Scompenso Cardiaco Acuto ed Insufficienza Renale:

L'importanza dei biomarkers per predire l'evoluzione

GREAT NETWORK IN THE WORLD

www.greatnetwork.org

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European Society Cardiology

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Biomerieux;

Ortho Clinical Diagnostics

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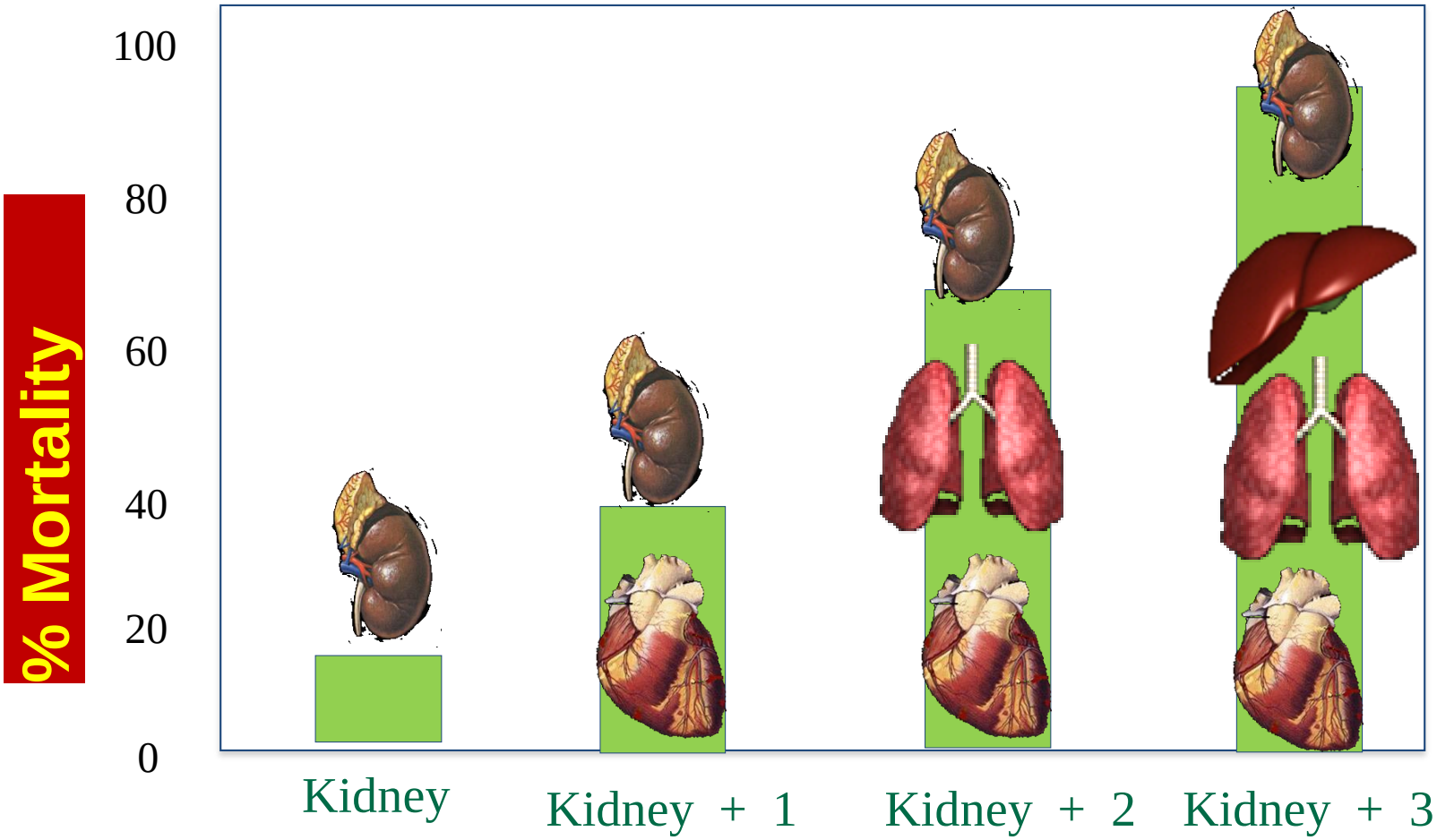
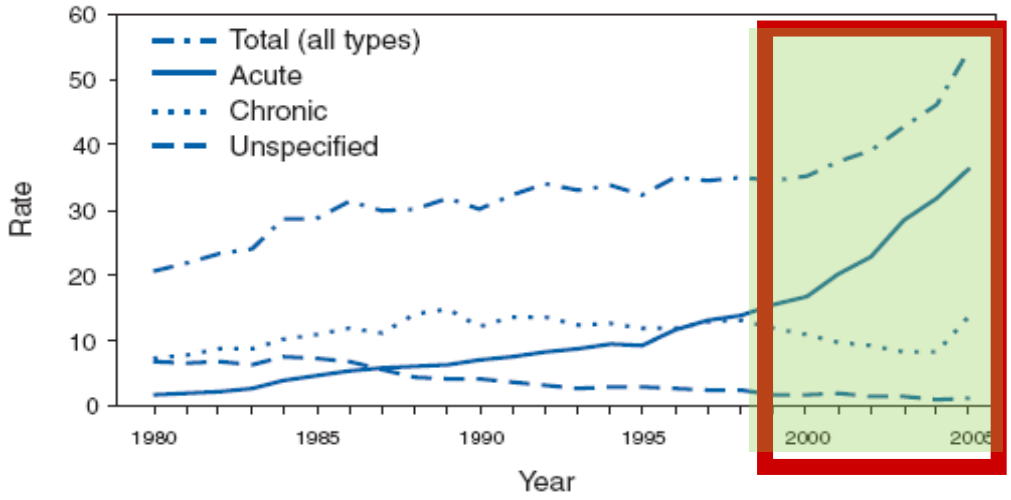
Number of Failing Organs for any acute disease



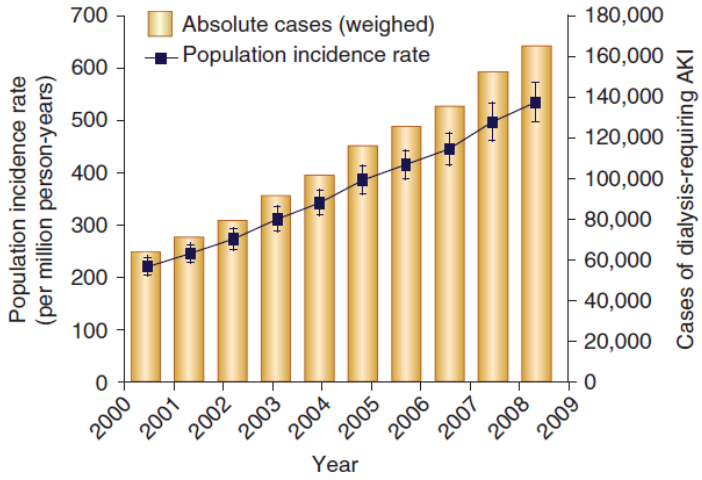
Increasing Frequency of Hospitalizations and Need for Dialysis because of Kidney Disease

FIGURE 2. Age-adjusted hospitalization rates* for kidney disease,† by type of kidney failure — National Hospital Discharge Survey, United States, 1980–2005



* Per 10,000 population.
† Based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 580–589, which include acute kidney disease, acute renal failure, end-stage renal disease, chronic kidney failure, and other kidney diseases.

Morb Mortal Wkly Rep, 57: 309-12, 2008.



Population incidence of dialysis-requiring AKI

Siew ED et al. Kidney international 2015.

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AKI: Epidemiology

- ✓ Over the past two decades, the increased availability of electronic health records and large prospective cohorts of patients with AKI have facilitated the study of this disease in different settings;

- ✓ Rapid increases in the incidence of AKI have been reported, highlighting a growing contribution to the public health burden of advanced kidney disease.

AKI (KDIGO definition) is estimated to occurs in:

- **18% of general hospitalizations and**
- **up to 50% of ICU cases worldwide;**

Bienholz A et al.From the nephrologist's point of view: diversity of causes and clinical features of acute kidney injury. Clinical Kidney Journal 2015.
Siew ED et al. The growth of acute kidney injury: a rising tide or just closer attention to details? Kidney international 2015.

Patients considered for eligibility in ED (n= 700)

Admission (T0)

- *Baseline clinical screening;*
- *Routine laboratory tests*;*
- *sCr , NGAL;*
- *ED physician clinical judgement for suspected AKI ;*
- *Medications, urine output , nephrology consults and disposition*

T:6-12-24-48 and 72 (hours after admission)

sCr, NGAL;
medications, urinary output, nephrology consults, dialysis,ICU admission and mortality;

Excluded (n= 35):
- *Did not consent (n = 8)*
- *Withdraws from study (n=21)*
- *Not admitted (n= 3)*
- *Incomplete data (n= 3)*

7%

Patients considered for statistical analisys (n= 665)

Catania (n= 193)
Genoa (n= 200)
Rome (n= 272)

Outcomes

NO AKI (n=616)
- *Preserved Renal Function (n = 461)*
- *Stable CKD (n=84)*
- *Renal Dysfunction* (n= 71)*

AKI (n=49)
- *RIFLE "R" (n= 9)*
- *RIFLE "I & F" (n=8)*
- *Recovery from RIFLE "I &F"(n= 6)*
- *AKIN Criteria (n = 10)*
- *Oliguria (n = 14)*
- RRT (n=2)

In-hospital deaths (n= 27)
ICU admission (n=11)

S. Di Somma et al. Critical Care 2013 ,17: R 29

*see in the text methods section

Figure 1

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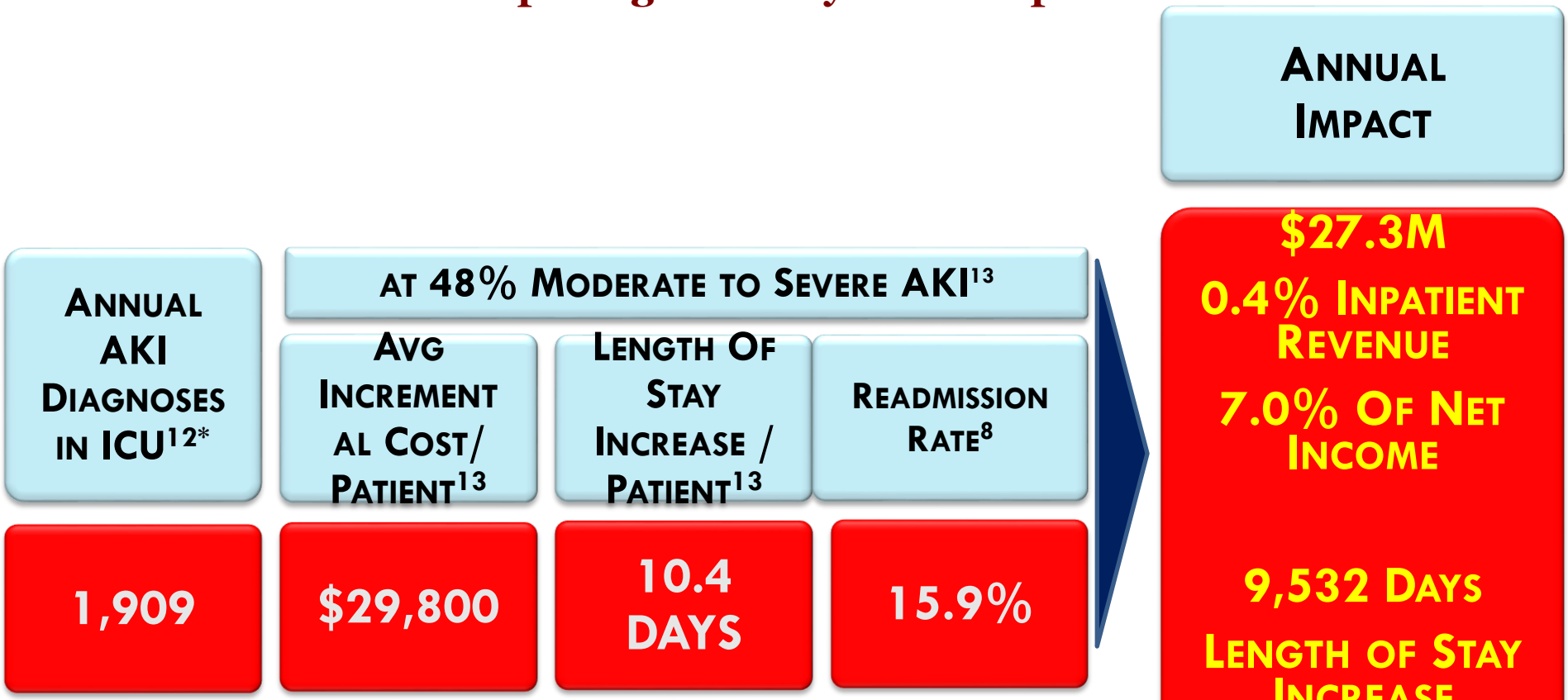
Why is AKI Important to Society

Drives Up Length of Stay And Hospital Costs



[8] Brown JR et al. Impact of perioperative acute kidney injury as a severity index for thirty-day readmission after cardiac surgery. *Ann Thorac Surg.* 2014;97(1):111-7

[11] Massicottee-Azarniouch, Magder S, Goldberg P, Alam A. Acute Kidney Injury in the Intensive Care Unit: Risk Factors and Outcomes of Physician Recognition Compared with KDIGO Classification. Poster presented at: Society of Critical Care Medicine; February 2016; Orlando, FL.

[12] American Hospital Directory Database, accessed Dec 2016 on 7,052 hospitals, data on file

*AKI diagnoses from AHD Database adjusted for diagnoses in ICU using assumptions from AHA Database (ICU beds per hospital bed), Wunsch et al. (ICU LOS, % cardiovascular/respiratory compromised), and Hobson et al. (% moderate/severe AKI).

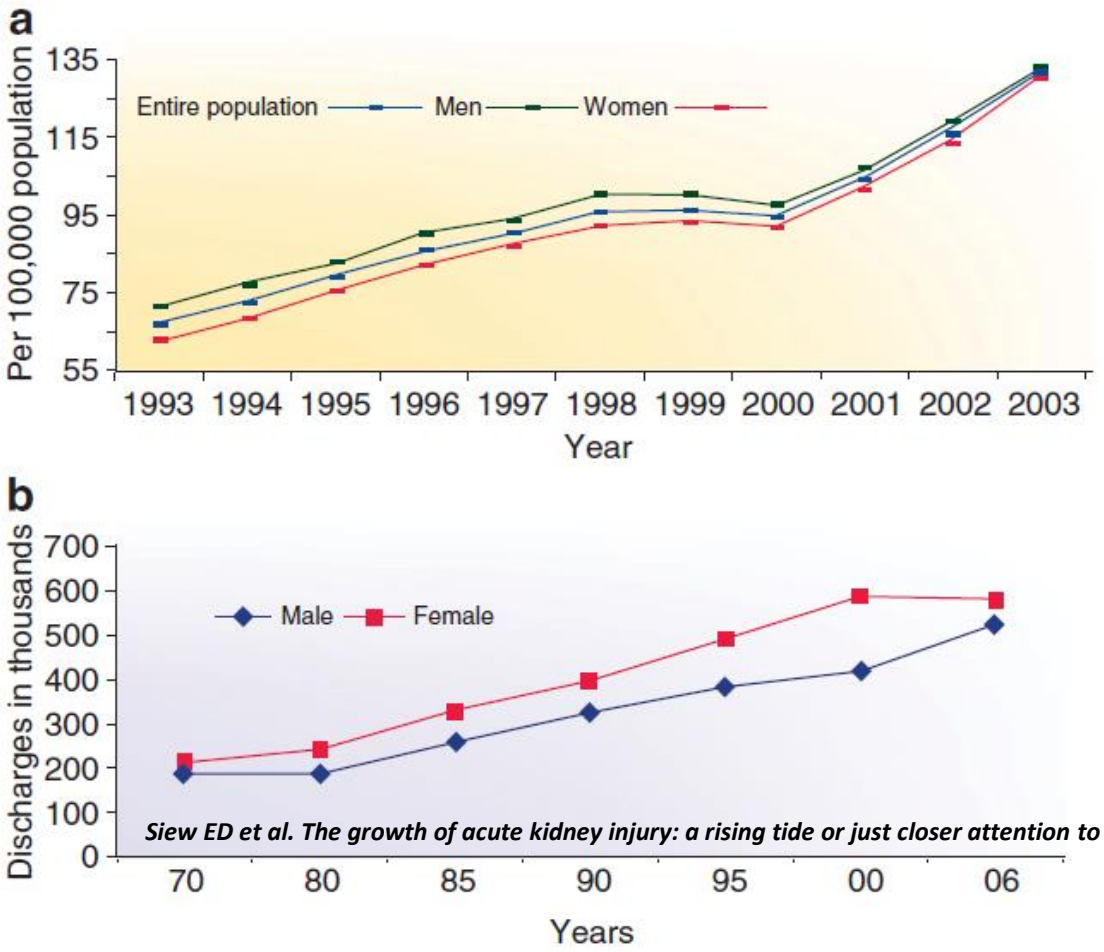
[13] Hobson CE, Ozrazgat-Baslanti T, Kuxhausen A, et. al. Cost and Mortality Associated With Postoperative Acute Kidney Injury Annals of Surgery. 2014;00:1–8

Acute conditions associated with AKI

Exposures	Susceptibilities
• Sepsis	• Dehydration and volume depletion
• Critical illness	• Advanced age
• Circulatory shock	• Female gender
• Burns	• Black race
• Trauma	• CKD
• Cardiac surgery (especially with cardio-pulmonary bypass)	• Chronic diseases (heart, lung, liver)
• Major non-cardiac surgery	• Diabetes mellitus
• Nephrotoxic drugs	• Cancer
• Radiocontrast agents	• Anaemia
• Poisonous plants and animals	• . . .
• Acute Heart Failure	Both Volume Depletion and or Congestion

Bienholz A et al.From the nephrologist's point of view: diversity of causes and clinical features of acute kidney injury. Clinical Kidney Journal 2015.
Siew DE et al. The inexorable rise of AKI: can we bend the growth curve? J Am Soc Nephrol 2013.

Temporal trends in **Sepsis (a)** and **Heart Failure (b)** hospitalizations in US



Siew ED et al. The growth of acute kidney injury: a rising tide or just closer attention to details? Kidney international 2015.

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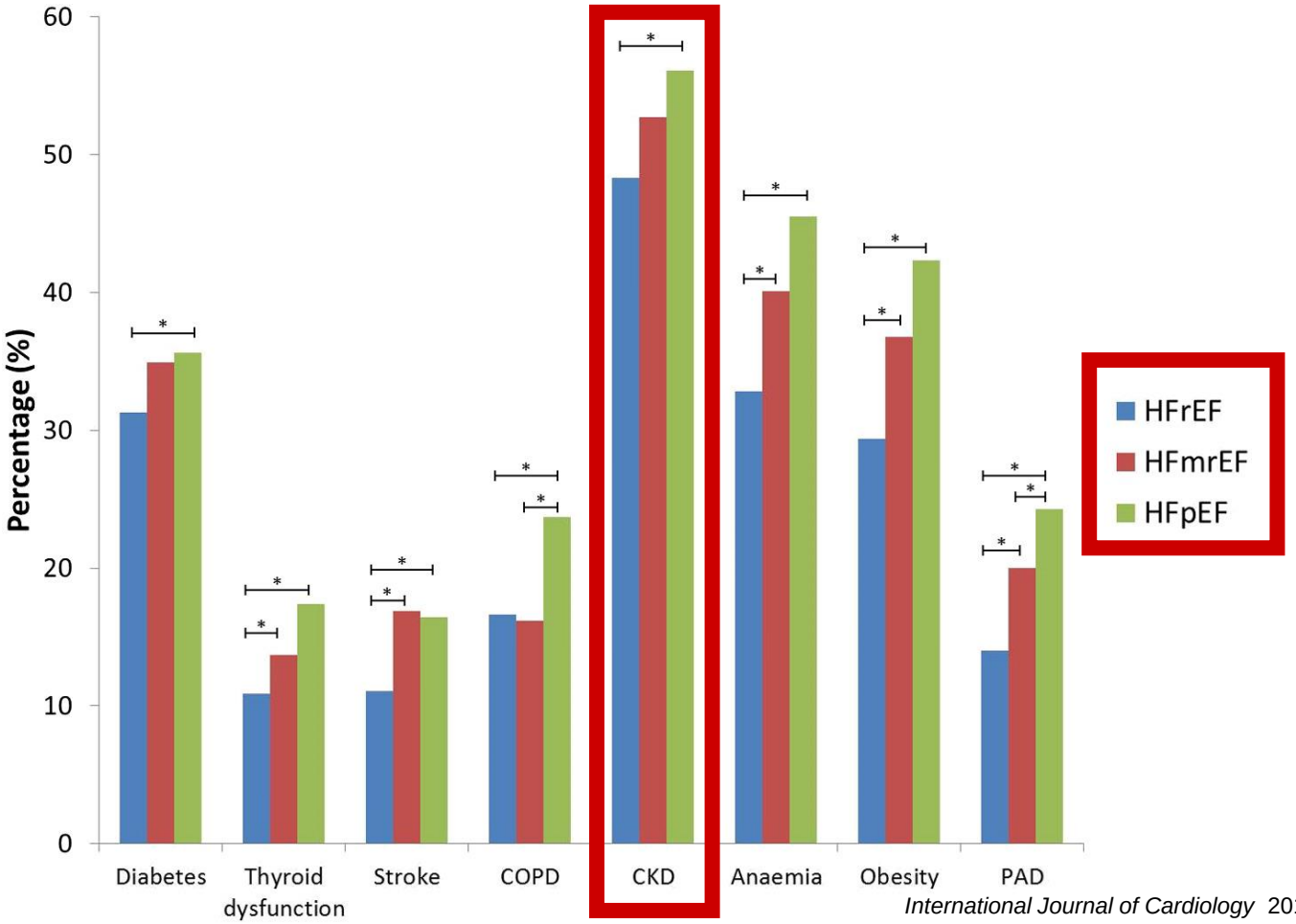
Comorbidities in heart failure with reduced, mid-range and preserved ejection fraction



International Journal of Cardiology 2018 271, 132-139

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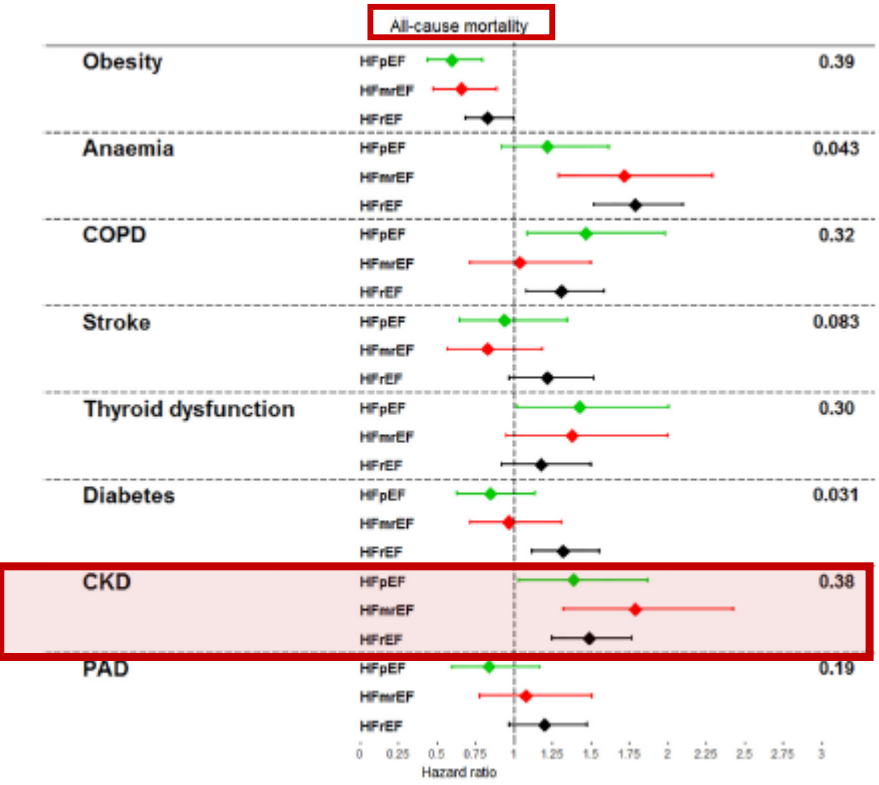
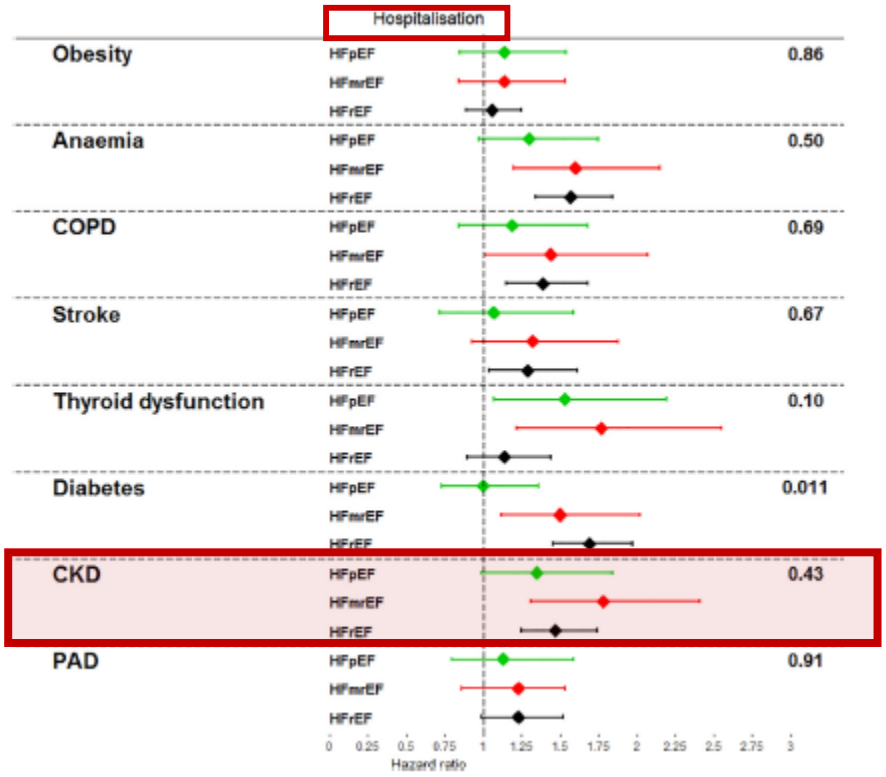
Kidney Disease and Outcome in Heart Failure





International Journal of Cardiology 2018 271, 132-139

Clinical Practice/Education

European Heart Journal Acute Cardiovascular Care

European Heart Journal: Acute Cardiovascular Care 1–10

DOI: 10.1177/2048872616633853
acc.sagepub.com
SAGE

European Society of Cardiology – Acute Cardiovascular Care Association position paper on safe discharge of acute heart failure patients from the emergency department

Òscar Miró[1], Frank W Peacock[2], John J McMurray[3], Héctor Bueno[4], Michael Christ[5], Alan S Maisel[6], Louise Cullen[7], Martin R Cowie[8], Salvatore Di Somma[9], Francisco J Martín Sánchez[10], Elke Platz[11], Josep Masip[12], Uwe Zeymer[13], Christiaan Vrints[14], Susanna Price[15], Alexander Mebazaa[16] and Christian Mueller[17] for the Acute Heart Failure Study Group of the ESC Acute Cardiovascular Care Association

Table 2. Variables included in the Emergency Heart Failure Mortality Risk Grade Model formulated by Lee et al.[41] Score calculation for a particular patient can be done through a web calculator (https://ehmrg.ices.on.ca/#/) which allocates patient in low (deciles 1 to 4), medium (deciles 5 to 7) or high (deciles 8 to 10) risk category.

Variable[a]	Unit of measurement
Age	Continuous in years
Transported by EMS	Categorical
Systolic blood pressure	Continuous in mmHg (max = 160 mmHg)
Heart rate	Continuous in beats/min (min = 80, max = 120 beats/min)
Oxygen saturation	Continuous as % (max = 92%)
Creatinine	Continuous as mg/dl
Potassium	Categorical: 4.0 to 4.5 mmol/l ⩾ 4.6 mmol/l ⩽ 3.9 mmol/l
Troponin	Categorical
Active cancer	Categorical
Metolazone at home	Categorical

Cardiorenal Syndrome(CRS)

"a pathophysiological disorder of the heart and kidneys, in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction to the other."

Although cardiorenal syndrome was usually referred to as acute kidney dysfunction following acute cardiac disease, it is now clearly established that impaired kidney function can have an adverse impact on cardiac function.

Ronco C et al. Adv Chronic Kidney Dis.2018 Sep;25(5):382-390.

Table 1. Classification of CRS

Type	Denomination	Description	Example
1	Acute cardiorenal	Heart failure leading to AKI	Acute coronary syndrome leading to acute heart and kidney failure
2	Chronic cardiorenal	Chronic heart failure leading to kidney failure	Chronic heart failure
3	Acute nephrocardiac	AKI leading to acute heart failure	Uremic cardiomyopathy AKI related
4	Chronic nephrocardiac	CKD leading to heart failure	Left ventricular hypertrophy and diastolic heart failure due to kidney failure
5	Secondary	Systemic disease leading to heart and kidney failure	Sepsis, vasculitis, diabetes mellitus

Cardiorenal Syndrome: Review

Ronco C Kidney Dis 2016;2:151–163

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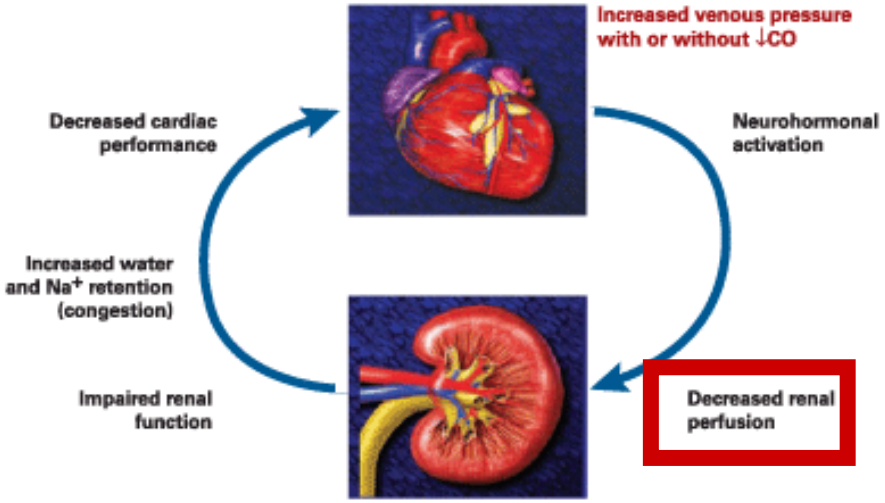
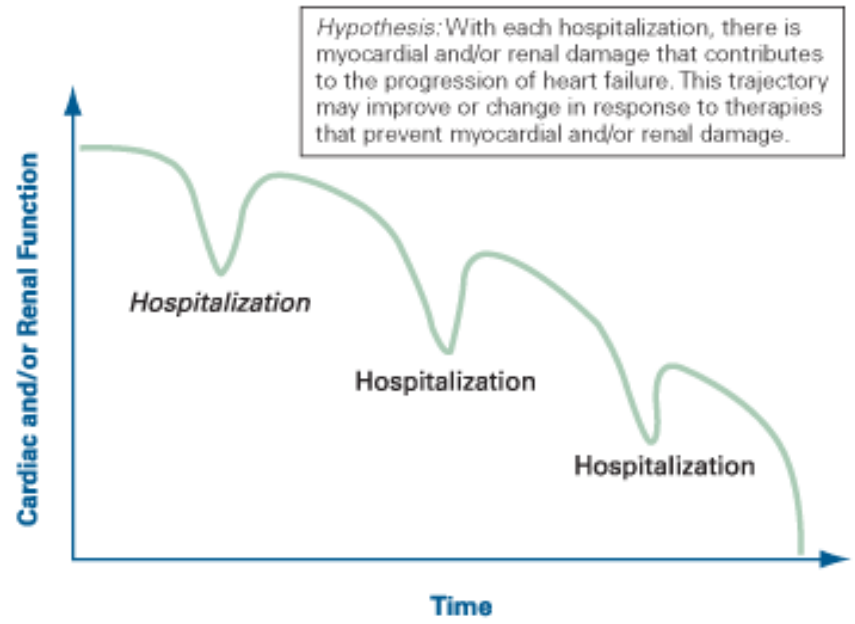
CRS Type 1:Acute CRS

Figure 1. Cardiac/Renal Syndrome[a] in Acute Heart Failure Syndrome[7]



Most patients do not have low cardiac output.
[a]Increasing blood urea nitrogen, in the presence of high filling pressures (edema) often related to high doses of loop diuretics.
Modified from Abraham WT, Schrier RW. *Adv Intern Med.* 1994;39:23-47.

Figure 2. Acute Heart Failure Syndrome and Heart Failure Progression as Related to Cardiac/Renal Function[10]



Am J Manag Care. 2008 Dec;14(12 Suppl Managed):S273-86

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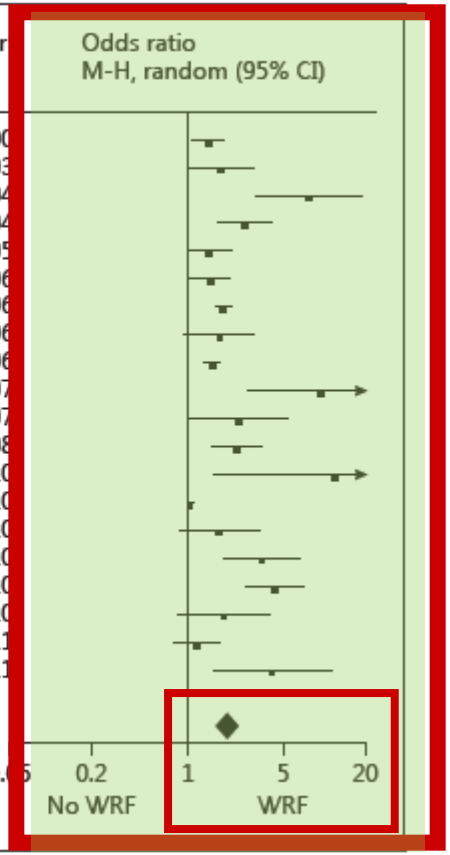
WRF and poor outcome in Heart Failure

Study or subgroup	WRF events	WRF total	No WRF events	No WRF total	weight, %	Odds ratio M-H, random (95% CI)	year
Krumholz	119	469	235	1,212	7.1	1.41 (1.10, 1.82)	200
Smith	35	185	27	227	5.0	1.73 (1.00, 2.98)	200
Forman	19	273	7	731	3.1	7.74 (3.21, 18.62)	200
Akhter	45	119	68	361	5.6	2.62 (1.66, 4.13)	200
De Silva	44	161	219	1,055	6.2	1.44 (0.98, 2.09)	200
Jose	58	223	316	1,631	6.6	1.46 (1.06, 2.02)	200
Khan	628	2,060	879	4,475	7.8	1.79 (1.59, 2.02)	200
Cowie	26	98	35	201	4.8	1.71 (0.96, 3.05)	200
Owan	1,095	1,419	3,215	4,633	7.7	1.49 (1.30, 1.71)	200
Cioffi	11	16	12	63	2.0	9.35 (2.73, 31.99)	200
Chittineni	10	107	17	402	3.4	2.33 (1.04, 5.26)	200
Iglesias	47	221	49	461	5.8	2.27 (1.47, 3.52)	200
Hata	29	275	1	101	0.9	11.79 (1.58, 87.72)	201
Kociol	1,261	3,581	5,601	16,482	7.9	1.06 (0.98, 1.14)	201
Lassus	18	46	67	246	4.3	1.72 (0.89, 3.31)	201
Herout	25	252	16	515	4.3	3.43 (1.80, 6.56)	201
Damman	30	106	76	894	5.4	4.25 (2.62, 6.89)	201
Belziti	12	46	25	154	3.5	1.82 (0.83, 3.99)	201
Breidthardt	49	136	171	521	6.1	1.15 (0.78, 1.71)	201
Voors	11	68	7	157	2.6	4.14 (1.53, 11.19)	201
Total (95% CI)		9,861		34,522	100	1.99 (1.63, 2.42)	
Total events	3,572		11,043				

Heterogeneity: $\tau^2 = 0.13$, $\chi^2 = 146.49$, d.f. = 19 ($p < 0.00001$), $I^2 = 87\%$

Test for overall effect: $Z = 6.81$ ($p < 0.00001$)



Blood Purif 2014;37:271–285
DOI: 10.1159/000360689

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CRS Type 1: outcome

Total enrolled patients (n = 103)

Patient's excluded:
- Missing data (n=3)

Statistical analysis group (n= 100)

Rome = 50 pts
Boston = 50 pts

NO WRF (n= 75)

WRF (n= 25)

Out come

In-hospital Death = 0
Death 30 days follow-up = 7
30 days rehospitalization = 14

L.O.S : 5 days

In-hospital Death = 5
Death 30 days follow-up = 6
30 days rehospitalizzation = 2

L.O.S : 12 days

40%

WRF: worsening renal function

Di Somma et al.Clin Chem Lab Med. 2015 Mar;53(4):613-21

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Importance of early therapies for AHF as consequence of prompt diagnosis

- In 46,599 patients with ADHF (ADHERE)
- ***a delay in Treatment*** was associated with:

- ***250% ↑ in acute mortality;***
- ***150% ↑ in Hospital length of stay***

W.F. Peacock,S. Di Somma et al. Congest Heart Fail. 2008

European Heart Journal Advance Access published May 20, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Recommendations for the management of patients with acute heart failure: pharmacotherapy

Recommendations	Class [a]	Level [b]	Ref [c]
Diuretics			
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.	I	C	

Recommendations regarding monitoring of clinical status of patients hospitalized due to acute heart failure

Frequent, often daily,measurement of renal function (blood urea, creatinine) and electrolytes (potassium, sodium) during i.v. therapy and when renin-angiotensin-aldosterone system antagonists are initiated is recommended.	I	C

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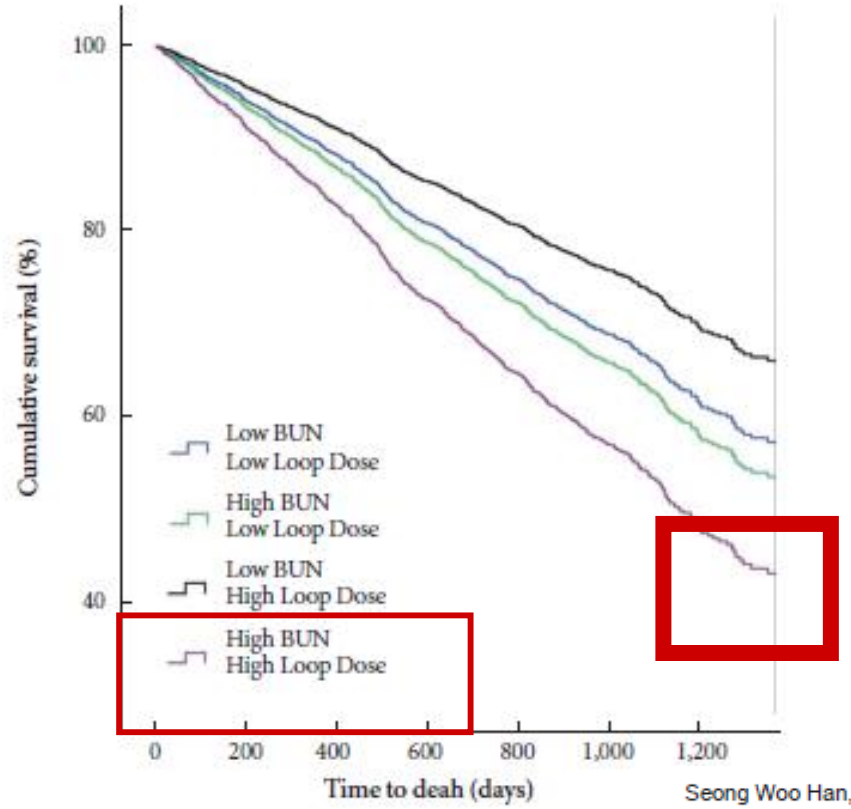
Diuretic dosage and kidney function



Seong Woo Han, et al. (Korean Circ J 2011;41:565-574)

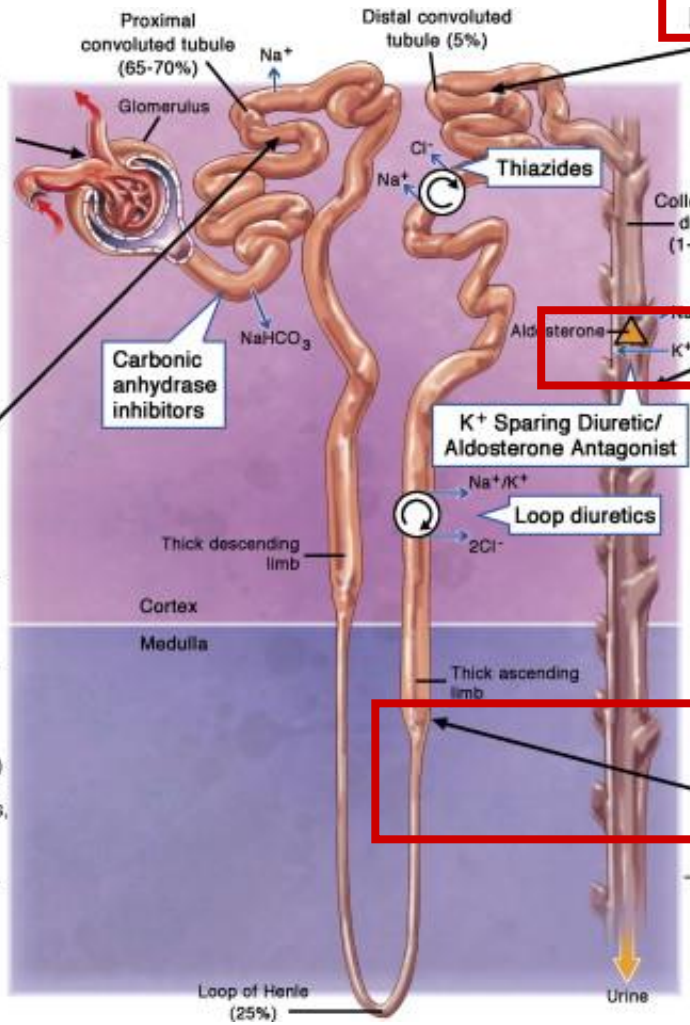
Diuretic Resistance

Reduced GFR:

Barriers	Potential solution
Abnormal glomerular hemodynamics	Discontinue NSAIDs, consider holding ACEI/ARB
Low cardiac output	Hemodynamic support
Chronic kidney disease or functional renal hypoperfusion	Increase LD dose

Proximal Tubule Hyperfunction:

Barriers	Potential solution
Neuro-hormonal activation	ACEI/ARB
Sodium-avid states	Increased LD doses, proximal tubule diuretics (i.e. acetazolamide)
Post-diuretic effect	Multiple daily doses, continuous LD infusion
Excessive daily sodium intake	Sodium restriction



Distal Tubule Hypertrophy

Barriers	Potential solution
Rebound sodium retention	Sequential nephron blockade (Combination diuretic therapy)

Distal Nephron Hyperfunction:

Barriers	Potential solution
Excessive aldosterone-mediated sodium retention	Aldosterone antagonist, K+ - sparing diuretic (ENaC blocker)
Excessive vasopressin-mediated water retention	Vasopressin antagonist, free water restriction

Loop of Henle Hyperfunction:

Barriers	Potential solution
Braking effect	Higher LD doses

Jentzer J.C. et al JACC Nov 2;56(19):1527-34. 2010

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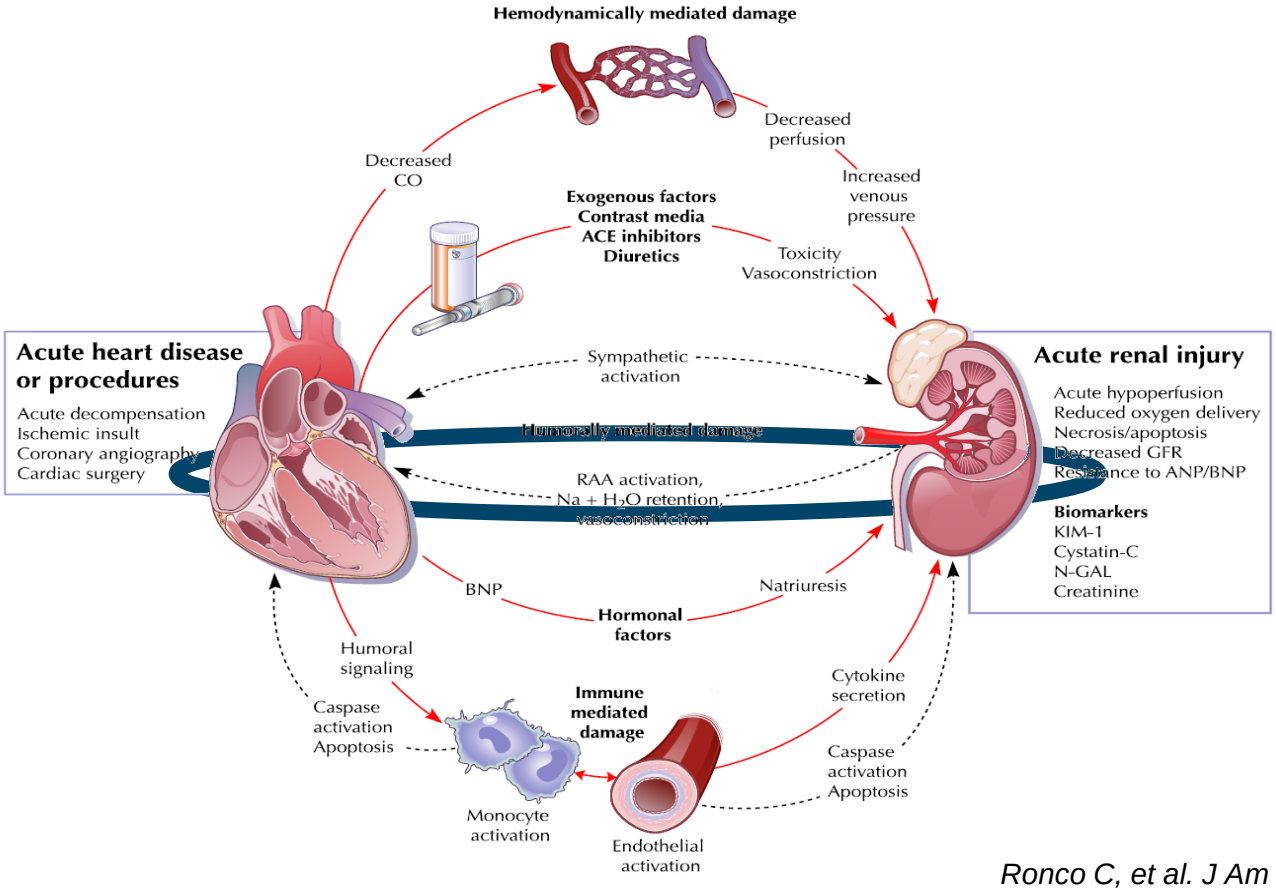
Type 1 Cardiorenal Syndrome: Biomarkers Utility



Ronco C, et al. J Am Coll Cardiol. 2008;52:1527-.

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AKI:Diagnosis

Criteria	RIFLE[25]	AKIN[26]	KDIGO[27,92]
Date of release	2004	2007	2012
Baseline	Not specifically defined. If not available, back-calculate a serum creatinine using an eGFR of 75 ml/min/1.73 m^2 using the MDRD equation	48-h window	Not specifically defined. If not available, use lowest serum creatinine during hospitalization, or calculate SCr using MDRD assuming baseline eGFR 75 ml/min/1.73 m^2 when there is no evidence of CKD
Time interval	Diagnosis and staging: within 1–7 days and sustained more than 24 h	Diagnosis: within 48 h Staging: 1 week	Diagnosis: 50% increase in SCr within 7 days or 0.3 mg/dl (26.5 µmol/l) within 48 h

Criteria		Creatinine	Urine output		Creatinine (urine output criteria same)		Creatinine (urine output criteria same)
Stage	Risk	Increased SCr 1.5–1.9 times baseline or GFR decrease >25%	<0.5 ml/kg/h for 6–12 h	1	Increased SCr 1.5–1.9 times baseline *OR* ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	1	Increased SCr 1.5–1.9 times baseline (7 days) *OR* ⩾0.3 mg/dl (⩾26.5 µmol/l) increase (48 h)
	Injury	2.0–2.9 times baseline or GFR decrease >50%	<0.5 ml/kg/h for ⩾12 h	2	Same as RIFLE minus eGFR criteria	2	same as AKIN
	Failure	3.0 times baseline, GFR decrease >75%, or SCr ⩾4.0 mg/dl (354 µmol/l) with an acute rise of ⩾0.5 mg/dl (44 µmol/l)	<0.3 ml/kg/h for ⩾24 h *OR* Anuria for ⩾12 h	3	Same as RIFLE or on RRT. eGFR criteria removed	3	3.0 times baseline, *OR* Increase in SCr ⩾4.0 mg/dl (354 µmol/l) *OR* Initiation of renal replacement therapy *OR* For <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2
	Loss	Persistent ARF = complete loss of kidney function (need for dialysis) >4 weeks			Notable differences: (1) Addition of 0.3 mg/dl absolute change in SCr to increase diagnostic sensitivity (2) eGFR criteria removed (3) 48-h time window to ensure acuity (also allows for inpatient baseline values) (4) Exclusion of Loss/ESKD categories as diagnostic criteria		Notable differences: (1) Time frame differences for absolute versus relative changes in serum creatinine (2) 0.5 mg/dl increase for those with SCr ⩾4.0 mg/dl (354 µmol/l) no longer required if minimum AKI threshold met (3) Inclusion of eGFR criteria for children
	ESKD	End-stage kidney disease (>3 months)					

Bienholz A et al.From the nephrologist's point of view: diversity of causes and clinical features of acute kidney injury. Clinical Kidney Journal 2015.

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Creatinine caveats

Ostermann and Joannidis *Critical Care* (2016) 20:299
DOI 10.1186/s13054-016-1478-z

Critical Care

REVIEW Open Access

Acute kidney injury 2016: diagnosis and diagnostic workup

Marlies Ostermann[1*] and Michael Joannidis[2*]

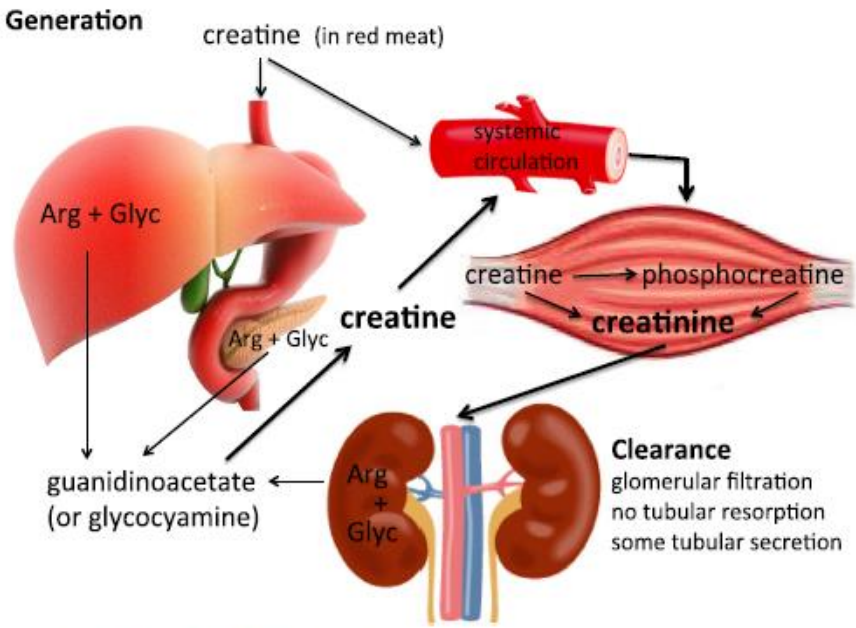

Fig. 1 Generation and clearance of creatinine. *Arg* arginine, *Glyc* glycine

Caveats in using BNP

Curr Emerg Hosp Med Rep
DOI 10.1007/s40138-013-0009-3

HEART FAILURE (F PEACOCK, SECTION EDITOR)

Biomarkers for Diagnosis and Prognosis of Acute Heart Failure

Rajiv Choudhary · Salvatore Di Somma · Alan S. Maisel

Table 1 Factors affecting natriuretic peptide levels in patients with HF along with "grey-zone" values in diagnosing HF

	BNP	NT-proBNP
Factors affecting NP levels		
Pulmonary disease[a]	↑	↑
Renal disease[b]	↑	↑
Diastolic dysfunction[c]	↑	↑
Obesity[d]	↓	↓
Flash pulmonary edema[e]	↓	↓
Other causes[f]	↓	↓
Diagnostic cut-off		
HF present (pg/ml)	>400	<50 years: >450 50–75 years: >900 >75 years: >1800
HF absent (pg/ml)	<100	<75 years: 125 >75 years: 450
Grey-zone (pg/ml)	100–400	<50 years: 300–450 50–75 years: 300–900 >75 years: 300–1800

BNP B-type natriuretic peptide, *NT-proBNP* amino-terminal B-type natriuretic peptide

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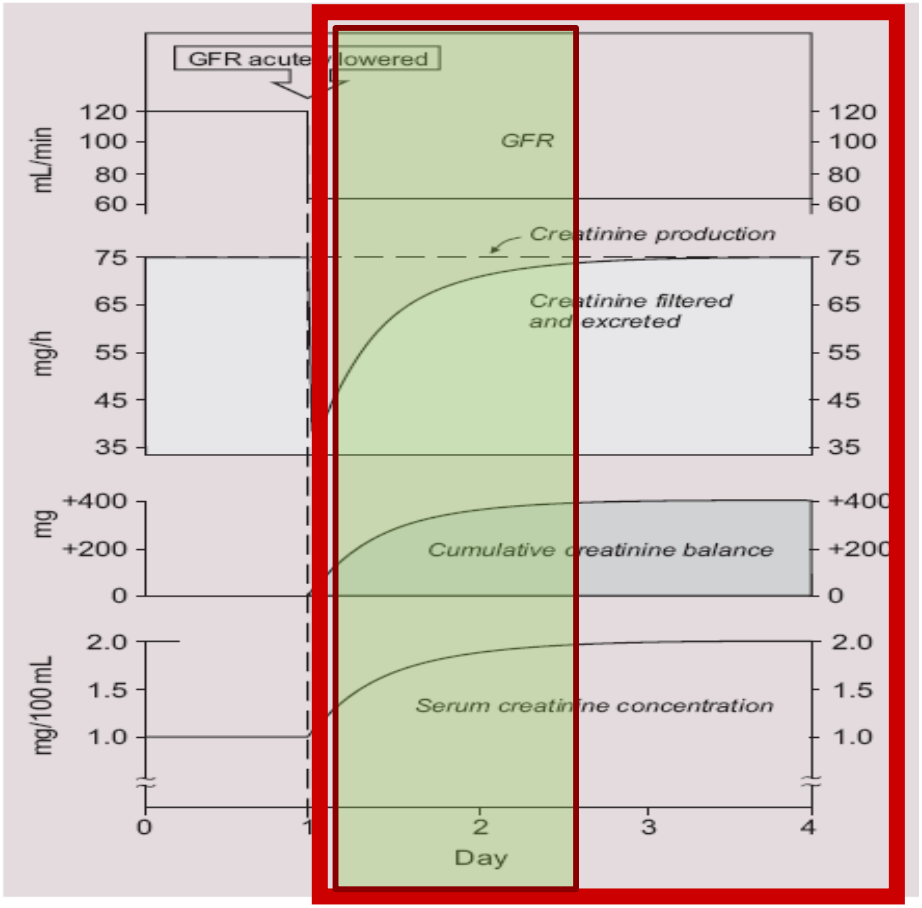
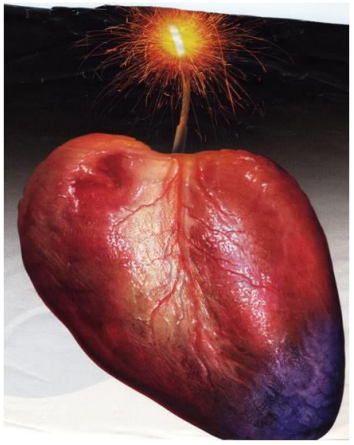
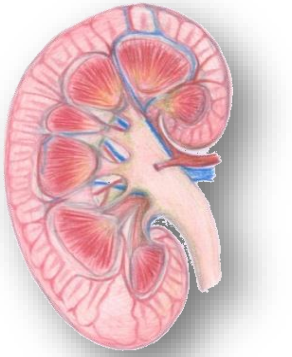
Importance of Time in Acute Kidney Injury: we need AKI biomarkers !







In ACS Time is Myocardium !!

And we have troponin…

IN AKI Time is important to stop the progression of nephrons death

We need Kidney troponin….

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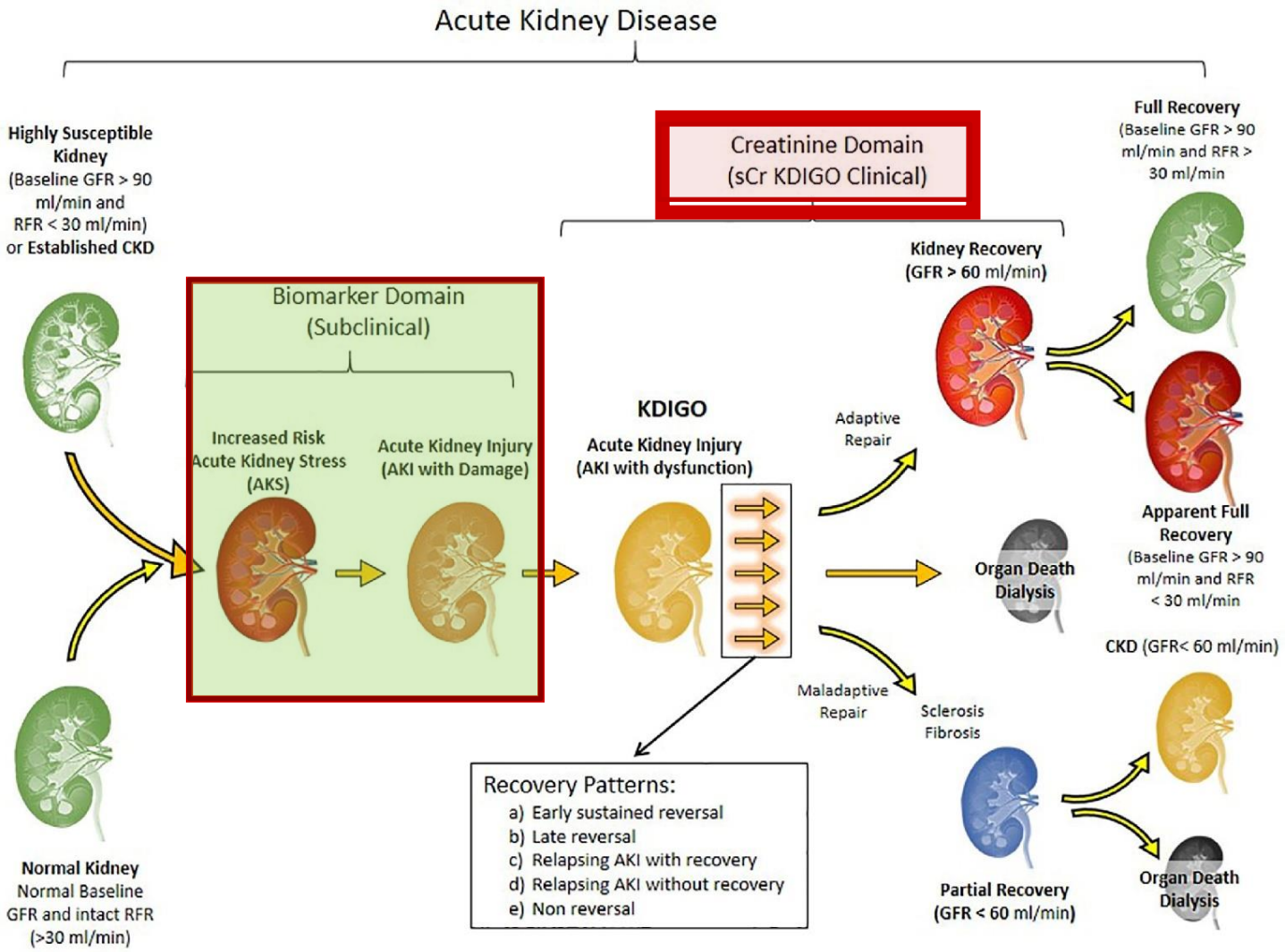

Seminars in Nephrology 2019 39, 31-40DOI: (10.1016/j.semnephrol.2018.10.003)

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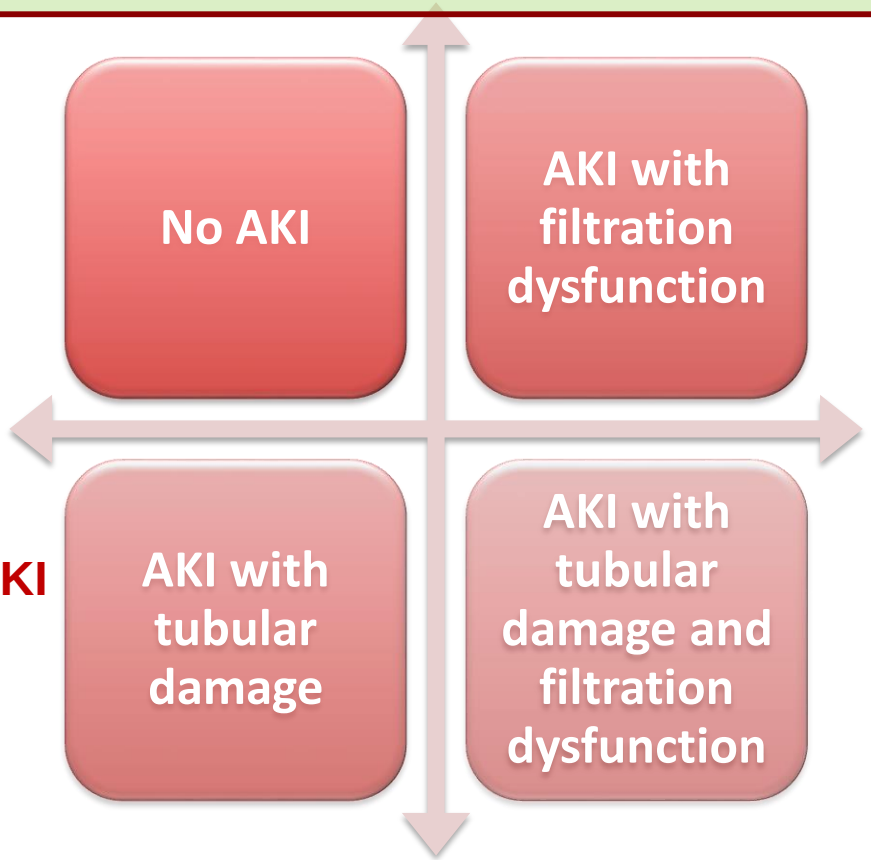
Entities of acute kidney injury syndrome

The most common and expensive kidney disease in hospital;



- AKI implies injury or damage but not necessarily dysfunction
- Functional criteria and damage criteria: new domain of AKI diagnosis

*Ronco et al. Critical Care 2012, **16**:313*

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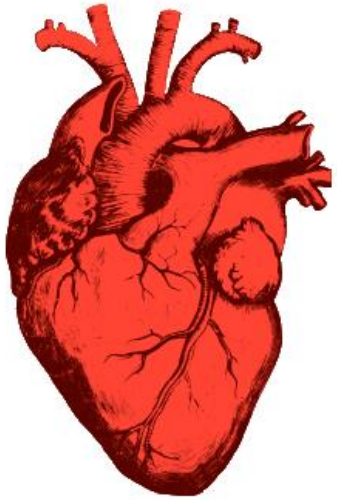
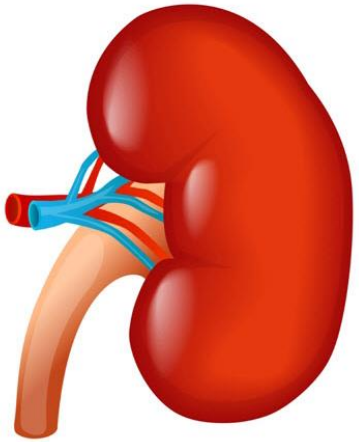
Biomarkers: Function x Lesion





- **Function marker** – Natriuretic Peptides.
- **Lesion marker** – Hs troponins

- **Function marker** – creatinine and urine output
- **Lesion marker** - TIMP-2 & IGFBP7

A lesion marker does not necessarily predict loss of function – nor should it !!!!

But a lesion marker STILL SHOULD GUIDE PATIENT MANAGEMENT!!!!!

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Functional and Damage Kidney Biomarkers

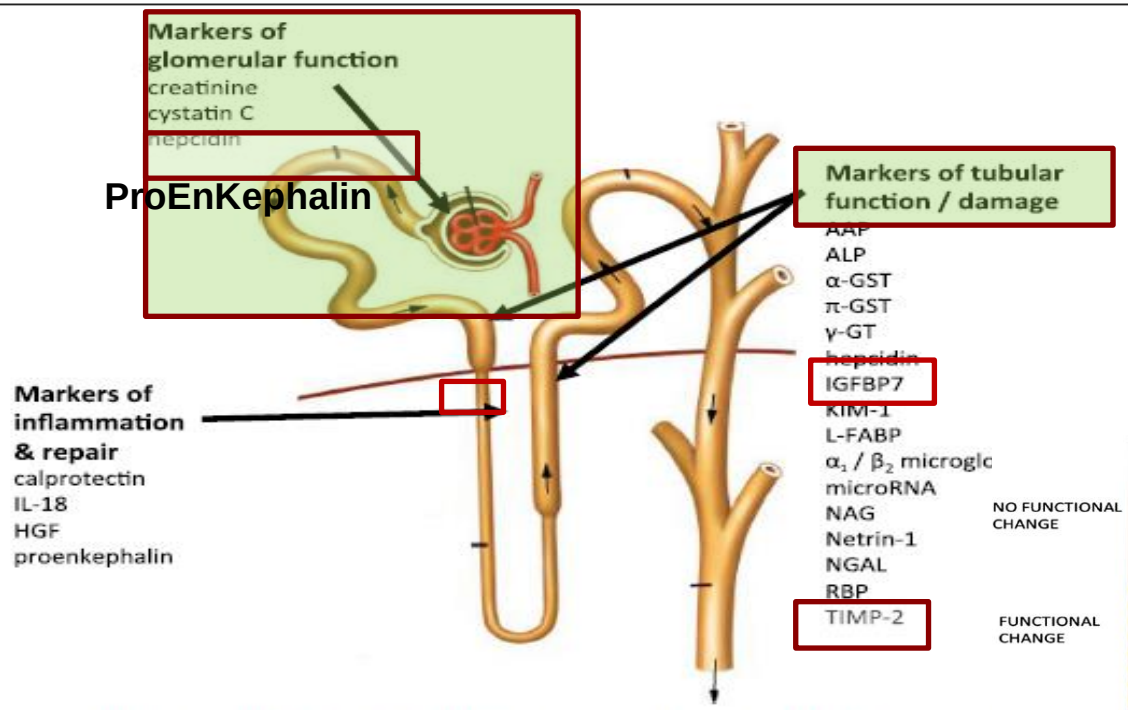

Fig. 2 Biomarkers of AKI. *α-GST* α glutathione S-transferase, *AAP* alanine aminopeptidase, *ALP* alkaline phosphatase, *γ-GT* γ-glutamyl transpeptidase, *π GST* π glutathione S-transferase, *HGF* hepatocyte growth fator, *IGFBP-7* insulin like growth factor binding protein 7, *IL-18* interleukin 18, *KIM-1* kidney injury molecule-1, *L-FAB* liver fatty acid-binding protein, *NAG* N-acetyl-β-D-glucosaminidase, *NGAL* neutrophil gelatinase-associated lipocalin, *RBP* retinol binding protein, *TIMP2* tissue inhibitor metalloproteinase 2

Ostermann and Joannidis *Critical Care* (2016) 20:299
DOI 10.1186/s13054-016-1478-z

AKINESIS Study

OBJECTIVES:

This study sought to determine whether NGAL is superior to creatinine for prediction and/or prognosis of WRF in hospitalized patients with AHF treated with intravenous diuretic agents.

METHODS:

This was a multicenter, prospective cohort study enrolling patients presenting with AHF requiring intravenous diuretic agents. The primary outcome was whether plasma NGAL could predict the development of WRF, defined as a sustained increase in plasma creatinine of 0.5 mg/dl or ≥50% above first value or initiation of acute renal-replacement therapy, within the first 5 days of hospitalization. The main secondary outcome was in-hospital adverse events.

RESULTS:

We enrolled 927 subjects (mean age, 68.5 years; 62% men). The primary outcome occurred in 72 subjects (7.8%). Peak NGAL was more predictive than the first NGAL, but neither added significant diagnostic utility over the first creatinine (areas under the curve: 0.656, 0.647, and 0.652, respectively). There were 235 adverse events in 144 subjects. The first NGAL was a better predictor than peak NGAL, but similar to the first creatinine (areas under the curve: 0.691, 0.653, and 0.686, respectively). In a post hoc analysis of subjects with an estimated glomerular filtration rate <60 ml/min/1.73 m(2), a first NGAL <150 ng/ml indicated a low likelihood of adverse events.

CONCLUSIONS:

Plasma NGAL was not superior to creatinine for the prediction of WRF or adverse in-hospital outcomes. The use of plasma NGAL to diagnose acute kidney injury in AHF cannot be recommended at this time.

A.Maisel et al.J ACC 2016

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Proenkephalin, Renal Dysfunction, and Prognosis in Patients With Acute Heart Failure

A GREAT Network Study

Leong L. Ng, MD,[a,b] Iain B. Squire, MD,[a,b] Donald J.L. Jones, PhD,[c] Thong Huy Cao, MD, PhD,[a,b] Daniel C.S. Chan, BMedSci, BM BS,[a,b] Jatinderpal K. Sandhu, MPhil,[a,b] Paulene A. Quinn, MPhil,[a,b] Joan E. Davies, PhD,[a,b] Joachim Struck, PhD,[d] Oliver Hartmann, PhD,[d] Andreas Bergmann, PhD,[d] Alexandre Mebazaa, MD, PhD,[e] Etienne Gayat, PhD,[e] Mattia Arrigo, MD,[e] Eiichi Akiyama, MD,[e] Zaid Sabti, MD,[f] Jens Lohrmann, MD,[f] Raphael Twerenbold, MD,[f] Thomas Herrmann, MD,[f] Carmela Schumacher, MSc,[f] Nikola Kozhuharov, MD,[f] Christian Mueller, MD,[f] on behalf of the GREAT Network

CONCLUSIONS PENK levels reflect cardiorenal status in acute HF and are prognostic for worsening renal function and in-hospital mortality as well as mortality during follow-up. (J Am Coll Cardiol 2017;69:56–69)

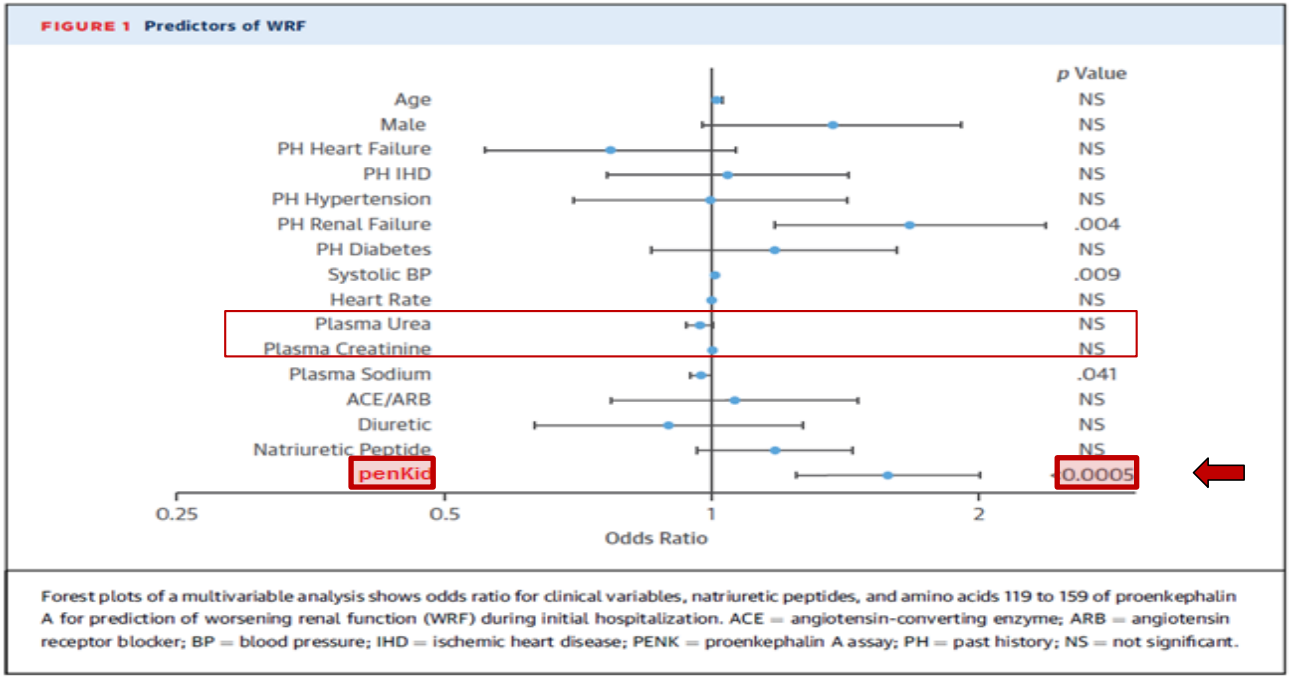
ProEnkepahlin (penKid) is the strongest predictor of WRF

in Acute Heart Failure patients

Forest plot of a multivable analysis

GREAT AHF Study
n = 1,908

- **Multicentric, observational study in patients with AHF presenting to the ED of participating university hospitals in 3 countries**
- **264 patients developed WRF (rise in plasma creatinine of >26.5 mmol/l or 50% higher than the admission value)**



Ng et al. (2017) J Am Coll Cardiol. 69(1):56-69.

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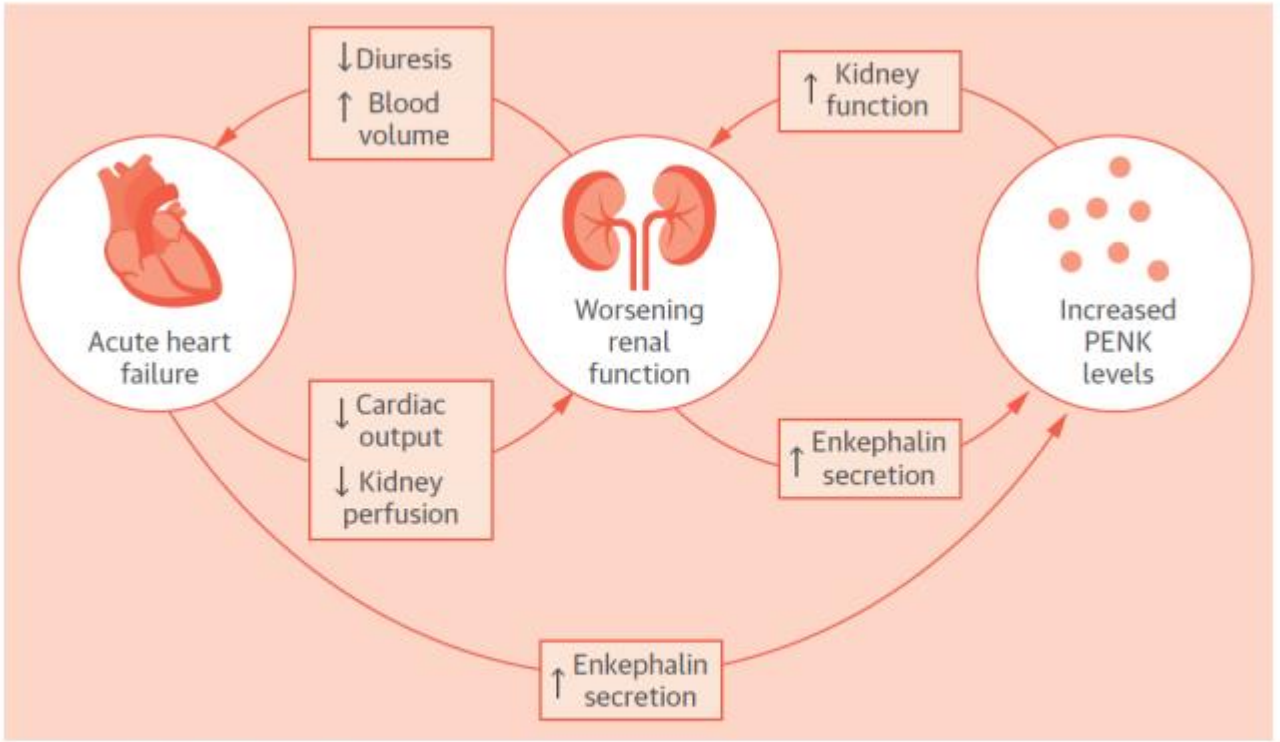
penKid in AHF

CENTRAL ILLUSTRATION Proenkephalin in Acute Heart Failure



Ng, L.L. et al. J Am Coll Cardiol. 2017;69(1):56-69.

Acute heart failure leads to reduced renal perfusion and worsening kidney function, which further exacerbates salt and fluid retention. Secretion of amino acids 119 to 159 of proenkephalin A (PENK) may be a counter-regulatory response to mitigate declining renal function, although extremely high levels may be cardiodepressive and lead to further decline in renal perfusion.

Ng et al. (2017) J Am Coll Cardiol. 69(1):56-69.

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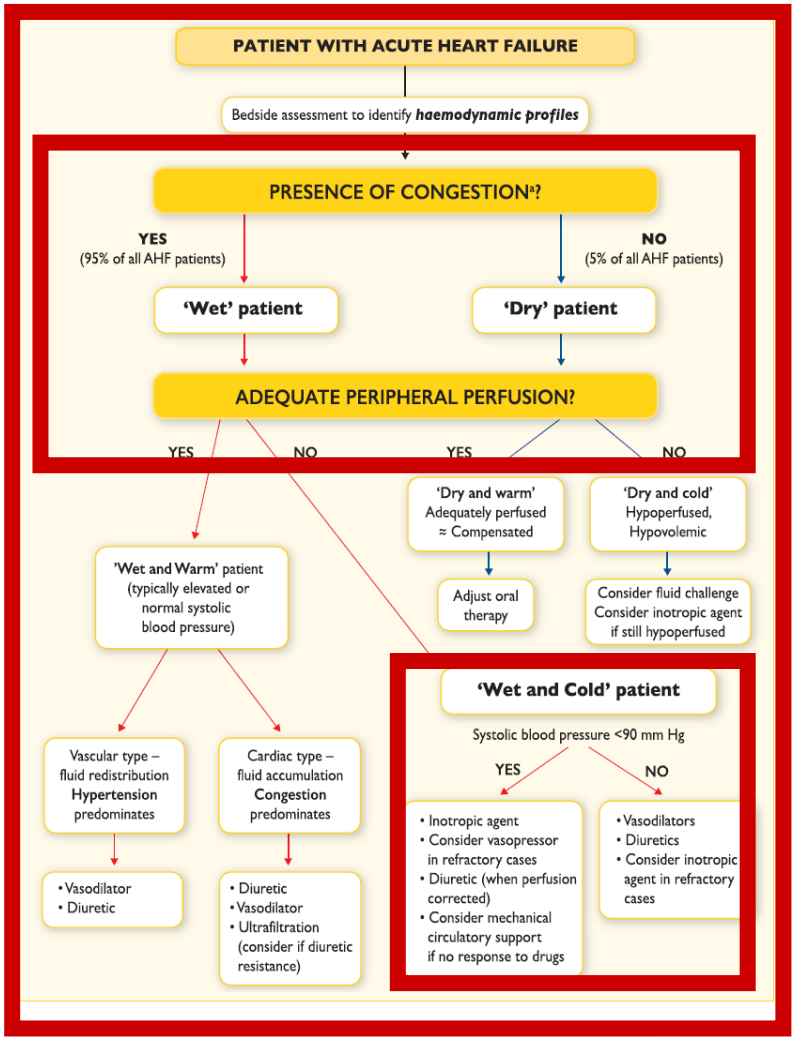
Need for Congestion and Perfusion assessment in AHF patients



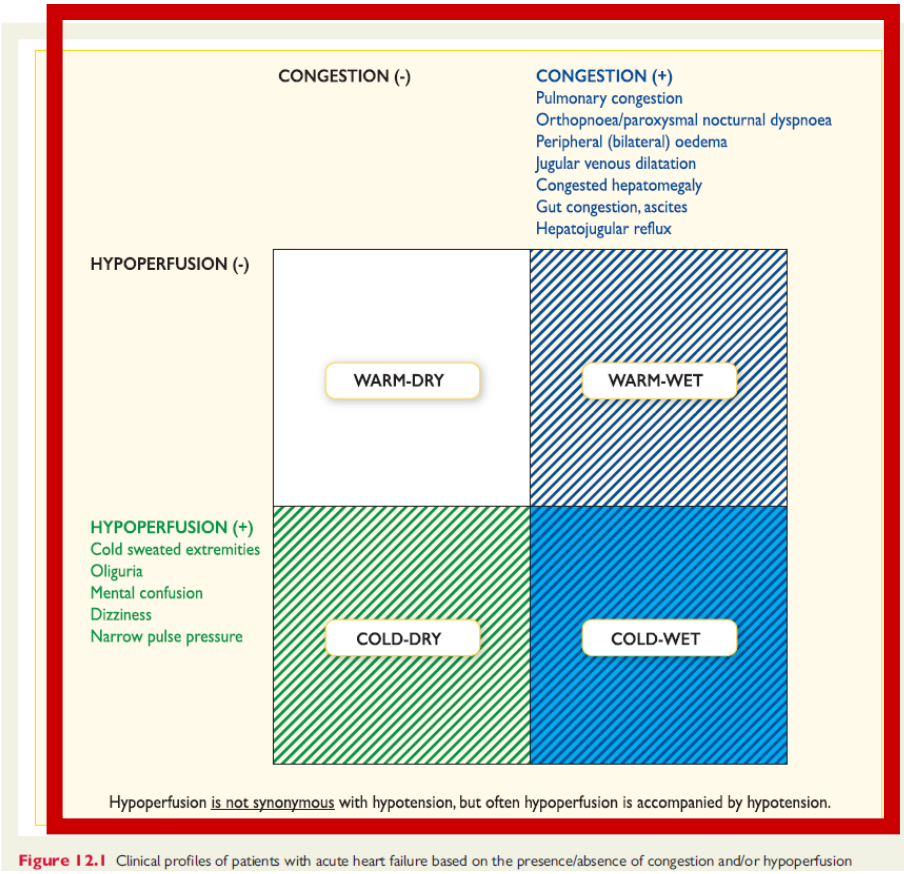


Figure 12.1 Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion

European Heart Journal Advance Access published May 20, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

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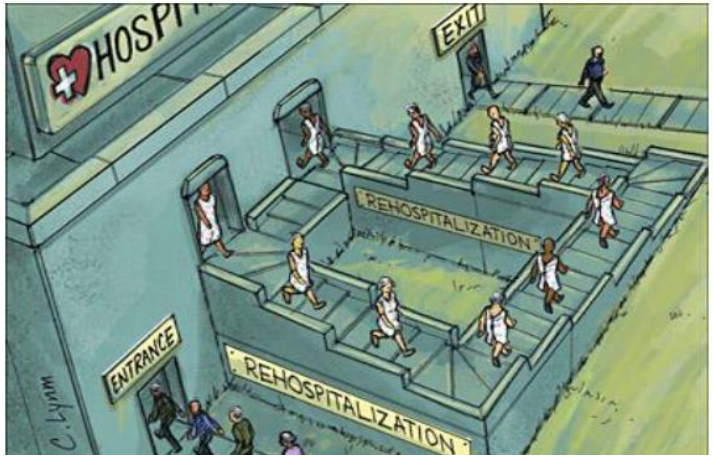
Congestion and Rehospitalization

Heart Failure Admissions- The Revolving Door



- Main reason for hospitalization for worsening HF is related to **symptoms of congestion**.

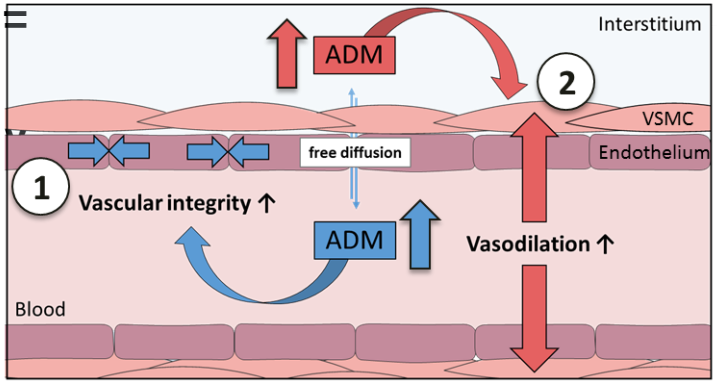
M. Gheorghiade et al. European Journal of Heart Failure (2010) 12, 423–433

Any Biomarker of Congestion?

Adrenomedullin (ADM)

Key regulator and Biomarker of vascular function & drug target for the causal treatment of vascular dysfunction

1. **Increase in plasma ADM = Response of the body to support vascular integrit**
2. **Interstitial ADM acts on vascular smooth muscle cells (VSMC) and regulates vasodilation**



Temmesfeld-Wollbrück et al. (2007) Thromb Haemost. 98(5):944-51.
Hirata et al. (1996) J Clin Endocrinol Metab. 81(4):1449-53.
Ishizaka et al. (1994) Biochem Biophys Res Commun. 200(1):642-6.

bio-ADM best reflects the degree of clinical congestion at baseline

Diagnosis

- **Severity of clinical congestion at baseline:**

OR = 1.76, 95% CI (1.56-1.99)

- **adjusted*: OR = 1.44**, 95% CI (1.25-1.65)

* adjusted for BMI, serum albumin, total cholesterol, BNP, history of atrial fibrillation and past heart failure hospitalization

Mild/moderate vs. Severe congestion at baseline

	OR (95% CI)	AUC (95% CI)
bio-ADM	**1.76 (1.56-1.99)**	**0.66 (0.63-0.69)**
Weight	1.53 (1.36-1.72)	0.60 (0.57-0.63)
BNP	**1.21 (1.09-1.35)**	**0.55 (0.52-0.58)**
Blood urea nitrogen	1.12 (1.00-1.24)	0.55 (0.50-0.56)
Creatinine	1.05 (0.95-1.17)	0.51 (0.48-0.54)
Hemoglobin	1.00 (0.89-1.12)	0.50 (0.47-0.53)
Serum Albumin	0.74 (0.66-0.83)	0.59 (0.56-0.62)
Cholesterol	0.74 (0.66-0.83)	0.59 (0.56-0.62)
...	...	...

Kremer D et al., Eur J Heart Fail. 2018 Jun 22. doi: 10.1002/ejhf.1245.
PROTECT Study: Massie et al. (2010) NEJM. 363(15):1419-28.

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Bioactive adrenomedullin, proenkephalin A and clinical outcomes in an acute heart failure setting

John Molvin,[1,2] Amra Jujic,[1,2] Silvia Navarin,[3,4] Olle Melander,[2,5] Giada Zoccoli,[3,4] Oliver Hartmann,[6] Andreas Bergmann,[6] Joachim Struck,[6] Erasmus Bachus,[2] Salvatore Di Somma,[3,4] Martin Magnusson[1,2]

Open Heart

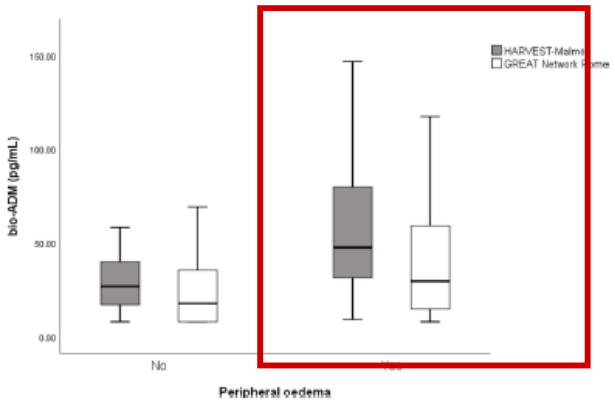

Figure 1 Distribution of bio-ADM according to signs of peripheral oedema within each centre. HARVEST-Malmö n=301, 215 events (p<0.001), GREAT Network Rome n=208, 123 events (p=0.080). bio-ADM, bioactive adrenomedullin, HARVEST, HeArt and bRain failure inVESTigation trial.

Table 4 Logistic regression model for in-hospital mortality for bio-ADM and penKid

	Univariable			Bivariable: BioADM			Bivariable: PenKid		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	1.04	0.99 to 1.09	0.067	1.54	1.03 to 2.31	0.037	2.16	1.49 to 3.13	<0.001
Sex	0.53	0.24 to 1.16	0.112	1.58	1.05 to 2.37	0.028	2.19	1.53 to 3.14	<0.001
Diabetes	0.85	0.37 to 1.92	0.689	1.52	1.01 to 2.28	0.045	2.23	1.56 to 3.19	<0.001
SBP	0.99	0.98 to 1.01	0.254	1.48	0.98 to 2.25	0.063	2.28	1.59 to 3.27	<0.001
ACE-i	0.60	0.26 to 1.36	0.217	1.49	0.99 to 2.23	0.056	2.24	1.56 to 3.21	<0.001
ARB	0.92	0.46 to 1.81	0.798	1.51	1.01 to 2.27	0.049	2.27	1.58 to 3.25	<0.001
Betablockers	0.20	0.09 to 0.46	<0.001	1.61	1.08 to 2.40	0.020	2.08	1.44 to 3.00	<0.001
Prior HF	0.54	0.25 to 1.19	0.127	1.63	1.09 to 2.46	0.018	2.22	1.56 to 3.15	<0.001
Creatinine	1.77	1.27 to 2.46	0.001	1.38	0.90 to 2.11	0.139	2.31	1.51 to 3.53	<0.001
BNP	1.28	0.85 to 1.92	0.235	1.42	0.93 to 2.15	0.105	2.29	1.56 to 3.35	<0.001
Smoking	0.43	0.10 to 1.84	0.255	1.47	0.97 to 2.21	0.067	2.25	1.57 to 3.23	<0.001
Prevalent AF	0.47	0.20 to 1.09	0.078	1.50	1.01 to 2.25	0.047	2.18	1.53 to 3.11	<0.001
Bio-ADM	1.50	1.00 to 2.26	0.051				2.19	1.52 to 3.15	<0.001

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bio-ADM: Companion Dx for ADRECIZUMAB

Targeted Therapy

Companion Diagnostic

ADRECIZUMAB

- Phase-II in Early Septic Shock & Acute Heart Failure
- **Expected Market Entry: 2021**

sphingotest® bio-ADM assay

- CE-marked IVD test for measurement of the bioactive target
- **Patients will be stratified according to their bio-ADM admission level**

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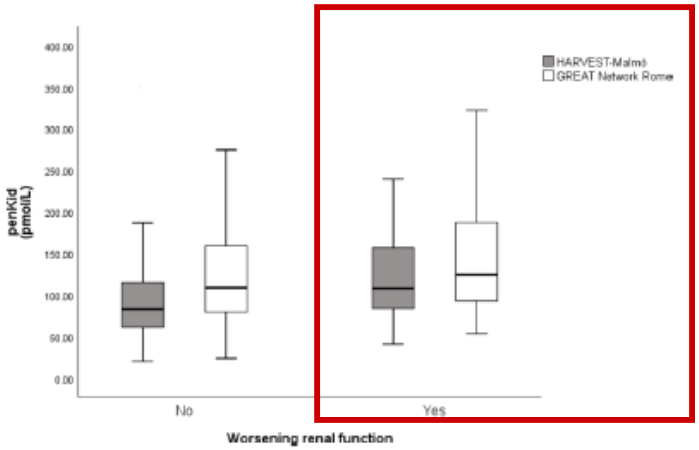

Figure 2 Distribution of penKid according to worsening renal function in each centre. HARVEST-Malmö n=323, 30 events (p=0.003), GREAT Network Rome n=178, 37 events (p=0.050). PenKid, proenkephalin A 119–159HARVEST, HeArt and bRain failure inVESTigation trial.

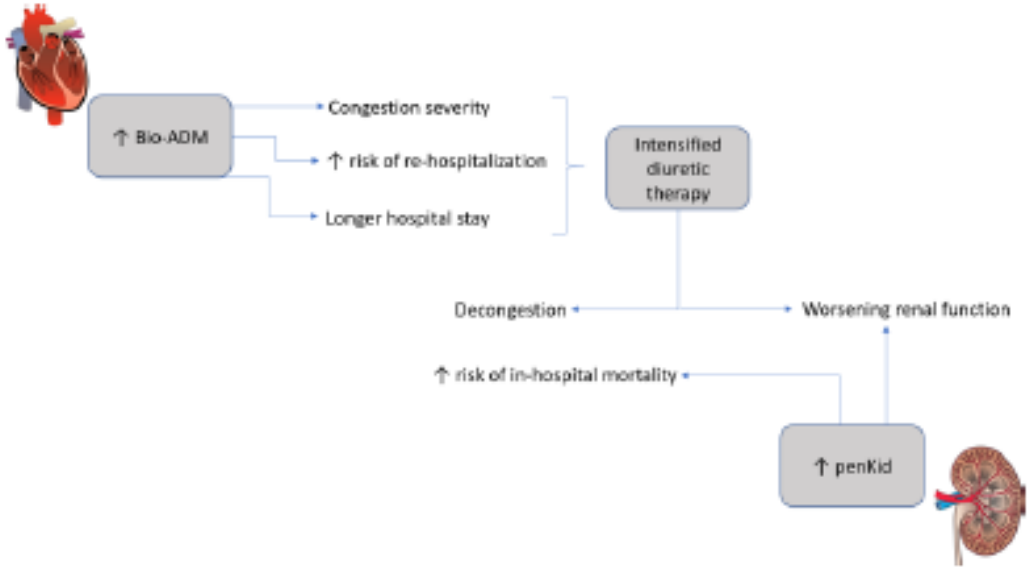

Figure 3 The clinical use of Bioactive adrenomedullin (bio-ADM) and proenkephalin A 119–159 (penKid) for management of heart failure.

Molvin J, *et al. Open Heart* 2019;6:e001048. doi:10.1136/openhrt-2019-001048

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Nexus IB 10Product Portfolio available 2019

Sphingotec Biomarker	Standard of Care Biomarker	Biomarker Combinations
sphingotest® penKid®	sphingotest® Troponin-99	sphingotest® Shortness of Breath: NT-proBNP – Troponin-99 – D-Dimer
sphingotest® bio-ADM®	sphingotest® NT-proBNP	sphingotest® 3-in-1 Cardiac: Troponin-99 – CKMB – Myoglobin
	sphingotest® D-Dimer	
	sphingotest® TSH	
	sphingotest® beta-hCG	

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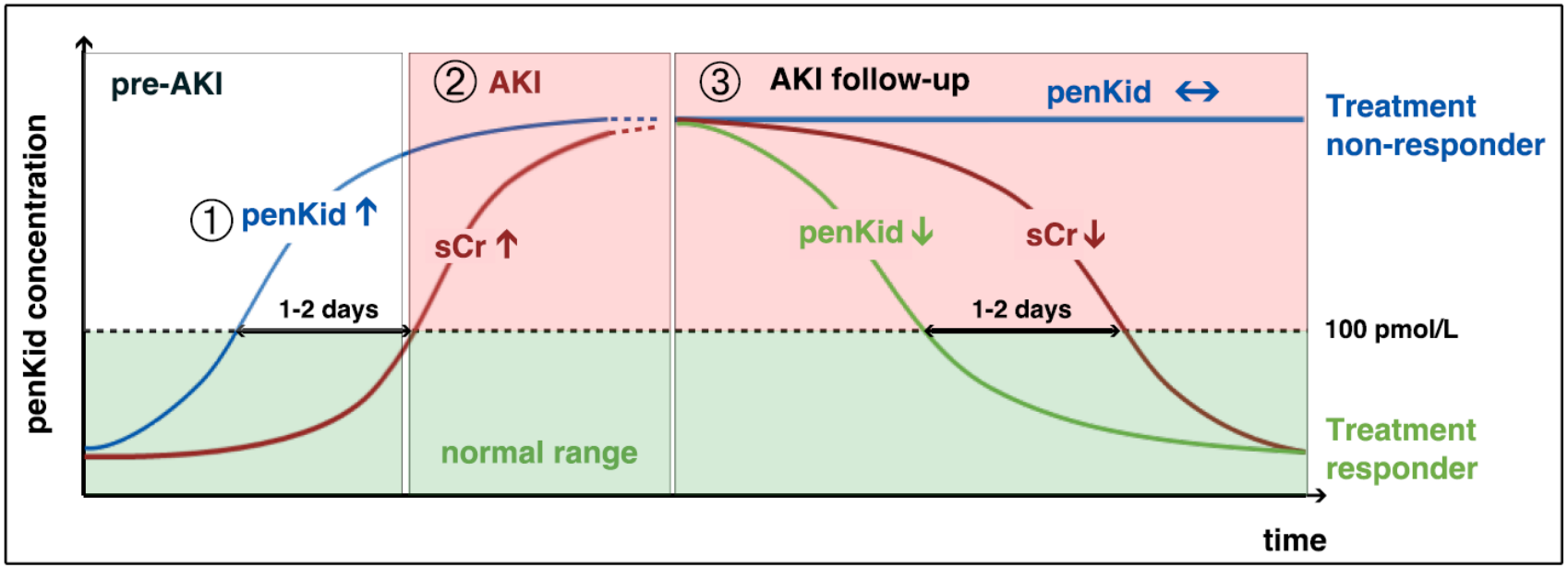
penKid® tracking AKI in AHF patients



① Relative Change

Relative changes in penKid® enables early assessment of worsening renal function

② Diagnosis

Independent of commorbidities or inflammation, penKid® is highly elevated in AKI patients

③ Monitoring

Dynamic penKid® level enables close monitoring of therapy success and kidney normalization

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Blood Purification

Editorial

Blood Purif 2014;38:I–III
DOI: 10.1159/000375470

Published online: February 13, 2015

Cell Cycle Arrest Biomarkers: New Weapons for A New Battle

Claudio Ronco

Department of Nephrology, Dialysis and Transplantation, International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy

Recently, the US Food and Drug Administration made an important step forward in the battle against AKI and its consequences. The FDA cleared the marketing of the NephroCheck Test (Astute Medical Inc., San Diego, USA), a rapid test for the quantitative measurement of the cell cycle arrest biomarkers Tissue Inhibitor of Metalloproteinase – 2 (TIMP2) and Insulin-Like Growth Factor Binding Protein – 7 (IGFBP7) [5]. The combination of the two biomarkers ([TIMP2]·[IGFBP7]) measured by the test seems to be highly predictive of which patients will develop moderate to severe AKI in the next 12–24 h.

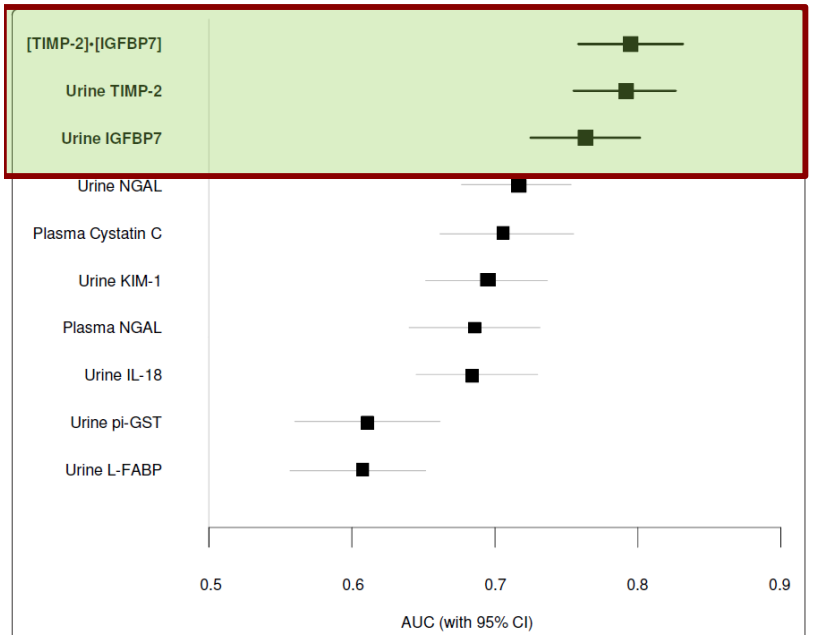
Kashani et al. Critical Care 2013, 17:R25
http://ccforum.com/content/17/1/R25

CRITICAL CARE

RESEARCH Open Access

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

Kianoush Kashani[1], Ali Al-Khafaji[2], Thomas Ardiles[3], Antonio Artigas[4], Sean M Bagshaw[5], Max Bell[6], Azra Bihorac[7], Robert Birkhahn[8], Cynthia M Cely[9], Lakhmir S Chawla[10], Danielle L Davison[10], Thorsten Feldkamp[11], Lui G Forni[12], Michelle Ng Gong[13], Kyle J Gunnerson[14], Michael Haase[15], James Hackett[16], Patrick M Honore[17], Eric AJ Hoste[18], Olivier Joannes-Boyau[19], Michael Joannidis[20], Patrick Kim[21], Jay L Koyner[22], Daniel T Laskowitz[23], Matthew E Lissauer[24], Gernot Marx[25], Peter A McCullough[26], Scott Mullaney[27], Marlies Ostermann[28], Thomas Rimmelé[29], Nathan I Shapiro[30], Andrew D Shaw[31], Jing Shi[32], Amy M Sprague[33], Jean-Louis Vincent[34], Christophe Vinsonneau[35], Ludwig Wagner[36], Michael G Walker[32], R Gentry Wilkerson[37], Kai Zacharowski[38] and John A Kellum[39*]



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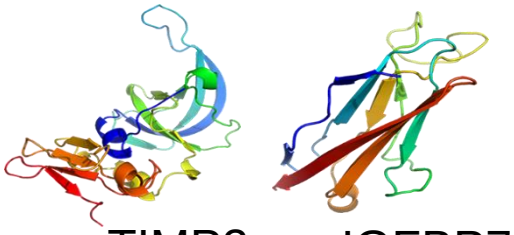
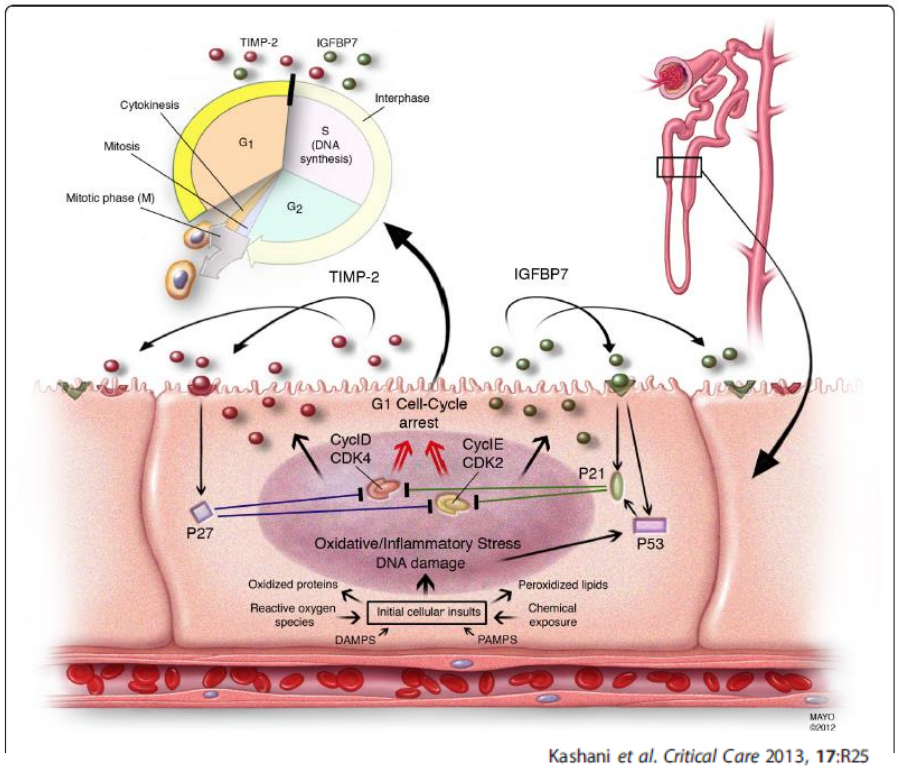


TIMP2 IGFBP7



Kashani *et al. Critical Care* 2013, **17**:R25
http://ccforum.com/content/17/1/R25

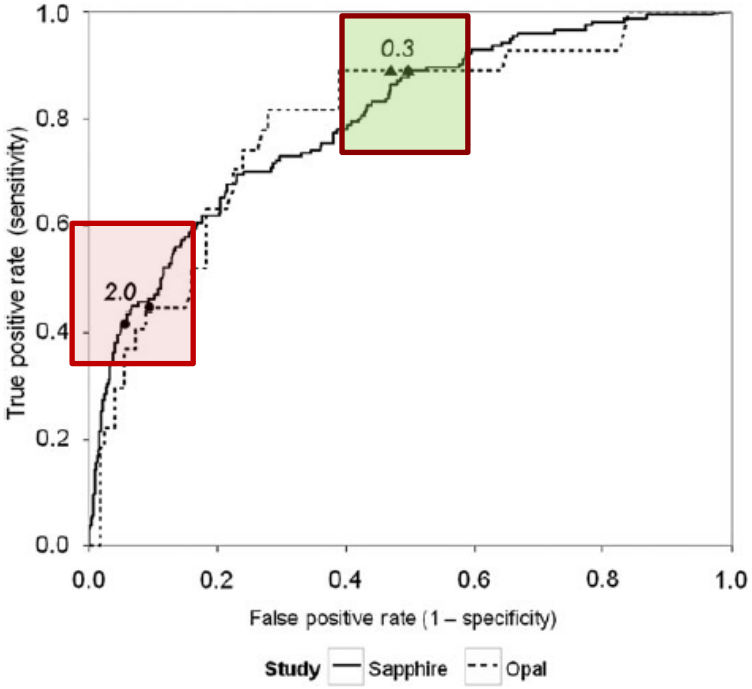
Nephrol Dial Transplant (2014) 29: 2054–2061
doi: 10.1093/ndt/gfu292
Advance Access publication 18 September 2014

ndt Nephrology Dialysis Transplantation

Original Articles

Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers

Eric A.J. Hoste[1], Peter A. McCullough[2,3], Kianoush Kashani[4], Lakhmir S. Chawla[5,6], Michael Joannidis[7], Andrew D. Shaw[8], Thorsten Feldkamp[9,10], Denise L. Uettwiller-Geiger[11], Paul McCarthy[12], Jing Shi[13], Michael G. Walker[13], John A. Kellum[14] on behalf of the Sapphire Investigators†



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BRAVA Study :Participant Centers

Konkuk University Medical Center –Seoul(**Korea**)
Ramathibodi Hospital – Bangkok(**Thailand**)
National University Hospital – Singapore(**Singapore**)
Yashoda Hospital – Secunderabad (**India)**
Prince of Wales Hospital – Sydney(**Australia)**

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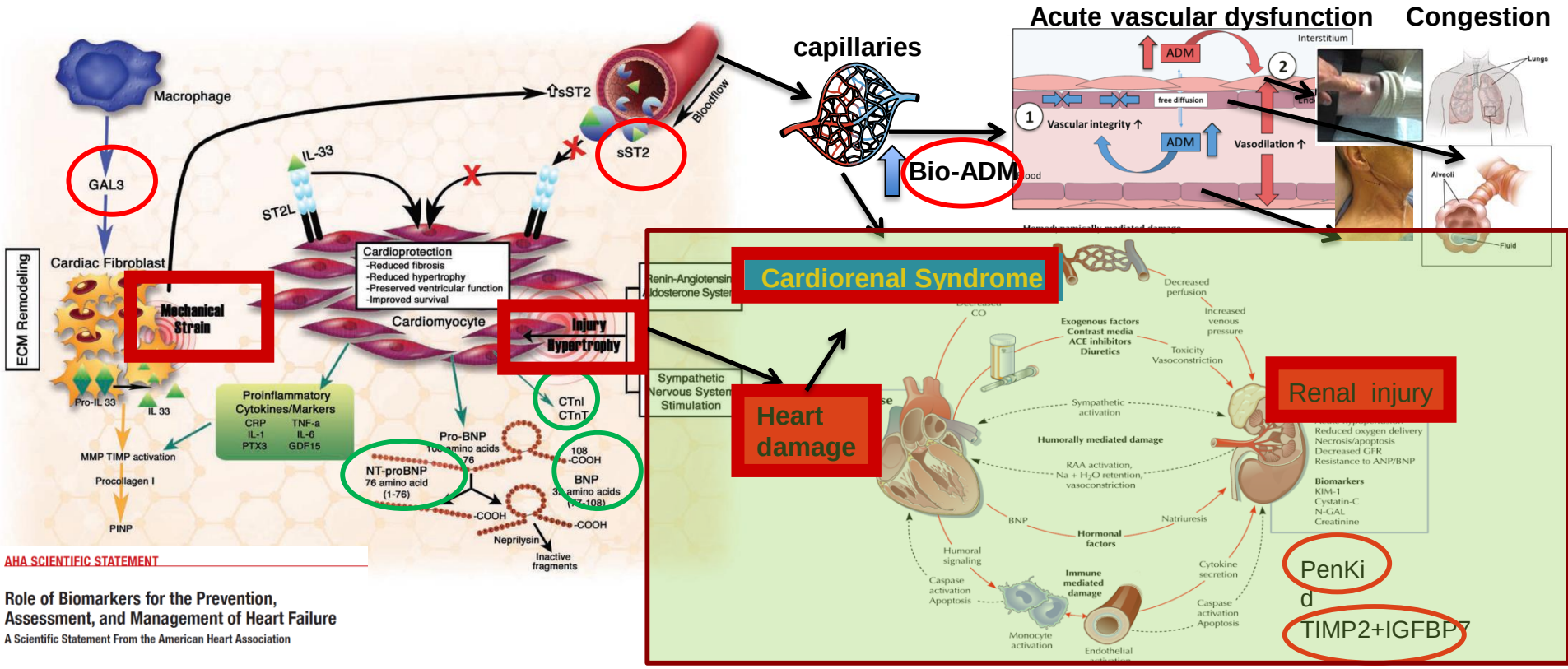
Mechanisms and responses to injury in heart failure:role of heart and Kidney biomarkers



AHA SCIENTIFIC STATEMENT

Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure

A Scientific Statement From the American Heart Association

Circulation. 2017;135 (Modified)

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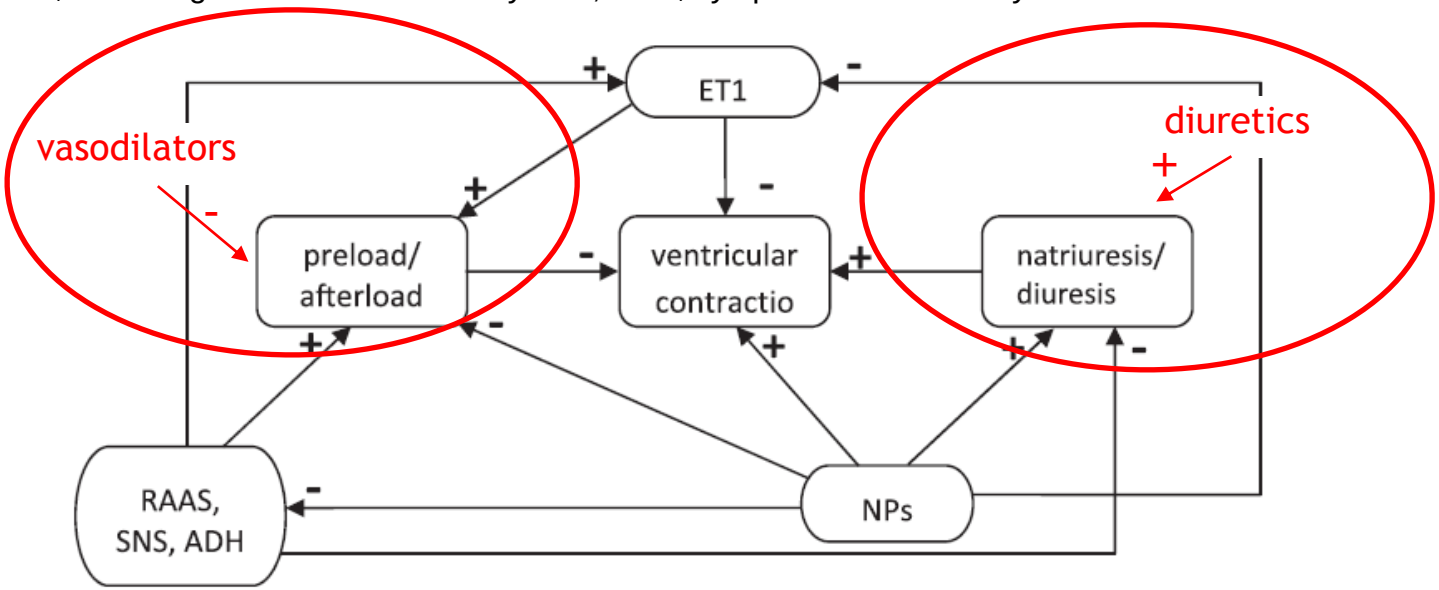
AHF: pathophysiology and treatment

Neurohormones can affect cardiac function either directly or by modulating preload, afterload, natriuresis, and diuresis.

<u>"afterload mismatch":</u>
interaction between a progressive decrease of systolic function and an acute increase of vascular resistance.

ADH, antidiuretic hormone; ET1, endothelin-1; NPs, natriuretic peptides
RAAS, renin-angiotensinaldosterone system; SNS, sympathetic nervous system



Vasodilators in ADHF • Carlson and Eckman Journal of Cardiac Failure Vol. 19 No. 7 July 2013

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Vena-Vena Ultrafiltration 24 hours monitoring in intensive Observation Unit for Cardiorenal Syndrome type I

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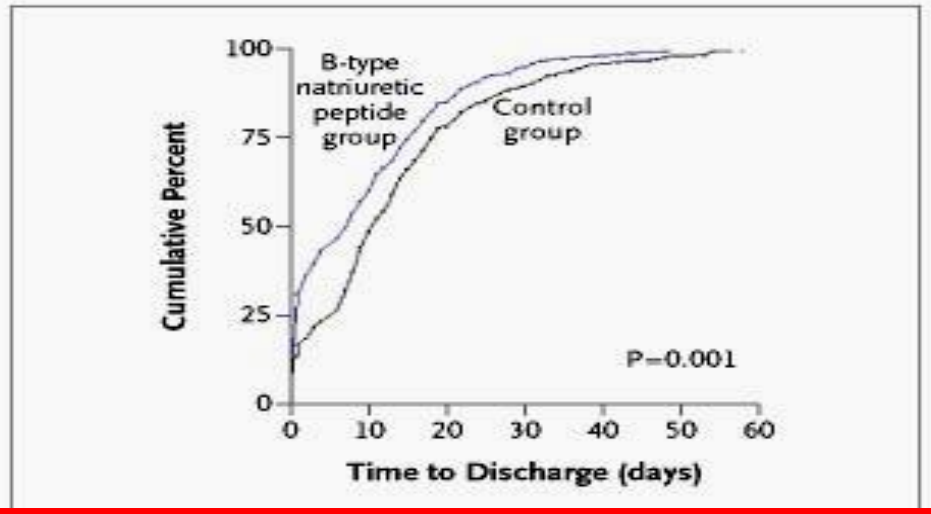
The (True) Value of Laboratory Medicine

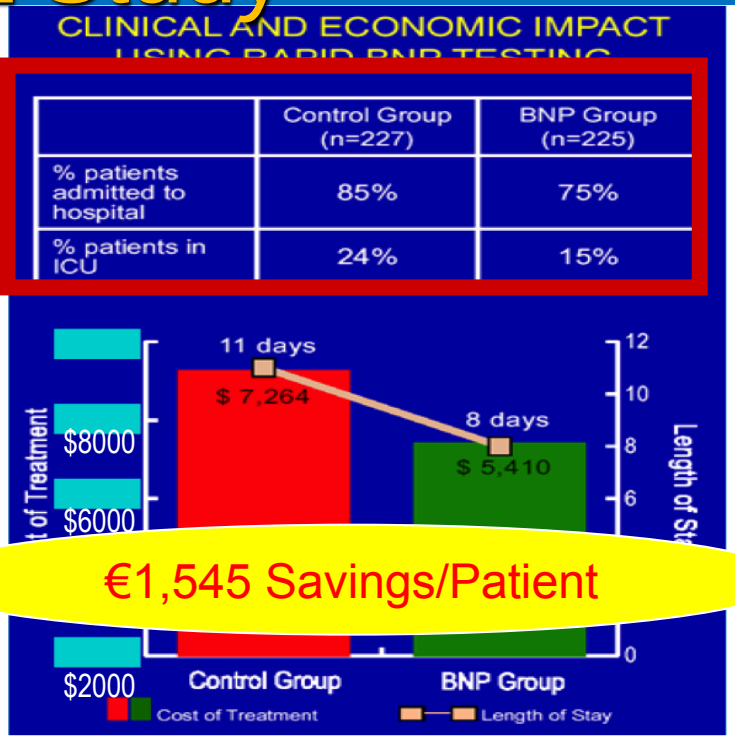
Laboratory medicine is often misquoted as having a role **in 70 percent of clinical decisions** –
but how can we measure the true value, and more importantly, **how can we improve it?**

Cost-Effectiveness of NPs use at ED: The BASEL Study



Fabourable effects on appropriate rule out and hospital admissions and LOS

Muller C, et al. *N Engl J Med.* 2004;350:647-654.



€1,545 Savings/Patient

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Hindawi
Disease Markers
Volume 2018, Article ID 4597489, 1 page
https://doi.org/10.1155/2018/4597489

Editorial

Biomarkers in Emergency Medicine

Patrizia Cardelli,[1] **Mina Hur**,[2] **and Salvatore Di Somma**[3]

[1]*Sapienza University of Rome, Rome, Italy*
[2]*Konkuk University, Seoul, Republic of Korea*
[3]*Facoltà di Medicina e Psicologia, Roma, Italy*

Researchers navigate the ocean of biomarkers searching for proper targets and optimal utilization of them. Emergency medicine builds up the front line to maximize the utility of clinically validated biomarkers and is the cutting edge field to test the applicability of promising biomarkers emerging from thorough translational researches. The role of biomarkers in clinical decision making would be of greater significance for identification, risk stratification, monitoring, and prognostication of the patients in the critical- and acute-care settings. No doubt basic research to explore novel biomarkers in relation to the pathogenesis is as important as its clinical counterpart. This special issue includes five selected research papers that cover a variety of biomarker- and disease-related topics.

There is still no substitute for a "Hands on" open-ended history and physical exam- all the while , demonstrating compassion and empathy

Biomarkers should be used wisely

- *They should be used <u>as a tool **together**</u>*
  <u>with clinical experience;</u>
- *You need to know:*
- *clinical indications,*
  cut-off ranges and limitations of the biomarker

A fool with a tool is still a fool...

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AISC STRUCTURE MULTICULTURAL

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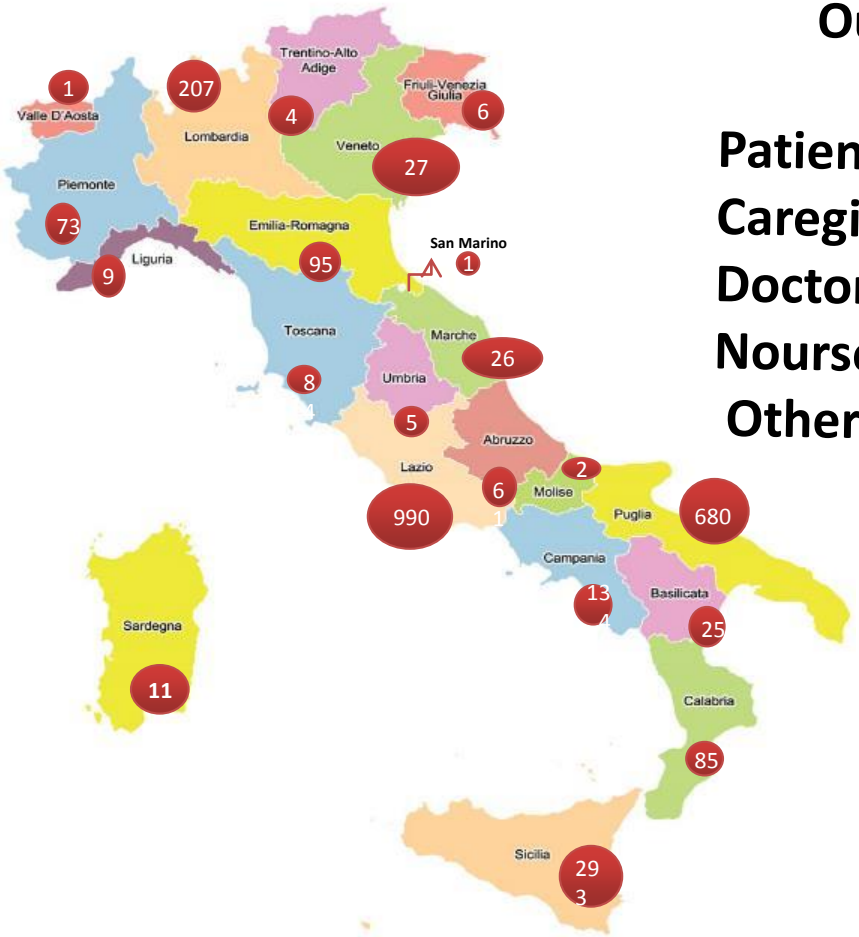

Our Associates:

Patients:3879
Caregivers:706
Doctors :103
Nourses: 91
Others:330

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• AIMS AND OBJECTIVES

• **With the Final goal to Ameliorate relationship between clinicians and Patients with Heart Failure**

1) **Promote information on heart failure, raising awareness of the disease and ensure the best prevention; Perform an educational function aimed at developing the ability to recognize the disease and follow the correct care, to improve the quality of patient life;**

2) **Improve the goals of medical research also in light of the practical needs of patients;**

3) **Create a national referral network for patients, to ensure the possibility of sharing information and receiving support throughout the territory;**

4) **Bring the attention of institutions and public opinion to the pathology and patients, to improve prevention, protection and care interventions;**

Encourage contact with patient associations at international level

•

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Perform an educational function: Books,Website,Video,Traveling vehicle Meetings,

http://associazioneaisc.org/

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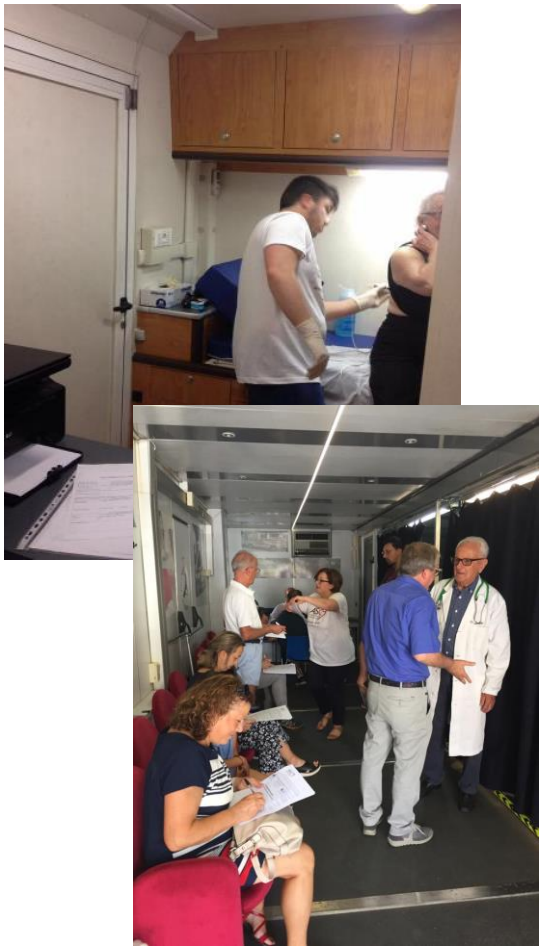
THE MOBILE CLINIC:
Different way of approach to Patients with Heart Failure



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