Antagonisti recettoriali dell'angiotensina, dall'ipertensione all'insufficienza cardiaca: ruolo del Candesartan

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Il sottoscritto GIANFRANCO SINAGRA
in qualità di (moderatore, relatore, formatore, tutor, docente)

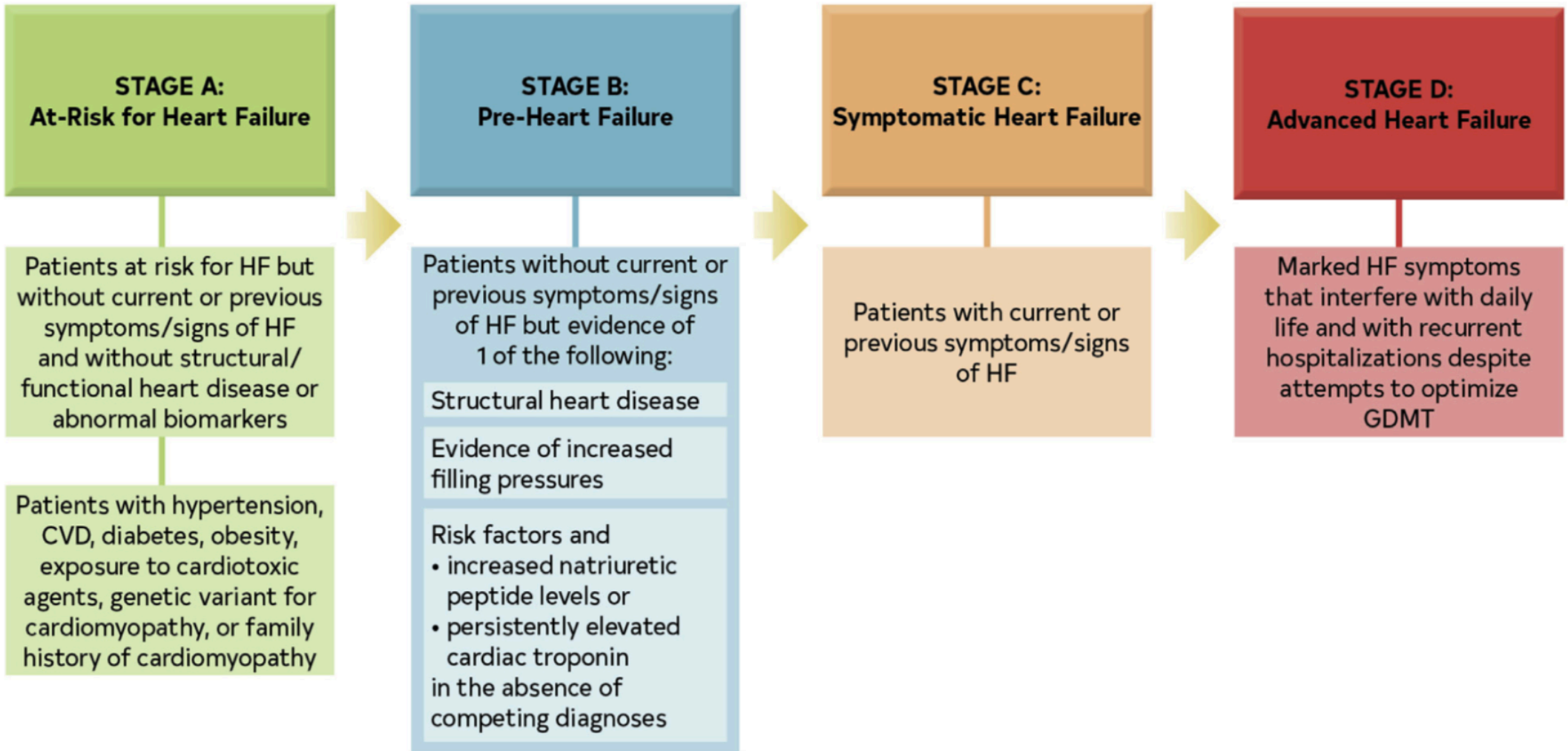
ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
Negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi in campo sanitario:

Bruno Farmaceutici, Novartis, Astrazeneca, Novo Nordisk, Boston Scientific, Menarini, Amgen, Sanofi, Boehringer Ingelheim, Pfizer, Alnylam (Relatore a congressi)

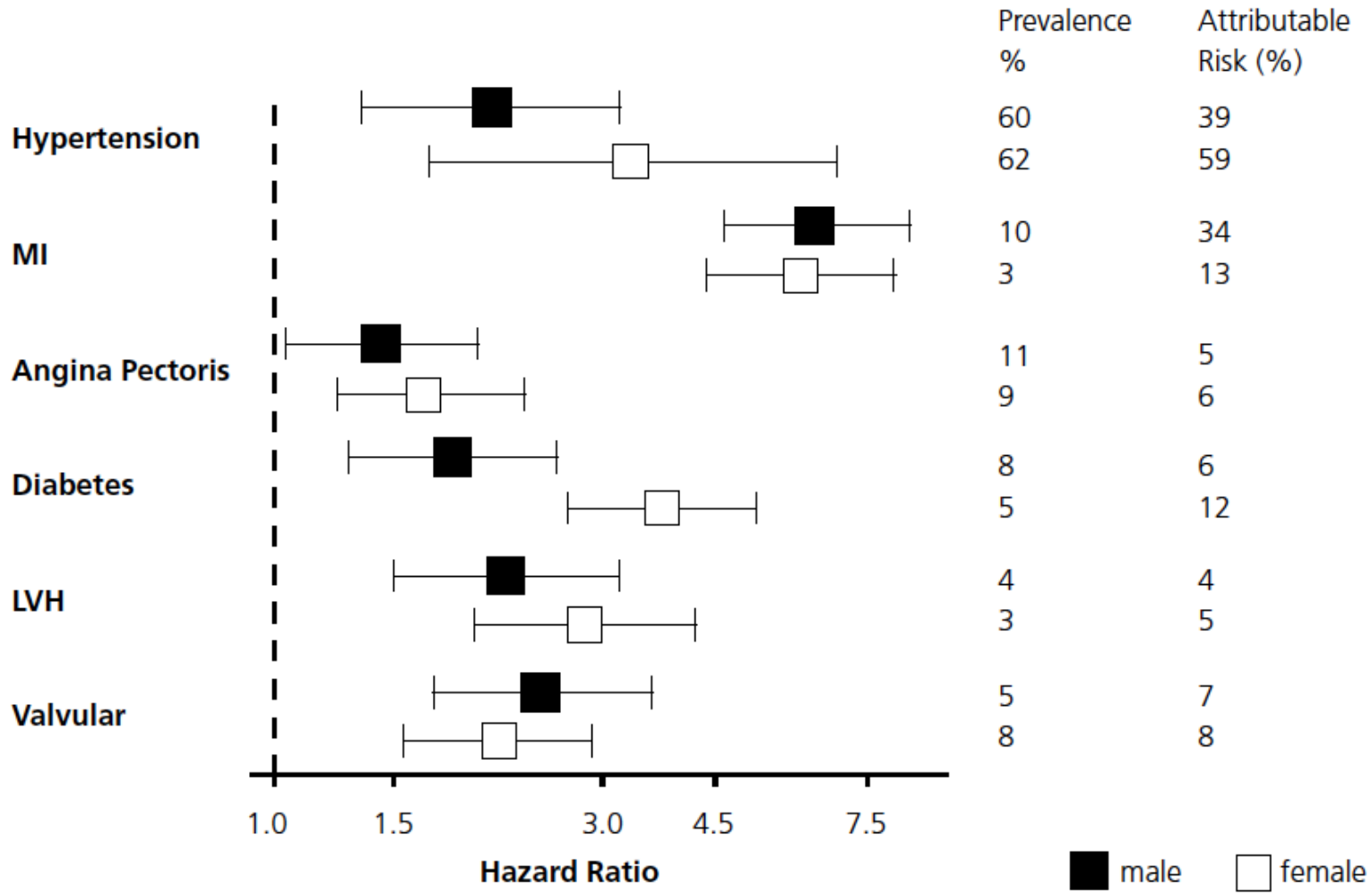
Bayer, BMS (Consulenze e Collaborazione scientifica occasionale)

FIGURE 1 ACC/AHA Stages of HF



From Hypertension to Heart Failure – Are There Better Primary Prevention Strategies?

Peter A Meredith, Jan Östergren†*



The hazard ratios for important risk factors for development of heart failure, their prevalence and the derived population-attributable risk

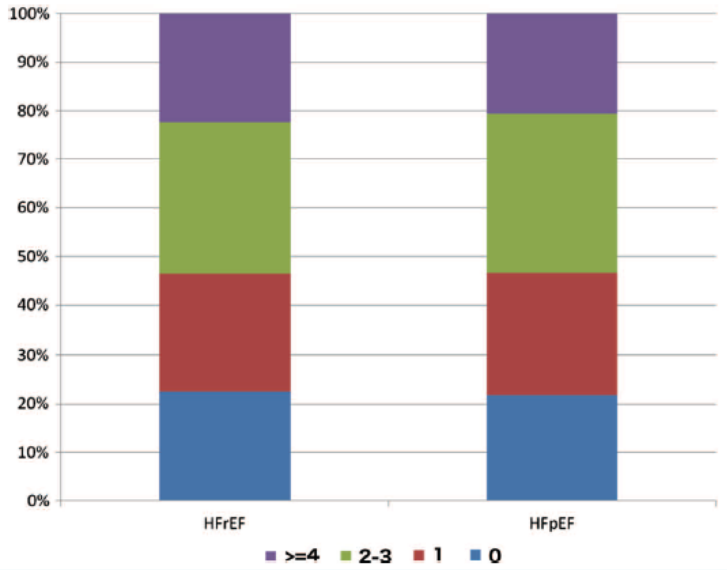
JRAAS 2006;7:64-73

Prevalence and prognostic impact of non-cardiac co-morbidities in heart failure outpatients with preserved and reduced ejection fraction: a community-based study

Iorio, Sinagra et al.
Eur J Heart Fail 2018

2314 pts
941 HFrEF
1373 HFpEF

Clinical characteristics	Overall ($n = 2314$)	HFrEF ($n = 941$; 41%)	HFpEF ($n = 1373$; 59%)	*P*-value (HFrEF vs. HFpEF)
Age, years, mean (SD)	77 (10)	76 (10)	79 (9)	<0.001
Male gender, *n* (%)	1325 (57)	658 (70)	667 (49)	<0.001
NYHA class, *n* (%)				
I	790 (34)	302 (32)	488 (35)	0.06
II	993 (43)	392 (42)	601 (44)	0.05
III–IV	531 (23)	178 (19)	235 (17)	0.05
Body mass index, kg/m^2, mean (SD)	28 (5)	27 (4)	28 (5)	0.001
Systolic blood pressure, mmHg, mean (SD)	134 (19)	130 (20)	136 (20)	<0.001
Heart rate, b.p.m., mean (SD)	73 (16)	73 (17)	73 (16)	0.42
Left ventricular ejection fraction, %, mean (SD)	51 (15)	36 (8)	61 (7)	
eGFR, mL/min/1.73 m^2, mean (SD)	66 (25)	65 (25)	66 (25)	0.37
Sodium, mEq/L, mean (SD)	139 (12)	139 (12)	139 (12)	0.91
Haemoglobin, g/dL, mean (SD)	13.2 (3)	13 (2)	13 (4)	0.32
Ischaemic heart disease, *n* (%)	1116 (46)	572 (61)	544 (40)	0.001
Atrial fibrillation, *n* (%)	1235 (54)	437 (46)	798 (58)	<0.001
Non-cardiac co-morbidities, *n* (%)				
Hypertension	1863 (80)	732 (79)	1131 (82)	0.01



From Hypertension to Heart Failure – Are There Better Primary Prevention Strategies?

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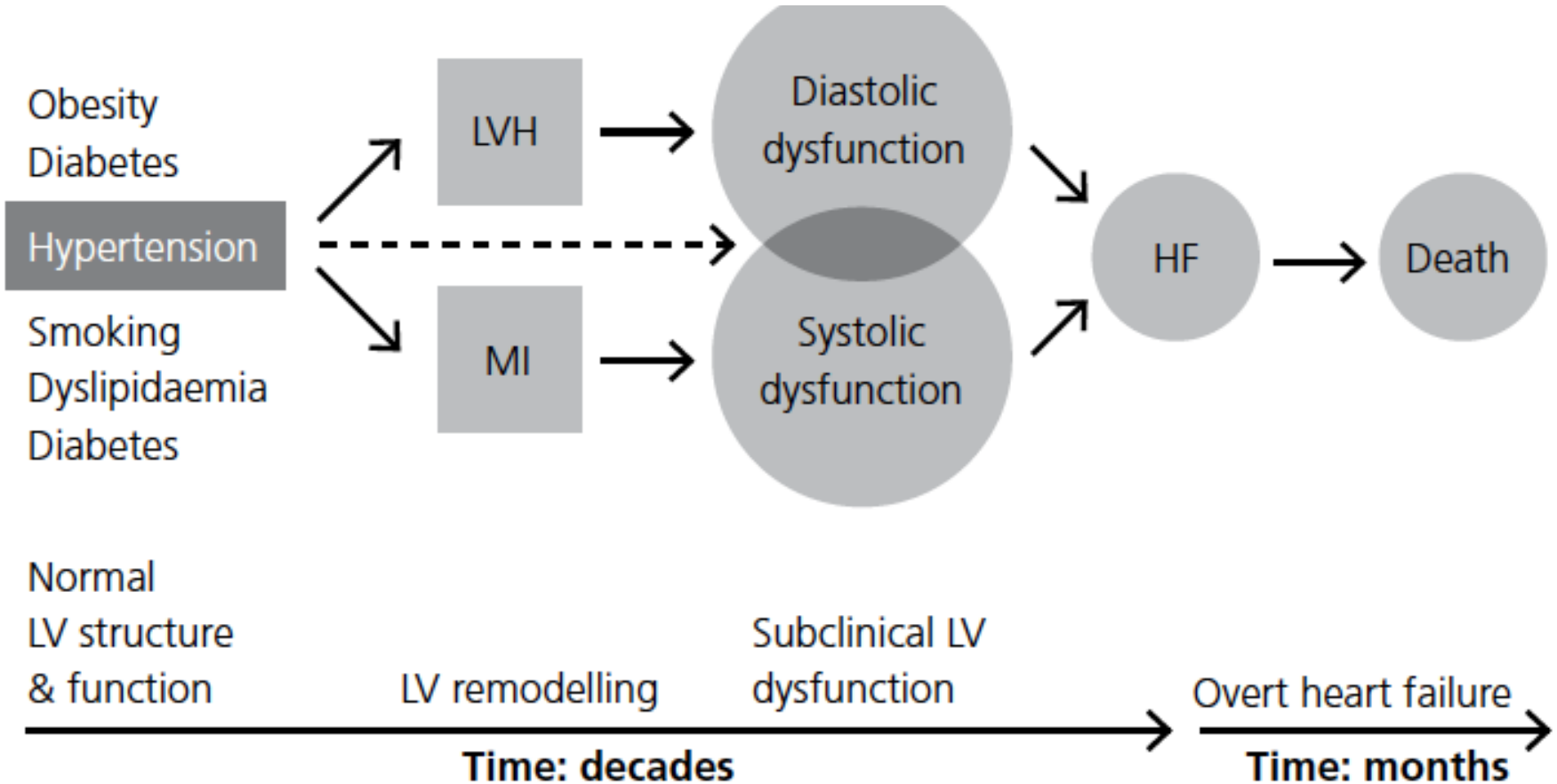


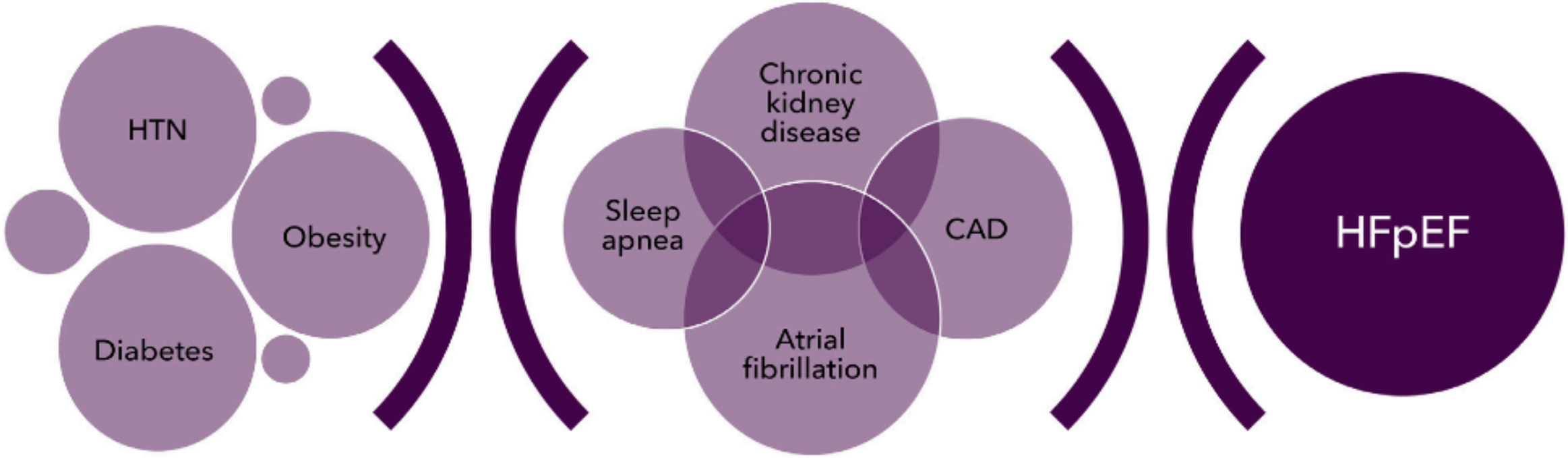
JRAAS 2006;7:64-73

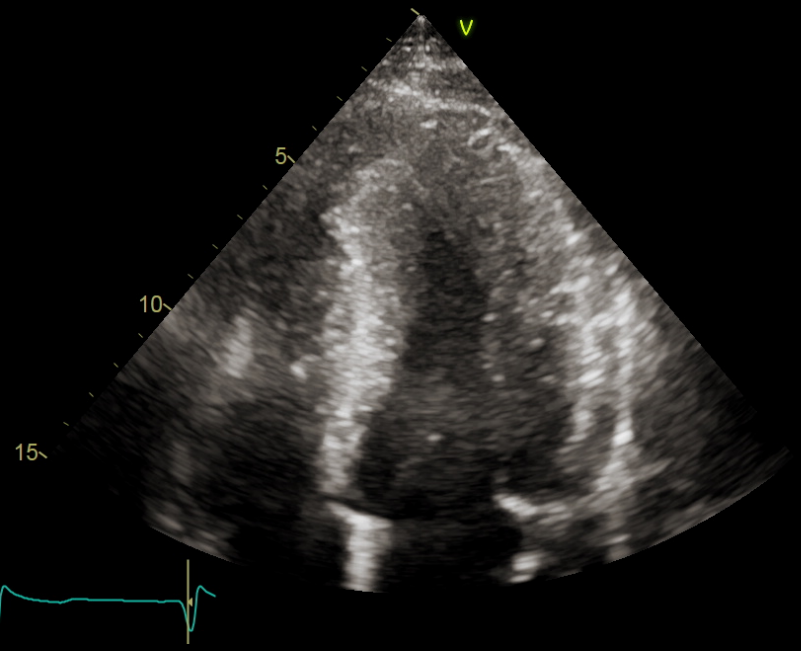
EXPERT CONSENSUS DECISION PATHWAY

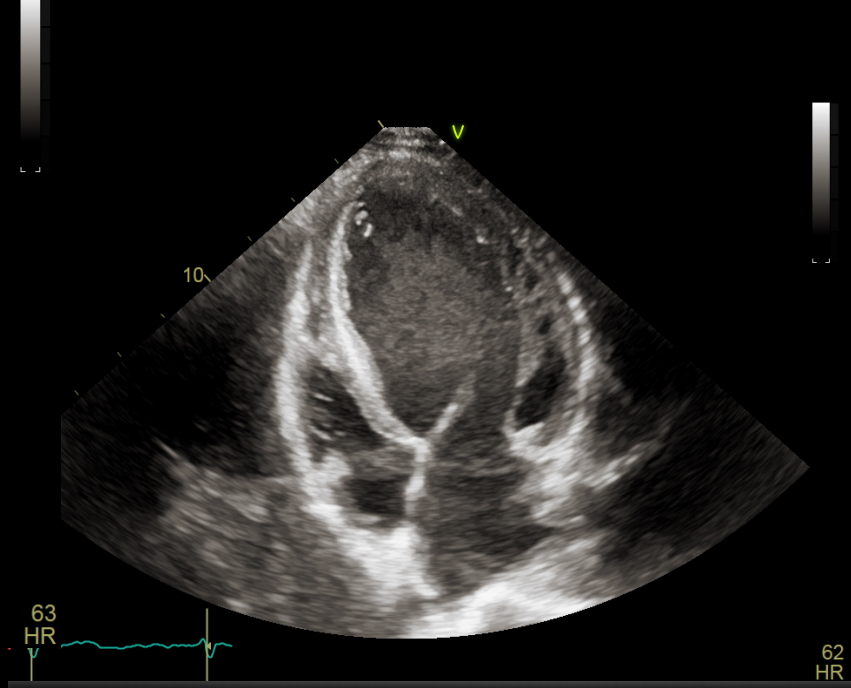
2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction

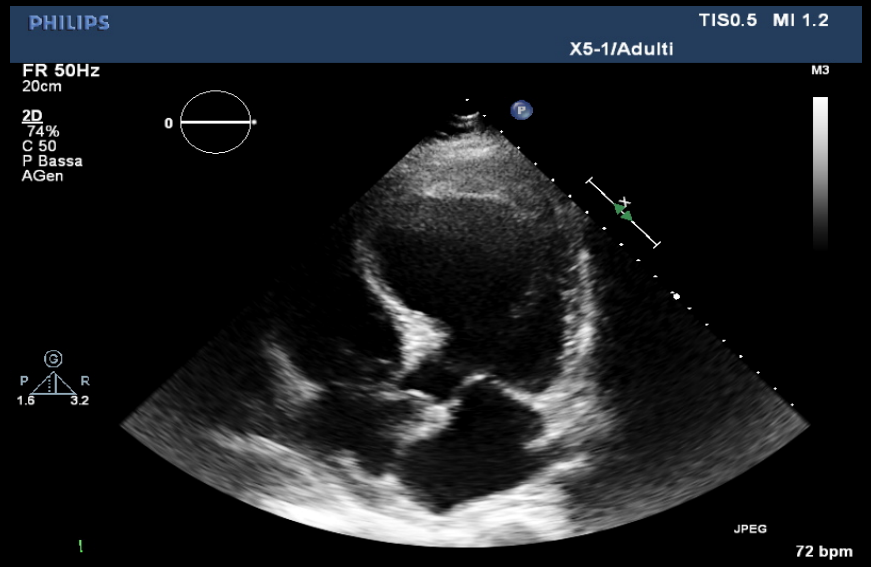
A Report of the American College of Cardiology Solution Set Oversight Committee

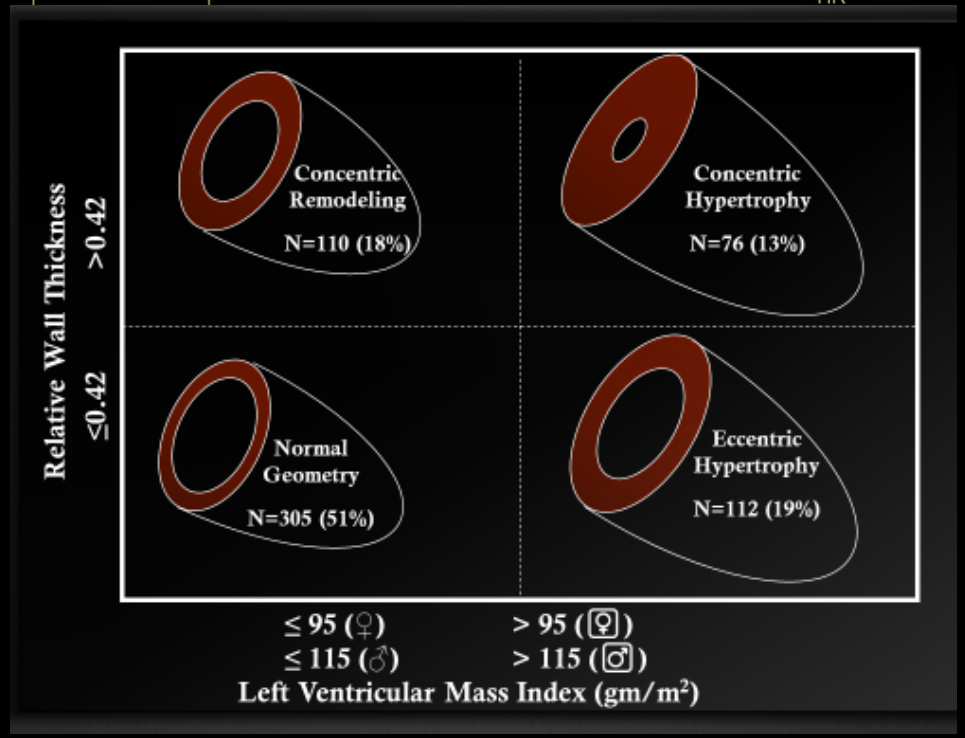
HFpEF



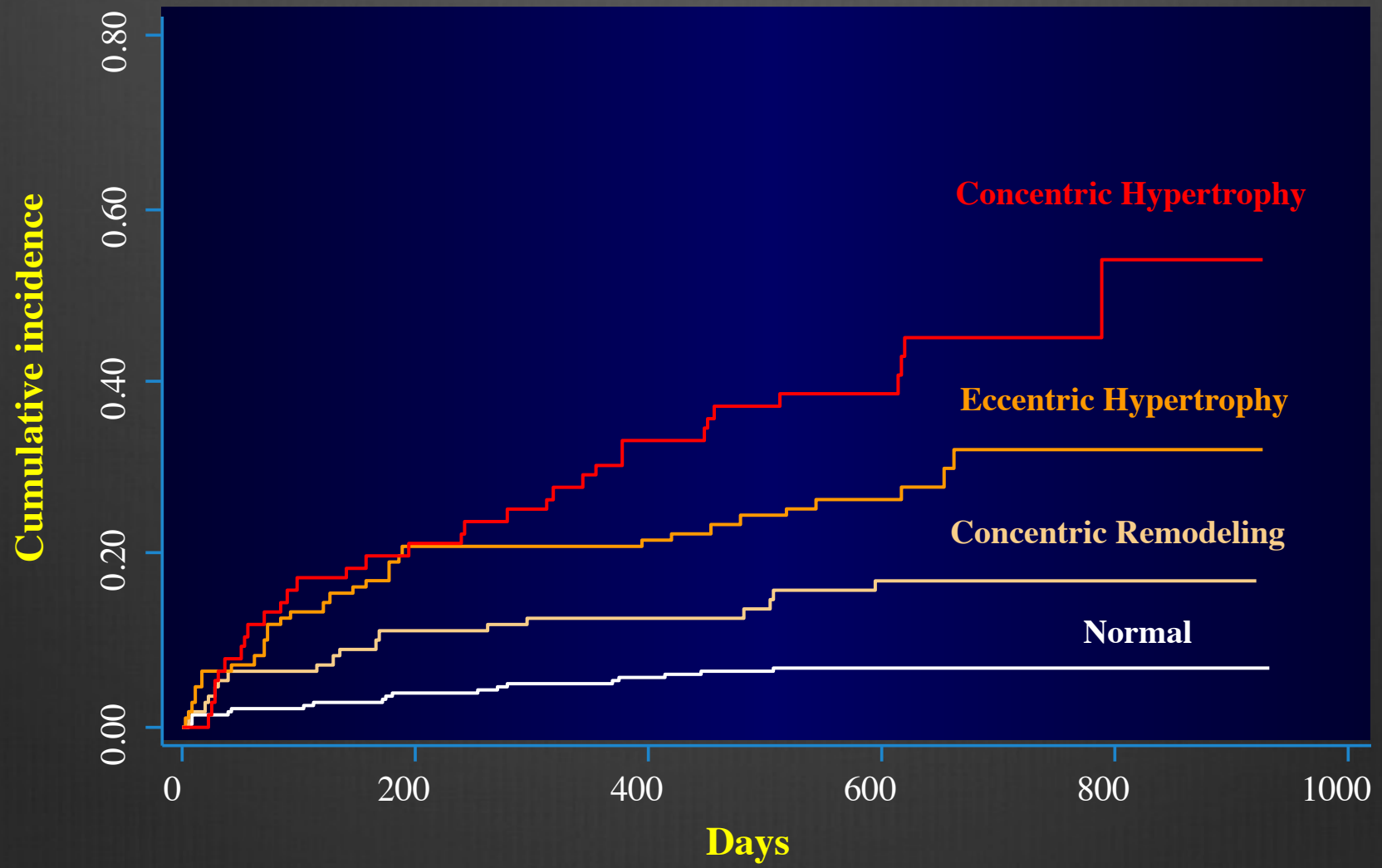

V
5
10
15


V
10
63
HR
62
HR


PHILIPS
TIS0.5 MI 1.2
X5-1/Adulti
FR 50Hz
20cm
2D
74%
C 50
P Bassa
AGen
M3
P
R
1.6
3.2
JPEG
72 bpm

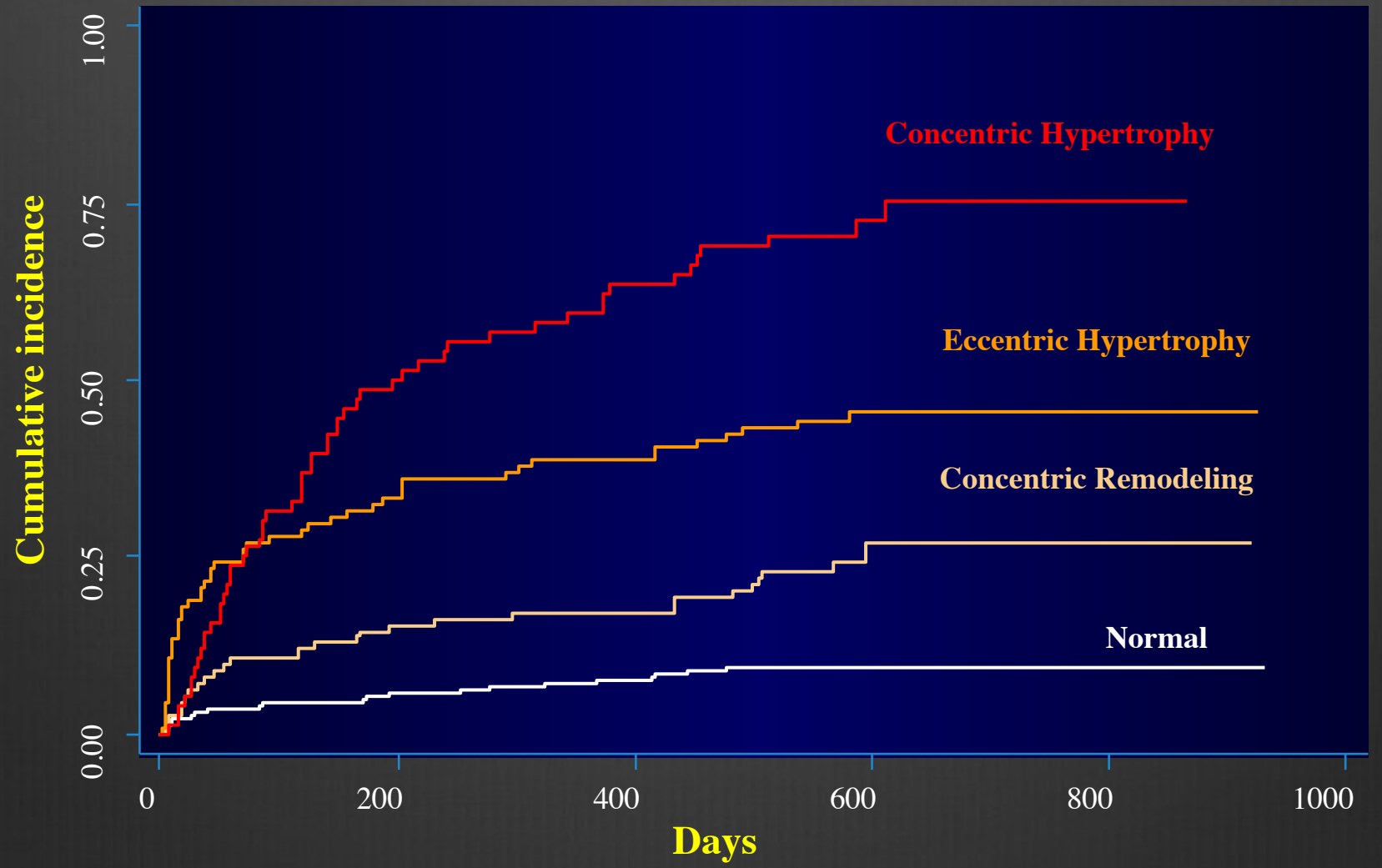

Relative Wall Thickness
>0.42
≤0.42
Concentric Remodeling
N=110 (18%)
Concentric Hypertrophy
N=76 (13%)
Normal Geometry
N=305 (51%)
Eccentric Hypertrophy
N=112 (19%)
≤ 95 (♀)
> 95 (♀)
≤ 115 (♂)
> 115 (♂)
Left Ventricular Mass Index (gm/m²)

Unadjusted Kaplan Meier Curves for ***All Cause Mortality***

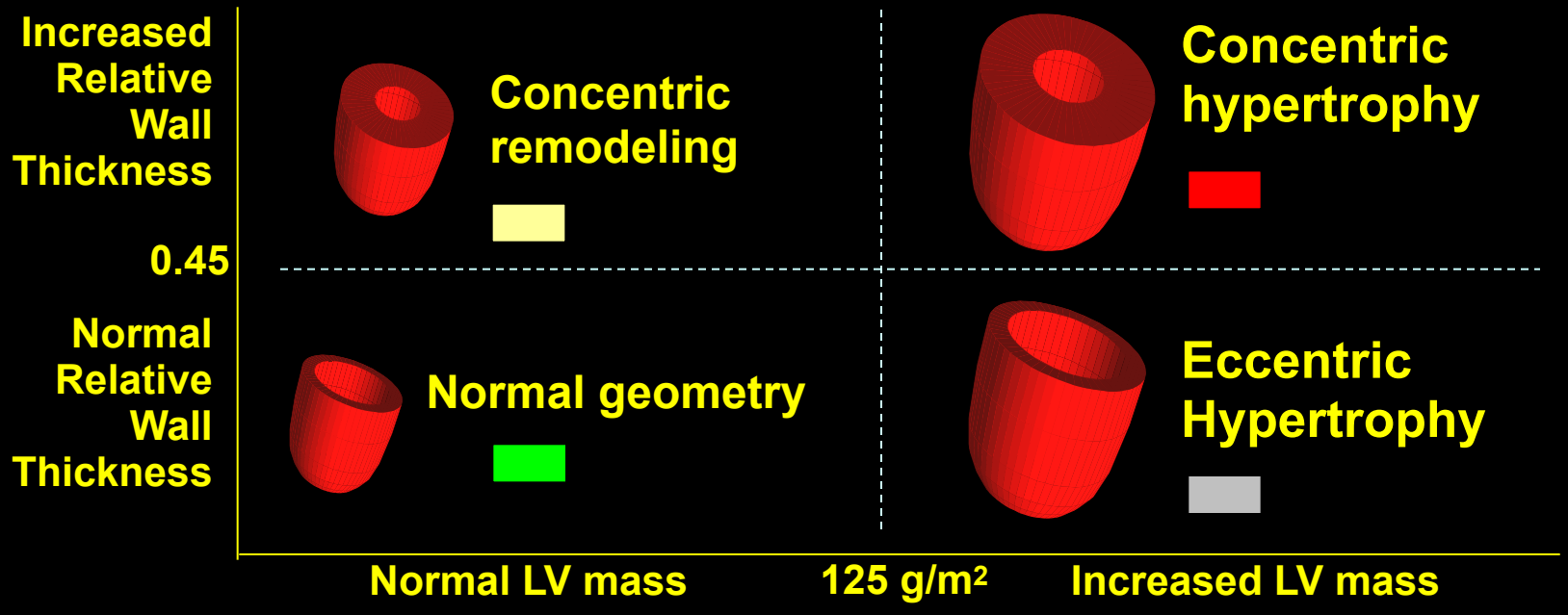


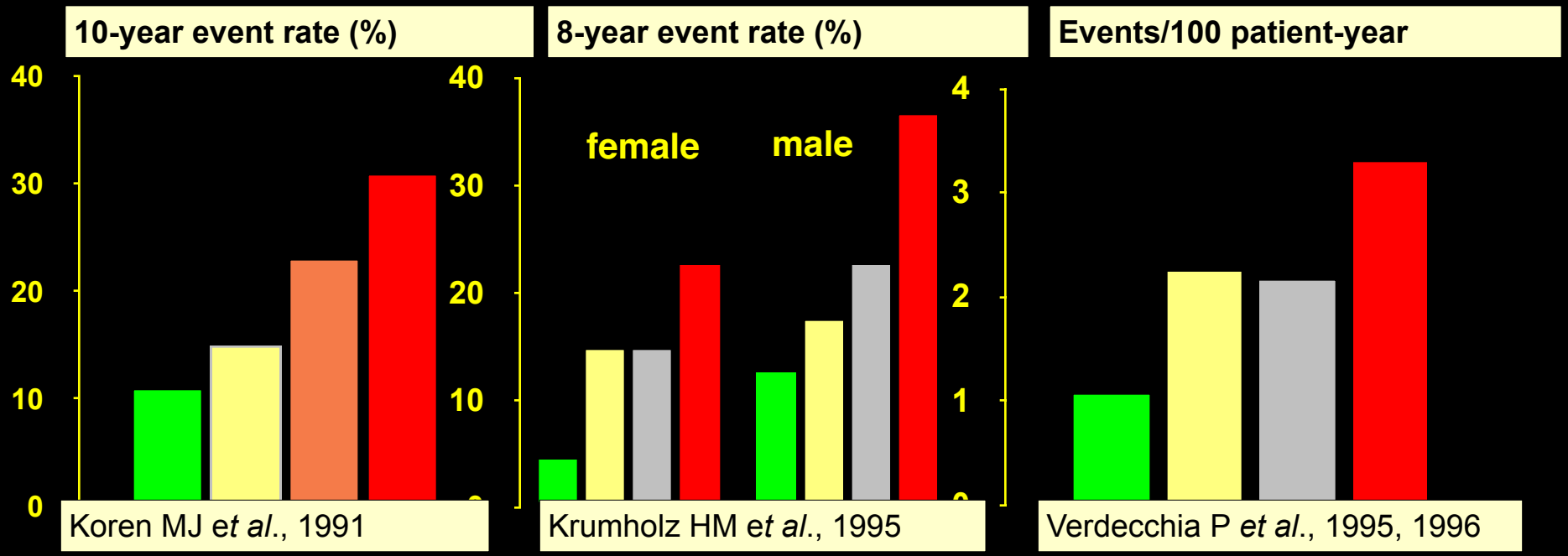
Verma A, et al. JACC Cardiovasc Img 2008;1:582–91

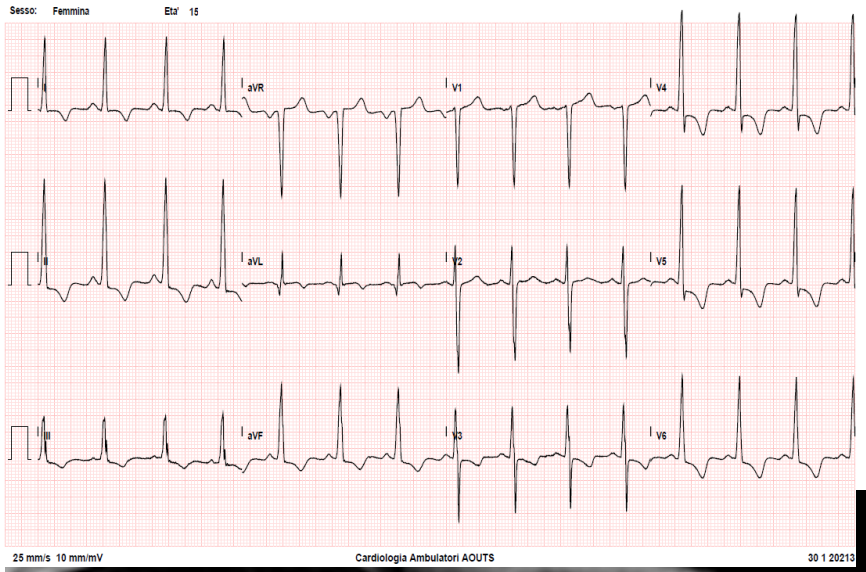
Unadjusted Kaplan Meier curves for *Death or Heart Failure*

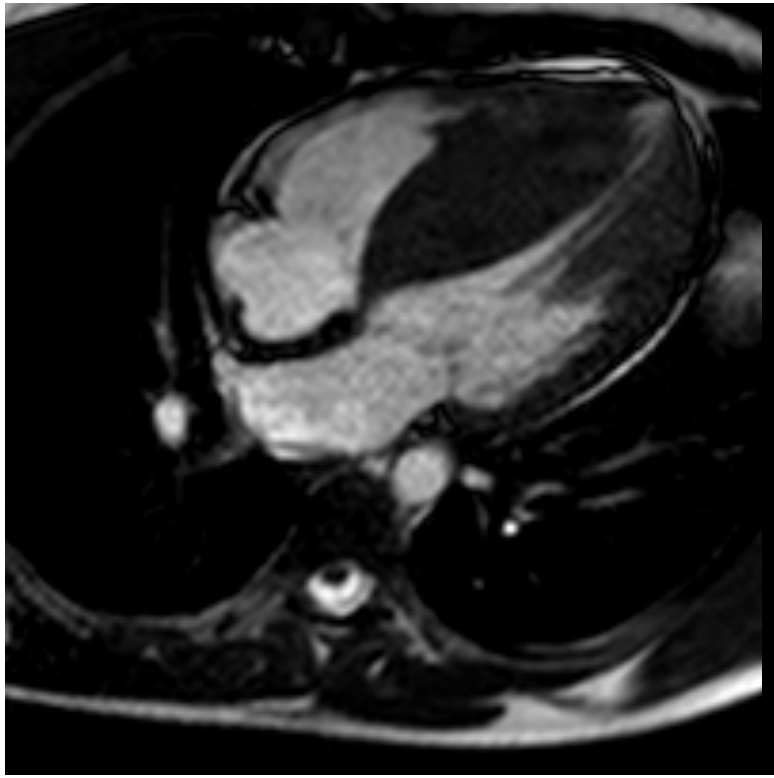


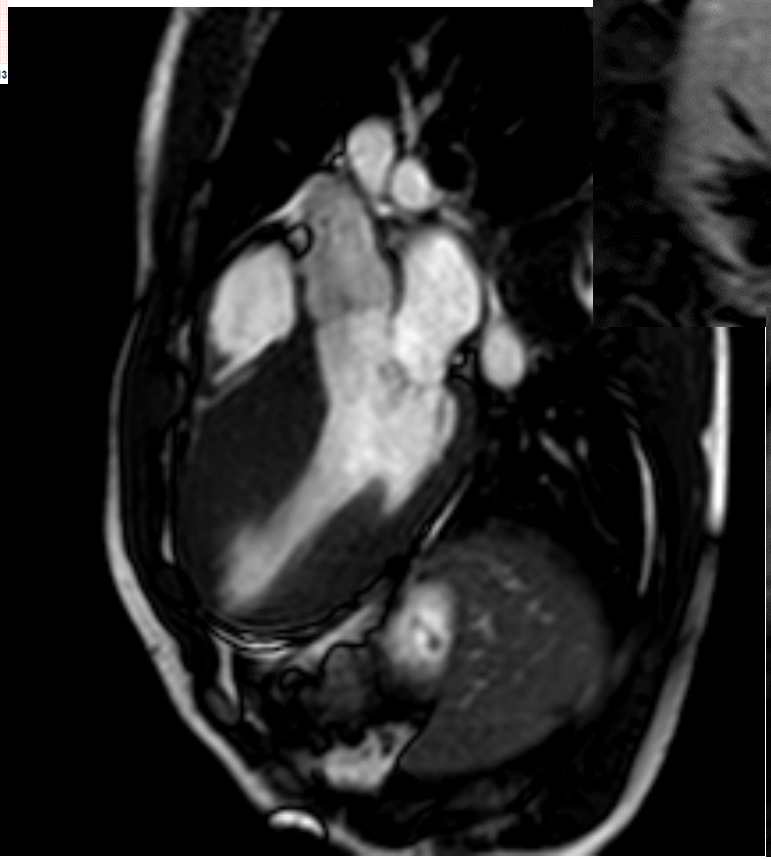
Verma A, et al. JACC Cardiovasc Img 2008;1:582–91

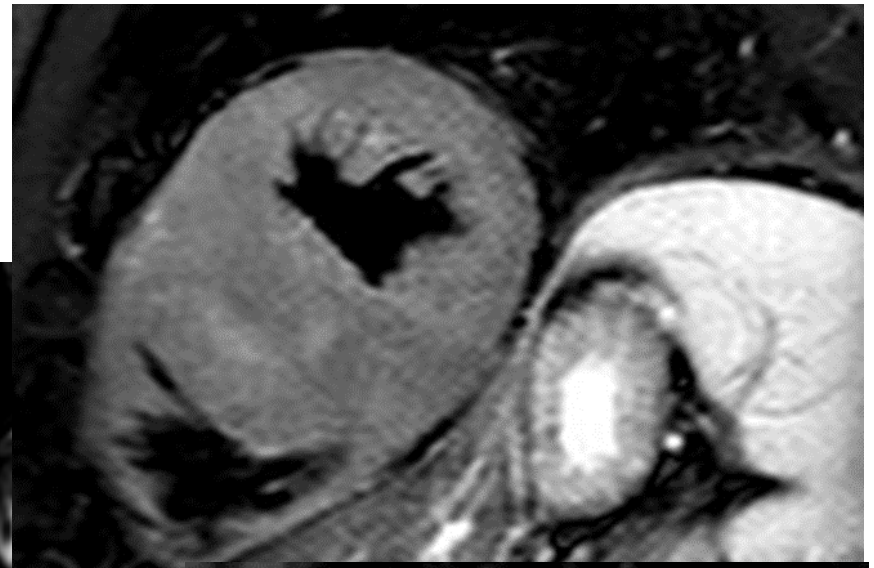

Increased Relative Wall Thickness
0.45
Normal Relative Wall Thickness
Concentric remodeling
Concentric hypertrophy
Normal geometry
Eccentric Hypertrophy
Normal LV mass
125 g/m2
Increased LV mass

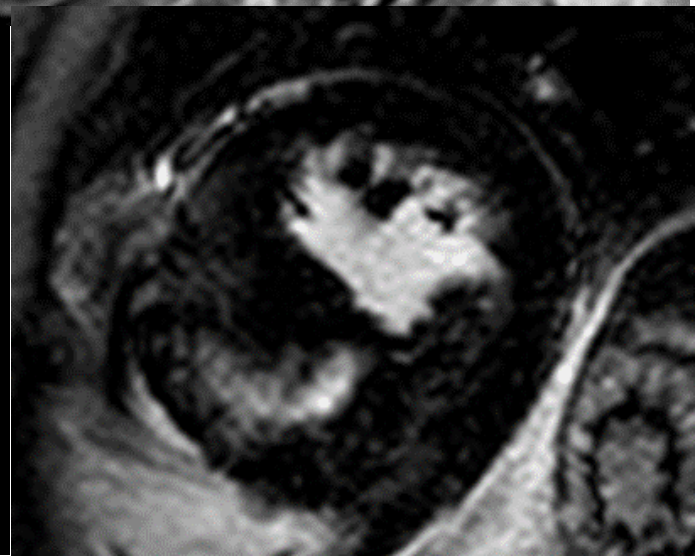

10-year event rate (%)
40
30
20
10
0
Koren MJ et al., 1991
8-year event rate (%)
female
male
4
3
2
1
Krumholz HM et al., 1995
Events/100 patient-year
Verdecchia P et al., 1995, 1996

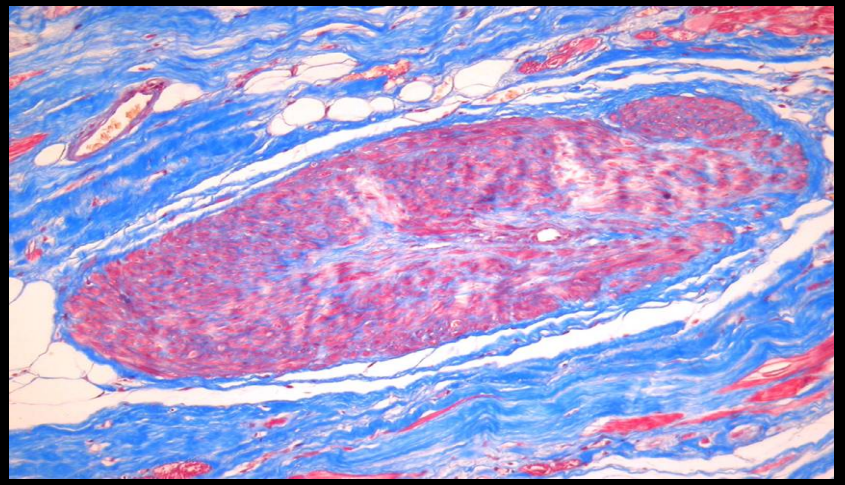

Sesso: Femmina
Eta' 15
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
25 mm/s 10 mm/mV
Cardiologia Ambulatori AOUTS
30 1 20213

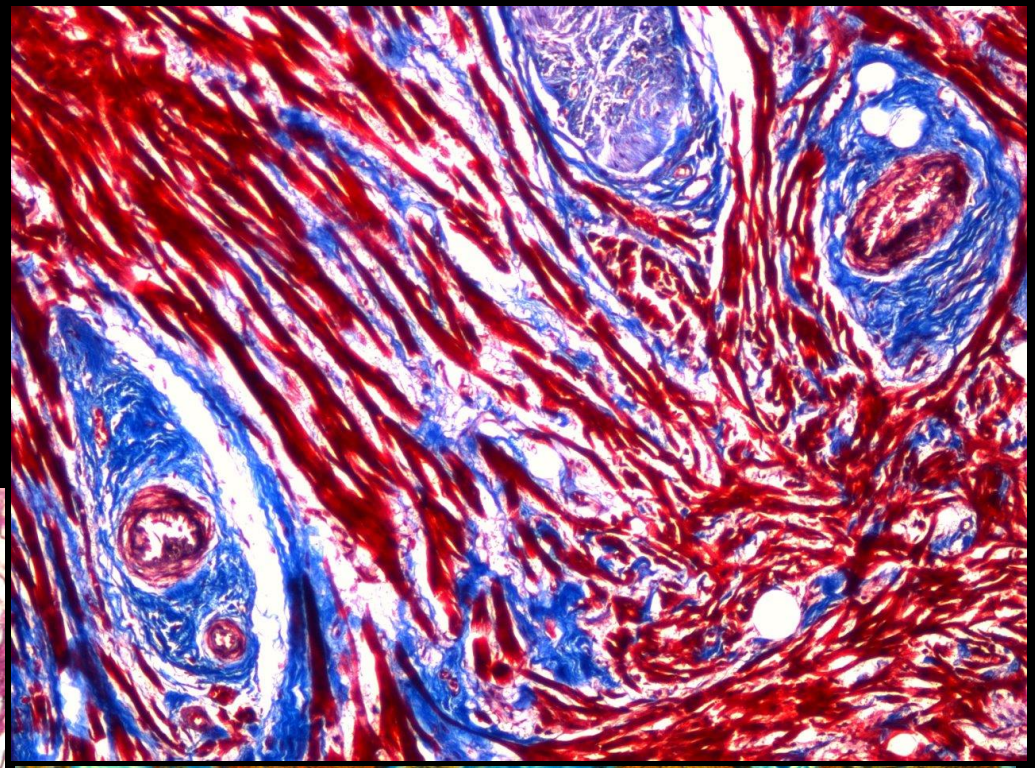


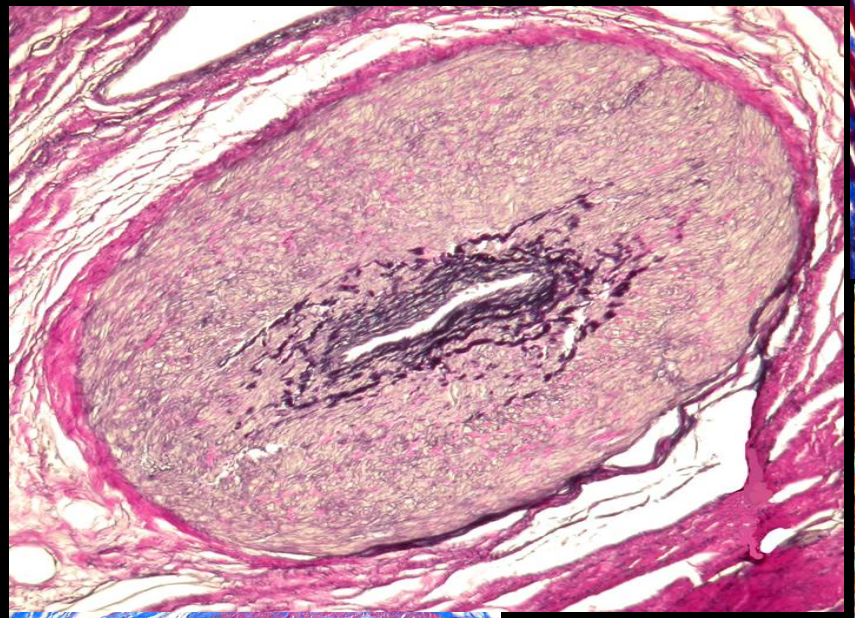


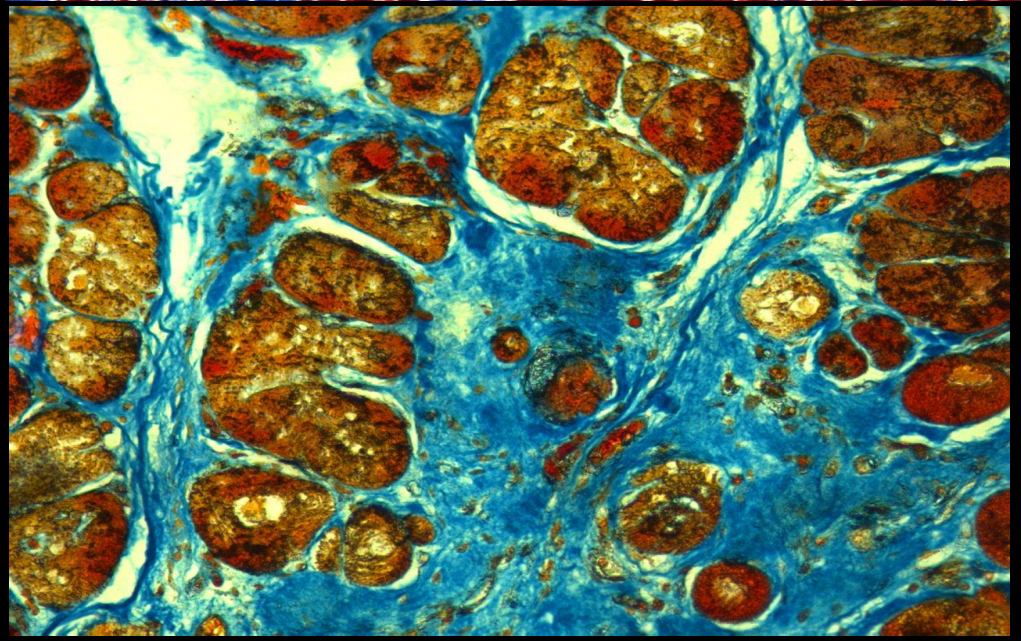


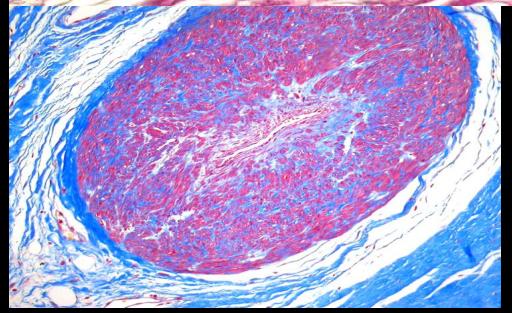










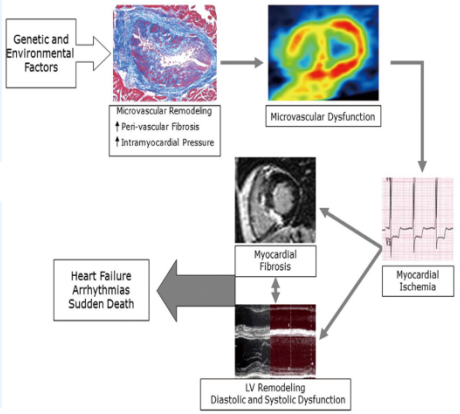


From Left Ventricular Hypertrophy to Dysfunction and Failure

Davide Lazzeroni, MD; Ornella Rimoldi, MD; Paolo G Camici, MD

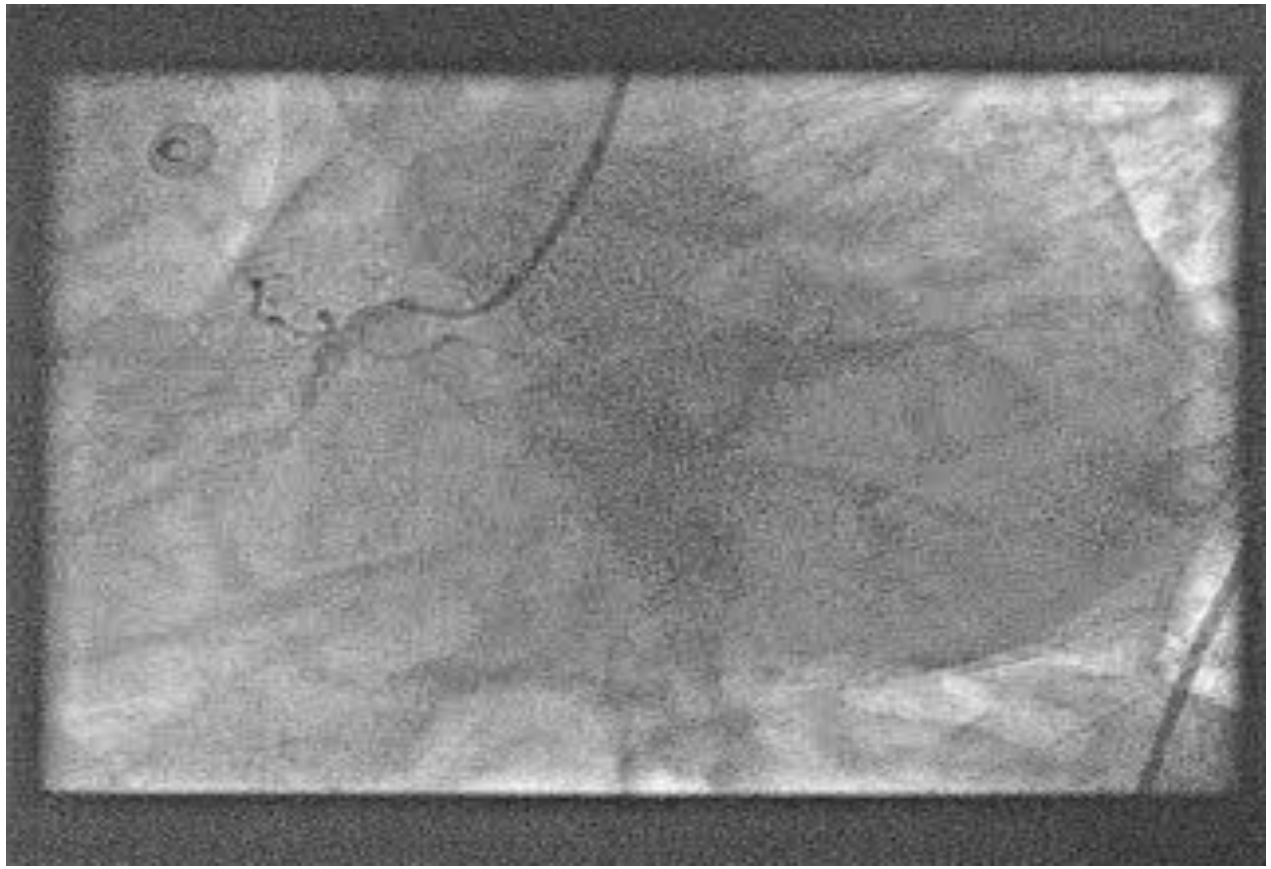
Table. Myocardial Perfusion and Coronary Flow Reserve in Normal Controls, and Primary and Secondary LVH Patients

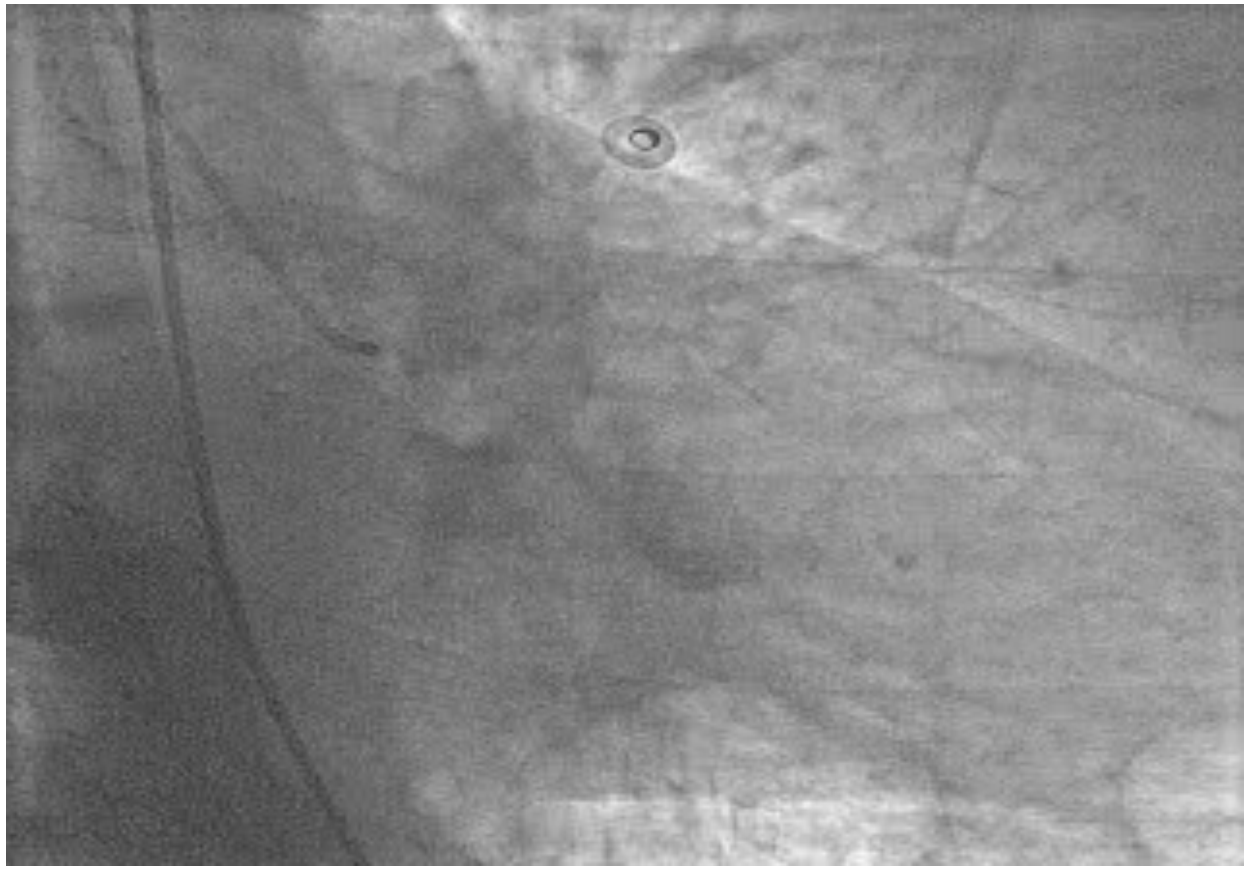
Method	n	MBFR (ml/g/min)	MBFH (ml/g/min)	CFR	Reference
Normal controls					
PET	3.484	0.82±0.06	2.86±1.29	3.55±1.36	Gould et al[38]
Physiologic					
LVH					
PET	10	0.74±0.17	2.69±1.15	3.58±1.02	Radvan et al[41]
PET	14	0.8±0.2	NA	6.1±1.9	Toraa et al[42]
Doppler	52	10.6±3.1 (ml/min)	61.9±17.8 (ml/min)	5.9±1.0	Hildick-Smith et al[43]
Primary LVH					
HCM					
PET	345	0.90±0.10	1.57±0.33	1.84±0.36	Gould et al[38]
PET	23	1.02±0.39	1.55±0.58	1.51±0.48	Camici et al[44]
PET	51	0.84±0.31	1.50±0.69	1.80±0.70	Cecchi et al[48]
PET	61	–	1.90±0.90	–	Olivotto et al[45]
DCM					
PET	22	0.80±0.25	1.91±0.76	2.38±0.5	Neglia et al[49]
PET	67	0.69±0.23	1.53±0.79	2.22±0.89	Neglia et al[50]
Secondary LVH					
Hypertensive heart					
PET	20	0.69±0.13	1.42±0.32	NA	Neglia et al[52]
PET	30	0.89±0.18	1.9±0.62	2.18±0.74	Rimoldi et al[51]
Aortic stenosis					
PET	20	1.05±0.26	1.99±0.78	1.9±0.6	Rajappan et al[54]
Doppler	24	23.3±10.1 (cm/s)	37.8±11.3 (cm/s)	1.76±0.5	Hildick-Smith et al[55]
Mitral regurgitation					
Doppler	31	28±8 (cm/s)	56±14 (cm/s)	2.1±0.5	Akasaka et al[56]



Circ J 2016; 80: 555 – 564

65 aa, Ipertensione (3 farmaci), LDL 135 mg/dl; HbA1C 6.2%; BMI 28; eGFR 58 ml/min/1.73; fumatore

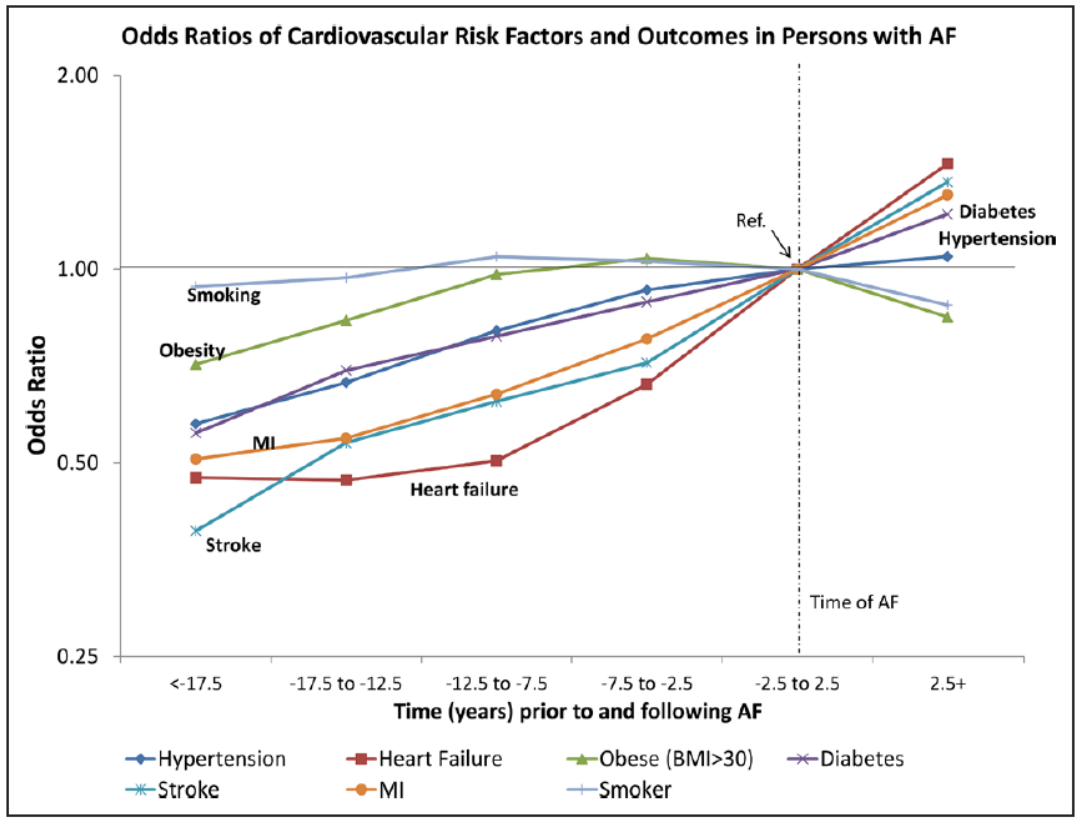




Circulation. 2016;134:599–610.

Trajectories of Cardiovascular Risk Factors and Incidence of Atrial Fibrillation Over a 25-Year Follow-Up

The ARIC Study (Atherosclerosis Risk in Communities)



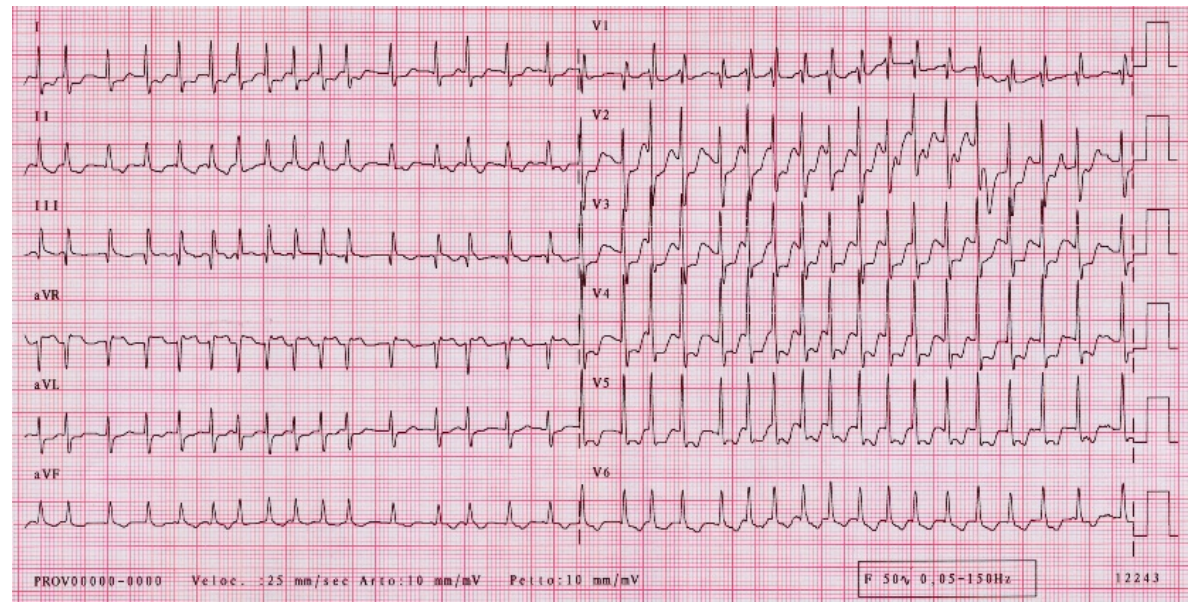
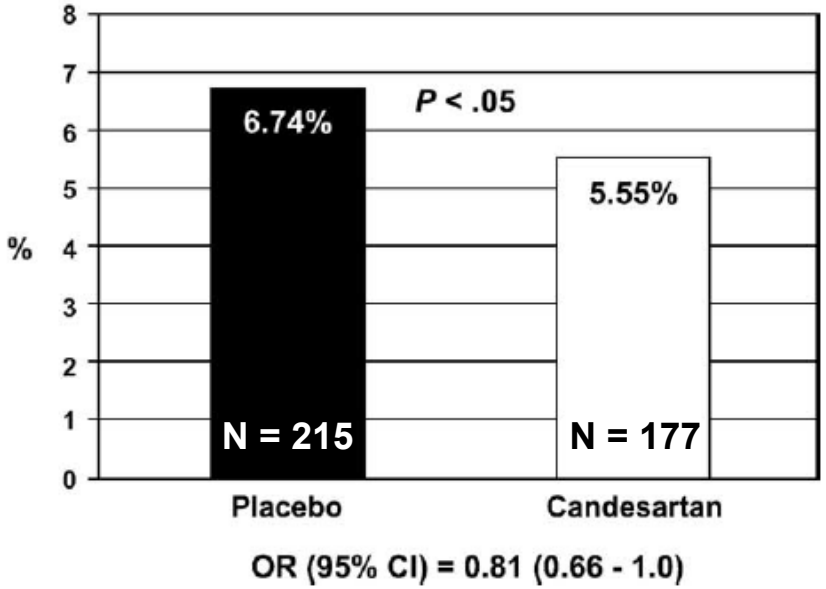


Figure 2. Odds ratios (ORs) of cardiovascular risk factors and outcomes over time based on atrial fibrillation (AF) status and adjusted for age, race, and sex.

An OR <1 or >1 can be interpreted as a lower or higher odds, respectively, of the risk factor or cardiovascular outcome at a particular time period compared with the odds at the time of AF diagnosis date. MI indicates myocardial infarction.

Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure (CHARM program)

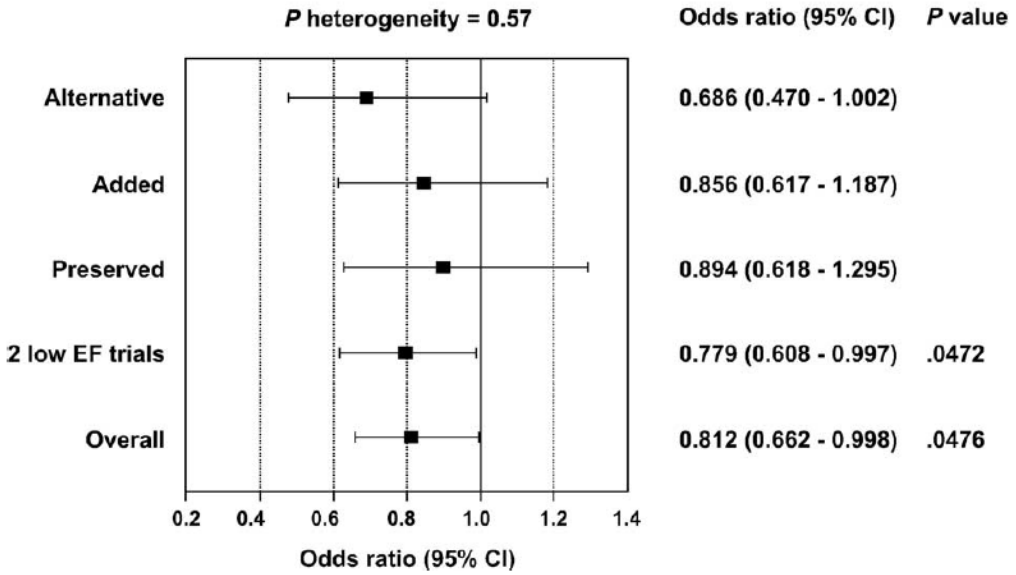
392 pts (6.15%) developed AF during FU



OR (95% CI) = 0.81 (0.66 - 1.0)

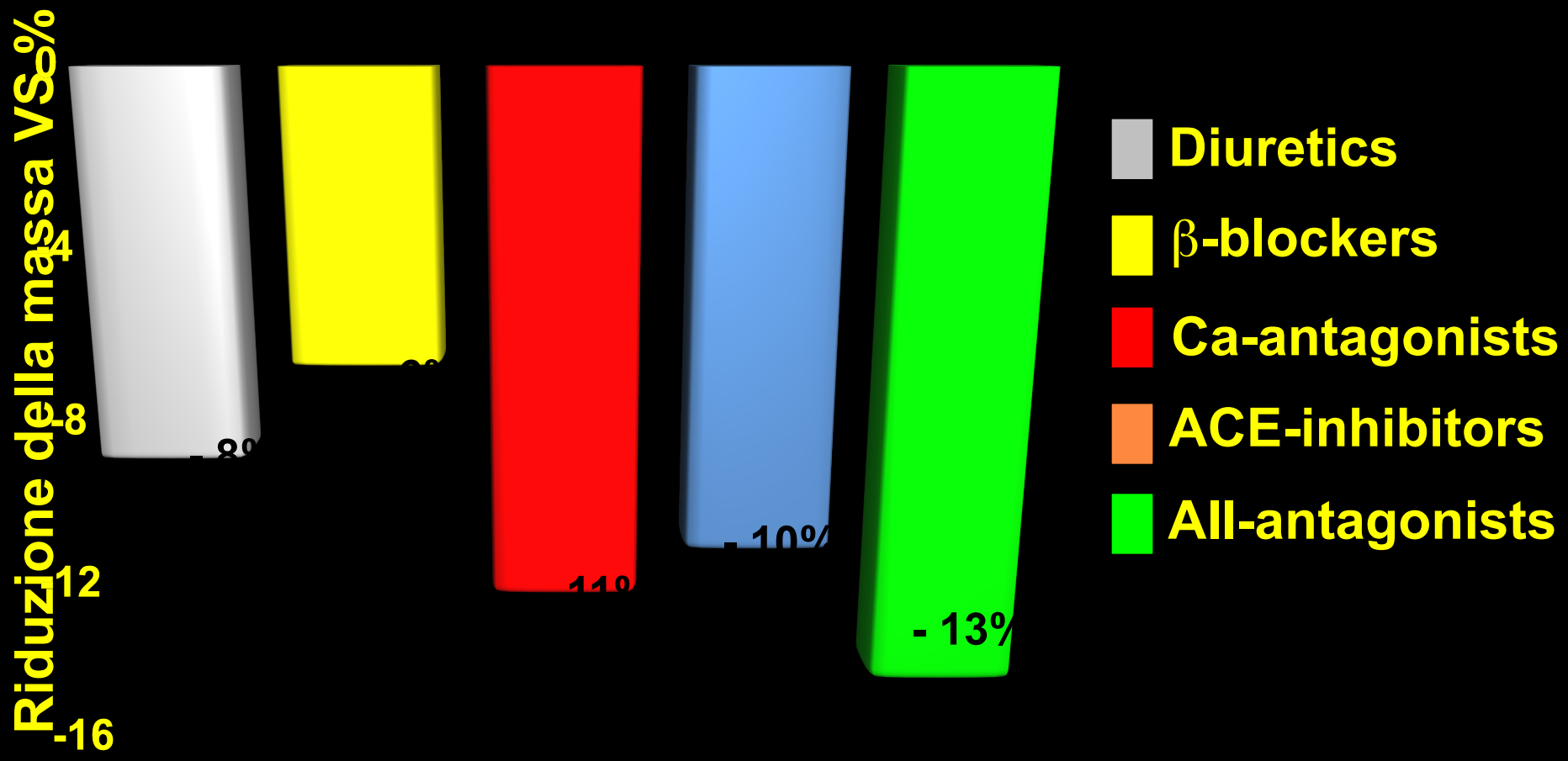
Adjst OR 0.802 (95% CI 0.650- 0.990, P = .039)

The effect of candesartan on the incidence of AF



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

Metanalisi di studi randomizzati e controllati sulla Regressione dell'Ipertrofia VS nell'ipertensione arteriosa

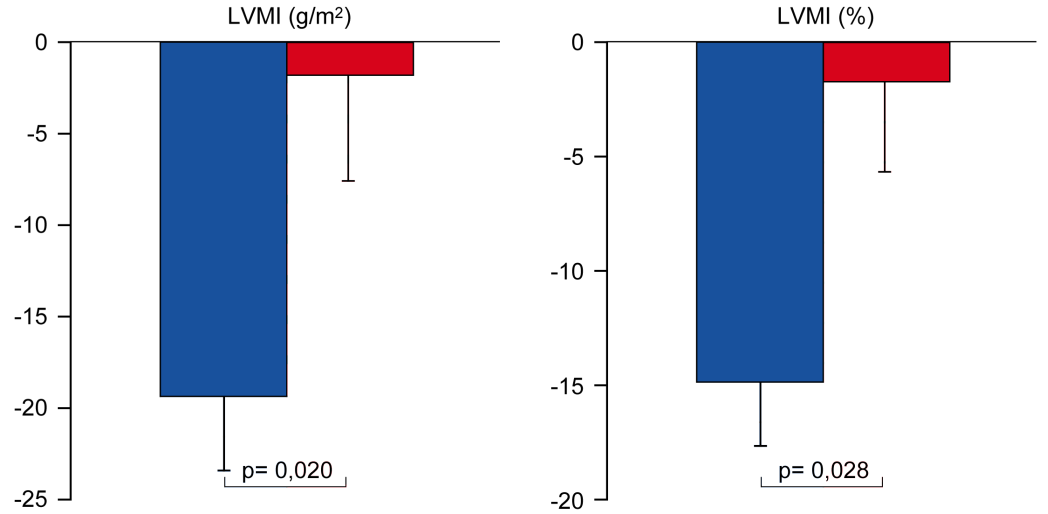


80 Trials
4113 patients

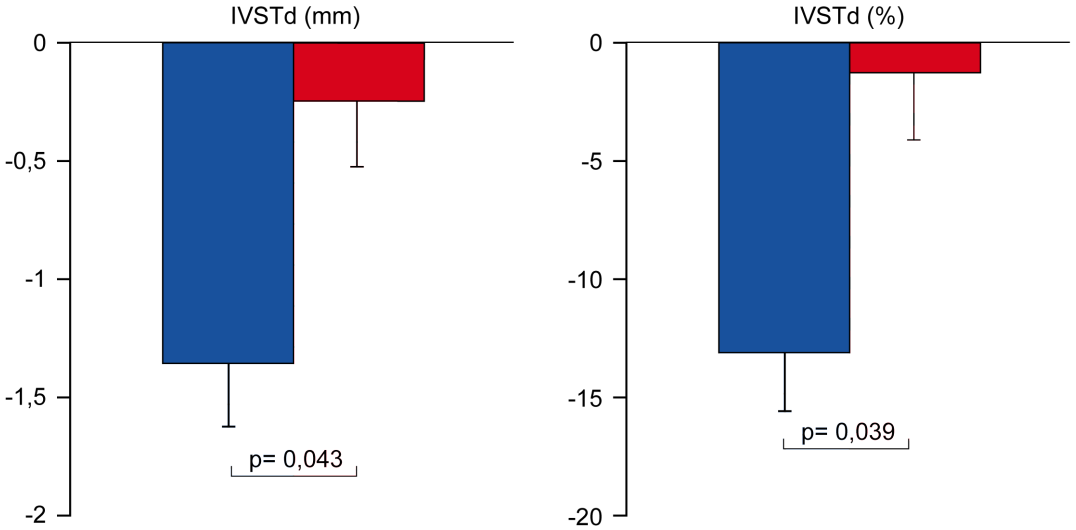
Schmieder RE et al. Am J Med 2003; 115:41-6

Effetti di Candesartan *vs.* Amlodipina su regressione dell'ipertrofia cardiaca, pz ipertesi con diabete di tipo 2 (n = 40)

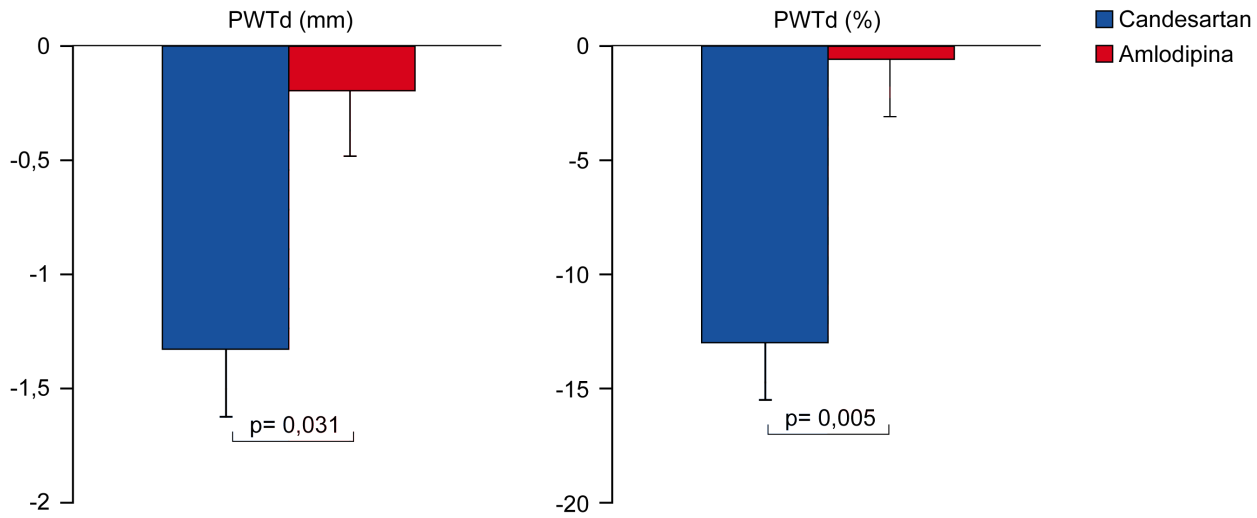
LVMI: indice massa ventricolo sinistro.



IVSTd: spessore setto interventricolare in diastole.



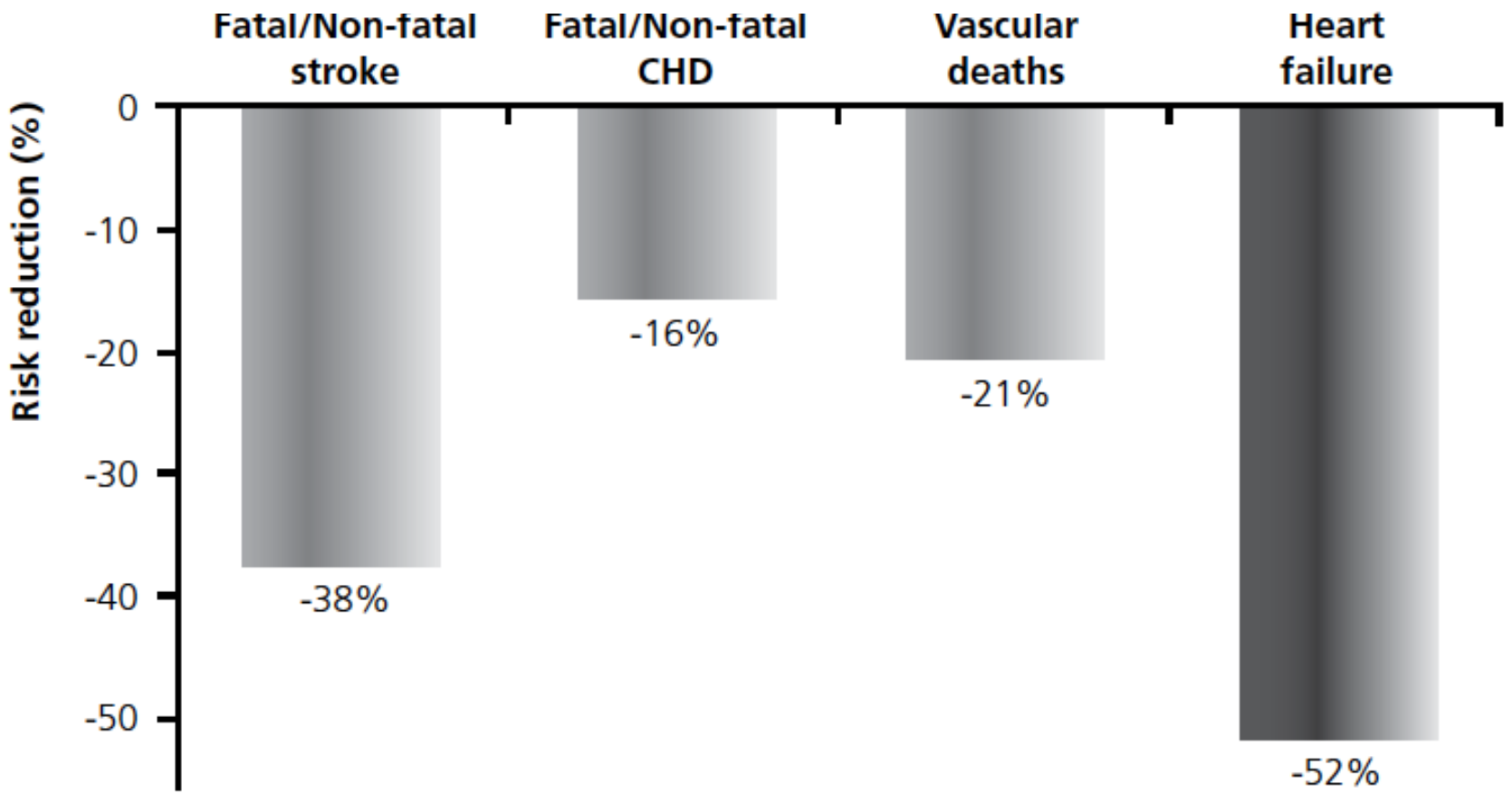
PWTd: spessore parete posteriore ventricolo sinistro in diastole.



Iwashima Y et al. Diabetes Research and Clinical Practice 2006;74:8-14

From Hypertension to Heart Failure – Are There Better Primary Prevention Strategies?

Peter A Meredith, Jan Östergren†*



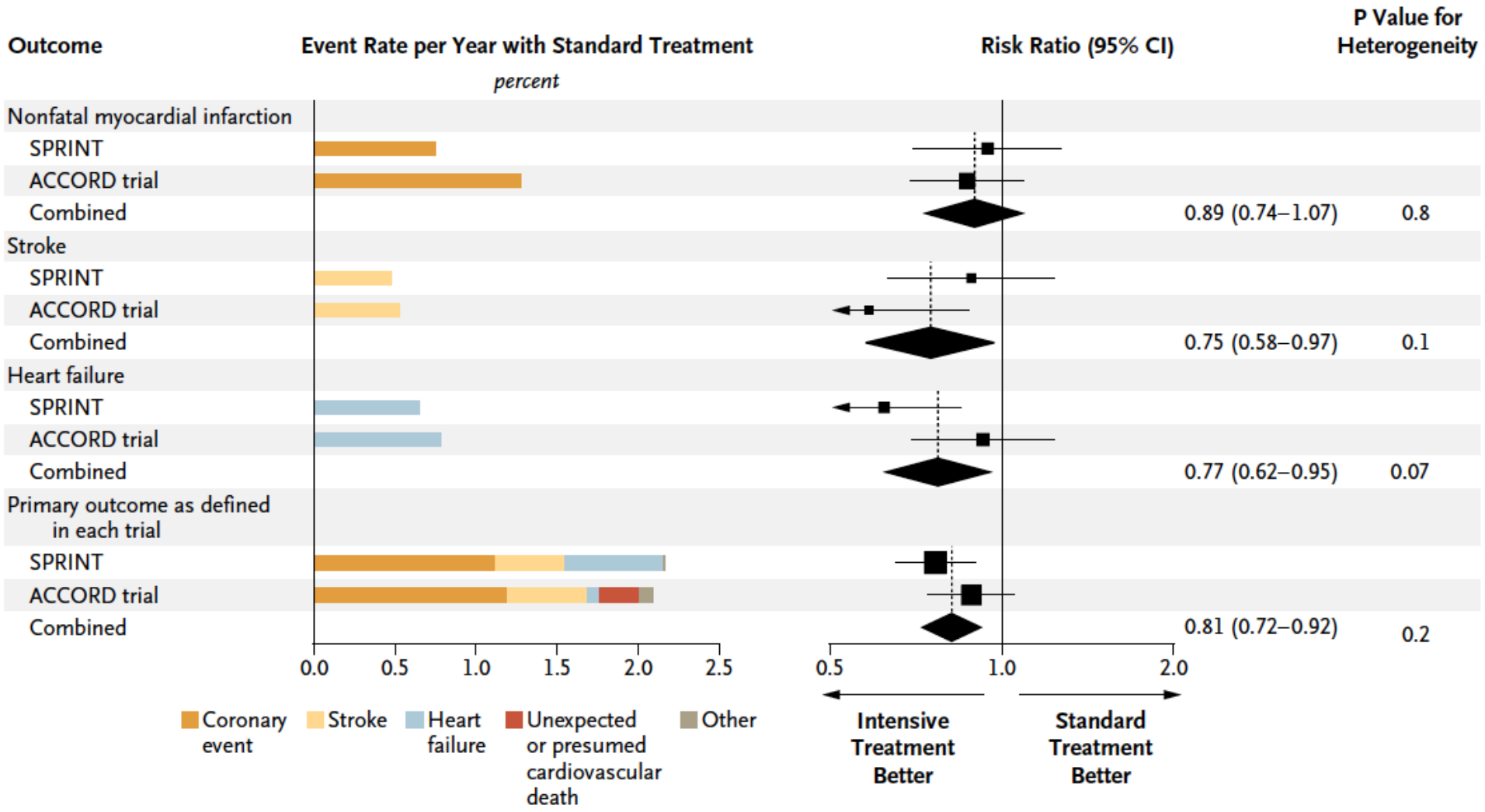
Results of meta-analyses of the randomised trials of antihypertensive drug therapy, demonstrating the reduction in cardiovascular events

JRAAS 2006;7:64-73

Redefining Blood-Pressure Targets — SPRINT Starts the Marathon

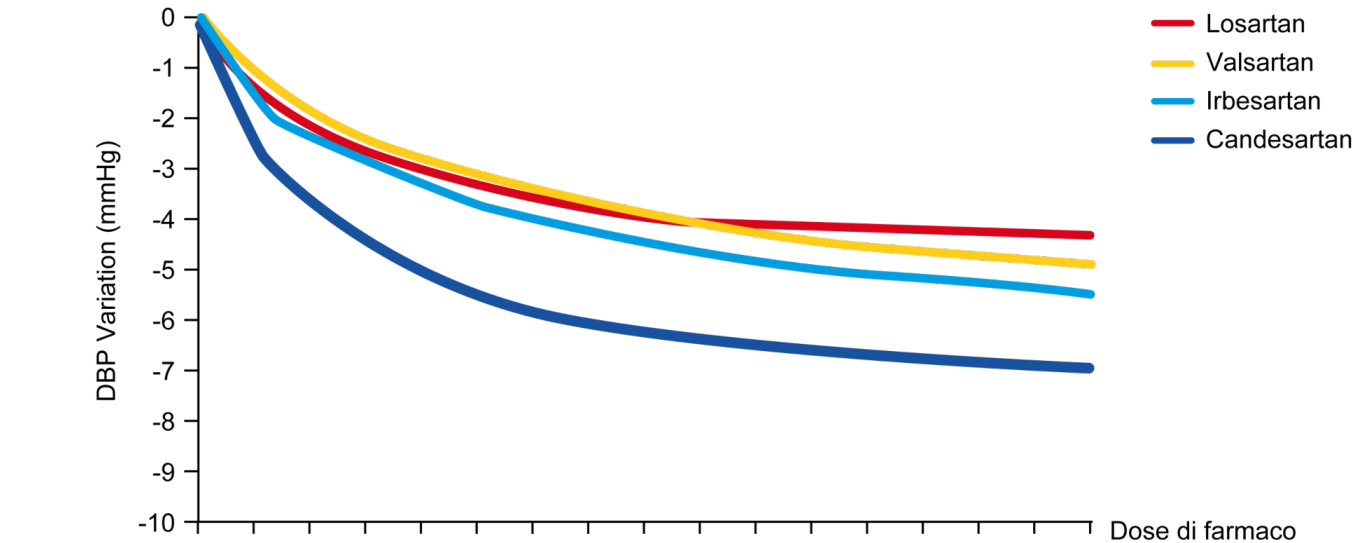
The NEW ENGLAND JOURNAL of MEDICINE

Outcomes Data from SPRINT and the ACCORD Trial and Combined Data from Both Trials



Pekrovic. NEJM 2015 373;22

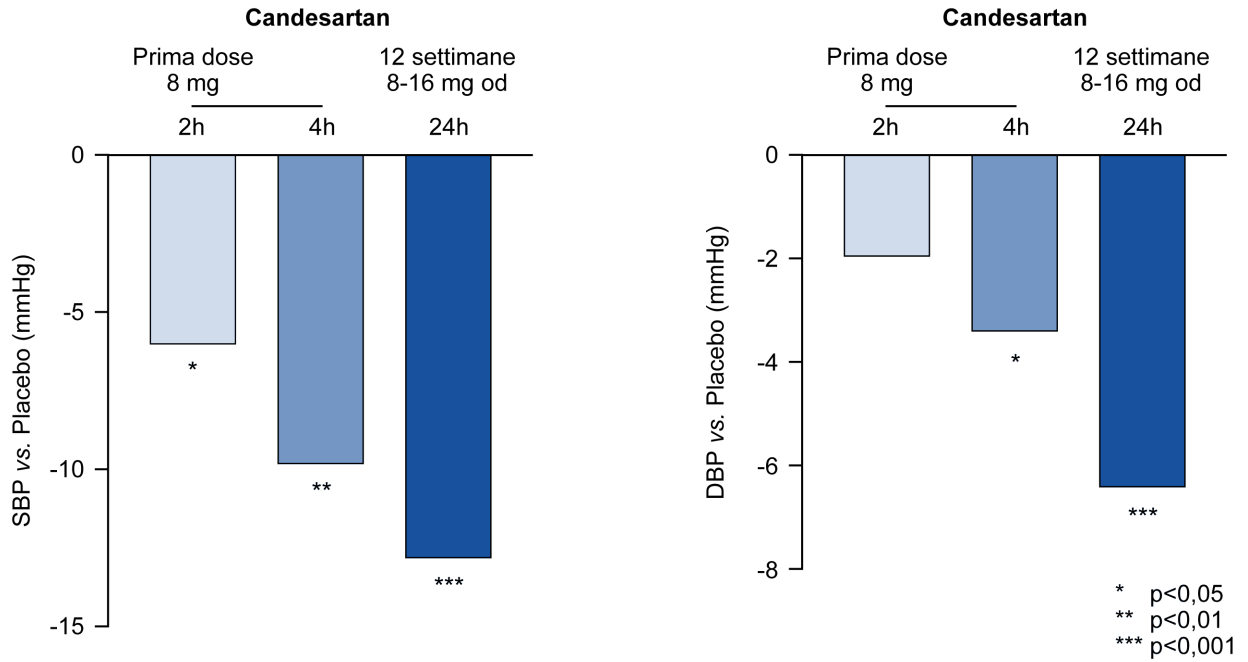
Curva dose-effetto nella ipertensione arteriosa: profilo di efficacia di 4 antagonisti recettoriali dell'angiotensina II (ARBs)



Losartan	0	25	50	75	100 mg
Valsartan	0	40	80	240	160 mg
Irbesartan	0	75	150	225	300 mg
Candesartan	0	4	8	12	16 mg

Elmfeldt D et al. Blood Pressure 2002;11:293-301

Efficacia antipertensiva di candesartan in pazienti anziani ipertesi (n = 350)



Candesartan produce una riduzione significativa di SBP e DBP (-13,6 mmHg/-7,5 mmHg rispettivamente)

McInnes GT *et al.* Journal of Human Hypertension 1997, Suppl. 2; S75-S80

CHARM TRIAL

7,601 patients with heart failure

3 Individual component randomized trials with the ARB **candesartan** (4 or 8 mg/day, titrated to target dose of 32 mg) or placebo

CHARM Added
- Patients with LVEF ≤40% and treated with an ACE-inhibitor

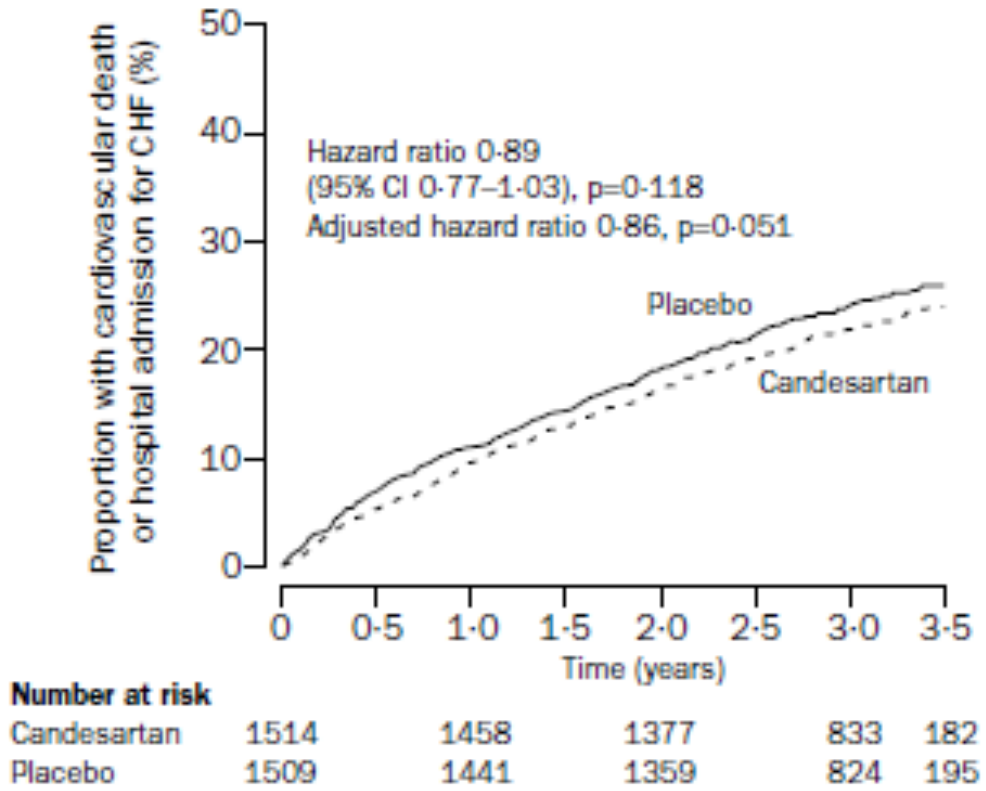
CHARM Alternative
- Patients with LVEF ≤40% and ACE-inhibitor intolerant

CHARM "Preserved"
- Patients with LVEF >40% with or without ACE-inhibitor

Endpoints (follow-up minimum 2 years):
- Primary – Component trials: cardiovascular mortality or CHF hospitalization
- Primary – Overall trial results: All-cause mortality

Lancet 2003 Sep 6;362(9386):759-66.

Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial



	Placebo	Candesartan
Number of patients	1509	1514
Total follow-up years	4374.03	4424.62
Number of deaths	237	244
Number of CV deaths	170	170
All-cause hospitalisation		
• patients with ≥ 1 admission	920	912
• patients with ≥ 2 admissions	552	556
• total admissions	2484	2463
Cardiovascular hospitalisation		
• patients with ≥ 1 admission	659	631
• patients with ≥ 2 admissions	339	311
• total admissions	1434	1304
• patients with (no. of hospitalisations)		
1	164	135
2	55	56
3	25	23
4	13	9
5	9	4
6	4	1
7	2	2
8	2	0
9	2	0
13	1	0
16	1	0
• patients with ≥ 1 admission	278	230
• patients with ≥ 2 admissions	114	95
• total admissions	547	392

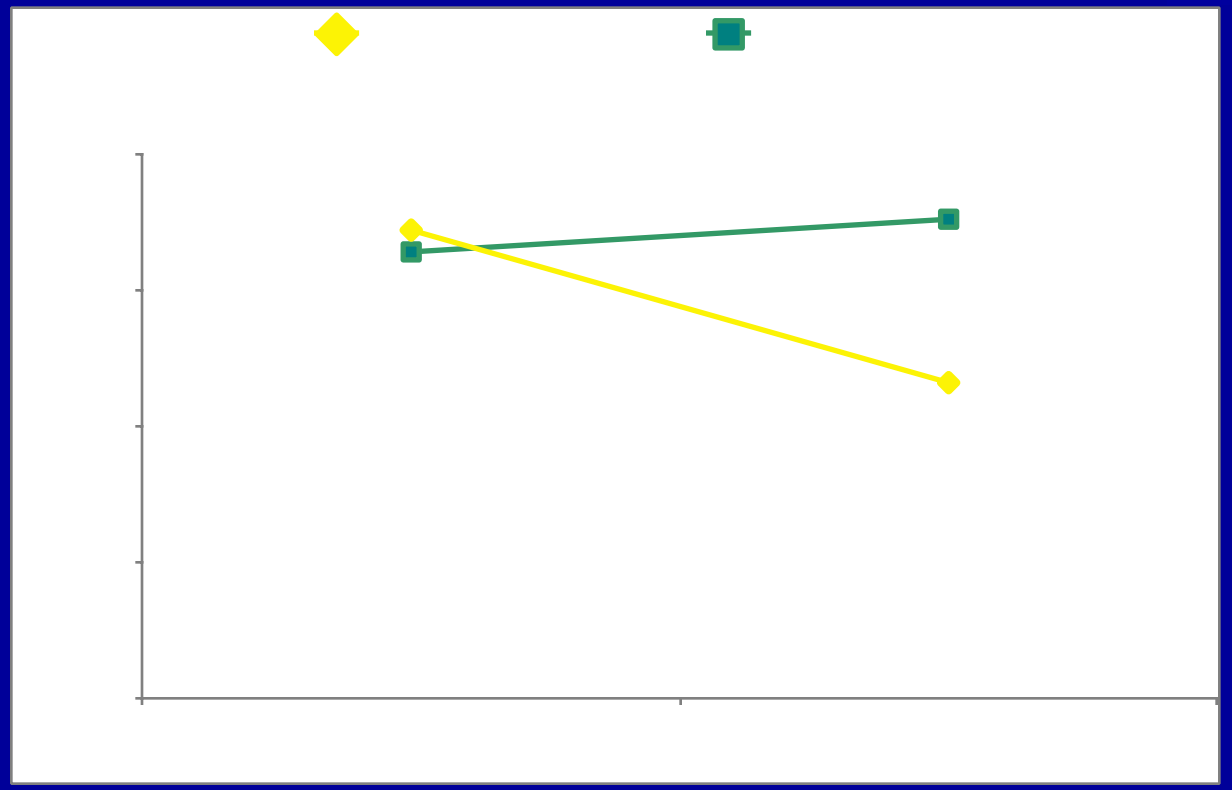
N° Hospital admission for HF

Yusuf et al Lancet 2003; 362: 777–81

	Candesartan (n=3803)	Placebo (n=3796)	p
Cause of discontinuation			
Hypotension	132 (3·5%)	66 (1·7%)	<0·0001
Increase in serum creatinine	234 (6·2%)	115 (3·0)	<0·0001
Hyperkalaemia	85 (2·2%)	21 (0·6%)	<0·0001

Lancet 2003 Sep 6;362(9386):759-66.

Aldosterone pg/mL (median)



Candesartan, median [25%-75%]	143 [87.8-216.3]	129 [83.0-187.0]
Control, median [25%-75%]	141 [90.0-201.0]	144 [105.0-229.5]

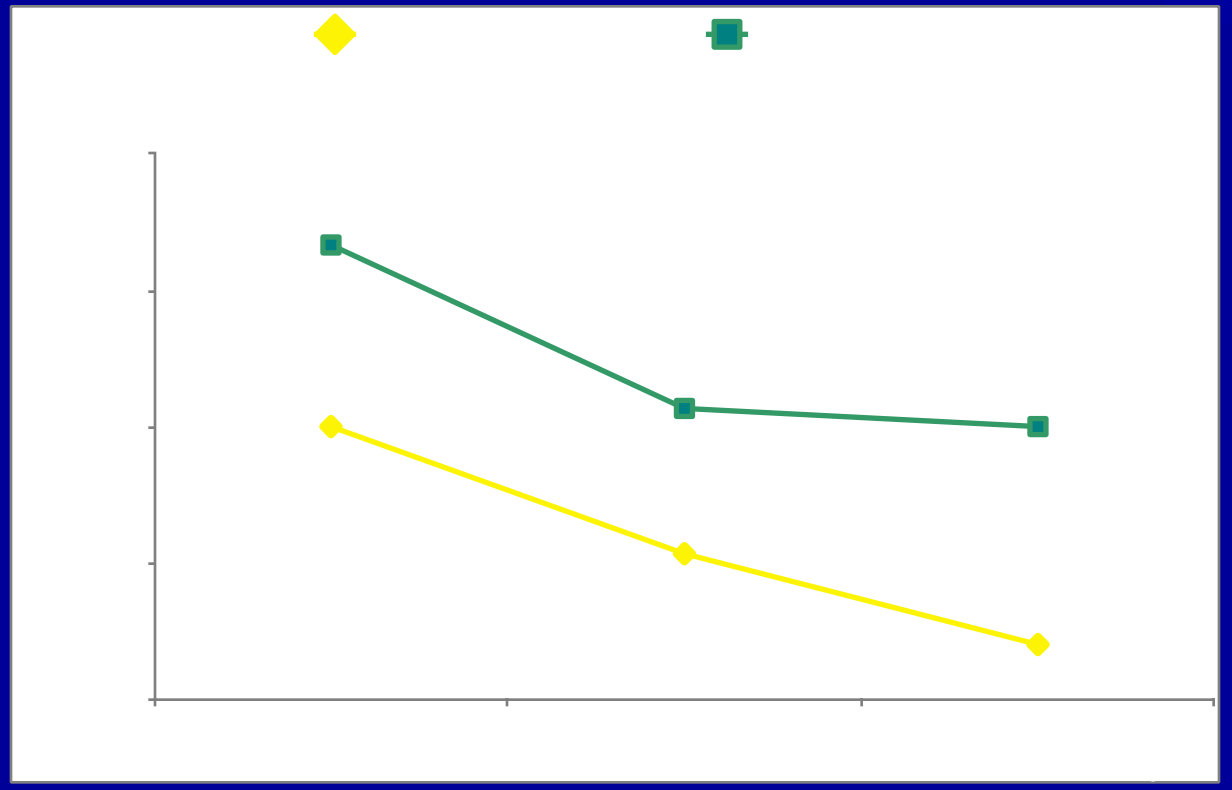
CandHeart Results

Differences between baseline and end of study: **p*=0.009**

** Mann Whitney*

Aleksova A, Sinagra G et al Cardiovasc Drugs Ther, 2012

LVIDd/BSA mm/m^2 (median)

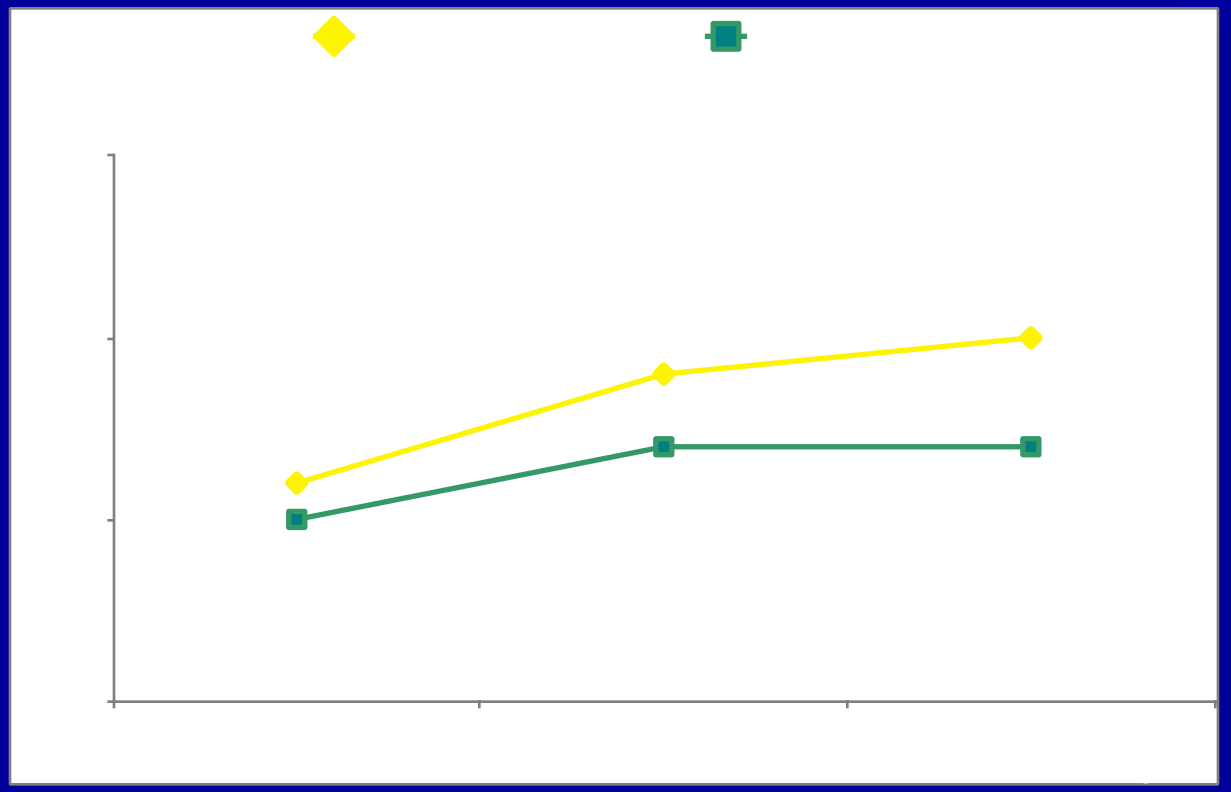


Candesartan, median [25%-75%]	32.5 [29.8-36.0]	31.8 [29.3-34.7]	31.3 [28.8-33.7]
Control, median [25%-75%]	33.5 [30.0-37.1]	32.6 [29.0-36.2]	32.5 [28.8-36.2]

Differences between baseline and 12 weeks: **p*=0.05**
Differences between baseline and end of study: **p*=0.12**
** Mann Whitney*

Aleksova A, Sinagra G et al
Cardiovasc Drugs Ther, 2012

Ejection fraction % (median)



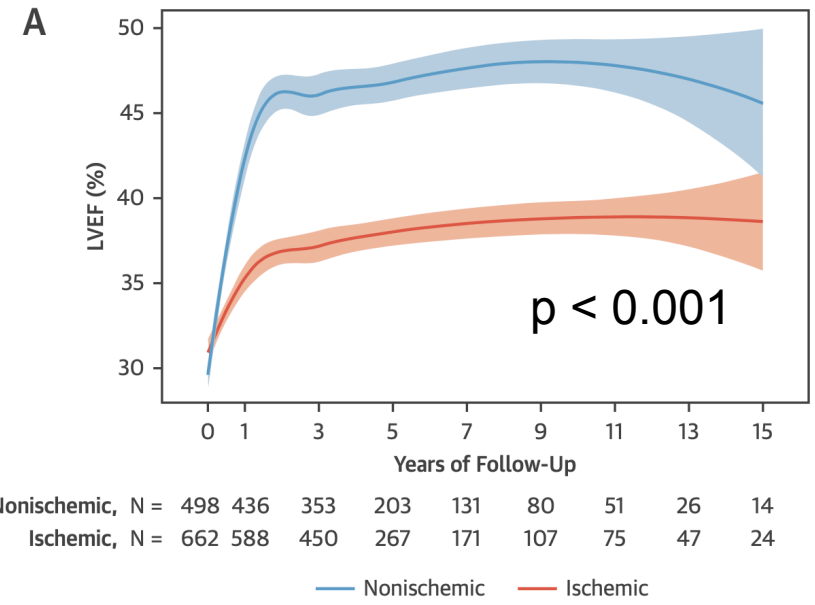
Candesartan, median [25%-75%]	36 [30-40]	39 [34-46]	40 [35-49]
Control, median [25%-75%]	35 [30-39]	37 [31-44]	37 [32-45]

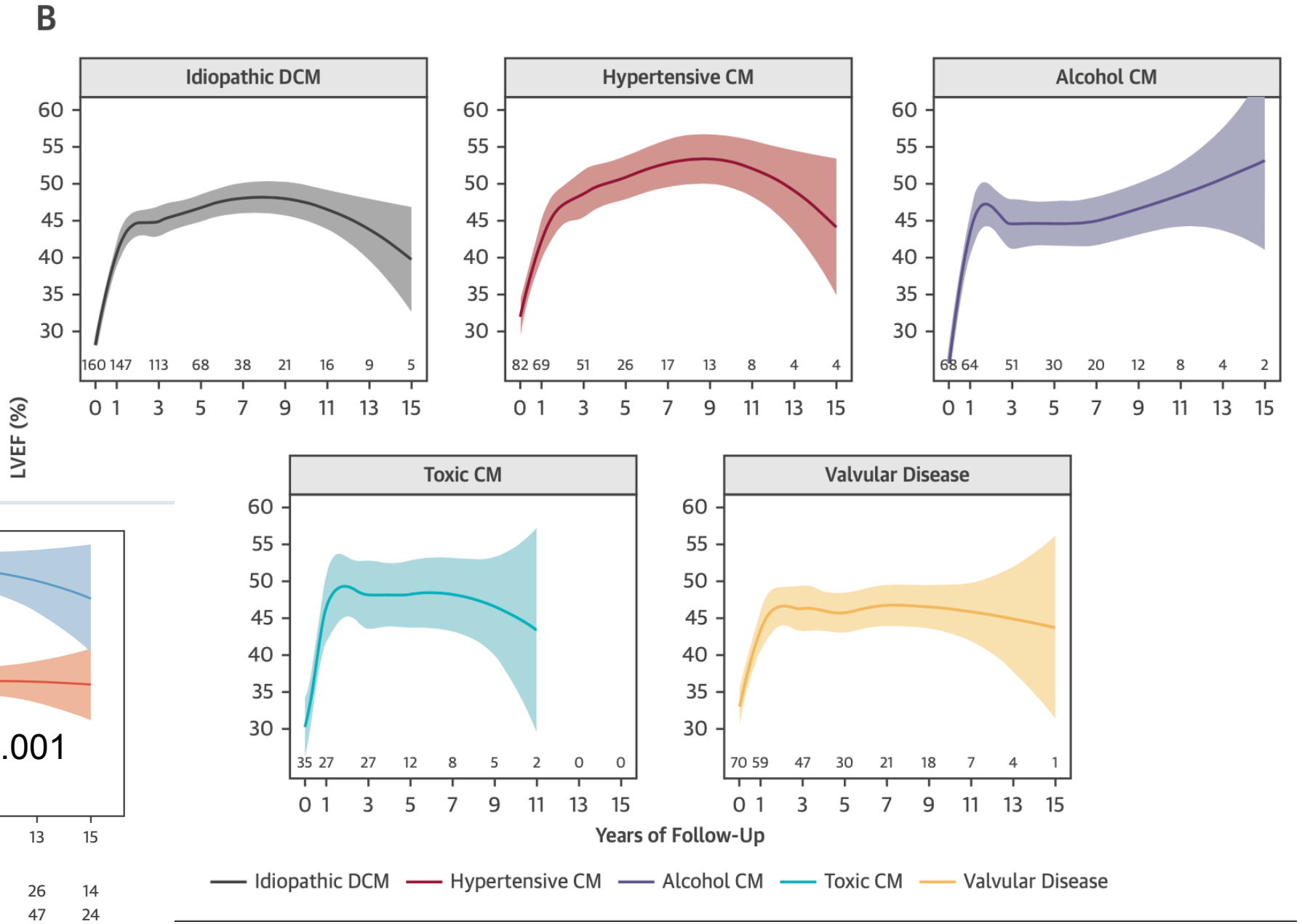
Differences between baseline and 12 weeks: **p*=0.09**
Differences between baseline and end of study: **p*=0.01**
** Mann Whitney*

Aleksova A, Sinagra G et al
Cardiovasc Drugs Ther, 2012

Dynamic Trajectories of Left Ventricular Ejection Fraction in Heart Failure

Josep Lupón, MD, PhD,[a,b,c,d] Giovana Gavidia-Bovadilla, MSc,[e,f] Elena Ferrer, MD,[b] Marta de Antonio, MD, PhD,[a,b] Alexandre Perera-Lluna, PhD,[f,g,h] Jorge López-Ayerbe, MD,[b] Mar Domingo, MD, PhD,[a] Julio Núñez, MD, PhD,[d,i,j] Elisabet Zamora, MD, PhD,[a,b,c,d] Pedro Moliner, MD,[a,b] Patricia Díaz-Ruata, MSc,[f,g] Javier Santesmases, MD,[a] Antoni Bayés-Genís, MD, PhD[a,b,c,d]





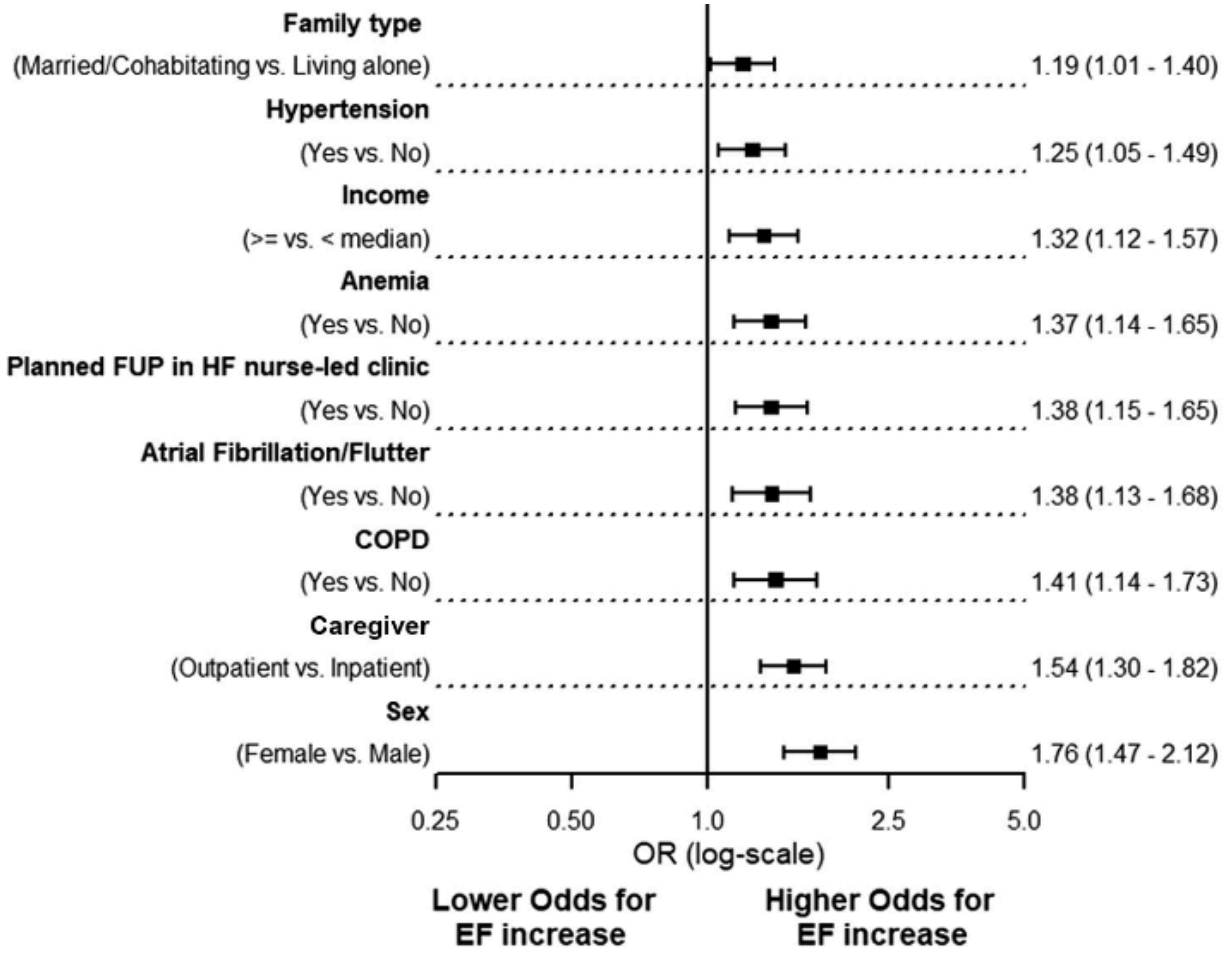
JACC vol 72, no 6, 2018:591-601

JACC: HEART FAILURE VOL. 7, NO. 4, 2019

Prevalence and Prognostic Implications of Longitudinal Ejection Fraction Change in Heart Failure

Gianluigi Savarese, MD, PhD,[a,*] Ola Vedin, MD, PhD,[b,c,*] Domenico D'Amario, MD, PhD,[d] Alicia Uijl, MD, PhD,[a,e] Ulf Dahlström, MD, PhD,[f] Giuseppe Rosano, MD, PhD,[g] Carolyn S.P. Lam, MD, PhD,[h] Lars H. Lund, MD, PhD[a]

Predictors of EF increase



JACC Heart Failure vol 7, 2019: 306-17

THM- Ipertensione Arteriosa e HF

- Ipertensione arteriosa conferisce HR 3 for HF;
- Riduzione RR HF in terapia fra il 30-60%;
- Rimodellamento VSin concentrico predittore eventi fatali e HF;
- Inibizione RAAS costituisce prima scelta nella prev HF;
- Fra gli ATIIRa Candesartan coniuga potenza d'inibizione recettoriale, controllo PA ed effetti su massa e spessori Vsin
- BB, SGLT2, GLP1A, CaAtg, diuretici;
- Target <130/80 mmHg; se HFrEF <120/70 mmHg;
- Presidio sul danno d'organo….e sull'aderenza!