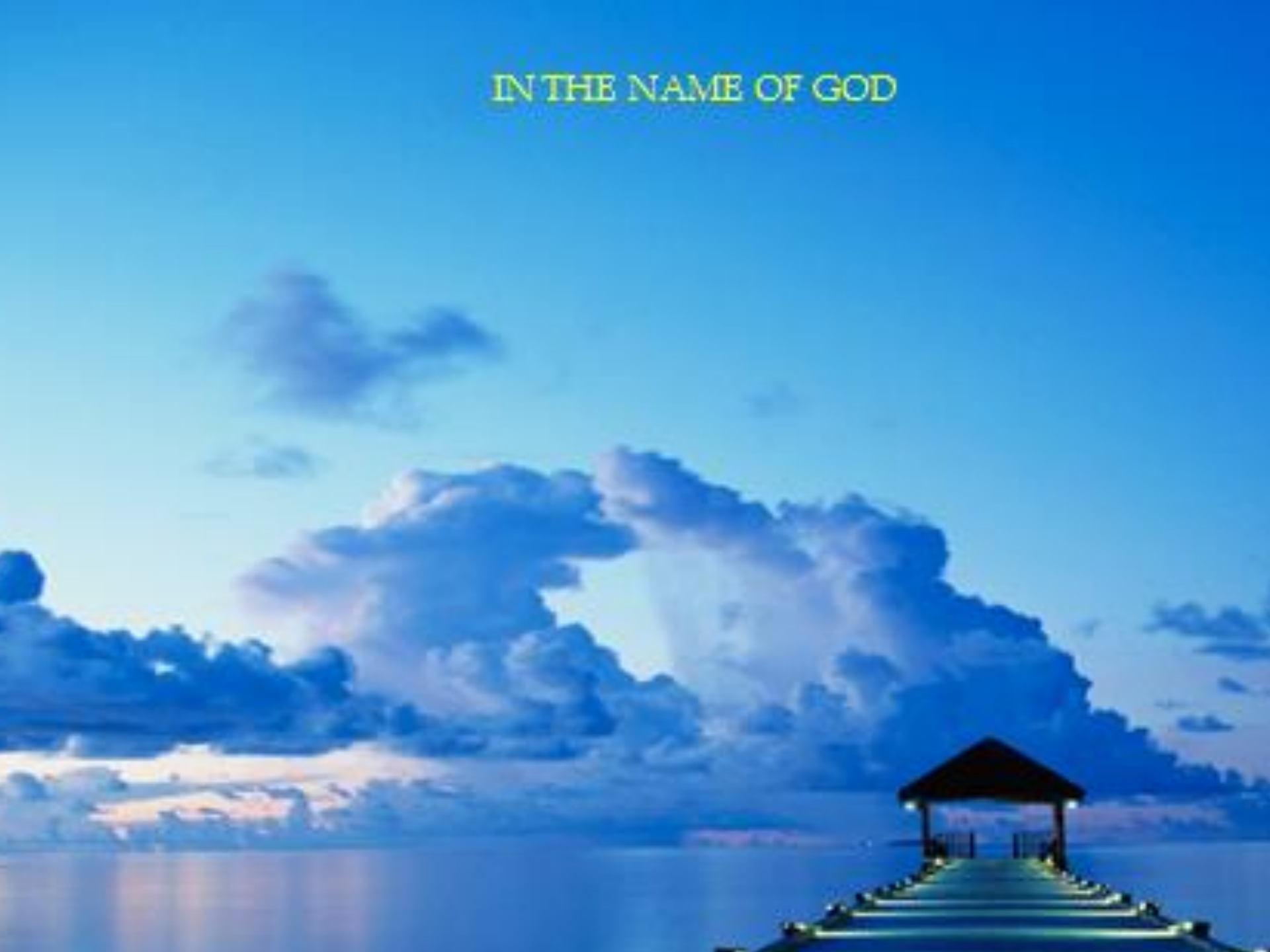
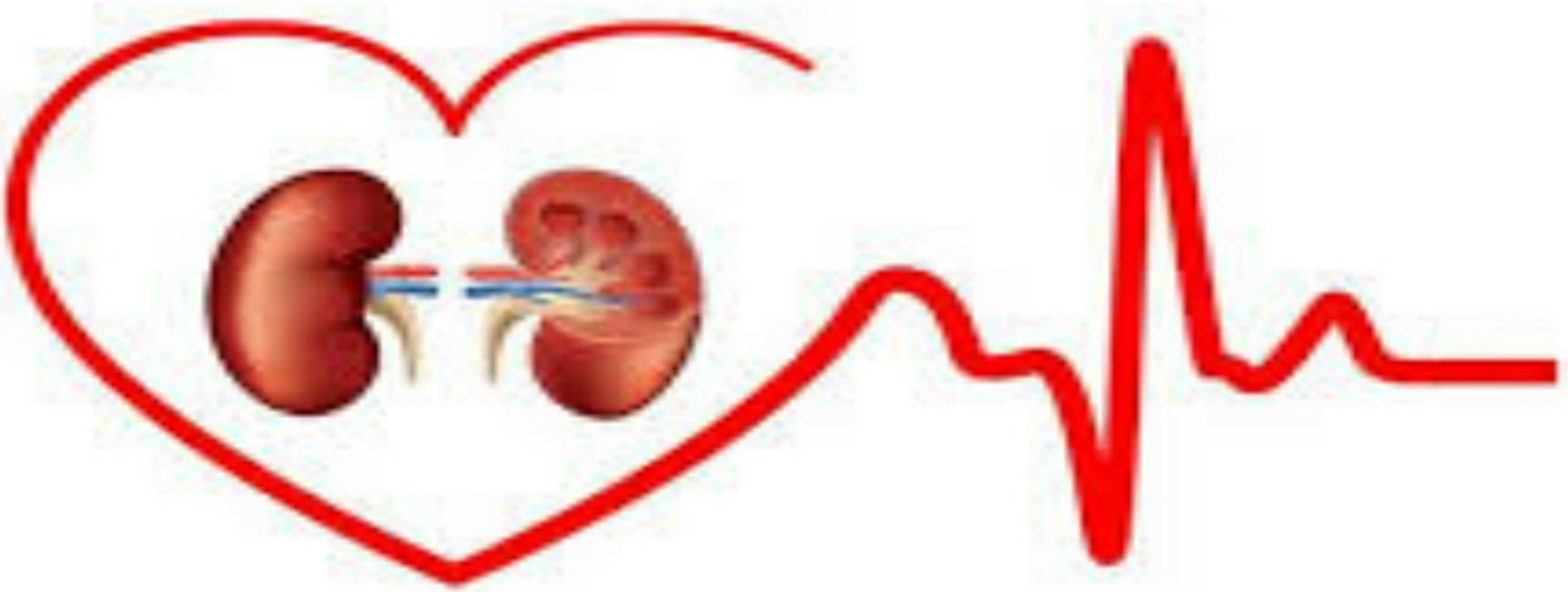
IN THE NAME OF GOD



Heart failure and Kidney disease



- **Dr.F.Haghverdi MD**

CASE:

- A 65-year- old man with history of HTN and systolic heart failure (EF=45%) presented with Acute MI and dyspnea (class 4) and admitted in CCU. Also he was known case of CKD (Cr= 2 mg/dl six month ago).
- 2 days after admission in CCU, his cardiologist noticed oliguria and creatinin rising.(Cr on admission day was 2 and now is 3).
- Cardiologist requested nephrology consult for AKI on CKD and Emergent coronary angiography.

CASE:

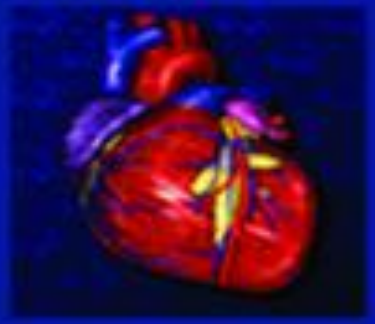
- **Drugs**: ASA 80/d, Losartan 50 mg Bd, Amp lasix 5 mg/h , sprinolacton 25 mg/d, TNG 5 mic g/ min,plavix75/d, atorvastatin 40mg/d , Heparin 1000 u/ h.

CASE:

- **Ph Exam:** BP=100/60 ,RR=30/min ,T=37 , PR=100/min , O2 sat=90% (3lit O2nasal), W=70 kg
- fine Rales in 1/3 of both lungs
- S3 sound, 2+ edema on legs, JVP=9 cm H2O
- **Lab: BUN=100 mg/dl, Cr=3 mg/dl**
- Hb= 8 g/dl, Na =125 meq/l, K= 4.9 meq/l
- FBS=100 mg/dl, Uric acid= 12 mg/dl
- ABG: PH =7.32 , PCO2 =25 , HCO3 =15
- Urine analysis :+ protein , Urine output= 350 cc / day
- SONO : RK=95 , LK =87 mm, EF= 25 %

- **As a Consultant nephrologist , What is your diagnosis and treatment plan?**

The Cardiorenal Syndrome of Heart Failure



Decreased Cardiac Output

Neurohormonal Activation

Diminished Blood Flow

Decreased Renal Perfusion

Impaired Renal Function

Increased Water & Na^+ Retention

Decreased Cardiac Performance

NEW YORK HEART ASSOCIATION CLASSES OF CARDIAC FAILURE: ASSOCIATED HEMODYNAMIC AND HORMONAL CHANGES

	CLASS II	CLASS III	CLASS IV
Cardiac Index	↓ or Normal	↓↓	↓↓↓
Plasma Hormones (AVP, Renin, Aldosterone, NE)	Normal	↑	↑↑
Plasma Volume	↑	↑↑	↑↑↑

Cardiorenal syndrome classification

Type	Definition
CRS type 1 (acute cardiorenal syndrome)	Abrupt worsening of cardiac function (e.g. acute cardiogenic shock, acute decompensation of chronic heart failure or acute coronary syndrome) leading to acute kidney injury.
CRS type II (chronic cardiorenal syndrome)	Chronic abnormalities in cardiac function (e.g. chronic heart failure) causing progressive chronic kidney disease.
CRS type III (acute renocardiac syndrome)	Abrupt worsening of renal function (e.g. acute kidney failure due to volume depletion or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, pulmonary edema).
CRS type IV (chronic renocardiac syndrome)	Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and / or increased risk of adverse cardiovascular events.
CRS type V (secondary cardiorenal syndrome)	Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

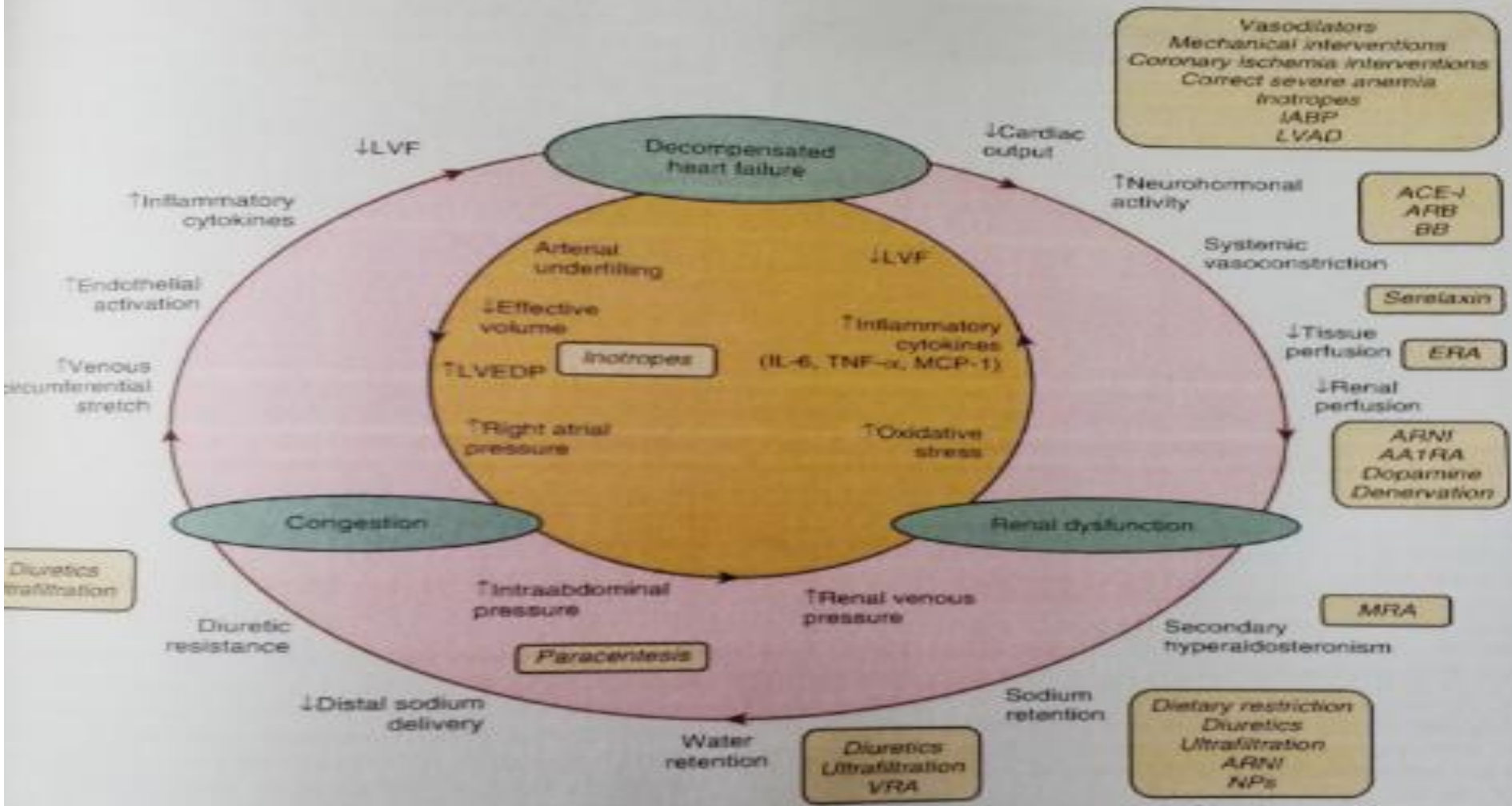


Fig. 72.1 Reciprocal pathophysiologic pathways linking heart failure, renal dysfunction, and congestion in cardiorenal syndrome. Decompensation of heart failure can lead to deterioration in renal function via exacerbated neurohormonal activity (i.e., low forward flow) or through fluid overload and renal venous congestion (i.e., high backward pressure). The impact of various pharmacologic and nonpharmacologic therapeutic options on the underlying pathophysiologic mechanisms is illustrated. *AA1RA*, Adenosine A1 receptor antagonist; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor neprilysin inhibitor; *BB*, β-blocker; *ERA*, endothelin receptor antagonist; *IABP*, intraaortic balloon pump; *IL-6*, interleukin-6; *LVAD*, left ventricular assist device; *LVEDP*, left ventricular end-diastolic pressure; *LVF*, left ventricular function; *MCP-1*, monocyte chemoattractant protein-1; *MRA*, mineralocorticoid receptor antagonist; *NPs*, natriuretic peptides; *TNF-α*, tumor necrosis factor-α; *VRA*, vasopressin receptor

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- 3-Hyponatremia management (Vaptan)?
- 4-Hyperurecemia management (Allopurinol)?
- 5- Anemia Management (CRAIDS and EPO)?
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?
- 8- New drugs?

Case problems:

- **1 -Volume overload (Diuretic therapy vs UF)?**
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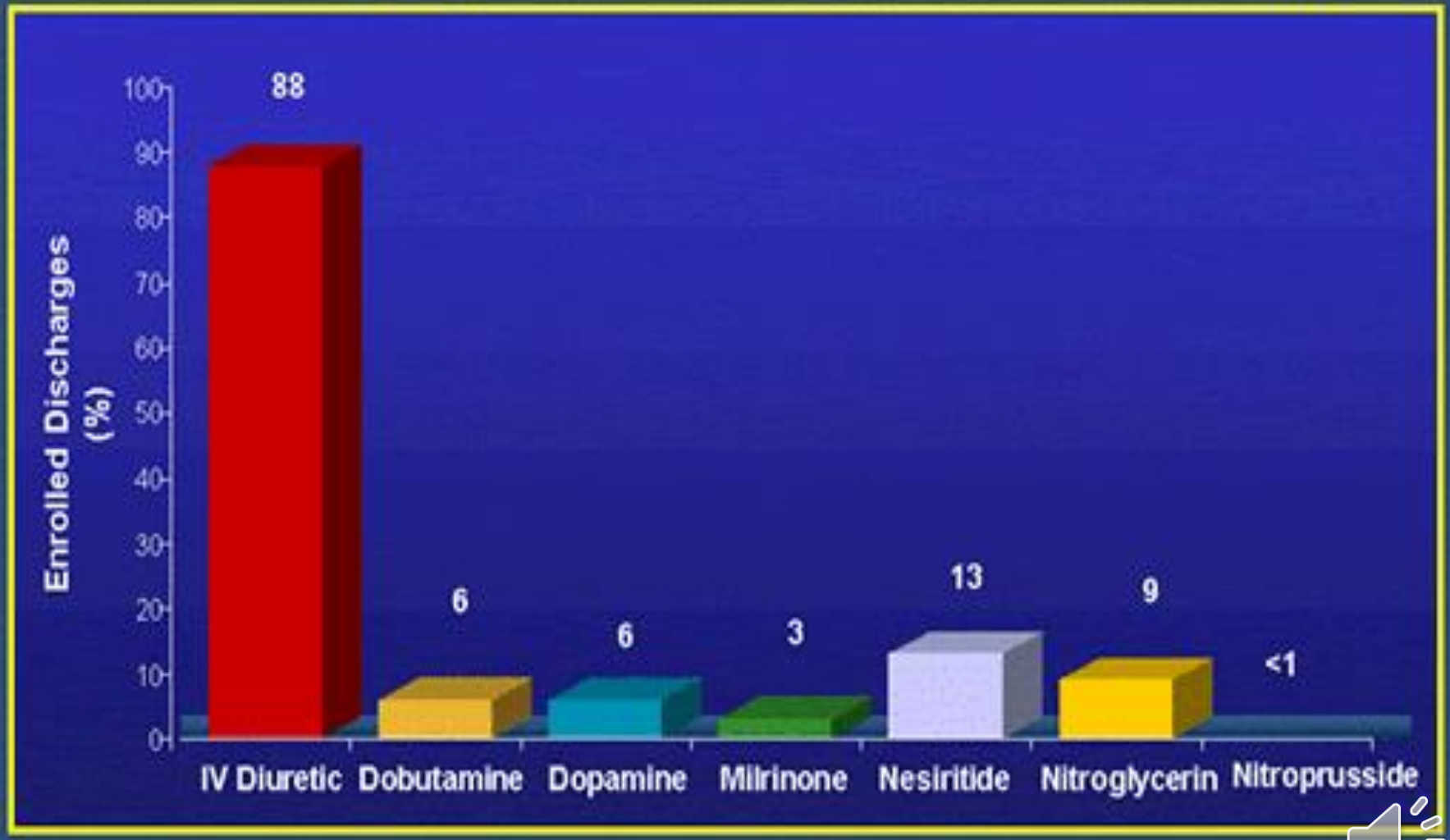
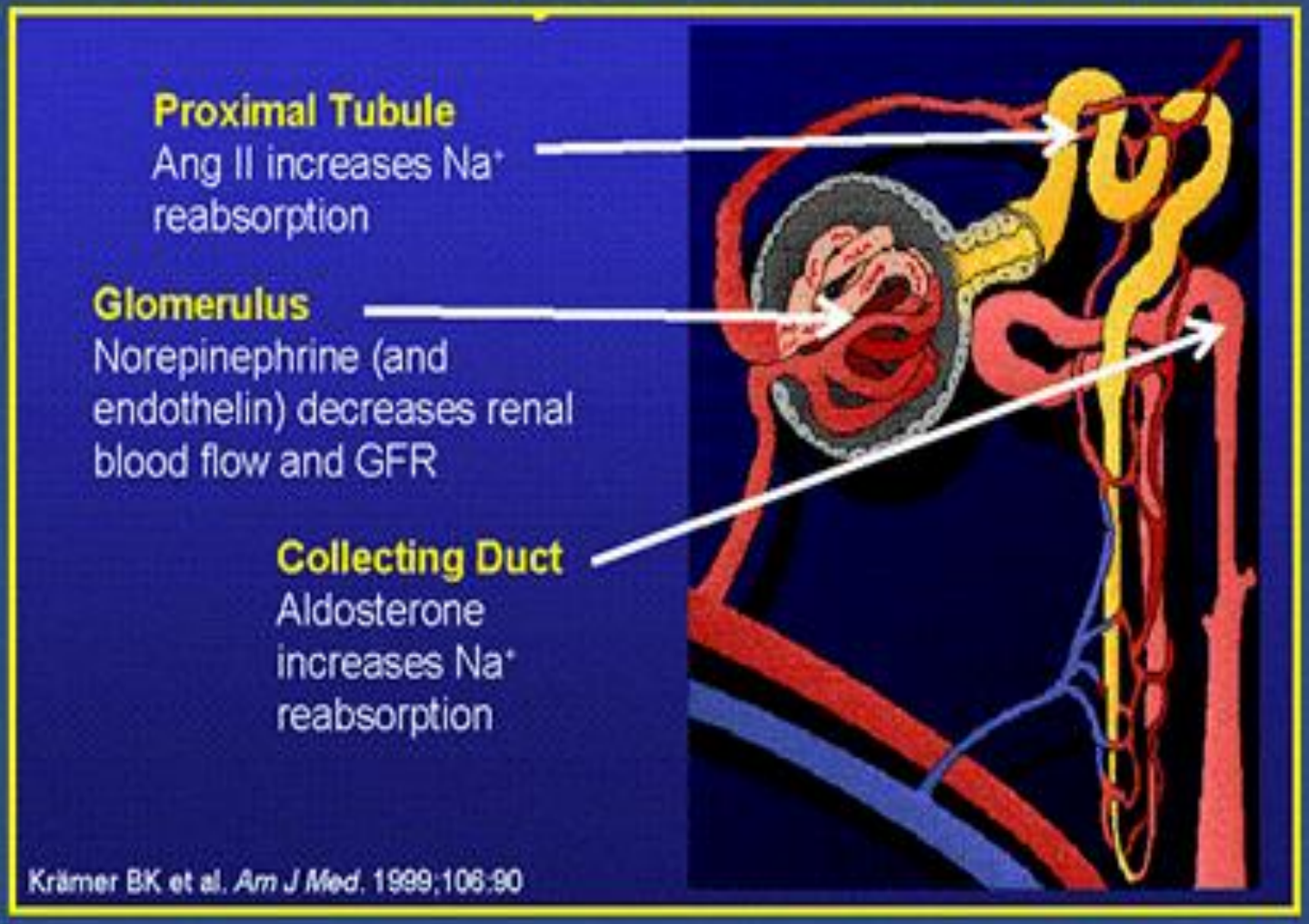
- **3-Hyponatremia management (Vaptan)?**
- **4-Hyperurecemia management (Allopurinol)?**
- **5- Anemia Management (CRAIDS , EPO)?**
- **6-Mineral receptor antagonist?**
- **7-Contrast nephropathy risk and prophylaxy?**
- **8-New drugs?**

ADHERE: Loop Diuretics Most Common IV Therapy, Often Used as Monotherapy



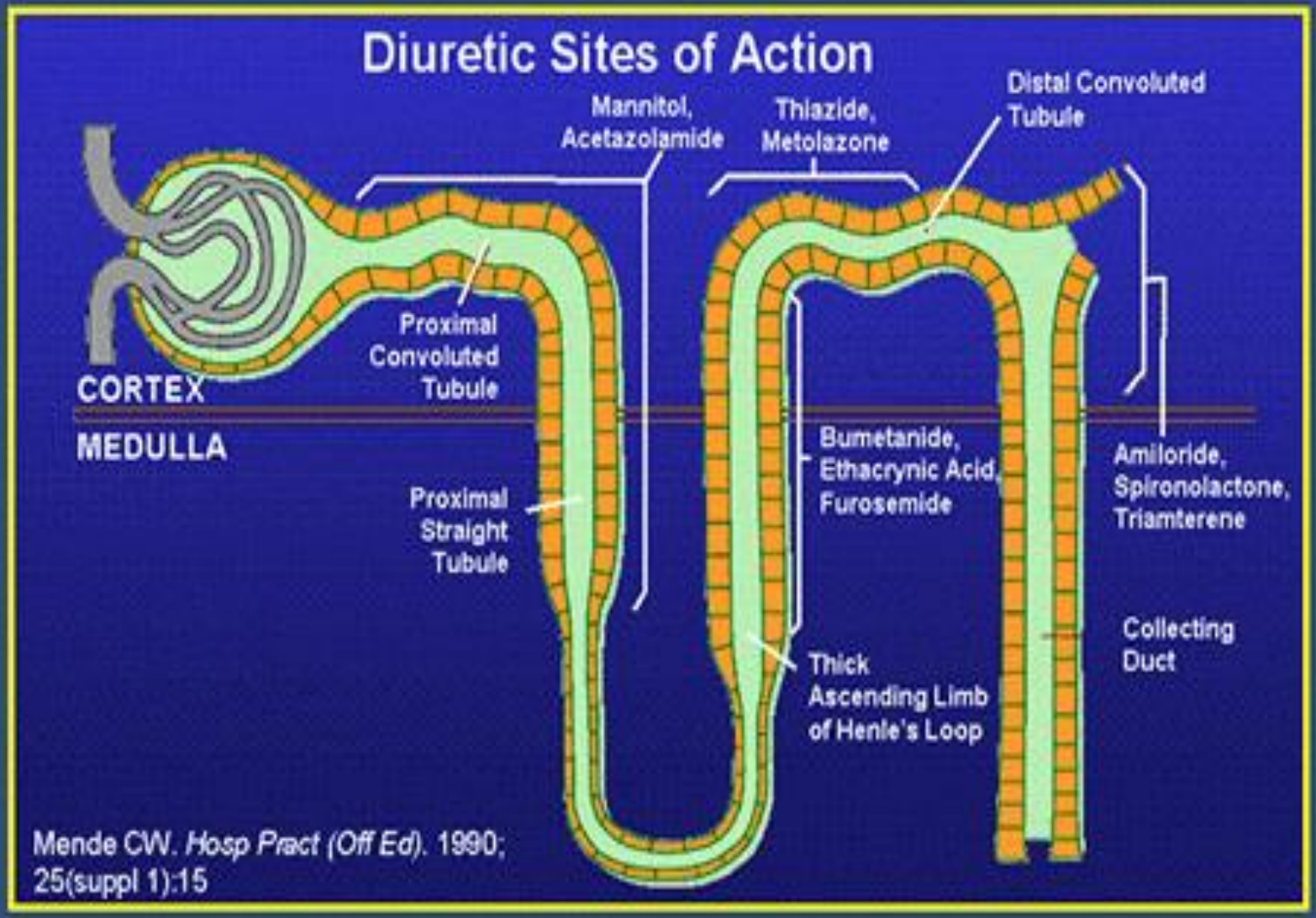
ADHERETM Registry Data. All Enrolled Discharges (n =150,745); October 2001 to December 2004

Neurohormonal Actions Leading to "Diurectic Refractoriness" and Renal Dufunction in HF



Kramer BK et al. Am J Med. 1999; 106:90

Diuretics: Comparison of Site of Action



Mende CW. Hosp Pract (Off Ed). 1990; 25 suppl. 1:15

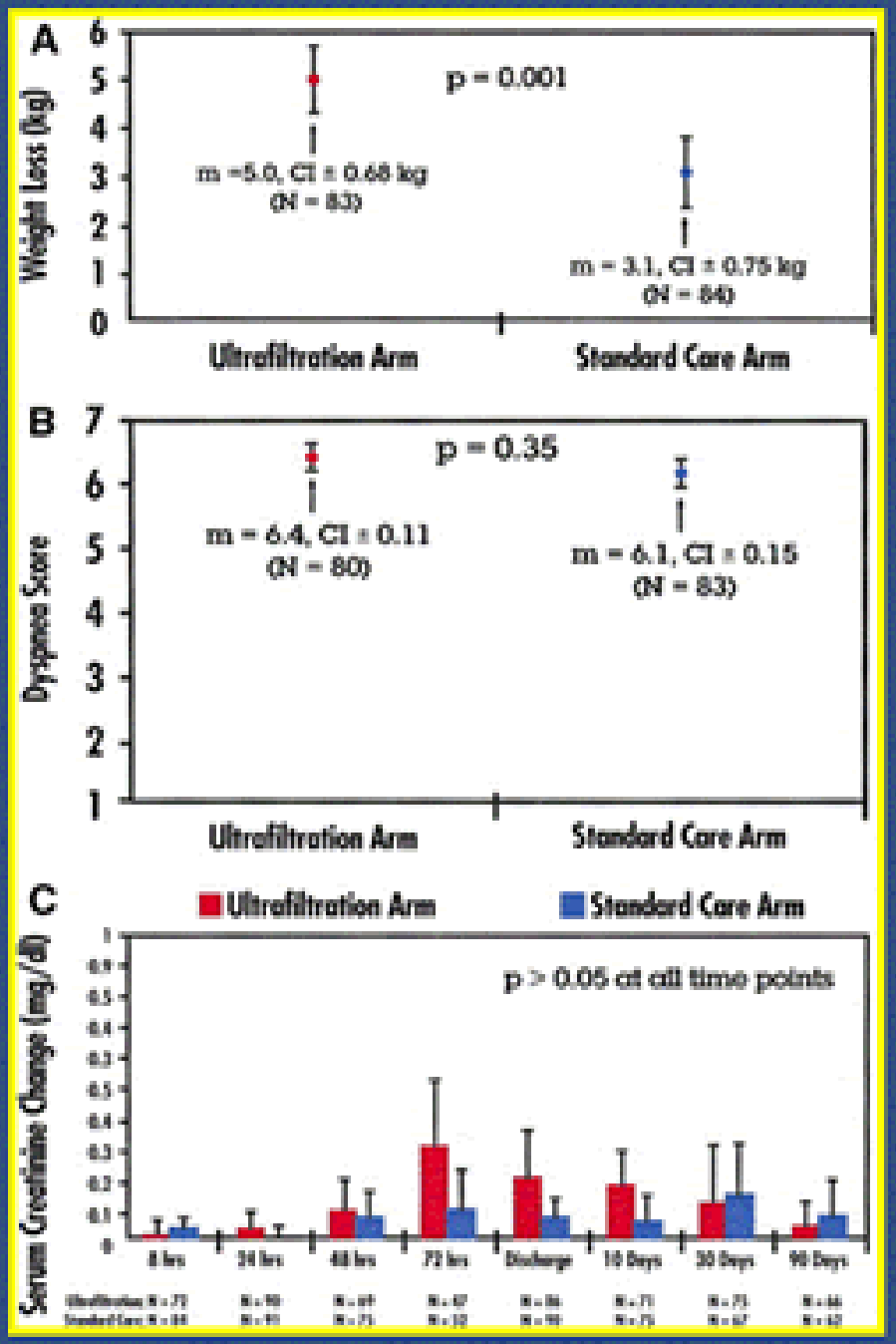
UF vs Diuretics for CHF: Theoretical Advantages

- More rapid and predictable fluid removal and negative fluid balance
- Greater loss of sodium and ECF per ml of ultrafiltrate
- Less potassium, magnesium loss per ml of ultrafiltrate
- Less activation of TG feedback, possibly better preservation of residual RBF and GFR
- Possible acute improvement in cardiac function by unloading LV/RV and moving on Starling curve
  - Secondary improvement in response to vasoactive drugs and diuretics
- Possible acute improvement in GFR by relieving elevated CVP, renal venous hypertension
  - Secondary improvement in response to diuretics

UNLOAD Trial

- 200 patient RCT: UF vs. Diuretic Rx for ADHF
- Mean serum creatinine in both groups was 1.5±0.5mg/dl (exclusion > 3mg/dl)
- ULTRAFILTRATION:
- Rx: UF with BFR 10-40ml/min, heparinization, UF ≤500ml/hour
- → Fluid removal rate averaged 241ml/hr for 12.3±12 hours
- DIURETICS:
- Rx: Intravenous route, minimum dosing of ≥ 2 double the prehospitalization oral diuretic dose for at least 48 hrs post-randomization
- → Received 181±121mg of furosemide (or equivalent bumetanide or torsemide doses), the majority by intermittent boluses

UNLOAD Trial: Efficacy



Primary Endpoint:

(A) Weight Loss

&

(B) Dyspnea Scores at 48 hours

Safety: no difference in AKI rates

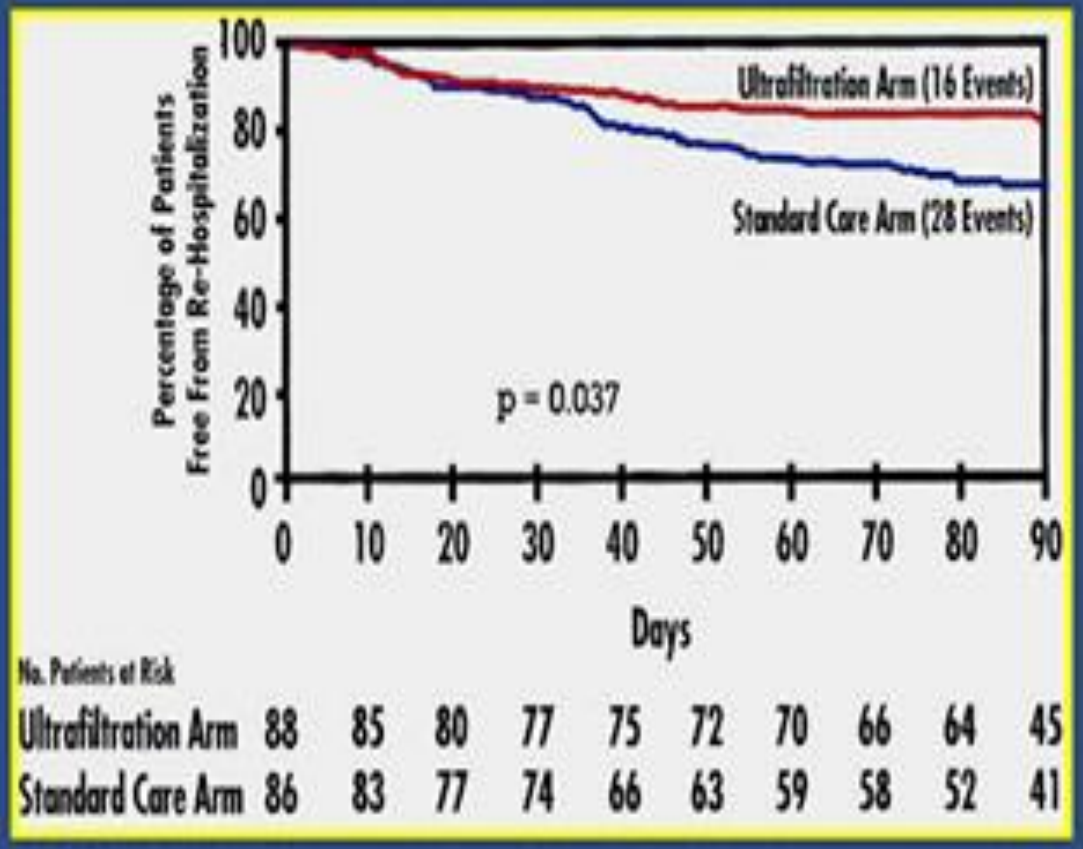
<or>

Hypotension rates

More hypokalemia in diuretic group

Constanzo MR, et al: JACC 2007;49:675-83

UNLOAD Trial: Outcomes



Lengths of index hospitalization did not differ between the ultrafiltration group (6.3±4.9 days) vs. diuretic group (5.8±3.8 days, p=0.979)

90 day rehospitalizations with heart failure were significantly more common in the diuretic group (32%) than the ultrafiltration group (18%, p=0.037)

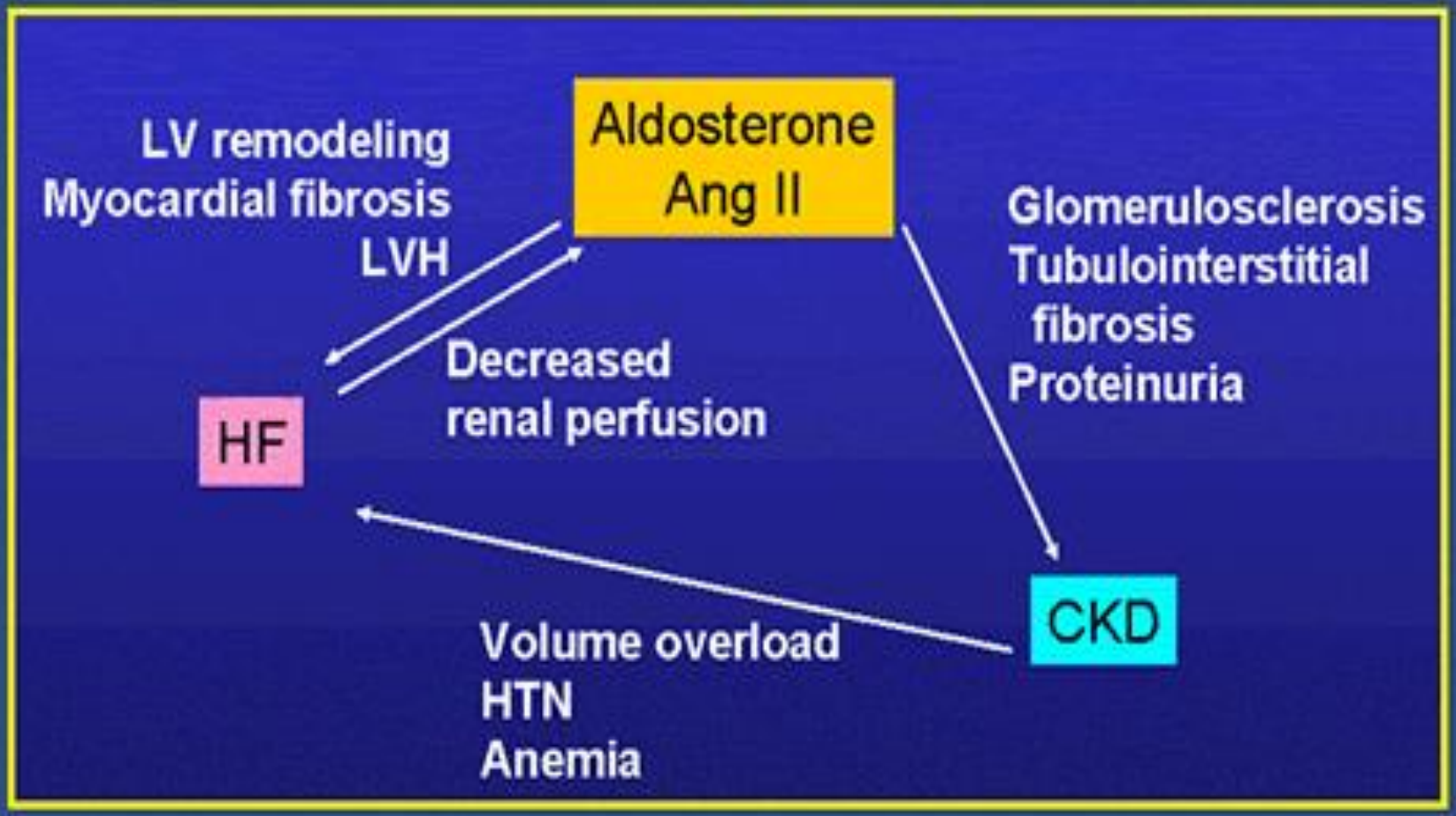
Mortality rates were not significantly different

Constanzo MR, et al: JACC 2007;49:675-83

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- **2- RAAS blockade and Neprylisin inhibitor (pseudo worsening of renal function)?**
- 3-Hyponatremia management (Vaptan)?
- 4-Hyperurecemia management (Allopurinol)?
- 5- Anemia Management (CRAIDS and EPO)?
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?
- 8-New drugs?

Central Role of RAAS in Progressive CKD and Cardiomyopathy



Volpe M et al. J Am Soc Nephrol. 2002; 13 (suppl 3): S173
Brewster UC et. al. Am J Med Sci. 200
Hirsch AT et al. Am J Cardiol. 1990;

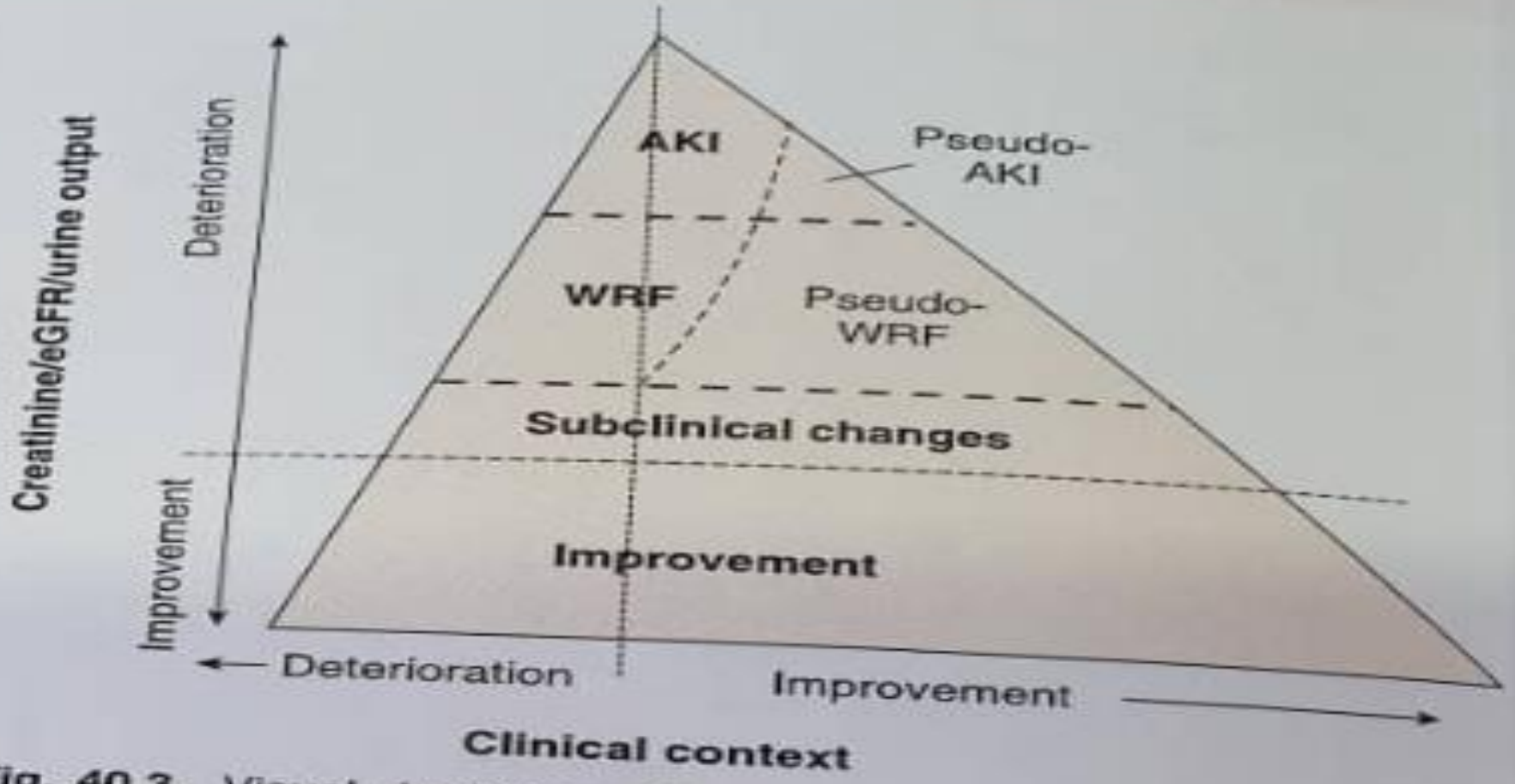
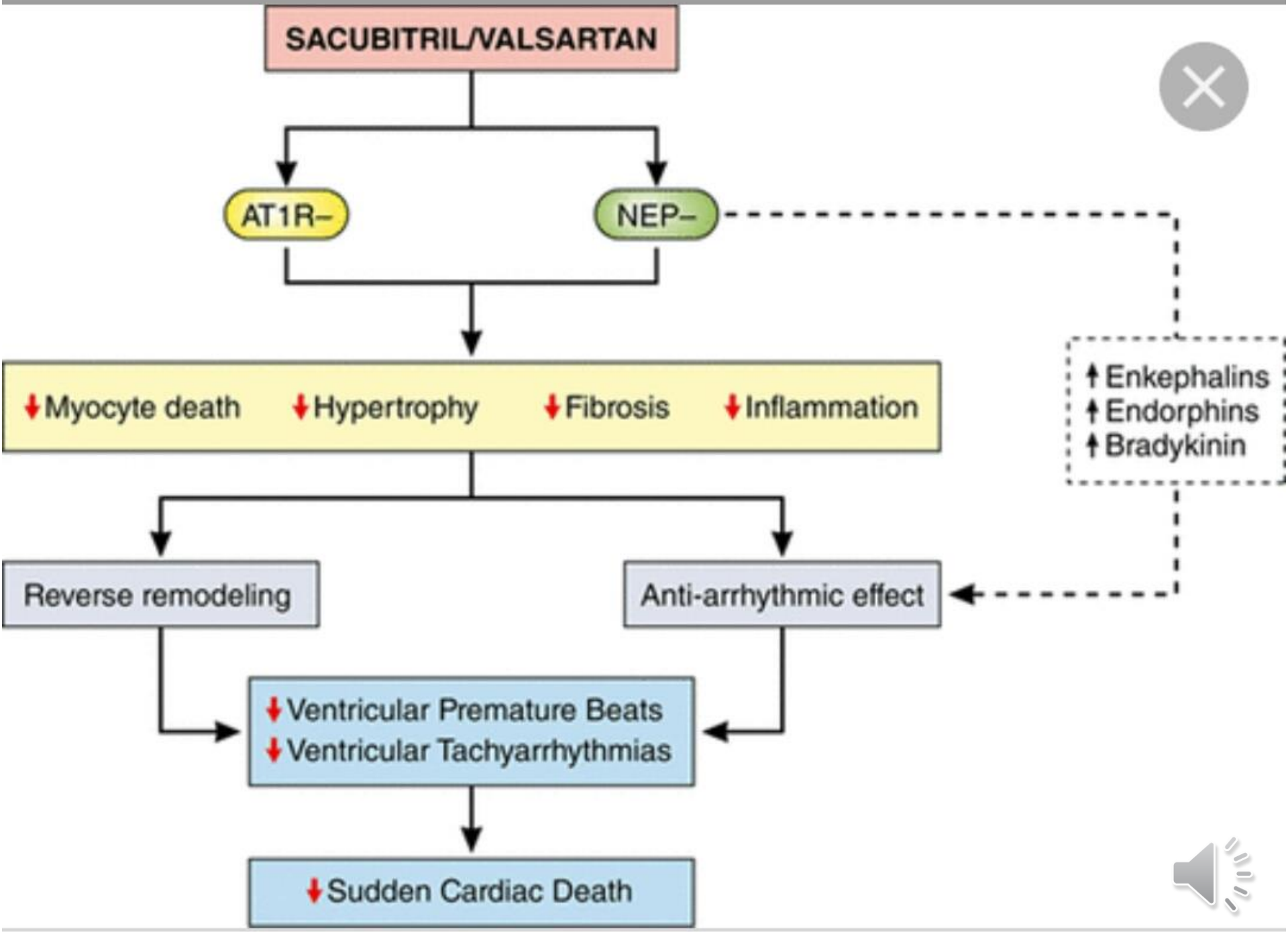
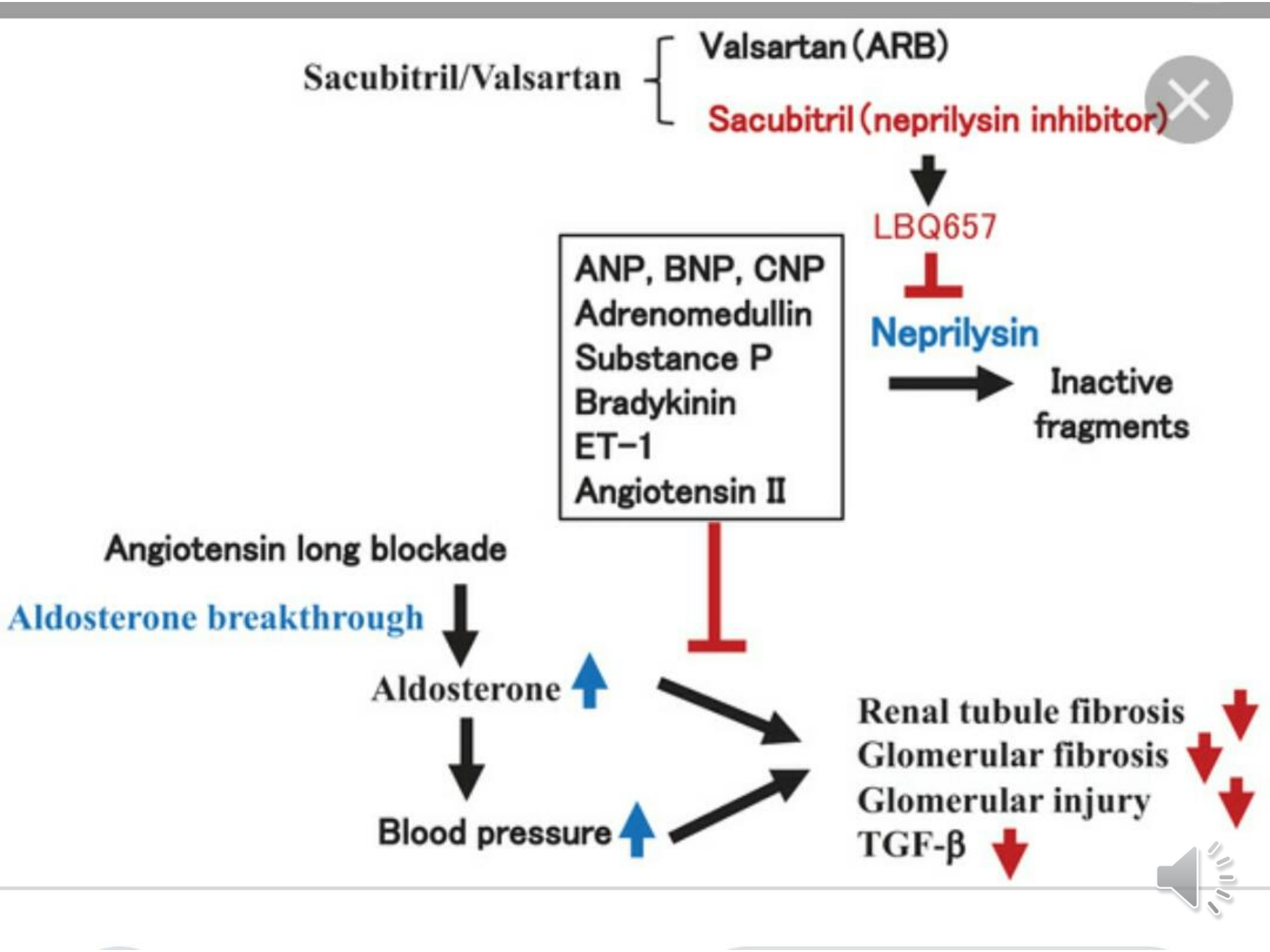


Fig. 40.3 Visual depiction of association among changes in renal function, clinical condition, and mortality risk. Only when both deterioration in clinical status and increase in the serum creatinine level (or decrease in renal function) track together is this associated with worse clinical outcomes in heart failure. *AKI*, Acute kidney injury; *GFR*, glomerular filtration rate; *WRF*, worsening renal function. *Darker colors* indicate higher mortality risk. (From Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J.* 2015;36:1437–1444. Reprinted with permission from Oxford University Press.)


SACUBITRIL/VALSARTAN
AT1R–
NEP–
↓Myocyte death
↓Hypertrophy
↓Fibrosis
↓Inflammation
↑Enkephalins
↑Endorphins
↑Bradykinin
Reverse remodeling
Anti-arrhythmic effect
↓Ventricular Premature Beats
↓Ventricular Tachyarrhythmias
↓Sudden Cardiac Death


Sacubitril/Valsartan
Valsartan (ARB)
Sacubitril (neprilysin inhibitor)
LBQ657
Neprilysin
Inactive fragments
ANP, BNP, CNP
Adrenomedullin
Substance P
Bradykinin
ET-1
Angiotensin II
Angiotensin long blockade
Aldosterone breakthrough
Aldosterone
Blood pressure
Renal tubule fibrosis
Glomerular fibrosis
Glomerular injury
TGF-β

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

ABSTRACT

BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.). Address reprint requests to Dr. Packer at the Department of Clinical Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, or at milton.packer@utsouthwestern.edu; or to Dr. McMurray at the BHF Cardiovascular Research Centre, University Pl., University of Glasgow, Glasgow, Scotland G12 8QQ, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of the investigators in the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) is provided in the Supplementary Appendix, available at NEJM.org.

Drs. McMurray and Packer contributed equally to this article.

This article was published on August 30, 2014, and updated on September 11, 2014, at NEJM.org.

N Engl J Med 2014;371:993-1004.
DOI: 10.1056/NEJMoa1409077

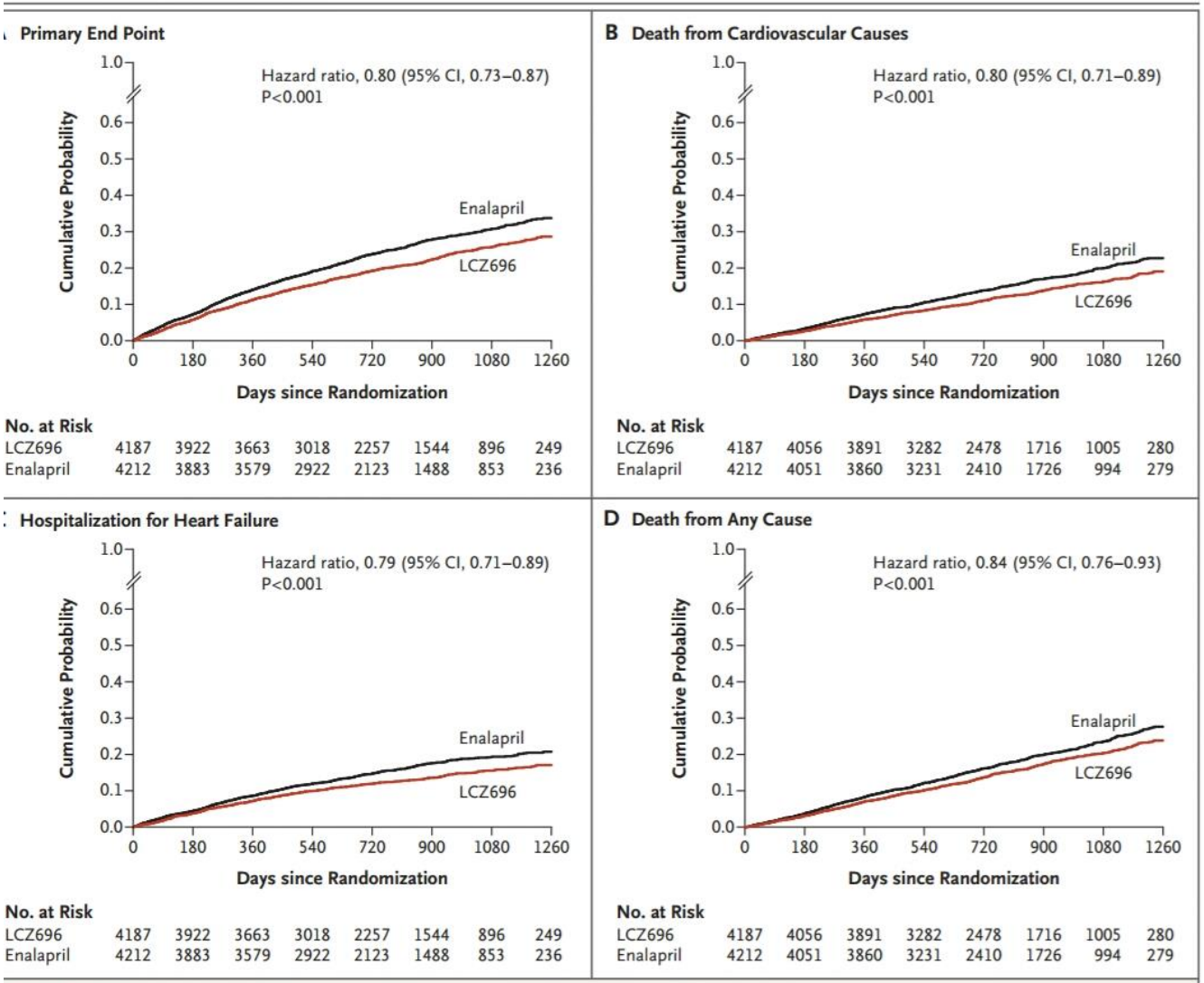


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

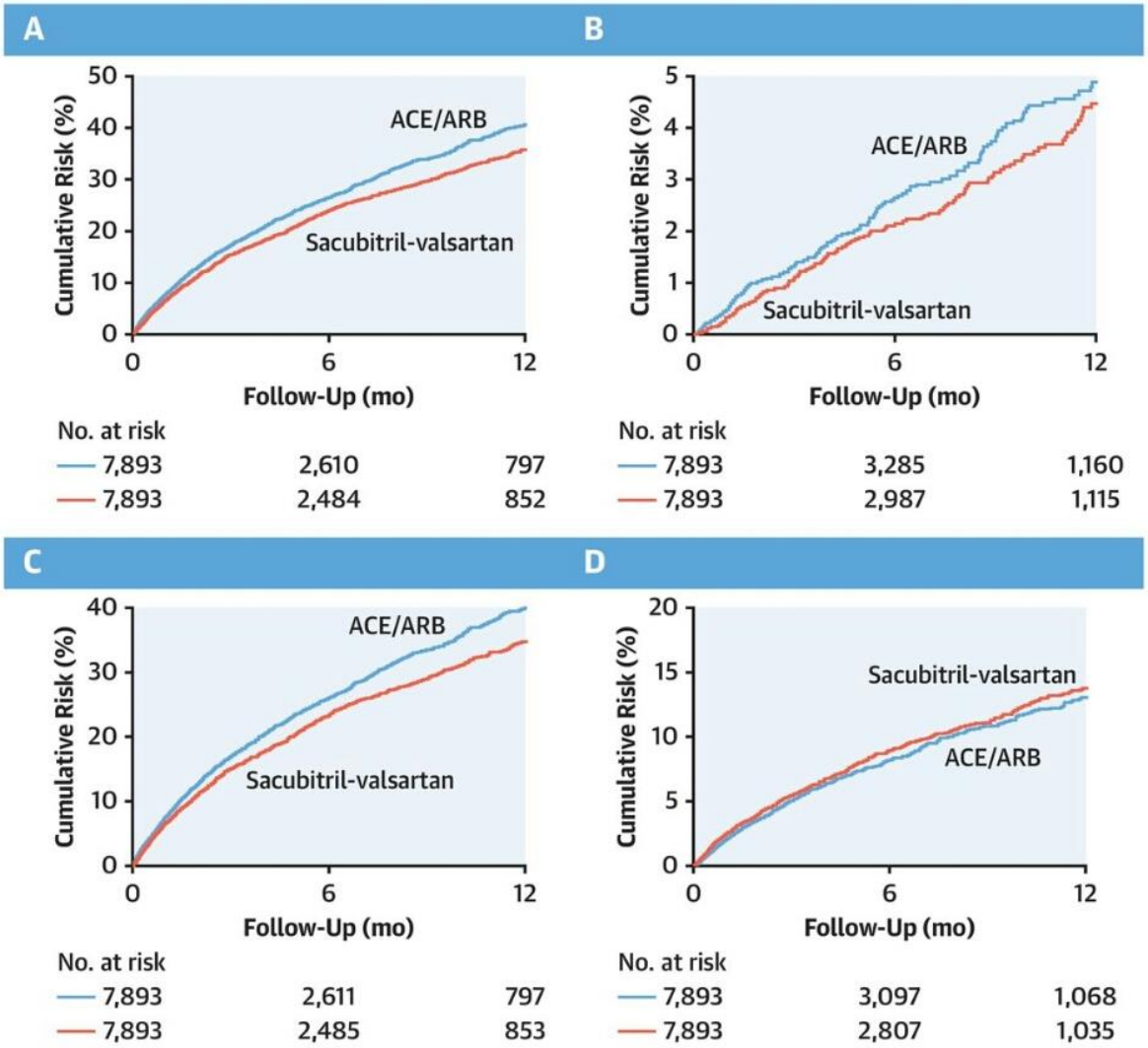
JACC: Heart Failure
Volume 8, Issue 1, January 2020 PDF Article
DOI: 10.1016/j.jchf.2019.08.003

CLINICAL RESEARCH

Comparative Effectiveness of Sacubitril-Valsartan Versus ACE/ARB Therapy in Heart Failure With Reduced Ejection Fraction

Nicholas Y. Tan, Lindsey R. Sangaralingham, S. Jeson Sangaralingham, Xiaoxi Yao, Nilay D. Shah and Shannon M. Dunlay

CENTRAL ILLUSTRATION: Cumulative Risk of Outcomes in Patients Treated With Sacubitril-Valsartan or ACE/ARB



Tan, N.Y. et al. J Am Coll Cardiol HF. 2020;8(1):43-54.

Table 40.3 Characteristics of Different Treatment in HFREF Patients With Chronic Kidney Disease

Therapy	Incidence of Worsening Renal Function and Adverse Events	Incidence of Hyperkalemia	Effectiveness in HFREF Patients*		Cautions and Remarks
			CKD Stage 1–3	CKD Stage 4 or 5	
ACE inhibitor	1.5%–13.7% (35% in NYHA IV)	1.1%–6.4% (7% in NYHA IV)	Yes	Unclear; possible	Induces early decline in eGFR; some increase in serum creatinine should be accepted. Very large increases should prompt further investigation and (temporary) stopping of drug.
ARB	5.5%–17% (24% with high-dose losartan)	1%–3% (10% with high-dose losartan)	Yes	Unclear	
MRA	1.9%–17%	2%–8%	Yes	Unclear; possible	
ARNI	2.2%	4.3% (potassium > 6 mmol/L)	Yes	Unclear; possible	Sacubitril/valsartan was superior to enalapril in reducing renal events and also slowing progression of decline in eGFR; increases urinary albumin excretion to some extent. Large increases should prompt further investigation.
Beta-blocker	7%–10.1%	NA	Yes	Probable	Effect on renal function negligible compared with placebo; should be continued if possible.
Loop diuretics	NA	Probably low	NA	NA	Use and dose associated with worsening renal function. Long-term effects on renal function unknown. Dose should be higher in patients with CKD stage 3–5.
CRT	NA	NA	Yes	Unclear; possible	Improvement in renal function in parallel—improvement in clinical symptoms can be expected.
LVAD	NA	NA	Yes	Unclear; possible	LVAD therapy improves renal function in the long term. However, risk of AKI is peri- and postoperatively higher in patients with CKD stage 3-5 at baseline. Risk contrast nephropathy at tir of implantation.

*Improvement in clinical outcome.

ARB, Angiotensin II receptor blocker; *ACE*, angiotensin-converting enzyme; *ARNI*, angiotensin receptor blocker neprilysin inhibitor; *CKD*, chronic kidney disease; *CRT*, cardiac resynchronization therapy; *eGFR*, estimated glomerular filtration rate; *HFREF*, heart failure reduced ejection fraction; *LVAD*, left ventricular assist device; *NYHA*, New York Heart Association.

Adapted from Damman K, Tang WH, Felker GM, et al. Current evidence on treat

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- **3-Hyponatremia management (Vaptan)?**
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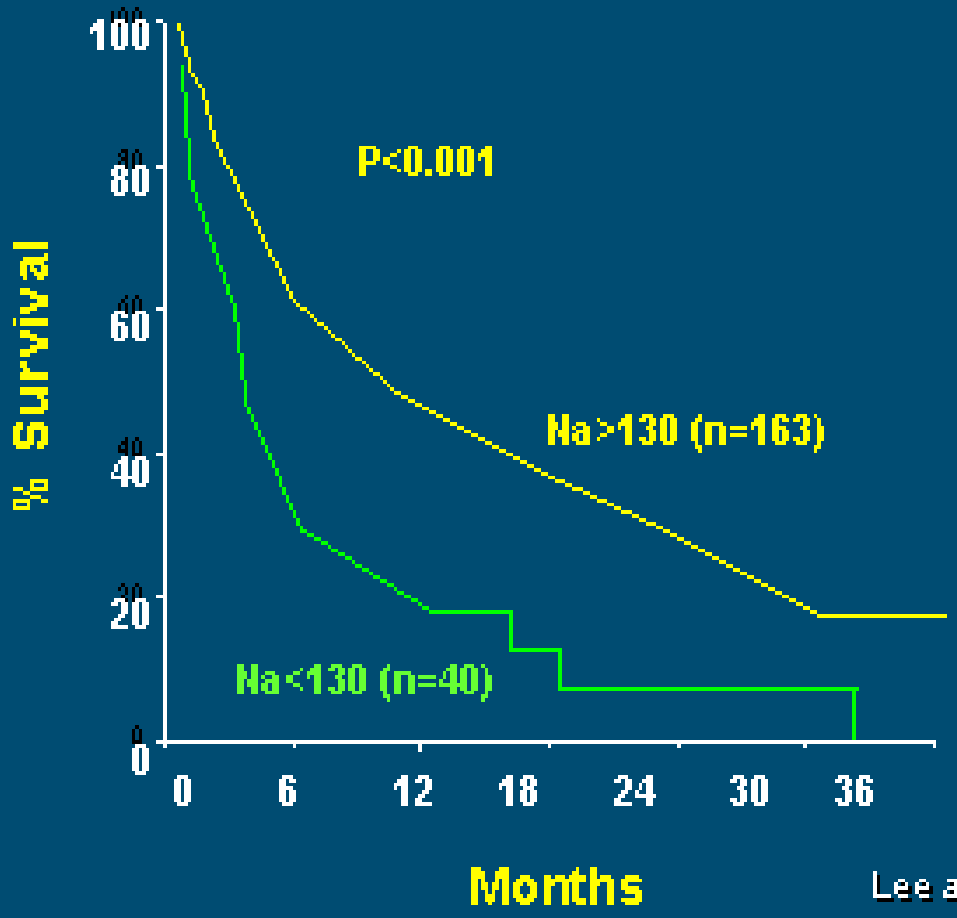
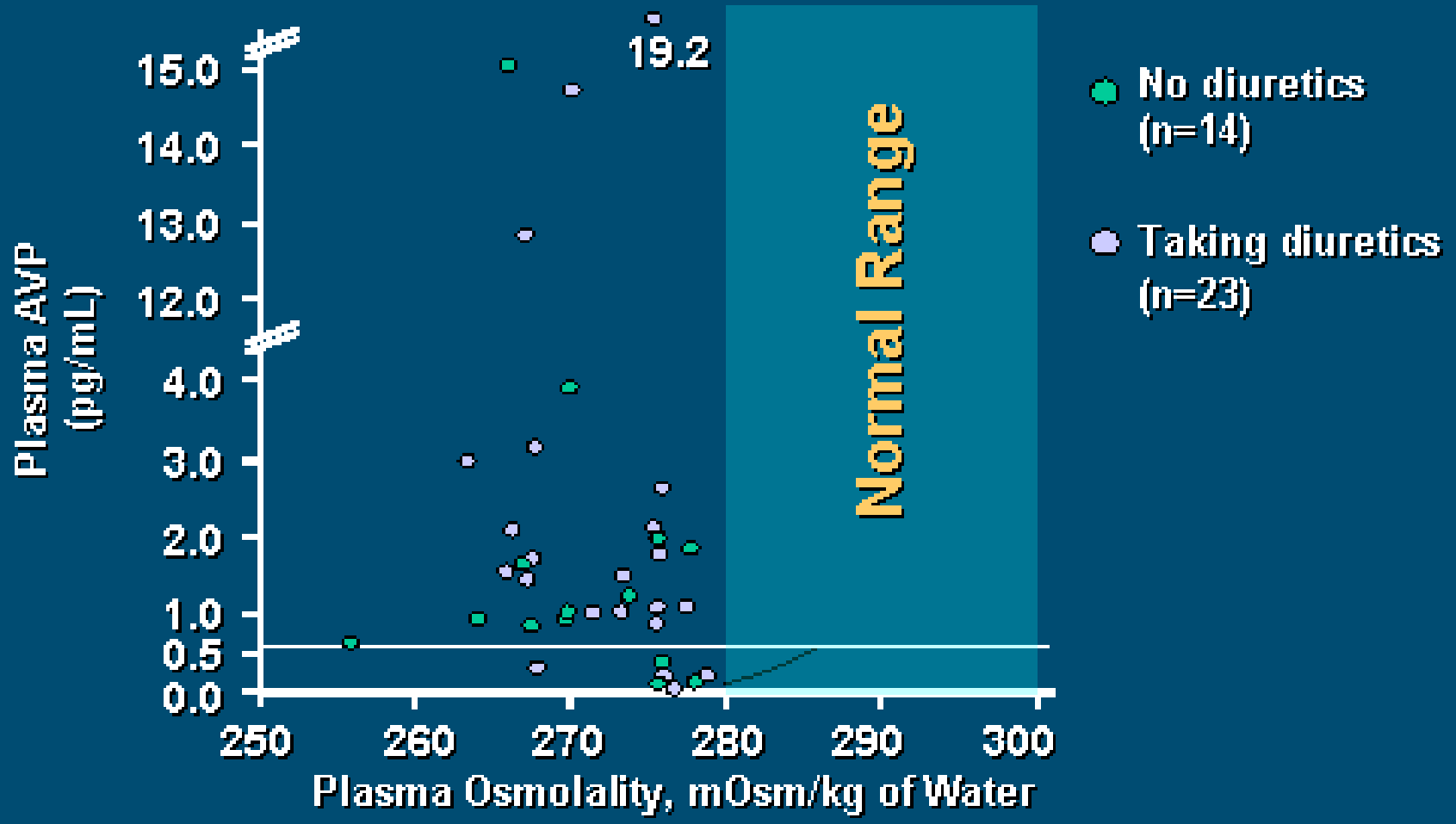
- 8- New drugs?

Pretreatment Hyponatremia Predicts an Unfavorable Prognosis in Patients with Heart Failure



Lee and Packer, Circulation, 73: 257-67, 1986

AVP Levels are also Elevated in Patients with CHF



Szatalowicz et al, N Engl J Med 305:263, 1981

Szatalowicz VL et al. *N Engl J Med. 1981 Jul 30;305(5):263-6.*

Vasopressin (AVP, ADH)

- Nonapeptide hormone synthesized in the hypothalamus
- Released into the circulation by the posterior pituitary
- V_1 vascular receptor:
  - vasoconstriction => increased peripheral vascular resistance, afterload
- V_2 renal tubular receptor:
  - water retention => increased intra- and extracellular volume overload
- Indirect mechanisms:
  - both AVP and AG II stimulate ET synthesis

Goldsmith and Gheorghiade JACC 2005;46:1785-91

Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

Table 3. Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

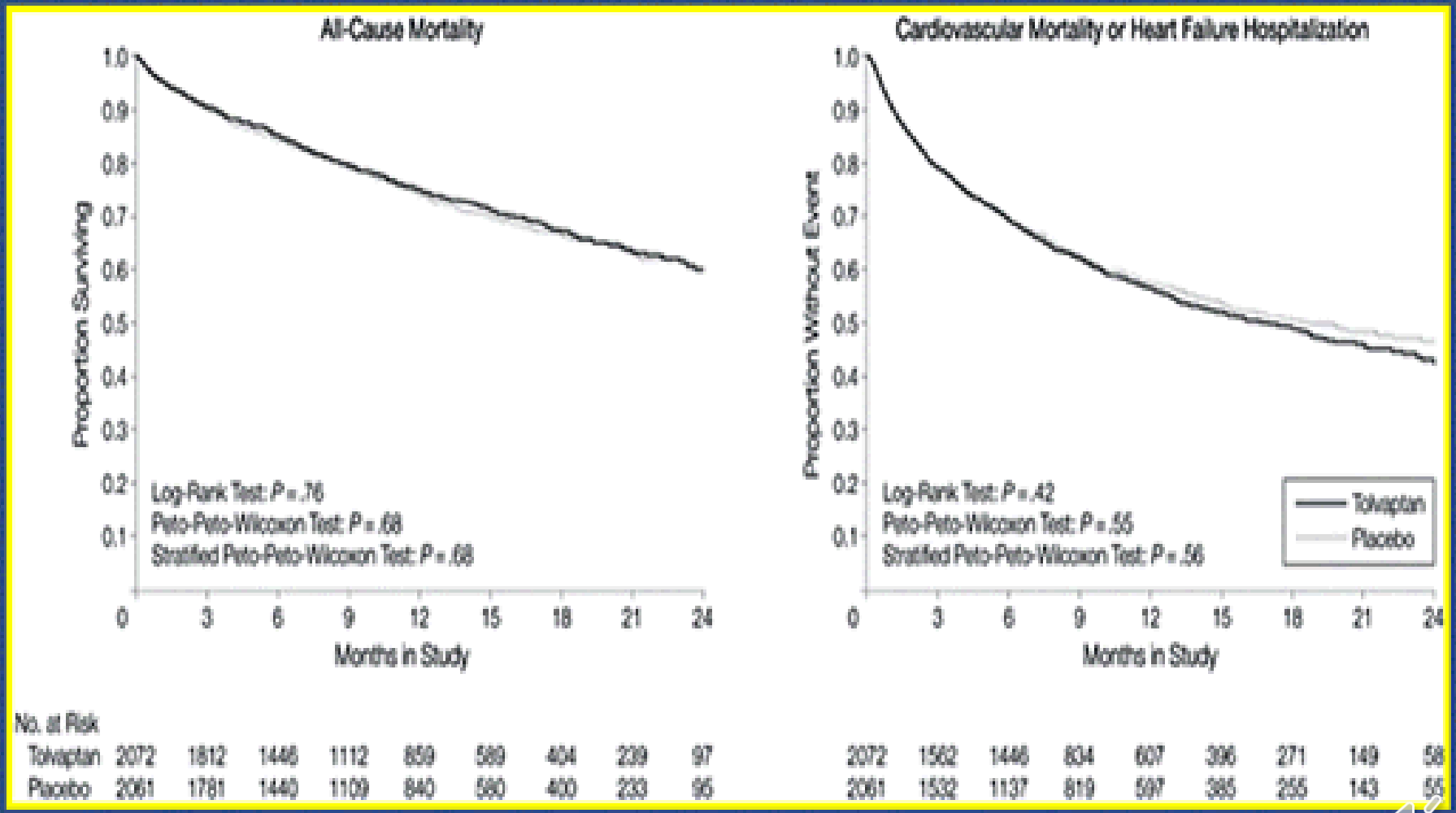
	Tolvaptan	Placebo	*P* Value
Change in body weight at 1 day, mean (SD), kg	−1.76 (1.91) [n = 1999]	−0.97 (1.84) [n = 1999]	<.001*
Change in dyspnea at 1 day, % showing improvement in dyspnea score†	74.3 [n = 1835]	68.0 [n = 1829]	<.001‡
Change in serum sodium at 7 days (or discharge if earlier), mean (SD), mEq/L§	5.49 (5.77) [n = 162]	1.85 (5.10) [n = 161]	<.001*
Change in edema at 7 days (or discharge), % showing at least a 2-grade improvement†	73.8 [n = 1600]	70.5 [n = 1595]	.003‡
Change in KCCQ overall summary score at postdischarge week 1, mean (SD)	19.90 (18.71) [n = 872]	18.52 (18.83) [n = 856]	.39*

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.
*Based on analysis of covariance model.
†Among patients with symptoms at baseline.
‡Based on van Elteren test.[28]
§Among participants with baseline sodium levels of less than 134 mEq/L.

JAMA

Konstam, M. A. et al. JAMA 2007;297:1319-1331.

EVEREST Trial: Tolvaptan, All-Cause Mortality and Cardiovascular Mortality or Hospitalization for Heart Failure



JAMA

Konstam, M. A. et al. JAMA 2007;297:1319-1331.

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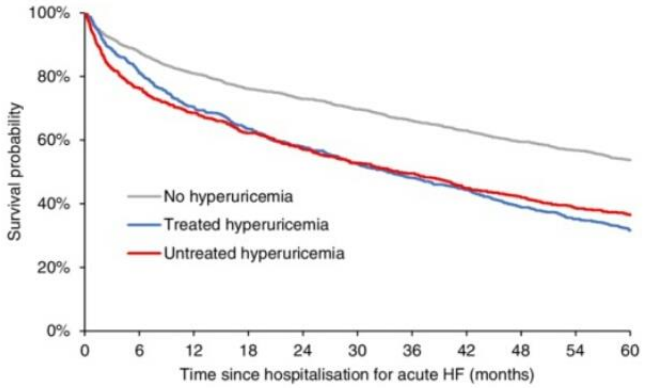
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?
- 8- New drugs?

Clinical Cardiology
Wiley-Blackwell

Hyperuricemia treatment in acute heart failure patients does not improve their long-term prognosis: A propensity score matched analysis from the AHEAD registry

Marie Pavlusova, Jiri Jarkovsky, [...], and Jiri Parenica



No. at risk:

No hyperuricemia	1,786	1,564	1,444	1,359	1,302	1,244	1,179	1,124	1,062	1,013	959
Treated hyperuricemia	793	643	558	504	460	416	382	352	309	279	251
Untreated hyperuricemia	583	444	399	362	332	307	288	261	245	225	212

	Overall survival (95% CI)		
	1-year	**2-year**	**5-year**
No hyperuricemia	80.9% (82.7%; 0.8%)	72.9% (75.0%; 0.7%)	53.7% (56.0%; 0.5%)
Treated hyperuricemia	70.4% (73.5%; 0.7%)	58.0% (61.4%; 0.5%)	31.7% (34.9%; 0.3%)
Untreated hyperuricemia	68.6% (72.3%; 0.6%)	57.0% (61.1%; 0.5%)	36.4% (40.3%; 0.3%)

Log-rank test: **$p < 0.001$**

Post-hoc comparison at 5 years: no hyperuricemia vs treated hyperuricemia **$p < 0.001$**, no hyperuricemia vs untreated hyperuricemia **$p < 0.001$**, treated hyperuricemia vs untreated hyperuricemia $p = 0.370$

Kaplan – Meier estimate of 5 – year overall survival in patients with acute heart failure according to hyperuricemia and its treatment (before propensity

ORIGINAL ARTICLE

Effects of Allopurinol on the Progression of Chronic Kidney Disease

Sunil V. Badve, Ph.D., Elaine M. Pascoe, M.Biostat., Anushree Tiku, M.B., B.S., Neil Boudville, D.Med., et al. for the CKD-FIX Study Investigators*

June 25, 2020

N Engl J Med 2020; 382:2504-2513

CONCLUSIONS In patients with chronic kidney disease and a high risk of progression, urate-lowering treatment with allopurinol did not slow the decline in eGFR as compared with placebo. (Funded by

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- 3-Hyponatremia management (Vaptan)?
- 4-Hyperurecemia management (Allopurinol)?
- **5- Anemia Management(CRAIDS and EPO)?**
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?
- 8- New drugs?

Anemia In The Cardiorenal Syndrome: Proposed Etiologies

- **Risk factors**
  - Bleeding associated with anti-platelet agents
  - Nutritional iron deficiency with cachexia
  - Hemodilution from volume overload
  - CKD with decreased EPO production
- **EPO resistance thought primary mechanism**
  - HF causes chronic inflammation
    - Elevates levels of multiple cytokines
      - Epo resistance
        - Anemia

Review Article

The Potential Role of Erythropoietin in Chronic Heart Failure: From the Correction of Anemia to Improved Perfusion and Reduced Apoptosis?

Stefan A.J. Timmer MSc ... A.C. Van Rossum MD, PhD

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
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The NEW ENGLAND JOURNAL of MEDICINE

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Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

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ABSTRACT

BACKGROUND

Aldosterone blockade reduces mortality and morbidity among patients with severe heart failure. We conducted a double-blind, placebo-controlled study evaluating the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

METHODS

Patients were randomly assigned to eplerenone (25 mg per day initially, titrated to a maximum of 50 mg per day; 3313 patients) or placebo (3319 patients) in addition to optimal medical therapy. The study continued until 1012 deaths occurred. The primary end points were death from any cause and death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia.

RESULTS

During a mean follow-up of 16 months, there were 478 deaths in the eplerenone group and 554 deaths in the placebo group (relative risk, 0.85; 95 percent confidence interval, 0.75 to 0.96; P=0.008). Of these deaths, 407 in the eplerenone group and 483 in the placebo group were attributed to cardiovascular causes (relative risk, 0.83; 95 percent confidence interval, 0.72 to 0.94; P=0.005). The rate of the other primary end point, death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (relative risk, 0.87; 95 percent confidence interval, 0.79 to 0.95; P=0.002). As was the secondary end point of death from any cause or any hospitalization (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.98; P=0.02). There was also a reduction in the rate of sudden death from cardiac causes (relative risk, 0.79; 95 percent confidence interval, 0.64 to 0.97; P=0.03). The rate of serious hyperkalemia was 5.5 percent in the eplerenone group and 3.9 percent in the placebo group (P=0.002), whereas the rate of hypokalemia was 8.4 percent in the eplerenone group and 13.3 percent in the placebo group (P<0.001).

CONCLUSIONS

The addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

From the University of Michigan, Ann Arbor (B.P.); STEMBIO, Cardiovascular Research Foundation, Rotterdam, the Netherlands (W.R.); the Centre of Investigation Clinique de Nancy, Nancy, France (F.Z.); the University of Minnesota, Minneapolis (J.N.); the Fundacion Favaloro, Cordoba, Argentina (F.M.); and Pharmacia, Skokie, IL (B.R., R.B., S.H., J.K., M.G.). Address reprint requests to Dr. Pitt at the Department of Internal Medicine, Division of Cardiology, University of Michigan Medical Center, 9220 Kresge, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0364, or at bpitt@umich.edu.

*Members of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Group are listed in the Appendix.

N Engl J Med 2003;348:1309-21.

Eplerenone vs Placebo

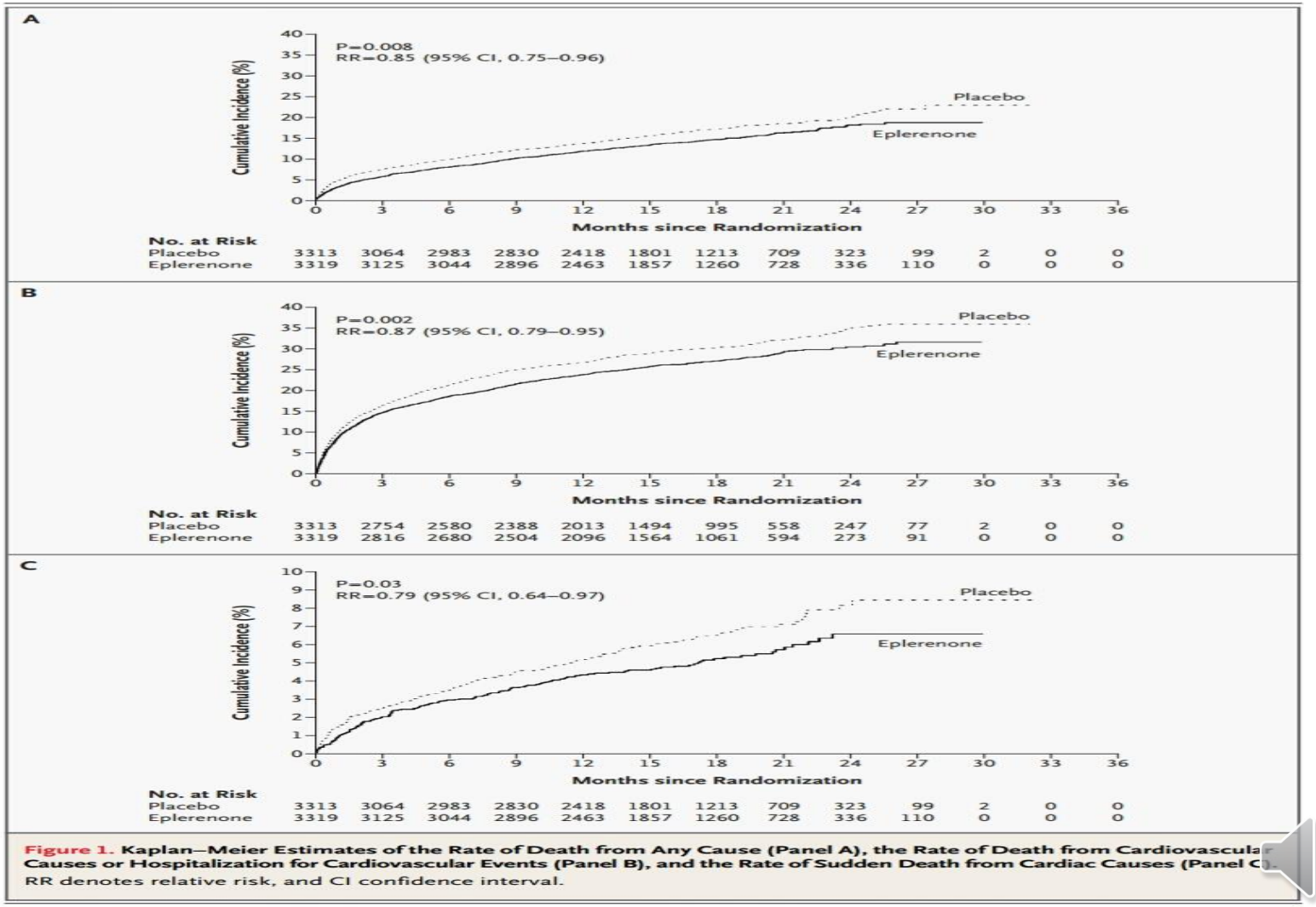

Figure 1. Kaplan–Meier Estimates of the Rate of Death from Any Cause (Panel A), the Rate of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B), and the Rate of Sudden Death from Cardiac Causes (Panel C).
RR denotes relative risk, and CI confidence interval.

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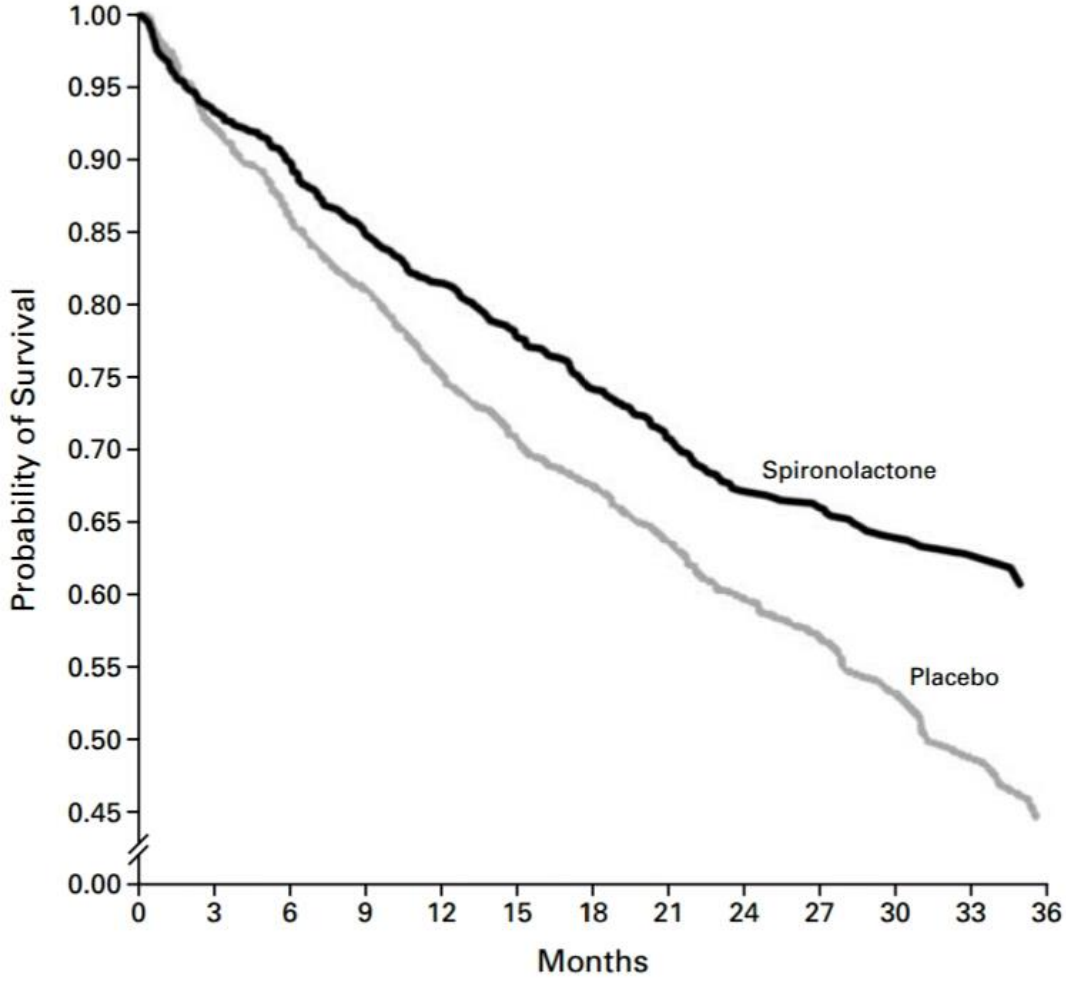
THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Figure 1. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group.

The risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group ($P<0.001$).

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- 3-Hyponatremia management (Vaptan)?
- 4-Hyperurecemia management (Allopurinol)?
- 5- Anemia Management (CRAIDS and EPO)?
- 6-Mineral receptor antagonist?
- **7-Contrast nephropathy risk and prophylaxy?**
- 8- New drugs?

CIN risk after PCI

developing CIN. This has mostly been done in patients undergoing percutaneous coronary intervention (PCI), especially those with preexisting risk factors. Mehran et al developed a scoring system based on points awarded to each of the following multivariate predictors [27] :

- Hypotension = 5 points
- Intra-aortic balloon pump (IABP) use = 5 points
- CHF = 5 points
- SCr >1.5 mg/dL = 4 points
- Age >75 years = 4 points
- Anemia = 3 points
- Diabetes mellitus = 3 points
- Contrast volume = 1 point for each 100 mL used

Risk categories by total calculated score, CIN rates, and requirements for dialysis were as follows:

- Low risk (score of ≤5): CIN rate 7.5%, dialysis in 0.04%
- Moderate risk (score of 6-10): CIN rate 14%, dialysis in 0.12%
- High risk (score of 11-15): CIN rate 26.1%, dialysis in 1.09%,
- Very high risk (score of ≥16): CIN rate 57.3%, dialysis in 12.6%

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- 3-Hyponatremia management (Vaptan)?
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- 5- Anemia Management (CRAIDS and EPO)?
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- **8- New drugs?**

BOX 72.1 Treatment Modalities for Refractory Heart Failure

Traditional Treatment

- Diuretics: Loop diuretics, long-acting thiazides
- Digoxin
- ACE inhibitors and ARBs
- Mineralocorticoid receptor antagonists
- β-Blockers
- Vasodilators
- Blood transfusions

Pharmaceuticals

- Neprilysin inhibitor/ARB combination for HFrEF
- Inotropes: For example, milrinone, dobutamine*
- Synthetic natriuretic peptides*
- Aquaretics: Vasopressin antagonists*
- Erythropoiesis-stimulating agents*
- Adenosine receptor blockade*

Mechanical Treatment

- Biventricular pacing
- Ventricular assist devices

Ultrafiltration

- Peritoneal dialysis
- Manual (CAPD) and automated using a cycler (APD)
- Extracorporeal therapies
- Intermittent short-duration ultrafiltration
- Slow continuous ultrafiltration (SCUF)

*No clinical benefit established.