

Manitoba Troponin Guideline

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Prepared by:

Dr. John Sokal, CCFP (EM)

Medical Director, Department of Emergency Medicine
Health Sciences Centre

Dr. Laurel Thorlacius, PhD, FCACB

Medical Director, Clinical Biochemistry and Genetics
Diagnostic Services of Manitoba

Dr. James Tam, FRCPC

Head of Cardiology
Director of Echocardiography
Health Sciences Centre and St. Boniface General Hospital

Note: This document was originally prepared for use within the WRHA that uses Troponin T only, due to differences in laboratory instrumentation. As most of the content is the same for either TnT or TnI this document has been modified to reflect the assays in use in other parts of Manitoba. Troponin I and T are of equivalent diagnostic use. Values reported by different Troponin assays will not be identical.

Abbreviations:

| | |
|-------------------|---|
| AMI | acute myocardial infarction |
| AUC | area under the curve |
| CAD | coronary artery disease |
| CRF | chronic renal failure |
| CV | coefficient of variation |
| ED | emergency department |
| ESC/ACC | European Society of Cardiology / American College of Cardiology |
| LOS | length-of-stay |
| MR | mitral regurgitation |
| NLR | negative likelihood ratio |
| NPV | negative predictive value |
| NSTEMI | non-ST segment elevation MI |
| ROC | receiver operating curve |
| STEMI | ST segment elevation MI |
| th ile | percentile |
| TnI | troponin I |
| TnT | troponin T |

Version 4: 2011 December

Version 3: 2010 October

Version 2: 2009 March

Version 1: 2007 June

OVERVIEW

1. In patients with a low likelihood of ACS:

- ⇒ Troponin must be measured at least six (6) hours after the onset of chest pain.
- ⇒ Troponin measurement may be deferred until six (6) hours after the onset of pain.
- ⇒ Troponin samples may be measured two (2) hours apart when measured at least 6 - 8 hours after the onset of chest pain (e.g. sample one at 6 hours after the onset of pain, sample two at 8 hours).
- ⇒ If Troponin measured $\geq 6 - 8$ hours after the onset of chest pain is negative, AMI may be safely ruled-out in patients with a low likelihood of ACS.

2. Troponin is considered negative: (when measured $\geq 6 - 8$ hrs after the onset of chest pain)

| hs TnT Roche | TnI i-STAT | TnI Dade |
|---|-------------------|-------------------|
| < 3 ng/L | < 0.08 mcg/L | < 0.07 mcg/L |
| <i>OR</i> | | |
| hs TnT Roche | TnI i-STAT | TnI Dade |
| ≥ 14 ng/L | ≥ 0.08 mcg/L | ≥ 0.07 mcg/L |
| <i>and</i> not rising on 2 samples measured at least 2 hours apart <i>and</i> in context of alternate etiology for elevated troponin | | |

3. **A rising troponin level is required in order to diagnose AMI.** While there is no current consensus recommendations for the hsTnT delta change in serial sampling, there is strong evidence to support an absolute change of **7 ng/L** (or 50% at the 99th ile) in samples measured **2 hours** apart.
4. **In patients with background elevations of troponin (e.g. patients with CRF), two (2) measurements are required to demonstrate a rising pattern.**
5. **No single serum marker used alone has sufficient sensitivity or specificity to reliably identify or exclude AMI within 6 hours after symptom onset.**
6. **Do not utilize cardiac serum marker tests to exclude unstable angina.**
7. **Document the time of onset of chest pain on all patients.**

Testing of low-risk patients presenting to the emergency department with chest pain: AHA Scientific Statement. Circulation 2010; 122:756–776.

1. The primary goal of evaluation of these patients in the acute setting is accurate **risk stratification** and identification by exclusion of ACS and other serious conditions rather than detection of coronary artery disease.
2. It has been demonstrated that among patients presenting to the ED with chest pain, those with **<5% probability of AMI can be identified from the presenting symptoms, past history, and ECG.**
3. Concomitant with the rapid exclusion of important noncardiac causes of chest pain, risk stratification into categories defined by the ACC/AHA criteria should be performed as indicated by the history, physical examination, ECG, and cardiac injury markers.

Low-risk patients for ACS are those with no hemodynamic derangements or arrhythmias, a normal or near-normal ECG, and negative initial cardiac injury markers, which correlate with low likelihood of ACS and a probability of AMI < 5%.

Recommended approach for a patient presenting with chest pain:

⇒ ***Document the time of onset of chest pain on all patients.***

⇒ If the time of onset of chest pain is not known, then the time of presentation must be utilized for cardiac marker interpretation.

⇒ ***Do not utilize cardiac serum marker tests to exclude unstable angina.***
(ACEP NSTEMI Clinical Policy, 2006)

- *For the definition of unstable angina, see appendix A*

⇒ ***Assess for likelihood of ACS and 30-day MACCE***

MACCE = *major adverse cardiovascular and cerebrovascular events*
(*death, MI, stroke, revascularization*)

Definitions

ESC/ACC Diagnostic Criteria for Acute Myocardial Infarction

Typical rise and/or fall of biochemical markers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following:

- a. symptoms of ischemia
- b. ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
- c. development of pathologic Q waves in the ECG
- d. imaging evidence of loss of viable myocardium or NEW regional wall motion abnormality

Universal Definition of Myocardial Infarction – Circulation 2007

Presentations of Unstable Angina

| | |
|-------------------|---|
| rest angina | angina occurring at rest or prolonged, usually > 20 minutes |
| new-onset angina | new onset angina of at least CCS Class III severity |
| increasing angina | previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e. increased by ≥ 1 CCS Class to at least Class III severity) |

Canadian Cardiovascular Society (CCS) Grading of Angina

| Class | Description of Stage |
|-------|---|
| I | "Ordinary physical activity does not cause... angina" such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation. |
| II | "Slight limitation with ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking >2 blocks on the level and climbing >1 flight of ordinary stairs at a normal pace and under normal conditions. |
| III | "Marked limitations of ordinary physical activity." Angina occurs on walking 1-2 blocks on the level and climbing >1 flight of stairs at a normal pace and under normal conditions. |
| IV | "Inability to carry on any physical activity without discomfort - anginal symptoms may be present at rest." |

ACC/AHA 2002 Unstable angina / NSTEMI guideline update

Assess Likelihood of ACS:

Low Likelihood (e.g. 1% - 14% likelihood)

- chest pain, “probably not angina” in patients with one or no risk factors for CAD, but not diabetes
- normal ECG
- T-wave flat or inverted < 1 mm

Intermediate Likelihood (e.g. 15% - 84% likelihood)

- “definite angina” in patients with no risk factors
- “probable angina” in patients with one or more risk factors
- “probably not angina” in patients with diabetes or with two or three other risk factors
- patients with extracardiac vascular disease
- ST depression 0.5 – 1 mm
- T-wave inversion \geq 1 mm

High Likelihood (e.g. 85% - 99% likelihood)

- known history of prior AMI or CAD
- “definite angina” in males \geq 60 or females \geq 70
- transient hemodynamic or ECG changes during pain
- ST elevation or depression \geq 1 mm
- Marked symmetrical T-wave inversion in multiple leads

UCLA 2005 Chest Pain and ACS Patient Management Guideline

Likelihood that Signs and Symptoms Indicate ACS secondary to ACS

| Feature | High Likelihood (greater than 85%) (any of the following) | Intermediate Likelihood (15%-85%) (absence of high-likelihood features and presence of any of the following) | Low Likelihood (less than 5%) (absence of high- or intermediate-likelihood features but may have) |
|-----------------|---|--|---|
| History | chest or left arm pain or discomfort as chief symptom reproducing prior documented angina known history of CAD, including MI | chest or left arm pain or discomfort as chief symptom over 70 years of age male gender diabetes | probable ischemic symptoms in absence of any of the intermediate likelihood characteristics recent cocaine use |
| Exam | transient MR, hypotension, diaphoresis, pulmonary edema or rales | extracardiac vascular disease | chest discomfort reproduced by palpation |
| ECG | new, or presumably new, transient ST-segment deviation (greater than or equal to 0.05 mV) or T-wave inversion (greater than or equal to 0.2 mV) with symptoms | fixed Q waves abnormal ST segments or T waves not documented to be new | normal or unchanged ECG during an episode of chest discomfort T-wave flattening or inversion in leads with dominant R waves) normal ECG |
| Cardiac markers | elevated Tnl, TnT | normal | normal |

Diagnosis and Treatment of Chest Pain and ACS: Institute for Clinical Systems Improvement 2009 (adapted from Braunwald et al. AHCPR Guideline, Unstable Angina: Diagnosis and Management 1994)

How do you interpret Troponin results?

| Troponin value (µg/L) | hs TnT Roche | TnI i-STAT | TnI Dade | Comment | Interpretation |
|--|---|--------------|--------------|---|--|
| Below 99 th ile | < 14 | < 0.08 | < 0.07 | Below 99 th ile | No myocardial necrosis, if > 6 hrs after onset of symptoms |
| Between 99 th ile and functional sensitivity (10% CV) | 14 is also the level at which <10% variation is reached | 0.08 to 0.10 | 0.07 to 0.21 | Troponin present and can be distinguished from background but cannot be quantified repeatedly at this level | Possible myocardial injury, in the context of suspected ACS, repeat after two (2) hours (<i>repeat must be > 6 hrs after onset of symptoms</i>) ⇒ if not rising, consider alternate etiology for elevated troponin (<i>see Appendix D</i>) |
| Above functional sensitivity (10% CV or less) | > 14 | > 0.10 | > 0.21 | Definite myocardial necrosis, measurements are reproducible | NSTEMI when seen in the context of suspected ACS |

- The fact that any troponin elevation exceeding the 99th ile is associated with an increased cardiac risk is reflected by the recommendation of this cutoff for diagnostic purposes (ESC/ACC diagnostic criteria for AMI).
- It is important to realize that no troponin assays currently available has a CV less than 10% for values than the 99th percentile of a normal reference population. Values between the 99th ile and the level at which a 10% CV are reached have low positive predictive values, resulting in a considerable risk for diagnostic misclassification.
- A rising troponin level is required in order to diagnose AMI.
- In patients with background elevations of troponin (e.g. patients with CRF), two (2) measurements are required to demonstrate a rising pattern.
- **Troponin is specific for heart cell damage - any detectable level indicates myocardial damage. However, the etiology may be other than ACS**
 - *see Appendix A for the differential diagnoses of an elevated troponin.*

In order to rule-out NSTEMI in a patient at low-risk for adverse outcomes:

- **TnI must be measured at least 6 hours after the onset of chest pain.**
- If the repeat is less than the 99th ile - AMI is unlikely. But if clinical suspicion remains high, a third TnI may be considered.

No**Should Troponin *always* be performed at the time of ED presentation?**

- Contemporary troponin assays have improved sensitivity, specificity, and precision at lower levels. When used serially to detect changes over short intervals, their sensitivity is higher than that of more traditional injury markers, which obviates the need for creatine kinase-MB or myoglobin measurement, even in patients with onset of symptoms shortly before presentation. **Current studies have confirmed that contemporary troponin assays can identify the majority (~80%) of MIs within 3 hours of ED arrival** (AHA Statement, Circ 2010).
- For patients with low likelihood of ACS, the diagnostic value of a Troponin drawn at the time of ED presentation (which is often less than 2 hours after the onset of chest pain) is very low and very unlikely to permit earlier consultation and/or admission decisions, or to improve ED throughput. The Troponin measurement may be deferred until six hours after the onset of chest pain, when a negative Troponin test result may be most helpful.
- In patients with recurrent chest pain, ECG abnormalities, or intermediate to high clinical suspicion, immediate treatment for presumed ACS should take place, including prompt consultation when appropriate. In these cases, performing Troponin earlier than six hours may be permissible.

What is the rationale for two hour intervals between hs Troponin T samples?

Table 3. Area Under the Receiver Operating Characteristic Curves for the Diagnosis of Acute Myocardial Infarction for Absolute and Relative Changes in Cardiac Troponin After 1 and 2 Hours From Presentation According to Baseline Cardiac Troponin Levels

| | AUC (95% CI) | P | ROC Cutoff | Sensitivity | Specificity | PPV | NPV |
|-----------------------------|------------------|-------|------------|-------------|-------------|-----|-----|
| hs-cTnT | | | | | | | |
| <0.014 µg/L at presentation | | | | | | | |
| 1 h (n=540, 7 with AMI) | | | | | | | |
| Absolute change (Δ) | 0.85 (0.61–1.00) | 0.027 | 0.004 | 86 | 95 | 19 | 100 |
| Relative change (Δ%) | 0.83 (0.59–1.00) | | 45 | 86 | 90 | 10 | 99 |
| 2 hours (n=396, 6 with AMI) | | | | | | | |
| Absolute change (Δ) | 0.98 (0.96–1.00) | 0.052 | 0.005 | 100 | 95 | 22 | 100 |
| Relative change (Δ%) | 0.95 (0.91–0.99) | | 39 | 100 | 86 | 10 | 100 |

Reichlin T et al. Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction. *Circulation*. 2011;124:136-145.

No**Can single markers be utilized to safely rule out AMI *less than 6 hours* after the onset of chest pain?**

- No single serum marker used alone has sufficient sensitivity or specificity to *reliably* identify or exclude AMI within 6 hours after symptom onset (ACEP 2006 NSTEMI Clinical Policy).

YES**Can TnT be utilized to safely rule out AMI ≥ 6 hours after the onset of pain?**

Collinson P - Annal Clin Biochem 2006

- TnT sample 1 was drawn at the time of presentation;
- TnT sample 2 was drawn at six (6) hours from the onset of chest pain *and* at least two (2) hours after sample 1.
- In this study, the optimal decision threshold from the ROC curves for TnT was 0.02 ug/L (~30 ng/L on hs TnT assay).

⇒ The sensitivity of TnT (0.02ug/L cutoff) exceeds 98% if measured at least six (6) hours after the onset of chest pain, with a negative predictive value (NPV) ≥ 99.9% and a negative likelihood ratio (NLR) of 0.02.

| 6 hour Troponin T measurement (TnT 0.02 ug/L) | | | | | |
|---|----------------------------------|----------------------------------|----------------------------------|------------------------------------|---------------------------------|
| TnT sample 2 was drawn: | Sensitivity % (95%CI) | Specificity % (95%CI) | Negative Likelihood Ratio | Negative Predictive Value % | AUC (95%CI) |
| only between 6 to 12 hrs after the onset of chest pain | 100 (90.7 - 100) | 98.2 (96.6 – 99.2) | < 0.001 | 100 | 1.000 (0.966 – 1.000) |
| all times after 6 hrs | 98 (89.4-99.9) | 98.3 (97.1 – 99.1) | 0.02 | 99.9 | 0.989 (0.999 – 1.000) |
| Interpretation: If TnT measured ≥ 6 hours is negative, AMI may be safely ruled-out in patients with a low likelihood of ACS. | | | | | |

Maybe

Can TnI be utilized to safely rule out AMI ≥ 6 hours after the onset of pain?

There are a variety of TnI assays on the market and they are not all calibrated the same way. The various TNI assays each have different specifications for the 99th percentile of a normal population and different specifications for the 10% CV – therefore, a more conservative approach may be warranted.

The 2007 “National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Characteristics and Utilization of Biochemical Markers in Acute Coronary Syndromes” state:

“Given the improvements in the analytic performance assay, testing up to 6 – 9 h after symptom onset is expected to deliver optimal sensitivity in most patients. However, in patients for whom these initial samples are negative and there is an intermediate or high clinical index of suspicion, or in whom plausibly ischemic symptoms have recurred, repeat testing at 12 – 24 h should be considered.”

No

Does the measurement of CK or CK-MB provide any additional information?

At six hours after the onset of chest pain, troponin alone has a sensitivity for the detection of AMI of >98%, which exceeds the sensitivity of other single markers or combinations of markers.

Numerous studies have demonstrated that measurement of CK and its isoforms does not improve diagnostic accuracy for AMI or facilitate more rapid decision-making than TnT or TnI alone.

In patients with a confirmed MI, serial CK total (not CK-MB) may be used to gauge the relative size of the infarct.

Recommendation: discontinue use of CK-MB as a cardiac biomarker.

No

Does the measurement of myoglobin provide any additional value?

Based on the analysis of the studies utilizing myoglobin as a cardiac biomarker, there is insufficient evidence to justify the potential use of myoglobin as an early marker for AMI.

Recommendation: discontinue use of myoglobin as a cardiac biomarker.

Risk Stratification into categories defined by ACC/AHA

Table 1. Likelihood that Signs and Symptoms Indicate ACS secondary to ACS

| Feature | High Likelihood (any of the following) | Intermediate Likelihood (absence of high-likelihood features and presence of any of the following) | Low Likelihood (absence of high- or intermediate-likelihood features but may have any of the |
|-------------------|--|--|---|
| History | <ul style="list-style-type: none"> accelerating tempo of ischemic symptoms in preceding 48 hours | <ul style="list-style-type: none"> prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use | |
| Character of pain | <ul style="list-style-type: none"> prolonged ongoing (>20 min) rest pain | <ul style="list-style-type: none"> prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD rest angina (>20 min) or relieved with rest or NTG | <ul style="list-style-type: none"> new-onset or progressive CCS Class III or IV angina the past 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD |
| Clinical findings | <ul style="list-style-type: none"> pulmonary edema, most likely due to ischemia new or worsening mitral regurgitation murmur S3 or new/worsening rales hypotension, bradycardia, tachycardia age >75 y | <ul style="list-style-type: none"> age >70 y | |
| ECG | <ul style="list-style-type: none"> angina at rest with transient ST-segment changes >0.05 mV bundle-branch block, new or presumed new sustained ventricular tachycardia | <ul style="list-style-type: none"> T-wave inversions ≥0.2 mV pathological Q waves | <ul style="list-style-type: none"> normal or unchanged ECG during an episode of chest discomfort |
| Cardiac markers | <ul style="list-style-type: none"> elevated troponin | <ul style="list-style-type: none"> normal troponin | <ul style="list-style-type: none"> normal troponin |

Risk of 30-day MACCE in low-likelihood patients is < 5% (AHA Statement. Circ 2010)

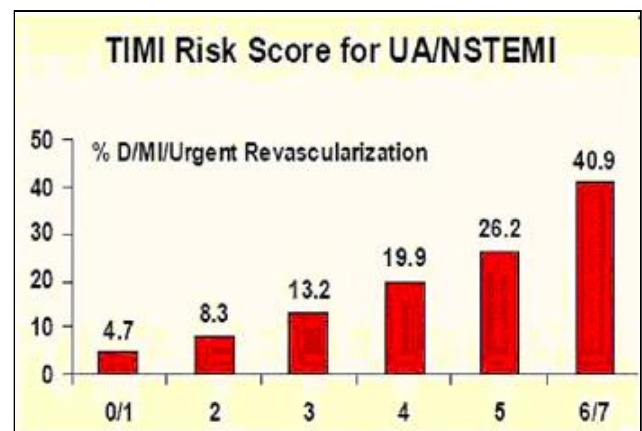
- 30-day MACCE risk in low-likelihood patients was 2.5% using AHCP criteria – above, without markers (Medicine, 2009).

Use TIMI risk score to further assess risk

TIMI risk score:

- age >65 years
- 3 or more risk factors for atherosclerosis
- known coronary artery disease
- 2 or more episodes of anginal chest pain in the preceding 24 hours
- Aspirin use in the preceding 7 days
- ST-segment deviation of ≥ 0.05 mV
- elevated troponin

To calculate the TIMI score, sum the number of positive variables (0–7)



- the incidence of 30-day MACCE in the lowest risk stratum (TIMI score 0) was 1.8%
- The TIMI (Thrombolysis in MI) risk score was developed in high-risk patients with ACS to indicate prognosis and is not intended to establish a diagnosis in a low-risk heterogeneous population of patients presenting with chest pain and no objective evidence of ACS (AHA Statement. Circ 2010).
- Although the TIMI risk score is an effective risk stratification tool for patients in the ED with potential ACS, it should not be used as the sole means of determining patient disposition.
(Diagnostic accuracy of the TIMI risk score in patients with chest pain in the ED: a meta-analysis, CMAJ 2010)

Algorithm for risk stratification of patients with unstable angina and NSTEMI

| | non-cardiac chest pain | stable angina | unstable angina | NSTEMI | STEMI |
|-------------------------|------------------------|-----------------|-------------------------------|--------------|-------|
| Clinical finding | atypical pain | exertional pain | rest pain, post-AMI, diabetes | ongoing pain | |
| ECG | negative | | ST-T wave changes | ST elevation | |
| TnT | negative | | | positive | |
| Risk assessment | low probability | low risk | medium - high risk | STEMI | |

Cannon – Circulation 2003

Troponin is considered negative:

(when measured $\geq 6 - 8$ hrs after the onset of chest pain)

| hs TnT Roche | TnI i-STAT | TnI Dade |
|---|-------------------|-------------------|
| < 3 ng/L | < 0.08 mcg/L | < 0.07 mcg/L |
| <i>OR</i> | | |
| hs TnT Roche | TnI i-STAT | TnI Dade |
| ≥ 14 ng/L | ≥ 0.08 mcg/L | ≥ 0.07 mcg/L |
| <i>and</i> not rising on 2 samples measured at least 2 hours apart <i>and</i> in context of alternate etiology for elevated troponin | | |

Consider discharge of patients with low risk of adverse outcomes if all of the following are met:

- no recurrent chest pain
- no ECG changes
- negative troponin measured six (6) hrs after the onset of chest pain

For patients with intermediate risk of adverse outcomes (and/or a TIMI risk score ≥ 1), consider the need of admission or a consult for an accelerated diagnostic protocol (such as stress testing to be performed prior to discharge or within 72 hours as an outpatient).

Each centre may need to develop local resources to accomplish an accelerated diagnostic protocol.

See Appendix B: WRHA algorithm for the management of patients with suspected ACS in the ED

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Appendix A

Differential Diagnosis of Elevated Troponin

Table 1 Examples of reported elevations of cardiac troponin

| | | |
|---|---|--|
| Primary ischaemic cardiac injury | | |
| Thrombotic coronary artery occlusion caused by platelets/fibrin | ST elevation MI Non-ST elevation MI (previously non-Q wave AMI plus troponin positive unstable angina) | |
| Secondary ischaemic cardiac injury | | |
| Coronary intervention | Primary PTCA | Distal embolisation from clot or atheroma; side branch occlusion |
| | Elective PTCA | Distal embolisation from atheroma or debris; side branch occlusion |
| | CABG | Global ischaemia from inadequate perfusion, myocardial cell protection or anoxia |
| Sympathomimetics | Cocaine Catecholamine storm | Head injury, stroke, intracerebral bleed |
| Pulmonary embolus | Presumed right heart strain or hypoxia | |
| Coronary artery spasm | Small percentage of patients only | |
| Coronary artery embolisation | Clot Air CABG | |
| Coronary artery inflammation with microvascular occlusion | Vasculitides Connective tissue disease SLE | |
| End stage renal failure | More severe CAD but 50% have normal coronaries | |
| Rhythm disturbances | Prolonged tachyarrhythmia or bradyarrhythmia with IHD | |
| Acute heart failure | Only if caused by IHD | |
| Direct coronary artery trauma | | |
| Extreme endurance exercise | Extreme marathons | Wall motion abnormalities |
| | Extreme training | cTn +ve deaths presumed caused by extreme oxygen debt producing ischaemia |
| Non-ischaemic cardiac injury | | |
| Known causes of myocarditis | Infection | Bacterial Viral |
| | Inflammation | |
| | Auto-immune | Polymyositis Scleroderma Sarcoid |
| | Drugs | Alcohol Chemotherapy |
| | Inflammation | |
| Cardiac trauma | Direct | RTA Stabbing |
| | Cardiac surgery | |
| Metabolic/toxic | Renal failure | |
| | Multiple organ failure | |

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; IHD, ischaemic heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; RTA, road traffic accident; SLE, systemic lupus erythematosus.

Appendix B

WRHA algorithm for the management of patients with suspected ACS in the ED

Algorithm for the Management of Patients with Suspected Acute Coronary Syndrome (ACS) in the Emergency Department

