

*Dangerous liaison*

# **Heart Failure & Renal Insufficiency**

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# Case

- 71-yrs-old male patients with dyspnea
- Orthopnea and coughing for 10 days
- Diagnosed as lung cancer at another hospital
- DM for 10 years
- Increased jugular venous pressure
- Crackle on both lung lower lung fields

HF

KYUNGHEE UNIV. HOSPITAL  
ADC 51xx  
Srs:1  
Img:1

MP:AP

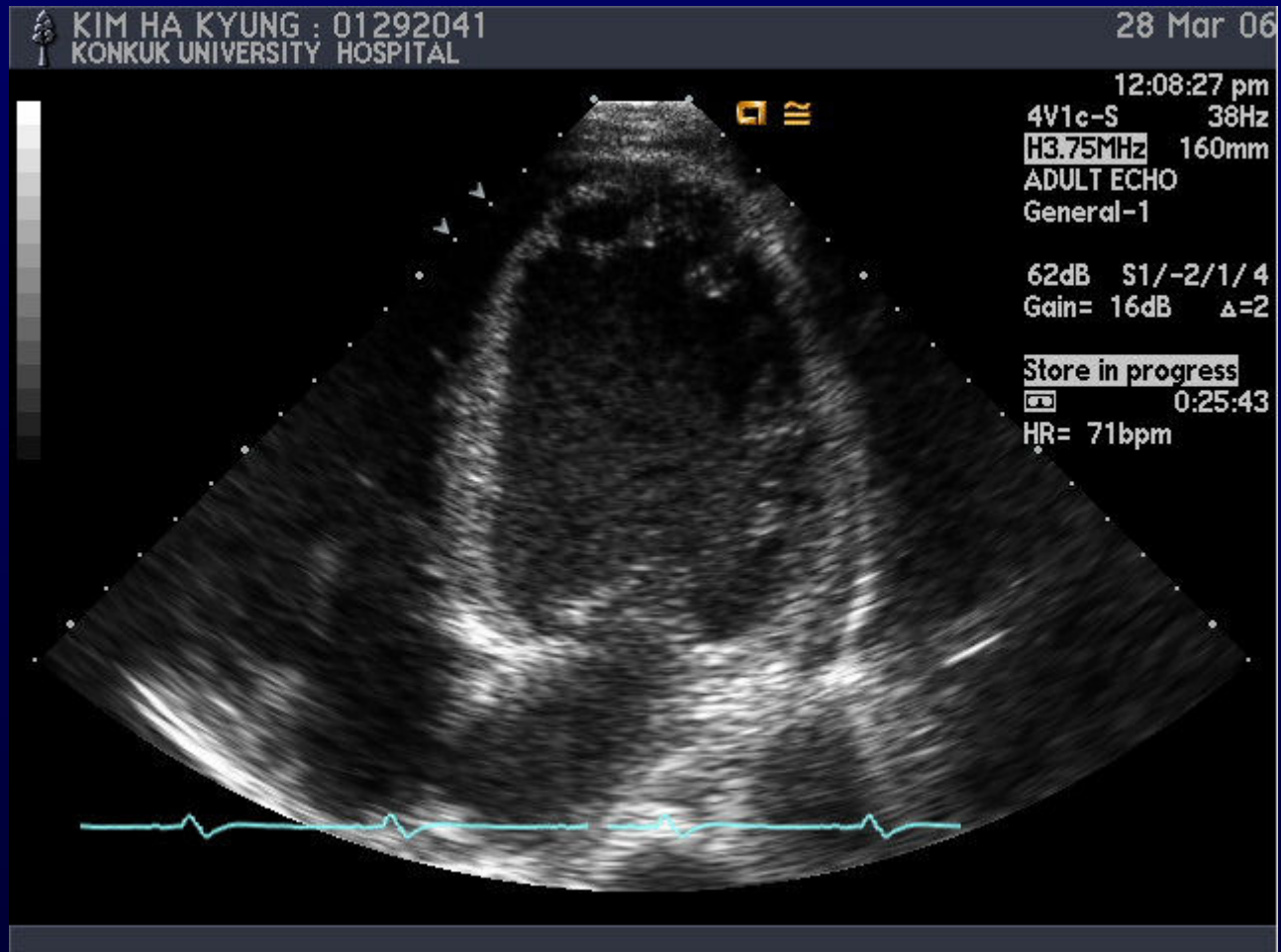


14 Cm

Sens:200.00

L:1600  
W:2800

*HF & renal insufficiency*



- Hgb 13.8g/dL
- BUN/Cr 24.7/2.3mg/dL
- Na/K/Cl 136/5.2/100 mEq/L
- Total protein/albumin 5.4/2.8g/dL
- Urine protein 1+

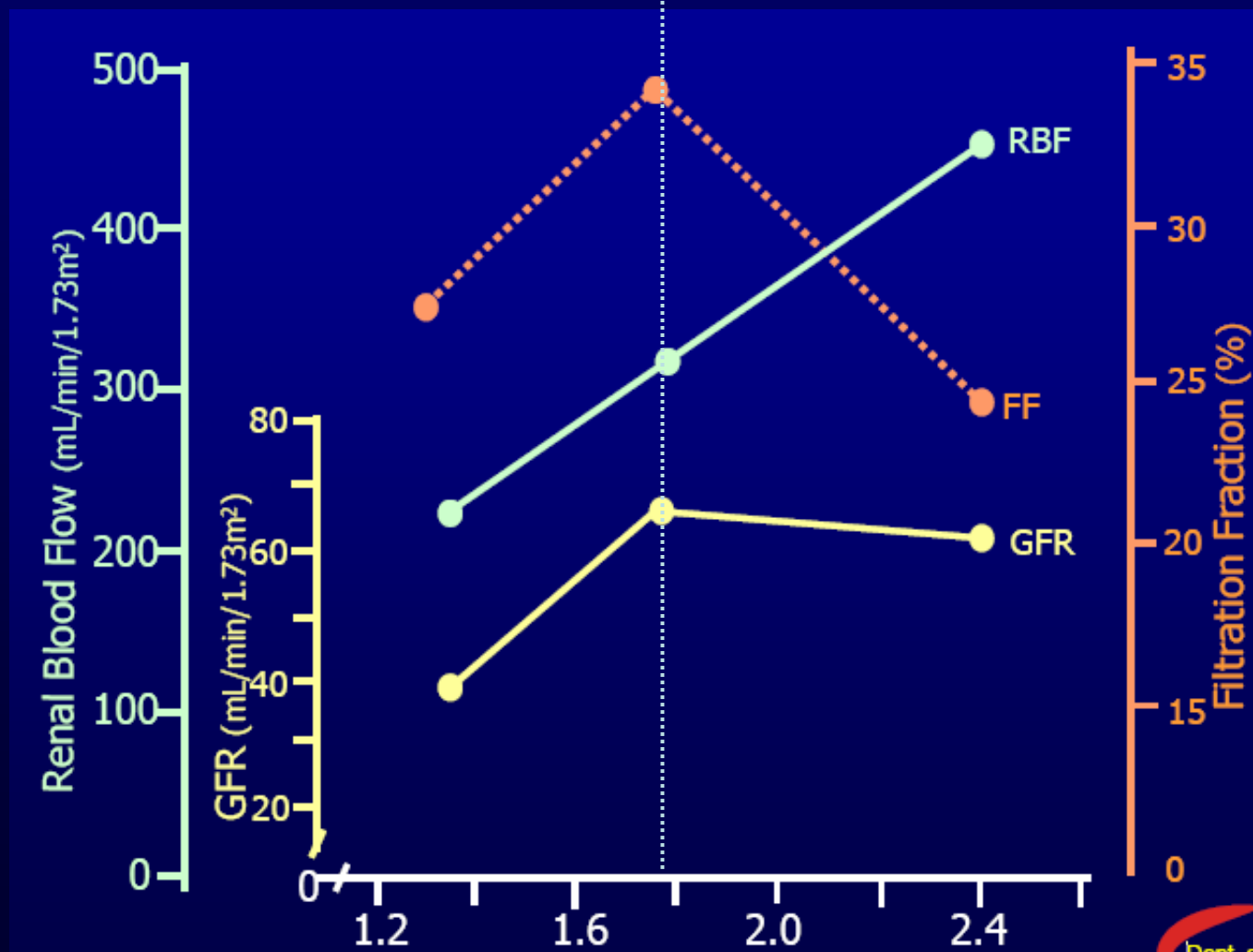
# Issues of Concern

- Cause of renal insufficiency
- Degree of renal insufficiency
- Relation between renal insufficiency and prognosis
- Limitation of treatment
- Optimal management strategy

# Causes of Renal Dysfunction in HF

- Underlying disease : diabetes, hypertension
- Sympathetic nervous system
- Renin-angiotensin-aldosterone system
- Activated cytokines, prostaglandins
  
- Hemodynamic alterations in heart failure

# Hemodynamic impairment and Renal Dysfunction



Cardiac index

Ljungman et al Drugs 1990



# Degree of Renal Dysfunction

## Terminologies for Dysfunctional Kidney

- Renal insufficiency
- Renal impairment
- Renal dysfunction
- Chronic renal disease
- Chronic renal failure

# Estimation of Glomerular Filtration Rate (GFR)

Prognostic value of formulas estimating renal function in CHF

Formula	Equation
Cockcroft-Gault (mL/min)	$[(140 - \text{age}) \times (\text{weight})] / 72 \times \text{sCr}$ Female: $\text{GFR}_{\text{cg}} \times 0.85$ BSA corrected: $\text{GFR}_{\text{cg}} \times 1.73 / \text{BSA}$
MDRD (mL/min/1.73m <sup>2</sup> )	$170 \times \text{sCr}^{-0.999} \times \text{age}^{-0.176} \times \text{sUrea}^{-0.170} \times \text{sAlb}^{-0.318}$ Female: $\text{MDRD} \times 0.76$ Black or non-white: $\text{MDRD} \times 1.180$
sMDRD (mL/min/1.73m <sup>2</sup> )	$186.3 \times \text{sCr}^{-1.154} \times \text{age}^{-0.203}$ Female: $\text{MDRD} \times 0.742$ Black or non-white: $\text{MDRD} \times 1.212$

# Prognostic value of Formulas Estimating Renal Function in HF Patients

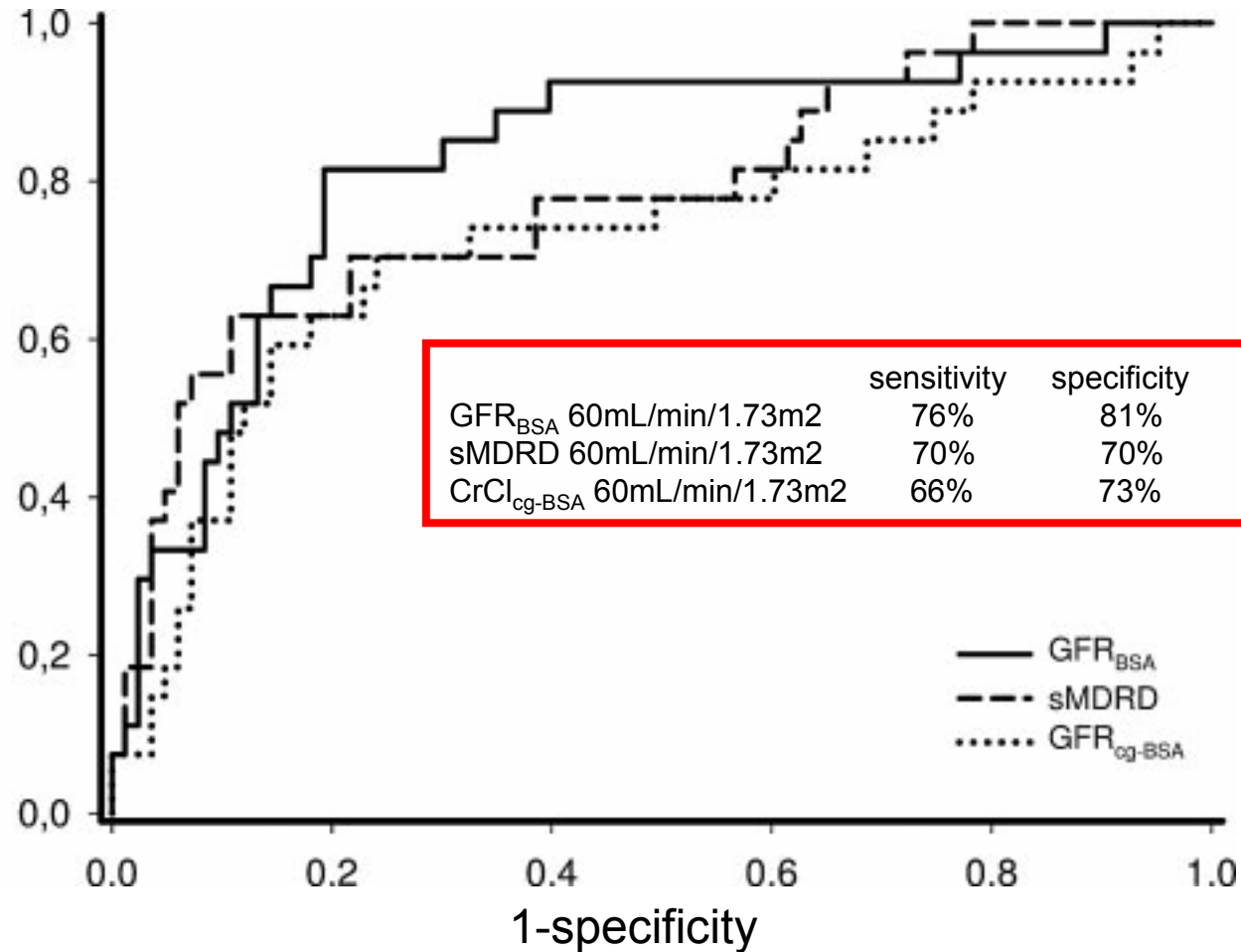
	Mean	Precision r2	Accuracy %
GFR <sub>BSA*</sub>	73±27	..	..
CrCl <sub>BSA</sub>	68±26	0.56	76
GFR <sub>cg-BSA</sub>	66±21	0.63	76
MDRD	62±19	0.72	83
sMDRD	62±18	0.68	80

\* 125I-iothalamate and 131I-hippuran method

# Prognostic value of Formulas Estimating Renal Function in HF Patients

Sensitivity for 12 months event

Smilde TDJ, Circulation 2006;114:1572



# Definition of Chronic Renal Disorder

ACC/AHA heart failure clinical data standards (2005)

History of reduced GFR  $\geq$  3 months, estimated by MDRD or sMDRD

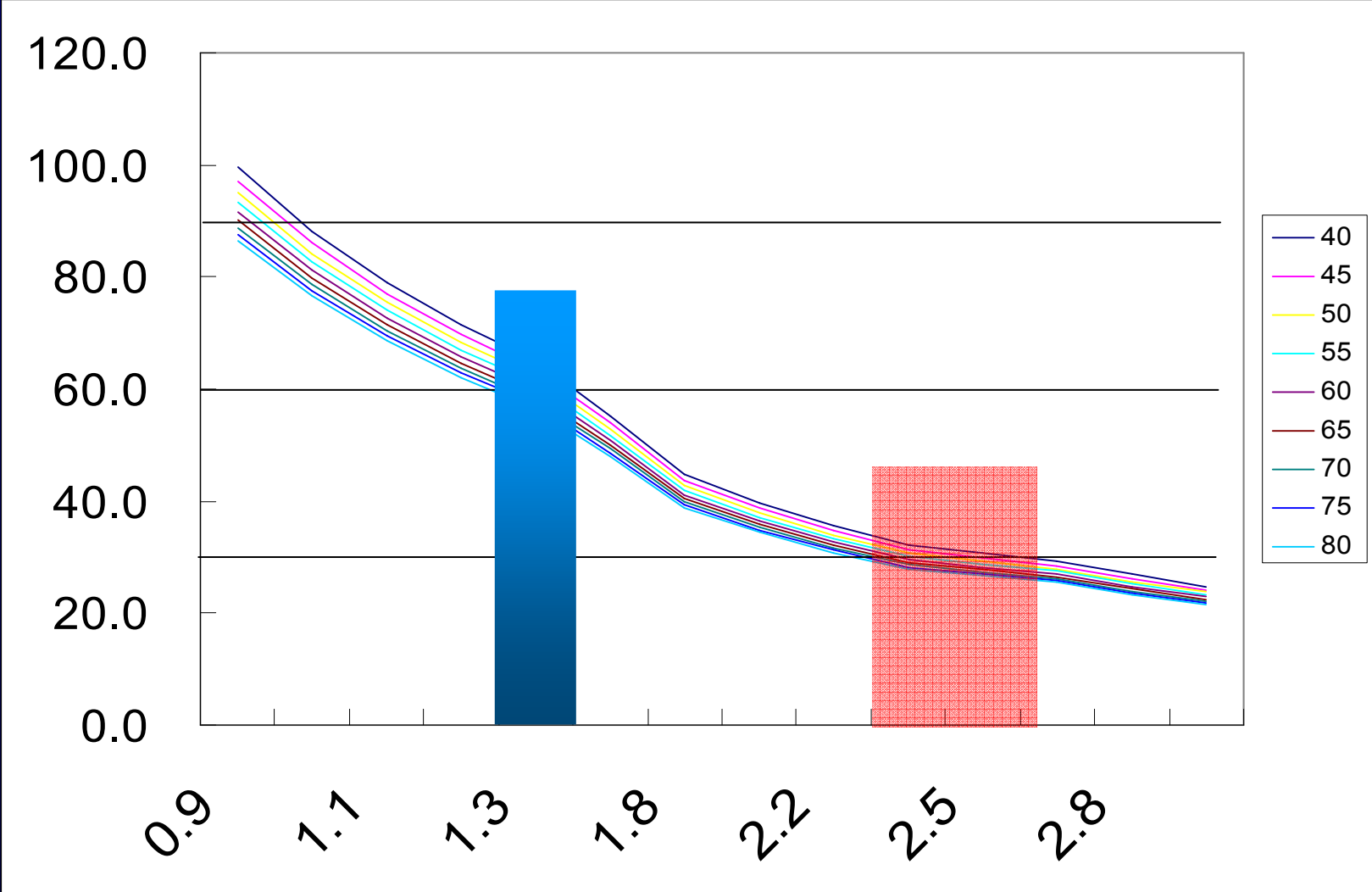
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Degree of renal insufficiency	Definition
Mild renal insufficiency	GFR 60-89mL/min/1.73m <sup>2</sup>
Moderate renal insufficiency	GFR 30-59mL/min/1.73m <sup>2</sup>
Severe renal insufficiency	GFR 15-29mL/min/1.73m <sup>2</sup>
Chronic renal failure	GFR <15mL/min/1.73m <sup>2</sup> or maintenance dialysis

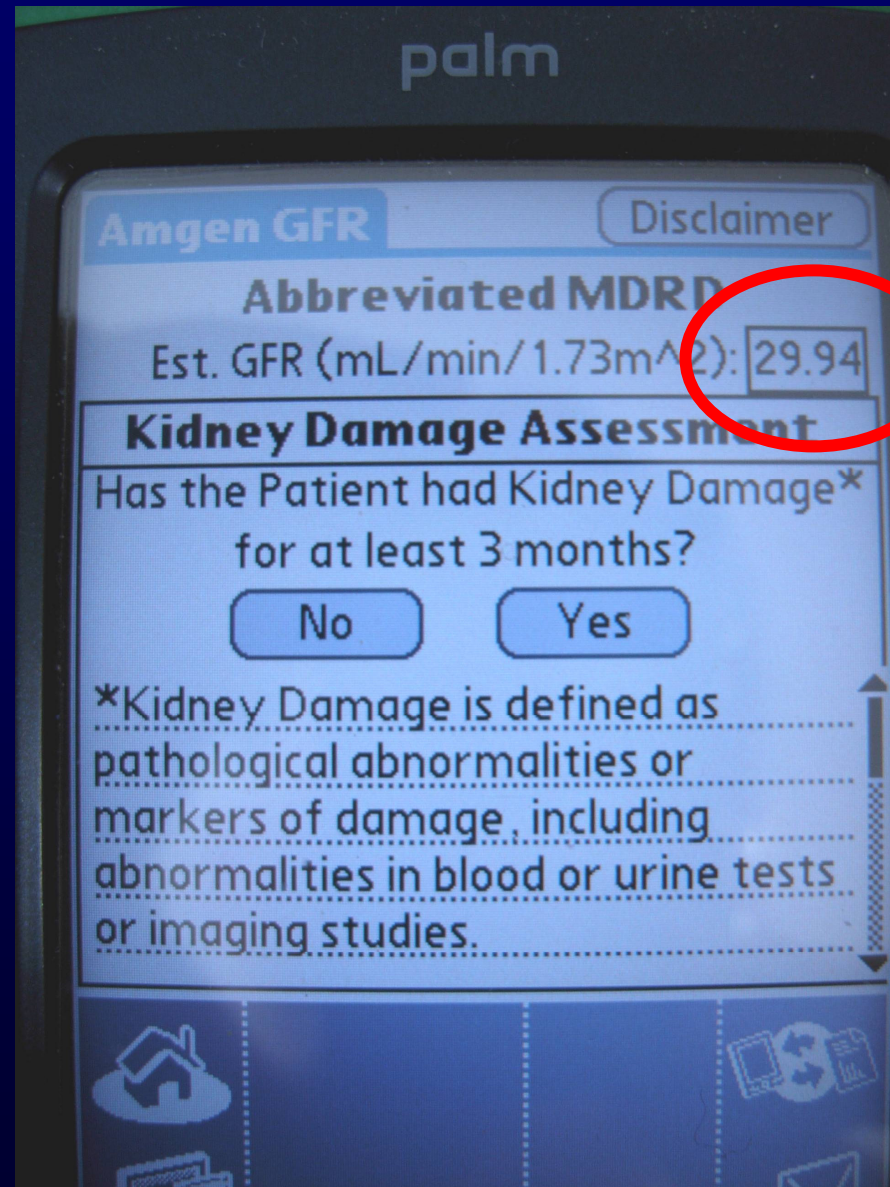
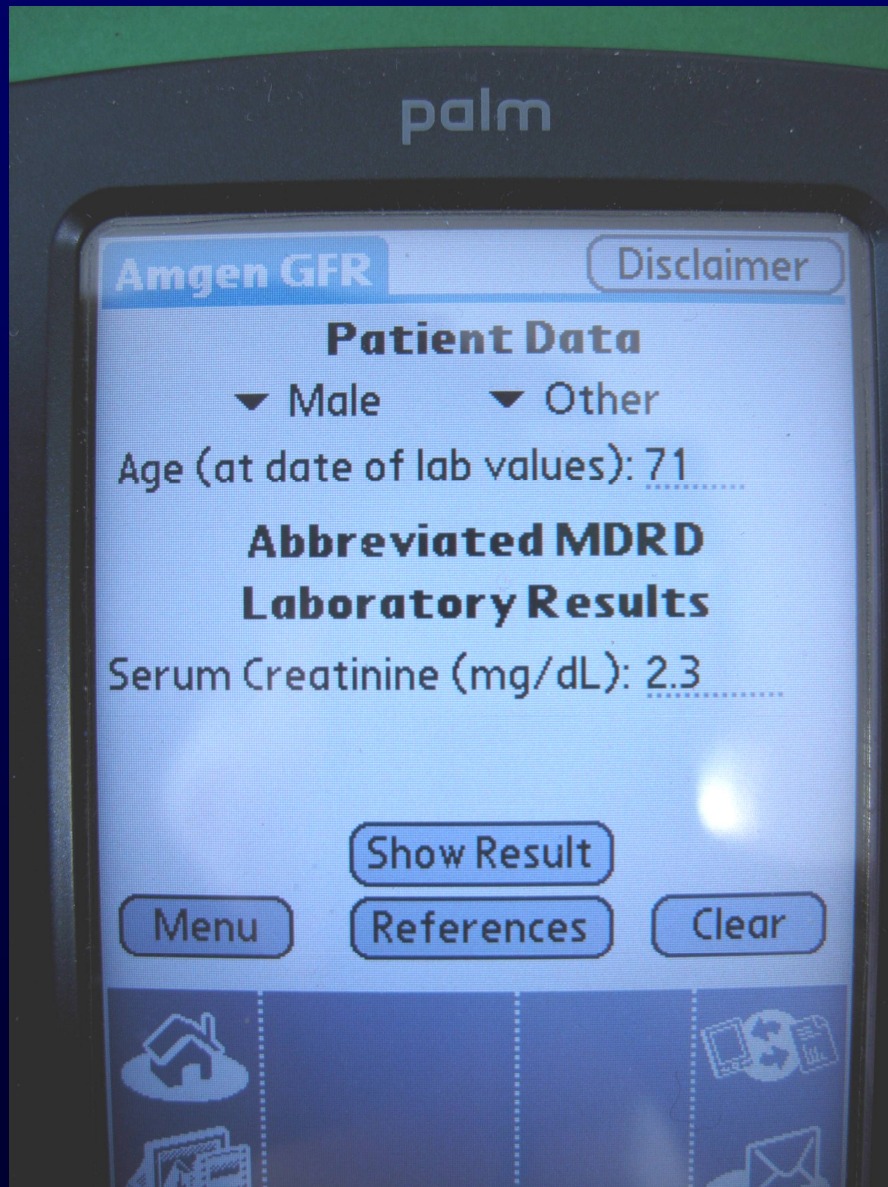
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HF & renal insufficiency





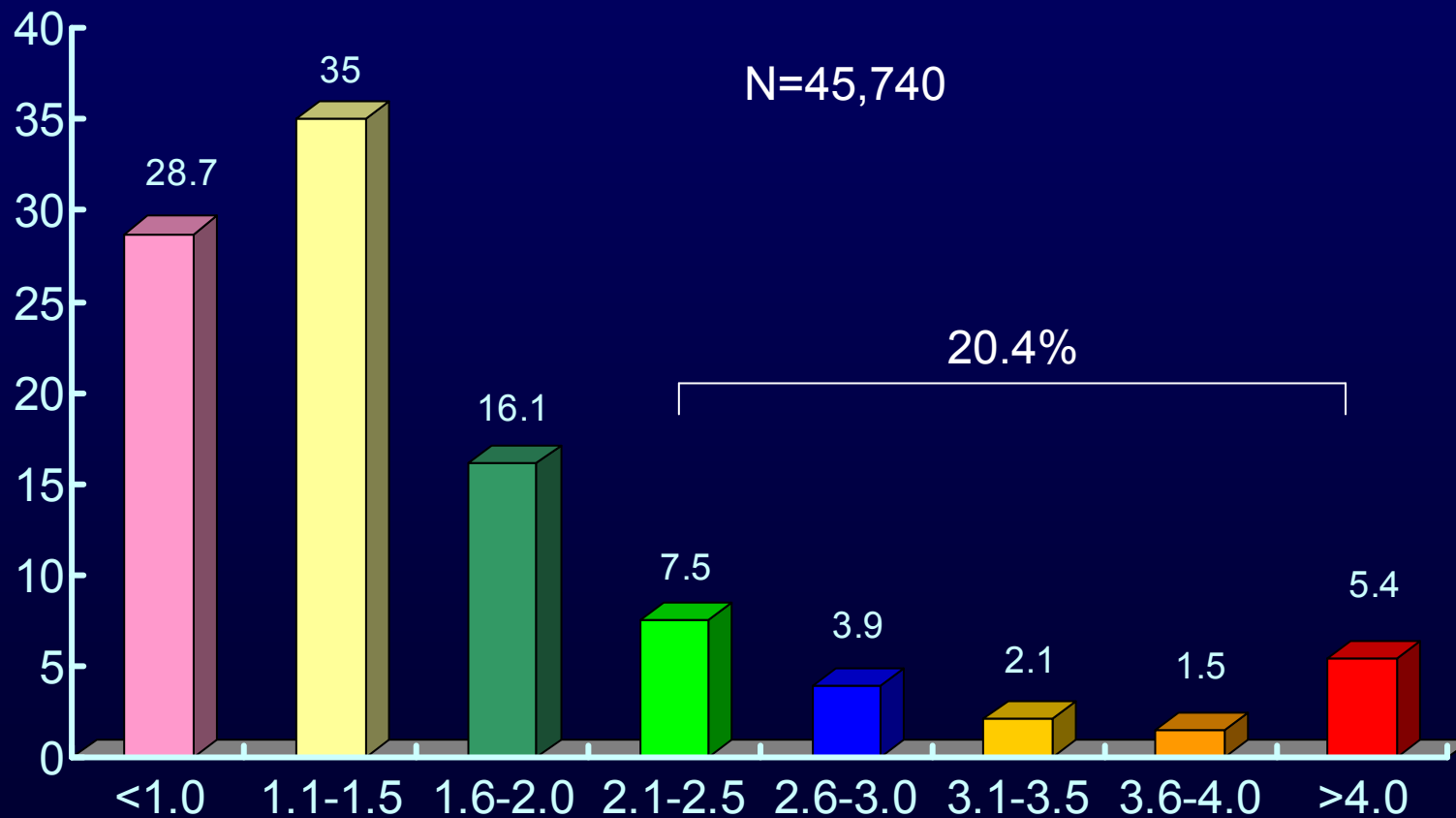


# Severe renal insufficiency (stage 3)

# Prevalence of Renal Dysfunction in Mega Registry

# ADHERE: Initial Creatinine Level

(enrolled 01.01.2002-12.31.2002)

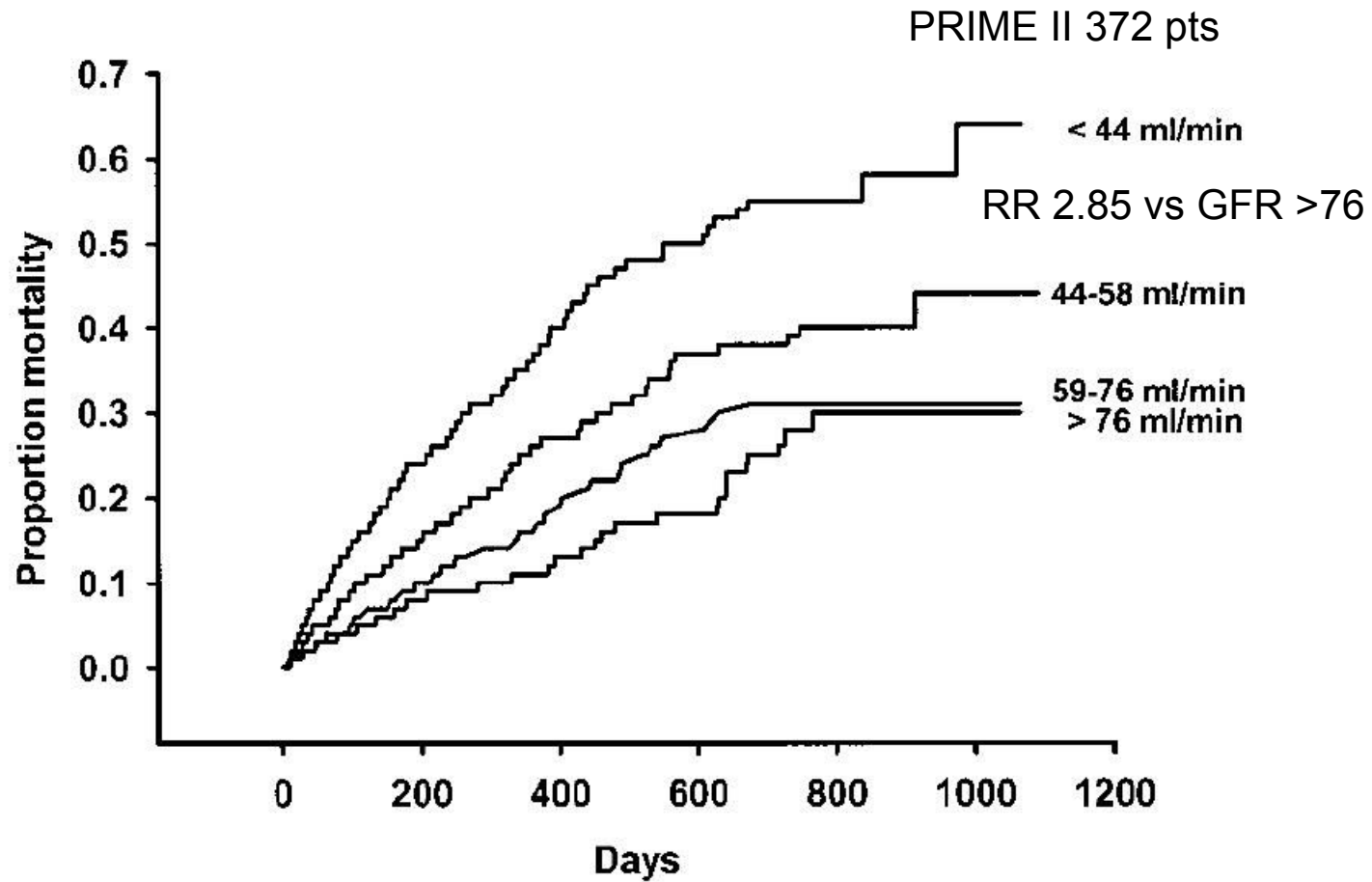


# Renal Dysfunction in Euro Heart Survey

- Total 11,327 pts.
- Renal dysfunction 18%
  - Russia, Hungary 6%
  - Old EU (Swiss, Netherland) up to 40%

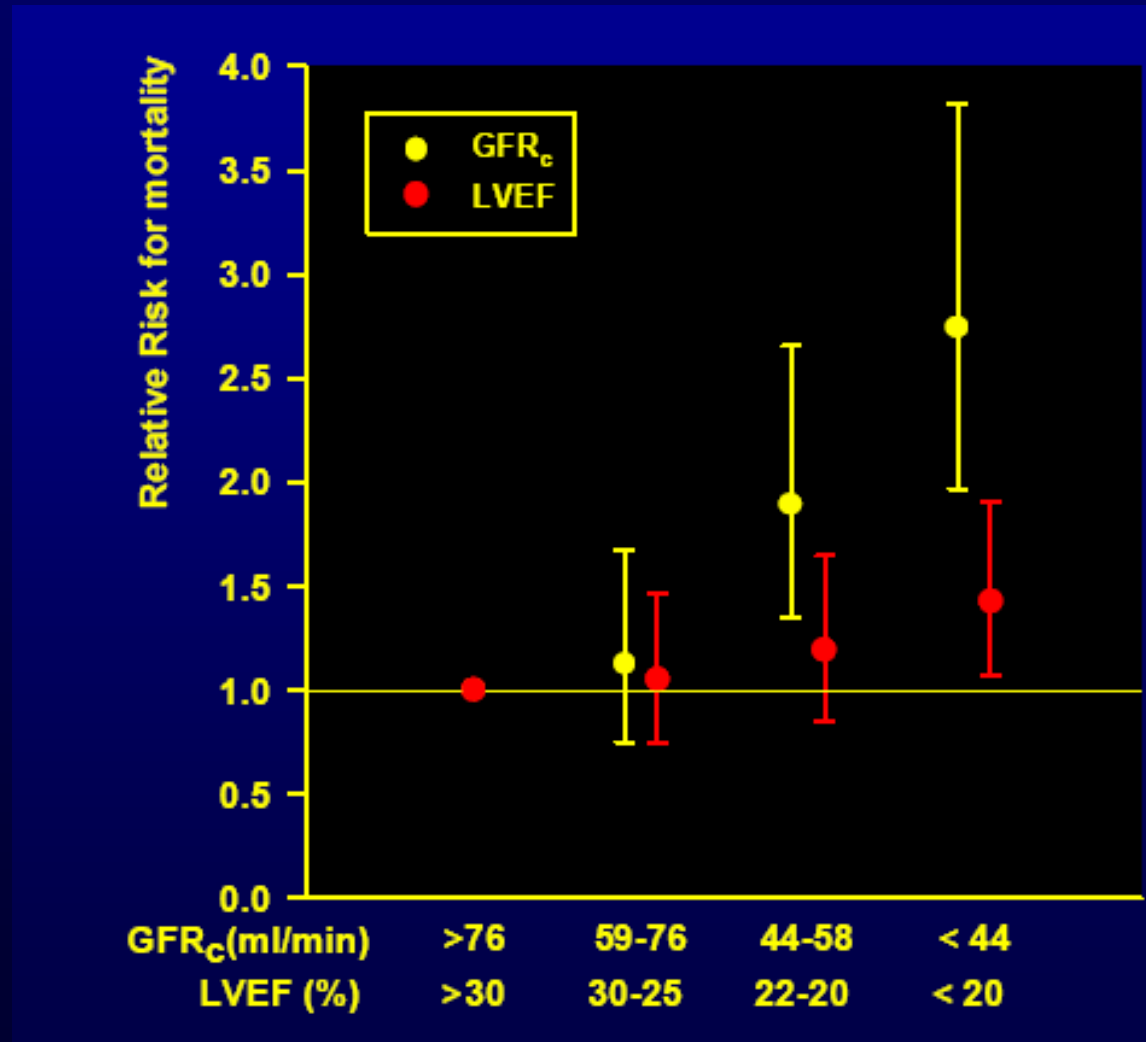
# Relation with Prognosis

# Prognostic Value of Renal Function in Advanced HF



Hillege et al Circulation 2000

# GFR more Predictable than LVEF

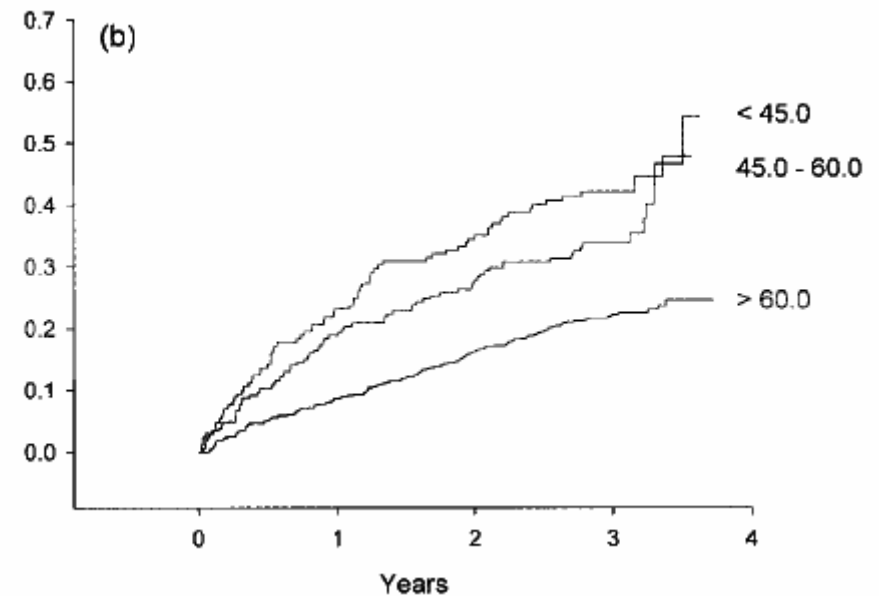
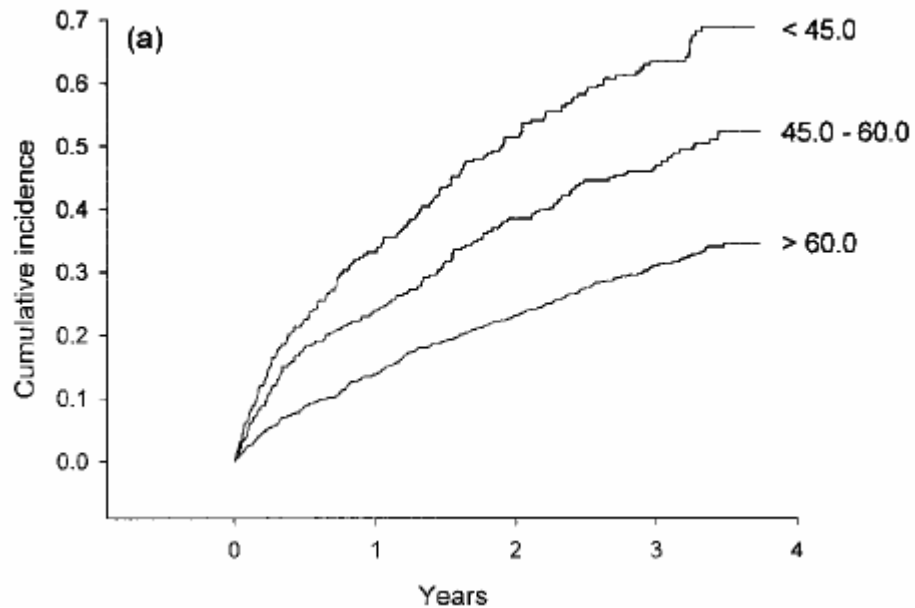




# Prognostic Factor even in Preserved LVEF CHARM subgroup analysis

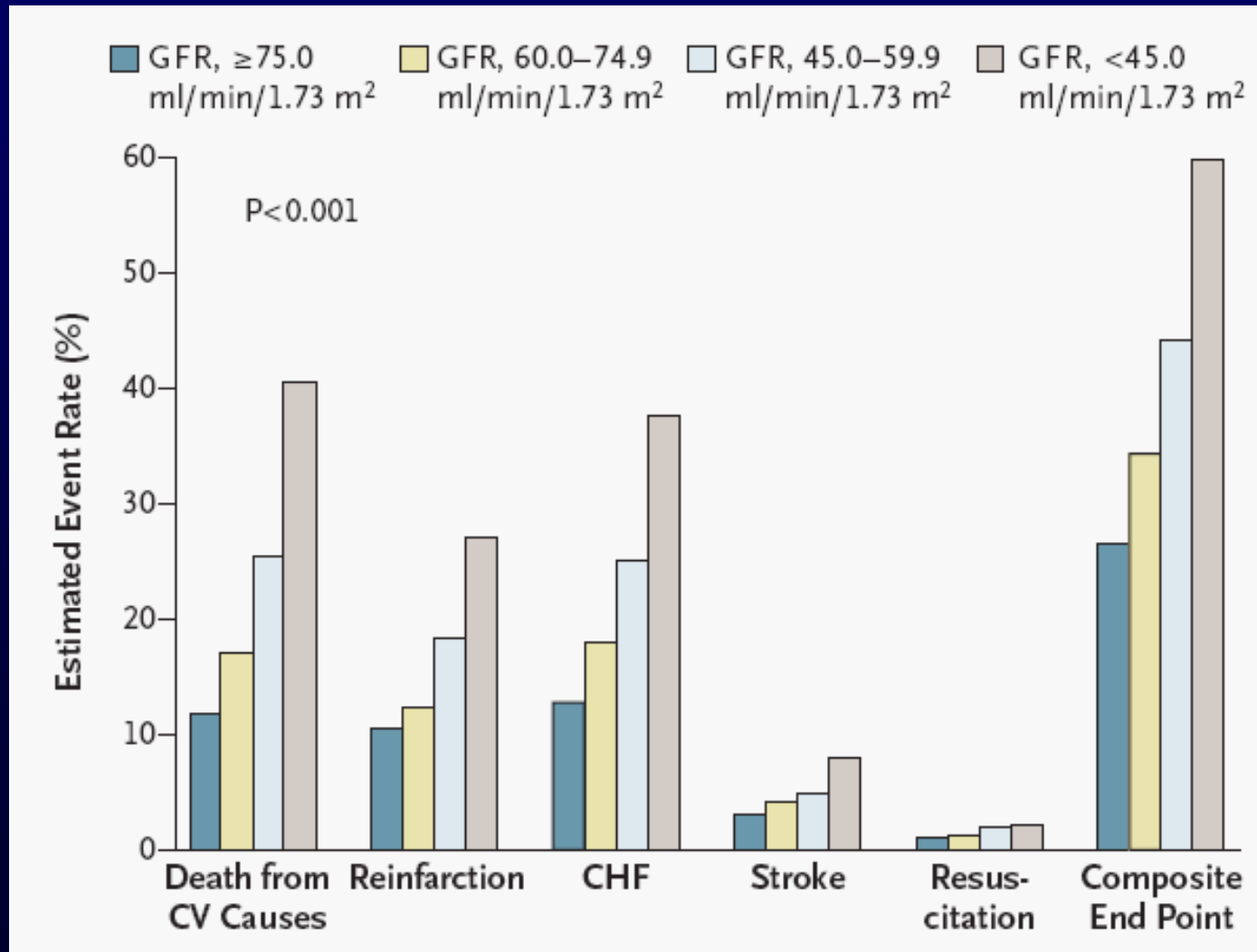
LVEF  $\leq$  40%

LVEF  $>$  40%



Hillege et al Circulation 2006

# Cardiovascular Outcome after MI with Renal Function (VALLIANT subgroup analysis, NEJM 2004)



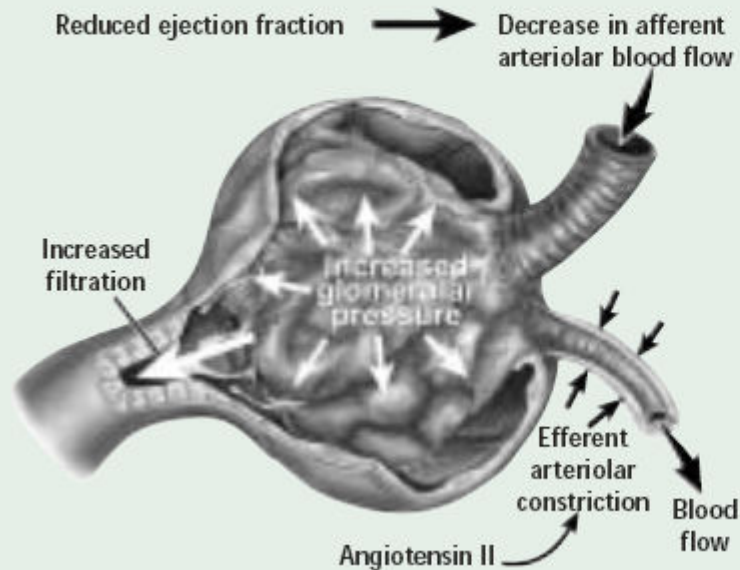
# Therapeutic Limitation

Excluded at major large RCT!  
Pathophysiologica Consideration

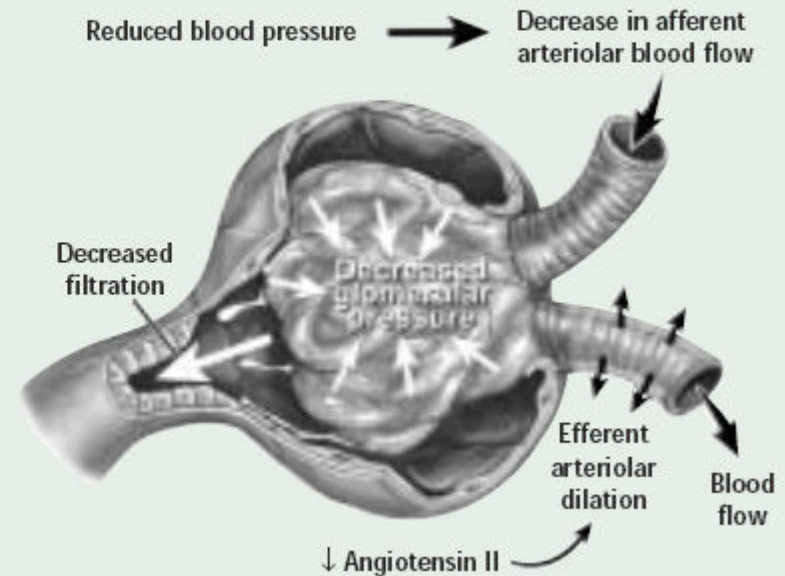
# Angiotensin II in Glomerulus

## Role of angiotensin II in glomerular function

### A Untreated heart failure



### B Treated heart failure



## Underrepresentation of Renal Disease in RCT of CV disease

Inclusion and exclusion of renal disease in CV disease trials

No of trials	153
<b>Trials excluding renal disease</b>	<b>86(56%)</b>
reported as excluded in original article	73(48%)
reported as excluded via personal communication	13(8%)
Threshold for exclusion	
serum Cr > 1.5-2.0mg/dL	19(12%)
serum Cr ≥ 2.0-2.9mg/dL	24(16%)
serum Cr ≥ 3.0mg/dL	16(10%)
eGFR ≤ 30mL/min/1.73m <sup>2</sup>	3(2%)

# Renal Dysfunction in Large RCT

Drug	Study (Reference)	Renal Function Exclusion Criteria: Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	Mean Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	All-Cause Mortality	Renal Insufficiency Subgroup Analysis?
ACE inhibitors					
Enalapril	CONSENSUS (11)	>300 (3.4)	124 (1.4) <sup>†</sup>	0.73	Yes
Enalapril	SOLVD Prevention (9)	>175 (2.0)	106 (1.2)	0.92 (0.79–1.08)	No
Enalapril	SOLVD Treatment (10)	>175 (2.0)	106 (1.2)	0.84 (0.74–0.95)	No
Captopril	SAVE (13)	>221 (2.5)	117 (1.3)	0.81 (0.68–0.97)	No
Trandolapril	TRACE (14)	>200 (2.3)	NA	0.78 (0.67–0.91)	No
Ramipril	AIRE (15)	NA	NA	0.73 (0.60–0.89)	No
Angiotensin-receptor blocker					
Valsartan	Val-HeFT (16)	NA	NA	1.02 (0.88–1.18)	No
$\beta$ -Blocker					
Metoprolol	MERIT-HF (17)	NA	NA	0.66 (0.53–0.81)	No
Bisoprolol	CIBIS-II (18)	>300 (3.4)	NA	0.66 (0.54–0.81)	No
Carvedilol	Australia/New Zealand Heart Failure Research Collaborative Group (19)	>250 (2.8)	NA	0.76 (0.42–1.36)	No
Carvedilol	U.S. Carvedilol Study Group (20)	Clinically important renal disease	NA	0.35 (0.20–0.61)	No
Carvedilol	COPERNICUS (21)	>250 (2.8)	133 (1.5) <sup>†</sup>	0.65 (0.52–0.81)	No
Spironolactone	RALES (22)	>221 (2.5)	106 (1.2) <sup>†</sup>	0.70 (0.60–0.82)	Yes
Hydralazine–Nitrates	V-HeFT (23)	NA	NA	0.66 (0.46–0.96)	No
Digoxin	DIG (24)	>265 (3.0)	110 (1.3)	0.99 (0.91–1.07)	No

# Incidence of Worsened Renal Function with ACE inhibitor

Study (Reference)	Drug	Patients <i>n</i>	New York Heart Association Class	Definition of Worsened Renal Function	Time to Follow-up	Incidence of Worsened Renal Function %	Discontinuation Rate for Worsened Renal Function
Packer et al. (34)	Captopril or enalapril	104	IV	Increase in BUN >7.14 $\mu\text{mol/L}$ (20 mg/dL) or increase in serum creatinine level, 35 $\mu\text{mol/L}$ (0.4 mg/dL)	1–3 mo	33	11.5
Gottlieb et al. (35)	Quinapril, 10 mg	20	III, IV	Any decrease in GFR	7 wk	25	0
CONSENSUS (11)	Enalapril, 40 mg	127	IV	Increase in serum creatinine level, 30%	6 mo	35	4.7
SOLVD (Treatment and Prevention Trials) (9, 10)	Placebo	126	I, II, III	Increase in creatinine level, 44 $\mu\text{mol/L}$ (0.5 mg/dL)	2.6 y	18	3.2
	Enalapril	3379				16	NA
TRACE (14)	Placebo	3379	Any	Renal dysfunction	2–4 y	12	3
	Trandolapril, 4 mg	876				14	
AIRE (15)	Placebo	873	I, II, III	NA	15 mo	11	1
	Ramipril, 10 mg	1004				NA	1.5
ATLAS (29)	Placebo	982	II, III, IV	Renal dysfunction/hyperkalemia†	54 mo	NA	1.2
	Creatinine level <133 $\mu\text{mol/L}$ (1.5 mg/dL)	2176				5.4	0.8
	Lisinopril 35 mg					4.1	1.6
	Lisinopril 5 mg	998				15.6	6.0
Creatinine level $\geq$ 133 $\mu\text{mol/L}$ (1.5 mg/dL)	Lisinopril 35 mg	998	15.6	3.8			
Lisinopril 5 mg							

# Incidence of Worsened Renal Function with Angiotensin type I Receptor Blocker(ARB)

Trial	Drugs	Number	Definition of renal impairment	Incidence of renal impairment	Withdrawal
ELITE	Captopril 150mg	370	Increased sCr 0.3mg/dL	10.5	0.8
	Losartan 50mg	352		10.5	1.4
Val-HeFT	Valsartan 160mg	2511	Renal impairment	NA	1.1
	Placebo	2499		NA	0.2

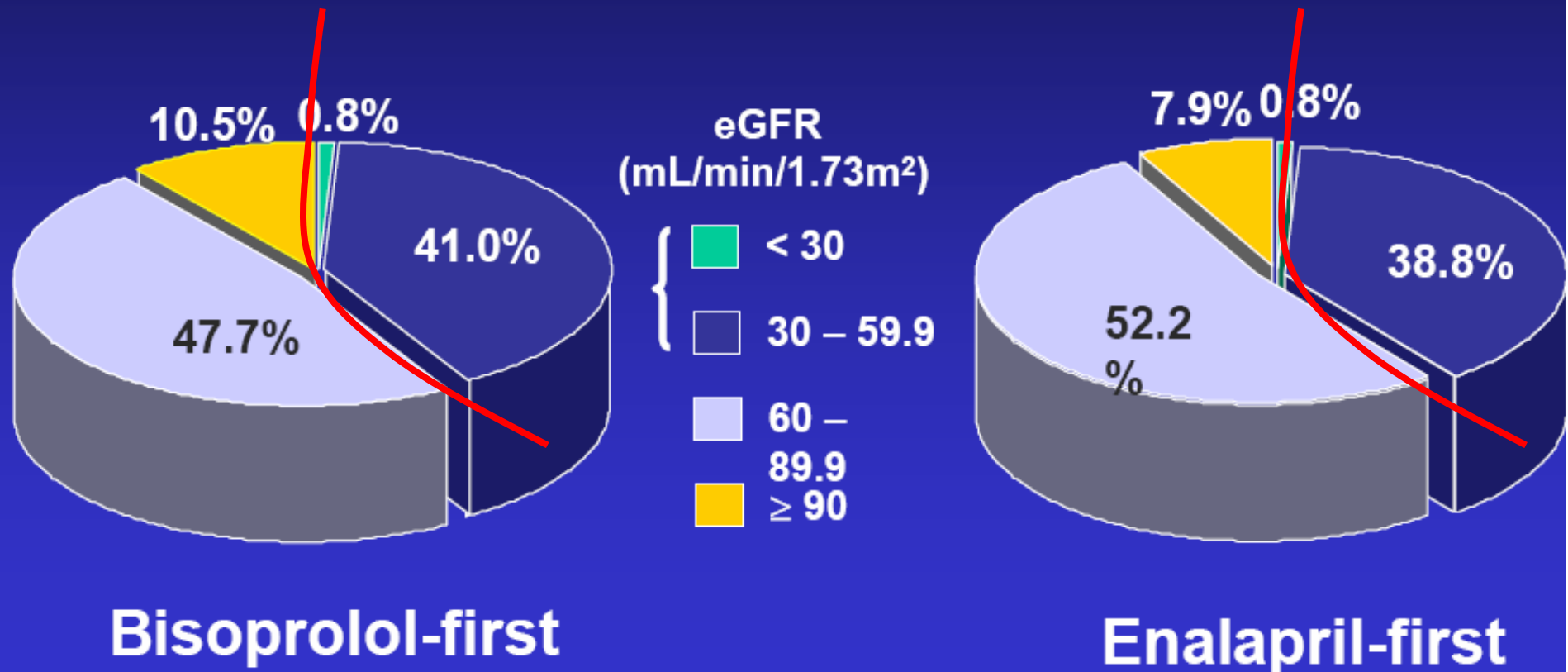


# CIBIS III population:

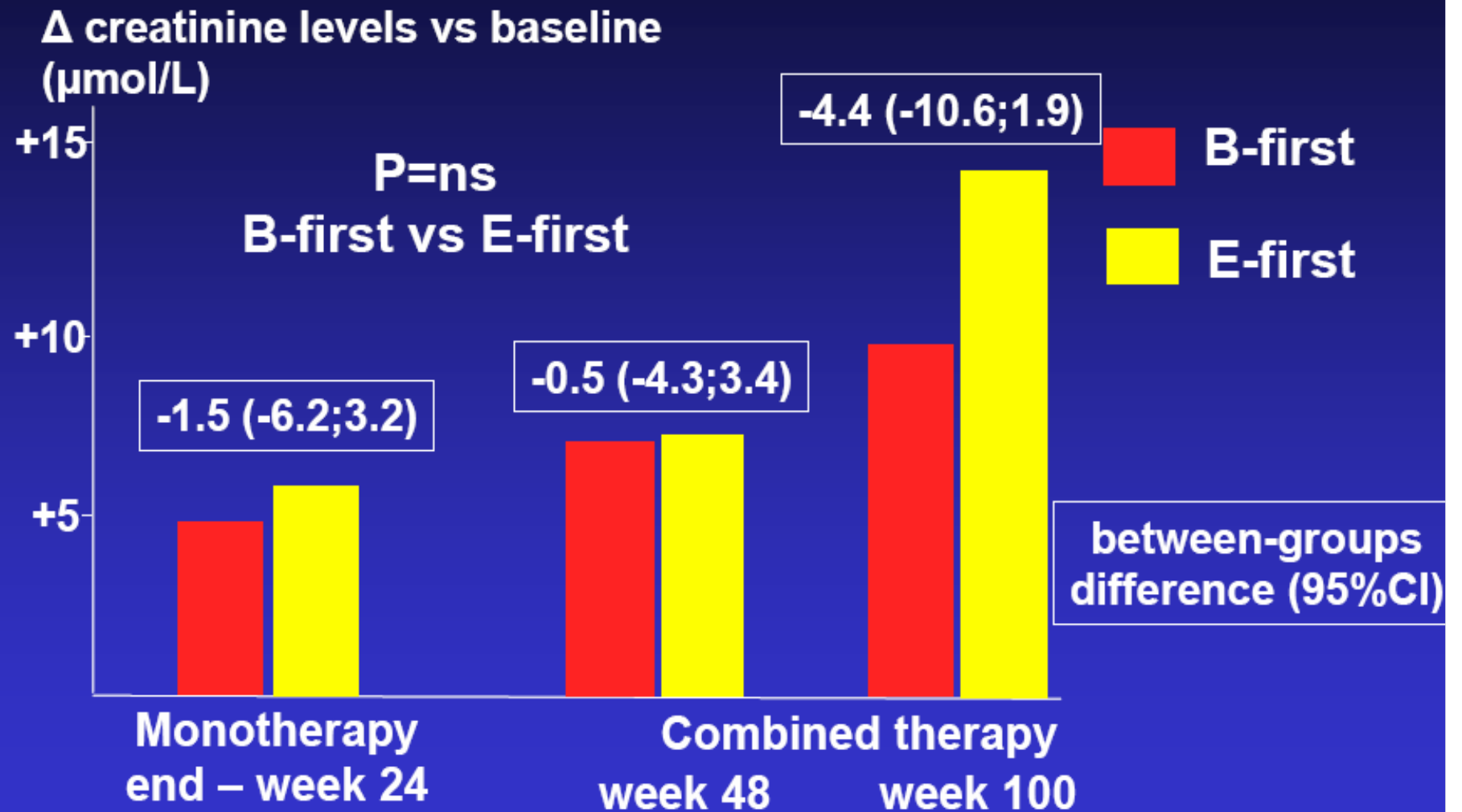
**411 (40.7%) pts with moderate-severe ↓ eGFR (< 60 ml/min/1.73m<sup>2</sup>)**

506 (50.1%) pts with mild ↓ eGFR (60 – 89.9 ml/min/1.73m<sup>2</sup>)

93 (9.2%) pts with normal eGFR (≥ 90 ml/min/1.73m<sup>2</sup>)



# CIBIS III: changes in creatinine levels during study



# Risk-therapy mismatch

## ACE inhibitor use according to comorbidity

Euro Heart Survey, Eur Heart J 2003;24:464

	%	P value
Age > 70	67.7	<0.0001
Age ≤ 70	57.9	
Diabetes		
yes	67.7	<0.0001
no	59.7	
<b>Renal dysfunction</b>		
yes	57	<0.0001
no	66.3	

# Risk Management Mismatch

	No. (%) of Patients					
	At Hospital Discharge (All Patients ≤79 y)			90 Days Postdischarge (Patients Aged 65-79 y)		
	Low Risk	Average Risk	High Risk	Low Risk	Average Risk	High Risk
Drug prescription						
No. of patients	784	473	161	436	428	156
ACE inhibitor	635 (81)	346 (73)	96 (60)	363 (83)	326 (76)	95 (61)
ACE inhibitor or ARB	677 (86)	380 (80)	105 (65)	389 (89)	354 (83)	104 (67)
β-Blocker	314 (40)	154 (33)	38 (24)	187 (43)	155 (36)	44 (28)
No ACE inhibitor, ARB, or β-blocker	76 (10)	73 (15)	43 (27)	33 (8)	60 (14)	41 (26)
Observed 1-y mortality rate, %	13.9	26.4	47.2	13.8	25.9	50.6

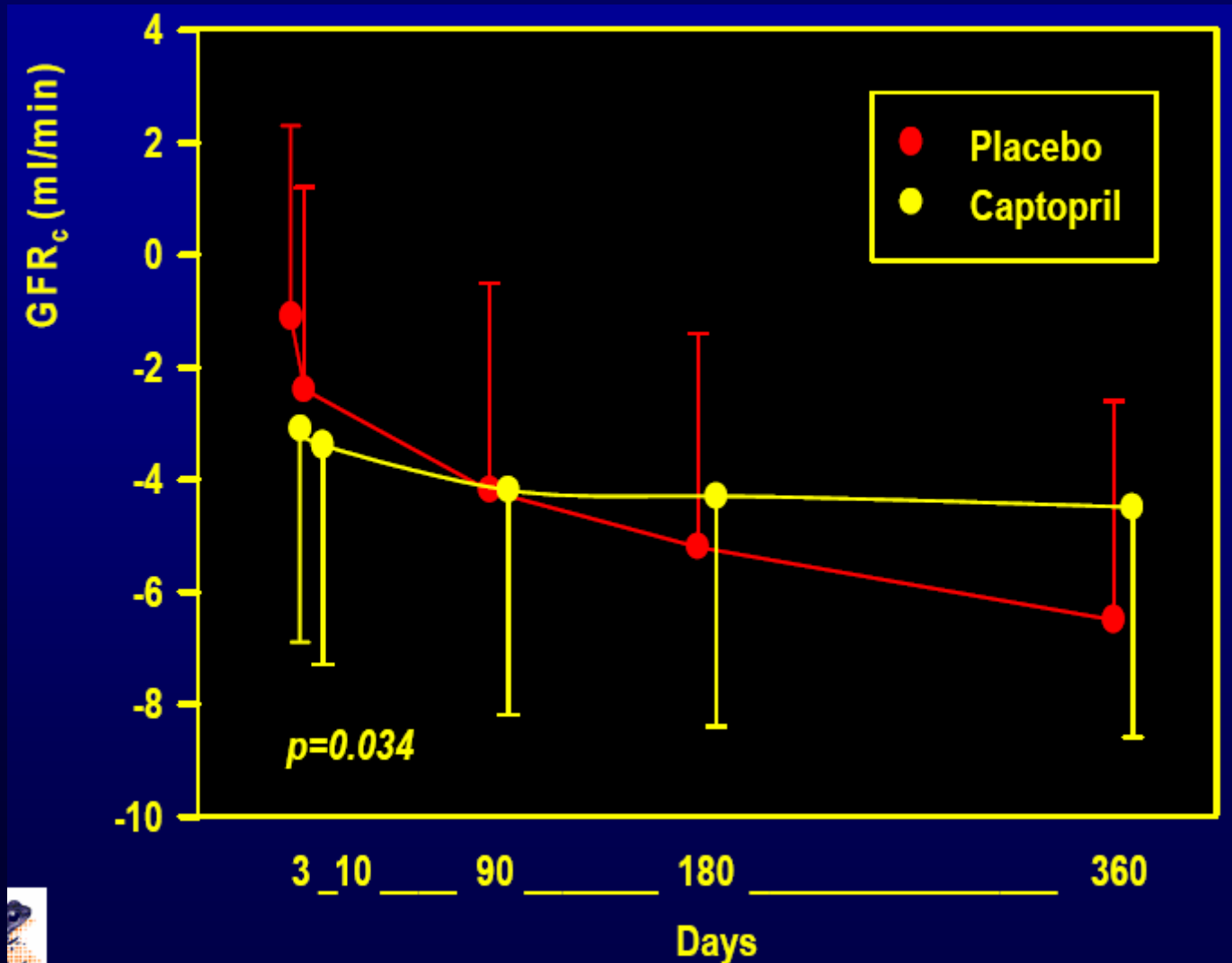
Lee DS et al. JAMA 2005;294:1240

# Efficacy of Therapy

# Preserved Renal function after Initial Loss with ACE i

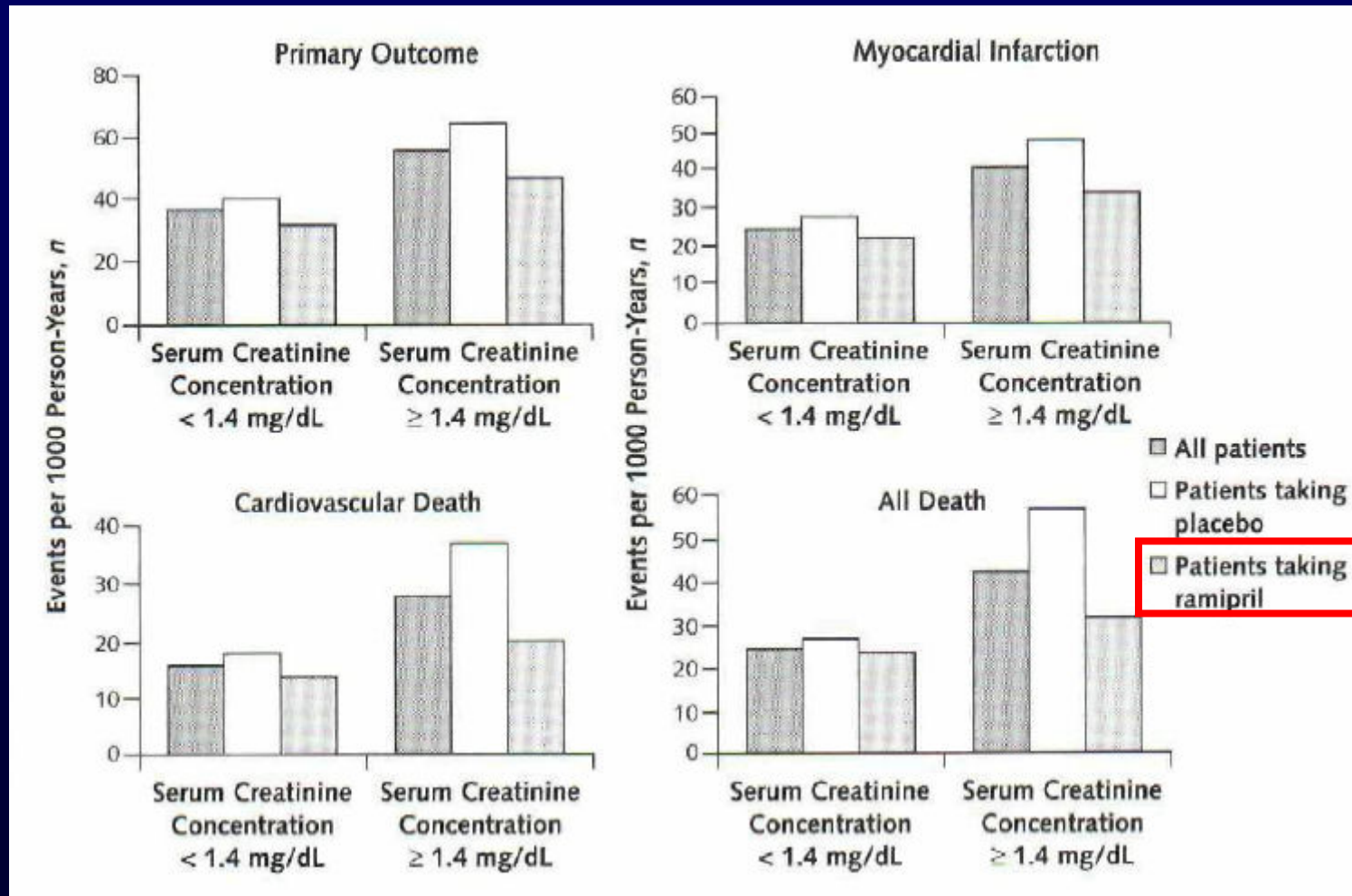
LV dysfunction after MI, CATS trial

Hillege et al Eur Heart J 2003



# HOPE Renal Insufficiency Subgroup Analysis

Mann JFE et al. Ann Intern Med 2001

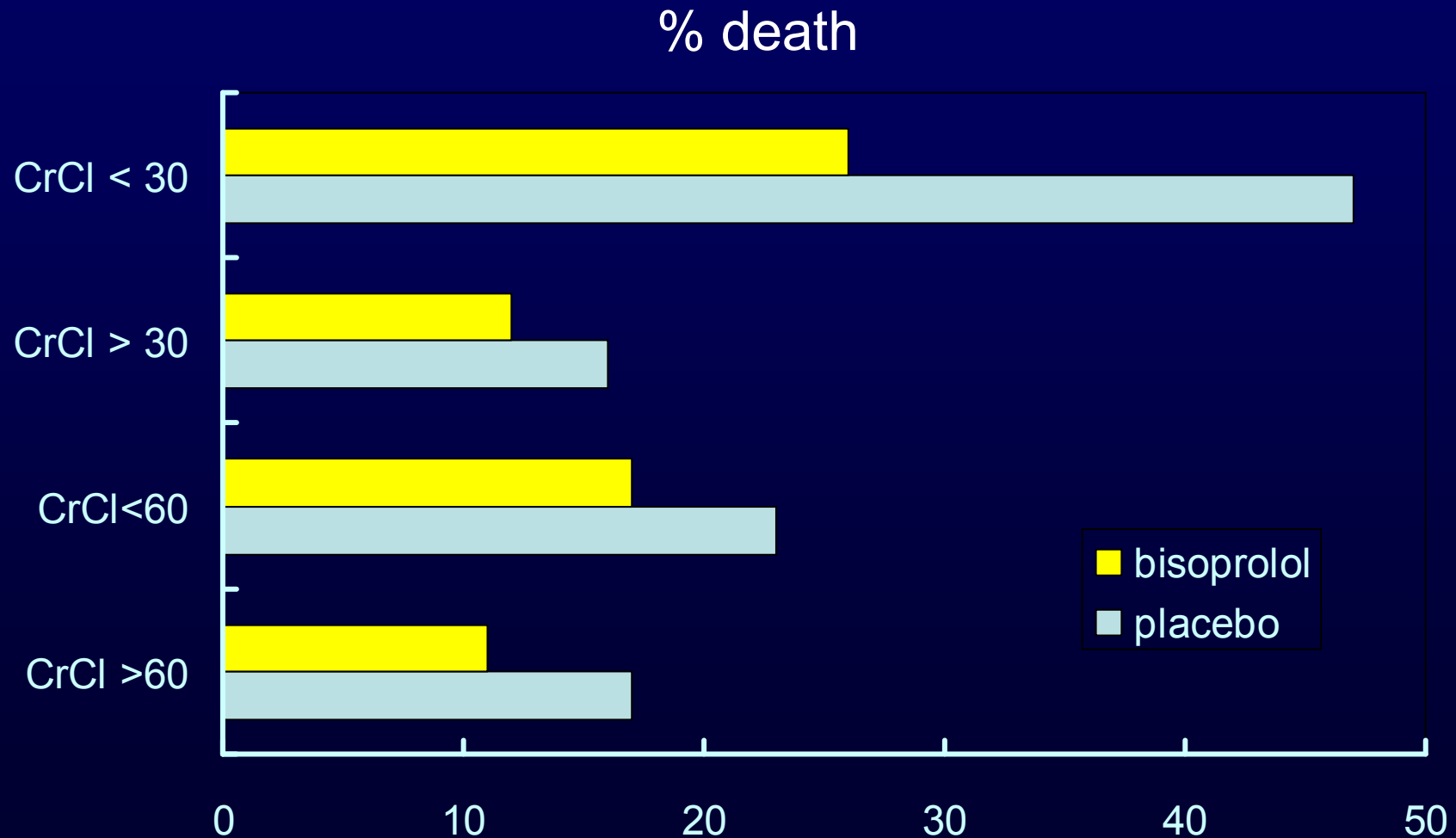




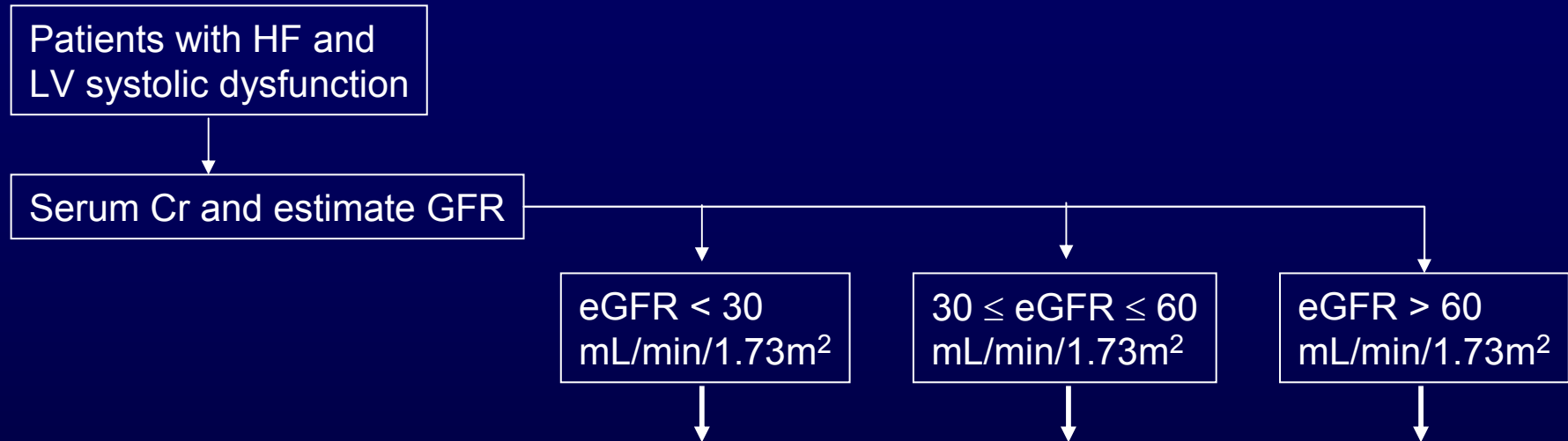
# CONSENSUS trial

- sCr exclusion criteria  $> 3.4\text{mg/dL}$
- Mean eGFR  $45\text{mL/min/1.73m}^2$   
-> moderate renal insufficiency group
- 31% reduction of mortality

# CIBIS II Subgroup Analysis



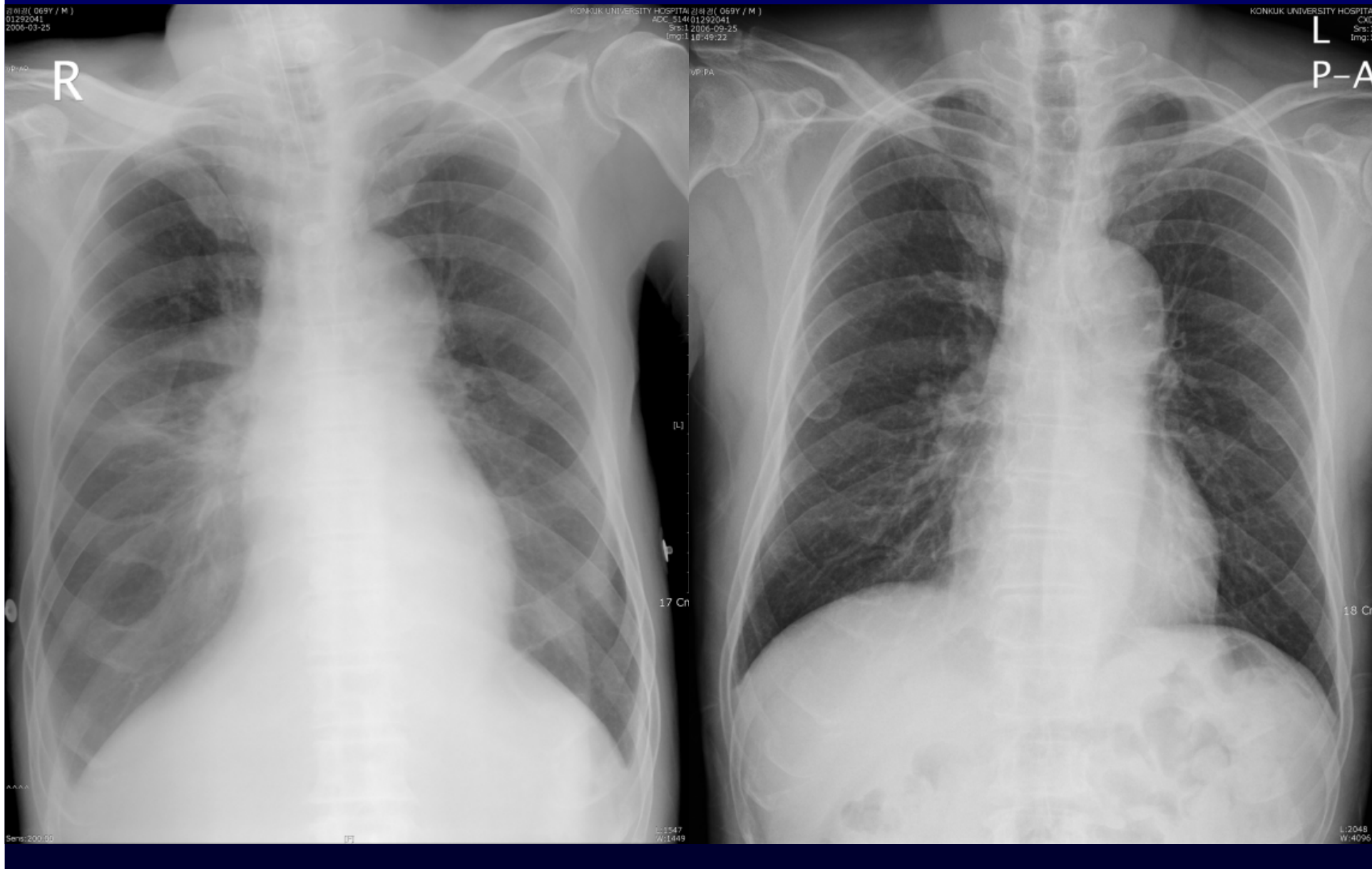
# Evidence of Treatment Based on Renal Function



Evidence for improving clinical outcomes			
ACEi (ARB for ACEi intolerance)	Possible	Definite	Definite
Beta blocker	Unknown	Definite	Definite
Spironolactone	Unknown	Possible	Definite
Digoxin	Unknown	Possible	Definite
Hydralazine-nitrate	Unknown	Possible	Definite

HF & renal insufficiency

# Hospital course



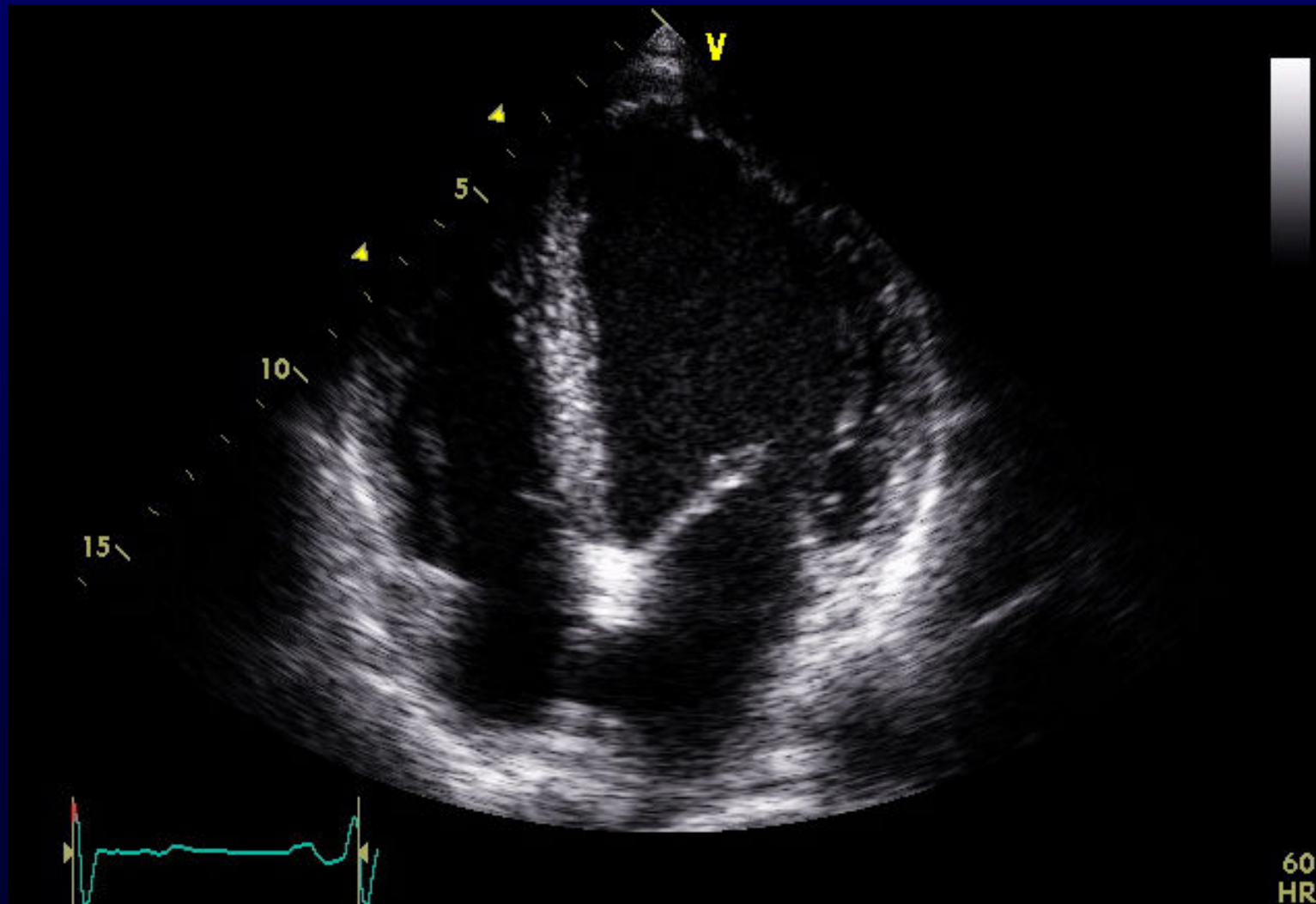
# Discharge medication

- Captopril 50mg bid
- Furosemide 40mg qd
- Carvedilol 6.25mg bid
- Warfarin 2mg

*HF & renal insufficiency*

**6 months later**

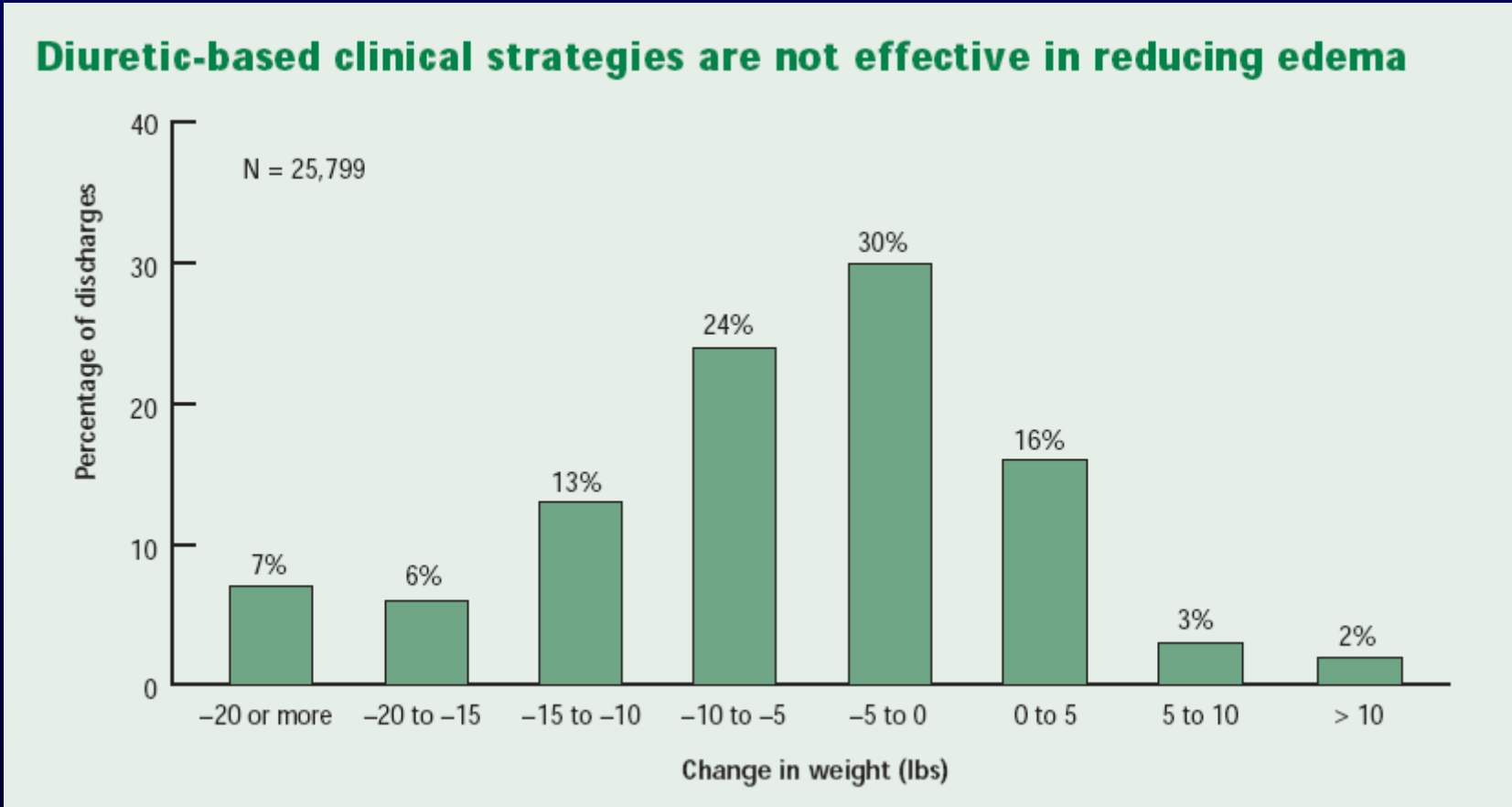
sCr 1.8mg/dL, K 4.7mEq/L



# Cardio-Renal Syndrome

## Limitation of Diuretics-Based Strategy

Data from ADHERE registry



# New Approaches to detect and manage edema & renal insufficiency

## Early detection of decompensation

Hemodynamic monitoring guided therapy

Intracardiac filling pressure(implantable)

Impedance cardiography

Biomarkers

BNP

Troponin T

Cystatin C



# New Approaches to detect and manage edema & renal insufficiency

## Strategy limiting Cardiorenal Syndrome

Diuretic sparing strategy

New drug classes

- Adenosine type 1 receptor antagonists

- Vasopressin receptor antagonists

New devices and non-drug interventions

- Early ultrafiltration

- Continuous aortic flow augmentation

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