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

## The past, present and future

KDIGO

**Christopher deFilippi, MD**
**Vice-Chair Academic Affairs**
**Inova Heart and Vascular Institute**
**Virginia, USA**

# Disclosures

Research grants: Abbott Diagnostics, Amgen, FujiRebio, Ortho Diagnostics, Prevencio, Roche Diagnostics
Advisory board/Consulting/Honorarium/Royalties: Alere, FujiRebio, Metabolomics, Ortho Diagnostics, Roche Diagnostics, Siemens Healthcare, UpToDate, WebMD
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"*

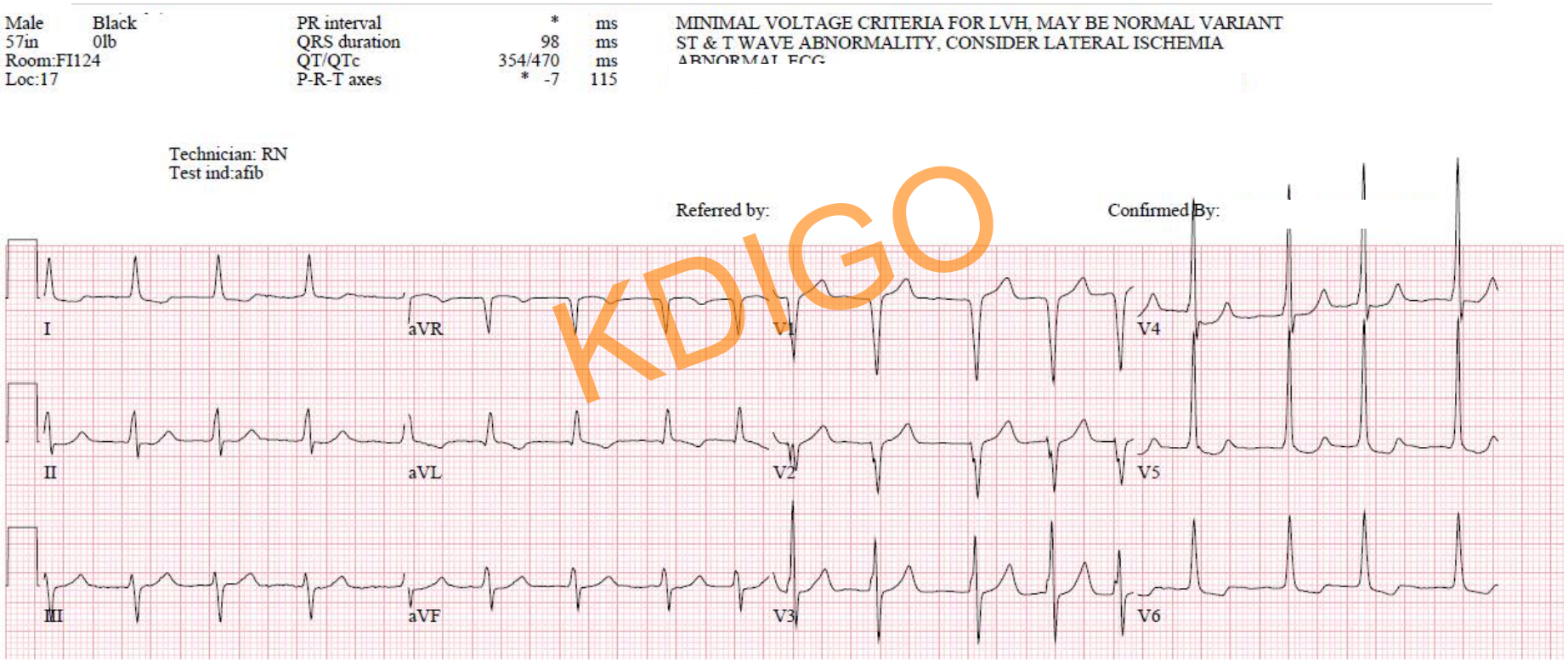
# Case presentation #1

## Physical Exam

*"BP 71/49, HR 158, respiration 22, Lungs clear to ausculation, cardiac tachy irregular rate and rhythm, 2/6 systolic murmur heard throughout the precordium, no rubs or gallops"*

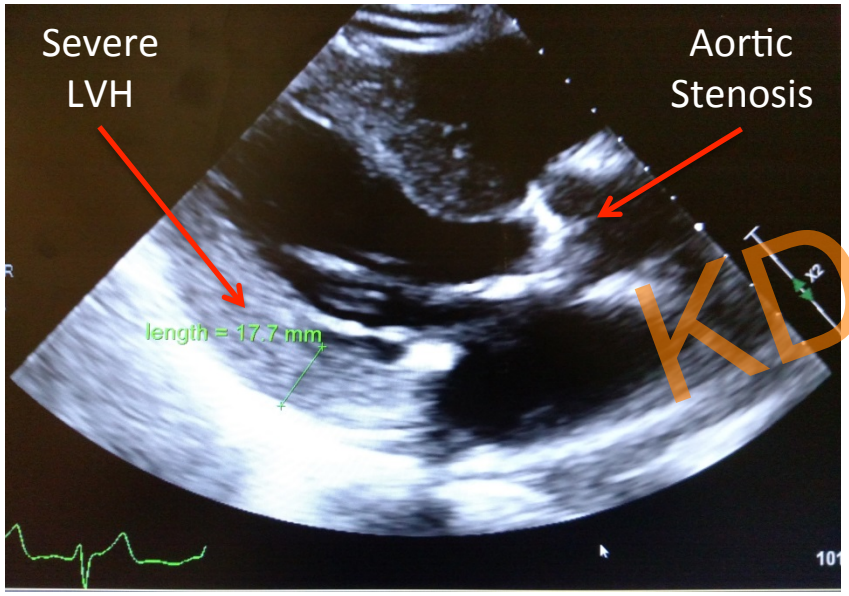
# Case presentation #1

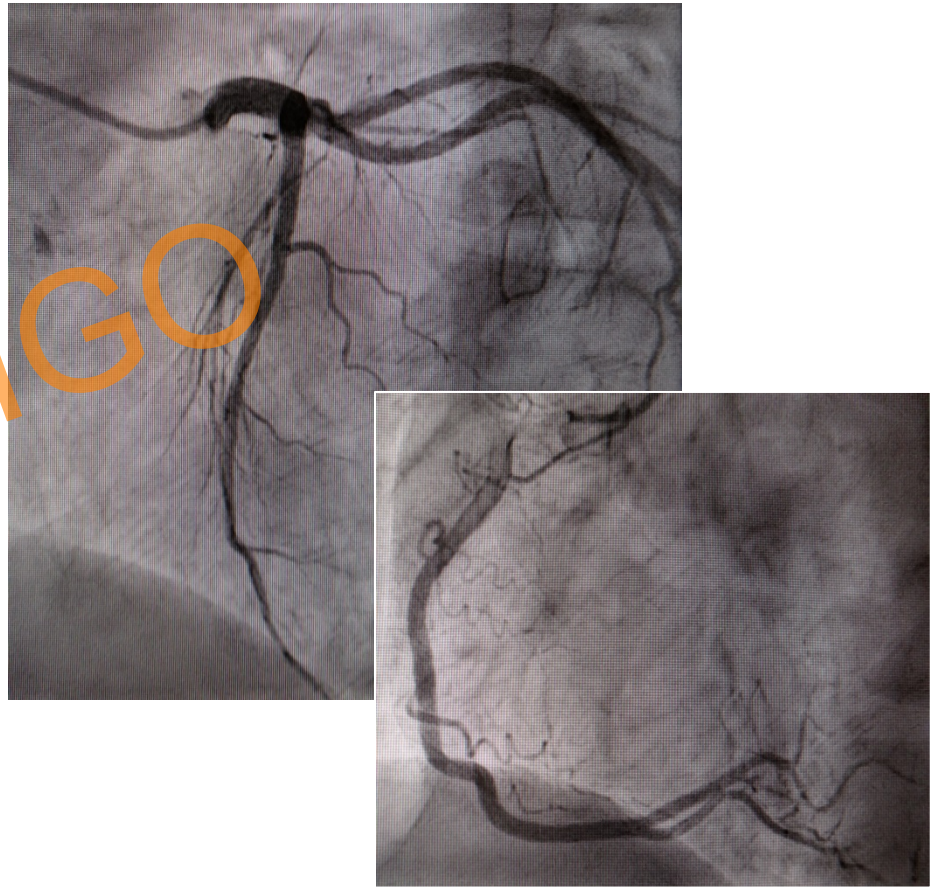
## ECG



# 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."*



Jaffe A, Sara J. Trends Cardiovasc Med. 2015;25:655-6

# Case presentation #2

## Physical Exam

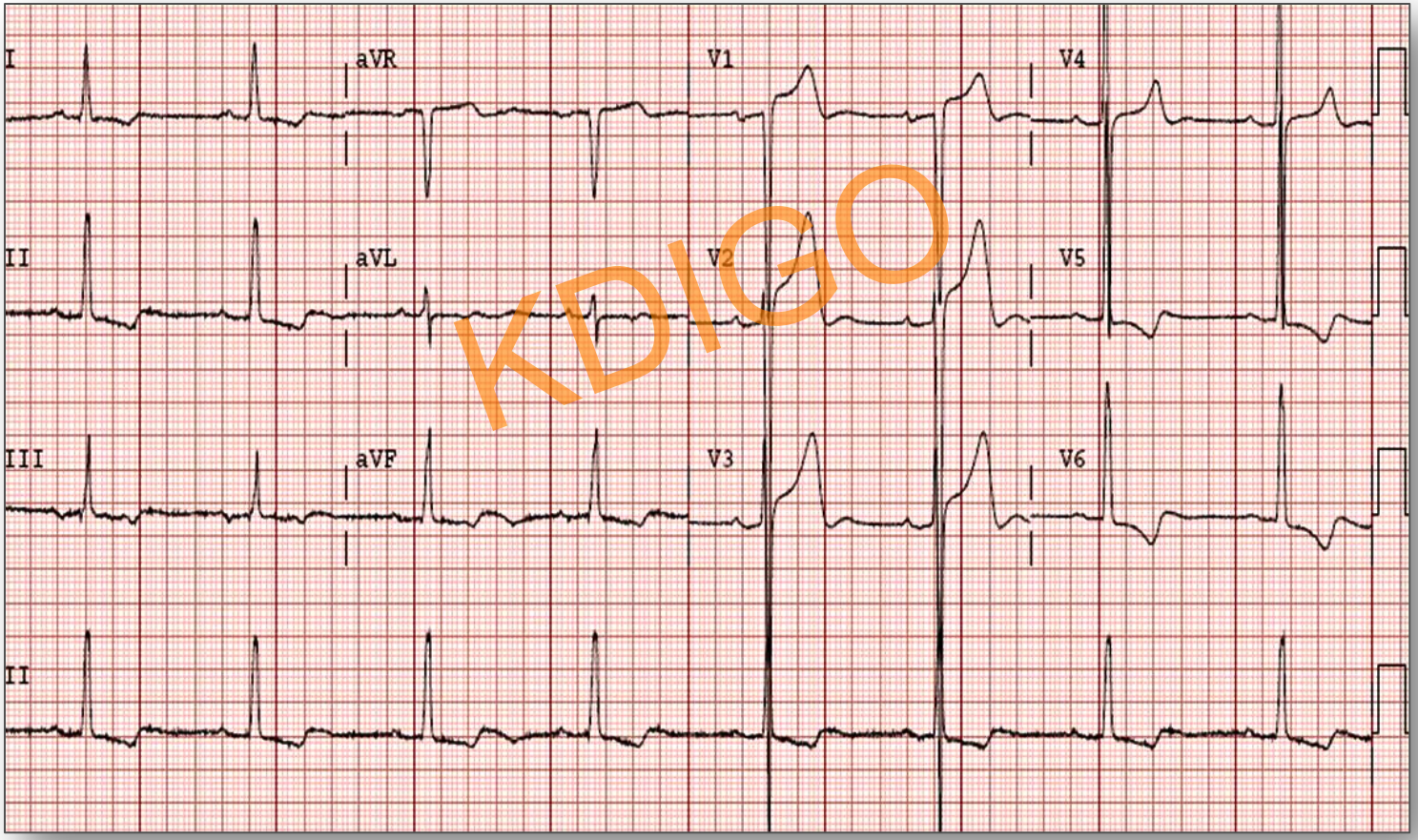
*"His blood pressure is 149/89 mmHg and heart rate is 86 bpm. On auscultation, both heart sounds are audible and normal, although you do notice a fourth heart sound and bibasilar rales on the chest posteriorly along with bilateral pedal edema to the level of the mid-shins and mild jugular venous distension."*



Jaffe A, Sara J. Trends Cardiovasc Med. 2015;25:655-6

# Case presentation #2

## ECG

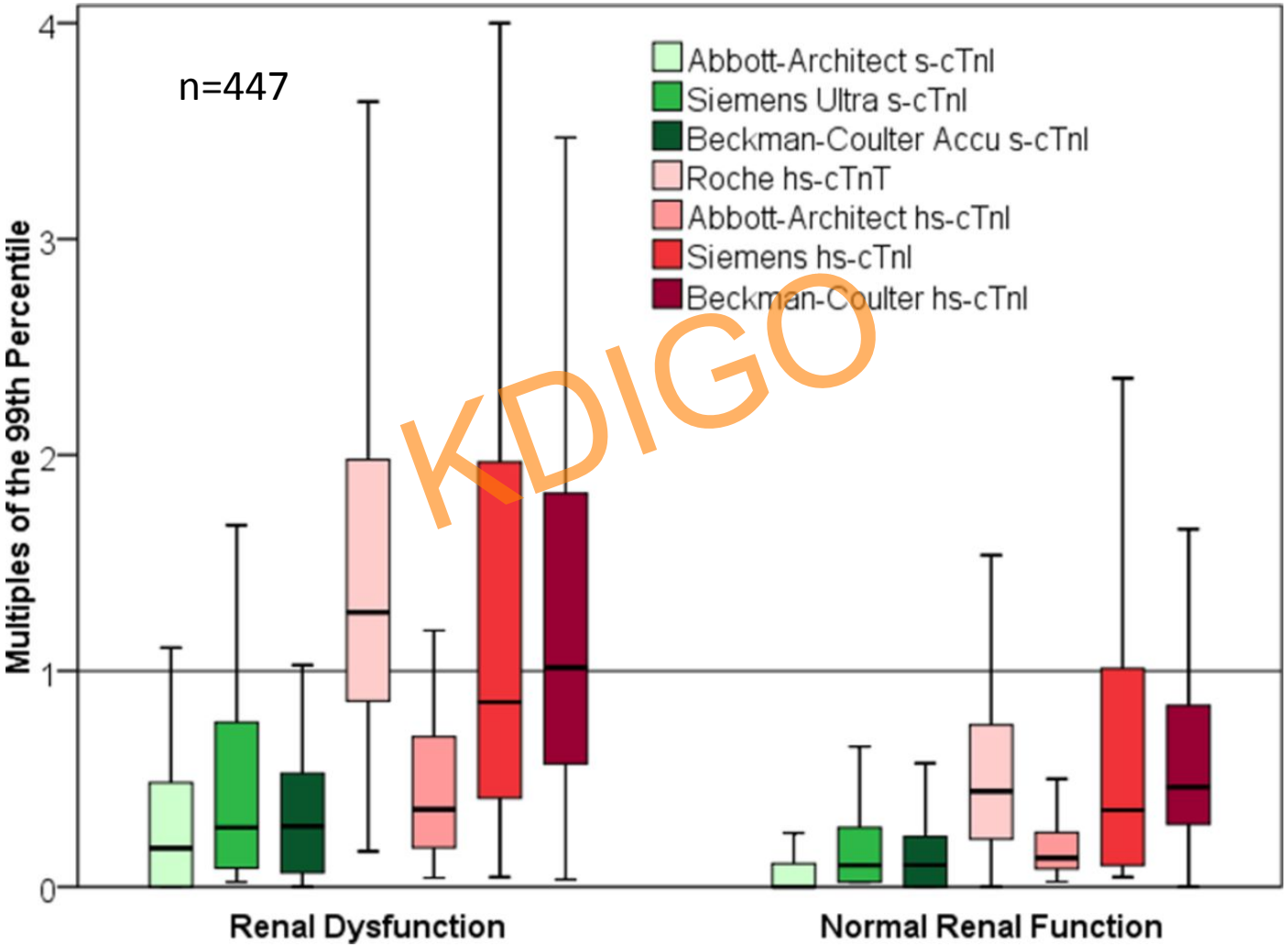


# Case presentations

## Relevant laboratory findings

| Case | Presenting cTn | | 2nd cTn | | eGFR |
|---|---|---|---|---|---|
| | cTnI (ng/ml) | hs-cTnT (ng/L) | cTnI | hs-cTnT | |
| #1 | 0.02 | | 14.5 | | ESRD on HD |
| #2 | | 36.2 | | 39.0 | 23 ml/min/1.73m$^2$ |

# Baseline levels of sensitive and hs cTn assays at presentation in patients with final diagnosis other than acute myocardial infarction






Twerenbold et al. Circulation. 2015;131:2041-2050

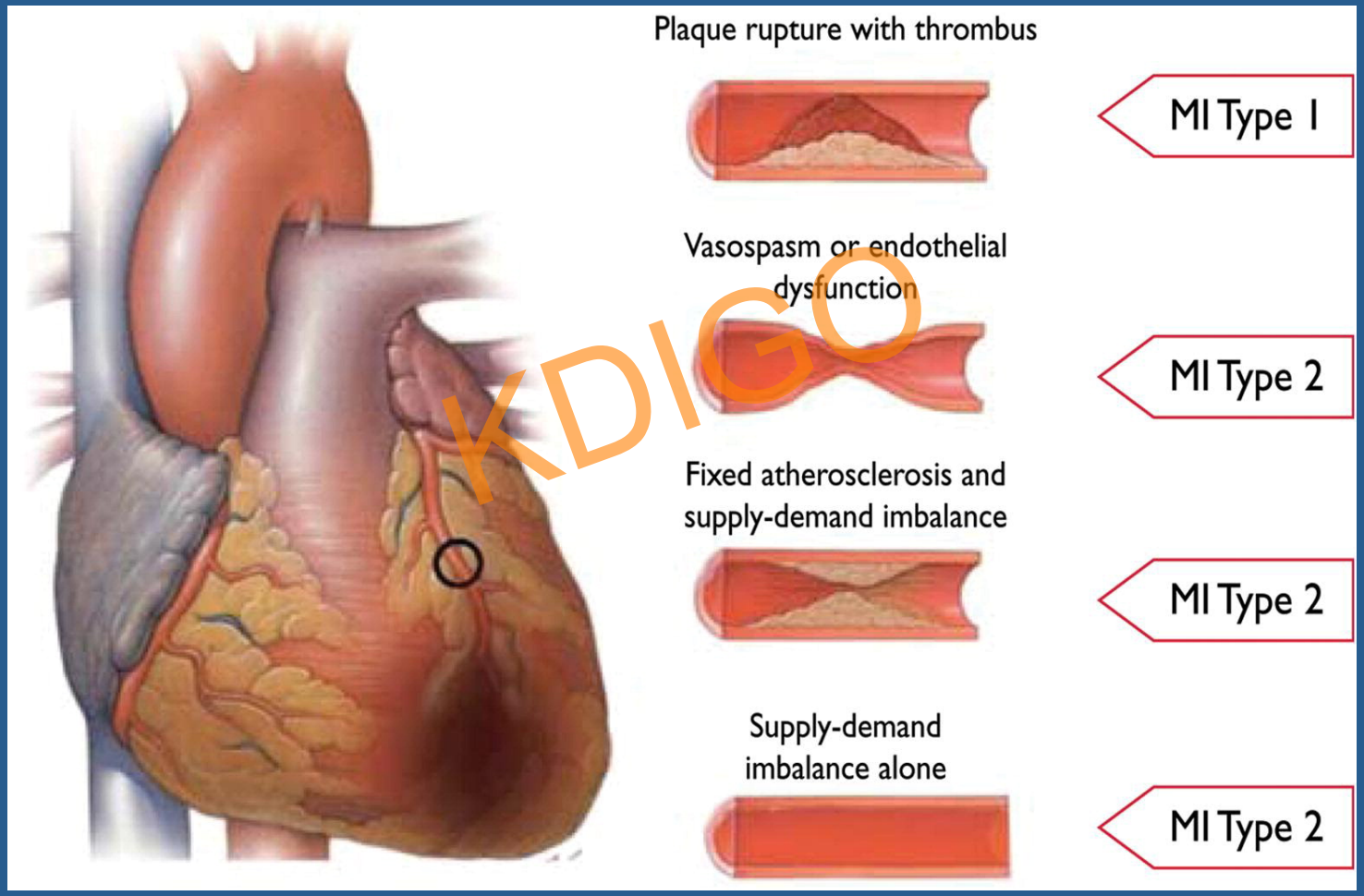
# Criteria for Acute Myocardial Infarction

- 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.



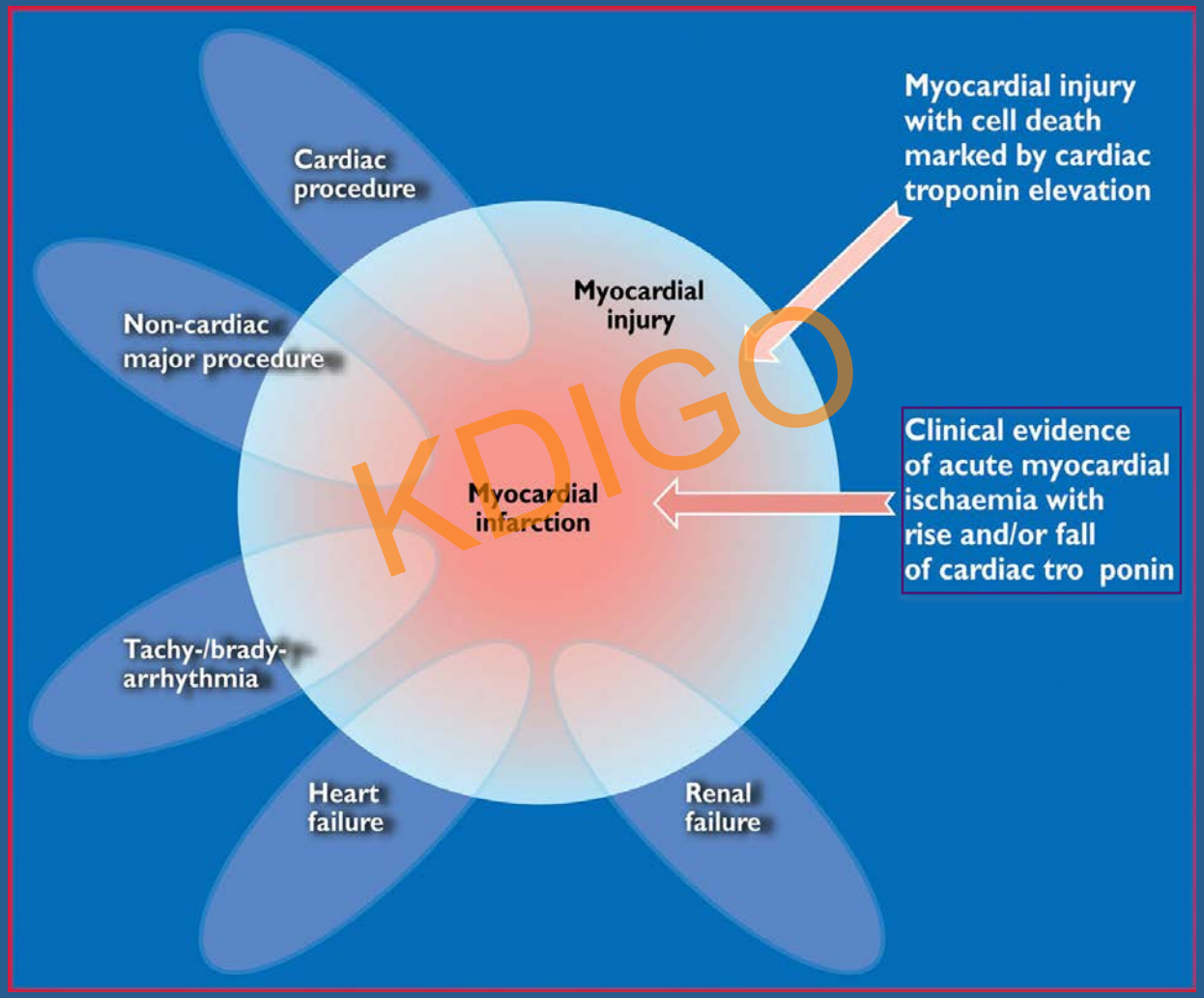
J Am Coll Cardiol. 2012;60:2427-63

# Differentiation of type of MI according to the condition of the coronary arteries




J Am Coll Cardiol 2012;60:1581-98

# Third Universal Definition of Myocardial Infarction

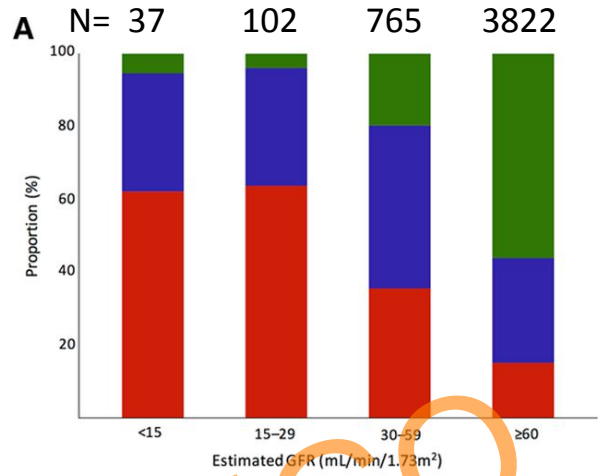





J Am Coll Cardiol 2012;60:1581-98
J Am Coll Cardiol. 2012;60:2427-63

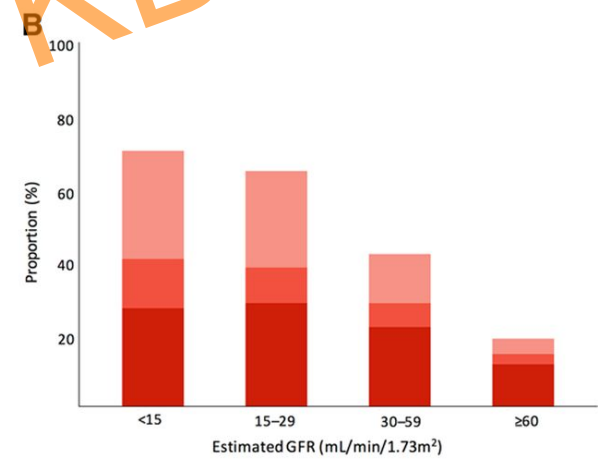
# hs-cTnI concentration at presentation in suspected ACS

## Stratified by renal function (A) and adjudicated index diagnosis stratified by renal function (B)




| Presentation troponin, number of patients (%) | | | | |
|---|---|---|---|---|
| <5ng/L | 2 (5) | 4 (4) | 151 (20) | 2144 (56) |
| 5ng/L - 99th centile | 12 (32) | 33 (32) | 342 (45) | 1100 (29) |
| >99th centile | 23 (62) | 65 (64) | 272 (36) | 578 (15) |

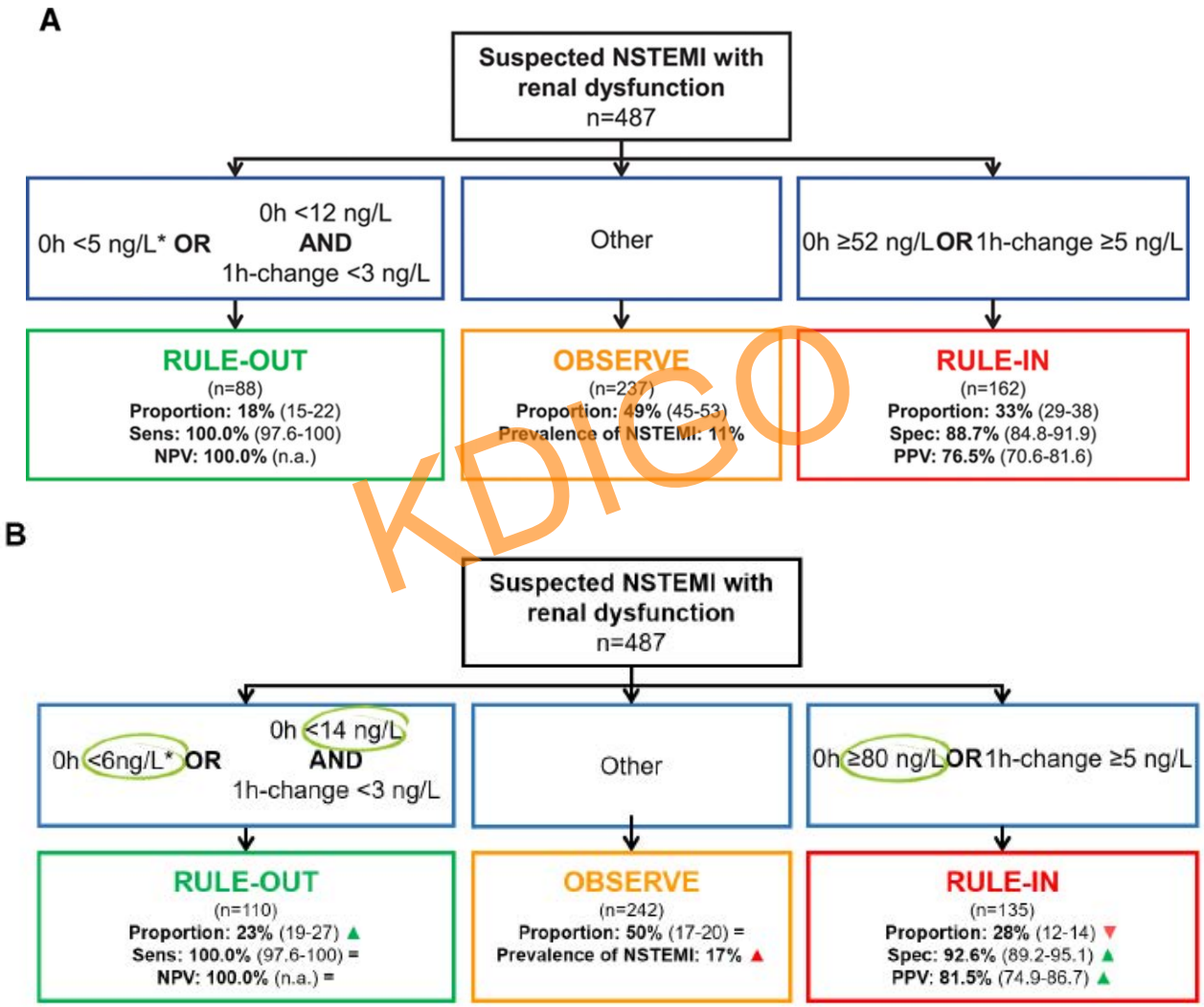





| Index diagnosis, number (%) | | | | |
|---|---|---|---|---|
| Type 1 MI | 10 (27) | 29 (28) | 167 (22) | 444 (12) |
| Type 2 MI | 5 (14) | 10 (10) | 50 (7) | 108 (3) |
| Myocardial Injury | 11 (30) | 27 (26) | 103 (13) | 160 (4) |

Miller-Hodges E et al. Circulation. 2018;137:425-435

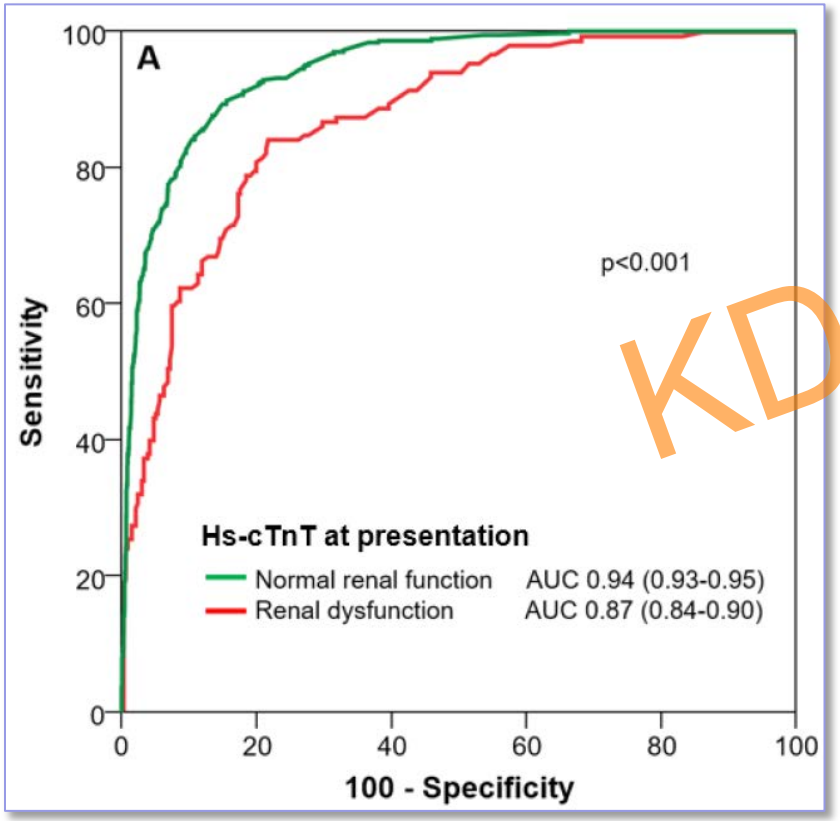
# Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T in patients with renal dysfunction and normal renal function

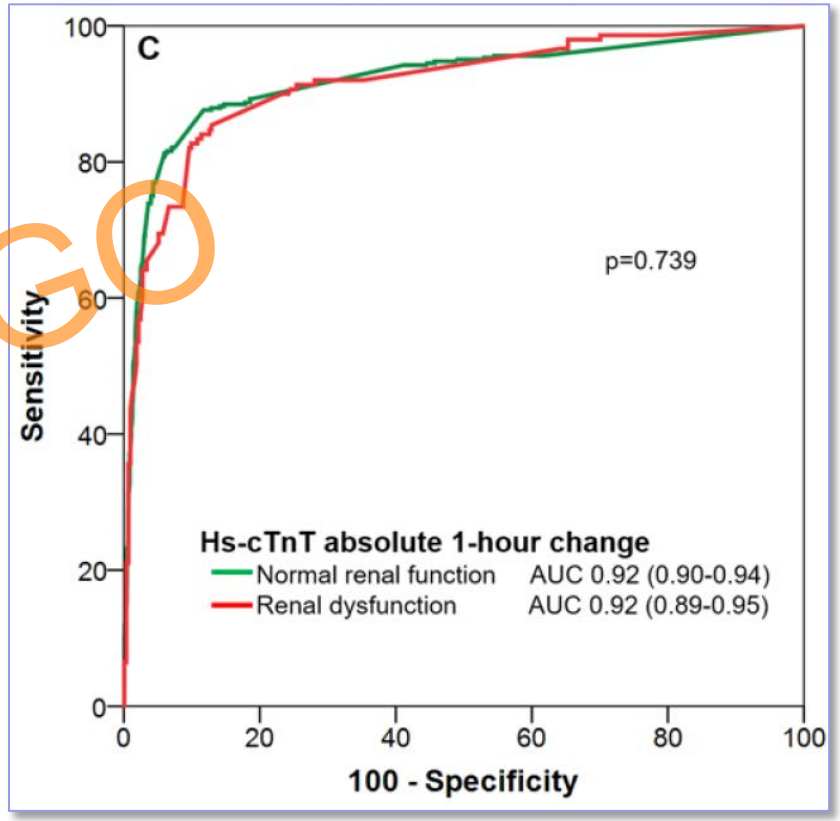





Twerenbold et al. Circulation. 2018;137:436-451

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





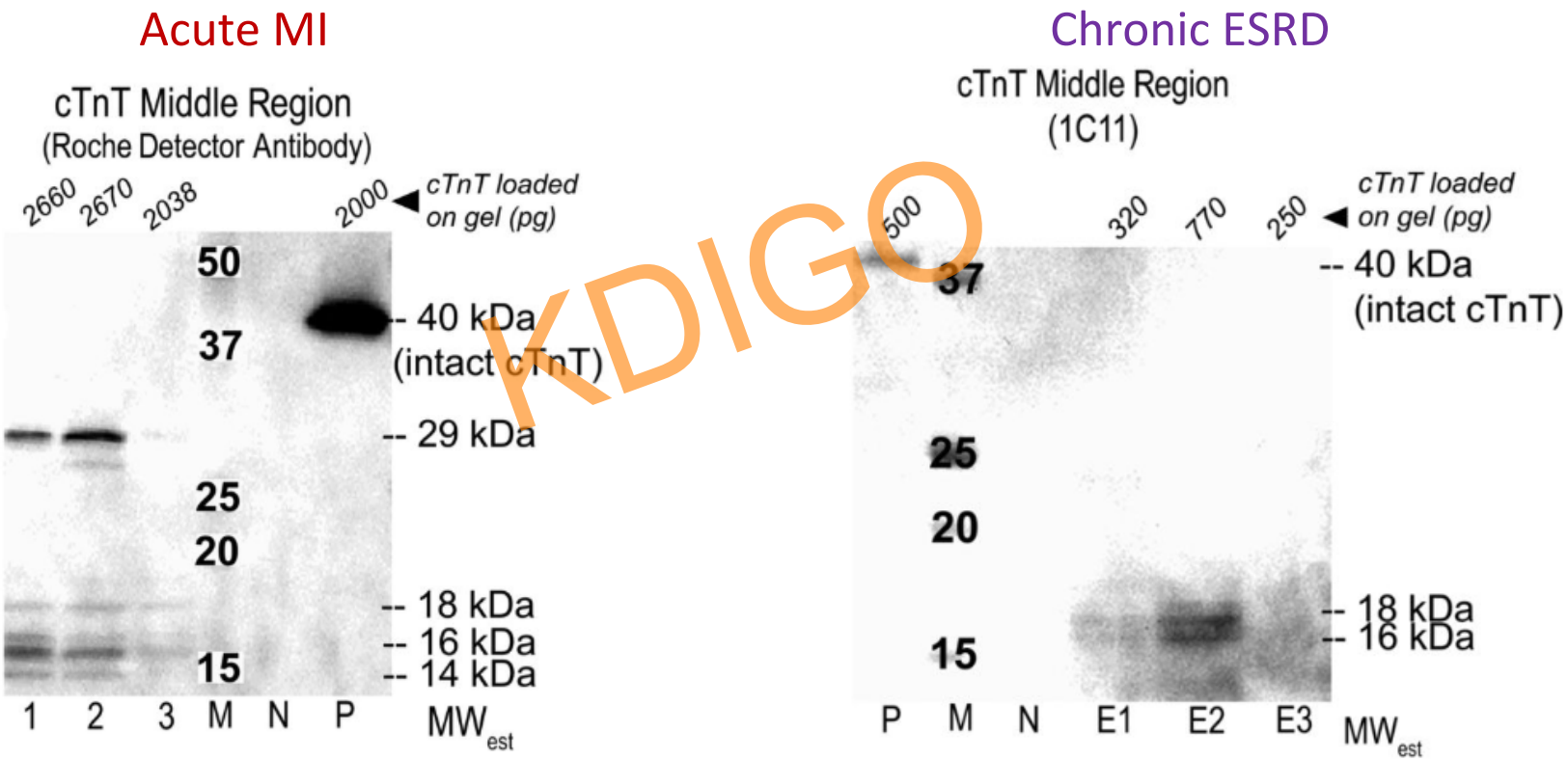

Twerenbold et al. Circulation. 2018;137:436-451

# 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

# Cardiac Troponin T: Smaller Molecules in Patients with End-Stage Renal Disease than after Onset of Acute Myocardial Infarction

## Western Blot Analysis






Mingles AM et al. Clin Chem. 2017;63:683–690

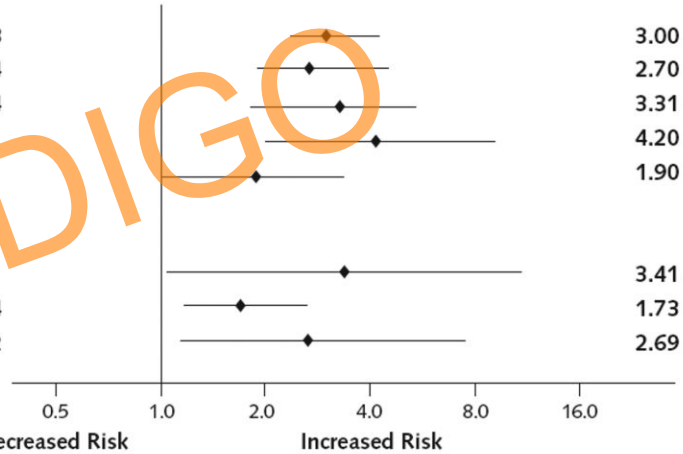
# Cardiac specific troponin assays

- ✓ 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

# Prognostic value of cardiac troponin in patients with CKD without suspected ACS

## A systemic review and meta-analysis

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



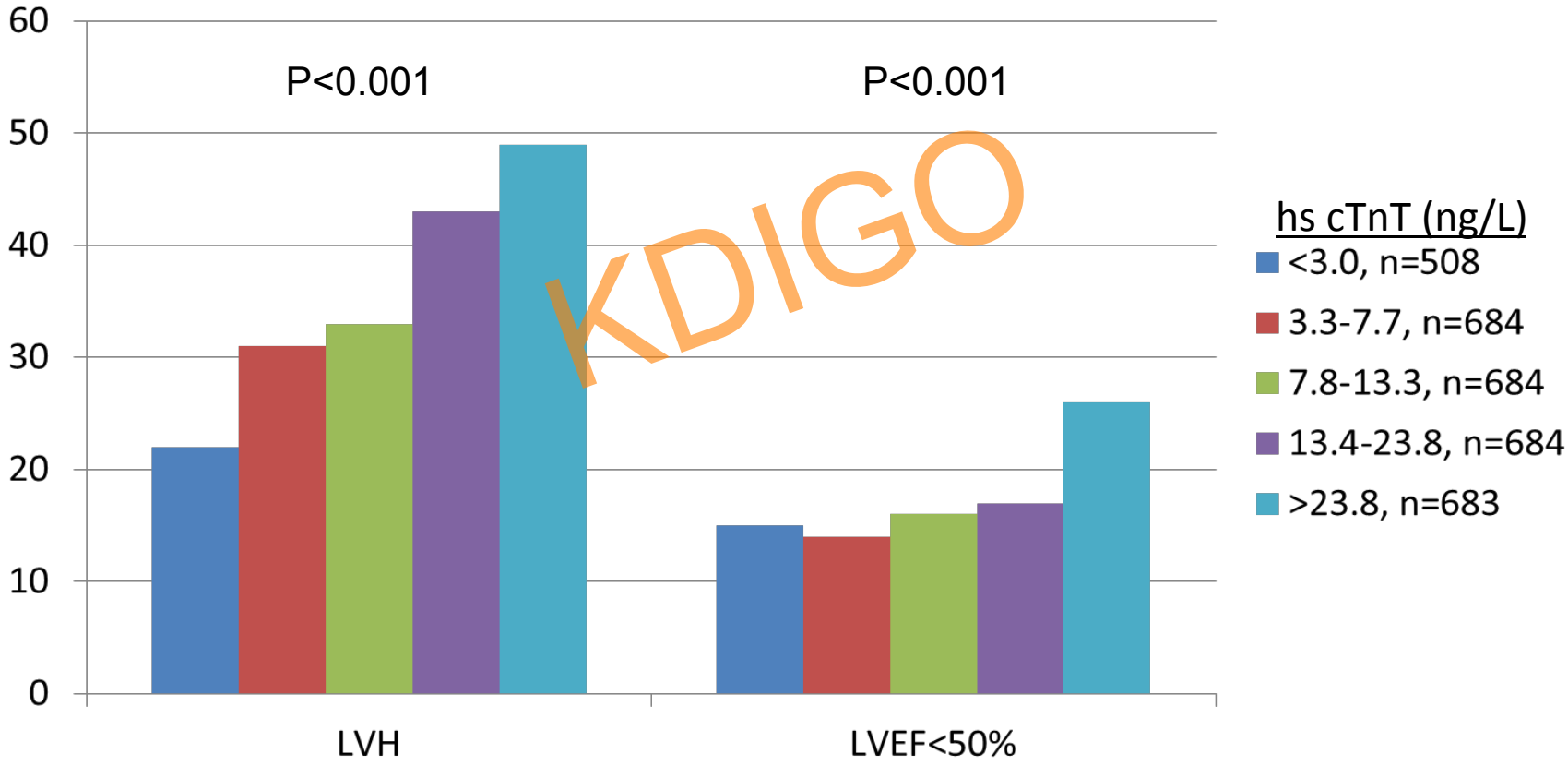



HRs were adjusted for age and coronary artery disease or a risk equivalent. The SOE for outcomes not listed was graded as low or insufficient because we did not find any studies addressing them or were unable to draw conclusions from the evidence. SOE = strength of evidence.

Michos ED et al. Ann Intern Med 2014;161:491–501

# Association of high sensitive cTnT with LVH and LVEF

## The CRIC Study

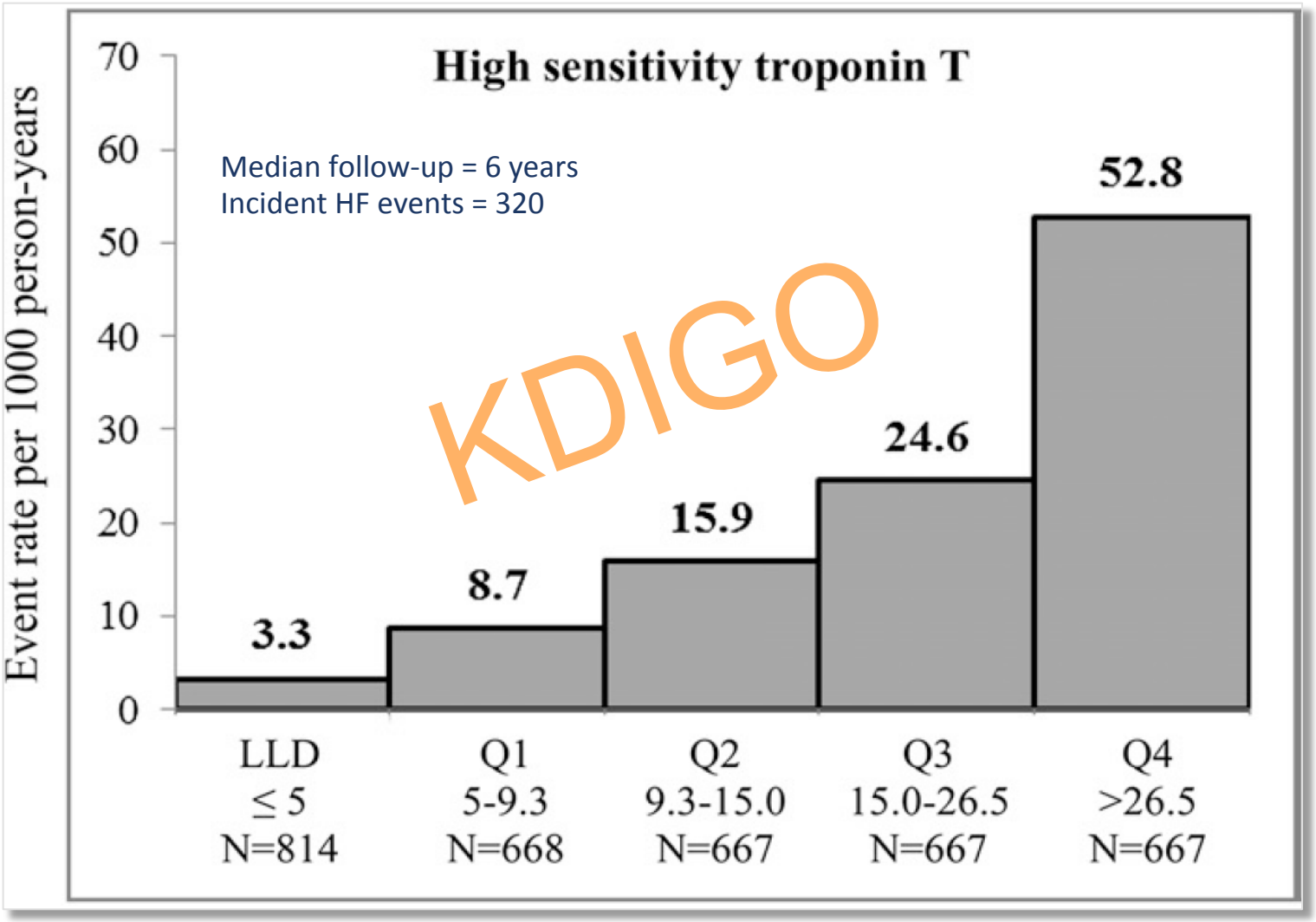





Mishra R. Am J kidney Dis 2013;61:701-9

# Incident heart failure based on hs-cTnT level

## The CRIC Study



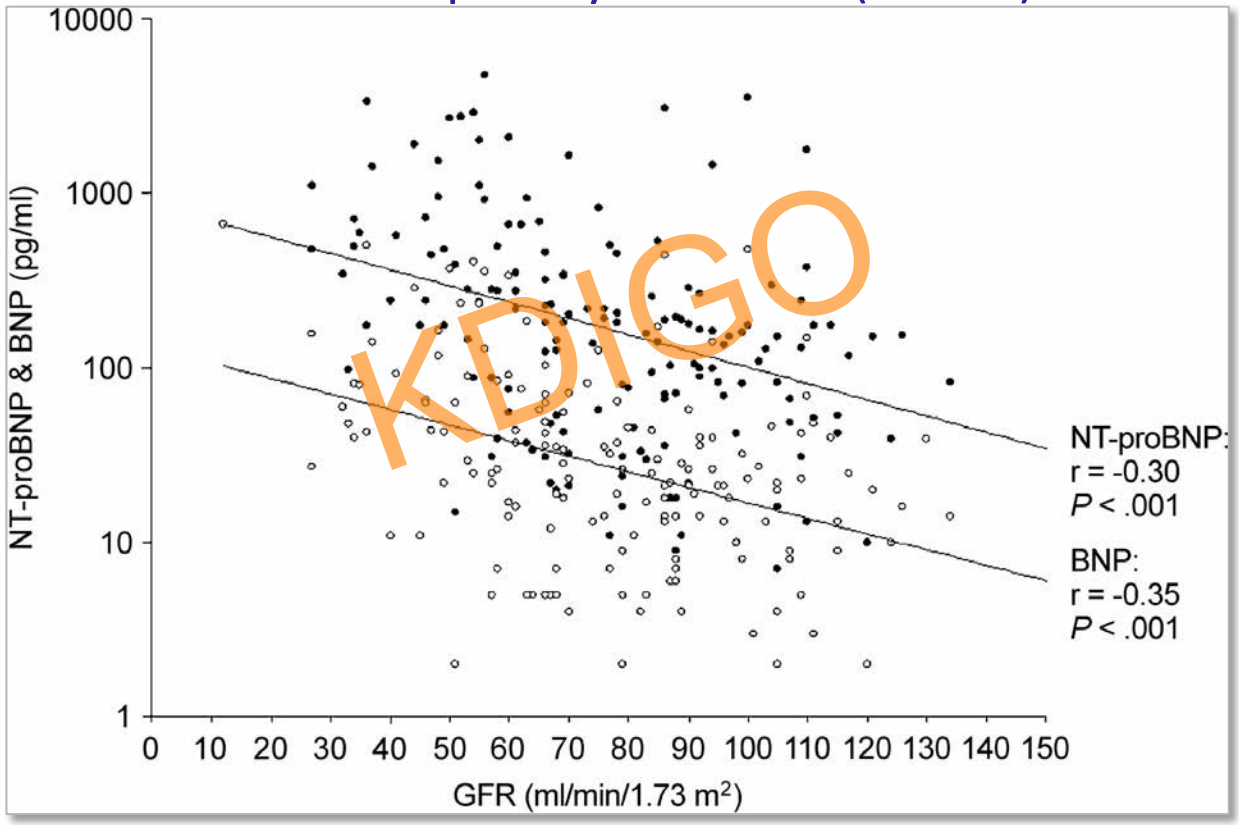

Bansal N. J Am Soc Nephrol 2015;26:946-56

# 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)

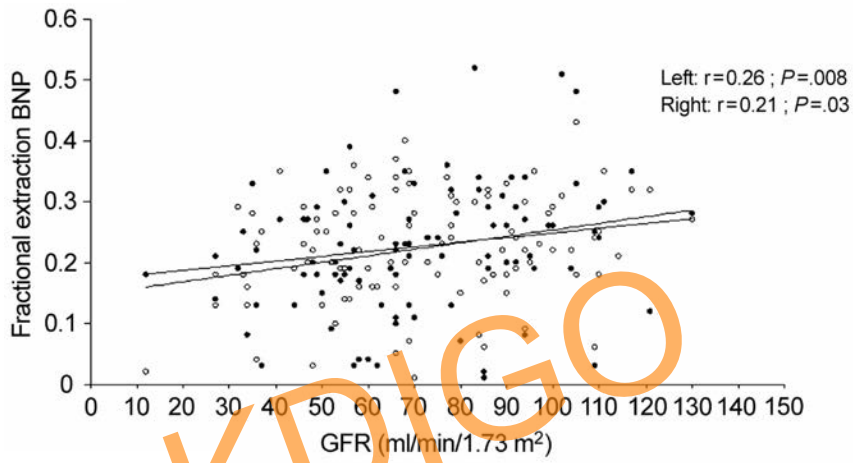



Solid dots indicate left kidney, open dots indicate right kidney

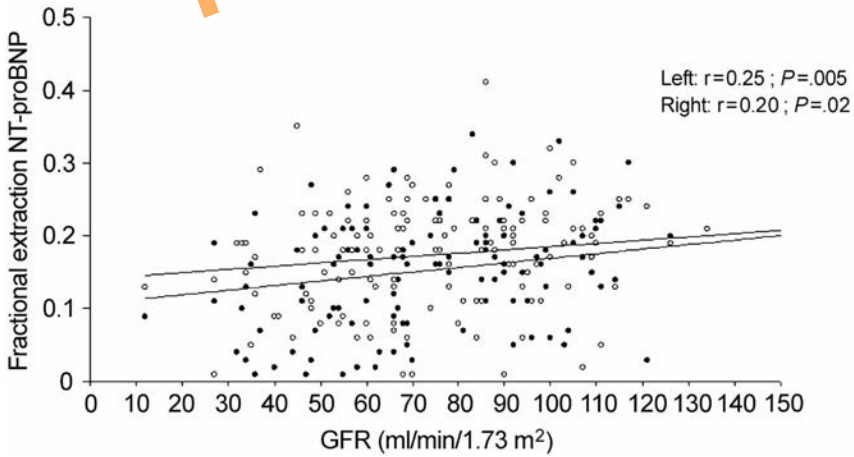
Roland R.J. van Kimmenade et al. JACC 2009;53:884-890

# Correlations Between Fractional Extraction and GFR in the Left and the Right Kidney

**BNP**




**NT-proBNP**





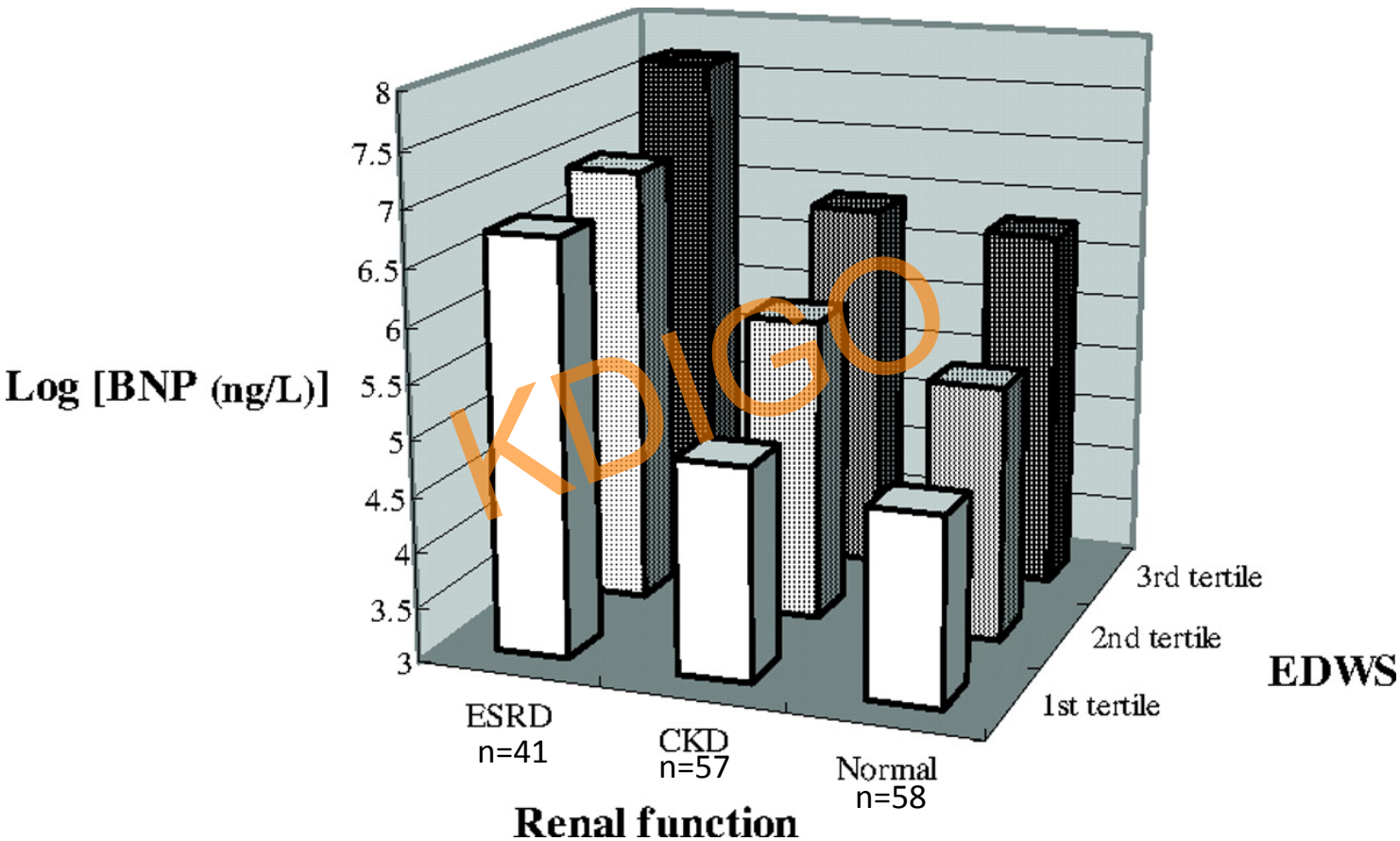

Solid dots indicate left kidney, open dots indicate right kidney

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



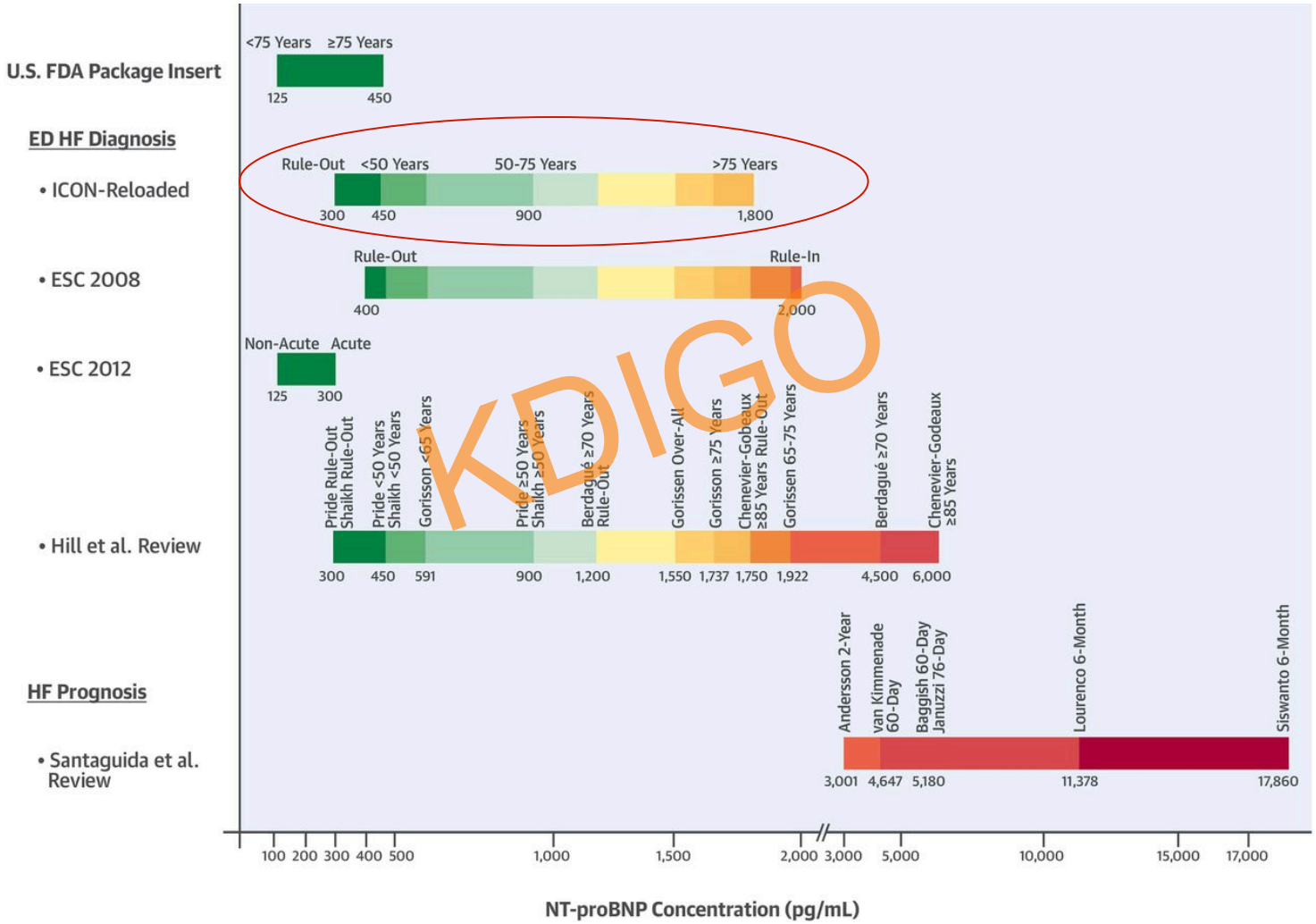

Patients were divided into tertiles according to the EDWS level
(first tertile: <33 kdynes/cm$^2$, second tertile: 33–55, third tertile: >55)
Mean eGFR: normals =78, CKD=44, ESRD=5

Niizuma S et al. Clin Chem 2009;55:1347-1353

# 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

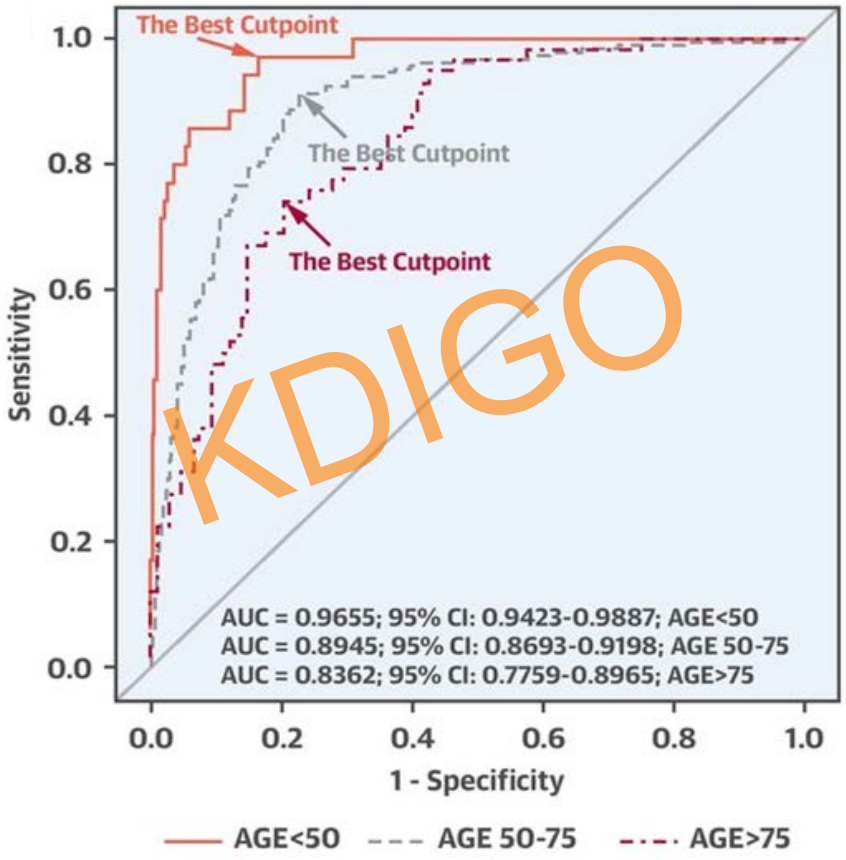
# Diagnosis and prognosis of acute heart failure with NT-proBNP




McCullough P et al. J Am Coll Cardiol 2018;71:1201-1203

# 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




| | AUC | p Value for Difference in AUC |
|---|---|---|
| 1.73 m$^2$ | 0.872 | 0.12 |
| 1.73 m$^2$ | 0.907 | |

Januzzi, JL et al. J Am Coll Cardiol 2018;71:1191-1200

# 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.