Misdiagnosis of Myocardial Infarction Related to Limitations of the Current Regulatory Approach to Define Clinical Decision Values for Cardiac Troponin

_Circulation June 2015_

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17.06.2016

SGK Congress
Disclosures

• Swiss National Science Foundation

• Swiss Herzstiftung

• University Hospital Basel

• Abbott

• Alere

• Beckman Coulter

• Bühlmann

• Brahms

• Critical Diagnostics

• Roche

• Schiller

• Siemens

• Novartis

• CardioRentis
- AMI major cause of death and disability worldwide
- 10% of ED consultations with symptoms suggestive of AMI. Only 10-20% AMI
- Rapid identification of paramount clinical importance
  Avoid Misdiagnosis of AMI
- Introduction of universal definition of AMI
  - harmonization worldwide
  - reduction in inconsistencies
  - cTnI or T >99th perc in healthy population (CDV)
Background

• Available assays: hs-cTnI (Abbott) and hs-cTnT (Roche)
  Challenging: define clinical decision values (CDV) for a each assay in diagnosis of AMI

• Manufacturers: establish the 99th percentile in a healthy reference population
  -different populations
  -lack of consensus: “healthy”
  -effect of age and gender

• Aim of this analysis:
  quantify inconsistencies in the diagnosis of AMI related to limitations of the current regulatory approach on how to define CDV for cTn
Methods

• Prospective international multicenter study (APACE)
• Consecutive patients presenting to the ED with acute chest pain (<12h)
• Hs-cTn I and T measured at presentation, after 1, 2, 3 and 6h
• Follow up 3M, 12M and 24M

• Final diagnosis by 2 independent cardiologists all available medical records (after 3M FU)
• Definition AMI:
  Evidence of myocardial necrosis* in association with a clinical setting consistent with myocardial ischemia
  *myocardial necrosis: at least 1 hs-cTnT value above the 99th perc and a significant rise and/or fall
Results

3030 patients included between April 2006 and September 2012

excluded

92 patients final diagnosis remained unclear after adjudication and at least one cTn elevated

638 patients hs-cTnl (Abbott) or hs-cTnT (Roche) levels were not available

n=2300

Final diagnosis AMI in 473 patients (21%)

16% STEMI, 84% NSTEMI
Results

Correlation hs-cTnT and hs-cTnI

no AMI: \( r = 0.799 \) (presentation), \( 0.808 \) (serial) (both \( p < 0.001 \))

AMI Patients:

A) \( r = 0.797, p < 0.001 \)

B) \( r = 0.770, p < 0.001 \)
Results

Similar results using sex-specific cutoffs

A) women: $r=0.832$, $p<0.001$

B) men: $r=0.849$, $p<0.001$
Results

Approved CDV for hs-cTnI not biologically equivalent to hs-cTnT: inconsistencies related to underdiagnosis with hs-cTnI

- hs-cTnT higher Sens
- hs-cTnI higher Spec

Biologically equivalent CDV for hs-cTnI (regression analysis) corresponding to the CDV of hs-cTnT

less than half the CDV for hs-cTnI (8.7ng/L instead of 26.2ng/L) reduced inconsistencies from 18.2% to 10% (p<0.001)
Discussion

- Hs-cTnI and hs-cTnT levels showed high correlation.
- Using approved CDV for hs-cTnT vs hs-cTnI: 1/5 patients with AMI with inconsistent diagnosis.
- Both similar diagnostic accuracy (prior studies).
- Inconsistencies not reduced with sex-specific CDVs.
- CDV for hs-cTnI not biologically equivalent to approved CVD.
Limitations

- Quantification of inconsistencies only in AMI
- Patients with terminal kidney failure excluded
- Cannot quantify the increase in morbidity or mortality possibly associated with missing these 18% of AMI patients with discordant CDVs
Conclusion

Current cut-offs (CDV) are not biologically equivalent, contribute to inconsistencies in the diagnosis of AMI in 1 of each 5 patients.
Thank you!!
Distribution of sensitive (s-Tn) and high-sensitivity cardiac troponin (hs-Tn) I and T values at presentation in quadrants according to the approved uniform CDVs in patients with an adjudicated diagnosis of AMI
A

Cumulative survival over days to death for different patient groups:

- Unstable angina: 216, 212, 211, 209, 205, 201, 201
- Inconsistent diagnosis of AMI: 86, 81, 80, 80, 79, 76, 74
- Consistent diagnosis of AMI: 387, 354, 341, 337, 329, 324, 321

Log rank values:
- Log rank < 0.001
- Log rank = 0.4
- Log rank = 0.05
Subgroup analysis regarding pre-analytical contributors

- Measurement of hs-cTnT and s-cTnI ultra: same tube, same day (1355 patients)
- 294 patients with AMI (22%), r=0.802
- 53 patients with inconsistent diagnosis (18%): nearly all related to under-diagnosis of AMI with s-cTnI ultra
- Using the s-cTnI ultra biologically equivalent CDV (9.4ng/l instead of 40ng/l) reduced inconsistencies to 9%