The Rapid Assessment of Possible ACS In the emergency Department with high sensitivity Troponin T (RAPID-TnT) Study

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Declaration of interest

- Others (Grant in Aid Roche Diagnostics)
**BACKGROUND**

- Suspected ACS in the Emergency Department
  - one of the most common presentations to emergency services
  - very resource intensive
  - equivocal benefit for the traditional ‘liberal’ approach to further testing

- High sensitivity troponins have the potential to improve the early diagnosis of myocardial infarction
  - High negative predictive value effective in ruling out MI.

- Increased sensitivity could lead to more downstream cardiac testing
  - Uncertain benefit and even potential harm.
KEY STUDY QUESTION

What is the clinical impact of the improved diagnostic precision of hs-cTnT assay incorporated into a rapid 0/1-hour protocol in terms of patient outcomes and/or greater emergency department efficiency when embedded within practice?

• Conditions needed to address this question:
  1. No prior access to hs-cTnT results to influence clinical decision-making
  2. Clinical practice where 0/1-hour protocols are not standard of care

Primary Hypothesis: Compared with our current standard practice, clinical care based on a 0/1-hour hs-cTnT protocol will provide non-inferior clinical outcomes at 30 days

Secondary hypothesis: Suspected ACS patients discharged from the ED under the 0/1-hour hs-cTnT protocol is safe (30-day death or new/recurrent MI of <1%)
STUDY DESIGN

Prospective “in practice” patient-level randomized non-inferiority evaluation of a 0/1-hour protocol using a hs-cTnT reporting format (LoD 5ng/L) compared with a 0/3-hour protocol using masked hs-cTnT reporting (≤29ng/L) in participants with suspected ACS

Conducted in four metropolitan public emergency departments in Adelaide, Australia from August 2015-April 2019

Funding: National Health and Medical Research Council of Australia (APP 1224471) and restricted educational grant from Roche Diagnostics International (Rotkreuz, Switzerland)
RAPID TnT: OUTCOME MEASURES

The primary outcome: the 30-days composite endpoint of:

- All-cause mortality
- Myocardial infarction adjudicated by the 4th Universal Definition of MI

*Excluding Index “presenting” MI

Major secondary clinical outcomes:

- The occurrence of all-cause mortality or new ACS at 12 months
- Cardiovascular mortality at 30 days and 12 months
- Unplanned hospital admission: non-elective coronary revascularization; CVA; atrial or ventricular arrhythmias; CCF without MI; as documented by a hospital discharge summary at 30 days and 12 months.
In 2011 Roche Diagnostics 5th generation hs-cTnT assay was introduced as the sole troponin assay in public hospitals in South Australia.

Due to concerns regarding a higher rate of abnormal troponin results and increased invasive testing, the reported lower limit was aligned to the 4th generation level of ≤29 ng/L.

- (N.B: an improvement in test performance recognized)

Local EDs remained masked to troponin T concentration below 29 ng/L; and clinicians had no prior clinical experience with hs-cTnT results below this level.
Staged Implementation of cTnT to hs-cTnT

(cTnT (ng/L))

(ULN: <29ng/L on 4th Gen Assay = ~44ng/L on 5th Gen Assay)

2011

(hs-cTnT (ng/L))

(ULN: <29ng/L, below 29ng/L masked)

(hs-cTnT (ng/L))

(ULN: <14 ng/L, >4 ng/L reported)

RAPID TnT: ELIGIBILITY CRITERIA

Inclusion Criteria
Patients presenting to the ED were eligible if they had:
• Clinical features of chest pain or suspected ACS as the principal cause for investigation;
• Baseline electrocardiogram (ECG) interpreted as not definitive for coronary ischemia;
• Are greater than 18 years of age or older;

Exclusion Criteria
Patients were considered ineligible if they:
• Require admission for non-chest pain related reasons;
• Presented as a result of a transfer from another hospital;
• Are representing with chest pain within 30 days of last presentation;
• Require permanent dialysis;
• Are unable to complete clinical history questionnaire due to language or comorbidity;
STANDARD 0/3-HOUR masked hs-cTnT PROTOCOL

Troponin >29ng/L on any sample
Prior Known CAD
Ongoing Chest Pain

Admit

Suggested Management:
• General Medicine or Cardiology Consult

Troponins ≤29ng/L
No ongoing chest pain

Discharge

Suggested Management:
• Risk stratify based on age >65 years and 3 or more Cardiac Risk factors
• Discretion and discussion with cardiology
• Intermediate risk: Discharge with early outpatient stress testing
• Low risk: Discharge for review in primary care
**0/1-HOUR hs-cTnT PROTOCOL**

**Baseline hsTnT ≥52ng/L**
- OR
- Delta hsTnT ≥5ng/L at 1hr

**Rule In** *(Treat as ACS)*
- Suggested Management:
  - Consult Cardiology for admission

**Baseline hsTnT 13-51ng/L**
- OR
- Delta hsTnT 3-4ng/L at 1 hr

**Observe** *(ACS Probability: 25%)*
- Requires further troponin testing in 4h
- Discuss further testing with ED Consultant or Registrar
- Consider extended care in ED admission

**Baseline hsTnT <5ng/L**
- OR
- Baseline hsTnT ≤12 ng/L AND
- Delta hsTnT <3ng/L at 1 hr

**Rule Out** *(ACS Probability: <1%)*
- Patient able to be discharged immediately
- Follow-up (GP or Cardiac Clinic) determined by cardiovascular risk factors

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RAPID TnT: SYSTEMATIZED DATA COLLECTION

- Leverage single state-wide patient administration system and pathology systems through data-linkage
  
  - All hs-cTnT results (index and subsequent) sourced from the pathology service
  
  - All representations to the ED/hospitals interrogated
  
  - All ECG, cardiac investigation reporting systems interrogated

- Index admission and subsequent event adjudication:
  
  - All episodes of care with at least 1 hs-cTnT result >14ng/L examined
  
  - All episodes of care with targeted ICD-10AM and DRG codes examined
RAPID TnT: STATISTICAL CONSIDERATIONS

Sample size targeted 1212 patients receiving a rule out-MI/discharge recommendation in the 0/1 hour arm to assess primary endpoint (97.5% C.I.) event rate of <1%

- Anticipated rate of rule out MI recommendation was 60% (observed 72%)
- Anticipated rate of initial troponin >29ng/L was 25% (observed rate 9%). Planned sample n=5400

Non-inferiority margin defined as upper 97.5% C.I. of 0/1 hour hs-cTnT arm not 0.5% worse than 0/3-hour masked hs-cTnT arm i.e. Number needed to harm with new protocol >200

Primary analysis: Poisson regression with robust standard errors using ITT population

- Key Sub-analysis: patients with initial troponin ≤29 ng/L

Sensitivity analysis: Poisson regression using PP population, defined as troponin reported as randomized and care aligned with recommendation

April 2019, DSMB informed the Steering Committee that there is no longer equipoise regarding the event rate in patients with Rule-out MI recommendation. Study stopped
Assessed for eligibility (n=12,157)

Excluded (n=8,779)

Randomized (n=3,378)

Allocated to standard care (n=1,689)
Deemed ineligible or self-withdrawn by 30 days (n=47)

Lost to follow-up (n=0)

Analysed (n=1,642)

Allocated to intervention (n=1,689)
Deemed ineligible or self-withdrawn by 30 days (n=43)

Lost to follow-up (n=0)

Analysed (n=1,646)
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard (n = 1642)</th>
<th>0/1-Hour (n = 1646)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>58.6 (48.8, 71.2)</td>
<td>58.7 (48.6, 69.4)</td>
</tr>
<tr>
<td>Female sex</td>
<td>46.8 %</td>
<td>46.8 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20.5 %</td>
<td>19.7 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.4 %</td>
<td>15.8 %</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>44.0 %</td>
<td>43.3 %</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35.6 %</td>
<td>34.6 %</td>
</tr>
<tr>
<td>Prior history of CAD</td>
<td>29.0 %</td>
<td>27.8 %</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>2.8%</td>
<td>3.0 %</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>8.4%</td>
<td>10.4 %</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min/1.73m², median (IQR)</td>
<td>86.0 (71.1, 98.1)</td>
<td>86.2 (71.6, 98.2)</td>
</tr>
<tr>
<td>EDACS, median (IQR)</td>
<td>15.0 (9.0, 21.0)</td>
<td>14.0 (9.0, 20.0)</td>
</tr>
<tr>
<td>GRACE score, median (IQR)</td>
<td>75.0 (56.1, 100.8)</td>
<td>74.1 (55.2, 97.2)</td>
</tr>
<tr>
<td>HEART score, median (IQR)</td>
<td>3.0 (2.0, 4.0)</td>
<td>3.0 (2.0, 4.0)</td>
</tr>
</tbody>
</table>
**TIME BETWEEN TROPOGIN T TESTING**

1.0 (1.0, 1.2) hours

3.1 (2.9, 3.5) hours

0/1-Hour

Standard

Cumulative Distribution (%)
Standard Protocol

- Recommended for Admission:
  - Troponin T >29 ng/L
  - Prior CAD
  - Number of Patients: 549
  - Unallocated: 10

- Recommended for Discharge:
  - Troponin T ≤29 ng/L
  - Number of Patients: 1083

0/1-Hour hs-cTnT Protocol

- Recommended for Admission:
  - Troponin T >29 ng/L
  - Number of Patients: 136

- Recommended for Discharge:
  - Troponin T ≤29 ng/L
  - Number of Patients: 1187

Unallocated: 15

N.B.: Actual management based on clinical discretion
INDEX CLINICAL DIAGNOSIS
All participants

- Myocardial Infarction
  - Standard: 4.0%
  - 0/1-Hour: 3.6%

- Other cardiac diagnosis
  - Standard: 25.9%
  - 0/1-Hour: 26.6%

- Non-cardiac diagnosis
  - Standard: 8.2%
  - 0/1-Hour: 9.3%

- Undifferentiated Chest Pain
  - Standard: 61.9%
  - 0/1-Hour: 60.3%


**PRIMARY ENDPOINT:**

30-day Death or MI

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**All-cause Death or MI (%)**

Days from randomization

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>1642</td>
<td>1635</td>
<td>1633</td>
<td>1628</td>
<td>1626</td>
</tr>
<tr>
<td>0/1-Hour</td>
<td>1646</td>
<td>1637</td>
<td>1634</td>
<td>1631</td>
<td>1629</td>
</tr>
</tbody>
</table>

0/1-Hour (%) : 1.04 (0.72-1.35)  
Standard (%) : 0.98 (0.50-1.46)

IRR: 1.06 (95% C.I.: 0.53-2.11)  
Non-inferiority p=0.006  
Log-rank p-value =0.886

*IRR=Incident rate ratio  
Poisson confidence intervals
CV RE-HOSPITALIZATION
30-day rehospitalization for non-elective coronary revascularization, heart failure, CVA and arrhythmias

Days from randomization

<table>
<thead>
<tr>
<th>Days</th>
<th>Standard</th>
<th>0/1-Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1642</td>
<td>1646</td>
</tr>
<tr>
<td>7</td>
<td>1636</td>
<td>1640</td>
</tr>
<tr>
<td>14</td>
<td>1634</td>
<td>1631</td>
</tr>
<tr>
<td>21</td>
<td>1631</td>
<td>1627</td>
</tr>
<tr>
<td>30</td>
<td>1627</td>
<td>1623</td>
</tr>
</tbody>
</table>

0/1-Hour (%): 1.41 (0.81-2.00)
Standard (%): 0.92 (0.57-1.27)

IRR: 1.53 (95% C.I.: 1.12-2.10)
Log-rank p-value: 0.194

*Poisson confidence intervals
0/1-HOUR PROTOCOL PERFORMANCE
Death or MI within 30 days

Sensitivity 88.1 %
Specificity 94.7%
PPV 38.2%
LR(+) MI 16.5

5/1187 (0.4 %)
2/630 (0.3%)*

NPV 99.6%
Spec. 73.2%

Rule In MI
Observe
Rule Out MI

* Basis for DSMB Recommendation
CUMULATIVE DISTRIBUTION OF TIME
First 12 hrs

ALL PATIENTS

Proportion of Participants

Hours in ED

Discharged from the ED

≤29 ng/L TROPONIN T

Proportion

0 25 50 75 100

5.6

4.6

3.4-6.4

3.4-6.2

4.0-7.0

4.0-7.1

12

0 25 50 75 100

5.6

4.6

3.4-6.4

3.4-6.2

4.0-7.0

4.0-7.1

12

\[ ≤29 \text{ ng/L} \]

\[ \text{TROPONIN T} \]

\[ \text{Discharged from the ED} \]

\[ \text{First 12 hrs} \]

\[ \text{ALL PATIENTS} \]

\[ \text{Standard} \]

\[ \text{0/1-Hour} \]

\[ p<0.001 \]

\[ \text{531/1642} \]

\[ 32.3\% \]

\[ \text{742/1646} \]

\[ 45.1\% \]

\[ \text{512/1493} \]

\[ 34.3\% \]

\[ \text{728/1515} \]

\[ 48.1\% \]

\[ p<0.001 \]
CARDIAC TESTS WITHIN 30 DAYS
All participants

No subsequent cardiac test

<table>
<thead>
<tr>
<th>Test</th>
<th>Standard</th>
<th>0/1-Hour</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional testing</td>
<td>11.0%</td>
<td>7.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>9.3%</td>
<td>8.6%</td>
<td>0.24</td>
</tr>
<tr>
<td>Coronary angiogram</td>
<td>9.3%</td>
<td>10.4%</td>
<td>0.30</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>3.4%</td>
<td>4.0%</td>
<td>0.36</td>
</tr>
</tbody>
</table>
CARDIAC TESTS WITHIN 30 DAYS
≤29 ng/L Troponin T

- Functional testing: 7.1% (Standard), 7.1% (0/1-Hour) [p = 0.002]
- Echocardiogram: 5.8% (Standard), 5.7% (0/1-Hour) [p = 0.92]
- Coronary angiogram: 5.3% (Standard), 7.1% (0/1-Hour) [p = 0.044]
- No subsequent cardiac test: 0.9% (Standard), 2.2% (0/1-Hour) [p = 0.002]

RAPID TNT
MYOCARDIAL INFARCTION AND INJURY

All patients

Myocardial Infarction

Standard 0.6%
0/1-Hour 0.9%

0.7%
0.4%

Chronic Injury

Type 4a/5 MI
Type 1/2 MI
Acute Injury

21
11
18

Chronic Injury

p = 0.004

1.6%
1.0%

Type 4a/5 MI
Type 1/2 MI
Acute Injury

3
7
11

6
9

RAPID TNT
CONCLUSIONS

- Patients classified as “Rule-out MI” are safe for early discharge and have low rate of death or MI within 30 days supporting the routine implementation of a 0/1-hour hs-cTnT protocol

- Implementing high-sensitivity troponin in routine practice does not appear to “improve” the diagnosis of MI, although the impact on late outcomes and cost-effectiveness await the 12-month analysis

- However, use of invasive coronary investigation is increased among patients with newly identified low-concentration troponin elevations and strategies to mitigate associated cardiac injury may require further refinements in acute coronary syndrome care.
Acknowledgements

Steering Committee:
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Australian Government