מחקרים חדשים באי ספיקת לב

דר' אברהם שוטן

מכון הלב

בי"ח הילל יפה

חדרה

Clinical Studies - Beta-Blockers

ANZ

BEST

CAPRICORN

CARMEN

Carvedilol-US

CIBIS I

CIBIS II

CIBIS III

COMET

COPERNICUS

Merit-HF

MDC

SENIORS

- **Cardiovascular Trial Review**
- **What's What**

Clinical Studies - ACE-Inhibitors

AIRE

AIRE-EX

ATLAS

CCS I

CONSENSUS I

CONCENSUS II

EUROPA

HOPE

GISSI III

ISIS IV

PEACE

PEP-CHF

SAVE

SMILE

SOLVD

TRACE

V-HeFT II

Clinical Studies - Angiotensin-Receptor Blockers

CHARM-Added

CHARM-Alternative

CHARM-Preservrd

CHARM-Overall

ELITE

ELITE II

OPTIMAAL

RESOLVD

STRETCH

Val-HeFT

VALIANT

Clinical Studies – Other Drugs

A-HeFT

AFFIRM

CORONA

GISSI-HF

DIG

RALES

EPHESUS

PRAISE I

PRAISE II

Neseritide

Levosimendan

LIDO

RUSSLAN

CASINO

REVIVE

SURVIVE

V-HeFT I

AF-CHF

Clinical Studies – Non Drug Treatment

CARE-HF

COMPANION

CTOPP

DEFINITE

MADIT I

MADIT II

MIRACLE

MUSTIC

MUSTT

REMATCH

GISSI-HF omega-3 fatty acid study: Primary and secondary outcomes

End point	Omega-3 fatty acids, n=3494 (%)	Placebo, n=3481 (%)	Adjusted hazard ratio (95% CI)
Primary end points			
•Mortality	27.3	29.1	0.91 (0.833–0.998)
•All-cause mortality or hospitalization for cardiovascular causes	56.7	59.0	0.92 (0.849–0.999)
Secondary end points			
•Death from cardiovascular causes	20.4	22.0	0.90 (0.81–0.99)
•Sudden cardiac death	8.8	9.3	0.93 (0.79–1.08)
•Patients admitted for cardiovascular causes	46.8	48.5	0.93 (0.87–0.99)
•Patients with fatal and nonfatal MI	3.1	3.7	0.82 (0.63–1.06)
•Patients with fatal and nonfatal stroke	3.5	3.0	1.16 (0.91–1.53)

GISSI-HF investigators. *Lancet* 2008; available at: http://www.thelancet.com.

GISSI-HF statin study: Primary outcomes

End point	Rosuvastatin 10 mg, n=2285 (%)	Placebo, n=2289 (%)	Adjusted hazard ratio (95% CI)
Mortality	29.0	28.0	1.00 (0.898–1.122)
All-cause mortality or hospitalization for cardiovascular causes	57.0	56.0	1.01 (0.908–1.112)

GISSI-HF investigators. *Lancet* 2008; available at: http://www.thelancet.com.

Table 2. Prespecified Composite Cardiovascular Outcomes and Fatal and Nonfatal Events.*

Variable	Placebo (N=2497)		Rosuvastatin (N=2514)		Hazard Ratio (95% CI)	P Value
	No. of Patients	Event Rate	No. of Patients	Event Rate		
Outcome						
Primary outcome	732	12.3	692	11.4	0.92 (0.83–1.02)	0.12
Death from cardiovascular causes	487		488			
Nonfatal myocardial infarction	141		115			
Nonfatal stroke	104		89			
Secondary outcome						
Death from any cause†	759	12.2	728	11.6	0.95 (0.86–1.05)	0.31
Any coronary event‡	588	10.0	554	9.3	0.92 (0.82–1.04)	0.18
Fatal event						
Death from cardiovascular causes§	593	9.6	581	9.3	0.97 (0.87–1.09)	0.60
Sudden death	327	5.3	316	5.0	0.96 (0.82–1.12)	0.57
In primary outcome	284		284			
In coronary events	283		272			
Worsening heart failure	191	3.1	193	3.1	1.00 (0.82–1.22)	1.00
In primary outcome	157		161			
Myocardial infarction§	9	0.2	15	0.2		
In primary outcome	8		9			
In coronary events	8		9			
Stroke§¶	32	0.5	35	0.6		
In primary outcome	11		14			
Pulmonary embolism	8	0.1	2	<0.1		
In primary outcome	7		1			
Aortic aneurysm	5	<0.1	0			
In primary outcome	5		0			
Other	21	0.3	20	0.3		
In primary outcome	15		19			
Death from noncardiovascular cause	159	2.6	138	2.2		
Infection	68	1.1	54	0.9		
Cancer	50	0.8	52	0.8		

CORONA

Rosuvastatin in Older Patients with Systolic Heart Failure

- 5011 patients
- ≥60 years of age
- NYHA class II-IV
- ischemic
- systolic heart failure

Rosuvastatin 10 mg / placebo

Kjekshus J et al. NEJM 2007; 357:2248-2261

AF-CHF trial

1376 HF patients

LVEF ≤35%, History of AF

Rhythm control vs rate control

Follow-up : 37 months

Similar results in AFFIRM & RACE in non-valvular, non-HF

Table 3. Cause of Death.

Cause	Rhythm-Control Group (N=682)	Rate-Control Group (N=694)	P Value
	no. (%)		
Total deaths	217 (32)	228 (33)	0.68
Cardiovascular	182 (27)	175 (25)	0.53
Presumed arrhythmic cause	71 (10)	88 (13)	0.19
Congestive heart failure	73 (11)	57 (8)	0.11
Myocardial infarction	15 (2)	9 (1)	0.20
Stroke	9 (1)	11 (2)	0.68
Other	14 (2)	10 (1)	0.39
Noncardiovascular	35 (5)	53 (8)	0.06
Cancer	14 (2)	20 (3)	0.32
Renal failure	1 (<1)	2 (<1)	1.0
Trauma	0	1 (<1)	1.0
Sepsis	11 (2)	26 (4)	0.01
Other	9 (1)	4 (1)	0.15

Roy D et al. N Engl J Med 2008;358:2667-2677

RALES: Study Design

Aldactone 25 mg/d

(n = 822)

NYHA III or IV

LVEF ≤ 35%

ACE-I + loop diuretics ± digoxin

3 years

Placebo

(n = 841)

Primary Endpoint

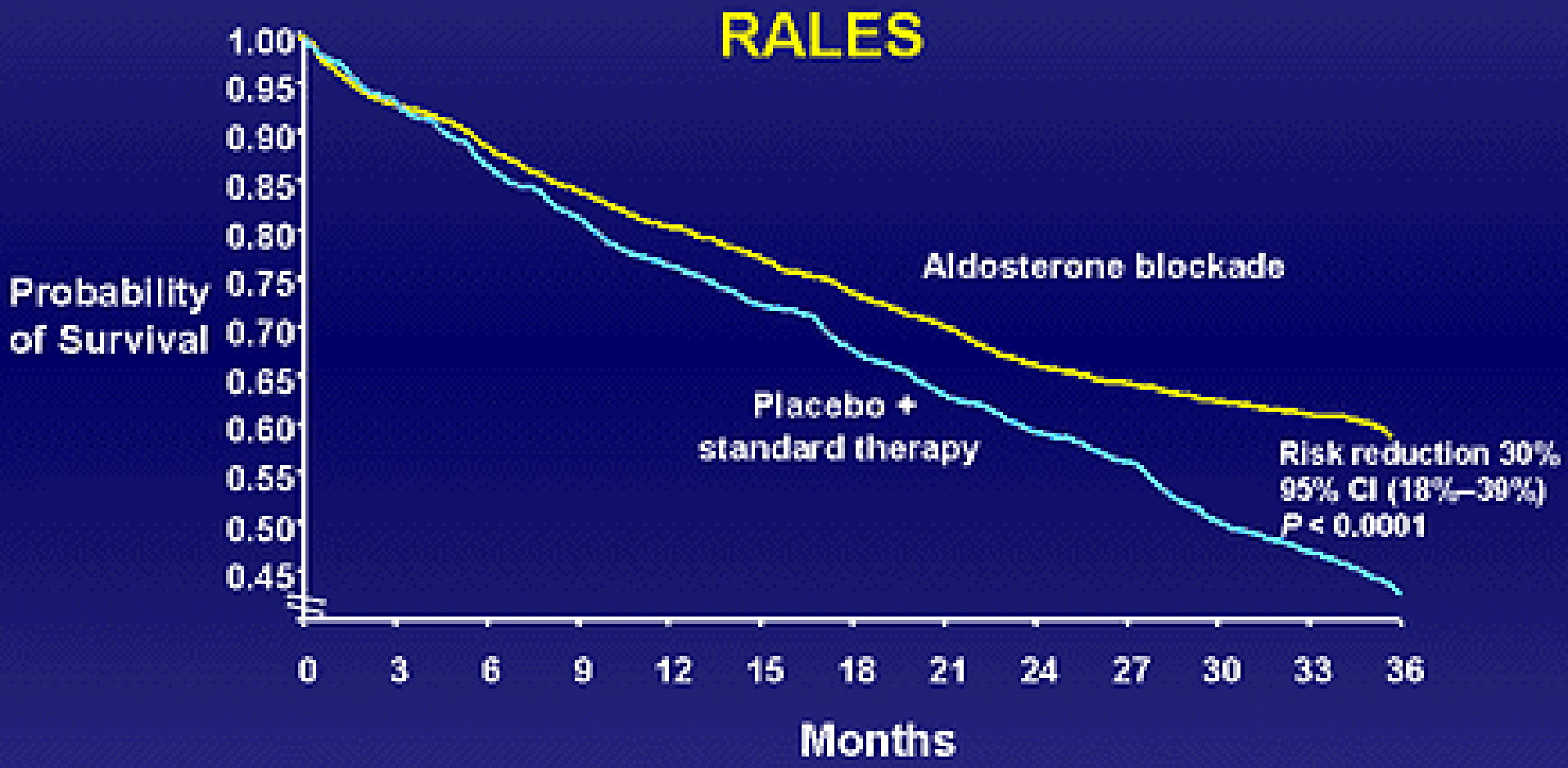
- Total Mortality

Secondary Endpoints

- Cardiac Mortality
- Non-Fatal Cardiac Hospitalization
- Cardiac Mortality or Non-fatal cardiac hospitalization
- Changes in NYHA

Pitt B et al. N Engl J Med 1999;341:709

Total Mortality in Patients with Severe Heart Failure Is Reduced with Aldosterone Blockade



Standard therapy = ACE inhibitor, loop diuretic ± digitalis.

Pitt B et al. *N Engl J Med.* 1999;341:709-17.

Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA:
Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

N Engl J Med 2004;351:543-51

Methods

A population-based time series analysis

to examine trends in the rate of spironolactone prescriptions **and**

rate of hospitalizations for hyperkalemia **in ambulatory patients**

before and after **the publication of** RALES **(1999).**

Prescription-claims data linked to hospital-admission records

Population: >1.3 million **adults** ≥ 66 yrs **in** Ontario, Canada (12.3×10^6)

Period: 1.1.1994 - 31.12.2001

Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA:
Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study
N Engl J Med 2004;351:543-51

Results

Among ACE-I treated hospitalized for HF – 20,820 (94) 32,283 (01)

Spironolactone rate

34/1000 **in** 1994 **increased to** 149/1000 **in** late 2001 (p<0.001)

Rate of hospitalizations for hyperkalemia

2.4/1000 **in** 1994 **rose to** 11.0/1000 **in** 2001 (p<0.001)

Associated mortality

0.3/1000 **in** 1994 **to** 2.0/1000 **in** 2001 (p<0.001)

2001 Additional hyperkalemia related hospitalizations 560 (285-754)

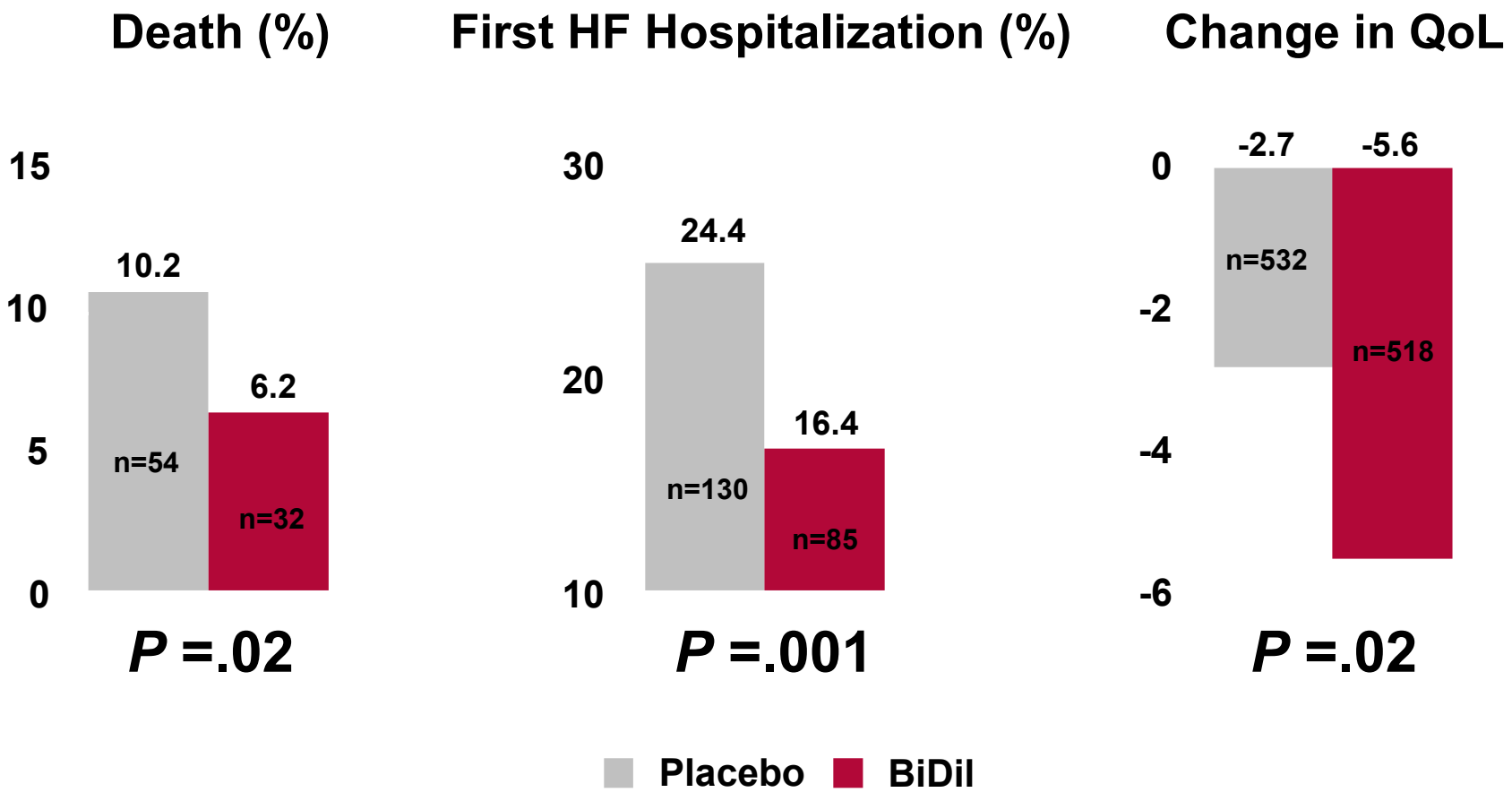
A-HeFT: Study Design

- African American Heart Failure Trial (A-HeFT)

  Hypothesis: Fixed-dose isosorbide dinitrate/hydralazine hydrochloride will improve outcomes in black patients with moderate to severe symptomatic HF

- 169 sites
- 1050 randomized patients (518 BiDil, 532 placebo)
- Up to 18 months of follow-up
- No patient lost to follow-up
- Study initiated 6/12/01, terminated early due to significant survival benefit in the BiDil group

A-HeFT: All Components of Composite Score



Taylor AL et al. *N Engl J Med.* 2004;351:2049-2057.

Therapeutic Efficacy in Heart Failure

	Symptoms Relief	LV Remodeling	Mortality
Diuretics	++	↔	?
Aldosterone Antagonists	+	++	++
ACE - I	+	+++	++
All Antagonists	+	+++	++
Nitrates/Hydralazine	++	++	+
Positive Inotropics	+	↔	↑
Digoxin	+	+ ?	↔
Beta Blockers	+ ↔	++	+++
CCB	↔ ↑	↔	↑ ?

HFSIS – Heart **F**ailure **S**urvey in **Is**rael **2003**

Study Population

25/25 Hospitals

93/98 Internal Medicine Departments

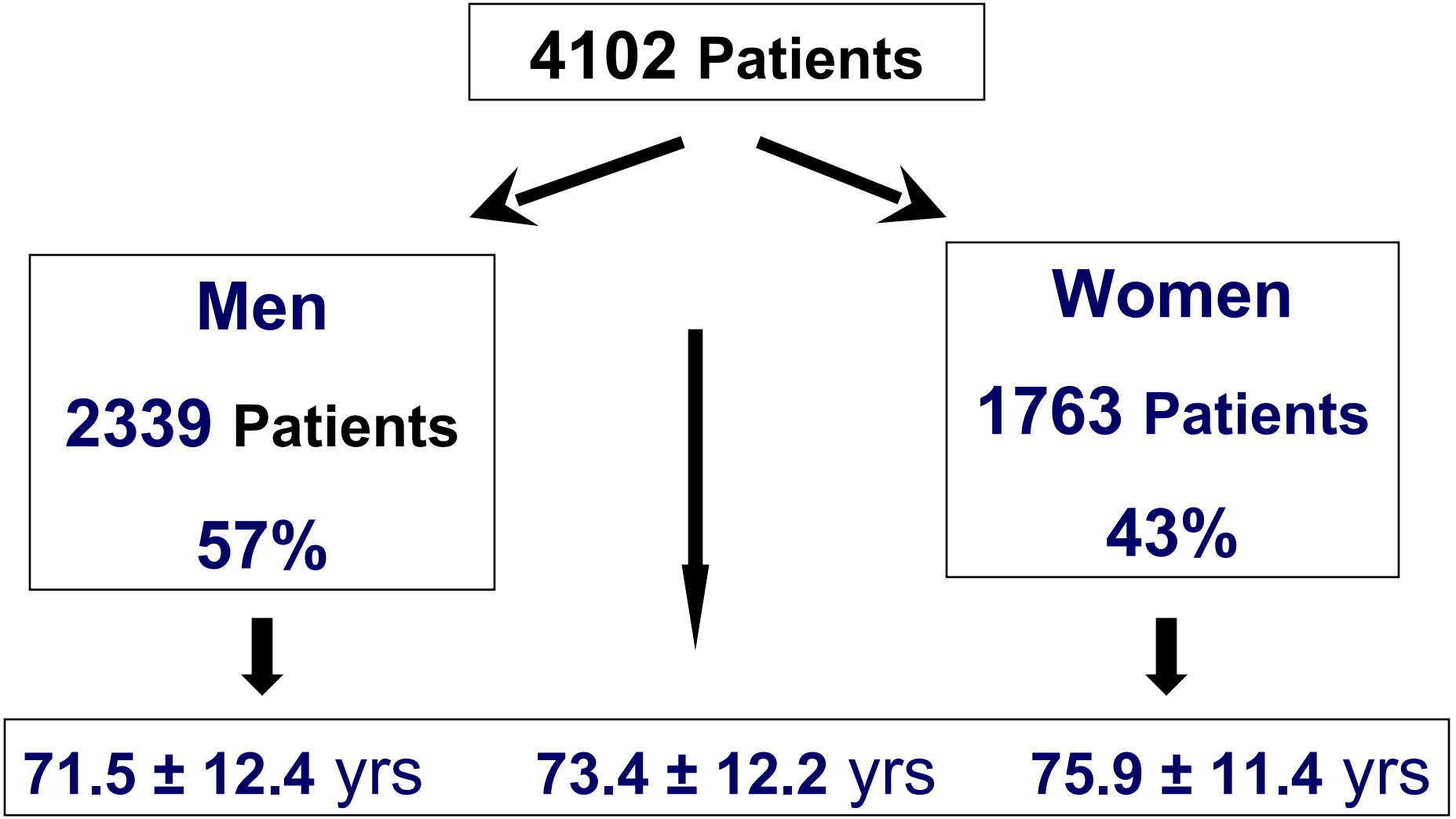
24/25 Cardiology Departments (24 ICCU, 16 Intermediate)

4872 Hospitalizations recorded

4514 Hospitalizations

4102 Patients

HFSIS 2003 – Age by Gender



HFSIS 2003 – Co-Morbidity

	n = 4,102	%
Ischemic Heart Disease	3,372	82.2
Acute Coronary Syndrome	1,505	36.7
Renal Failure (creat ≥1.5 mg%)	1,672	40.8
Anemia (Hb ≤ 12.0 gr%)	2,026	49.4
COPD	803	19.6
PVD	374	9.1
Stroke / TIA	511	12.5
Atrial Fibrillation	1,360	33.2
PAF	398	9.7 (29.3)

HFSIS 2003 – Risk Factors for ASCVD

	n = 4,102	%
Hypertension	3,088	75.3
Dyslipidemia	2,403	58.6
Diabetes Mellitus	2,050	50.0
Insulin treated	514	12.5 (25.1)
P.O.	1,059	25.8 (51.7)
Obesity	949	23.1
Current Smokers	417	10.2

HFSIS 2003 – Left Ventricular Ejection Fraction

LVEF

	n = 2,842*	%
Normal (≥50%)	763	26.8
Mild (40-49%)	601	21.1
Preserved (≥40%)	1,364	48.0
Moderate (30-39%)	735	25.9
Severe (<30%)	743	26.1

***Missing 1,260 (echo done – 394)**

HFSIS 2003 – All-Cause Mortality

Period	Mortality n = 4,102 %
Hospital	4.7
day-30	7.6
month-6	18.7
year-1	28.2
year-2	40.2
year-3	50.3
year-4	57.7

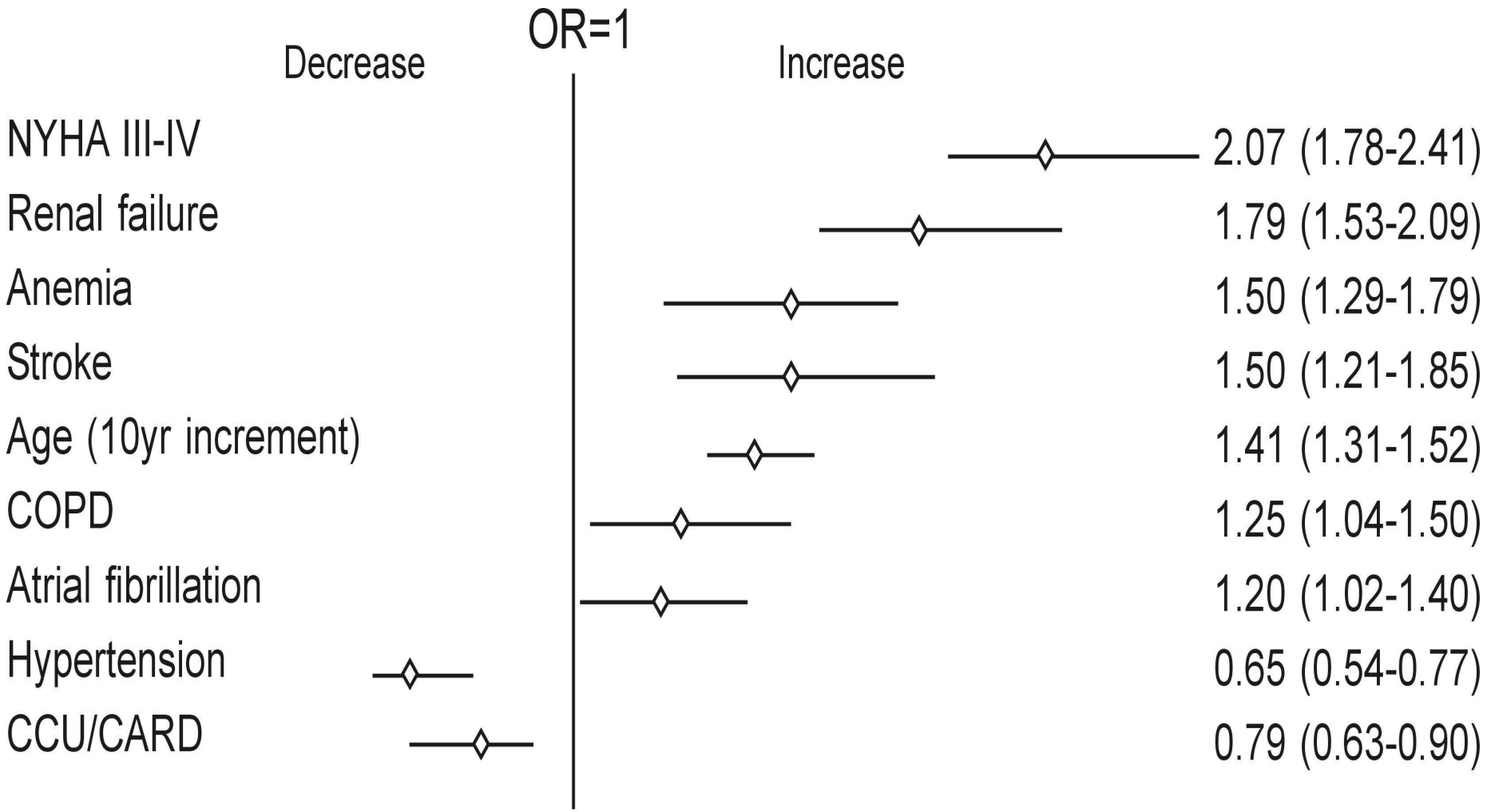


Fig.2: parameters associated with1year mortality

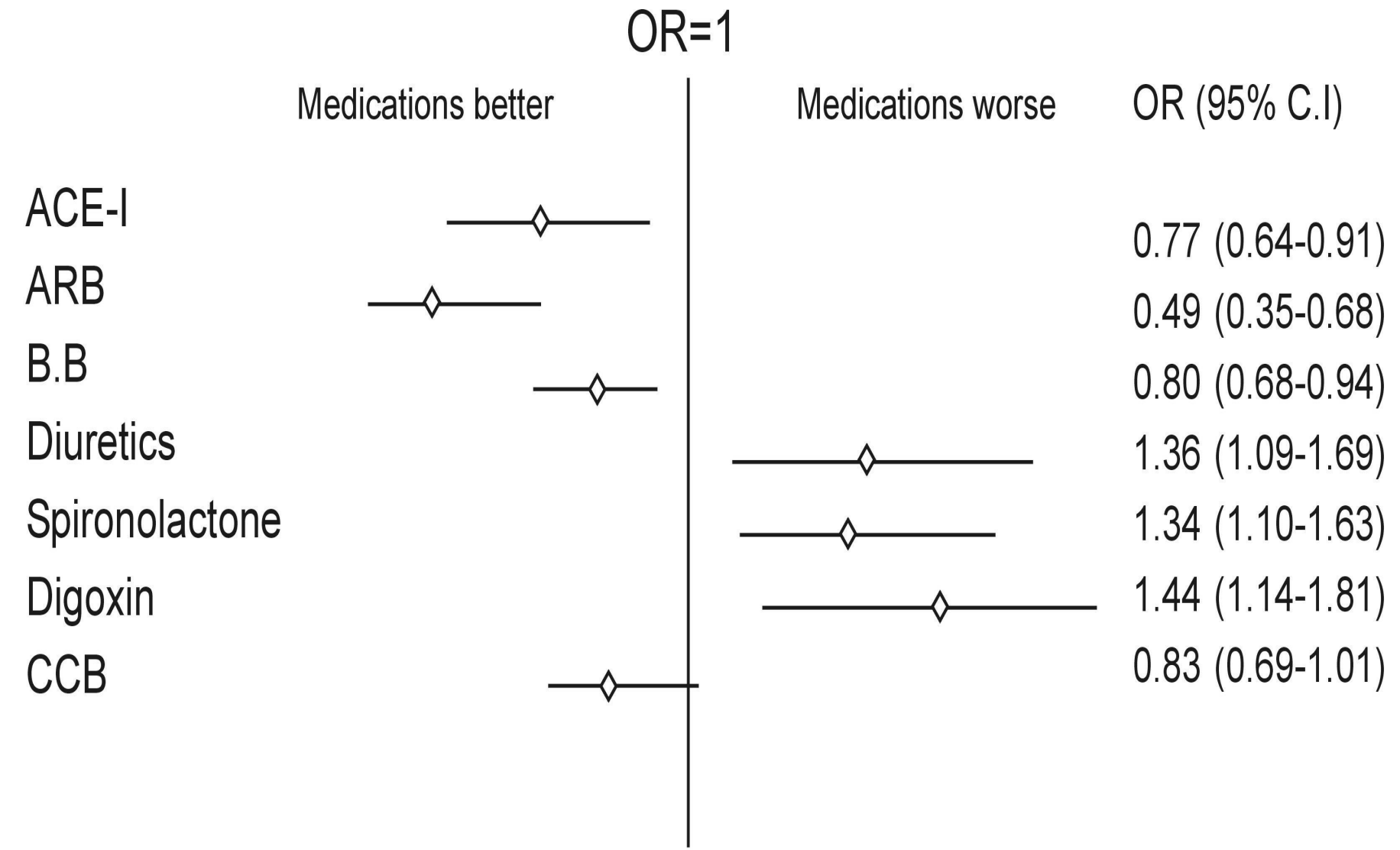
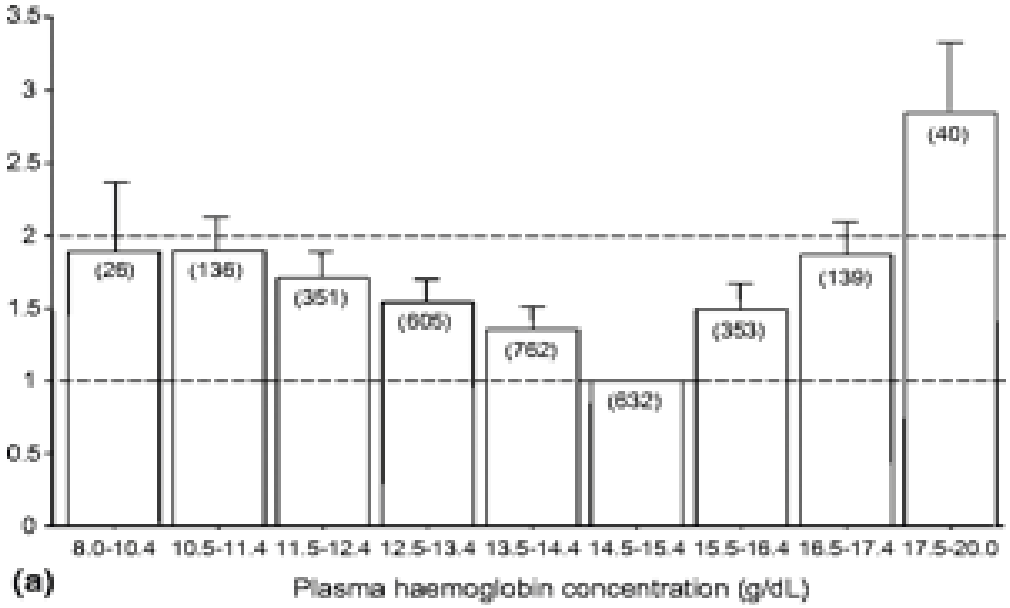


Fig. 3: medications at discharge associated with 1 year mortality

Sharma R et al: Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. **EHJ 2004; 25:1021**



ELITE II :Evaluation of Losartan In The Elderly trial
(Captopril vs. Losartan)

3044 pts enrolled 6.1997 – 5.1998

FU for survival 1–780 (median 551) days

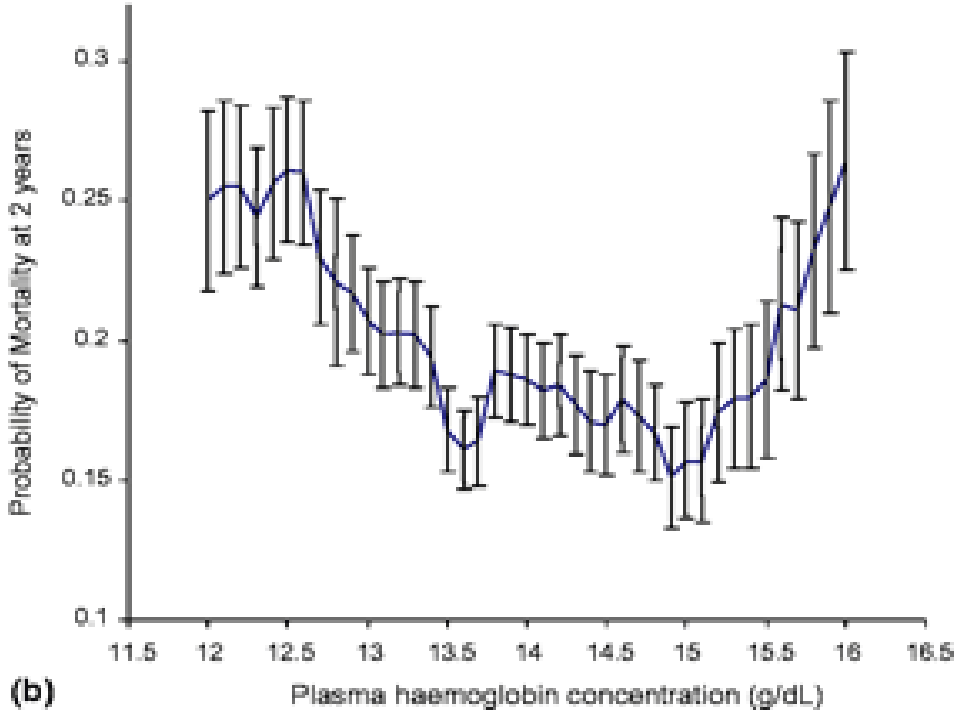
Mean age 71.5±6.8 years

NYHA class 2.5±0.6

LVEF 31±7%

haemoglobin 14.0±1.6 g/dL

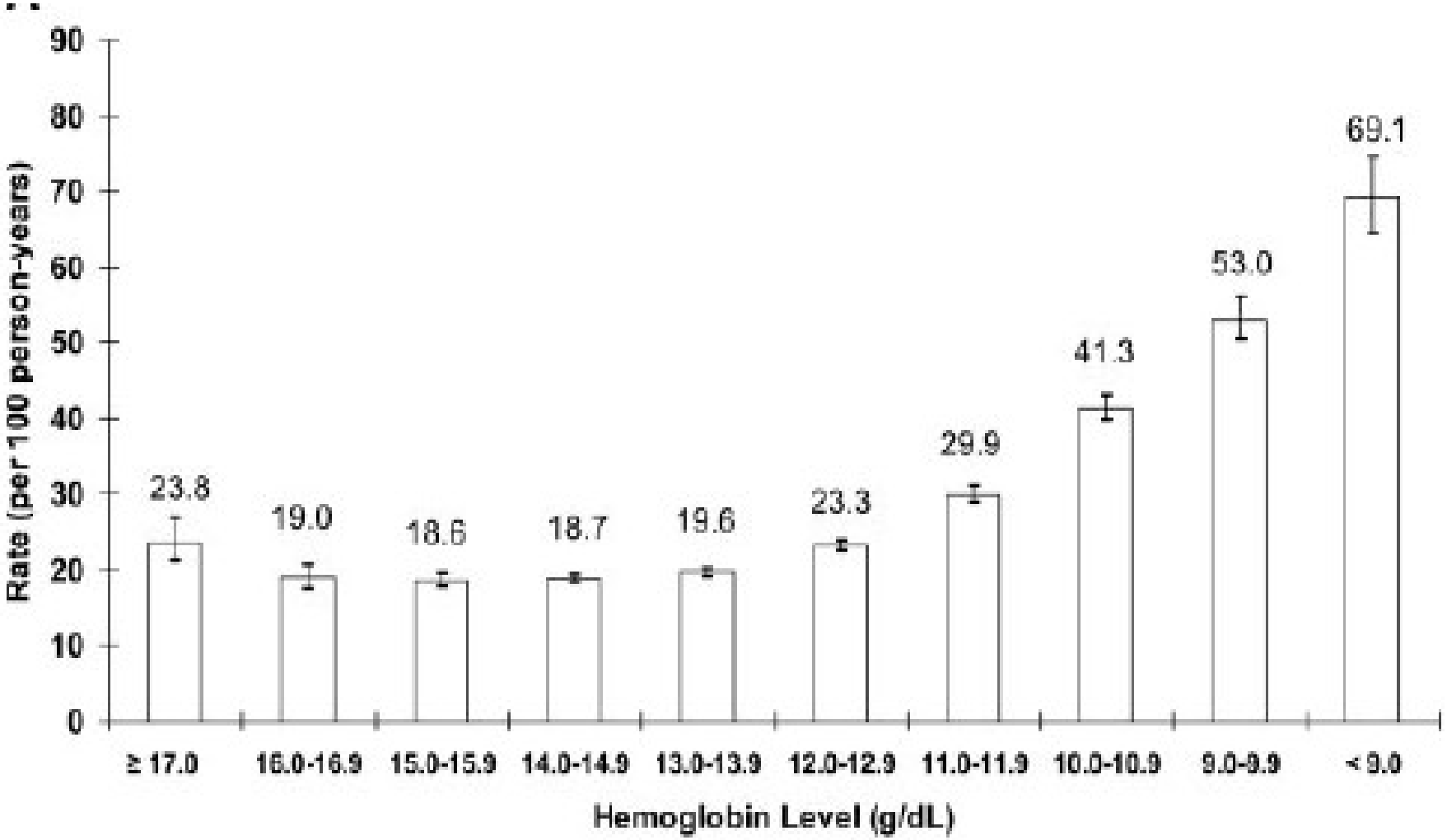
haematocrit 42±5%



Go AS et al: Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure.

The Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study

Circ 2006;113:2713



Go AS et al: Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure.

The Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study

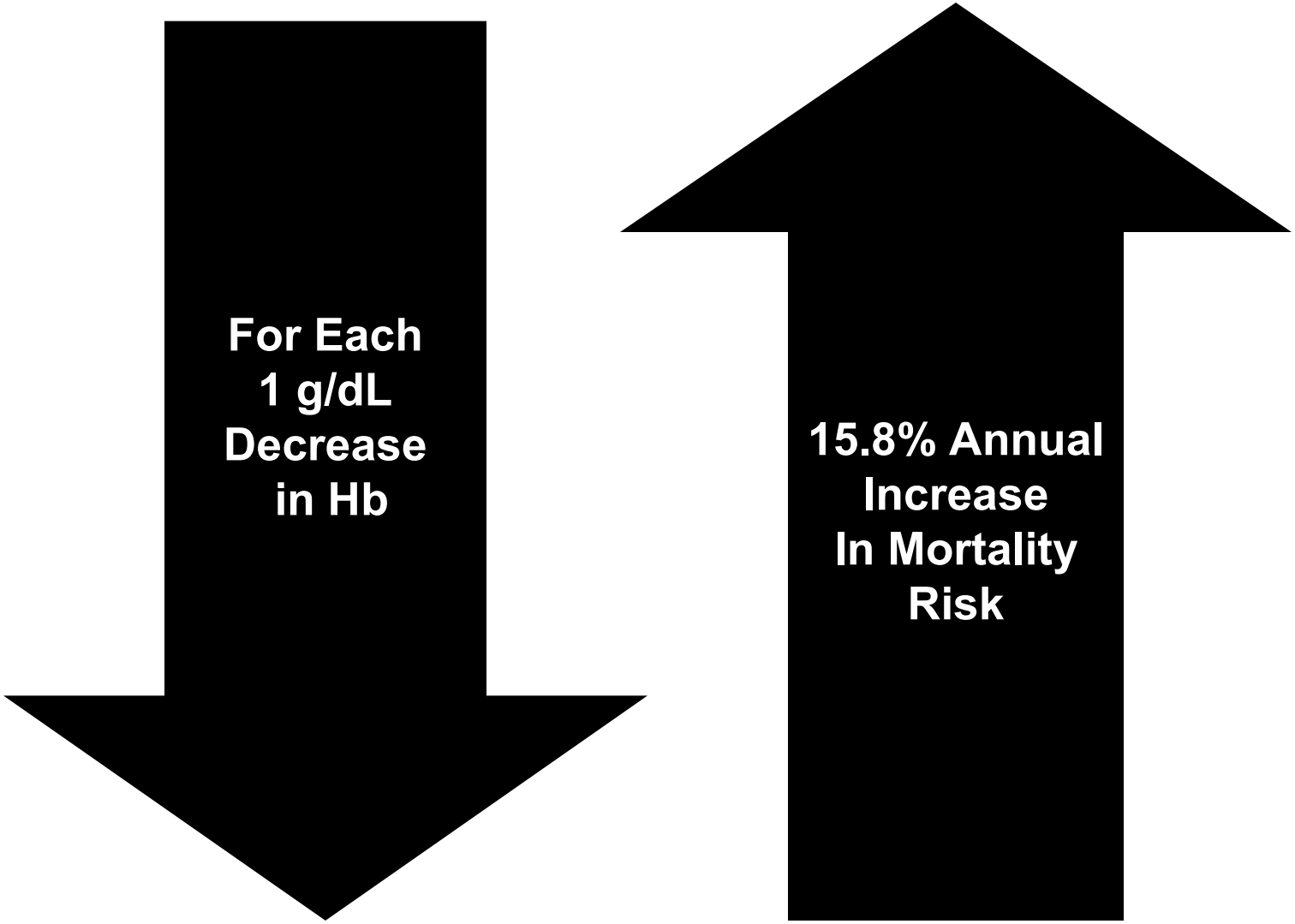
Circ 2006;113:2713

59 772 adults with heart failure, Kaiser Permanente of Northern California,

During 1.1.1996-31.12.2002, mean age was 72 years and 46% were women

	Death From Any Cause*	Hospitalization for Heart Failure*
	Adjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)
Hemoglobin level (g/dL)		
≥17	1.42 (1.24-1.63)	1.14 (1.03-1.27)
16.0-16.9	0.94 (0.85-1.03)	0.95 (0.89-1.02)
15.0-15.9	0.94 (0.88-1.00)	0.96 (0.92-1.01)
14.0-14.9	0.92 (0.88-0.97)	0.98 (0.94-1.01)
13.0-13.9	Reference	Reference
12.0-12.9	1.16 (1.11-1.21)	1.12 (1.09-1.16)
11.0-11.9	1.50 (1.44-1.57)	1.33 (1.28-1.38)
10.0-10.9	1.89 (1.80-1.98)	1.64 (1.58-1.71)
9.0-9.9	2.31 (2.18-2.45)	1.89 (1.80-1.99)
<9.0	3.48 (3.25-3.73)	1.99 (1.86-2.13)

Hemoglobin in HF Patients



Anand et al Circulation 2004;110:149-154

Late-Breaking Clinical Trials – AHA Sessions 2008

Tuesday 11/11/2008

HF-ACTION Study: Morbidity and Mortality Outcomes From Aerobic Exercise Training in Heart Failure: Results of the HF and A Controlled Trial Investigating Outcomes of Exercise Training

I-PRESERVE: A Randomized Double-Blind Placebo-Controlled Trial of Irbesartan in the Treatment of Heart Failure in Patients with Preserved EF

BACH Multinational: Mid-Regional pro-Adrenomedullin (proADM) vs BNP and NTproBNP as Prognosticator in Heart Failure Patients

The effect of s.c. treatment with interferon-beta-1b over 24 weeks on safety, virus elimination & clinical outcome in patients with chronic viral cardiomyopathy

אס"ק לב – שאלה מס' 1

מתן איזו תרופה מוריד את התמותה בחולי אס"ק לב עם הפרעה בתפקוד הסיסטולי

א. אמלודיפין

ב. וראפמיל

ג. דיגוקסין

ד. ספירונולקטון

ה. דובוטמין

אס"ק לב – שאלה מס' 2

באיזה מחקר מתן ניטראטים עם או ללא הידרלאזין הביא לירידה מובהקת סטטיסטית בתמותה?

א. V-HeFT I

ב. V-HeFT II

ג. GISSI III

ד. ISIS IV

ה. A-HeFT