TROPONIN TESTING FOR DIAGNOSIS OF ACUTE CORONARY SYNDROMES IN WESTERN AUSTRALIAN URBAN PRIMARY CARE

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ABSTRACT

Objective: To examine primary care use of cardiac troponin (cTn) testing for acute coronary syndrome (ACS) diagnosis.

Design: Prospective cohort study.

Setting: General practitioner-initiated cTn tests conducted from 24 September 2009 to 3 September 2010 in Perth, Western Australia.

Participants: 369 patients with samples collected at laboratory community collection centres. Requesting GPs provided the clinical context for testing (124 GPs, response rate 38%). Patient outcomes were obtained from linked data sources for 12 months following the final test. Clinical information and outcomes were compared with data from emergency department patients with ACS symptoms.

Main outcome measures: Cardiovascular risk status, symptoms prompting cTn testing; estimated ACS likelihood and referral decision before and after testing; result turnaround time; hospital presentations, procedures and mortality.

Results: Of the 328 GPs who received a survey request, 124 (37.8%) responded. 122/124 (98.4%) of test results were negative. 71/104 patients (69%) were at high or intermediate risk of ACS based on clinical risk factors. 69/124 patients (55.6%) had typical ischaemic pain and 62/124 patients (50.0%) were tested within 48 h of symptom onset (23.4% within 12 h, with no serial testing). Test results affected GPs' estimation of ACS likelihood ($P < 0.01$) but not referral decisions ($P = 0.23$). 94/355 patients (26.5%) presented to hospital with cardiovascular symptoms or diagnoses during follow-up; 27/355 patients (7.6%) had at least one ACS, 13/255 (3.7%) within 1 month of testing.

Conclusions: GP-initiated cTn testing involves patients at high risk of ACS. ACS and associated adverse outcomes can occur in patients undergoing testing, even when the cTn test result is negative. Potential gaps exist in physicians' understanding of the limitations of cTn testing, and results have minimal influence on their patient management. GPs may benefit from guidance in ordering cTn testing.

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GLOSSARY

AAA	Abdominal aortic aneurysm
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AO	Adverse outcome
AV	Atroventricular
CABG	Coronary artery bypass graft surgery
CASP	Critical Appraisal Skills Programme
CHD	Coronary heart disease
CK	Creatine kinase
Cr	Creatinine
CVS	Cardiovascular
Dx	Diagnosis
ECG	Electrocardiogram
ED	Emergency department
EDDC	Emergency Department Data Collection
eGFR	estimated glomerular filtration rate
GP	General practitioner
HMDC	Hospital Morbidity Data Collection
hsTn	high sensitivity troponin
ICU	Intensive care unit
IQR	Interquartile ratio
LBBB	left bundle branch block
MI	Myocardial infarction
MRDC	Mortality Record Data Collection
NA	Not applicable
NHMRC	National Health and Medical Research Council
NR	Not reported
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
POCT	Point of care testing
RACGP	Royal Australian College of General Practitioners
RCT	randomised controlled trial
SJOG	St John of God
STEMI	ST elevation myocardial infarction
SVT	supraventricular tachycardia
TIMI	Thrombolysis in Myocardial Infarction
TnI	Troponin I
TnT	Troponin T
UA	Unstable angina
URL	upper reference limit
VT	ventricular tachycardia
WADLS	Western Australian Data Linkage service
+ve	Positive
-ve	negative

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STATEMENT OF CANDIDATE CONTRIBUTION

I, Helen Wilcox, hereby declare that:

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Location in thesis: Components located in Methods, Results and Discussion

Further, I declare that:

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or institution and;

to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Student Signature

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Helen Wilcox

23 December 2015

CHAPTER ONE: BACKGROUND

1. ACUTE CORONARY SYNDROMES IN AUSTRALIA

1.1 Acute coronary syndromes: prevalence and burden

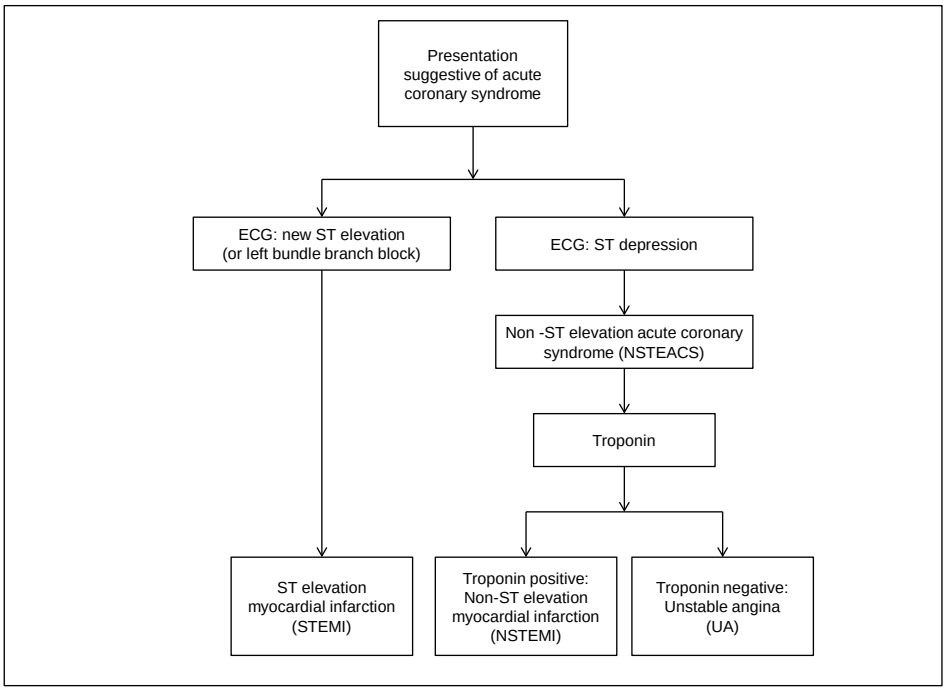
Acute coronary syndromes (ACS) are a life threatening form of coronary heart disease (CHD) and a leading cause of illness and death in Australia, with 69,900 Australians experiencing an ACS in 2011[1]. While mortality due to ACS is declining, due to better control of CHD risk factors and the introduction of new treatments[2-4], at least 10,000 Australians still die each year from ACS[1]. ACS also place a large burden on tertiary hospital resources, with $8 billion of health care expenditure spent annually on inpatient care of the condition[5]. Excluding the diagnosis in a patient with ACS symptoms also commands resources; ACS symptoms are one of the most common reasons for a patient to present to an emergency department (ED), even though 75 to 85% of these patients do not ultimately have a diagnosis of ACS[6].

1.2 ACS: pathogenesis, classification and diagnosis

The spectrum of ACS includes unstable angina (UA), where atherosclerotic plaque rupture leads to arterial occlusion and myocardial ischaemia, and acute myocardial infarction (AMI), where ischaemia progresses to myocardial cell necrosis. Further classification into ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) is based on electrocardiographic (ECG) findings, as shown in Figure 1.

The diagnosis of ACS is suggested by typical clinical features in the presence of CHD risk factors, and confirmed by the presence of supportive ECG and biochemical abnormalities[7-9]. The typical pain of ACS is a severe, retrosternal pressure or heaviness which occurs at rest, is prolonged or recurrent, radiates to the back, neck or arm, and is not relieved by sublingual nitrates[8-10]. Atypical presentations do occur, more commonly in women, the elderly, and diabetics[11,12] and are associated with delayed presentations to medical care and missed diagnoses[13,14]. Such presentations include pain that is unusual in location, being felt in the back, neck, arm, or epigastrium without chest pain, or unusual in nature, being sharp or pleuritic. Atypical presentations also include symptoms of syncope, presyncope, dyspnoea, nausea and vomiting. When present as part of an atypical picture, these symptoms may overshadow the pain or be present in the absence of pain[8-10]. Additionally, it is possible to have no symptoms at all, with the diagnosis of ACS made on ECG or cardiac imaging[11].

Figure 1: Classification of acute coronary syndromes



Adapted from: White HD, Chew DP. Acute myocardial infarction. Lancet. 2008 Aug 16;372(9638)[15]. Figure 2, Classification of acute coronary syndromes, p572.

Multiple prospective studies have shown that clinical features alone are not reliable predictors of ACS[16-18], especially in older patients[19]. Additionally, for the majority of patients with symptoms of ACS, an initial ECG will not show ST segment elevation[20]. Consequently, biochemical investigations are required for diagnosis.

2. TROPONIN

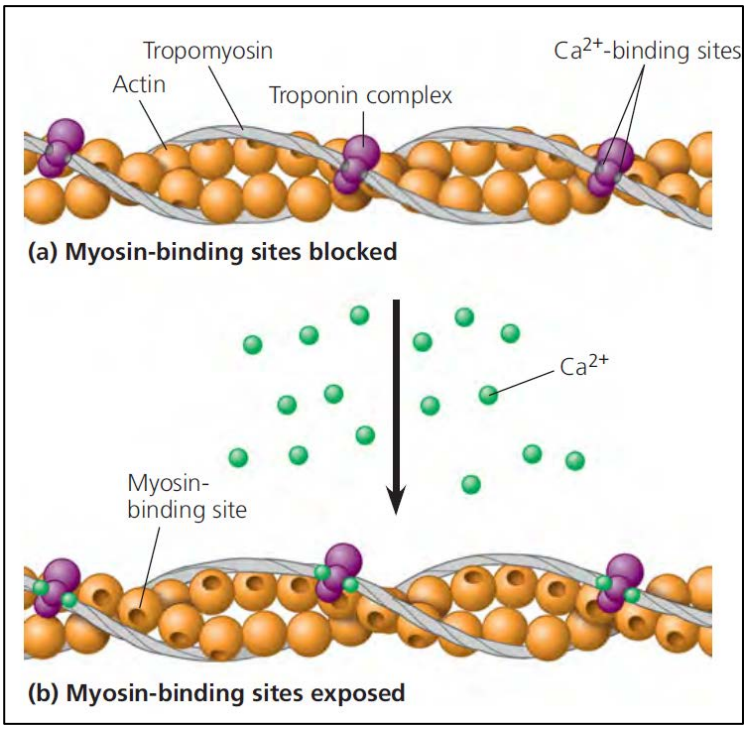
2.1 The troponin complex

Cardiac troponin (cTn) is the main biomarker for the diagnosis of AMI[9,11,21,22]. It is a structural protein complex in skeletal muscle and myocardial cells, comprising the subunits TnT, TnI and TnC[9]. The three subunits are located along the length of actin filaments in myofibrils and play an important regulatory role in the calcium-dependent activation of muscle contraction, as shown in Figure 2.

In ACS, initial myocardial ischaemia results in release of the TnT and TnI subunits into the blood. This release can be detected by biochemical assay as early as two hours after the onset of ischaemia. The magnitude and duration of cTn elevation are proportional to the severity of the myocardial injury[23]. Elevations in TnI levels can persist for seven to ten days in patients with large AMI, probably due to the ongoing release of cTn during myonecrosis and the subsequent remodelling process[24].

Conversely, cTn elevation in smaller infarctions might last several hours only at a time, due to its short circulating half-life and an absence of ongoing necrosis.

Figure 2: The troponin complex.



In a resting muscle fibre, the troponin complex inhibits actin–myosin interaction (a). Calcium release from intracellular stores causes a conformational change in the complex which allows tropomyosin bound along the actin strands to shift position and expose the myosin-binding sites (b). Myosin then binds to actin, actin and myosin slide past each other, and muscle contraction results.

From: Reece JB Campbell NA. Campbell Biology: Australian Version 9th ed: Pearson Education Australia; 2011[25]. Figure 50.29, The role of regulatory proteins and calcium in muscle fiber contraction, p1106.

2.2 Troponin in diagnosis and risk stratification of ACS

The diagnostic criteria for AMI, as defined by the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction[11], comprise the presence of a rise and/or fall in at least one cTn level above the 99th centile for the reference population, combined with symptoms suggestive of ischaemia and findings supportive of ischaemia on ECG, functional imaging and/or angiography (Table 1). A elevated cTn level may be the only feature in addition to history that permits the diagnosis of NSTEMI to be made, as the majority of patients experiencing a NSTEMI will have a normal physical examination, and half will have a normal ECG[8].

The use of a rise or fall in cTn levels, known as a dynamic change, allows detection of new onset AMI with increasing values, and resolving AMI with decreasing values[26]. The minimum change required, and whether an absolute or relative change is preferable, varies between guidelines. A change of at least 50% is recommended by Australian

Table 1: Definition of myocardial infarction

The term acute myocardial infarction (MI) should be used when there is myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following diagnoses meets the criteria for MI:

1. Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn] with at least one value above the 99th percentile upper reference limit [URL]) and with at least one of the following:

- Symptoms of ischaemia
- Development of pathologic Q waves in the electrocardiogram (ECG)
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
- Identification of an intracoronary thrombus by angiography or autopsy
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

2. Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemia ECG changes or new LBBB:

- Death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3. Percutaneous coronary intervention (PCI)-related MI:

- Elevation of biomarker values (cTn is preferred) >5 x 99th percentile URL) in patients with normal baseline values (<99th percentile URL) or a rise of values >20 percent if the baseline values are elevated but stable or falling.
- In addition, either (i) symptoms suggestive of myocardial ischaemia, (ii) new ischaemic ECG changes or new LBBB, (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. Stent thrombosis associated with MI:

- Detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers, with at least one value above the 99th percentile

5. Coronary artery bypass graft surgery (CABG)-associated MI:

- Elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values.
- In addition, either (i) new pathologic Q waves or new LBBB, (ii) angiographic documented new graft or native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Adapted from: Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal Definition of Myocardial Infarction. Circulation 2012 Oct; 126(16): 2020-2035. Definition of myocardial infarction, p2022.

authors[27] (based on reported intra-individual variation of up to 46%) and a change of at least 20% is required elsewhere[11], though a greater relative increase than this is suggested if the initial value is close to the upper limit of normal[28]. The exact algorithm used can vary between laboratories depending on the precision of their assay[29].

In addition to its role in diagnosis, cTn levels contribute to the assessment of risk of adverse outcomes in patients with ACS, with increasing cTn levels correlating with a proportional increase in mortality[9,21,30-32]. Such adverse outcomes are not infrequent, with a 4.5% rate of in-hospital mortality for patients with AMI and a 5.1% rate of recurrent AMI. Figures are even higher in patients with STEMI[33]. Overall, the rate of an in-hospital major adverse cardiac event as a consequence of ACS (such as death, cardiac arrest, recurrent MI, worsening heart failure, major bleeding or stroke)

approaches 30% for STEMI and 20% for NSTEMI[33]. Patients with UA also have an increased risk of cardiac death and subsequent MI despite the lack of myonecrosis[9].

2.3 Troponin in non-ACS contexts

cTn can be elevated in clinical contexts apart from ACS, and elevation in these situations also confers a higher risk of adverse outcomes. Firstly, patients with stable CHD and elevated cTn are at higher risk of major adverse events[34-37]. Additionally, patients with normal coronary arteries on angiography and elevated cTn retain a higher risk of mortality than similar patients with a normal cTn level[26]. The mechanism of increased risk in these settings may be coronary artery vasospasm, embolisation or dissection, or early aggressive antithrombotic therapies removing visible thrombus by the time the vessels are demonstrated angiographically[15,38].

Non-coronary conditions which increase myocardial oxygen requirement or decrease oxygen supply can also cause cTn elevation in the absence of atherosclerosis, as listed in Table 2. In some of these disease states the cTn elevation may be stable and chronic, and use of dynamic cTn levels will help with their differentiation from MI. However, the more acute conditions such as sepsis may also produce a dynamic cTn level due to acute cardiac injury in the absence of MI[39]. The presence of heterophile antibodies in certain individuals and assay calibration errors may also lead to an elevated result[11].

For these reasons, the diagnosis of ACS relies on a supportive clinical picture in addition to cTn elevation, and in the absence of a history suggestive of ACS or of CHD risk factors other causes of the cTn rise should be sought.

Table 2: Non-coronary causes of elevated cTn

Ischaemic	Non-ischaemic	
Non-ACS causes of MI	**Cardiac**	**Systemic**
Hypoxia	Heart failure	Pulmonary embolism
Global ischaemia	Infection (e.g. viral cardiomyopathy)	Anthracycline toxicity
Hypoperfusion	Inflammation (e.g. myocarditis)	Trauma (e.g. chest wall injury)
Cardiothoracic surgery	Trauma (e.g. surgery)	Renal failure
	Ablation procedures	Sepsis
	Malignancy	Stroke
	Stress cardiomyopathy	Subarachnoid haemorrhage
	Infiltrative diseases	

Adapted from: Newby LK, Jesse RL, Babb JD, Christenson RH, De Fer TM, Diamond GA, et al. ACCF 2012 Expert Consensus Document on Practical Clinical Considerations in the Interpretation of Troponin Elevations - A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2012 Dec 11; 60(23): 2427-2463. Figure 1: Conceptual Model for Clinical Distribution of Elevated Troponin

2.4 Delays in cTn testing

Early, rapid diagnosis of ACS is vital[40]. The overall mortality rate for ACS within one month of the event is approximately 50%, with half of these deaths occurring within two hours of the event[10]. Despite this need for early diagnosis of ACS, there are multiple delays inherent in ACS diagnosis using cTn testing. Standard laboratory based cTn testing has been limited by a lack of sensitivity for diagnosis of ACS in the early hours following infarction, with elevation not detectable for four to six hours[8,45]. Consequently, a cTn result is only considered to be sufficiently sensitive when tested at least eight hours after onset of symptoms[27,46].

There are also delays associated with sample collection and transportation to the laboratory. Such delays are minimal for patients who present to hospitals with co-located laboratories, but can be significant when the laboratory is at a distant site. Once the sample has been transported to the laboratory, sample preparation, analysis and result reporting need to occur before a result is available[47]. For patients with possible ACS, the time taken for this sequence of events should be no more than 60 minutes, according to Australian and international guidelines[27,48].

Point of care testing (POCT) devices using cTn testing have much shorter turn-around times than laboratory based testing regimes. POCT results are available within 15 to 26 minutes, due to elimination of transportation time and minimal sample preparation time, as most devices use whole blood[26]. A POCT strategy might alleviate some issues with delay and has been shown in the ED setting to reduce ED length of stay for patients with a normal cTn result, when used in conjunction with clinical risk scoring systems[6,49-51]. The downside of POCT is the limited sensitivity of the assays, with some assays having lower accuracy than laboratory based tests[52,53]. Additionally, analytical variability exists between POCT cTn assays, posing a risk of misinterpretation of results if the performance of the particular assay used is not taken into consideration.

2.5 Monitoring during cTn testing

Until a cTn result is known to be negative, major Australian and international guidelines recommend continuous cardiac monitoring for patients with suspected ACS[7,27,54]. The rationale for monitoring includes the need to identify evolving ECG changes that would indicate eligibility for reperfusion. In addition, abnormalities of the ST segment on ECG also provide prognostic information, being independently associated with an increased risk of adverse outcomes[55]. Cardiac monitoring may also identify complications of evolving infarction such as cardiac arrhythmias and hemodynamic instability.

2.6 Highly sensitive troponin in ACS diagnosis

Recently, highly sensitive troponin (hsTn) assays have been developed that that have 10 to 100 fold lower limit of detection of ACS compared with standard methods of testing[56,57]. This improved sensitivity lowers morbidity and mortality rates for ACS patients with detectable hsTn levels, presumably due to improved access to reperfusion therapy with earlier diagnosis[58]. When incorporated into established risk stratification scoring systems, hsTn can reliably rule out MI as early as six hours after symptom onset[27], resulting in shorter emergency department transition times for those with normal hsTn levels who can safely be designated as being at low risk of adverse outcomes[57,59-61]. This approach is also cost effective when compared with testing in the standard eight hour time period[62]. hsTn testing early after presentation is not yet included in National Heart Foundation guidelines[27] but its inclusion is predicted in the future[63,64].

The lower limit of detection of hsTn assays comes at the cost of reduced specificity, with measurable concentrations of hsTn detectable in significant numbers of asymptomatic individuals[28,65]. Conventional assays have been shown to detect circulating hsTn in 0.7% of the community population without known CHD[66], with newer hsTn assays increasing this to 50-66% of the population aged over 65[37,67] and up to 80% of a younger age group[68]. In addition, other factors affect the interpretation of hsTn results, such as individual biological variation in cTn levels over time[26], the heterogeneity of assays available[26,69,70] and whether an appropriate reference range is that of a younger healthy population or that of an aged matched population[71].
As a result, the use of hsTn continues to be a topic of debate[28,72-77].

3. TROPONIN AND ACS IN AUSTRALIAN GENERAL PRACTICE

3.1 Clinical diagnosis of ACS in general practice

The challenge of ACS diagnosis exists in primary care as well as in the tertiary setting. In Australia, primary care presentations with symptoms associated with ACS such as chest pain are common, with 15% of patients experiencing an acute MI first contacting their general practitioner with their symptoms[78]. The number of such consultations is substantial: there are over 126 million general practice all cause encounters each year in Australia and at least 1% of these presentations involve chest pain as a reason for the encounter[79]. The Bettering the Evaluation And Care of Health (BEACH) Program[80] reports that:

i. 8% of patients seeking GP care have established CHD with a high risk of ACS;
ii. 3.6% have a history of acute myocardial infarction in the last three years, and;
iii. 60% of patients in general practice have at least one CHD risk factor.

The typical ACS presentation of acute prolonged or recurrent central chest pain with unequivocal ischaemic changes on ECG in a patient with multiple CHD risk factors is well known to GPs. The decision to refer to hospital for a definitive diagnosis, rather than proceed with outpatient investigations, is usually clear in these patients[81]. In less typical presentations, ACS diagnosis in primary care is not always straightforward, as there are limitations to the clinical tools that can be used within the consultation to assess the risk of ACS. Evidence from systematic reviews shows that in the pre-hospital population, signs and symptoms alone are neither sensitive nor specific for the diagnosis of ACS[81-84]. Additionally, risk stratification tools such as the Thrombolysis in Myocardial Infarction (TIMI)[85] and the Global Registry of Acute Coronary Events (GRACE)[86] scores were developed using secondary care populations which limit their generalisability to patients in primary care.

GPs seem to use a combination of strategies in diagnosis of serious illness and in managing diagnostic uncertainty: their initial impression or “gut feeling”, the combination of clinical factors which are of limited value in isolation but highly sensitive when applied together, and development of a safety netting strategy[87,88]. Attempts to formalise this approach have led to the development of clinical prediction rules for ACS in the general practice setting. These report negative predictive values of 94.8% to 97.9%[89-91] for the diagnosis of ACS. However, guidance directed at Australian primary care doctors suggest their validation has been limited and their accuracy cannot be relied upon[63]. The inclusion of ECG findings does not always improve accuracy of

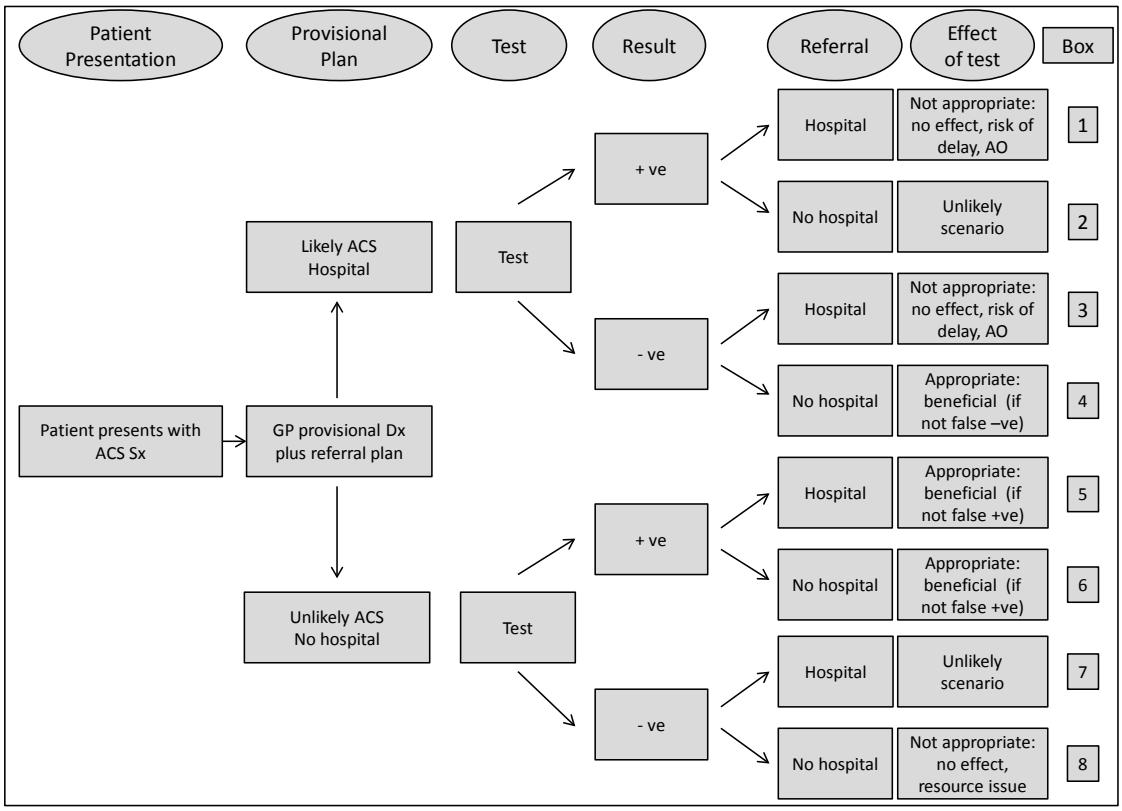
diagnosis. GPs do not always interpret key findings on ECGs correctly, with estimates of correct interpretation ranging from 59 to 70%[92,93].

3.2 Benefits and limitations of cTn testing in general practice

Given the limitations of the above clinical tools in primary care, cTn testing in primary care should theoretically improve accuracy of diagnosis of ACS. Even so, cTn interpretation in primary care can be as complex as in the hospital setting. Appropriate use requires an understanding of its sensitivity and specificity as well as consideration of technical and practical issues.

According to the American College of Cardiology, *"the concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics"*[94]. Figure 3 describes the potential effects of differing cTn test results on GP management decisions.

Figure 3: Potential effects of GP-initiated cTn test results on management



+ve = positive, –ve = negative, AO = adverse outcome, Dx = diagnosis, hospital = emergency department evaluation.

Only some of the decisions in Figure 3 can be considered appropriate. When this definition is applied to cTn, appropriate use of cTn should:

(a) avoid the risk of adverse outcomes of ACS which may occur if cTn testing delays hospital referral (Boxes 1 and 3)

(b) benefit the patient by excluding ACS in those at low risk of ACS (Box 4)

(c) benefit the patient by allowing diagnosis of ACS and expedited referral to hospital where ACS was initially not suspected due to atypical presenting features (Box 5)

(d) benefit the patient by providing valuable diagnostic and prognostic information in patients not suitable for admission, such as those in residential care or with significant comorbidities (Box 6)

(e) be interpreted with an understanding of specificity and sensitivity (Boxes 4, 5 and 6)

(f) conserve emergency department resources by avoiding attendance at hospital emergency departments [95] (Box 8). It is worth noting that use in this context may not translate to a substantial conservation of ED resources, as the total burden of GP patients in ED is reportedly overestimated[96].

Multiple authors have expressed concern that cTn is used inappropriately by GPs. These concerns relate to delay in hospital referral, an over-interpretation of positive results and an overreliance on negative results[21,94-99].

3.2.1 Delay in hospital referral

The first situation where cTn use may be inappropriate is when hospital referral is required regardless of test outcome. In this context, cTn testing may cause unnecessary delay (Figure 3, Boxes 1 and 3). Patients with ACS whose first medical contact is a community physician rather than emergency services experience greater pre-hospital delay[14,97-99] especially if presenting with atypical symptoms[100,101]. There is a risk of misdiagnosis[102], greater haemodynamic instability[103] and delayed access to thrombolysis[104,105] as well as increased mortality in these patients[106].

Adverse cardiac events of the ACS may occur during this period of delay, and urban GPs do not always have access to the equipment and other resources needed to detect and manage complications such as cardiac arrhythmias. Access to continuous ECG monitoring is limited to the tertiary inpatient setting[8,9] and is not routinely required in urban primary care. Accredited GP practices in Australia do not need an ECG machine for accreditation purposes, nor are they required to have an onsite defibrillator for management of cardiac arrhythmias[107].

Theoretically, point of care troponin testing (POCT) in primary care, as used in the ED setting, may go some way towards resolving the issue of delay in ACS diagnosis. Such a strategy would require validation on an Australian primary care population, as the prevalence of ACS is lower than in the ED setting, thereby affecting the predictive value of the test[108]. There are also problems with POCT assay standardization, staff training and a lack of Medicare subsidies, which limit use in primary care[52,109-111].

It is worth noting that if patients present to GPs late in the course of the ACS (after the 48 hour period of maximum risk for short term adverse outcomes) there may be no increase in adverse outcomes. In late-presenting patients in whom invasive management is less time-critical, delay due to cTn testing may not be relevant.

3.2.2 Over-interpretation of positive results

The type of chest pain seen in primary care differs from that seen in ED. The prevalence of ACS in primary care populations, and consequently the pretest probability of ACS, is lower than in secondary care. Pain due to a musculoskeletal cause is the most common diagnosis for primary care chest pain, with only 10-34% of presentations having CHD as their cause[112-114].

Additionally, non-coronary conditions that cause detectable cTn levels are prevalent in general practice and falsely positive test results are therefore likely[115]. Increasing use of hsTn will add to uncertainty, with many primary care patients returning elevated hsTn results having non-ACS conditions that do not warrant ED attendance. Detectable hsTn values may be solely a result of recent exercise or increasing age, with positive results in the very old being the norm[71]. Without laboratory provision of age-related cut-off values, such results may trigger unnecessary intervention.

3.2.3 Overreliance on negative results

Recent Australian literature has suggested that GPs have incomplete understanding of the need for serial cTn testing, as serial testing is underutilised[95]. Even with serial testing, negative results in the context of chest pain do not obviate the need for second-line evaluation. ED patients with chest pain, normal ECGs and normal cTn levels remain at risk of adverse outcomes, with an outcome of ACS, urgent coronary revascularisation or death of cardiac origin in 1 of 40 such cases at 30 days after an episode of chest pain, and in 1 of 14 cases at 6 months[116].

A further complication for GPs is the variability of cTn assays. Available tests have different sensitivities and use differing reference populations to define the cutoff value at the 99th percentile[52,117]. This is particularly relevant when comparing serial results

from different laboratories, as a significant rise or fall in cTn values may not be appreciated if GPs use multiple laboratories for one patient episode.

3.3 Practical issues in cTn testing in primary care

There are practical implications of cTn testing in primary care. While a request for cardiac biomarkers is regarded as urgent by the laboratory, it may be some hours before a result is available, potentially only after the GP's surgery is closed. Difficulties then arise if the requesting doctor is not contactable, as it falls to the pathologist, a locum service or a colleague of the requesting GP to contact the patient and arrange further investigation. A 2005 Coronial Inquest examined a patient death following a cTn test ordered in general practice that was not attended to in a timely manner due to the result being notified after office hours[118]. The conclusion was that there was a failure of systems in place at the medical centre for the patient's test results to be accessed, assessed and appropriate action taken[118]. While systems can be established within group practices to allow successful follow up of abnormal life threatening results outside opening hours, and accreditation of general practices requires after hours cover to be available[107], not all practices may consistently operate to this standard.

Pathology providers across Australia recognize the potential risks to patients in undergoing cTn testing in primary care. Historically, some Queensland laboratory collection centres will not collect blood samples for outpatient cTn testing, referring patients to ED instead (Dr Narelle Hadlow, pers.comm.). In Western Australia major pathology providers have stressed the need to exercise caution in ordering cTn on community patients, reminding GPs of the delays inherent in non-hospital cTn testing and stating that in cases with a high index of suspicion it may be more appropriate to refer patients to a tertiary care facility for assessment[119-121].

3.4 Estimates of frequency of cTn testing in primary care

Despite these limitations, cTn testing for the diagnosis of ACS remains available for use by GPs in the primary care setting under the Australian Medicare Benefits Schedule[122]. Across Australia in 2012, 481,322 cTn tests were ordered outside public hospitals[123] at a cost to Medicare of over $10 million. While this figure includes tests performed in private hospital and by specialists other than GPs, the majority are likely to have been requested by GPs, given that pathology tests requested by GPs account for 70% of Medicare pathology services[124].

4. GUIDELINES FOR PRIMARY CARE USE OF TROPONIN

4.1 Australian guidelines

Recent reviews have made suggestions on the use of cTn testing in general practice[63,95]. Authors suggest that a single cTn test may be used in general practice to exclude the possibility of AMI in asymptomatic patients whose symptoms resolved at least 12 hours prior to the test, so long as they have no features placing them at high risk of ACS, and a normal ECG. Serial tests are advised in patients presenting within 12 hours of symptom onset who are at low risk of ACS and/or have atypical symptoms. Despite this, there is no formal guideline addressing appropriate use of cTn testing directed at Australian GPs from the Heart Foundation, the Royal Australian College of General Practitioners (RACGP) or the Royal College of Pathologists Australasia (RCPA). The RACGP-supported point of care database – Dynamed[125]– does not address how to use cTn in primary care as opposed to the hospital setting. A recent review in the RACGP's own journal[126] advises cTn testing as part of the investigation of possible ACS but makes no mention of the attendant risks and limitations. The RCPA Manual speaks in general terms of the complementary nature of laboratory investigations for diagnosis of MI but does not discuss their application in primary care[127]. Locally, the Western Australian Health Department ACS Model of Care acknowledges that some patients with possible ACS may present to GPs but it does not advise GPs on management other than hospital referral[40].

4.2 International guidelines

In the international literature, few of the major European or United States guidelines on ACS contain recommendations to GPs about cTn testing. Authors of such guidelines include the Scottish Intercollegiate Guidelines Network[128], the National Institute for Health and Care Excellence[129], the European Society of Cardiology[7], the National Academy of Clinical Biochemistry and the American College of Cardiology Foundation[130]. The Guidance on chest pain of recent onset from the National Institute for Health and Care Excellence[129] advises obtaining a blood cTn level only if a recent ACS is suspected in people whose last episode of chest pain was more than 72 hours ago and who have no complications of ACS such as pulmonary oedema, and that clinical judgement should be used to decide whether referral is necessary and how urgent this should be.

Only one other guideline is directed at GPs to inform safe practice in cTn testing, produced by NHS Quality Improvement Scotland[131]. It recommends that cTn should not

be measured in primary care, except where the clinical episode of pain is between 24 and 72 hours earlier, or where the patient has other medical conditions precluding admission to hospital. This advice is at odds with that of the Australian authors[63,95]. Other international guidelines for GPs to use in diagnosis of chest pain intentionally exclude cTn, citing its perceived limited value in primary care[89].

5. CONCLUSION

In summary, ACS is common and carries a high risk of death and adverse outcomes. While cTn testing is central to the diagnosis of ACS, there are a number of pitfalls and practical considerations in its interpretation. POCT and the use of high sensitivity cTn do not entirely resolve these issues. Urban GPs frequently encounter patients with symptoms suggestive of ACS, and cTn testing is frequently performed in the community to investigate these presentations. However, urban general practice is not structured to minimise delays in cTn testing and does not have the capabilities to detect and manage complications of ACS. It has also been suggested that GPs have incomplete knowledge of the limitations of cTn testing.

It is not known if the above issues with GP-initiated cTn testing actually result in adverse outcomes of ACS. If the test is ordered often in an unsupported setting on patients at high risk of ACS, adverse outcomes may eventually occur. Alternatively, cTn testing in primary care might be beneficial if it permits diagnosis of ACS that would have otherwise been overlooked on clinical grounds. Additionally, if GP-initiated cTn testing rules out ACS, use of the test might alter GP management, reduce the number of referrals to ED and so conserve ED resources.

This study aims to explore these issues by examining the use of cTn testing for ACS diagnosis in primary care. The study will describe a population of patients who undergo cTn testing in general practice and assess whether they have a lower risk of ACS than those who present directly to ED. GP knowledge of cTn testing's use and limitations and the influence of cTn testing on GPs' diagnosis and management will be explored. Finally, the outcomes of patients who undergo cTn testing in primary care will be examined.

AIMS

1. To **describe** the clinical characteristics of a patient group who undergo cTn testing in primary care, specifically:
   i. The nature and duration of presenting symptoms;
   ii. The coronary risk status of the patient prior to testing;
   iii. An assessment of whether patients in the group are clinically different and at a lower risk of ACS to those who present directly to emergency departments with ACS symptoms.

2. To examine GPs' **knowledge** of cTn's use and limitations of the test in general practice, specifically the risk of false positive and negative results.

3. To assess the **effect of the test result** on the GP's:
   i. **estimation of likelihood** of ACS prior to test ordering and following receipt of results;
   ii. **management** of that patient prior to test ordering and following receipt of results.

4. To document the **outcomes** of patients in this group who underwent cTn testing in general practice. Specific outcomes sought would be:
   i. Hospital presentation or admission with cardiac symptoms or diagnoses;
   ii. Hospital procedures relating to ACS;
   iii. Occurrence of significant events representing adverse outcomes of ACS;
   iv. Delay in diagnosis of ACS.

HYPOTHESES

1. Patients undergoing cTn testing in primary care are clinically different to those who present directly to emergency departments

2. CTn testing in primary care does influence a GP's management of their patient.

3. CTn testing in primary care is associated with adverse patient outcomes.

CHAPTER TWO: TROPONIN TESTING FOR ACUTE CORONARY SYNDROME IN PRIMARY CARE - A SYSTEMATIC REVIEW

1. RATIONALE

GPs have a key role in assessment of patients with symptoms suggestive of ACS. They must integrate clinical findings and investigation results, which may include cTn, in order to determine the need for hospital referral or to exclude ACS[7-9]. Because cTn interpretation is complex, GPs require an understanding of its sensitivity and specificity as well as of its technical and practical considerations in order to use cTn testing appropriately. It is important to know if GPs have this understanding and are able to use cTn appropriately, as inappropriate use could place patients at risk of adverse outcomes.

2. OBJECTIVES

1. To describe the outcomes of patients who presented with ACS symptoms in general practice and had cTn testing performed;
2. To examine GPs' understanding of cTn testing's limitations, and the influence of cTn test result on GP management.

3. METHODS

3.1 Theoretical and methodological approach

The standard methodology for systematic reviews was followed according to guidelines published by the National Health and Medical Research Council[132] and the York Centre for Reviews and Dissemination[133]. The development of a theoretical model to assist with the search strategy and the process for narrative synthesis were guided by the ESRC Methods Program Guidance on the Conduct of Narrative Synthesis for Systematic Reviews[134]. Findings are reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[135,136]. Methods of the analysis were pre-specified and documented in a protocol.

3.2 Eligibility criteria

Table 3 presents the inclusion criteria for the review with reference to standardised data definitions used in Australasian ACS research[137].

Table 3: Eligibility criteria for systematic review

Criteria	Included	Excluded
Participant related:		
Definition of disease/condition	1.ACS and synonyms (Acute myocardial infarction, STEMI, NSTEMI, Unstable angina) 2.Ischaemic heart disease	Non-ischaemic heart failure.
Presentation (Note 1)	Symptom(s) of ACS without a previous ACS diagnosis for this episode of symptoms	No symptoms; cTn used as screening test
Demographic factors	All	None
Setting	Urban primary care	1.Wholly presenting to Emergency department 2.Hospital inpatient at time of testing 3.Populations where time taken to perform test is greater than time taken to present to inpatient setting 4.Test ordered by paramedical services
Intervention related:		
Intervention	1. cTn (including TnI, TnT, hsTn) requested by GP 2. Laboratory or point of care testing	ECG only
Control	No cTn test ordered by GP	
Outcome related:		
Survival (Note 2)	1. Death from cardiovascular cause 2. Death of uncertain cause 3. Cardiac arrest	
Adverse events (Note 3)	1. Cardiogenic shock 2. Ventricular arrhythmia within 48 hours 3. High degree AV block within 48 hours 4. AMI within 30 days diagnosed on ECG 5. STEMI within 30 days diagnosed on ECG 6. NSTEMI within 30 days diagnosed on ECG 7.AMI plus NO Emergency revascularization procedure NOR Urgent revascularization procedure NOR thrombolysis	
Delay (Note 4)	Delay greater than 30 minutes or 90 minutes depending on time from medical contact to PCI	
Beneficial effects (Note 5)	Late or atypical presentation PLUS any of: 1.ACS or synonyms 2.Emergency revascularization procedure 3.Urgent revascularization procedure 4.Elective revascularization procedure	

Note 1: Symptoms consistent with possible ACS include acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without an apparent non-cardiac source. Atypical presentations of ACS may include back pain, sharp and pleuritic pain and the following symptoms in the absence of pain: dyspnoea, palpitations, nausea, vomiting, diaphoresis, fatigue, syncope or presyncope[137].

Note 2: The relevant time period in survival is the first 48 hours where inpatient monitoring is indicated.

Note 3: Australian consensus guidelines list of important outcomes to monitor in patients with ACS[137]. The relevant time period is the first 30 days after ACS where there is the greatest risk of progression to MI or the development of recurrent MI or death. Following this phase most patients with ACS resume a clinical course similar to that of patients with stable coronary disease[9,138].

Note 4: In general, the maximum acceptable delay from first medical contact to balloon inflation (marking the commencement of PCI) is 60 minutes if a patient presents within 1 hour of symptom onset; or 90 minutes if a patient presents within 1-12 hours of symptom onset. PCI is still considered in those who present more than 12 hours after onset of symptoms if there are ongoing symptoms, haemodynamic instability or a contraindication to fibrinolysis.[8]

Note 5: Late presentation is defined as greater than 48 hours after symptom onset as this is window where inpatient monitoring is indicated.

3.3 Information sources

An initial search was conducted for existing or ongoing reviews of cTn testing in primary care in the following registers of systematic reviews:

1. Database of Abstracts of Reviews of Effects (DARE)[139]
2. Cochrane Database of Systematic Reviews (CDSR)[140]
3. National Institute for Health and Clinical Excellence (NICE)[141]
4. NIHR Health Technology Assessment (NIHR HTA)[142]
5. National Guidelines Clearinghouse (NGC)[143]
6. Scottish Intercollegiate Guidelines Network (SIGN)[144]

No existing systematic reviews were identified in this process.

3.4 Search

A search strategy was then designed in consultation with a medical librarian. The search involved the following database list:

1. Web of Science
2. MEDLINE
3. Evidence Based Medicine Reviews Multifile Database:
    3.1. ACP Journal Club
    3.2. Database of Abstracts of Reviews of Effects
    3.3. Cochrane Central Register of Controlled Trials
    3.4. Health Technology Assessment
    3.5. Cochrane Database of Systematic Reviews
    3.6. National Health Service Economic Evaluation
    3.7. Cochrane Methodology Register
4. Embase
5. Scopus
6. TRIP

Table 4 shows the final list of potential search terms.

Table 4: List of terms used in electronic search strategy

ACS symptoms	Pre-hospital care	Troponin	General Practice	Delay
Cardiovascular diseases	Emergency Medical Services	Point of care testing	General Practitioner	Diagnostic Errors
Acute Coronary Syndrome	Pre-hospital Care	Troponin I	Primary Health Care	Misdiagnosis
Coronary Artery Disease	Resuscitation	Troponin T	Family Physician	Time Factors
Coronary Disease		Troponin	Family Practice	Delay
Coronary Thrombosis			General Practice	
Unstable Angina			Primary Care	
Myocardial Infarction				
Angina Pectoris				
Chest Pain				
Arrhythmia				
Fatigue				
Syncope				

The search strategy for relevant papers was customised for each database using a combination of MeSH and free text non-indexed keywords including truncations and wildcards. The search was piloted with the aim of obtaining four papers known to be relevant for the review. The strategy was refined following this initial exercise.

Related links, citing articles and reference lists for key papers were reviewed. Hand-searching was performed in full text journals in the fields of primary care, cardiology, emergency medicine and pathology. Reports from the Australian Institute of Health and Welfare and the Heart Foundation were assessed for relevance. Grey literature sources listed in the Cochrane Handbook were reviewed. Reference tracking and citation tracking using Scopus, Medline, Web of Science and Google Scholar were performed to complete the search.

The search was limited from January 1990 to December 2013, 1990 being the first year that the use of the cTn assay in diagnosis of ACS was described. No language or document format restrictions were applied. The full search strategy for each database, lists of journals hand-searched and grey literature sources are included as an Appendix.

3.5 Study selection

A flow diagram of the study selection process is shown in Figure 4 (see Section 4.1 Study selection). Search results were merged and duplicates removed using EndNote X6 reference management software[145]. Each title and abstract was examined by one researcher (HW) to exclude irrelevant reports. Full text versions of remaining reports were examined in full using the eligibility criteria in Table 3. Reports of unclear significance were discussed with the other researcher (JE) and consensus obtained on inclusion in the review.

3.6 Data collection process

A data extraction form was designed for the specific purpose of the review. The list of items included was derived from the Cochrane Handbook of Systematic Reviews of Interventions[146]. It was piloted and refined further using two papers that were highly likely to be included and two of uncertain relevance.

3.7 Data items

Data were extracted from each included paper on:

1. Source (lead author, title, year published, citation)
2. Aims
3. Methods (design, setting, duration, year performed, study inclusion and exclusion criteria)
4. Participant characteristics - patients (number, age, sex, symptoms, timing of presentation, diagnosis)
5. Participant characteristics – GPs (number)
6. Intervention (Troponin T or I, laboratory based or POCT, number of tests performed, timing of tests relative to symptom onset)
7. Quality assessment
8. Results of cTn test
9. Patient outcomes (hospital referral, hospital admission, survival, adverse events, delay, beneficial effects)
10. Management before and after test result

3.8 Risk of bias in individual studies

All included studies were assessed for quality according to the Critical Appraisal Skills Programme UK (CASP) checklist for cohort or qualitative research as applicable to design of that study[147]. The NHMRC criteria for quality appraisal[132] were also considered in the formulation of results. Results of this assessment are summarised in Table 6.

Due to the small volume of relevant studies retrieved, no studies were excluded on methodological grounds. A grading system was used to rank the methodological quality and relevance of each study according to the structured appraisal approach described by Dixon-Woods[148] and endorsed by the Cochrane Handbook[146].

A search was undertaken for any published protocols for each study. None were found.

3.9 Synthesis of results

Given the diverse evidence types in the included papers a narrative synthesis approach was used[148] employing the framework described in the UK ERSC Guidance on the Conduct of Narrative Synthesis in Systematic Reviews[134]. Steps in the framework include:

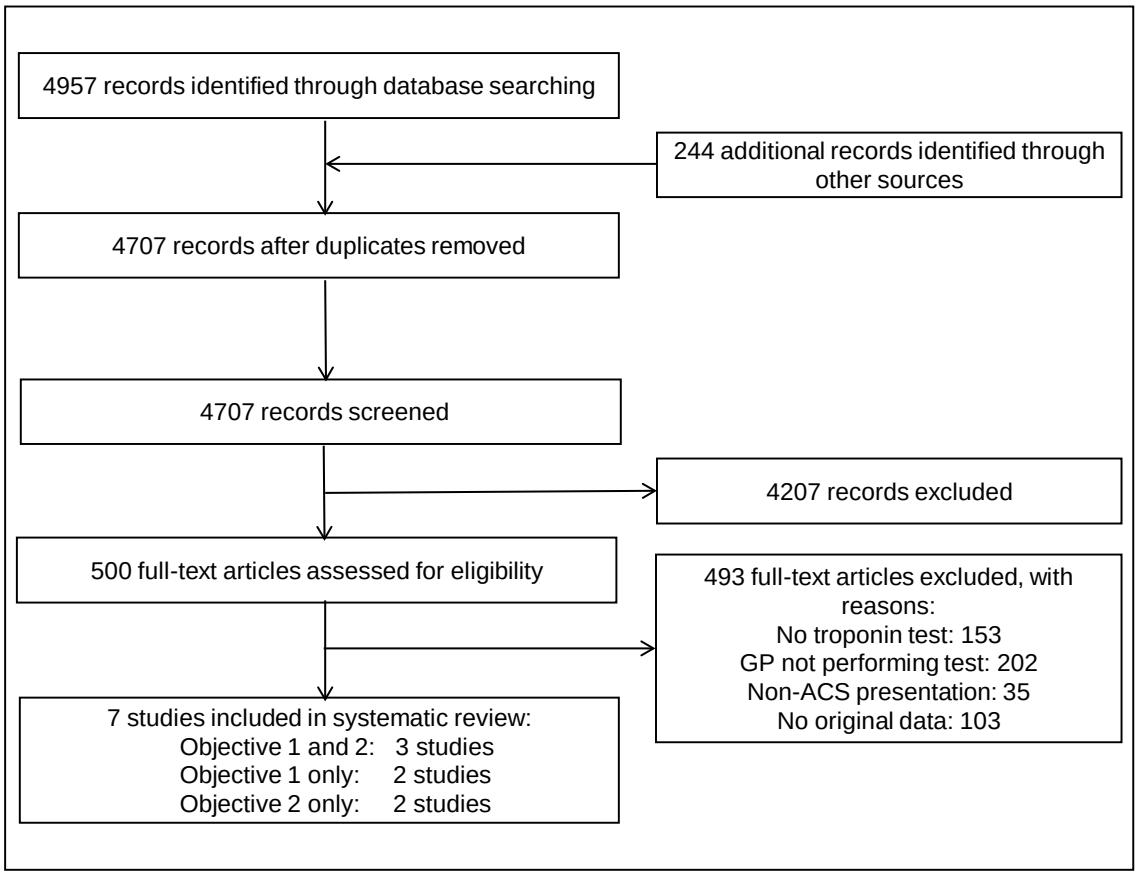
1. Developing a theoretical framework
2. Developing a preliminary synthesis of findings of included studies
3. Exploring relationships within and between studies
4. Assessing the robustness of the synthesis.

4. RESULTS

4.1 Study selection

Figure 4 describes the study selection process. A total of seven studies were identified for inclusion in the review. There was marked heterogeneity of these studies which limited the ability to undertake meta-analysis, prompting a narrative synthesis approach to analysis.

Figure 4: Flow diagram of study selection process.



A description of included studies is provided in Table 5. Table 6 presents an assessment of the risk of bias in each study.

Table 5: List of included studies

Study	Aim	Method				Participants					Intervention	Follow up
		Country	Setting	Source of outcome information	Exclusion criteria	Number	Age	Sex	Symptom	Number of GPs	Country	
Aldous (2012)	To assess utilisation of troponin testing in the community	New Zealand (NZ)	Laboratory audit	National health events database	Admission to hospitals outside NZ	2662 tests 2575 patients	63 (51-74)	M 45%	NR	NR	Laboratory based Troponin I Standard sensitivity	6 months
Mann (2006)	To document clinical circumstances and medical outcomes where troponin is used to assess chest pain in general practice	New Zealand	Laboratory audit	GP survey	Test added by laboratory and not requested by GP	433 tests 278 tests with survey data Number of patients NR	NR	NR	Chest pain in 245/278 surveys NR in 23/278 surveys	201	Laboratory based Troponin T Standard sensitivity	3 days
Planer (2005)	To evaluate the diagnostic value of troponin T kit testing in the community setting for the assessment of patients presenting with chest pain	Israel	GP clinics	GP diagnosis prior to test result, emergency physician diagnosis for positive tests, patient phone call follow up 2 months after study entry for all test results.	Age <30 years <20 consecutive mins chest pain Interval symptom onset to presentation <8hours or >6days Renal failure, ECG ST elevation ACS or revascularisation within previous 2 weeks	349 tests 349 patients	59 (+/-14)	M 58%	Chest pain in 104/349 patients	NR	POCT Troponin T	2 months
Tanner (2006)	To study behaviour of patients prior to admission to hospital with symptoms of ACS	New Zealand	Coronary care unit inpatients	Patient recall of time intervals	Patients transferred from other centres Language barrier Patients discharged or died prior to interview	11 tests 100 patients	65 (32-88)	M 69%	Chest pain in 91/100 patients	NA	Laboratory based Troponin T Standard sensitivity	NR – data obtained during hospital admission
Tomonaga (2011)	To analyse the diagnostic accuracy of POCT in general practice for diagnosis of ACS, heart failure and thromboembolic events	Switzerland	GP clinics	GP requesting test	Interval symptom onset to presentation >5days Anticoagulant therapy Renal failure Cancer therapy Practices within 8-10km of Zurich where rapid laboratory troponin results available	147 tests 151 controls	65 (+/-16)	M 58%	Chest pain in195/369 patients	79	POCT Troponin T	3 weeks

Table 5(cont'd.): List of included studies

Study	Aim	Method				Participants					Intervention	Follow up
		Country	Setting	Source of outcome information	Exclusion criteria	Number	Age	Sex	Symptoms	Number of GPs		
Law (2006)	To investigate GP knowledge and use of troponin testing in primary healthcare	Wellington region, New Zealand	GP clinics	GP survey	NR	NA	NA	NA	NA	299 30 GPs rural	NA	NA
Sodi (2007)	To undertake an audit of troponin tests requested by GPs with a view to developing an informed strategy regarding assay provision and reporting of results	Liverpool, United Kingdom	Laboratory audit	GP telephone interview	NR	18 tests 16 tests with interview data	NR	NR	Chest pain 9/16	16	Laboratory based Troponin T Standard sensitivity	1 week
Tandjung (2012)	To survey infrastructure and the performance in diagnostics and therapy of cardiologists and GPs who encounter ACS in an outpatient setting	Switzerland	GP and cardio-logist clinics	Postal survey	NR	NA	NA	NA	NA	467 GPs 35 cardio-logists	NA	NA

GP = general practitioner; NR = not recorded; POCT = point of care troponin; ECG = electrocardiogram; ACS = acute coronary syndrome; NA = not applicable

Table 6: Assessment of risk of bias in included studies using CASP tools

Cohort Study Appraisal

Study	Clearly focused issue	Appropriate method	Recruitment acceptable	Exposure accurately measured	Outcome accurately measured	Confounders identified, accounted for	Follow up long, complete	Result presentation	Result precision	Results believable	Result applicability	Results fit with other evidence	Quality assessment
Aldous	Y	Y	Y	Y	U	N	Y	U	U	U	Y	Y	SAT
Mann	Y	Y	Y	Y	N	U	U	U	U	U	Y	Y	?
Planer	Y	Y	Y	Y	U	U	Y	U	Y	U	U	U	SAT
Tanner	U	Y	U	U	U	U	Y	U	Y	U	Y	N	SAT

Diagnostic Test Appraisal

Study	Clear study question	Appropriate reference standard comparison	Diagnostic test, reference standard applied	Reference standard influenced test results	Disease status described	Test methods described	Result presentation	Result applicability	Test applicability	All important outcomes considered	Impact of test use on population	Quality assessment
Tomonaga	Y	N	Y	N	U	U	Y	Y	N	Y	U	SAT

Qualitative Research Appraisal

Study	Clear statement of aims	Qualitative methodology appropriate	Research design appropriate	Recruitment strategy appropriate	Data collection addressed research aims	Researcher – participant relationship examined	Ethical issues taken into consideration	Clear statement of findings	Results valuable	Quality assessment
Law	Y	Y	Y	Y	Y	N	Y	Y	Y	SAT
Sodi	Y	Y	Y	U	Y	N	N	Y	N	?
Tandjung	Y	Y	Y	Y	Y	N	Y	Y	N	SAT

CASP = Critical Appraisal Skills Program[147];Y = yes; N= no; U= unclear; SAT = Satisfactory include in review; ?= Unclear if paper warrants inclusion in review

4.2 Objective 1: To describe the outcomes of patients who present in general practice with ACS symptoms and undergo cTn testing

4.2.1 Study characteristics

Five studies that addressed this review objective were included in the final analysis[149-153]. The intervention examined in all studies was that of a cTn test requested by GPs, with Aldous et al., Mann et al. and Tanner et al. examining laboratory based cTn testing and Planer et al. and Tomonaga et al. assessing point of care cTn testing (POCT) ordered by GPs in primary care.

One randomised controlled trial (RCT) was found (Tomonaga et al.) comparing POCT to conventional diagnosis using best clinical practice, and the remainder were observational cohort studies. While RCTs are preferable to observational studies when evaluating interventions due to a lesser susceptibility to bias[133], the RCT examined POCT which is of less relevance to the review question. Hence the key messages of the discussion of this section are drawn largely from findings of the observational studies.

Across all studies, 3447 cTn test results were included in final analyses. The number of participants overall is not known as this information was not provided by Mann et al.

4.2.2 Assessment of risk of bias within studies

Table 6 describes the assessment of risk of bias for the included studies.

4.2.3 Results of individual studies

The numbers of tests performed, results of tests and referral decisions in each study are reported in Table 7.

All studies provided mortality data for patients with positive results, but only Aldous et al. provided death rates for those with negative test results. The incidence of ACS and other cardiovascular diagnoses were stated, with Aldous describing revascularisation rates also. The two POCT studies also provided information on hospitalisation rates. The period of follow up for outcomes varied from 5 weeks (Mann et al.) to 12 months (Planer et al).

Table 7: Results of studies describing outcomes (Objective 1)

Study	Number						Hospital status – positive tests		Hospital status – negative tests	
	Number of tests performed	Number positive	Number negative	% positive	Positive on serial measure	Negative test serial measures	Hospital referral	Hospital admission	Hospital referral	Hospital admission
Aldous	2662	223	2439	8.4%	11/223 (4.9%)	297/2439 (12.2%)	NR	184/223 (82.5%)	NR	344/2439 (14%)
Mann	278	8	270	2.9%	NR	12/270 (4.4%)	4/8 (50%)	4/8 (50%)	9/270 (3.3%)	NR
Planer	349	5	344	1.4%	NR	NR	5/5 (100%)	5/5 (100%)	107/344 (31.1%)	42/344 (16%)
Tanner	11	11	0	100%	NR	NA	11/11 (100%)	11/11 (100%)	NA	NA
Tomonaga	147	19‡	128	12.9%	NR	NR	NR	NR	NR	NR

Study	ACS		Delay		Adverse events – positive tests				Adverse events – negative tests					Beneficial effects
	Positive tests	Negative tests	Patients with delay	Median delay	Died	Died within 48h	Died, admitted	Died, not admitted	Died	Died within 48h	Died, admitted	Died, not admitted	Other	NR
Aldous	101/223 (45.3%)	42/2439 (1.7%)	NR	NR	19/223 (8.5%)	NR	17/223 (7.6%)	28/223 (12.8%)	34/2439 (1.10%)	NR	NR	NR	Arrhythmia 10%* Heart failure 5%*	NR
Mann	6/7 (86%)^	12/270 (4.4%)^	1	350 mins	0	0	0	0	0	0	0	NR	Arrhythmia 1/270 (0.3%)	71/138 (51.4%)§
Planer	5/5 (100%)	18/344 (5.2%)	NR	NR	0	0	0	0	0	0	0	0	NR	NR
Tanner	11/11 (100%)	NA	11	485 mins	0	0	0	0	NA	NA	NA	NA	NR	NR
Tomonaga	10/19 (52.6%)	7/128 (5.5%)	NR	NR	0	0	0	0	NR	NR	NR	NR	NR	NR

* approximate values only;
^ GP likelihood of MI >10%
‡ 9 false positive results
§ 71/138 (51.4%) likelihood pretest >10%, post test <10%. Data only provided for 138/270 negative tests
NR Not recorded
NA Not applicable

4.2.4 Synthesis of results

4.2.4.1 Deaths

Mortality rates in patients who had cTn testing were provided by Aldous et al., six months after the test. The six month death rates were 8.5% in patients with positive cTn tests and 1.1% for patients with negative test results. As the remaining studies obtained complete follow up information by interview for patients with positive tests after at least three days, it may be inferred that there were no early fatalities in the other studies in patients with positive results.

4.2.4.2 ACS diagnoses

The rates of ACS in patients with positive cTn levels were over 50% in four of five studies. The rate of ACS in the fifth study, by Mann et al., is not known with certainty, with the rate of likely ACS reported as the GP's estimation of likelihood of MI as the cause for presentation.

4.2.4.3 Hospital admission, ACS complications and procedures

Across four studies, admission occurred in 50 -100% of patients with positive tests and for 14-16% of patients with negative tests. Admission data were not provided by Tomonaga et al. In the study by Aldous et al., not all patients with positive test results were referred to hospital, with 17.5% being managed in the community. In regard to ACS complications, Aldous et al., Mann et al. and Planer et al. reported incidences of patients with heart failure or arrhythmias as discharge diagnoses, though exact figures were not provided.

4.2.4.4 Delay

Delay was recorded by Tanner et al. and by Mann et al. In the study by Tanner et al., 11 patients were sent for a cTn test prior to hospital. They were then referred to hospital after a positive cTn result was returned, in a median time of 7.5 hours (range, 1 to 25 hours) after seeing the GP. The median time from symptom onset to hospital arrival was 9.5 hours for this group, significantly longer than the 1.8 hours (range, zero to 17 hours) for patients whose first health professional contact was with emergency medical services.

Only one patient in the study by Mann et al. was thought to have had their admission delayed by cTn testing, with a delay of five hours before admission.

4.2.4.5 Beneficial effects

There were potential beneficial effects of GP based cTn testing noted in the study by Mann et al., with positive results returned in patients with late or atypical presentations.

4.3 Objective 2: To examine GPs' understanding of cTn testing's limitations, and the influence of cTn test result on management.

4.3.1 Study characteristics

A description of included studies is provided in Table 3. The studies by Aldous et al. and Mann et al. were also assessed as part of Objective 1 of the review. Both used the frequency of serial testing and timing of test ordering relative to symptom onset as markers of GP understanding of limitations. Additionally Mann et al. used the difference in GP assessment of likelihood of MI as a marker of management change.

Three new studies were examined as part of Objective 2. Law et al.[154] used a postal survey to all GPs listed on a university Department of General Practice database to present nine hypothetical scenarios of MI likelihood, and to enquire whether a cTn test would be ordered and whether the GP would wait for the result before referring patient. The study by Sodi et al.[155] consisted of a telephone survey of GPs who had ordered a cTn test on a patient through one urban laboratory, to enquire about indications for the test and proposed management before and after the test result. Tandjung et al.[156] also used a hypothetical scenario of a patient with a diagnosed ACS and a known cTn test result to assess a GP's action. The GPs' responses were compared with those of a group of cardiologists as a reference standard.

4.3.2 Assessment of risk of bias within studies

Table 6 describes the assessment of risk of bias for the included studies.

4.3.3 Results of individual studies

Table 8 reports the results of each study.

Table 8: Results of studies describing GP understanding and use of cTn (Objective 2)

Study	GP understanding of test				Effect on management		
	Sensitivity		Specificity	Indications			
	Number (%) of tests ordered during window period	Number (%) of pts with serial testing	Number (%) of patients with comorbidities causing false positive result	Number (%) ordered with inappropriate indication	Change in hospital referral decision	No change in hospital referral decision	Hospital referral despite negative result
Aldous (2012)	NR	308/2439 (12.6%)	NR*	NR	NR	NR	14% of patients
Law (2006)	34% of GPs order with <5% risk MI 16% of GPs order with 5-50% risk MI 6% of GPs order with >50% risk MI	NR	Heart failure identified by 25% GPs PE identified by 25% GPs Renal failure identified by 39% GPs	NR	31-64% of GPs with <5% risk MI^ 10-78% of GPs with 5-50% risk MI^ 1-32% of GPs with >50% risk MI^	0-3% of GPs with <5% risk MI‡ 4-10% of GPs with 5-50% risk MI‡ 5-16% of GPs with >50% risk MI‡	NR
Mann (2006)	29 patients (12%) had tests performed; number of tests NR	3/29 (10.3%)	NR	NR	102/151 (67.6%)†	49/151 (32.4%)	9/270 (3.3%)
Sodi (2007)	NR	0/16 (0%)	NR	6/16 (37.5%) no indication provided 1/16 (6.25%) inappropriate (increased lipid level)	5/16 (31.25%)	NR	NR
Tandjung (2012)	NR	NR	NR	175/471 (41.4%) inappropriate (to make diagnosis of known STEACS)	NR	NR	6.7% of GPs

* Discharge diagnoses of admitted patients included heart failure, pulmonary embolism, arrhythmias
^ Percentage who would wait for result before referral; percent varies depending on duration ofsymptoms
† Percentage with change in estimation of likelihood
‡ Percentage who would refer without waiting for result; percent varies depending on duration of symptoms
GP General practitioner
NR Not recorded
MI Myocardial infarction
PE Pulmonary embolism
STEACS ST elevation acute coronary syndrome

4.3.4 Synthesis of results

4.3.4.1 Knowledge of limitations

GP understanding of cTn's limited sensitivity within the first 10 hours after symptom onset was assessed directly by Law et al. and indirectly by Mann et al. and Aldous et al.

Aldous et al. reported that 308 of 2439 (12.6%) had serial tests performed. The interval of symptom onset to presentation was not reported so it is unclear how many patients had an indication for serial tests. Notably, 11 of 223 (4.9%) patients with positive tests had serial measures performed after elevation was detected on the first test. Law et al. also posed hypothetical questions to respondents about the specificity of cTn testing. Only a minority of GPs identified heart failure (25% of GPs), pulmonary embolism (25% of GPs) and renal failure (39% of GPs) as causes of false positive results. One scenario in the study by Tandjung et al. obtained useful information about GP understanding of the indications for cTn, with 41.4% of GPs ordering a cTn test in a patient with current chest pain and a STEMI on ECG, when cTn testing is not required to make the diagnosis of ACS and would only delay referral to hospital.

4.3.4.2 Effect on management

The papers by Law et al., Mann et al., Sodi et al. and Tandjung et al. all collected information about the effect of a cTn test result on GP estimation of likelihood of ACS and on management of ACS.

In the scenario of a less than 5% likelihood of MI, most GPs in the study by Law et al. would order the test and wait for the result before making a decision about referral.

In the Mann et al. group, 67.6% (102/151) of GPs would change their estimation of likelihood of MI based on the test result. Three out of ten patients whose pre-test clinical likelihood of MI was <10% moved to confirmed infarction after receipt of test results, showing a definite change in estimation of likelihood of MI. Mann et al. also reported that 86% of cTn tests were ordered on patients with a pre-test likelihood of MI of less than 25%, and that pre-test likelihood fell substantially after the test result, with 84% of cases having a post-test likelihood of MI of less than 1%. In the scenario used by Tandjung et al. of a patient with chest pain due to ACS that has been resolved for 8 hours, 93.8% of GPs would refer to hospital with a positive result, compared with 6.7% with a negative result.

5. DISCUSSION

5.1 Summary of evidence

ACS and its complications were reported in all studies. While deaths occurred in patients with positive cTn results, it was not clear if the deaths occurred early after ACS, nor whether they were related to ACS. There were no early deaths in the studies which specifically sought mortality data in the first few days following an ACS. This provides some reassurance about the safety of test ordering. However, as Mann et al. noted, “the overall number of positive tests was too small to conclude that management of ACS was never adversely affected by cTn testing and waiting for results”.

Hospital admission occurred for over 50% of those with positive results and for 14 to 16% of those with negative results. Many non-admitted patients were over 75 years of age, where a conservative medical or palliative approach due to age-related comorbidities may have been more appropriate than admission and invasive management. This could be considered a beneficial outcome if confirming ACS diagnosis in a patient not suitable for hospital management allows progression to a palliative stage of care. However, 2.6% of non-admitted patients underwent invasive management with revascularisation within six months, suggesting that at least some of the non-admitted patients may have been suitable for active management at their initial presentation. Without knowing the residential and functional status of these patients, or the timing of their symptoms, it is not possible to describe the late revascularisations as either delayed or as adverse events.

A number of arrhythmias were described in the studies, including atrial fibrillation, supraventricular tachycardia and complete heart block. Certain patients with these arrhythmias may be at risk of adverse outcomes should the arrhythmias occur in the community, as some treatments such as cardiac pacing are usually only available in hospital. In order to classify these arrhythmias as adverse events they would need to occur early while test results were awaited and while the patients were unmonitored in the community, and this level of clinical information was not provided.

Similarly, heart failure was listed as an outcome for some patients. This is relevant in that patients with heart failure manifesting as acute pulmonary oedema or cardiogenic shock require urgent intervention not available in the community. Again, the limited clinical information obtained in these studies prevents heart failure occurring early and as an emergency being confirmed as an adverse outcome.

There was evidence of delay in diagnosis of ACS with some patients having their admission deferred for some hours while awaiting a test result.

In patients with late or atypical presentations, both positive cTn test results and diagnoses of ACS were seen, representing beneficial outcomes and therefore appropriate test use. Due to the small numbers of patients in the included studies, these benefits relate to individual patient cases rather than a systemic effect. There was limited clinical information on the causes of these late positive results, and some could have been due to conditions which may cause falsely positive results. Nevertheless, some of the causes of false positive elevations, such as pulmonary embolism or subarachnoid haemorrhage, carry a risk of death or major morbidity and need intervention in their own right, and so their detection could be considered a beneficial outcome, although cTn testing is not the preferred method to diagnose these conditions.

In each study, some GPs showed evidence of inappropriate use of cTn testing. There were instances of poor understanding of the limitations of cTn testing, with failure to identify situations where false positive or false negative results were likely or where there had been incomplete indications for ordering the test. It was evident that cTn testing occurred within the 10 hour period of limited sensitivity, and certainly within the 24-72 hour period in which community based cTn testing is discouraged by major guidelines[129,131]. Additionally, some patients with positive tests had serial measures performed unnecessarily, as elevation was detected on the first test. This suggests a need for education on the contraindications to serial testing as well as the indications. It would be helpful to know if these tests were ordered by different providers, in which case requesting of the second test may have been understandable if the first test result was not available.

Many GPs in the studies would perform the test and wait for a result before acting in a possible or probable MI scenario within 2 hours of symptom onset. As well as the risk of being insufficiently sensitive, this delay raises the issue of safety for the unmonitored patient. Other GPs in this context would order a cTn test but would send the patient to hospital immediately without waiting for the results. This at least addresses patient safety and reduces the chance of a missed diagnosis, even if the test is potentially an inappropriate use of resources by not influencing management. There might be a rationale for facilitating earlier diagnosis by hospital staff if the test is already being

processed while the patient is being transported to hospital, but this benefit is likely to be lost given the time taken to collect and transport the specimen in the community.

CTn testing appeared to reduce the estimated likelihood of ACS in patients at low risk of ACS, and to influence management in all four of the studies which collected information from GPs. This would count as appropriate usage, though no measures of statistical significance were provided.

5.2 Limitations

The studies within this review had a number of limitations and the above findings should be interpreted with these in mind.

Selection and response bias affected a number of the papers. The study by Law et al. was undertaken in collaboration with a University Department of General Practice. This allowed the researchers to design the survey instrument in collaboration with GPs affiliated with the department, and also to pilot the survey with a variety of GPs. The high response rate of 72% shows the success of these measures. However, there were acknowledged inaccuracies in the university database used to provide names of participants. Furthermore, the design of this study carried the risk of response bias; the identifiability of respondents to authors who were known to them as GP colleagues increased the likelihood of the reporting of desired outcomes. The use of non-identifiable data may have overcome this issue.

The nature of the cTn assay used was not described for the POCT studies. There was initial training in the use of the POCT kit but no quality assurance process for the GPs' ability to perform or interpret the test kit result. This is relevant as the majority of false negative results in the study by Tomonaga et al. came from the same practice, with the authors suspecting misuse of the device. The exact method of cTn testing for all patients was not stated by Law et al. or Tandjung et al., which affects the generalisation of their findings to the urban laboratory based GP testing. Though not specifically mentioned as POCT, Tandjung et al.'s scenario involved "perform(ing) a troponin test in my practice". POCT is known to be widely used in northern Europe and 76.3% of respondents in this study had POCT for cTn as part of their practice infrastructure. Nineteen GPs in the study by Tandjung et al. stated that they would perform cTn testing despite not having this available in their practice, implying use of laboratory based cTn in these cases. Similarly, in the scenario by Law et al. where there was a greater than 50% likelihood of MI, 68 GPs (32%) of GPs would wait for a cTn result, which was raised as a concern by the authors. It is known that five GPs in this group came from rural areas where POCT may have been used. The rapid result obtained by POCT means that waiting a shortened time for a result would be an appropriate management option in this situation.

The accuracy of assessment of outcomes was low in all laboratory studies. Questionnaires to GPs about their clinical practice may be unreliable and this was a risk in the three studies using survey data, with no independent verification of

questionnaire responses despite key conclusions being based on this information. The main study addressing delay, by Tanner et al., failed to obtain objective measurements of time intervals beyond those recalled by the patients, nor was there corroboration of presenting symptoms as reported by the patient to the GP. These authors concluded that cTn testing by GPs represented a failure to understand the risks of delay in diagnosis and treatment of suspected ACS. However, if the presenting symptoms described to the GP were more benign than those recalled by the patient after hospital admission, the GP's decision not to refer may have been appropriate. Additionally, while the questionnaire used by Mann et al. was sent to GPs within 3 days of ordering of the test, there is still the possibility of recall bias in the case of incomplete medical records. There were missing data from the group of patients with negative results in Mann et al. which affects the number of patients with a potential beneficial outcome.

The use of hospital databases would have improved the accuracy of assessment of outcomes, but these were underutilitised. Instead, Mann et al. relied on the questionnaire response of GP estimate of MI likelihood as a surrogate marker for diagnosis in most patients. When hospital databases were used in the laboratory studies to verify GP responses, the databases and items used to arrive at a diagnosis of ACS were not specified. Even with the use of health record databases, actual information on delays in inpatient therapy may only be obtained by detailed review of hospital medical notes, and there are significant privacy considerations in obtaining this clinical information which may have deterred the authors from proceeding with such research.

The accuracy of outcome measurement in the POCT studies was variable. A major weakness of the study by Tomonaga et al. was the lack of reliability of the reference standard of conventional best practice diagnosis. It was unclear if guidelines or other education were used to direct best practice or if diagnosis was left to the individual doctor's clinical judgement. In this study there was a lack of independence of the index test and reference standard and a failure to involve an independent blinded assessor, with the same clinician performing the clinical diagnosis, cTn test and the final diagnosis. It is likely that these clinicians incorporated additional information into the final diagnosis 3 weeks after the test, as specialist reports and hospital data were provided to GPs on patient discharge for those admitted to hospital. Practical and data protection reasons were cited as the reasons for this aspect of the study design.

The paucity of clinical information reduces the ability to draw conclusions for either objective of the review. Regarding Objective 1, a clinical context for each test would have assisted in classifying outcomes as adverse or beneficial. Additionally, clinical and demographic information would also allow assessment for confounding, which was not fully identified or addressed in any study. Non-coronary comorbidities causing false positive results could have accounted for any or all of the positive tests. Regarding Objective 2, many GPs found it difficult to indicate management based on cTn testing alone, stating that clinical factors would influence their decision making and risk stratification. Removing this clinical context from decision making does not mirror actual GP practice, limiting the strength of study findings. Tandjung et al. did supply GPs with this information, making the findings in that study more representative of real world practice.

Additionally, no study recorded the patient's contribution to the decision to have cTn testing. In the study by Tanner et al., 27 of 47 patients who chose to see a GP did not believe their condition was serious and six of 47 believed the hospital system was too busy to provide their care. It may have been that this reluctance on the part of the patient to attend hospital was the driver for the GP to find evidence of current ACS and to use this evidence to convince the patient that hospital attendance was necessary. Previous studies have used carer surveys, hospital records[157], data from the referring GP[138] and benchmarking processes[103] to improve the accuracy of recorded times and the inclusion of these processes in the design of the study by Tanner et al. would add weight to the authors' conclusions.

The review itself is limited by the small number of eligible studies, as well as the marked heterogeneity of patient populations and outcome measures in studies that were the included. Participant numbers were low in all studies and most reported data from single centres. Publication bias might account for this paucity of data. Laboratory audits and audits as part of GP quality improvement cycles are often performed for the purposes of internal review, and evidence of good practice, while reassuring for individual clinicians and laboratories, may not merit wider dissemination.

5.3 Implications for future research

The optimal study method to address this review's objectives would firstly address the risk of bias by using non-identifiable data from a group of GPs who are representative of the wider GP population. In terms of the intervention used, the involvement of multiple pathology providers would strengthen findings of further studies. Results from the studies included in this review can only be generalised to the wider population if the population serviced by that laboratory is representative of the region, and only Mann et al. claimed to have a representative cohort. The ideal study would also use laboratory testing rather than POCT in order to be to be generalisable to urban Australian GPs, as this is the common method of cTn testing in urban primary care in this country.

Obtaining clinical context for the patient undergoing testing would be crucial to classification of events subsequent to the ACS as adverse or beneficial outcomes. Clinical information would also contribute to the understanding of the incidence of false positive and negative results and to the rationale for the GPs' referral decisions.

Deficiencies in outcome measurement could be addressed by making wider use of linked data sources to provide objective measures of hospital events and assist with the reporting of outcomes, for a defined period of follow up. The results of outpatient investigations confirming a diagnosis of ACS, such as positive dynamic testing that was not confirmed with inpatient angiography, would need to be captured to obtain a true picture of ACS events. However this would be a challenge in Australia given the abundance of private providers of cardiology investigations.

The preferred method of investigating adverse outcomes would be a randomised controlled trial designed to detect rates of adverse outcomes in patients who did and did not undergo testing. The observational nature of the three laboratory based studies in this review means that a comparison of outcomes with patients who did and did not undergo GP investigation was not possible. However randomisation of a patient with symptoms suggestive of ACS to community care would be unethical and unacceptable to both patient and doctor. Additionally, the heterogeneous nature of ACS presentations in general practice poses a risk of bias and if the low absolute numbers of positive tests in the studies included in this review are a guide, a fully powered study would need to be very large and therefore probably unfeasible. An observational design remains the realistic method to evaluate patient outcomes.

6. CONCLUSION

In summary, knowledge about the appropriateness of GP initiated cTn testing is limited due to a small number of published studies, the heterogeneity of these studies and the small number of patients in existing studies. The understanding of GP cTn test use would be improved if there were clinical data on patients in the existing studies, as well as precise and complete outcome data.

What is evident from this review is that information on the outcomes of GP cTn testing and the effect of cTn testing on management needs to be interpreted within a clinical context. While it appears from this review that cTn testing occurs in all clinical scenarios regardless of likelihood of pain and recency of symptoms, the majority of these data comes from hypothetical scenarios, and the findings based on actual GP practice involve such small cohorts that their validity is limited.

This provides justification for the research presented in this thesis evaluating cTn testing by GPs, where non-identifiable clinical information has been provided by GPs on patient presentation and risk status, and linked with outcome data from hospital record databases. This will account for some of the limitations in the literature detected by this review and should further the understanding of what is appropriate use of cTn testing by GPs.

CHAPTER THREE: METHODS

1. STUDY DESIGN

This study was a prospective cohort design.

2. SETTING

The study recruited patients who had cTn blood tests ordered by a general practitioner in a non-hospital setting and who had their sample collected at community collection centres of two laboratories in urban Perth, Western Australia. The laboratories were PathWest and St John of God Pathology, two of the five pathology laboratories in Perth. Together, these laboratories cover all Perth regions. The period of recruitment was 24 September 2009 to 3 September 2010, with recruitment ceasing so that follow up could be completed within the four year period specified by UWA for the completion of the research.

Ethical approval to conduct the survey was obtained from Human Research Ethics Committee at the University of Western Australia (RA/4/1/2275; 13 July 2009), St John of God Hospital (370; 7 May 2009), the Department of Health Western Australia (2013.04.02; 9 April 2013) and the South Metropolitan Health Services Board (08.136; 28 August 2014). The Medical Directors of St John of God Pathology and PathWest gave written consent for provision of laboratory data.

3. PARTICIPANTS

3.1 GP cohort

Consecutive patients with samples collected at collection centres of the two laboratories were included in this study. Both laboratories used the standard sensitivity cTnI assay. A Research Assistant employed by the laboratories then approached requesting GPs to complete a survey which described the clinical scenario leading to the test request, and the clinical course of the patient following the test result.

3.2 ED cohort

The Multiple Infarct Markers in Chest Pain (MIMiC) study dataset[158] was used to compare clinical presentations and outcomes in the GP survey cohort with an Emergency department cohort. This prospective cohort study was conducted between September 2008 and June 2009 in two tertiary referral hospitals and three general hospitals in urban Perth. The urban catchment areas of these five hospitals were similar to those of the collection centres used in the GP survey phase.

Participants were a representative sample of patients undergoing evaluation for possible ACS with serial cTn testing. Exclusions were patients aged less than 18 years, those who were pregnant or those where ECG criteria called for urgent reperfusion therapy, such as patients with ST segment elevation ACS on their initial ECG.

3.3 Linked data

The Department of Health Western Australia Data Linkage System (WADLS) uses computerised probabilistic matching supported by clerical officers to connect all available health and related information for the WA population[159]. Connections, or linkages, are created by comparing the personal information available and calculating the likelihood that records belong to the same person, place or event, while at the same time protecting personal privacy[160].

Linked data were obtained for all patients for a minimum twelve month period following the date of the test, regardless of whether the GP responded to the survey. The final cTn test included in the study was performed in September 2010, and follow-up continued until October 2011. The Emergency Department Data Collection, the Hospital Morbidity Data Collection and the Mortality Register Data Collection were searched for the period from 24 September 2009 to 3 October 2011. Linkage and extraction were performed in November 2013 to compensate for delay in updating of Department of Health records.

Patients who had samples collected at rural and regional centres were excluded, since it was thought that GPs in these centres may use cTn testing differently to urban GPs. Reduced access to tertiary hospital EDs in rural and regional centres may result in the need to obtain greater evidence of ACS before instigating transfer of patients to larger centres. Additionally, point of care assays may substitute for laboratory based testing in rural areas, and so the prevalence of cTn testing may have been underestimated if laboratory results alone were examined. If the collection centre location was unknown, as occurred when the specimen was collected within doctor's rooms or by domiciliary collection, the patient's postcode was used for allocation to rural, regional or urban areas.

4. VARIABLES

4.1 GP cohort

Tables 9 and 10 list the data variables obtained from each source in this phase. A copy of the questionnaire used in the GP survey phase is provided as an appendix.

Table 9: Data variables obtained by laboratories

Variables obtained from GPs	Variables obtained from laboratory records
GP name and contact details	Time from sample collection to registration
Patient name, address, gender	Time from registration to result availability
Patient date of birth	cTn result (quantitative)
Collection centre ID code	Interpretation of cTn result
Collection centre postcode	Renal function where available (Cr or eGFR)
Date of test request	
Date and time of sample collection	

Cr = plasma creatinine eGFR = estimated glomerular filtration rate

Table 10: Data variables obtained by laboratories from requesting GP

Patient's symptoms prompting ordering of cTn test
Duration of symptoms prior to test ordering
Nature of any pain Typical of cardiac ischemia Atypical of cardiac ischemia
Non-pain symptoms that may represent cardiac ischemia Dyspnoea Syncope Dizziness Palpitations Fatigue
Cardiovascular risk factors known to be present at the time of presentation Current smoker or previous smoker of more than10 pack years Hyperlipidaemia Hypertension Diabetes Personal history of CHD or equivalent Family history of CHD (1st or 2nd degree relative less than 60years old at onset)
Assessment by the GP of the likelihood of ACS before and after the test* Less than 5% 5-10% Greater than 10%
Intended management before and after receipt of test result Referral to Emergency Department. Cardiology review as an outpatient Ongoing management by GP without referral

CHD= coronary heart disease; ACS = acute coronary syndrome; * = category scores chosen to be the same as those used in two of four articles in the systematic review which examined GPs' estimation of likelihood[149, 154]

4.2 ED cohort

Variables obtained from the ED cohort data set are listed in Table 11.

4.3 Linked data

Table 12 lists specific outcomes provided by the Data Linkage System.

Table 11: Data variables obtained from the ED cohort dataset

Age
Gender
Cardiovascular risk factors
Current smoker
Hyperlipidaemia
Hypertension
Diabetes
Personal or family history of coronary heart disease or equivalent
Presenting symptom
Admission status
Outcomes
All-cause mortality
MI
Unplanned revascularisation

MI = myocardial infarction

Table 12: Data variables from Data Linkage System

Emergency Department Data Collection
Hospital type
Presentation date and time (DDMMYYYY)
Transport mode (arrival)
Referral Source
Triage category
Presenting problem
Principal diagnosis
Departure destination
Hospital Morbidity Data Collection
Admission age
Gender
Hospital category
Admission date
Separation date
Length of stay
Days in Intensive Care Unit
Hours on continuous ventilatory support
Mode of separation (method and destination of patient discharge)
Principal diagnosis
Co-diagnosis
Additional diagnoses
Principal procedure
Additional procedures
WA Mortality Register
Date of death
Cause of death

4.4 Outcomes

Information on hospital presenting problems, diagnoses and procedures are listed in Tables 13 to 18. This information was obtained from the Emergency Department Data Collection (EDDC) dataset and the Hospital Morbidity Data Collection (HMDC). Outcomes were defined according to standardised data definitions recommended for use in Australasian ACS research[137]. Specific diagnosis and procedure codes representing these outcomes were selected from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification, 6th and 7th editions[161,162], and the Australian Classification of Health Interventions 7th edition[163].

Significant clinical events representing adverse outcomes of ACS, as listed in Table 18, were those occurring within a 30 day time period following ACS, as this is the interval where there is the greatest risk of death, progression to MI or the development of recurrent MI. After 30 days, most patients with ACS resume a clinical course similar to that of patients with stable coronary disease[9,138].

If a specific diagnosis was recorded that excluded a cardiovascular cause for a presenting problem or diagnosis, such as chest pain with a coexistent diagnosis of chest wall trauma or dyspnoea with a coexistent diagnosis of asthma, that patient's data was reclassified as non-cardiovascular.

Table 13: EDDC cardiovascular presenting problems

Problem group	Specific symptom
Chest pain	Presence of acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without apparent non-cardiac source
Associated symptoms	Symptoms that developed since pain/discomfort started, and cannot otherwise be explained by a non -cardiac condition, including: Nausea, vomiting, Sweating, clamminess Syncope, blackout, unexplained loss of consciousness Palpitations, arrhythmia Shortness of breath, dyspnoea, breathlessness
General/atypical symptoms	Fatigue, nausea, vomiting, diaphoresis, faintness, back pain
Symptom recorded as provisional diagnosis	Cardiac arrest Acute myocardial infarction, unstable angina Heart failure, pulmonary oedema Hypotensive, hypertensive Arrhythmia Cardiomyopathy

Table 14: EDDC cardiovascular presenting problems – ICD-10AM codes

Symptom group	ICD-10AM code				
Chest pain	QG000	QGA00	QGB00	QGC00	
Associated symptoms	HJ000	HQ000	HQA00	KF000	KN000
	BE000	BEA00	BEB00	BEC00	
	CF000	CFA00			
General/atypical symptoms	BD000	CJ000			
Cardiac arrest	BA000	BAA00	BAB00		
Acute myocardial infarction	SDB00	SXB00			
Unstable angina	SDV00	SXP00			
Heart failure, pulmonary oedema	SDM00	SXG00			
Hypotensive, hypertensive	BB000	BC000	BD000		
Arrhythmia	SDC00	SDCA0	SDD00	SDE00	SDG00
	SDU00	SDW00	SXC00	SXCA0	SXCB0
	SXCC0	SXCD0	SXCE0	SXCF0	

Table 15: EDDC and HMDC principal and additional diagnoses

Diagnosis group	Specific diagnosis
ACS	STEMI, NSTEMI, AMI, unstable angina
CHD	CHD, Angina NOS, atherosclerosis of autologous bypass graft
Atherosclerosis	TIA
	Hypertensive heart disease
	Intracerebral haemorrhage
	Cerebral infarction
	AAA rupture
	Acute vascular disorder of intestine
Arrhythmia	VT, SVT, Atrial fibrillation
	Atrioventricular block
	Bradycardia
	Cardiac arrhythmia - other
Other CVS diagnosis	Cardiogenic shock
	Symptomatic aortic stenosis
	Cardiomyopathy
	Heart failure
	Syncope
	Mechanical complication of cardiac device
	Other breathing abnormality
	Dizziness
	Palpitations
	Chest pain - anterior chest wall
	Chest pain on breathing
	Chest pain unspecified
	Precordial pain

ACS = acute coronary syndrome, STEMI = ST elevation myocardial infarction, NSTEMI = Non-ST elevation myocardial infarction, AMI= acute myocardial infarction, CHD = coronary heart disease; NOS = not otherwise specified, VT = ventricular tachycardia, SVT = supraventricular tachycardia, AAA = abdominal aortic aneurysm, TIA= transient ischaemic attack

Table 16: EDDC and HMDC principal and additional diagnoses - ICD-10AM codes

Diagnosis group	ICD-10AM code				
ACS	I20.0	I21	I22	I23	
CHD	I20.1	I20.8	I20.9	I24	I25
Arrhythmia	I44	I45	I47	I48	I49
Atherosclerosis	G45	I11	I61	I63	I70
	I71	I72	I73.8	I73.9	I74
	K55				
Other CVS diagnosis	I30	I31	I32	I33	I50
	I51	I52	I95.1	J81	R01
	R01	R02	R03	R42	R50
	R53	R55	R57.0		

ACS = acute coronary syndrome, CHD = coronary heart disease, CVS = cardiovascular

Table 17: ACHI codes for procedures

Outcome	ACHI code				
Emergency or urgent revascularization procedure*	30500-04	30500-05	30306-00	35303-01	38215-00
	38218-00	38218-01	38218-02	38300-00	38300-01
	38303-00	38306-01	38306-02	38306-03	38306-04
	38306 -05	38497-00	38497-01	38497-02	38497-03
	38497-04	38497-05	38497-06	38497-07	38500-00
	38500-01	38500-02	38503-00	38503-01	38503-02
	38503-03	38503-04	90201-00	90201-01	90201-02
	90201-03	90201-00			

*ACHI codes apply to all revascularisation procedures irrespective of urgency

Table 18: Adverse outcomes and ICD-10AM codes

Outcome	ICD-10AM code				
Death from cardiovascular cause	I21	I22	I23	I24	I25
Death of uncertain cause	R96	R98	R99		
Cardiac arrest	I46				
Cardiogenic shock	R57.0				
Unstable angina	I20				
Acute myocardial infarction	I21	I22	I23	I24	I25
Ventricular arrhythmia	I47.2				
High degree AV block	I44.3	I44.3			
Heart failure requiring intervention	I50				

AV= atrioventricular

5. MEASUREMENT

5.1 GP cohort

Information was collected using a one page survey sent and returned by facsimile, with an information sheet and consent form sent at the same time. GPs were contacted within one week of testing, with telephone follow up to non-responders performed one week after initial contact. GPs who had previously indicated that they did not wish to be involved with the study were not contacted in regard to subsequent tests that they requested.

All identifying information for patients and GPs, including patient name, address, gender and date of birth was removed from laboratory data before the data were

provided to the researchers. Each test result was given a unique project number, being the laboratory's sample identification number.

The use of a unique project number for each sample, rather than a number for each patient, meant that additional methods were required to identify patients who had more than one test performed. The unique identifier assigned by the WADLS as part of the linkage process described below was used for this purpose.

5.2 ED cohort

Clinical data had been obtained by the treating clinician in ED at the time of presentation. Outcome information had been sought by a research nurse who made telephone contact with patients, relatives, GPs or cardiologists, supplementing from these sources with the hospital discharge summary as necessary.

Non-identifiable data were provided to the researchers of this study by the MIMiC study investigators via encrypted Excel documents.

5.3 Linked data

Identifying information from the laboratories was retained by Research Assistants working within the laboratories and provided to the WADLS, along with a unique project number. Following linkage and extraction, identifying data variables were removed by the WADLS before delivery to the researcher, who used the unique project number to merge the non-identifiable data from the laboratories with the non-identifiable data from the WADLS.

The unique identifier assigned by the WADLS as part of the linkage process was used to identify patients who had more than one test performed. Records were excluded from analysis if there was no principal diagnosis stated. Records were also excluded if the presenting symptom or principal diagnosis was insufficiently specific to allow classification as a possible ACS symptom (for example, pain or respiratory complaint without additional information). Duplicate records with more than one hospital admission for the same patient on the same day were considered as one admission for the purposes of statistical analysis, for example inter-hospital transfer recorded as a new admission.

All data transfers between laboratories, the WADLS and the researchers used Winzip 256bit AES encryption.

6. STUDY SIZE

A retrospective review of GP-initiated cTn tests was performed by the two pathology providers for the purposes of estimating sample size. It showed that over a five month period in 2008, 1,596 cTn tests were requested by GPs, at a rate of approximately 45 tests per week, 55 of these tests (3.4%) being positive results. Urban GPs requested approximately 35 urban tests per week with a 5% rate of positive tests. On this basis a sample size of 1400 tests was expected with 70 tests expected to be positive.

7. QUANTITATIVE VARIABLES

Outcomes were grouped into adverse or beneficial as shown in Table 19.

Late presentation was defined as greater than 48 hours after symptom onset, 48 hours being the time period following ACS where inpatient continuous cardiac monitoring is indicated[7,27,54].

Atypical presentations included atypical pain and the presence of non-pain symptoms in the absence of pain. Atypical pain was defined as back pain, sharp pain or pleuritic pain. Non-pain symptoms included dyspnoea, palpitations, nausea, vomiting, sweating, fatigue, syncope or presyncope[137].

Table 19: Grouping of quantitative variables

Outcome	Event
Adverse	Death from cardiovascular cause Death from uncertain cause Cardiac arrest Cardiogenic shock AMI - revascularisation AMI – no revascularisation Unstable angina – revascularisation Unstable angina – no revascularisation Ventricular arrhythmia High degree AV block Heart failure requiring intervention STEMI and delay greater than 120 minutes from time of presentation to GP to revascularisation, if performed. STEMI and delay greater than 12 hours from onset of symptoms to revascularisation, if performed.
Beneficial	Late or atypical presentation plus any of: AMI or unstable angina Emergency revascularization procedure Urgent revascularization procedure Elective revascularization procedure

AMI = acute myocardial infarction, AV = atrioventricular, STEMI = ST elevation myocardial infarction,

8. STATISTICAL METHODS

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA)[164] and XLSTAT-Pro (Version 2014.2, Addinsoft Inc., Brooklyn, NY, USA[165].) Categorical outcomes were summarized using frequency distributions. Tests of normality were applied to the continuous outcomes using Anderson-Darling test and P-P graphs. For normally distributed variables, the differences between group characteristics were assessed using the two sample t test for continuous variables and the chi squared test and Fisher's exact test where appropriate, based on expected frequencies for dichotomous variables.. A p value of <0.05 was considered statistically significant.

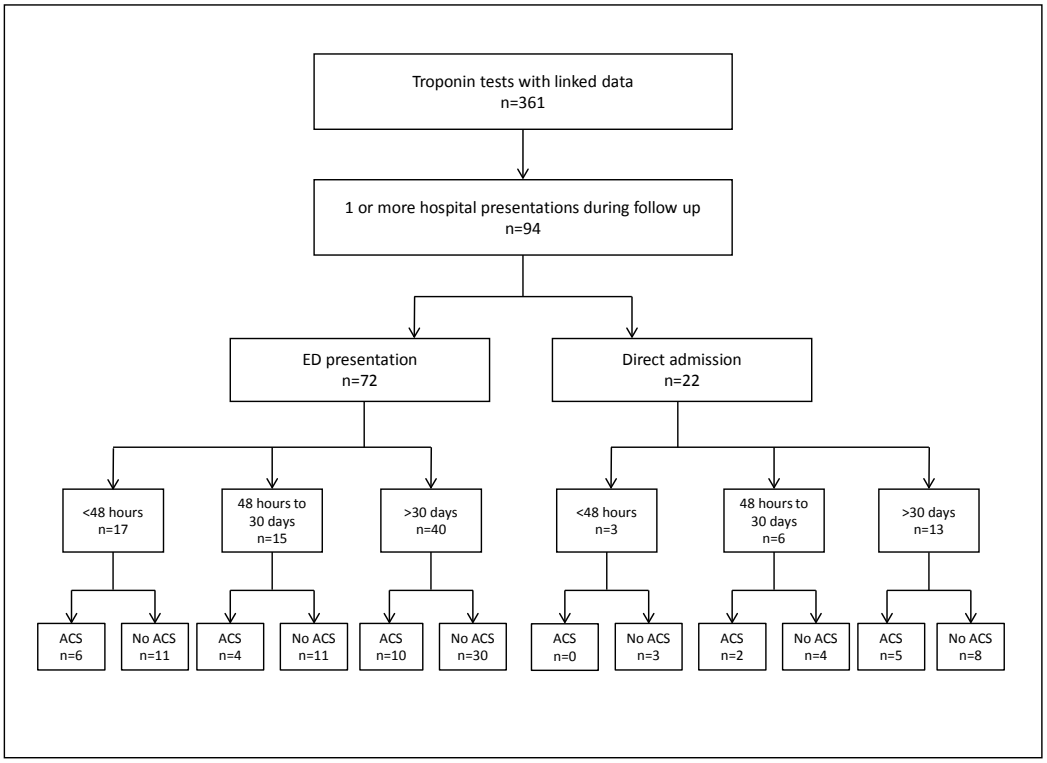
CHAPTER FOUR: RESULTS

1. PARTICIPANTS

Figure 5 describes the flow of participants through the phases of the study. 369 surveys were sent to 127 GPs. 124 surveys, each on a unique patient, were completed by 57 GPs, representing a response rate of 38%. There were no significant differences between included and excluded patients in respect of age or gender (each *P* >0.10).

Two GPs declined to participate after receiving the first survey and requested that no further surveys be sent to them, with no reason provided for their decision. These two GPs requested 41 tests on 39 patients.

Figure 5: Flow chart of participants



2. DESCRIPTIVE DATA

2.1 Characteristics of GP cohort with survey data

Table 20 presents characteristics of the 124 patients in the GP cohort for whom survey data were available. The most common presentation was pain typical of cardiac ischemia, with 56% of patients reporting this symptom. Twenty two per cent had pain atypical of ACS and 19% had no pain, instead presenting with dyspnoea, syncope, dizziness, palpitations or fatigue. Two per cent had no symptoms of ACS prior to cTn testing. Reasons given for cTn testing in these patients were: monitoring of cardiac side effects in one patient on antipsychotic medication, monitoring of cardiac symptoms in one patient on lipid-lowering therapy, and monitoring for emergence of ACS in one patient with ongoing creatine kinase elevation.

Sixty-two patients (51%) had the onset of symptoms prompting the test request within 48 hours of test requesting, and 29 patients (23%) had symptoms within 12 hours of the request for the cTn test.

Data concerning CHD risk factors were available for 104 patients. Two or more risk factors were present in 38% of patients, placing them at increased risk of ACS, according to the NHF/CSANZ risk stratification framework[8,27,166]. Nineteen per cent were automatically at high risk of ACS, including 7% with a personal history of CHD, 6% with typical symptoms and diabetes and a further 7% aged over 60 years with diabetes. Of the 85 patients who had renal function recorded by the laboratory, 26% had some degree of renal impairment with an eGFR of less than 60mls/min/1.73m^2, another factor that elevates risk[8].

Twenty-one patients did not have complete data for all CHD risk factors; 20 St John of God (SJOG) patient surveys did not provide information on the presence of a personal history or family history of CHD.

2.2 Comparison with Emergency Department cohort

A comparison with the ED cohort of 1758 patients showed significant differences in the prevalence of all individual CHD risk factors with the exception of diabetes, with greater proportions for all risk factors in the ED cohort (Table 21).

There was a significant difference in the proportions of participants with no known risk factors (P <0.01), one or more risk factors (P <0.01) and two or more risk factors (P <0.01).

Table 20: Characteristics of included patients

		GP (n=124)		ED (n=1758)		
		n	**%**	**n**	**%**	***P***
Median age (IQR)		61 (45-73)		62 (50-74)		0.38
Male		55	44	984	56	<0.01
Test result	Positive	2	1.6	168	10.7	<0.01
	Negative	122	98.4	1408	89.3	<0.01
Risk factors*	Smoker	15	12	425	24	0.01
	Hypertension	51	41	923	53	0.02
	Dyslipidaemia	47	38	842	48	0.03
	Diabetes	15	12	327	19	0.07
	Past Hx CHD	8	6	621	35	<0.01
	Family Hx CHD	24	19	879	50	<0.01
Presenting symptoms	Typical pain	69	56			
	Atypical pain	27	22			
	Non-pain symptoms	24	19			
	No symptoms	3	2			
	NR	1	1			
Pain duration	Less than 12h	29	23			
	12-48h	33	28			
	More than 48h	57	46			
	NR	5	2			
eGFR	<30	3	2			
	30-60	19	15			
	>60	63	5			
	NR	39	31			

*104 patients with complete risk factor data; **1576 patients with 8-12 hour cTn levels; Hx = history, CHD = coronary heart disease; NR = not recorded

Table 21: Comparison of risk factors between GP and ED cohorts

	GP (n=104)		**ED (n= 1758)**		
Number of risk factors	**n**	**proportion (CI)**	**n**	**proportion (CI)**	***P***
Zero	25	0.24 (0.17, 0.33)	167	0.09 (0.08, 0.11)	<0.01
One	40	0.38 (0.30, 0.48)	408	0.23 (0.21, 0.25)	0.01
Two	19	0.18 (0.12, 0.27)	445	0.25 (0.23, 0.27)	0.10
Three	17	0.16 (0.10, 0.25)	373	0.21 (0.19, 0.23)	0.20
Four	3	0.03 (0.01, 0.08)	365	0.21 (0.19, 0.23)	<0.01

2.3 Patients presenting within 12 hours of symptom onset

Data for a subgroup of 29 patients of the GP cohort who presented within 12 hours of symptom onset is shown in Table 22. The majority (69%) of these patients had pain typical of cardiac ischemia. Twenty four patients (83%) had at least one CHD risk factor including five patients (19%) with a personal history of CHD. Figure 6 shows patients who had a combination of these characteristics. Fifteen patients (52%) had typical pain as well as at least one CHD risk factor.

Ten patients in this subgroup of 29 (34%) had accurate information on the timing of sample collection, with nine patients (34%) having specimens collected less than one

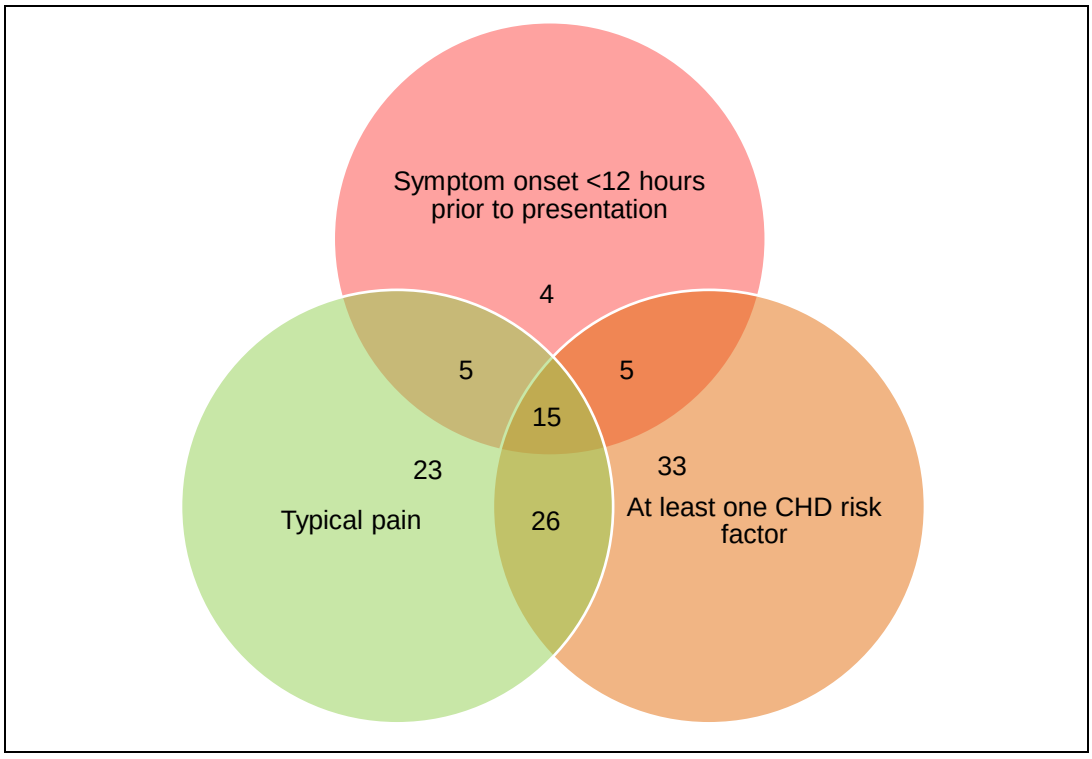
hour after presentation. This represents a maximum 13 hour interval between symptom onset and specimen collection. The median time taken for result provision for this group was 121 minutes (range, 23-1466).

Table 22: Characteristics of GP patients presenting within 12 hours

		Total (n=29)	%
Presenting symptoms	Typical pain	20	69
	Atypical pain	6	21
	Any pain	26	90
	No pain	3	10
	No symptoms	0	0
	NR	0	0
Risk factors	Smoker	3	10
	Hypertension	10	34
	Dyslipidaemia	15	52
	Diabetes	3	10
	Family history CHD	8	28
	Personal history CHD	5	17
Cumulative risk factors	Zero	5	17
	One	13	45
	Two	6	21
	Three	5	17
	Four	0	0

CHD = coronary heart disease; NR = not recorded

Figure 6: Number of patients with typical ACS pain, symptom onset <12hours and CHD risk factors



2.4 Test result availability

The time taken for result availability is shown in Table 23. The total time from specimen collection to a result being available was divided into two intervals. First, the time from specimen collection to registration represented the time taken for transport of the specimen from a specimen collection centre to a processing laboratory, including any delay at the collection centre awaiting specimen being collected by the laboratory's courier. This interval varied depending on the location of the specimen collection centre, with collection centres that were co-located with laboratories having the shortest time interval. The median time for specimen collection to registration was 31 minutes (range, 0-1465).

Second, the time from specimen registration to result availability represented the processing time for the specimen. The median time for this interval was 59 minutes (range, 1 - 391). Overall the total median time from specimen collection to result availability was 128 minutes (range, 23 -1466).

Table 23: Time in minutes from specimen collection to result availability

Interval	**Median (IQR)**	**Pathwest**	**SJOG**
Specimen collection to result availability	128 (78-190)	93(50-186)	135 (94-192)
Collection to registration	31 (12-88)	11 (6-29)	51 (21-113)
Registration to availability	59 (30-111)	77(41-148)	52 (27-101)

2.5 Effect of test result on GPs' estimation of likelihood of ACS

One hundred and twenty GPs provided a response to this item. Results are shown in Table 24. The majority of GPs (80, or 67%) estimated the likelihood of ACS to be low, or less than 5%, prior to receipt of test results. This proportion increased to 110 GPs (92%) after test results were received. Of the two patients with positive results, one GP estimated the likelihood as intermediate before the test, the other as high, and both GPs estimated the likelihood as high after receipt of test results.

For the 39 patients with an estimated intermediate or high likelihood, seven (18%) had symptom onset within 12 hours of presentation, and 20 (51%) had symptom onset within 48 hours of presentation.

A significant proportion of GPs (27.5%) changed their assessment of the likelihood of ACS, in response to a negative test result (chi-square test, *P* <0.01). No further information on the clinical circumstances was available where the estimation of likelihood of ACS increased following a negative test result.

Table 24: Effect of test result on GPs' estimation of likelihood of ACS

Estimated likelihood	No. (%) before test	No. (%) after test	*P*
Low (<5%)	80 (67)	110 (92)	<0.01
Intermediate (5-10%)	31 (26)	6 (5)	<0.01
High (>10%)	9 (7)	4 (3)	0.25

2.6 Effect of test result on GPs' intended management

One hundred and eighteen GPs responded to this question, as shown in Table 25. Most GPs (85, or 72%) intended to manage the patient themselves before the test result. This increased to 97 GPs (82%) after the test results were known.

Despite the test result having a significant effect on estimated likelihood of ACS, the test result did not significantly influence a GP's intended management, with 22.9% of GPs changing their intended management (chi-square test, *P* =0.23).

Table 25: Effect of test result on GPs' intended management

Intended management	No. (%) before test	No. (%) after test	*P*
GP	85 (72)	95 (82)	0.17
Outpatient cardiology	15 (13)	11 (9)	0.53
ED	18 (15)	10 (8)	0.16

3. OUTCOME DATA

3.1 Emergency Department cardiovascular presentations

Linked data were available for 361 tests performed on 355 patients, with eight patients unable to be linked due to insufficient identifying information from the requesting GP.

Table 26 shows ED cardiovascular (CVS) presentations for this group. There were 112 presentations to ED with CVS symptoms by 76 patients (21.4% of those with linked data available) during follow up. Symptoms were: chest pain (84 patients), dyspnoea (15), palpitations (8), dizziness (7) and syncope (5).

112 presentations had an ED diagnosis of a CVS condition, of which 20 presentations in 16 patients were due to ACS and 92 presentations were for other conditions, as described in Table 27. Eighty-seven presentations were given a triage category of 1 or 2, requiring immediate medical review or review within 10 minutes. 20 of these high triage category presentations had an eventual diagnosis of ACS.

Within 30 days of cTn testing, 24 patients (21.4%) who presented to ED with a CVS symptom were given a CVS diagnosis, of whom nine (8%) had an diagnosis of ACS and 15 (13%) had other CVS diagnoses (two with 2nd degree atrioventricular block, one with heart failure, one with atrial fibrillation and the remainder with unspecified chest pain.)

By comparison, the ED cohort included 357 patients (20.3%) with an ED diagnosis of definite ACS, and 984 (56.0%) with an ED diagnosis of definite or possible ACS.

Table 26: ED presentations – GP cohort (n=355)

	Diagnosis	n (%)
Number of ED presentations	ACS	20 (17.9)
	Non-ACS	92 (82.1)
	Total	112 (100)
Number of patients presenting to ED	ACS	16 (14.3)
	Non-ACS	60 (53.6)
	Total	76 (67.9)
Age of patients presenting (median, IQR)	ACS	64 (55,80)
	Non-ACS	60 (46,77)
	Total	66 (52,78)
ED presentations with CVS diagnosis within 1 month of test	ACS	9 (8.0)
	Non-ACS	15 (13.4)
	Total	24 (21.4)
ED presentations requiring admission	ACS*	19
	Non-ACS	38
	Total	57

*One patient with UA was not admitted; ACS = acute coronary syndrome; CVS = cardiovascular

Table 27: ED CVS diagnoses – GP cohort (n=112)

Diagnosis	n	Specific diagnosis	n
ACS	20	AMI	9
		Unstable angina	11
CHD	1	Angina NOS	1
Atherosclerosis	7	TIA	2
		Hypertensive heart disease	1
		Intracerebral haemorrhage	1
		AAA rupture	2
		Acute vascular disorder of intestine	1
Arrhythmia	9	SVT	2
		Atrial fibrillation	3
		AV block 2nd degree	1
		Bradycardia	2
		Cardiac arrhythmia - other	1
Other CVS diagnosis	75	Syncope	8
		Mechanical complication of cardiac device	1
		Other breathing abnormality	5
		Dizziness	3
		Palpitations	3
		Chest pain - anterior chest wall	10
		Chest pain on breathing	2
		Chest pain unspecified	43
		None (later Dx STEMI)	1
		Delirium (later Dx AMI)	1

ACS = acute coronary syndrome; AMI= acute myocardial infarction; CHD = coronary heart disease; NOS = not otherwise specified; TIA = transient ischaemic attack; AAA = abdominal aortic aneurysm; SVT = supraventricular tachycardia; AV = atrioventricular; CVS = cardiovascular; STEMI = ST elevation myocardial infarction

3.2 Admissions and procedures

There were 114 patient admissions with either an ED or hospital principal CVS diagnosis, 40 of which were for ACS (Tables 28 and 29). This represents 66 unique patients, or 18.6% of the cohort. While some patients had hospital admission as their ED departure destination, this was not always reflected in hospital morbidity information; 29 patient admissions for which the ED discharge destination was admission had no admission data in morbidity records.

Twenty-seven admissions with cardiac diagnoses occurred within one month of the test being performed, 10 of which had a discharge diagnosis of ACS. Ten patients had a previous admission with a cardiac diagnosis before the date of the test, including six with ACS, three with IHD and one with heart failure. Of the 40 ACS patient admissions, 36 had admission data available. Six patients were diagnosed with STEMI, 18 with NSTEMI, six with AMI not otherwise specified and six with UA.

Procedures performed on admitted patients are described in Table 30. Twenty one patients with ACS underwent angiography at that admission, with 14 undergoing revascularisation. A total of 19 patients required intensive care unit admission. There

were three patients who were admitted with ACS within one month of the test who did not undergo revascularisation, all aged 85 and above.

Table 28: Admissions with CVS diagnoses – GP cohort (n=114)

	Diagnosis	n (%)
Number of admissions	ACS	40 (35.1)
	Non-ACS	74 (64.9)
	All CVS diagnoses	114 (100)
Admission with ED presentation	ACS*	25 (21.9)
	Non-ACS	30 (26.3)
	All CVS diagnoses	55 (48.2)
Admission directly to hospital	ACS	15 (13.2)
	Non-ACS	44 (38.6)
	All CVS diagnoses	59 (51.8)
Admissions within 1 month of test	ACS	10 (8.8)
	Non-ACS	17 (14.9)
	All CVS diagnoses	27(23.7)
Age of patients admitted (median, IQR)	ACS	66 (54,76)
	Non-ACS	71 (47,83)
	All CVS diagnoses	69 (62,83)

*5 patients with non-ACS ED diagnoses were subsequently diagnosed with ACS during hospital admission; ACS = acute coronary syndrome; CVS = cardiovascular

Table 29: Details of admission CVS diagnoses– GP cohort (n=114)

Diagnosis	Detailed diagnosis	n
ACS	STEMI	6
	NSTEMI	18
	AMI	6
	UA*	6
CHD	Angina NOS	1
	CHD NOS	19
	Atherosclerosis of autologous bypass graft	2
Cardiomyopathy		1
Cardiogenic shock		1
Arrhythmia	VT	2
	AF	3
Valvular disease	Symptomatic aortic stenosis	1
Heart failure		6
Chest pain NOS		6
Admission data NR		36

*4 patients with UA had no admission data in hospital morbidity data collection; ACS = acute coronary syndrome; STEMI = ST elevation myocardial infarction; NSTEMI = Non-ST elevation myocardial infarction; AMI= acute myocardial infarction; UA = unstable angina; CHD = coronary heart disease; NOS = not otherwise specified; VT= ventricular tachycardia; AF = atrial fibrillation; NR = not recorded

Table 30: Procedures performed on admitted patients - GP cohort (n=67)

	ACS	CHD, no ACS	No ACS or CHD	Total
Revascularisation	14	9	1	24
Revascularisation within 1 month of test	8	0	1	9
Angiography alone	7	13	9	29
Other CVS procedure*				4
ICU admission				19

*2 electrophysiological studies, 1 testing of defibrillator, 1 cardioversion; ACS = acute coronary syndrome; CHD = coronary heart disease; CVS = cardiovascular; ICU = intensive care unit

3.3 Time to first hospital presentation

In total, 92 patients (25.9%) presented to hospital at least once during the follow up period with a CVS symptom or diagnosis, whether by attendance at ED or by direct admission. The median time to presentation was 33 days (range, zero to 551). Twenty patients (5.6%) presented to hospital within 48 hours of testing.

Twenty seven patients (7.6%) had at least one ACS during the follow up period, ten of whom had the ACS within 30 days of testing. The median time to presentation was 42 days (range, zero to 498). For the six patients who presented to hospital with ACS within 48 hours of testing, the median time from specimen collection to hospital presentation was 382 minutes (range, 80 to 1312).

3.4 Adverse events

Thirteen patients (3.7%) had an ACS or other adverse event within 30 days of testing, as summarized in Table 31. The events included one death from a CVS cause, which occurred outside of hospital within one week of the test being performed, in a patient aged 59 years. The troponin result on this patient was negative, and survey or other linked data were available on this patient. There was one cardiac arrest in a patient with CHD, one episode of cardiogenic shock and one episode of an unspecified cardiac arrhythmia. Three ACS patients did not undergo revascularisation.

The ED cohort had follow up information at 30 days for 1575 participants. 317 patients (20.1%) had an ACS or another adverse event within 30 days of cTn testing, significantly more than the ten patients (3.5%) with ACS in the GP cohort (*P* <0.001).

There were six deaths during the total follow up period, two of which had a CVS cause. Three deaths occurred outside of hospital. All patients had comorbidities and were aged 85 years or older.

Table 31: Adverse events within 30 days – GP and ED cohorts

		GP (n=355)	ED (n=1575)
ACS or other adverse event within 1 month		13	317
Types of adverse events:			
Death from CVS cause		1	8
Death from uncertain cause		0	0
Cardiac arrest		1	0
Cardiogenic shock		1	0
AMI - revascularisation	STEMI	1	128
	NSTEMI, AMI NOS	3	
AMI - no revascularisation	STEMI	0	84
	NSTEMI, AMI NOS	3	
UA - revascularisation		3	86
UA - no revascularisation		0	
Emergency revascularisation		NR	NR
Urgent revascularisation		NR	NR
Ventricular arrhythmia		0	NR
High degree AV block		0	NR
Heart failure requiring intervention*		NR	11

*3 admissions with heart failure, but intervention NR. ACS = acute coronary syndrome; CVS = cardiovascular, AMI= acute myocardial infarction, STEMI = ST elevation myocardial infarction, NSTEMI = Non-ST elevation myocardial infarction, NOS = not otherwise specified; AV block = atrioventricular block

3.4 Outcomes for survey patients in GP cohort

Of the 124 patients with both survey and linked data, there were 45 admissions or presentations to ED, including 18 ACS occurring in eleven patients.

Six ACS occurred within one month of the test, including one STEMI. All had pain onset more than 48 hours prior to testing and at least one CHD risk factor.

Two of these six ACS patients in this group had positive cTn results. One had typical pain with onset more than 48 hours before the test, three risk factors and an admission diagnosis of NSTEMI. One had atypical pain symptoms for more than 48 hours before the test was performed with one risk factor, and a diagnosis of STEMI. Both underwent revascularisation at that admission.

CHAPTER FIVE: DISCUSSION

1. KEY FINDINGS

1.1 Clinical characteristics of GP cohort

This study's first aim was to describe clinical characteristics of patients undergoing GP-initiated cTn testing, hypothesising that such patients are clinically different and at a lower risk of ACS to those who present directly to ED. The GP cohort were not all at low risk of ACS, with a majority having at least one CHD risk factor, and one in five having a risk factor profile placing them at high risk of ACS and associated adverse outcomes. Furthermore, most patients had pain typical of cardiac ischaemia, and most tests were performed within the 48 hour window where the risk of complications of ACS is highest.

However, in comparison to the ED cohort, the GP cohort did have a significantly lower prevalence of CHD risk factors, with the exception of diabetes, where the prevalence was similar.

1.2 GPs' knowledge of cTn's use and limitations

The second aim of this study was to examine GPs' knowledge of the use of cTn testing and its limitations. There was insufficient information from which to make firm conclusions about GP's knowledge of the test's sensitivity and specificity. Seventeen per cent of patients had impaired kidney function, one cause of a falsely positive result. Additionally, outcome data showed that cTn testing was performed on patients who had previously been admitted to hospital with heart failure, another cause of a false positive result. Unfortunately, it was not possible to assess whether these diagnoses were known to the requesting GPs, nor whether the renal impairment was a new finding on a test performed concurrently with the cTn test.

Regarding cTn's sensitivity, one in five cTn tests were ordered on patients who presented within 12 hours of symptoms when the test may be insufficiently sensitive. No serial testing was performed.

1.3 Effect of cTn on GP estimation of ACS likelihood and management

This study found that one third of GPs felt there was an intermediate or high pre-test likelihood of ACS as the cause of their patient's symptoms. A significant number of

GPs changed their assessment of likelihood of ACS in response to the test result. Despite this, there was no significant change in the GPs' intended management in response to the test result.

1.4 Outcomes of patients who underwent cTn testing in primary care

This study's final objective was to describe outcomes of patients who had a cTn test in general practice, specifically seeking outcomes of the occurrence of complications of an ACS and delay in diagnosis of ACS. Adverse events occurred within one month of testing in one in 25 patients, significantly less than in the ED cohort. An important finding was that one in four patients with negative test results presented to hospital with a cardiovascular symptom or diagnosis during follow up, and one in 25 presented within 48 hours of the test. One in ten patients with negative test results were admitted to hospital with ACS, one third of which were within one month of testing.

There were too few positive results to assess the risk of adverse or beneficial outcomes in patients who had a positive cTn test result, as only five tests were positive, of which only two had survey data available. Only one patient had a beneficial outcome of a positive test result contributing to ACS diagnosis, with an increase in estimated likelihood of ACS as a result of the test.

Regarding delay, the median time from patient presentation to specimen collection was over one hour and the median time from specimen collection to result availability was over two hours, although not all patients had this information supplied. In patients presenting with ACS within 48 hours of their test, the median delay from specimen collection to hospital presentation was over six hours.

2. INTERPRETATION

2.1 Clinical characteristics of GP cohort

The finding that the majority of patients undergoing cTn testing have typical pain of ACS or pain of short duration was unexpected, and there may have been other factors not detected by the survey that reduced the risk status of patients. Examples of such information include ECG findings or previous negative invasive investigations for CHD.

The cumulative number of CHD risk factors in the ED cohort was significantly greater than the GP cohort. This may be explained by high risk patients heeding earlier advice to present to ED in the event of ACS symptoms. Certainly, there are substantial National Heart Foundation awareness campaigns marketed to high risk patients and their GPs about the warning signs of ACS, advising them to call emergency services in the event of the development of ACS symptoms[168]. Additionally, patients with multiple CHD risk factors are more likely to present with STEMI[169,170], and patients with STEMI or symptoms of haemodynamic instability are more likely to call emergency services rather than present to a GP[157,171]. Regardless, it is concerning that cTn was requested on GP cohort patients who were automatically at high risk of ACS and adverse outcomes based on a past history of CHD, as prior CHD is a well-known predictor of short term mortality due to ACS[172,173].

Some tests were clearly ordered on low risk patients in response to patient request, as has been reported elsewhere[174,175]. Requesting GPs commented that “the test was mainly arranged to satisfy the patient that this was unlikely cardiac in origin”, that “the likely diagnosis was anxiety and panic but the patient felt that the chest pain was a prominent symptom”, and that “in this case the cTn test was expected to be negative and it provided some reassurance to the patient”. It is worth noting that a negative test in this context may not resolve the patient’s worry about illness, as doctors are known to overestimate the value of testing in reassuring the patient when the probability of serious disease is low[176].

2.2 GPs’ knowledge of cTn’s use and limitations

There were instances suggesting incomplete understanding of cTn’s reduced sensitivity early after symptom onset, shown by the lack of serial tests ordered in patients presenting within 12 hours. This correlates with findings of other authors[149,154,167]. Similarly, there were instances of the test being performed in the presence of comorbidities that reduce the test’s specificity. Laboratory advice was not provided to the requesting doctor with the test result about these limitations. There is

an opportunity for education to GPs by laboratory-initiated advice, as such notifications have been shown consistently to alter GP practice[177].

2.3 Effect of cTn on GP estimation of ACS likelihood and management

cTn testing occurred most often in the setting of a less than 5% pre-test likelihood of ACS, to further reduce the probability of ACS as a diagnosis. This is consistent with other literature stating that cTn testing in primary care substantially reduces the clinical likelihood of ACS[178], with the findings of this this study having the added weight of statistical significance. Interestingly, when a GP retained an intermediate or high post-test likelihood in the face of a negative test result, the patient did not have a high risk clinical picture; few patients in this setting had typical pain, multiple risk factors or the recent onset of symptoms. It is possible that there were other patient factors not detected by the survey that were influencing the GP to maintain a higher estimation of likelihood in these situations, such as a low pre-test probability of other, non-ACS diagnoses.

In contrast to studies in the systematic review[156,179], this study showed that cTn test results did not significantly affect GP management. Perhaps requesting GPs may have been practising in a defensive manner, out of a fear of litigation. A cTn test is likely to be ordered in this context given that a high proportion of medical negligence claims relate to myocardial infarction[180], and that the fear of litigation is a powerful motivator for diagnostic test requesting[177,181].

2.4 Outcomes of patients who underwent cTn testing in primary care

Over the course of the study, rates of ACS and other adverse outcomes were higher than reported elsewhere[150], though the period of follow up was longer. Although cTn tests were ordered on patients having some risk of short term adverse outcomes, such outcomes did not eventuate in large numbers in the period of this study, with few positive tests or adverse outcomes within one month of the test. There were too few deaths for a meaningful comparison of mortality rates in this study with other reports in the literature.

The rate of presentation to hospital with CVS symptoms was high, and a number of patients presented within hours of a negative test, suggesting the negative test result may not have been reassuring for the patient or the GP. This finding also underscores the difficulty in excluding serious causes of CVS symptoms in the community – even if

a negative cTn is taken to exclude ACS, other serious causes of CVS symptoms requiring hospital assessment remain in the differential diagnosis[114,182-184].

The admission rate for patients with negative test results was higher than expected from the literature, with admissions in 19% of the patients in this study, compared with 14 to 16% elsewhere[150,151]. Possible reasons for the higher admission rate in this study include a longer period of follow up, and a higher number of patients who were admitted with unspecified chest pain and subsequently discharged. It was not clear if the admissions in this study were to short stay emergency observation wards. These wards are used increasingly since the 2009 introduction of the Four Hour Rule in Perth tertiary hospital EDs, where a target of 85% of patients presenting to ED would be either discharged home or admitted to a ward within four hours of presentation[185]. Previously, some patients would have remained in ED for their period of observation, and therefore not been classed as admitted. The studies reporting lower rates were located in cities where the Four Hour Rule had not yet been implemented.

There was evidence of delay at multiple points for patients undergoing cTn testing. This is despite guidance from laboratories to GPs about the need to avoid delay in cTn testing, and despite recommendations from pathology bodies about the need for timely communication of cTn test results to the requesting doctor[120,186]. Firstly, the median time from patient presentation to specimen collection was over one hour, where the interval from patient presentation to specimen collection was supplied. Even allowing for time taken to complete the consultation and to undergo an ECG (if one was performed) this suggests an under-appreciation of the urgent nature of the test by either the patient or the GP, and possibly no triage for test urgency performed at the specimen collection centre. Notably, laboratory specimen collection guides, where available, do not indicate the urgent nature of cTn testing[187].

Secondly, patients tended to present to the GP in the early part of the day, but wait some time before having blood collected, as most specimens were collected after 12 midday. In these cases it is likely that results would not be available until outside surgery hours. This poses a risk to the patient if systems are not in place for handling such results, and indeed deaths have occurred in the absence of such systems[118].

Thirdly, there was potential for pre-hospital delay due to laboratory factors, with the median time from specimen collection to result availability being over two hours. This is substantially outside the recommended 60 minute period suggested by National Heart

Foundation guidelines[27]. For the most part, though, turnaround times were less than 60 minutes where the laboratory was co-located with the specimen collection centre. This suggests that much of the delay due to laboratory factors relates to the geographical location of the specimen collection centre at which the patient chooses to present, which is of course out of the control of the laboratory.

Finally, the median time from specimen collection to hospital presentation was over six hours in patients presenting with ACS within 48 hours of their test. This is comparable to delay reported elsewhere[153]. Again, this falls outside the recommended two hour interval from presentation to reperfusion, if reperfusion is indicated[10,27,42]. Admittedly, none of the patients in this study who presented with ACS within 48 hours were ultimately diagnosed with STEMI, making early reperfusion less critical to their long term outcomes.

3. STRENGTHS AND LIMITATIONS

3.1 Strengths

A strength of this research was consecutive recruitment of an unselected group of GPs requesting cTn tests in order to reduce the risk of selection bias, as opposed to use of a database of selected GPs in other studies[179]. Although the laboratories providing results were only two of five laboratories in Perth, posing a risk of selection bias, it was confirmed before study commencement that collection centres were distributed evenly over the metropolitan area. It was also noted that one laboratory (St John of God) required a patient co-payment which may have led to participants from this laboratory being of a higher socioeconomic status. With this in mind, a government funded laboratory (PathWest) was used for the second laboratory.

Measurement bias was minimised in the survey design by the provision of an explicit definition of clinical factors, such as family history, smoking status and the nature and location of pain. Using linked data sources to obtain outcome data, rather than relying upon patient or GP recall, also increased the precision of results.

3.2 Limitations

3.2.1 Selection bias

The survey response rate was not as high as predicted, lower than in other studies[178,179]. The construction of the survey may be responsible for this, as it included a question about events in the next 30 days. Some GPs may have been waiting for the 30 days interval to lapse before completing it, and GP survey response rates are known to decrease over time[188]. All GPs volunteering to take part in this study were followed up once in order to increase response rates. A third contact would have been valuable, as two follow up contact attempts have been shown to be more effective at increasing response rates than a single follow up[189]. Other proven methods to increase response could have been the use of a mixed mode survey, such as a response tool built into electronic medical record result systems[189]. This would have avoided relying upon the manual work involved in responding to a facsimile. The limited resources available for this study did not permit the additional time taken for a second follow up, nor design of an electronic tool.

It would have been ideal to compare the GP cohort with a group of patients who initially presented to their GP but were referred directly to ED. The ED dataset was chosen for its comparable geographic data, demographics and outcome measures, but referral source was not collected as part of that dataset. No local research collecting this

information could be identified, and budgetary constraints precluded collection of ED data specifically for this study.

The linked data had some omissions. Admission data were not provided for some patients who had hospital admission as the ED discharge destination. Attempts were made to track such patients using age and date of presentation but this was not completely effective.

Most importantly, the number of adverse outcomes in the linked data was very small. The retrospective study recorded approximately 35 urban tests per week with 5% of these positive. This led to an initial assessment that an appropriately sized study was possible. It is likely that many of the results in the retrospective dataset which were classified as urban were in fact from Bunbury, a larger regional centre. At the time of designing the study, it was planned to include patients in Bunbury. That centre is served by a tertiary emergency department and has access to interventional cardiology services, so was felt to be sufficiently similar to tertiary centres in urban Perth. However, once the prospective study was underway it soon became apparent that the patients attending collection centres in Bunbury lived in outlying rural areas. As a result, the GP's decision making was likely to be influenced by the patient's increased travel time, and therefore not comparable to that of urban GPs. Had this issue been recognised in the design stage of the study, additional efforts would have been made to recruit patients from other urban pathology providers.

3.2.2 Information bias

There were issues with the accuracy of time intervals recorded as part of the assessment of delay. No objective measurements of time intervals were obtained beyond those recalled by the patients. Many GPs provided the same time for presentation and specimen collection, and with hindsight this wording was not clear on the survey. Also in respect of time measurement, the interval between result availability and the GP taking action upon the results was not measured on the survey, and it would have been valuable to do this in order to assess the component of pre-hospital delay due to doctor behaviour.

The accuracy of clinical information was suboptimal, as there was no corroboration of presenting symptoms as reported by the patient to the GP. There were also incomplete data fields for risk factors in some of the surveys from one laboratory, which in retrospect related to an error in the paper layout of the survey that was subsequently

corrected. Independent verification of questionnaire responses for clinical information and time intervals would have reduced the risk of this source of bias, but it was decided not to proceed with independent verification in the interests of confidentiality.

It would have been valuable to extract information on potential confounders, such as diagnoses causing falsely positive cTn results. Review of the outcome data revealed patients undergoing cTn testing who had previously been admitted to hospital with heart failure, but it was not clear from the data collections whether this was chronic heart failure, nor whether this diagnosis was known to requesting GPs. While some patients had renal impairment demonstrated by a reduced eGFR, it was not possible to assess whether this was a new finding at the same time as cTn testing or whether this information was already known. Only a minority of patients had previously documented renal function tests from that laboratory. It was decided while designing the survey that adding an exhaustive list of causes of false positive cTn would have lengthened the survey unacceptably. Despite this, many causes of non-coronary cTn on a comprehensive list are of very low frequency in GP, so an edited list of conditions likely to present in primary care could have been included.

The survey did not collect ECG results. Again, it was felt that this would lengthen the survey unacceptably and discourage participation. Additionally, the reliability of GP interpretation of ECG data is not certain[92]. The task of providing the original ECG rather than an interpretation was felt to be too onerous for the GP and also posed a risk of patient identification. Similarly, quantitative data on blood pressure or lipid levels was not sought from GPs, due to the effort required to provide this information being a possible disincentive to participate in the study. Without this information, it was not possible to apply measures of cardiovascular risk such as the TIMI score or the National Health Foundation risk assessment criteria and the absence of these measures of risk limits the populations to which this study's data can be compared.

In regard to the accuracy of the linked data, it was not possible to classify outcomes fully according to standardised data definitions for ACS research. As an example, standardised definitions only include heart failure as an adverse outcome if it requires intervention. Identification of this subgroup would have required access to medication charts in hospital records, compromising patient confidentiality. There were also instances where CHD was not accurately classified as ACS or otherwise, instead being classed as CHD or angina not otherwise specified. This is likely to have led to underestimation of the true numbers of ACS, though the scale of this is small.

4. GENERALISABILITY AND FUTURE IMPLICATIONS

4.1 Generalisability of findings

The findings of this study have important implications for patient safety. It shows that there are inherent delays in GP-initiated cTn testing. Some of these delays can be shortened, for example by GPs directing patients to a collection centre located close to a laboratory. Further, GPs could impress upon patients the need to have their sample collected as soon as practicable, and must arrange to follow up results in a timely manner. However, even with optimal practices, some delay is unavoidable.

This study also shows that patients undergoing GP cTn testing often have CHD risk factors. The prevalence of obesity, diabetes and hyperlipidaemia in general practice has risen since this study was undertaken, and the presence of these risk factors substantially increases the likelihood of short term ACS complications. It follows, then, that the risk of ACS adverse outcomes in the GP population may also rise in the future[190-192]. Although this study was too small to identify adverse outcomes occurring early in the course of the ACS caused by a period of pre-hospital delay, such adverse outcomes may well occur eventually.

There is a clear need to inform GPs about the limited sensitivity of cTn testing, as based on this study understanding may be suboptimal. A negative cTn test does not confer freedom from ACS, as shown by the finding that one in 25 patients with a negative cTn was admitted with ACS within a month of the test. This finding supports results of other research which state that patients deemed at low risk of ACS still carry a residual risk of subsequent events[193]. GPs have been known to underestimate five-year risk of a cardiovascular event on clinical grounds[194], and must be particularly careful to avoid equating a negative cTn test result with the absence of CHD. Instead, they should proceed with more sensitive investigations for CHD if there is any clinical uncertainty, and clearly communicate safety netting strategies to the patient[87].

4.2 Future use of cTn testing in primary care

Point of care testing (POCT) for cTn is an attractive option which might reduce delay and its attendant risks. There is evidence showing the efficacy of POCT in control of chronic conditions such as diabetes and conditions requiring anticoagulation[110]. Australian GPs are certainly keen to use POCT for cTn, with 43% of GPs in a 2013 survey indicating they would make use of the test if it were available[**195**]. However, a recent systematic review of POCT of cTn levels in the pre-hospital setting reported

insufficient sensitivity of the test, with a negative predictive value of 57-95%[108]. In addition, there is currently no Medicare rebate for POCT for cTn in general practice, further limiting its uptake in the short to medium term[196].

Another issue that emerges from this study's findings is that cTn is ordered frequently on patients with conditions that cause a detectable highly sensitive cTn level (hsTn). Some authors have foreshadowed a plague of 'troponinitis' from indiscriminate hsTn use in hospital patients[22,197,198]. It is also known that there is a progressive increase in rates of GP pathology test ordering in general[124]. Consequently, as laboratory uptake of hsTn becomes widespread, the rates of positive hsTn tests in primary care are likely to increase. Unnecessary hospital referrals may result, if referral is initiated by GPs in response to a single elevated value, which seems likely based on the suboptimal rates of serial testing in this and other studies[150,167]. While recent research states that hsTn does not increase the diagnosis of ACS and the burden of possible ACS patients in emergency departments[199] , that work was conducted in a controlled hospital setting with easy access to testing protocols and a frequent throughput of ACS patients, such that requesting hospital doctors would be very familiar with the hsTn testing algorithm used at that site. GPs appear to require education about the need for serial cTn testing in order to become equally familiar with the process of hsTn testing in the community.

4.3 Future implications for primary care research

This study has shown that conducting primary care research on an adequate scale on low prevalence conditions such as ACS is challenging. For example, the ideal design to address the objectives of this study would be randomisation of general practices to either having access to cTn testing or not having access to cTn testing. However, an appropriately sized study of this design would require many thousands of patients. Moreover, it is difficult to gather clinical data on low prevalence conditions by survey, as GP response rates to surveys are low, often 30% or less[200]. Recruitment rates for survey based studies are falling, with time and workload pressures cited as reasons[188,189]. Non-monetary incentives do not appear to influence response rates[189].

In future investigation of low prevalence conditions, it might be possible to increase sample sizes by using computerised research databases. The National Prescribing Service (NPS) MedicineInsight program[201] and the UK Clinical Practice Research Datalink[202] are examples of established multicentre groups which contribute data to a common database. However, the routine data collected do not include textual descriptions of the nature of the clinical presentation, as was required for this study.

One option is to collect more detailed information from selected practices within such networks[87]. Research could be conducted concurrently into the diagnostic approach to other serious low prevalence causes of chest pain, such as pulmonary embolism and use of D-dimer testing. Another method is the use of a web-based survey. GPs could be invited to participate by the laboratory when they check electronic results, with any cTn test result including a link to the survey. Advantages would be a shorter response time, improved accuracy of data around timing of presentation, and the ease of obtaining clinical information, as the GP would be accessing the patient's electronic record in order to note and action the result. There is the potential for coverage error as not all practices use electronic medical records. This effect would be small, with at least 93% of GPs using computers for pathology test ordering based on 2012 data[203]. Security of patient data would need to be considered if pursuing this approach.

5. CONCLUSION

This study concludes that GP use of cTn testing for ACS diagnosis in primary care does not meet the definition of appropriateness on a number of grounds. cTn is ordered on patients at high risk of ACS and adverse outcomes of ACS occur in patients who undergo GP-initiated cTn testing, including some events which occur within days of testing. cTn testing adds to delay in hospital presentation, though whether this delay contributes to adverse outcomes remains unclear. Furthermore, GP-initiated cTn testing has not been shown to be beneficial by detecting unexpected ACS, due to low numbers of positive tests. Most importantly, a negative cTn test is not reassuring and does not equate to no risk of ACS.

There are potential gaps in GP understanding of cTn testing's limitations. Additionally, GP management of patients with possible ACS does not change as a result of cTn testing, despite influencing estimation of likelihood of ACS. While the test is most often used to justify GP management rather than hospital referral, this benefit is likely to be small, as the ED burden of general practice patients is not great in any case[96].

GPs are left in a difficult situation. The consequences of missing a diagnosis of ACS can be grave, yet there are no reliable clinical predictors of ACS[81,82,84], and the investigations available in primary care have limitations, as this study shows. At the same time, GPs have an important role as gatekeepers of the health system[204-206]. A failure to accept any uncertainty may lead to unnecessary investigation and referral, which themselves are potential causes of patient harm and health system costs.

What a GP can do is to employ other strategies in the diagnosis of ACS, such as their their initial impression or "gut feeling", their knowledge of the cumulative effect of clinical risk factors, and the use of safety netting, all of which have supporting evidence. Additionally, they should counsel patients at risk to present to hospital in the event of ACS symptoms, and initiate primary and secondary prevention strategies for CHD. In this way, GPs will still fulfil their key role in ACS management without the use of cTn. The appropriate use of cTn testing for ACS diagnosis in primary care, then, may well be to not use cTn tests at all.

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APPENDICES

Appendix 1: Search strategy

1.1 Medline, EBM Review and Embase combined search strategy

1. exp Cardiovascular diseases/ (4224045)
2. exp Acute Coronary Syndrome/ (34096)
3. exp Angina, Unstable/ or exp Myocardial Infarction/ or exp Coronary Disease/ or exp Acute Coronary Syndrome/ (684955)
4. exp Coronary Artery Disease/ (228567)
5. exp Coronary Thrombosis/ (11895)
6. exp Dyspnea/ (80823)
7. exp Arrhythmia/ (444708)
8. exp Fatigue/ (142053)
9. exp syncope/ (15776)
10. 8 and heart.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (20123)
11. exp Chest Pain/ (102494)
12. general practitioner.mp. or exp General Practitioners/ (80222)
13. family practice.mp. or exp Family Practice/ (121024)
14. primary health care.mp. or exp Primary Health Care/ (191722)
15. exp Physicians, Primary Care/ or exp Physicians, Family/ (72149)
16. 12 or 13 or 14 or 15 or primary care.mp (411562)
17. troponin.mp. or exp Troponin C/ or exp Troponin/ or exp Troponin T/ or exp Troponin I/ (47191)
18. 16 and 17 (159)
19. delay.mp. or exp delay/ (252335)
20. Time Factors.mp (1029166)
21. misdiagnosis.mp. or Diagnostic Errors/ (77207)
22. Resuscitation/ or Emergency Medical Services/ or Time Factors/ or prehospital.mp. (1462509)
23. Heart Arrest/di [Diagnosis] (2236)
24. prehospital care.mp. (2496)
25. Point-of-Care Systems/og, st, td, ut [Organization & Administration, Standards, Trends, Utilization] (1322)
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 9 or 10 or 11 (4380798)
27. 22 or 23 or 24 (1464347)
28. 19 or 20 or 21 (1612065)
29. 16 and 17 and 26 (150)
30. 16 and 17 and 26 and 28 (10)
31. 17 and 26 and 28 (1682)
32. 16 and 17 and 28 (11)
33. 16 and 26 and 28 (1756)
34. 17 and 27 and 28 (1690)
35. 16 and 17 and 25 (1)
36. 16 and 25 and 27 (4)
37. 16 and 17 and 27 (24)

38. 17 and 25 and 27 (9)

39. 16 and 26 and 27 and 28 (433)

40. 18 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (3915)

41. limit 40 to (humans and yr="1995 -Current") (3223)

42. remove duplicates from 41 (2709)

1.2 Web Of Science search strategy

#1 Topic=(general pract* or family pract* or primary care or family physician) (282671)

#2 ts =(acute coronary syndrome) OR ts=(chest pain) or ts=(cardiovascular disease) or ts=(coronary artery disease) or ts=(coronary heart disease) or ts=(Angina) or ts=(Myocardial Infarction) (466241)

#3 ts =(Coronary Thrombosis) or ts=(Dyspnea) or ts=(arrhythmia) or ts=(Fatigue) or ts=(syncope) (224322)

#4 #3 OR #2 (659247)

#5 ts =(troponin) (20445)

#6 ts =(delay) or ts =(error*) (1083775)

#7 ts =(Point-of-Care Systems) (2582)

#8 ts =(prehospital care) (3077)

#9 #5 and #2 and #1 (187)

#10 #9 and #6 (11)

#11 #6 and #5 and #2 (246)

#12 #6 and #5 and #1 (13)

#13 #8 and #6 and #5 (7)

#14 #7 and #5 and #1 (4)

#15 #8 and #7 and #1 (3)

#16 #8 and #5 and #1 (8)

#17 #8 and #7 and #5 (5)

#18 #7 and #6 and #5 and #1 (2)

#19 #5 and #1 (243)

#20 #6 and #5 and #2 and #1 (11)

#21 #8 and #6 and #2 and #1 (118)

#22 #6 and #2 and #1 (694)

#23 #22 or #21 or #20 or #19 or #18 or #17 or #16 or #15 or #14 or #13 or #12 or #11 or #10 or #9 (1163)

#24 topic=(poct) (573)

#25 #24 or #7 (2976)

#26 #25 and #2 and #1 (35)

#27 #23 or #26 (1167)

.2.3 Scopus search strategy

1. (TITLE-ABS-KEY(Cardiovascular diseases) OR TITLE-ABS-KEY(Acute Coronary Syndrome) OR TITLE-ABS-KEY(Angina,Unstable) OR TITLE-ABS-KEY(Myocardial Infarction) OR TITLE-ABS-KEY(Coronary Disease) OR TITLE-ABS-KEY(Coronary Artery Disease) OR TITLE-ABS-KEY(Coronary Thrombosis) OR TITLE-ABS-KEY(Dyspnea) OR TITLE-ABS-KEY(chest pain) OR TITLE-ABS-KEY(Arrhythmia) OR TITLE-ABS-KEY(Fatigue) OR TITLE-ABS-KEY(syncope/)) AND PUBYEAR > 1989 (985,377)

2. (TITLE-ABS-KEY(General practice) OR TITLE-ABS-KEY(Physicians,Family) OR TITLE-ABS-KEY(Physicians,Primary Care) OR TITLE-ABS-KEY(Primary Health Care) OR TITLE-ABS-KEY(General Practitioners)) (430,531)

3. TITLE-ABS-KEY(troponin) AND PUBYEAR > 1989 (24,847)

4. (TITLE-ABS-KEY(delay) OR TITLE-ABS-KEY(misdiagnosis) OR TITLE-ABS-KEY(Diagnostic Errors)) (520,036)

5. (TITLE-ABS-KEY(Resuscitation) OR TITLE-ABS-KEY(prehospital) OR TITLE-ABS-KEY(Time Factors) OR TITLE-ABS-KEY(Emergency Medical Services)) (1,900,643)

6. 1 and 2 and 3 (209)

7. 1 and 2 and 3 and 4 (15)

8. 1 and 3 and 4 (328)

9. 2 and 3 and 4 (18)

10. 3 and 4 and 5 (111)

11. TITLE-ABS-KEY(point of care testing) (9,804)

12. 2 and 5 and 11 (167)

13. 2 and 3 and 5 (67)

14. 3 and 5 and 11 (77)

15. 2 and 3 and 4 and 5 (9)

16. 2 and 3 (253)

17. 1 and 2 and 4 and 5 (404)

18. 6 or 7 or 8 or 9 or 10 or 12 or 13 or 14 or 15 or 16 or 17 (1081)

Appendix 2: Additional literature sources

2.1 Grey literature sources

SIGLE (System for Information on Grey Literature) database. Available at www.opensigle.inist.fr
NTIS (National Technical Information Service). Available at www.ntis.gov
Proquest Dissertations and Theses
BIOSIS Previews

2.2 Journals and conference proceedings handsearched:

2.1.1 Australian primary care, emergency medicine and cardiology journals

1. Emergency Medicine Australasia
2. Medical Journal of Australia
3. Australian Family Physician
4. New Zealand Medical Journal

2.2.2 International primary care journals (chosen according to impact factor)

1. Annals of Family Medicine
2. Scandinavian Journal of Family Practice
3. Family Practice
4. Journal of the American Board of Family Medicine
5. Biomed Central Family Practice
6. British Journal of General Practice
7. Quality and safety journals
8. BMJ Quality and Safety
9. Clinical risk

2.2.3 Other journals

1. Journal of Clinical Pathology

Appendix 3: GP cohort questionnaire

INFORMATION SHEET AND CONSENT FORM

Troponin testing for diagnosis of acute coronary syndromes in primary care

Dear Colleague,

Last week you were sent an information sheet and a questionnaire relating to troponin testing ordered by you.

This test was requested on (date) on your patient (name).

The study is being conducted by the School of Primary, Aboriginal and Rural Health Care (SPARHC) at the University of Western Australia in collaboration with the laboratories of St John of God Pathology and Pathwest.

We are analysing all troponin test results ordered by general practitioners in the six month period starting from March 2009. We are collecting information on the clinical characteristics of these patients, their cardiovascular risk factors, the GP's perception of the cause of their symptoms and their management after the test result was known.

From this we hope to understand if troponin testing is safe to be done in general practice. We hope to show that:

- Troponin testing can be safely used in general practice on a certain group of patients, who are likely to be those who present late in the course of their illness or with atypical symptoms;
- GPs have good knowledge of the use and limitations on troponin testing.

We would be very grateful if you could complete this survey. We estimate that it will take less than 5 minutes to complete including time to access records. Thank you very much for your assistance.

Dr Helen Wilcox
Senior Lecturer, Discipline of General Practice

Professor Jon Emery
Head of School

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University of Western Australia
328 Stirling Highway, Claremont, WA 6010
Telephone 08 9449 5121
Facsimile 08 93846238
helen.wilcox@uwa.edu.au

Consent form

I, (Name of GP), have read the information provided and any questions I have asked have been answered to my satisfaction. I agree to participate in this activity, realising that I may withdraw at any time without reason and without prejudice. I understand that all information provided is treated as strictly confidential and will not be released by the investigator. The only exception to this principle of confidentiality is if documents are required by law. I have been advised as to what data is being collected, what the purpose is, and what will be done with the data upon completion of the research.

I agree that research data gathered for the study may be published provided my name or other identifying information is not used.

_____ _____

Participant Date

PLEASE FAX THIS CONSENT FORM WITH COMPLETED QUESTIONNAIRE TO:……..

The Human Research Ethics Committee at the University of Western Australia requires that all participants are informed that, if they have any complaint regarding the manner, in which a research project is conducted, it may be given to the researcher or, alternatively to the Secretary, Human Research Ethics Committee, Registrar's Office, University of Western Australia, 35 Stirling Highway, Crawley, WA 6009 (telephone number 6488-3703). All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

This information will be sent to a researcher who is employed within (laboratory). In order to maintain your privacy and that of your patient, the researcher will remove all identifying information prior to forwarding test requests and results to the Chief Investigator who will analyse the data.

The patients on whom the test was performed will not be made aware of their, or your, involvement in the study. Data will be kept within secure storage facilities at the laboratory and at the School of Primary, Aboriginal and Rural Health Care and access to this is only available to the study investigators. The data will be destroyed after the completion of the study which is estimated to take two years. Information will not be released to any third party unless required by law.

Approval has been granted by the University of Western Australia's Human Ethics Research Committee for this study. The study conforms to the NHMRC National Statement on Ethical Conduct in Human Research (2007). Funding for the project has been granted through the Primary Health Care Research, Evaluation and Development which is supported by the Commonwealth Government. Neither of the participating laboratories have any financial interest in the project.

Voluntary participation and withdrawal from this project

You are free at any time to withdraw consent to further participation without prejudice in any way. You need give no reason for your decision and the record of your participation will be destroyed on your request.