Pharmacological therapy of AF in Pts with impaired LV function

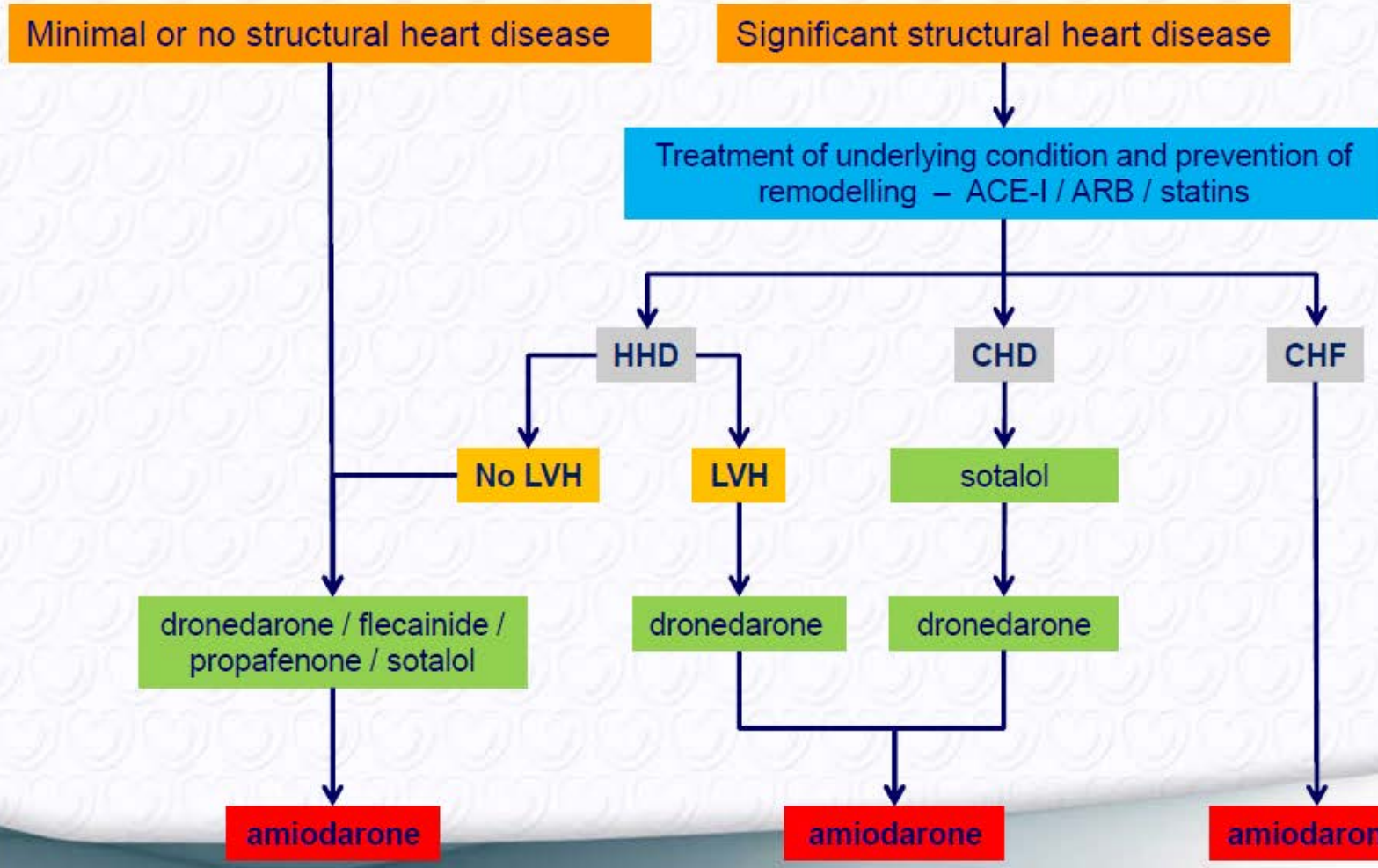
- Robustness of guidelines (?)
- The «Dronedarone saga»
- Ventricular dysfunction vs Heart Failure
- Sistolic vs diastolic HF
- Residual chances of upstream therapy (?)
- Optimal heart rate values

New /Modified Recommendations

Topic	A	B	C	I	IIa	IIb	III
Anticoagulation risk stratification	6	7		6	7		
Anticoagulation	2	5	1	3	4		1
Left atrial appendage occlusion		1	1			2	
Pharmacological cardioversion	1	2		1	2		
Oral antiarrhythmic therapy	1	2		1		1	1
Left atrial catheter ablation	2	3		1	4		
Total n (%)	12 (35%)	20 (59%)	2 (9%)	12 (35%)	17 (50%)	3 (9%)	2 (9%)

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

Antiarrhythmic drug management of *non-permanent* AF



ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CHD = coronary heart disease; CHF = congestive heart failure; HHD = hypertensive heart disease; LVH = left ventricular hypertrophy.

www.escardio.org/guidelines

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

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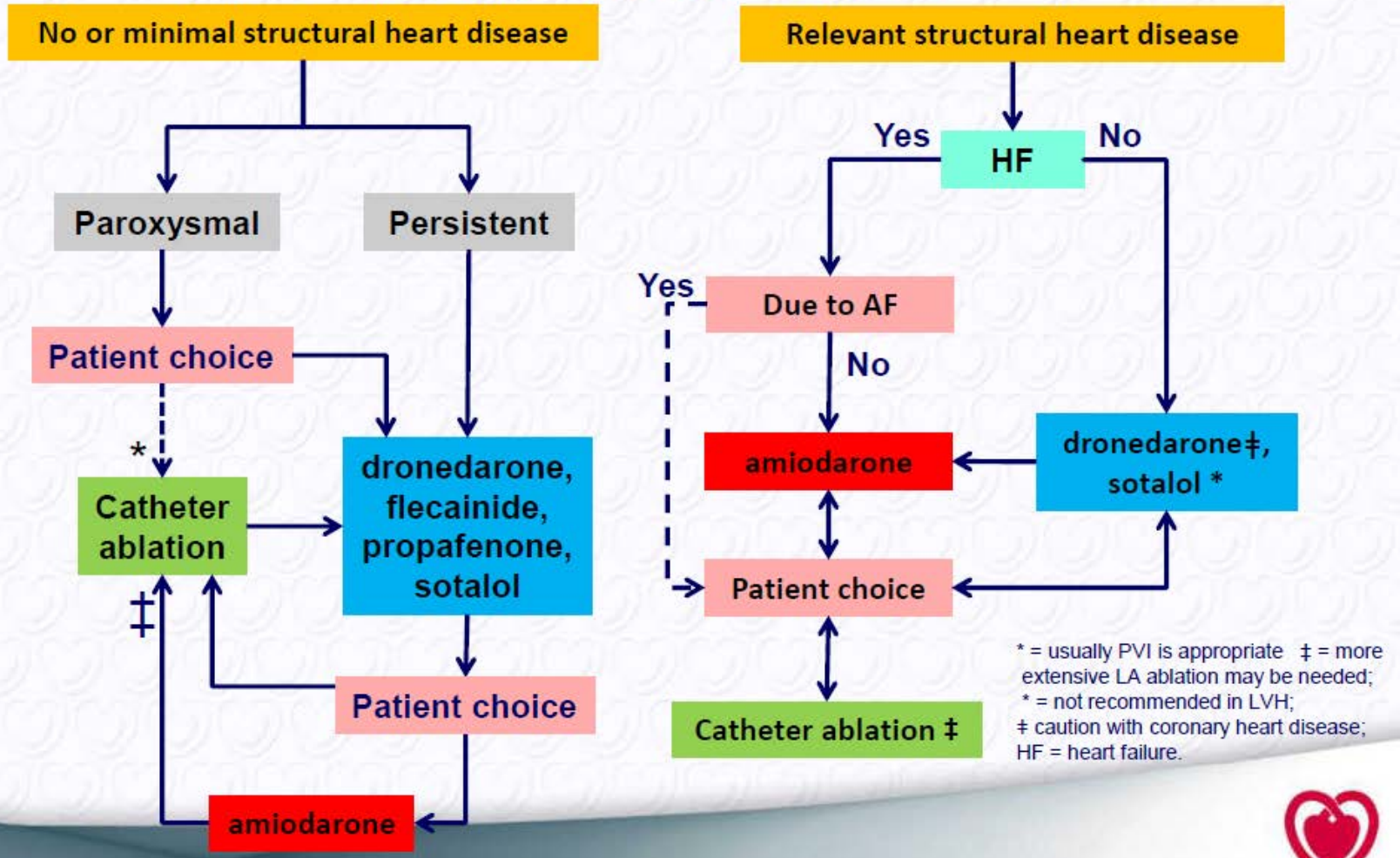
Antiarrhythmic drugs and/or left atrial ablation for rhythm control in AF



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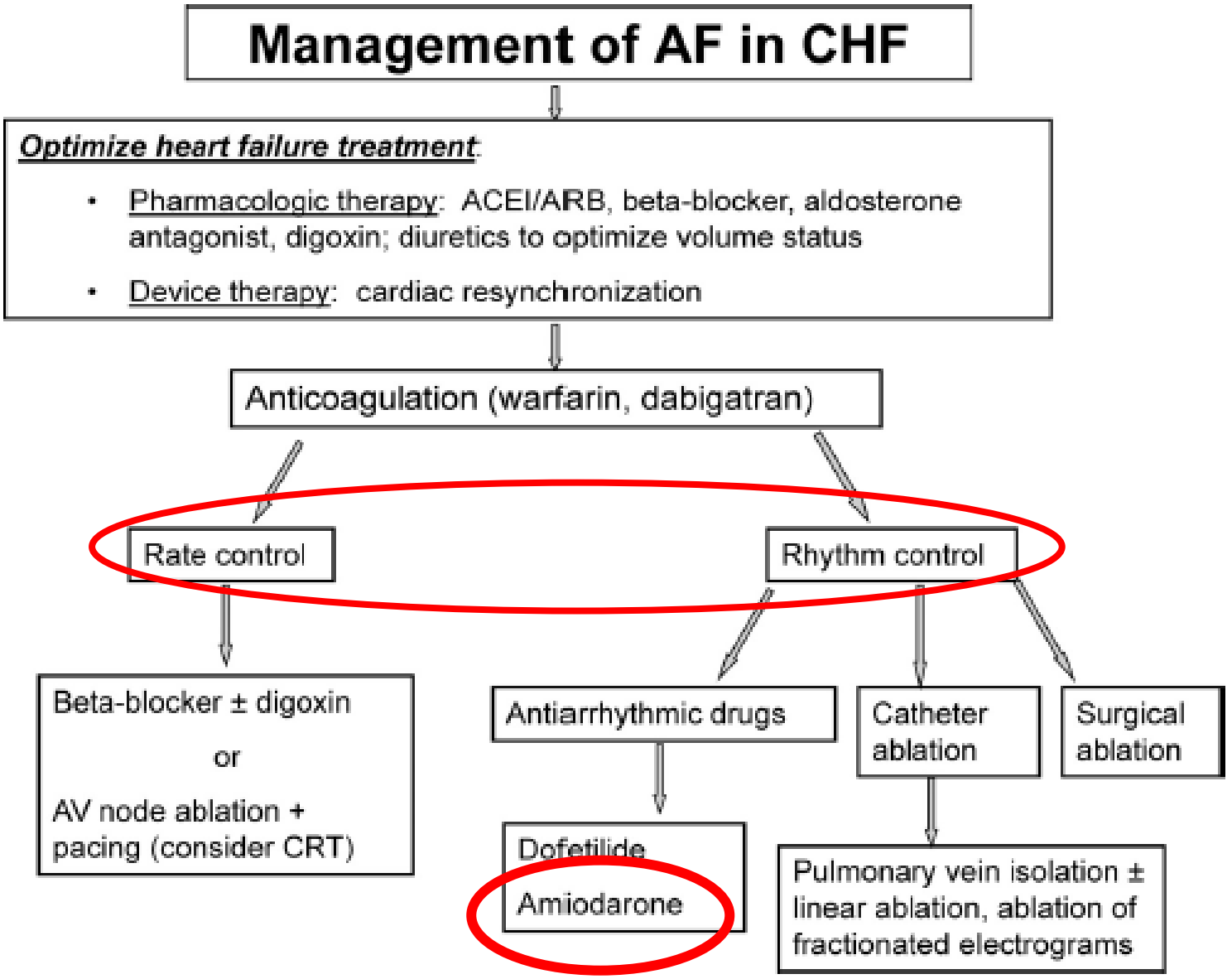

Darby AE et al, Circulation 2012;125:945-57

Suggested doses and main caveats for commonly used antiarrhythmic drugs

Drug	Dose	Main contraindications and precautions	ECG monitoring	AV nodal slowing
Disopyramide	100-250 mg t.i.d.	Contraindicated in ~~cystolic~~ heart failure, SND, and AVB II and III without PM. Caution when using concomitant medication with QT-prolonging drugs.	QT interval	None
Flecainide	100-200 mg b.i.d.	Contraindicated if creatinine clearance < 50 mg/mL, in coronary artery disease, ~~reduced LV ejection fraction,~~ heart failure.	QRS duration increase > 25% above baseline	None
Flecanide XL	200 mg o.d.	Caution in the presence of conduction system disease.		
Propafenone	150-300 mg t.i.d.	Contraindicated in coronary artery disease, heart failure.	QRS duration increase > 25% above baseline	Slight
Propafenone SR	225-425 mg b.i.d.	Caution in the presence of conduction system disease and renal impairment.		

Changes from 2010 Guidelines

AF = atrial fibrillation; AV = atrioventricular; bpm = beats per minute; CYP = cytochrome P; ECG = electrocardiogram; LV = left ventricular; NYHA = New York Heart Association.

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Suggested doses and main caveats for commonly used antiarrhythmic drugs

Drug	Dose	Main contraindications and precautions	ECG features prompting lower dose or discontinuation	AV nodal slowing
d,l-Sotalol	80-160 mg b.i.d..	Contraindicated in the presence of significant LV hypertrophy, ~~systolic~~ heart failure, pre-existing QT prolongation, hypokalaemia, significant renal impairment ~~Creatinine clearance < 50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose.~~	QT interval > 500 ms	Similar to high-dose β-blockers
Amiodarone	600 mg o.d. for 4 weeks, 400 mg o.d. for 4 weeks then 200 mg o.d.	Caution when using concomitant medication with QT-prolonging drugs, heart failure. Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced. Creatinine, liver enzymes, thyroid hormones, & lung function should be monitored	QT interval >500 ms	10–12 bpm in AF

Changes from 2010 Guidelines

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EUROPEAN SOCIETY OF CARDIOLOGY®

Suggested doses and main caveats for commonly used antiarrhythmic drugs

Drug	Dose	Main contraindications and precautions	ECG features prompting lowerdose or discontinuation	AV nodal slowing
Dronedarone	400 mg b.i.d.	Contraindicated in NYHA class III–IV or unstable heart failure, during concomitant medication with QT-prolonging drugs, powerful CYP 3A4 inhibitors, if creatinine clearance < 30 mg/mL. Not advised in other forms of heart failure, unless no appropriate alternative. Cautious use in CHD. Regular monitoring of liver function. Dose of digitoxin/digoxin should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect reduced renal function.	QT interval > 500 ms	10–12 bpm in AF

Changes from 2010 Guidelines

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European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

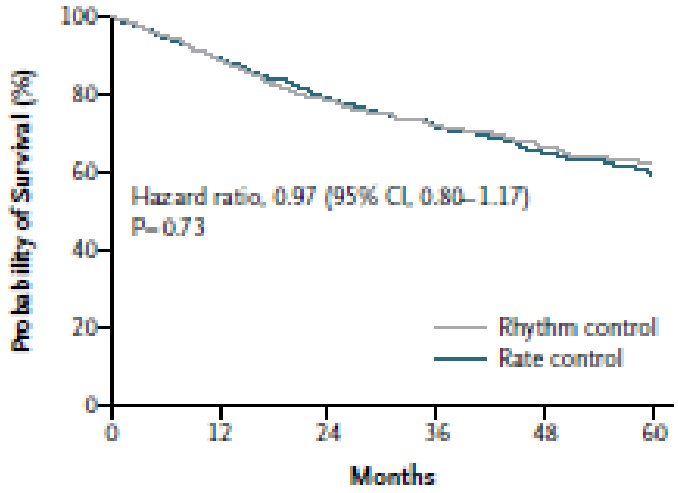
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 19, 2008 VOL. 358 NO. 25

Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure

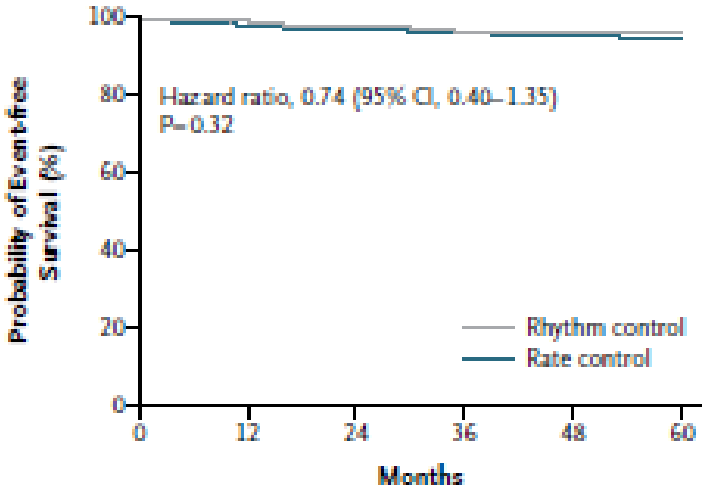
Denis Roy, M.D., Mario Talajic, M.D., Stanley Nattel, M.D., D. George Wyse, M.D., Ph.D., Paul Dorian, M.D., Kerry L. Lee, Ph.D., Martial G. Bourassa, M.D., J. Malcolm O. Arnold, M.D., Alfred E. Buxton, M.D., A. John Camm, M.D., Stuart J. Connolly, M.D., Marc Dubuc, M.D., Anique Ducharme, M.D., M.Sc., Peter G. Guerra, M.D., Stefan H. Hohnloser, M.D., Jean Lambert, Ph.D., Jean-Yves Le Heuzey, M.D., Gilles O'Hara, M.D., Ole Dyg Pedersen, M.D., Jean-Lucien Rouleau, M.D., Bramah N. Singh, M.D., D.Sc., Lynne Warner Stevenson, M.D., William G. Stevenson, M.D., Bernard Thibault, M.D., and Albert L. Waldo, M.D., for the Atrial Fibrillation and Congestive Heart Failure Investigators*

A Death from Any Cause



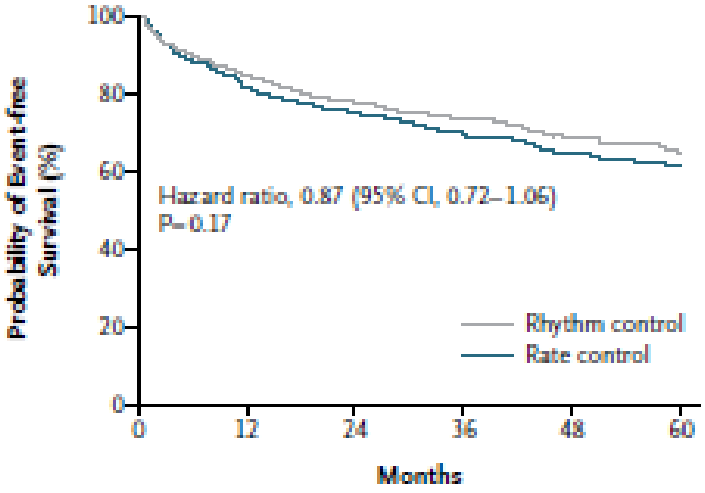
No. at Risk					
Rhythm control	593	514	378	228	82
Rate control	604	521	381	219	69

B Stroke



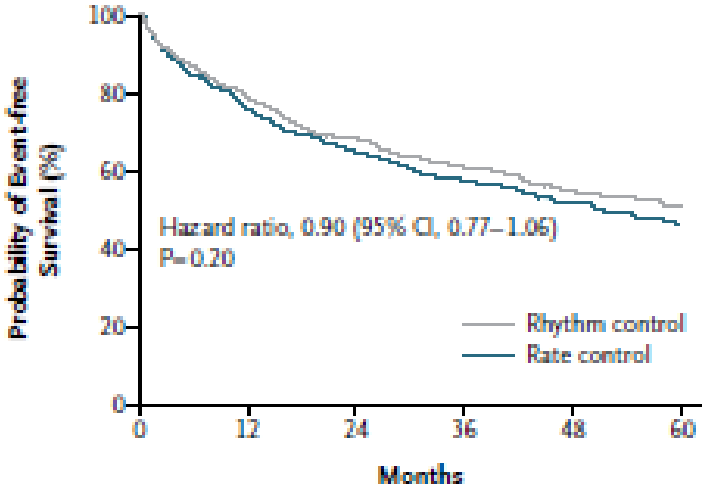
No. at Risk					
Rhythm control	589	507	367	221	79
Rate control	596	512	373	216	68

C Worsening Heart Failure



No. at Risk					
Rhythm control	523	436	311	174	63
Rate control	509	419	289	165	54

D Composite Outcome



No. at Risk					
Rhythm control	518	432	303	169	60
Rate control	502	412	281	162	53

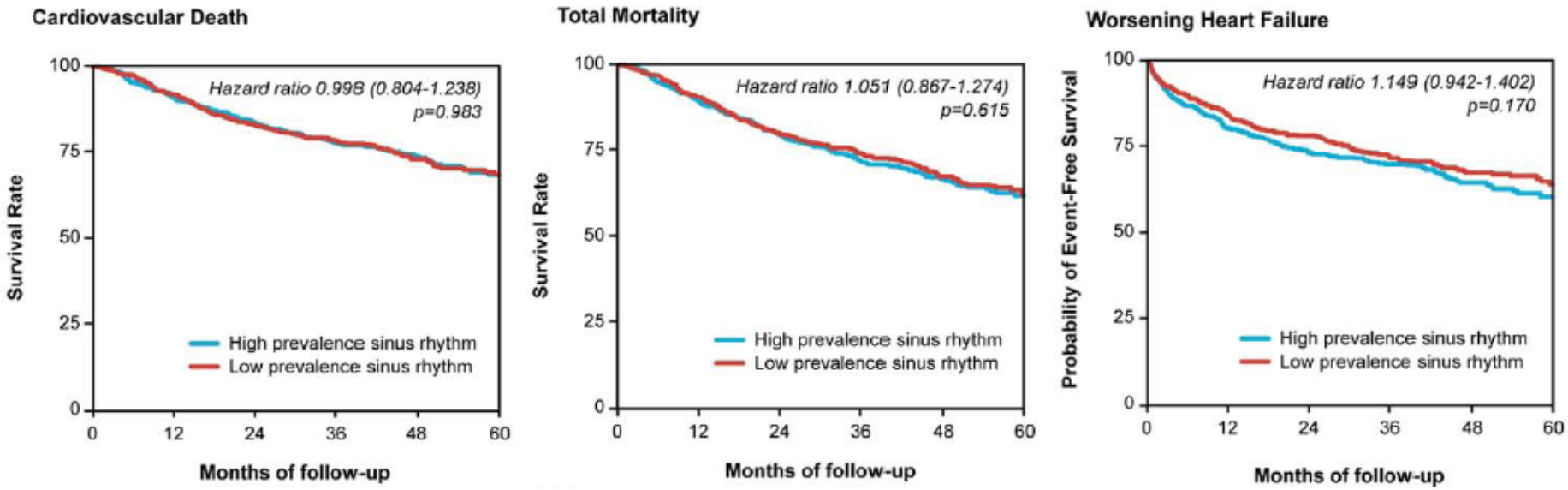
Maintenance of Sinus Rhythm and Survival in Patients With Heart Failure and Atrial Fibrillation

Mario Talajic, MD,* Paul Khairy, MD, PHD,* Sylvie Levesque, MSC,* Stuart J. Connolly, MD,† Paul Dorian, MD,‡ Marc Dubuc, MD,* Peter G. Guerra, MD,* Stefan H. Hohnloser, MD,§ Kerry L. Lee, PHD,‖ Laurent Macle, MD,* Stanley Nattel, MD,* Ole D. Pedersen, MD,¶ Lynne Warner Stevenson, MD,# Bernard Thibault, MD,* Albert L. Waldo, MD,** D. George Wyse, MD, PHD,†† Denis Roy, MD*

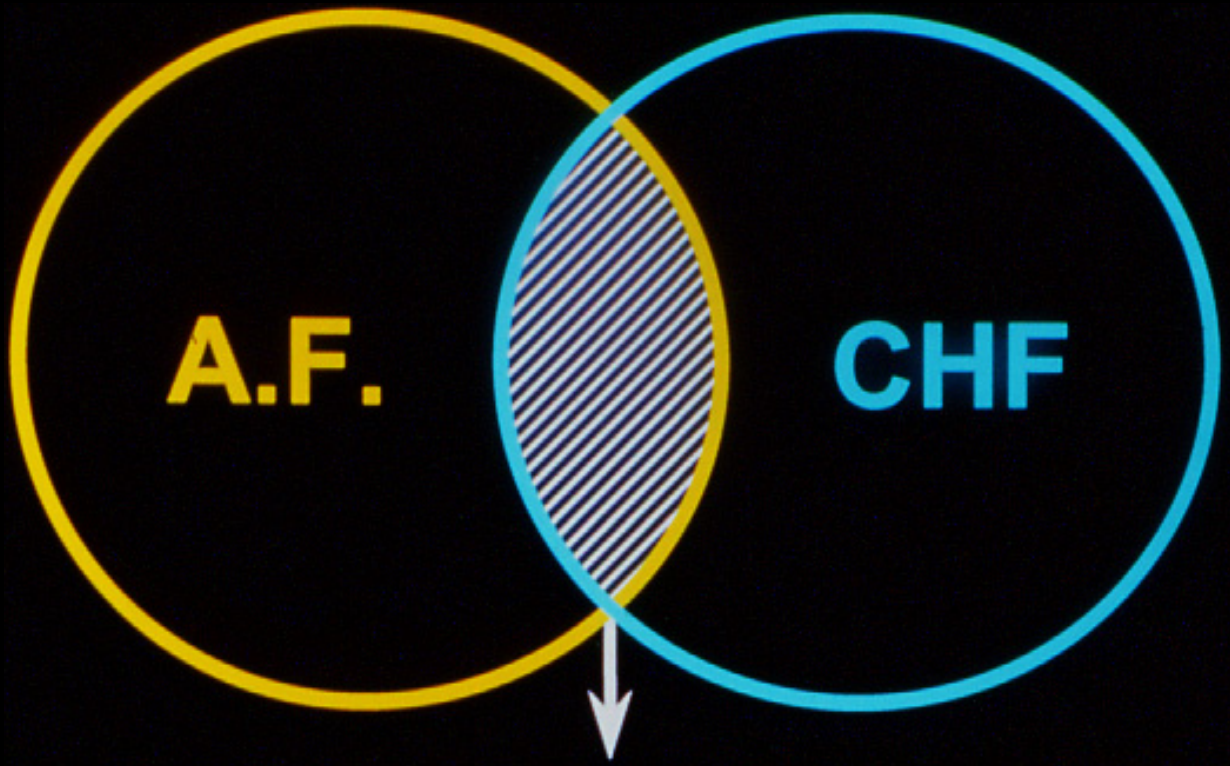
Montreal, Quebec, Hamilton and Toronto, Ontario, and Calgary, Alberta, Canada; Frankfurt, Germany; Durham, North Carolina; Copenhagen, Denmark; Boston, Massachusetts; and Cleveland, Ohio

J Am Coll Cardiol 2010;55:1796–802

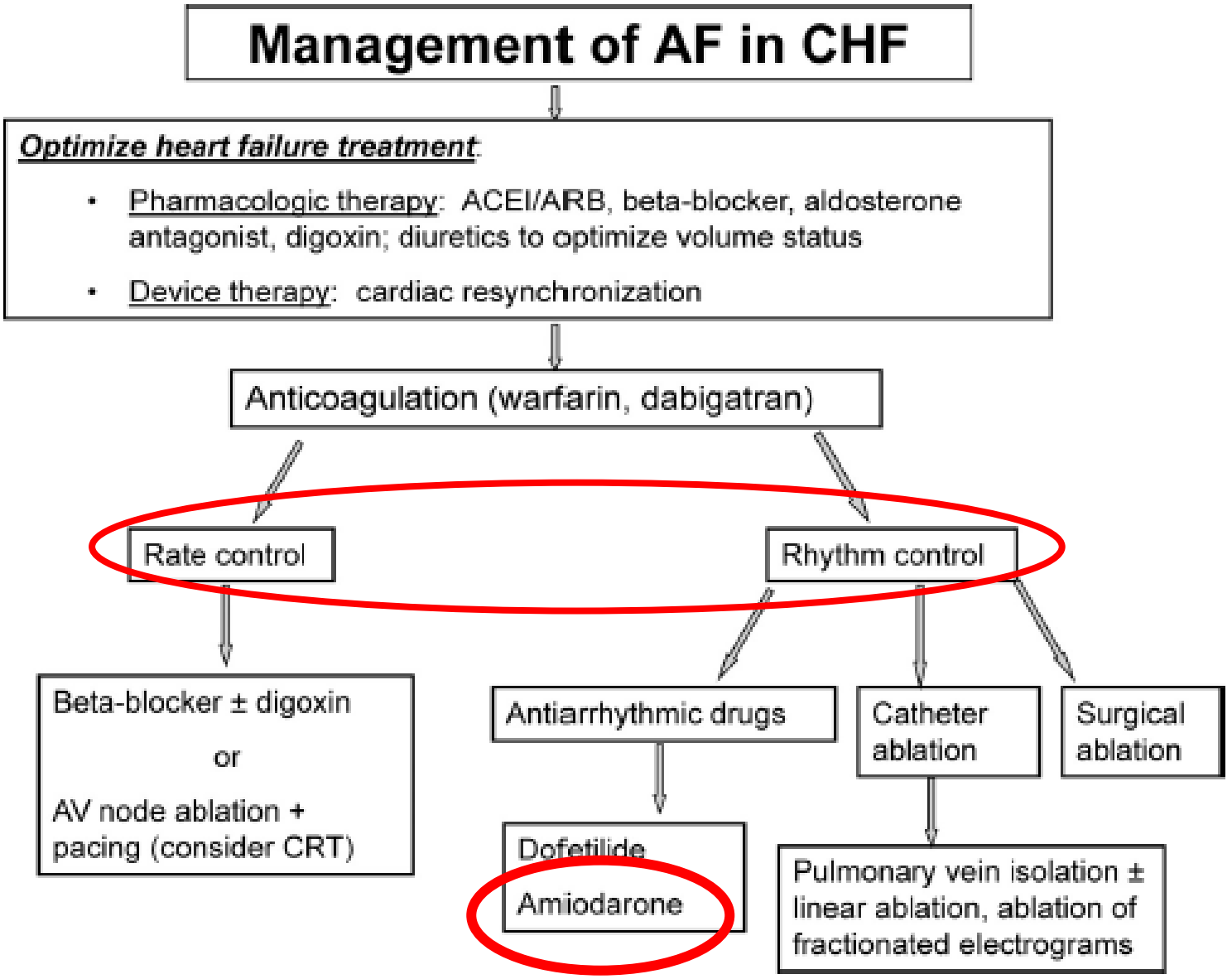
AF-CHF Trial



Talajic M et al, J Am Coll Cardiol 2010;55:1796–802



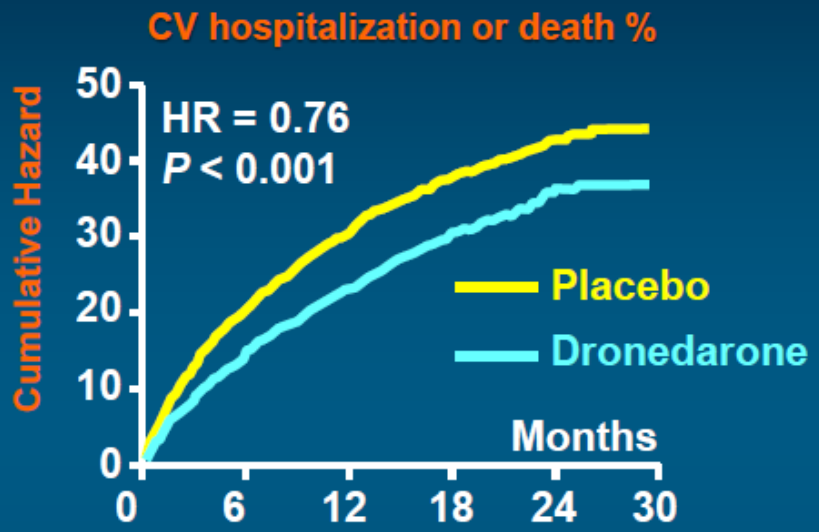
1. A.F. as a cause of CHF
2. CHF as a cause of A.F.
3. A.F. and CHF as consequences of a common cause

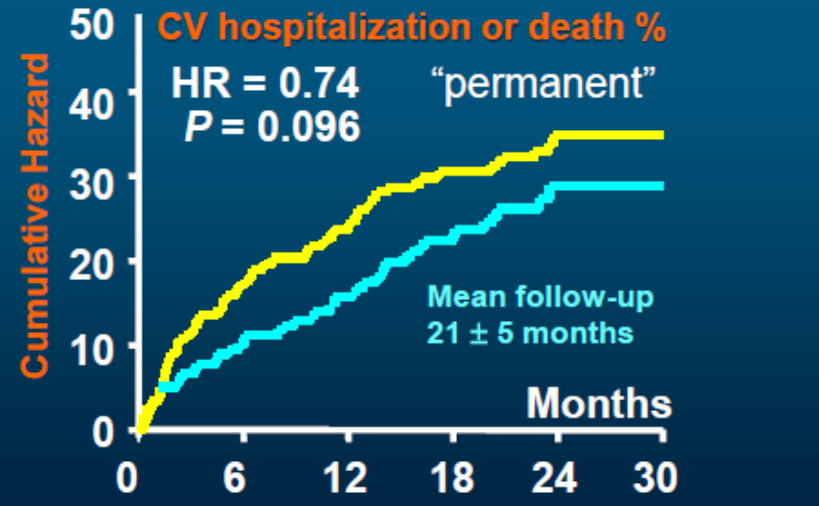


Darby AE et al, Circulation 2012;125:945-57

Permanent versus Non-Permanent AF

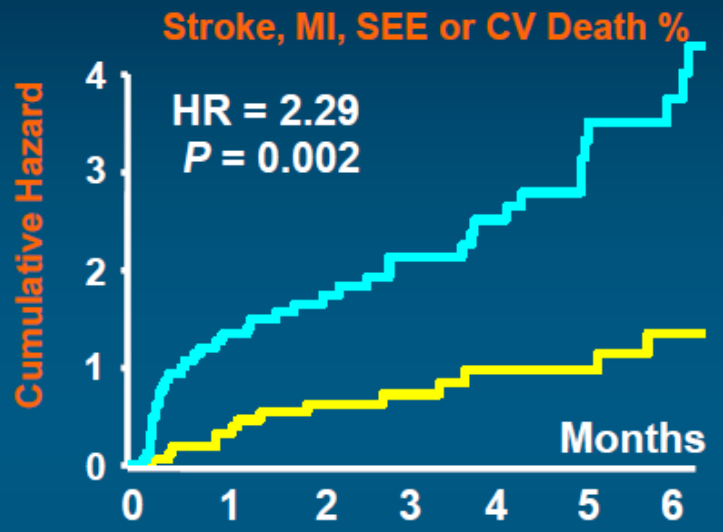
ATHENA

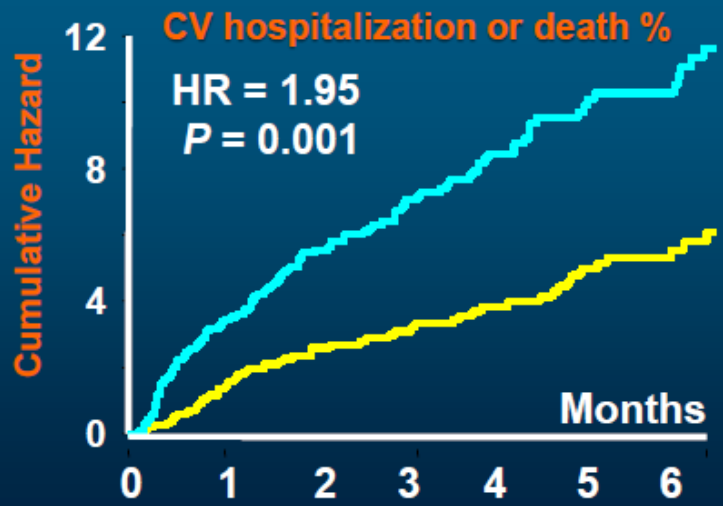




Hohnloser SH et al. N Engl J Med. 2009;360:668-78

PALLAS





Connolly S et al. N Engl J Med. 2011;365:2268-76

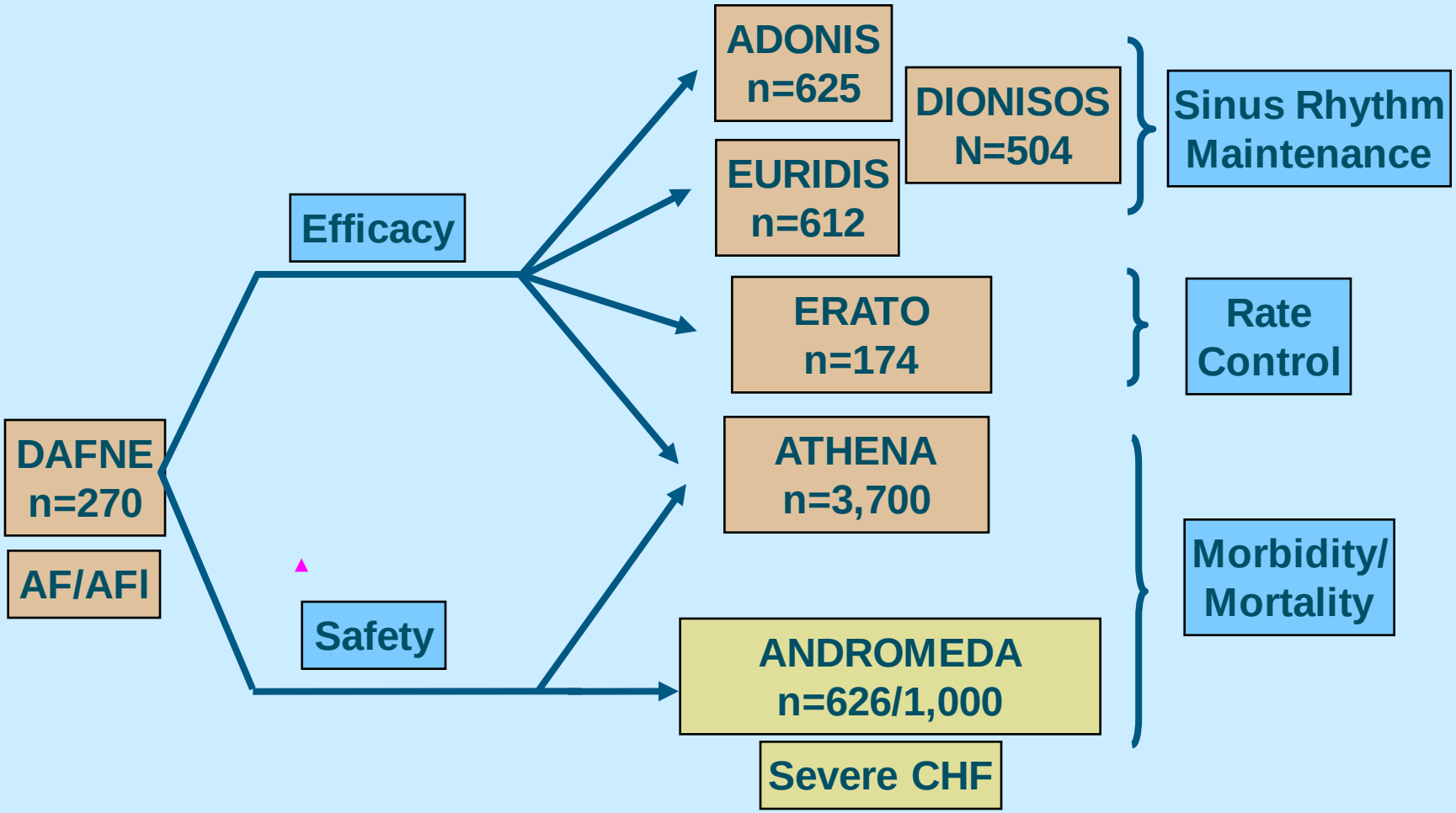
Summary of Recommendations Regarding the Use of Dronedarone

Recommendations	Class[a]	Level[b]
Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm.	I	A
Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.	IIa	B
Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.	III	B
Dronedarone is not recommended in patients with permanent AF	III	B

[a]Class of recommendation. [b]Level of evidence.
AF = atrial fibrillation; LoE = level of evidence.

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

Dronedarone Clinical Overview



ANDROMEDA

Objective

- ANDROMEDA was conducted in high-risk congestive heart failure (CHF) patients with left ventricular dysfunction and a recent acute decompensation and aimed to evaluate the potential benefit of dronedarone on all cause death or hospitalisation for worsening heart failure

- Patients were not selected based on AF / AFL history

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA

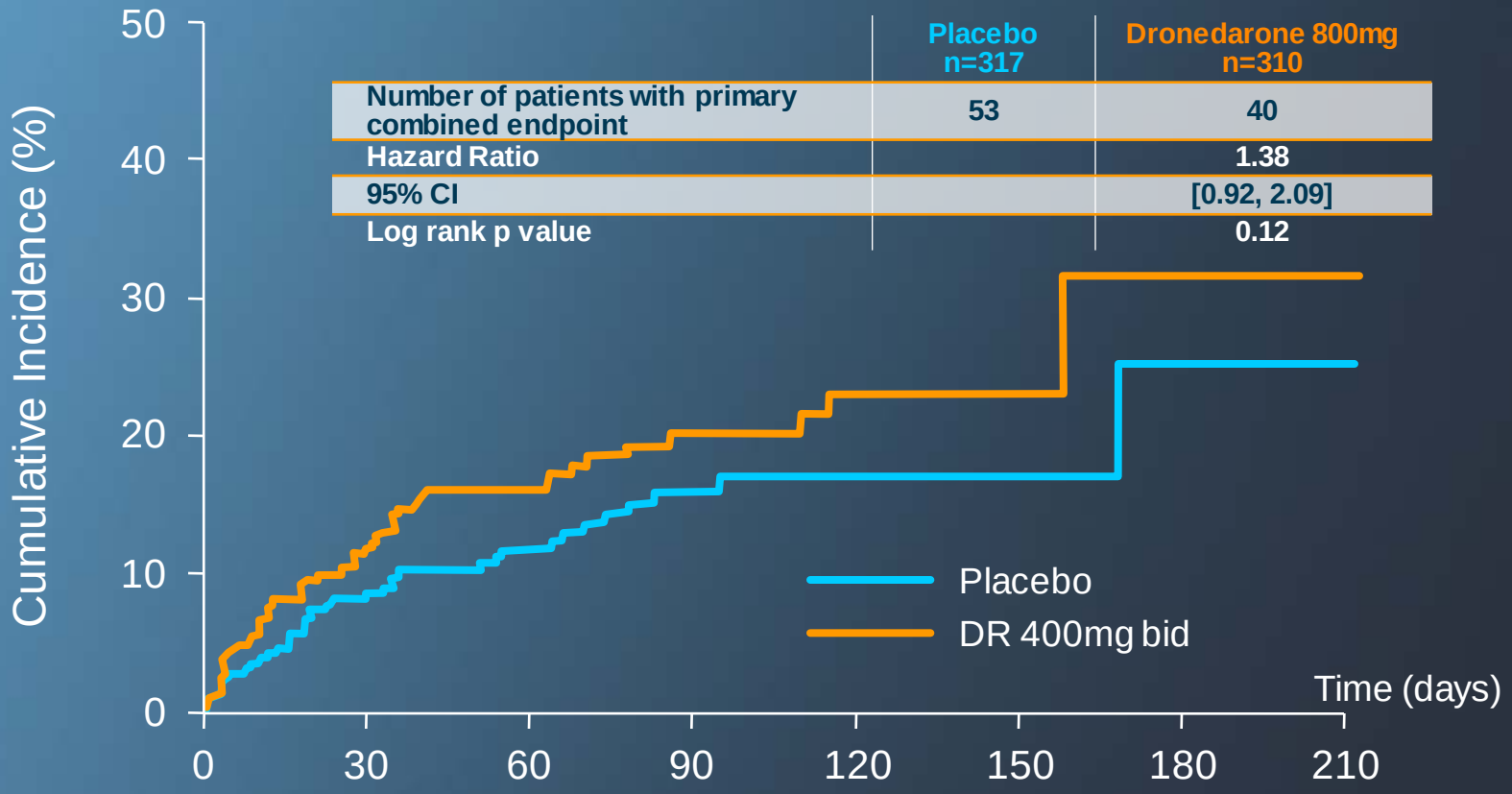
Study endpoints

- **Primary endpoint**
  - Death from any cause or hospitalisation for worsening heart failure
- **Secondary endpoints**
  - Death from all causes
  - Hospitalisation for cardiovascular causes
  - Hospitalisation for worsening heart failure
  - Occurrence of atrial fibrillation or flutter
  - Death from arrhythmia
  - Sudden death

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA

	Placebo n=317	Dronedarone 800mg n=310
Number of patients with primary combined endpoint	53	40
Hazard Ratio		1.38
95% CI		[0.92, 2.09]
Log rank p value		0.12



Patients at risk:

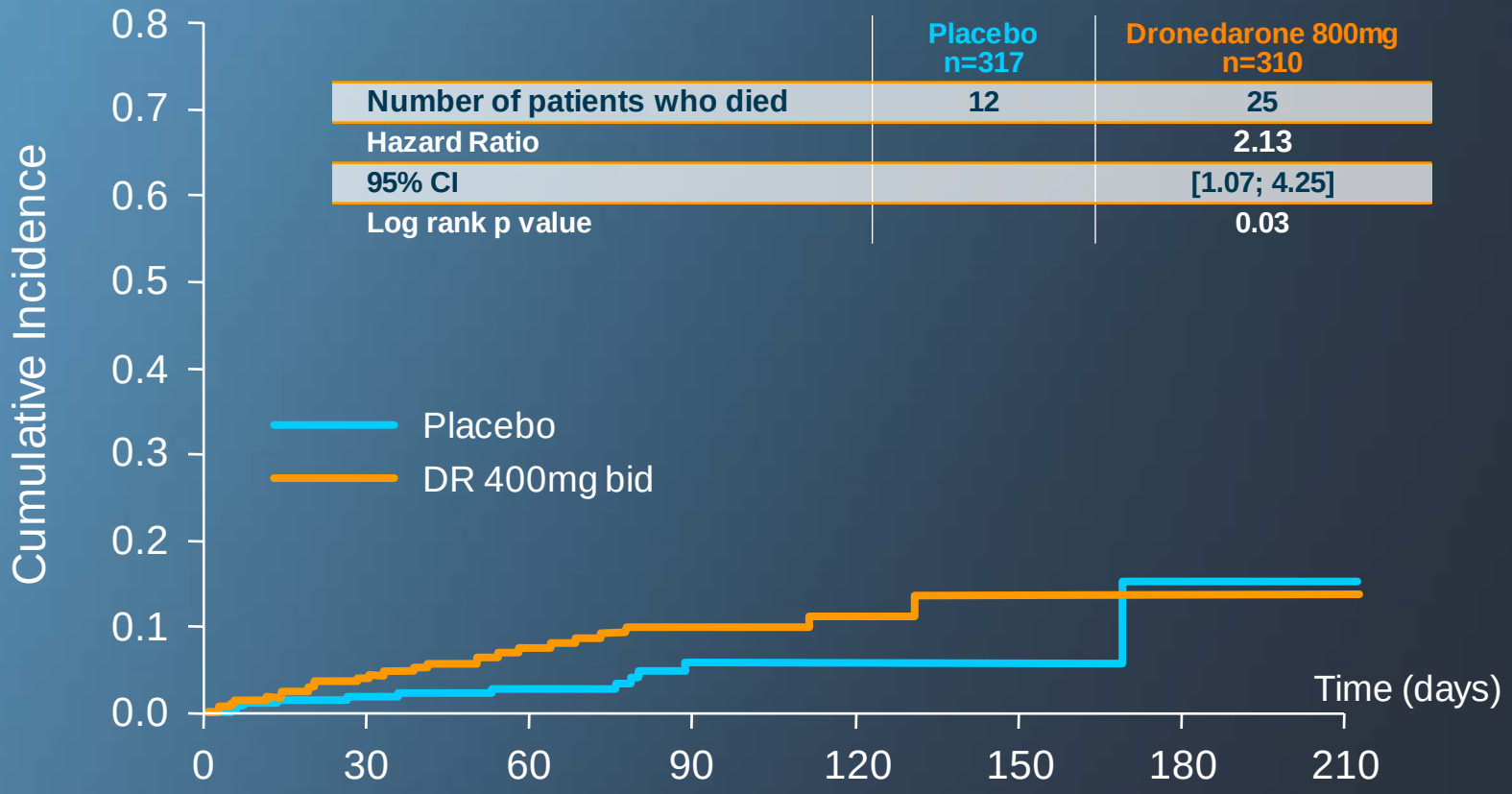
Placebo	317	234	159	87	41	16	6	1
DR 400mg bid	310	232	151	87	49	19	4	1

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA

Cumulative Incidence of All-cause Mortality

	Placebo n=317	Dronedarone 800mg n=310
Number of patients who died	12	25
Hazard Ratio		2.13
95% CI		[1.07; 4.25]
Log rank p value		0.03



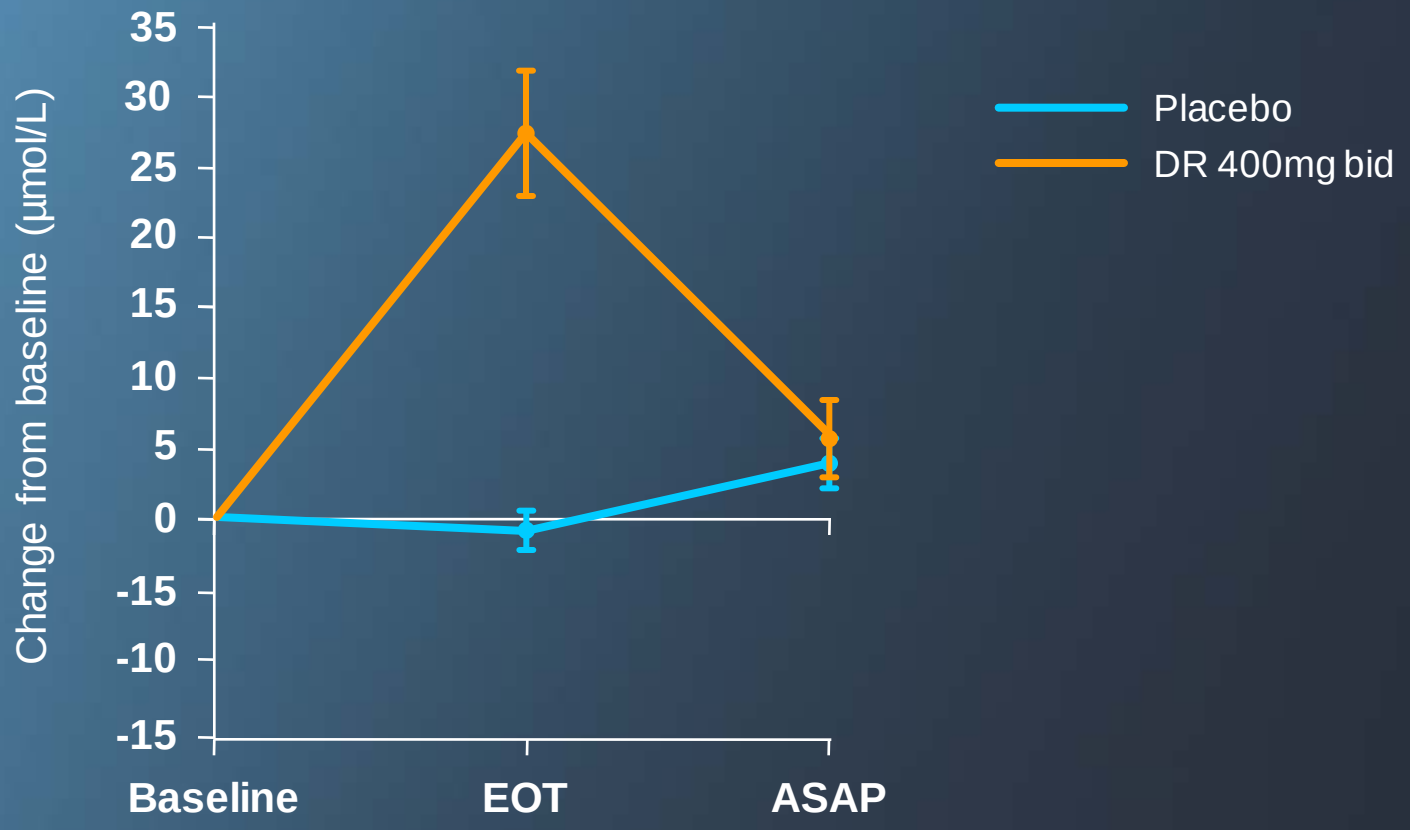
Patients at risk:

Placebo	317	256	181	103	50	18	6	1
DR 400mg bid	310	257	174	104	59	22	5	1

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA

Increases in Serum Creatinine were more Frequent in the Dronedarone Group vs Placebo



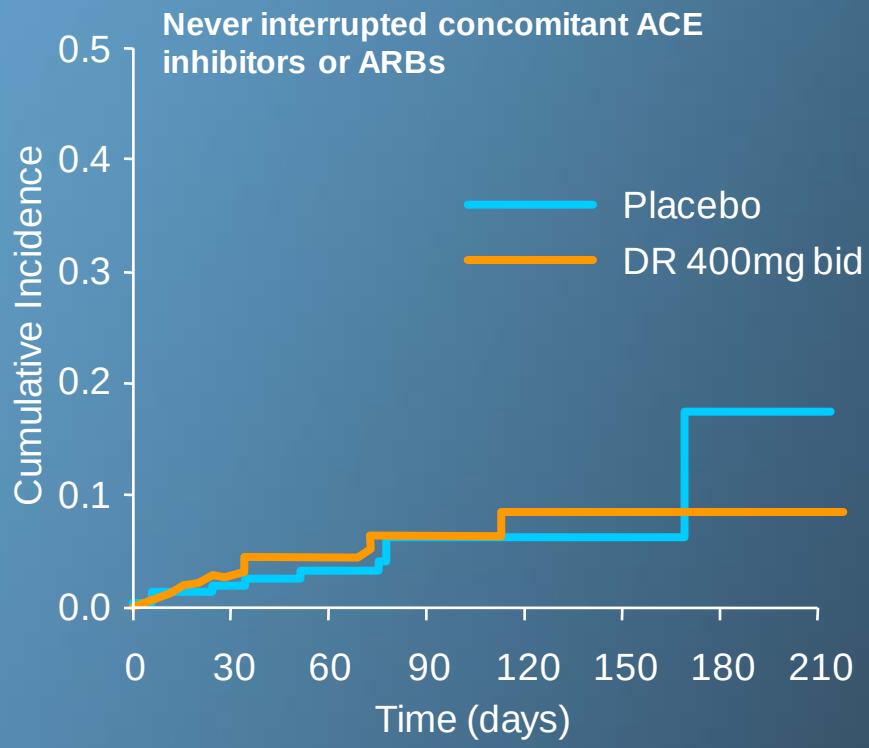
Patients at risk:

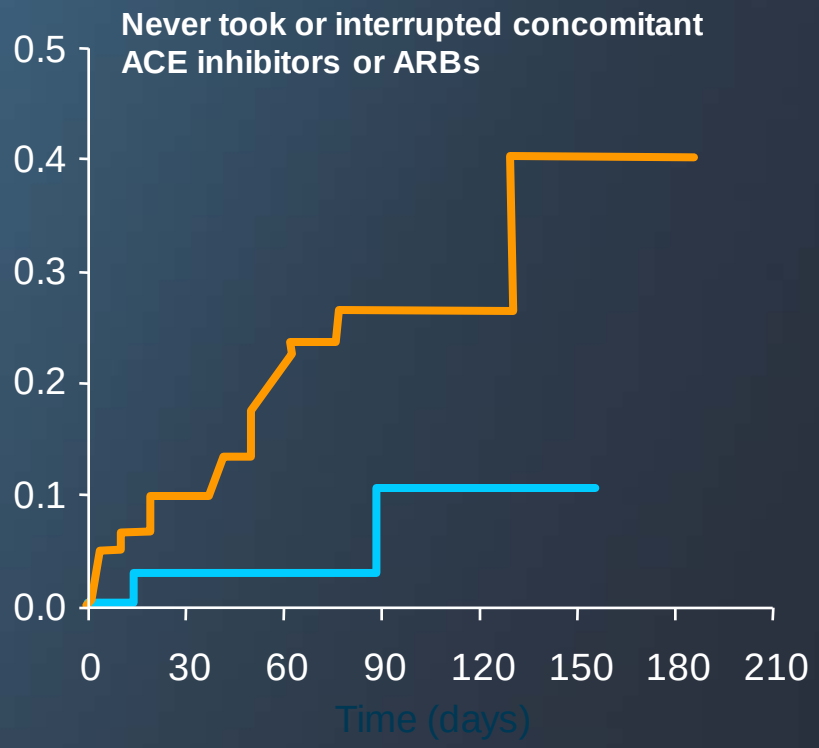
Placebo	218	218	218
DR 400mg bid	199	199	199

EOT=End Of Treatment; ASAP=As Soon As Possible.
Data on file.

ANDROMEDA

Cumulative Incidence of Death According to ACE-inhibitor or ARB treatment





Patients at risk:								
Placebo	281	223	157	92	45	15	6	1
DR 400mg bid	249	207	141	85	46	19	4	1

Placebo	36	33	24	11	5	3	0	0
DR 400mg bid	61	50	33	19	13	3	1	0

Data on file.

Variable	ATHENA	ANDROMEDA
Demographic characteristic		
• Mean age (yr)	72	72
• Female sex (%)	47	25
Clinical characteristic (%)		
• Baseline atrial fibrillation	25	25
• Hypertension	86	37
• Coronary artery disease	30	65
• CHF	21	97
Treatment		
• Beta-blocker	71	61
• Digoxin	14	31
• ACE-i/ARBs	70	86
• Oral anticoagulant	60	32

Pharmacological therapy of AF in Pts with impaired LV function

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- The «Dronedarone saga»
- Ventricular dysfunction vs Heart Failure
- Sistolic vs diastolic HF
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Amiodarone	600 mg o.d. for 4 weeks, 400 mg o.d. for 4 weeks then 200 mg o.d.	Caution when using concomitant medication with QT-prolonging drugs, heart failure. Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced. Creatinine, liver enzymes, thyroid hormones, & lung function should be monitored	QT interval >500 ms	10–12 bpm in AF

Changes from 2010 Guidelines

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Changes from 2010 Guidelines

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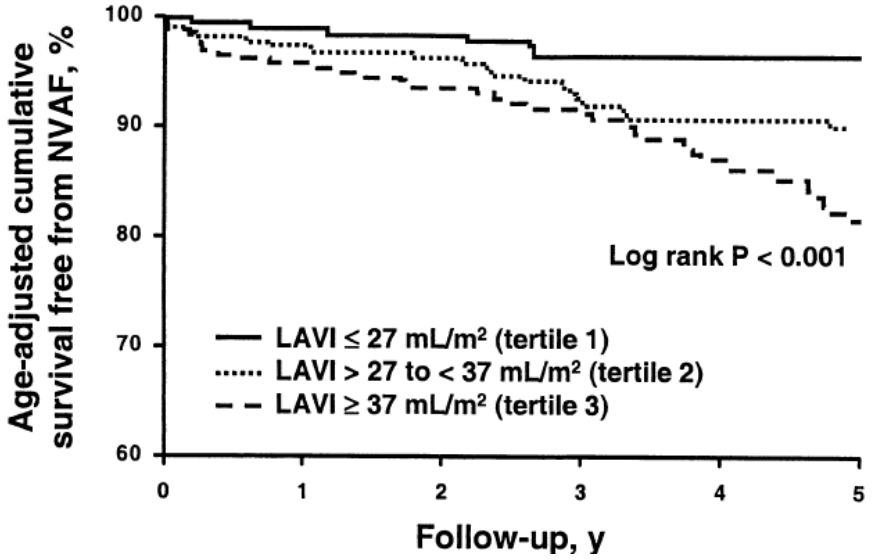
European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

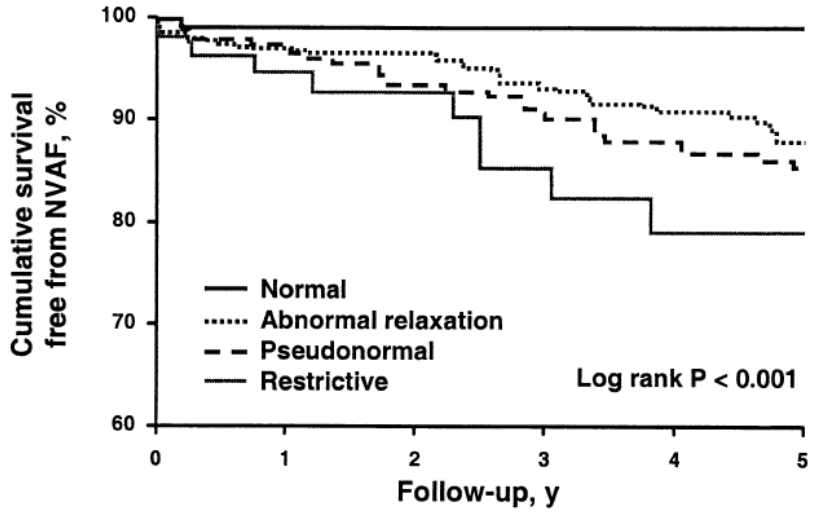
Left Ventricular Diastolic Dysfunction as a Predictor of the First Diagnosed Nonvalvular Atrial Fibrillation in 840 Elderly Men and Women

Tsang TSM et al, (J Am Coll Cardiol 2002;40:1636–44)

LA Volume



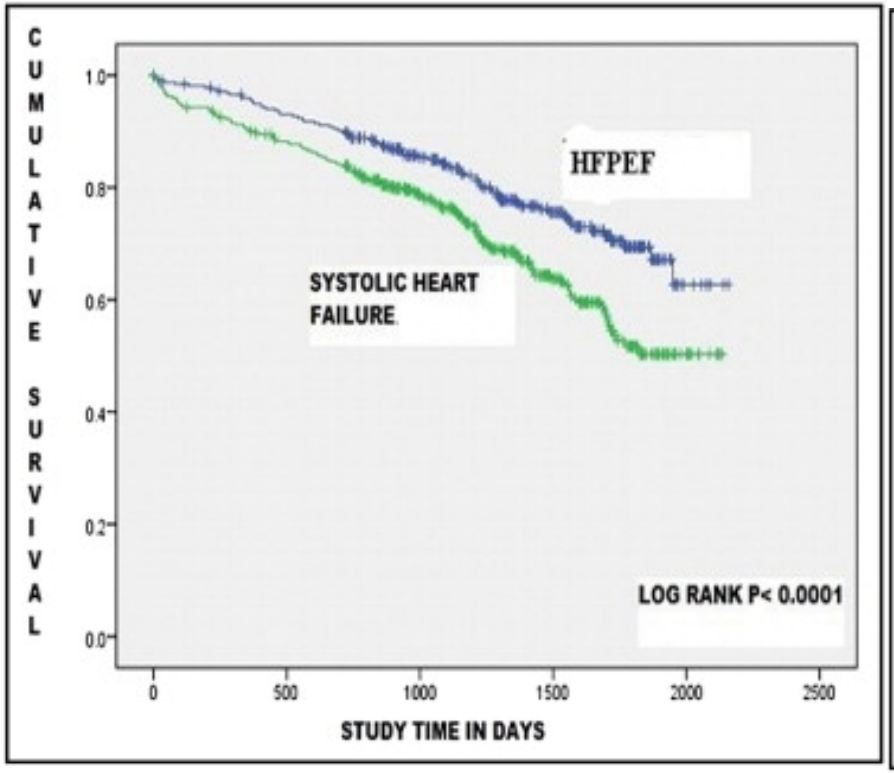
Diastolic function



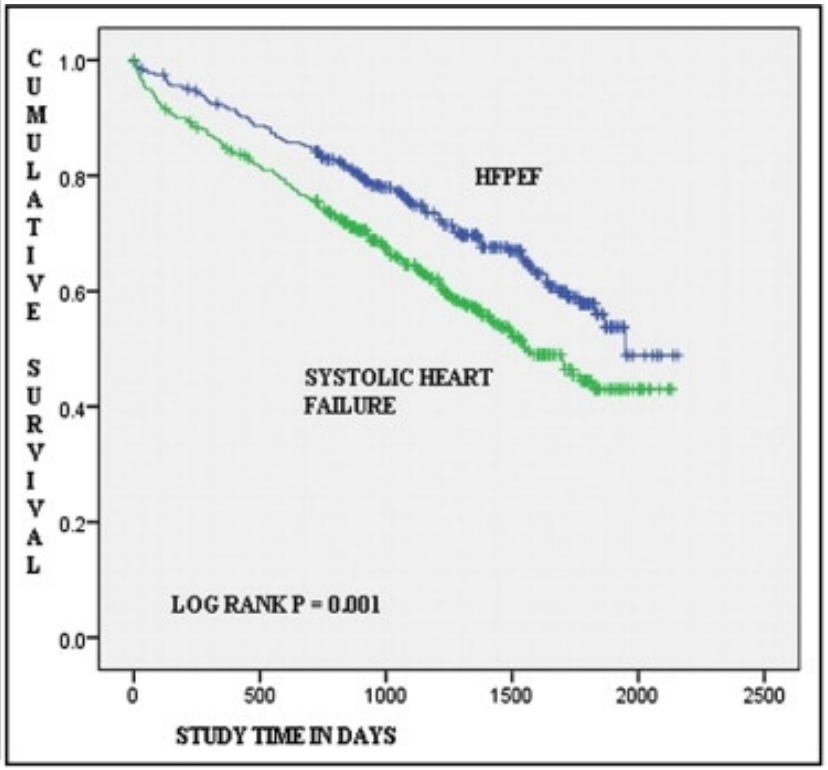
Comparison of Mortality and Morbidity in Patients With Atrial Fibrillation and Heart Failure With Preserved Versus Decreased Left Ventricular Ejection Fraction

Am J Cardiol 2011;108:1283–1288

All cause mortality



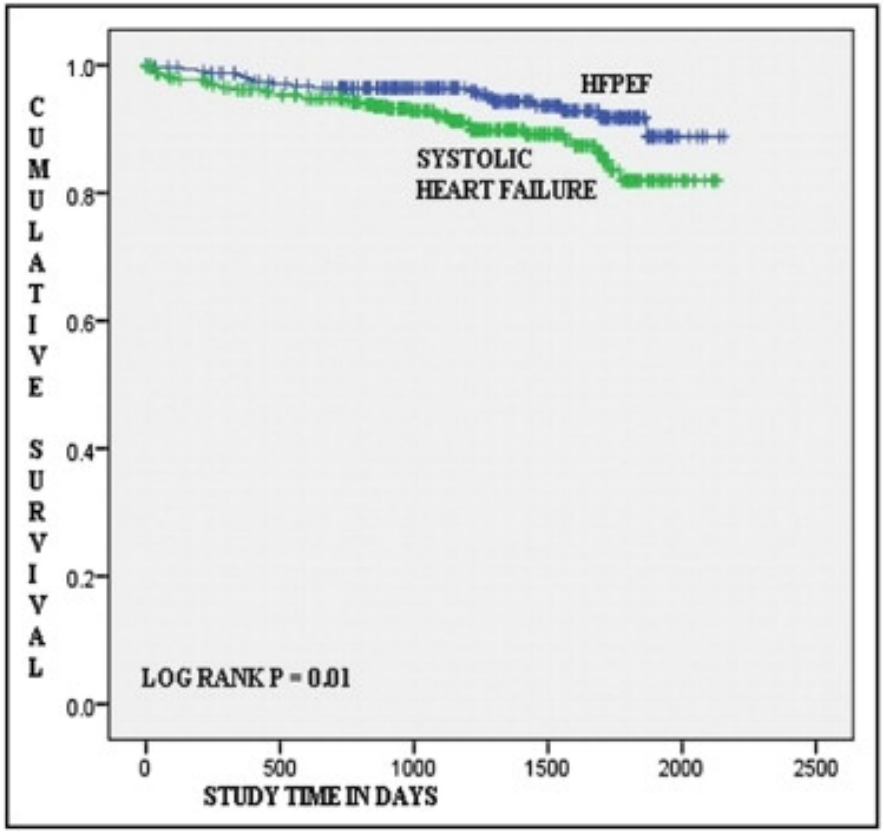
Combined endpoint



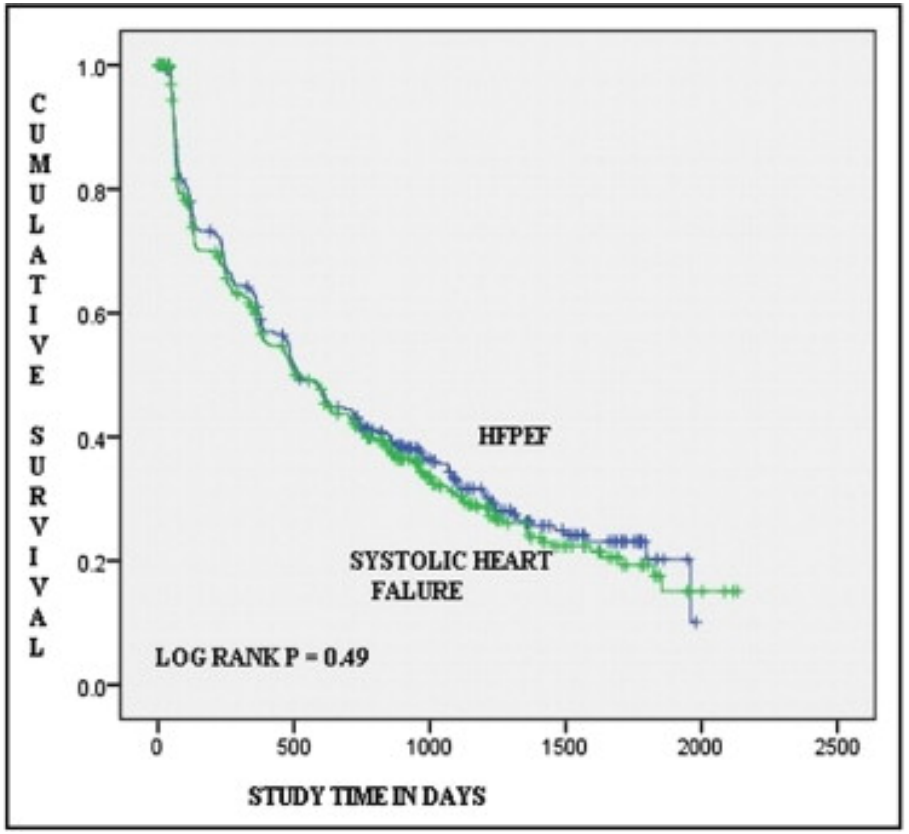
Comparison of Mortality and Morbidity in Patients With Atrial Fibrillation and Heart Failure With Preserved Versus Decreased Left Ventricular Ejection Fraction

Am J Cardiol 2011;108:1283–1288

Cardiovascular mortality

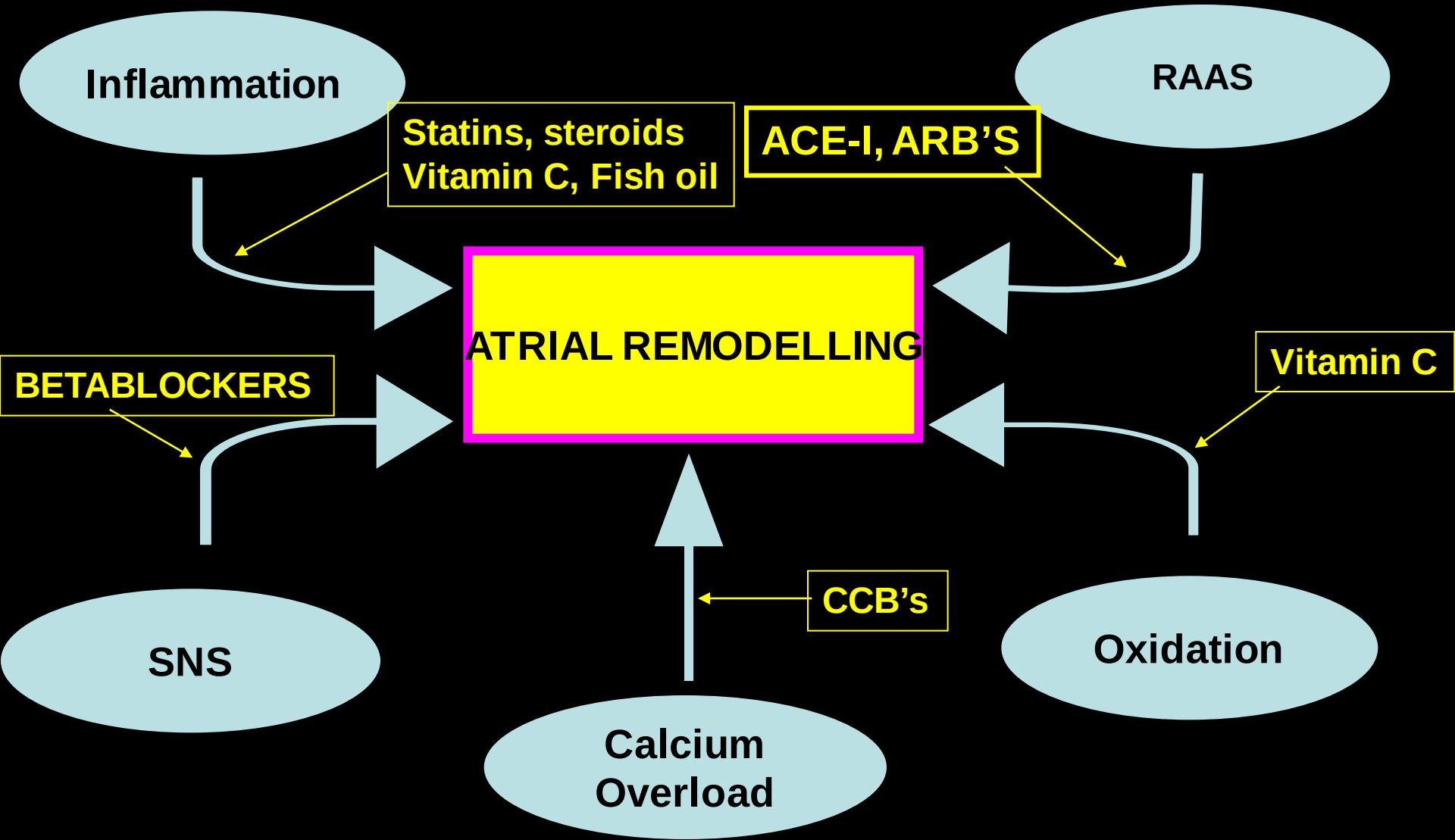


Rehospitalization

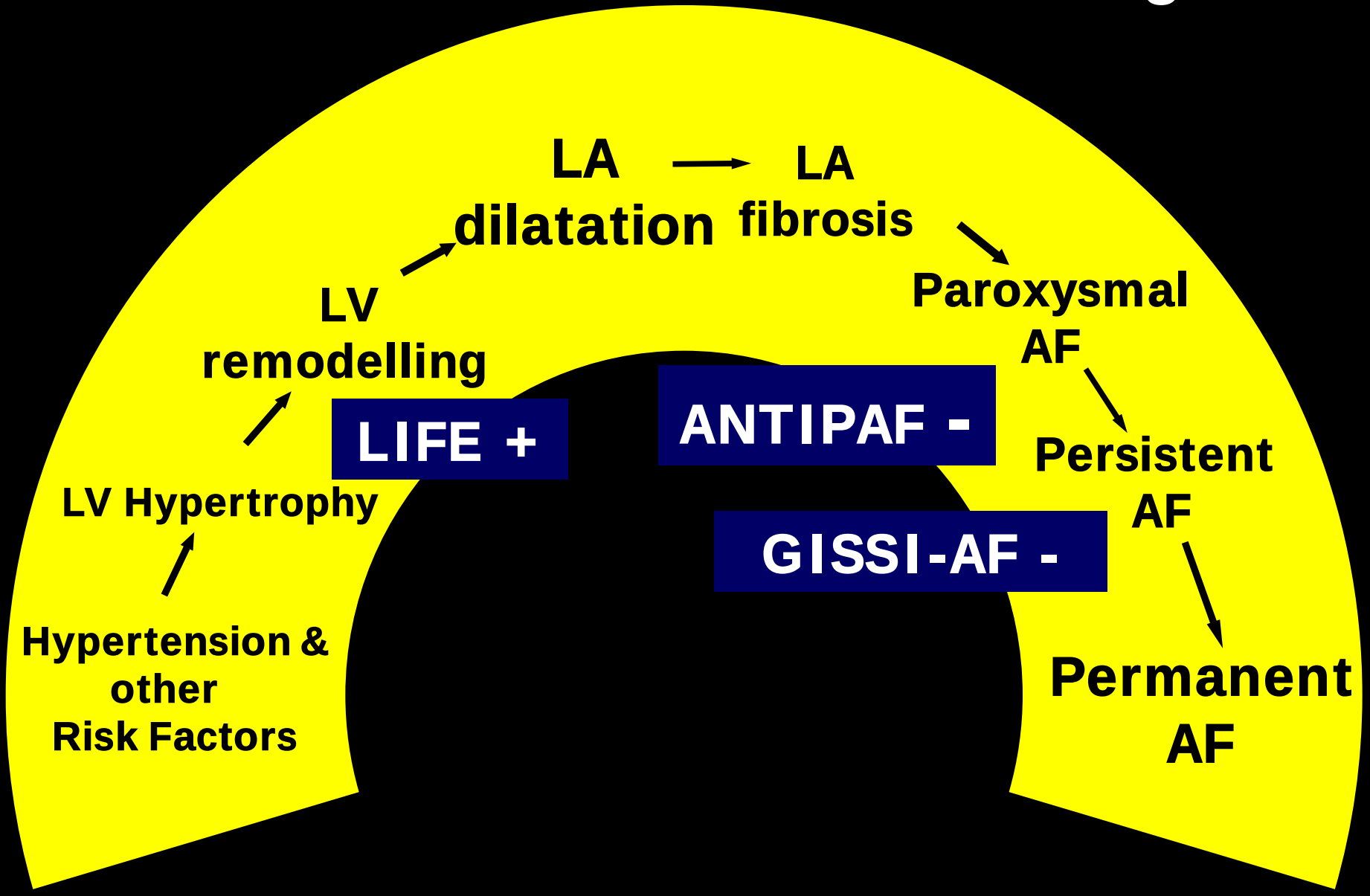


Non-Antiarrhythmic Drugs in Atrial Fibrillation

Mod. from Lally J Cardiovascular Elettrophysiol 2007;18:1222



From anatomical to electrical irreversible remodeling



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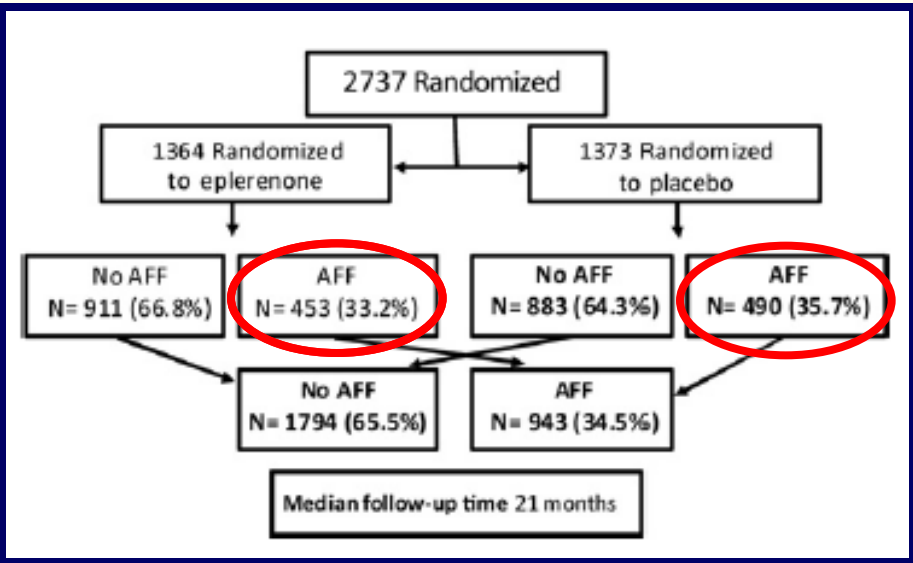
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.11.063

Eplerenone and Atrial Fibrillation in Mild Systolic Heart Failure

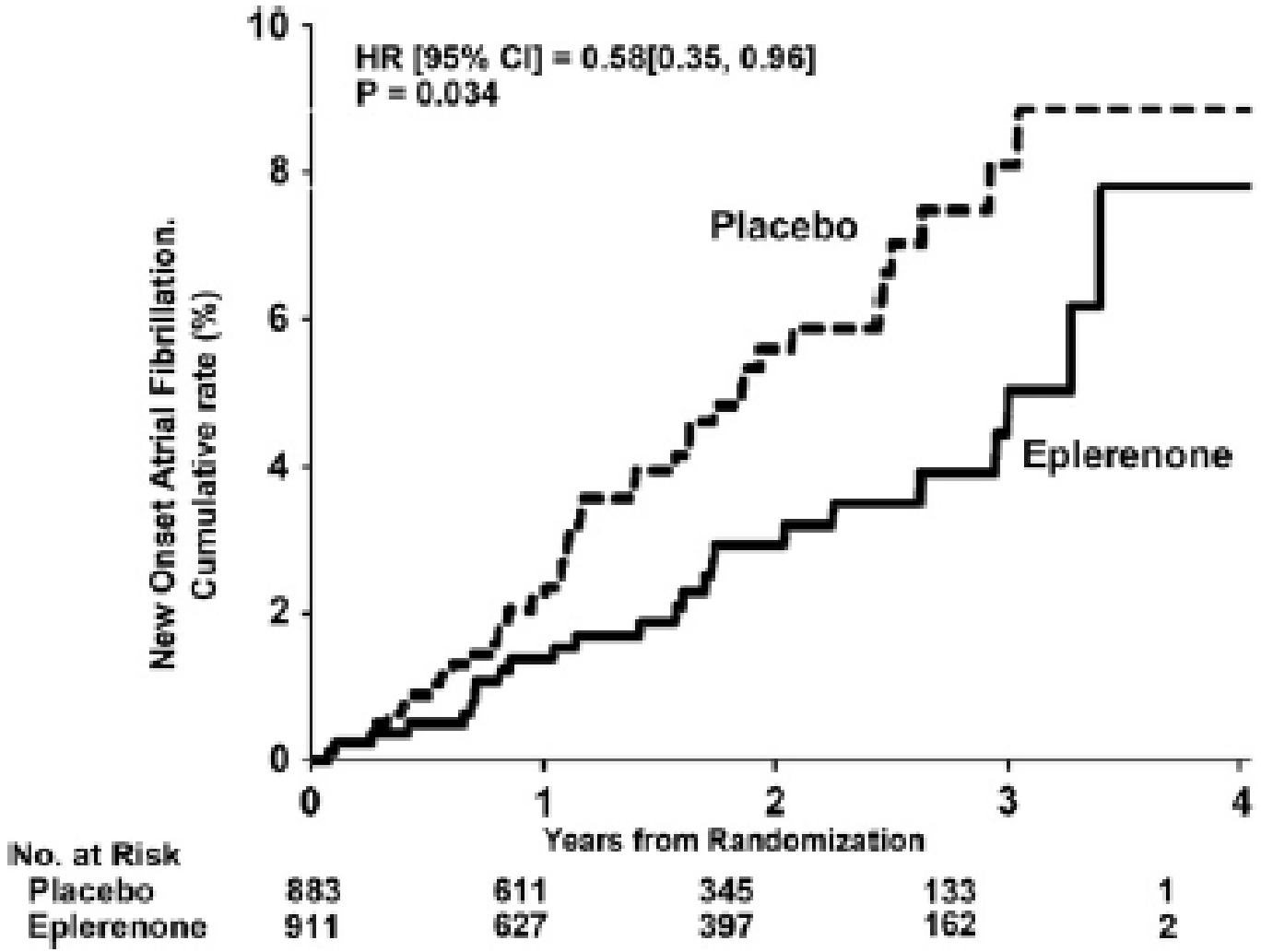
Results From the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) Study

Karl Swedberg, MD, PHD,* Faiez Zannad, MD, PHD,† John J. V. McMurray, MD,‡
Henry Krum, MB, PHD,§ Dirk J. van Veldhuisen, MD, PHD,‖ Harry Shi, MS,¶
John Vincent, MB, PHD,¶ Bertram Pitt, MD,# for the EMPHASIS-HF Study Investigators

Goteborg, Sweden; Nancy, France; Glasgow, United Kingdom; Melbourne, Australia; Groningen, the Netherlands; New York, New York; and Ann Arbor, Michigan



Incidence of Atrial Fibrillation or Flutter



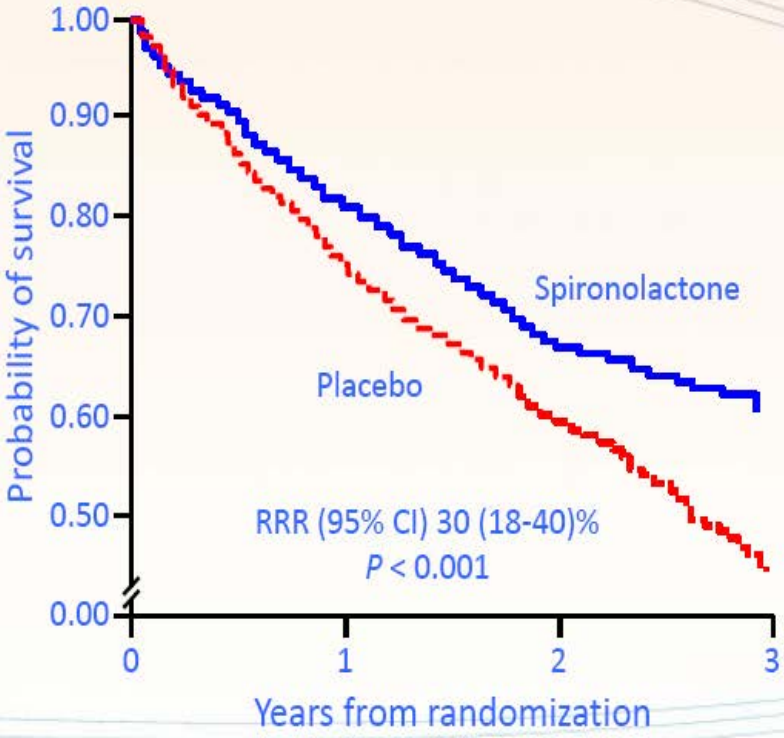
EMPHASIS-HF, 2012

Aldosterone/MR antagonists beneficial across the spectrum of severity

RALES

1663 NYHA class III/IV patients

95% ACE-I/10% β-blocker

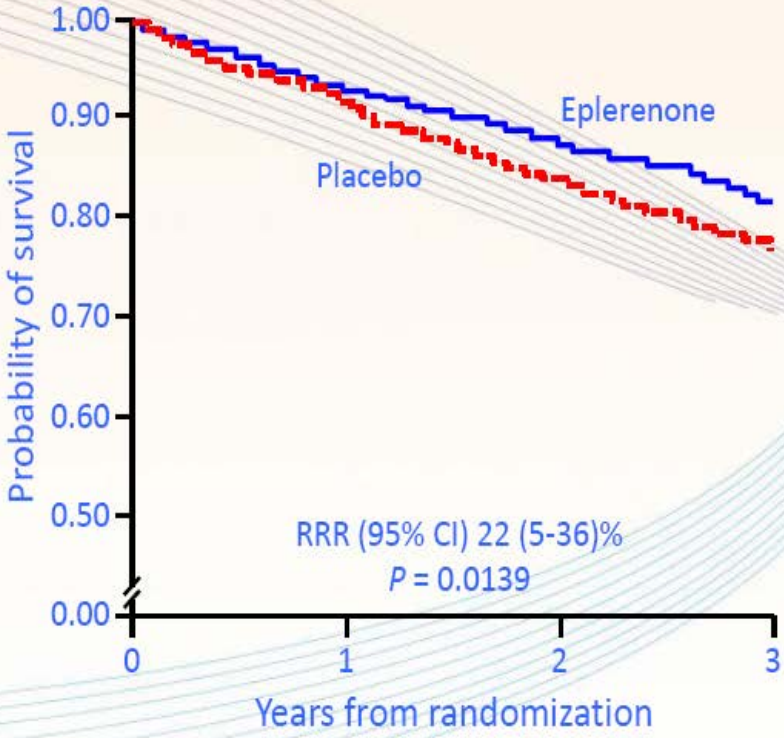


Pitt B, et al. *N Engl J Med.* 1999;341:709-717.

EMPHASIS-HF

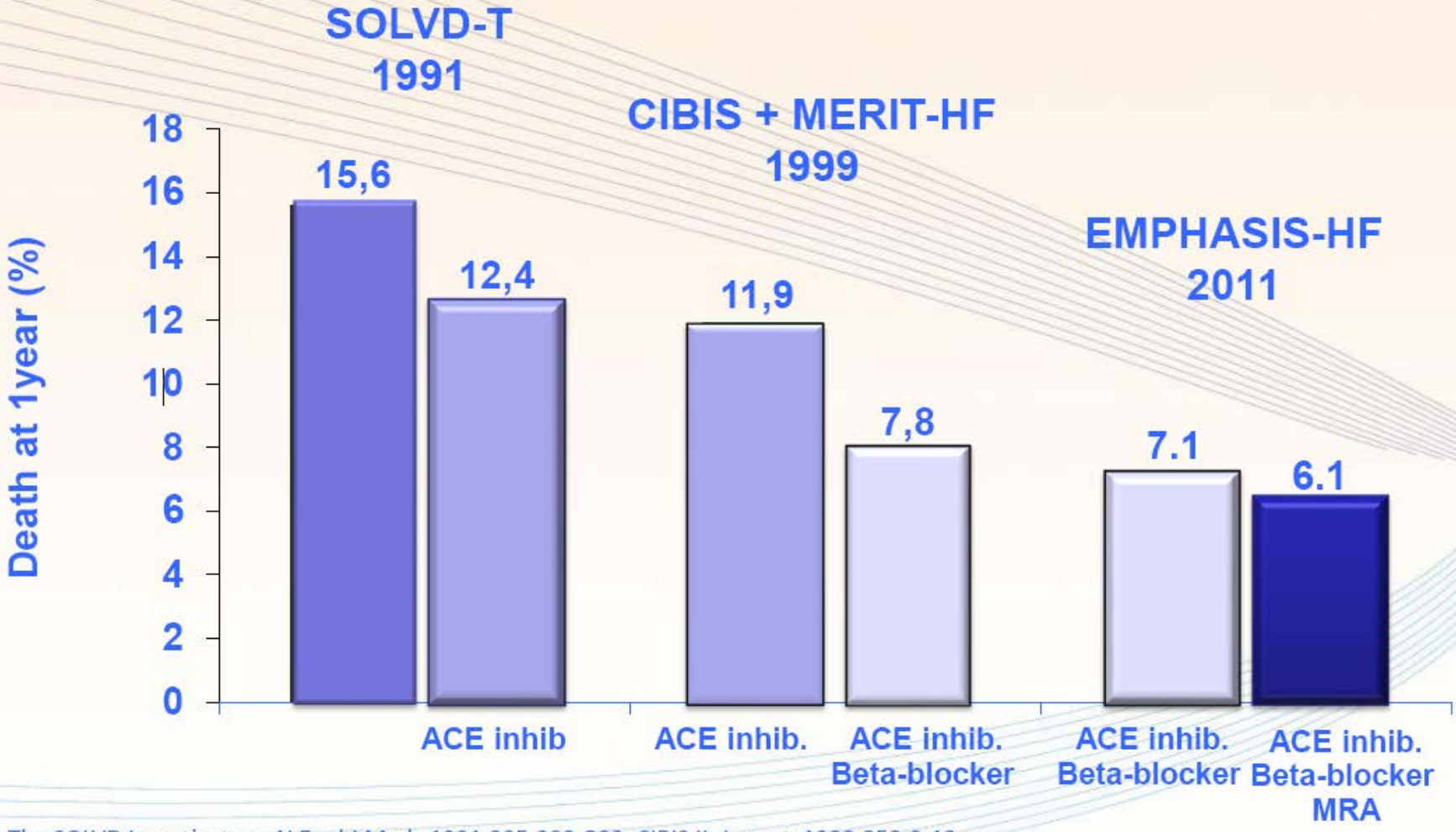
2737 NYHA class II patients

93% ACE-I or ARB/87% β-blocker



Zannad F, et al. *N Engl J Med.* 2010;364:11-21.

Opitimization of Neurohumoral blockade in systolic heart failure. Mild symptoms.



The SOLVD Investigators. *N Engl J Med*.. 1991;325:293-302. CIBIS II. *Lancet*. 1999;353:9-13. MERIT-HF. *Lancet*. 1999;353:2001-2007. Zannad F, et al. *N Engl J Med*. 2011;364:11-21.

TOPCAT: Trial Design

Funded by the NHLBI

- AGE ≥ 50 YRS
- EF ≥ 45% WITHIN 6 MONTHS
- HEART FAILURE SYMPTOMS AND SIGNS
- CONTROLLED SYSTOLIC BP (< 140 mm Hg)*
- SERUM K^+ ≤ 5.0 MMOL/L

PLUS ONE OF THE FOLLOWING:

- HF HOSPITALIZATION WITHIN 12 MONTHS
- BNP ≥ 100 PG/ML
- N-TERMINAL PRO-BNP ≥ 360 PG/ML

N=4500
(3,200 enrolled)

↓

RANDOMIZE

↓

PLACEBO 15 MG | **SPIRONOLACTONE 15 MG**

Week 0

↓

DOSE TITRATION (TARGET 30 MG)
** Optional Titration to 45 mg at 4 mos*

Week 4

↓

COMPOSITE PRIMARY ENDPOINT
CV death, Aborted cardiac arrest, Hospitalization for management of HF

~ 3.25 yrs

Aldosterone Receptor Blockade in **D**iastolic **H**eart **F**ailure

The **Aldo-DHF** Trial

Frank Edelmann, M.D., Rolf Wachter, M.D., Albrecht Schmidt, M.D., Elisabeth Kraigher-Krainer,M.D., Caterina Colantonio, M.D., Wolfram Kamke, M.D., André Duvinage, M.D., Raoul Stahrenberg, M.D., Kathleen Dustewitz, M.D., Markus Löffler, M.D., Hans-Dirk Düngen, M.D., Carsten Tschöpe, M.D., Christoph Herrmann-Lingen, M.D., Martin Halle, M.D., Gerd Hasenfuss, M.D., Götz Gelbrich,Ph.D., and Burkert Pieske, M.D.

For the Aldo-DHF Investigators

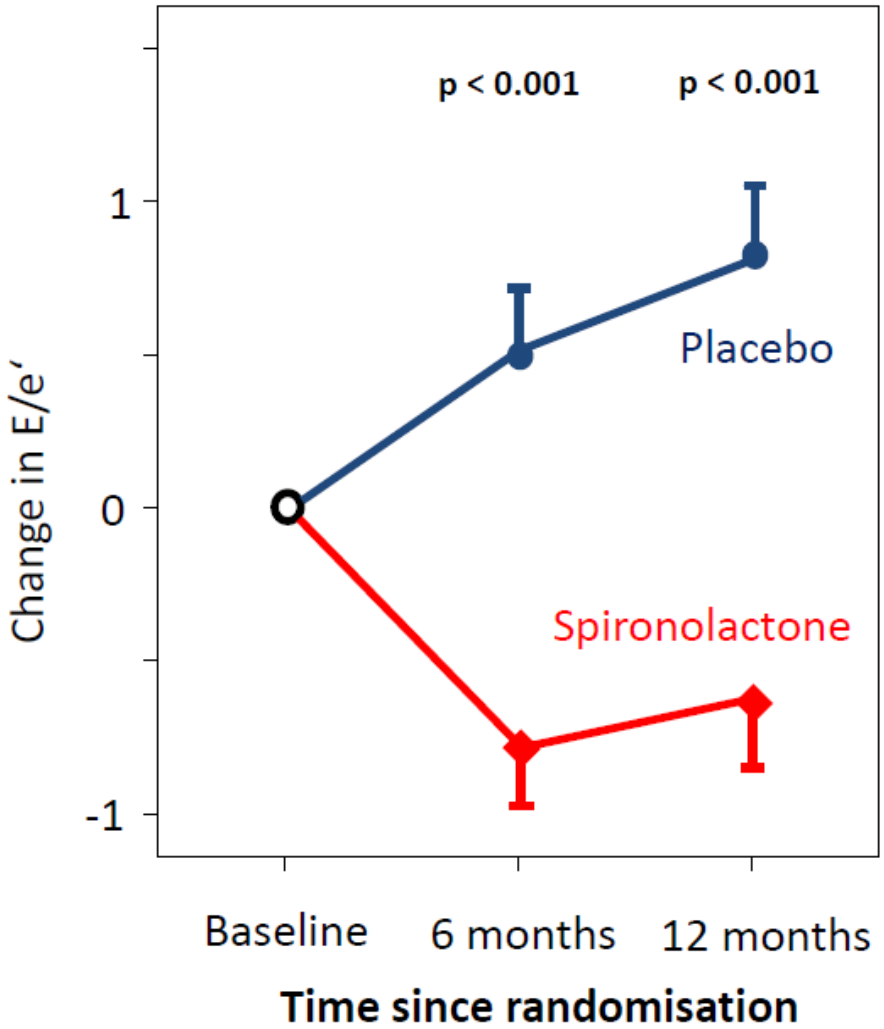
Registered at *www.controlled-trials.com*: ISCRTN94726526; Eudra-CT no. 2006-002605-31

Primary endpoint - E/é

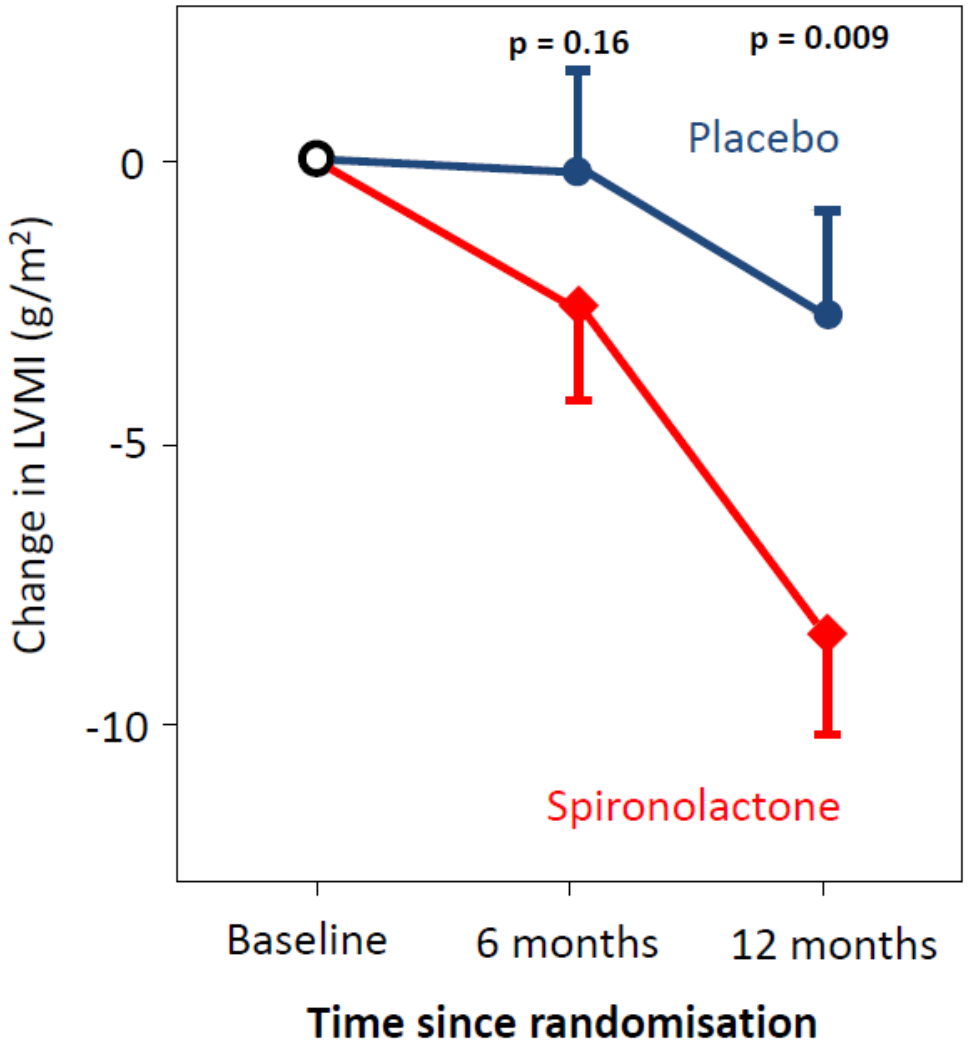
Spironolactone: 12.7±3.6 to 12.1±3.7

Placebo: 12.8±4.4 to 13.6±4.3

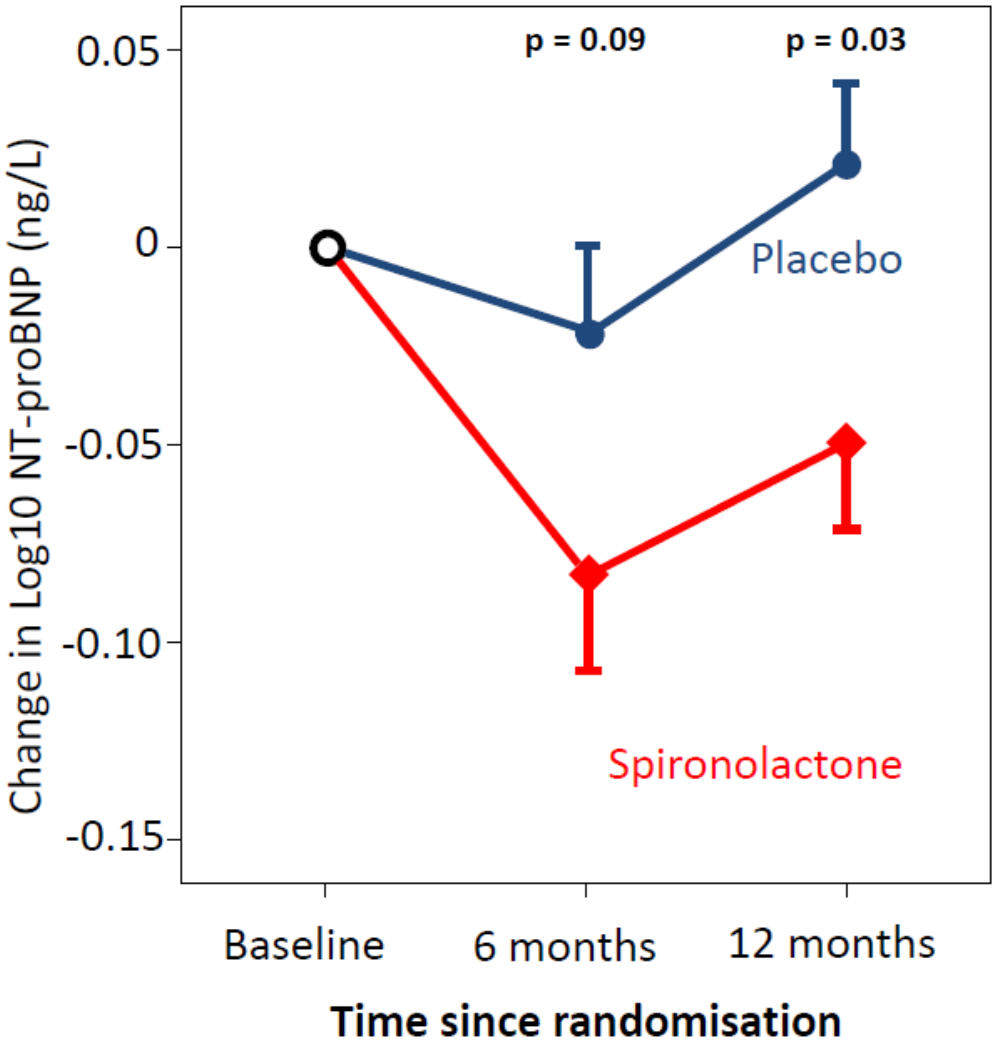
(**P<0.001** for difference between groups)



Secondary endpoint - LV mass index

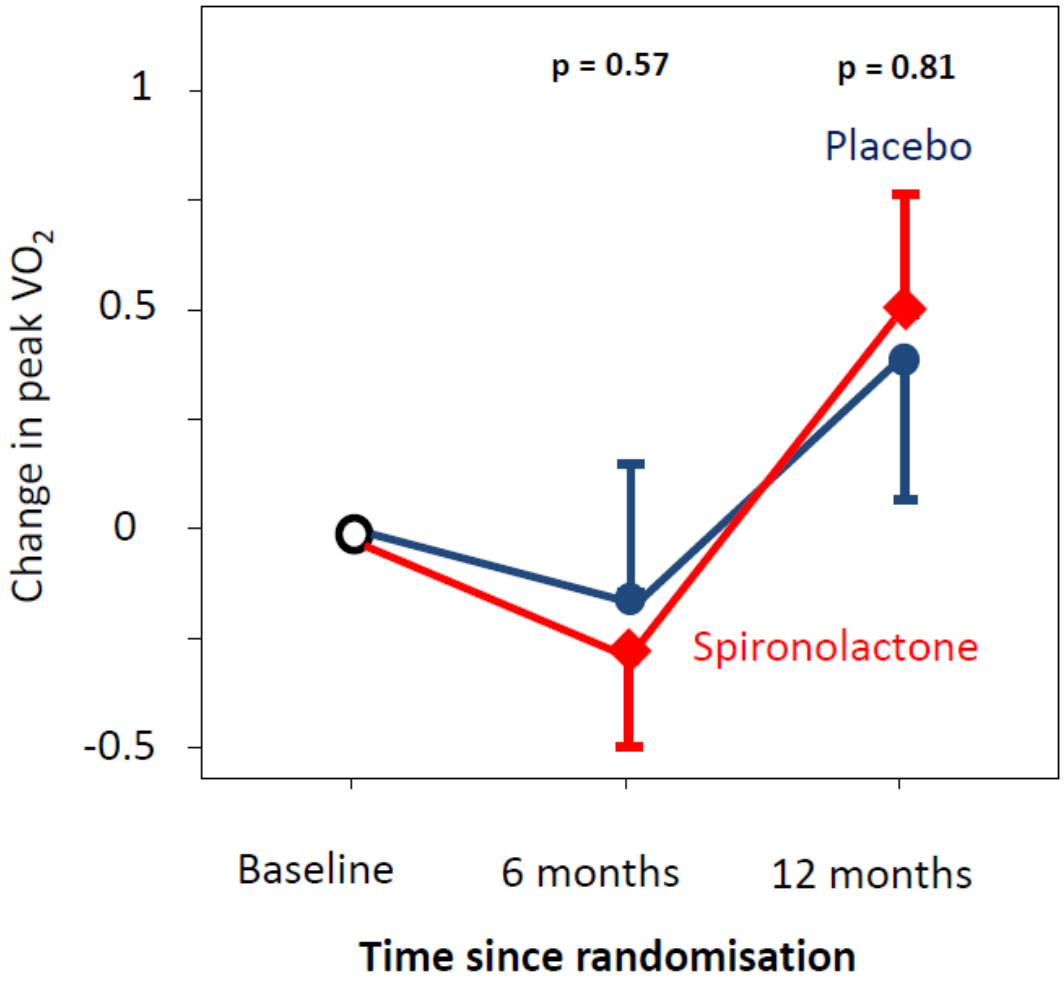


Secondary endpoint: NT-proBNP

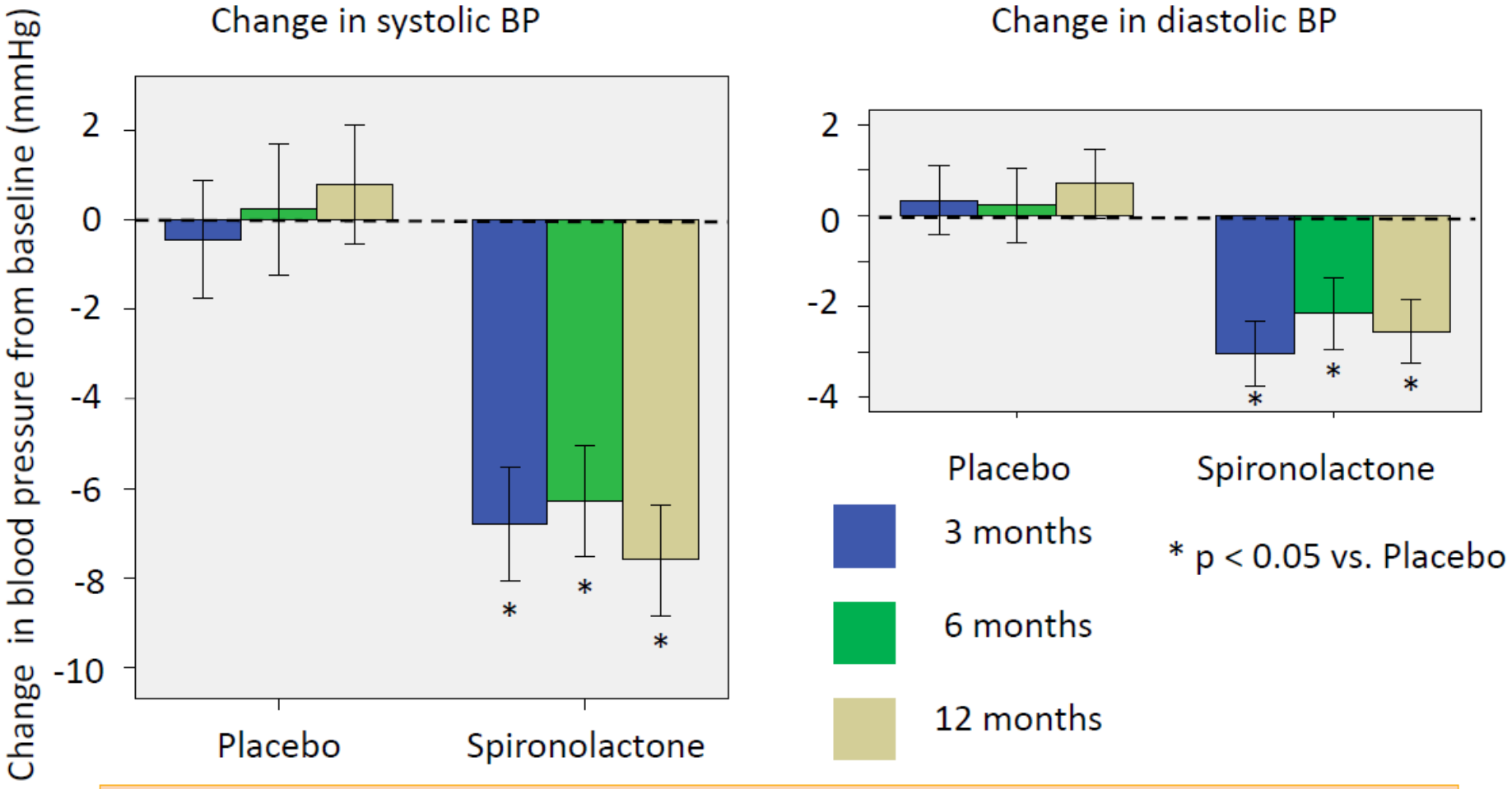


Primary endpoint - peak VO_2

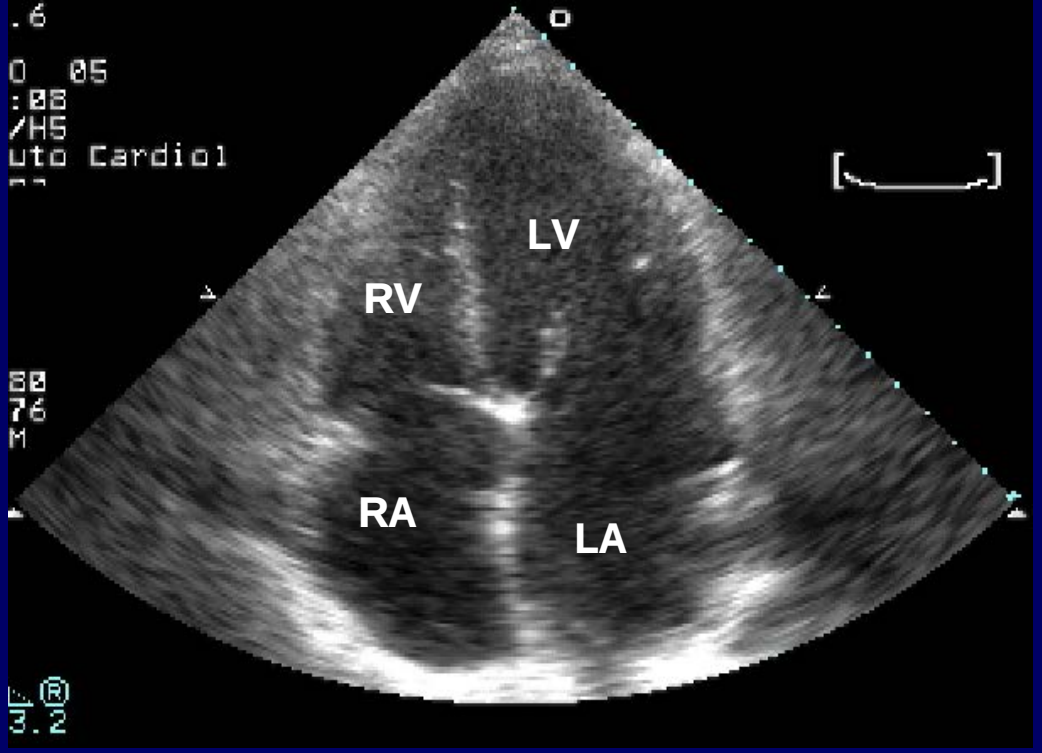
Spironolactone: 16.3±3.6 to 16.8±4.6mL/min/kg
Placebo: 16.4±3.5 to 16.9±4.4mL/min/kg
(**P=0.67** for difference between groups)

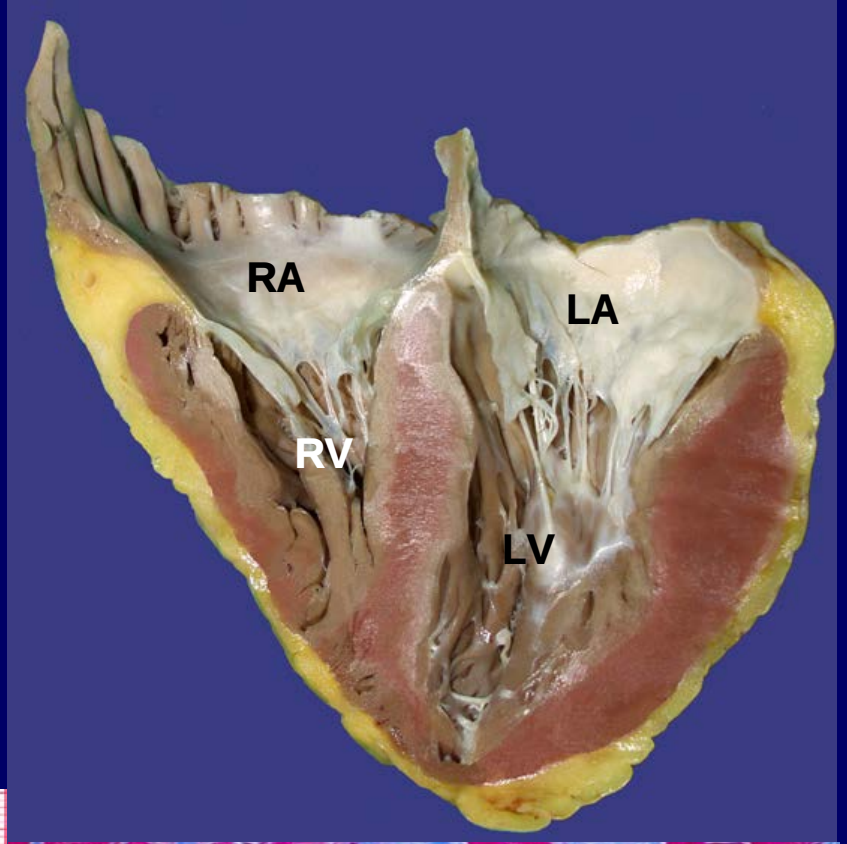


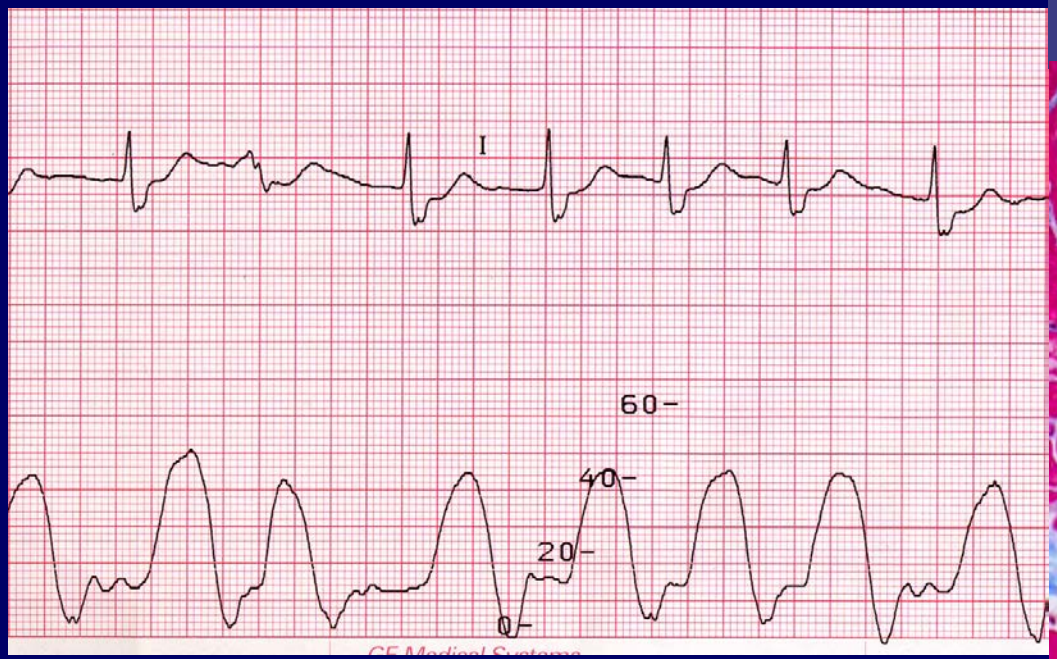
Blood Pressure (BP)

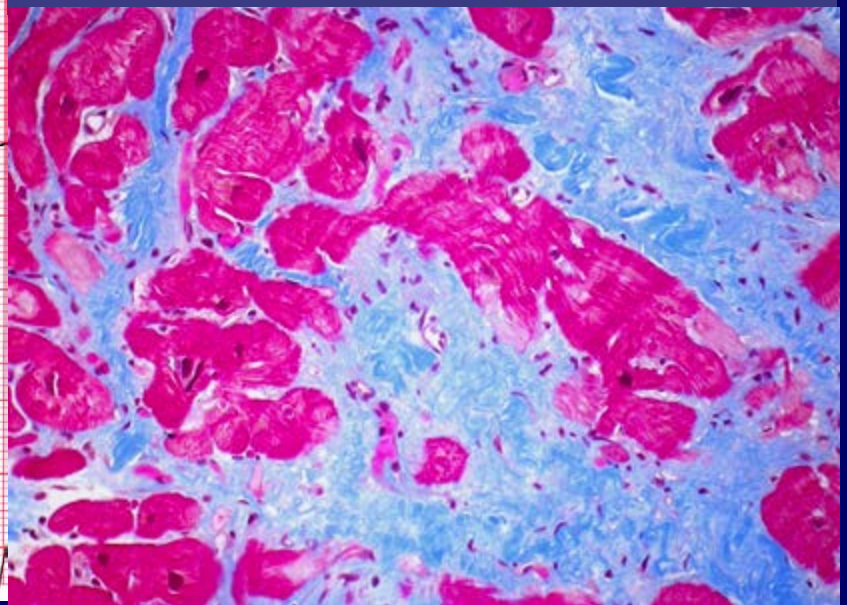


Results for functional and structural reverse remodelling remained significant after adjusting for blood pressure effects

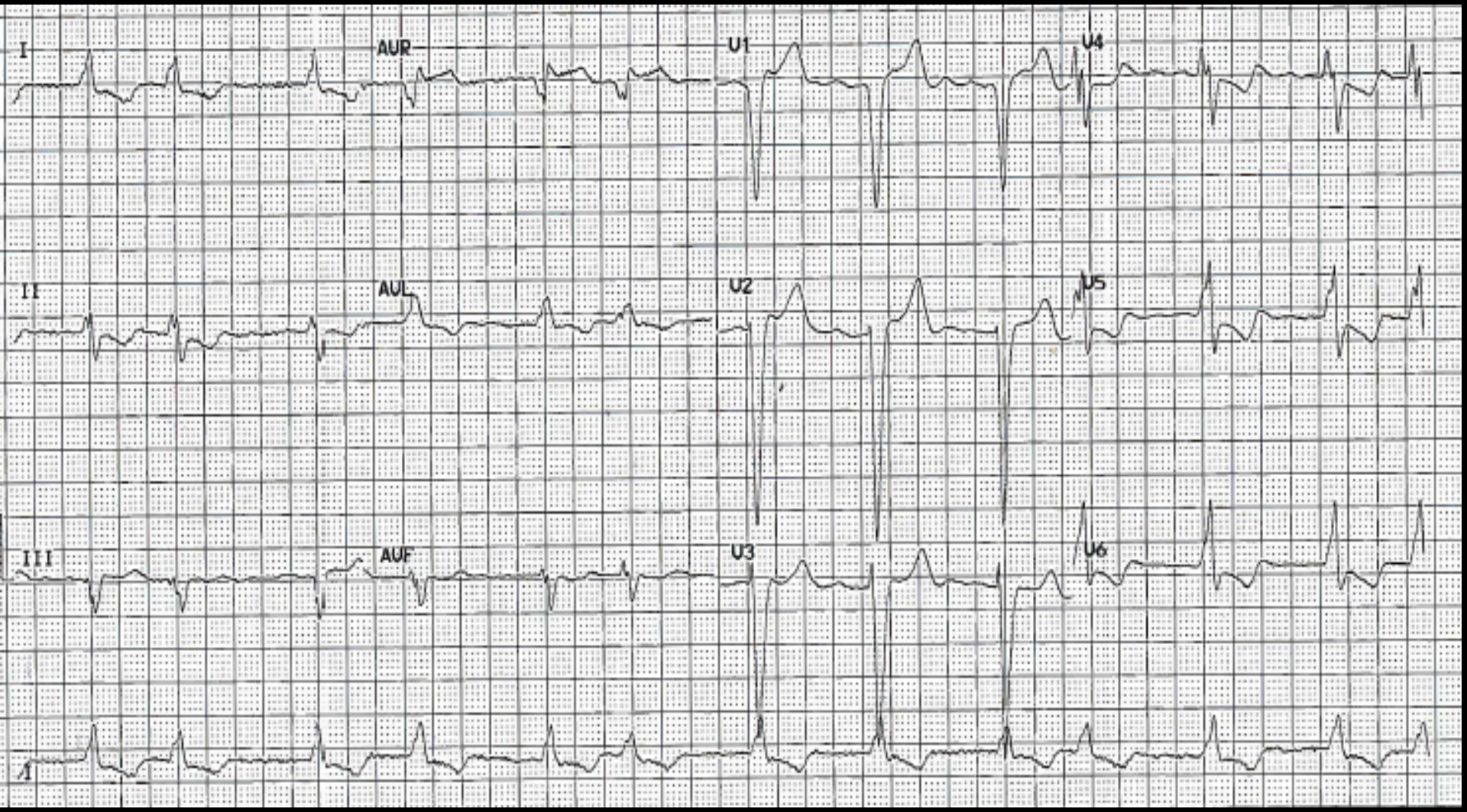

LV
RV
RA
LA

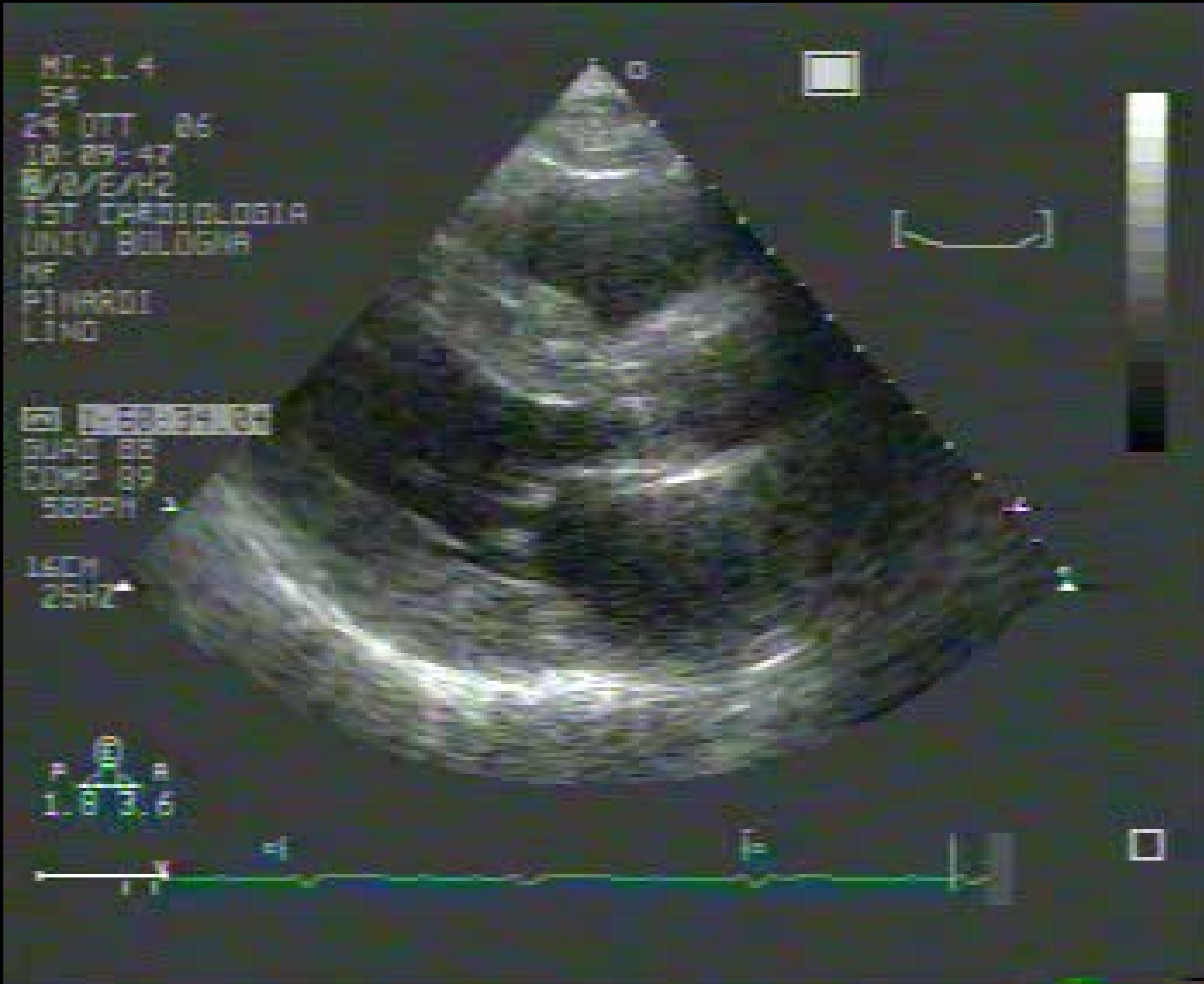

RA
LA
RV
LV


I
60
40
20
0

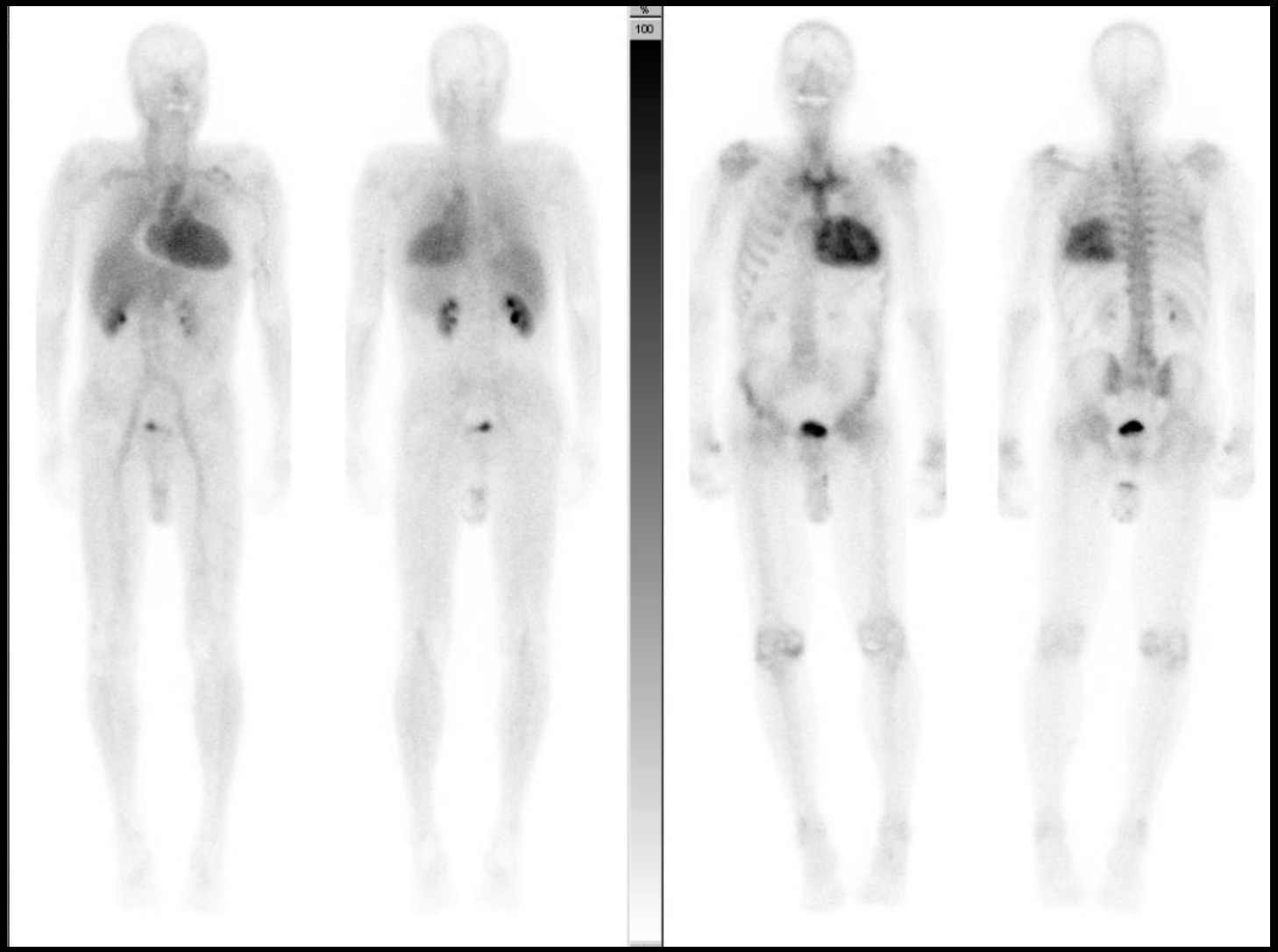


PL ♂ 70 yrs old



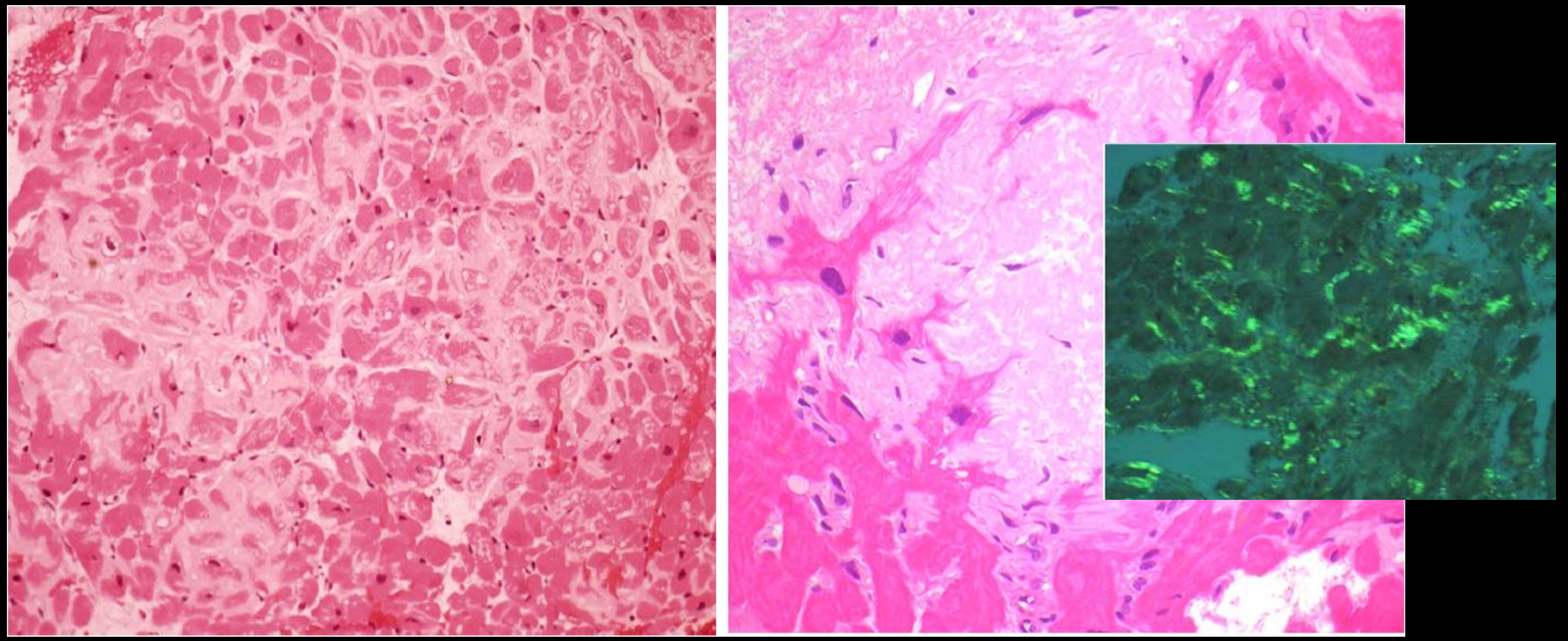

MI 1.4
24 OTT 06
IST CARDIOLOGIA
UNIV BOLOGNA
14CM
25HZ

^{99m}Tc-DPD scintigraphy

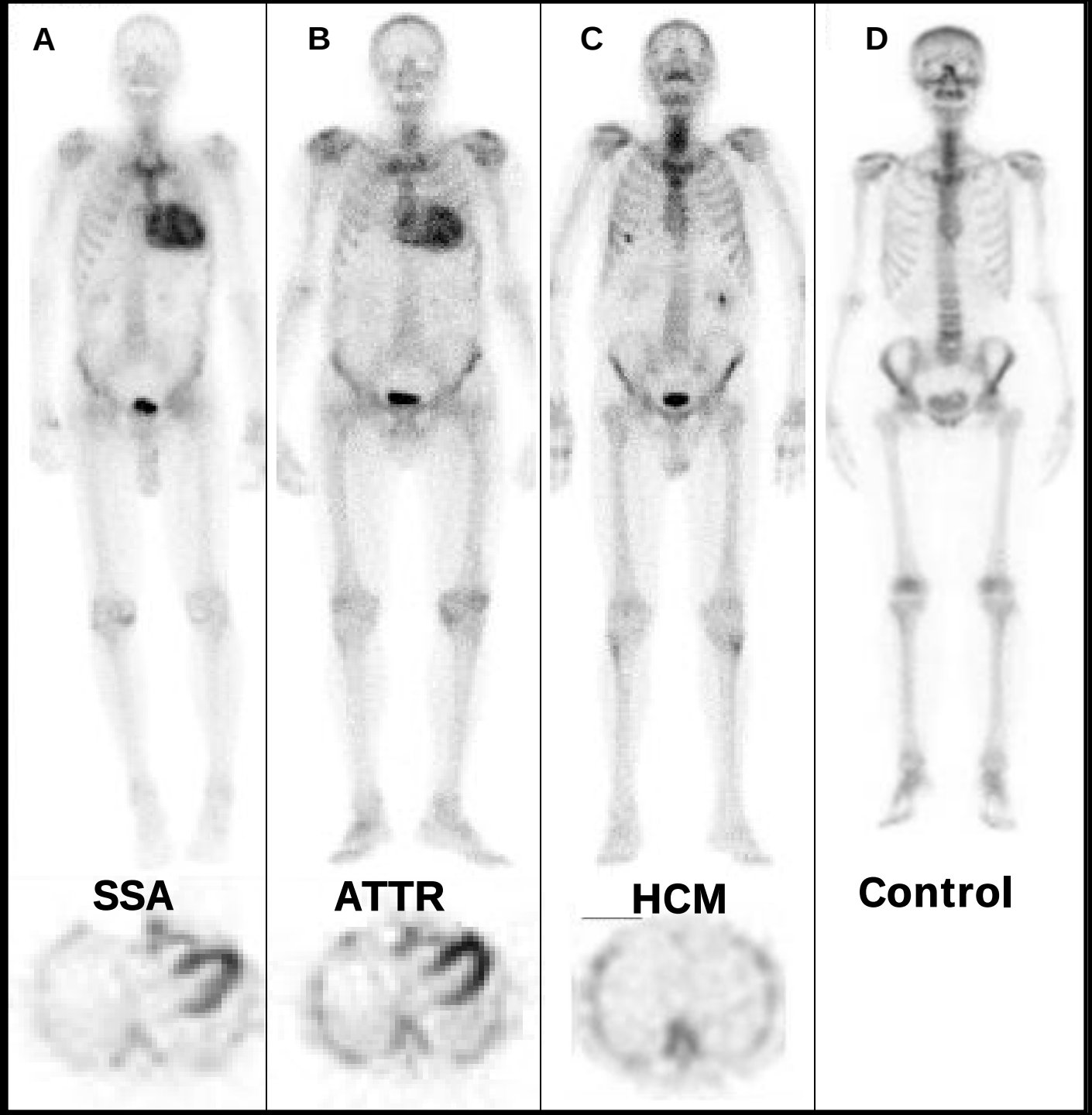


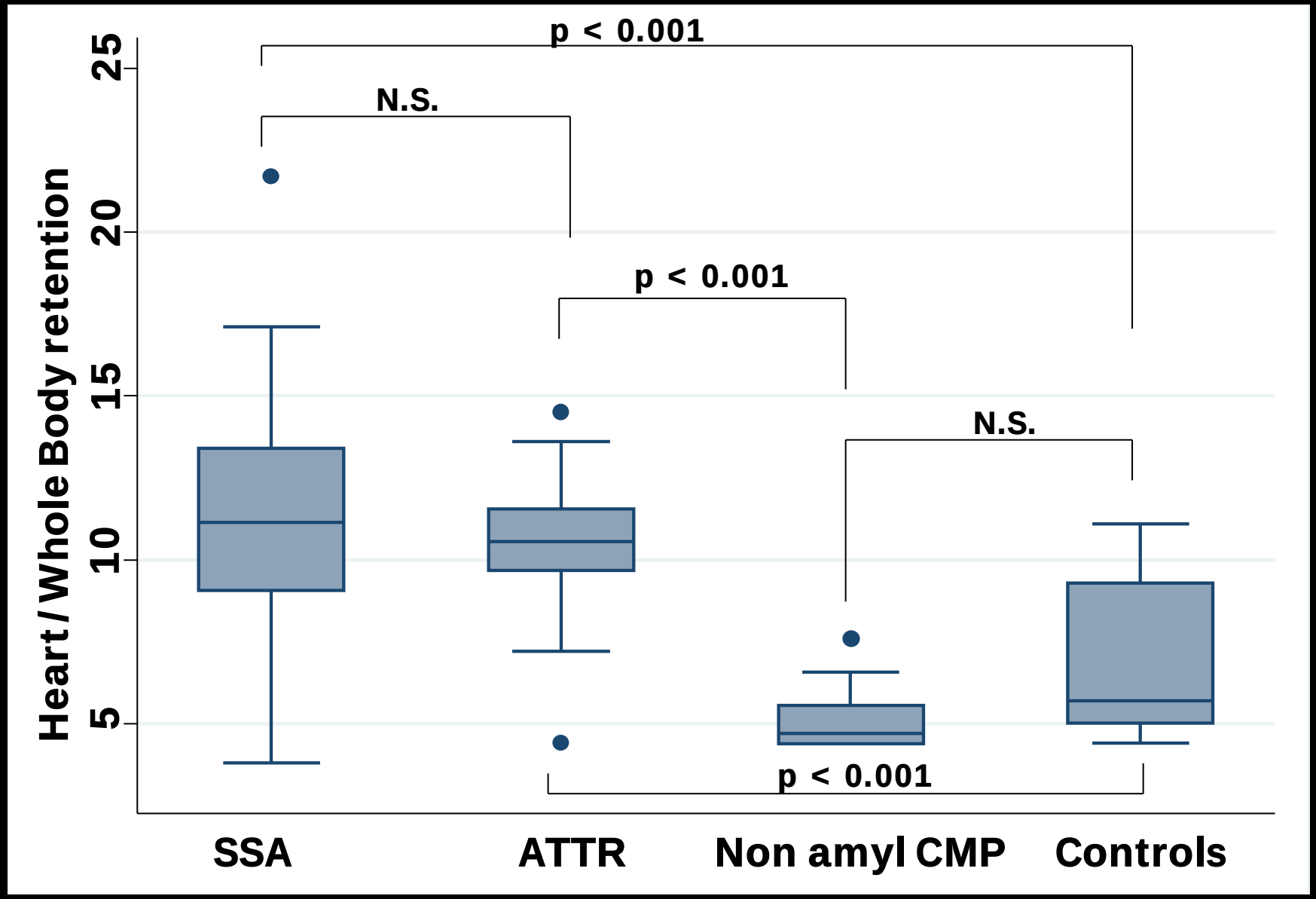
Early scan (5 min)

Late scan (3 h)



EMB : cardiac amyloidosis. Severe entity of deposition. Interstitial and endocardial localization. Moderate myocytes damage.


A
B
C
D
SSA
ATTR
HCM
Control

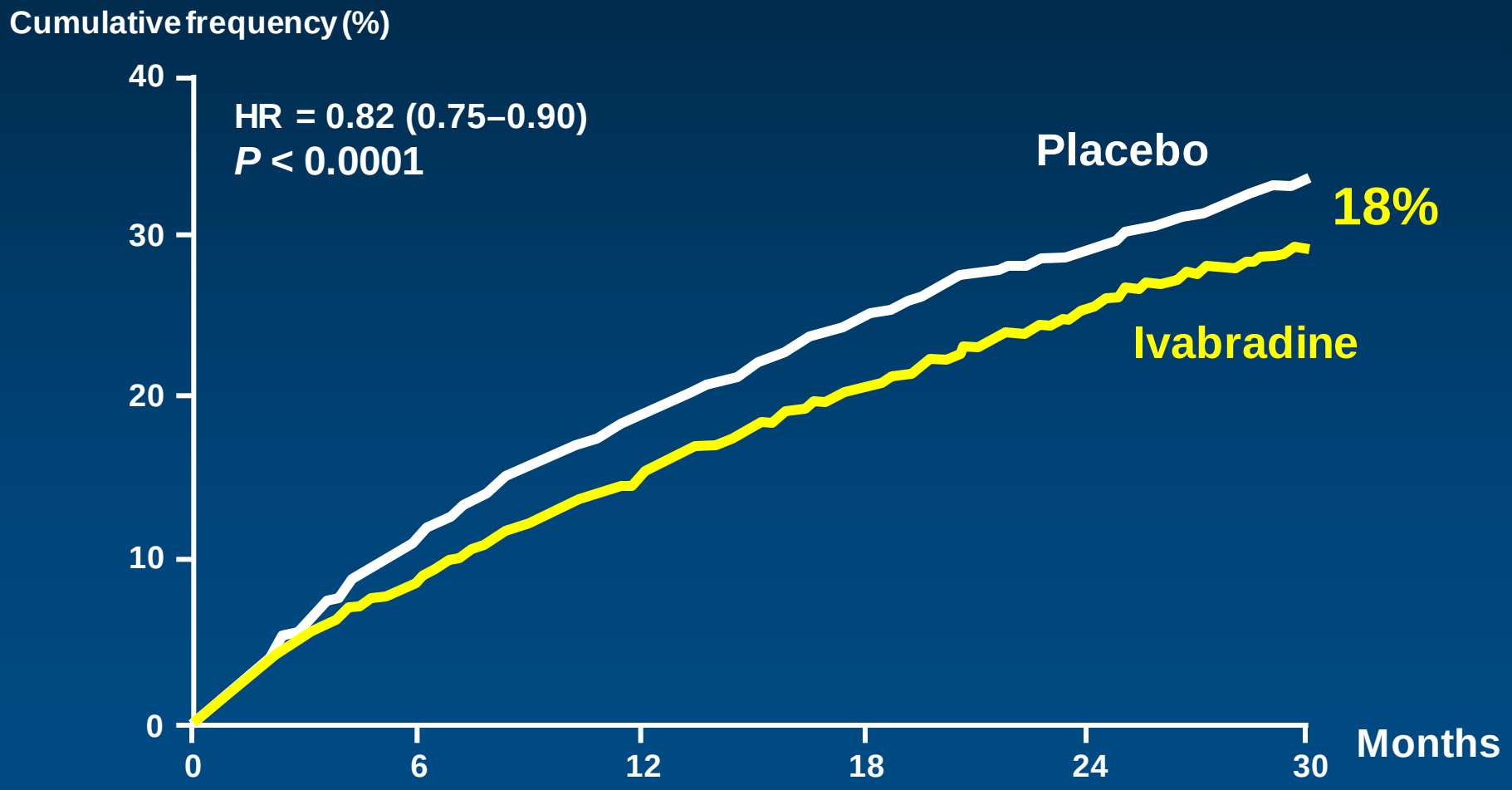


Quarta CC et al, J Am Coll Cardiol Img in press

Pharmacological therapy of AF in Pts with impaired LV function

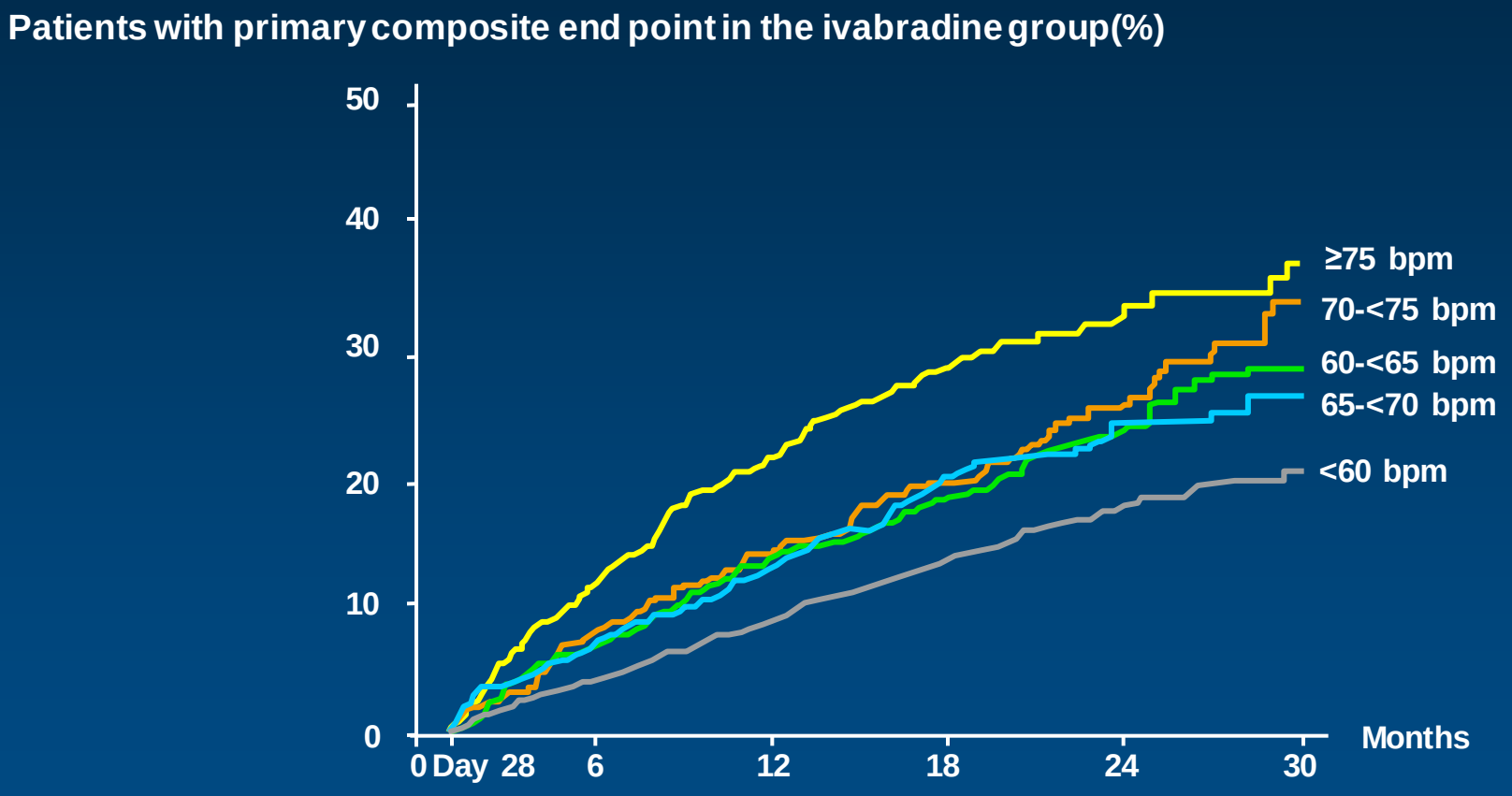
- Robustness of guidelines (?)
- The «Dronedarone saga»
- Ventricular dysfunction vs Heart Failure
- Sistolic vs diastolic HF
- Residual chances of upstream therapy (?)
- Optimal heart rate values

Primary composite end point (CV death or hospital admission for worsening HF)



Swedberg K, et al. *Lancet*. 2010;376:875-885.

Primary composite end point according to HR achieved at D28*

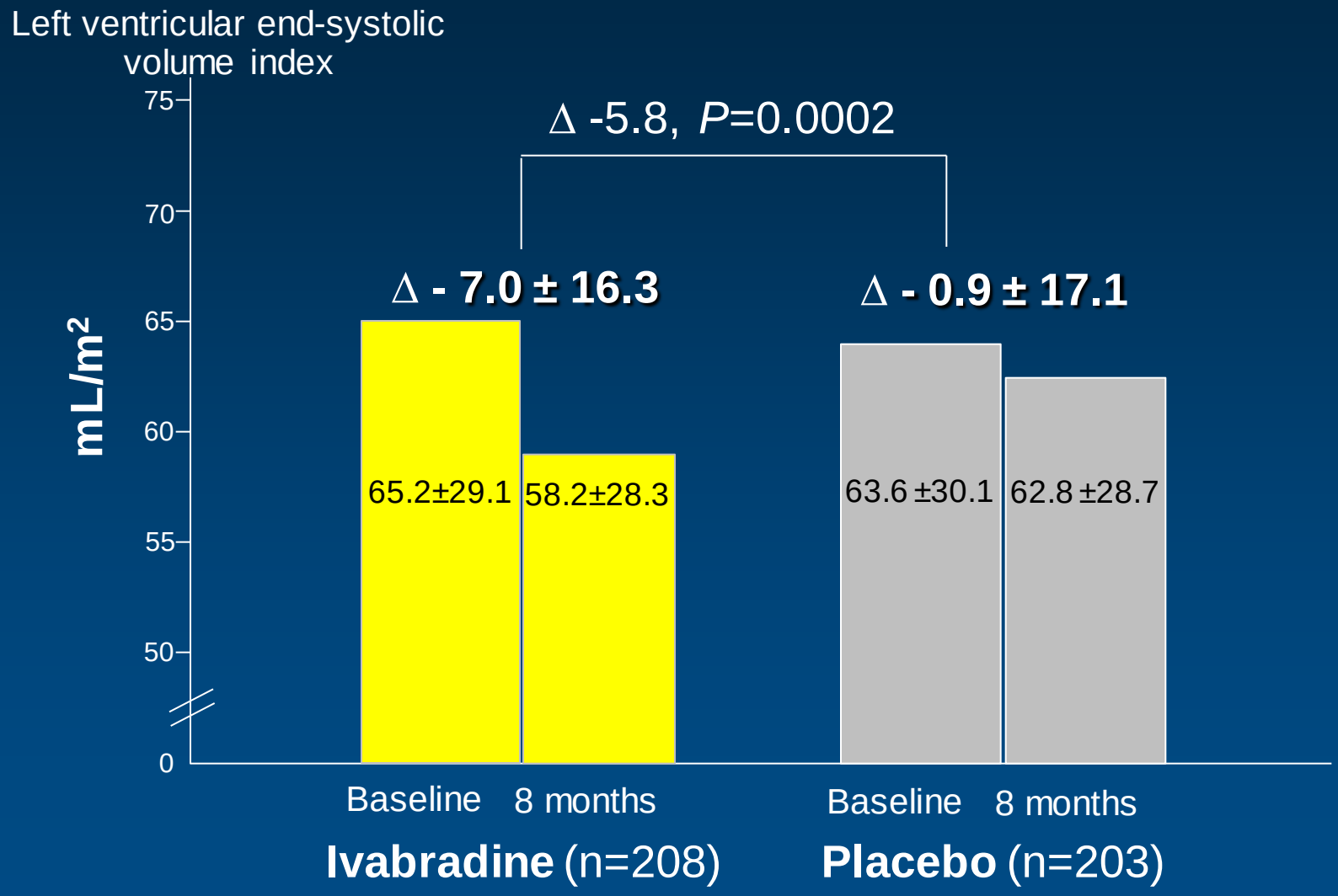


**Data exclude patients reaching primary composite end point in the first 28 days*

Böhm M, et al. *Lancet.* 2010;376:886-894.

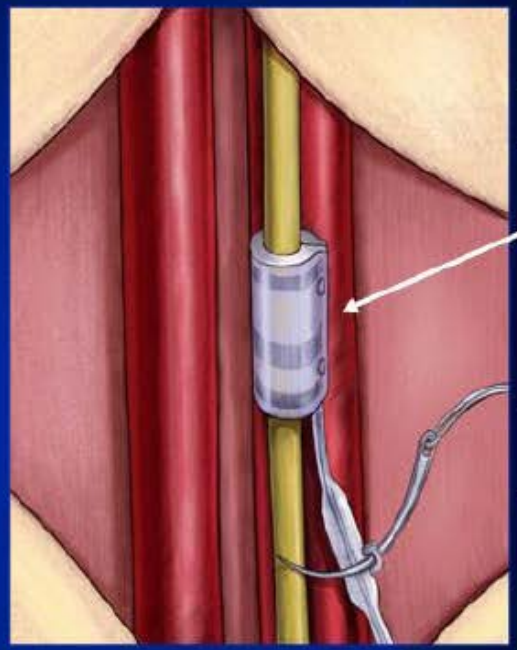
Heart Rate reduction is a positive inotropic intervention in HF !!

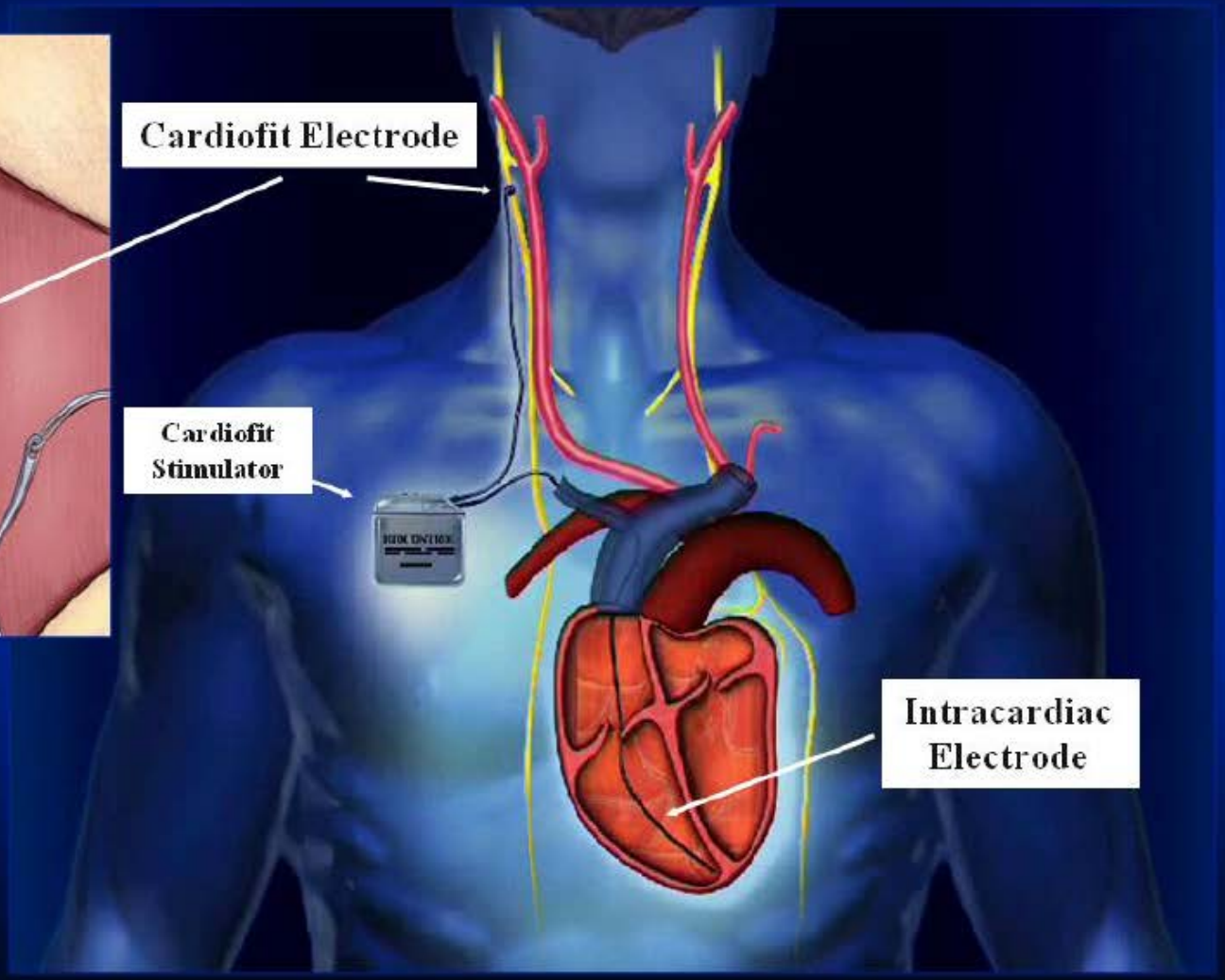
Primary endpoint: change in LVESVI from baseline to 8 months



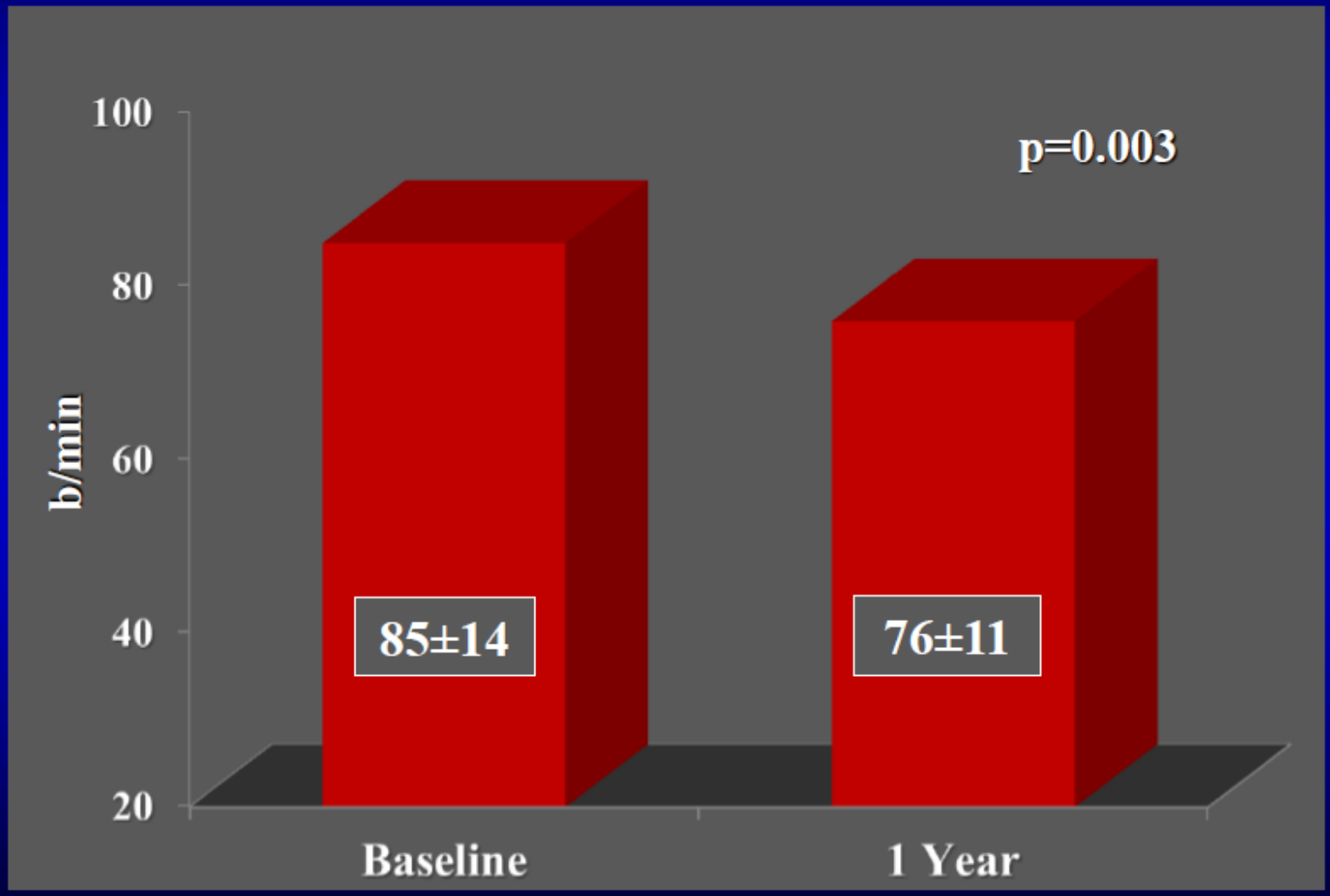
SHIFT Echocardiography substudy: Eur.Heart J. doi:10.1093/eurhearti/ehr311

Device Components

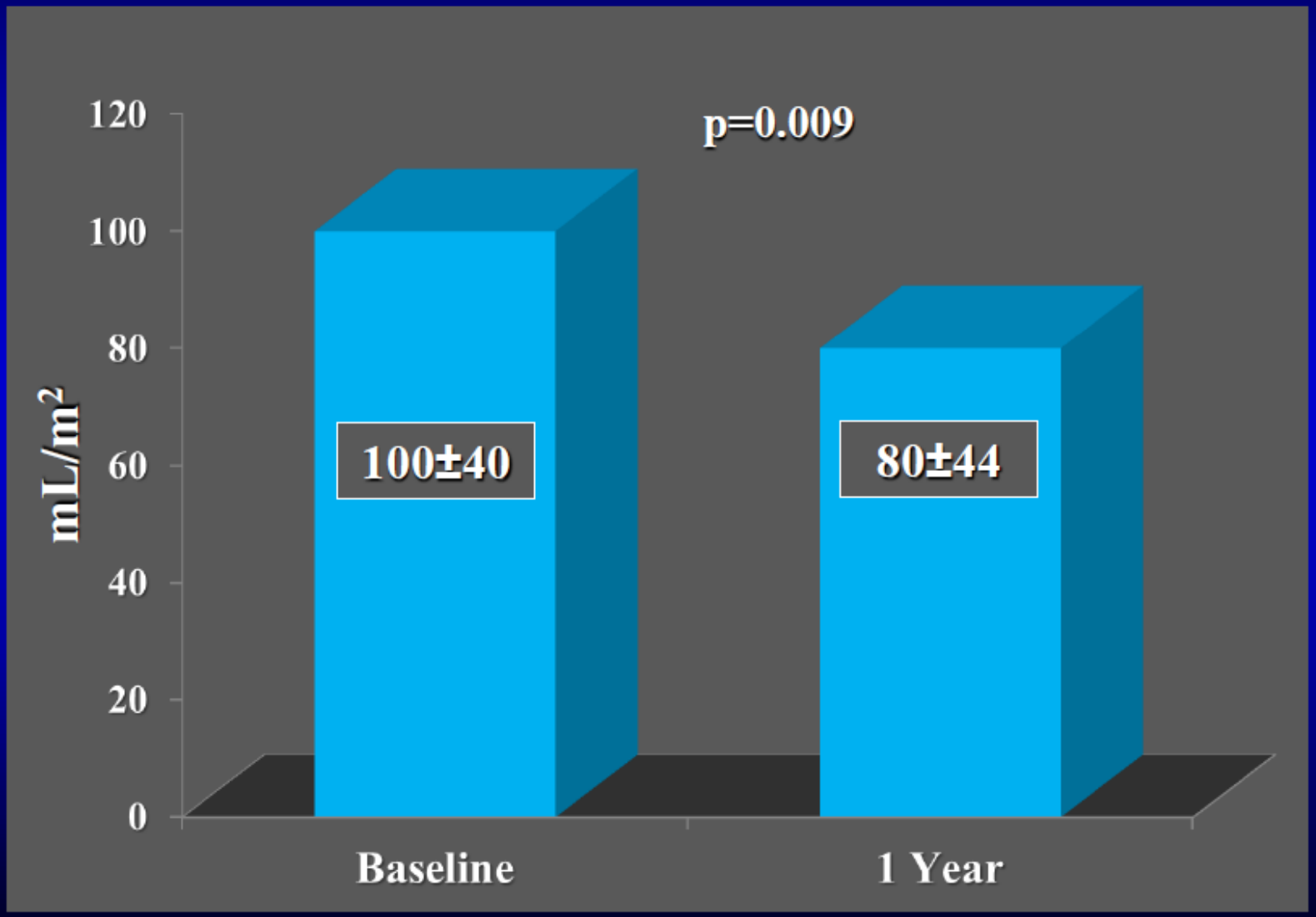




Heart Rate (n=23)

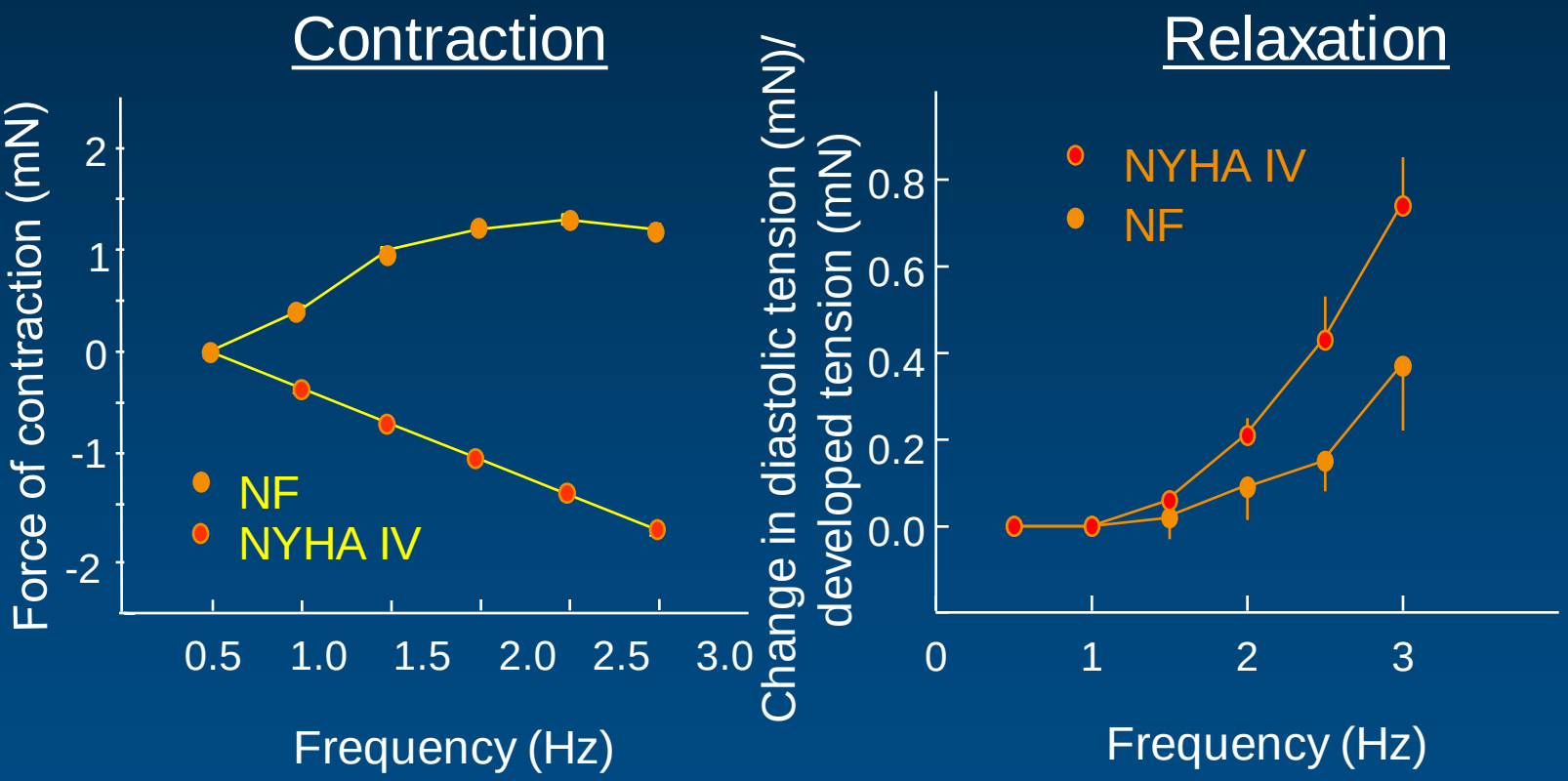


Left Ventricular End-Systolic Volume Index (n=23)



Pathophysiological background

Human Papillary Muscle Strips



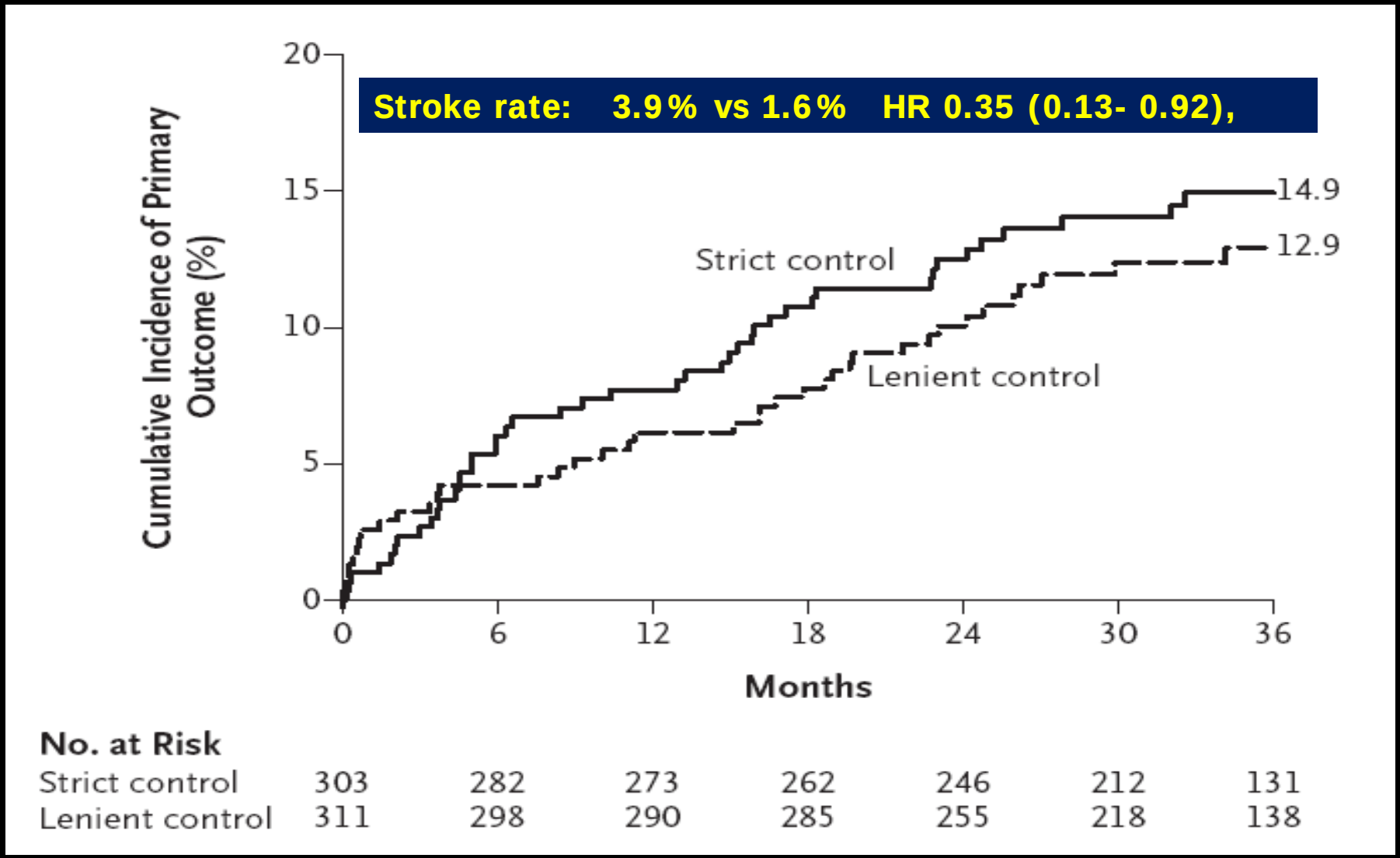
Böhm et al., *Clin Invest,* 1992

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 15, 2010 VOL. 362 NO. 15

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Isabelle C. Van Gelder, M.D., Hessel F. Groenveld, M.D., Harry J.G.M. Crijns, M.D., Ype S. Tuininga, M.D., Jan G.P. Tijssen, Ph.D., A. Marco Alings, M.D., Hans L. Hillege, M.D., Johanna A. Bergsma-Kadijk, M.Sc., Jan H. Cornel, M.D., Otto Kamp, M.D., Raymond Tukkie, M.D., Hans A. Bosker, M.D., Dirk J. Van Veldhuisen, M.D., and Maarten P. Van den Berg, M.D., for the RACE II Investigators*



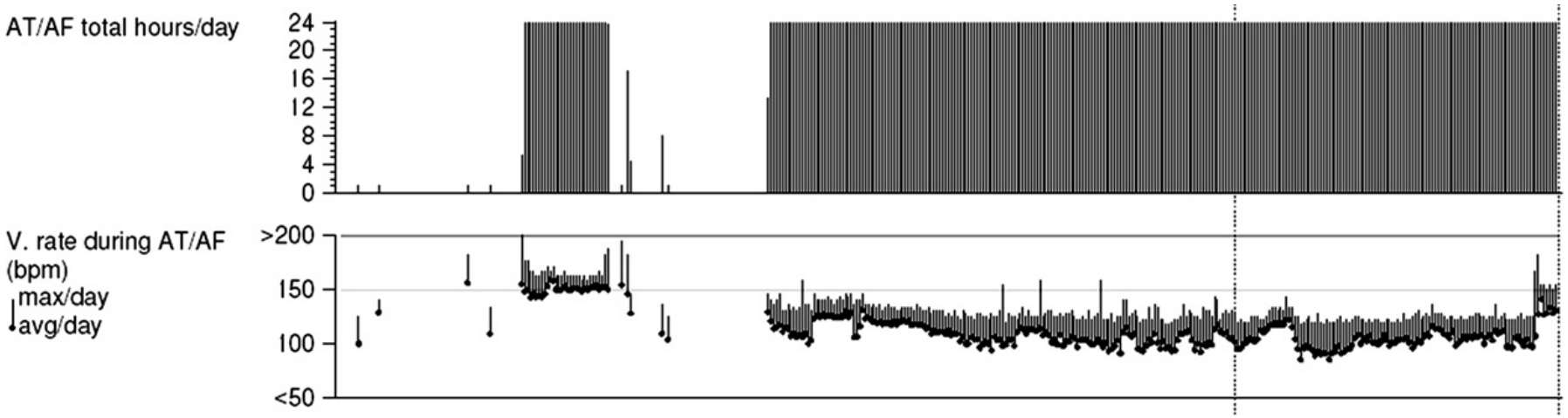
Strict rate control: HR < 80 / min at rest
HR < 110 / min during exercise

Van Gelder IC et al, N Engl J Med 2010;362:1363-73

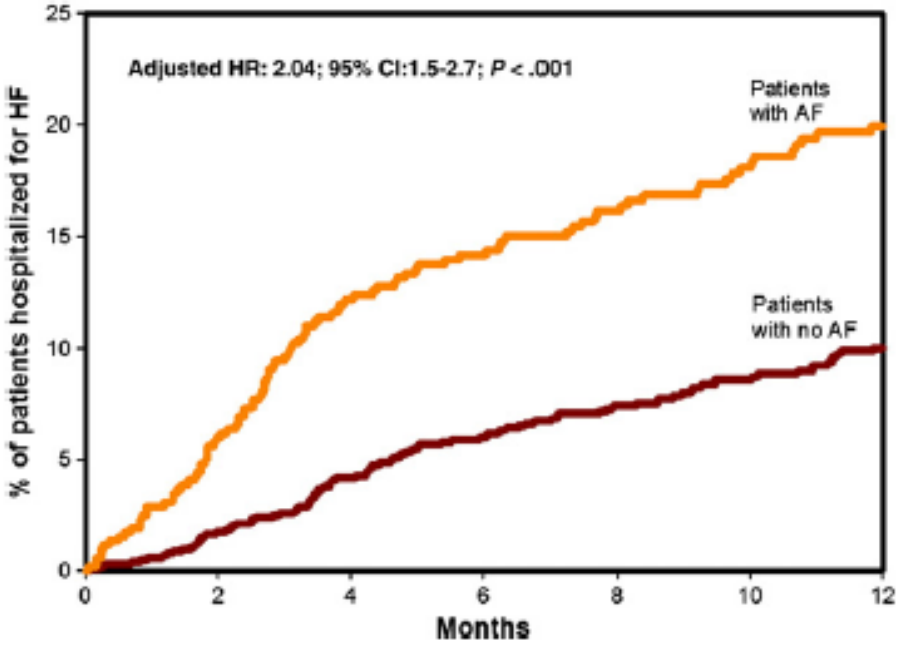
Burden of atrial fibrillation and poor rate control detected by continuous monitoring and the risk for heart failure hospitalization

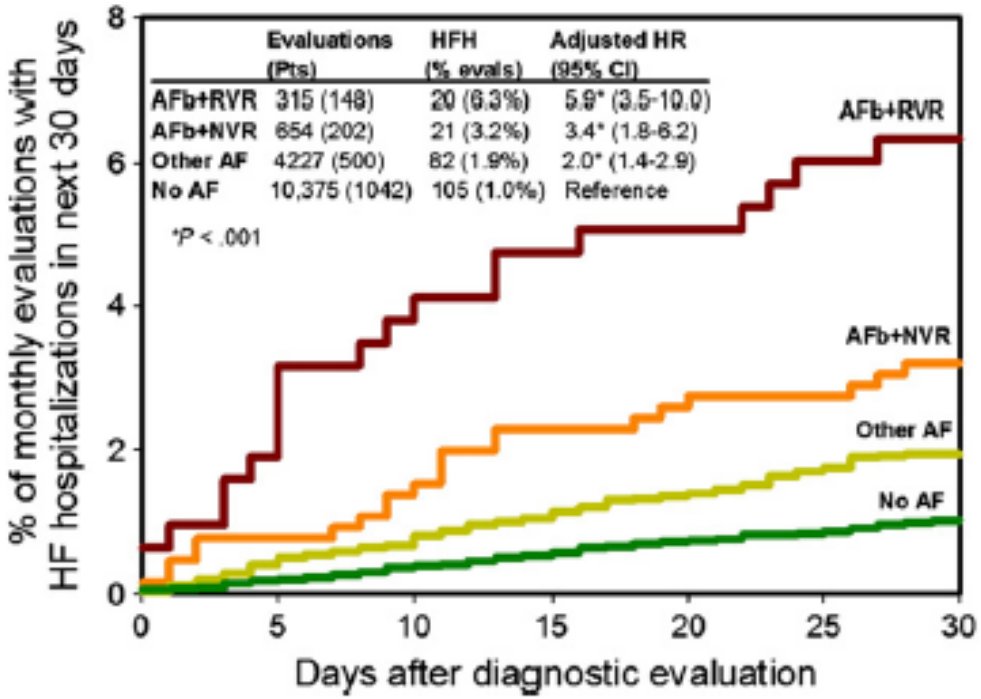
Shantanu Sarkar, PhD,[a] Jodi Koehler, MS,[a] George H. Crossley, MD,[b] W. H. Wilson Tang, MD,[c] William T. Abraham, MD,[d] Eduardo N. Warman, PhD,[a] and David J. Whellan, MD[e] *Mounds View, MN; Nashville, TN; Cleveland, and Columbus, OH; and Philadelphia, PA*

Am Heart J 2012;164:616-24



Time to first hospitalization





Sarkar S et al, Am Heart J 2012;164:616-24

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