Future Diagnostic & Therapeutic Targets in Cardiorenal Syndromes

(Biomarkers, advanced monitoring, advanced imaging, novel therapies)

EDGAR V. LERMA, MD

Clinical Professor of Medicine

Section of Nephrology

UIC/ Advocate Christ Medical Center

Oak Lawn, IL

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Disclosure of Interests

- Honoraria: UpToDate, McGraw-Hill Publishing, Elsevier Publishing, Springer Publishing, Wolters-Kluwer Publishing, ACP Smart Medicine, Emedicine
- Editorial Boards: American Journal of Kidney Diseases, ASN Kidney News, Clinical Journal of the American Society of Nephrology, Clinical Reviews in Bone and Mineral Metabolism, International Urology and Nephrology, Journal of Clinical Lipidology, Prescribers Letter, Renal and Urology News, Reviews in Endocrinology and Metabolic Disorders, Seminars in Dialysis
- Speaker/ Advisory Board: Astute Medical, Mallinckrodt, Otsuka Pharmaceuticals, ZS Pharma

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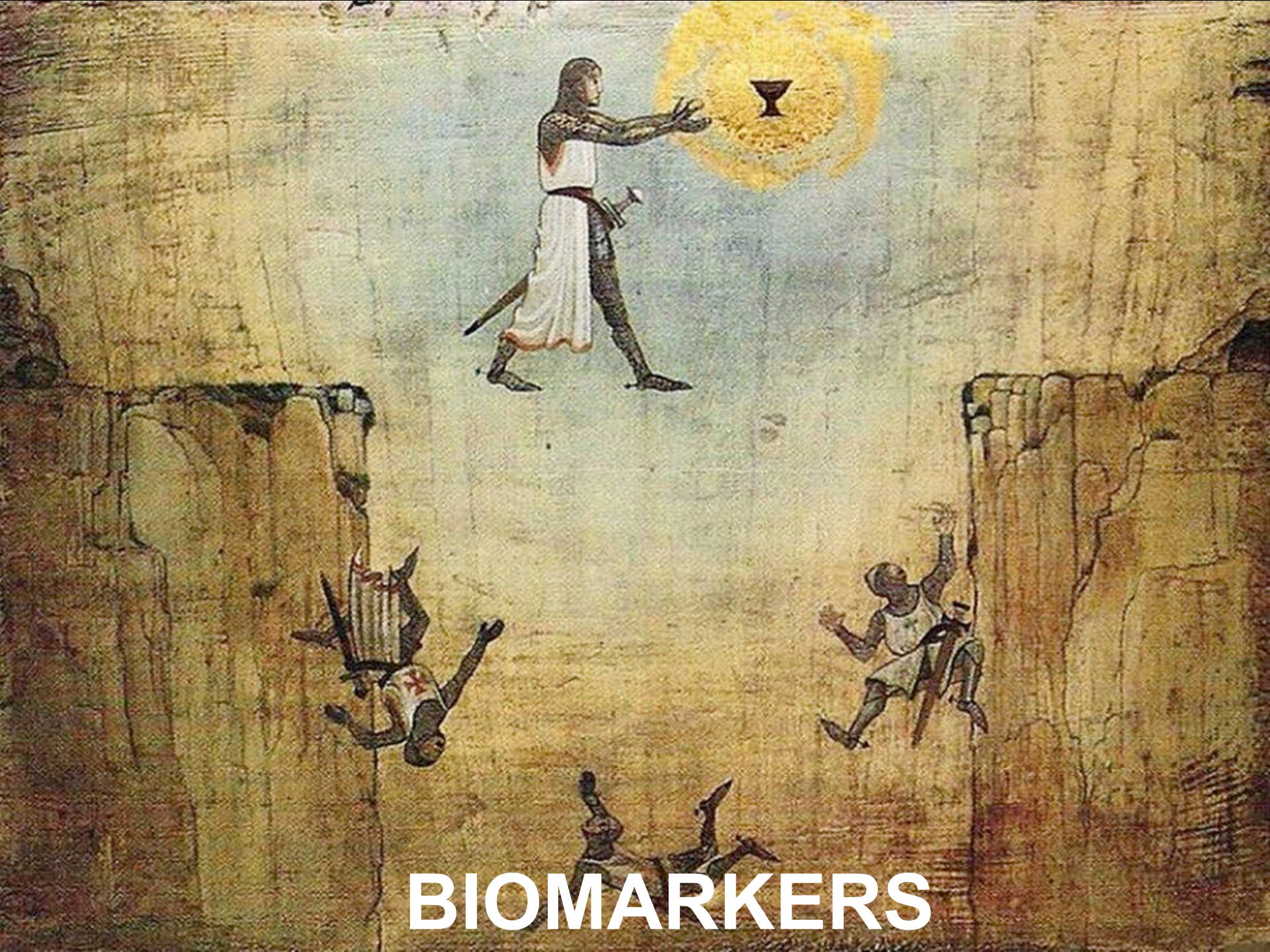
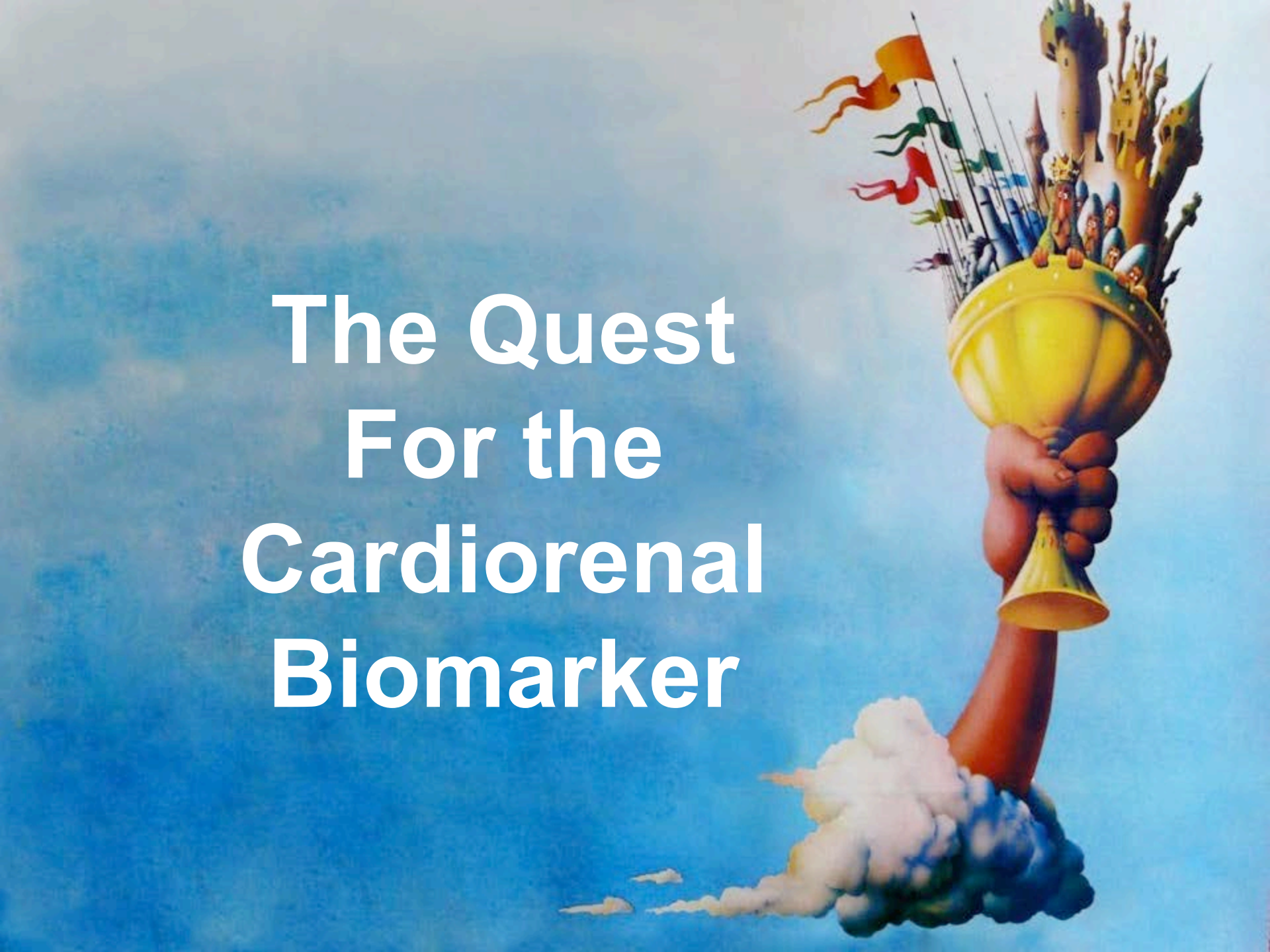

BIOMARKERS

The Quest For the Cardiorenal Biomarker



BIOMARKERS AND ADVANCED MONITORING

Table 1. Characteristics of an ideal blood or urinary biomarker

- Easy to measure with validated, reproducible technologies
- Stable in the blood or urine for time consistent with routine clinical use
- Devoid of interferences with other substances present in the biological fluid
- Unaffected by chemical composition of the fluid (e.g., urinary ionic strength and pH)
- Reflects risk, injury, outcome, and chronic sequelae with high sensitivity and high specificity
- Changes in measurements reflect efficacy of an intervention and/or recovery
- Identifies the specific site of injury (e.g., kidney tubule segment, glomerulus, endothelium, or interstitium)
- Understandable function of the marker in the kidney

BIOMARKERS AND ADVANCED MONITORING

Table 2. Classification of biomarkers

- **Predictive**—Identify subpopulations of subjects at higher risk for developing an outcome or more likely to respond to a therapy
- **Prognostic**—Informs likely course of disease progression or outcome
- **Diagnostic**—Characterizes onset and severity of a disease state
- **Efficacy**—Tracks the effectiveness of a treatment to mitigate a disease process
- **Pharmacodynamic**—Measures whether a particular biological response has occurred in response to a treatment
- **Surrogate**—Substitutes for a clinical end point ("a characteristic or variable that reflects how a patient feels, functions, or survives")

BIOMARKERS AND ADVANCED MONITORING

Evidence-Based Nephrology

Biomarkers for the Early Detection and Prognosis of Acute Kidney Injury

Rakesh Malhotra and Edward D. Siew[†‡§]*

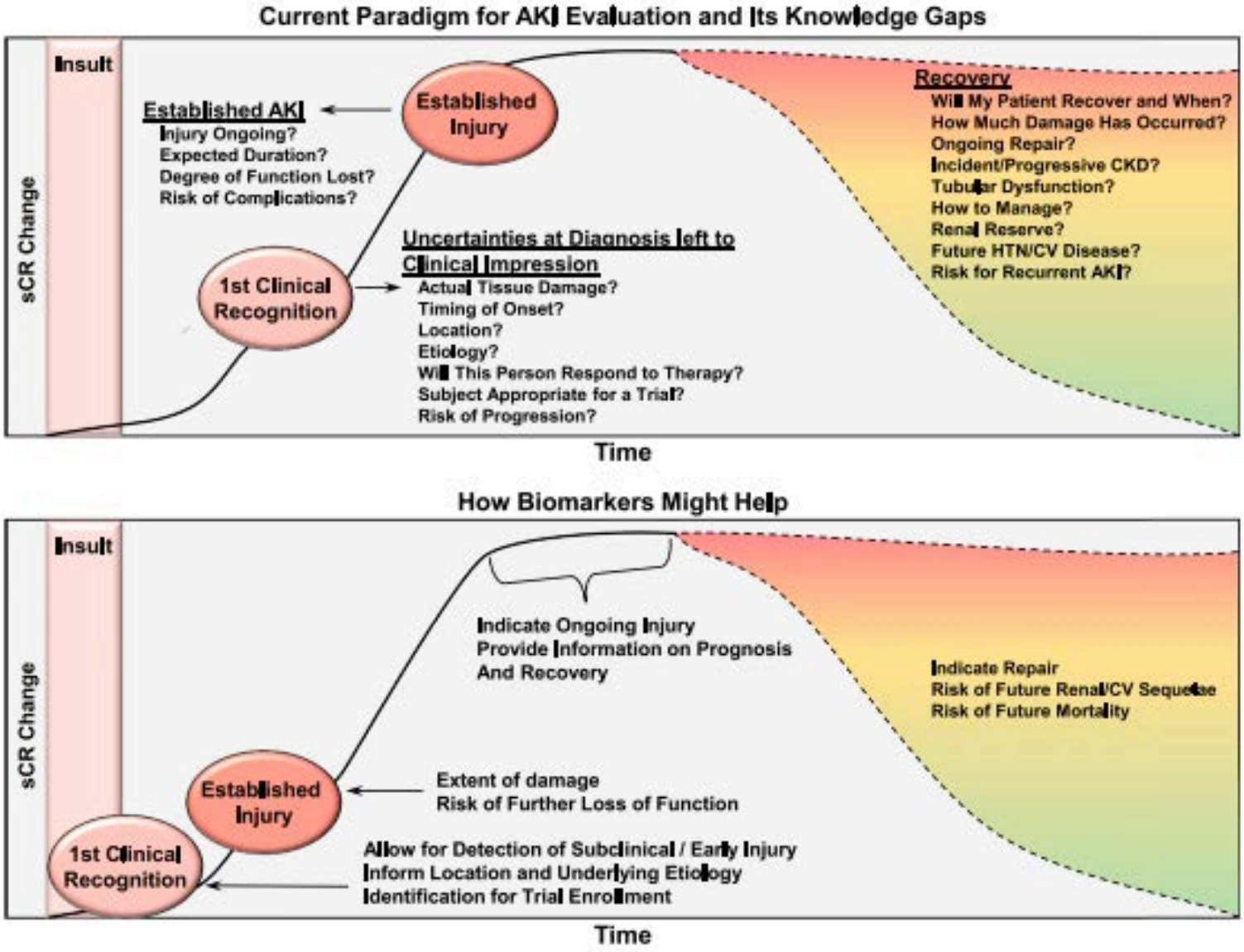
Abstract

AKI is an increasingly common disorder that is strongly linked to short- and long-term morbidity and mortality. Despite a growing heterogeneity in its causes, providing a timely and certain diagnosis of AKI remains challenging. In this review, we summarize the evolution of AKI biomarker studies over the past few years, focusing on two major areas of investigation: the early detection and prognosis of AKI. We highlight some of the lessons learned in conducting AKI biomarker studies, including ongoing attempts to address the limitations of creatinine as a reference standard and the recent shift toward evaluating the prognostic potential of these markers. Lastly, we suggest current gaps in knowledge and barriers that may be hindering their incorporation into care and a full ascertainment of their value.

Clin J Am Soc Nephrol ■: ●●●–●●●, 2016. doi: 10.2215/CJN.01300216

*Division of Nephrology and Hypertension, Department of Medicine, University of California San Diego, San Diego, California; †Division of Nephrology and

BIOMARKERS AND ADVANCED MONITORING



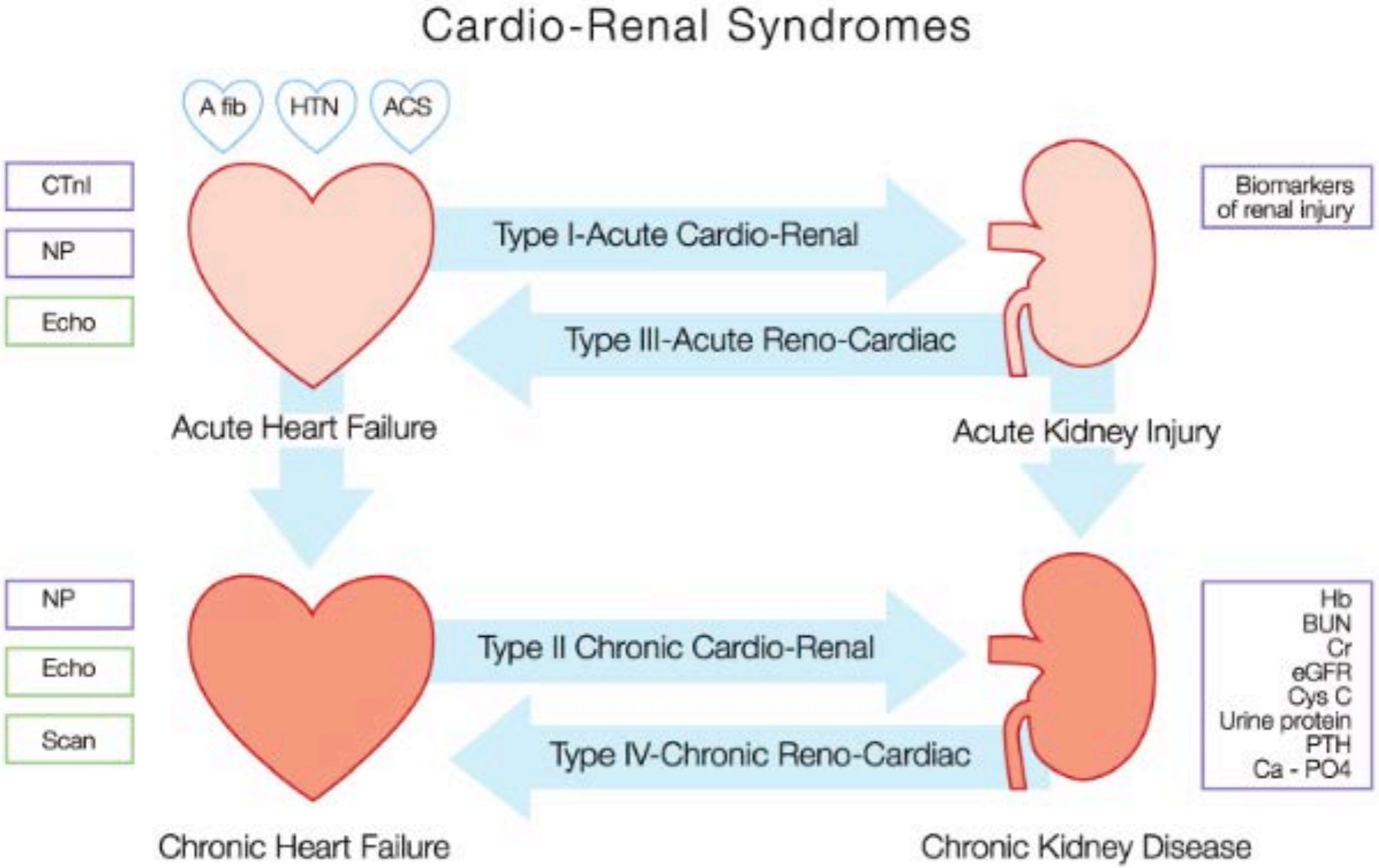


Fig. 2. Biomarkers that are currently used in various cardiorenal syndromes. Acute coronary syndrome (ACS), atrial fibrillation (A fib), blood urea nitrogen (BUN), calcium (Ca), creatinine (Cr), cystatin C (Cys C), estimated glomerular filtration rate (eGFR), haemoglobin (Hb), hypertension (HTN), natriuretic peptides (NP), parathyroid hormone (PTH), phosphate (PO4).

Journal of Cardiovascular Diseases & Diagnosis
McCullough et al., J Cardiovasc Dis Diagn 2015, 3:5
http://dx.doi.org/10.4172/2329-9517.1000221

Review Article Open Access

Cardiorenal Syndromes: Advances in Determining Diagnosis, Prognosis, and Therapy

Peter A. McCullough[1*], James A. Tumlin[2], Harold Szerlip[3], Krishnaswami Vijayaraghavan[4], Sathya Jyothinagaram[5], John F. Rausch Jr[6], Bhupinder Singh[7], Jun Zhang[8] and Mikhail Kosiborod[9]

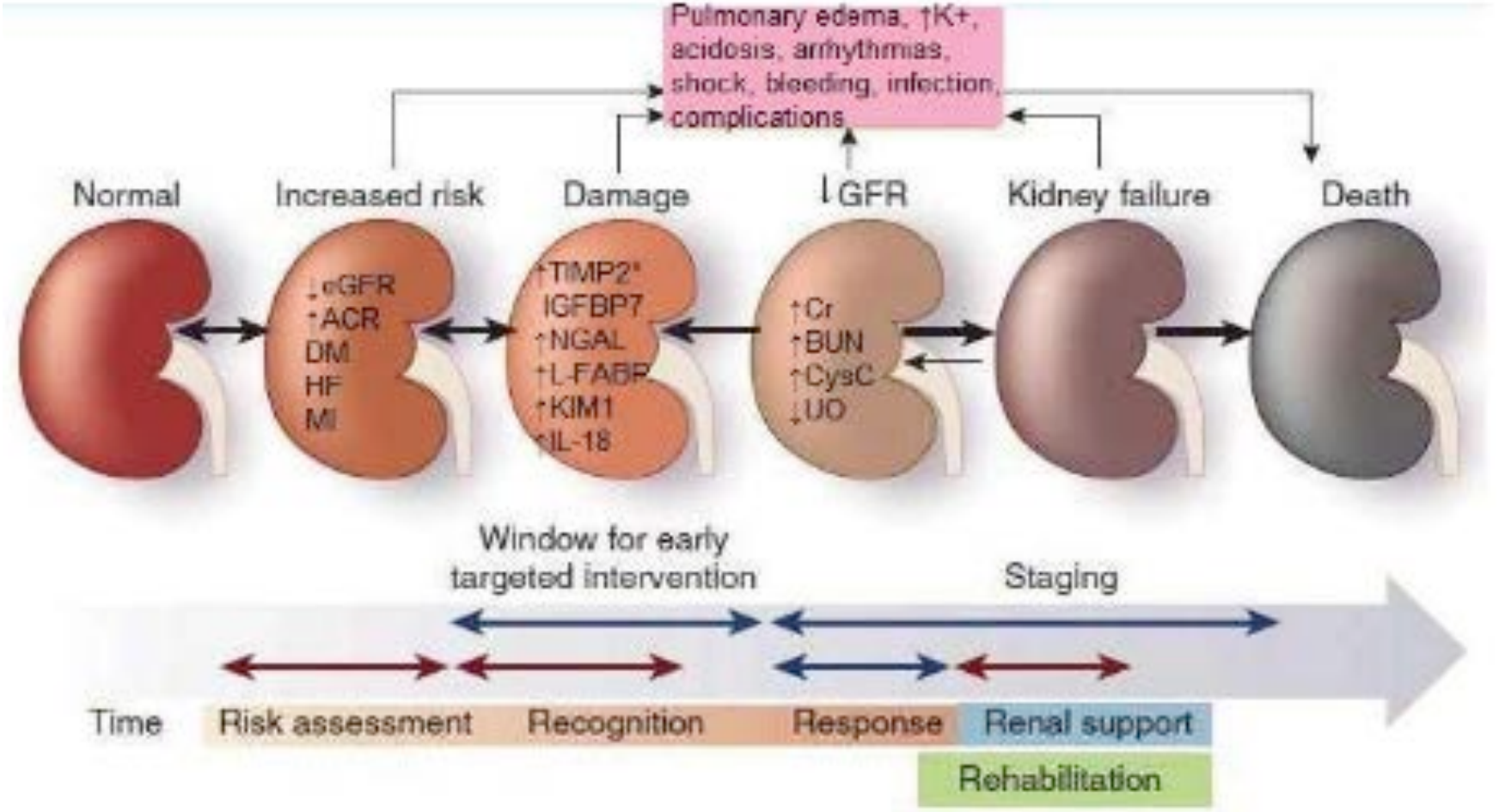


Figure 6: Continuum of kidney function in the setting of CRS.

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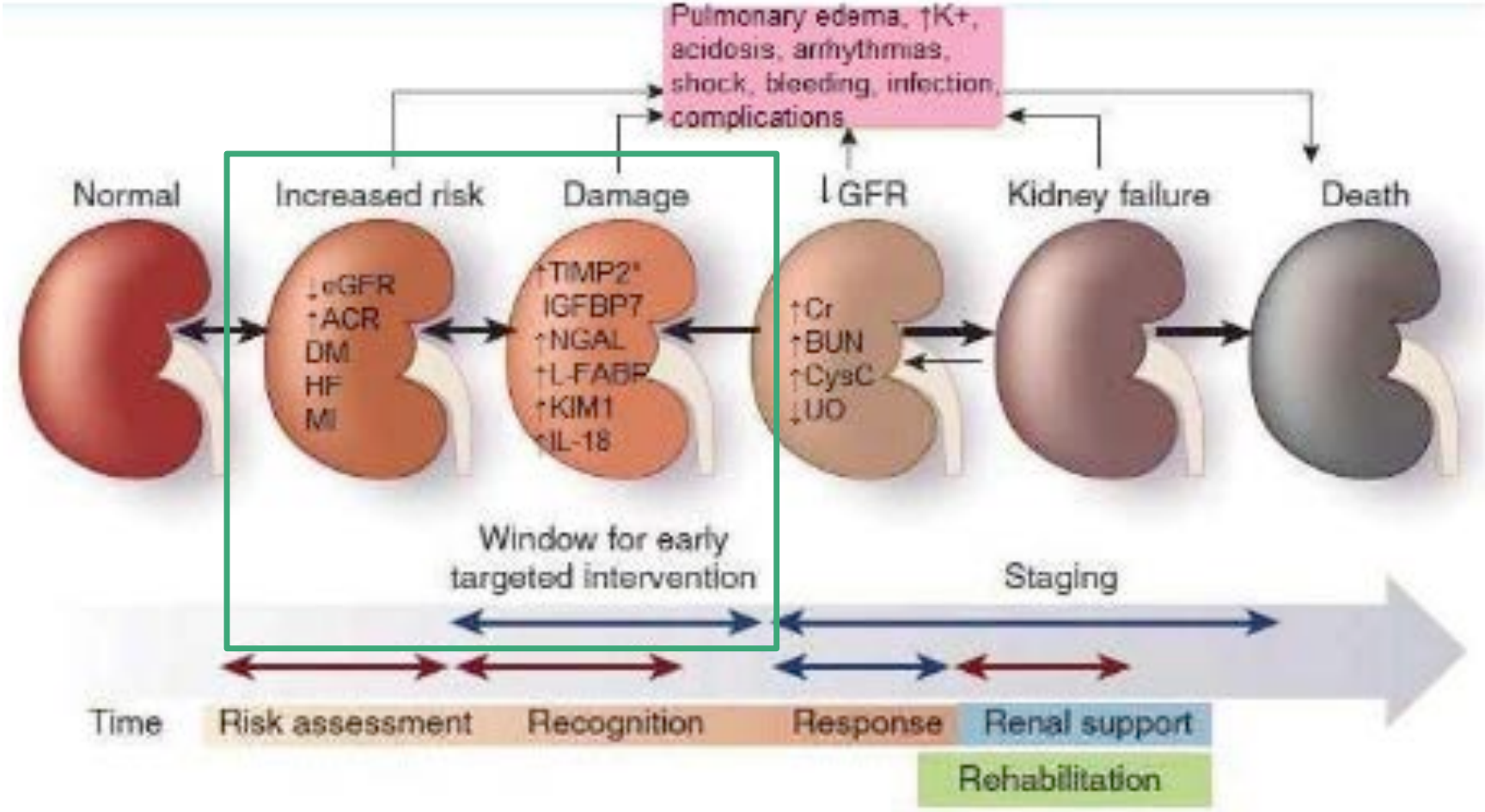


Figure 6: Continuum of kidney function in the setting of CRS.

Biomarkers of acute kidney injury and associations with short- and long-term outcomes [version 1; referees: 2 approved]

Jennifer A. Schaub, Chirag R. Parikh

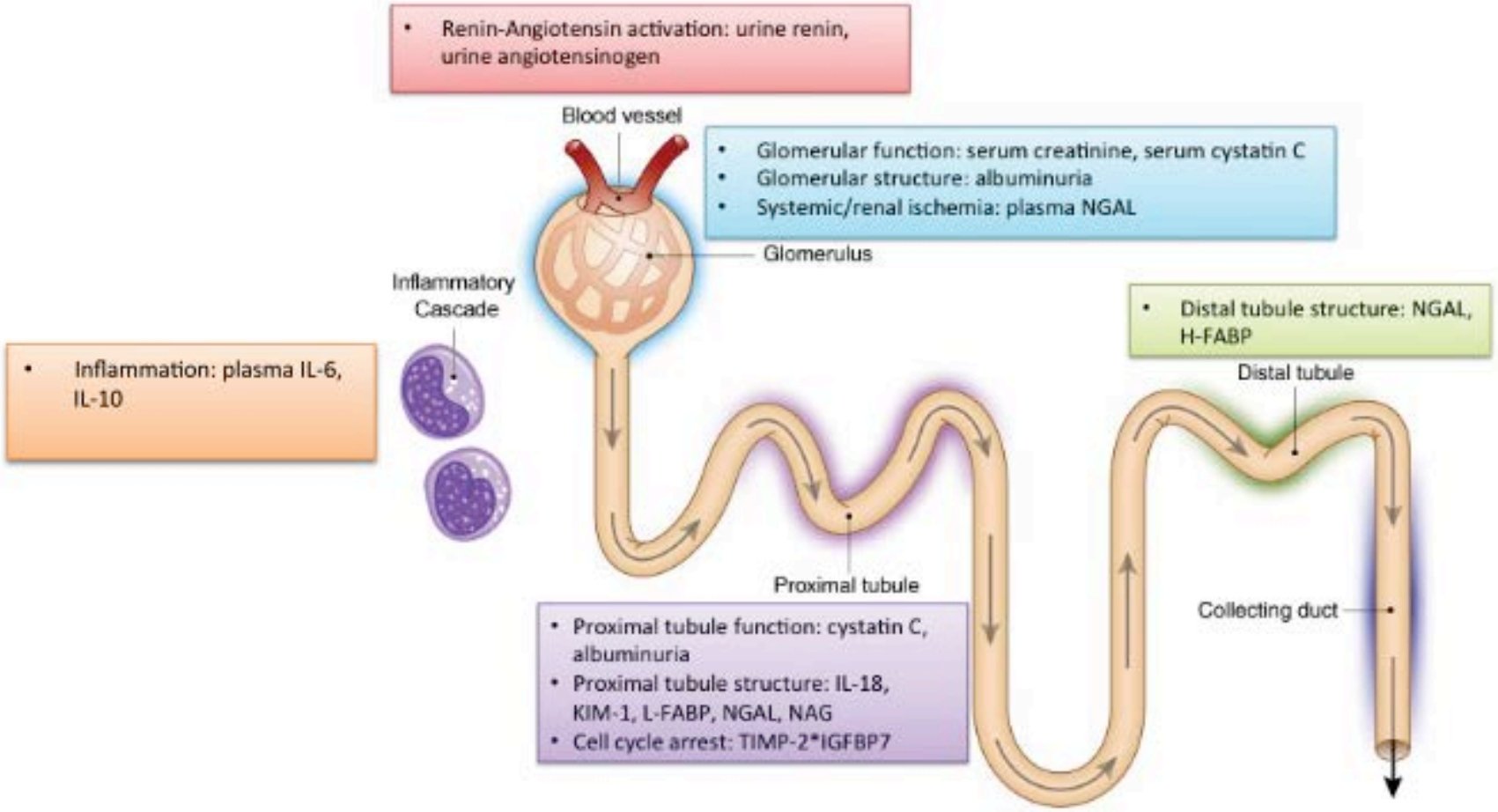


Figure 1. Physiology of biomarkers of AKI. Adapted from 73. AKI, acute kidney injury; H-FABP, heart fatty acid binding protein; IGFBP-7, insulin-like growth factor binding protein 7; IL-6, interleukin-6; IL-10, interleukin-10; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor metalloproteinase-2.

BIOMARKERS

CARDIAC BIOMARKERS

- Natriuretic peptides
- Cardiac Troponins
- Cytokines
- Myeloperoxidase

RENAL BIOMARKERS

- GFR
  - Serum Creatinine/ Creatinine Clearance
  - BUN
  - Cystatin C
- Glomerular Permeability
  - Albuminuria
- Tubulointerstitial injury
  - NAG
  - **KIM-1**
  - **NGAL**
  - IL-18
  - **FABP**
  - Klotho
- OTHER Biomarkers
  - hs-CRP
  - Procalcitonin
  - Adrenomedullin
  - Copeptin
  - ADMA

RENAL BIOMARKERS

TUBULAR INJURY: Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- 25 kDa protein
- Found in granules of neutrophils
- Steady state
  - Serum: < 20 ng/mL
  - Urine: < 20 ng/mL
- Elevated in chronic inflammatory conditions
- Freely filtered in the glomerulus
- Nearly completely resorbed in the PCT (unless tubular damage exists)

- KIDNEY INJURY
  - **Serum and urine NGAL are precipitously increased, peaking within 24-48 hours following injury**
- Involved in Fe transport
  - Plasma levels are inversely related with anemia indices

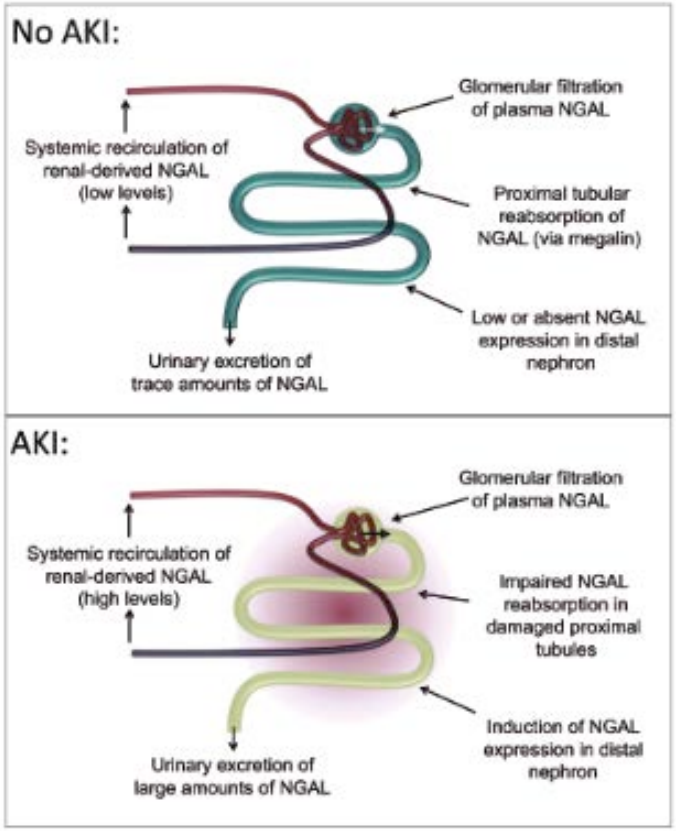
RENAL BIOMARKERS

TUBULAR INJURY: Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury—where do we stand today?

Kai M. Schmidt-Ott[1,2]

[1]Experimental and Clinical Research Center, Charité—Universitätsmedizin Berlin, Berlin, Germany and [2]Max-Delbrück Center for Molecular Medicine, Berlin, Germany



Urine NGAL reflects primarily intra-renal production from the thick ascending loop of Henle and collecting ducts

Systemic NGAL reflects extra-renal synthesis and potentially some renal-derived NGAL

RENAL BIOMARKERS

TUBULAR INJURY: Neutrophil Gelatinase-Associated Lipocalin (NGAL)

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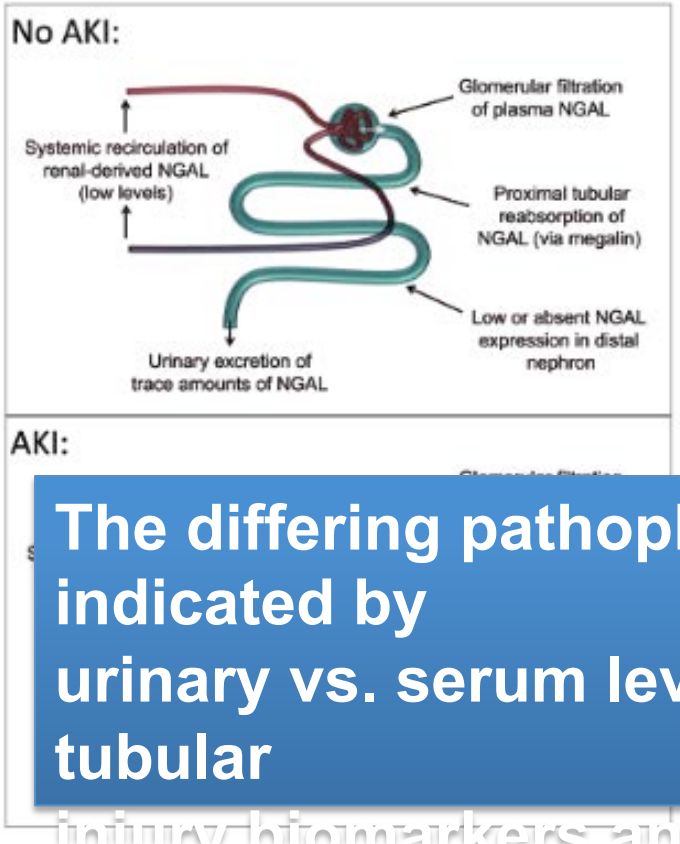


Urine NGAL reflects primarily intrarenal production from the thick ascending loop of Henle and collecting ducts

Systemic NGAL reflects

The differing pathophysiology of renal damage indicated by urinary vs. serum levels of NGAL is unique among tubular

injury biomarkers and may ultimately prove vital for

RENAL BIOMARKERS

TUBULAR INJURY: Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- Early biomarker for **ischemic and nephrotoxic AKI**
- Increases significantly in **AKI** (but not in controls)
- Increases during the **first 24-48 hours before the onset of rise in creatinine**
- NGAL levels on the day of transplant **predicts DGF and requirement for RRT (2-4 days later)**

RENAL BIOMARKERS

TUBULAR INJURY: Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- Urine NGAL predicts the **severity of AKI and dialysis requirement in the pediatric population**
- **Measurements may be influenced by co-existing variables, e.g., systemic infections, underlying CKD**

RENAL BIOMARKERS

TUBULAR INJURY: Neutrophil Gelatinase-Associated Lipocalin (NGAL)

There are currently 3 analytic platforms for NGAL measurement in patient samples

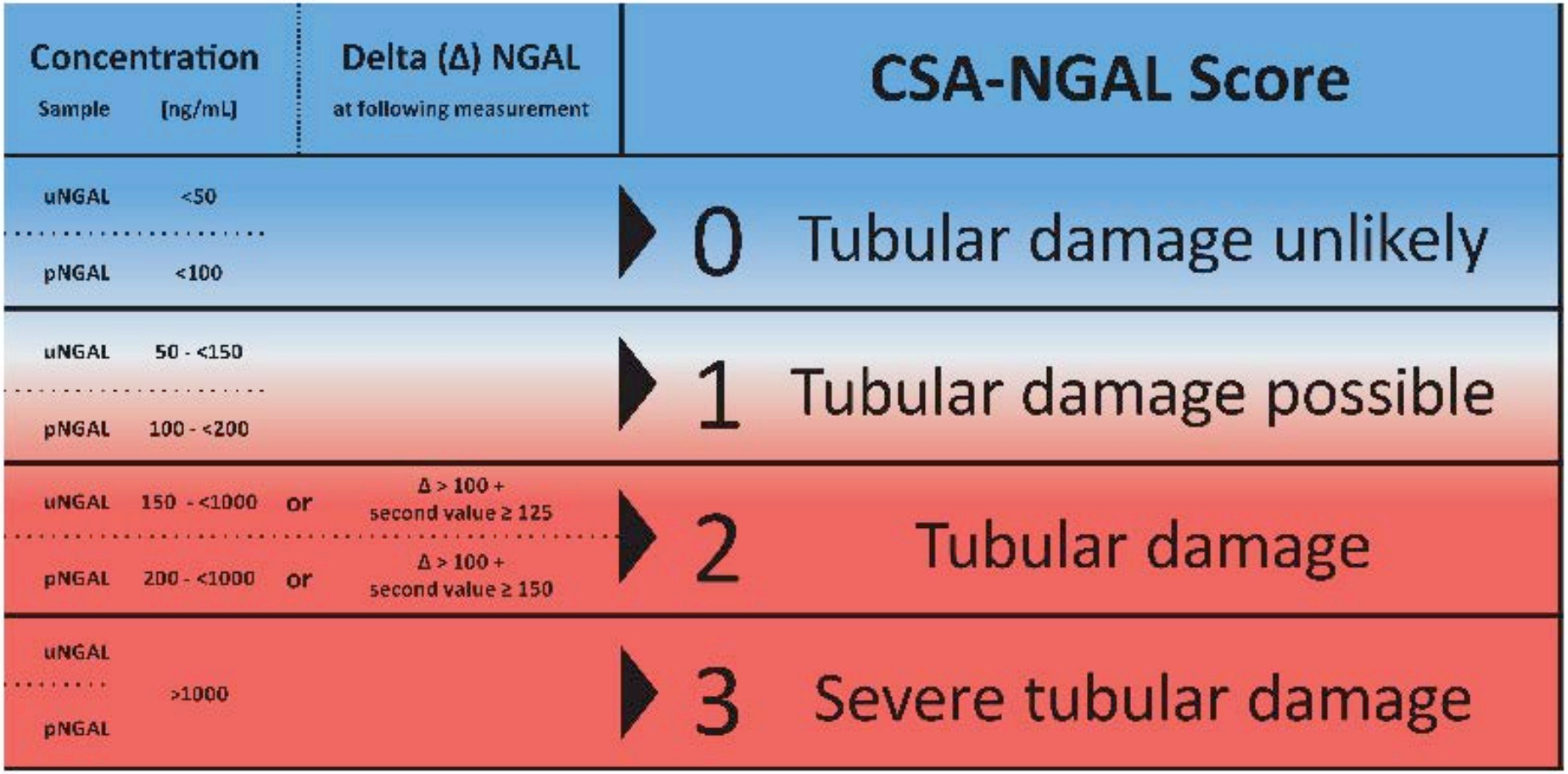
(Results available within 15-30 mins)

- Alere Triage NGAL Test
  - POC immunoassay for plasma
- Abbott Diagnostics ARCHITECT
  - Urine immunoassay
- Bioporto Diagnostics NGAL TestTM
  - Particle-enhanced turbidimetric immunoassay for urine and plasma

COMMERCIALLY-AVAILABLE BIOMARKERS

The cardiac surgery–associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage

Hilde R. H. de Geus, MD, PhD,[a] Claudio Ronco, MD, PhD,[b] Michael Haase, MD, PhD,[c] Laurent Jacob, MD, PhD,[d] Andrew Lewington, MD, PhD,[e] and Jean-Louis Vincent, MD, PhD[f]



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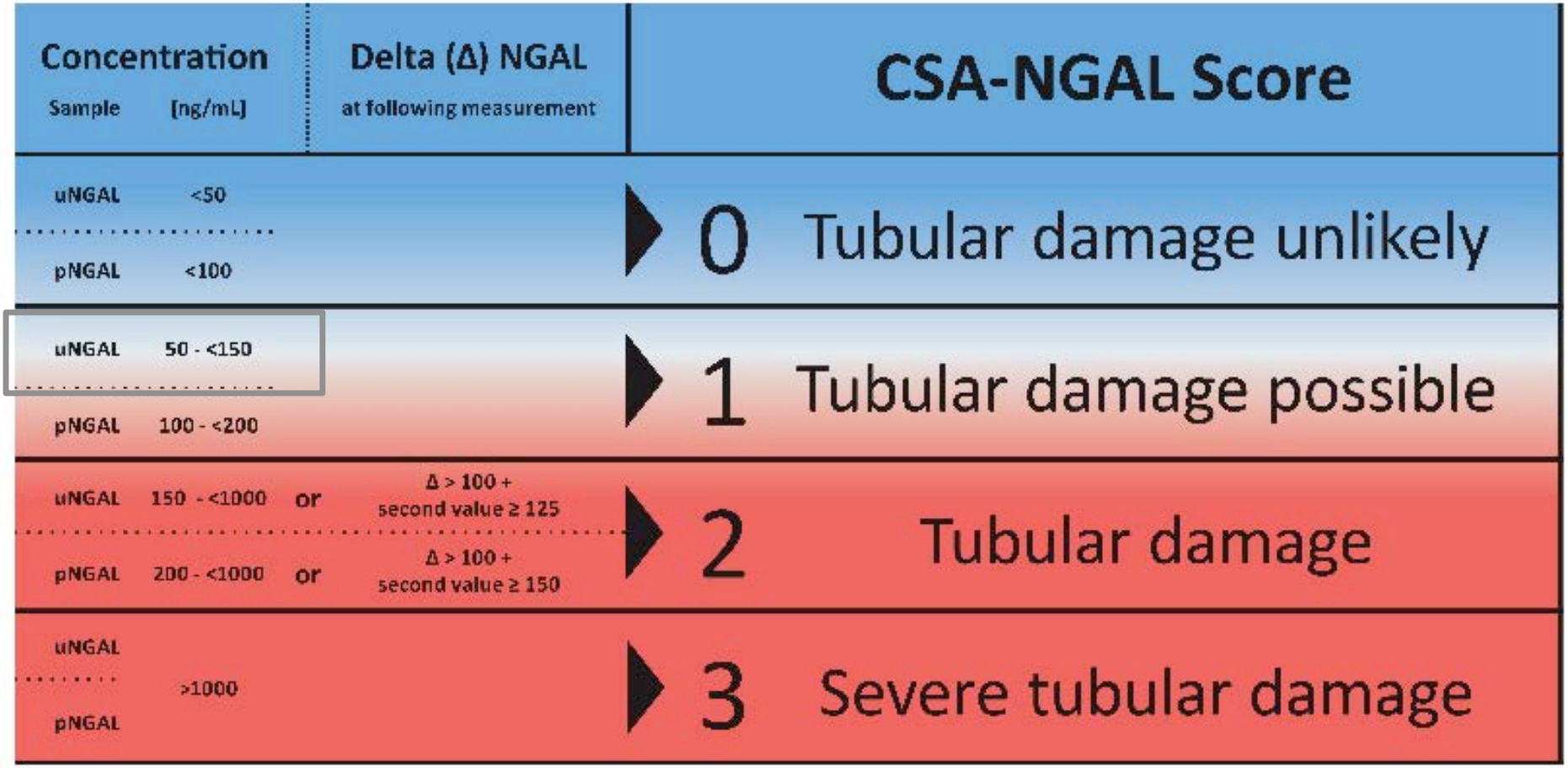


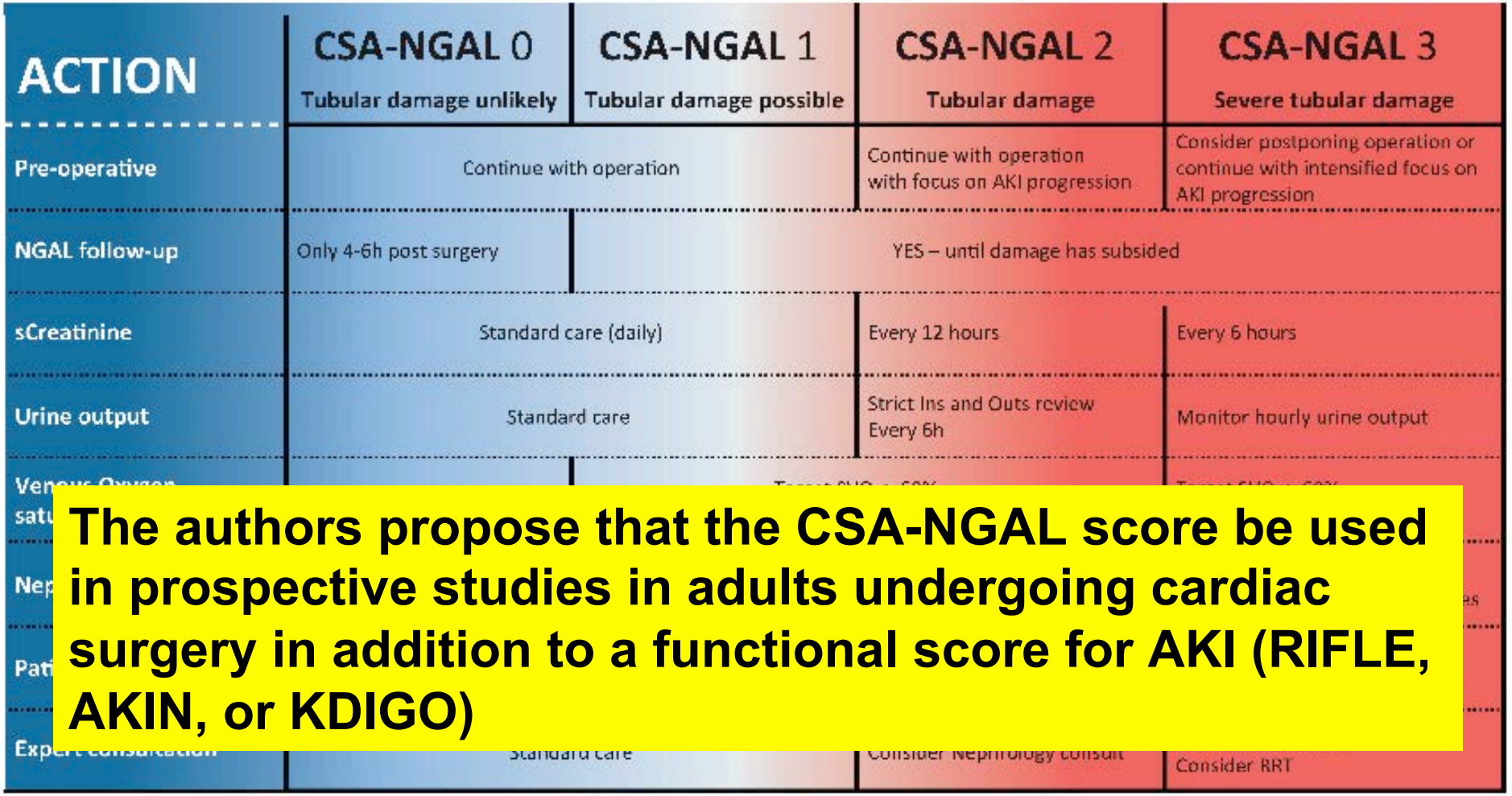
CSA-NGAL Score based management considerations

Acute kidney tubular damage in cardiac surgery

ACTION	CSA-NGAL 0 Tubular damage unlikely	CSA-NGAL 1 Tubular damage possible	CSA-NGAL 2 Tubular damage	CSA-NGAL 3 Severe tubular damage
Pre-operative	Continue with operation		Continue with operation with focus on AKI progression	Consider postponing operation or continue with intensified focus on AKI progression
NGAL follow-up	Only 4-6h post surgery	YES – until damage has subsided		
sCreatinine	Standard care (daily)		Every 12 hours	Every 6 hours
Urine output	Standard care		Strict Ins and Outs review Every 6h	Monitor hourly urine output
Venous Oxygen saturation	Standard Care	Target SVO_2 > 60% Review SVO_2 trend every 3h		Target SVO_2 > 60% Hourly review of SVO_2 trend
Nephrotoxic medication	Standard care		Consider alternatives Adjust dosing	Move to alternatives if possible Close attention to renal responses
Patient location	Discharge to floor from ICU as per standard care	Discharge to floor from ICU	Consider step-down unit	Consider keeping patient in ICU
Expert consultation	Standard care		Consider Nephrology consult	Nephrology consult Consider RRT

CSA-NGAL Score based management considerations

Acute kidney tubular damage in cardiac surgery



The authors propose that the CSA-NGAL score be used in prospective studies in adults undergoing cardiac surgery in addition to a functional score for AKI (RIFLE, AKIN, or KDIGO)

RENAL BIOMARKERS

TUBULAR INJURY: Kidney Injury Molecule-1 (KIM-1)

- Type 1 cell membrane glycoprotein
- Expressed in regenerating proximal tubular cells and facilitates phagocytosis of neighboring apoptotic tubular epithelial cells
- **Not expressed in the normal kidney**

- **Within 24-hours of tubular injury:**
  - **KIM-1 increases dramatically** (normal < 200 ng/g/Cr) and sheds its ectodomain which is **detected in the urine**

RENAL BIOMARKERS

TUBULAR INJURY: Kidney Injury Molecule-1 (KIM-1)

- Excellent predictive marker for the **detection of acute tubular injury in chronic HF after the suspension and introduction of diuretic therapy**
- KIM-1 levels increased significantly as early as 8 hours after diuretics were discontinued, remained elevated within 3 days, and then returned to normal levels as early as 4 hours after furosemide was resumed.

RENAL BIOMARKERS

TUBULAR INJURY: Kidney Injury Molecule-1 (KIM-1)

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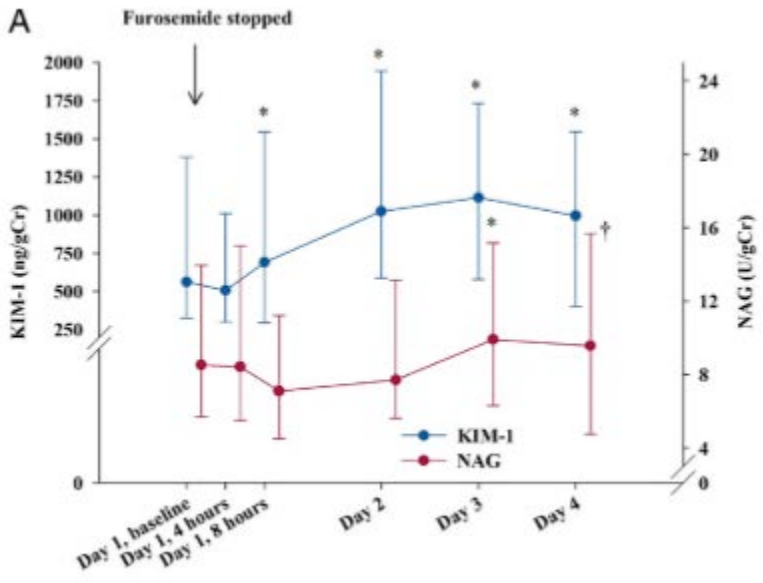
Heart Failure

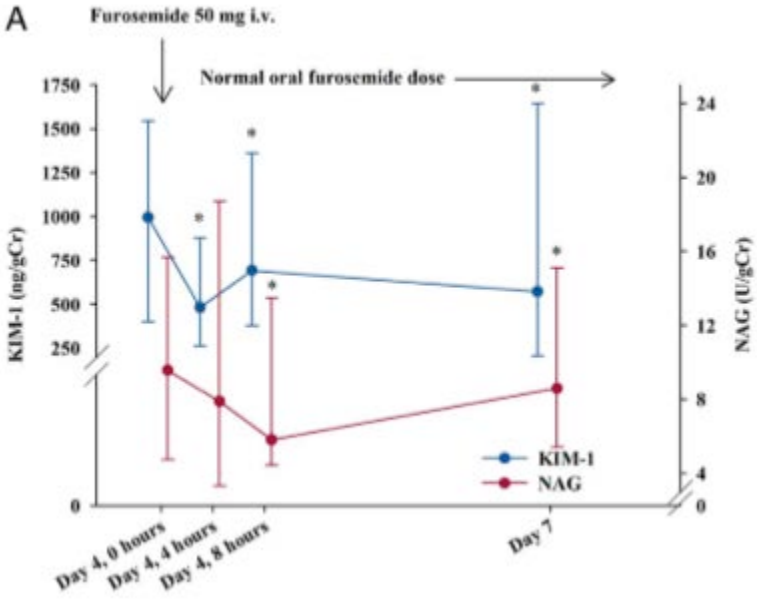
Volume Status and Diuretic Therapy in Systolic Heart Failure and the Detection of Early Abnormalities in Renal and Tubular Function

Kevin Damman, MD, PHD,* Marie J. Ng Kam Chuen, MD,§ Robert J. MacFadyen, MD, PHD,§
Gregory Y. H. Lip, MD,§ David Gaze, PHD,†‖ Paul O. Collinson, MD,†‖
Hans L. Hillege, MD, PHD,*†‖ Wim van Oeveren, PHD,‡ Adriaan A. Voors, MD, PHD,*
Dirk J. van Veldhuisen, MD, PHD*

Groningen, the Netherlands; and Birmingham and London, United Kingdom

The concentration of KIM-1 **increases with diuretic withdrawal** and **subsequently returns to normal with re-institution of diuretic therapy.**





RENAL BIOMARKERS

TUBULAR INJURY: Kidney Injury Molecule-1 (KIM-1)

- The sensitivity of KIM-1 to **changes in fluid status and diuretic use** coupled with its strong **association with WRF in *chronic HF*** suggests that **it may be valuable in phenotyping CRS**, however, **the lack of relationship between KIM-1 and WRF in decompensated HF** may in turn limit its utility and therefore deserves further exploration.

RENAL BIOMARKERS

TUBULAR INJURY: Kidney Injury Molecule-1 (KIM-1)

- Urinary KIM-1 was associated with **increased risk of death or hospitalization, independent of GFR in patients with chronic HF.**
- **One advantage of KIM-1 as a urinary biomarker is that its expression seems to be limited to the injured or diseased kidney**, although **its value may be affected by a number of confounding variables, e.g., chronic proteinuric, inflammatory and fibrotic disease states.**

RENAL BIOMARKERS

TUBULAR INJURY: Kidney Injury Molecule-1 (KIM-1)

- **It is yet to be determined whether the changes described in tubular function captured with KIM-1 are actually due to HF.**

COMMERCIALLY-AVAILABLE BIOMARKERS

TechNotes

HyTest

Clinical and Research Area | Kidney Diseases

Kidney Injury Molecule-1 (KIM-1)

Ordering information

ANTIGEN

Product name	Cat. #	Purity	Source
Kidney injury molecule-1 (KIM-1), ectodomain, recombinant	8KR6	>92%	Recombinant

MONOCLONAL ANTIBODY

Product name	Cat. #	MAb	Subclass	Remarks
Kidney injury molecule-1 (KIM-1)	4KM1	KIM70	IgG1	EIA, WB
		KIM75	IgG1	EIA, WB

RENAL BIOMARKERS

TISSUE INHIBITOR OF METALLOPROTEINASE-2

INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7

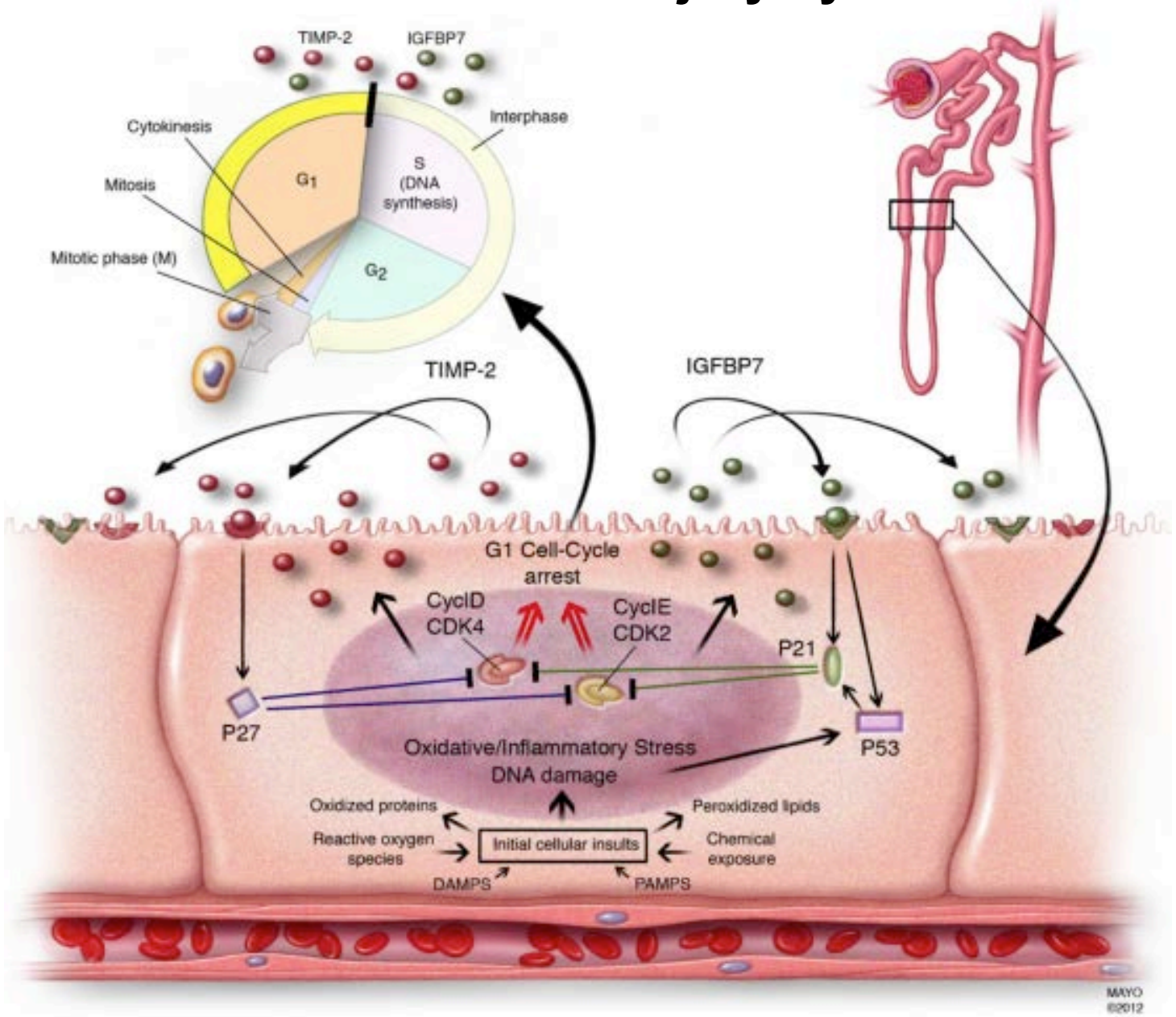
Kashani *et al. Critical Care* 2013, **17**:R25
http://ccforum.com/content/17/1/R25

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*]

Proposed mechanistic involvement of novel biomarkers in AKI: initial tubular cells sustain injury by various insults



RENAL BIOMARKERS

TISSUE INHIBITOR OF METALLOPROTEINASE-2
INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7

- 520 adults in 3 different ICUs who have no AKI
- 340 biomarkers
- Which biomarker will **best predict AKI 12 hours later**
- **RESULTS: Urine TIMP2 and Urine IGFBP7 best predicted AKI in 12 hours with AUCs 0.75 and 0.77, respectively.**

RENAL BIOMARKERS

TISSUE INHIBITOR OF METALLOPROTEINASE-2
INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7

SAPPHIRE

- 728 adults admitted to ICU within 24 hours, without AKI
- 20 sites in North America and 15 sites in Europe
- Urine and blood were collected within 18 hours of enrollment, biomarkers were measured and correlated with the **development of AKI 12 hours later.**

RENAL BIOMARKERS

TISSUE INHIBITOR OF METALLOPROTEINASE-2

INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7

SAPPHIRE

- **RESULTS: Urine TIMP2 X IGFBP7 (Nephrocheck) best predicted AKI in 12 hours with AUC 0.80 ($p<0.002$)**
- The highest tertile of TIMP2 X IGFBP7 levels had a 10-fold relative risk of developing AKI vs the lowest tertile
- **Higher levels of TIMP2 X IGFBP7 were associated with a higher risk of developing AKI**

RENAL BIOMARKERS

TISSUE INHIBITOR OF METALLOPROTEINASE-2

INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7

ORIGINAL ARTICLE

Validation of Cell-Cycle Arrest Biomarkers for Acute Kidney Injury Using Clinical Adjudication

Azra Bihorac[1], Lakhmir S. Chawla[2], Andrew D. Shaw[3], Ali Al-Khafaji[4], Danielle L. Davison[2], George E. DeMuth[5], Robert Fitzgerald[6], Michelle Ng Gong[7], Derrel D. Graham[8], Kyle Gunnerson[9,10], Michael Heung[11], Saeed Jortani[12], Eric Kleerup[13], Jay L. Koyner[14], Kenneth Krell[15], Jennifer LeTourneau[16], Matthew Lissauer[17], James Miner[18], H. Bryant Nguyen[19], Luis M. Ortega[20], Wesley H. Self[21], Richard Sellman[22], Jing Shi[23], Joely Straseski[24], James E. Szalados[25], Scott T. Wilber[26], Michael G. Walker[23], Jason Wilson[27], Richard Wunderink[28], Janice Zimmerman[29], and John A. Kellum[30]

[1]Department of Anesthesiology, University of Florida, Gainesville, Florida; [2]Department of Anesthesiology and Critical Care Medicine, George Washington University Medical Center, Washington, District of Columbia; [3]Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee; [4]Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [5]Stat-Tech Services, LLC, Chapel Hill, North Carolina; [6]University of California, San Diego, San Diego, California; [7]Department of Medicine, Montefiore Medical Center, Bronx, New York; [8]Louisiana State University, Shreveport, Louisiana; [9]Department of Anesthesiology and [10]Department of Emergency Medicine, Virginia Commonwealth University, Richmond, Virginia; [11]Division of Nephrology, University of Michigan, Ann Arbor, Michigan; [12]Department of Pathology, University of Louisville, Louisville, Kentucky; [13]Division of Pulmonary and Critical Care, University of California, Los Angeles, Los Angeles, California; [14]Department of Medicine, University of Chicago, Chicago, Illinois; [15]Eastern Idaho Medical Consultants, LLC, Idaho Falls, Idaho; [16]Portland VA Medical Center, Portland, Oregon; [17]Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland; [18]Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota; [19]Loma Linda University, Loma Linda, California; [20]Department of Nephrology, AGH Nephrology Associates, Pittsburgh, Pennsylvania; [21]Department of Emergency Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; [22]The International Heart Institute of Montana, Missoula, Montana; [23]Statistical Consultant, Carlsbad, California; [24]University of Utah and ARUP Laboratories, Salt Lake City, Utah; [25]Rochester General Medicine, Rochester, New York; [26]Department of Emergency Medicine, Summa Health System Akron City Hospital, Akron, Ohio; [27]Tampa General Hospital, Tampa, Florida; [28]Division of Pulmonary and Critical Care Medicine, Northwestern University, Chicago, Illinois; [29]The Methodist Hospital, Houston, Texas; and [30]Department of Critical Care Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania

RENAL BIOMARKERS

TISSUE INHIBITOR OF METALLOPROTEINASE-2
INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7

TOPAZ

- 420 patients admitted to ICU within 24 hours who had no evidence of AKI.
- **RESULTS: Urine TIMP2 X IGFBP7 (Nephrocheck) best predicted AKI in 12 hours with AUC 0.82.**
- **The higher the value, the higher the relative risk of developing AKI.**

Proposed clinical application of risk assessment for patients immediately after cardiac surgery

Clinical Evidence of AKI	Clinical Suspicion	STS Predicted Mortality	Urinary [TIMP-2]• [IGFBP7]	Risk Assessment
Negative	Low or Moderate	Any	≤ 0.3	LOW
Negative	Low or Moderate	<4%	>0.3 <2.0	Moderate
Any	Any	≥ 4%	>0.3 <2.0	High
Positive	Any	Any	Any	High
Any	High	Any	Any	High
Any	Any	Any	≥ 2.0	High

Action	Low Risk	Moderate Risk	High Risk
Monitor sCr	Standard Care (daily)	Every 12 hrs until decrease	Every 12hrs until decrease
Monitor Urine Output	(I/Os reviewed every 12 hours)	Strict I/Os keep Foley	Strict I/Os keep Foley
Ensure volume status	Standard Care Lasix as needed	For Oliguria, may use balanced fluid IF CVP < 8; Hold Lasix unless pulmonary edema	May use balanced fluid IF CVP < 8 AND evidence of hypovolemia (not just oliguria); hold Lasix
Avoid Nephrotoxic meds	Standard care	No NSAIDS or ACE/ARBs	No NSAIDS or ACE/ARBs Adjust doses (narcotics)*
Cardiac management	Usual care	Monitor SCVO2 if h/o abnormal LV Fx	Monitor SVO2, Echo or PA catheter if < 55% – Inotropes to keep CI >2.2
Recheck markers	NA	24 hrs	12 hrs

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RENAL BIOMARKERS

L-TYPE FATTY ACID BINDING PROTEIN

H-TYPE FATTY ACID BINDING PROTEIN

LIVER-TYPE FATTY ACID BINDING PROTEIN

- 14 kDa
- Binds unsaturated fatty acids and lipid peroxidation products in hypoxic tissue
  - Plays a putative **anti-oxidant** and **renoprotective** role predominantly in the proximal tubule cells, which use FA as their major source of energy

HEART-TYPE FATTY ACID BINDING PROTEIN

- Found in cardiomyocytes and distal tubule cells

RENAL BIOMARKERS

L-TYPE FATTY ACID BINDING PROTEIN

Early urinary marker of AKI

AJKD

Original Investigation

Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis

Julie Ho, MD,[1,2] Navdeep Tangri, MD, PhD,[1,3,4] Paul Komenda, MD,[1,3] Amit Kaushal, MD,[1,3] Manish Sood, MD,[5] Ranveer Brar, BSc,[3] Kamal Gill, BSc,[3] Simon Walker, BSc,[3] Kerry MacDonald, MLIS,[6] Brett M. Hiebert, MSc,[7] Rakesh C. Arora, MD,[7,8] and Claudio Rigatto, MD, MSc[1,3]

Table 6. Sensitivity Analyses Showing Recalculated Composite AUROC When Studies Restricted to Those Measuring Biomarkers Earlier Versus Later

	All Studies		Earlier: ≤6 Hours		Later: >6 Hours	
Biomarker	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies
Urine						
NGAL	0.72 (0.66-0.79)	16	0.74 (0.65-0.83)	11	0.69 (0.59-0.79)	5
Cystatin C	0.63 (0.37-0.89)	3	—	—	—	—
NAG	0.69 (0.60-0.79)	4	—	—	—	—
KIM-1	0.72 (0.59-0.84)	6	0.68 (0.61-0.75)	5	—	—
IL-18	0.66 (0.56-0.76)	5	—	—	0.66 (0.51-0.80)	4
L-FABP	0.72 (0.60-0.85)	6	0.73 (0.50-0.96)	4	—	—
α-GST	0.57 (0.46-0.68)	3	0.57 (0.46-0.68)	3	—	—
π-GST	0.65 (0.48-0.82)	3	0.65 (0.48-0.82)	3	—	—
Plasma						
NGAL	0.71 (0.64-0.77)	6	0.73 (0.44-1.00)	3	0.69 (0.60-0.78)	3
Cystatin C	0.69 (0.63-0.74)	5	0.65 (0.51-0.79)	4	—	—

In the setting of **cardiac surgery**, **L-FABP peaks after 6 hours and shows an overall AUC of 0.73 in predicting AKI**

European Journal of Clinical Investigation

ESCI

DOI: 10.1111/j.1365-2362.2011.02620.x

ORIGINAL ARTICLE

Urinary liver-type fatty acid-binding protein level as a predictive biomarker of contrast-induced acute kidney injury

Kenichi Manabe, Hiroshi Kamihata, Masayuki Motohiro, Takeshi Senoo, Susumu Yoshida, and Toshiji Iwasaka

Cardiovascular Division, Department of Medicine II, Kansai Medical University, Hirakata Hospital, Hirakata, Japan

Heart and Vessels

March 2014, Volume 29, Issue 2, pp 191–197

Elevation of urinary liver-type fatty acid-binding protein as predicting factor for occurrence of contrast-induced acute kidney injury and its reduction by hemodiafiltration with blood suction from right atrium

Authors Authors and affiliations

Hiromasa Katoh ✉, Tsuyoshi Nozue, Yuya Kimura, Sei Nakata, Taku Iwaki, Mitsuhiro Kawano, Masa-aki Kawashiri, Ichiro Michishita, Masakazu Yamagishi

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Cardiovascular Division, Department of Medicine II, Kansai Medical University, Hirakata Hospital, Hirakata, Japan

- 200 patients
- Urinary L-FABP ≥ 24.5 ug/g creatinine was an **independent predictor of CI-AKI development [OR = 9.1; 95% CI: 3.2-2.89]**

Post-procedural rise in urinary L-FABP 24 hours after exposure to contrast media was **greater in the CI-AKI group vs those without WRF**
[25.2 ± 31.5 vs 8.9 ± 16.3 ng/mL; p = 0.04]

Post-procedural rise in urinary L-FABP 24 hours after exposure to contrast media was greater in the CI-AKI group
vs those without WRF
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ORIGINAL ARTICLE

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Heart and

March 2

Even a baseline increase of urinary L-FABP prior to contrast media administration identified patients at risk for CI-AKI.

Elevation of urinary liver-type fatty acid-binding protein as predicting factor for occurrence of contrast-induced acute kidney injury and its reduction by hemodiafiltration with blood suction from right atrium

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For the differentiation of severity of acute kidney injury (AKI)

Clinical effectiveness

For the differentiation of severity of acute kidney injury (AKI)

Key words : AKI (Acute Kidney Injury), Cardiorenal Syndrome

ROC analysis of 14-day mortality rate

nephron
Clinical
Practice

Nephron Clin Pract 2014;127:106–112
DOI: 10.1159/000363705

Cardiac and Renal Fibrosis in Chronic Cardiorenal Syndromes

Aneley Hundae[a] Peter A. McCullough[a, b]

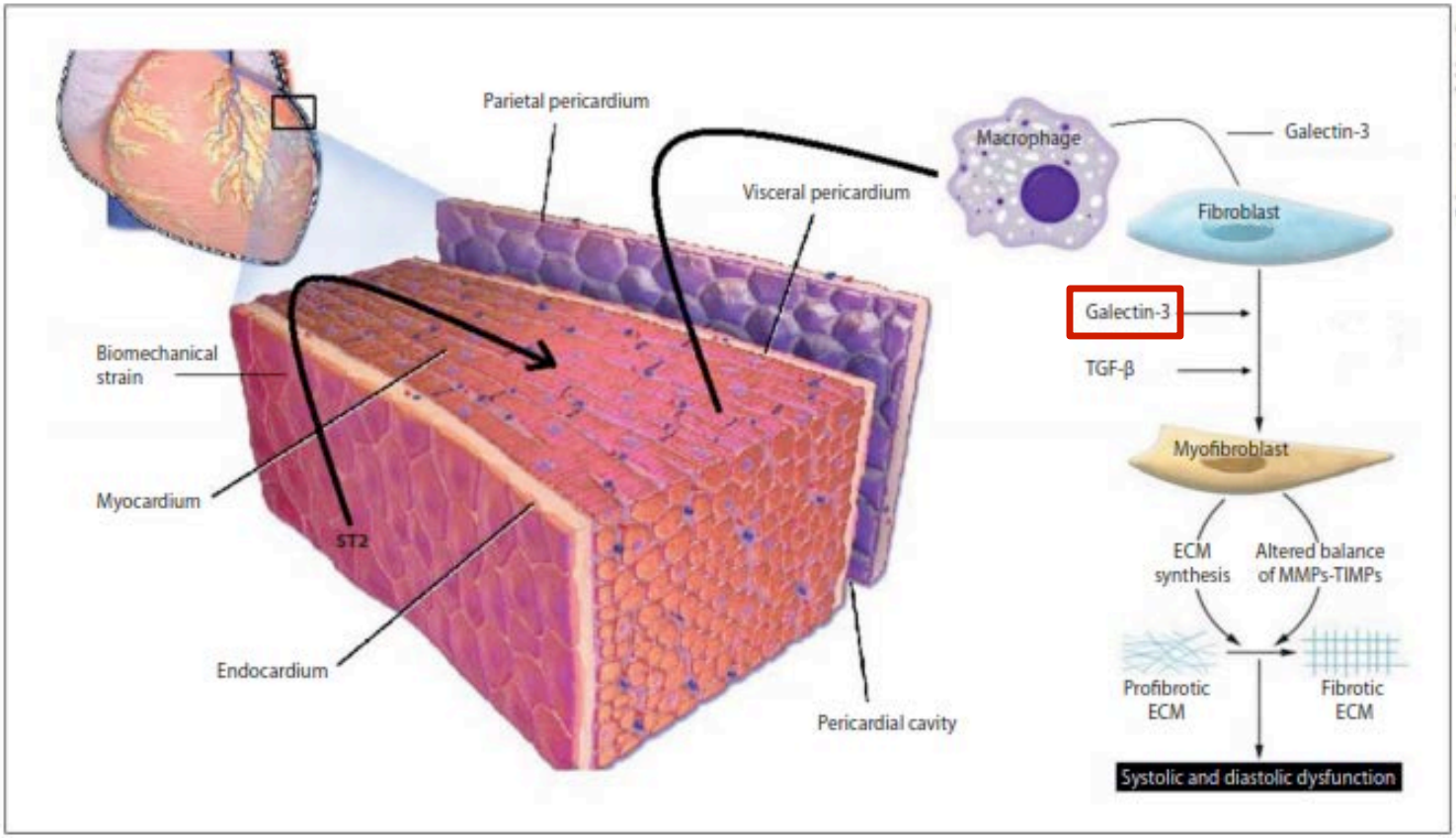


Fig. 3. Roles of ST2 and galectin-3 in pathogenic cardiac fibrosis. MMP = Matrix metalloproteinase; TIMP = tissue inhibitor of metalloproteinase.

RENAL BIOMARKERS
TISSUE FIBROSIS: Galectin-3

- A β-galactosidase-binding lectin
- Expressed both intracelluarly and extracellularly
- Involved in cell proliferation, apoptosis, inflammation and cell-growth
- Package Insert: Serum Galectin-3 ≥ 17.8 ng/mL is considered elevated.
- Predominantly hepatically-cleared

- **In the kidney**, its role appears to be **protective in AKI, attenuating fibrosis**, yet also **activates kidney fibrosis in the setting of persistent renal injury**
- **In the myocardium**, it has binding sites on cardiac fibroblasts and induces their proliferation and ultimately collagen deposition leading to **ventricular dysfunction and myocardial fibrosis.**

RENAL BIOMARKERS
TISSUE FIBROSIS: Galectin-3

- There is a strong relationship between galectin-3 and **increased mortality in both stable chronic and decompensated HF patients**

Clin Res Cardiol (2010) 99:323–328
DOI 10.1007/s00392-010-0125-y

ORIGINAL PAPER

Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study

Dirk J. A. Lok · Peter Van Der Meer · Pieta W. Bruggink-André de la Porte · Erik Lipsic · Jan Van Wijngaarden · Hans L. Hillege · Dirk J. van Veldhuisen

Table 2 Univariate and adjusted multivariable hazard ratios for galectin-3 association with mortality

	HR (95% CI) for galectin-3	*P* value
Univariate (galectin-3 only) per standard deviation (7.8 ng/mL)	1.24 (1.08–1.43)	0.003
+NT-proBNP	1.28 (1.07–1.52)	0.006
+NT-proBNP + age + gender	1.25 (1.05–1.49)	0.014
+NT-proBNP + age + gender + GFR	1.24 (1.03–1.50)	0.026

The stated *P* value is associated with the regression coefficient of galectin-3 in each model

RENAL BIOMARKERS
TISSUE FIBROSIS: Galectin-3

Heart Failure

Elevated plasma galectin-3 is associated with near-term rehospitalization in heart failure: A pooled analysis of 3 clinical trials

Wouter C. Meijers, MD,[a] James L. Januzzi, MD,[b] Christopher deFilippi, MD,[c] Aram S. Adourian, PhD,[d] Sanjiv J. Shah, MD,[e] Dirk J. van Veldhuisen, MD, PhD,[a] and Rudolf A. de Boer, MD, PhD[a] *Groningen, The Netherlands; Boston, and Waltham, MA; Baltimore, MD; and Chicago, IL*

Table IV. Net reclassification improvement and discrimination change metrics upon the addition of galectin-3, for HF rehospitalization and fatal event, at 30, 60, 90, and 120 days

Time point	NRI, continuous (95% CI)	P	NRI, categorical (95% CI)	P	Base model, AUROC (95% CI)	Base model + galectin-3, AUROC (95% CI)	P
30 d	+42.6% (+19.9%-65.4%)	<.001	+13.3% (+0.3%-26.3%)	.044	0.682 (0.624-0.740)	0.698 (0.644-0.749)	.17
60 d	+39.2% (+19.2%-59.1%)	<.001	+19.3% (+6.8%-31.7%)	.002	0.673 (0.619-0.727)	0.693 (0.642-0.744)	.12
90 d	+40.1% (+22.7%-57.6%)	<.001	+10.8% (+1.2%-20.5%)	.027	0.684 (0.642-0.736)	0.703 (0.657-0.749)	.15
120 d	+38.4% (+21.9%-54.9%)	<.001	+10.7% (+2.1%-19.3%)	.015	0.689 (0.642-0.735)	0.700 (0.654-0.744)	.27

Base model comprises age, gender, NYHA class, LVEF, eGFR, and $\log_e$(BNP) value. Continuous NRI and categorical NRI are for base model plus galectin-3 (dichotomized variable, defined by the cutoff value of 17.8 ng/mL). Categories for categorical NRI are defined by tertiles of predicted risk at each time point.

When measured at discharge following a HF exacerbation, galectin-3 has been shown to **predict 30, 60, 90 and 120-day risk for HF re-hospitalization**, significantly improving **patient re-classification in re-admission models**

Circulation
Heart Failure

American Heart Association.

Prognostic Value of Changes in Galectin-3 Levels Over Time in Patients With Heart Failure: Data From CORONA and COACH

A. Rogier van der Velde, Lars Gullestad, Thor Ueland, Pål Aukrust, Yu Guo, Aram Adourian, Pieter Muntendam, Dirk J. van Veldhuisen and Rudolf A. de Boer

Table 3. Predictive Value of Relative Changes (by Percentage Category) in Galectin-3, in CORONA and COACH, Adjusted for Baseline Covariates

	CORONA		COACH	
Variables in Model	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality and HF hospitalization end point				
Increase in galectin-3 by +15% or more*	1.549 (1.247–1.925)	<0.001	2.036 (1.087–3.813)	0.026
+ age, sex, diabetes mellitus, LVEF, eGFR, NT-proBNP	1.500 (1.173–1.917)	0.001	1.973 (1.026–3.794)	0.042
Decrease in galectin-3 by −15% or more*	0.714 (0.435–1.110)	0.112	0.792 (0.570–1.068)	0.072
+ age, sex, diabetes mellitus, LVEF, eGFR, NT-proBNP	0.790 (0.371–1.262)	0.165	0.837 (0.488–1.174)	0.178
All-cause mortality				
Increase in galectin-3 by +15% or more*	1.432 (1.095–1.872)	0.009	2.290 (1.100–4.768)	0.027
+ age, sex, diabetes mellitus, LVEF, eGFR, NT-proBNP	1.381 (1.012–1.886)	0.042	2.401 (1.099–5.245)	0.028
Decrease in galectin-3 by −15% or more*	0.802 (0.393–1.159)	0.123	0.763 (0.467–1.265)	0.178
+ age, sex, diabetes mellitus, LVEF, eGFR, NT-proBNP	0.747 (0.403–1.056)	0.082	0.781 (0.452–1.347)	0.265
Cardiovascular mortality and HF hospitalization end point				
Increase in galectin-3 more than +15%*	1.596 (1.274–1.999)	<0.001	ND†	ND

Patients whose galectin-3 levels increased by > 15% over 3-6 months had a **significantly increased adjusted risk for all-cause mortality and HF hospitalization (CORONA HR = 1.54, p < 0001; COACH HR = 2.04, p = 0.026)**

RENAL BIOMARKERS
URINARY ANGIOTENSINOGEN

- Reflects intra-renal renin-angiotensin system activation
- Currently being investigated as a **biomarker of renal hemodynamic alterations** as well as **hypertension** and **CKD progression**

RENAL BIOMARKERS
URINARY ANGIOTENSINOGEN

CLINICAL RESEARCH www.jasn.org

Urinary Angiotensinogen Level Predicts AKI in Acute Decompensated Heart Failure: A Prospective, Two-Stage Study

Xiaobing Yang,* Chunbo Chen,*† Jianwei Tian,* Yan Zha,‡ Yuqin Xiong,* Zhaolin Sun,‡ Pingyan Chen,* Jun Li,* Tiecheng Yang,§ Changsheng Ma,‖ Huafeng Liu,¶ Xiaobin Wang,** and Fan Fan Hou*

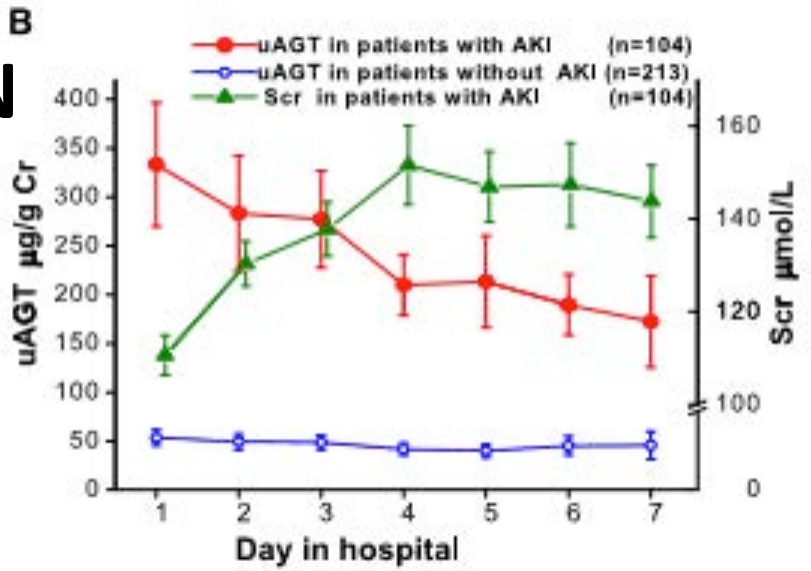


Table 5. NRI and IDI analyses for risk reclassification of AKI and 1-year mortality in the stage I cohort

Outcome	AUC			IDI			NRI[a]	
	Biomarker	Biomarker+Clinical Model	Clinical Model[b]	*P* Value[c]	Value (SEM)	*P* Value	Value (SEM)	*P* Value
AKI								
uAGT	0.84	0.86	0.77	0.01	0.06 (0.02)	0.003	0.13 (0.06)	0.03
uNGAL	0.78	0.84		0.04	0.05 (0.02)	0.03	0.08 (0.04)	0.05
uAGT+uNGAL	0.86	0.90		<0.001	0.09 (0.03)	<0.001	0.19 (0.09)	0.01
Mortality								
uAGT	0.77	0.81	0.75	0.03	0.06 (0.02)	0.01	0.16 (0.07)	0.02
NT-proBNP	0.63	0.77		0.22	0.02 (0.01)	0.08	0.07 (0.03)	0.10
uAGT+NT-proBNP	0.79	0.82		0.02	0.09 (0.03)	<0.001	0.16 (0.07)	0.01

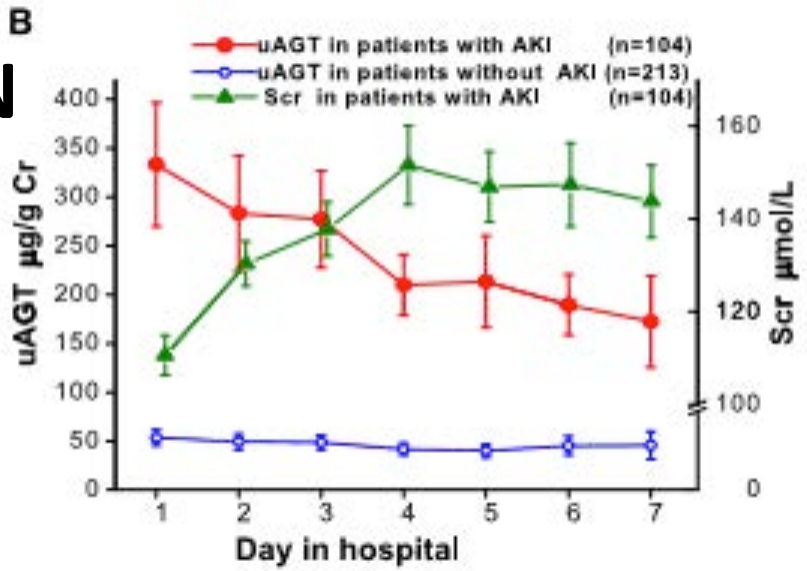
LVEF, left ventricular ejection fraction.
[a]The NRI is calculated through two-way category by using the event rate of AKI and mortality in the stage I cohort as thresholds.
[b]The clinical model for predicting AKI is composed of age, hypertension, diabetes, preadmission eGFR, LVEF, NT-proBNP, hemoglobin, and UACR. The clinical model for predicting mortality is composed of age, sex, hypertension, preadmission eGFR, LVEF, serum Na, and hemoglobin.
[c]Biomarker+clinical model versus clinical model.

RENAL BIOMARKERS
URINARY ANGIOTENSINOGEN

CLINICAL RESEARCH www.jasn.org

Urinary Angiotensinogen Level Predicts AKI in Acute Decompensated Heart Failure: A Prospective, Two-Stage Study

Xiaobing Yang,* Chunbo Chen,*† Jianwei Tian,* Yan Zha,‡ Yuqin Xiong,* Zhaolin Sun,‡ Pingyan Chen,* Jun Li,* Tiecheng Yang,§ Changsheng Ma,‖ Huafeng Liu,¶ Xiaobin Wang,** and Fan Fan Hou*



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	Biomarker	Biomarker+Clinical Model	Clinical Model[b]	*P* Value[c]	Value (SEM)	*P* Value	Value (SEM)	*P* Value
AKI								
uAGT	0.84	0.86	0.77	0.01	0.06 (0.02)	0.003	0.13 (0.06)	0.03
uNGAL	0.78	0.84		0.04	0.05 (0.02)	0.03	0.08 (0.04)	0.05
uAGT+uNGAL	0.86	0.90		<0.001	0.09 (0.03)	<0.001	0.19 (0.09)	0.01
Mortality								
uAGT	0.77	0.81	0.75	0.03	0.06 (0.02)	0.01	0.16 (0.07)	0.02
NT-proBNP	0.63	0.77		0.22	0.02 (0.01)	0.08	0.07 (0.03)	0.10
uAGT+NT-proBNP	0.79	0.82		0.02	0.09 (0.03)	<0.001	0.16 (0.07)	0.01

In **Type 1 CRS**, urinary angiotensinogen **peaks on Day 1 (admission)** and appears to be a **strong prognosticator for AKI [AUC], 0.84**

RENAL BIOMARKERS

URINARY microRNA

- Endogenous and noncoding RNA molecules containing 18-22 nucleotides in AKI
- **CARDIAC SURGERY: Both urine and plasma miR-21 concentrations** (which orchestrated a microRNA-controlled apoptosis of renal tubular epithelial cells and promoted cellular proliferation in response to renal ischemia-reperfusion injury) **may be helpful in detection of AKI and AKI progression**

RENAL BIOMARKERS IN CKD

URINARY microRNA

OPEN ACCESS Freely available online

PLOS | ONE

MicroRNA-21 and Risk of Severe Acute Kidney Injury and Poor Outcomes after Adult Cardiac Surgery

Juan Du[1,2,3], Xiaoqing Cao[1,2,3], Liang Zou[1,2], Yi Chen[1,2], Jin Guo[1,2], Zujun Chen[1,2], Shengshou Hu[1,2,3*], Zhe Zheng[1,2,3*]

Table 3. Predictive power for AKI progression (urine and plasma miR-21 versus routine measurements).

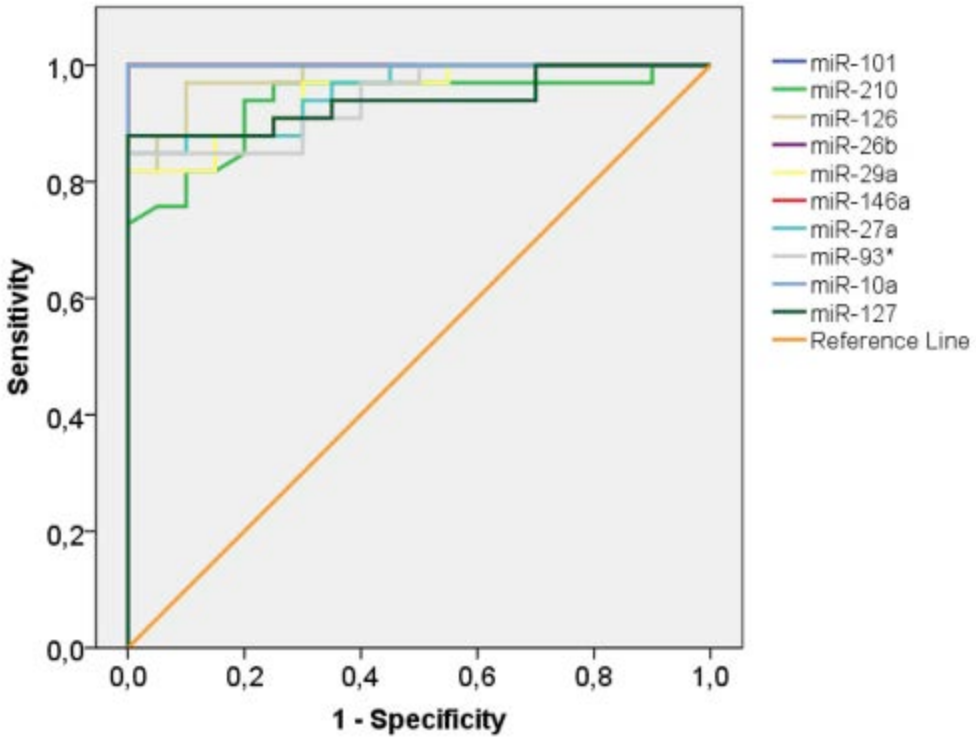
Biomarkers	unadjusted				Adjusted [a]			
	AUC (SE)	95%CI	OR(95%CI)	*P* Value	AUC (SE)	95%CI	OR(95%CI)	*P* Value
Urine miR-21	0.72 (0.06)	0.61–0.83	1.38(1.14. - 1.67)	0.001	0.81 (0.05)	0.72–0.91	1.35(1.10–1.67)	0.005
Plasma miR-21	0.72 (0.06)	0.60–0.83	1.08(1.03–1.14)	0.002	0.83 (0.05)	0.74–0.92	1.10(1.03–1.17)	0.003
SCr	0.62 (0.06)	0.50–0.75	1.02(1.00–1.03)	0.06	0.76 (0.05)	0.66–0.87	1.01(0.99–1.03)	0.48
Percent change in SCr[b]	0.50 (0.07)	0.37–0.63	1.00(0.99–1.02)	0.52	0.79 (0.05)	0.69–0.89	1.02(1.00–1.04)	0.132
Heavy proteinuria[c]	0.57 (0.04)	0.50–0.63	4.27(0.83–21.98)	0.08	0.77 (0.05)	0.66–0.87	3.92(0.65–23.55)	0.135

PLOS ONE

RESEARCH ARTICLE

A Pilot Study Identifying a Set of microRNAs As Precise Diagnostic Biomarkers of Acute Kidney Injury

Ella Aguado-Fraile[1]*, Edurne Ramos[1], Elisa Conde[1], Macarena Rodríguez[1], Laura Martín-Gómez[1], Aurora Lietor[2], Ángel Candela[3], Belen Ponte[4], Fernando Llaño[5], María Laura García-Bermejo[1]*



ICU: Other sets of microRNAs were altered **several days prior to the increase in serum creatinine**, indicating their potential as **prognostic AKI biomarkers**

Circulating miR-210 Predicts Survival in Critically Ill Patients with Acute Kidney Injury

Johan M. Lorenzen,[*†] *Jan T. Kielstein,*[†] *Carsten Hafer,*[†] *Shashi K. Gupta,*[*] *Philipp Kümpers,*[‡] *Robert Faulhaber-Walter,*[†] *Hermann Haller,*[†] *Danilo Fliser,*[§] *and Thomas Thum*[*]

Table 3. Univariate and multivariate Cox regression analyses for survival

Variables	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
miR-210 (log10)	1.868	1.079 to 3.232	0.03[a]	1.692	1.001 to 2.861	< 0.05[a]
CRP (mg/L)	1.000	0.997 to 1.004	0.8			
Ang-2 (ng/ml)	1.014	1.003 to 1.025	0.02[a]	1.005	0.990 to 1.019	0.5
Age (years)	0.994	0.969 to 1.020	0.7			
BMI (kg/m^2)	0.972	0.897 to 1.054	0.5			
Gender (male/female)	0.909	0.433 to 1.907	0.8			
Sepsis (yes/no)	2.257	1.071 to 4.753	0.03[a]	0.457	0.206 to 1.016	0.06
Surgery (yes/no)	2.024	0.947 to 4.324	0.07	0.363	0.158 to 0.831	0.02[a]
SOFA score	1.203	1.066 to 1.357	0.003[a]	1.133	0.997 to 1.287	0.06
APACHE II score	1.055	1.007 to 1.106	0.03[a]	1.010	0.944 to 1.081	0.8

Ang-2, Angiopoietin-2; HR, hazard ratio; CI, confidence interval.
[a]$P < 0.05$.

Elevated levels of plasma miR-210 (microRNA upregulated by hypoxia-inducible factor) was an **independent predictor of mortality.**

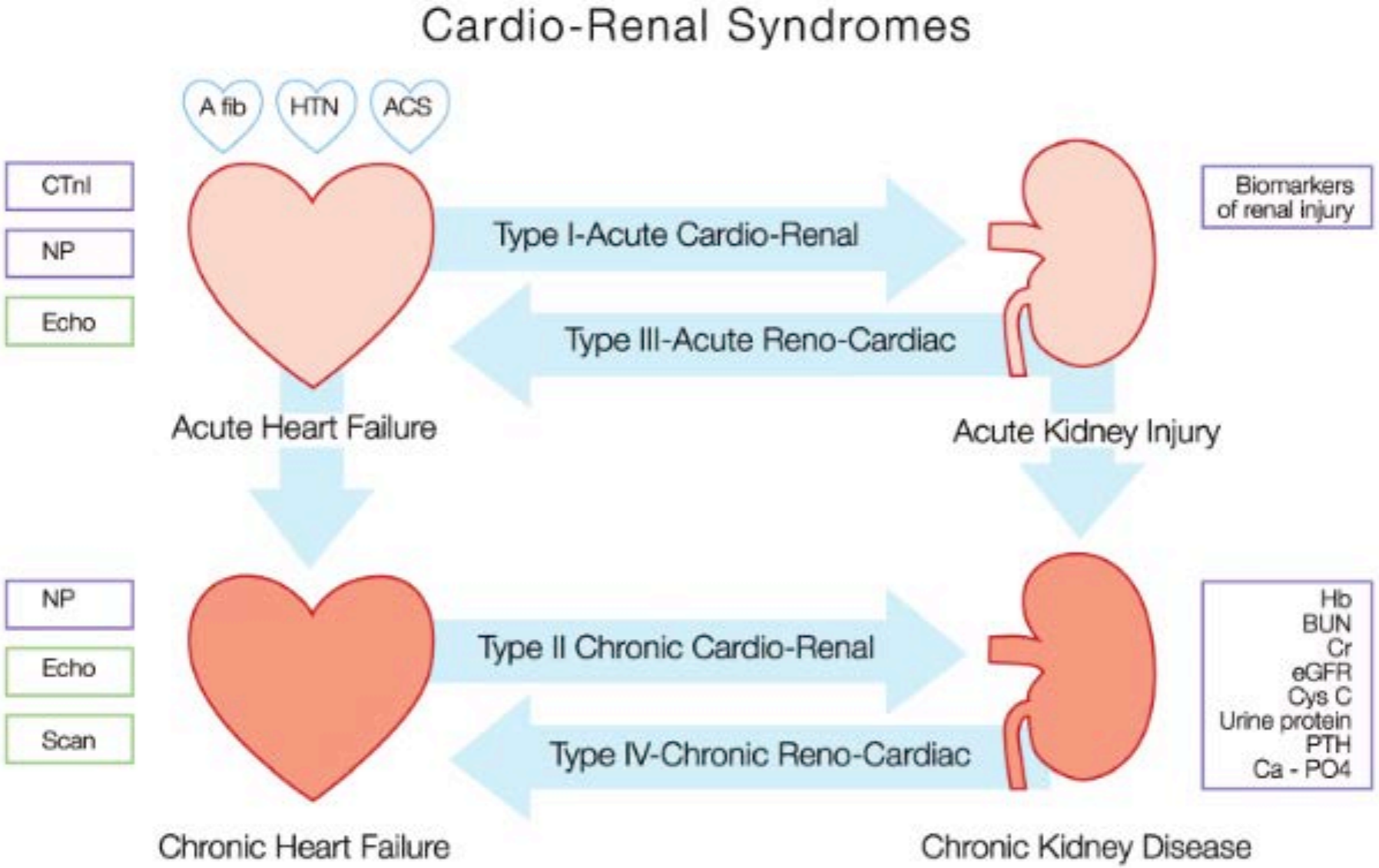


Fig. 2. Biomarkers that are currently used in various cardiorenal syndromes. Acute coronary syndrome (ACS), atrial fibrillation (A fib), blood urea nitrogen (BUN), calcium (Ca), creatinine (Cr), cystatin C (Cys C), estimated glomerular filtration rate (eGFR), haemoglobin (Hb), hypertension (HTN), natriuretic peptides (NP), parathyroid hormone (PTH), phosphate (PO4).

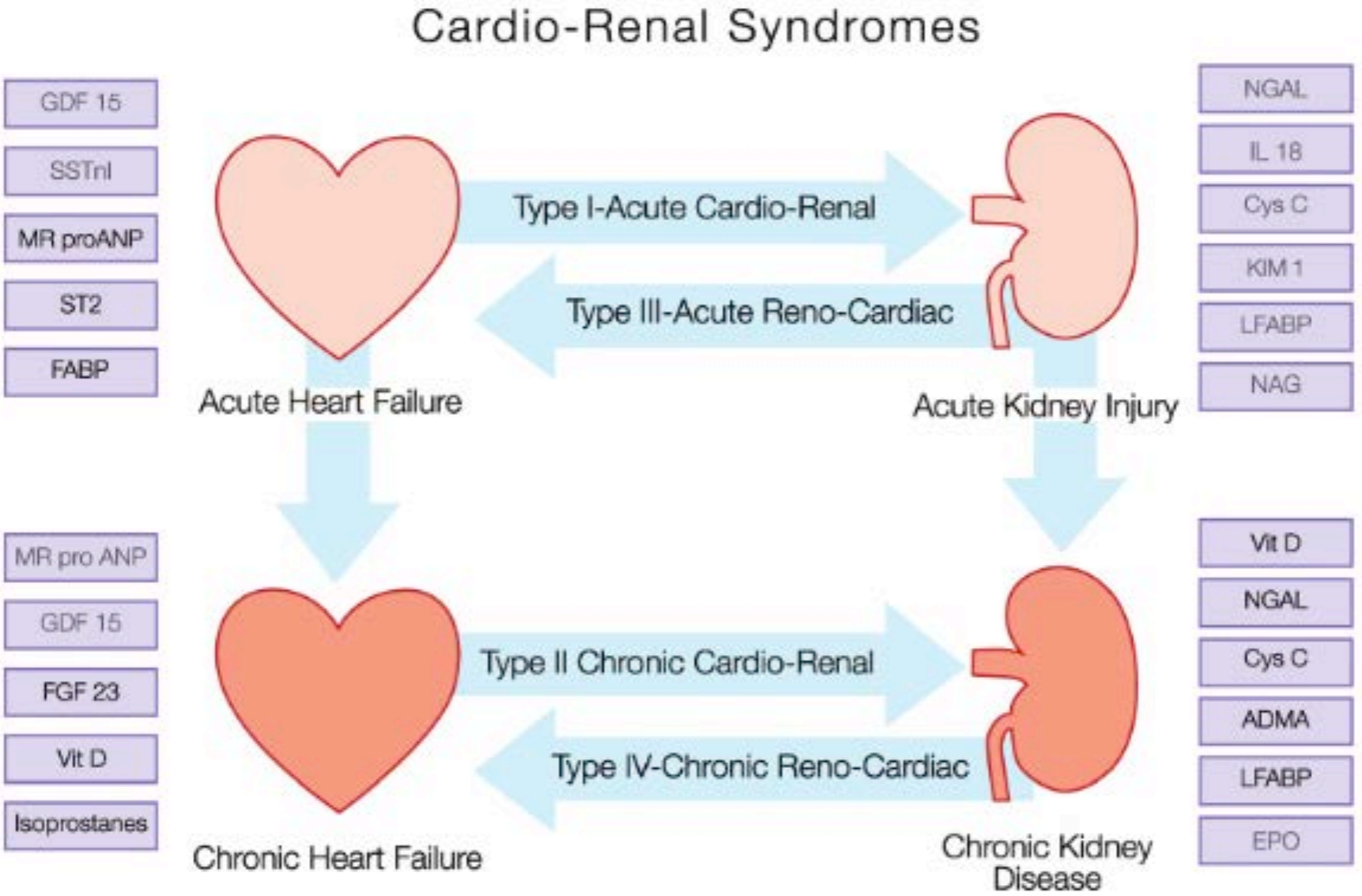


Fig. 6. Cystatin C (Cys C), erythropoietin (EPO), fatty acid binding protein (FABP), interleukin (IL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), *N*-acetyl-β-D-glucosaminidase (NAG), natriuretic peptides (NP).

BIOMARKERS AND ADVANCED MONITORING

Table 2. Classification of biomarkers

- **Predictive**—Identify subpopulations of subjects at higher risk for developing an outcome or more likely to respond to a therapy
- **Prognostic**—Informs likely course of disease progression or outcome
- **Diagnostic**—Characterizes onset and severity of a disease state
- **Efficacy**—Tracks the effectiveness of a treatment to mitigate a disease process
- **Pharmacodynamic**—Measures whether a particular biological response has occurred in response to a treatment
- **Surrogate**—Substitutes for a clinical end point ("a characteristic or variable that reflects how a patient feels, functions, or survives")

BIOMARKERS AND ADVANCED MONITORING

Opportunities to use biomarkers in late phase clinical trials

clinical investigation www.kidney-international.org

Application of new acute kidney injury biomarkers in human randomized controlled trials

Chirag R. Parikh[1,2], Dennis G. Moledina[1], Steven G. Coca[3], Heather R. Thiessen-Philbrook[1] and Amit X. Garg[4,5]

[1]Program of Applied Translational Research, Department of Medicine, Yale University, New Haven, Connecticut, USA; [2]Veterans Affairs Medical Center, West Haven, Connecticut, USA; [3]Section of Nephrology, Mount Sinai School of Medicine, New York, New York, USA; [4]Department of Medicine, Western University, London, Ontario, Canada; and [5]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

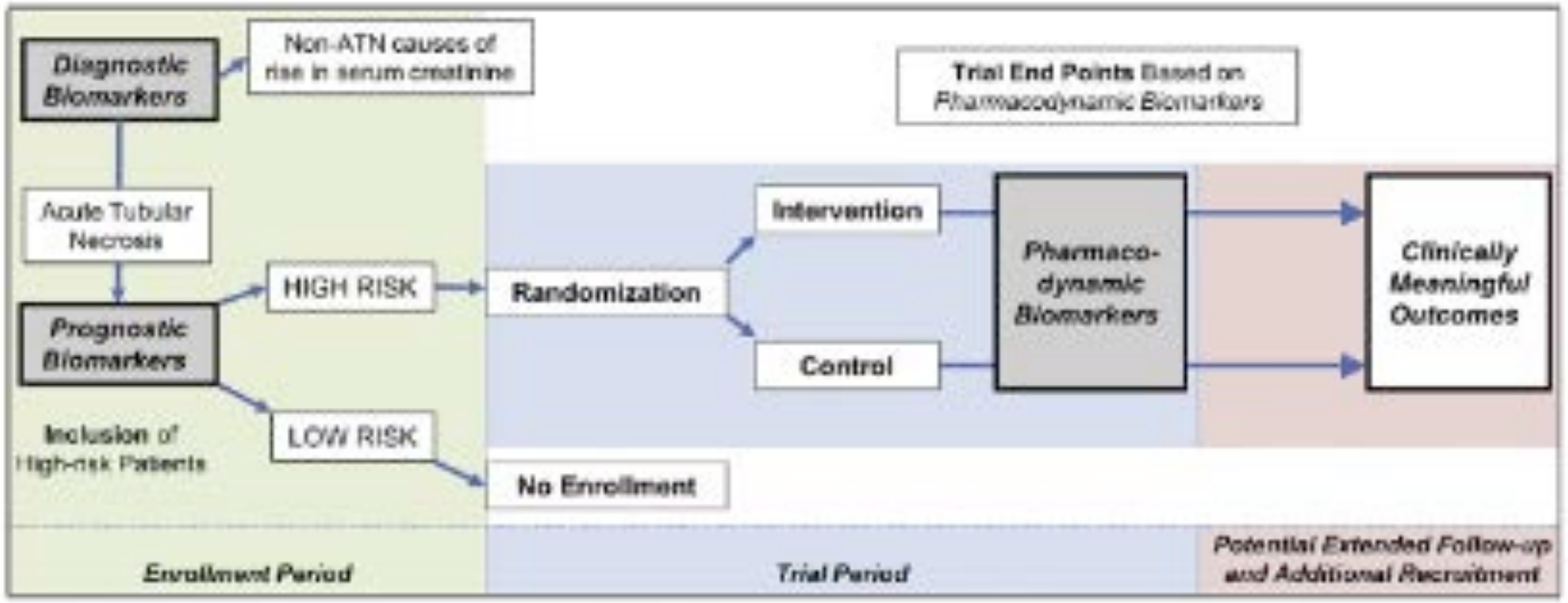


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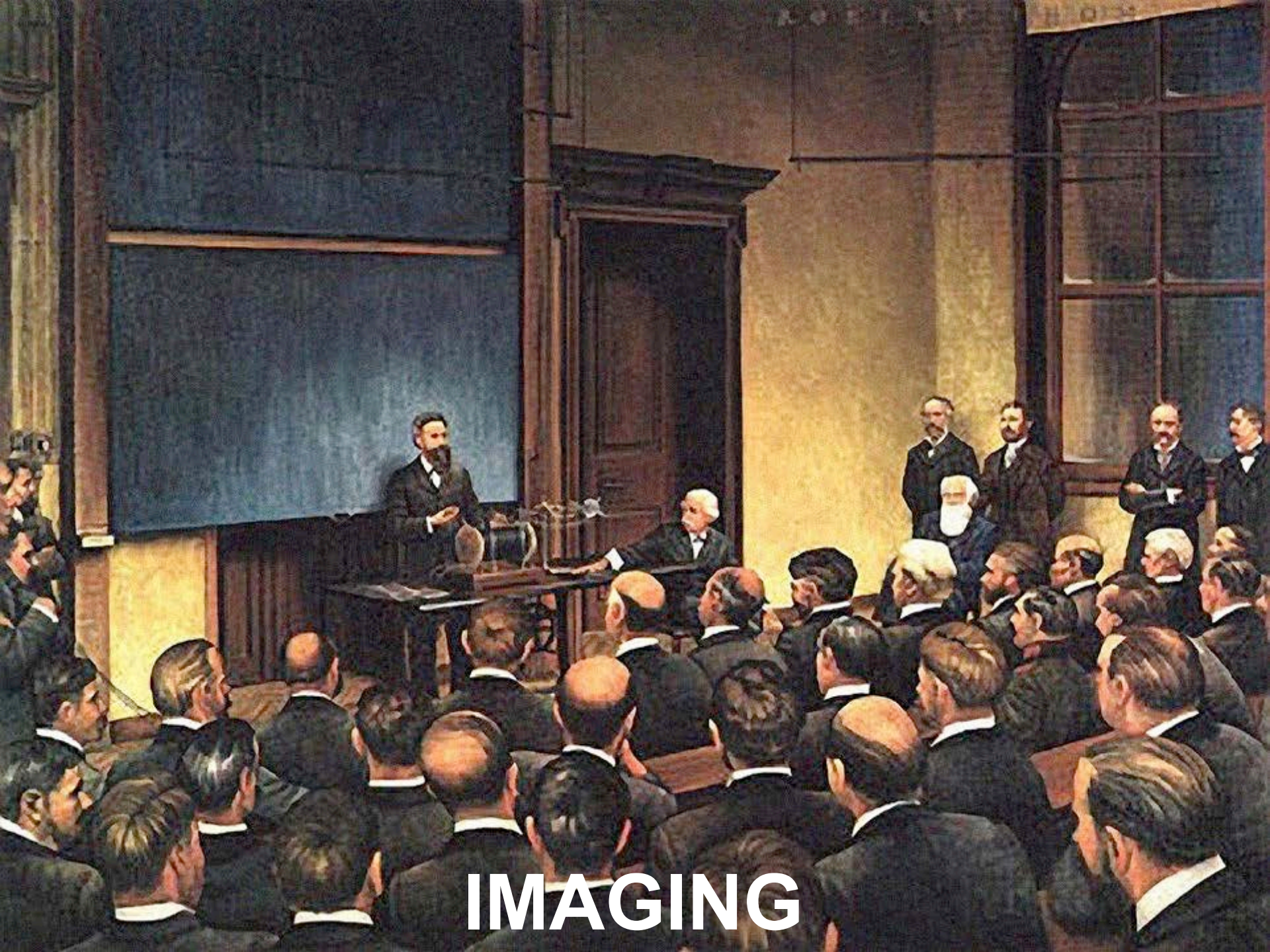
Table 4| Impact of biomarkers on future acute kidney injury trials

Problems with current trial design	Role of biomarkers
1. Misclassification: inaccurate definition of "true AKI" or ATN	***Diagnostic biomarkers:*** Use of urine biomarkers can lead to more accurate diagnosis of AKI and recruitment of a more homogenous patient population
2. Enrollment of large proportion of low-risk patients who do not reach progression end points	***Prognostic biomarkers:***[a] Identification of high-risk patients likely to reach trial end points
3. All patients enrolled in trials are given similar therapy	***Predictive biomarkers:***[a] Patients most likely to respond to a particular therapy are identified
4. Current outcomes of efficacy and progression take months or years to develop; potentially beneficial therapies are terminated before reaching end points *or* harmful therapies are continued without recognition of harm	***Pharmacodynamic biomarkers:*** Trials can be continued to harder end points or terminated early based on their effect on biomarkers. Such biomarkers may serve to monitor *safety or efficacy*.



IMAGING

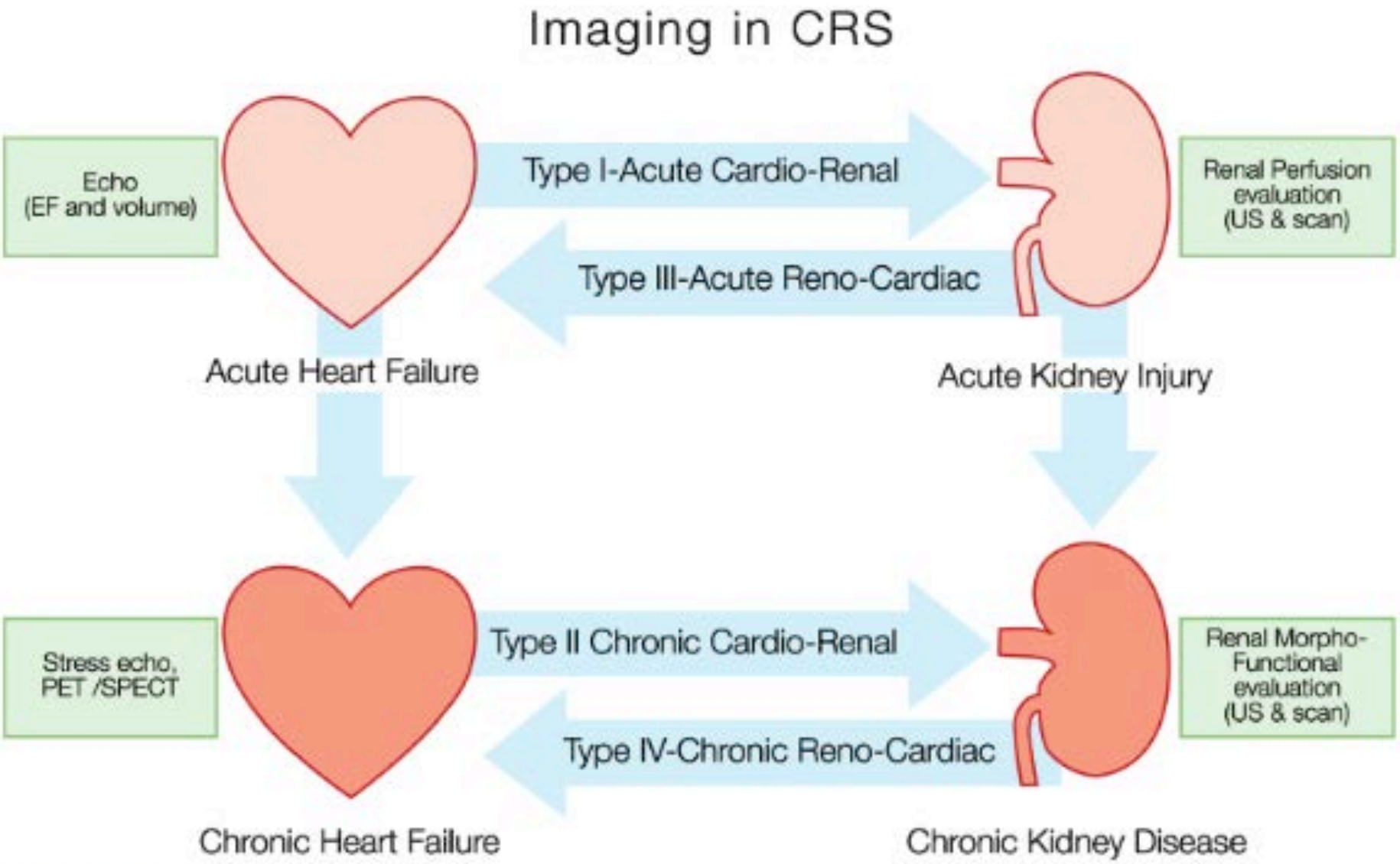


Fig. 7. Imaging in cardiorenal syndromes.

Novel Imaging Techniques for Heart Failure

Josep L Melero-Ferrer, Raquel López-Vilella, Herminio Morillas-Climent, Jorge Sanz-Sánchez, Ignacio J Sánchez-Lázaro, Luis Almenar-Bonet and Luis Martínez-Dolz

Advanced Heart Failure and Heart Transplantation Unit, Cardiology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain

Abstract

Imaging techniques play a main role in heart failure (HF) diagnosis, assessment of aetiology and treatment guidance. Echocardiography is the method of choice for its availability, cost and it provides most of the information required for the management and follow up of HF patients. Other non-invasive cardiac imaging modalities, such as cardiovascular magnetic resonance (CMR), nuclear imaging-positron emission tomography (PET) and single-photon emission computed tomography (SPECT) and computed tomography (CT) could provide additional aetiological, prognostic and therapeutic information, especially in selected populations. This article reviews current indications and possible future applications of imaging modalities to improve the management of HF patients.

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Table 1: Main Indications and Applications for Each one of the Available Imaging Modalities in the Assessment of Heart Failure Patients

	2D ECO	3DE	Strain	Cardiovascular Magnetic Resonance	Nuclear	Computed Tomography
LV/RV volumes	RU	AI		AI (GS)		AI
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LV diastolic function	RU (GS)		AI	AI		
RV function	RU	AI	AI	AI (GS)		
Ischaemia	RU		AI	AI (GS)	AI (GS)	
Viability	RU		AI	AI (GS)	AI (GS)	
Cardiomyopathies and other heart failure aetiologies	RU		AI	AI (GS)		AI
Risk assessment (arrhythmia)						
Therapy guidance (cardiac resynchronisation therapy)						
Follow-up	RU					

Green: best performance of the technique for this indication; yellow: the technique could provide useful information for this indication; red: no/little use for this indication. AI = provides additional information to that obtained with 2D echocardiogram; GS = gold standard; RU = routinely used for this indication. LV = left ventricular; RV = right ventricular.

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Viability	RU		AI	AI (GS)	AI (GS)	
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Risk assessment (arrhythmia)						
Therapy guidance (cardiac resynchronisation therapy)						
Follow-up	RU					

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European Heart Journal (2016) **37**, 1196–1207
doi:10.1093/eurheartj/ehv529

REVIEW

Imaging

Myocardial strain imaging: how useful is it in clinical decision making?

Otto A. Smiseth[1]*, Hans Torp[2], Anders Opdahl[1], Kristina H. Haugaa[1], and Stig Urheim[1]

- **Myocardial strain is a principle for quantification of LV function which is now feasible with <u>speckle-tracking ECHO</u>**

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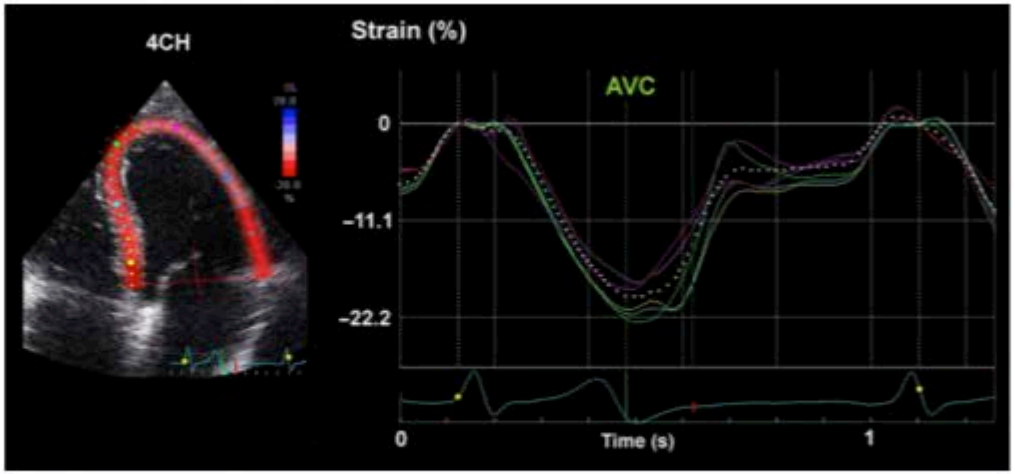

Figure 1 Segmental strains in apical four-chamber view, showing normal contractions. The color of each trace corresponds to anatomical points on the 2-D color image to the left. The white dotted line represents average strain.

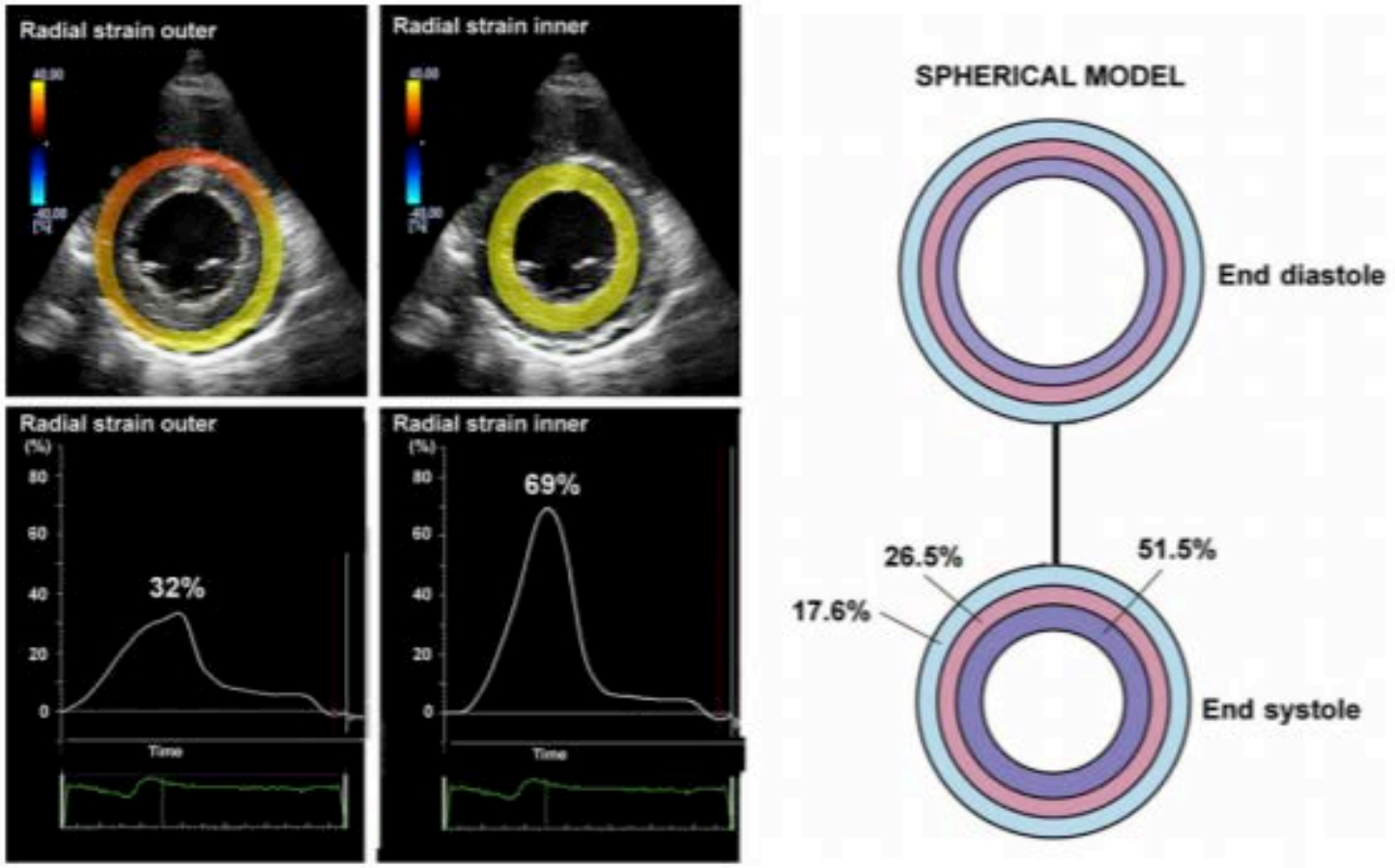

Figure 2 Left panels: left ventricular short-axis view from a healthy individual showing higher radial strains in inner than outer layer. Right panel: Transmural difference in radial strain is a pure geometrical effect, since reduction in external diameter of a passive circular structure leads to more thickening of inner than outer layers. The figure simulates reduction of inner radius by 25% and the numbers indicate the resulting thickening in inner, mid and outer wall layers.[11]

The best evaluated strain parameter is **global longitudinal strain (GLS)**.

- **More sensitive than LVEF as a measure of systolic function**

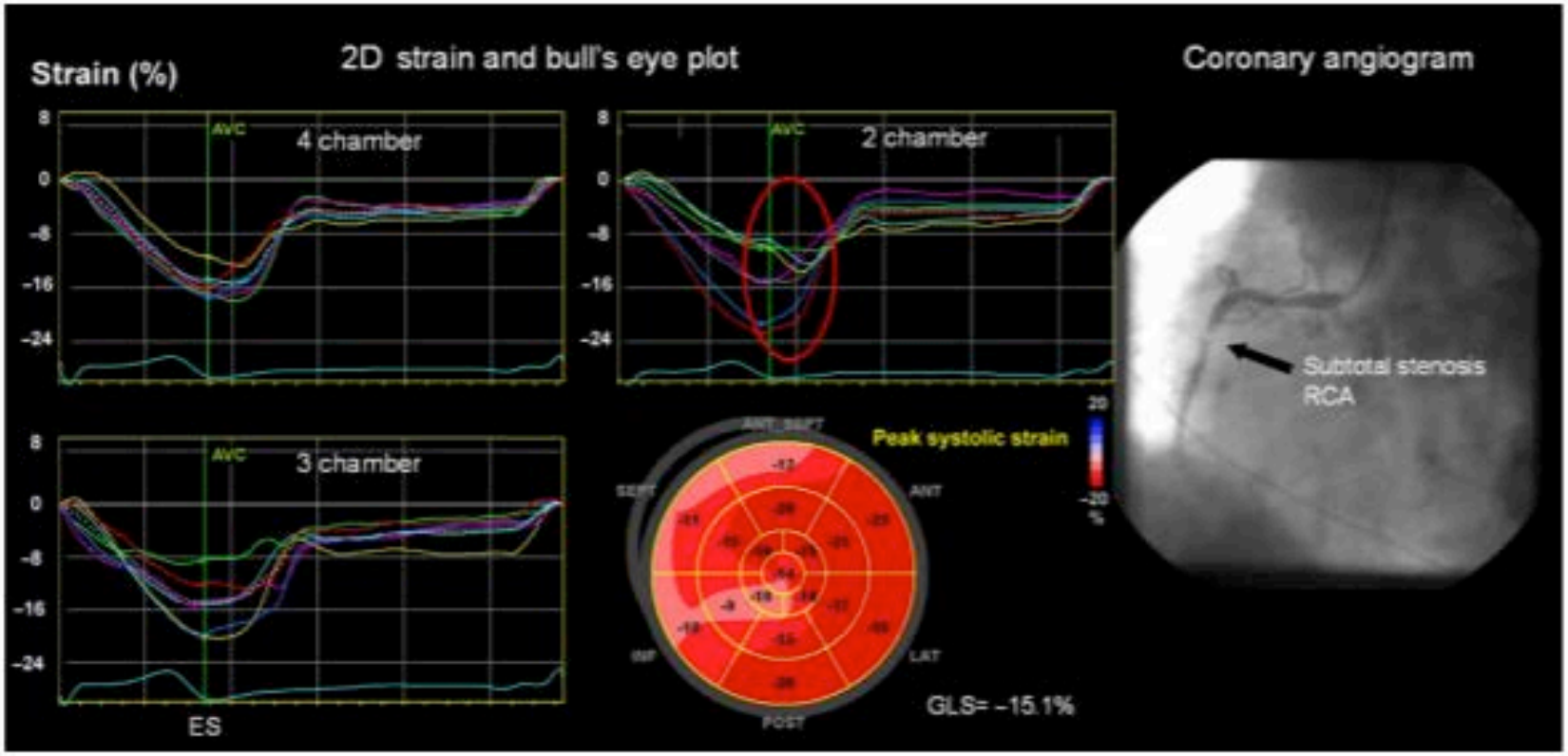

Figure 5 Strain imaging in patient with atypical symptoms, no chest pain and no signs of ischaemia in electrocardiogram. Each trace represents one LV segment. Possible inferior wall hypokinesia on grey scale imaging. Strain imaging showed moderately reduced systolic shortening and marked post-systolic shortening in the inferior wall (red circle). The patient was referred for angiography which revealed a subtotal stenosis of the right coronary artery (right panel) and was successfully treated with percutaneous coronary intervention. ES = end systole.

May be used to identify **sub-clinical LV dysfunction** in cardiomyopathies.

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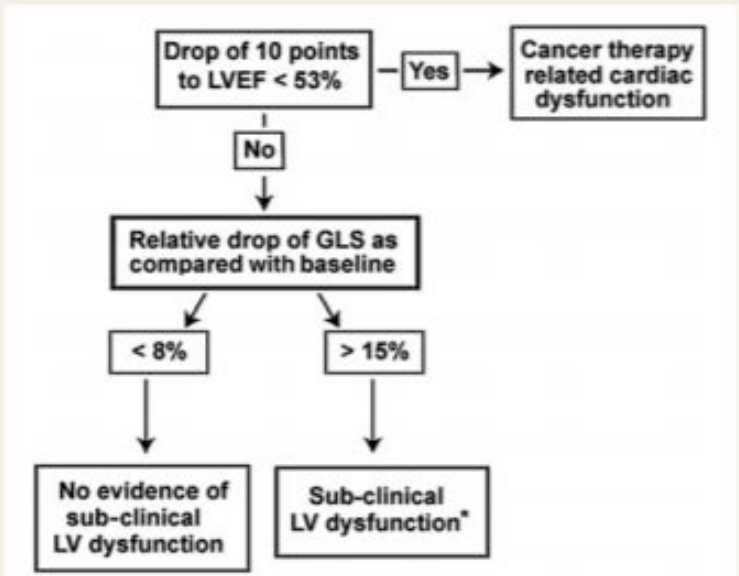

Figure 8 Strain imaging for early detection of sub-clinical left ventricular dysfunction during chemotherapy. Modified from Plana *et al.*[43] *The data supporting the initiation of cardioprotection for the treatment of sub-clinical left ventricular dysfunction is limited.

Recommended as routine measurement in **patients undergoing chemotherapy to detect reduction in LV function prior to fall in LVEF.**

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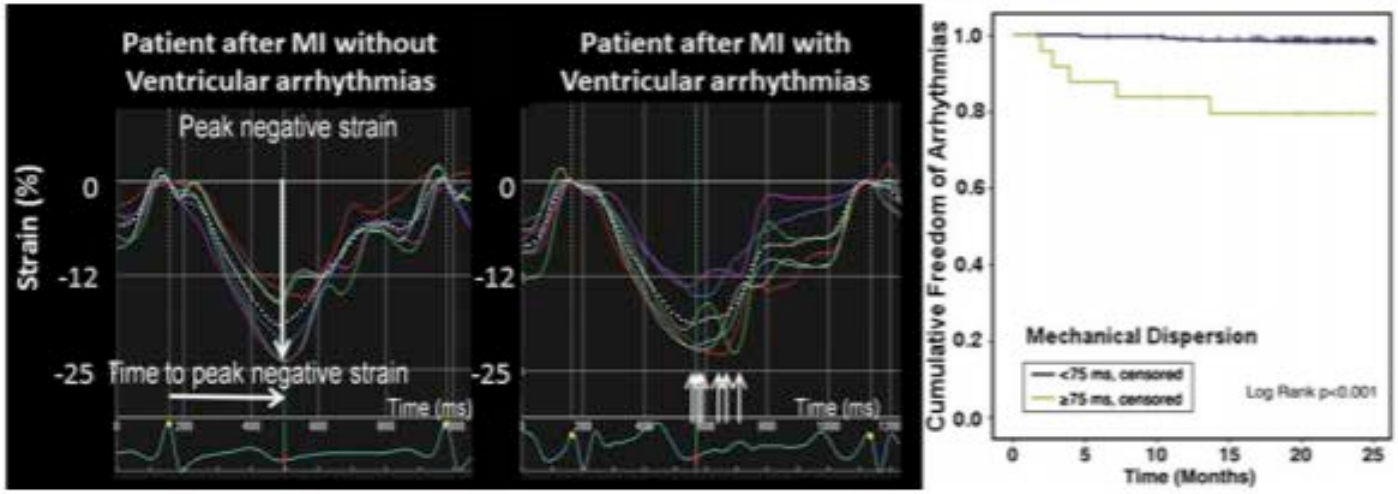

Figure 10 Left panel shows synchronous contraction by longitudinal strain in a patient after myocardial infarction. Mid panel shows heterogeneous timing of contraction and pronounced mechanical dispersion in a patient after myocardial infarction with ventricular arrhythmias. Right panel shows better arrhythmia free event rate in those with mechanical dispersion <75 ms.[47]

<u>Intersegmental variability in timing</u> of peak myocardial strain: proposed as **predictor of risk of ventricular arrhythmias**.

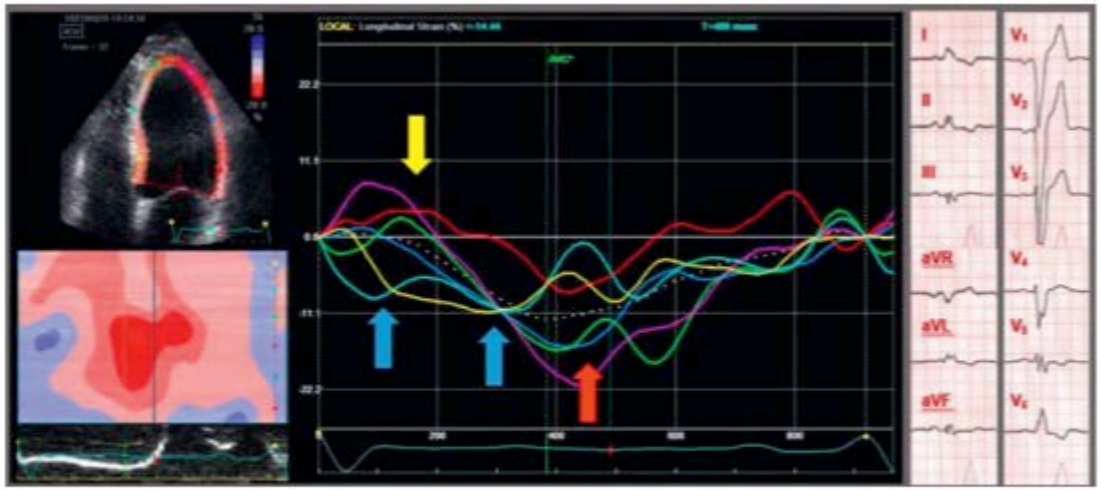

Figure 12 Recording of left ventricular longitudinal strain by speckle-tracking echocardiography in a patient with heart failure and left bundle branch block: there is a characteristic left bundle branch block pattern with early-systolic shortening in the septum (blue arrows), combined with early (pre-stretch) in the lateral wall (yellow arrow), and late peak contraction in the lateral wall (red arrow). AVC, aortic valve closure. Modified from Risum *et al.*[68]

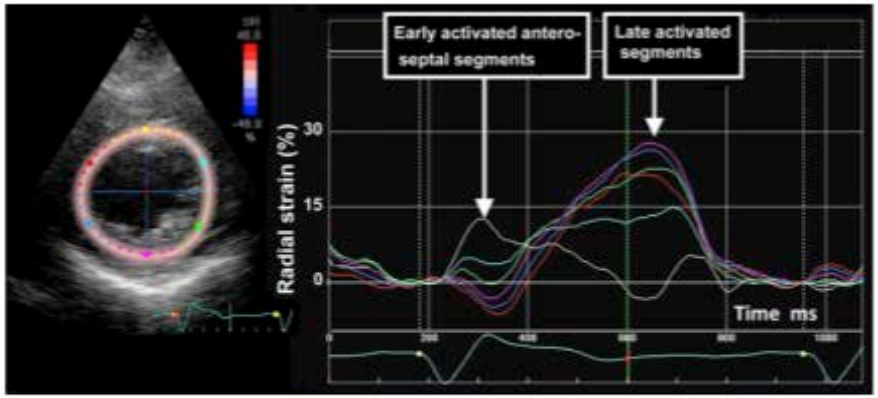

Figure 13 The figure illustrates how radial strain may be used to determine which segments have latest mechanical activation. A left ventricular parasternal short-axis recording is displayed. Strain in anteroseptal segment shows early-systolic thickening (yellow curve). Lateral (light blue), posterior (green and pink), and posterioseptal segments (blue and red) show late thickening, indicating latest activation.

May be applied **to guide placement of the LV pacing lead** in patients receiving cardiac resynchronization therapy.

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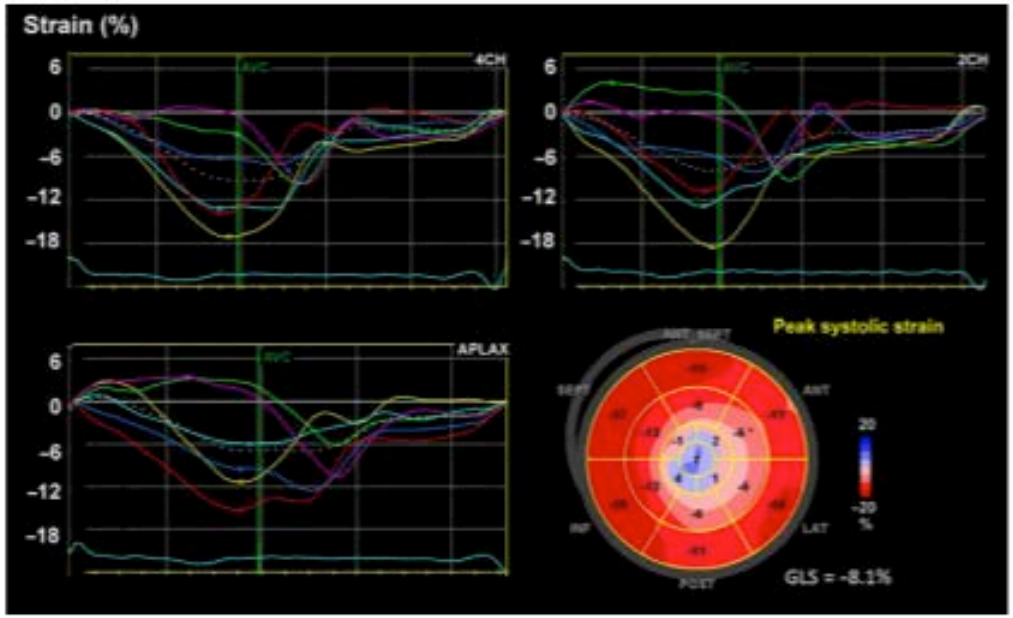

Figure 4 Patient with anterior myocardial infarction. Each trace represents one LV segment. Apical segments are dyskinetic (blue colour in bull's eye plot) while other segments are hypokinetic.

May also be used to **diagnose myocardial ischemia**

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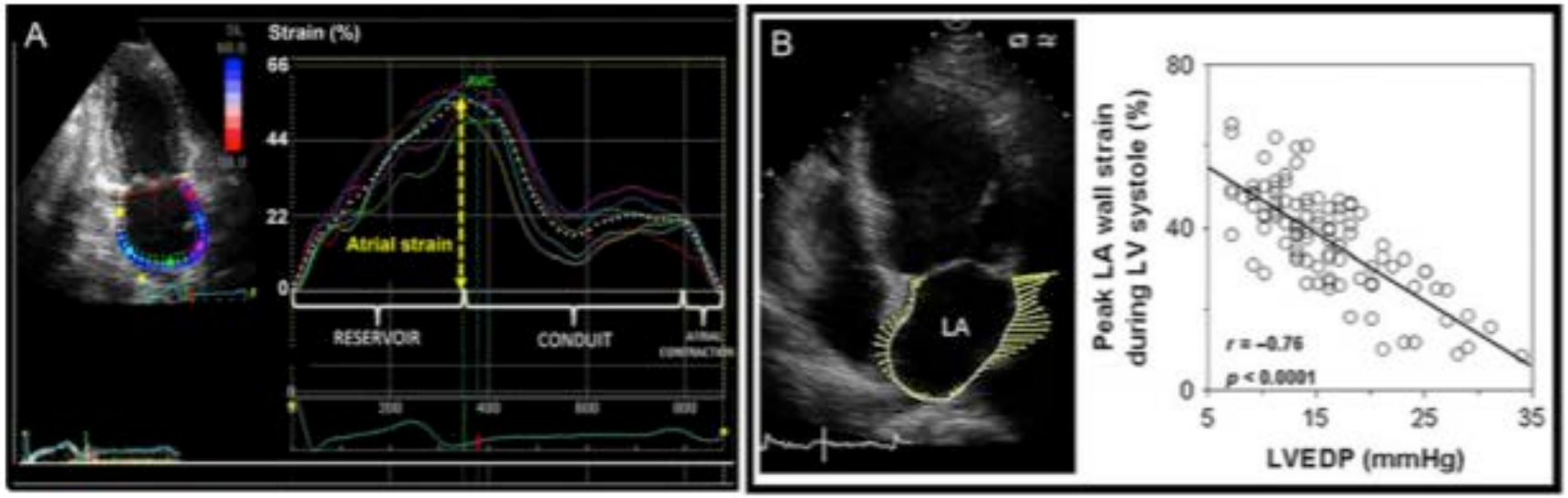

Figure 14 (*A* and *B*) Left atrial (LA) strain by two different speckle-tracking software. (*A*) Segmental traces of LA strain and average strain (white-dashed trace). Yellow arrow indicates peak strain. Modified from Cameli *et al.*[74] (*B*) Relationship between LA strain and left ventricular end-diastolic pressure.[73]

Peak systolic LA strain: suppl. index of **LV filling pressure**

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- **Myocardial strain is a principle for quantification of LV function which is now feasible with speckle-tracking ECHO**
  - ❑ **Quantification of global and LV function**
  - ❑ **CAD: Detection of myocardial ischemia and viability**
  - ❑ **Cardiomyopathies and sub-clinical LV dysfunction**
  - ❑ **Cardiotoxicity during chemotherapy**
  - ❑ **Risk assessment and prognosis**

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Viability	RU		AI	AI (GS)	AI (GS)	
Cardiomyopathies and other heart failure aetiologies	RU		AI	AI (GS)		AI
Risk assessment (arrhythmia)						
Therapy guidance (cardiac resynchronisation therapy)						
Follow-up	RU					

Green: best performance of the technique for this indication; yellow: the technique could provide useful information for this indication; red: no/little use for this indication. AI = provides additional information to that obtained with 2D echocardiogram; GS = gold standard; RU = routinely used for this indication. LV = left ventricular; RV = right ventricular.

CARDIAC MAGNETIC RESONANCE (CMR)

- Assess cardiac, great vessels and coronary anatomy and flow, ventricular function, myocardial viability and perfusion
- High accuracy and reproducibility for determination of ventricular volumes, stroke volume and EF
- Can detect fibrosis, scarring and inflammation in the myocardium

- **ADVANTAGES OVER ECHO**:
  - Can image the heart in **any desired plane in an unrestricted view**
  - **Allows ease in studying the RV** due to its inherent 3-D nature and superior border detection between ventricular blood pool and the myocardium

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STATE-OF-THE-ART PAPER

The Role of Cardiovascular Magnetic Resonance Imaging in Heart Failure

Theodoros D. Karamitsos, MD, PHD,* Jane M. Francis, DCC(R), DNM,* Saul Myerson, MD,*
Joseph B. Selvanayagam, MBBS, DPHIL,† Stefan Neubauer, MD*

Oxford, United Kingdom; and Adelaide, Australia

Noninvasive imaging plays a central role in the diagnosis of heart failure, assessment of prognosis, and monitoring of therapy. Cardiovascular magnetic resonance (CMR) offers a comprehensive assessment of heart failure patients and is now the gold standard imaging technique to assess myocardial anatomy, regional and global function, and viability. Furthermore, it allows assessment of perfusion and acute tissue injury (edema and necrosis), whereas in nonischemic heart failure, fibrosis, infiltration, and iron overload can be detected. The information derived from CMR often reveals the underlying etiology of heart failure, and its high measurement accuracy makes it an ideal technique for monitoring disease progression and the effects of treatment. Evidence on the prognostic value of CMR-derived parameters in heart failure is rapidly emerging. This review summarizes the advantages of CMR for patients with heart failure and its important role in key areas. (J Am Coll Cardiol 2009;

In some institutions where CMR is available, it is considered as the *alternative diagnostic test to ECHO* in cases with poor US images or when myocarditis or infiltrative diseases of the heart is suspected

LATE ENHANCEMENT IMAGING

- **The volume of bright 'late enhancement' correlates with the size of sub-endocardial scar following myocardial infarction**
- Also **distinguishes regions of myocyte disarray and replacement fibrosis**, e.g., CKD-associated cardiomyopathy

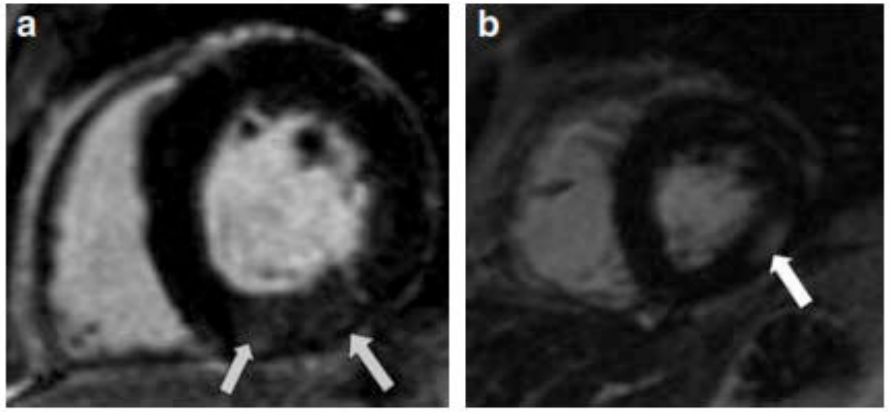


Figure 2 | (a) Short axis view of the left ventricle of hemodialysis patient demonstrating a diffuse area of gadolinium enhancement in the inferior wall of the left ventricle (arrowed). Signal intensity of this area is 17.6 compared to the 6.9 for the LGE-negative area. (**b**) Short axis view of the left ventricle of another hemodialysis patient demonstrating a diffuse area of gadolinium enhancement in the lateral wall of the left ventricle. Signal intensity of the area of late gadolinium enhancement is 32.0 compared to 8.4 for the LGE-negative area. This patient had normal coronary arteries at angiography performed as transplant assessment.

LATE ENHANCEMENT IMAGING

http://www.kidney-international.org original article

see commentary on page 1711

Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging

PB Mark[1,2], N Johnston[3], BA Groenning[3], JE Foster[3], KG Blyth[3], TN Martin[3], T Steedman[3], HJ Dargie[3] and AG Jardine[1,2]

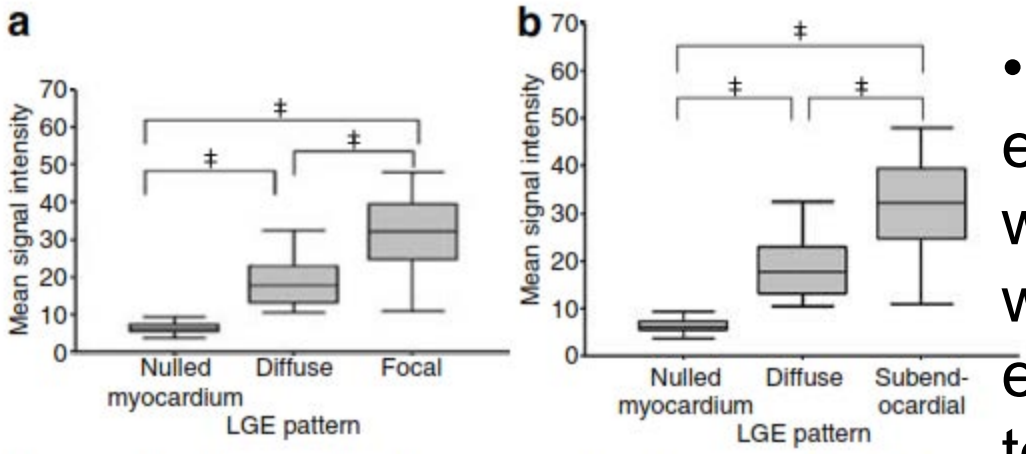


Figure 3 | (a–b) Box plots demonstrating the mean signal intensity (with 95% confidence intervals) for each area of gadolinium enhancement. ‡$P<0.001$ compared to areas of alternate patterns of LGE (paired samples *t*-test).

- Cross-sectional study
- 134 patients with ESRD
- Sub-endocardial 'late-enhancement' consistent with myocardial infarction was found in 14% but an equal number were found to have **mid-wall 'late-enhancement' consistent with non-ischemic replacement fibrosis**

T1 MAPPING

- **‘Native’ (non-contrast) T1 relaxation time** of myocardium varies with **water content** and **increases with interstitial fibrosis**.
- This is ideal in CKD because no contrast is required to detect DIF

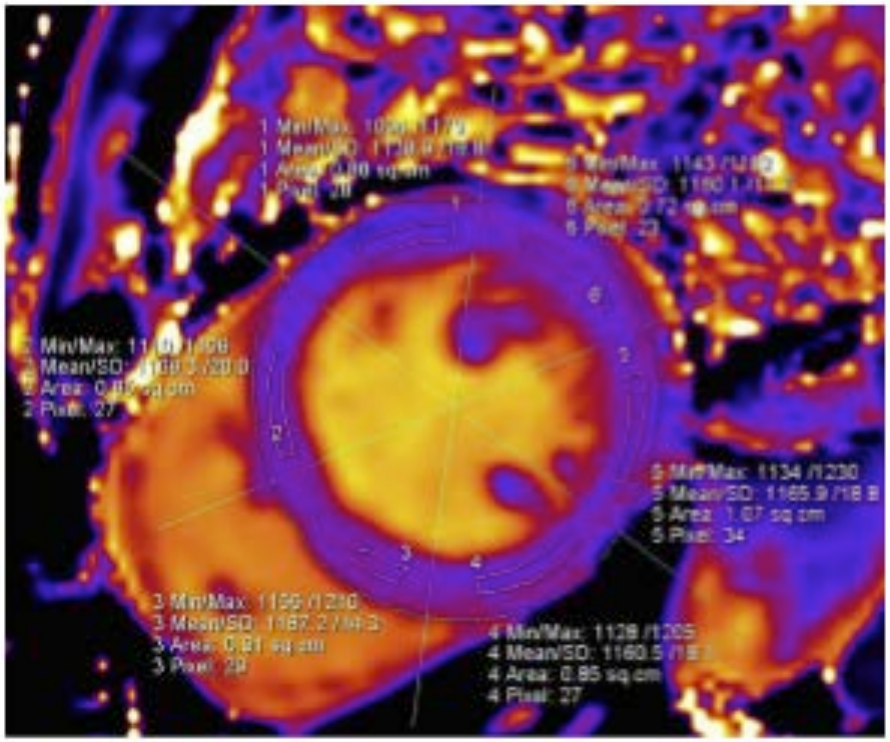


Figure 3| A typically segmented T1 map of a basal myocardial slice in a hemodialysis patient. Min/Max, minimum/maximum.

UNIVERSITY OF LEICESTER

Loughborough University

University Hospitals of Leicester NHS
NHS Trust

Native T1 mapping is a highly reproducible measure of myocardial fibrosis in hemodialysis patients independent of hydration status

MPM Graham-Brown[1,2], DR Churchward[1,3], DS March[1,3], DJ Stensel[2], GP McCann[4], JO Burton[1,3]

[1]John Walls Renal Unit, University Hospitals Leicester NHS Trust, UK; [2]National Centre for Sport and Exercise Medicine, Loughborough University, UK; [3]Department of Infection Immunity and Inflammation, University of Leicester, UK; [4] Department of Cardiovascular Sciences, University of Leicester, UK

Introduction

Myocardial fibrosis occurs frequently in hemodialysis (HD) patients and is associated with poor prognosis. Native T1 mapping is a novel cardiac MRI (CMR) technique that measures longitudinal proton relaxation to characterize tissue with great specificity. Native T1 mapping correlates well with myocardial fibrosis in many diseases, but concerns remain about its use in HD patients due to the potential impact of changes in hydration status on T1 time. We examined the inter-study and inter-observer variability of native T1 mapping in HD patients to assess reproducibility and the effects of changes hydration on native T1 time.

Methods

3-Tesla CMR was performed twice on non-dialysis days for 10 patients. Native T1 values were acquired using the modified look-locker inversion recovery (MOLLI) sequence and analysed using the software package CMR[42] (Circle Cardiovascular Imaging, Alberta, Canada) (Figure 1).

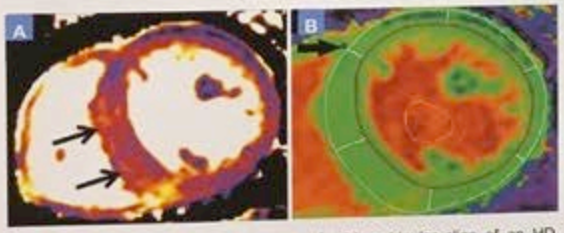


Figure 1A: Native T1 parametric map of mid-ventricular slice of an HD patient. Arrows represent discretely increased native T1 signal likely to represent replacement fibrosis. ***1B:*** Native T1 map divided into the 6-segment AHA model, defined by RV insertion point (Arrow)

Inter-study variability of native T1 values was established by assessing the variability of native T1 values analysed by a single, blinded observer. Inter-observer variability between two, blinded observers was also assessed.

Results: Demographics

All 10 HD patients completed this test-retest CMR study. Median interval between scans was 7±4 days. Mean age of participants was 57.8±15 years. 80% patients were male. Mean dialysis vintage of patients was 26±2.6 months. 30% of patients had diabetes. All scans were suitable for analysis, with T1 map image quality being either excellent (no artefact) (n=18) or good (minimal artefact) (n=2).

Results: Native T1 reproducibility

Inter-study reproducibility	*Study 1 (Mean±SD)*	*Study 2 (Mean±SD)*	*CoV*
Mid-ventricular native T1 (ms)	1267.8 ±35.4	1270.7 ±30.5	0.7%
Inter-observer reproducibility	*Observer 1 (Mean±SD)*	*Observer 2 (Mean±SD)*	*CoV*
Mid-ventricular native T1 (ms)	1267.6 ±35.4	1271 ±34.8	0.3%

Table 1: Interstudy and interobserver variability of native T1 mapping. CoV: Co-efficient of Variation.

Bland-Altman analyses showed for both inter-study and inter-observer variability of native T1 analyses showed narrow limits of agreement with no systematic bias (Figure 2).

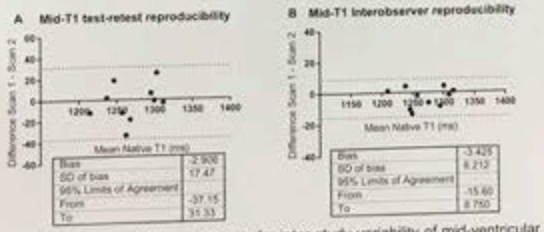


Figure 2A: Bland-Altman analysis for inter-study variability of mid-ventricular native T1 values. ***B:*** Bland-Altman analysis for inter-observer variability of mid-ventricular native T1 values

Results: Effects of hydration status on native T1 values

Changes in left ventricular end-diastolic volume (ΔLVEDV) and changes in weight (Δweight) between scans were used as surrogates of changes in hydration status and the effects these on change in native T1 (ΔT1) between scans was assessed. Whilst ΔLVEDV and Δweight correlated with each other (r=0.682, P=0.03) , there was not relationship between either ΔLVEDV or Δweight and ΔT1 (Figure 3).

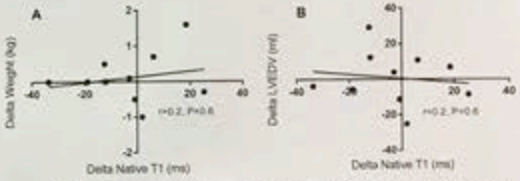


Figure 3A: Relationship between Δweight and ΔT1 between test-retest scans. ***B:*** Relationship between ΔLVEDV and ΔT1 between test-retest scans.

Linear regression confirmed ΔT1was unaffected by both ΔLVEDV and Δweight (adj R2=0.1, P=0.71 and adj R2=0.08, P=0.59).

Conclusion

Native T1 mapping is an extremely reproducible imaging biomarker in HD patients. Myocardial native T1 is affected by myocardial water content and the finding that changes in native T1 values were not affected by the changes in fluid status between scans is reassuring and goes some way to addressing concerns about the possible influence of volume overload on native T1 values in HD patients.

Further work is required to determine whether native myocardial T1 is related to prognosis in ESRD and whether interventions that reduce T1 are associated with improved outcomes.

@CycleHD15
@DrMattGB

Matthew Graham-Brown: mpmgb1@le.ac.uk

T1 MAPPING

- **LIMITATIONS**
  - 'Native' T1 relaxation values include **signals from cells and interstitium**
    - In ESRD, it is not known how variable T1 values may be in the myocardium when there may be variation in water content
  - 'Native' mapping has been most successful **when there is a large pathophysiological change**, e.g., infiltrative accumulation in Amyloid, Fabry, etc.
    - In CKD, 'native' T1 relaxation times overlap between cases and controls and its not established whether the difference in the signal from DIF will be large enough to track in individuals over time or in response to treatment

IMAGING INTRARENAL HEMODYNAMICS AND O_2 METABOLISM

Frontiers in Research Review:
Kidney Oxygenation in Health and Disease

Imaging of intrarenal haemodynamics and oxygen metabolism

Per Liss,* Eleanor F Cox,† Per Eckerbom* and Sue T Francis†

Table 1 Comparison of each imaging method showing quantitative measures, advantages, disadvantages and applications

MR method	Quantitative measure	Advantage	Disadvantage	Applications
BOLD	R2* as marker of oxygenation	Non-invasive	Indirect measure of renal oxygenation	Renal hypoxia,[26] renal artery stenosis,[31] dynamic challenges[13,28]
PC-MRI	Renal artery flux, velocity and area	Non-invasive, contrast free Blood flow curve provides method to grade stenosis	Breath hold Requires image slice to be perpendicular to vessel	Detection of renal artery stenosis[83] Global renal perfusion by combination with renal volume[43]
DCE-MRI	Perfusion, blood volume, transit time and filtration	Well-established and validated technique	Invasive contrast agent with risk of NSF Arterial input function required	DCE first-pass perfusion to assess renal artery stenosis[84] or renal parenchymal disease
ASL	Tissue perfusion and transit times	Non-invasive, contrast free Free breathing technique	Low signal-to-noise ratio, sensitive to motion	Renal parenchymal disease,[62] dynamic challenges[43]
DWI/DTI	DWI: ADC, D, D* and f_p DTI: FA, MD and λ	Non-invasive, contrast free Free breathing technique	Fitted parameters depend on choice and number of *b*-values	Detection of fibrosis, incoherent water flow and anisotropic microstructure in CKD[16,70]

IMAGING INTRARENAL HEMODYNAMICS AND O_2 METABOLISM

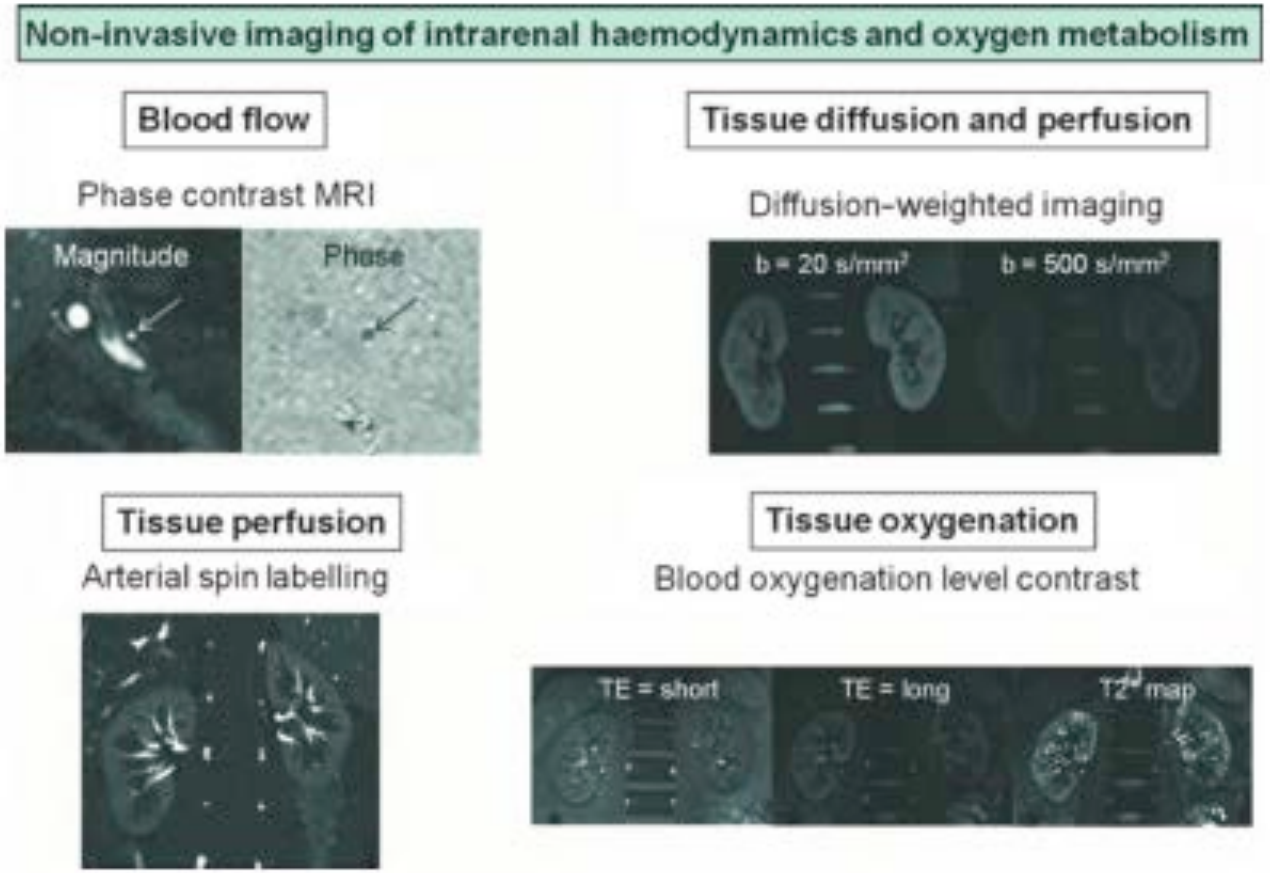


Fig. 1 Schematic illustrating non-invasive magnetic resonance imaging methods to assess intrarenal haemodynamics and oxygen metabolism. MRI, magnetic resonance imaging; TE, echo time; T2*, transverse relaxation time.

BLOOD OXYGEN LEVEL-DEPENDENT (BOLD) MRI

- The future use of non-invasive MR techniques to assess hemodynamic alterations and oxygenation in the kidney would make clinical daily MR routine work much easier, and because potential side effects of injected MR contrast media do not have to be taken into consideration, these techniques could be substituted for contrast media in most examinations

BLOOD OXYGEN LEVEL-DEPENDENT (BOLD) MRI

- It has been proposed that renal hypoxia and the development of fibrosis may be the mechanisms causing DM and HTN nephropathy; these non-invasive techniques to **detect <u>early fibrotic alterations</u> together with changes in intrarenal O_2 availability** may be able to **identify those who are at risk for developing kidney failure.**

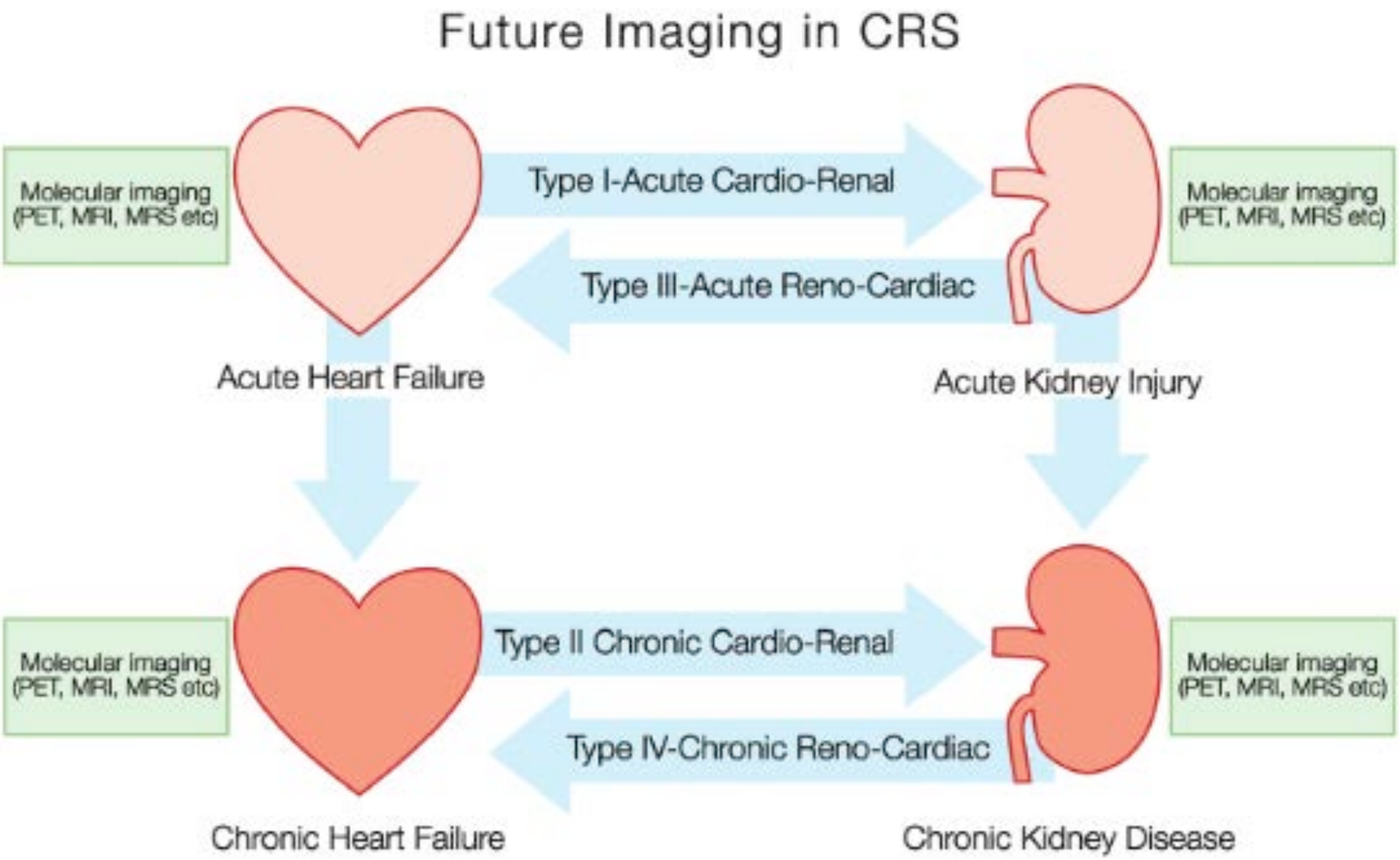
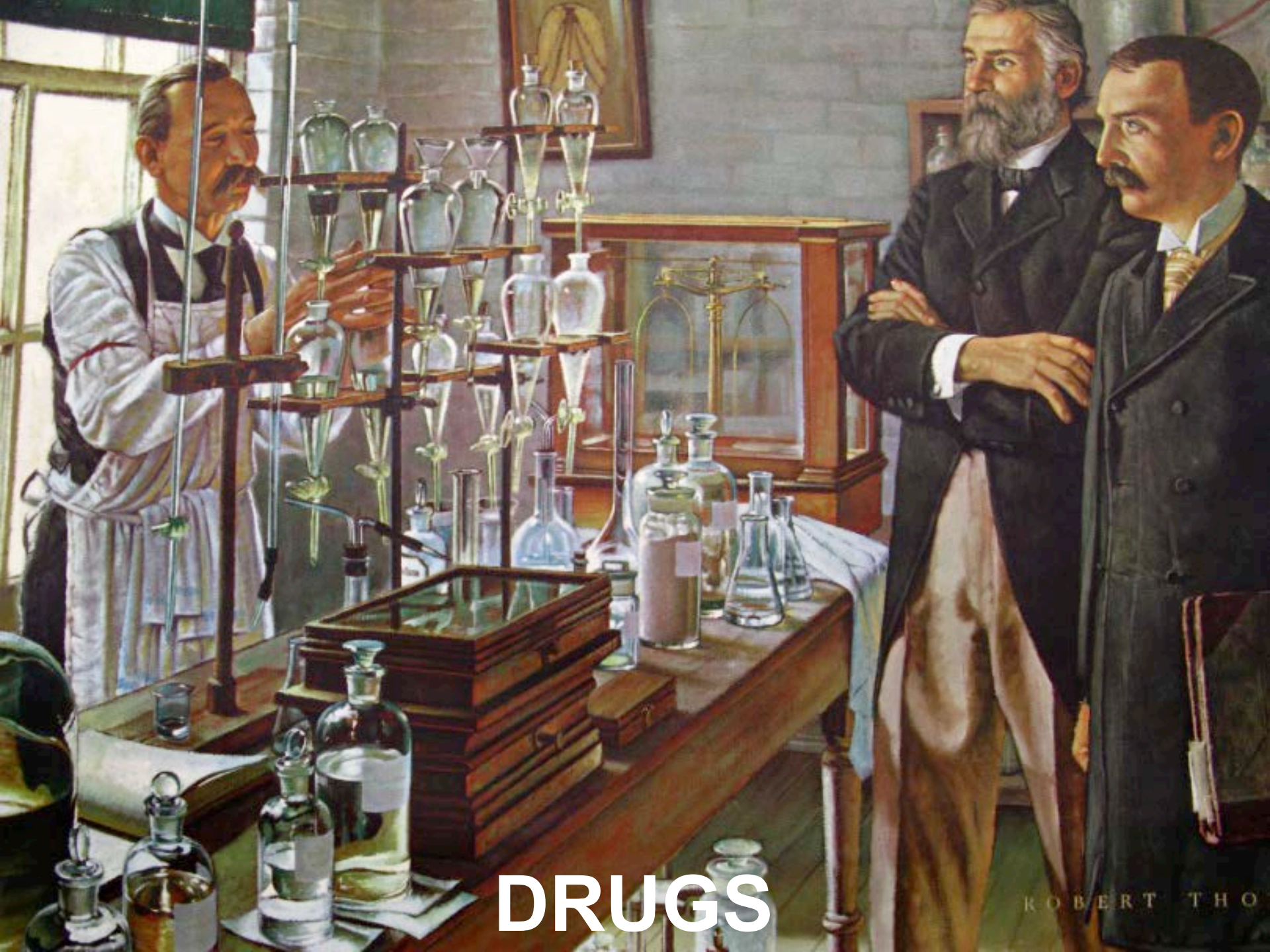
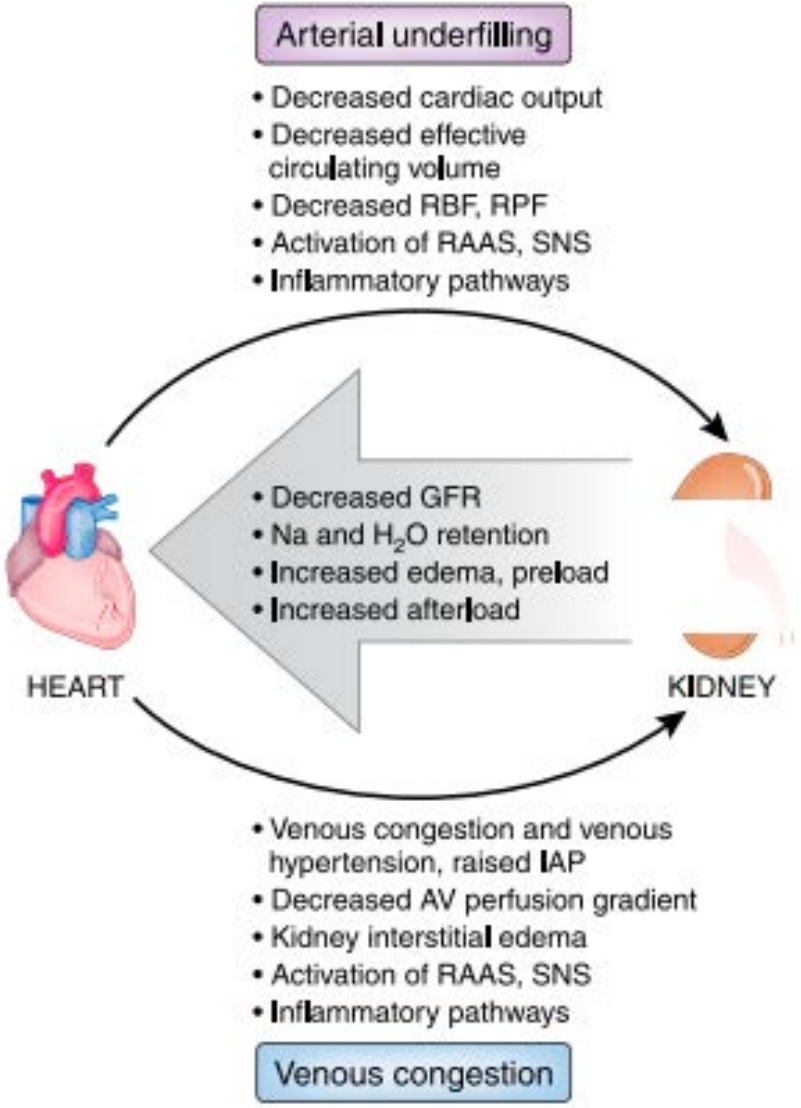


Fig. 8. Future imaging in cardiorenal syndromes.



DRUGS

NOVEL THERAPIES



TREATMENT STRATEGIES

NOVEL VASODILATOR

- Nesiritide
- Rolofylline
- Recombinant human relaxin-2

NOVEL INOTROPES

- Levosimendan
- Omecamtiv
- Istaroxime

NEUTRAL ENDOPEPTIDASE INHIBITORS

SOLUBLE GUANYLATE CYCLASE INHIBITORS

SGLT2 inhibitors

GLP-1 agonists

TREATMENT STRATEGIES

- Mechanical Support
  - Left Ventricular Assist Devices (LVAD)
- Cardiac Resynchronization Therapy

CardioRenal Medicine

Cardiorenal Med 2014;4:176–188
DOI: 10.1159/000366168
Published online: October 3, 2014

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www.karger.com/crm

Review

Management of the Cardiorenal Syndrome in Decompensated Heart Failure

Frederik Hendrik Verbrugge[a, b] Lars Grieten[a, c] Wilfried Mullens[a, c]

CardioRenal Medicine

Cardiorenal Med 2014;4:176–188
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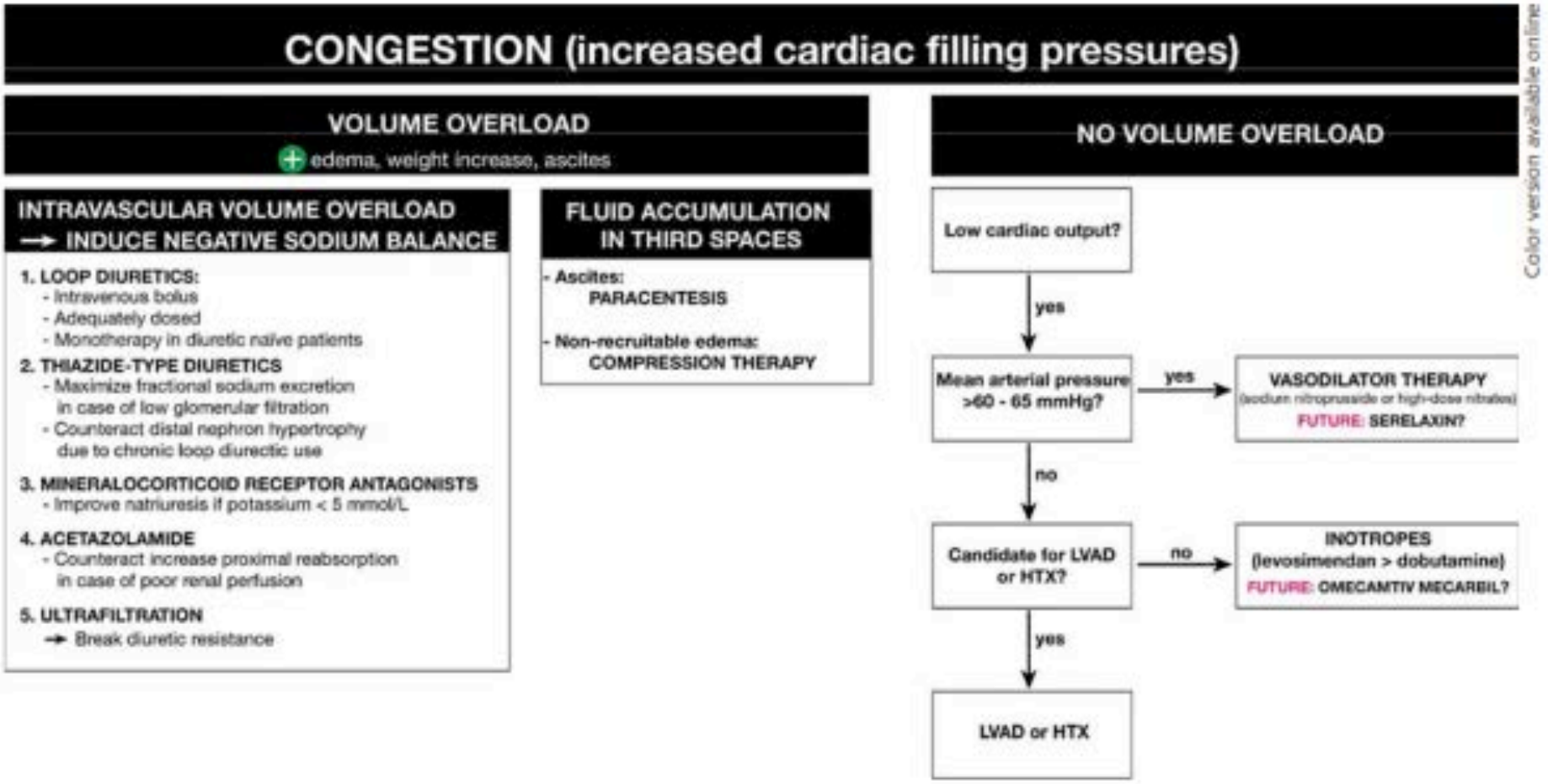

Fig. 2. Flowchart of the treatment of patients with CRS. HTX = Heart transplantation; LVAD = left ventricular assist device.

SERELAXIN

RELAXIN

- Endogenous endopeptide
- Plays a role in the maternal circulatory changes associated with pregnancy
- **Effects on arterial compliance, cardiac output, and renal blood flow** that could counterbalance the maladaptive changes in CRS

SERELAXIN

THE LANCET

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

Prof John R Teerlink, MD, Gad Cotter, MD, Beth A Davison, PhD, G Michael Felker, MD, Prof Gerasimos Filippatos, MD, Prof Barry H Greenberg, MD, Prof Piotr Ponikowski, MD, Elaine Unemori, PhD, Prof Adriaan A Voors, MD, Kirkwood F Adams Jr, MD, Prof Maria I Dorobantu, MD, Liliana R Grinfeld, MD, Prof Guillaume Jondeau, MD, Prof Alon Marmor, MD, Prof Josep Masip, MD, Peter S Pang, MD, Prof Karl Werdan, MD, Sam L Teichman, MD, Angelo Trapani, PhD, Christopher A Bush, PhD, Rajnish Saini, MD, Christoph Schumacher, PhD, Thomas M Severin, MD, Prof Marco Metra, MD, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

- > 1100 patients
- **Standard care + 48-hour IV infusion of placebo or serelaxin (30 mcg/kg/day) within 16 hours of presentation with acute HF**
- There was a **statistically significant improvement in visual analogue scale AUC dyspnea scores and fewer deaths at 180 days (HR 0.63, p = 0.019)**
- **More patients receiving placebo had adverse events related to renal impairment vs serelaxin (placebo 51 patients [9%]; serelaxin 32 [6%], p = 0.03)**

SERELAXIN

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http://dx.doi.org/10.1016/j.jacc.2012.11.005

EXPEDITED PUBLICATION

Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program

Correlation With Outcomes

Marco Metra, MD,* Gad Cotter, MD,† Beth A. Davison, PHD,† G. Michael Felker, MD, MHS,‡ Gerasimos Filippatos, MD,§ Barry H. Greenberg, MD,‖ Piotr Ponikowski, MD, PHD,¶ Elaine Unemori, PHD,# Adriaan A. Voors, MD, PHD,** Kirkwood F. Adams, JR, MD,†† Maria I. Dorobantu, MD,‡‡ Liliana Grinfeld, MD,§§ Guillaume Jondeau, MD, PHD,‖‖ Alon Marmor, MD,¶¶ Josep Masip, MD,## Peter S. Pang, MD,*** Karl Werdan, MD,††† Margaret F. Prescott, PHD,‡‡‡ Christopher Edwards, BS,† Sam L. Teichman, MD,# Angelo Trapani, PHD,‡‡‡ Christopher A. Bush, PHD,‡‡‡ Rajnish Saini, MD,‡‡‡ Christoph Schumacher, PHD,§§§ Thomas Severin, MD,§§§ John R. Teerlink, MD,‖‖‖ for the RELAX-AHF Investigators

Table 2 Association of Continuous Biomarker Changes From Baseline With 180-Day Mortality in the RELAX-AHF Study

Biomarker	HR (95% CI)*	p Value
Troponin (log2)		
Day 2	1.66 (1.24–2.02)	0.0002
Day 5	1.22 (1.01–1.47)	0.039
Day 14	1.68 (1.40–2.01)	<0.0001
Cystatin-C (log2)		
Day 2	2.28 (1.02–5.10)	0.046
Day 5	1.77 (0.87–3.59)	0.11
Day 14	1.34 (0.64–2.81)	0.44
Creatinine (log2)		
Day 2	1.64 (0.83–3.26)	0.15
Day 5	1.63 (0.88–3.00)	0.12
Day 14	1.12 (0.58–2.17)	0.74
NT-proBNP (log2)		
Day 2	1.73 (1.42–2.12)	<0.0001
Day 5	1.56 (1.30–1.88)	<0.0001
Day 14	1.48 (1.20–1.82)	0.0002

- Blood was sampled at days 2, 5 and 14 for creatinine and Cystatin C (CysC)
- Acute CRS: Defined as increases in serum creatinine and plasma CysC values of 0.3 mg/dL and 0.03 mg/L respectively

SERELAXIN

Table 4 Baseline Values and Changes From Baseline in Biomarkers Related to Organ Damage in the RELAX-AHF Study

Variable	Placebo (n = 580)	Serelaxin (n = 581)	Treatment Effect (95% CI)	p Value
Cardiac damage				
hs-cTnT (μg/l)				
Baseline geometric mean	0.036	0.034		
Below LLOQ (0.013 μg/l) at baseline	34/541 (6.3%)	40/533 (7.5%)		
Day 2 geometric mean	0.037	0.033		
Below LLOQ at day 2	32/534 (6.0%)	37/523 (7.1%)		
Relative change to day 2 (geometric mean change)	1.035	0.966	0.933 (0.883 to 0·985)*	0.013
≥20% increase at day 2	145/534 (27.2%)	86/522 (16.5%)	0.53 (0.39 to 0.71)†	<0.0001
Worsening renal function				
Serum creatinine (μmol/l)§				
Baseline mean	117	117		
Day 2 mean	123	113		
Mean change to day 2	6.2	−3.4	−9·5 (−12.4 to −6.6)‡	<0.001
≥0.3 mg/l (27 nmol/L) increase from baseline to day 2	108/545 (19.8%)	59/541 (10.9%)	0.50 (0.35 to 0.70)†	<0.0001
Cystatin C (nmol/l)‖				
Baseline geometric mean	109	109		
Day 2 geometric mean	118	112		
Relative change to day 2 (geometric mean change)	1.080	1.027	0.950 (0.931 to 0.970)*	<0.001
≥0.3 mg/l (22 nmol/l) increase from baseline to day 2	126/542 (23.2%)	86/539 (16.0%)	0.63 (0.46 to 0.85)†	0.0027

SERELAXIN

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≥0.3 mg/l (22 nmol/l) increase from baseline to day 2	126/542 (23.2%)	86/539 (16.0%)	0.63 (0.46 to 0.85)†	0.0027

At day 2, 19.8% treated with placebo vs. 10.9% treated with serelaxin had experienced an **increase in serum creatinine ≥ 0.3 mg/dL (p < 0.001)**

Novartis provides update on Phase III study of RLX030 (serelaxin) in patients with acute heart failure

MAR 22, 2017

- *Phase III RELAX-AHF-2 study did not meet primary endpoints of reduced cardiovascular death or worsening heart failure in patients with acute heart failure*

- *Novartis remains committed to improving and extending the lives of patients with cardiovascular disease and will continue to invest in ways to improve their outcomes*

Basel, March 22, 2017 - Novartis today announced results from the global Phase III RELAX-AHF-2 study investigating the efficacy, safety and tolerability of RLX030 (serelaxin) in patients with acute heart failure (AHF).

LEVOSIMENDAN

Crit Care Med. 2012 Feb;40(2):634-46. doi: 10.1097/CCM.0b013e318232962a.

Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies.

Landoni G[1], Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, Guarracino F, Zangrillo A.

Author information

Abstract

OBJECTIVE: Catecholaminergic inotropes have a place in the management of low output syndrome and decompensated heart failure but their effect on mortality is debated. Levosimendan is a calcium sensitizer that enhances myocardial contractility without increasing myocardial oxygen use. A meta-analysis was conducted to determine the impact of levosimendan on mortality and hospital stay.

DATA SOURCES: BioMedCentral, PubMed, Embase, and the Cochrane Central Register of clinical trials were searched for pertinent studies. International experts and the manufacturer were contacted.

STUDY SELECTION: Articles were assessed by four trained investigators, with divergences resolved by consensus. Inclusion criteria were random allocation to treatment and comparison of levosimendan vs. control. There were no restrictions on dose or time of levosimendan administration or on language. Exclusion criteria were: duplicate publications, nonadult studies, oral administration of levosimendan, and no data on main outcomes.

DATA EXTRACTION: Study end points, main outcomes, study design, population, clinical setting, levosimendan dosage, and treatment duration were extracted.

DATA SYNTHESIS: Data from 5,480 patients in 45 randomized clinical trials were analyzed. The overall mortality rate was 17.4% (507 of 2,915) among levosimendan-treated patients and 23.3% (598 of 2,565) in the control group (risk ratio 0.80 [0.72; 0.89], p for effect <.001, number needed to treat = 17 with 45 studies included). Reduction in mortality was confirmed in studies with placebo (risk ratio 0.82 [0.69; 0.97], p = .02) or dobutamine (risk ratio 0.68 [0.52-0.88]; p = .003) as comparator and in studies performed in cardiac surgery (risk ratio 0.52 [0.35; 0.76] p = .001) or cardiology (risk ratio 0.75 [0.63; 0.91], p = .003) settings. Length of hospital stay was reduced in the levosimendan group (weighted mean difference = -1.31 [-1.95; -0.31], p for effect = .007, with 17 studies included). A trend toward a higher percentage of

Levosimendan **might reduce mortality in cardiac surgery and cardiology settings of adult patients**

LEVOSIMENDAN

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

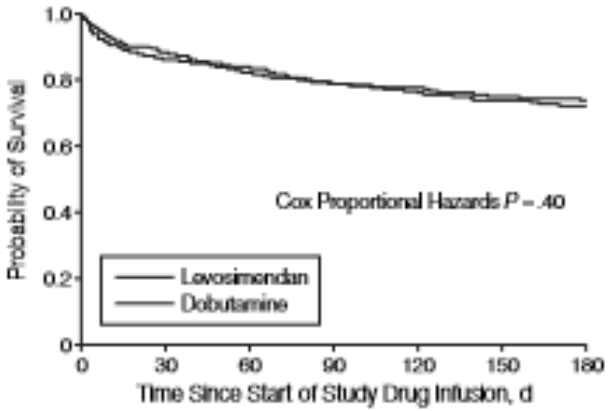
The SURVIVE Randomized Trial

Alexandre Mebazaa, MD, PhD
Markku S. Nieminen, MD, PhD
Milton Packer, MD
Alain Cohen-Solal, MD, PhD

Context Because acute decompensated heart failure causes substantial morbidity and mortality, there is a need for agents that at least improve hemodynamics and relieve symptoms without adversely affecting survival.

Objective To assess the effect of a short-term intravenous infusion of levosimendan or dobutamine on long-term survival.

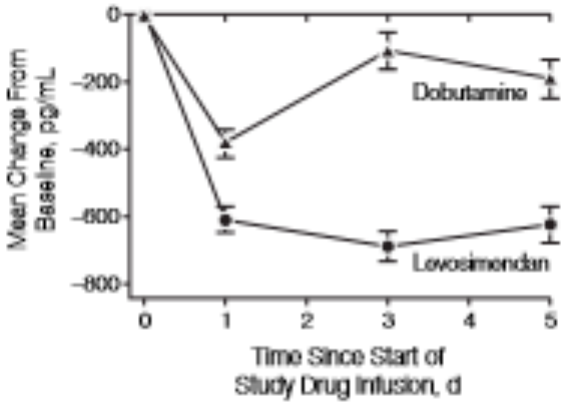
Figure 2. Effect of Dobutamine and Levosimendan Treatment on All-Cause Mortality During 180 Days Following the Start of Study Drug Infusion



No. at Risk

Levosimendan	664	606	586	525	462
Dobutamine	663	596	568	519	454

Figure 3. Mean Change From Baseline in B-Type Natriuretic Peptide Levels at 1, 3, and 5 Days by Treatment Group



There was a significantly greater mean (SE) change from baseline in plasma B-type natriuretic peptide levels in the levosimendan group compared with the dobutamine group at 1, 3, and 5 days after initiation of study drug infusion. $P<.001$ at all 3 time points. Statistical significance was determined using Kruskal-Wallis test with treatment effect.

Despite an **initial reduction in plasma BNP** in the Levosimendan group, **it did not significantly reduce all-cause mortality at 180 days.**

LEVOSIMENDAN

Cardiovascular Drugs and Therapy
December 2007, Volume 21, Issue 6, pp 431–435

Levosimendan Improves Renal Function in Patients with Acute Decompensated Heart Failure: Comparison with Dobutamine

Authors | Authors and affiliations

Mehmet Birhan Yilmaz, Kenan Yalta, Can Yontar, Filiz Karadas, Alim Erdem, Okan Onur Turgut, Ahmet Yilmaz, Izzet Tandogan

- **LVEF increased** and **24 hour UO improved** in both groups
- Those in L showed a **significant improvement in calculated GFR after 24 h**, whereas those in D showed no significant change (**median change in L:+15.3%,** median change in D: -1.33%).
- In the L group a **significant improvement was observed in calculated GFR after 72 h compared to baseline levels**; in D no significant change (**median change in L:+45.45%,** median change in D: +0.09%) was seen

LEVOSIMENDAN

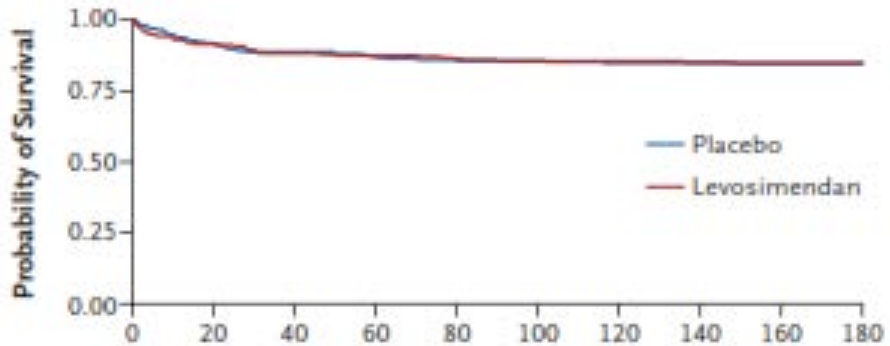
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

In patients who required **perioperative hemodynamic support after cardiac surgery,** low-dose levosimendan in addition to standard care **did not result in lower 30-day mortality than placebo.**



No. at Risk

Placebo	258	237	229	225	222	221	219	219	219	219
Levosimendan	248	227	219	217	214	212	212	211	210	210

Figure 2. Kaplan–Meier Survival Estimates of All-Cause Mortality.

OMECAMTIV MECARBIL

- CK-1827542
- First **selective cardiac myosin activator** to be studied in humans
- Specifically targets and activates myocardial ATPase and improves energy utilization, thereby **enhancing effective myosin cross-bridge formation and duration**, while the velocity of contraction remains the same
- Also **increases the rate of PO_4 release from myosin**, thereby accelerating the rate-determining step of the cross-bridge cycle (which is the transition of the actin-myosin complex from the weakly bound to the strongly bound state)

OMECAMTIV MECARBIL

- **EFFECTS:**
  - **Increases LV systolic ejection time, sarcomere shortening and stroke volume,** while systolic pressure remains the same **→ decrease in heart rate** while myocardial O_2 consumption is unaffected

OMECAMTIV MECARBIL

THE LANCET

Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial

Prof John R Teerlink, MD, Prof G Michael Felker, MD, Prof John J V McMurray, MD, Prof Scott D Solomon, MD, Kirkwood F Adams Jr, MD, Prof John G F Cleland, MD, Justin A Ezekowitz, MBBCh, Prof Assen Goudev, MD, Prof Peter Macdonald, MD, Prof Marco Metra, MD, Prof Veselin Mitrovic, MD, Prof Piotr Ponikowski, MD, Prof Pranas Serpytis, MD, Prof Jindrich Spinar, MD, Prof János Tomcsányi, MD, Hans J Vandekerckhove, MD, Prof Adriaan A Voors, MD, Maria Laura Monsalvo, MD, James Johnston, PhD, Fady I Malik, MD, Narimon Honarpour, MD for the COSMIC-HF Investigators

- Double blind, placebo controlled
- 45 patients on a stable HF regimen and LVEF < 40%
- Received OM for 2, 24, or 72 hours in a dose-escalating fashion (to ensure tolerability of the infusion)
- **DOSES > 100 ng/mL: Significant increase in the duration of LV systole, stroke volume and fractional shortening**

This trend **continued in a dose-dependent manner and plateaued > 400 ng/mL**

OMECAMTIV MECARBIL

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http://dx.doi.org/10.1016/j.jacc.2016.01.031

Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

The ATOMIC-AHF Study

John R. Teerlink, MD,[a,b] G. Michael Felker, MD,[c] John J.V. McMurray, MD,[d] Piotr Ponikowski, MD, PhD,[e] Marco Metra, MD,[f] Gerasimos S. Filippatos, MD,[g] Justin A. Ezekowitz, MBBCh, MSc,[h] Kenneth Dickstein, MD, PhD,[i,j] John G.F. Cleland, MD,[k] Jae B. Kim, MD,[l] Lei Lei, PhD,[l] Beat Knusel, PhD,[l] Andrew A. Wolff, MD,[m] Fady I. Malik, MD, PhD,[m] Scott M. Wasserman, MD,[l] on behalf of the ATOMIC-AHF Investigators

- Omecamtiv mecarbil vs placebo
- 606 patients with HF symptoms, with LVEF < 40%, elevated plasma concentrations of natriuretic peptides
- **Randomized 1:1**
  - ✓ 48-hour infusion of placebo or OM
  - ✓ Target mean plasma OM concentrations at 48 hours: 114, 230 and 310 ng/ mL using 3 dose escalating regimens

OMECAMTIV MECARBIL

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Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

The ATOMIC-AHF Study

John R. Teerlink, MD,[a,b] G. Michael Felker, MD,[c] John J.V. McMurray, MD,[d] Piotr Ponikowski, MD, PhD,[e] Marco Metra, MD,[f] Gerasimos S. Filippatos, MD,[g] Justin A. Ezekowitz, MBBCh, MSc,[h] Kenneth Dickstein, MD, PhD,[i,j] John G.F. Cleland, MD,[k] Jae B. Kim, MD,[l] Lei Lei, PhD,[l] Beat Knusel, PhD,[l] Andrew A. Wolff, MD,[m] Fady I. Malik, MD, PhD,[m] Scott M. Wasserman, MD,[l] on behalf of the ATOMIC-AHF Investigators

- OM **did not improve the primary endpoint of dyspnea relief or any secondary endpoints (p = 0.331)**
- OM was well-tolerated and did have significant physiological effects on systolic ejection time
- **Study was underpowered** to determine if there was **any effect on clinical outcomes**

OMECAMTIV MECARBIL

COSMIC-HF - Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure. (COSMIC-HF)

This study has been completed.

Sponsor:
Amgen

Collaborator:
Cytokinetics

Information provided by (Responsible Party):
Amgen

ClinicalTrials.gov Identifier:
NCT01786512

First received: January 18, 2013
Last updated: May 5, 2016
Last verified: April 2016
History of Changes

- **Clinical effectiveness of omecamtiv mecarbil**

ISTAROXIME

- **INOTROPIC:** Due to inhibition of Na-K ATPase at the sarcolemma, leading to an **increase in cytosolic Ca ~ improve contractility**
- **LUSITROPIC:** Related to stimulation of the sarcoplasmic reticulum Ca ATPase isoform 2 (SERCa2), leading to **rapid sequestration of cytosolic Ca into the sarcoplasmic reticulum during diastole ~ promoting myocardial relaxation**

The American Journal of Cardiology

ISTAROXIME

A Phase 1–2 Dose-Escalating Study Evaluating the Safety and Tolerability of Istaroxime and Specific Effects on Electrocardiographic and Hemodynamic Parameters in Patients with Chronic Heart Failure with Reduced Systolic Function

Jalal K. Ghali, MD, William B. Smith, MD, Guillermo Torre-Amione, MD, William Haynos, MD, Barry K. Rayburn, MD, Antonino Amato, MD, Dan Zhang, MD, Doug Cowart, PharmD, Giovanni Valentini, MD, Paolo Carminati, MD, Mihai Gheorghiade, MD

- Multi-center, randomized, double blind, placebo-controlled dose-escalation study designed to evaluate tolerability and safety
- Chronic HF with LVEF ≤ 40%
- Randomized to 1 of 3 groups receiving istaroxime or placebo, each with escalating doses over 3 hours within each low-, medium-, or high-dose cohort

The American Journal of Cardiology

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- **No effect on hemodynamic parameters in low- or medium-dose cohorts**
  - In **high dose-cohort**, there was a **dose-dependent increase in CI, acceleration index and velocity index**
- **SBP did not decrease** but there was an **increase in PP**
- **No significant change in mean HR, supraventricular ectopy or ventricular ectopy** between istaroxime or placebo

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- There was a **trend towards QTc shortening during the infusion period**
- **No significant changes in routine clinical data or BNP**
- ***Hemodynamic effects appeared to disappear rapidly within 6 hours after termination of infusion***

ISTAROXIME

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Vol. 51, No. 23, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.03.015

EXPEDITED PUBLICATIONS

Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent

A Randomized Controlled Trial in Patients Hospitalized With Heart Failure

Mihai Gheorghiade, MD, FACC,* John E. A. Blair, MD,* Gerasimos S. Filippatos, MD, FACC,†
Cezar Macarie, MD,‡ Witold Ruzyllo, MD,§ Jerzy Korewicki, MD,§
Serban I. Bubenek-Turconi, MD,¶ Maurizio Ceracchi, MS,‖ Maria Bianchetti, PHD,‖
Paolo Carminati, MD,‖ Dimitrios Kremastinos, MD,† Giovanni Valentini, MD,‖
Hani N. Sabbah, PHD, FACC,# for the HORIZON-HF Investigators

- Randomized, double blind, placebo controlled, dose escalation study (3 European countries)
- 120 patients hospitalized with HF who had
  - ✓ LVEF ≤ 35
  - ✓ SBP < 150 and > 90 mmHg
  - ✓ HR < 110 and > 60
  - ✓ Maintained on standard therapy for HF

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Hani N. Sabbah, PHD, FACC,# for the HORIZON-HF Investigators

- **MAIN EXCLUSION CRITERIA**
  - ✓ IV Inotropes
  - ✓ Serum Digoxin > 0.5 ng/mL
  - ✓ Recent ACS or coronary revascularization
  - ✓ Atrial fibrillation
  - ✓ L BBB
  - ✓ Implanted electrical devices
  - ✓ Serum Creatinine > 3.0 mgs/dL
  - ✓ Severe Liver enzyme abnormalities

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- **PCWP was significantly reduced with all 3 doses of istaroxime** during the entire length of the infusion
- **BP increased**
- **HR trended downward** in a dose-dependent manner
- **CI increased** in the high-dose cohort vs placebo
- **ECHO: Dose-dependent decrease in LVEDV (reached statistical significance in high-dose cohort)** vs placebo

ISTAROXIME

- Istaroxime **has not undergone further testing**, but has **potential in patients hospitalized with HF and reduced LVEF**, in whom inotropy and lusitropy are desired without the potential side effects of hypotension and tachycardia

NEUTRAL PEPTIDASE INHIBITORS

- Metallopeptidase that is upregulated in HF patients
- Responsible for metabolism of peptides: bradykinin, substance P, endothelin-1 and ANPs
- **EFFECTS:**
  - ✓ **Vasodilation**
  - ✓ **Decrease Na retention**
  - ✓ **Slow down ventricular hypertrophy and remodeling**

NEUTRAL PEPTIDASE INHIBITORS

Circulation

American Heart Association.

Comparison of Omapatrilat and Enalapril in Patients With Chronic Heart Failure: The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)

Milton Packer, Robert M. Califf, Marvin A. Konstam, Henry Krum, John J. McMurray, Jean-Lucien Rouleau and Karl Swedberg
for the OVERTURE Study Group

- **Ompatrilat (ACEi + NEP) vs Enalapril**: symptomatic patients with chronic HF
- 5770 patients with NYHA class II to IV HF and reduced EF
- **Randomized 1:1**
  - ✓ **Enalapril 10 mgs BID**
  - ✓ **Omipatrilat 40 mgs daily**
- **Average of 14.5 months**
- **PRIMARY ENDPOINT: Combined risk of death or hospitalization for HF requiring IV therapy**

NEUTRAL PEPTIDASE INHIBITORS

Circulation

American Heart Association.

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- **PRIMARY ENDPOINT: Combined risk of death or hospitalization for HF requiring IV therapy**
  - ✓ **Omipatrilat was found to be non-inferior** to enalapril
    Omipatrilat: 914 patients
    Enalapril: 973 patients
    [HR 0.94; 95% CI 0.86-1.03, p = 0.187]
- **Significant incidence of angioedema in omipatrilat group**

MECH: Inhibition of 3 enzymes that breakdown bradykinin

NEUTRAL ENDOPEPTIDASE INHIBITORS

Eur J Heart Fail. 2015 May;17(5):510-7. doi: 10.1002/ejhf.232. Epub 2015 Feb 6.

Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction.

Voors AA[1], Gori M, Liu LC, Claggett B, Zile MR, Pieske B, McMurray JJ, Packer M, Shi V, Lefkowitz MP, Solomon SD; PARAMOUNT Investigators.

Author information

Abstract

BACKGROUND: Increases in serum creatinine with renin-angiotensin-aldosterone system (RAAS) inhibitors can lead to unnecessary discontinuation of these agents. The dual-acting angiotensin receptor neprilysin inhibitor LCZ696 improves clinical outcome patients with heart failure with reduced ejection fraction, and pilot data suggest potential benefit in heart failure with preserved ejection fraction (HFpEF). The effects of LCZ696 on renal function have not been assessed.

METHODS AND RESULTS: A total of 301 HFpEF patients were randomly assigned to LCZ696 or valsartan in the PARAMOUNT trial. We studied renal function [creatinine, estimated glomerular filtration rate (eGFR), cystatin C, and urinary albumin to creatinine ratio (UACR)] at baseline, 12 weeks, and after 36 weeks of treatment. Worsening renal function (WRF) was determined as an serum creatinine increase of >0.3 mg/dL and/or >25% between two time-points. Mean eGFR at baseline was 65.4 ± 20.4 mL/min per 1.73 m(2) . The eGFR declined less in the LCZ696 group than in the valsartan group (-1.5 vs. -5.2 mL/min per 1.73 m(2) ; P = 0.002). The incidence of WRF was lower in the LCZ696 group (12%) than in the valsartan group (18%) at any time-point, but this difference was not statistically significant (P = 0.18). Over 36 weeks, the geometric mean of UACR increased in the LCZ696 group (2.4-2.9 mg/mmol), whereas it remained stable in the valsartan group (2.1-2.0 mg/mmol; P for difference between groups = 0.016).

CONCLUSION: In patients with HFpEF, therapy with LCZ696 for 36 weeks was associated with preservation of eGFR compared with valsartan therapy, but an increase in UACR.

PARAMOUNT: Prospective comparison of ARNI with ARB On Management Of heart failure with preserved ejection fracTion

NEUTRAL ENDOPEPTIDASE INHIBITORS

PARAMOUNT: LCZ696

- **Reduced NT-proBNP** to a greater extent
- **Reduced LA size and improved remodeling**
- **Decreased BP**
- **Improved HF symptoms**
- **Preserved eGFR to a greater extent**
  - ✓ **36-week decline in LCZ696 group of 1.6 mL/min/1.73 m^2** vs 5.2 mL/min/1.73 m^2 in the valsartan group, p = 0.007

NEUTRAL ENDOPEPTIDASE INHIBITORS

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In patients with HFpEF, therapy with LCZ696 for 36 weeks was associated with preservation of GFR (vs valsartan) but had an increase in UACR.

PARAMOUNT: Prospective comparison of ARNI with ARB On Management Of heart failure with preserved ejection fracTion

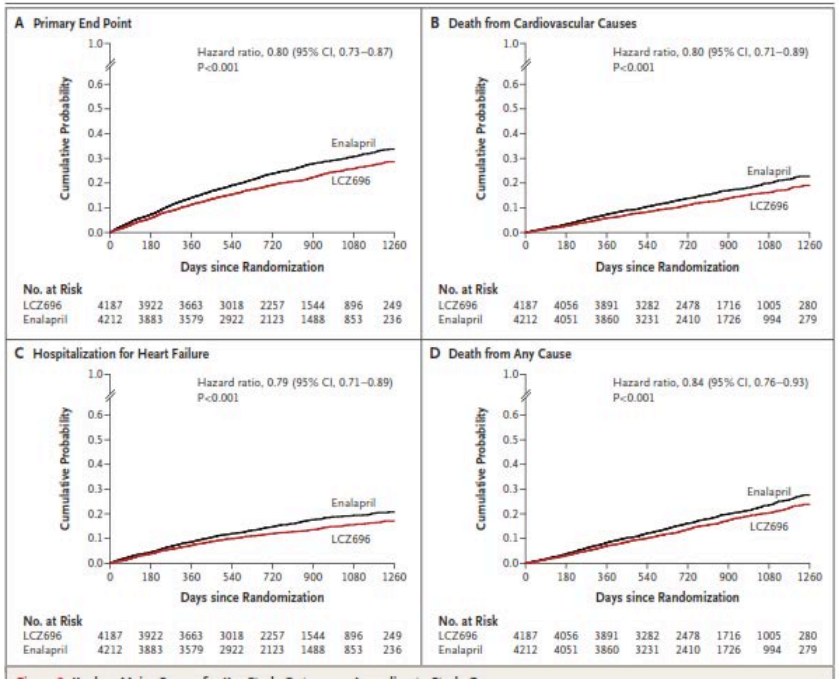
NEUTRAL ENDOPEPTIDASE INHIBITORS

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*



- Double blind
- 8442 patients with chronic NYHA class II-IV HF and LVEF ≤ 40%
- **Randomized 1:1**
  - ✓ **LCZ696 200 mg BID**
  - ✓ **Enalapril 10 mg BID**
- **PRIMARY OUTCOME: Composite of death from CV causes or a first Hospitalization for HF**
- **STOPPED EARLY after median F/U of <u>27 months</u>**

NEUTRAL ENDOPEPTIDASE INHIBITORS

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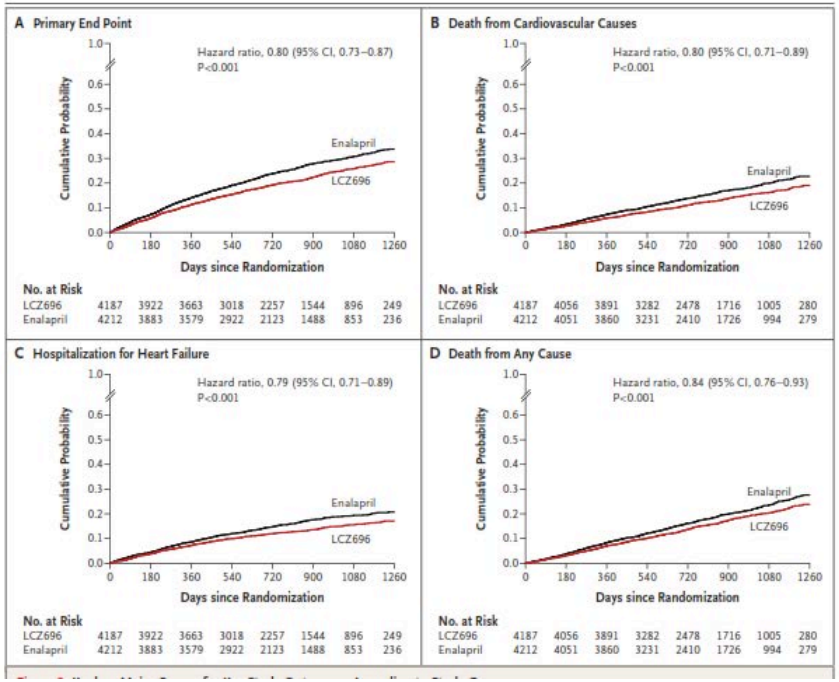


- **Remarkable efficacy in reducing both mortality and re-hospitalization in patients with symptomatic chronic HF.**
- HOWEVER, its **potential in advanced HF has not yet been prospectively studied**
- **Further investigation is into whether initiation of LCZ696 during an index ADHF hospitalization is an efficacious strategy in preventing morbidity and mortality is warranted.**

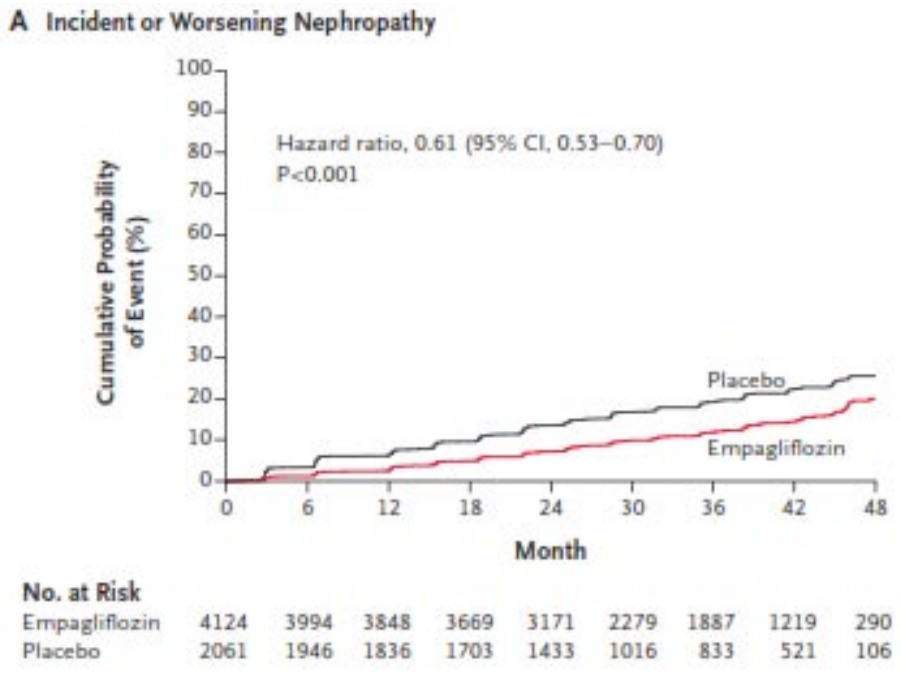
SGLT2-INHIBITORS

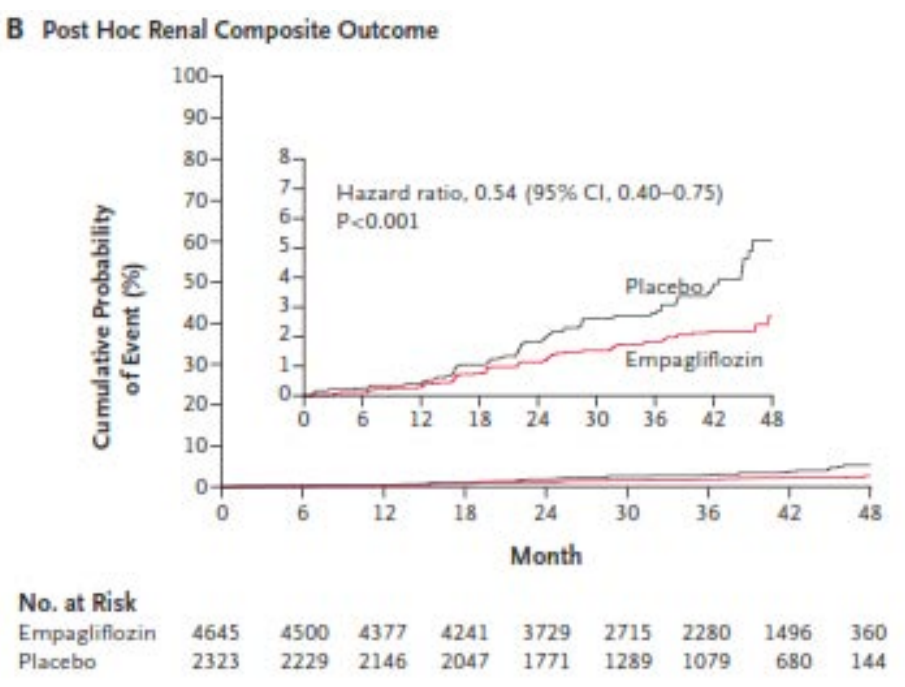
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*





SGLT2-INHIBITORS

- Decreased development of macroalbuminuria.
- Reduced slope of eGFR decline.
- Prevented serum creatinine doubling and ESRD.
- Benefit of empagliflozin occurred in sub-groups with and without pre-existing CKD.

SGLT2-INHIBITORS

Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis

Diabetes Care 2016;39:1115–1122 | DOI: 10.2337/dc16-0542

Table 1—Cardiovascular outcomes in the EMPA-REG OUTCOME study

CV outcome	Placebo group (n = 2,333)	Pooled empagliflozin group (n = 4,687)	Relative risk reduction
CV death, nonfatal MI/stroke	12.1	10.5	−14*
Death from any cause	8.3	5.7	−32*
CV death	5.9	3.7	−38*
Hospitalization for HF	14.5	9.4	−35*
Fatal/nonfatal MI (excludes silent MI)	5.4	4.8	−13**
Nonfatal stroke	3.0	3.5	+24**

Data are %. *Significant. **Nonsignificant.

Table 2—Renal outcomes in the EMPA-REG OUTCOME study

Renal outcome	Pooled empagliflozin group (n = 4,687) vs. placebo (n = 2,333)		
	Hazard ratio	Relative risk reduction (%)	P value
New-onset or worsening nephropathy	0.61	39	0.0001
Composite of: Doubling of serum creatinine Initiation of renal replacement therapy (includes dialysis/transplantation) Death due to renal disease	0.54	46	0.0002

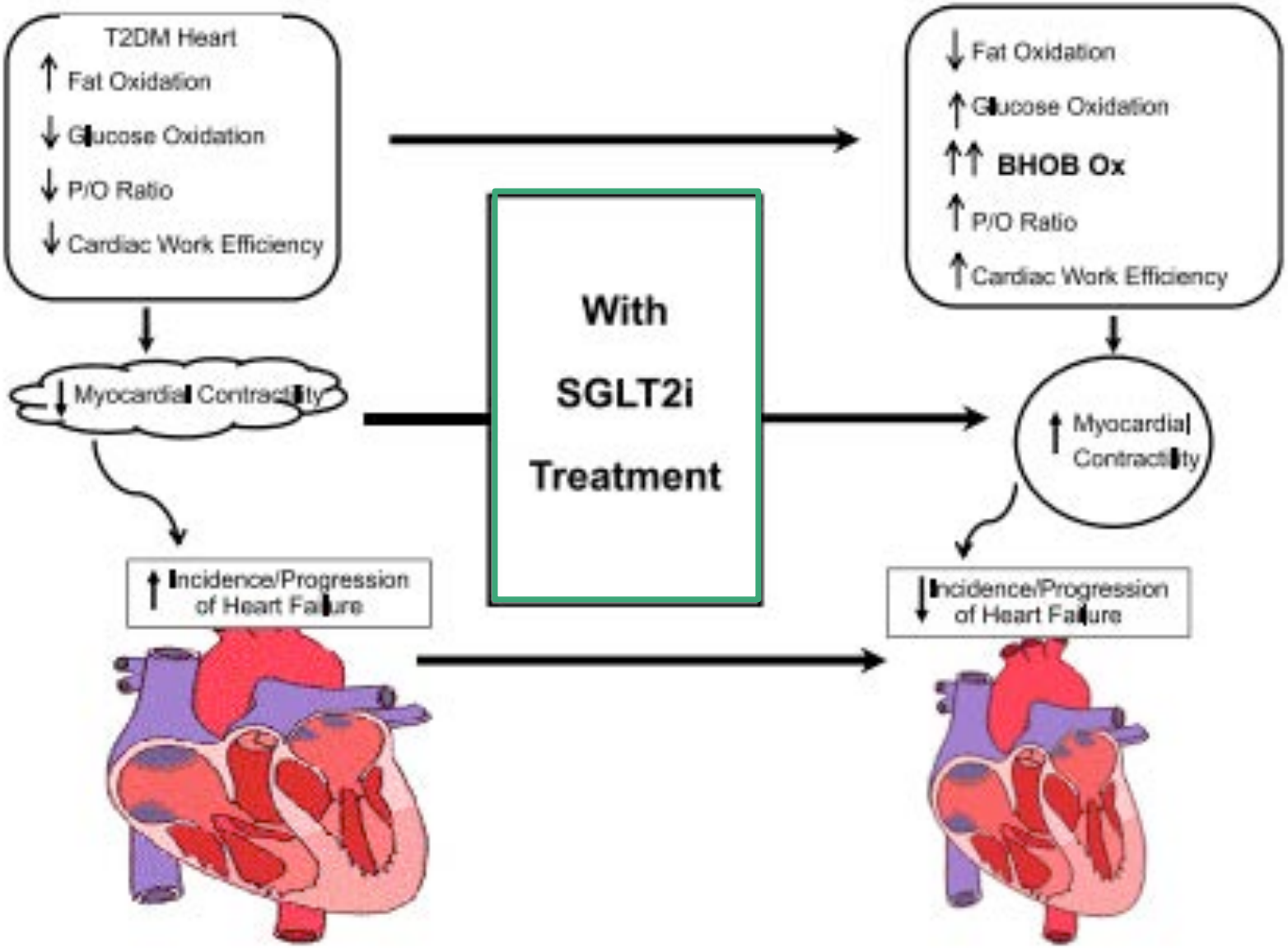
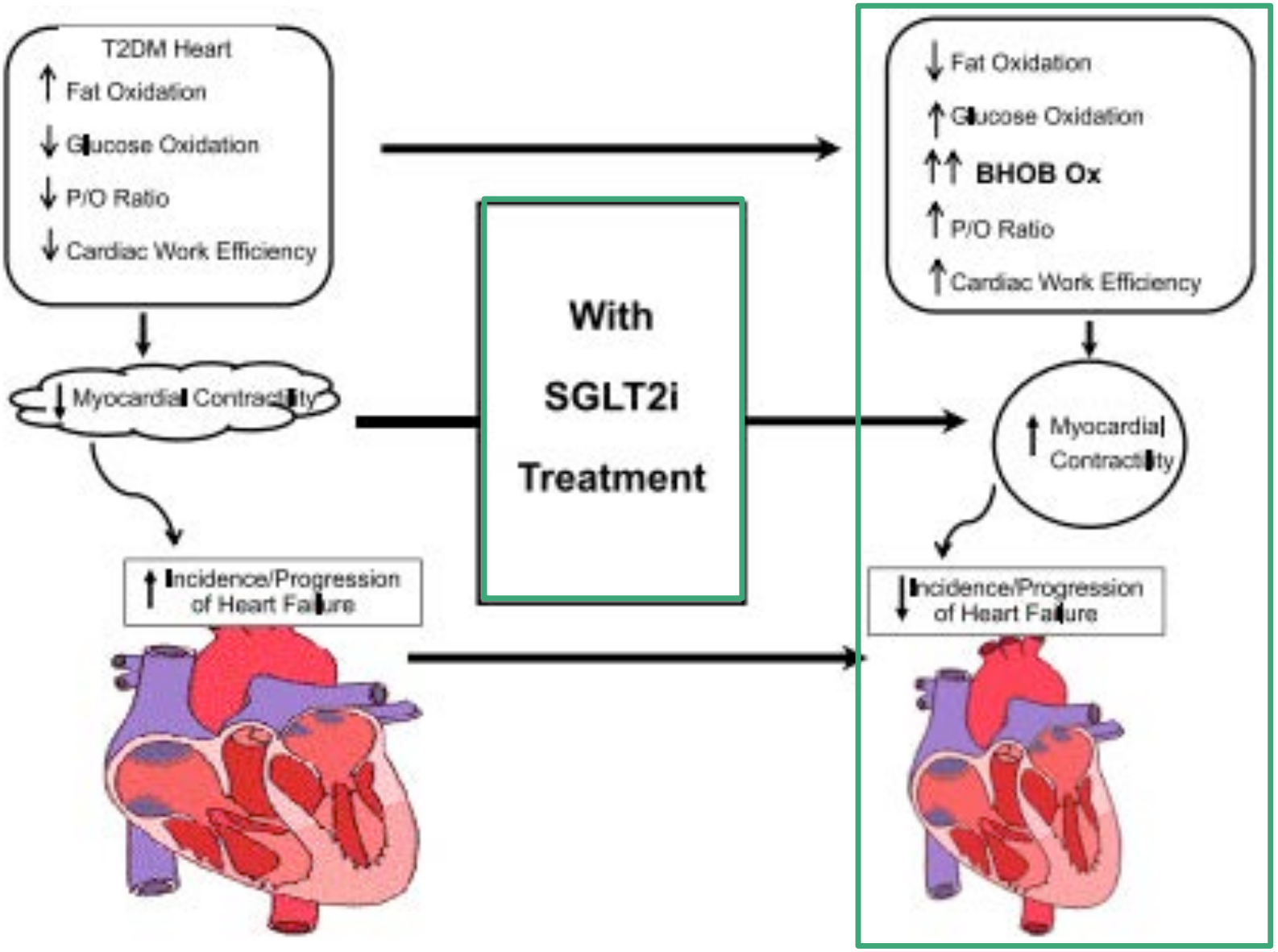


Figure 1—Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.



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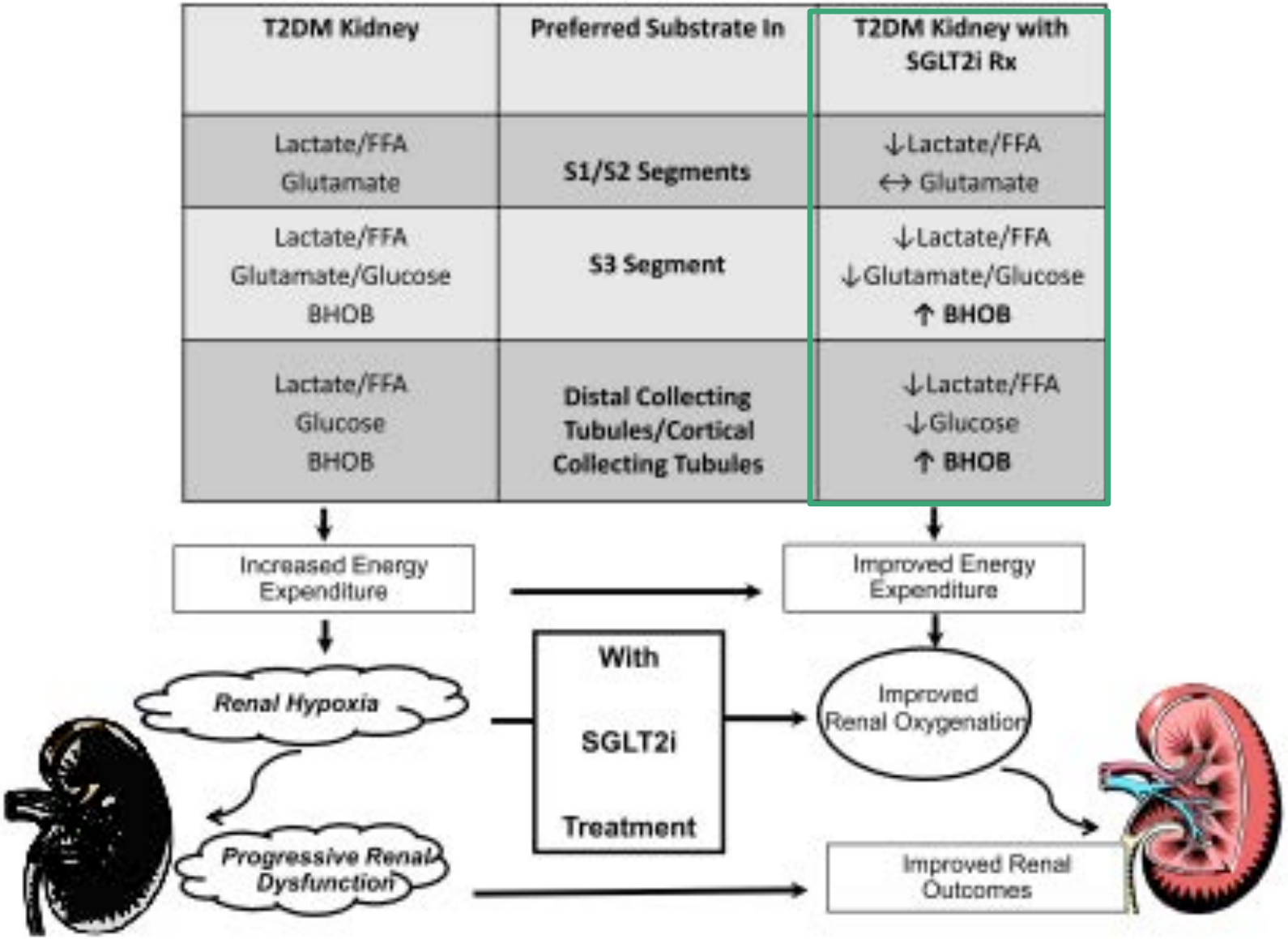
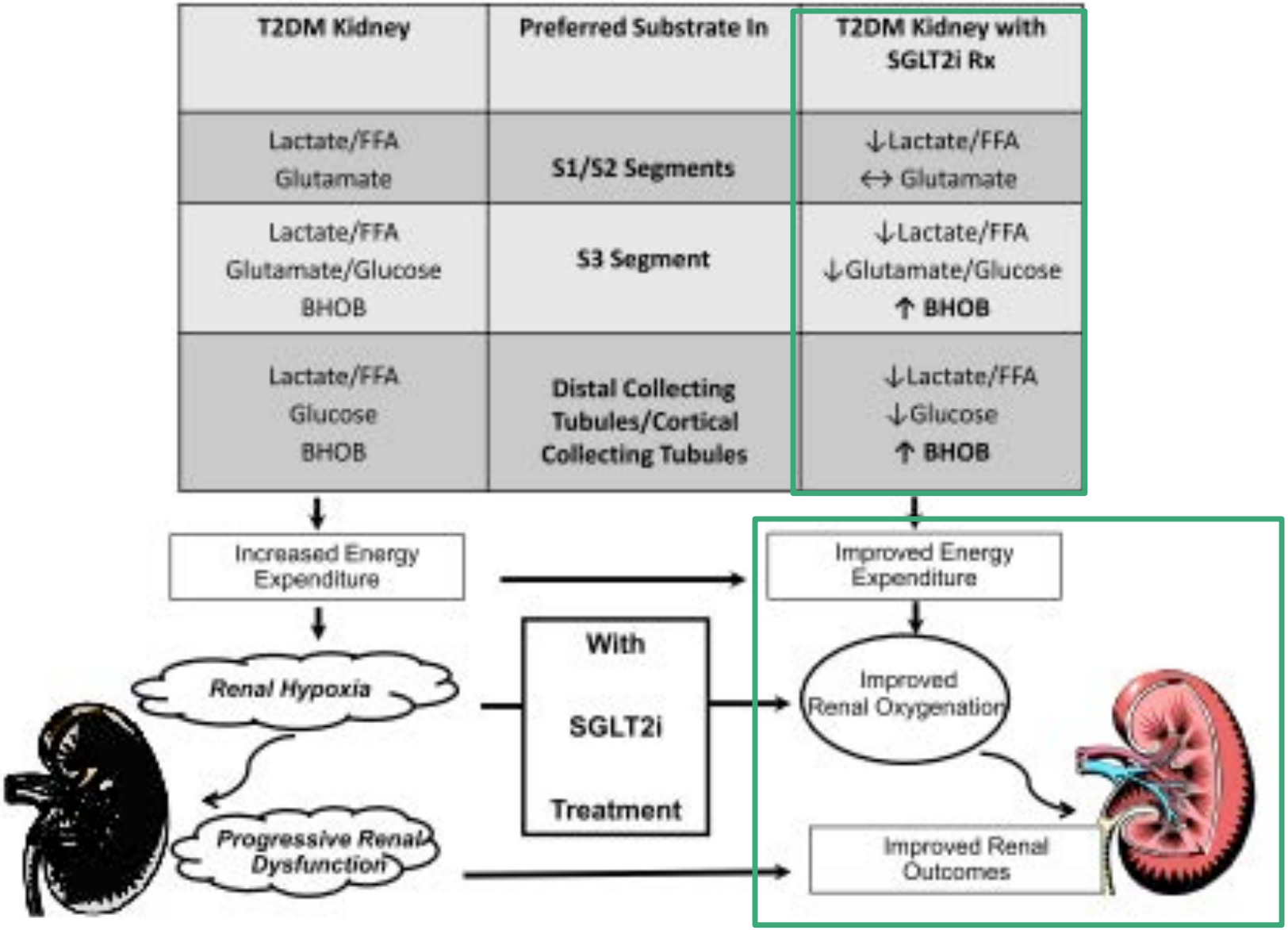


Figure 3—Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. Rx, treatment.



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GLP-1 AGONISTS

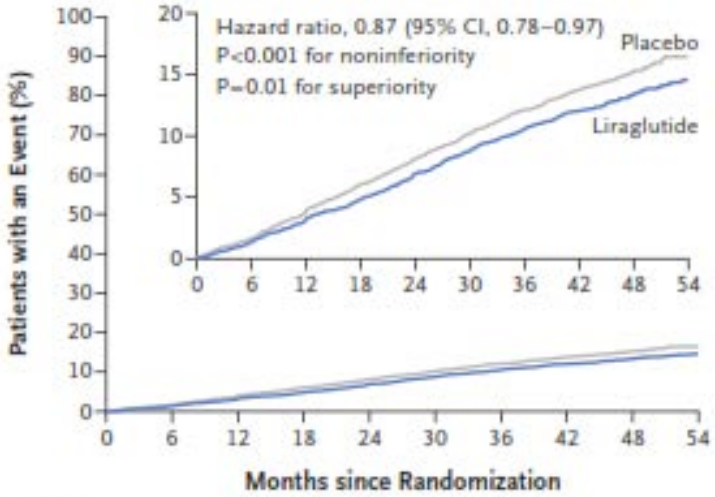
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

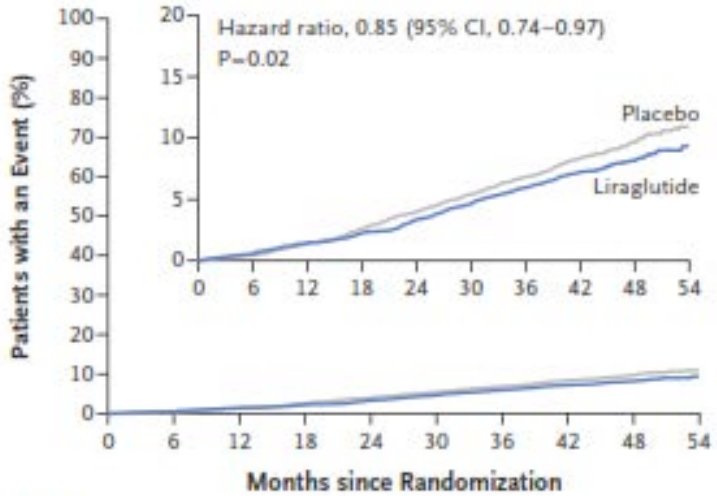
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

A Primary Outcome



No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

E Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

GLP-1 AGONISTS

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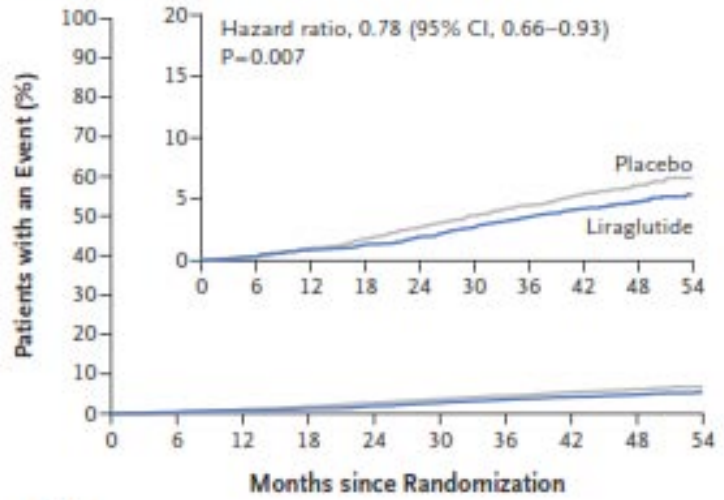
B Death from Cardiovascular Causes



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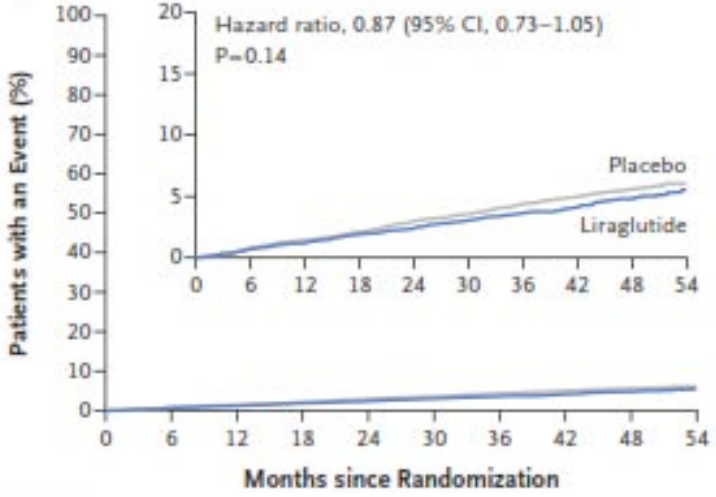
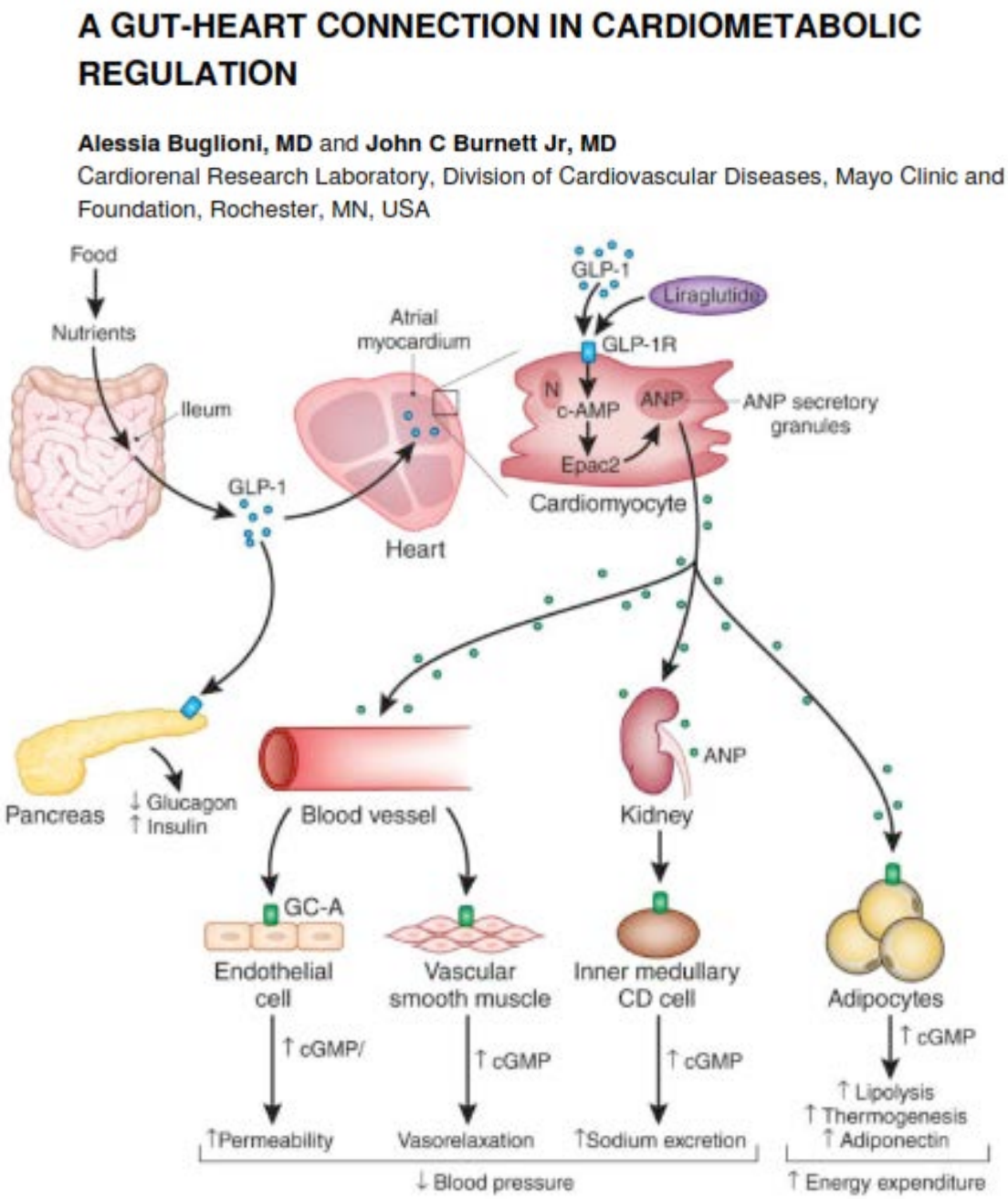
F Hospitalization for Heart Failure



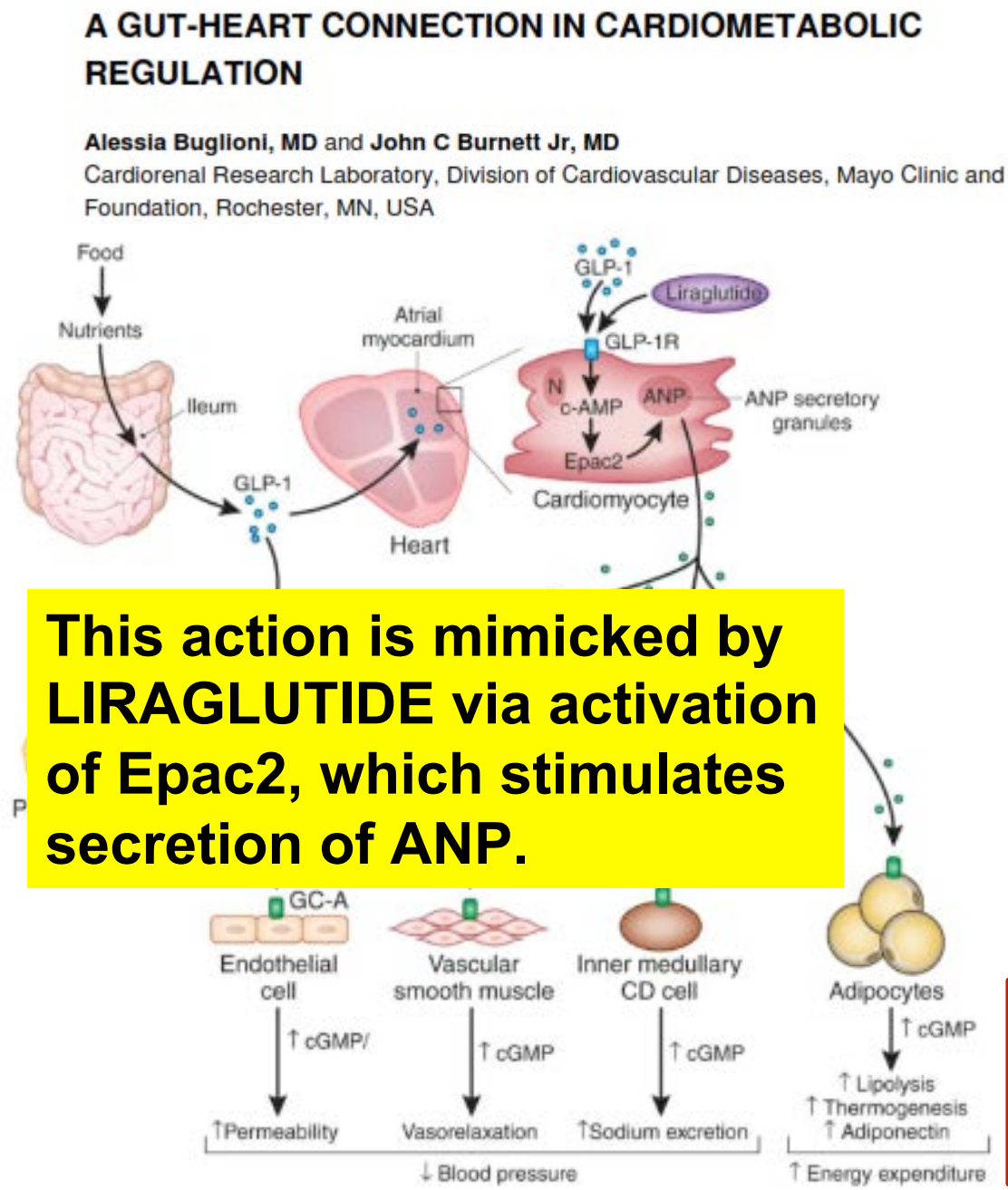
No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

GLP-1 AGONISTS



- **ILEUM: Nutrients are absorbed; GLP-1 is released from the secretory vesicles in ileum epithelial cells**
- **PANCREAS: GLP-1 decreases glucagon secretion & increases insulin release via GLP-1R**
- **HEART: GLP-1 activates GLP1-Rs in the atrial myocardium which induces ANP secretion from atrial secretory granules**

GLP-1 AGONISTS



This action is mimicked by LIRAGLUTIDE via activation of Epac2, which stimulates secretion of ANP.

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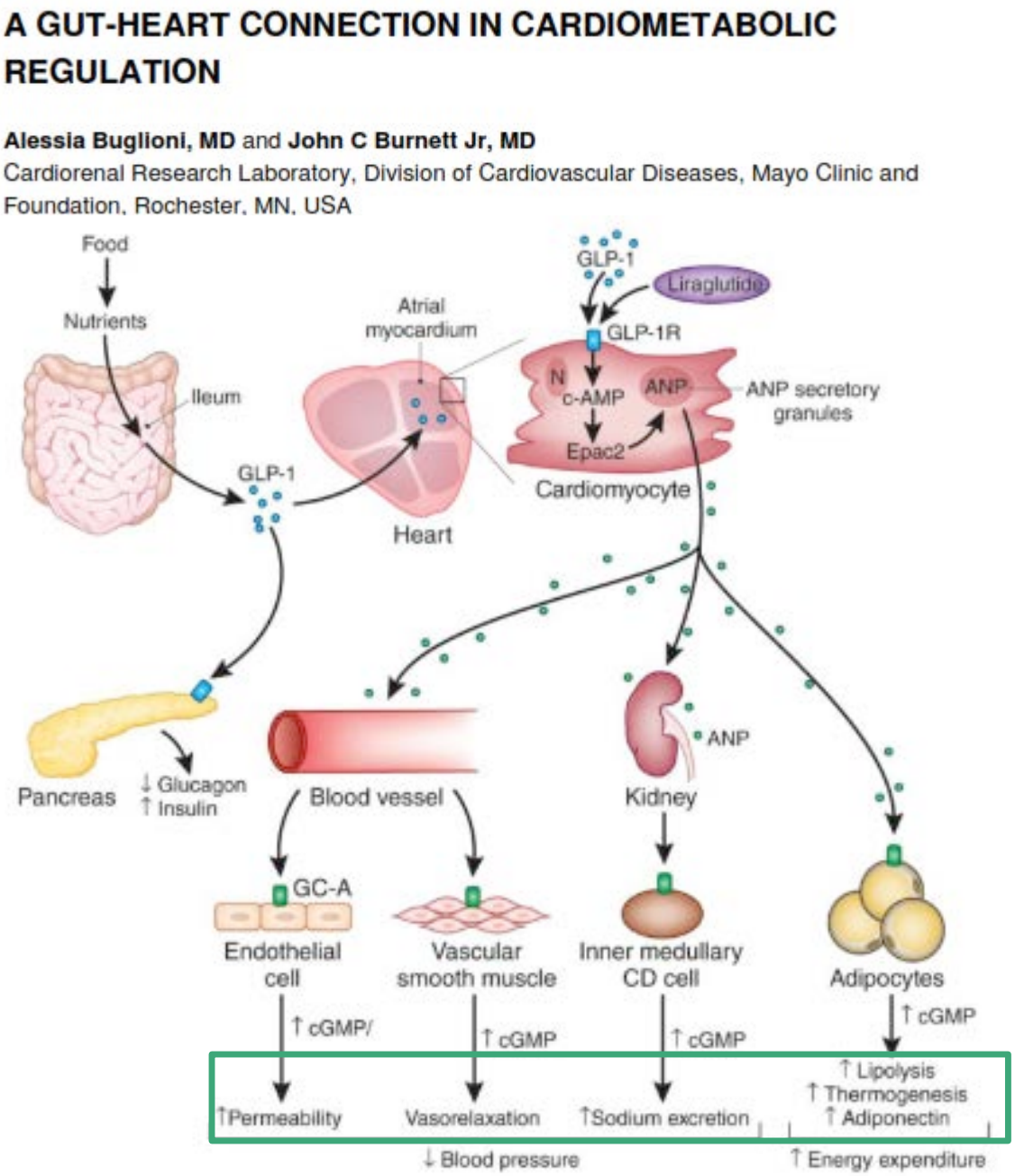
GLP-1 AGONISTS



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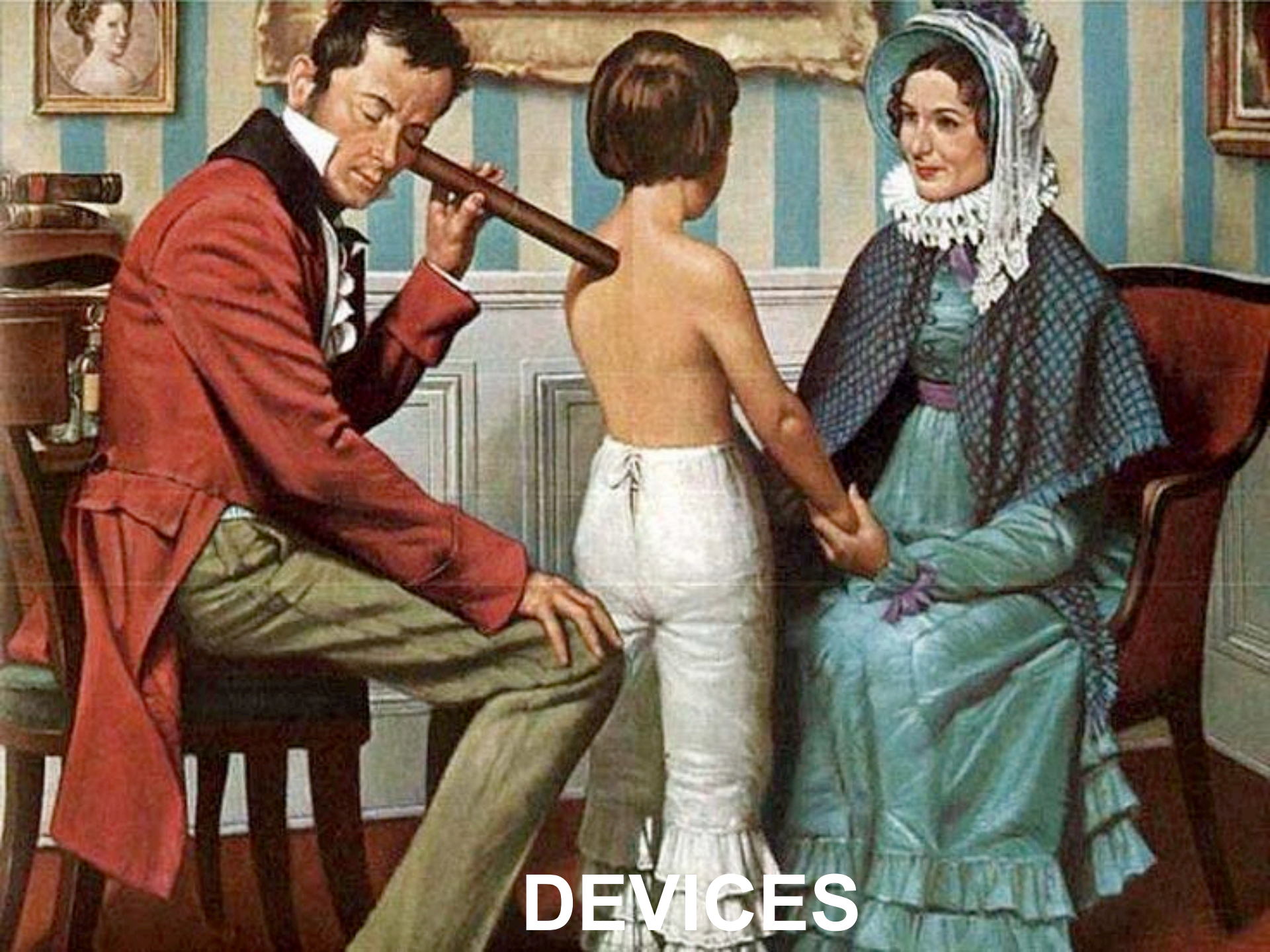
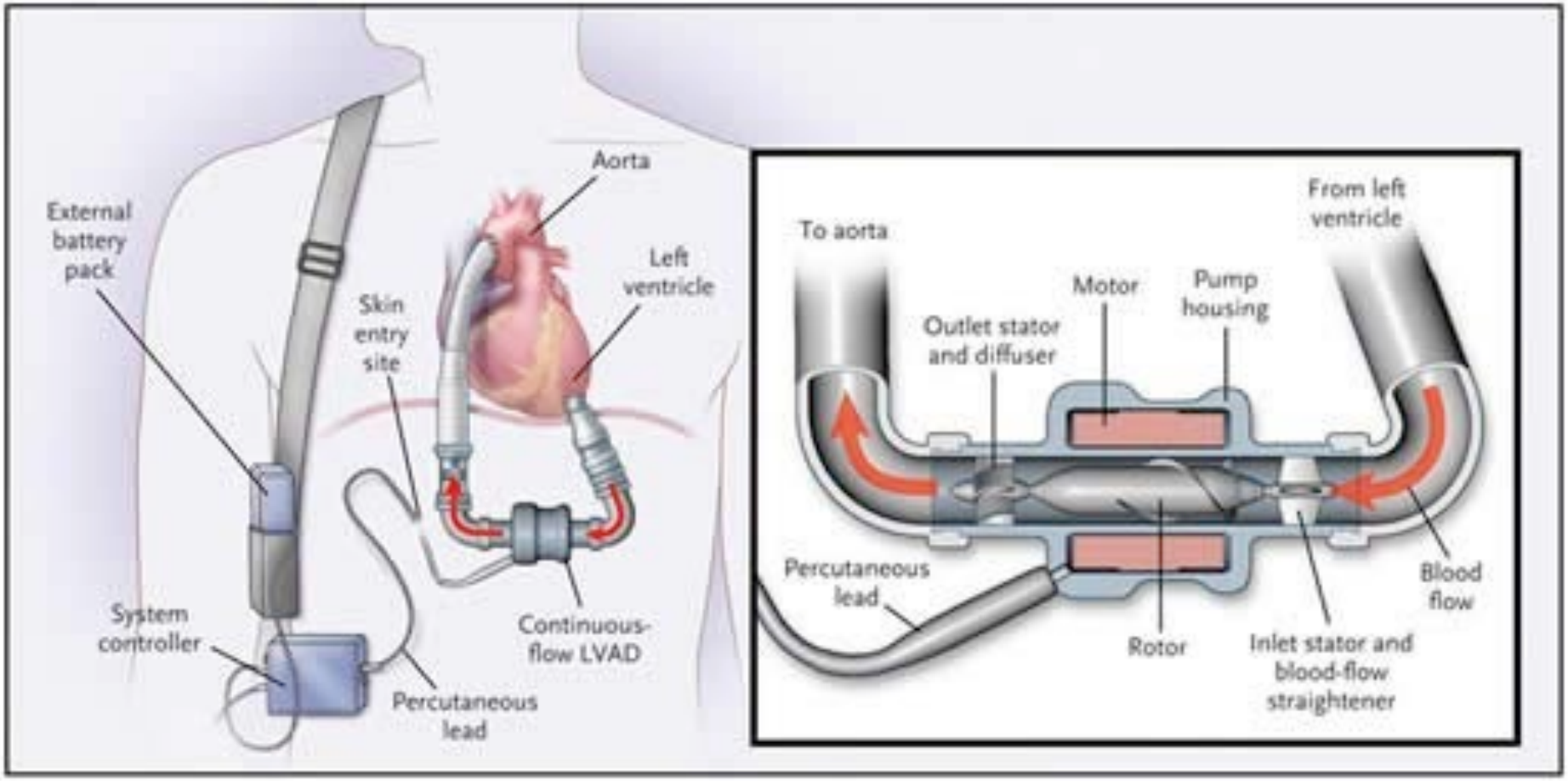
GLP-1 AGONISTS

- GLP-1 receptor agonists have **extra-pancreatic effects**, including **primary and secondary mechanisms for kidney protection**.
- **Lower risk of albuminuria onset and progression** have been observed across GLP-1 receptor agonists in clinical trials for CVD safety and drug registration in type 2 diabetes.
- Clinical trials of GLP-1 receptor agonists to test **effects on kidney function and clinical endpoints, eGFR thresholds and ESRD**, on-going.
- Both kidney and CVD safety have held-up in clinical trials as well as in real-world data.


DEVICES

LEFT VENTRICULAR ASSIST DEVICES (LVAD)



LEFT VENTRICULAR ASSIST DEVICES (LVAD)

The Journal of Heart and Lung Transplantation

J Heart Lung Transplant. 2013 Dec;32(12):1205-13. doi: 10.1016/j.healun.2013.09.001. Epub 2013 Oct 8.

Quantifying the effect of cardiorenal syndrome on mortality after left ventricular assist device implant.

Kirklin JK[1], Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, Givertz MM, Young JB.

Author information

Abstract

BACKGROUND: Comorbidities complicate recovery and contribute to mortality after implant of a left ventricular assist device (LVAD). Coexistent cardiac and renal dysfunction (so-called cardiorenal syndrome) increases the risk of death, both with advanced heart failure and after LVAD implantation. We analyzed patients from the Interagency Registry for Mechanically Assist Circulatory Support to better estimate postimplant mortality according to the severity of renal dysfunction.

METHODS: Patients with a continuous-flow LVAD were grouped according to their pre-implant level of renal dysfunction: severe was defined as dialysis and/or estimated glomerular filtration rate (eGFR) < 30 ml/min; moderate if eGFR was 30 to 59 ml/min or blood urea nitrogen (BUN) was > 60 mg/dl; and mild or no renal dysfunction if eGFR was ≥ 60 ml/min and BUN was < 60 mg/dl.

RESULTS: Of the 4,917 patients with a continuous-flow LVAD implanted between June 2006 and March 2012, 3,160 (64%) were identified with mild or no renal dysfunction, 1,475 (30%) with moderate dysfunction, and 282 (6%) with severe dysfunction. Worsening renal dysfunction correlated with decreased survival, with nearly a 20% reduction in the 2-year survival going from low to severe dysfunction. The major negative survival effect occurred during the first 3 months. Combination of severe renal dysfunction and cardiogenic shock predicted the highest early mortality.

CONCLUSIONS: Pre-implant renal dysfunction predicts higher mortality after LVAD implant. The progressive reduction in survival with higher grades of renal dysfunction supports consideration of LVAD implant before cardiorenal syndrome is advanced. For patients with severe renal dysfunction and other major comorbidities, initial support with a temporary device while awaiting organ recovery before implanting a durable pump could be considered.

LEFT VENTRICULAR ASSIST DEVICES (LVAD)

The Journal of Heart and Lung Transplantation

J Heart Lung Transplant. 2013 Dec;32(12):1205-13. doi: 10.1016/j.healun.2013.09.001. Epub 2013 Oct 8.

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- 4917 patients with continuous-flow LVADs enrolled in the INTERMACS registry (baseline moderate to severe renal dysfunction
- **Improvements in serum creatinine**
- **Reductions in BUN**

LEFT VENTRICULAR ASSIST DEVICES (LVAD)

Circulation
Heart Failure

American Heart Association®

Prevalence and Prognostic Importance of Changes in Renal Function After Mechanical Circulatory Support

Meredith A. Brisco, Stephen E. Kimmel, Steven G. Coca, Mary E. Putt, Mariell Jessup, Wilson W.H. Tang, Chirag R. Parikh and Jeffrey M. Testani

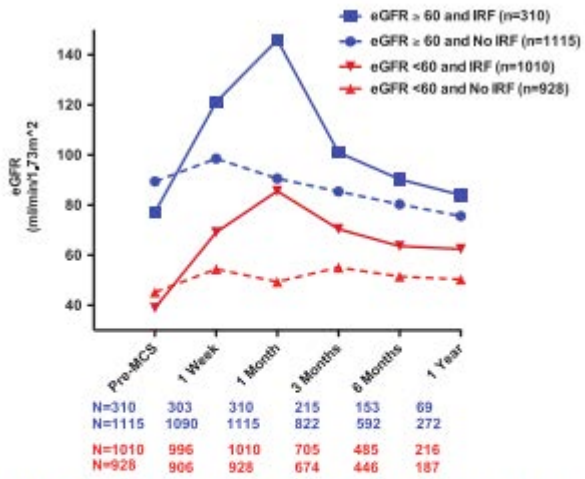


Figure 2. Mean eGFR over time in patients with and without pre-MCS renal dysfunction and post-MCS IRF. Mean eGFR according to presence or absence of baseline renal dysfunction further stratified by IRF at 1 mo post-MCS. Renal dysfunction defined as a pre-MCS eGFR <60 mL/min per 1.73 m². IRF is defined as a ≥50% improvement in eGFR from pre-MCS to 1 mo post-MCS. Sample sizes (N) refer to the number of patients with data available at all time points. eGFR indicates estimated glomerular filtration rate; IRF, improvement in renal function; and MCS, mechanical circulatory support.

This separate analysis of data from the INTERMACS registry found that **early improvements in eGFR with LVAD use were transient and typically only sustained for a period of weeks to months.**

CARDIAC RESYNCHRONIZATION

PACE
Pacing And Clinical Electrophysiology

Pacing Clin Electrophysiol. 2010 Jul;33(7):850-9. doi: 10.1111/j.1540-8159.2010.02705.x. Epub 2010 Feb 19.

Response to cardiac resynchronization therapy in patients with heart failure and renal insufficiency.

Adelstein EC[1], Shalaby A, Saba S.

Author information

Abstract

BACKGROUND: Renal insufficiency (RI) adversely impacts prognosis in heart failure (HF) patients, partly because renal and cardiac dysfunction are intertwined, yet few cardiac resynchronization therapy (CRT) studies have examined patients with moderate-to-severe RI.

METHODS: We analyzed 787 CRT-defibrillator (CRT-D) recipients with a glomerular filtration rate (GFR) measured prior to implant. Patients were grouped by GFR (in mL/min/1.73 m(2)): >or=60 (n = 376), 30-59 (n = 347), and <30 (n = 64). Overall survival, changes in left ventricular (LV) ejection fraction and LV end-systolic diameter, and GFR change at 3-6 months were compared among CRT-D groups and with a control cohort (n = 88), also stratified by GFR, in whom LV lead implant was unsuccessful and a standard defibrillator (SD) was placed. All patients met clinical criteria for CRT-D.

RESULTS: Among CRT-D recipients, overall survival improved incrementally with higher baseline GFR (for each 10 mL/min/1.73 m(2) increase, corrected hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.13-1.30, P < 0.0001). Survival among SD and CRT-D patients within GFR < 30 and GFR >or= 60 groups was similar, whereas CRT-D recipients with GFR 30-59 had significantly better survival compared to SD counterparts (HR 2.23, 95% CI 1.34-3.70; P = 0.002). This survival benefit was associated with improved renal and cardiac function. CRT recipients with GFR >or= 60 derived significant echocardiographic benefit but experienced a GFR decline, whereas those with GFR < 30 had no echocardiographic benefit but did improve GFR.

CONCLUSIONS: CRT may provide the largest survival benefit in HF patients with moderate RI, perhaps by improving GFR and LV function. Severe baseline RI predicts poor survival and limited echocardiographic improvement despite a modest GFR increase, such that CRT may not benefit those with GFR < 30 mL/min/1.73 m(2). CRT recipients with normal renal function derive echocardiographic benefit but no overall survival advantage.

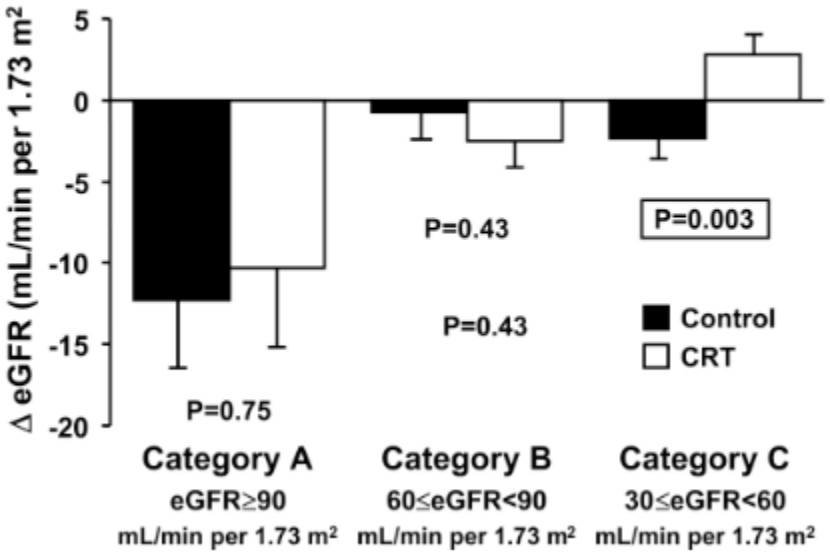
CARDIAC RESYNCHRONIZATION

Cardiac Resynchronization Therapy Improves Renal Function in Human Heart Failure With Reduced Glomerular Filtration Rate

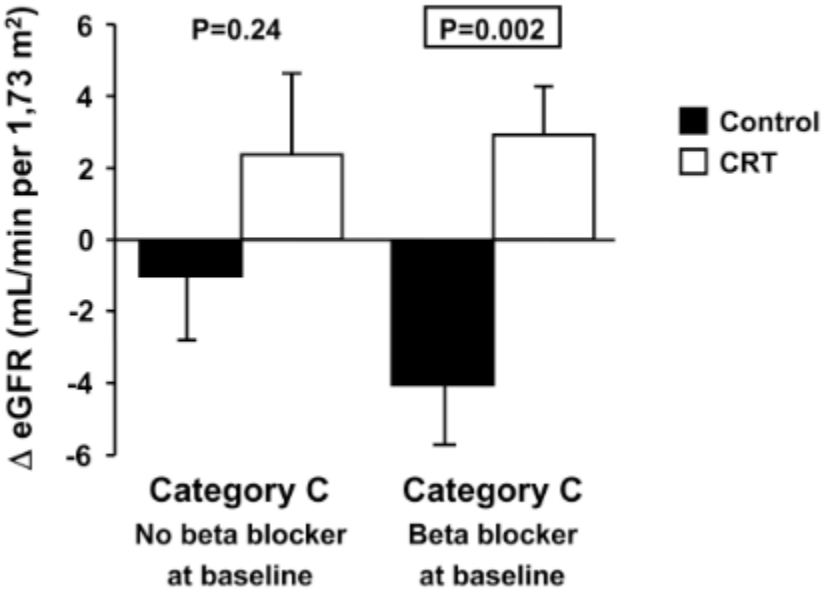
Guido Boerrigter, MD*, Lisa C. Costello-Boerrigter, MD, PhD*, William T. Abraham, MD†, Martin G. St. John Sutton, MD‡, Denise M. Heublein*, Kristin M. Kruger, BSN§, Michael R.S. Hill, PhD§, Peter A. McCullough, MD, MPH||, and John C. Burnett Jr, MD*

*Cardiorenal Research Laboratory, Mayo Clinic and Mayo Clinic College of Medicine, Rochester, MN, USA

1A Change from Baseline to 6 months: Estimated Glomerular Filtration Rate



2A Change from Baseline to 6 months: Estimated Glomerular Filtration Rate



CARDIAC RESYNCHRONIZATION

Cardiac Resynchronization Therapy Improves Renal Function in Human Heart Failure With Reduced Glomerular Filtration Rate

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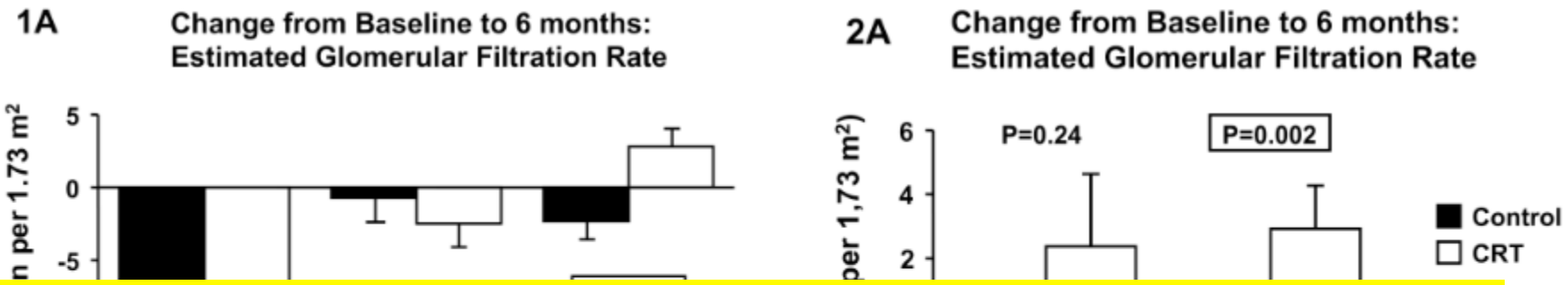
[*]Cardiorenal Research Laboratory, Mayo Clinic and Mayo Clinic College of Medicine, Rochester, MN, USA



Analyses of data from the observational study (preceding slide) and from the MIRACLE trial found that cardiac resynchronization therapy **improved LVEF and the eGFR in selected patients with HF and moderately reduced baseline eGFR (eGFR 30-59 mL/min)**

CARDIAC RESYNCHRONIZATION

- Implantation of the LV typically requires contrast administration in order to locate the ostium of the coronary sinus and to define coronary venous anatomy
  - Epicardial LV lead placement, via an open surgical procedure, has been suggested as an alternative in patients with CKD
    - More invasive
    - Longer ICU stay

Journal of Cardiovascular Diseases & Diagnosis

McCullough et al., J Cardiovasc Dis Diagn 2015, 3:5
http://dx.doi.org/10.4172/2329-9517.1000221

Review Article Open Access

Cardiorenal Syndromes: Advances in Determining Diagnosis, Prognosis, and Therapy

Peter A. McCullough[1*], James A. Tumlin[2], Harold Szerlip[3], Krishnaswami Vijayaraghavan[4], Sathya Jyothinagaram[5], John F. Rausch Jr[6], Bhupinder Singh[7], Jun Zhang[8] and Mikhail Kosiborod[9]

CHALLENGES	CONSEQUENCES	POTENTIAL SOLUTIONS
Lack of CRS-specific symptoms and reliable intermediate markers of disease progression	• Reliance on binary "hard" endpoints • Obligatory large, expensive, long-term trials, not feasible for many potential treatments	• Develop reliable intermediate outcomes, clearly linked to hard endpoints • Smaller, more focused trials
Focus on average treatment effects to determine if intervention works	• Failure to provide personalized treatment approach, so patients most likely to benefit are also most likely to be treated	• Rigorous assessment of treatment heterogeneity (benefit and risk) • Targeting interventions to patients most likely to benefit
Highly selective patient populations	• Lack of generalizability	• Long-term registries to monitor benefits and risks in "real-world" clinical practice

Figure 8: Change in priorities needed in future studies to help advance CRS.

European Heart Journal (2015) **36**, 1437–1444
doi:10.1093/eurheartj/ehv010

REVIEW

Clinical Update

The kidney in heart failure: an update

Kevin Damman[1]* and Jeffrey M. Testani[2]

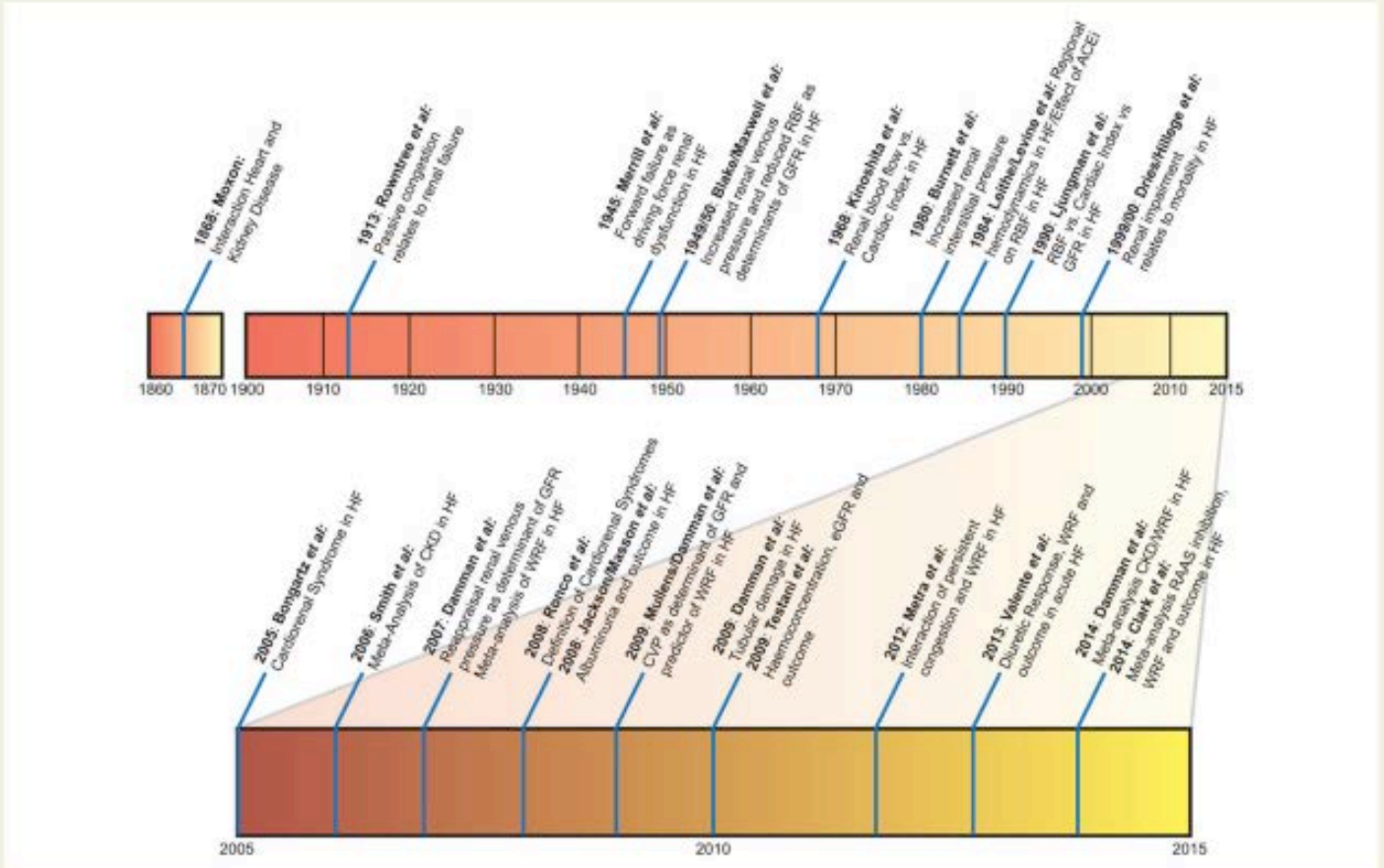


Figure 1 History of research in cardiorenal interaction. Overview of some key investigations in cardiorenal research. For reference list, see Supplementary material online, files.

European Heart Journal (2015) 36, 1437–1444
doi:10.1093/eurheartj/ehv010

REVIEW

Clinical Update

The kidney in heart failure: an update

Kevin Damman[1]* and Jeffrey M. Testani[2]

- Research needs to focus on further characterizing why some patients with impaired renal function and WRF fair pretty well, while others struggle to survive

- Studies should be conducted to differentiate between true and pseudo-WRF, and how we can possibly (early) distinguish between both, possibly via markers of tubular or glomerular damage, or yet to be discovered biomarkers or imaging modalities

- It is clear that renal dysfunction does not mean the same thing in each patient; we need strategies to determine the individual response

European Heart Journal (2015) 36, 1437–1444
doi:10.1093/eurheartj/ehv010

REVIEW

Clinical Update

The kidney in heart failure: an update

Kevin Damman[1]* and Jeffrey M. Testani[2]

- ❑ If possible, we need treatment options that can prevent significant deteriorations in renal function.

- ❑ In acute HF, we need strategies that improve diuretic response in patients that are most likely to benefit from the therapy, without compromising renal function

- To do so, we need more information on
  - ✓ Changes in hemodynamics
  - ✓ Cardiorenal connectors
  - ✓ Renal function and structure during and possibly before hospitalization
  - ✓ Whether specifically targeting renal function with therapies alters prognosis (in acute and chronic HF)

European Heart Journal (2015) 36, 1437–1444
doi:10.1093/eurheartj/ehv010

REVIEW

Clinical Update

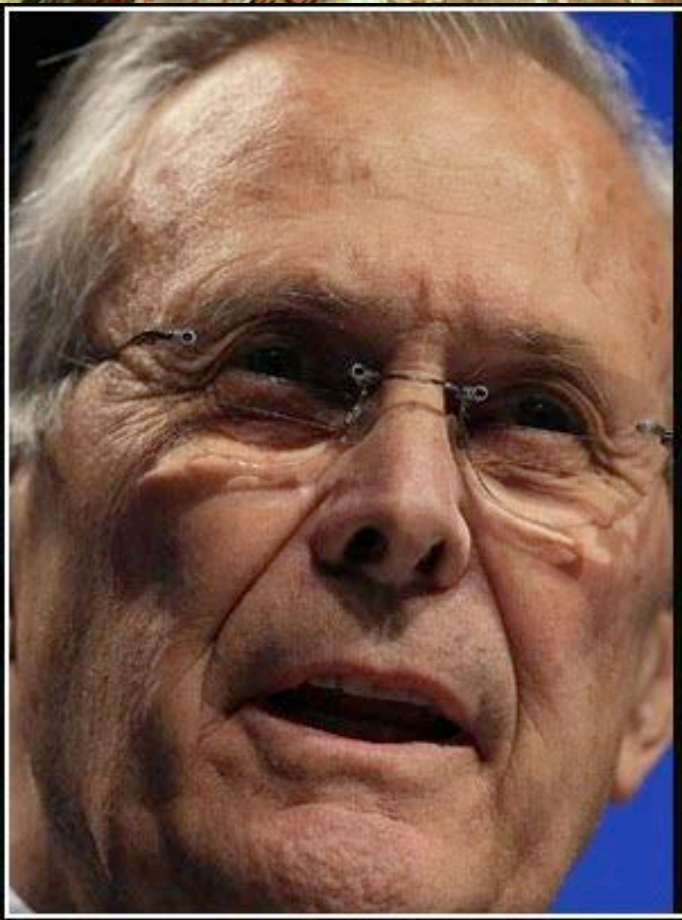
The kidney in heart failure: an update

Kevin Damman[1]* and Jeffrey M. Testani[2]

- In chronic HF, where the incidence of severe renal dysfunction is increasing, we need evidence-based treatments or strategies that are specifically designed and executed in HF patients with low GFR

- We need more information on how modulation of congestion in patients with chronic HF may alter renal function and structure

- To help determine where progress is made or needed, researchers should embark on a voyage to redesign and define cardiorenal syndrome in HF with evidence of the last 10 years



There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

— Donald Rumsfeld —

AZ QUOTES

One of the things I learned in medical school is “how to say ‘I don’t know,’ “ confidently … ain’t no shame in it …


ThankYou
Merci
Salamat
Kop
Hvala
Xie
Gra
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Tack
Dhanyavad
Khopjai
Gomapsupnida
Kruthagnathalu
Arigatou
Dhonnobaad
Asante
Dhan
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Hain
Kun
Euxaristo
Danke
dank
Enkosi
Terima
Fyrir
Blagodariya
Gracias
Nandree
Grazzi
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