Clinical question.
In patients with suspected ACS in various settings (eg. prehospital, emergency or in-hospital) (P), do abnormal protein markers (I), compared with normal levels (C) allow the clinician to accurately diagnose acute coronary ischemia? (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis?  DIAGNOSIS
State if this is a proposed new topic or revision of existing worksheet: REVISION 2005 GUIDELINE

Existing Guideline: 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

New cardiac biomarkers, which are more sensitive than the myocardial muscle creatine kinase isoenzyme (CK-MB), are useful in diagnosis, risk stratification, and determination of prognosis. An elevated level of troponin correlates with an increased risk of death, and greater elevations predict greater risk of adverse outcome. Patients with increased troponin levels have increased thrombus burden and microvascular embolization.

Cardiac biomarkers should be obtained during the initial evaluation of the patient, but therapeutic decisions and reperfusion therapy for patients with STEMI should not be delayed pending the results of these tests. Important limitations to these tests exist because they are insensitive during the first 4 to 6 hours of presentation unless continuous persistent pain has been present for 6 to 8 hours. For this reason cardiac biomarkers are not useful in the prehospital setting.

Serial marker testing (CK-MB and cardiac troponin) over time improves sensitivity for detection of myocardial infarction but remains insensitive in the first 4 to 6 hours.


Class I
“Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS.” (Level of Evidence: B)
“A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients who present with chest discomfort consistent with ACS.” (Level of Evidence: B)
“Patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 h after symptom onset. (The exact timing of serum marker measurement should take into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized as well as the release kinetics of the marker being measured.)” (Level of Evidence: B)

Class IIa
“It is reasonable to remeasure positive biomarkers at 6- to 8-h intervals 2 to 3 times or until levels have peaked, as an index of infarct size and dynamics of necrosis.” (Level of Evidence: B)

Class IIb
“For patients who present within 6 h of the onset of symptoms consistent with ACS, assessment of an early marker of cardiac injury (e.g., myoglobin) in conjunction with a late marker (e.g., troponin) may be considered.” (Level of Evidence: B)
“For patients who present within 6 h of symptoms suggestive of ACS, a 2-h delta CK-MB mass in conjunction with 2-h delta troponin may be considered.” (Level of Evidence: B)
“For patients who present within 6 h of symptoms suggestive of ACS, myoglobin in conjunction with CK-MB mass or troponin when measured at baseline and 90 min may be considered.” (Level of Evidence: B)
“Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS.” (Level of Evidence: B)

Class III
“Total CK (without MB), aspartate aminotransferase (AST, SGOT), alanine transaminase, beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be utilized as primary tests for the detection of myocardial injury in patients with chest discomfort suggestive of ACS.” (Level of Evidence: C)

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?  NO

Search strategy (including electronic databases searched).
Last search: August 4, 2009
Database: PUBMED
Search Strategy:
-------------------------------------------------------------------------------
1. exp “Biological Markers”[Mesh]/ (403243)
2. exp “Clinical Enzyme Tests”[Mesh]/ (11390)
3. exp “Isoenzymes”[Mesh]/ (69152)
4. exp “Troponin”[Mesh]/ (7688)
5. exp “Creatine Kinase”[Mesh]/ (20411)
6. “Natriuretic Peptide, Brain”[Mesh]/ (5024)
7. “Atrial Natriuretic Factor”[Mesh]/ (13061)
8. “Myoglobin”[Mesh]/ (7921)
9. “C-Reactive Protein”[Mesh]/ (16627)
10. "myeloperoxidase"[All Fields]/(10936)
11. "Pregnancy-Associated Plasma Protein-A”[Mesh]/ (784)
12. "Resistin”[Mesh]/ (688)
13. "NT-proBNP"[All Fields] OR "NTproBNP”[All Fields]/ (1086)
14. "cystatin C”[Substance Name]/ (1204)
15. "Neopterin”[Mesh]/ (1820)
16. "thrombus precursor protein, human”[Substance Name]/ (18)
17. "FABP3 protein, human”[Substance Name]/ (84)
18. "Leptin”[Mesh]/ (11079)
19. "von Willebrand Factor”[Mesh]/ (8072)
20. "growth differentiation factor 15”[Substance Name]/ (168)
21. "ischemia modified albumin”[All Fields] OR "ima”[All Fields]/ (1579)
22. "1-Alkyl-2-acetylglycerophosphocholine Esterase”[Mesh]/ (943)
23. "Matrix Metalloproteinase 9”[Mesh]/ (6728)
24. "soluble CD40 ligand”[All Fields] OR "sCD40L”[All Fields]/ (503)
25. "Choline”[Mesh]/ (42532)
26. "product placenta growth factor”[Substance Name]/ (406)
27. OR/1-26 (603583)
28. exp “Emergency Service, Hospital”[Mesh]/ (31750)
29. exp “Emergency Medical Services”[Mesh]/ (65691)
30. exp “Emergency Treatment”[Mesh]/ (73395)
31. exp “Ambulances”[Mesh]/ (5093)
32. exp “Critical Care”[Mesh]/ (32194)
33. pre-hospital[All Fields] OR prehospital[All Fields] OR "pre hospital”[All Fields]/ (6108)
34. exp “Emergencies”[Mesh]/ (29595)
35. “emergency” AND department/ (65311)
36. "inpatients”[All Fields] OR "inpatient”[All Fields] OR "in-patients”[All Fields] OR "in-patient”[All Fields]/ (807023)
37. inhospital[All Fields] OR in-hospital[All Fields]/ (34058)
38. OR/28-37 (1025411)
39. exp “Myocardial Ischemia”[Mesh]/ (284910)
40. 27 AND 38 AND 39 (6308)
42. 40 AND 41/ (3227)
43. limit 42 to publications 2004 or later, human studies and English/ (1240)

Database: OVID Medline
Search Strategy:
-------------------------------------------------------
1. exp Biological Markers/  
2. exp Troponin/  
3. exp Creatine Kinase/  
4. exp Troponin I OR exp Troponin T/  
5. exp Myoglobin/  
6. exp Clinical Enzyme Tests/  
7. exp Isoenzymes/  
8. exp Natriuretic Peptide, Brain/  
9. exp Atrial Natriuretic Factor/  
10. exp C-Reactive Protein/  
11. myeloperoxidase.mp.  
12. exp Pregnancy-Associated Plasma Protein-A/  
13. exp Resistin/  
14. nt-probnp.mp.  
15. ntprobn.mp.
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<tr>
<th>No.</th>
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<tr>
<td>16.</td>
<td>exp Cystatins/</td>
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<td>17.</td>
<td>exp Neopterin/</td>
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<td>18.</td>
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<tr>
<td>19.</td>
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<td>20.</td>
<td>exp Leptin/</td>
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<td>21.</td>
<td>exp von Willebrand Factor/</td>
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<td>exp Cytokines/</td>
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<td>25.</td>
<td>exp Matrix Metalloproteinase 9/</td>
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<td>exp CD40 Ligand/</td>
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<td>exp Myocardial Ischemia/</td>
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<td>33.</td>
<td>exp Emergency Service, Hospital/ or emergency department.mp.</td>
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<td>34.</td>
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<td>exp Emergency Treatment/</td>
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<td>30 and 41 and 31</td>
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<td>43.</td>
<td>limit 42 to (humans and (&quot;diagnosis (sensitivity)&quot; or &quot;diagnosis (specificity)&quot; or &quot;diagnosis (optimized)&quot; or &quot;clinical prediction guides (sensitivity)&quot; or &quot;clinical prediction guides (specificity)&quot; or &quot;clinical prediction guides (optimized)&quot;))</td>
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**Database: EMBASE <1980 to 2008 Week 42>**

Search Strategy:

```
1  exp Biological Marker/ (30606)
2  exp Isoenzyme/ (19576)
3  exp TROPONIN/ (10254)
4  exp Creatine Kinase/ (15773)
5  exp Brain Natriuretic Peptide/ (6317)
6  exp Atrial Natriuretic Factor/ (13540)
7  exp MYOGLOBIN/ (6502)
8  exp C Reactive Protein/ (27633)
9  exp MYELOPEROXIDASE/ (9316)
10 exp Pregnancy Associated Plasma Protein A/ (656)
11 exp RESISTIN/ (1199)
12 NT-proBNP.mp. (985)
13 NTproBNP.mp. (62)
14 exp Cystatin C/ (1597)
15 exp NEOPTERIN/ (2314)
16 thrombus precursor protein.mp. (25)
17 FABP3 protein.mp. (2)
18 fatty acid binding protein 3.mp. (24)
19 exp LEPTIN/ (13433)
20 exp Von Willebrand Factor/ (10297)
21 growth differentiation factor 15.mp. (48)
22 ischemia modified albumin.mp. (116)
23 exp 1 Alkyl 2 Acetylglycerophosphocholine Esterase/ (650)
24 Matrix Metalloproteinase 9.mp. or exp Matrix Metalloproteinase/ (10738)
25 exp Cd40 Ligand/ or soluble CD40 ligand.mp. (3115)
26 sCD40L.mp. (301)
27 exp CHOLINE/ (8220)
28 product placenta growth factor.mp. (1)
29 or/1-28 (177347)
30 exp Emergency Health Service/ (12784)
31 exp EMERGENCY MEDICINE/ or exp EMERGENCY NURSE PRACTITIONER/ or exp EMERGENCY PATIENT/ or exp EMERGENCY TREATMENT/ or AGENTS USED IN EMERGENCY MEDICINE/ or exp EMERGENCY NURSING/ or exp EMERGENCY CARE/ or exp
```
EMERGENCY/ or exp EMERGENCY PHYSICIAN/ or exp EMERGENCY WARD/ or exp "EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT"/ (96655)
32 exp AMBULANCE/ (2599)
33 exp Intensive Care/ (194667)
34 exp (pre-hospital or prehospital or pre hospital).mp. (4772)
35 exp (emergency and department).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (22251)
36 exp Hospital Patient/ (19421)
37 exp inpatient*.mp. (36043)
38 exp (emergenc* or triage or arrmigent* or ems or transport).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (438710)
39 or/32-38 (659512)
40 exp Heart Muscle Ischemia/ (43390)
41 exp Acute Coronary Syndrome/ (4585)
42 exp "SENSITIVITY AND SPECIFICITY"/ (47215)
43 exp DIFFERENTIAL DIAGNOSIS/ or exp "DIAGNOSIS, MEASUREMENT AND ANALYSIS"/ or exp DIAGNOSIS/ (5318183)
44 di.fs. (1361265)
45 exp (sensitiv* or diagnos*).ti,ab. (1367170)
46 or/42-45 (5952709)
47 40 or 41 (47507)
48 39 and 46 and 29 and 47 (681)
49 limit 48 to (human and english language and yr="2004 - 2009") (353)

Database: All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED

Search Strategy:

1. (Biological Marker* or abnormal protein marker* or biomarker* or clinical enzyme test* or Isoenzyme* or troponin or Creatine Kinase or Brain Natriuretic Peptide or Atrial Natriuretic Factor or myoglobin or C Reactive Protein or myeloperoxidase or Pregnancy Associated Plasma Protein A or resistin or NT-proBNP or NTproBNP or Cystatin C or neopterin or thrombus precursor protein or FABP3 protein or fatty acid binding protein 3 or leptin or Von Willebrand Factor or growth differentiation factor 15 or ischemia modified albumin or 1 Alkyl 2 Acetylglycerophosphocholine Esterase or Matrix Metalloproteinase 9 or Matrix Metalloproteinase or Cd40 Ligand or soluble CD40 ligand or sCD40L or choline or product placenta growth factor).ti,ab. (7361)
2. (Heart Muscle Ischemia or acute Coronary Syndrome or myocardial ischemia or myocardial infarct* or ACS or AMI or acute cardiac infarct* or heart attack*).ti,ab. (11978)
3. 1 and 2 (928)
4. limit 3 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] (924)
5. limit 4 to yr="2004 - 2008" [Limit not valid in DARE; records were retained] (358)

State inclusion and exclusion criteria

Inclusion criteria:
1. Human studies
2. Peer-reviewed
3. Studies that enrolled patients with MI, ACS or signs and symptoms suggestive of ACS
4. Biomarker determinations in either pre-hospital phase or in-hospital (emergency department or ward)
5. Studies evaluating CK, CKMB, myoglobin and troponins in the diagnosis of ACS for “common markers”
6. Studies evaluating all “novel markers” (e.g. BNP, ANP, CRP, PAPP, FABP, IMA, MMP, D-dimer, CD40L, etc.)
7. English language or translated papers
8. Manuscript available

Exclusion criteria:
1. Publications earlier than 2004
2. Expert opinion reviews
3. Abstract-only publications or availability
4. Studies evaluating biomarkers for prognostication

Number of articles/sources meeting criteria for further review:
359 articles were identified for further review after screening titles for relevance to topic.
152 articles included for final review after review of abstracts.
71 articles met criteria and were included for final review.
### Summary of evidence of common markers

(TnI, TnT, CK, CKMB, myoglobin)

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Christenson(06)b,f,h,l</th>
<th>Collinson(04)a,b,f,g,h,l</th>
<th>Fesmire(04)b,c,f,h</th>
<th>Keller(09)f,h,m</th>
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<tr>
<td>Fair</td>
<td>Collinson(06-1)a,b,f,h</td>
<td>Collinson(06-2)a,b,d,f,h</td>
<td>Eggers(05)a,b,c,d,f,h</td>
<td>Nagurney(05)a,b,c,f,h</td>
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<td>Hamilton(08)a,b,e,g,h,l</td>
<td>Macrae(06)f,h,m</td>
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<tr>
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<tr>
<td>D3</td>
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<tr>
<td>D4</td>
</tr>
<tr>
<td>D5</td>
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</tbody>
</table>

**a =** study primarily evaluates TnI and/or TnT  
**b =** study primarily evaluates CK or CKMB  
**c =** study primarily evaluates myoglobin  
**d =** multimarker testing  
**e =** single time point testing  
**f =** serial time points testing  
**g =** point of care testing (POCT)  
**h =** ED patients and evaluating tests primarily in the ED, short stay unit or CCU (or similar)  
**i =** evaluating tests in prehospital setting  
**j =** evaluating tests in outpatient/office setting  
**k =** evaluating tests in inpatient setting  
**l =** other evaluating modalities/specific protocol used (e.g. ECG, echocardiography, CT, MRI, etc.)  
**m =** sensitive Tn
### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planer(06)a,e,g,j</td>
<td>Bassan(05)a,b,e,h</td>
<td>Amodio(07)a,c,e,g,h</td>
</tr>
<tr>
<td></td>
<td>Sallach(04)c,f,h</td>
<td>Schuchert(99)a,g,i</td>
<td>Anwaruddin(05)a,b,c,d,e,h</td>
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<td>Bar-Or(05)a,e,h</td>
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<td>Bucciarrelli-Ducci(04)a,b,d,f,h,l</td>
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<td>Hallani(05)a,g,h</td>
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</table>

**Level of evidence**

- **a** = study primarily evaluates TnI and/or TnT
- **b** = study primarily evaluates CK or CKMB
- **c** = study primarily evaluates myoglobin
- **d** = multimarker testing
- **e** = single time point testing
- **f** = serial time points testing
- **g** = point of care testing (POCT)
- **h** = ED patients and evaluating tests primarily in the ED, short stay unit or CCU (or similar)
- **i** = evaluating tests in prehospital setting
- **j** = evaluating tests in outpatient/office setting
- **k** = evaluating tests in inpatient setting
- **l** = other evaluating modalities used (e.g. ECG, echocardiography, CT, MRI, etc.)
# Summary of evidence of “novel” markers

## Evidence Supporting Clinical Question

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<tr>
<th>Good</th>
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<td>Fair</td>
<td>Brown(07-1)a,e,g,1 Collinson(06-2)a,e,g,i Peacock(06)a,e,i Sinha(04)a,f,i Abadie(05)a,f,i</td>
</tr>
<tr>
<td></td>
<td>Cavus(06)a,e,g,q Ecollan(07)b,e,f,q Keating(06)a,e,f,i Liyan(08)a,f,i Seino(04)a,c,f,h,q</td>
</tr>
<tr>
<td>Poor</td>
<td>D1</td>
</tr>
</tbody>
</table>

**Level of evidence**

- **a** = ED patients and evaluating tests primarily in the ED, short stay unit or CCU (or similar)
- **b** = evaluating tests in prehospital setting
- **c** = evaluating tests in outpatient/office setting
- **d** = evaluating tests in inpatient setting
- **e** = multimarker testing
- **f** = single time point testing
- **g** = serial time points testing
- **h** = point of care testing (POCT)
- **i** = study primarily evaluates IMA
- **j** = study primarily evaluates PO4-cTnI
- **k** = study primarily evaluates neutrophil count
- **l** = study primarily evaluates BNP
- **m** = study primarily evaluates APC
- **n** = study primarily evaluates PAPP-A
- **o** = study primarily evaluates BNP
- **p** = study primarily evaluates ST2
- **q** = study primarily evaluates H-FABP
- **r** = study primarily evaluates IL-6
- **s** = study primarily evaluates hs-CRP/CRP
- **t** = study primarily evaluates E-selectin
- **u** = study primarily evaluates NT-proBNP
- **w** = study primarily evaluates tryptase
- **x** = study primarily evaluates D-dimer
- **y** = study primarily evaluates MPO
- **z** = study primarily evaluates monocyte chemoattractant
- **aa** = study primarily evaluates CD40 ligand
- **bb** = study primarily evaluates fibrinogen
- **cc** = study primarily evaluates placental growth factor
- **dd** = study primarily evaluates adhesion-1
- **ee** = study primarily evaluates P-selectin
- **ff** = study primarily evaluates vascular adhesion-1
- **gg** = study primarily evaluates prothrombin fragment
- **hh** = study primarily evaluates thrombin-antithrombin (TAT)
- **ii** = study primarily evaluates soluble tissue factor
- **jj** = study primarily evaluates tissue factor inhibitor
- **kk** = study primarily evaluates plasminogen activator inhibitor
- **ll** = study primarily evaluates IL-1Ra
- **mm** = study primarily evaluates MMP-9
nn = study primarily evaluates glycogen phosphorylase BB
oo = study primarily evaluates copeptin

### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Mitchell(05)a,k,l,n,q,r,s,t,u,x,y,z,aa,bb,cc,dd,ee,ff</th>
<th>Bassan(05)a,e,f,l</th>
<th>Kwan(07)a,e,g,l,u</th>
<th>Nagahara(06)a,f,q</th>
<th>Roy(04)a,e,g,i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td>Brown(07-2)a,f,p Body(09)a,f,h,q</td>
<td>Kervinen(05)a,f,w Moons(05)a,f,gg,hh,ii,ij,kk</td>
<td>Anwaruddin(05)a,f,i Bar-Or(05)a,e,f,j Basili(04)a,g,k Bhiladvala(06)a,f,m Elsber(07)a,f,n Ferroni(07)a,f,r,s Kavsak(08)a,e,f,r,t,u Lippi(08)a,f,x Liyan(08)a,f,s Mad(07)a,g,h,q Mitchell(06)a,l,s,y,z Nikolaou(05)a,g,l Patti(04)a,f,ll Potsch(06)a,g,s Valle(08)a,f,q Liao(08)a,f,q McCann(08)a,f,h,n,q,s,x,y,aa,mm,nn Plaikner(09)a,f,aa</td>
<td>Tokita(09)a,f,x</td>
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<td>Poor</td>
<td>Body(06)a,n</td>
<td>Talwakar(08)a,f,i</td>
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<table>
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<th>Level of evidence</th>
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<tbody>
<tr>
<td>a = ED patients and evaluating tests primarily in the ED, short stay unit or CCU (or similar)</td>
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<tr>
<td>b = evaluating tests in prehospital setting</td>
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<td>e = multimarker testing</td>
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<td>f = single time point testing</td>
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<td>g = serial time points testing</td>
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<td>h = point of care testing (POCT)</td>
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<td>i = study primarily evaluates IMA</td>
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<td>j = study primarily evaluates PO4-cTnI</td>
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<td>k = study primarily evaluates neutrophil count</td>
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<td>l = study primarily evaluates BNP</td>
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<td>m = study primarily evaluates APC</td>
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<td>p = study primarily evaluates ST2</td>
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<td>q = study primarily evaluates H-FABP</td>
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<td>r = study primarily evaluates IL-6</td>
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s = study primarily evaluates hs-CRP/CRP
 t = study primarily evaluates E-selectin
 u = study primarily evaluates NT-proBNP
 w = study primarily evaluates tryptase
 x = study primarily evaluates D-dimer
 y = study primarily evaluates MPO
 z = study primarily evaluates monocyte chemoattractant
 aa = study primarily evaluates CD40 ligand
 bb = study primarily evaluates fibrinogen
 cc = study primarily evaluates placental growth factor
 dd = study primarily evaluates adhesion-1
 ee = study primarily evaluates P-selectin
 ff = study primarily evaluates vascular adhesion-1
 gg = study primarily evaluates prothrombin fragment
 hh = study primarily evaluates thrombin-antithrombin (TAT)
 ii = study primarily evaluates soluble tissue factor
 jj = study primarily evaluates tissue factor inhibitor
 kk = study primarily evaluates plasminogen activator inhibitor
 ll = study primarily evaluates IL-1Ra
 mm = study primarily evaluates MMP-9
 nn = study primarily evaluates glycogen phosphorylase BB
 oo = study primarily evaluates copeptin
**REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

The importance of cardiac marker testing has been widely accepted and has been included in the recent ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction ([J Am Coll Cardiol, 2007; 50:1-157.]). Moreover, in an expert consensus document, a Joint ESC/ACCF/AHA/WHF Task Force revised the universal definition of myocardial infarction to include a rise in cardiac biomarkers above the 99th percentile as a primary criterion ([Circulation, 2007;116:2634-2653.]). Cardiac markers are useful in the evaluation of patients presenting with symptoms suggestive of cardiac ischemia when they are highly sensitive to safely “rule out” cardiac ischemia or when they are highly specific to capture patients with ACS that otherwise have non-diagnostic tests (e.g. ECG). Accordingly, I have rated studies as “supportive” for diagnosis if they provided evidence of their respective index test having a sensitivity>~95% or having a specificity>92% combined with a sensitivity>90%.

The studies on “common” cardiac markers (troponin I or T, CK/CK-MB and myoglobin) included in this evidence review were variable in their study design and methodology. Although the majority of the studies were in patients presenting to the emergency department, there were 2 studies in the prehospital setting using point-of-care testing (POCT) [Ecollan(07) LOE D4, Goddet(07) LOE D4], 2 studies in an outpatient clinic setting using POCT [Planer(06) LOE D2, Seino(04) LOE D4], and 1 study in an inpatient ICU setting [Lim(05) LOE D4]. None of these studies showed adequate diagnostic yield for the use of common markers outside of the emergency department/short stay cardiac units. There was also varying inclusion/exclusion criteria used in these studies, ranging from studies that excluded “high risk” patients to including all comers with symptoms suggestive of cardiac ischemia, which undoubtedly affected the sensitivities/specificities of their respective index tests. Several studies also used receiver operator curve (ROC) analyses to alter cut-off levels in order to optimize their index test sensitivities. Many also identified their “gold standard” or reference standard to be the criteria published by the ESC/ACC in 2000: Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction ([J Am Coll Cardiol, 2000; 36:959-969.]). This was a confounder with a number of studies that included their index test as part of the reference standard. Overall, the comparison of different studies of the same cardiac marker was difficult.

In addition to the “common” markers, there has been growing interest in the study of “novel” markers over recent years. This was inspired by the search for more sensitive and more specific markers of myocardial ischemia, including markers of inflammatory processes. There was also a great demand for studies of markers that predicted ACS/AMI at earlier time intervals than Tn and CK/CKMB. The literature search of “novel” markers yielded a large number of articles on a variety of markers, including but not limited to BNP, NT-BNP, APC, PAPP-A, IMA, H-FABP, CRP, MPO, neutrophil count, CD40 ligand, etc. A total of 43 studies evaluated, at least in part, “novel” cardiac markers. Although the vast majority of these studies did not show adequate sensitivities/specificities according to the stated criteria above, eleven studies of varying levels of evidence and quality supported the use of IMA [Collinson(06-2) LOE D2, Peacock(06) LOE D2, Sinha(04) LOE D2, Abadie(05) LOE D3, Keating(06) LOE D4, Liyan(08) LOE D4], H-FABP [Cavus(06) LOE D4, Seino(04) LOE D4], BNP [Brown(07-1) LOE D2] and copeptin [Reichlin(09) LOE D2]. There were no studies that showed adequate diagnostic significance for the use of other “novel” markers.

A large number of articles evaluated the use of point-of-care testing (POCT) of various markers, including multimarker panels, with varying results. Although this type of testing reduces delays of central laboratory assays, it must be weighed against the need of appropriate ED training and quality control. Bedside testing has not been widely accepted. Furthermore, the results from this review were not adequately consistent to make any recommendations. Further studies are needed.

**Comments related to individual markers for diagnosis**

Troponin I and T:
The cardiac-specific troponins (I and T) are derived from heart-specific genes and are regarded as the diagnostic markers of choice. There is a wealth of studies that have shown both TnI and TnT are both highly sensitive and specific for myocardial necrosis. Although they can be detected in serum as early as 2h from the onset of myocardial necrosis, elevation may be delayed for up to 8 to 12h. Clinicians must be particularly mindful to the timing of troponin testing for MI. There is also heterogeneity of existing assays for both TnI and TnT with newer generation assays being able to detect lower troponin levels. This review reinforces these differences. Eight studies showed adequate sensitivity of troponin testing alone when serum testing was drawn at least 6h from time of symptom onset or ED presentation or serially [Collinson(06-1) LOE D2, Collinson(06-2) LOE D2, Eggers(05) LOE D2, Hamilton(08) LOE D3, Cavus(06) LOE D4, Saki(07) LOE D4, Storrow(06) LOE D4, Zarich(04) LOE D4]. Six studies did not support the use of Tn overall [Keller(09) LOE D2, Reichlin(09-2) LOE D2, Beyne(04) LOE D3, Bassan(05) LOE D4, Bucciarelli-Ducci(04) LOE D4,
Nagurney(05) LOE D4), one in the ICU setting [Lim(05) LOE D4] and five studies in patients presenting <6h of onset [Brown(07-1) LOE D2, Bhiladvala(06) LOE D4, Nagahara(06) LOE D4, Valle(08) LOE D4, Liao(08) LOE D4]. The use of cardiac troponins is limited in the ICU setting due to troponin leak/release in various disease states and their physiological kinetics in complex patients with multiple co-morbidities.

Sensitive Tn:
A new generation of sensitive Tn assays has been developed with 10% coefficient of variation for levels below or very close to the 99th percentile. They are touted to overcome the low sensitivities of conventional Tn assays in the first few hours of chest pain in ACS/AMI. There were three studies in this review that evaluated the use of sensitive Tn assays and all three supported their use to diagnose AMI [Keller(09) LOE D2, Reichlin(09-2) LOE D2, Macrae(06) LOE D3] but sensitive Tn assays were not adequately sensitive to detect UA [Keller(09) LOE D2, Reichlin(09-2) LOE D2]. These new assays appeared to be more sensitive than conventional troponin assays and show promise for earlier detection of cardiac ischemia. Sensitivities increased significantly when serial samples were taken at time 0 and 3h regardless to time of symptom onset [Keller(09) LOE D2]. However, further evaluation of a 3h delta troponin is needed. It is reasonable to suggest that the adoption of more sensitive assays be recommended.

CK/CK-MB:
CK-MB has long been the standard diagnostic marker of myocardial ischemia. However, it is less sensitive and specific than the cardiac troponins. Elevated CK-MB levels may be present in healthy individuals and in processes involving skeletal muscle damage. The sensitivity of CK-MB testing alone reached significance in two studies when serial levels were drawn or in “late presenters” with symptoms occurring 6-24h prior to presentation or drawn serially [Nagurney(05) LOE D2, Cavus(06) LOE D4]. Six studies showed inadequate sensitivities [Bassan(05) LOE D2, Collinson(06) LOE D2, Eggers(05) LOE D2, Hamilton(08) LOE D3, Liao(08) LOE D4, Nagahara(06) LOE D4]. Four studies supported the use of CK-MB when combined with Tn and/or other markers [Brown(07-1) LOE D2, Eggers(05) LOE D2, Peacock(06) LOE D2, Storrow(06) LOE D4]. Newer studies have rekindled interest in the use of CK-MB in the evaluation of myocardial ischemia. Two well-done studies evaluated the change of CK-MB levels (delta CK-MB) within a relatively short period of time with sensitivities>95% [Christenson(06) LOE D2, Fesmire(04) LOE D2] and one study did not [Collinson(06) LOE D2]. This approach showed promise but was part of a chest pain protocol evaluating a low risk population [Christenson(06) LOE D2] and the authors accordingly recommended prospective validating studies in the future.

Myoglobin:
Myoglobin is found in both cardiac and skeletal muscle. It is released as early as 2h after the onset of myocardial infarction and is possible to make earlier detection of MI compared to CK-MB and the cardiac troponins. However, there is good evidence showing myoglobin to be less sensitive and specific than troponins and CK-MB. All studies in this review that evaluated myoglobin were rated as opposing evidence for the use of single or serial myoglobin testing [Eggers(05) LOE D2, Nagurney(05) LOE D2, Amodio(07) LOE D4, Melanson(04) LOE D4] or delta myoglobin [Fesmire(04) LOE D2, Sallach(04) LOE D4]. The evidence from this review suggested that myoglobin testing alone is inadequate for the diagnosis of myocardial ischemia. However, when used as part of a multimarker approach, there were two studies that supported the use of myoglobin [Brown(07-1) LOE D2, Peacock(06) LOE D2].

IMA:
Ischemia-modified albumin has been recognized as a marker of inflammation and myocardial ischemia. It is thought that IMA will rise to detectable levels prior to markers of myocardial necrosis. There were five studies of varying quality that supported a multimarker approach with the addition of IMA to Tn to detect AMI [Collinson(06-2) LOE D2, Peacock(06) LOE D2, Sinha(04) LOE D2, Anwaruddin(05) LOE D4, Keating(06) LOE D4]. One study showed adequate sensitivity for IMA alone but was used in high risk patients requiring angiography [Liyan(08) LOE D4]. There was one study that showed inadequate sensitivities when IMA was used in combination with TnT to diagnose ACS [Roy(04) LOE D4] and three studies opposed the use of IMA alone [Sinha(04) LOE D2, Anwaruddin(05) LOE D4, Talwakar(08) LOE D4] for ACS or AMI. The evidence from this review suggests IMA may be helpful when combined with Tn in the diagnosis of AMI.

H-FABP:
Heart-type fatty acid binding protein is a regulator of the oxidative system of cardiac myocytes. It is increased to detectable levels after myocardial ischemia. There were two studies that showed adequate sensitivities for the use of H-FABP alone in the diagnosis AMI [Cavus(06) LOE D4, Seino(04) LOE D4]. The Cavus(06) study measured H-FABP at time 0 and 4h for patients presenting to the ED < 1h of symptom onset but also included STEMI patients. The Seino(04) study showed adequate sensitivity/specificity for the use of POCT in outpatient cardiology clinic settings when patients present <3h and >6h but not between 3 to 6h of symptom onset. There were eight studies including two meta-analyses [Mitchell(05) LOE D2, Body(09) LOE D2], that did not show adequate sensitivities when used <3-4h of
symptom onset [Liao(08) LOE D4, McCann(08) LOE D4, Mad(07) LOE D4, Nagahara(06) LOE D4, Valle(08) LOE D4] or in the prehospital setting [Ecollan(07) LOE D4]. There is inconclusive evidence to make recommendations for the use of H-FABP.

**BNP:**
Beta-type natriuretic peptide is expressed after ventricular wall stress and myocardial hypoxia. There is some evidence that showed BNP to be an independent prognostic indicator for poor outcomes in ACS/AMI. In this review, there is one study that showed the addition of BNP to a multimarker panel of TnI, CKMB and myoglobin at time=0 and 90min improved sensitivities adequately to diagnose AMI in patients with a median time=240min of symptom onset to ED presentation [Brown(07-1) LOE D2]. Importantly, the study also included STEMI patients in their sample population. However, there were five studies, including a meta-analysis [Mitchell(05) LOE D2], that did not support the use of BNP alone [Kwan(07) LOE D4, Mitchell(06) LOE D4, Nikolaou(05) LOE D4] or as part of a multimarker approach [Bassan(05) LOE D4]. The evidence from this review does not support the use of BNP to diagnose ACS or AMI.

**Copeptin:**
Copeptin is the c-terminal portion of the vasopressin prohormone and was markedly increased in AMI in one previous study. In the review, there was only one study included and Reichlin et al. showed adequate sensitivities to rule out AMI with the addition of copeptin to TnT when TnT<0.01 at time=0 in patients presenting to the ED < 12h of symptom onset [Reichlin(09-1) LOE D2]. Interestingly, copeptin levels were inversely proportional to time of symptom onset. Although the results are impressive, further studies are required prior to making clear recommendations for the use of copeptin.

**Other “novel markers”:**
This review also included studies evaluating the following markers: PO4-cTnI, neutrophil count, APC, PAPP-A, ST2, IL-6, hs-CRP/CRP, E-selectin, NT-proBNP, trypptase, D-dimer, MPO, monocyte chemoattractant, CD40 ligand, fibrinogen, placental growth factor, adhesion-1, P-selectin, vascular adhesion-1, prothrombin fragment, thrombin-antithrombin (TAT), soluble tissue factor, tissue factor inhibitor, plasminogen activator inhibitor, IL-1Ra, MMP-9 and glycogen phosphorylase BB. No studies in this review supported the use of these markers. Further evidence would be required to make clear recommendations for the use of these “novel” markers.

**Acknowledgements:**
None.
## Citation List

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Notes: Retrospective case control study (n=200) evaluating albumin cobalt binding assay of ischemia-modified albumin (IMA). ROC curves analyzed for best optimal result. Marker drawn at t=0h. Inadequate information about chest pain characteristics (i.e. timing) or reference standard (Tnl>5ng/L)  
Sensitivity/specificity of IMA>97U/mL for ACS = 98/45%.  
LOE D3  
Fair quality.  
Supporting evidence for IMA at time=0. Inadequate information re: timing of chest pain. |
Notes: Retrospective study in 516 NSTEMI comparing cTnI > 0.03microg/L (99th percentile), myoglobin vs. ESC/ACC 2000 definition of AMI. Sensitivity of cTnI >0.03 to diagnose AMI with single early POCT (median 5h) = 77.3  
Specificity of cTnI >0.03 = 84.0  
Sensitivity of myoglobin = 36.4  
Specificity of myoglobin = 87.7  
LOE D4  
Fair quality study  
Opposing evidence for single early (<6h) POCT cTnI testing for diagnosis  
Opposing evidence for single early (<6h) POCT myoglobin testing for diagnosis |
Notes: Prospective study of 200 consecutive patients (193 total for analysis) suspicious for myocardial ischemia as defined by ESC/ACC 2000 definitions. Includes STEMI, NSTEMI, UA. Markers drawn at time of admission. Inadequate information on chest pain characteristics. Sensitivity of combination of all myoglobin, CK-MB, and TnI +ve with single POCT testing at ED admission (no absolute definition of timing) = 57%  
Sensitivity of IMA > 90U/mL with single POCT testing at ED admission = 80%  
Specificity of IMA > 90U/mL = 31%  
Sensitivity of combination of all myoglobin, CK-MB, TnI and IMA = 97%  
LOE D4  
Fair study  
Opposing evidence for use of IMA for diagnosis. |
## Opposing evidence for multimarker POCT (myoglobin, CK-MB, TnI) for diagnosis

Supporting evidence for multimarker POCT (myoglobin, CK-MB, TnI and IMA) for diagnosis

**inadequate information on chest pain characteristics**

### Apple(06)


**Notes:**
- Retrospective study following implementation of cTnI POCT showing similar 1-year all cause mortality rates vs. central lab testing.
- Improved cost effectiveness
- No control comparisons
- No sensitivity/specificity data for diagnosis

LOE D4

Poor quality study

Insufficient quality for further review.

### Bar-Or(05)


**Notes:**
- Retrospective study (n=61) comparing sensitivity of phosphorylated cTnI by immunoassay vs cTnI in diagnosing ACS.
- Sensitivity overall PO4-cTnI to diagnose ACS = 82%, vs. cTnI = 50%, vs. PO4-cTnI or cTnI = 91%, vs. PO4-cTnI or cTnI or ECG = 94%
- Specificity overall PO4-cTnI to diagnose ACS = 81%, vs. cTnI = 92%, vs. PO4-cTnI or cTnI = 72%, vs. PO4-cTnI or cTnI or ECG = 64%
- Sensitivity <4h symptom onset PO4-cTnI to diagnose ACS = 79%, vs. cTnI = 26%, vs. PO4-cTnI or cTnI = 84%, vs. PO4-cTnI or cTnI or ECG = 89%
- Specificity <4h symptom onset PO4-cTnI to diagnose ACS = 75%, vs. cTnI = 100%, vs. PO4-cTnI or cTnI = 73%, vs. PO4-cTnI or cTnI or ECG = 55%

LOE D4

Fair quality study

Opposing evidence for use of PO4-cTnI immunoassay for diagnosis of ACS (sensitivity<95%)

Opposing evidence of TnI

### Basili(04)


**Notes:**
- Retrospective study (n=292) comparing sensitivities of elevated neutrophil, fibrinogen and CK-MB in patients diagnosed with AMI according to ESC/ACC 2000 definition of AMI.
- Blood tests drawn at 4, 12, 24h.
- Sensitivity of elevated neutrophil > 8.5x109 = 52.6%
- Sensitivity of CK-MB = 50%
- Sensitivity of CK-MB and/or elevated neutrophil = 69.8%

LOE D4

Fair quality study
### Bassan(05)


**Notes:**
- Prospective study (n=631) of patients presenting to ED with chest pain suggestive of ACS comparing sensitivities of BNP, CK-MB and troponin-I at time of admission in diagnosing ACS (excluding STEMI).
- Timing of cardiac markers relative to chest pain not reported.
- Sensitivity/Specificity/PPV/NPV of BNP > 100pg/mL at time=0 for NSTEMI= 70.8/68.9/22/94.8%
- Sensitivity/Specificity/PPV/NPV of CKMB at time =0 for NSTEMI= 45.8/98.4/78/93.4%
- Sensitivity/Specificity/PPV/NPV of troponin-I at time=0 for NSTEMI= 50.7%/98.8/85/93%
- Sensitivity/Specificity of BNP, CKMB or troponin-I for NSTEMI= 87.3%/65.7%

**LOE D4**

Good quality

Opposing evidence of addition of admission BNP to cardiac markers (troponin-I and CKMB) for diagnosis

Opposing evidence for admission TnI, CKMB for AMI

### Beyne(04)


**Notes:**
- Prospective study (n=106) of patients presenting to ED with symptoms suggestive of ACS to determine the sensitivity and specificity of new cTnI cutoffs (.04, .06, .08, .16) using a new Beckman Coulter Access AccuTnI assay to diagnose ACS using ESC/ACC 2000 definition.
- Timing of markers on admission, 6h and 12h. Inadequate information on timing of symptoms to serum testing.
- Sensitivity/Specificity of highest reading of cTnI > 0.04 for diagnosis of = 87%/48%
- Sensitivity/Specificity of highest reading of cTnI > 0.06 = 83%/75%
- Sensitivity/Specificity of highest reading of cTnI > 0.08 = 76%/83%
- Sensitivity/Specificity of highest reading of cTnI > 0.16 = 70%/98%

**LOE D3**

Fair quality study

Opposing/Neutral evidence for use of cTnI > 0.16 cutoff for diagnosis (99th percentile of control group)

### Bhiladvala(06)


**Notes:**
- Prospective study (n=340) of “high risk” patients presenting to the ED with chest pain in combination with ECG changes or previous cardiac disease evaluating activated protein C – protein C inhibitor complex (APC-PCI) to diagnose AMI defined as troponin I >0.3.
- Chest pain lasted >30min with 6h of hospital presentation. Serum markers were obtained on admission, 6h and 12h.
- Sensitivity of APC-PCI >0.32mcg/L on admission to diagnose AMI = 39%
- Sensitivity of troponin I >0.3 on admission to diagnose AMI = 51%
- Specificity of APC-PCI >0.32mcg/L on admission to diagnose AMI = 78%
- Odds ratio of APC-PCI >0.32mcg/L on admission of AMI = 3.7.
- Authors state “value of APC-PCI should be among those where Troponin I is normal”.

Opposing evidence for elevated neutrophil count for diagnosis (sensitivity<95%)
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Notes:  
Retrospective study (n=7473) of all patients admitted to hospital for increased TnI. No data on timing of blood collection.  
35% increase unrelated to ACS/STEMI/NSTEMI  
Sensitivity/specificity of increased TnI for ACS = 78/44% |  
**LOE D5**<br>Fair quality<br>Inappropriate for further review. Various disease states can increase TnI unrelated to cardiac ischemia. |
Notes:  
In patients presenting to the ED receiving TnI testing, this study compared 5909 +ve TnI POCT using i-STAT1 device (Abbott Point-of-Care) and a random selection of 137 –ve results to central lab testing using TnI-Ultra method (ADVIA Centaur analyzer, Siemens Medical Solutions Diagnostics).  
Inadequate information on reasons for and timing of TnI testing.  
POCT 99th percentile = 0.08mcg/L.  
Central lab testing 99th percentile = 0.04mcg/L = gold standard used in study.  
Sensitivity of TnI POCT >.08mcg/L in accuracy with central lab testing = 63.3%  
Specificity of TnI POCT >.08mcg/L in accuracy with central lab testing = 99.5% |  
**LOE D4**<br>Poor quality study<br>Neutral/opposing evidence for POCT TnI for diagnosis. |
Notes:  
Systematic review of prospective studies evaluating pregnancy-associated plasma protein A (PAPP-A) in ACS.  
Adequate search strategy in multiple databases and limited methodological characteristics included.  
No specific objectives, study design, inclusion/exclusion criteria stated. |  
**LOE D2**<br>Poor quality study<br>Opposing evidence for the use of pregnancy-associated plasma protein A in diagnosis of ACS. |
**Notes:**  
Meta-analysis of studies evaluating H-FABP on ED presentation for diagnosis of AMI. Studies included both POCT and quantitative testing.  
Pooled sensitivity/specificity/PPV/PPV = 71/82/66/82%  
LOE D2  
Fair quality  
Opposing evidence for H-FABP for diagnosis of AMI. |
|---|---|
**Notes:**  
Prospective observational study (n=493) of patients presenting to the ED with non-traumatic chest pain prompting an ECG evaluating beta-type natriuretic peptide (BNP) in the diagnosis of ACS and 30-day cardiac events. Includes STEMI patients.  
Median time of onset upon ED admission = 240min. Median time of chest pain duration = 120min. Serum markers obtained at time of hospital admission and 90min.  
Sensitivity/Specificity of myoglobin, CK-MB and cTnI at t=0 or 90min in patients without CHF to diagnose AMI = 85.7%/67.5%  
Sensitivity/Specificity of addition of BNP to myoglobin, CK-MB and cTnI at t=0 or 90min in patients without CHF to diagnose AMI = 100%/54.5%  
Sensitivity/Specificity of myoglobin, CK-MB and cTnI at t=0 or 90min in patients without CHF to diagnose ACS = 67.2%/71.4%  
Sensitivity/Specificity of addition of BNP to myoglobin, CK-MB and cTnI at t=0 or 90min in patients without CHF to diagnose ACS = 81.3%/53.9%  
Sensitivity/Specificity of myoglobin, CK-MB and cTnI at t=0 or 90min in all suspected patients to diagnose AMI = 87.2%/62.3%  
Sensitivity/Specificity of addition of BNP to myoglobin, CK-MB and cTnI at t=0 or 90min in all suspected patients to diagnose AMI = 97.4%/47.8%  
Sensitivity/Specificity of myoglobin, CK-MB and cTnI at t=0 or 90min in all suspected patients to diagnose ACS = 75.2%/68%  
Sensitivity/Specificity of addition of BNP to myoglobin, CK-MB and cTnI at t=0 or 90min in all suspected patients to diagnose ACS = 88.1%/48.6%  
Authors state, “the increased sensitivity and trends toward increased NPV suggest that BNP may prove useful in populations without definitive dispositions”.  
LOE D2  
Fair quality study  
Supporting evidence for the addition of BNP to multimarker (myoglobin, CK-MB and cTnI) testing for diagnose of AMI not ACS.  
**Timing remains an issue**  
***Opposing evidence for TnI, CKMB, myoglobin at t<=90min*** |
**Notes:** |
<table>
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| Prospective observational study (n=348) of patients presenting to the ED with chest pain prompting an ECG evaluating ST2 in the diagnosis of AMI, ACS and 30-day cardiac events. Includes STEMI patients. Median time of onset upon ED admission = 260min. Serum markers obtained at time of hospital admission. No significant differences between ST2 levels in all groups and outcomes. | LOE D2  
Fair quality study.  
Opposing evidence for the use of ST2 in the diagnosis of ACS. |
Notes:  
Retrospective study (n=166) of patients diagnosed with NSTEMI in the ED with elevated TnI on multiple measurements and with ECG changes (excluding ST elevations) evaluating diagnostic value of TnI. Serum markers (TnI, CK-MB, CK) drawn at time of admission and q6h. Inadequate information on characteristics of presentation. Wall motion abnormalities screened between 24-48h of presentation.  
PPV of TnI>0.5 --> >3.0 = 53% --> 65%  
Sensitivity of TnI=0.5ng/mL = 60.8%  
PPV of TnI and WMSI = 72%  
PPV of TnI+CKMB+WMSI = 74%  
LOE D4 – case series w/o controls, index test used as part of inclusion criteria  
Fair quality study  
Opposing evidence for TnI in diagnosis. |
Notes:  
Prospective observational study (n=425) of patients presenting to the ED with suspected ACS to evaluate correlation of initial BNP and NT-proBNP to TnI. No specific cut-offs.  
Inadequate information on chest pain characteristics.  
Good correlation of BNP and NT-proBNP at t=0h with TnI.  
LOE D4  
Fair quality study.  
Supportive evidence but can not make recommendations because of specific evidence criteria and no set cut-offs. |
Notes:  
Prospective observational study (n=67) of ED patients presenting with chest pain <1h of onset. Markers (TnT, CKMB, myoglobin) drawn at t=0, 4, 8, 12h and H-FABP at t=0, 4h. Reference standard cTnT at 8h >0.1. Included STEMI patients.  
Small study and CP<1h of presentation with +ve Tn suggests severe ischemia |
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| **Sensitivity/specificity of TnT at t=0, 4h = 100/23.1, 100/88.5%**  
**Sensitivity/specificity of CKMB at t=0, 4h = 97.6/34.6, 97.6/88.5%**  
**Sensitivity/specificity of myoglobin at t=0, 4h = 85.4/34.6, 90.2/73.1**  
**Sensitivity/specificity of H-FABP at t=0, 4h = 97.6/38.5, 97.6/88.5%** |  |
| **LOE D4**  
**Fair quality study**  
**Supportive for H-FABP at t=0, 4h in early onset**  
**Supportive for TnT and CKMB**  
**Opposing for myoglobin** |  |
**Notes:**  
Prospective study (n=769) of patients presenting to the ED with chest pain suggestive of ACS deriving a CDR to rule out ACS in very low to low risk patients and be safely discharged.  
Cardiac markers (CK, TnI, TnT, myoglobin and CKMB) were drawn at time 0 and 2 hours. Timing and duration of chest pain not defined.  
Rule includes initial CKMB<3.0mcg/L or delta CKMB<=0 in very low to low risk patients.  
Sensitivity/Specificity of clinical decision rule = 98.8%/32.5%  
PPV/NPV = 28.5%/99.0%  
**LOE D2**  
**Good quality study**  
**Supporting evidence for use of CKMB (including delta CKMB) testing in very low to low risk patients to rule out ACS.** |  |
**Notes:**  
Prospective study (n=263) of patients presenting to the ED with symptoms suggestive of ACS to evaluate the diagnostic value of POCT vs. central lab testing of TnT (cutoff 0.2mcg/L).  
CK testing was done at time of CCU admission and at 4h, and TnT at 12h. Timing of chest pain within 48h without mention of duration.  
Sensitivity of TnT>0.2mcg/L POCT in diagnosis of STEMI, NSTEMI = 97.6%  
Significant reduction of length of hospital stay in POCT testing in low risk ACS as defined by a structured decision rule.  
**LOE D2**  
**Good quality study**  
**Supporting evidence for use of POCT TnT testing in diagnosis of AMI** |  |
**Notes:**  
Prospective study (n=786) of “low-risk” patients presenting to the ED with undifferentiated chest pain requiring admission to an observation unit or medical unit to evaluate the diagnostic value of CKMB and TnT. If chest pain<12h prior to presentation, cardiac markers drawn at time 0 (CKMB) and at least 2h and 6h (CKMB, TnT) of chest pain. If chest pain>12h from presentation, then markers (CKMB, TnT) drawn at time 0h. |  |
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<th>Worksheet No. ACS-013B.doc</th>
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</table>


**Notes:**
Prospective observational study (n=539) of “low-risk” patients presenting to the ED with undifferentiated chest pain requiring admission to an observation unit or medical unit to evaluate the additive diagnostic value of IMA to TnT.  
If chest pain <12h prior to presentation, cardiac markers drawn at time 0 (CKMB) and at least 2h and 6h (CKMB, TnT) of chest pain.  If chest pain >12h from presentation, then markers (CKMB, TnT) drawn at time 0h.  
IMA sampling taken from first sample.  
Sensitivity/specificity of TnT or IMA positive for AMI = 100%/34.5%  
Sensitivity of TnT at t=0 = 94.6%  
Sensitivity/specificity of TnT and CKMB = 94.6%/91.8%  
Sensitivity of CKMB = 67.6%  
LOE D2  
Fair quality study  
Supporting evidence for TnT in diagnosis of AMI  
Supportive for addition of IMA to Tn but from 94.6 to 100%  
Opposing evidence for CKMB  
Opposing evidence for addition of CKMB and Tn  


**Notes:**
Prospective observational study (n=108) of pre-hospital patients presenting with chest pain. **MI defined by increased cTnI in any sample in first 24h. Pre-hospital POCT performed assessing H-FABP, cTnI, myoglobin and CKMB.  
Sensitivity/specificity of H-FABP overall and <3h = 87.3/94.3% and 85.7/92.7%  
Sensitivity/specificity of CKMB overall and <3h = 41.5%/93% and 37.5%/93.8%  
Sensitivity/specificity of myoglobin overall and <3h = 64.2/67.4% and 57.5/71.9%  
Sensitivity/specificity of prehospital cTnI overall and <3h = 21.8/100% and 14.3/100%  
Sensitivity/specificity of H-FABP overall and <3h with –ve prehospital cTnI = 83.3/93.3%  
LOE D4  
Fair quality study  
Supporting evidence for troponin T for diagnosis of AMI  
Neutral/opposing evidence for CKMB and delta CKMB for diagnosis of AMI.  

**Sensitivity/Specificity**

- **initial (<12h) CKMB>5mcg/L = 36.8%/95.7%**
- **6h sample (<12h) CKMB>5mcg/L = 68.4%/96.4%**
- **(>12h) CKMB>5mcg/L = 75%/99.5%**
- **(<12h) delta CKMB>1.6mcg/L = 65.8%/99.2%**
- **6h (<12h) TnT>0.05mcg/L = 92.1%/100%**
- **(>12h) TnT>0.05mcg/L = 83.3%/100%**
<table>
<thead>
<tr>
<th><strong>Opposing evidence for the use of pre-hospital H-FABP POCT overall and &lt;3h of symptom onset (note MI defined as +ve TnI in 24h)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Opposing evidence for pre-hospital TnI, CKMB and myoglobin POCT</td>
</tr>
</tbody>
</table>

**Eggers(05)**


**Notes:**
- Prospective study (n=191) of patients presenting to the ED with chest pain without STE on ECG to evaluate the diagnostic and prognostic values of TnI, CK-MB and myoglobin in AMI according to the ESC/ACC 2000 definitions.
- Chest pain >15min within 24h of presentation warranting suspicion of ACS. Serum marker testing at time 0, 0.5, 1, 1.5, 2, 3, 6 and 12h.
- Sensitivity/specificity of TnI>0.1mcg/L at 6h for AMI = 98%/77%.
- Sensitivity/specificity of CK-MB>3.5mcg/L at 6h for AMI = 85%/88%.
- Sensitivity/specificity of myoglobin>98mcg/L(men) or >56mcg/L(women) at 6h for AMI = 73%/85%.
- Sensitivity/specificity of TnI>0.1mcg/L at 6h for ACS = 75%/82%.
- Sensitivity/specificity of CK-MB>3.5mcg/L at 6h for ACS = 52%/86%.
- Sensitivity/specificity of myoglobin at 6h for ACS = 46%/83%.
- Sensitivity/specificity of TnI or CK-MB at 6h for AMI = 100%/70%.
- Sensitivity/specificity of TnI or CK-MB at 6h for ACS = 77%/73%.

**LOE D2**
- Fair quality of study
- Supportive evidence for TnI at 6h for the diagnosis (rule-out) of AMI but not ACS

**Eisenman(05)**


**Notes:**
- Prospective study (n=54) of patients presenting to the ED with chest pain suggestive of ACS with normal or equivocal ECGs to evaluate the diagnostic value of bedside TnI and TnT.
- Time of cardiac markers drawn is unclear. Chest pain lasted >4h.
- Sensitivity/Specificity of bedside TnI>0.4mcg/L = 100%/74%
- Sensitivity/Specificity of bedside TnT>0.3mcg/L = 55%/95%

**LOE D4**
- Poor quality study
- Supporting evidence for use of POCT TnI for diagnosis. Important to note high TnI cutoff at 0.4mcg/L.

**Elesber(07)**


**Notes:**
- Prospective observational study (n=59) of “intermediate-high risk” patients presenting to ED with chest pain (undefined time of CP onset) to assess PAPP-A at time = 0 of ED admission.
- MI diagnosed by multiple criteria.
- Odds ratio = 2.093

**LOE D4**
- Fair quality
### Opposing evidence for use of PAPP-A in diagnosis of MI

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Title</th>
<th>Publication Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engel(07)</td>
<td>Engel G, Rockson SG. Rapid diagnosis of myocardial injury with troponin T and CK-MB relative index. Molecular Diagnosis and Therapy11(2)(pp 109-116), 2007</td>
<td>Date of Publication: 2007. 2007(2):109-16.</td>
<td>Prospective observational study (n=171) of ED NSTE chest pain patients. Evaluated TnT, CKMB, CKMB relative index or multimarker (TnT &amp; CKMB index). Markers drawn at 0, 3, 6, 8 and 16h from presentation. Insufficient information on chest pain characteristics. Reference standard: TnT &gt; 0.03ng/mL (index test as part of reference standard) Sensitivity/specificity TnT at 0, 3, 6h = 80/94, 96/90, 98/90 Sensitivity/specificity CKMB&gt;5ng/mL at 0, 3, 6h = 36/97, 57/96, 59/96 Sensitivity/specificity CKMB index at 0, 3, 6h = 77/74, 89/67, 89/64 Sensitivity/specificity TnT and CKMB at 0, 3, 6h = 84/93, 96/89, 100/88 Sensitivity/specificity TnT and CKMB index at 0, 3, 6h = 91/72, 98/64, 100/61</td>
</tr>
<tr>
<td>Ferroni(07)</td>
<td>Ferroni P, Rosa A, Di Franco M, Palmirotta R, Guadagni F, Davi G, Bertazzoni G, Basili S. Prognostic significance of interleukin-6 measurement in the diagnosis of acute myocardial infarction in emergency department. Clin Chim Acta. 2007 Jun;381(2):151-6.</td>
<td>Prospective observational study (n=88) of patients presenting to ED with chest pain &lt;6h and assessed for IL-6 and hs-CRP. MI defined by ECC guidelines. IL-6 and hs-CRP drawn at time =0. Other markers (TnI, CKMB, myoglobin) drawn at time 0 and then every 4h until diagnosis or for 24h.</td>
<td>Sensitivity/specificity of IL-6 using low and high cutoff = 74/66 and 48/90.6% Sensitivity/specificity of hs-CRP using low and high cutoff = 68/58 and 45/88.7%</td>
</tr>
<tr>
<td>Fesmire(04)</td>
<td>Fesmire FM, Christenson RH, Fody EP, Feintuch TA. Delta creatine kinase-MB outperforms myoglobin at two hours during the emergency department identification and exclusion of troponin positive non-ST-segment elevation acute coronary syndromes. Ann Emerg Med. 2004 Jul;44(1):12-9.</td>
<td>Prospective study (n=975) of patients presenting to the ED with chest pain suggestive of ACS and initial troponin&lt;1.0ng/mL(gold standard) to evaluate the diagnostic value of CKMB and myoglobin. Adequate exclusion criteria. Cardiac markers (CKMB, myoglobin, TnI) drawn at time 0h and 2h. Chest pain lasting &gt;20min within 24h of presentation included.</td>
<td>Sensitivity/Specificity of delta myoglobin &gt;9.4ng/mL = 77.3%/83.8% +ve/-ve LR of delta myoglobin = 4.8/0.27 Sensitivity/Specificity of delta CKMB &gt;0.7ng/mL = 93.2%/94.4% +ve/-ve LR of delta CKMB = 16.7/0.07</td>
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<tr>
<td>Supporting evidence for use of CKMB (2h delta CKMB) in diagnosis of AMI of low risk patients. Opposing evidence for use of myoglobin in diagnosis of AMI.</td>
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Notes: Prospective study (n=69) of patients presenting with chest pain suggestive of ACS in the prehospital setting to evaluate the diagnostic value of POCT (qualitative and quantitative) TnT, myoglobin, CKMB in ACS. Cardiac marker testing not specified but within prehospital setting. Chest pain lasting >3h were included. ACS gold standard based on history, physical exam and ECG. No biomarkers used. Sensitivity/Specificity of qualitative +ve test for all markers (TnT, CKMB, myoglobin) = 27.8%/100% Sensitivity/Specificity of qualitative +ve TnT = 60%/96.9%  
LOE D4  
Poor quality of study  
Opposing evidence for POCT marker testing in the prehospital setting. |
Notes: Prospective observational study (n=741) of chest patient presenting to ED. Evaluated POCT TnT and myoglobin vs. central lab. Markers drawn at 0h and 2-6h. Chest pain >20min within 12h of presentation.  
Sensitivity of POCT TnT (including STEMI) at 0h and 4h = 62, 97%  
Sensitivity of POCT TnT (NSTE) at 0h and 4h = 65.5, 84%  
Sensitivity of POCT myoglobin (NSTE) at 0h and 4h = 59.3, 81.2%  
LOE D4  
Fair quality study  
Supportive evidence for POCT TnT at 4h for AMI  
Opposing evidence for POCT TnT, myoglobin for ACS |
Notes: Random sample (n=133) of patients presenting to the ED or CCU with chest pain suggestive of ACS were evaluated with POCT TnT compared to central lab testing. Inadequate information about timing of blood drawn or characteristics of chest pain. Sensitivity/Specificity of TnT>0.1ng/mL POCT = 75%/100% POCT false positive with TnT values between 0.03 to 0.1.  
LOE D4  
Fair quality of evidence  
Neutral/opposing evidence for use of POCT TnT in diagnosis of ACS. |
Hamilton(08)


Notes:
Prospective study (n=351) of low risk patients presenting with chest pain suggestive of ACS and admitted to hospital for further evaluation to evaluate POC protocol TnI, CKMB, myoglobin and BNP vs central TnT at 12h >0.09ng/mL (gold standard).
Inadequate information about timing of cardiac markers drawn. Chest pain of ischemic nature at time of presentation or within last 24h.
Sensitivity/Specificity of POC myoglobin>150ng/mL = 73.0%/88.7%
Sensitivity/Specificity of POCKM>4.3ng/mL = 81.1%/93.4%
Sensitivity/Specificity of central lab at 12h CKMB>24IU/L = 70.5%/89.3%
Sensitivity/Specificity of POC CKMB>4.3ng/mL = 81.1%/93.4%
Sensitivity/Specificity of POC TnI>0.09ng/mL = 78.9%/96.7%
Sensitivity/Specificity of initial central lab TnT>0.09ng/mL = 66%/96.6%
Sensitivity/Specificity of 12h central lab TnT>0.09ng/mL = 95.7%/95.7%
Sensitivity/Specificity of POC BNP at low and high cutoffs = 66/71 and 77/65%

LOE D3
Fair quality study
Supporting evidence for POCT CKMB, TnI as part of protocol for diagnosis of AMI.
Supporting evidence for TnT for diagnosis of AMI.
Opposing evidence for POCT BNP.

Hindle(05)


Notes:
Retrospective chart review (n=235) of patients who underwent qualitative POCT TnI testing at time 0h and 6h for AMI in a rural setting where quantitative CKMB or TnI testing is not readily available.
No controls used in study.
Sensitivity/Specificity of POCT qualitative TnI = 100%/98.6%
Sensitivity/Specificity of quantitative CK = 88.2%/84.7%

LOE D4
Poor quality study.
Supporting evidence for POCT qualitative TnI for diagnosis.

Kavsak(08)


Notes:
Retrospective analysis of stored serum (n=216) from 1996 for E-selectin, IL-6 and NT-proBNP for diagnosis of AMI. Unclear of timing of samples drawn and time of symptom onset.
Sensitivity/Specificity of 2 of 3 panel test = 60/74%

LOE D4
Poor quality
Opposing evidence for E-selectin, IL-6 and NT-proBNP panel testing.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Details</th>
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Notes: Prospective observational study (n=277) to assess IMA and TnI at time 0 in ED patients presenting with low risk CP < 8h onset. Reference standard defined by +ve TnI at 8h of presentation.  
Sensitivity/Specificity of index test (+ve IMA or +ve TnI) at time 0 = 97/13.6%  
LOE D4  
Fair quality  
Supporting evidence for addition of IMA to TnI at time =0 to improve sensitivity but highly non-specific. |
Notes: Prospective observational study (n=1818) of patients presenting to the ED with symptoms suggestive of cardiac ischemia evaluating new sensitive TnI assay. Samples taken at time 0, 3, 6h in ED. Appropriate definitions of AMI according to universal definition.  
Sensitivity/specificity/PPV/NPV of sensitive TnI on admission < 3h onset = 84/93/82/94%  
Sensitivity/specificity/PPV/NPV of sensitive TnI on admission < 6h onset = 87/92/79/94%  
Sensitivity/specificity/PPV/NPV of sensitive TnI on admission < 12h onset = 88/92/78/96%  
Sensitivity/specificity/PPV/NPV of sensitive TnI on admission overall = 90/90/76/96%  
Serial testing at 0, 3, and 6h of admission, rate of overall detection = 100%  
LOE D2  
Good quality study  
Supporting evidence for the use of sensitive TnI when serial testing done. |
Notes: Case control study to assess diagnostic value of tryptase levels in patients presenting to ED. Average time of bloods drawn = 7h from symptom onset.  
Stable levels in normal and in MI.  
LOD D3  
Fair study  
Opposing evidence for use of tryptase. |
Notes: Prospective observational study of chest pain patients presenting to ED to evaluate diagnostic value of BNP and NT-proBNP. Levels drawn at time 0 and up to 5 times in 24h.  
ROC analyses showed equivocal results for the diagnosis of ACS |
<table>
<thead>
<tr>
<th>LOE D4</th>
<th>Good quality</th>
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<tbody>
<tr>
<td>Opposing evidence for BNP and NT-proBNP in diagnosis of ACS.</td>
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<td>Notes:</td>
<td>Prospective observational study (n=74) to evaluate a whole-blood H-FABP in presenting ED pts &lt; 3h of symptom onset for &gt; 20min. Median time between time of onset and blood drawn = 2.3+/-.7h. Unclear criteria for Dx of AMI.</td>
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<tr>
<td>Sensitivity/specificity/PPV/NPV of H-FABP = 83/30/76/40%</td>
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<tr>
<td>Sensitivity/specificity/PPV/NPV of myoglobin = 76/25/73/27%</td>
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<tr>
<td>Sensitivity/specificity/PPV/NPV of TnI = 64/50/77/34%</td>
<td></td>
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<tr>
<td>Sensitivity/specificity/PPV/NPV of CKMB = 65/35/73/27%</td>
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<thead>
<tr>
<th>LOE D4</th>
<th>Fair quality</th>
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<tbody>
<tr>
<td>Opposing evidence for use of H-FABP, myoglobin, TnI and CKMB for diagnosis &lt; 3h symptom onset.</td>
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<tr>
<td>Notes:</td>
<td>Prospective observational study (n=93) of admitted consecutive ICU patients with both troponin and ECG performed with or without symptoms suggestive of ACS. No controls. Gold standard based on TnT, ECG and echocardiography by 2 independent reviewers using adapted AHA definitions.</td>
</tr>
<tr>
<td>LOE D4</td>
<td>Fair quality study</td>
</tr>
<tr>
<td>Opposing evidence for use of TnT alone for diagnosis of AMI in the ICU. Recommend multimodal diagnostic criteria for AMI in the ICU.</td>
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<tr>
<td>Notes:</td>
<td>Prospective observational study (n=741) to assess the use of D-dimer compared to TnT in chest pain patients presenting to the ED. MI defined by ACC/ECC guidelines. Blood drawn 12-24h of admission. No references to timing of symptom onset.</td>
</tr>
<tr>
<td>Sensitivity/specificity of D-dimer&gt;500 – 95/27%</td>
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<tr>
<td>PPV/NPV = 92/41%</td>
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<tr>
<td>Linear regression showed no significant association with TnT</td>
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<thead>
<tr>
<th>LOE D4</th>
<th>Fair quality</th>
</tr>
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<tbody>
<tr>
<td>Neutral evidence for use of D-dimer in diagnosis of AMI</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Title</td>
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</tbody>
</table>
| Liyan(08) | Liyan C, Jie Z, Yonghua W, Xiaozhou H. Assay of ischemia-modified albumin and C-reactive protein for early diagnosis of acute coronary syndromes. Journal of Clinical Laboratory Analysis 22(1)(pp 45-49), 2008. | Prospective observational study (n=113) high-risk CP patients requiring coronary angiography. Assessed utility of IMA in these patients with cutoffs determined by ROC analysis. Markers drawn within 12h of symptom onset. | Sensitivity/Specificity of IMA = 94.4/82.6%  
Sensitivity/Specificity of CRP = 70/73.9% | LOE D4  
Fair quality | Supporting evidence for IMA for diagnosis of AMI **in high risk pts**  
Opposing evidence for CRP |
| Macrae(06) | Macrae AR, Kavsak PA, Lustig V, Bhargava R, Vandersluis R, Palomaki GE, et al. Assessing the requirement for the 6-hour interval between specimens in the American Heart Association Classification of Myocardial Infarction in Epidemiology and Clinical Research Studies.[see comment]. Clin Chem. 2006 May;52(5):812-8. | Retrospective analysis of serum from patients (n=258) presenting to the ED with chest pain suggestive of ACS to evaluate the diagnostic value of various time intervals between TnI serum testing. |  | LOE D3  
Fair quality of study. | Supporting evidence for use of sensitive TnT >=6h of symptom onset for diagnosis of AMI.  
Supporting evidence for shortening time intervals >=3h for TnT testing for diagnosis. |
Sensitivity/specificity of POCT H-FABP < 2h = 65/78%  
Sensitivity/specificity of POCT H-FABP 2-6h = 58/70%  
Sensitivity/specificity of POCT H-FABP > 6h = 91/73% | LOE D4  
Fair quality | Opposing evidence for POCT H-FABP |
| McCann(08) | McCann CJ, Glover BM, Menown IB, Moore MJ, McEneny J, Owens CG, Smith B, Sharpe PC, Young IS, Adgey JA. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T.[see comment]. |  |  |  |  |
Prospective observational study (n=664) presenting to early coronary care/ED units with CP<24h. Median time of symptom onset to time of arrival was 2.9h in the mobile CCU and 6.5h in the ED. AMI was defined as cTnT>0.03**. H-FABP, glycogen phosphorylase-BB, NT-proBNP, D-dimer, hsCRP, MPO, MMP-9, PAPP-A, CD40 ligand were compared to initial cTnT or cTnt at 12hours.

Sensitivity/specificity/PPV/NPV of H-FABP = 76/61/64/74%
Sensitivity/specificity/PPV/NPV of initial cTnT = 75/94/92/81%
Sensitivity/specificity/PPV/NPV of H-FABP at time=0 = 93/60/68/91%
Sensitivity/specificity/PPV/NPV of H-FABP <4h = 73/71/71/73%
Sensitivity/specificity/PPV/NPV of cTnT <4h = 55/95/92/68%
Sensitivity/specificity/PPV/NPV of H-FABP at cTnT <4h = 85/69/73/83%
Sensitivity/specificity/PPV/NPV of H-FABP >4h = 78/56/61/75%
Sensitivity/specificity/PPV/NPV of cTnT >4h = 88/94/92/90%
Sensitivity/specificity/PPV/NPV of H-FABP or cTnT >4h = 98/55/66/97%

LOE D4
Fair quality
Supporting evidence for cTnT >4h of CP
Opposing evidence for H-FABP, glycogen phosphorylase-BB, NT-proBNP, D-dimer, hsCRP, MPO, MMP-9, PAPP-A, CD40 ligand at time=0.
Small increase to sensivity/specificity when H-FABP added to cTnT.


Notes:
Prospective observation cohort (n=537) of patients presenting to the ED with chest pain suggestive of ACS to evaluate POCT of myoglobin, CKMD and TnI at time 0h.
Inadequate information for timing and duration of chest pain. Gold standard not specified.
Sensitivity/Specificity of myoglobin>200ng/mL = 69%/74.8%
Sensitivity/Specificity of CKMB>7.5ng/mL = 57.6%/92.7%
Sensitivity/Specificity of TnI>0.4ng/mL = 33.3%/99.4%

LOE D4
Fair quality study
Neutral/opposing evidence for POCT myoglobin for diagnosis at time 0h.
Neutral/opposing evidence for POCT for TnI and CKMB for diagnosis at time 0h.


Notes:
Meta-analysis of studies assessing the diagnostic accuracy of novel markers (myeloperoxidase, CRP, CD40 ligand, D-dimer, BNP, NT-proBNP, fibrinogen, H-FABP, IL-6, monocyte chemoattractant 1, WBC, placental growth factor, PAPP, E-selectin, soluble intercellular adhesion-1, P-selectin, soluble vascular adhesion-1) in low risk patients. Used appropriate inclusion/exclusion criteria.
No studies reached diagnostic criteria/significance

LOE D2
Good quality
Opposing evidence for all novel markers in low risk patients.

Notes:
Prospective observational study (n=414) to assess novel markers (MCP, MPO, CRP, BNP) in low risk chest pain pts presenting to the ED. Average time of single blood test drawn = 27h. Blinded independent assessment.

Sensitivity/Specificity of TnT = 43/99%
Sensitivity/Specificity of MPO = 71/32%
Sensitivity/Specificity of CRP = 29/91%
Sensitivity/Specificity of BNP = 14/95%
Sensitivity/Specificity of MCP = 85/72%

LOD D4
Fair quality
Opposing evidence for TnT, MPO, CRP, BNP and MCP.


Notes:
Nested case-control study of suspected but TnT –ve pts (n=33), +ve ACS with +ve TnT (n=65) and controls (n=62) to examine prothrombin fragment (F1+2), thrombin-antithrombin (TAT), soluable TF, tissue factor pathway inhibitor (TFPI) and plasminogen activator inhibitor (PAI) in diagnosis of ACS.

All markers did not reach significant sensitivity/specificity.

LOE D3
Fair quality
Opposing evidence for use of prothrombin fragment (F1+2), thrombin-antithrombin (TAT), soluable TF, tissue factor pathway inhibitor (TFPI) and plasminogen activator inhibitor (PAI).


Notes:
Prospective observational study (n=74) to assess TnT, H-FABP, CKMB and myoglobin in low risk ACS. Standard was according to guidelines as well as imaging studies. Time of blood samples within 30min of ED arrival and median time=5.8h of symptom onset.

All markers (TnT, H-FABP, CKMB and myoglobin) did not reach significance.

LOE D4
Good quality
Opposing evidence of TnT, H-FABP, CKMB and myoglobin.

Notes:
Prospective study of 2 subpopulations of patients presenting to the ED with chest pain onset 6-24h (late) prior to admission vs. <6h (early) to evaluate the diagnostic value of TnI, CKMB and myoglobin testing.
Cardiac markers drawn at time 0h and 2h. Adequate blinding of investigators and treating physicians.
Sensitivity of CKMB>5ng/mL in <6h patients at time 0h/2h = 43%/82%
Sensitivity of TnI>1ng/mL in <6h patients at time 0h/2h = 21%/68%
Sensitivity of myoglobin>110ng/mL in <6h patients at time 0h/2h = 54%/82%
Sensitivity of CKMB>5ng/mL in 6-24h patients at time 0h/2h = 95%/94%
Sensitivity of TnI>1ng/mL in 6-24h patients at time 0h/2h = 80%/82%
Sensitivity of myoglobin>110ng/mL in 6-24h patients at time 0h/2h = 90%/82%

LOE D2
Fair quality study.

Supporting evidence for serial marker testing with CKMB.
Neutral/opposing evidence for TnI and myoglobin.

Nikolaou(05)

Notes:
Prospective observational study (n=101) of chest pain pts presenting to the ED to assess BNP at time 0, 2 and 6h. Unclear time of onset.
Sensitivity/specificity = 84/94% highest in ongoing chest pain pts at 6h but low PPV/NPV = 0.87/0.93.

LOE D4
Fair quality

Opposing evidence for BNP.

Patti(04)

Notes:
Prospective observational study (n=44) of STEMI patients to assess sensitivity of IL-1Ra compared to CK, CKMB, TnI, myoglobin and CRP. Levels drawn at time of admission to ED. Median time of chest pain prior to ED admission 228+-170min.
Sensitivity of IL-1Ra in STEMI < 3h duration vs heralded STEMI = 86% vs. 91%

LOE D4
Fair study

Opposing evidence for IL-1Ra

Peacock(06)

Notes:
Meta-analysis of the diagnostic value of IMA in presenting chest pain pts within 3h of onset and markers drawn using the same blood samples. Studies taken from Medline and Pubmed.
<table>
<thead>
<tr>
<th>Study</th>
<th>LOE</th>
<th>Quality</th>
<th>Evidence</th>
<th>Notes</th>
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</thead>
</table>
| Plaikner(09)| D2   | Fair    | Supporting evidence for the addition of IMA in multimarker testing with Tn. | Sensitivity/NPV of –ve ECG, Tn and IMA = 94.4/97.1%  
  Sensitivity/NPV of –ve Tn, CKMB, myoglobin and IMA = 96/92%  
  Notes: Prospective observational study (n=1089) to evaluate sCD40L in CP Pts presenting to the ED. No information regarding time of symptom onset. Blood drawn at time=0. Physicians blinded to sCD40L results. Diagnosis by retrospective review.  
  No association.  
  Notes: Prospective study (n=349) of patients presenting to 44 family physician offices in Jerusalem to evaluate the diagnostic value of POCT TnT in a community clinic setting. Chest pain lasting >20min starting >8h to 6d prior to presentation. Adequate blinding of treating physicians. Gold standard was +ve central TnT testing. Sensitivity/Specificity of POCT TnT >0.08mcg/L = 83%/100%  
  Notes: Prospective observational study (n=980) of chest pain pts presenting to the ED<12h of symptom onset. Cardiac markers(TnI, CKMB and CRP) drawn at appropriate times. Dx according to ACC/ESC guidelines.  
  Sensitivity/PPV of +ve CRP = 30/61%  
  Sensitivity/NPV of –ve CRP = 80/96% |

Notes:  
Prospective observational study (n=487) to evaluate copeptin levels in pts presenting to the ED. Chest pain onset < 12h of presentation. No mean/median time of onset given. TnT drawn at time 0, 3, 6, 9h. Copeptin drawn at time 0 and at 1, 2, 3, 6h until Dx made. Cardiologists blinded to copeptin results and made Dx according to current guidelines.  
Copeptin levels inversely proportional to time of symptom onset. Increase AUC levels for TnT.  
Sensitivity/specificity/PPV/NPV of copeptin >14pmol/L when TnT<.01 at time 0 = 98.8/77/46/99.7%  
LOE D4  
Good quality  
Supporting evidence for copeptin at time=0 when troponin<0.01. Time of onset <12h but no delineation. **Note: availability of test** |
Notes:  
Prospective observational study (n=718) of patients presenting to the ED with symptoms <12h to evaluate various sensitive Tn assays vs standard assay. Sample taken on admission. Appropriate definition of AMI.  
Sensitivity/specificity/PPV/NPV of sensitive Tn overall = 75-95/80-97/50-73/95-99%  
Sensitivity/specificity/PPV/NPV of sensitive Tn <3h onset = 41-85/84-98/42-71/92-98%  
Serial testing did not significantly improve accuracy  
LOE D2  
Fair study  
Supporting evidence for the use of sensitive Tn (dependant on assay) for AMI not ACS. |
Notes:  
Prospective observational study (n=131) to assess IMA in chest pain pts presenting to the ED <3h of symptom onset with non-diagnostic ECG and –ve TnT. Prior to heparin tx, single venous IMA drawn. AMI defined accordingly.  
Sensitivity/specificity/NPV of IMA>93.5 = 75/74/75.8%  
Sensitivity/specificity/NPV of IMA>85 = 90.6/49/84.5%  
Sensitivity/specificity/NPV of IMA>85 in combination with serial TnT = 92.2/49/86%  
LOE D4  
Good quality  
Opposing evidence for IMA but helped improved sensitivity when combined with TnT |

Notes:
Prospective observational analysis (n=144) of chest pain pts presenting to the ED <3h symptom onset to assess WBC, albumin and hsCRP drawn at time=0. TnT drawn at time 0 and 6-12h later. AMI defined appropriately.

OR WBC 20.9
OR albumin 0.1
OR hs-CRP 2.1

LOE D4
Fair quality
Supporting but insufficient analysis of sensitivity/specificities


Notes:
Retrospective study (n=1023) of patients presenting to the ED and had TnI testing. Gold standard was diagnosis by a cardiologist. Inadequate information on timing of chest pain—known to have occurred within 24h of presentation.
Sensitivity/Specificity of TnI>0.03ng/mL for AMI = 94.6%/61.9%
Sensitivity of TnI for UA = 77.1%

LOE D4
Fair quality study.
Supporting evidence for TnI testing for diagnosis.


Notes:
Prospective study (n=817) of patients presenting with chest pain to evaluate the diagnostic value of delta myoglobin at 90min when initial TnI and myoglobin tests are normal.
Serum testing done at time 0, 90min, 3h and 9h. Inadequate information on timing or characteristics of chest pain. Gold standard used was ESC/ACC 2000 definitions with emphasis on TnI>0.4ng/mL.
Sensitivity/Specificity of delta myoglobin >20ng/mL = 83.3%/88.6%
NPV of delta myoglobin >20ng/mL = 99.5%

LOE D4
Good quality study.
Opposing/neutral evidence of delta myoglobin for diagnosis.


Notes:
Prospective observational study (n=158) to evaluate TnT POCT in the prehospital setting and confirmed in central lab testing.
<table>
<thead>
<tr>
<th>Study</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Sn/Sp = 18/97%</strong>&lt;br&gt;LOE D4&lt;br&gt;Good quality.</td>
<td>Opposing evidence for the use of TnT POCT in the prehospital setting.</td>
</tr>
<tr>
<td><strong>Seino(04)</strong></td>
<td>Seino Y, Tomita Y, Takano T, Ohbayashi K, Tokyo Rapid-Test Office Cardiologists S. Office cardiologists cooperative study on whole blood rapid panel tests in patients with suspicious acute myocardial infarction: comparison between heart-type fatty acid-binding protein and troponin T tests. Circ J. 2004 Feb;68(2):144-8. &lt;br&gt;&lt;br&gt;Notes: &lt;br&gt;Prospective observational study (n=129) to compare the rapid POCT H-FABP vs POCT TnT tests in chest pain pts presenting to office cardiologists. AMI defined by WHO definition (using CKMB criteria).&lt;br&gt;&lt;br&gt;Sensitivity/specificity/NPV of H-FABP (&lt;3h onset) = 100/63/100&lt;br&gt;Sensitivity/specificity/NPV of H-FABP (3-6h onset) = 75/93/94&lt;br&gt;Sensitivity/specificity/NPV of H-FABP (6-12h onset) = 100/72/100&lt;br&gt;Sensitivity/specificity/NPV of H-FABP (&gt;12h onset) = 100/75/100&lt;br&gt;Sensitivity/specificity/NPV of TnT (&lt;3h onset) = 50/96/86&lt;br&gt;Sensitivity/specificity/NPV of TnT (3-6h onset) = 0/93/79&lt;br&gt;Sensitivity/specificity/NPV of TnT (6-12h onset) = 60/100/84&lt;br&gt;Sensitivity/specificity/NPV of TnT (&gt;12h onset) = 100/87/100</td>
</tr>
<tr>
<td><strong>Serdar(05)</strong></td>
<td>Serdar MA, Tokgoz S, Metinyurt G, Tapan S, Erinc K, Hasimi A, et al. Effect of macro-creatine kinase and increased creatine kinase BB on the rapid diagnosis of patients with suspected acute myocardial infarction in the emergency department. Mil Med. 2005 Aug;170(8):648-52.&lt;br&gt;&lt;br&gt;Notes: &lt;br&gt;Retrospective analysis of patients presenting to ED (n=3290) evaluating CK isoenzymes. Markers drawn at 0h and every 4-6h.&lt;br&gt;&lt;br&gt;Sensitivity/specificity of CKMB for AMI = 96/99%</td>
</tr>
<tr>
<td><strong>Sinha(04)</strong></td>
<td>Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of &quot;Ischemia modified albumin&quot;, a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes.[see comment]. Emerg Med J. 2004 Jan;21(1):29-34.&lt;br&gt;&lt;br&gt;Notes: &lt;br&gt;Prospective observational study (n=208) to assess IMA in patients presenting with chest pain &lt;3h of onset to the ED. Serum tests drawn within 2h of admission. Appropriate definitions of ACS and AMI.</td>
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<tr>
<td>Study</td>
<td>Title</td>
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<tr>
<td>Straface (08)</td>
<td>Straface AL, Myers JH, Kirchick HJ, Blick KE. A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department. Am J Clin Pathol. 2008 May;129(5):788-95.</td>
</tr>
</tbody>
</table>
Sensitivity/specificity/PPV/NPV of IMA on admission = 52/79/46/79%

LOE D4
Poor quality
Opposing evidence for IMA


Notes:
Prospective observational study (n=279) of pts presenting to the ED with symptoms suggestive of acute cardiovascular diseases (ACVD) including ACS, PE and dissection to assess utility of admission D-dimer. Unclear time of onset. Appropriate ACS diagnosis criteria.

Sensitivity/specificity/PPV/NPV of D-dimer of ACS = 68/55/31/85%
Sensitivity/specificity/PPV/NPV of TnT of ACS = 45/98/87/83%
Sensitivity/specificity/PPV/NPV of H-FABP of ACS = 70/82/58/88%

LOE D5
Fair study
Opposing evidence for D-dimer


Notes:
Prospective observational study (n=212) of angina pts undergoing angiography after 12h fast. Total plasma cholesterol and erythrocyte membrane cholesterol sampled.

+ve correlation of CEM and ACS.

LOE D5
Good quality
Insufficient evidence for use of erythrocyte membrane cholesterol in diagnosis of ACS.


Notes:
Prospective multicentre observational study (n=419) of CP pts presenting to the ED within 3h onset. H-FABP taken at time 0. TnT taken at time 0 then 6-12h after. Appropriate definition of ACS.

Sensitivity/specificity/PPV/NPV of H-FABP in ACS = 47/94/91/56%
Sensitivity/specificity/PPV/NPV of TnT in ACS = 12/100/100/47%
Sensitivity/specificity/PPV/NPV of H-FABP in AMI = 60/88/72/80%
Sensitivity/specificity/PPV/NPV of TnT in AMI = 19/99/97/69%

LOE D4
Fair quality
Opposing evidence for H-FABP and TnT in diagnosis of ACS or AMI with CP <3h.
Notes:  
Case control study of patients presenting to the ED with chest pain comparing RAMP TnI POCT to the Triage and RxL central lab testing systems. Inadequate information on timing of serum testing or characteristics of chest pain.  
Sensitivity/Specificity of POCT TnI = 90%/86%  
LOE D3  
Fair quality study.  
Opposing evidence for POCT TnI for diagnosis. |
|---|---|
Notes:  
Prospective study (n=420) of patients presenting to the ED with symptoms suggestive of ACS to evaluate the diagnostic value of various TnT cutoffs.  
Marker testing at time 0h, 3h and 12h (not all subjects). Chest pain last >30min and median time was 5.4h prior to presentation.  
Sensitivity/Specificity of TnT>0.03 =98.3%/88.4%  
Sensitivity/Specificity of TnT>0.067 =75.9%/96.7%  
Sensitivity/Specificity of TnT>0.1 =60.3%/98.3%  
LOE D4  
Fair quality study.  
Supporting evidence for TnT for diagnosis. |