



Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

Ms. S. is a 69 yo woman with a PMHx of ESRD (on HD T, Th, Sat, last HD session 2 days prior to admission), type 2 DM, HTN and HLD presenting with one day of nausea, vomiting (3-4 episodes, nbnb), diarrhea (4-5 episodes, non-bloody) and epigastric pain. Symptoms began suddenly around noon the day of admission and worsened around midnight with accompanying dizziness, HA and a sudden “clouding” of vision (resolved after one hour). Denies fever, chills, sick contacts, new or raw foods, chest pain, palpitations and SOB. Home BP: 200/107 (systolics the day prior to dialysis generally in the 180s, diastolics unknown) so she activated EMS. ED vitals: T 37.1, HR 100, BP 187/90, RR 18 satting 95% (room air). Physical exam unremarkable. Labs notable for troponins of 0.03 → 0.05 → 0.04. EKG: sinus rhythm with premature atrial complexes but no ST or T wave changes. She was admitted for work up of her elevated troponins.

Clinical Question: What is the clinical significance of a slight troponin elevation? Are the clinical implications of such an elevation different in patients with vs. without ESRD?

**Search Strategy:** PubMed: “subclinical troponins” → 48 results

Wilson Tang WH, Wu Y, Britt EB, Iqbal N, Hazen SL. Detectable subclinical myocardial necrosis is associated with cardiovascular risk in stable patients with diabetes. *Diabetes Care* 2013; 36(5): 1126-31.

**Background**

Epidemiology of renal failure

- In the US more than 10% of people (more than 20 million) ≥ 20 years old have CKD
- In 2009 > 871,000 people undergoing ESRD treatment

Cardiovascular disease in renal failure: the cardio-renal syndrome

- Cardio-renal syndrome: kidney failure and heart failure; either can be primary
- After adjusting for traditional cv risk factors, patients with decreased renal function and increased albumin in urine have 2-4 times the likelihood of developing cv disease of patients without CKD.
- Individuals with CKD 16-40 times more likely to die than to reach ESRD
- CAD in patients w/ CKD → often atypical presentation or asymptomatic
- Treatment: no effective evidence based treatment

Cardiac effects of hemodialysis

- HD induces myocardial ischemia → recurrent ischemic insults → myocardial structural and functional changes → systolic dysfunction and heart failure

What are troponins? How are they cleared?

- Complex of three proteins involved in skeletal and cardiac muscle contraction
  - cTnT and cTnI—cardiac specific troponins used in assays
- Troponins T and I used to detect acute MI: increase 3-12 hours post MI, peak at 24hrs, remain elevated several days
- Elevated in any damage to heart muscle (not just MI)
- Both cTnT and cTnI renally cleared but exact mechanisms unknown: cTnT more commonly elevated in ESRD patients → one theory: cTnT glycosylated so less easily cleared by kidney

Prior studies of troponins in renal failure

- Previously troponins thought to be of no significance in ESRD patients
- Now considered a prognostic marker
- In one study of 733 patients with ESRD on HD 82% had cTnT levels above 99<sup>th</sup> percentile of referent (0.01 μg/l)

- Global Use of Strategies to Open Occluded Coronary Arteries IV trial: 7033 patients with ACS, cTnT elevation associated with death or MI across all quartiles of creatinine clearance
- Trended troponins (especially cTnI) *can* be used to diagnose acute MI in ESRD patients



## COLUMBIA UNIVERSITY MEDICAL CENTER

### DIVISION OF GENERAL MEDICINE

#### Senior Medicine Rotation: Evidence-Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened	Participants in the Cleveland Clinic GeneBank Study: a single center prospective cohort study from 2001 to 2006 examining subjects undergoing elective diagnostic coronary angiography.	15,000
Inclusion criteria	Consecutive consenting subjects with clinical diagnosis of DM and with 3-year follow up data.	1,275
Exclusion criteria	Clinical evidence of ACS Cardiac troponin I $\geq 0.03$ ng/ml Revascularization within 30 days of enrollment	?

#### Are the results of the study valid?

##### Primary Guides

- *Representative patients at similar point in disease?*
  - **Yes:** the two patient groups did not differ significantly on HbA<sub>1c</sub>, systolic blood pressure, history of HTN, HLD
  - **No:** the subclinical myocardial necrosis group had a significantly greater percentage of patients with hx of heart failure, MI, maximal stenosis  $\geq 50\%$  and three-vessel coronary artery disease, they tended to be older and they had slightly lower renal function at baseline
- *Follow-up sufficiently long and complete?*
  - **Yes:** data from the Cleveland GeneBank study. Selected only subjects with three full years of follow up

##### Secondary Guides

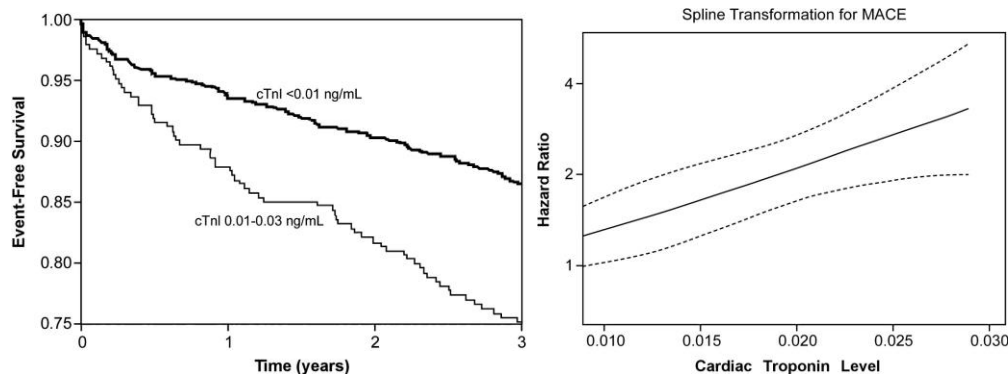
- *Objective and unbiased outcome criteria?*
  - **Yes:** outcomes were major adverse cardiovascular event, or MACE, (defined as any death, MI or stroke)
- *Adjustment for important prognostic factors?*
  - **Yes:** adjustments were made for individual traditional cardiac risk factors (age, sex, cigarette smoking, LDL cholesterol, HDL cholesterol and systolic blood pressure)
  - Further, the authors used a number of different models to control for additional factors

#### Results

Likelihood of outcome event(s) in specified period of time? How precise are estimates of likelihood?

Hazard ratio for outcomes at three years:

	cTnI < 0.01	cTnI 0.01-0.03	CI	p
Death	1	2.39	1.68-3.40	<0.001
Nonfatal MI or Stroke	1	1.70	1.09-2.66	0.019
MACE	1	1.98	1.48-2.65	<0.001



### Will the results help me in caring for my patients?

- *Study patients similar to my own?*
  - Yes: Ms. S had DM2, no clinical evidence of ACS
  - No: Troponins slightly too high, not considering elective angiography
- *Results lead directly to selecting or avoiding therapy/ results useful for reassuring or counseling patients?*
  - Although results do not specifically implicate a therapy, they do identify patients at elevated risk for MACE → careful follow up and reduction of risk factors

### Study Conclusions

Subclinical myocardial necrosis was associated with decreased renal function (estimated by creatinine clearance). Although past studies have suggested that this may be due to reduced renal clearance of cTnI, this did not appear to be the case. The prognostic value of cTnI remained strong even when controlling for creatinine clearance implying an underlying cardiovascular process that disproportionately affects patients with decreased renal function.

### Limitations

The patients in the subclinical myocardial necrosis group were sicker, which may explain greater rates of MACE (which includes death from any cause) in this patient population. The rates of nonfatal stroke and MI alone were not significantly different between the two study groups. Further, when cardiovascular history was controlled for, the hazard ratio for MACE was 1.49 with a confidence interval of 1.06 to 2.09 ( $p < 0.05$ ) representing only a slight increase in risk for the group with subclinical myocardial necrosis. Although evidence is convincing enough to promote increased surveillance and risk factor reduction, further study is necessary to fully understand the significance of slightly elevated troponins in patients with and without ESRD.

### References

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