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ORIGINAL ARTICLE

What is the Yield of Testing for Coronary Artery Disease after an Emergency Department Attendance with Chest Pain?

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Background Guidelines recommend testing for coronary artery disease (CAD) for emergency department (ED) patients with a negative workup for acute coronary syndrome (ACS). The rationale is that, although myocardial infarction has been ruled out, the presentation could still indicate cardiac ischaemia. Evidence supporting this recommendation is weak.

Methods Planned sub-study of prospective cohort study of ED chest pain patients with a negative ACS workup who were discharged. Primary outcome of interest was occurrence of major adverse cardiac events (MACE) within 30 days. Secondary outcomes were rate of combined MACE or revascularisation and rates and outcome of referral for CAD testing. Analyses were descriptive.

Results 742 patients were included; median age 56, 52% male. There were two MACE within 30 days (0.3%; 95% CI 0.07–1%). Two patients had revascularisation without ACS - combined MACE or revascularisation rate 0.5% (95% CI 0.2-1.4%). Seventy-five per cent of patients with adverse events had previously known CAD. There was no statistically significant difference in outcome between those referred for testing and those who were not. Age, TIMI score 0-1 and absence of known CAD performed well as potential discriminators for selective testing.

Conclusions In our study the rate of MACE within 30 days was very low, coronary intervention was rare and most patients with MACE or revascularisation had previously known CAD. For young patients, those without known CAD and those with a low TIMI score, the risk of clinically significant CAD appears to be very low. It adds to the case for abandoning routine testing for CAD.

Keywords Chest pain • Emergency Department • Non-invasive testing

Introduction

Chest pain is a common reason for presentation to Australasian emergency departments (ED). The vast majority of patients investigated for acute coronary syndrome (ACS) have a negative ACS workup; only approx. 13-23% rule in for ACS [1–3]. Current Australasian guidelines [4] recommend consideration of testing for myocardial ischaemia or coronary artery disease (CAD) for ED patients with a negative workup for ACS who are discharged from ED. Such testing may be functional or anatomic. The rationale is that although myocardial infarction (MI) has been ruled out, the presentation could still indicate coronary ischaemia or CAD which might benefit from treatment. The guideline authors acknowledged that this was a consensus recommendation and that evidence supporting this recommendation is weak [4].

Routine testing is resource intensive [5] and may result in false positive tests and further unnecessary investigations

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and procedures. Since the guidelines were published a small body of evidence has challenged the need for routine testing showing adverse event rate <1% and low rates of identification of clinically relevant CAD [6–8]. Some authors have suggested clinical characteristics for the identification of very low risk groups including age and absence of known CAD [9,10].

The aim of this study was to determine the rate of major adverse cardiac events (MACE; defined as death, new MI, survived cardiac arrest, cardiogenic shock, life-threatening arrhythmia) in patients who underwent a rule-out ACS process in ED and were discharged home and to compare outcomes between those who were referred from ED for testing for CAD and those who were not.

Methods

This was a planned sub-study of a prospective cohort study conducted in the ED of a community teaching hospital with an annual adult ED census of approximately 36,000 between 16 April 2012 and 3 February 2013.

Patients were screened for inclusion if they presented with chest pain. Exclusion criteria were chest pain due to trauma, aged <18 years, no chest pain within 24 hours of the index ED visit, chest pain lasting <10 minutes, no ECG or no troponin assay performed within 24 hours of index ED visit, a clear alternative diagnosis at initial medical officer assessment, ischaemic ECG changes at ED presentation, haemodynamic instability, advanced terminal disease, inability to communicate in English and declined/unavailable for follow-up. Patients transferred to other hospitals and self-discharging against advice were also excluded because of inability to obtain accurate follow-up data.

For this sub-study, patients admitted to hospital wards or transferred to another hospital for admission were also excluded; i.e. only patients with a negative ACS workup who were discharged from ED (including ED observation unit) were included. The ACS workup included clinical assessment, serial ECG and serial biomarker analyses (Troponin I, TnI-Ultra by Siemens Diagnostics performed on an Advia Centaur analyser). Biomarker assays were taken at ED arrival and at least three to four hours later or six hours from symptom onset in accordance with current guidelines [4]. Decision to admit was made by the treating ED clinician in consultation with the duty cardiology team. During the study period, doctors were encouraged (using educational sessions, pre-printed forms and pathway reminders) to refer patients for outpatient testing for myocardial ischaemia/CAD directly from ED however clinical judgment was allowed to guide discharge and follow-up planning.

In the study hospital the pathway for care for patients with chest pain suspicious of ACS is clinical assessment and risk stratification by an ED clinician, serial ECG and biomarker assays with observation including continuous cardiac monitoring in ED or in the Emergency Department Observation Unit. Patients with negative ACS workup who are assessed as non-high risk are discharged for further testing (if required) or follow-up in the community. Those assessed as high risk or with positive ECG or biomarkers are referred to Cardiology. The study hospital does not have a chest pain unit.

Data collected included demographics, cardiac risk factors, biomarker assay results, ED disposition, final diagnosis, data to calculate GRACE risk and freedom from events scores and TIMI score, referral to and attendance at outpatient testing for CAD and seven- and 30-day outcome. Known CAD was defined as previous MI or coronary artery bypass grafts, known coronary artery stenosis >50% or previously diagnosed angina pectoris. Seven- and 30-day outcome was assessed by review of medical records and structured telephone follow-up.

The primary outcome of interest was the occurrence of MACE within 30 days, comparing patients referred for testing for myocardial ischaemia/CAD with those who were not. MACE was defined as death, new MI, survived cardiac arrest, cardiogenic shock or life-threatening arrhythmia. These mirror adverse events as reported in similar studies. Final diagnosis was as assigned by the treating clinician. An independent cardiologist adjudicated on final diagnosis and outcome for the subgroups where patients with troponin elevations on any assay exceeded the 99th centile and were coded as non-ACS and for patients without troponin elevations who were coded as ACS. The secondary outcomes of interest were the composite of MACE or revascularisation at 30 days between referred and non-referred group and rates of compliance with ED referral for CAD testing. We also conducted an exploratory analysis for adverse outcomes using age (<40 and <50), absence of known CAD and TIMI score 0-1 as potential discriminators in an attempt to identify a very low risk group in whom testing might not be required.

Analysis was by descriptive statistics and intention to treat analysis. No formal sample size calculation was performed. The study was approved by the institutional ethics panel and was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12612000990820). Patients provided verbal consent to telephone follow-up.

Results

742 patients were included in the analysis. (Figure 1) Median age was 56 (IQR 46-67) and 52% were male. Characteristics of patients are shown in Table 1.

There were two MACE within 30 days (0.3%; 95% CI 0.07 – 1%); both non-ST segment elevation MI within one week of index visit. A further two patients had revascularisation without ACS within 30 days giving a composite MACE or revascularisation rate of 0.5% (95% CI 0.2-1.4%). Clinical features of these patients are shown in Table 2.

340 patients were referred from ED for CAD testing (46%). Of these, 265 completed testing (78%; 95% CI 73-82%). There was no statistically significant difference in MACE or combined MACE or revascularisation rates between those referred for testing and those who were not.

265 patients underwent testing for CAD; 53 stress ECG, 176 stress radionucleotide scan, 26 stress echocardiography, four

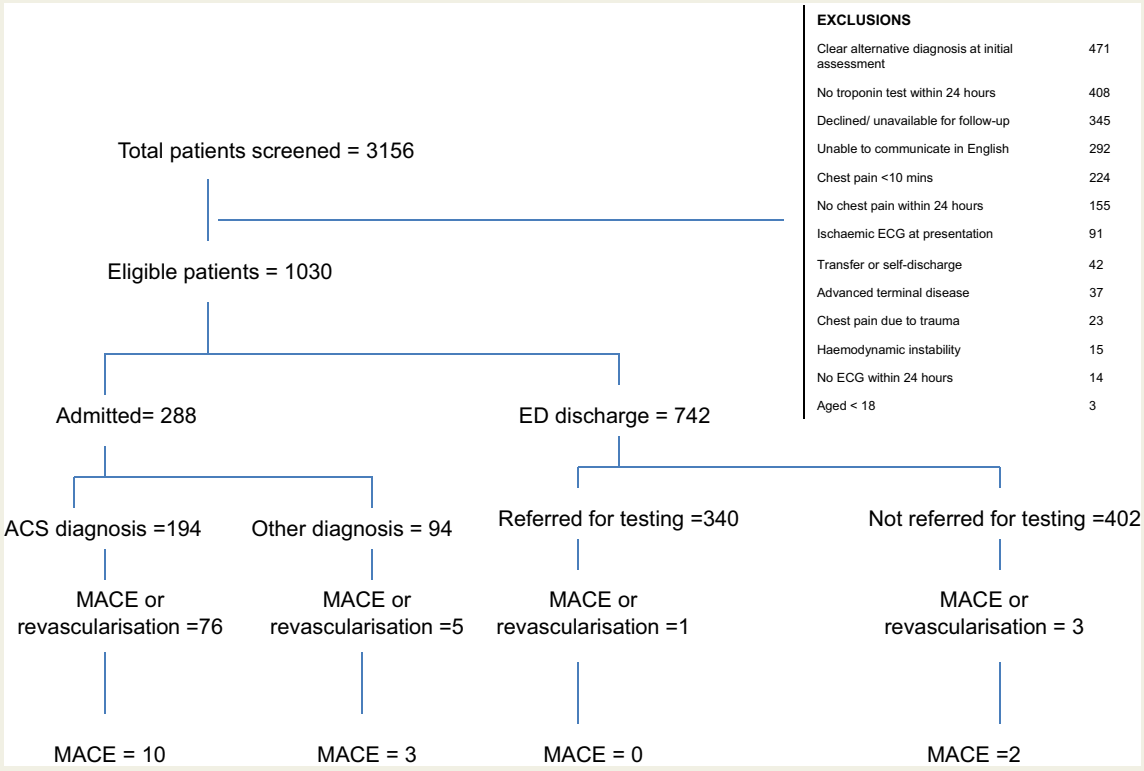

Figure 1 Sample derivation.
ACS = acute coronary syndrome; MACE = major adverse cardiac events.

Table 1 **Characteristics of the patient cohort.**

Variable	Overall (N = 742)	Referred for testing (N = 340)	Not referred (N = 402)	Statistical significance
Age (median, IQR)	56 (46-67)	54 (46-65)	57 (45-70)	<0.0001
Gender male (N, %)	386 (52%)	178 (52%)	208 (52%)	NS
Arrival by ambulance (N, %)	579 (78%)	267 (79%)	312 (78%)	NS
History of HT (N, %)	387 (52%)	172 (51%)	215 (54%)	NS
Diabetes (N, %)	157 (21%)	68 (20%)	89 (22%)	NS
Smoker (N, %)	174 (24%)	96 (28%)	78 (19%)	0.005
Cholesterol (N, %)	372 (50%)	159 (47%)	213 (53%)	NS
Previous MI (N, %)	160 (22%)	48 (14%)	112 (28%)	<0.0001
Known pre-existing CAD (N, %)	206 (28%)	61 (18%)	145 (36%)	<0.0001
TIMI score (median, IQR)	1 (0-3)	1 (0-2)	1.5 (0-3)	<0.0001
TIMI score 0-1	415 (56%)	214 (63%)	201 (50%)	0.0003
GRACE risk score (median, IQR)	88 (70-110)	86 (67-107)	89 (73-114)	<0.0001
GRACE Freedom from Events score (median, IQR)	312 (288-327)	314 (293-328)	311 (281-326)	<0.0001
MACE at 30 days (N, %)	2 (0.3%)	0	2 (0.5%)	NS
MACE or revascularisation at 30 days (N,%)	4 (0.5%)	1 (0.3%)	3 (0.8%)	NS

CAD = coronary artery disease; HT = hypertension; MACE = major adverse cardiac event; MI = myocardial infarction; NS = not significant; TIMI = thrombolysis in myocardial infarction.

Table 2 Characteristics of patients with MACE or revascularisation within 30 days.

Patient No.	Age & gender	Known CAD	TIMI score	GRACE score	Patient journey	Outcome
1	74 male	Yes	5	156	Not referred for testing by ED. Represented to ED within 1 day with recurrent chest pain, had troponin rise indicative of NSTEMI and underwent inpatient revascularisation	NSTEMI & revascularisation
2	54 female	No	2	88	Referred for testing by ED but did not attend; private cardiologist did angiogram and PCI	Revascularisation
3	66 male	Yes	5	81	Not referred for testing by ED. Private referral for stress test which was positive; private angiogram and PCI	Revascularisation
4	75 male	Yes	3	132	Not referred for testing by ED. Patient had recent angiogram showing <50% stenosis	NSTEMI within 7 days; no revascularisation

coronary CT and four coronary angiography. Note, some patients had more than one test. A breakdown of results and interventions is shown in Table 3. Fourteen per cent of patients (36/265) had a positive or equivocal test. Three of these underwent further investigation and none underwent a coronary intervention.

Results of the exploratory analysis regarding potential discriminators to identify groups at very low risk in whom testing for CAD may not be required are shown in Table 4. All discriminators had high negative predictive value for MACE, but varied in specificity. Both TIMI score 0-1 and the combination of absence of known CAD and TIMI score 0-1 would classify >54% of patients as very low risk with very high negative predictive value for MACE or the combination of MACE or revascularisation.

Discussion

Consideration of routine testing for myocardial ischaemia or CAD is recommended for patients with a negative ACS workup who are discharged from ED [4]. Our findings show that the rate of MACE within 30 days for this group is very low, that coronary intervention is rare and that most patients

Table 3 Distribution and outcome of testing for coronary artery disease.

Test	No.	Negative	Positive	Equivocal	Further tests	Coronary intervention
Stress ECG	53	46	5	2	No positive tests had further testing in follow-up period. One equivocal test had coronary angiography which was normal	0
Stres radionucleotide scan (RNS)	176	147	12	17	No positive tests had further testing in follow-up period. One equivocal test had echocardiography	0
Stress echocardiography (SE)	26	25	1	0	Positive test had coronary angiography	0
Coronary CT	4	4	0	0	One patient had coronary angiography	0
Coronary angiography#	4	4	0	0	All followed previous test(s): 1 equivocal stress ECG; I positive SE, 1 positive RNS and 1 negative stress ECG and CT	0
Echocardiography	14	11	3	0		
Total*	277	237	21	19		0

negative = <50% stenosis; * = note some patients had more than one test.

Table 4 Exploratory analysis of potential discriminators for requirement for testing for CAD.

Subgroup	Analysis	Overall	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Negative predictive value (%, 95% CI)
Age ≤ 40	Number	99			
	MACE at 30 days	0	100%; 20-100%	13%; 11-16%	100%; 95-100%
	MACE/revascularisation at 30 days	0	100%; 40-100%	13%; 11-16%	100%; 95-100%
Age <50	Number	260			
	MACE at 30 days	0	100%; 20-100%	35%;32-39%	100%; 98-100%
	MACE/revascularisation at 30 days	0	100%; 40-100%	35%;32-39%	100%; 98-100%
No known pre-existing CAD	Number	536			
	MACE at 30 days	0	100%; 20-100%	73%; 69-76%	100%; 99-100%
	MACE/revascularisation at 30 days	1	75%; 22-99%	73%; 69-76%	100%; 99-100%
TIMI = 0-1	Number	415			
	MACE at 30 days	0	100%; 20-100%	56%; 52-60%	100%; 99-100%
	MACE/revascularisation at 30 days	0	100%; 40-100%	56%; 52-60%	100%; 99-100%
No known CAD and TIMI 0-1	Number	402			
	MACE at 30 days	0	100%; 20-100%	54%; 51-58%	100%; 99-100%
	MACE/revascularisation at 30 days	0	100%; 40-100%	54%; 51-58%	100%; 99-100%

CAD = coronary artery disease.

with MACE or revascularisation have previously known CAD. For young patients, those without known CAD and those with a low TIMI score, our data suggests that the risk of clinically significant CAD is very low indeed. The low rate of MACE makes it unlikely that any current testing regime could identify these without resulting in a large number of false positive tests and their flow-on effects.

Our data concurs with the findings of others. Foy et al. [6] studied insurance claims data for patients attending ED and having a primary or secondary diagnosis of chest pain without an ACS diagnosis. The percentage of patients experiencing MI at seven and 190 days was low (0.11% and 0.33% respectively). Patients who did not undergo testing were no more likely to experience a MI than were those who did. Compared with no testing, non-invasive testing was associated with significantly higher odds of cardiac catheterisation, revascularisation procedure or a second non-invasive test without a concomitant improvement in the odds of experiencing an MI.

Hermann [7] et al. studied 4181 ED chest pain patients without a known history of CAD who had normal ECG and biomarker assays in ED. All received non-invasive testing; mostly myocardial perfusion imaging. 11.2% of patients had tests suggestive of inducible myocardial ischaemia, 2.9% underwent coronary angiography, 1.5% had obstructive coronary disease and 0.7% had disease potentially amenable to revascularisation. They concluded that routine testing had a small therapeutic yield, new diagnoses of coronary artery disease were uncommon and false-positive results were common.

In the Australian context Paoloni et al. [8] retrospectively studied patients referred from ED for exercise stress testing. Fourteen per cent of patients tested had a positive test and 13% an inconclusive result however only 0.8% of patients were diagnosed with major coronary artery disease. There were no deaths or MI at 30 days.

Low rates of MI were found in studies employing CT coronary angiography in ED chest pain. In the ACRIN-PA trial, [12] only two of 1356 (0.15%; 95% CI 0.03-0.6%) patients who did not have MI identified at the index visit had a MI at 28-day follow-up; there were no deaths. In the ROMICAT II study, [13] five of 964 patients without a MI diagnosed at index visit and without known CAD had a MI within 28 days (0.5%; 95% CI 0.2-1.3%). Again there were no deaths. In an unselected UK ED chest pain cohort, the rate of MACE was 1% at three months in patients discharged after a negative ACS workup – one nonfatal MI, two re-admissions with ACS, one supraventricular tachycardia and one non-cardiac death in 504 patients [14]. In an unselected Australian chest pain cohort, of 388 patients with troponin assays below the 99th centile one patient had MACE at 30 days (0.26%, 95% CI 0.05-1.5%); a non-ST elevation MI [15].

Interpreted together, the available evidence suggests that testing has a very low yield and potential downsides in

increased rates of additional testing or revascularisation without evidence of outcome benefit. Coupled with concerns about sensitivity and specificity of provocative tests for CAD/inducible ischaemia, in particular false positive tests that may generate unnecessary patient anxiety and further tests/interventions, it adds to the case for reconsidering routine testing in favour of selective testing.

A recent study [5] has reported the costs associated with assessing ED chest pain patients. Costs varied across guideline-defined [4] risk groups with high-risk patients having both the highest cost per patient and the highest rate of ACS. In contrast, the intermediate risk group was the most resource-intensive as it was by far the largest group but it had a very low rate of ACS (1.9%). The authors suggest the development of strategies to shorten diagnostic process and safely reduce the need for testing for myocardial ischaemia/CAD as ways to improve resource management.

The low risk characteristics identified by Hess et al. [10] and Belardinelli et al. [11] also performed well as did TIMI score 0-1. All had NPV >99%. These characteristics could inform the development of a selective testing strategy. Another approach to selective testing might be using the presence of diabetes or metabolic syndrome (high fasting glucose, hypertension, high waist circumference, high triglycerides and low HDL) as these groups have been shown to have higher ACS event rates [16].

This study was not designed to explore the reasons for referral or non-referral for CAD testing. That said, only 30% of patients with known CAD were referred for testing. Anecdotally, most are referred back to their treating cardiologist to determine if further testing would be of value. In some patients, the presentation may have been so atypical that clinicians judged the risk to be very low. Others may have had previous or recent testing.

This study has some limitations that should be considered when interpreting its results. It was a single centre study so may not be generalisable to other sites, although its results are consistent with those of other centres. While patients were identified prospectively, some data regarding risk factors, etc. was collected retrospectively so may have been subject to documentation error. It was a non-randomised study, therefore subject to bias, particularly in referral for testing. For example, those not referred may have been perceived by clinicians as negligible risk. There are also significant differences between the referred and non-referred groups in risk score distribution, the proportion with previous MI and smoking rates. Follow-up was limited to 30 days. It is possible that MACE could have occurred after this time.

Conclusion

In our study the rate of MACE within 30 days was very low, coronary intervention was rare and most patients with MACE or revascularisation had previously known CAD. For young patients, those without known CAD and those with a low TIMI score, the risk of clinically significant CAD appears to be very low. It adds to the case for abandoning routine testing for CAD.

Competing Interests

Professor Kelly was a member of the core writing group of the National Heart Foundation ACS guidelines 2005-14. This study was funded by departmental funds only.

Authors' Contribution

AMK had the concept for the study; contributed to development of the study design and methodology; performed the analysis; contributed to interpretation of results; drafted the manuscript and contributed to its refinement. SK contributed to development of the study design and methodology; managed data collection and entry; contributed to interpretation of results and contributed to refinement of the manuscript.

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