Appendix to: The Troponin-only Manchester Acute Coronary Syndromes (T-MACS) Decision Rule: Derivation and Validation

Other analyses published from these cohorts:

1. Body R, Carley S, Wibberley C, McDowell G, Ferguson J, Mackway-Jones K. The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. Resuscitation. 2010;81(2):281–6.

2. Body R, McDowell G, Carley S, Mackway-Jones K. Do risk factors for chronic coronary heart disease help diagnose acute myocardial infarction in the Emergency Department? Resuscitation. 2008;79:41–5.

3. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, et al. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014;100:1462–8.

4. Body R, McDowell G, Carley S, Wibberley C, Ferguson J, Mackway-Jones K. A FABP-ulous "rule out" strategy? Heart fatty acid binding protein and troponin for rapid exclusion of acute myocardial infarction. Resuscitation. 2011 Aug;82(8):1041–6.

5. Body R, Pemberton P, Ali F, McDowell G, Carley S, Smith A, et al. Low soluble P-selectin may facilitate early exclusion of acute myocardial infarction. Clin Chim Acta. 2011 Mar 18;412(7-8):614–8.

6. Body R, Carley S, McDowell G, Ferguson J, Mackway-Jones K. Can a modified thrombolysis in myocardial infarction risk score outperform the original for risk stratifying emergency department patients with chest pain? Emergency Medicine Journal. 2009;26:95–9.

7. Body R, Burrows G, Carley S, Lewis PS, Jarvis J. The Manchester Acute Coronary Syndromes (MACS) decision rule: validation with a new automated assay for heart-type fatty acid binding protein. Emergency Medicine Journal [Internet]. 2014 Dec 24 [cited 2015 Feb 27]; Available from: http://emj.bmj.com/cgi/doi/10.1136/emermed-2014-204235

8. Body R, Lewis PS, Carley S, Burrows G, Haves B, Cook G. Chest pain: if it hurts a lot, is heart attack more likely? European Journal of Emergency Medicine. 2014 Oct;[Online first]:1.

9. Body R, Cook G, Burrows G, Carley S, Lewis PS, Jarvis J, et al. Can emergency physicians "rule in" and "rule out" acute myocardial infarction with clinical judgement? Emergency Medicine Journal. 2014 Jul 12;31:872–6.

10. Carlton EW, Cullen L, Than M, Gamble J, Khattab A, Greaves K. A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. Heart [Internet].

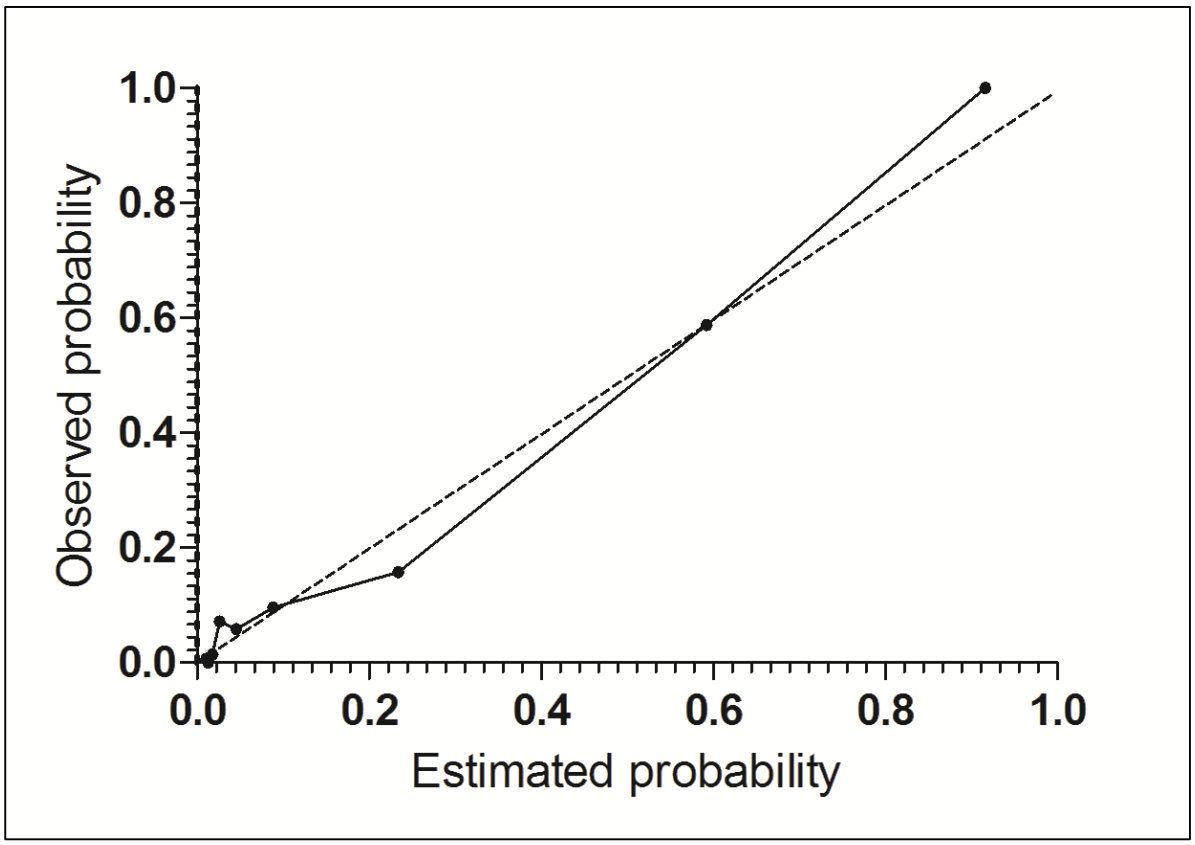
2015 Feb 17 [cited 2015 Mar 5]; Available from: http://heart.bmj.com/cgi/doi/10.1136/heartjnl-2014-307288

11. Carlton EW, Khattab A, Greaves K. Identifying Patients Suitable for Discharge After a Single-Presentation High-Sensitivity Troponin Result: A Comparison of Five Established Risk Scores and Two High-Sensitivity Assays. Ann Emerg Med. 2015 Dec;66(6):635–645.e1.

12. Carlton EW, Than M, Cullen L, Khattab A, Greaves K. "Chest pain typicality" in suspected acute coronary syndromes and the impact of clinical experience. Am J Med. 2015 Oct;128(10):1109–1116.e2.

13. Carlton E, Body R, Greaves K. External Validation of the Manchester Acute Coronary Syndromes Decision Rule. Smith S, editor. Academic Emergency Medicine. 2016 Feb;23(2):136–43.

14. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, et al. Absolute and Relative Kinetic Changes of High-Sensitivity Cardiac Troponin T in Acute Coronary Syndrome and in Patients with Increased Troponin in the Absence of Acute Coronary Syndrome. Clinical Chemistry. 2011 Dec 1;58(1):209–18.



Supplementary Figure 1: Calibration plot of observed versus expected probability for the refined T-MACS rule, stratified into deciles

Supplementary Table 1: Full details of the inclusion and exclusion criteria for each study

<table>
<tr><th>Study</th><th>Inclusion criteria</th><th>Exclusion criteria</th></tr>
<tr><td>Derivation study (Manchester)</td><td rowspan="2">Adults (>25 years) presenting to the Emergency Department (ED) with suspected cardiac chest pain occurring within the last 24 hours</td><td rowspan="2">Another medical condition requiring hospital admission; renal failure needing dialysis; significant chest trauma with suspicion of myocardial contusion; pregnancy; unable to speak English; prisoners</td></tr>
<tr><td>Validation study 1 (Stockport)</td></tr>
<tr><td>Validation study 2 (Manchester)</td><td>Adults (>16 years) presenting to the ED with suspected cardiac chest pain occurring within the last 12 hours</td></tr>
<tr><td>Validation study 3 (Poole)</td><td>Patients aged >18 years with at least 5 minutes of chest pain suggestive of an acute coronary syndrome, for whom the attending physician determined inpatient evaluation was required</td><td>ST elevation myocardial infarction; ECG changes diagnostic of ischaemia; arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second degree or complete heart block, or sustained or recurrent ventricular tachyarrhythmias); age ≥80 years; atypical symptoms in the absence of chest discomfort; a clear non-acute coronary syndrome cause identified at presentation; another medical condition requiring hospital admission; unable to speak English; renal failure needing dialysis; inability to be contacted after discharge</td></tr>
</table>

NB: All patients were also required to provide written informed consent for inclusion in any of the four studies. Thus patients lacking capacity to provide written informed consent were excluded.

Supplementary Table 2: Details of the assay and delta criteria used to adjudicate acute myocardial infarction in each study

<table>
<tr><th>Study</th><th>Criteria for establishing a rise and/or fall</th><th>Timing of tests</th><th>Assay used for adjudication of AMI</th></tr>
<tr><td>Derivation (Manchester)</td><td>Absolute change of at least 20ng/L (based on the analytical characteristics of the assay)</td><td rowspan="3">Admission and ≥12 hours after peak symptoms</td><td>Roche 4th generation cTnT (contemporary assay). 99th percentile 10ng/L; co-efficient of variation <10% at 30ng/L</td></tr>
<tr><td>Validation 1 (Stockport)</td><td rowspan="2">Absolute change of at least 9.2ng/L (1)</td><td rowspan="3">Roche 5th generation hs-cTnT (high sensitivity assay). 99th percentile 14ng/L; co-efficient of variation <10% at 13ng/L</td></tr>
<tr><td>Validation 2 (Manchester)</td></tr>
<tr><td>Validation 3 (Poole)</td><td>Relative change of at least 20%</td><td>Admission and ≥6 hours after peak symptoms</td></tr>
</table>

Supplementary Table 3: Proportion of patients with AMI and ACS in each individual validation cohort

		Very low risk	Low risk	Moderate risk	High risk
Validation cohort 1	Total number of patients (%)	143 (31.0)	80 (17.3)	198 (42.9)	41 (8.9)
	Number (%) with AMI	0 (0.0)	1 (1.3)	38 (19.2)	40 (97.6)
	Number (%) with MACE	0 (0.0)	2 (2.5)	52 (26.3)	40 (97.6)
Validation cohort 2	Total number of patients (%)	85 (44.5)	25 (13.1)	66 (34.6)	15 (7.9)
	Number (%) with AMI	1 (1.2)	0 (0.0)	14 (21.2)	14 (93.3)
	Number (%) with MACE	1 (1.2)	4 (16.0)	18 (27.3)	14 (93.3)
Validation cohort 3	Total number of patients (%)	362 (44.9)	277 (34.4)	154 (19.1)	13 (1.6)
	Number (%) with AMI	1 (0.3)	13 (4.7)	41 (26.6)	9 (69.2)
	Number (%) with MACE	3 (0.8)	18 (6.5)	51 (33.1)	9 (69.2)

Supplementary Table 4: Diagnostic performance of the T-MACS rule in each individual validation cohort for ACS

	Validation cohort 1	Validation cohort 2	Validation cohort 3
Sensitivity	100.0 (96.2 – 100.0)	97.3 (85.8 – 99.9)	96.3 (89.6 – 99.2)
Specificity	38.9 (33.9 – 44.1)	54.6 (46.3 – 62.6)	49.7 (46.0 – 53.4)
Positive predictive value	29.5 (24.5 – 34.8)	34.0 (25.0 – 43.8)	17.6 (14.1 – 21.4)
Negative predictive value	100.0 (97.5 – 100.0)	98.8 (93.6 – 100.0)	99.2 (97.6 – 99.8)
Positive likelihood ratio	1.64 (1.51 – 1.77)	2.14 (1.79 – 2.57)	1.92 (1.76 – 2.08)
Negative likelihood ratio	0.00	0.05 (0.01 – 0.34)	0.07 (0.02 – 0.23)

Supplementary Table 5: Results of the paired comparison between T-MACS and the LoD strategy

	LoD strategy	T-MACS	Absolute difference (95% CI), p value*
Sensitivity	98.1% (95.2 – 99.5)	98.1% (95.2 – 99.5)	0.0% (-2.2 – 2.2) p=1.00
Specificity	37.2% (34.5 – 40.0)	47.0% (44.2 – 49.8)	9.8% (6.7 – 12.7) p<0.0001