



#### **Fifty shades of Troponin**

Dr Liam Penny

The Queens Hotel, Cheltenham 4<sup>th</sup> October 2012

## Sir Arthur Conan Doyle Lesson

BEETON'S CHRISTMAS ANNUN

(The Boscombe Valley Mystery) ".It seems, from what I gather, to be one of those simple cases which are so extremely difficult." "That sounds a little paradoxical."



MONTHLY MAGAZINE.

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#### PRICE ONE SHILLING.

Ladon WARD, LOCK AND CO. Solidery Beneve E.C. Blacking J. 3. Lower Co.



## **Plaque-fissure and intracoronary thrombus**



Courtesy Prof. MJ Davies

### Acute Coronary Syndromes Plaque-fissure and intracoronary thrombus



### Acute Coronary Syndromes Plaque-fissure and intracoronary thrombus



### **Coronary Embolism in patient dying with ACS**



(From Falk E: Coronary thrombosis: Pathogenesis and clinical manifestations. Am J Cardiol 68:28B, 1991.)

## Acute Coronary Syndromes

## Why Troponin ? Main value is for Risk stratification

#### Any rise in Troponin Predicts Risk of complications in ACS



#### **Increasing Troponin Predicts increasing Risk**



Wright, R. S. et al. J Am Coll Cardiol 2011;57:e215-e367

# Troponin predicts which ACS patients benefit from Invasive strategy



Postgrad Med J 2012;88:437-442 doi:10.1136/postgradmedj-2011-130466

**Original article** 

# Early and late mortality in hospitalised patients with raised cardiac troponin T

Peter Sze Chai Wong<sup>1</sup>, Julia Dawn Jones<sup>1</sup>, <u>Reza Ashrafi<sup>1</sup></u>, Omer Khanzada<sup>1</sup>, Upul Wickramarachchi<sup>1</sup>, Touran Heidi Keen<sup>1</sup>, Derek Richard Robinson<sup>2</sup>

1021 patients 7 yr follow up study

## Comparison of Kaplan–Meier Survival for the 2 ACS groups and with the reference population.



Wong P S C et al. Postgrad Med J 2012;88:437-442

## Comparison of Kaplan–Meier Survival for the two non ACS groups and with the reference population.



#### Comparison of Kaplan–Meier Survival for the four troponin groups Tn + , non ACS had worst prognosis.



Wong P S C et al. Postgrad Med J 2012;88:437-442

# Definition of AMI

## WHO definition of AMI 1971

• CPK raised > 2 normal

- arbitrary level
- assay was unreliable with wide inter-individual and intra-individual variations
- many other causes of raised CPK

### ESC/ AHA 2000 definition of AMI

Either of the following criteria satisfies the diagnosis for acute, evolving, or recent MI:

- Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following:
  - a) Ischemic symptoms
  - b) Development of pathological Q waves in the ECG
  - c) ECG changes indicative of ischemia (ST segment elevation or depression)
  - d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- 2. Pathological findings of an acute myocardial infarction

### NB Any rise or fall of Tn

## New clinical classification of MI

#### Classification Description

3

- 1 Spontaneous MI related to ischemia due to a primary coronary event, such as plaque erosion and/or rupture, fissuring, or dissection
- 2 MI secondary to ischemia due to an imbalance of O<sub>2</sub> supply and demand, as from coronary spasm or embolism, anemia, arrhythmias, hypertension, or hypotension
  - Sudden unexpected cardiac death
- 4a MI associated with PCI
- 4b MI associated with documented in-stent thrombosis
- 5 MI associated with CABG surgery

#### Thygesen K et al. Circulation 2007;

# ESC/ ACC definition of AMI

 Based on more sensitive and more specific Tn assays but ....

## Problems with ESC /ACC definition

- Wide variation in early Tn assays at low levels
  - Eg same patient assayed in 2 different laboratories one will determine AMI other will not

## Problems with ESC /ACC definition

- Tn raised in other conditions apart from ACS
  - 68% of marathon runners
    Ann Emerg Med. 2007;49:137-143
  - 19.6% of angioplasties but normal CKMB
     J Am Coll Cardiol 2006;48:1765–70
  - Treadmill exercise test ie reversible ischemia not necessarily necrosis
  - 'Healthy' population

**RAISED TROPONINS ON A STROKE UNIT:** 

412 patients with Stroke

70 (29%) patients had positive Tn levels (>0.032 ng/l)

NB Must view clinical context to interprete rise in Tn

doi:10.1136/heartjnl-2011-300198.4

#### **BRITISH CARDIAC SOCIETY**

# British Cardiac Society Working Group on the definition of myocardial infarction

K A A Fox, J Birkhead, R Wilcox, C Knight, J Barth

The British Cardiac Society commissioned this report to help address inconsistencies in the terminology for acute coronary syndromes and wide variations in the threshold for the diagnosis of myocardial infarction (MI) depending on the assay performed, the precision, and the sensitivity. In addition, several publications have highlighted potential problems with the application of the European Society of Cardiology(ESC)/American College of Cardiology (ACC) consensus document published in 2000. A revision process has been initiated under the guidance of the ESC, the ACC, and the American Heart Association (AHA). The purpose of this report is to help inform the next revision of the ESC/ ACC/AHA guidelines for the diagnosis of MI.

Heart 2004;90:603-609. doi: 10.1136/hrt.2004.038679

#### The remit of the British Cardiac Society Working Group on MI is:

- To establish a nomenclature for acute coronary syndromes to meet current treatment and prognostic needs of patients
- To recommend a diagnostic threshold to distinguish patients with MI from patients with acute coronary syndromes with minor but prognostically important increases of troponin concentrations
- To recommend a strategy for establishing a reference standard for troponin assays.

# BCS Working Group proposals

- 1. ACS with unstable angina Tn –
- 2. ACS with myocyte necrosis Tn + transient ECG changes
- 3. ACS with clinical MI evolving ECG changes
  - Tn I >1.0ng/ml or Tn T >0.5ng/ml
    - Roughly corresponds with 1971 WHO definition CPK x2 Arbitrary cut-off

### **2007 Expert Consensus Document**

### **Universal Definition of Myocardial Infarction**

Kristian Thygesen; Joseph S. Alpert; Harvey D. White; on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

- Symptoms of ischaemia;
- ECG changes indicative of new ischaemia [new 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.

Thygesen K et al. Circulation. 2007 Nov 27;116(22):2634-53





**Third Universal Definition of Myocardial Infarction** 

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and Harvey D. White

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#### Circulation 2012

Cardiac procedure

Non-cardiac major proce Myocardial

Myocardial infarction

Tachy-/brady arrhythmia

> Heart failure

Renal

Myocardial injury with cell death marked by cardiac troponin elevation

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

# Electrocardiogram (ECG)









# ECG Evolution in ST Elevation Myocardial Infarction



### ECG can also be non-specific for diagnosing MI

#### False positives

- Early repolarization
- LBBB
- Pre-excitation
- J point elevation syndromes, e.g. Brugada syndrome
- Peri-/myocarditis
- Pulmonary embolism
- Subarachnoid haemorrhage
- Metabolic disturbances such as hyperkalaemia
- Cardiomyopathy
- Lead transposition
- Cholecystitis
- Persistent juvenile pattern
- Malposition of precordial ECG electrodes
- Tricyclic antidepressants or phenothiazines

#### **False negatives**

- Prior MI with Q-waves and/or persistent ST elevation
- Right ventricular pacing
- LBBB

## **Diagnostic criteria for AMI**

- Evidence of myocardial necrosis (rise in Tn) in the clinical setting consistent with AMI
- At least 1 of the following
  - Symptoms of Ischaemia
  - New ST T or LBBB or Q waves
  - Imaging evidence of new WMA
  - \*Coronary Thrombus at angio or PM

Special situations eg Sudden death, PCI/CABG related MI

#### Wide variation between laboratories in Tn I assay

Table 14 UK National External Quality Assessment Service between laboratory comparisons<sup>34</sup>; lowest concentrations at which between laboratory coefficients of variation are ≤10%

Assay	Concentration (ng/ml)
Tnl	
Abbott AxSYM	4.4
Bayer Immuno 1	NA
Bayer Advia Centaur	1
Beckman Coulter AccuTnl	0.65
Dade Dimension	1.75
Dade Stratus	1.25
DPC Immulite	NA
DPC Immulite 2000	2.75
Ortho CD Vitros ECi	2.0
Tosch Biascience AIA	7.5
TnT	
Roche Elecsys 1010	0.25
Roche Elecsys 2010	0.33

Note that many manufacturers are changing and improving their assay methods.

NA, not available.

NB: CV data on the Abbott AxSYM, Vitros Eci, and Tosoh AIA systems are derived from <10 data points.

#### Troponin level (mcg/L) depends on assay The diagnostic cut-offs used in new definition (99th centile) are one order of magnitude lower than those proposed by BCS

Method	99 <sup>th</sup> centile	Original AMI cut off
	mcg/l	mcg/l
Abbott AxSym Trop I	0.4 (95 <sup>th</sup> centile)	2.0
Abbott ARCHITECT Trop I	0.012	0.3
ADVIA Centaur cTnl	0.07 (95 <sup>th</sup> centile)	1.5
ADVIA Centaur Tnl-Ultra	0.04	0.78
Access Accu Tnl	0.04	0.5
Dade Behring Dimension Trop I	0.07	0.6
Dade Behring Stratus Trop I	0.07	0.6
IMMULITE 2500 Trop I	0.2	0.9
Ortho VITROS cTnl	0.08	0.4
Ortho VITROS Tropl		0.12
Tosoh AIA Trop I	0.1	0.1
Roche Elecsys Troponin T	<0.01	0.1-0.2

## Elevation of TN

- > 99 upper percentile
- COV 5%





Ravkilde J, et al Scand J Clin Lab Invest 1993 Nov;53(7):677-85
### **Impact of Cardiac Troponins**



Ravkilde J et al, Scand J Clin Lab Invest 1993 Nov;53(7):677-85 37

## Acute Coronary Syndromes

## What about high sensitivity Troponin ?

# Raised hs TN

- 2% "healthy" adults
- Stable Angina
- Pulmonary Hypertension
- LVH
- Heart Failure
- Renal Failure

# Diagnosis of AMI with hsTn

- Requires 2 samples
- Show 20% to 50% rise after 3 hrs

## High Sensitivity Troponin

Detects levels 10X lower than older assays

- 1. Greater sensitivity
- 2. Greater precision than older assays
- 3. Peaks earlier post MI (3hrs)
- 4. ?positive in some 'well' individuals

Christ M et al, American J Med (2010) 123, 1134-1142 Mohammed AA et al. Cardiology in Review 2010;18: 12–19

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Ortho VITROS TropI		0.12	
Tosoh AIA Trop I	0.1	0.1	
Roche Elecsys Troponin T	<0.01	0.1-0.2	

High Sensitivty Troponin T 99<sup>th</sup> percentile = 0.014 mcg/L (an order of magnitude lower again!!)

#### hs Troponin detected in 70% 'well' subjects > 65 yrs

**Baseline Tn predicted Death over 10 yrs.** 

deFilippi, C. R. et al. JAMA 2010;304:2494-2502

#### hs Troponin elevated in 70% 'well' subjects > 65 yrs

#### Baseline Tn predicted Death over 10 yrs.

Cardiovascular death	(n = 222)	(n = 153)	(n = 204)	(n = 239)	(n = 285)	
Adjusted for demographic factors, traditional risk factors, and NT-proBNP and CRP	1 [Reference]	1.30 (1.05-1.60)	1.45 (1.19-1.78)	1.58 (1.29-1.93)	2.10 (1.70-2.60)	

#### Subsequent Change in hs Tn predicts development of Heart Failure and Cardiovascular Death



deFilippi, C. R. et al. JAMA 2010;304:2494-2502

### Accuracy of Troponin depends on time since pain onset hs Troponin accurate at 2 hrs, standard Tn 12 hrs



## **Impact of Troponins on MI Incidence**

Studies of CK-MB and Troponin Comparison								
n	Characteristics	Positive CK-MB, n (%)	Positive Troponin, n (%)	% Troponi Troponin/CK-				
801	Acute myocardial ischemia admissions	216 (27)	289 (36)	+34%				
292	Possible myocardial ischemia in emergency ward	15 (5)	34 (12)	+127%				
14 777	MI discharge diagnosis plus biomarker, ECG, and pain algorithm	4157 (28)	4661 (32)	+12%				
1719	All ACS admissions	373 (22)	430 (25)	+15%				
80	All ACS admissions except with diagnostic ECG of MI	23 (29)	32 (40)	+ 39%				
798	ACS admits to cardiology service	189 (23)	228 (28)	(21%)				

#### Circulation 2003;108:2543-9

### Impact hsTn vs Tn STEMI diagnosis by 20%

#### Classification of patients using TnT gen 4<sup>th</sup> at 10% CV & cTnT-hs 99<sup>th</sup> percentile value



 After serial sampling with cTnT-hs assay, the number of patients with a final diagnosis of UA decreased from 31 to 22 with a corresponding increase of the number of NSTEMI

# In Edinburgh introducing hsTn increased myocardial infarction diagnosis by 33%

Conclusions In patients with suspected acute coronary syndrome, implementation of a sensitive troponin assay increases the diagnosis of myocardial infarction by a third, and identi- es those at high-risk of reinfarction and death. Lowering the diagnostic threshold of plasma troponin is associated with major reductions in morbidity and mortality.

Heart 2011

# Acute Myocardial Infarction

### Other markers to define AMI?

## Role of other Biomarkers to define AMI: Copeptin

Skip to content   Vision impaired   Login   Glossary   Contact   Sitemap         Search:         Site help       Site help         National Institute for       Institute for         Health and Clinical Excellence       Image: Search im							
Home	Find guidance	Putting guidance into practice Get involved News and press About NICE					
Home	News room Press	releases NICE consults on new test for heart attacks					
NICE p	ress office						
NICE n alerts	ewsletters and	NICE consults on new test for heart attacks					
Press r	eleases						
Press	release archive	The National Institute for Health and Clinical Excellence (NICE) has today (7 March), opened a consultation on its <b>draft</b> medical technology guidance on the use of a test to rule out myocardial infarction (heart attack) in patients who have acute chest pain. The medical technology guidance draft, produced by the independent Medical Technologies Advisory Committee (MTAC), concludes that the BRAHMS copeptin assay shows potential to reduce the time taken to rule out myocardial infarction but more evidence on its impact in clinical practice is					
News							
Fact sh	leets						
NICE s	tatistics	required to support the case for its routine adoption in the NHS.					
NICE a	nnual conference	The BRAHMS copeptin assay is intended to be used in conjunction with standard cardiac troponin testing (a biochemical marker, raised levels of which might indicate a heart attack) to reduce the time needed to exclude					
Events		acute myocardial infarction. MTAC was asked to consider whether the combination of the values resulting from the copeptin test and first troponin test may provide a reliable basis for earlier ruling out of myocardial					
Featur	es	infarction in patients, thereby reducing the need for intensive in-patient monitoring and further tests. Currently, the exclusion of myocardial infarction requires at least two troponin tests 9 -12 hours apart.					
Guidan	ce in Focus						

#### Copeptin and Tn Levels in Relation to Time Since Onset of Symptoms Copeptin is an early marker



Reichlin, T. et al. J Am Coll Cardiol 2009;54:60-68

# Acute Myocardial Infacrtion

What about adefinition based on Ejection Fraction?

#### Comparison between Echo and Nuclear EF in same subject



## Inter-observer variation



Echo mean diff = 18.1%

Nuclear mean diff = 3.1%

# **Other Factors Influencing EF**

### • Load on LV

- HT reduces EF (Normal = 0.45)
- Optimal treatment (3 months post MI)
- Mitral Regurgitation increases EF
   If MR, even EF < 0.6 is impaired</li>

### Conclusions

•Level of Tn which can now be reliably measured (99<sup>th</sup> Percentile and 10% CV) is 1% of original definition recommended by BCS

•Consequently in ACS spectrum less Unstable AP and more MI diagnose TN increased MI diagnosis by 33% hs TN increased MI diagnosis by further 33%

•Hs Tn measured in many 'normals' and non ACS patients

Interpretation relies not on level but on clinical context

# Case Study 1 Modern Treatment further complicates • RP male 55yrs Smoker Admitted 22.20hrs 2011 Pain onset 20.00 hrs ECG ST elevation inferior leads Tn on admission <0.03mcg/L Pain and ECG resolved with nitrates 09.3 Ohrs Pain ECG changes recurred Cath lab

# **Case Studies**

• RP male 55yrs Smoker

ECG ?small q waves
Echo Normal EF 70%
? Small area inf hypokinesia
Conclusion
Treated in early hrs of ?threatened inferior MI







Case Study2 Is this a valid claim ? 69 yrs female

While standing off stage just before a Ball Room dancing competition became distressed with palpitations and a tightness in her chest. She collapsed.

PMH – b/l mastectomy Non smoker, no FH of note

Meds - Tamoxifen 20mg /Omeprazole 20mg

**Examination** – unremarkable

X - ECG

**Troponin T – 0.02** 

### **ECG on admission**



# ECG at 12 hrs



• Diagnosis : Acute Coronary Syndrome

• Transferred that day to UHW because of ongoing pain and ECG changes despite IV Nitrates and LMW Heparin



### Normal right coronary anatomy



### Normal left coronary anatomy



### Normal left coronary anatomy










#### <u>TAKO - TSUBO SYNDROME</u>

# **'Transient LV apical ballooning' 'Reversible cardiomyopathy'**

### **First Article: Original Paper**

#### 4. 多枝 spasm により特異な左心室造影像 「ツボ型」を示した stunned myocardium Kagakuhyoronsha 1990:56-44

きりしてくるととがある。そして、ターしたつとまたわからなくなってくるのだが、"Downed myosardiam" という構造もその典型的な一つといえよう。Stanned myosardiam とは、prolonged postichemic ventricular dynamics without segmeandial second と定義される。心理 虚白に長時間で発展になると心影響形をひき起こすが、それに言われ stan 記憶があり、moreable であるという影響である。

おおおおの龍家御勧さら、malliple spanneに変換さ infernite エエッてひき起こされた result ed surgeardiam の変現を呈示したら、

#### 且 虚 例

(虚例1) V.K., 60歳, 列作,

7.30分、総会時に発展発作、可能回路を作う、30分裂の立身で解決やす。近時に受益、急 性心剤提進と診断され、12時15分入取。

AEM9, 白山道 19, 500, CFK 1, L1( o/U/a), LDR (F0 o/U), 1時間前に血清酸素油を置 定したが、入院時 が最高波 であった。 発生後 5時時 30 分で記動製造動を当行。C.O. 3.57/ min, LVEDF ElsenHg, FA 22/15 mmHg, RA 2mmHg, LVEF 405;

○電路は入設時に活業時の %T 上将 を示して (篇1)、左心協商新では、禁一利位請単で ang 2, 3, 4 dl aklannik を注1、通信の、いわゆる吉吉伊県や下居居室ではみられぬ「タッゴ 半型」ともいえる吉里像を示した (篇2)。

三組織通書では、全体に悪く spaces な学家を受けた、Togenerine 0.2 mg 掛法、左向下行 我はさらに悪くなり、正記状態制も 30% 以上の analight stansis を勝免した、Nicroglyceniae 0.5 mg 知動振行法人によう者しく必須した(第3)、 Published in Japan.
No translation.
First description.
The term "takotsubo" was named.

## Why Tako-Tsubo?

多枝 spasm により特異な左心室造影像
 「フボ型」を示した stunned myocardium

#### 上法正的规

一つの概念が展示されると、これまでわかっているようで、わからなかった問題が急には一 きりしてくることがある。そして、少したつとまたわからたくなってくるのだが、"manared myorardinan" という構まもその典型的な一つといえよう。Stanard myorardinan とは、prolonged postedomic ventricular dynamics without myopardial accresis 上定置される。 心理 虚白は長時間で展測になると心影響形をひき起こすが、それに至らな stan 記録があり、moresible であるという振動である。

おおおろの龍家朝鮮から、 moligie spannel空間の infemia と エーてひき起こされた mouti ed myonardium の空的を呈示したい。



# Tako=octopus Tsubo=pot

### **First Article: Patients**



#### Tako-tsuba Syndrome: Peculiar LV End systolic shape



#### **Key Questions**



# **1.- Absence of luminal coronary artery obstructions**

# 2.- Large LV akinetic area.

against this hypothesis is the observation that the area of akinesia does not correspond nicely to the perfusion territory of a single epicardial coronary artery—that is, in most patients it extends well beyond the perfusion territory of the left anterior

Heart 2003;89:1027-31

# Tako-tsubo Syndrome Incidence

Probably accounts for >5% ACS

Eur Heart J. 2006 Jul;27(13):1523-9.

#### Left ventricular EF independently predicts prognosis



#### New Terminology in ACS



Cannon CP. J Thromb Thrombolysis. 1995;2:205-218.

#### Importance of very small elevations in Tn



Kontos et al



●69 yrs female Christmas Eve shopping her purse was stolen and she became very distressed and collapsed with Chest pain





# Peculiar End-Systolic Shape



典型的な「ツボ型」左心室造影である.

Sato et al. Kagakuhyoronsha 1990:56-44



5 days later



●79 yrs female while picking blackcurrants in her garden had a bee sting, became distressed and then about 1 hr later developed chest pain and husband called 999

#### Histology of Ruptured plaque



#### Causes of Increased Troponin

Mohammed AA et al,Cardiology in Review 2010;18: 12–19

TABLE 2. Causes of Troponin Elevation in the Absence of Acute Coronary Syndrome

Cardiac diseases and interventions Cardiac amyloidosis Cardiac contusion Cardiac surgery Cardioversion Implantable cardioverter defibrillator shocks Closure of atrial septal defects Coronary vasospasm Dilated cardiomyopathy Heart failure Hypertrophic cardiomyopathy Left ventricular hypertrophy Myocarditis Pericarditis Percutaneous coronary intervention Post cardiac transplantation Radiofrequency ablation Supraventricular tachycardia Noncardiac diseases Critically ill patients High dose chemotherapy Primary pulmonary hypertension Pulmonary embolism Pulmonary edema Chronic renal insufficiency Stroke Subarachnoid hemorrhage Scorpion envenoming Sepsis and septic shock Sympathomimetic agents Ultra-endurance exercise Jelly fish sting Severe scorpion envenoming False-positive Heterophilic antibodies Rheumatoid factors Fibrin clots Microparticles Analyzer malfunction