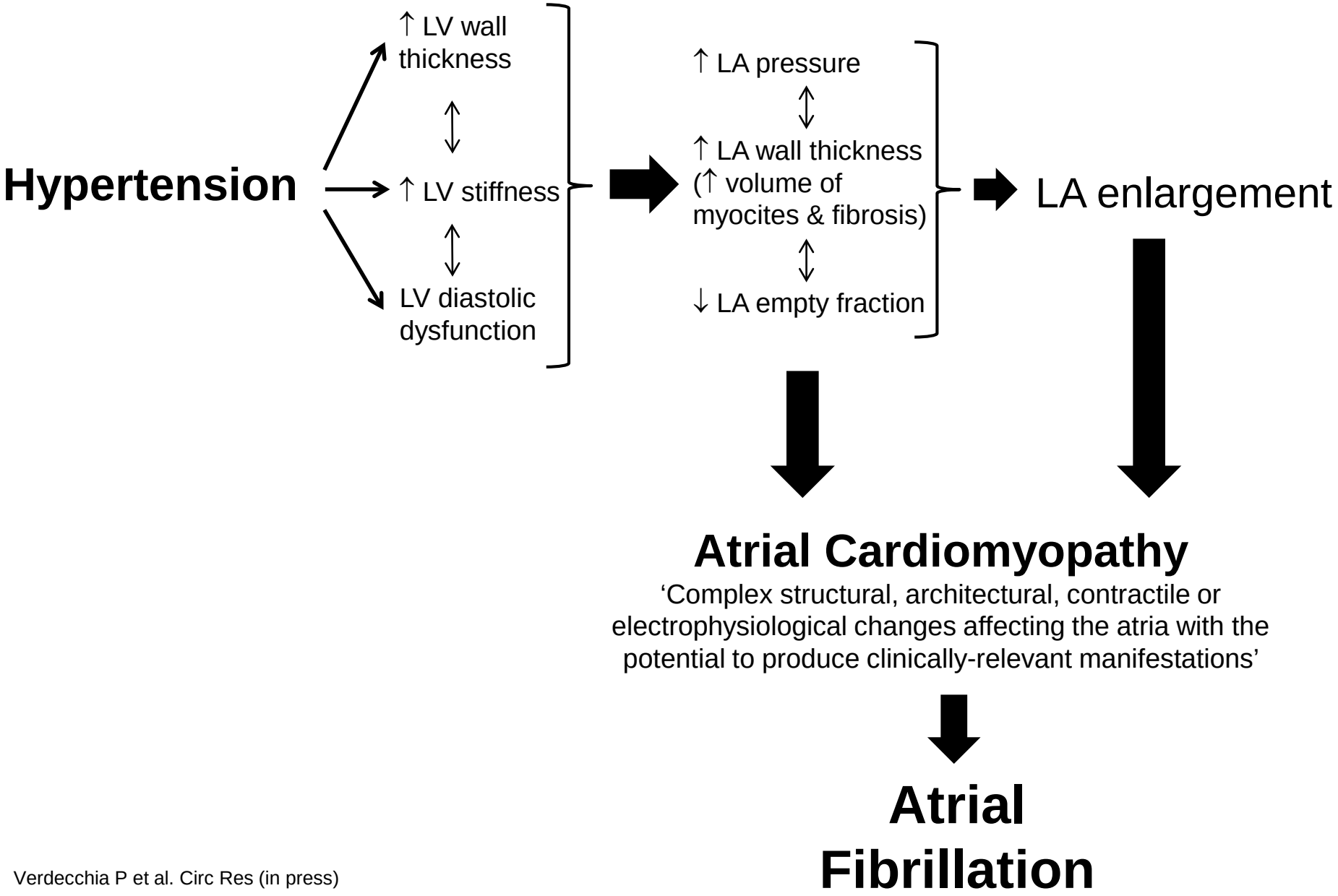
Agenda

- 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

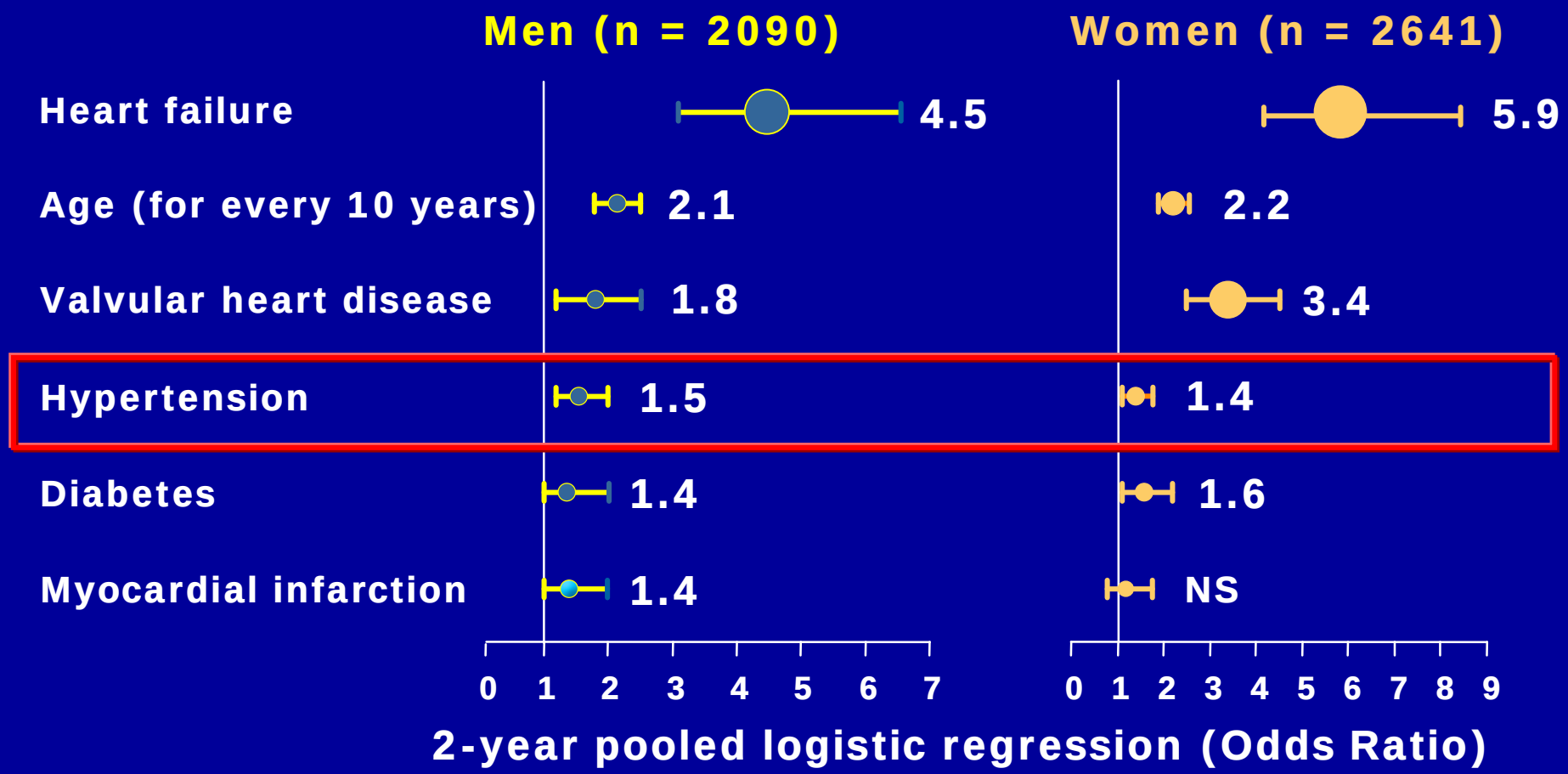
Potential Mechanisms of the Transition from Hypertension to AF



Verdecchia P et al. Circ Res (in press)

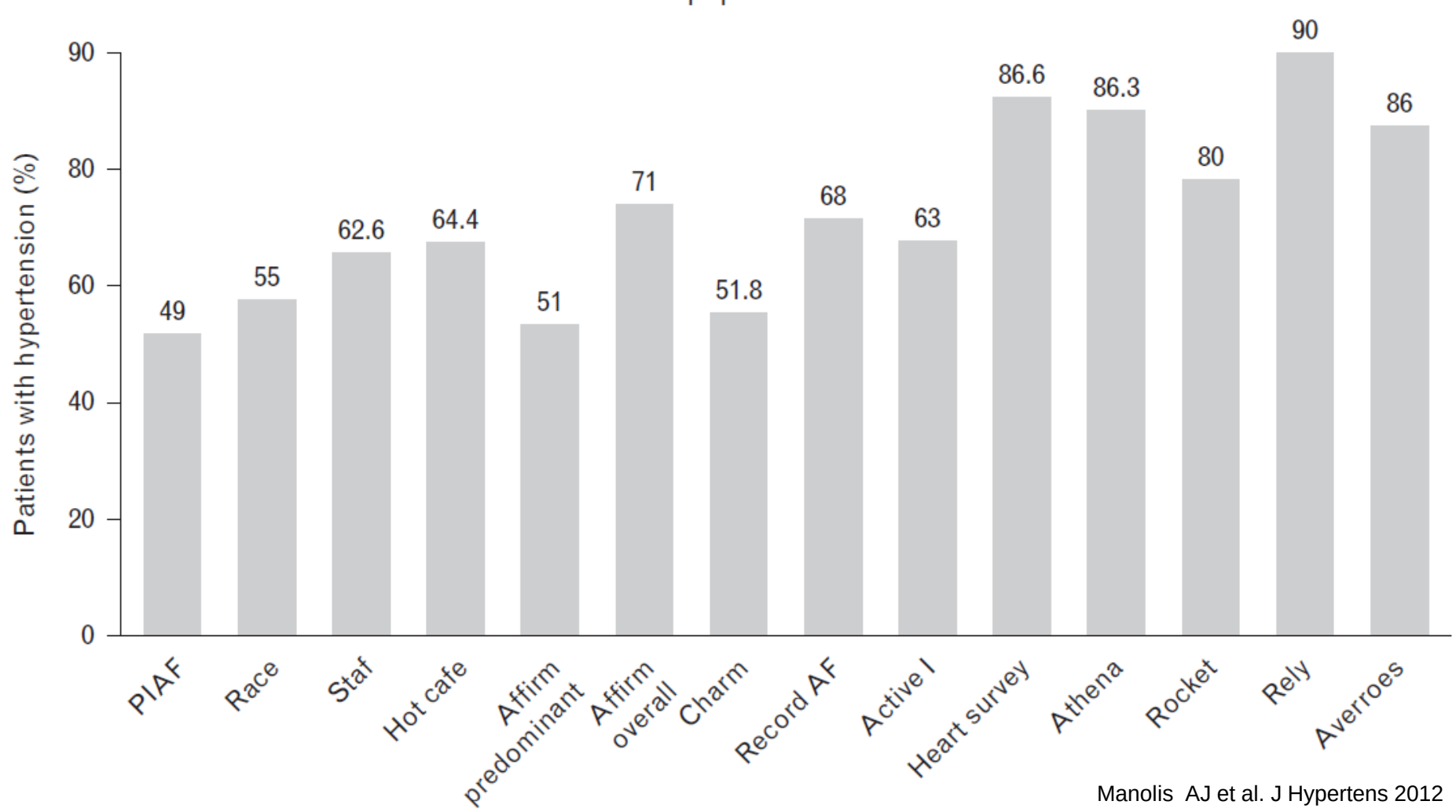
Independent risk factors for AF in subjects in sinus rhythm

The Framingham Heart Study



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

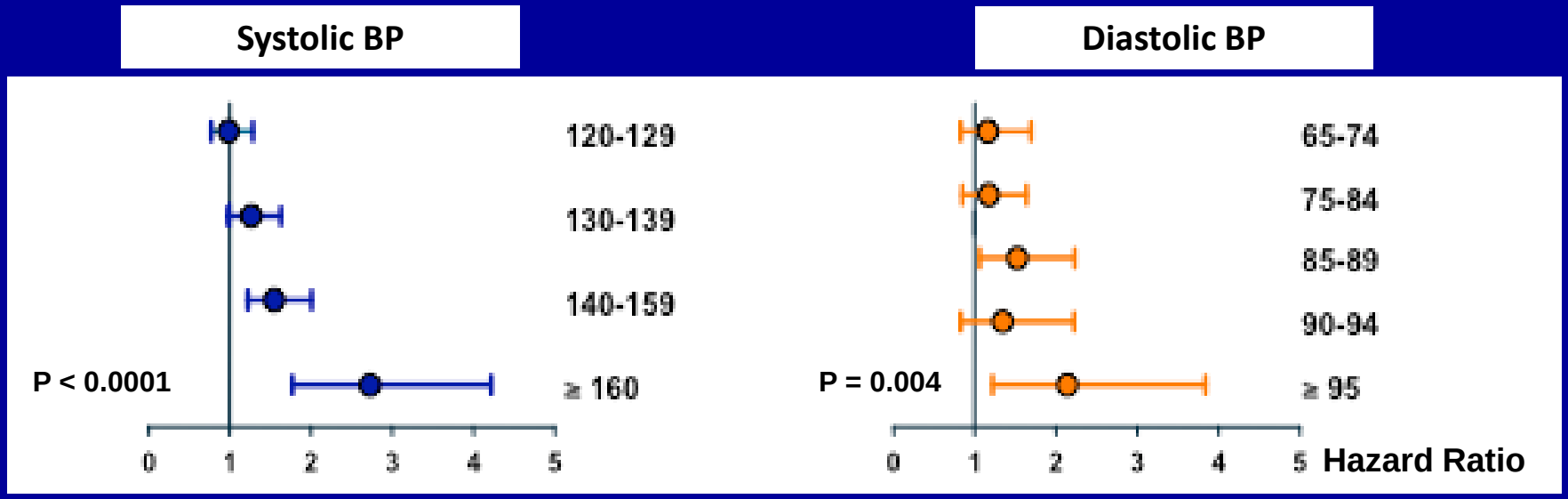
Prevalence of hypertension in patients with atrial fibrillation



Manolis AJ et al. J Hypertens 2012

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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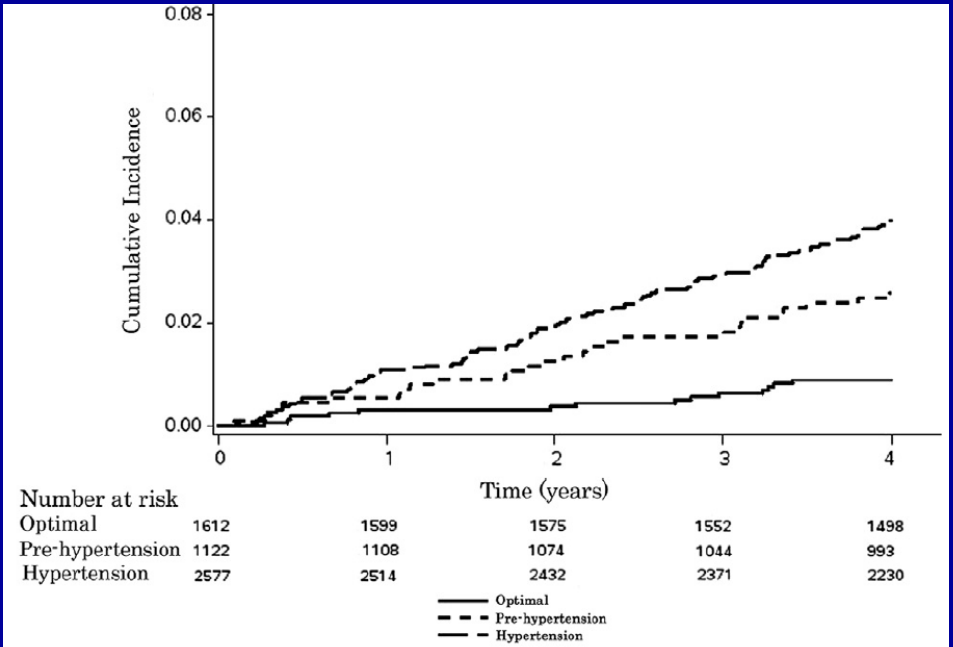
[e]*Cardiovascular Health Research Unit and, Department of Epidemiology, University of Washington, and Group Health Research Institute, Seattle, WA, USA*

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

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

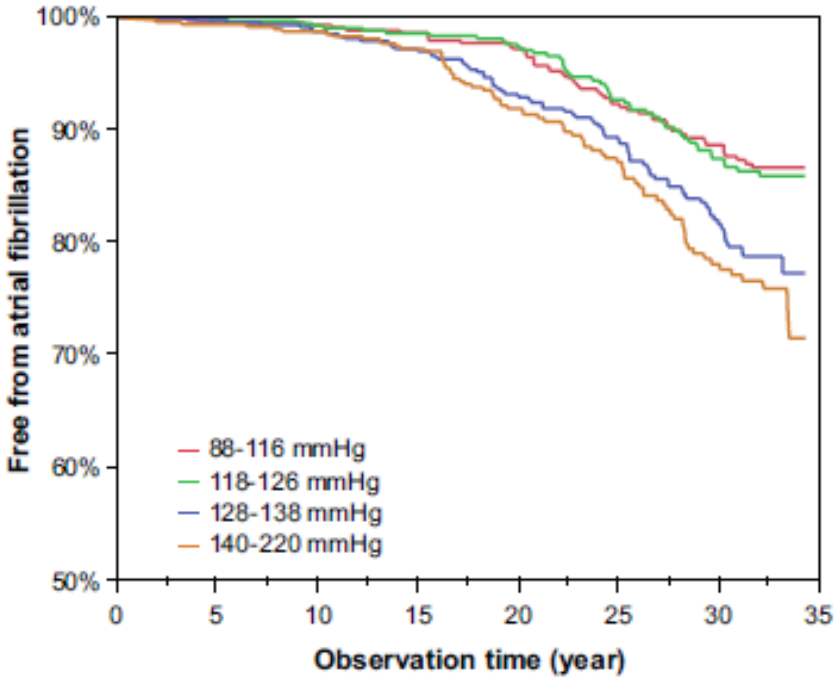


Figure 1. Kaplan-Meier curves show survival (%) free from AF among 1997 initially healthy middle-aged men according to quartiles of systolic blood pressure during 35 years of follow-up.

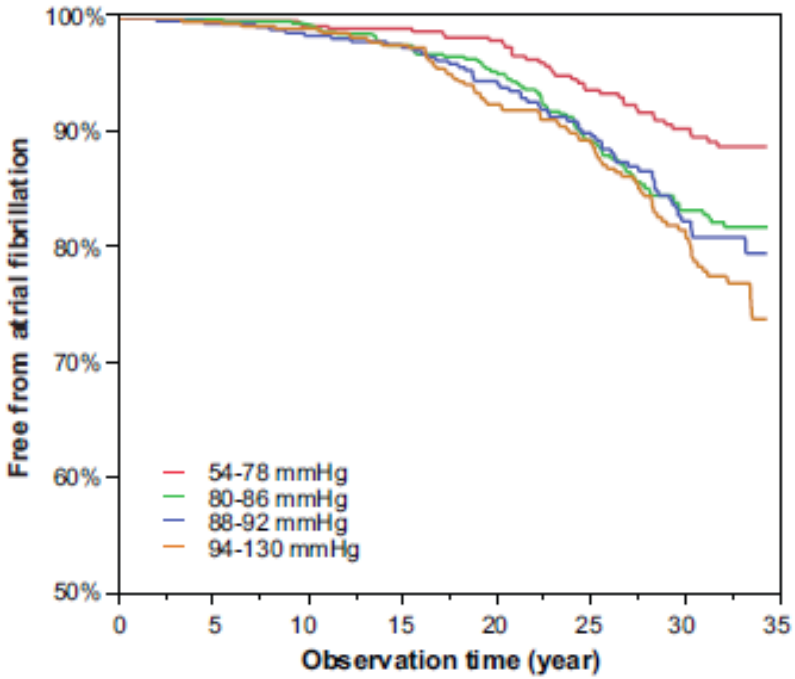


Figure 2. Kaplan-Meier curves show survival (%) free from AF among 1997 initially healthy middle-aged men according to quartiles of diastolic blood pressure during 35 years of follow-up.

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

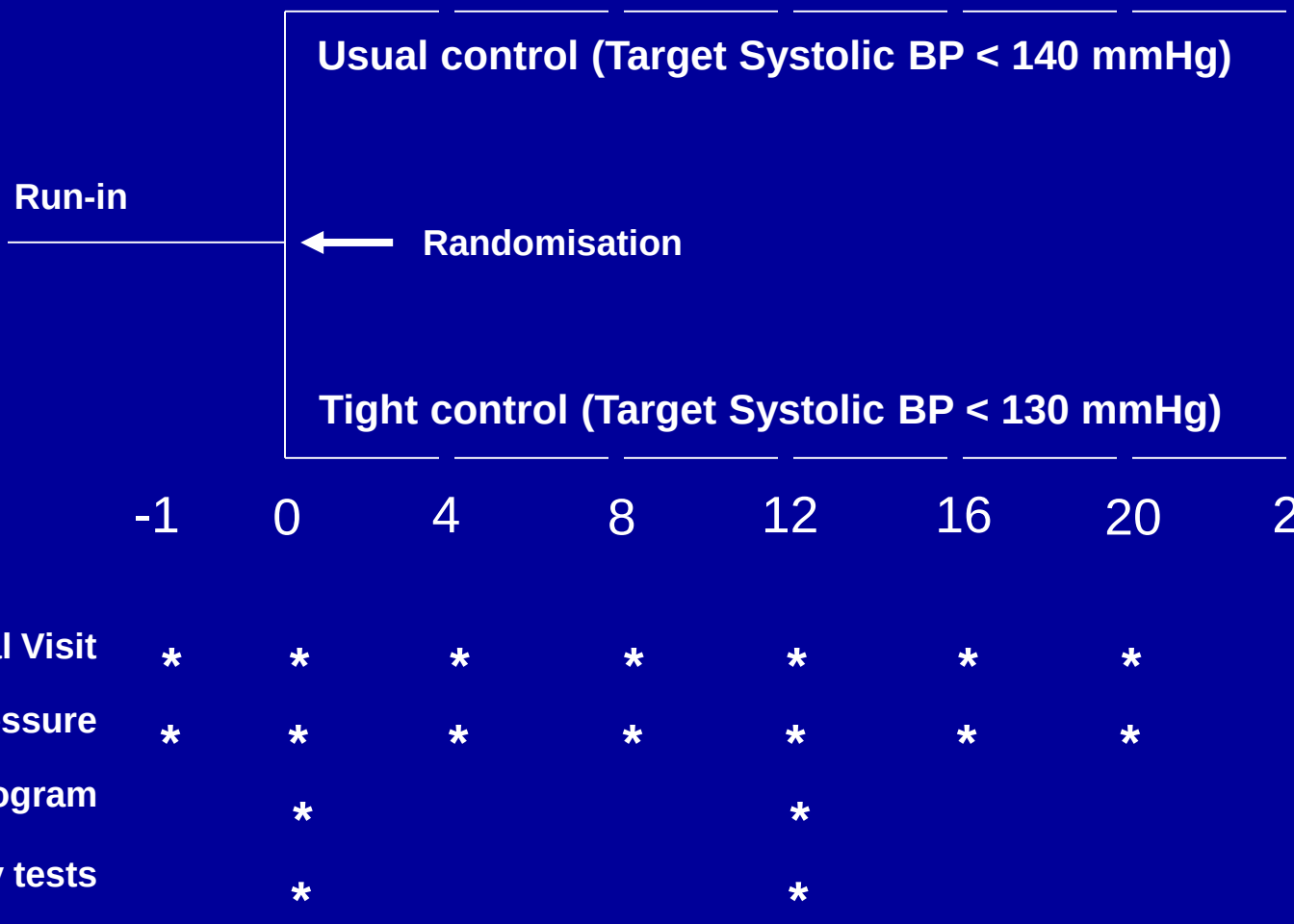
enced 28% and 53% excess risk of incident AF when compared with women with systolic BP <120 mm Hg or diastolic BP <65 mm Hg, respectively.[7]

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 !

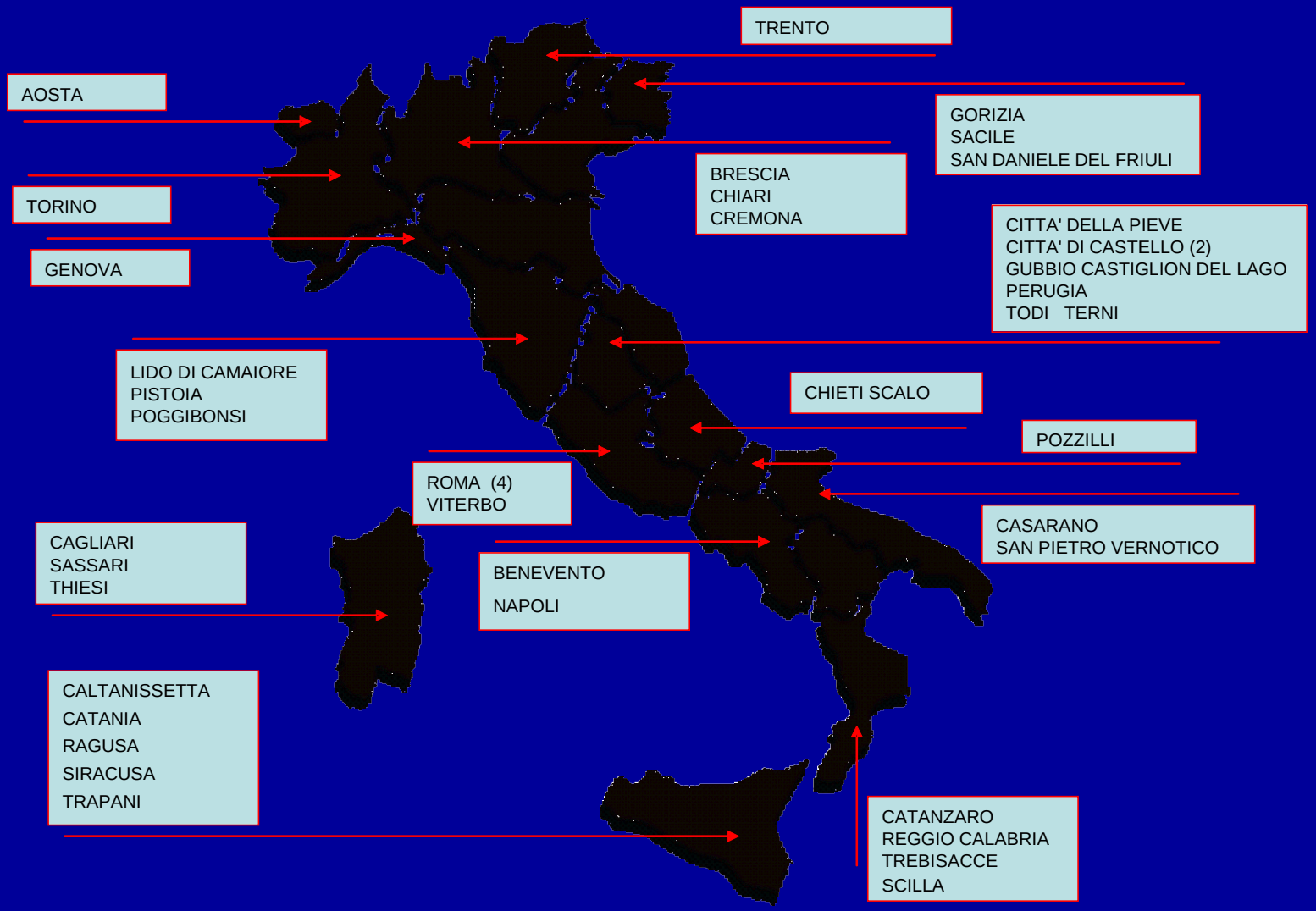
Hypertension 2012;59:184-185

Cardio-Sis



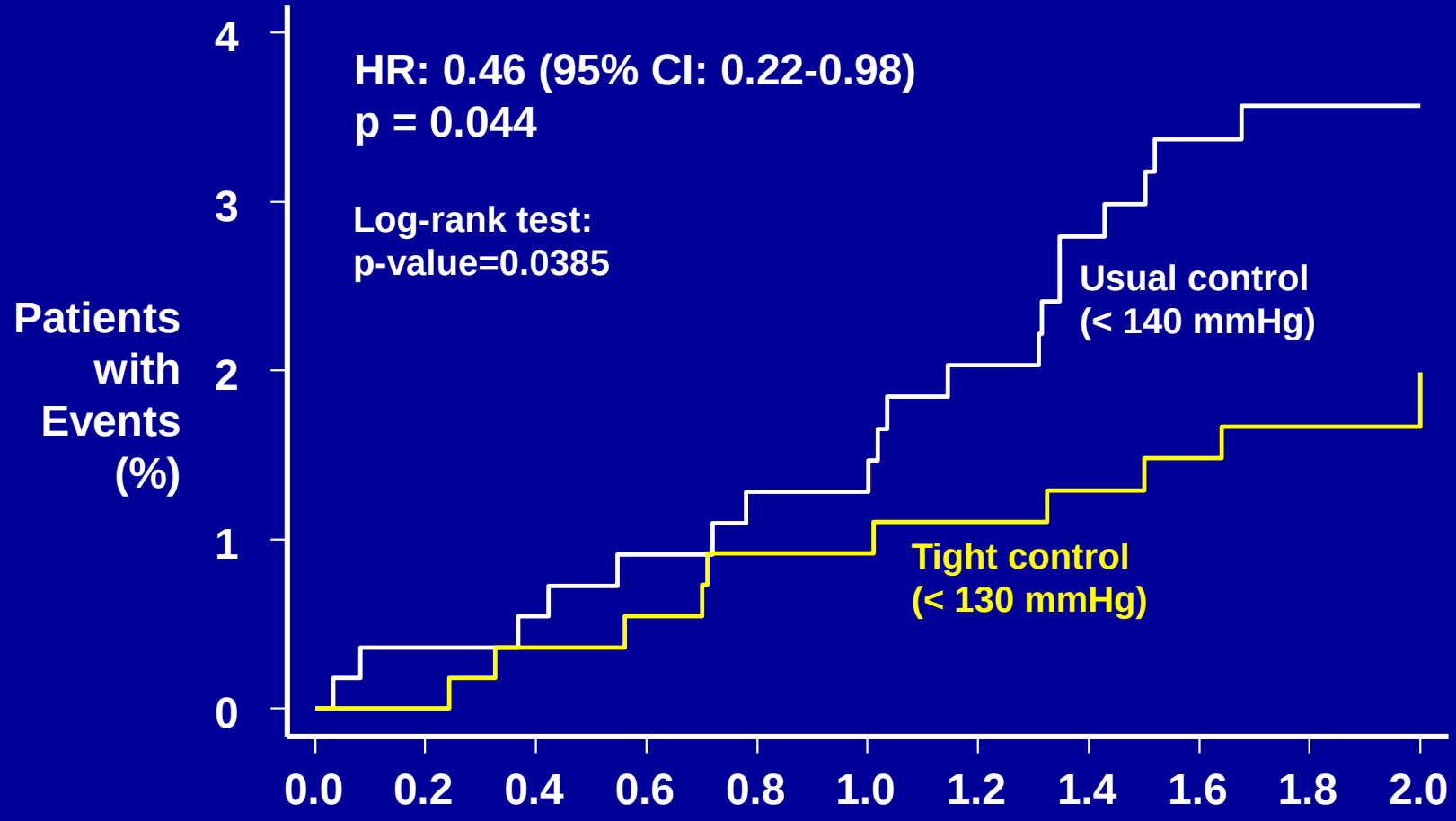
Verdecchia P et al Lancet 2009; 374: 525–33

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

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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Atrial Fibrillation at Baseline and During Follow-Up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)

L. Julian Haywood, MD,* Charles E. Ford, PHD,† Richard S. Crow, MD,‡ Barry R. Davis, MD, PHD,† Barry M. Massie, MD,§ Paula T. Einhorn, MD,‖ Angela Williard, RN, BSN,¶ for the ALLHAT Collaborative Research Group

Los Angeles and San Francisco, California; Houston, Texas; Minneapolis, Minnesota; Bethesda, Maryland; and New Orleans, Louisiana

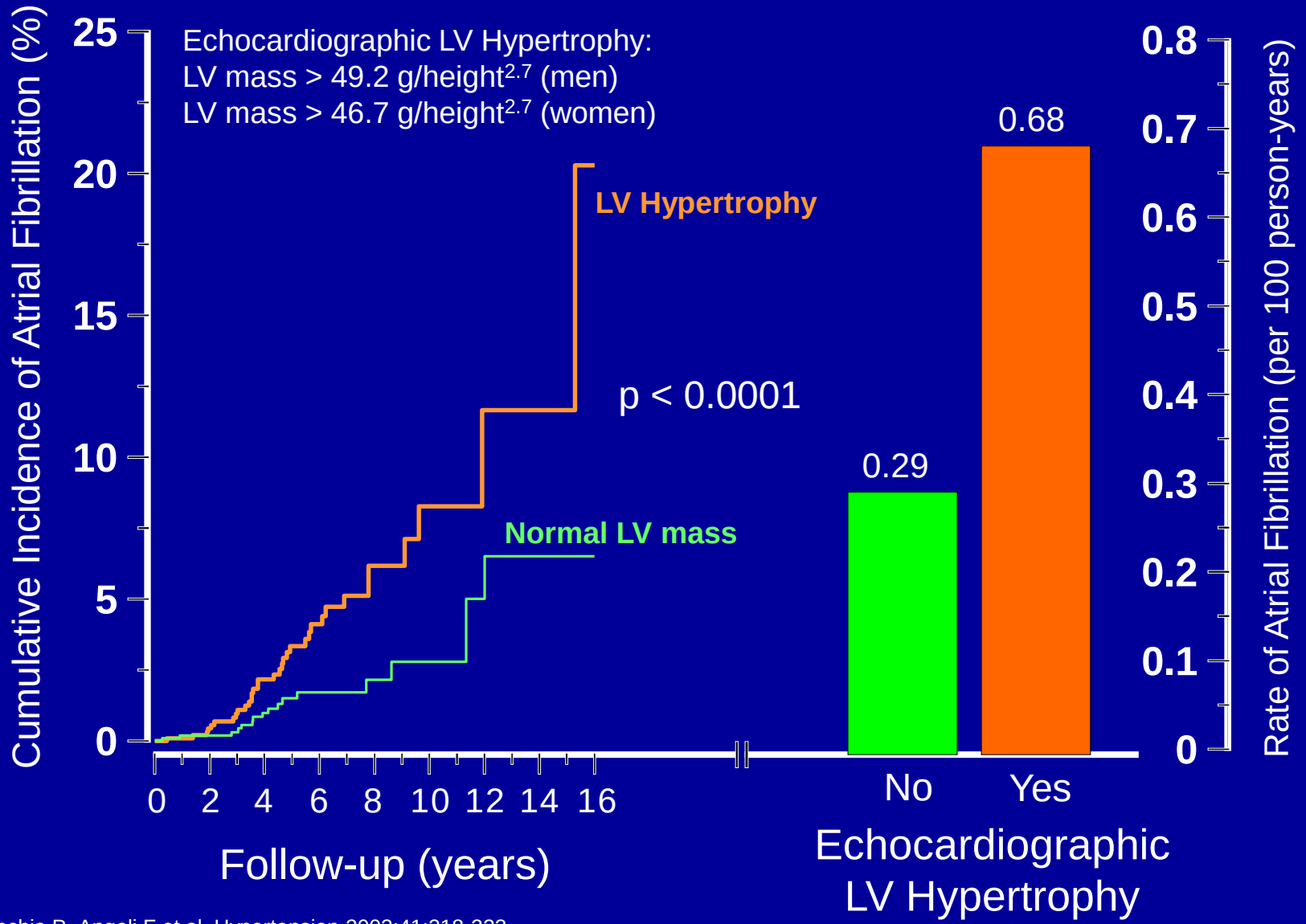
Table 3 Development of AF/AFL During Follow-Up per 1,000 Participants by Treatment Group

Treatment Group (Mean Follow-Up)	Sample Size	New* AF/AFL	Events† per 1,000	Univariable Logistic Model		Multivariable Logistic Model†		Kaplan-Meier Rate/1,000 Participants
				OR	p Value	OR	p Value	
Full trial (4.9 yrs)								6 yrs
Chlorthalidone	11,695	244	20.9	1.000	—	1.000	—	23.5
Amlodipine	6,935	155	22.4	1.073	0.50	1.083	0.48	28.3
Lisinopril	6,702	138	20.6	0.987	0.90	0.939	0.59	24.9
Doxazosin-Chlorthalidone (3.2 yrs)								4 yrs
Chlorthalidone	11,695	142	12.1	1.000	—	1.000	—	13.3
Doxazosin	6,392	104	16.3	1.346	0.02	1.326	0.05	19.3
Lipid-lowering trial (4.8 yrs)								6 yrs
Usual care	4,255	82	19.4	1.000	—	1.000	—	27.8
Pravastatin	4,327	85	19.8	1.020	0.90	1.108	0.54	25.9

Agenda

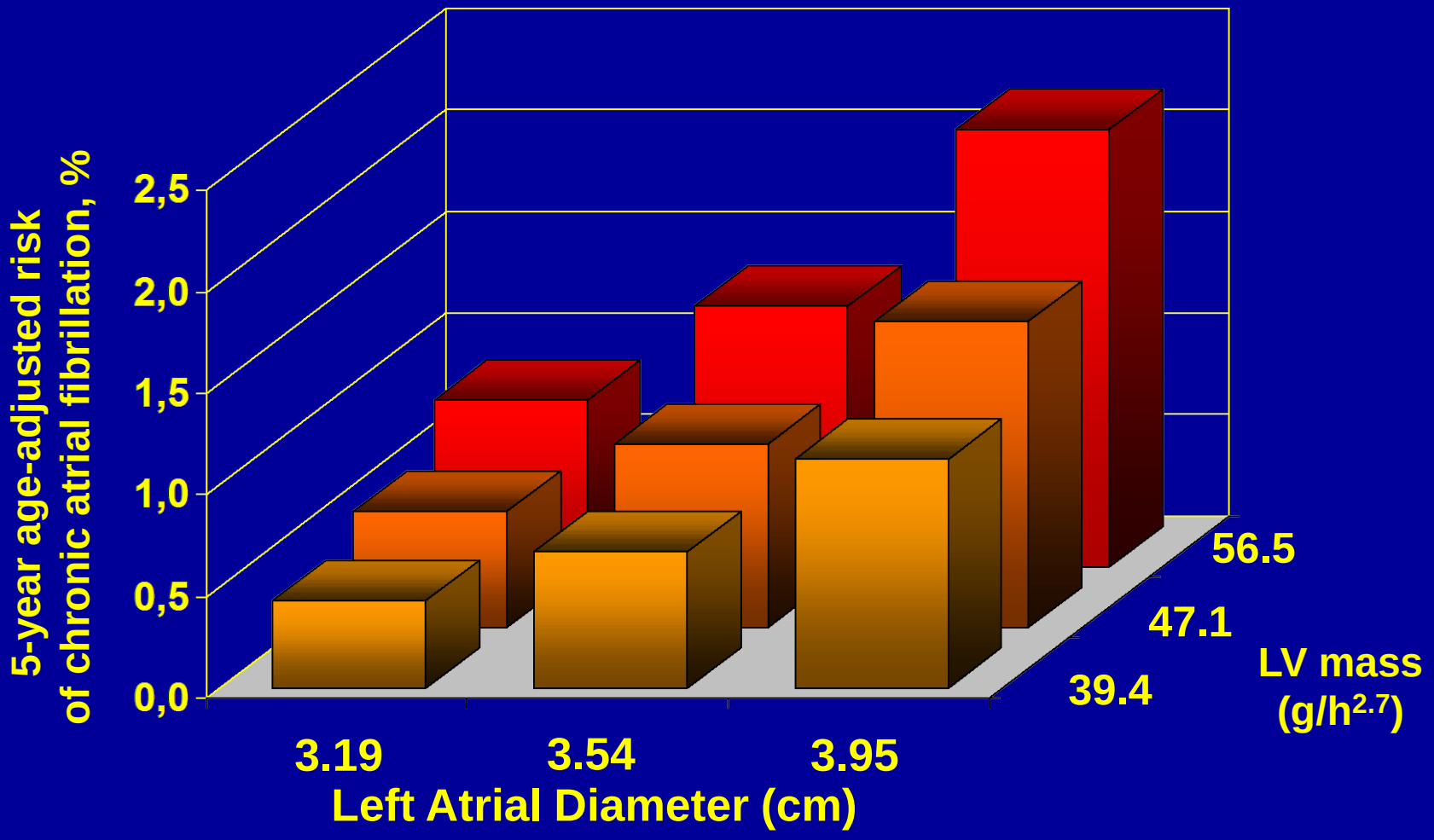
- Hypertensive LVH as a risk factor for AF

Incidence of Atrial Fibrillation in relation to LVH



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

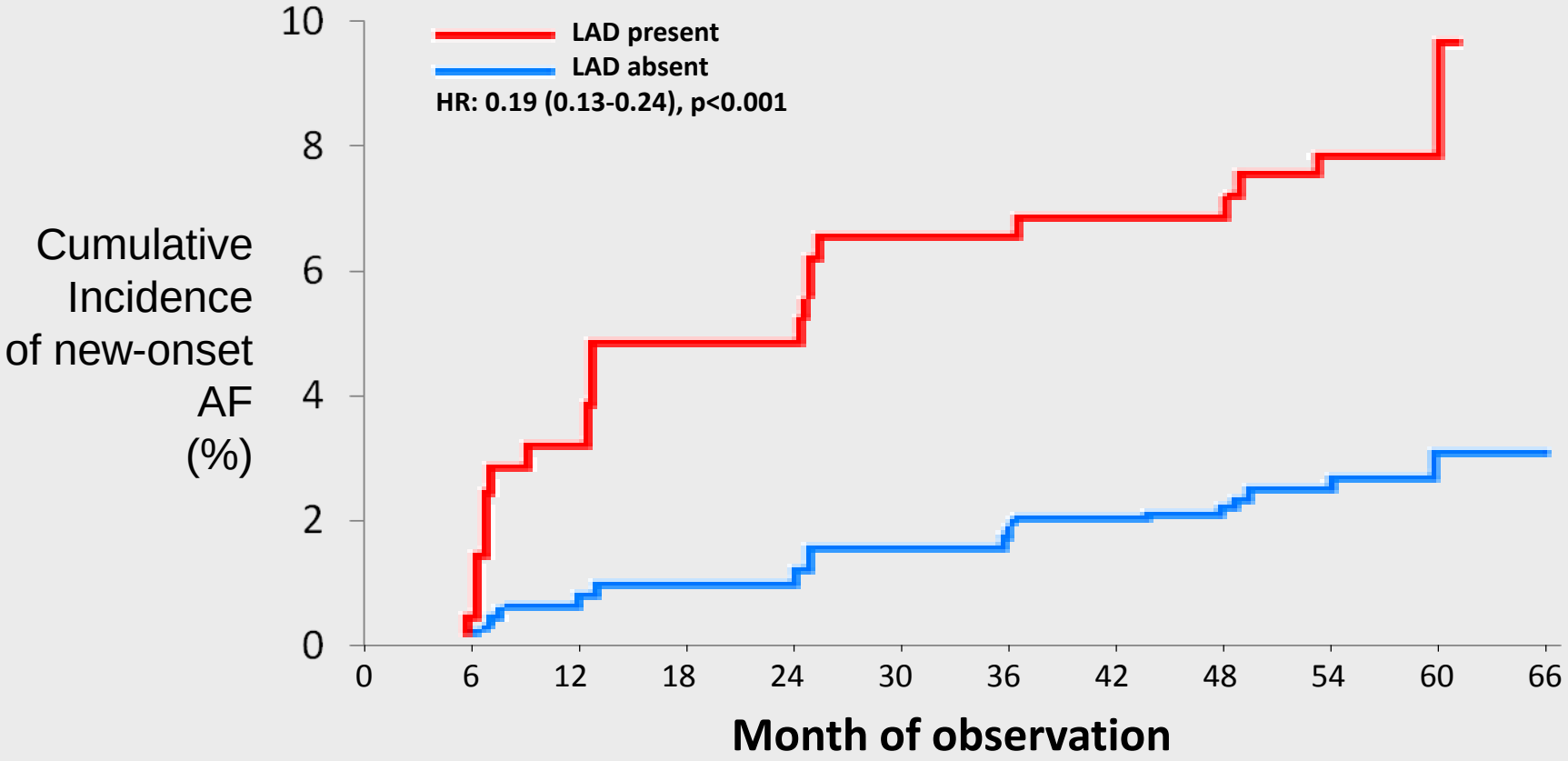
Age-adjusted 5-year risk of permanent atrial fibrillation



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

Left atrial dilatation and atrial fibrillation

The LIFE Study



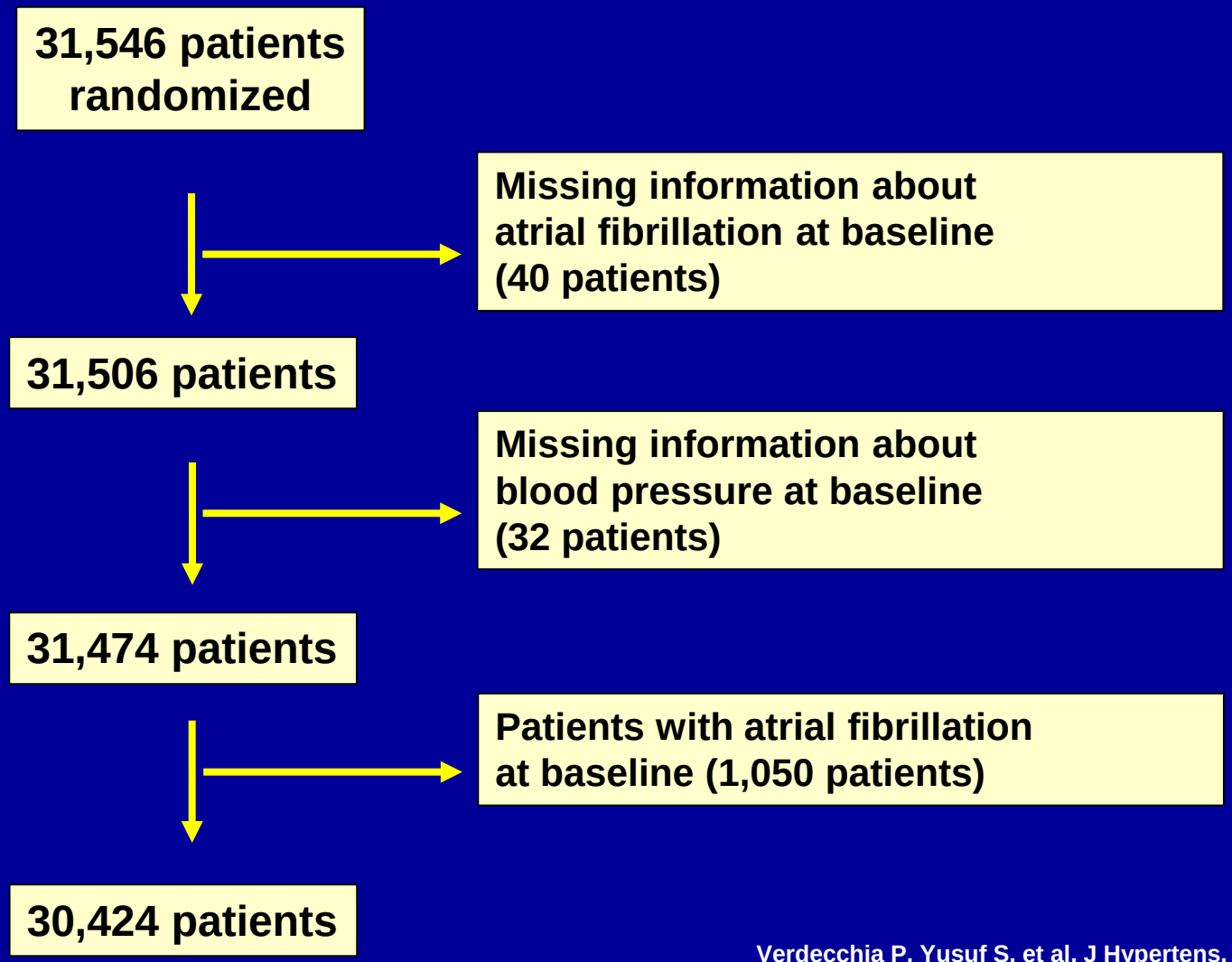
N. at risk						
LAD present	296	293	281	277	276	99
LAD absent	643	641	636	633	631	204

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

Agenda

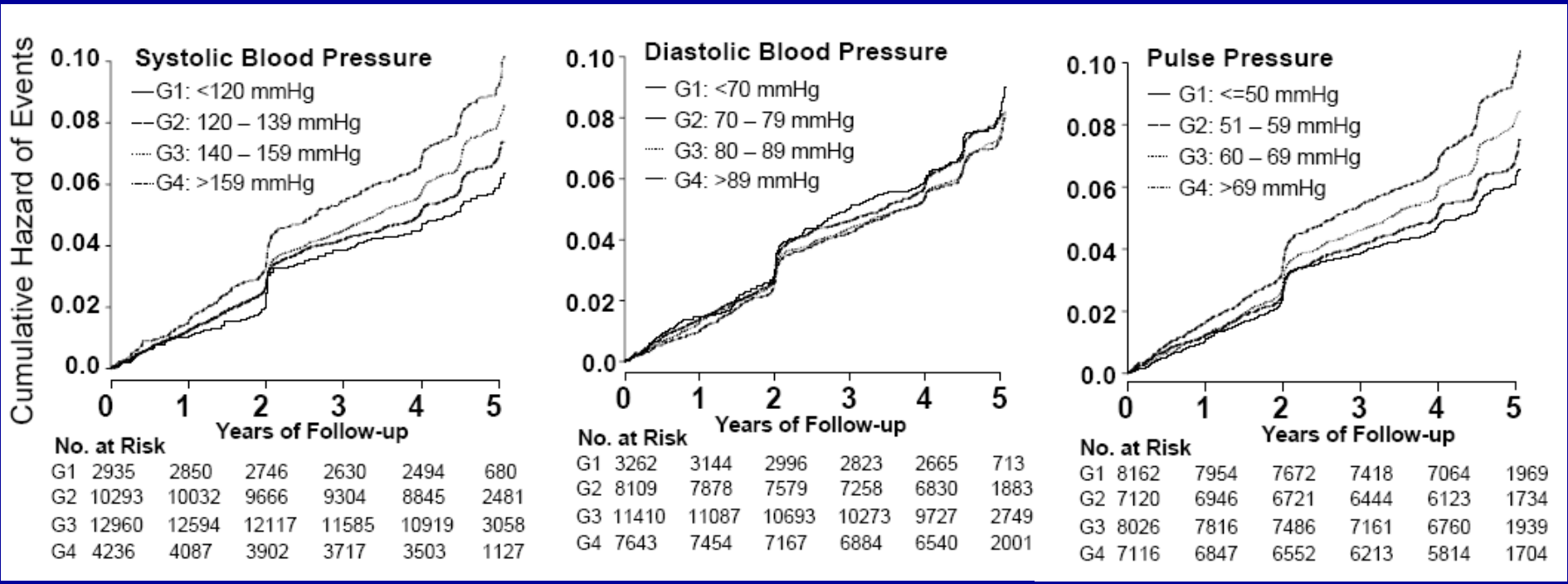
- Impact of AF in high-risk patients

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)

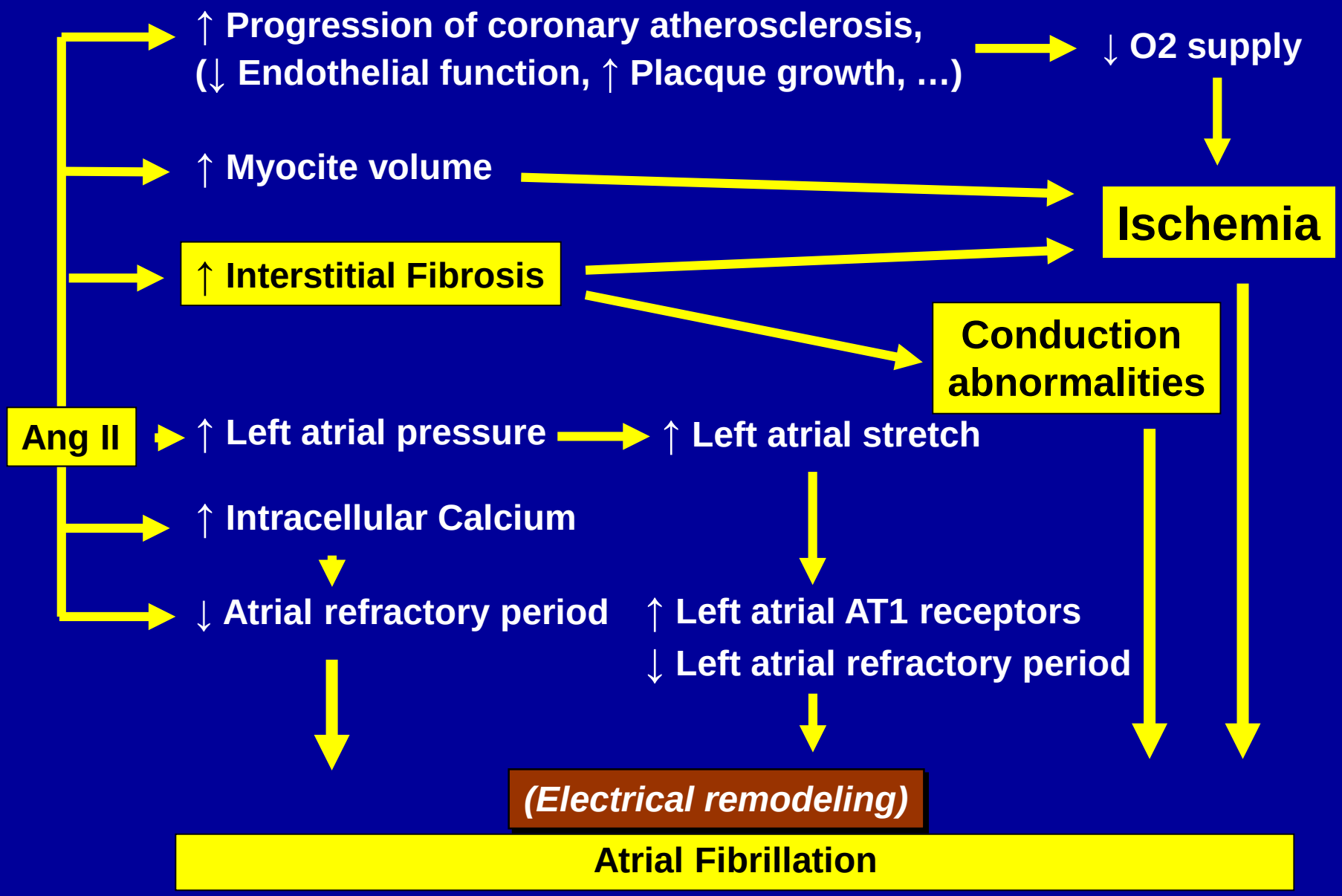


Verdecchia P, Yusuf S, et al. J Hypertens. 2012;30:1004-1014

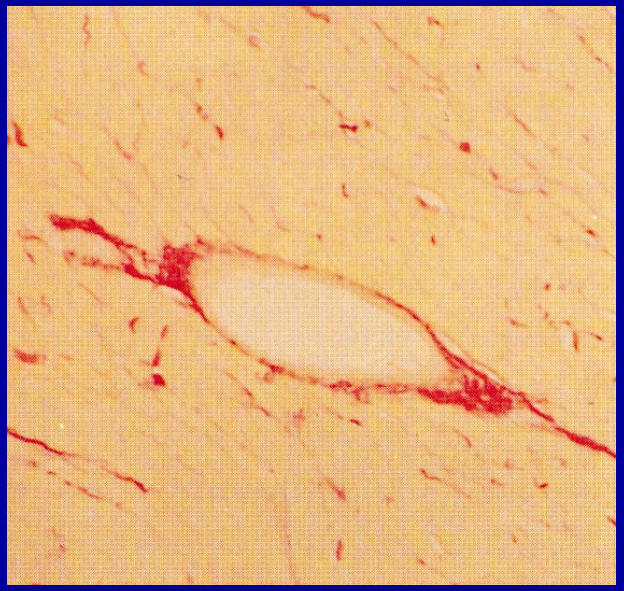
Agenda

- Inhibition of the RAS and AF

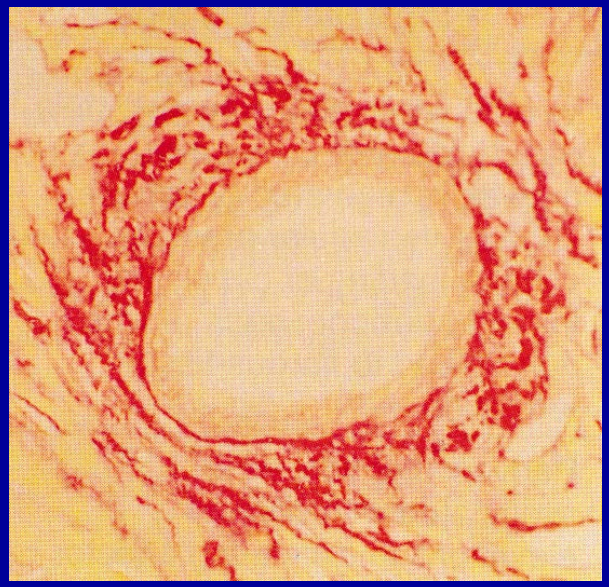
Angiotensin II and Atrial Fibrillation



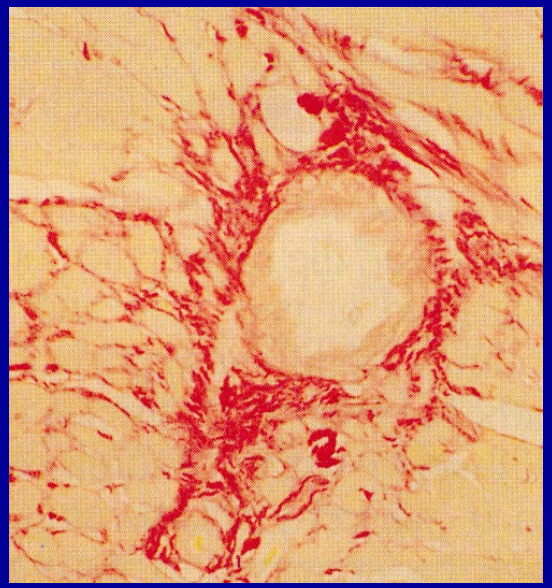
Effects of Sub-pressor Doses of Angiotensin II and Aldosterone Infused Through Implanted Minipump



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

Brief Review

Arterial Hypertension, Atrial Fibrillation, and Hyperaldosteronism

The Triple Trouble

Teresa M. Seccia, Brasilina Caroccia, Gail K. Adler, Giuseppe Maiolino, Maurizio Cesari, Gian Paolo Rossi

The complex relations between aldosterone and AF in hypertension have been recently reviewed. In particular, an impressive 12-fold higher risk of AF has been reported in patients with primary hyperaldosteronism when compared with patients with essential hypertension. This is in line with the known effect of aldosterone on cardiac inflammation, fibrosis and hypertrophy.

Seccia TM, et al. *Hypertension*. 2017;69:545-550.
Milliez P et al. *J Am Coll Cardiol*. 2005;45:1243-1248.
Rocha R et al*Am J Physiol Heart Circ Physiol*. 2002;283:H1802-1810.
Sun Y et al. *Am J Pathol*. 2002;161:1773-1781.

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

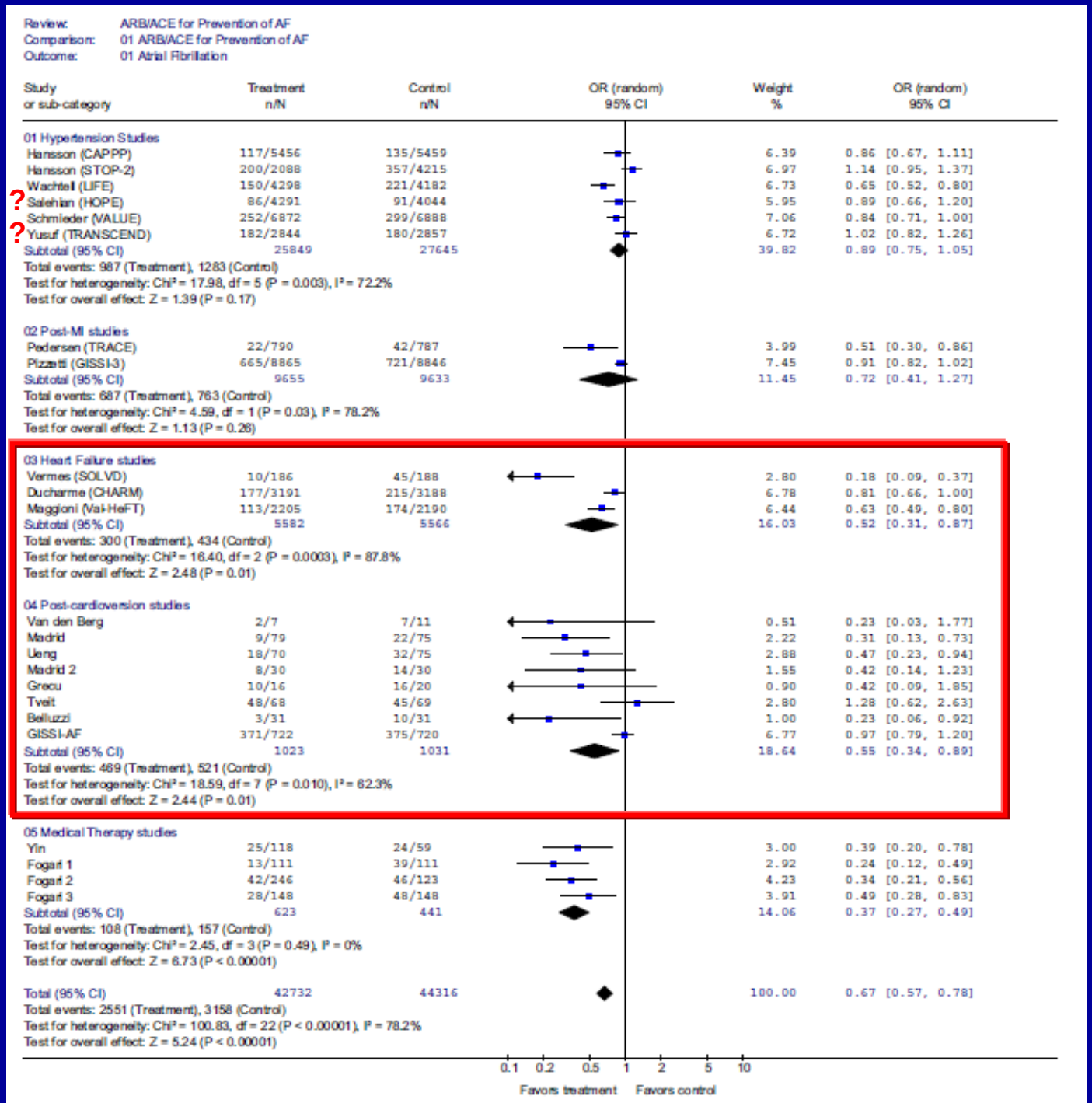
Objectives The authors reviewed published clinical trial data on the effects of renin-angiotensin system (RAS) inhibition for the prevention of atrial fibrillation (AF), aiming to define when RAS inhibition is most effective.

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

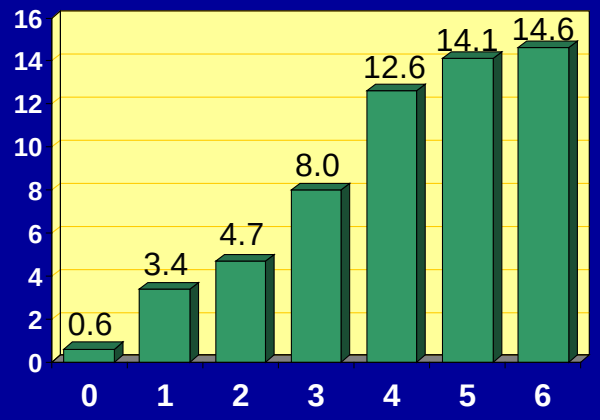
1) **Prior stroke / TIA**
   RR 2.5, 95% CI 1.8-3.5
2) **Increasing age**
   RR 1.5 per decade, 95% CI 1.3-1.7
3) **Hypertension**
   RR 2.0, 95% CI 1.6-2.5
4) **Diabetes mellitus**
   RR 1.7, 95% CI 1.4-2.0

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

Ischemic Stroke in relation to $CHADS_2$ and CHA_2DS_2VASc

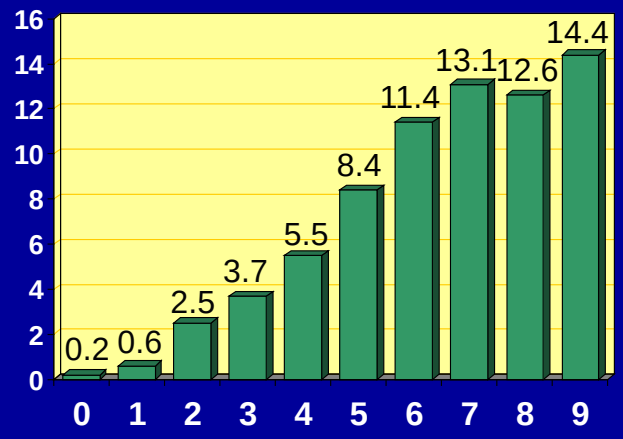
$CHADS_2$		CHA_2DS_2VASc
1	Congestive Heart Failure/LV dysfunction	1
1	Hypertension (or treated hypertension)	1
1	Age ≥ 75 years	2
1	Diabetes	1
2	Prior stroke or TIA	2
0	Vascular Disease (Prior MI, PAD, aortic plaque)	1
0	Age 65-74	1
0	Sex category (female sex)	1

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

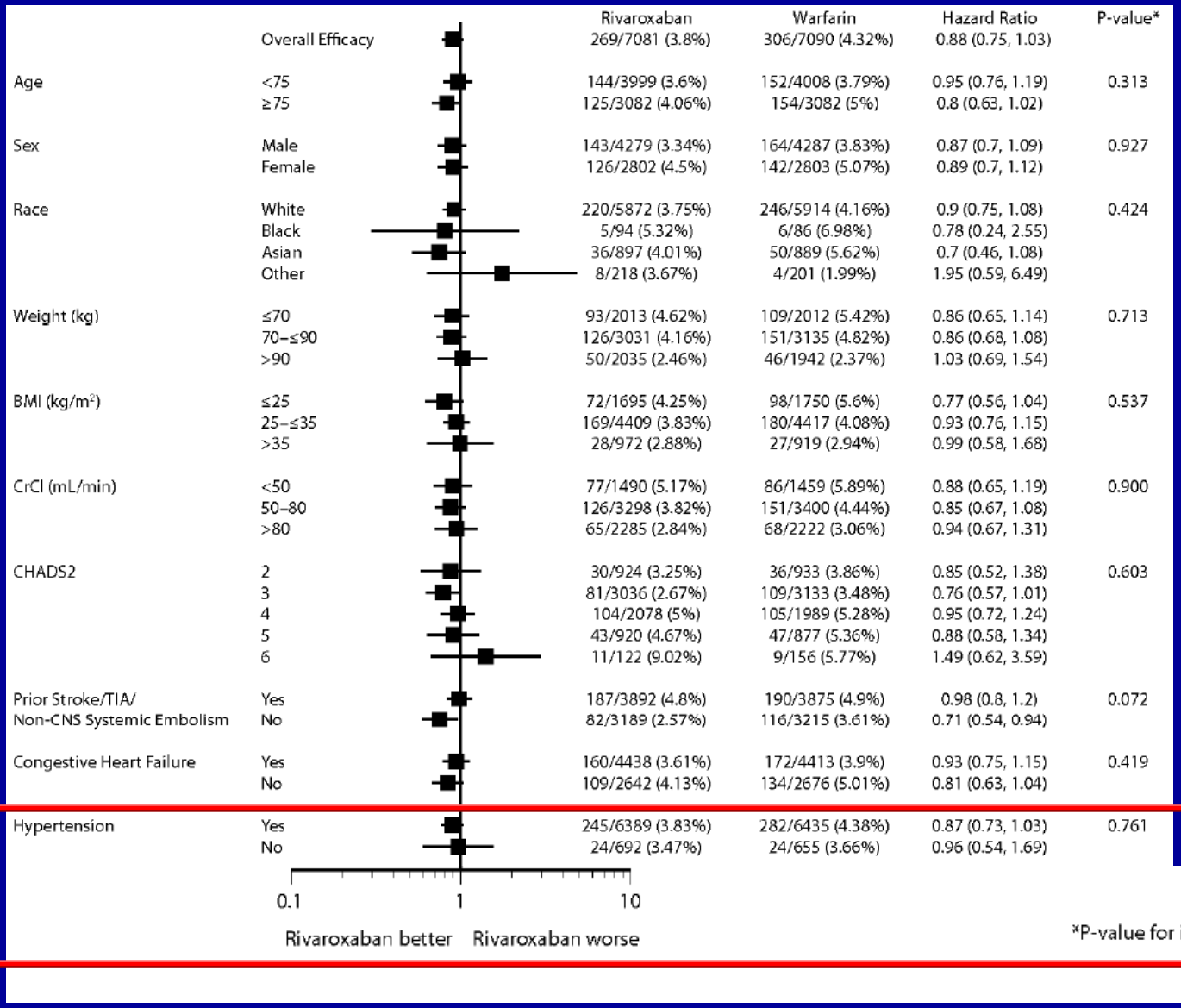
Subgroup analyses on the 1^{ry} outcome:

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

Dabigatran:
No significant interaction with hypertension status

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)	

*P-value for interaction

Blood Pressure Control and Risk of Stroke or Systemic Embolism in Patients With Atrial Fibrillation: Results From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

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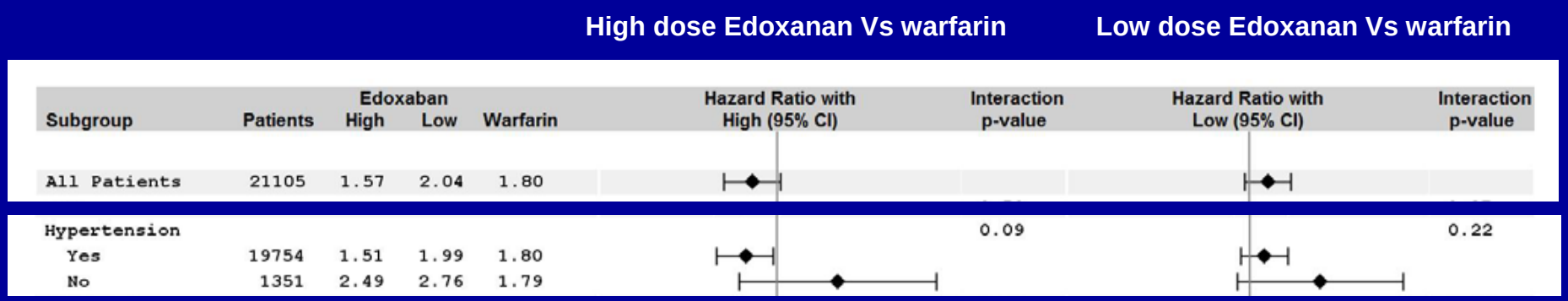
	History of Hypertension			No History of Hypertension			
	Apixaban Rate* (n)	Warfarin Rate* (n)	HR (95% CI)	Apixaban Rate* (n)	Warfarin Rate* (n)	HR (95% CI)	Interaction *P* Value
Efficacy endpoints							
Stroke/SE	1.31 (191)	1.59 (231)	0.82 (0.68–0.10)	0.99 (21)	1.67 (34)	0.60 (0.35–1.02)	0.27
Ischemic/uncertain type of stroke	1.00 (146)	1.04 (151)	0.96 (0.77–1.21)	0.75 (16)	1.17 (24)	0.64 (0.34–1.21)	0.24
Hemorrhagic stroke	0.24 (36)	0.48 (70)	0.51 (0.34–0.76)	0.19 (4)	0.39 (8)	0.49 (0.15–1.61)	0.93
Death from any cause	3.38 (505)	3.77 (562)	0.90 (0.79–1.01)	4.53 (98)	5.09 (107)	0.89 (0.67–1.17)	0.96
CV death	1.75 (262)	1.91 (285)	0.92 (0.77–1.08)	2.13 (46)	2.81 (59)	0.76 (0.51–1.11)	0.38
MI	0.51 (75)	0.66 (96)	0.78 (0.57–1.05)	0.71 (15)	0.29 (6)	2.44 (0.95–6.28)	0.02
Safety endpoints							
ISTH major bleeding	2.07 (277)	3.00 (394)	0.69 (0.59–0.80)	2.60 (50)	3.73 (68)	0.70 (0.48–1.00)	0.96
Major or CRNM bleeding	4.00 (527)	5.94 (761)	0.68 (0.61–0.76)	4.54 (86)	6.50 (116)	0.70 (0.53–0.93)	0.82
Any bleeding	17.91 (2042)	25.76 (2680)	0.71 (0.67–0.75)	19.29 (314)	26.31 (380)	0.75 (0.64–0.87)	0.55

Rao MP et al JAHA 2015

Edoxaban:
No significant interaction with hypertension status



Giugliano RP et al. N Engl J Med 2013;369:2093-2104

Take Home Points

1. Hypertension and atrial fibrillation (AF) are two important health priorities which often coexist in the same patient.
2. Hypertension increases the risk of AF and, because of its high prevalence in the population, it accounts for more cases of AF than other risk factors.
3. Hypertension is present in 60-80% of individuals with AF.
4. Although hypertension is the main modifiable risk factor for AF, there is a surprising paucity of intervention studies comparing different BP targets and strategies for the prevention of new-onset AF in hypertensive patients in sinus rhythm.
5. The potential impact of RAAS inhibitors is uncertain.

Areas for Future Studies

1. To identify, through remote ECG monitoring, the hypertensiove patients with silent AF who might benefit from an anticoagulant therapy.
2. Strategy trials should define an optimal BP target which may balance the risk of thrombotic and hemorrhagic complications in anticoagulated patients with AF, as well as the risk of AF recurrence after catheter ablation.

Thank you for your attention