Future Diagnostic & Therapeutic Targets in Cardiorenal Syndromes

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

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 Disclosure of Interests

- Speaker/ Advisory Board: Astute Medical, Mallinckrodt, Otsuka Pharmaceuticals, ZS Pharma

KDIGO Controversies Conference on Heart Failure in CKD
May 25-28, 2017 | Athens, Greece
Disclosure of ABIM Service: Edgar V. Lerma, M.D.

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The Quest
For the Cardiorenal Biomarker
**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
### 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 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.

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

Peter A. McCullough, James A. Tumlin, Harold Szerlip, Krishnaswami Vijayaraghavan, Sathya Jyothinagaram, John F. Rausch Jr, Bhupinder Singh, Jun Zhang and Mikhail Kosiborod

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

1Experimental and Clinical Research Center, Charité—Universitätsmedizin Berlin, Berlin, Germany and 2Max-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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Systemic NGAL reflects extrarenal synthesis and potentially some renal-derived NGAL.

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

The NGAL Test – first diagnostic acute kidney injury biomarker which can be measured in both human urine and plasma.

Important Note: (Not available in the USA for in vitro diagnostic use)

Introducing the CSA-NGAL score: A potential tool to monitor acute tubular damage

The Cardiac Surgery-Associated NGAL score - as presented in a new article by an expert group

Article in The Journal of Thoracic and Cardiovascular Surgery

Authored by an expert group chaired by Dr. Jean-Louis Vincent.
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, Claudio Ronco, MD, PhD, Michael Haase, MD, PhD, Laurent Jacob, MD, PhD, Andrew Lewington, MD, PhD, and Jean-Louis Vincent, MD, PhD

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Delta (Δ) NGAL at following measurement</th>
<th>CSA-NGAL Score</th>
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<tbody>
<tr>
<td>uNGAL &lt;50</td>
<td></td>
<td>0 Tubular damage unlikely</td>
</tr>
<tr>
<td>pNGAL &lt;100</td>
<td></td>
<td></td>
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<tr>
<td>uNGAL 50 - 150</td>
<td></td>
<td>1 Tubular damage possible</td>
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<tr>
<td>pNGAL 100 - 200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNGAL 150 - 1000 or second value ≥ 125</td>
<td>2 Tubular damage</td>
<td></td>
</tr>
<tr>
<td>pNGAL 200 - 1000 or second value ≥ 150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNGAL &gt;1000</td>
<td></td>
<td>3 Severe tubular damage</td>
</tr>
<tr>
<td>pNGAL &gt;1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The cardiac surgery–associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage

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<td></td>
<td></td>
</tr>
<tr>
<td>uNGAL 150 - &lt;1000 or pNGAL 200 - 1000</td>
<td>Δ &gt; 100 + second value ≥ 125</td>
<td>2 Tubular damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
# CSA-NGAL Score based management considerations

Acute kidney tubular damage in cardiac surgery

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<tr>
<th>ACTION</th>
<th>CSA-NGAL 0</th>
<th>CSA-NGAL 1</th>
<th>CSA-NGAL 2</th>
<th>CSA-NGAL 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tubular damage unlikely</td>
<td>Tubular damage possible</td>
<td>Tubular damage</td>
<td>Severe tubular damage</td>
</tr>
<tr>
<td>Pre-operative</td>
<td></td>
<td>Continue with operation</td>
<td>Continue with operation with focus on AKI progression</td>
<td>Consider postponing operation or continue with intensified focus on AKI progression</td>
</tr>
<tr>
<td>NGAL follow-up</td>
<td>Only 4-6h post surgery</td>
<td></td>
<td>YES – until damage has subsided</td>
<td></td>
</tr>
<tr>
<td>sCreatinine</td>
<td>Standard care (daily)</td>
<td>Every 12 hours</td>
<td>Every 6 hours</td>
<td>Monitor hourly urine output</td>
</tr>
<tr>
<td>Urine output</td>
<td>Standard care</td>
<td>Strict In's and Out's review Every 6h</td>
<td></td>
<td>Monitor hourly urine output</td>
</tr>
<tr>
<td>Venous Oxygen saturation</td>
<td>Standard Care</td>
<td>Target SVO$_2$ &gt; 60% Review SVO$_2$ trend every 3h</td>
<td>Target SVO$_2$ &gt; 60% Hourly review of SVO$_2$ trend</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxic medication</td>
<td>Standard care</td>
<td>Consider alternatives Adjust dosing</td>
<td>Move to alternatives if possible Close attention to renal responses</td>
<td></td>
</tr>
<tr>
<td>Patient location</td>
<td>Discharge to floor from ICU</td>
<td>Discharge to floor from ICU</td>
<td>Consider step-down unit</td>
<td>Consider keeping patient in ICU</td>
</tr>
<tr>
<td>Expert consultation</td>
<td>Standard care</td>
<td></td>
<td>Consider Nephrology consult</td>
<td>Nephrology consult Consider RRT</td>
</tr>
</tbody>
</table>
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.
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

Kidney Injury Molecule-1 (KIM-1)

Ordering information

<table>
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<tr>
<th>ANTIGEN</th>
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<tr>
<td>Product name</td>
<td>Cat. #</td>
<td>Purity</td>
<td>Source</td>
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<td>Kidney injury molecule-1 (KIM-1), ectodomain, recombinant</td>
<td>8KR6</td>
<td>&gt;92%</td>
<td>Recombinant</td>
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<tr>
<td>Product name</td>
<td>Cat. #</td>
<td>MAb</td>
<td>Subclass</td>
</tr>
<tr>
<td>Kidney injury molecule-1 (KIM-1)</td>
<td>4KM1</td>
<td>KIM70</td>
<td>IgG1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KIM75</td>
<td>IgG1</td>
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Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury
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

• 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

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


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

• 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

<table>
<thead>
<tr>
<th>Clinical Evidence of AKI</th>
<th>Clinical Suspicion</th>
<th>STS Predicted Mortality</th>
<th>Urinary [TIMP-2]-[IGFBP7]</th>
<th>Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Low or Moderate</td>
<td>Any</td>
<td>≤ 0.3</td>
<td>LOW</td>
</tr>
<tr>
<td>Negative</td>
<td>Low or Moderate</td>
<td>&lt;4%</td>
<td>&gt;0.3 &lt;2.0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>≥ 4%</td>
<td>&gt;0.3 &lt;2.0</td>
<td>High</td>
</tr>
<tr>
<td>Positive</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>High</td>
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<tr>
<td>Any</td>
<td>High</td>
<td>Any</td>
<td>Any</td>
<td>High</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>≥ 2.0</td>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

**Action**
- Monitor sCr
- Monitor Urine Output
- Ensure volume status
- Avoid Nephrotoxic meds
- Cardiac management
- Recheck markers

**Low Risk**
- Standard Care (daily)
- (I/Os reviewed every 12 hours)

**Moderate Risk**
- Every 12 hrs until decrease
- Strict I/Os keep Foley
- For Oliguria, may use balanced fluid IF CVP < 8; Hold Lasix unless pulmonary edema
- No NSAIDS or ACE/ARBs
- Monitor SCVO2 if h/o abnormal LV Fx

**High Risk**
- Every 12hrs until decrease
- Strict I/Os keep Foley
- May use balanced fluid IF CVP < 8 AND evidence of hypovolemia (not just oliguria); hold Lasix
- No NSAIDS or ACE/ARBs
- Adjust doses (narcotics)*
- Monitor SVO2, Echo or PA catheter if < 55% – Inotropes to keep CI >2.2

* Adjust doses (narcotics) if necessary.
COMMERCIALLY-AVAILABLE BIOMARKERS

Innovative biomarkers. Smarter healthcare.

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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

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

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

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

Hiromasa Katoh, Tsuyoshi Nozue, Yuya Kimura, Sei Nakata, Taku Iwaki, Mitsuhiro Kawano, Masa-aki Kawashiri, Ichiro Michishita, Masakazu Yamagishi
• 200 patients
• Urinary L-FABP $\geq$ 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]
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Even a baseline increase of urinary L-FABP prior to contrast media administration identified patients at risk for CI-AKI.
COMMERCIALLY-AVAILABLE BIOMARKERS

EARLY DIAGNOSIS OF KIDNEY DISEASES

L-FABP

Home  About L-FABP  Clinical Utilities  News  Published works  Nonclinical data

Product information

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

KDIGO Controversies Conference on Heart Failure in CKD
May 25-28, 2017 | Athens, Greece
Cardiac and Renal Fibrosis in Chronic Cardiorenal Syndromes

Aneley Hundae, Peter A. McCullough

Fig. 3. Roles of ST2 and galectin-3 in pathogenic cardiac fibrosis. MMP = Matrix metalloproteinase; TIMP = tissue inhibitor of metalloproteinase.
RENNAL BIOMARKERS
TISSUE FIBROSIS: Galectin-3

- A β-galactosidase-binding lectin
- Expressed both intracellularly 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.
There is a strong relationship between galectin-3 and increased mortality in both stable chronic and decompensated HF patients.
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.
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 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AUC</th>
<th>IDI Value (SEM)</th>
<th>P Value</th>
<th>NRI* Value (SEM)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uAGT</td>
<td>0.84</td>
<td>0.06 (0.02)</td>
<td>0.003</td>
<td>0.13 (0.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>uNGAL</td>
<td>0.78</td>
<td>0.05 (0.02)</td>
<td>0.03</td>
<td>0.08 (0.04)</td>
<td>0.05</td>
</tr>
<tr>
<td>uAGT+uNGAL</td>
<td>0.90</td>
<td>0.09 (0.03)</td>
<td>&lt;0.001</td>
<td>0.19 (0.09)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uAGT</td>
<td>0.77</td>
<td>0.06 (0.02)</td>
<td>0.01</td>
<td>0.16 (0.07)</td>
<td>0.02</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.63</td>
<td>0.02 (0.01)</td>
<td>0.08</td>
<td>0.07 (0.03)</td>
<td>0.10</td>
</tr>
<tr>
<td>uAGT+NT-proBNP</td>
<td>0.79</td>
<td>0.09 (0.03)</td>
<td>&lt;0.001</td>
<td>0.16 (0.07)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction.

*The NRI is calculated through two-way category by using the event rate of AKI and mortality in the stage I cohort as thresholds.

†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.

=Biomarker+clinical model versus clinical model.
In Type 1 CRS, urinary angiotensinogen peaks on Day 1 (admission) and appears to be a strong prognosticator for AKI [AUC], 0.84
• 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**
# MicroRNA-21 and Risk of Severe Acute Kidney Injury and Poor Outcomes after Adult Cardiac Surgery

Juan Du¹,²,³, Xiaqing Cao¹,²,³, Liang Zou¹,², Yi Chen¹,², Jin Guo¹,², Zujuan Chen¹,², Shengshou Hu¹,²,³, Zhe Zheng¹,²,³

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

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (SE)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Urine miR-21</td>
<td>0.72 (0.06)</td>
<td>0.61–0.83</td>
</tr>
<tr>
<td>Plasma miR-21</td>
<td>0.72 (0.06)</td>
<td>0.60–0.83</td>
</tr>
<tr>
<td>SCR</td>
<td>0.62 (0.06)</td>
<td>0.50–0.75</td>
</tr>
<tr>
<td>Percent change in SCR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.50 (0.07)</td>
<td>0.37–0.63</td>
</tr>
<tr>
<td>Heavy proteinuria&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.57 (0.04)</td>
<td>0.50–0.63</td>
</tr>
</tbody>
</table>
ICU: Other sets of microRNAs were altered several days prior to the increase in serum creatinine, indicating their potential as prognostic AKI biomarkers.
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-$\beta$-D-glucosaminidase (NAG), natriuretic peptides (NP).
<table>
<thead>
<tr>
<th>Table 2. Classification of biomarkers</th>
</tr>
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<tbody>
<tr>
<td>• <strong>Predictive</strong>—Identify subpopulations of subjects at higher risk for developing an outcome or more likely to respond to a therapy</td>
</tr>
<tr>
<td>• <strong>Prognostic</strong>—Informs likely course of disease progression or outcome</td>
</tr>
<tr>
<td>• <strong>Diagnostic</strong>—Characterizes onset and severity of a disease state</td>
</tr>
<tr>
<td>• <strong>Efficacy</strong>—Tracks the effectiveness of a treatment to mitigate a disease process</td>
</tr>
<tr>
<td>• <strong>Pharmacodynamic</strong>—Measures whether a particular biological response has occurred in response to a treatment</td>
</tr>
<tr>
<td>• <strong>Surrogate</strong>—Substitutes for a clinical end point (“a characteristic or variable that reflects how a patient feels, functions, or survives”)</td>
</tr>
</tbody>
</table>
Application of new acute kidney injury biomarkers in human randomized controlled trials

Chirag R. Parikh¹,², Dennis G. Moledina¹, Steven G. Coca³, Heather R. Thiessen-Philbrook¹ and Amit X. Garg⁴,⁵

¹Program of Applied Translational Research, Department of Medicine, Yale University, New Haven, Connecticut, USA; ²Veterans Affairs Medical Center, West Haven, Connecticut, USA; ³Section of Nephrology, Mount Sinai School of Medicine, New York, New York, USA; ⁴Department of Medicine, Western University, London, Ontario, Canada; and ⁵Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada
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Table 4 | Impact of biomarkers on future acute kidney injury trials

<table>
<thead>
<tr>
<th>Problems with current trial design</th>
<th>Role of biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Misclassification: inaccurate definition of “true AKI” or ATN</td>
<td><strong>Diagnostic biomarkers:</strong> Use of urine biomarkers can lead to more accurate diagnosis of AKI and recruitment of a more homogenous patient population</td>
</tr>
<tr>
<td>2. Enrollment of large proportion of low-risk patients who do not reach progression end points</td>
<td><strong>Prognostic biomarkers:</strong> Identification of high-risk patients likely to reach trial end points</td>
</tr>
<tr>
<td>3. All patients enrolled in trials are given similar therapy</td>
<td><strong>Predictive biomarkers:</strong> Patients most likely to respond to a particular therapy are identified</td>
</tr>
<tr>
<td>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</td>
<td><strong>Pharmacodynamic biomarkers:</strong> 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.</td>
</tr>
</tbody>
</table>
Fig. 7. Imaging in cardiorenal syndromes.
Novel Imaging Techniques for Heart Failure


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 aetiologial, 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.
# Novel Imaging Techniques for Heart Failure


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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>2D ECO</th>
<th>3DE</th>
<th>Strain</th>
<th>Cardiovascular Magnetic Resonance</th>
<th>Nuclear</th>
<th>Computed Tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV/RV volumes</td>
<td>RU</td>
<td>AI</td>
<td></td>
<td>AI (GS)</td>
<td></td>
<td>AI</td>
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<td>LV systolic function</td>
<td>RU</td>
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<tr>
<td>Risk assessment (arrhythmia)</td>
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*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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Myocardial strain imaging: how useful is it in clinical decision making?

Otto A. Smiseth¹*, Hans Torp², Anders Opdahl¹, Kristina H. Haugaa¹, and Stig Urheim¹

- Myocardial strain is a principle for quantification of LV function which is now feasible with speckle-tracking ECHO
**Imaging**

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

Otto A. Smiseth¹*, Hans Torp², Anders Opdahl¹, Kristina H. Haugaa¹, and Stig Urheim¹

---

**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.
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.
Imaging

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

Recommended as routine measurement in patients undergoing chemotherapy to detect reduction in LV function prior to fall in LVEF.
Intersegmental variability in timing of peak myocardial strain: proposed as predictor of risk of ventricular arrhythmias.
May be applied to guide placement of the LV pacing lead in patients receiving cardiac resynchronization therapy.
Imaging

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

May also be used to diagnose myocardial ischemia.
Myocardial strain imaging: how useful is it in clinical decision making?

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
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
# Novel Imaging Techniques for Heart Failure


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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk assessment (arrhythmia)</td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
<td></td>
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</tr>
</tbody>
</table>
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
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

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

MPM Graham-Brown1,2, DR Churchward1,3, DS March1,3, DJ Stensel2, GP McCann4, JO Burton1,3

1 John Watts 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 in hydration status 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 CMR42 (Circle Cardiovascular Imaging, Alberta, Canada) (Figure 1).

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

Table 1: Inter-study and inter-observer variability of native T1 mapping. CoV: Co-efficient of Variation.

<table>
<thead>
<tr>
<th></th>
<th>Study 1 (Mean±SD)</th>
<th>Study 2 (Mean±SD)</th>
<th>CoV</th>
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<tbody>
<tr>
<td>Mid-ventricular T1</td>
<td>1267.8±35.4</td>
<td>1270.7±30.5</td>
<td>0.7%</td>
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<tr>
<td>Inter-observer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-ventricular T1</td>
<td>1267.6±35.4</td>
<td>1271±34.8</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

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).

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 no relationship between either ΔLVEDV or Δweight and ΔT1 (Figure 3).

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

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

Linear regression confirmed ΔT1 was 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.

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

@CycleHD15
@DrMattGB
T1 MAPPING

• LIMITATIONS
  o ‘Native’ T1 relaxation values include signals from cells and interstitium
  o In ESRD, it is not known how variable T1 values may be in the myocardium when there may be variation in water content
  o ‘Native’ mapping has been most successful when there is a large pathophysiological change, e.g., infiltrative accumulation in Amyloid, Fabry, etc.
  o 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
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>
<thead>
<tr>
<th>MR method</th>
<th>Quantitative measure</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOLD</td>
<td>$R_2^*$ as marker of oxygenation</td>
<td>Non-invasive</td>
<td>Indirect measure of renal oxygenation</td>
<td>Renal hypoxia,\textsuperscript{26} renal artery stenosis,\textsuperscript{31} dynamic challenges\textsuperscript{13,28}</td>
</tr>
<tr>
<td>PC-MRI</td>
<td>Renal artery flux, velocity and area</td>
<td>Non-invasive, contrast free Blood flow curve provides method to grade stenosis</td>
<td>Breath hold Requires image slice to be perpendicular to vessel</td>
<td>Detection of renal artery stenosis\textsuperscript{83} Global renal perfusion by combination with renal volume\textsuperscript{43}</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Perfusion, blood volume, transit time and filtration</td>
<td>Well-established and validated technique</td>
<td>Invasive contrast agent with risk of NSF Arterial input function required</td>
<td>DCE first-pass perfusion to assess renal artery stenosis\textsuperscript{84} or renal parenchymal disease</td>
</tr>
<tr>
<td>ASL</td>
<td>Tissue perfusion and transit times</td>
<td>Non-invasive, contrast free Free breathing technique</td>
<td>Low signal-to-noise ratio, sensitive to motion</td>
<td>Renal parenchymal disease,\textsuperscript{62} dynamic challenges\textsuperscript{43}</td>
</tr>
<tr>
<td>DWI/DTI</td>
<td>DWI: ADC, D, D* and $f_p$ DTI: FA, MD and $\lambda$</td>
<td>Non-invasive, contrast free Free breathing technique</td>
<td>Fitted parameters depend on choice and number of $b$-values</td>
<td>Detection of fibrosis, incoherent water flow and anisotropic microstructure in CKD\textsuperscript{16,70}</td>
</tr>
</tbody>
</table>
IMAGING INTRARENAL HEMODYNAMICS AND O₂ 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 early fibrotic alterations together with changes in intrarenal $O_2$ availability may be able to identify those who are at risk for developing kidney failure.
Future Imaging in CRS

Type I-Acute Cardio-Renal

Type III-Acute Reno-Cardiac

Acute Heart Failure

Acute Kidney Injury

Type II-Chronic Cardio-Renal

Type IV-Chronic Reno-Cardiac

Chronic Heart Failure

Chronic Kidney Disease

Molecular imaging (PET, MRI, MRS etc)

Molecular imaging (PET, MRI, MRS etc)

Fig. 8. Future imaging in cardiorenal syndromes.
DRUGS
NOVEL THERAPIES

Arterial underfilling:
- Decreased cardiac output
- Decreased effective circulating volume
- Decreased RBF, RPF
- Activation of RAAS, SNS
- Inflammatory pathways

Heart:
- Decreased GFR
- Na and H₂O retention
- Increased edema, preload
- Increased afterload

Kidney:
- Venous congestion and venous hypertension, raised IAP
- Decreased AV perfusion gradient
- Kidney interstitial edema
- Activation of RAAS, SNS
- Inflammatory pathways

Venous congestion
TREATMENT STRATEGIES

NOVEL VASODILATOR
• Nesiritide
• Rolofylline
• Recombinant human relaxin-2

NOVEL INOTROPES
• Levosimendan
• Omecamtv
• Istaroxime

NEUTRAL ENDOPEPTIDASE INHIBITORS

SOLUBLE GUANYLATE CYCLASE INHIBITORS

SGLT2 inhibitors

GLP-1 agonists
TREATMENT STRATEGIES

• Mechanical Support
  o Left Ventricular Assist Devices (LVAD)

• Cardiac Resynchronization Therapy
Management of the Cardiorenal Syndrome in Decompensated Heart Failure

Frederik Hendrik Verbrugge, Lars Grieten, Wilfried Mullens
**CONGESTION (increased cardiac filling pressures)**

**VOLUME OVERLOAD**
+ edema, weight increase, ascites

**INTRAVASCULAR VOLUME OVERLOAD**

1. LOOP DIURETICS:
   - Intravenous bolus
   - Adequately dosed
   - Monotherapy in diuretic naive patients
2. THIAZIDE-TYPE DIURETICS:
   - Maximize fractional sodium excretion in case of low glomerular filtration
   - Counteract distal nephron hypertrophy due to chronic loop diuretic use
3. MINERALOCORTICOID RECEPTOR ANTAGONISTS
   - Improve natriuresis if potassium < 5 mmol/L
4. ACETAZOLAMIDE
   - Counteract increase proximal reabsorption in case of poor renal perfusion
5. ULTRAFILTRATION
   → Break diuretic resistance

**FLUID ACCUMULATION IN THIRD SPACES**
- Ascites: PARACENTESIS
- Non-recrutable edema: COMPRESSION THERAPY

**NO VOLUME OVERLOAD**

Low cardiac output?

- yes
  - Mean arterial pressure >60 - 65 mmHg?
    - yes
      → VASODILATOR THERAPY (nitrates or high-dose nitrates)
      → FUTURE: SERELAXIN?
    - no
      → INOTROPES (levosimendan > dobutamine)
      → FUTURE: OMECMATIV MECABIL?
  - no

Candidate for LVAD or HTX?

- yes
  - LVAD or HTX
- no

**Fig. 2.** Flowchart of the treatment of patients with CRS. HTX = Heart transplantation; LVAD = left ventricular assist device.
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)
• 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
Table 4: Baseline Values and Changes From Baseline in Biomarkers Related to Organ Damage In the RELAX-AHF Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 580)</th>
<th>Serelaxin (n = 581)</th>
<th>Treatment Effect (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac damage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-cTnT (µg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline geometric mean</td>
<td>0.036</td>
<td>0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below LLOQ (0.013 µg/l) at baseline</td>
<td>34/541 (6.3%)</td>
<td>40/533 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2 geometric mean</td>
<td>0.037</td>
<td>0.033</td>
<td></td>
<td></td>
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<td>Relative change to day 2 (geometric mean change)</td>
<td>1.035</td>
<td>0.966</td>
<td>0.933 (0.883 to 0.985)^*</td>
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<td>≥20% increase at day 2</td>
<td>145/534 (27.2%)</td>
<td>86/522 (16.5%)</td>
<td>0.53 (0.39 to 0.71)^†</td>
<td>&lt;0.0001</td>
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<td><strong>Worsening renal function</strong></td>
<td></td>
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<tr>
<td>Serum creatinine (µmol/l)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>117</td>
<td>117</td>
<td></td>
<td></td>
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<tr>
<td>Day 2 mean</td>
<td>123</td>
<td>113</td>
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<tr>
<td>Mean change to day 2</td>
<td>6.2</td>
<td>-3.4</td>
<td>-9.5 (-12.4 to -6.6)^‡</td>
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<td>0.0027</td>
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At day 2, 19.8% treated with placebo vs. 10.9% treated with serelaxin had experienced an increase in serum creatinine $\geq 0.3$ mg/dL ($p < 0.001$).

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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


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

Landoni G¹, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, Guarracino F, Zanirillo 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
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

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

Authors
Mehmet Birhan Yılmaz, Kenan Yalta, Can Yontar, Filiz Karadas, Alim Erdem, Okan Onur Turgut, Ahmet Yılmaz, 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.
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.
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:
  o Increases LV systolic ejection time, sarcomere shortening and stroke volume, while systolic pressure remains the same → decrease in heart rate while myocardial O₂ 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, G Michael Felker, MD, John V McMurray, MD, Scott D Solomon, MD, Kirkwood F Adams Jr, MD, John G Cleland, MD, Justin A Ezekowitz, MBBCh, Assen Goudev, MD, Peter Macdonald, MD, Marco Metra, MD, Veselin Mitrovic, MD, Piotr Ponikowski, MD, Pranas Serpytis, MD, Jindrich Spinar, MD, János Tomcsányi, MD, Hans J Vandekerckhove, MD, 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

- 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

- 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
| **This study has been completed.** | **ClinicalTrials.gov Identifier:**  
| | NCT01786512 |
| **Sponsor:** Amgen | **First received:** January 16, 2013  
| **Collaborator:** Cytokinetics | **Last updated:** May 5, 2016  
| **Information provided by (Responsible Party):** Amgen | **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
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
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

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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
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

- 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

• 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
ISTAROXIME

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
• 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

Omapatrilat (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

• 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

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


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 (HFrEF). The effects of LCZ696 on renal function have not been assessed.

METHODS AND RESULTS: A total of 301 HFrEF 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 m². The eGFR declined less in the LCZ696 group than in the valsartan group (-1.5 vs. -5.2 mL/min per 1.73 m²; 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 HFrEF, 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 m² vs 5.2 mL/min/1.73 m² in the valsartan group, p = 0.007
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

- 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 27 months
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.
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∗

A Incident or Worsening Nephropathy

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

B Post Hoc Renal Composite Outcome

Hazard ratio, 0.54 (95% CI, 0.40–0.75)
P<0.001
SGLT2-INHIBITORS

- Decreased development of macroalbuminuria.
- Reduced slope of eGFR decline.
- Prevented serum creatinine doubling and ESRD.
- Benefit of empagliflozin occurred in subgroups 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

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

Data are %. *Significant. **Nonsignificant.

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

<table>
<thead>
<tr>
<th>Renal outcome</th>
<th>Pooled empagliflozin group (n = 4,687) vs. placebo (n = 2,333)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>New-onset or worsening nephropathy</td>
<td>0.61</td>
</tr>
<tr>
<td>Composite of:</td>
<td></td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.54</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td></td>
</tr>
<tr>
<td>(includes dialysis/transplantation)</td>
<td></td>
</tr>
<tr>
<td>Death due to renal disease</td>
<td></td>
</tr>
</tbody>
</table>
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.
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.
Figure 3—Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. Rx, treatment.
Figure 3—Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. Rx, treatment.
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

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

Placebo
Liraglutide

Patients with an Event (%)

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

Months since Randomization

E Death from Any Cause

Hazard ratio, 0.85 (95% CI, 0.74–0.97)
P=0.02

Placebo
Liraglutide

Patients with an Event (%)

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

Months since Randomization
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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B  Death from Cardiovascular Causes

F  Hospitalization for Heart Failure

For the LEADER Trial Investigators on behalf of the LEADER Steering Committee.
**GLP-1 AGONISTS**

A GUT-HEART CONNECTION IN CARDIOMETABOLIC REGULATION

Alessia Buglioni, MD and John C Burnett Jr, MD
Cardiorenal Research Laboratory, Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, MN, USA

- **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

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- HEART: GLP-1 activates GLP1-Rs in the atrial myocardium which induces ANP secretion from atrial secretory granules

This action is mimicked by LIRAGLUTIDE via activation of Epac2, which stimulates secretion of ANP.
GLP-1 AGONISTS

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• HEART: GLP-1 activates GLP1-Rs in the atrial myocardium which induces ANP secretion from atrial secretory granules
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)

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

Kirklin JK¹, Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, Givertz MM, Young JB.

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

Kirklin JK¹, Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, Givertz MM, Young JB.

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

Adelstein EC¹, 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 m²): >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 m²) 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 >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 >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 m². CRT recipients with normal renal function derive echocardiographic benefit but no overall survival advantage.
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
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
    o More invasive
    o Longer ICU stay
**Cardiorenal Syndromes: Advances in Determining Diagnosis, Prognosis, and Therapy**

Peter A. McCullough, James A. Tumlin, Harold Szerlip, Krishnaswami Vijayaraghavan, Sathya Jyothisnagaram, John F. Rausch Jr, Bhupinder Singh, Jun Zhang, and Mikhail Kosiborod

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

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

The kidney in heart failure: an update

Kevin Damman¹ and Jeffrey M. Testani²

Figure 1 History of research in cardiorenal interaction. Overview of some key investigations in cardiorenal research. For reference list, see Supplementary material online, files.
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.
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)
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 —
One of the things I learned in medical school is “how to say ‘I don’t know,’” confidently … ain’t no shame in it …