Cardiac specific biomarkers for diagnosis and prognosis in patients with kidney disease

The past, present and future

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Disclosures

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Endpoint Committee/DSMB: Radiometer, Quintiles
Cardiac specific troponin assays

• Diagnosis of non ST elevation myocardial infarction in the era of the high sensitive assays
• Future directions to improve diagnostic accuracy
• Evolution from “false positive” to independent prognosticator
• Associations with underlying structural heart disease in the absence of myocardial infarction
Case presentation #1

History

“62 yr male with ESRD develops palpitations and chest pain within 2-3 hours of completing dialysis. Cardiac cath and echocardiogram 14 months earlier showed no CAD, moderate aortic stenosis and a Normal LVEF”
Case presentation #1

Physical Exam

“BP 71/49, HR 158, respiration 22, Lungs clear to auscultation, cardiac tachy irregular rate and rhythm, 2/6 systolic murmur heard throughout the precordium, no rubs or gallops”
Case presentation #1

ECG

Male
57in 0lb
Room: F1124
Loc: 17

Black
PR interval
* ms

QRS duration
98 ms

QT/QTc
354/470 ms

P-R-T Axs
* -7 115

MINIMAL VOLTAGE CRITERIA FOR LVH. MAY BE NORMAL VARIANTS
ST & T WAVE ABNORMALITY, CONSIDER LATERAL ISCHEMIA
ABNORMAL ECG

Technician: RN
Test ind: afib

Referred by:

Confirmed By:

KDIGO
Case presentation #1
Echo and Cardiac Catheterization
Case presentation #2

History

“A 62-year-old male presented to the emergency department with chest pain radiating down his left arm that lasted 40 minutes and awakened him 3 hours prior to arrival. It was associated with shortness of breath, nausea, and diaphoresis.

You note a history of hypertension and hypercholesterolemia controlled with hydrochlorothiazide and atorvastatin.

In addition, he has chronic renal failure, for which he tells you that his doctor thinks he might soon require dialysis.”
Case presentation #2

Physical Exam

“His blood pressure is 149/89 mmHg and heart rate is 86 bpm. On auscultation, both heart sounds are audible and normal, although you do notice a fourth heart sound and bibasilar rales on the chest posteriorly along with bilateral pedal edema to the level of the mid-shins and mild jugular venous distension.”
Case presentation #2
ECG
Case presentations
Relevant laboratory findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Presenting cTn</th>
<th>2nd cTn</th>
<th>eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cTnI (ng/ml)</td>
<td>hs-cTnT (ng/L)</td>
<td>cTnI</td>
</tr>
<tr>
<td>#1</td>
<td>0.02</td>
<td></td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>36.2</td>
<td></td>
<td>39.0</td>
</tr>
</tbody>
</table>
Baseline levels of sensitive and hs cTn assays at presentation in patients with final diagnosis other than acute myocardial infarction

n=447

Twerenbold et al. Circulation. 2015;131:2041-2050
Criteria for Acute Myocardial Infarction

• Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  – Symptoms of ischemia.
  – New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  – Development of pathological Q waves in the ECG.
  – Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  – Identification of an intracoronary thrombus by angiography or autopsy.

J Am Coll Cardiol. 2012;60:2427-63
Differentiation of type of MI according to the condition of the coronary arteries

- Plaque rupture with thrombus (MI Type 1)
- Vasospasm or endothelial dysfunction (MI Type 2)
- Fixed atherosclerosis and supply-demand imbalance (MI Type 2)
- Supply-demand imbalance alone (MI Type 2)
Third Universal Definition of Myocardial Infarction

Myocardial injury with cell death marked by cardiac troponin elevation

Clinical evidence of acute myocardial ischaemia with rise and/or fall of cardiac troponin

Cardiac procedure
Non-cardiac major procedure
Tachy-brady-arrhythmia
Heart failure
Renal failure
hs-cTnI concentration at presentation in suspected ACS
Stratified by renal function (A) and adjudicated index diagnosis stratified by renal function (B)
Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T in patients with renal dysfunction and normal renal function


KDIGO
Diagnostic performance of hs-cTnT in patients with renal dysfunction and normal renal function

Cardiac specific troponin assays

 ✓ Diagnosis of non ST elevation myocardial infarction in the era of the high sensitive assays

 • Future directions to improve diagnostic accuracy
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Cardiac Troponin T: Smaller Molecules in Patients with End-Stage Renal Disease than after Onset of Acute Myocardial Infarction

Western Blot Analysis

Cardiac specific troponin assays

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✔ Future directions to improve diagnostic accuracy

• Evolution from “false positive” to independent prognosticator

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Prognostic value of cardiac troponin in patients with CKD without suspected ACS
A systemic review and meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Troponin assay</th>
<th>Studies, n</th>
<th>Patients, n</th>
<th>HR (95% CI)</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>cTnT</td>
<td>11</td>
<td>2783</td>
<td>3.00 (2.36–4.26)</td>
<td>Moderate</td>
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<tr>
<td>All-cause mortality</td>
<td>cTnI</td>
<td>7</td>
<td>1514</td>
<td>2.70 (1.90–4.57)</td>
<td>Moderate</td>
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<tr>
<td>CVD mortality</td>
<td>cTnT</td>
<td>5</td>
<td>1634</td>
<td>3.31 (1.81–5.43)</td>
<td>Moderate</td>
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<tr>
<td>CVD mortality</td>
<td>cTnI</td>
<td>3</td>
<td>390</td>
<td>4.20 (2.01–9.20)</td>
<td>Moderate</td>
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<tr>
<td>MACE</td>
<td>cTnT</td>
<td>1</td>
<td>258</td>
<td>1.90 (1.02–3.40)</td>
<td>Moderate</td>
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<tr>
<td>Patients not receiving dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>cTnT</td>
<td>2</td>
<td>357</td>
<td>3.41 (1.06–10.99)</td>
<td>Moderate</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>cTnI</td>
<td>2</td>
<td>2594</td>
<td>1.73 (1.17–2.65)</td>
<td>Moderate</td>
</tr>
<tr>
<td>MACE</td>
<td>cTnT</td>
<td>4</td>
<td>2012</td>
<td>2.69 (1.14–7.60)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

HRs were adjusted for age and coronary artery disease or a risk equivalent. The SOE for outcomes not listed was graded as low or insufficient because we did not find any studies addressing them or were unable to draw conclusions from the evidence. SOE = strength of evidence.

Association of high sensitive cTnT with LVH and LVEF

The CRIC Study

Incident heart failure based on hs-cTnT level

The CRIC Study

Median follow-up = 6 years
Incident HF events = 320
Natriuretic peptide assays

• Influence of GFR on levels and fractional extraction of BNP and NT-proBNP
• Physiologic associations of natriuretic peptide levels in patients with kidney disease
• Diagnostic accuracy of natriuretic peptide levels for acute decompensated heart failure
Natriuretic peptide levels across the eGFR continuum

HTN patients undergoing evaluation for renal artery stenosis, but subsequently excluded (n=165)

Solid dots indicate left kidney, open dots indicate right kidney

Roland R.J. van Kimmenade et al. JACC 2009;53:884-890
Correlations Between Fractional Extraction and GFR in the Left and the Right Kidney

Solid dots indicate left kidney, open dots indicate right kidney

Roland R.J. van Kimmenade et al. JACC 2009;53:884-890
Natriuretic peptide assays

✓ Influence of GFR on levels and fractional extraction of BNP and NT-proBNP

• Physiologic associations of natriuretic peptide levels in patients with kidney disease
• Diagnostic accuracy of natriuretic peptide levels for acute decompensated heart failure
Relationship of renal function with left ventricular end-diastolic wall stress with BNP

Patients were divided into tertiles according to the EDWS level (first tertile: <33 kdynes/cm², second tertile: 33–55, third tertile: >55)
Mean eGFR: normals =78, CKD=44, ESRD=5

Natriuretic peptide assays

- Influence of GFR on levels and fractional extraction of BNP and NT-proBNP
- Physiologic associations of natriuretic peptide levels in patients with kidney disease
  - Diagnostic accuracy of natriuretic peptide levels for acute decompensated heart failure
Diagnosis and prognosis of acute heart failure with NT-proBNP

Influence of renal function and age on NT-proBNP for diagnosis of acute heart failure in patients with shortness of breath

The Icon Reloaded Study

Conclusions

✓ The cardiac specific biomarkers cTnI, cTnT, BNP, and NT-proBNP are frequently increased in patients with CKD with and without an acute event.

✓ Elevated cardiac specific biomarkers typically reflect cardiovascular pathophysiology more than impaired renal clearance.

✓ The tests remain accurate for AMI and acute heart failure, respectively, albeit with a modest reduction in accuracy and often a need to consider higher cutoffs.