«Актуальные вопросы диагностики и лечения фибрилляции предсердий»
Москва, 28. 11. 2014

Фибрилляция предсердий и артериальная гипертония

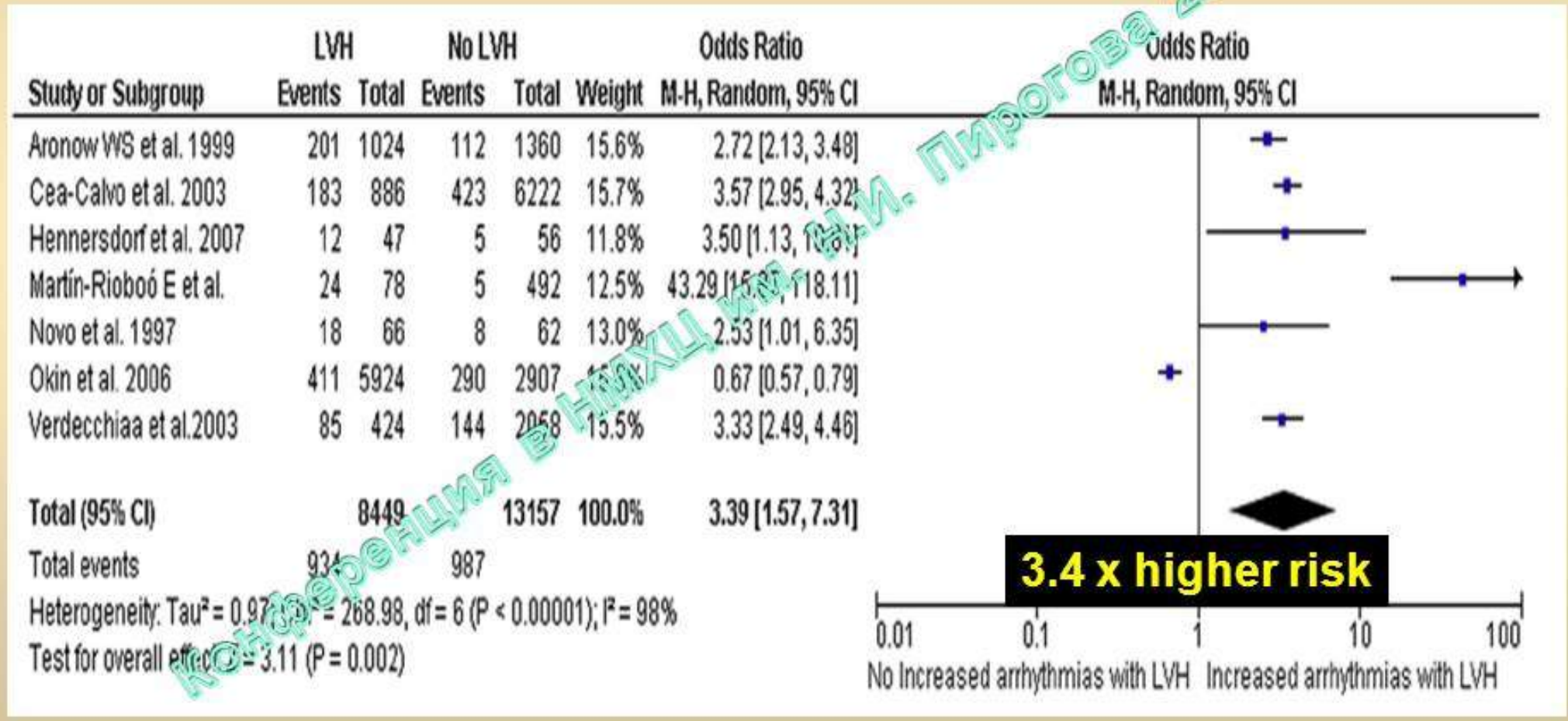
РОБЕРТ ГАТАЛА
НАЦИОНАЛЬНЫЙ КАРДИОВАСКУЛЯРНЫЙ ИНСТИТУТ
СЛОВАЦКИЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
БРАТИСЛАВА, СЛОВАКИЯ

HYPERTENSIVE HEART DISEASE

- The most prevalent arrhythmogenic condition
- Wide spectrum of arrhythmias – from sinus tachycardia to sudden death
- Little attention paid to efficient antiarrhythmic strategies to prevent and treat arrhythmias in hypertensive patients

Association of LVH and supraventricular arrhythmias

(meta-analysis 27 141 pts)

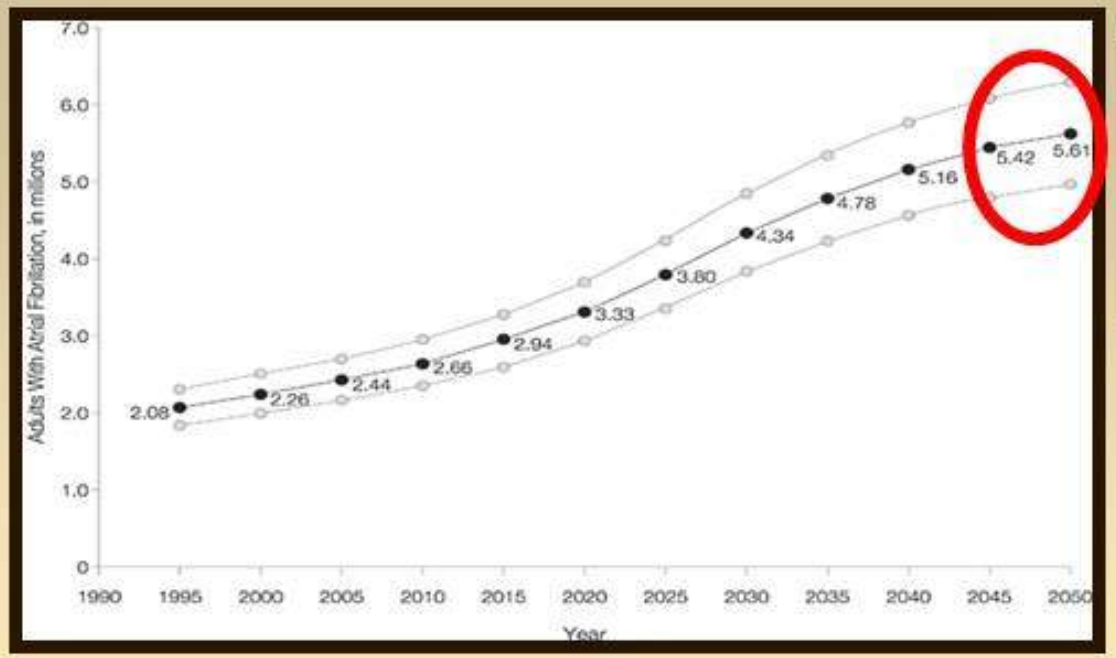


Chatterjee S et al., Am J Cardiol 2014

Hypertension and AFIB

a couple frequently unrecognized

- **Hypertension is the leading risk factor for atrial fibrillation (AFIB)**
- **AFIB is the leading arrhythmia associated with hypertension**



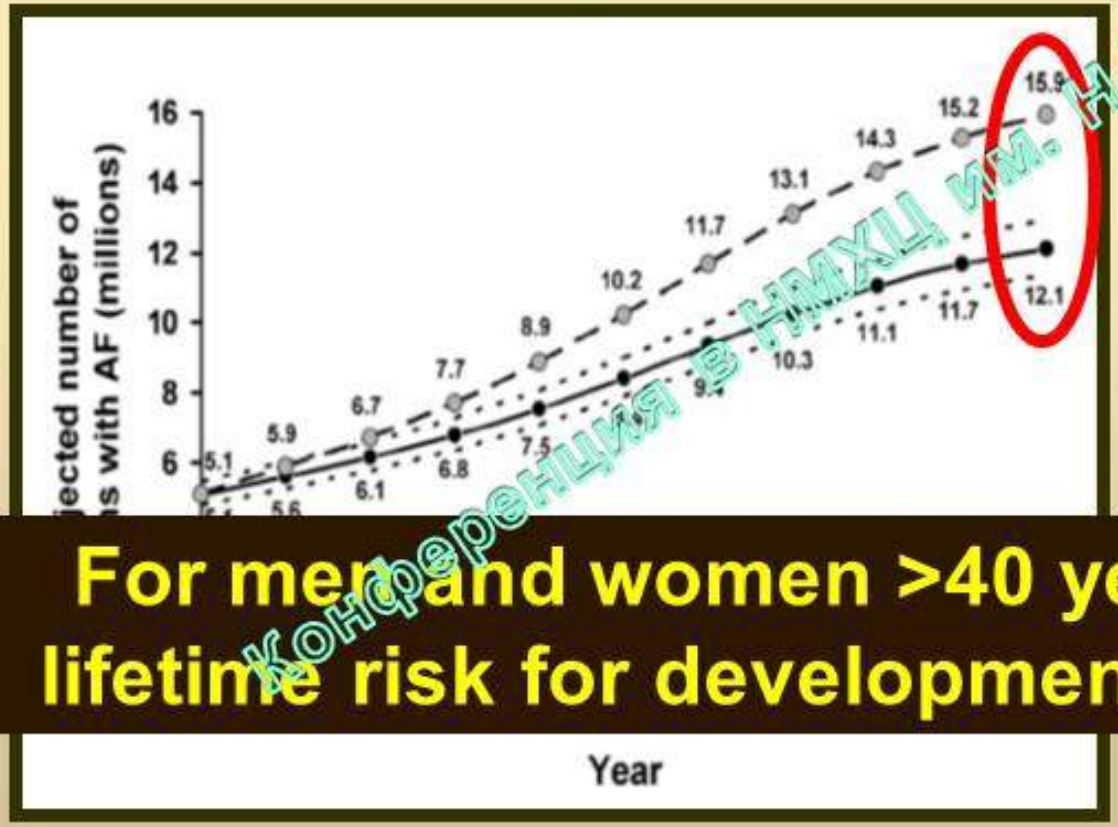

The New England Journal of Medicine

Special Article

SHATTUCK LECTURE — CARDIOVASCULAR MEDICINE AT THE TURN OF THE MILLENNIUM: TRIUMPHS, CONCERNS, AND OPPORTUNITIES

EUGENE BRAUNWALD, M.D.

Expecting the AFIB Epidemics…



For men and women >40 years old, the remaining lifetime risk for development of AF is approx. 1 in 4

AFIB – do we know the true extent of the epidemic ?

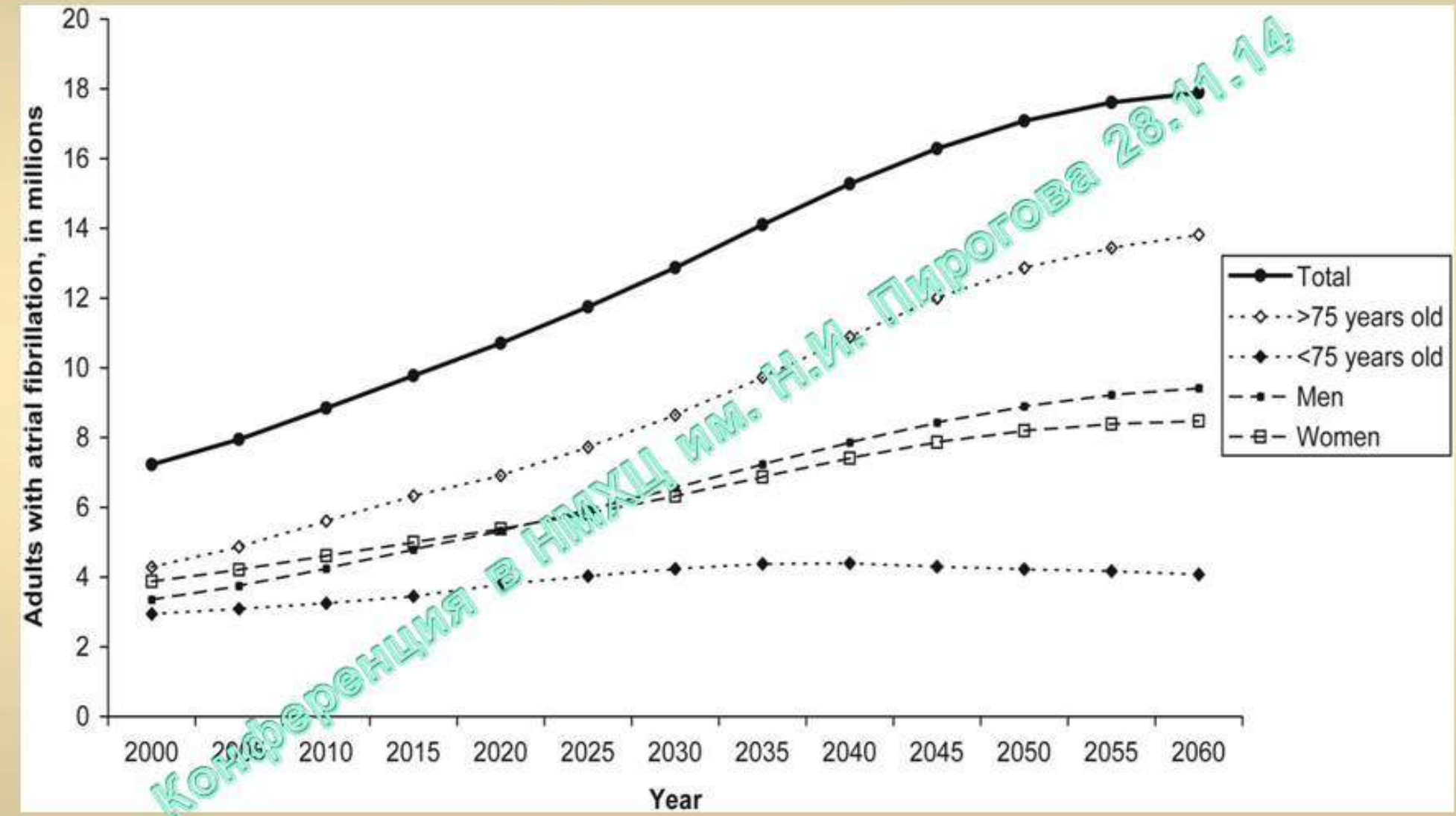
- **Absence of symptoms**: 70% - 95% of all AFIB episodes remain asymptomatic
- **Electrocardiographic „undersampling"** AFIB typically detected in 30-45% accidentaly
- **substantial underestimation of the true extent of AFIB very probable !**

AFIB and Hypertension

An outline

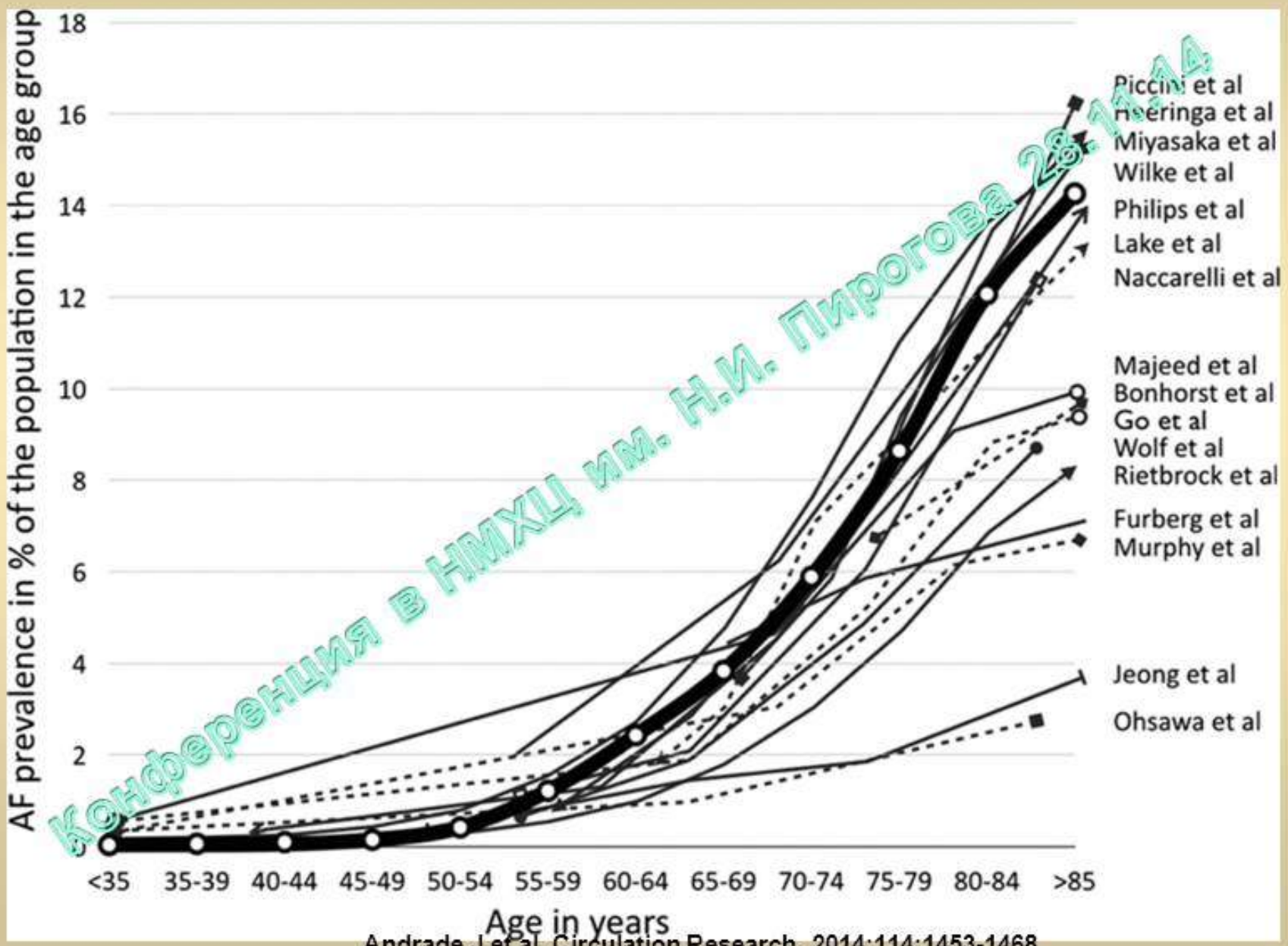
- **What is the role of hypertension in the etiology of AFIB ?**
- What are pathophysiological mechanisms promoting AFIB in hypertension ?
- Are there any risk factors for AFIB in hypertensive patients ? How to detect AFIB early in order to act early?
- Can we prevent the occurrence and progression of AFIB in hypertension ?
- How to treat hypertensive patients with AFIB?

Projected number of adults with AFIB in the EU 2000 - 2060



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

Prevalence rates of AFIB in the published studies



Andrade J et al. Circulation Research. 2014;114:1453-1468

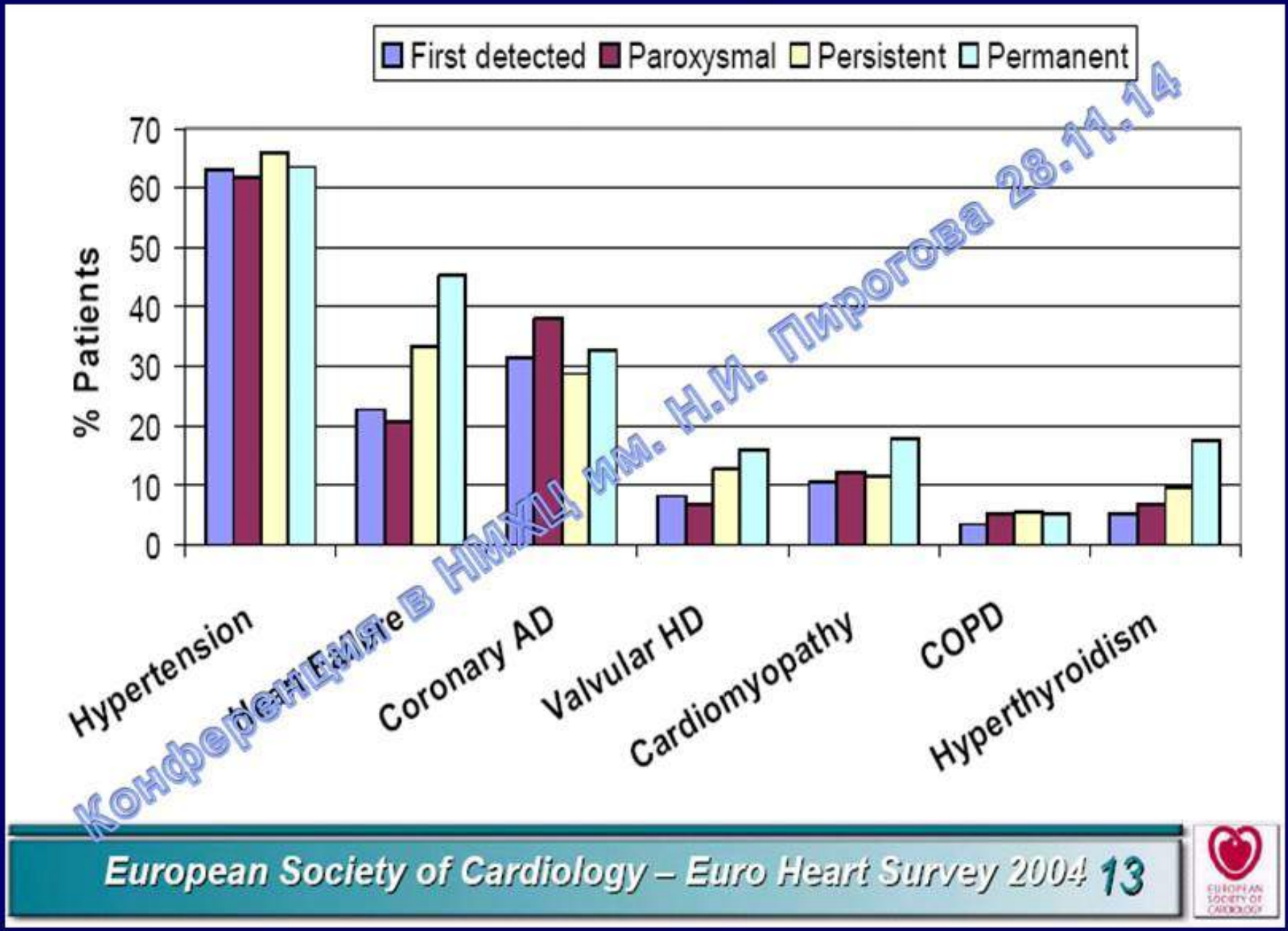
Risk Factors for Development of AFIB: Framingham Study, 38-Year Follow-Up

Risk Factors	Age-Adjusted OR		Risk Factor–Adjusted OR	
	Men	Women	Men	Women
Cigarettes	1.0	1.4†	1.1	1.4
Diabetes	1.7‡	2.1§	1.4†	1.6‡
ECG–LVH	3.0§	3.8§	1.4	1.3
Hypertension	1.8‖	1.7§	1.5‡	1.4†
BMI	1.03	1.02	—	—
Alcohol	1.01	0.95	—	—

BMI = body mass index; ECG–LVH = echocardiographic left ventricular hypertrophy; OR = odds ratio.

Kannel WB et al., Am J Cardiol 1998

COMORBIDITY in pts with AFIB

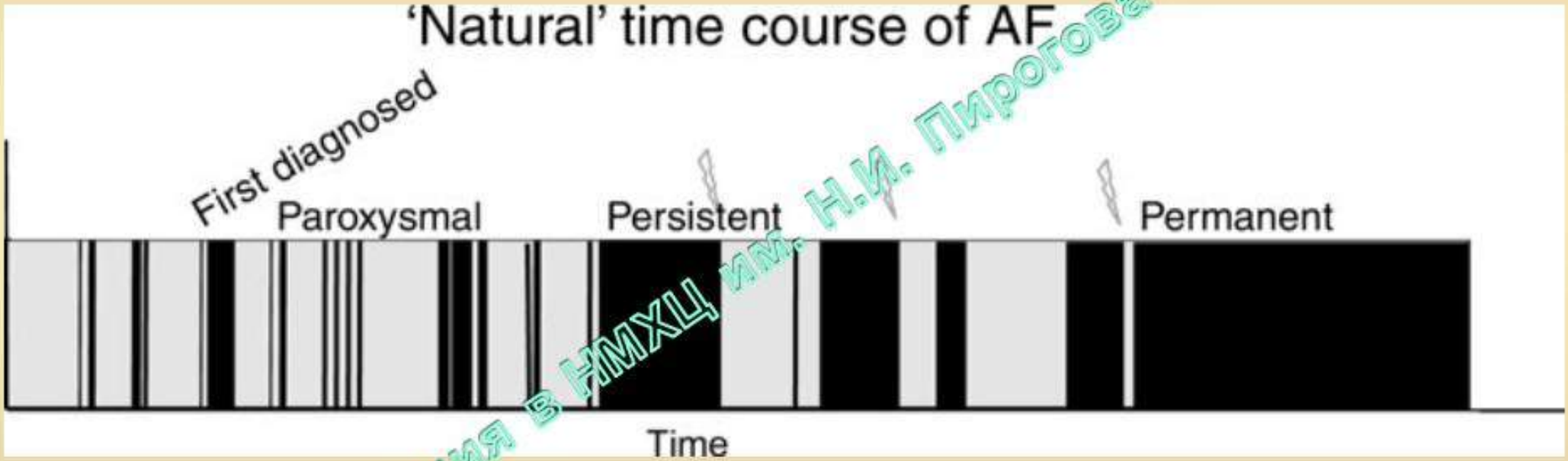


Concomitant diseases in AFIB patients
(German AFNET Registry)

	First detected 10.8% (*n* = 1035)	Paroxysmal 30.2% (*n* = 2893)	Persistent 19.5% (*n* = 1873)	Permanent 32.8% (*n* = 3141)
Demographics				
Age (years)	67.0 ± 12.3	65.5 ± 11.3	67.6 ± 11.2	71.7 ± 9.2
Female gender (%)	40.1	41.2	35.2	38.7
Concomitant disease				
Hypertension (%)	68.9	[illegible]	70.6	71.1
Coronary artery disease (%)	26.8	25.0	28.4	31.0
Old infarction (%)	14.5	11.2	14.0	14.5
Previous PCI/CABG (%)	14.7	16.7	16.6	17.6
Angina (%)	15.5	12.9	13.2	13.1
Heart failure (%)	31.6	24.1	41.4	45.2
Valvular heart disease (%)	27.7	25.1	37.0	48.1
Rheumatic origin (%)	3.1	2.5	3.3	5.3
Non-rheumatic origin (%)	24.6	22.6	33.7	42.7
Valve replacement (%)	2.4	3.9	4.3	7.6
Cardiomyopathy (%)	7.2	6.8	13.6	13.8

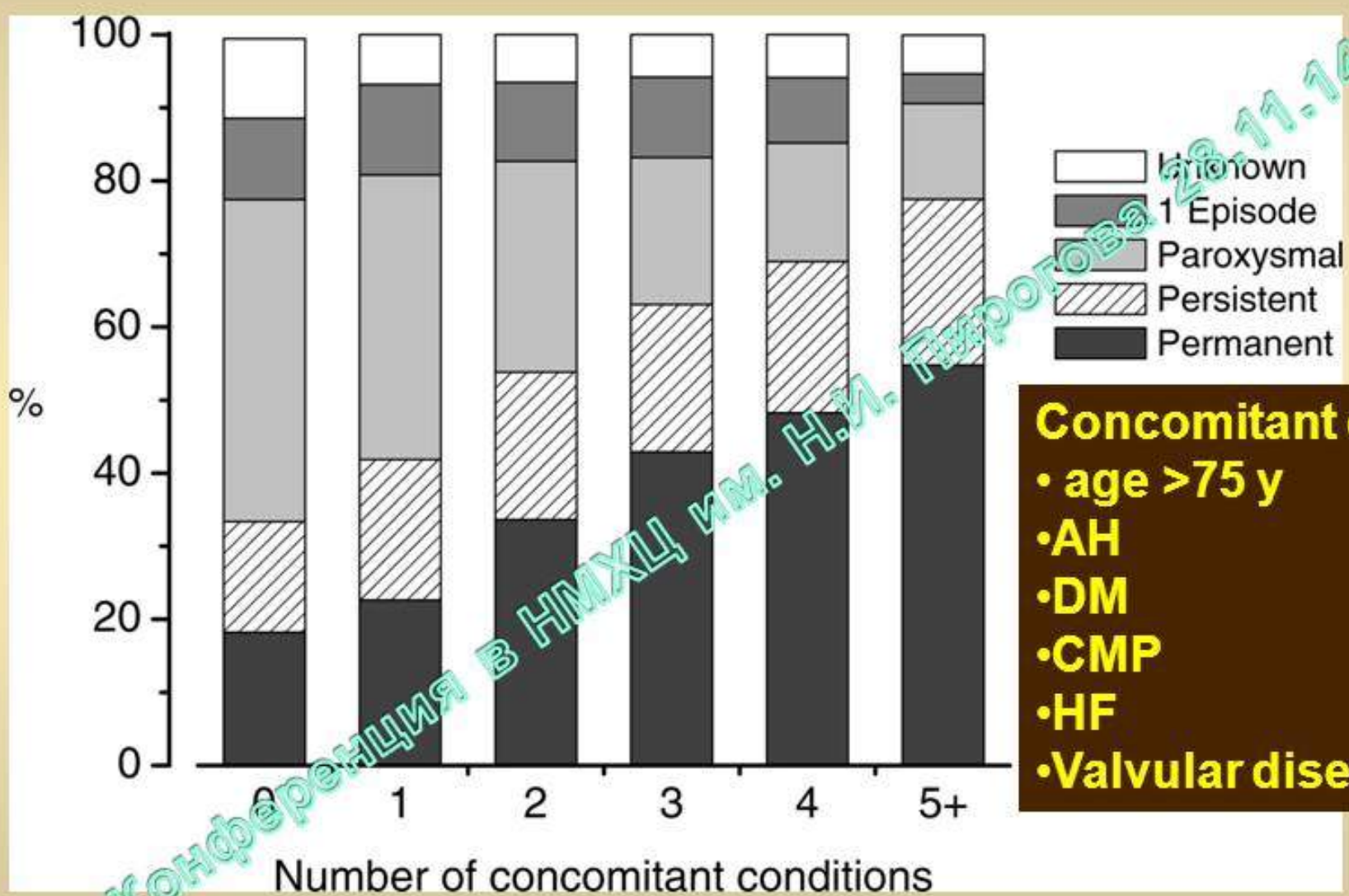
Nabauer M et al., Europace 2009

Natural course of AFIB



Kirchhof P,et al., Europace (2007) 9, 1006–1023

Shift of AFIB type from paroxysmal to permanent in relation to concomitant conditions known to promote AFIB



Concomitant conditions:

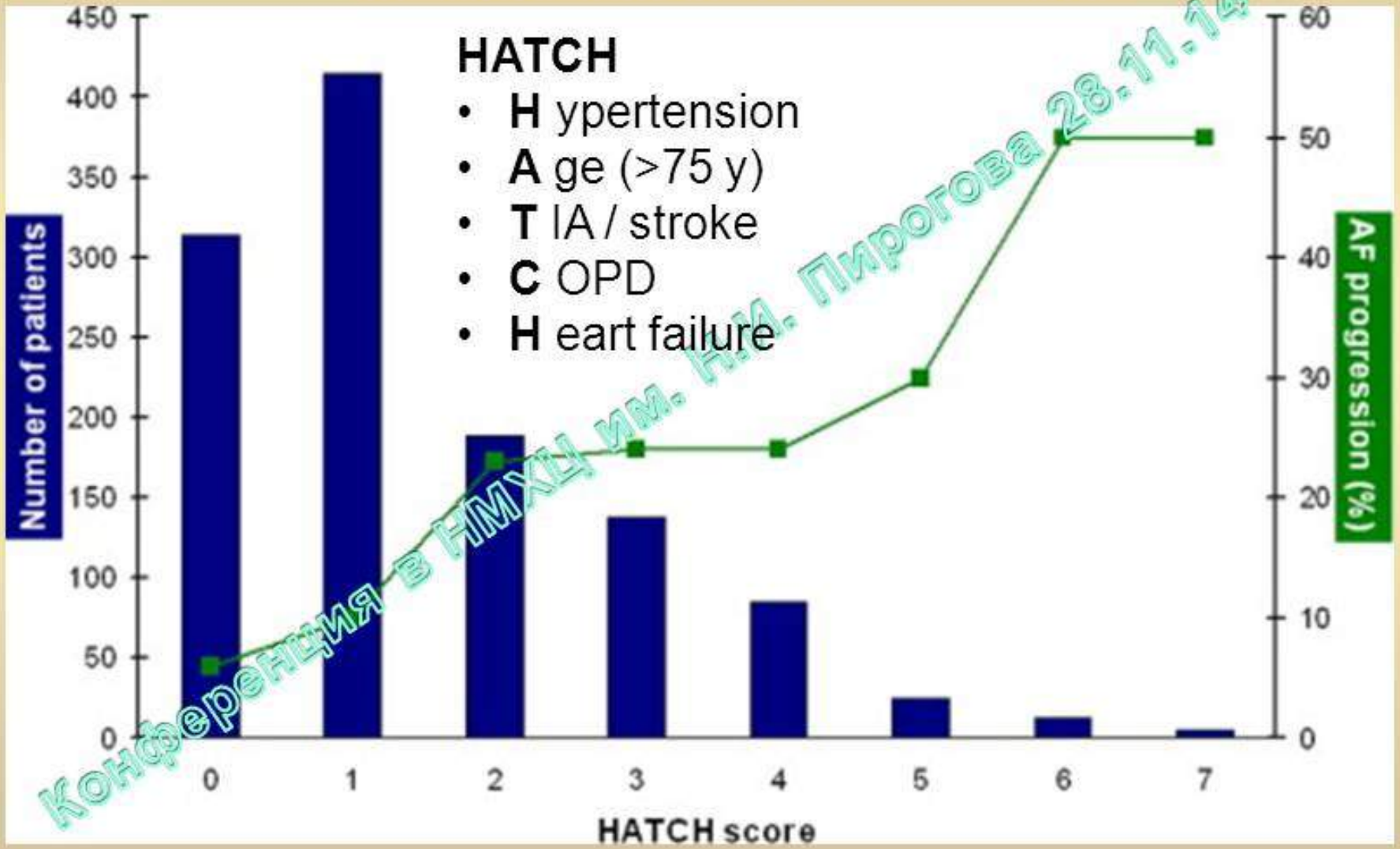
- age >75 y
- AH
- DM
- CMP
- HF
- Valvular disease

Nabauer, M. et al. Europace 2009 11:423-434

Progression From Paroxysmal to Persistent AFIB
Prevalence of HATCH score and progression of AFIB after 1 y F-U

(1219 pts from Euro Heart Survey on AF)

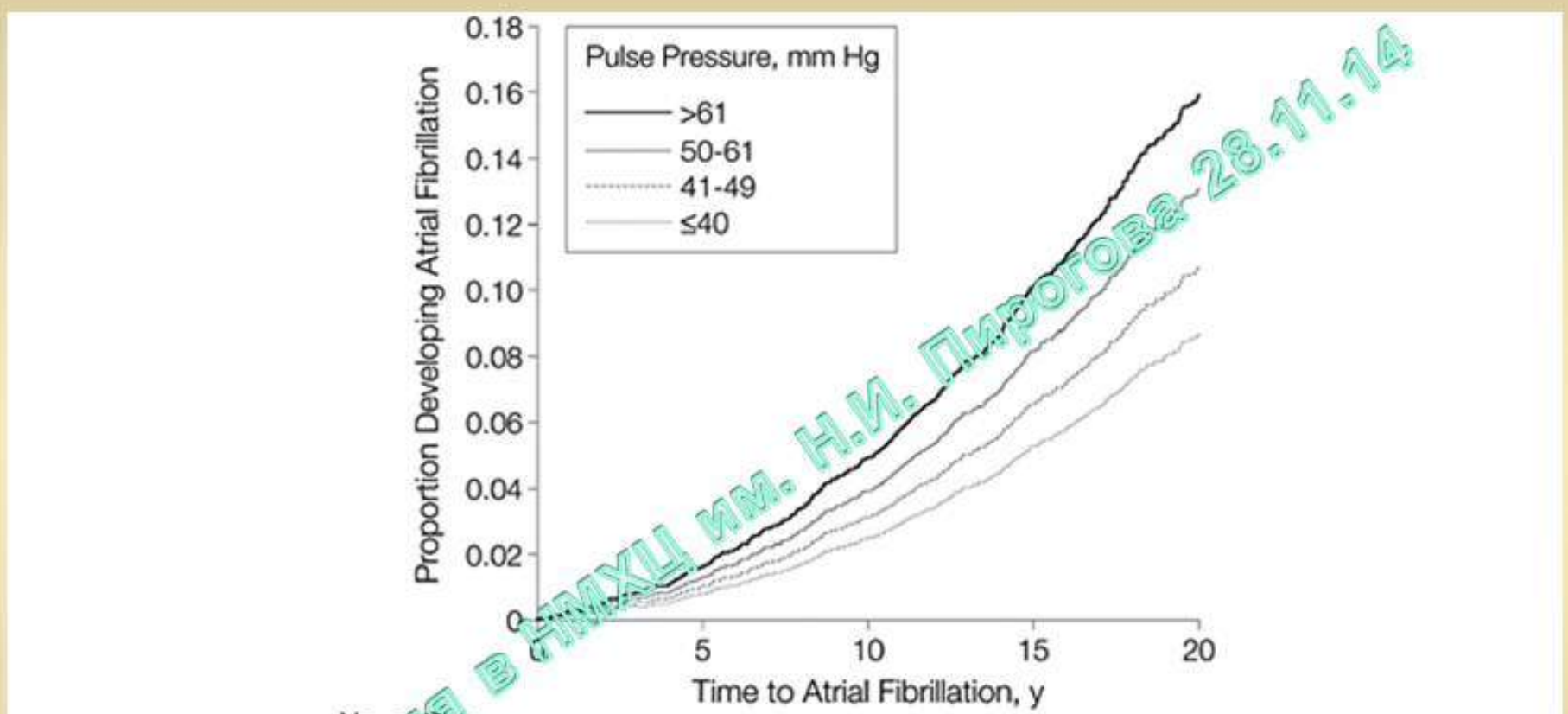
AF progression after 1 year = 15%



De Vos et al., JACC 55, 2010, 725

CATEGORY	AFIB RISK FACTOR	RISK	
ESTABLISHED	**AGE**	2	Per decade
	MALE SEX	1.5	
	HYPERTENSION	1.2 -1.5	BP>140/90 mmHg
	VHD	1.8-3.4	
	LV systolic dysfunction	4.5-5.9	
	OBESITY	1.4-2.4	
	ALCOHOL	1.3-1.5	>36 g/l
EMERGING	DIASTOLIC DYSFUNCTION	3.3-5.3	BPs 130-139
	PREHYPERTENSION	1.3	
	PULSE PRESSURE	1.3	per 20 mm Hg
	OSA	2.8-5.6	
	HEAVY PHYSICAL ACTIVITY	3.3-5.3	cumulative >1500 h
	FAMILIAL / GENETIC	1.9	
	HCMP	4-6	
INCONCLUSIVE	CORONARY HEART DIS.	-	
	…..		

Incidence of Atrial Fibrillation According to Quartiles of Pulse Pressure

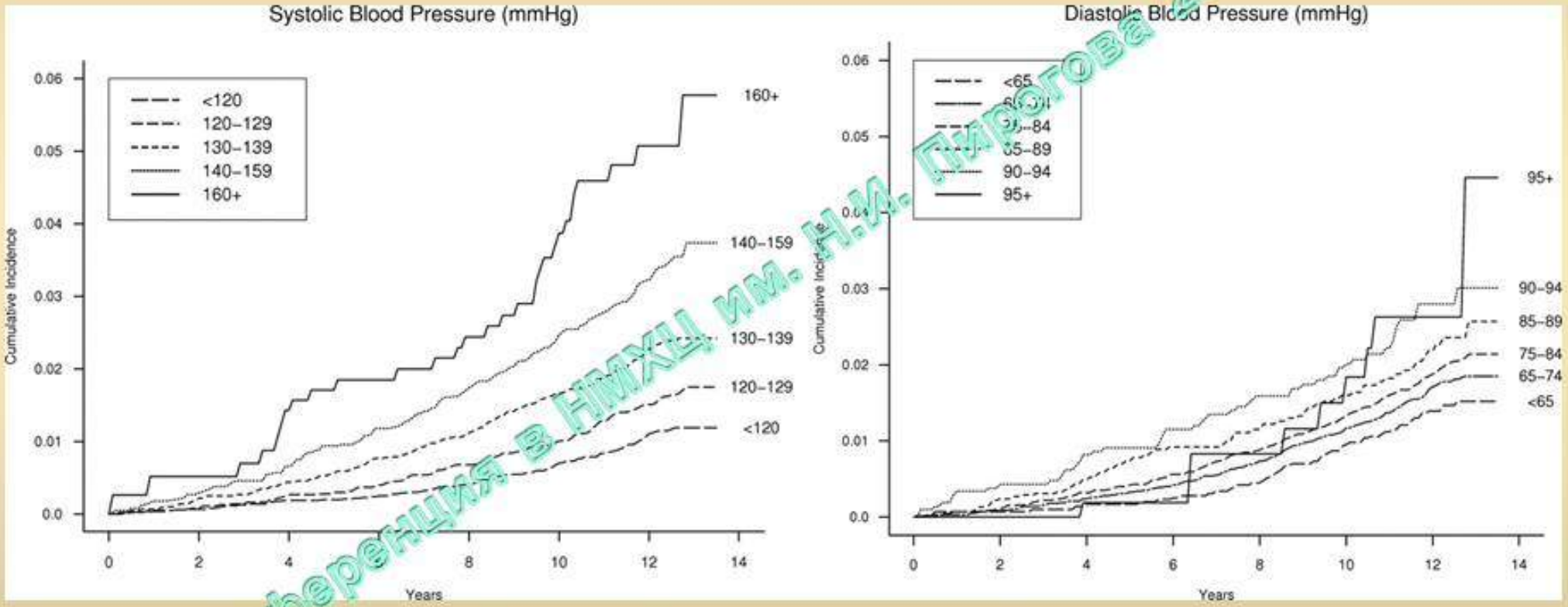


No. at Risk

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

Mitchell, G. F. et al. JAMA 2007;297:709-715.

Cumulative incidences of AFIB in various BP strata (BP value most recent before the event was considered)



Womens Health Study - 34 221 pts

Conen, D. et al. Circulation 2009;119:2146-2152

Hypertension and AFIB

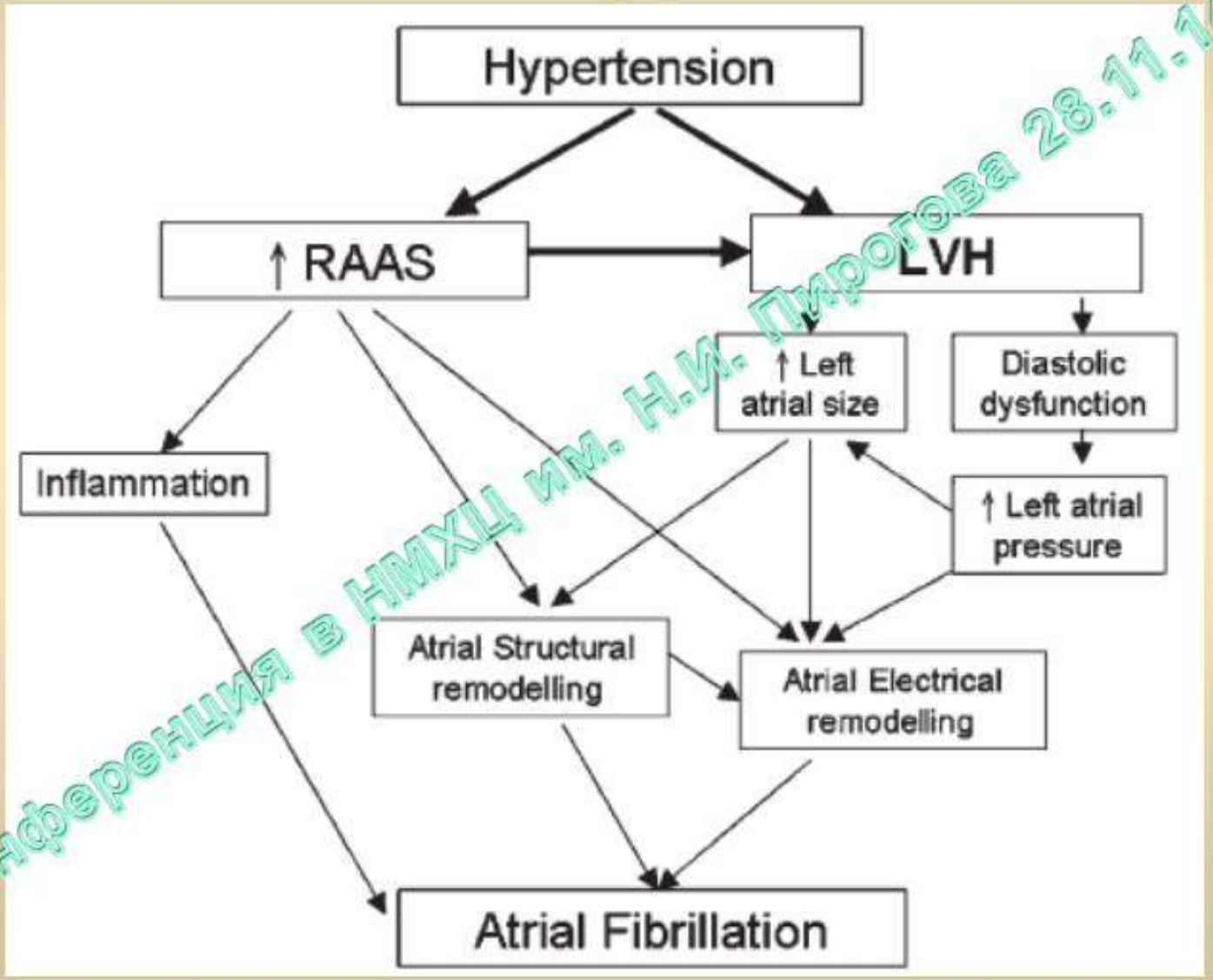
An outline

- What is the role of hypertension in the etiology of AFIB ?
- **What are pathophysiological mechanisms promoting AFIB in hypertension ?**
- Are there any risk factors for AFIB in hypertensive patients ? How to detect AFIB early in order to act early?
- Can we prevent the occurrence and progression of AFIB in hypertension ?
- How to treat hypertensive patients with AFIB?

AF – heterogenous arrhythmia with variable origin, clinical profile and natural history

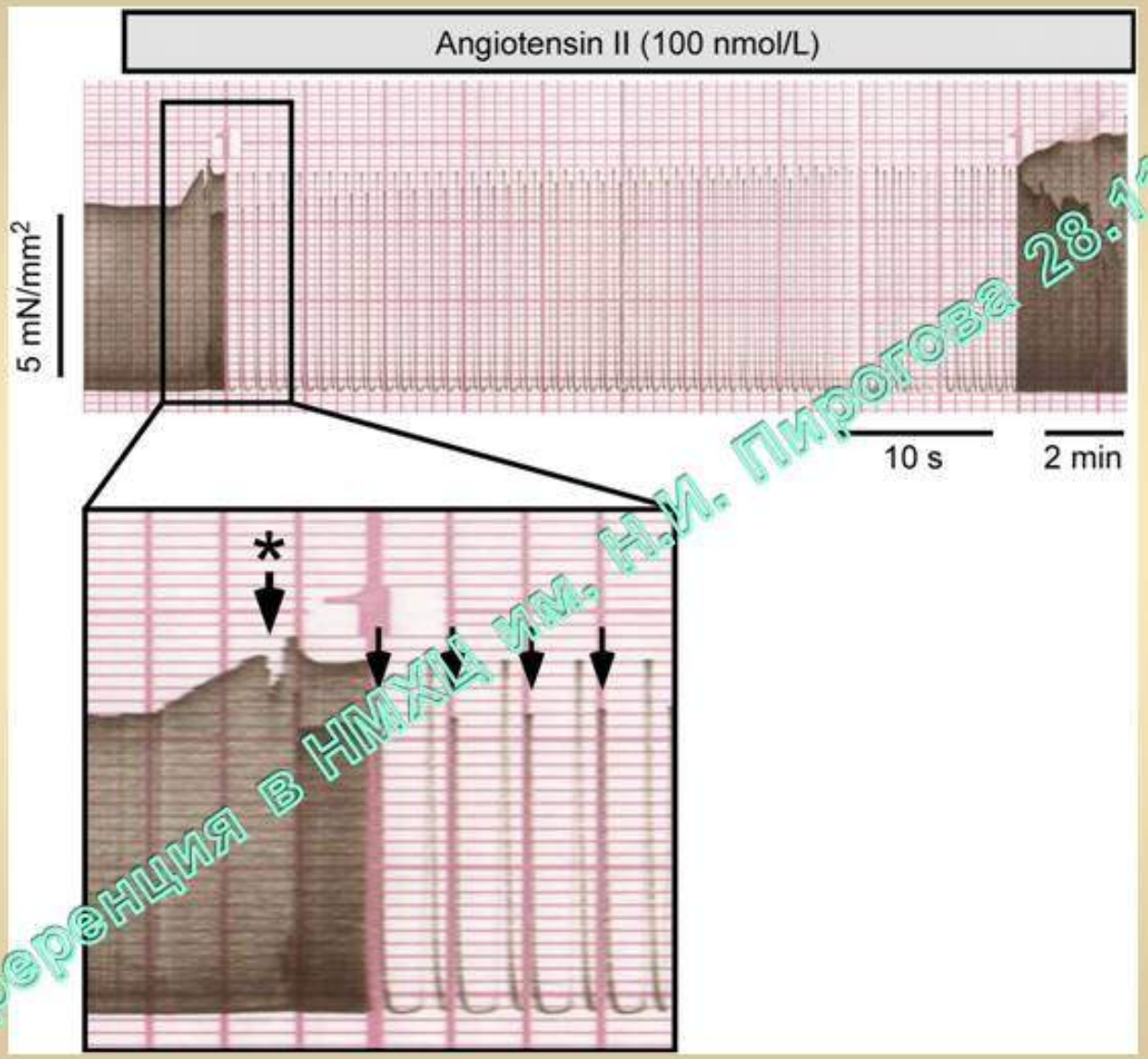
- heterogenous range of therapeutic actions needed
- **Atrial structural remodeling = common denominator of different AF forms**
- Atrial remodeling = any persistent change in atrial structure and / or function

Potential mechanisms of AFIB related to hypertension



Ziu and Tse, JHH 2008

Original recording demonstrating typical effects of Ang II in a human atrial muscle strip

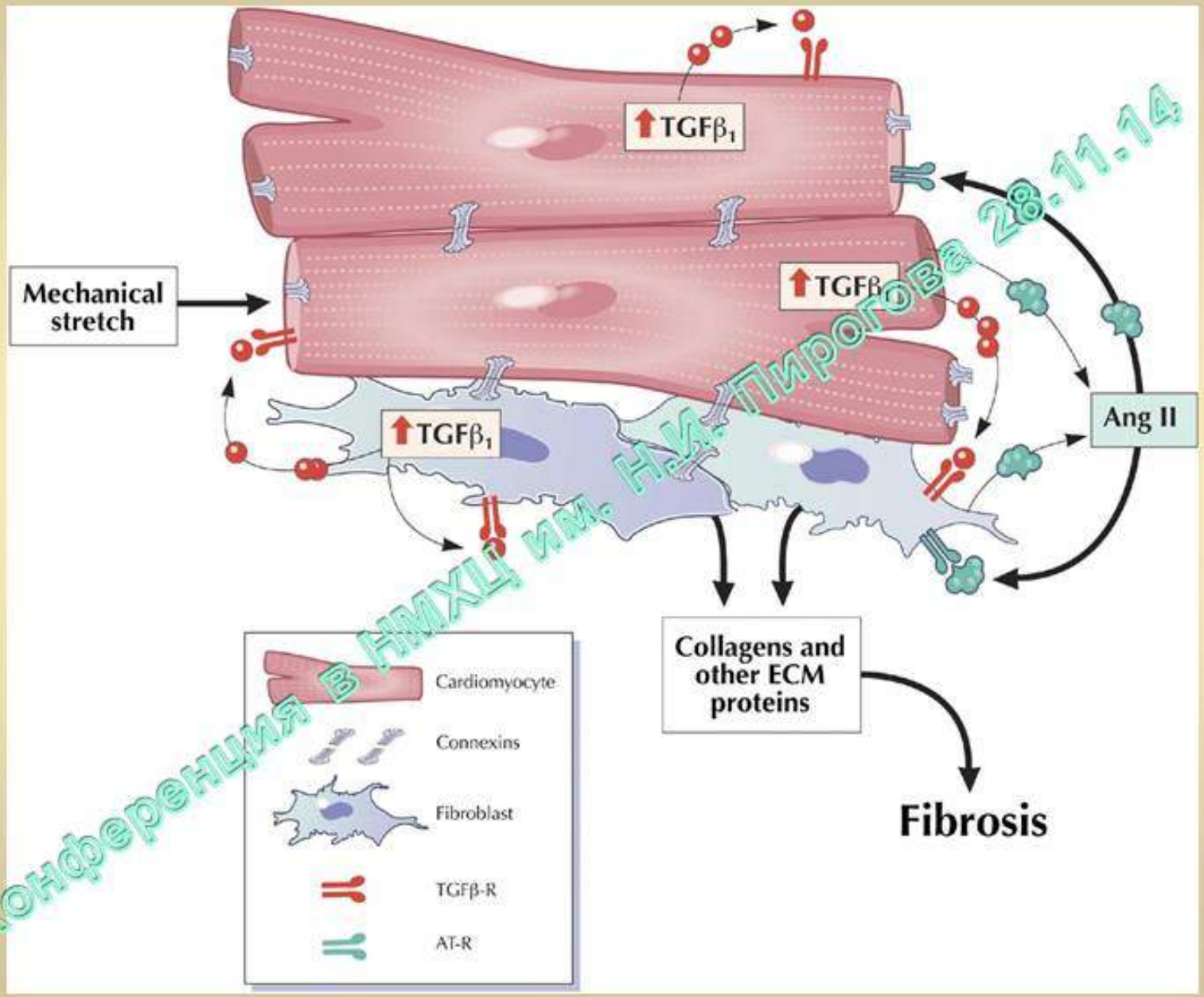


von Lewinski, D. et al. Eur J Heart Fail 2008 10:1172-1176;

Pathophysiology of fibrillating atria

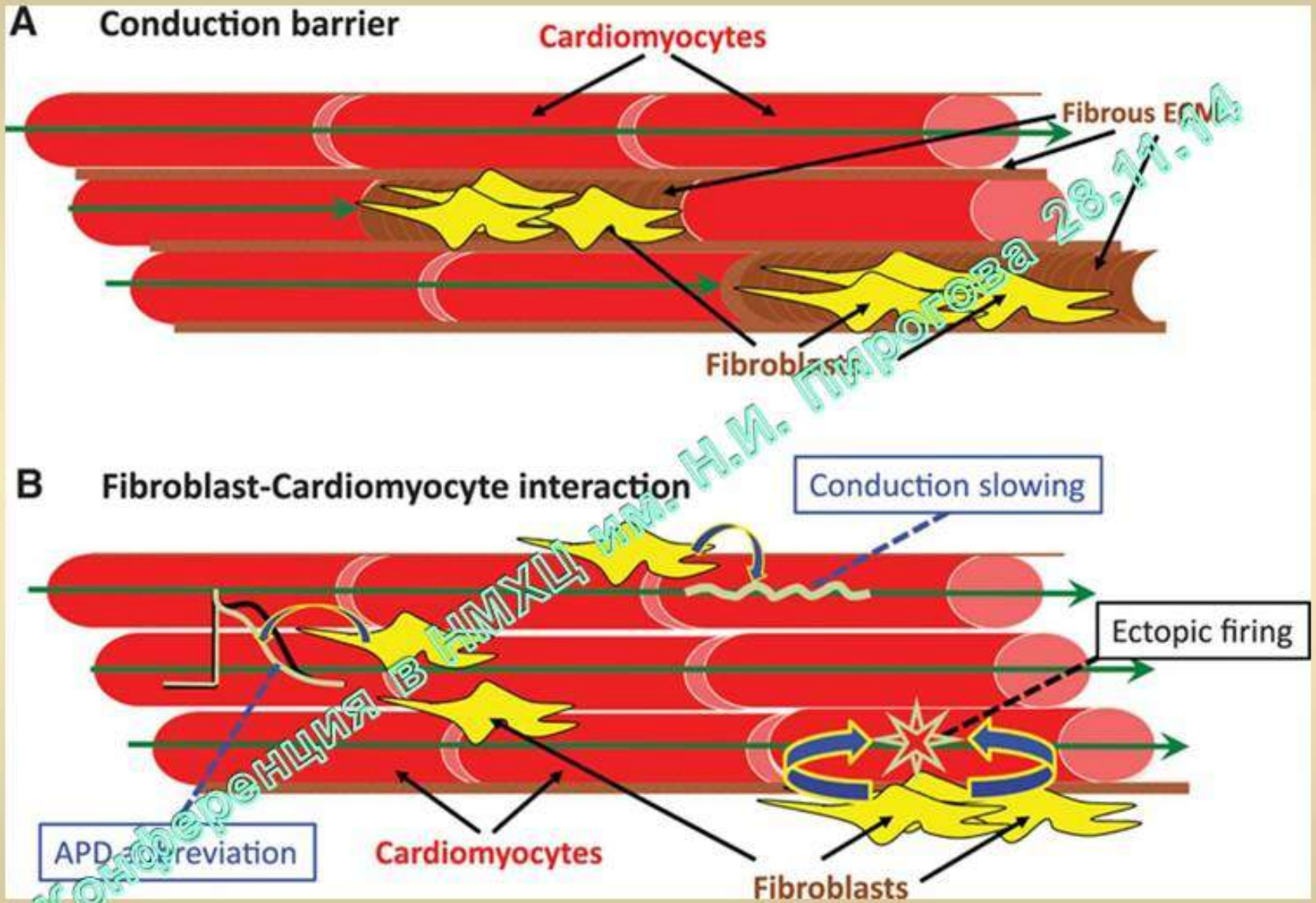
- **Hallmark of arrhythmogenic structural remodeling = atrial fibrosis**
- **Atrial structural remodeling = common denominator of different AF forms**
- Tissue fibrosis = accumulation of fibrillar collagen deposits
  - Usually reparative process to replace degenerating myocardial parenchyma
  - Concomitant reactive fibrosis causes interstitial expansion

Cardiomyocyte-Fibroblast Crosstalk

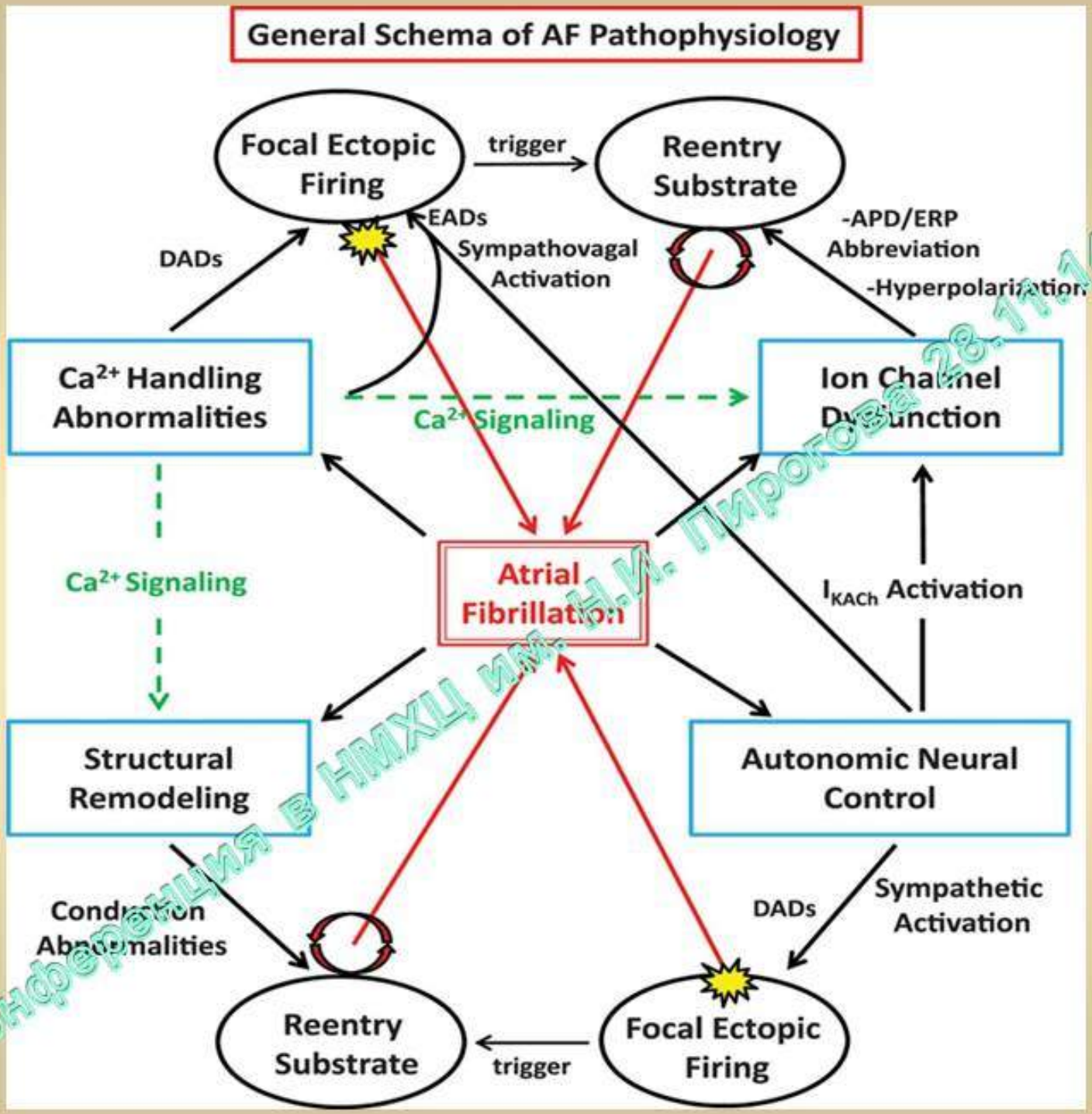


Burstein, B. et al. J Am Coll Cardiol 2008;51:802-809

Mechanisms by which fibrosis can promote atrial arrhythmogenesis leading to AFIB



Andrade J et al. Circulation Research. 2014;114:1453-1468



Andrade J et al. Circulation Research. 2014;114:1453-1468

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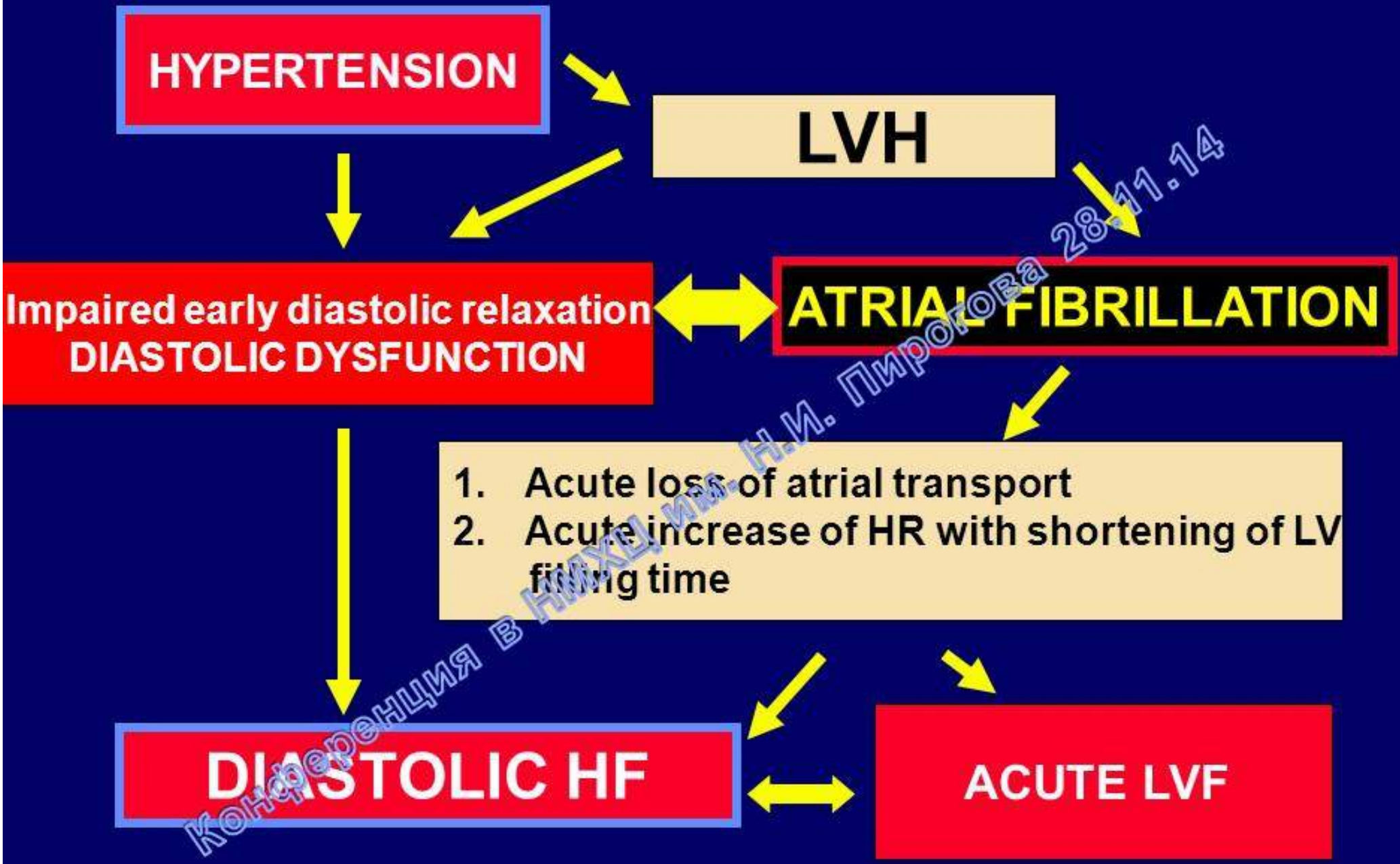
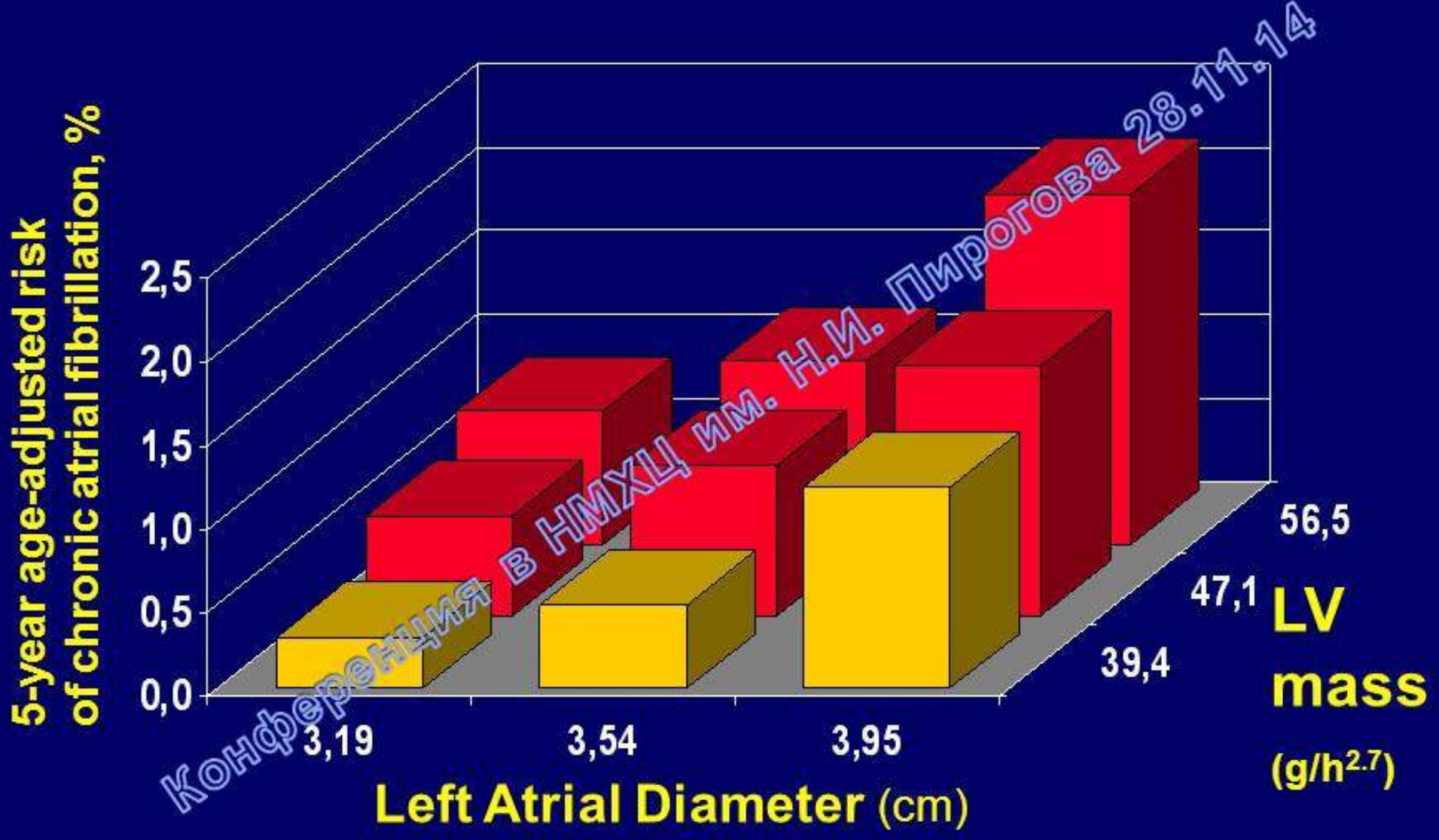
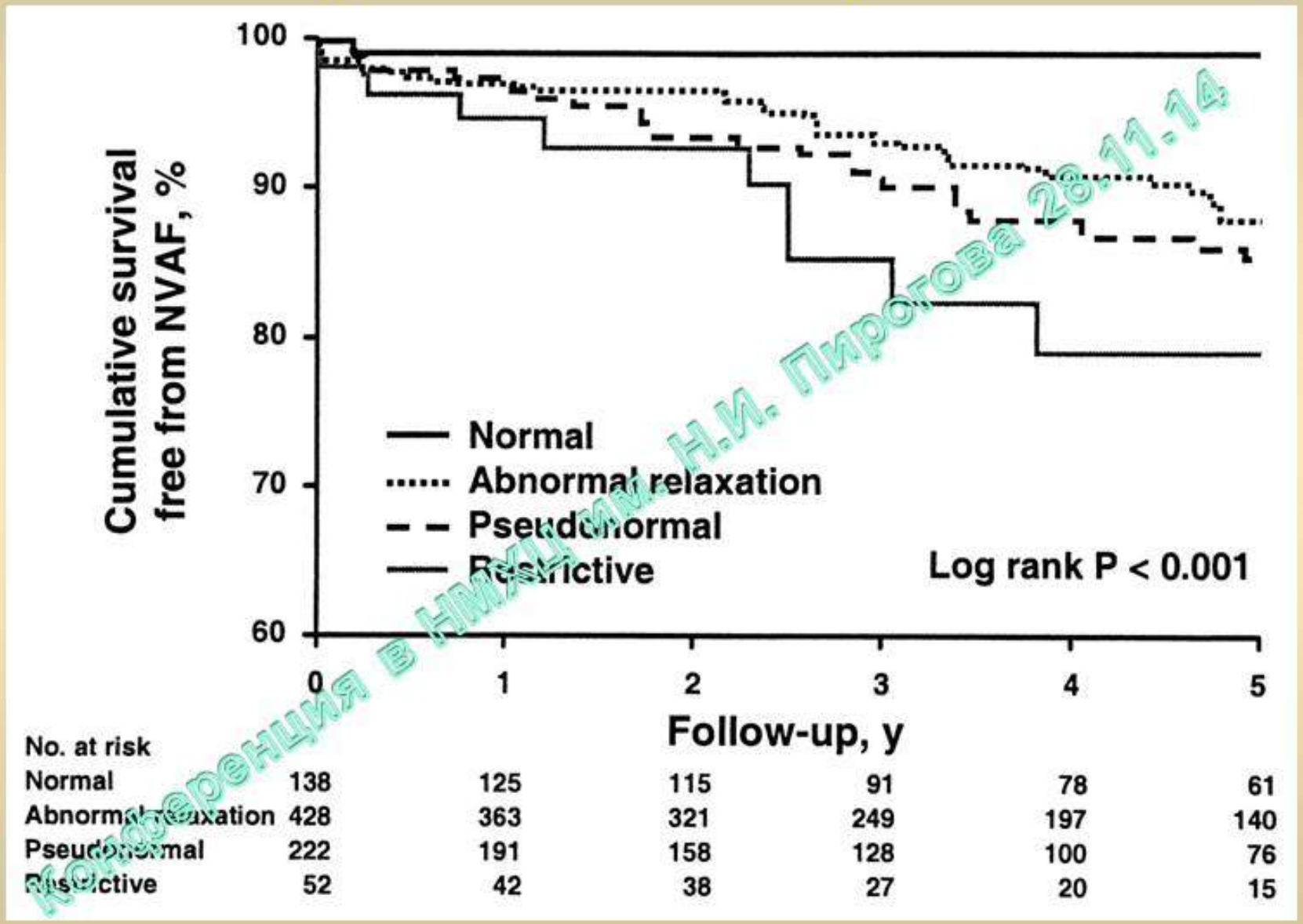


5-year risk of chronic AFIB occurrence (age corrected) in the PIUMA trial



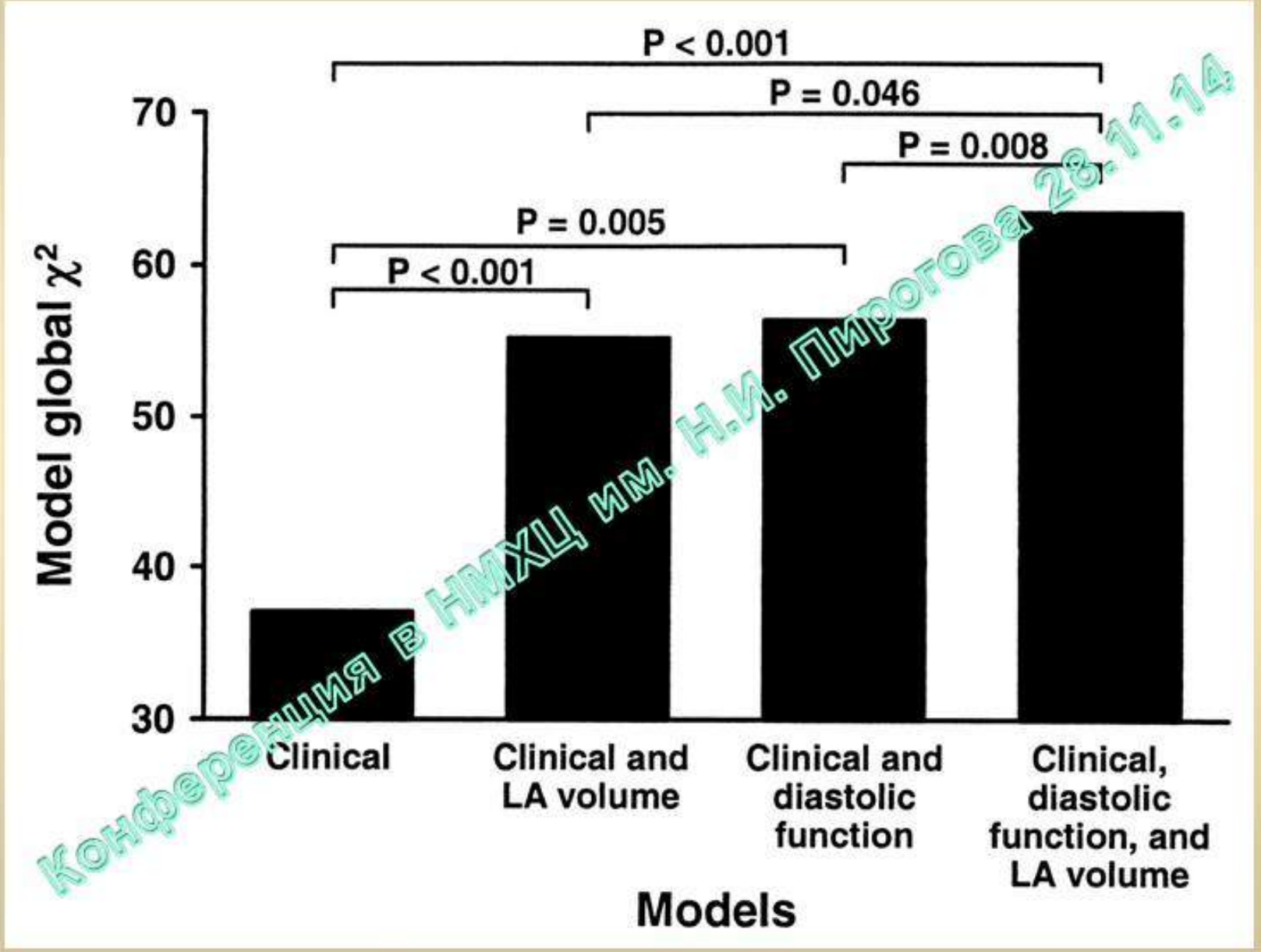
Verdecchia P, Angeli F et al. Hypertension 2003;41:218-223

Age-adjusted cumulative survival without nonvalvular AFIB by diastolic function profile



Tsang, T. S. M. et al. J Am Coll Cardiol 2002;40:1636-1644

Predictive power of four models for nonvalvular AFIB

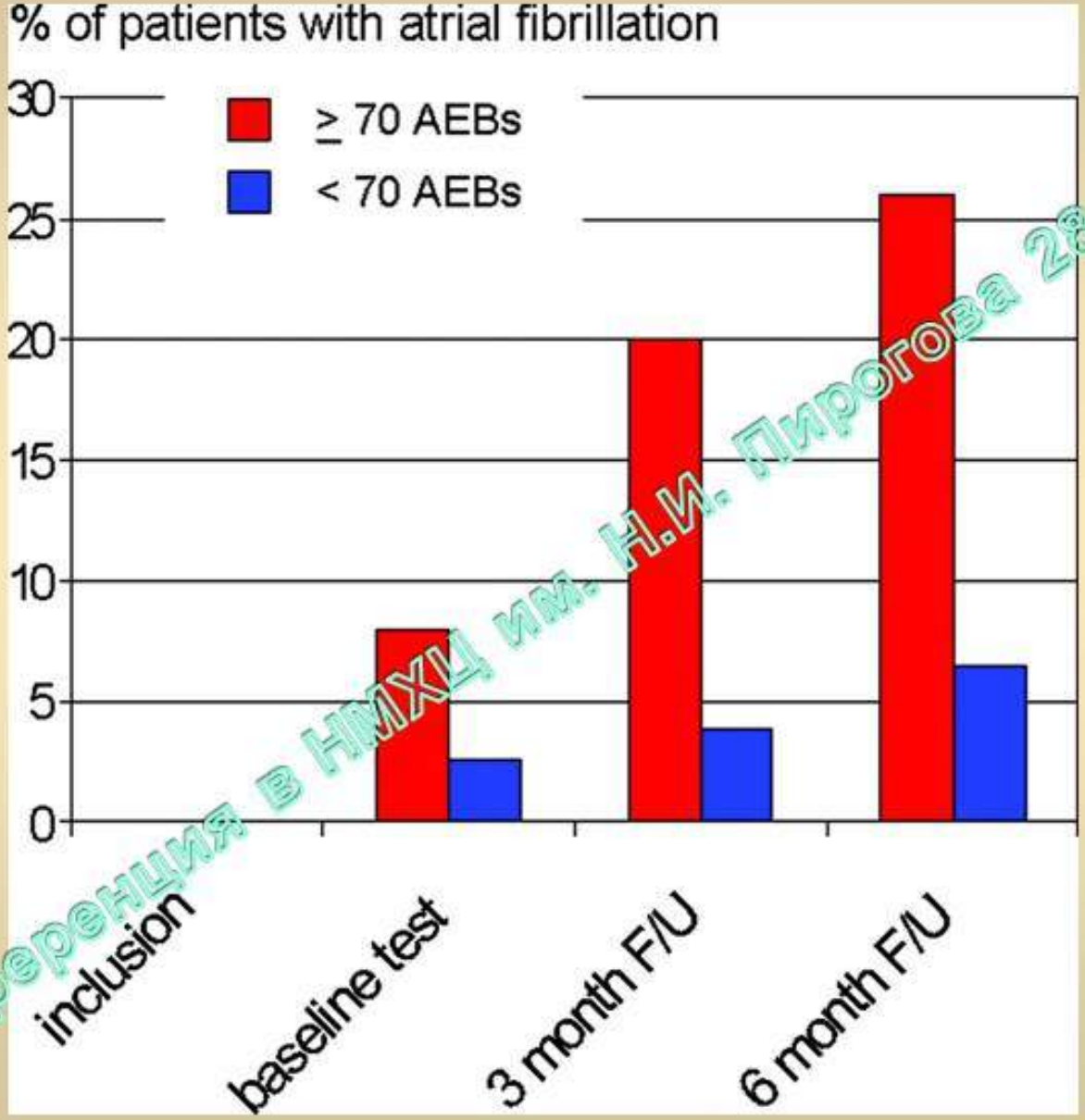


Tsang, T. S. M. et al. J Am Coll Cardiol 2002;40:1636-1644

Atrial extrasystoles – part of „atrial arrhythmic continuum“

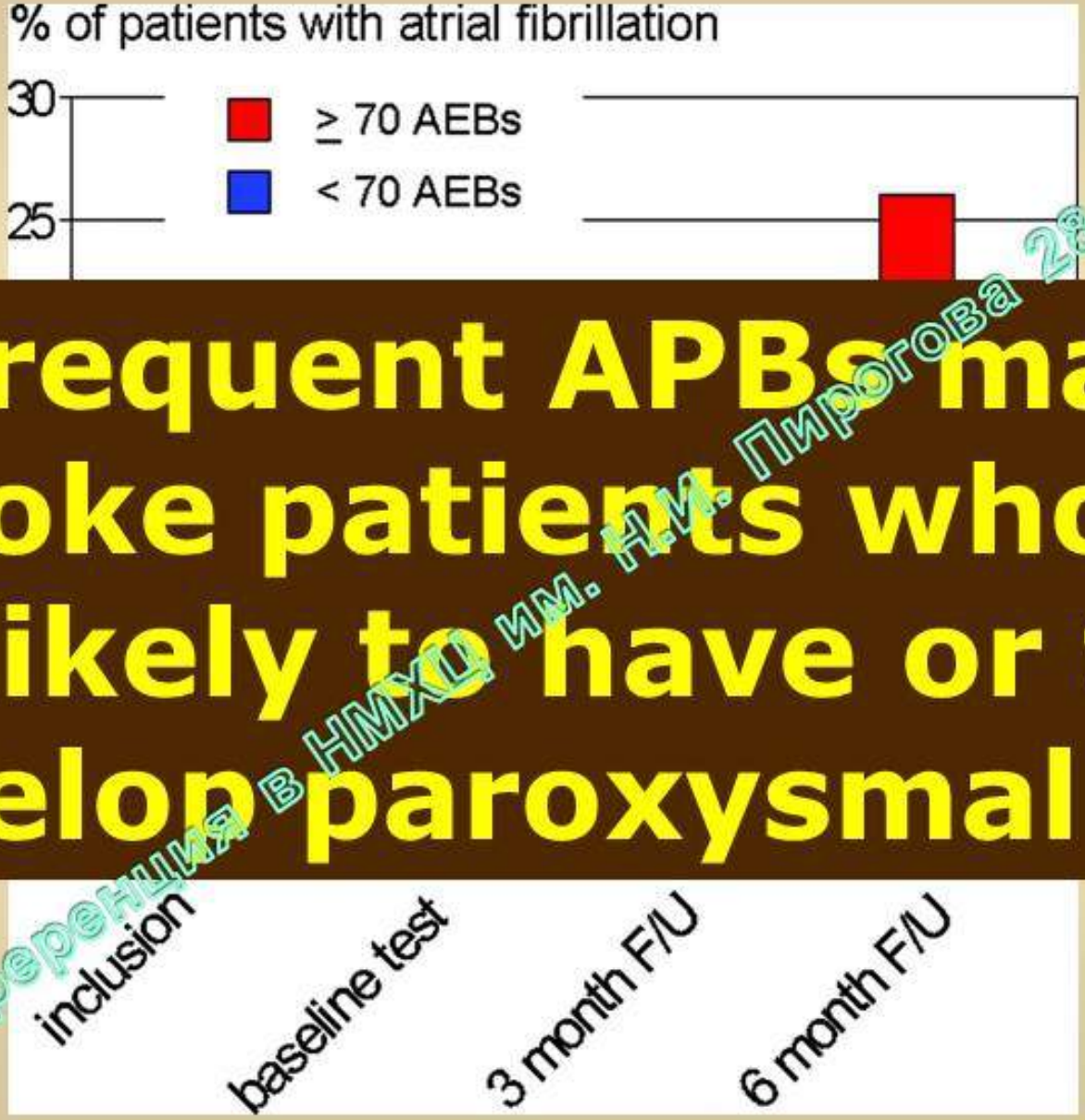
- Enormous expansion of knowledge on atrial ectopy (mechanisms, localization of origin, prognosis)
- **APC *(while per se benign)* can be regarded as harbingers of clinically relevant AFIB**

Cumulative incidence of paroxysmal AFIB (in %) detected at serial follow-up (F/U) with 7-day event recording in stroke patients



Wallmann, D. et al. Stroke 2007;38:2292-2294

Cumulative incidence of paroxysmal AFIB (in %) detected at serial follow-up (F/U) with 7-day event recording in stroke patients



Frequent APBs mark stroke patients who are likely to have or to develop paroxysmal AFIB

Wallmann, D. et al. Stroke 2007;38:2292-2294

APPROACH TO HYPERTENSIVE PATIENT WITH APCs

- APCs in the context of hypertension (w/wo stroke) should trigger
  - **active search for AFIB** and – if detected - its **appropriate management**
  - consideration of safe preventative therapeutic interventions
    - **upstream substrate therapy** (ACEI, ARB, statins,...
    - **thromboembolic prohylaxis** - frequent PAC can be a surrogate marker for PAF in stroke patients without detected AFIB

Hypertension and AFIB

An outline

- What is the role of hypertension in the etiology of AFIB ?
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- **Can we prevent the occurrence and progression of AFIB in hypertension ?**
- How to treat hypertensive patients with AFIB?

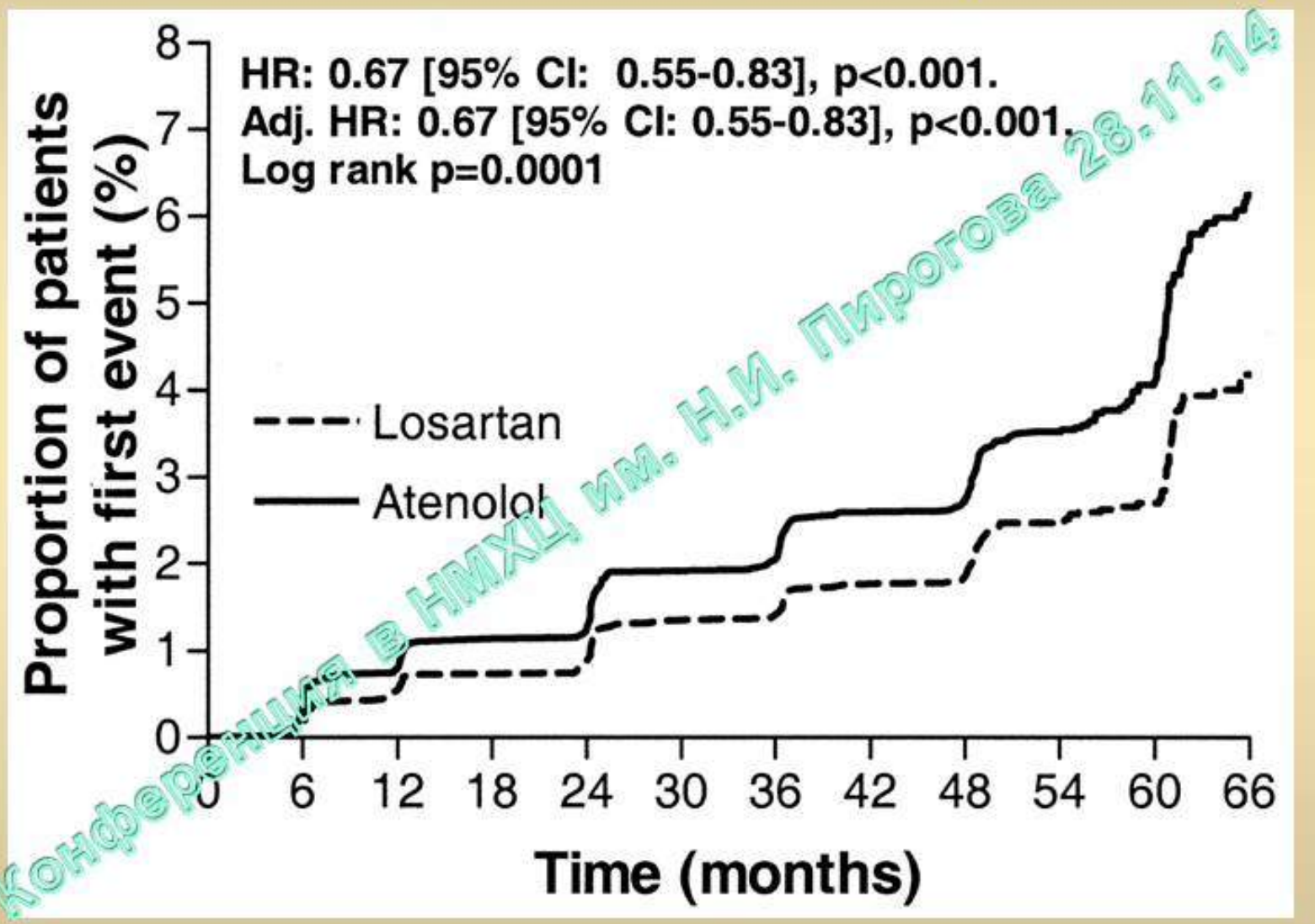
Reversal of atrial remodeling ?

- Growing evidence that LA remodeling is preventable and reversible (!), particularly in the earlier stages
- Any drug capable to control atrial stretch, angiotensin II and inflammation has a potential for anti-arrhythmic efficacy in AFIB
  - **ACEI / ARB** / (aldosterone antagonists ?)
  - Statins
  - PUFA

Possible mechanisms of anti-arrhythmic efficacy of ACEI / ARB

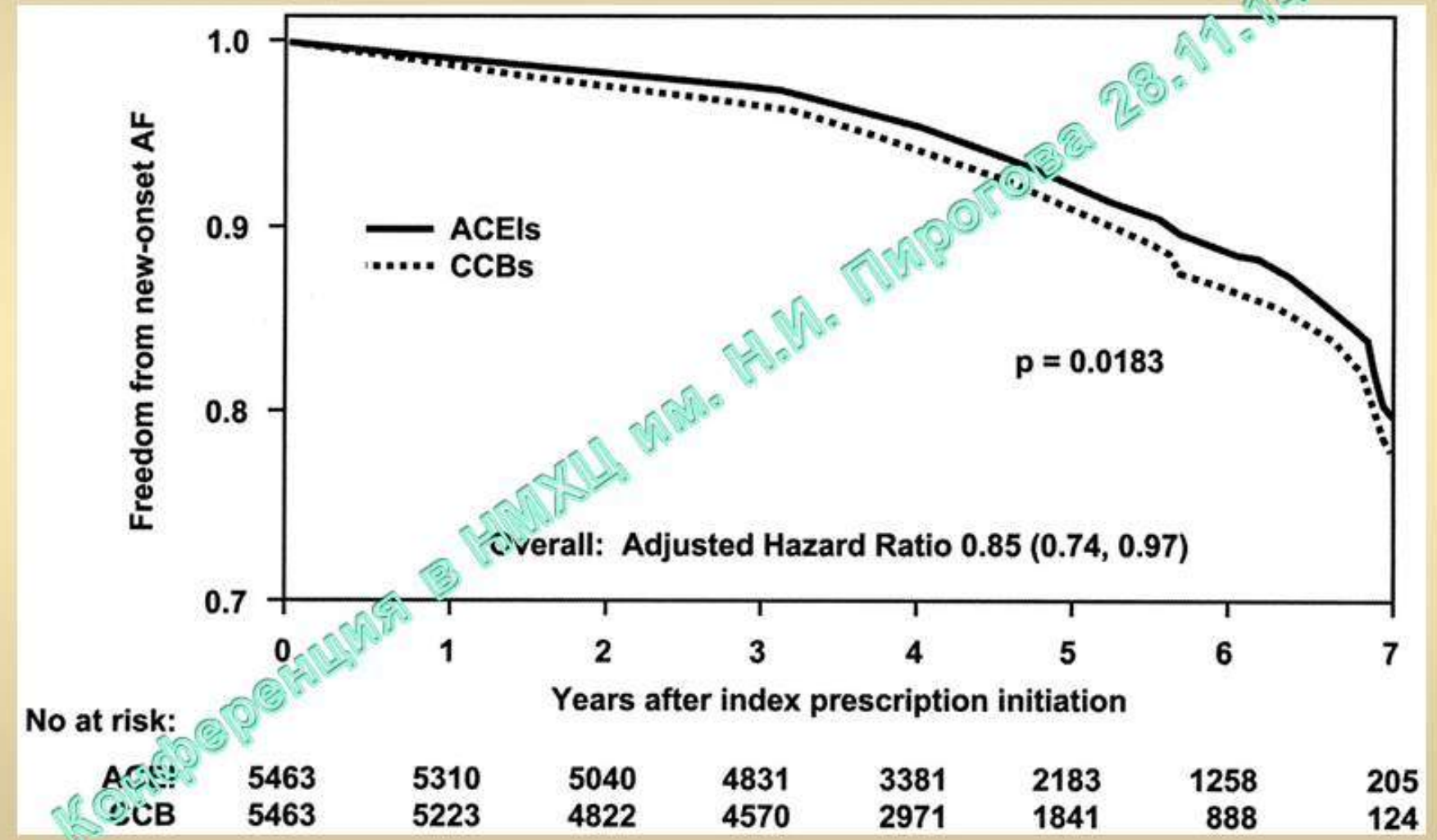
- **improved LV haemodynamics – decrease of wall stress** (stretch activated channels)
- **regression of myocardial fibrosis**
- **modulation of the inflammatory process**
- modification of sympathetic tone
- modulation of refractoriness
- interference with ion currents
- stabilization of electrolyte concentrations

Kaplan-Meier curves of occurrence of new-onset AF in the LIFE rct (n=9193)



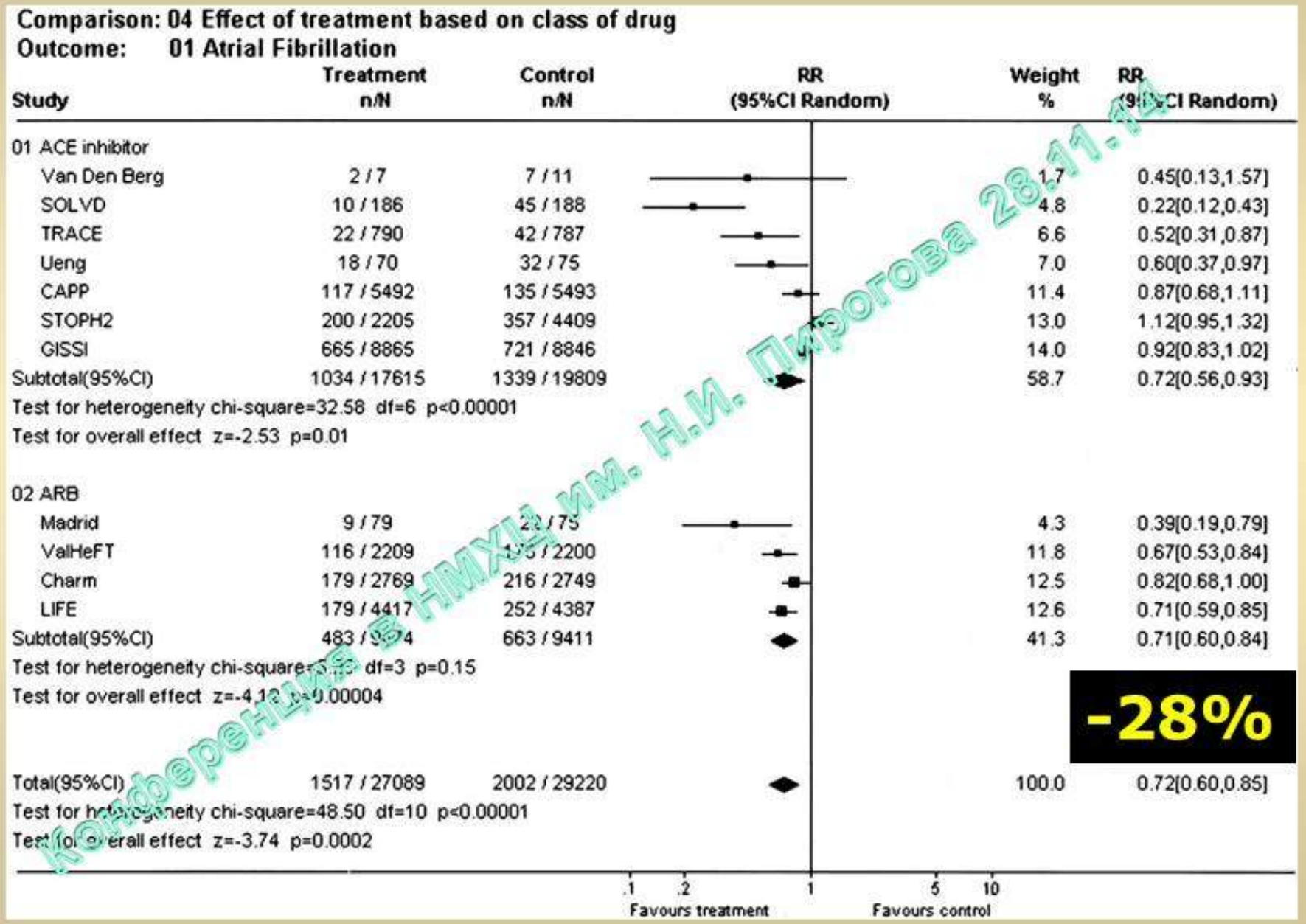
Wachtell, K. et al. J Am Coll Cardiol 2005;45:712-719

Kaplan-Meier curves for the time to first AF occurrence – ACEI vs. CCB



L'Allier, P. L. et al. J Am Coll Cardiol 2004;44:159-164

Reduction of AF occurrence by ACEI / ARB



Healey, J. S. et al. J Am Coll Cardiol 2005;45:1832-1839

ACEI/ARBs combined with AAD on the prevention of AF recurrence

(meta-analysis 13184 pts)

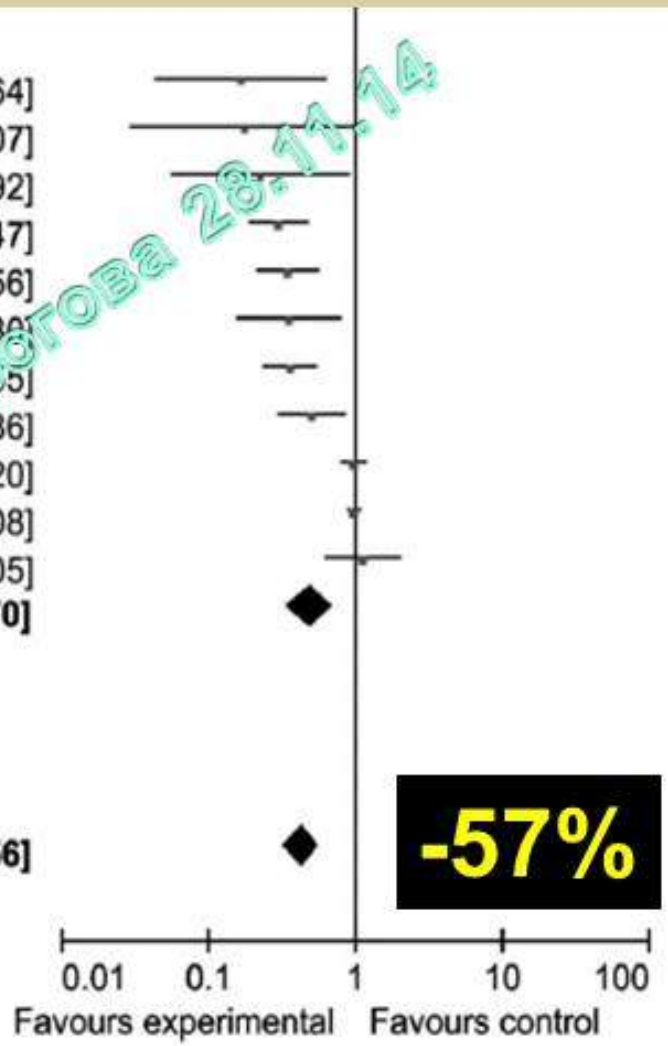
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4.1.1 combine with AAD						
Xie [38]	3	27	6	14	2.2%	0.17 [0.03, 0.8]
Fogari [42]	13	111	39	111	5.1%	0.24 [0.1 0.49]
Madrid [40]	9	79	22	75	4.4%	0.31 [0.13, 0.73]
Ji [39]	13	48	25	47	4.4%	0.33 [0.14, 0.77]
Ding [37]	10	32	18	31	3.7%	0.33 [0.12, 0.92]
Cao [36]	9	46	19	45	4.1%	0.33 [0.13, 0.85]
Yin [23]	25	118	24	5	5.2%	0.39 [0.20, 0.78]
Ueng [35]	18	70	32	75	5.1%	0.47 [0.23, 0.94]
Madrid [41]	19	60	1	30	4.2%	0.53 [0.22, 1.30]
Kawamura [43]	15	52	42	101	5.0%	0.57 [0.28, 1.17]
Subtotal (95% CI)				**588**	**43.4%**	**0.37 [0.29, 0.48]**
Total events	13		241			
Heterogeneity: Tau² = 0.0 Chi² = 5.07, df = 9 (P = 0.83); I² = 0%						
Test for overall effe Z = 7.41 (P < 0.00001)						

-63%

Han M et al., J Cardiovasc Pharamcol 2013

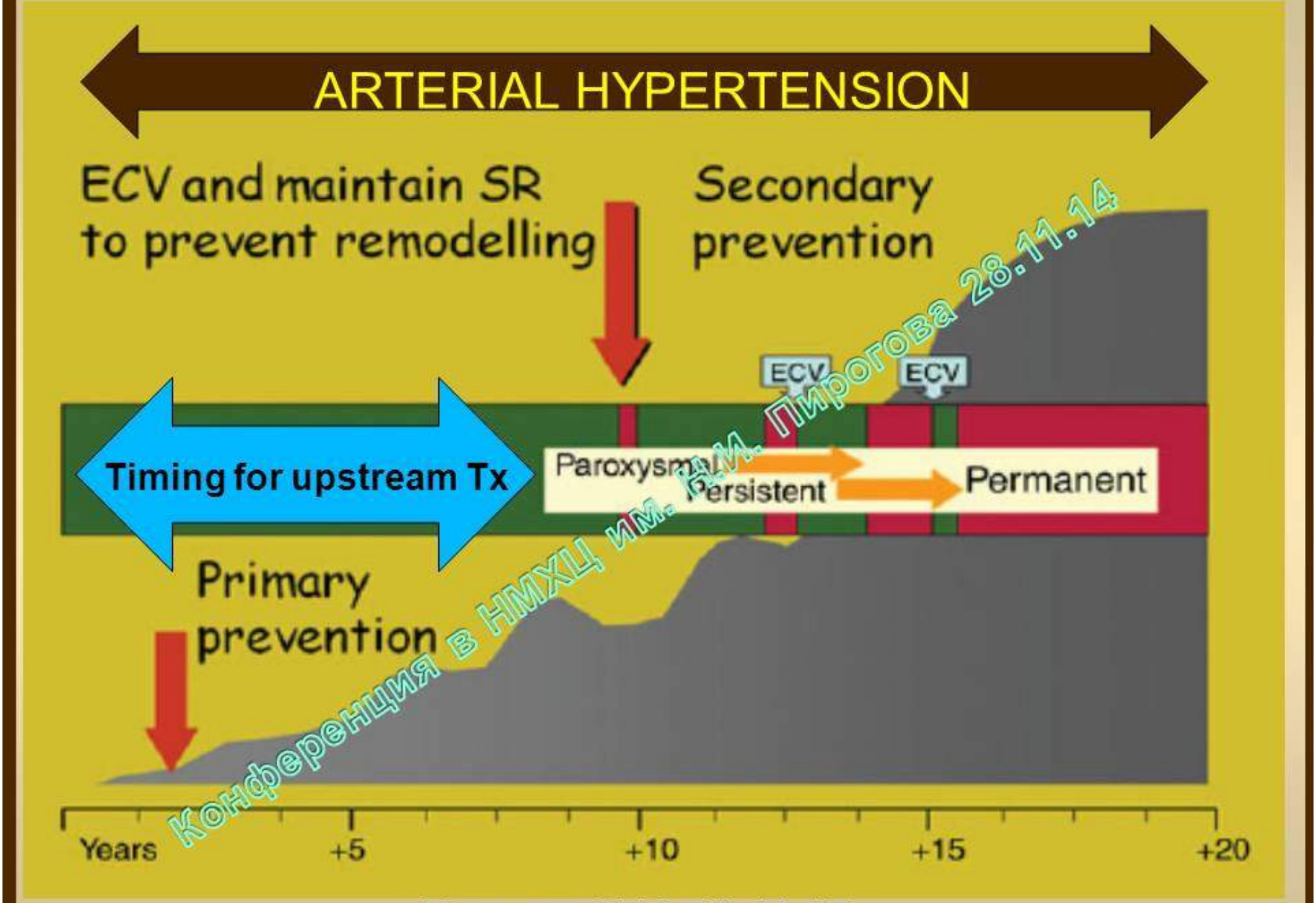
ACEI/ARBs without AAD on the prevention of AF recurrence

4.1.2 without AAD						
Wang [27]	3	42	13	41	2.7%	0.17 [0.04, 0.64]
Berg [34]	2	15	7	15	1.8%	0.18 [0.03, 1.07]
Belluzzi [33]	3	31	10	31	2.6%	0.23 [0.05, 0.92]
Fogari [24]	50	262	57	129	6.2%	0.30 [0.19, 0.47]
Fogari [22]	42	246	46	123	6.1%	0.34 [0.21, 0.56]
Galzerano [25]	10	77	23	77	4.5%	0.35 [0.15, 0.80]
Fogari [26]	52	188	98	190	6.4%	0.36 [0.23, 0.55]
Fogari [21]	28	148	47	148	5.9%	0.50 [0.29, 0.86]
GISSI-AF [20]	371	722	375	720	7.3%	0.87 [0.79, 1.20]
ACTIVE I [19]	3403	4304	3397	4273	7.5%	0.97 [0.88, 1.08]
Tveit [18]	48	86	45	85	5.6%	1.12 [0.61, 2.05]
Subtotal (95% CI)		**6121**		**5832**	**56.1%**	**0.49 [0.34, 0.70]**
Total events	4012		4118			
Heterogeneity: Tau² = 0.24; Chi² = 77.06, df = 10 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 3.96 (P < 0.0001)						
Total (95% CI)		**6761**		**6420**	**100.0%**	**0.43 [0.32, 0.56]**
Total events	4146		4359			
Heterogeneity: Tau² = 0.27; Chi² = 115.64, df = 20 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 8.00 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.48, df = 1 (P = 0.22), I² = 32.4%						



-57%

Han M et al., J Cardiovasc Pharamcol 2013



Europace 2008, 10: 21-27

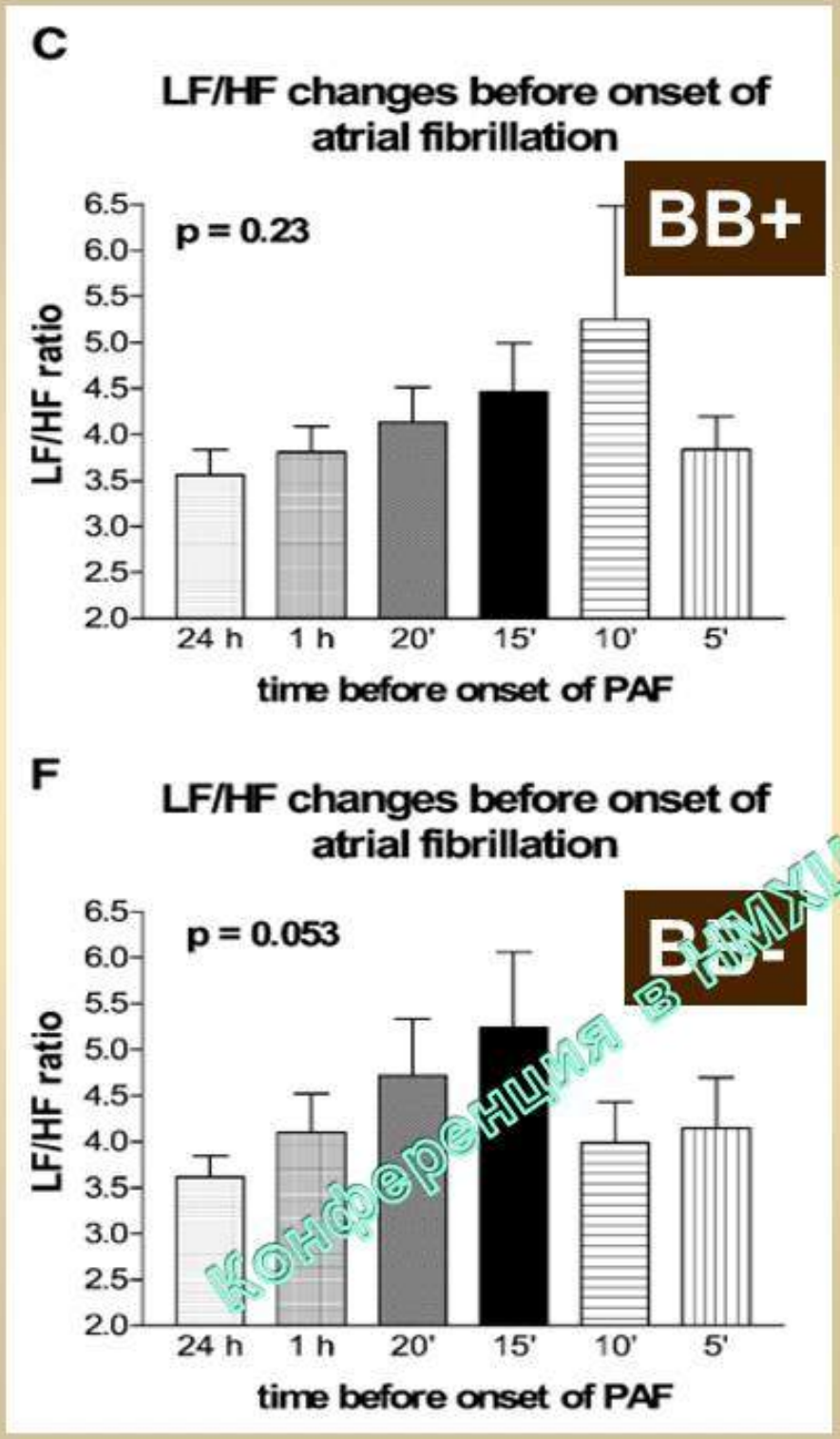
What can we expect from ACEI/ARB therapy in hypertensive AF pts beyond BP control ?

- Reduction of the incidence of new-onset AF
- Prevention of AF relapse after electrical cardioversion
- Decrease AF burden
- Prevention of AF progression to permanent form
- Reduction of „hard“ endpoints (mortality, major CV events) in pts with SHD more pronounced in those with AF

Hypertension and AFIB

An outline

- What is the role of hypertension in the etiology of AFIB ?
- What are pathophysiological mechanisms promoting AFIB in hypertension ?
- Are there any risk factors for AFIB in hypertensive patients ? How to detect AFIB early in order to act early?
- Can we prevent the occurrence and progression of AFIB in hypertension ?
- **How to treat hypertensive patients with AFIB?** (specifically)



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association.

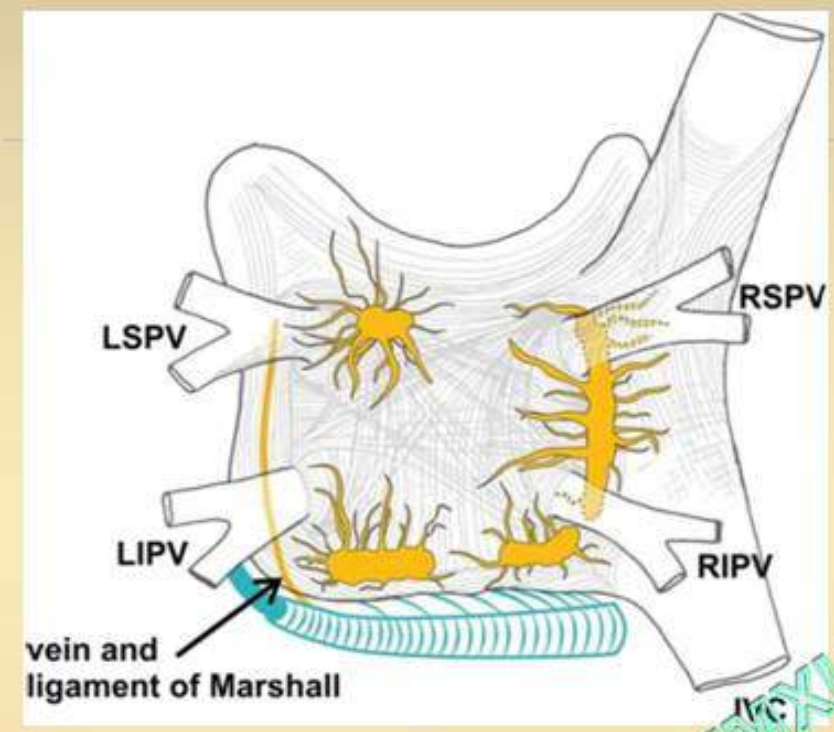
Autonomic Tone Variations Before the Onset of Paroxysmal Atrial Fibrillation

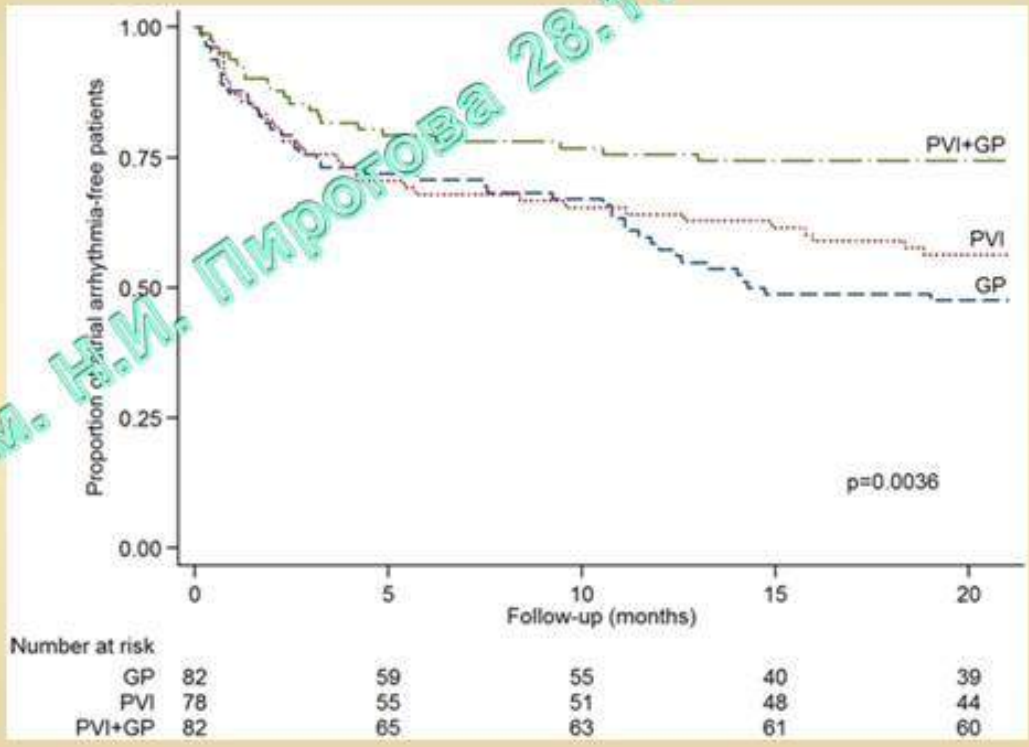
Marco Bettoni and Marc Zimmermann

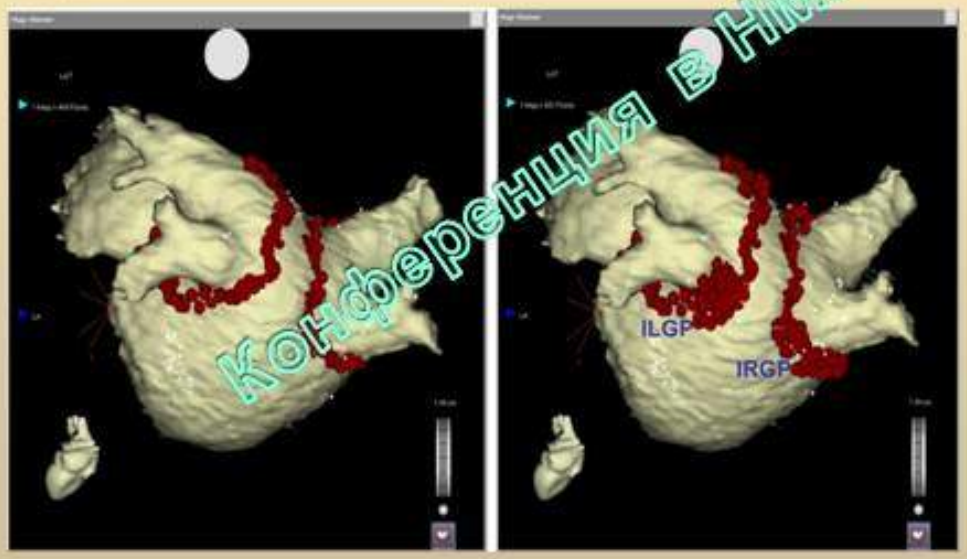
Circulation. 2002;105:2753-2759; originally published online May 13, 2002;

Dynamic changes in autonomic innervation (expressed as LF/HF ratio in HRV) before onset of PAF in patients with and w/o betablockers

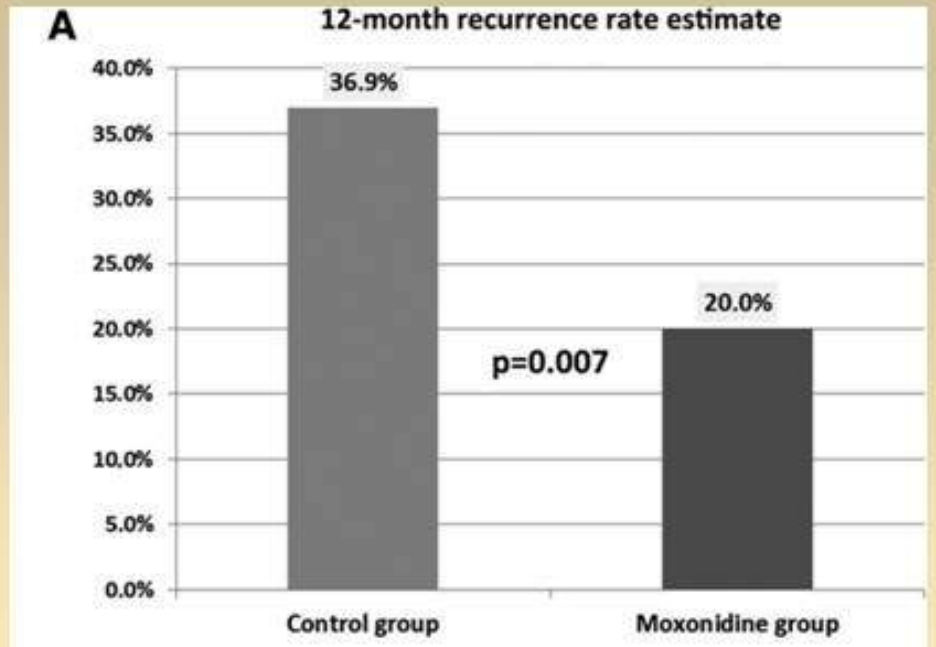
Autonomic Denervation Added to Pulmonary Vein Isolation for Paroxysmal AFIB Improved Maintenance of SR

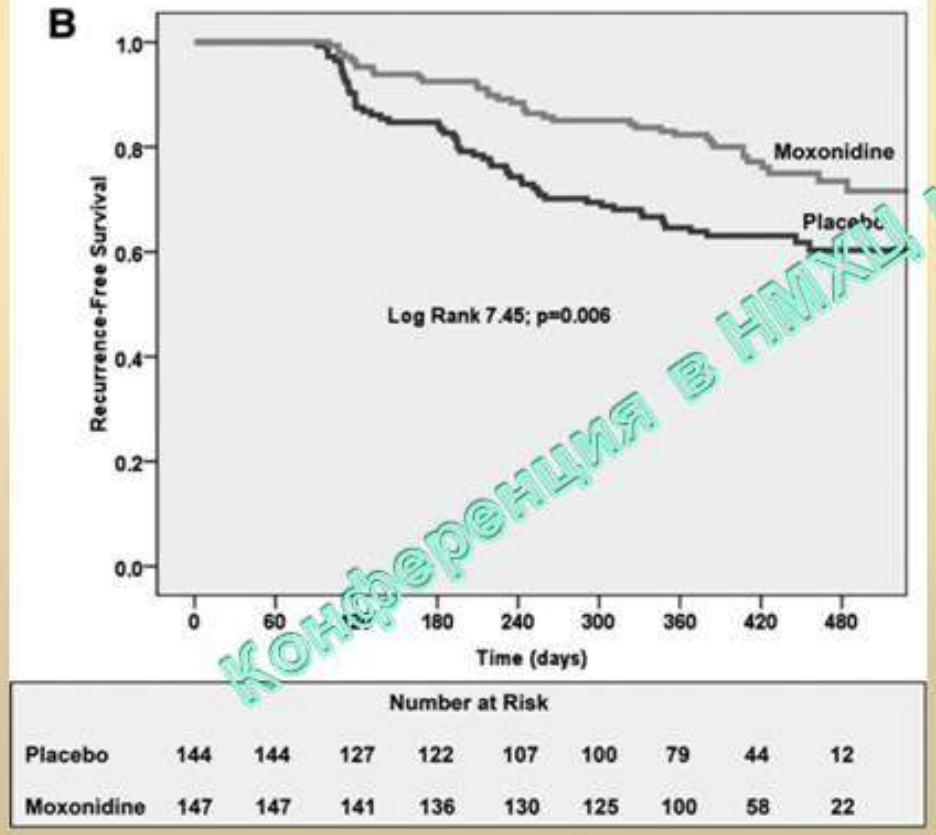






J Am Coll Cardiol. 2013;62(24):2318





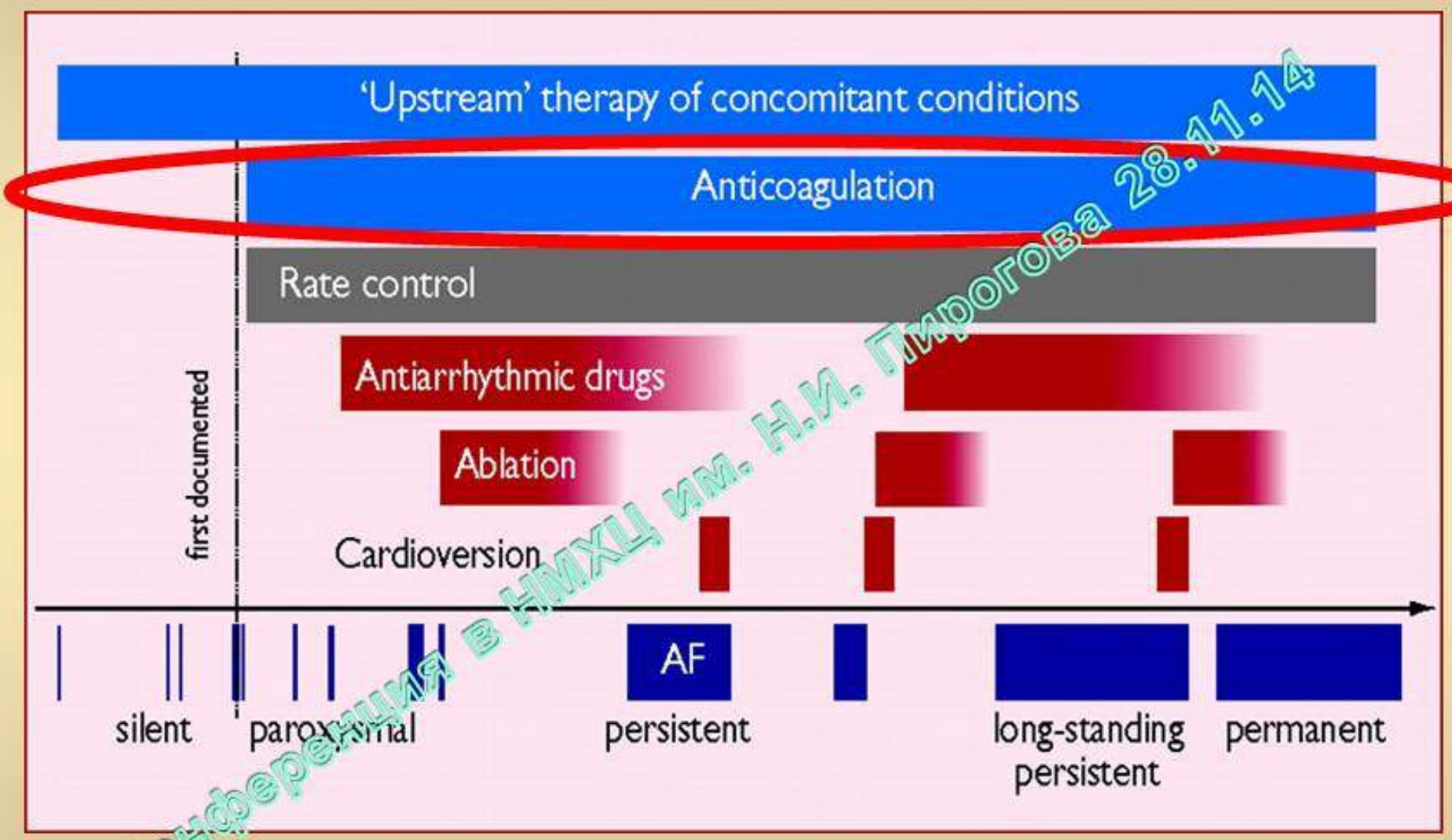
- N=291 hypertensive pts with paroxysmal AFIB
- on standard AH therapy
- randomized to moxonidine
- No difference in BP after randomization

Annualized AFIB recurrence rate estimates in the moxonidine vs. placebo groups

Message: Central symphathetic inhibition is effective in AFIB supression (-75%) independently from BP

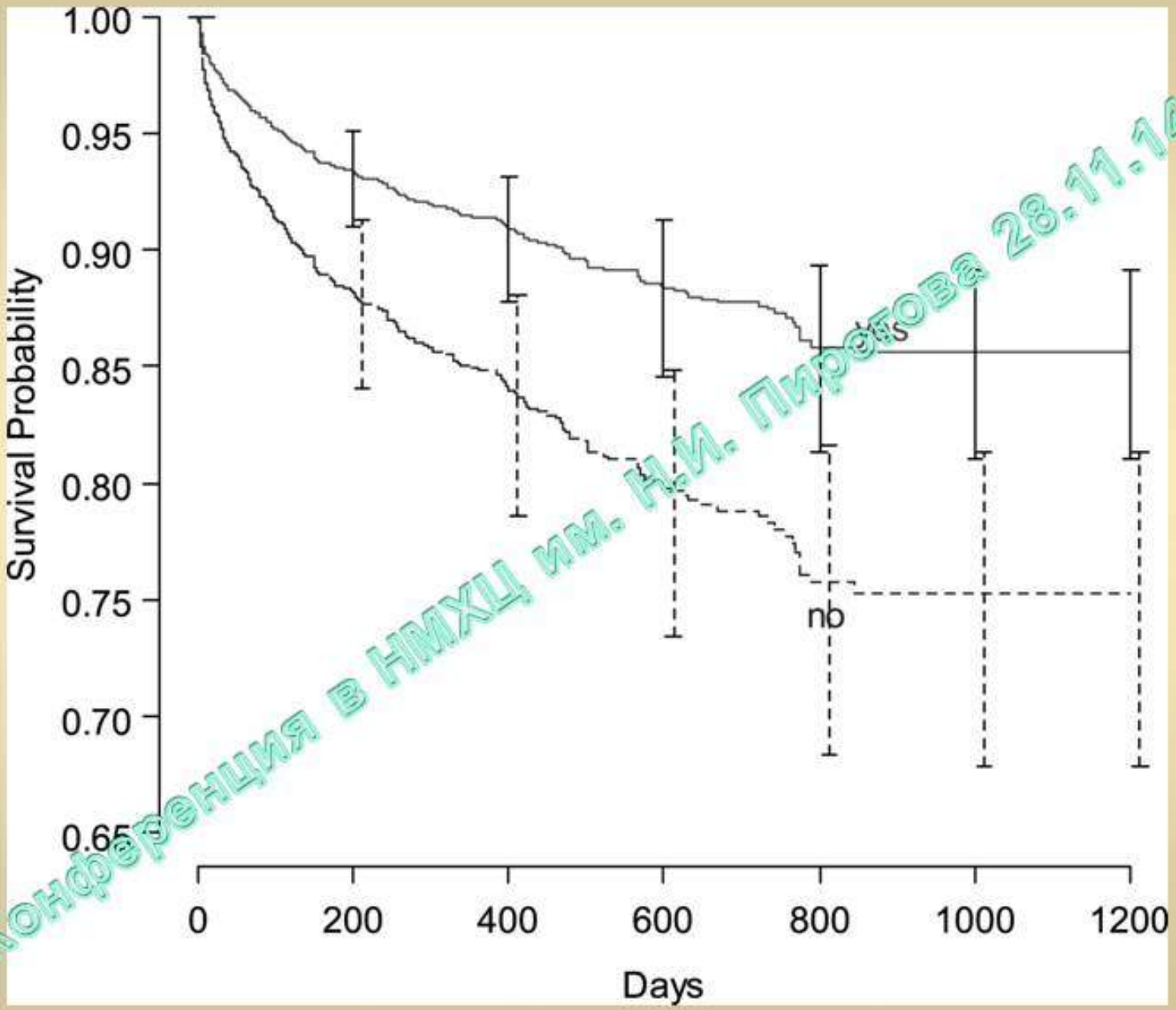
Giannopoulos G et al. Circulation. 2014;130:1346-1352

‘Natural’ time course and Tx approaches in AF



Camm et al. Eur Heart J 2010;31:2369-2429

Survival curves stratified by anticoagulation treatment



Andersen, K. K. et al. Stroke 2007;38:259-263

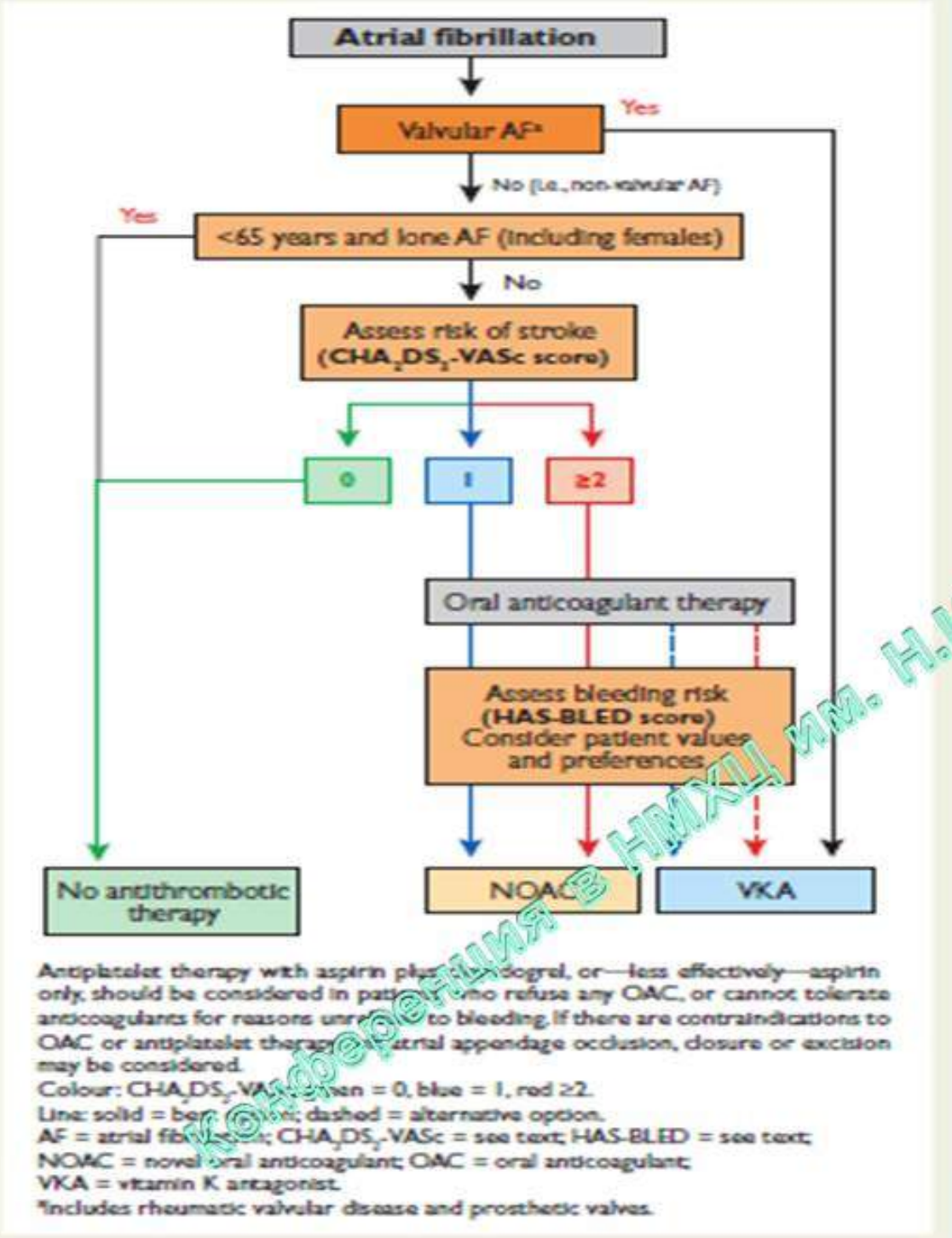
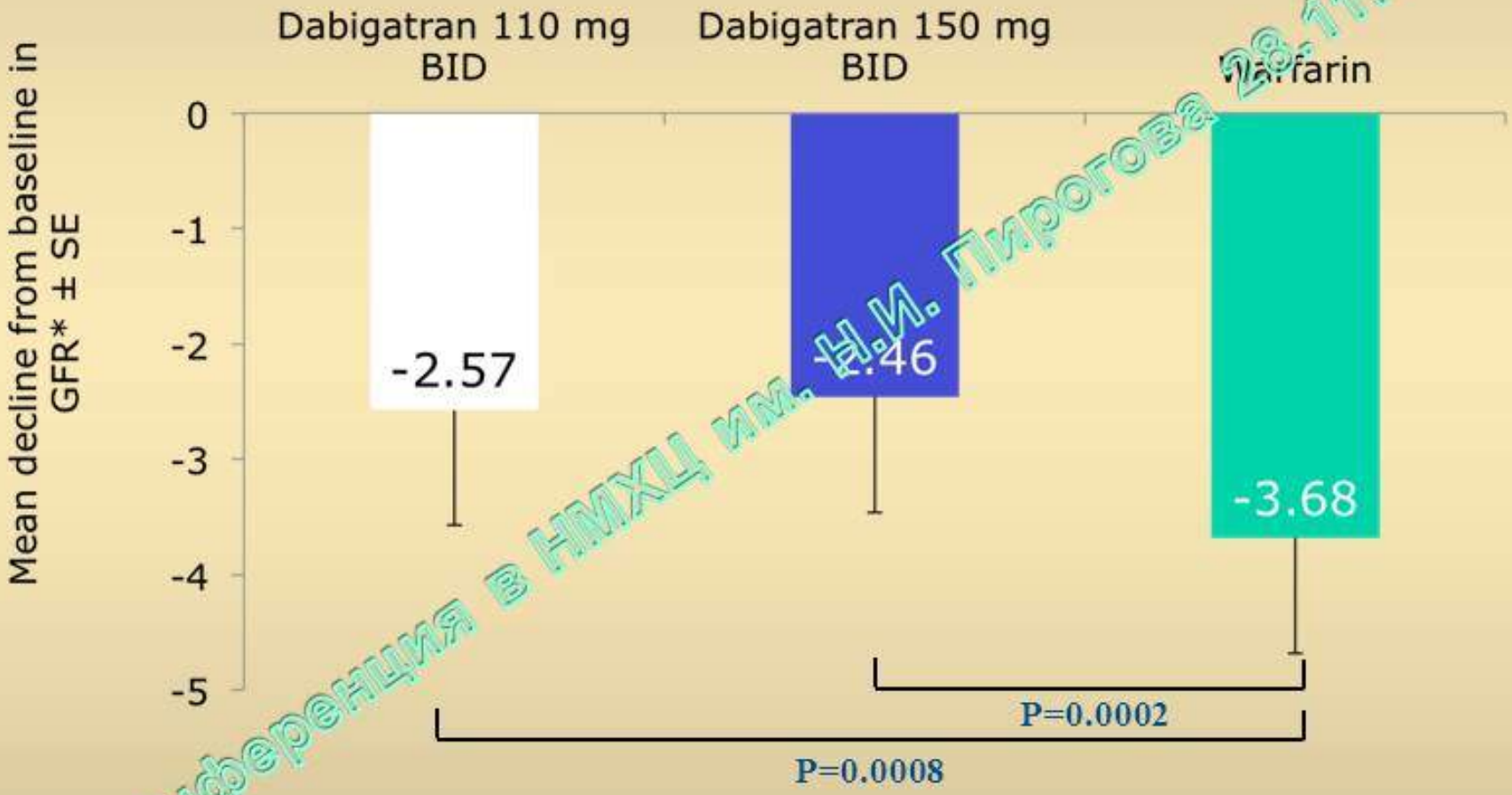


Figure 1 Choice of anticoagulant.

Guidelines for the management of atrial fibrillation **Update 2012**

EUROPEAN SOCIETY OF CARDIOLOGY®

Decline in GFR at 30 months was significantly reduced with both doses of dabigatran vs VKA



*According to CKD-EPI equation

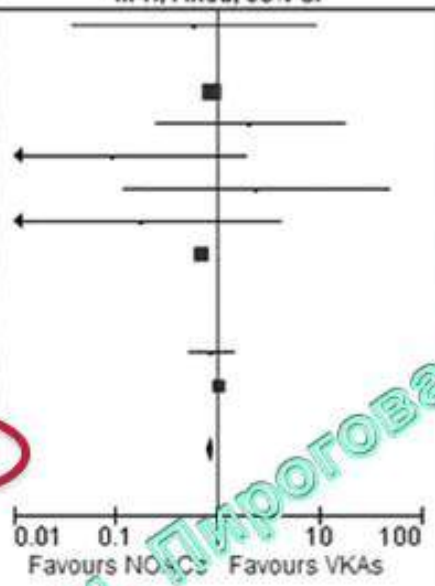
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; HR = hazard ratio; SE = standard error

Böhm M et al. Presented at ESC 2014

A Major bleeding

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	1	104	1	62	0.1%	0.60 [0.04, 9.36]
PETRO	0	166	0	70		Not estimable
RE-LY	741	12091	421	6022	38.8%	0.88 [0.78, 0.98]
WEITZ	6	713	1	250	0.1%	2.10 [0.25, 17.39]
CHUNG	0	159	2	75	0.2%	0.10 [0.00, 1.95]
YAMASHITA	2	260	0	125	0.0%	2.41 [0.12, 49.90]
ARISTOTLE-J	0	143	1	75	0.1%	0.18 [0.01, 4.27]
ARISTOTLE	327	9088	462	9052	31.9%	0.70 [0.61, 0.81]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	26	639	30	639	2.1%	0.87 [0.52, 1.45]
ROCKET-AF	395	7111	386	7125	26.6%	1.03 [0.89, 1.18]
Total (95% CI)		30599		23548	100.0%	0.86 [0.80, 0.93]
Total events	1498		1304			

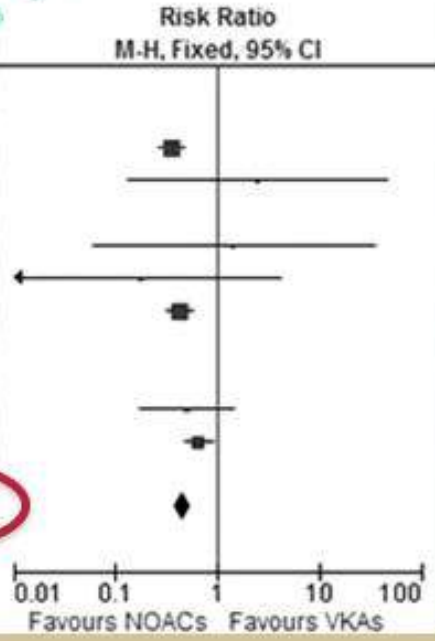
Heterogeneity: Chi² = 18.58, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 4.03 (P < 0.0001)



B Intracranial bleeding

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	0	62		Not estimable
PETRO	0	166	0	70		Not estimable
RE-LY	64	12091	90	6022	35.4%	0.35 [0.26, 0.49]
WEITZ	3	713	0	250	1.2%	2.46 [0.13, 47.47]
CHUNG	0	159	0	75		Not estimable
YAMASHITA	1	260	0	125	0.2%	1.45 [0.06, 35.30]
ARISTOTLE-J	0	143	0	75	0.6%	0.18 [0.01, 4.27]
ARISTOTLE	52	9088	122	9052	36.0%	0.42 [0.31, 0.59]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	10	639	10	639	2.9%	0.50 [0.17, 1.45]
ROCKET-AF	65	7111	84	7125	24.7%	0.66 [0.47, 0.92]
Total (95% CI)		30599		23548	100.0%	0.46 [0.39, 0.56]
Total events	180		307			

Heterogeneity: Chi² = 9.15, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 8.22 (P < 0.00001)

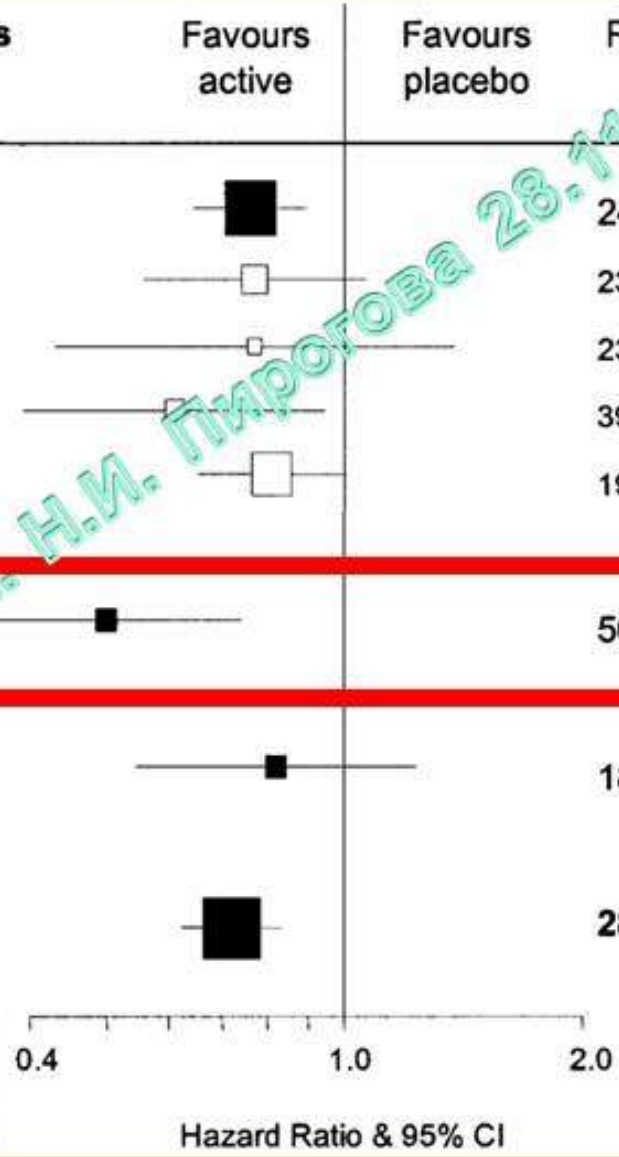


Major (A) and intracranial (B) bleeding on OAC

Dentali F et al. Circulation 2012;126:2381-2391

PROGRESS – risk of stroke with perindopril based therapy

Outcome event	Number of events/ total participants active	placebo	Risk Reduction (95%CI)
All Ischemic	246/3051	319/3054	24% (10 to 35%)
Lacunar	64/3051	83/3054	23% (-7 to 44%)
Cardio-embolic	20/ 3051	26/3054	23% (-38 to 57%)
Large artery	32/ 3051	52/3054	39% (5 to 61%)
Unknown ischemic	150/3051	184/3054	19% (0 to 35%)
Hemorrhagic	37/3051	74/3054	50% (26 to 67%)
Stroke of Unknown Type	42/3051	51/3054	18% (-24 to 45%)
OVERALL	**307/3051**	**420/3054**	**28% (17 to 38%)**



Decrease in BPs 9 mm Hg !

Chapman N et al., Stroke 2004

PROGRESS – risk of stroke with perindopril based therapy

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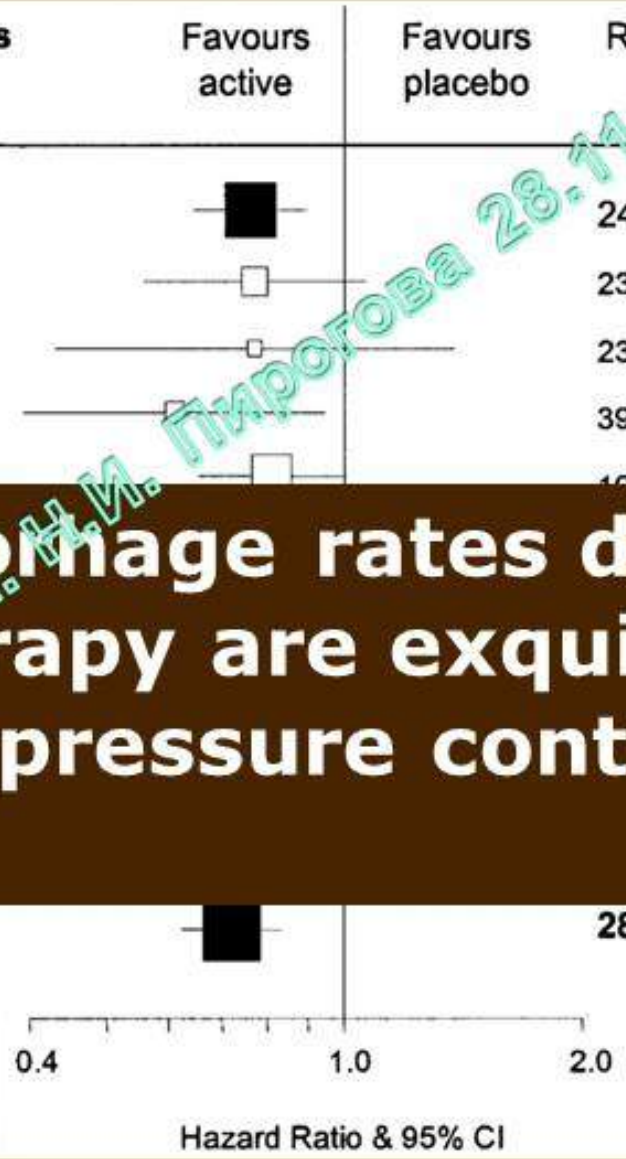

Intracranial haemorrhage rates during antithrombotic therapy are exquisitely sensitive to blood pressure control !!

Decrease in BPs 9 mm Hg !

Chapman N et al., Stroke 2004

Perspectives in hypertension and AFIB

- There is a tight association between BP, incident AFIB and subsequent CV events
- Future guidelines should assign a more important role to AFIB for CV risk stratification in hypertension
- **Tight BP control is a *conditio sine qua non* for the control of AFIB epidemics and of its impact (stroke)**

Management of AF in AH in 2014

Message for the clinician (1)

- Prevention is the key approach to manage AF epidemics in the near future
- Population-wide, **arterial hypertension** plays the crucial pathogenetic role for AF
  - Search for hypertension in every AF patients
  - Treat it vigorously to target levels
  - Block the RAAS always when possible - focus on ACEI / ARB - “upstream” effects
- **Hypertensive heart – AF is frequent cause of HF with preserved LVEF**

Management of AF in AH in 2014

Message for the clinician (2)

- **Assess and manage thromboembolic risk**
  - Most hypertensive pts are indicated for anticoagulation
  - use NOACs if possible + treat hypertension to lower targets (130/80 mm Hg) in order to protect against intracranial hemorrhage !

Гипертензия и ФП-

это пара, держащаяся за руки-

... в хорошем, плохом, до тех пор, пока ее смерть не разделит…