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ORIGINAL ARTICLE

Long Term Prognostic Value of a Negative Work-Up for Acute Coronary Disease in Emergency Department Chest Pain Patients Without Known Coronary Artery Disease: A Cohort Study

Anne-Maree Kelly, MD, FACEM, FFCP [*], **Sharon Klim, BN**

Joseph Epstein Centre for Emergency Medicine Research at Western Health, Melbourne, Vic, Australia

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Background To determine the rate of all cause and cardiac death, new myocardial infarction (MI) or coronary revascularisation at over three years from index visit in emergency department chest pain patients without known coronary artery disease (CAD) at index presentation who had a negative electrocardiogram (ECG) and biomarker workup for acute coronary syndrome (ACS).

Methods An unplanned sub-study of a prospective observational study of consecutive adult patients presenting to the ED with atraumatic chest pain (or equivalents). The primary outcome of interest was the predictive performance of a negative ECG and biomarker work-up for ACS for all cause and cardiac mortality over more than three years' follow-up in patients not known to have pre-existing CAD presenting to the ED with chest pain. Secondary outcomes were rate of new MI or revascularisation not related to the index visit.

Results 237 patients were studied. Median age was 52 years (IQR 42 – 62) and 55.3% were male. Median follow-up was 48 months. There were seven deaths (3%, 95% CI 1.4 – 6%), one of which was potentially cardiac in origin with cause of death given as pulmonary hypertension and cardiac failure (0.4%, 95% CI 0.02 – 2.3%). There was one confirmed MI (0.6%, 95% CI 0.03 – 3.8%). The rate of revascularisation not related to the index visit was 3.1% (95% CI 1.1 – 7.4%).

Conclusion Patients who present to ED with potentially cardiac chest pain but who do not have known CAD, and have non-ischaemic ECGs and troponin assays below the 99th percentile are at low risk of cardiac death or MI in long-term follow-up. This challenges the recommendation for routine functional or anatomic testing.

Keywords Prognosis • Chest pain • Coronary artery disease • ED

Introduction

Emergency department (ED) based processes to identify patients presenting with chest pain who are at low risk of acute coronary syndrome (ACS) or adverse cardiac events have been shown to have a low rate of, and high negative predictive value for, major adverse cardiac events (MACE) in short-term follow-up [1–4]. Less is known about the predictive performance of these processes in longer term follow-up, particularly in the subgroup of patients without known pre-existing coronary artery disease (CAD). Current guidelines suggest that patients with a negative ACS work-up should have provocative functional testing (e.g. exercise stress test, myocardial perfusion imaging or stress echocardiography) or

*Corresponding author at: JECEMR, Sunshine Hospital, Furlong Road, St Albans 3021, Vic, Australia, Email: anne-maree.kelly@wh.org.au

anatomical imaging (e.g. CT coronary angiography (CTCA)) to identify 'silent' CAD [5]. However if the rate of events in long-term follow-up is low and not cardiac-related, there may be a case for testing of selected patients only.

The aim of this study was to determine the rate of all cause and cardiac death, new myocardial infarction (MI) or coronary revascularisation, at over three years from index visit in patients without known CAD at index presentation who had a negative ECG and biomarker work-up for ACS in the ED.

Methods

Design and Setting

This is an unplanned sub-study of a prospective observational study of consecutive adult patients (aged over 18 years) presenting to the ED of two community teaching hospitals between 19 January 2009 and 30 June 2009 with chest pain.

Participants

Adult patients presenting with non-traumatic chest pain (or equivalents) and undergoing evaluation for potential ACS were eligible for inclusion in the parent study. For this sub-study, additional inclusion criteria were absence of known coronary artery disease at index ED visit, no ischaemic ECG features and all troponin assays during the index ED evaluation being below the 99th percentile for the test. Known coronary artery disease was as reported by the patient (confirmed where possible from medical records) and defined as any of: previous myocardial infarction (MI), physician-diagnosed angina, percutaneous coronary intervention, coronary artery bypass grafts or coronary angiogram showing stenosis >50%. Patients were not eligible for inclusion if they had clearly ischaemic ECG features identified by the treating clinician at initial assessment (including STEMI), they did not have a troponin assay or ECG performed within 24 hours of pain onset, there was a clear non-ACS diagnosis made by the treating clinician at initial assessment, they had a serious arrhythmia pre-hospital or at ED presentation (including cardiac arrest), language barrier or lack of telephone details precluded follow-up or they were aged under 18 years. Patients were also excluded if they declined consent to follow-up or records could not be found.

Data Collection

Clinical and investigational data regarding the index presentation were collected on a piloted data collection form. Data collected included demographics, cardiac risk factors, history of CAD, cardiac failure, atrial fibrillation or peripheral vascular disease, clinical features at ED presentation, use of warfarin, aspirin or statins, results of biochemical analyses including cardiac biomarkers, ECG findings, interventions during hospitalisation and in-hospital clinical course. In the parent study, patients were contacted by telephone at 7 and 30 days after the index ED visit to determine occurrence of defined MACE (defined as all cause and cardiac death, new MI or coronary revascularisation).

Regarding long-term follow-up, we chose to determine patient outcome as at 31 March 2013, representing approximately four years from the index ED visit. The choice of this date was arbitrary. Initially a review of the medical record was undertaken during 2014 to determine if the patient had died (including whether the cause of death was cardiac, non-cardiac or unknown) or treatment for a new MI or coronary revascularisation had occurred in the study health service during the follow-up period. If complete data was not available covering the relevant period, patients were contacted by telephone. If patients could not be contacted by telephone, a death registry search (Victorian Registry of Births, Deaths and Marriages) was undertaken. For patients who had died and the cause of death was unclear, clarification was made by contact with their family doctor. Deaths of unknown cause were assumed to be cardiac.

The primary outcome of interest was the predictive performance of a negative ECG and biomarker work-up for ACS for all cause and cardiac mortality. Secondary outcomes were the rate of new MI or revascularisation.

The troponin assay used was TnI-Ultra by Siemens Diagnostics performed on an ADVIA Centaur analyser. The test has a reported range of 0.006 to 50 microg/L. Co-efficient of variation is 10% at TnI 0.03 microg/L, 5.3% at 0.08 microg/L and 4.1% at 0.18 microg/L. The 99th percentile is 0.04 microg/L (95%CI 0.03 – 0.05 microg/L) (manufacturer's information). Timing of biomarkers was in accordance with the Australasian guidelines for contemporary troponin assays at the time of the index presentation [5]. Tests are taken at presentation and three to four hours later, as long as the latter test is more than six hours from symptom onset. If a patient presented more than six hours from symptom onset, a single assay was deemed sufficient to rule out ACS.

Analysis and Sample Size

Data analysis is descriptive. Continuous variables are reported as medians and interquartile ranges (IQR). Categorical data is reported as proportions, with 95% confidence intervals where relevant. Mortality is reported for the whole sample. Myocardial infarction or revascularisations are only reported for patients with full follow-up. No sample size calculation was undertaken as this was an unplanned post-hoc study.

Ethical Approval

The project was approved by the institution's low risk ethics panel as a quality assurance project under the National Health and Medical Research Council (Australia) guidelines [6]. Patient consent for data collection from medical records was not required. Participants provided verbal consent to telephone follow-up.

Results

Two hundred and thirty seven patients met inclusion criteria. Sample derivation is shown in Figure 1. Median age was

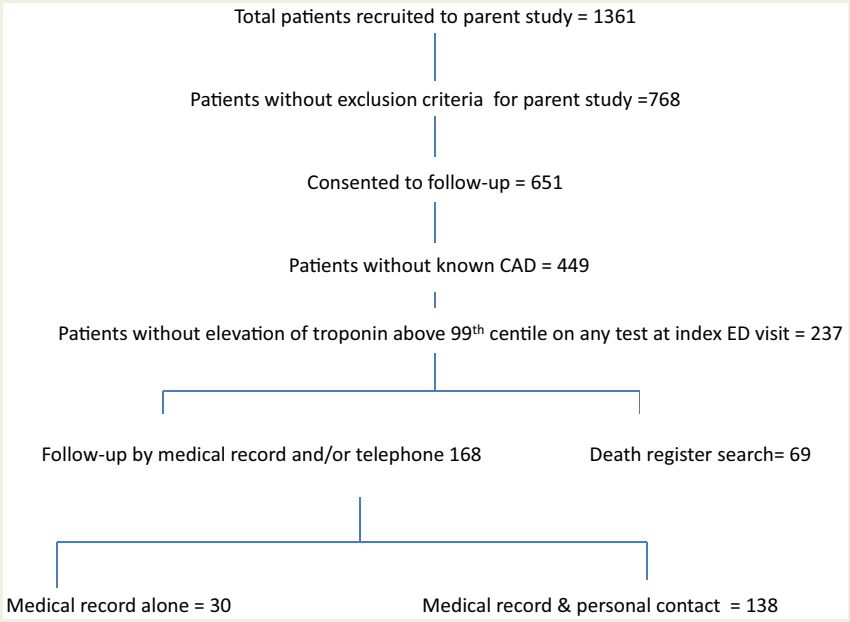

Figure 1 Sample derivation.

52 (IQR 42 – 62), 55.3% were male and 49.6% arrived by ambulance. Patient characteristics are summarised in Table 1.

There were seven deaths during the follow-up period (3%, 95% CI 1.4 – 6%), one of which was potentially cardiac in origin with cause of death given as pulmonary hypertension and cardiac failure (0.4%, 95% CI 0.02 – 2.3%). The deaths are summarised in Table 2.

Of the 168 patients with detailed follow-up data (i.e. complete medical record at 2014 and/or telephone follow-up), one had a confirmed MI (0.6%, 95% CI 0.03 – 3.8%). Nine

Table 1 **Characteristics of study sample**

Variable	Missing data	Result
Age (median, IQR)	0	52 (42-62)
Gender (N male, %)	0	131 (55.3%)
Arrival by ambulance (N, %)	1	117 (49.6%)
Risk factors		
Hypertension (N, %)	0	101 (42.6%)
Diabetes (N, %)	0	42 (17.7%)
Smoker (N, %)	0	117 (49.4%)
Renal impairment (N, %)	0	3 (1.3%)
Family history (N, %)	0	78 (32.9%)
Hypercholesterolaemia (N, %)	0	93 (39.2%)
Usual medications		
Aspirin (N, %)	0	38 (16%)
Warfarin (N, %)	0	6 (2.5%)
Statin (N, %)	0	63 (26.6%)
Risk scores		
TIMI (median, IQR)	0	0 (0-1)
GRACE risk (median, IQR)	1	75 (57-94)
GRACE freedom from events (median, IQR)	1	298 (278-314)
Disposition (N, discharged, %)	0	
Discharged (N,%)	0	170 (71.7%)
Admitted to hospital (N, %)	0	67 (28.3%)
30-day revascularisation (N, %)	0	4 (1.7%)
Duration of follow-up (months, median, IQR)	0	48 (47-49)

Table 2 Cause of death

Patient	Year of death	Months from presentation to death	Certified cause of death
A	2009	4	Malignant pulmonary neoplasm
B	2009	6	Pulmonary fibrosis
C	2009	8	Malignant pulmonary neoplasm
D	2010	10	Cerebral infarction
E	2010	11	Malignant pulmonary neoplasm
F	2011	27	Pulmonary hypertension/ cardiac failure
G	2012	37	Malignant melanoma

patients had revascularisation, four related to the index ED visit and five more than 30 days from the index ED visit, only one of which was preceded by MI. That MI occurred in March 2012 – 37 months after the index ED visit — in a 63-year-old male smoker with known hypercholesterolaemia. The rate of revascularisation related to the index event (within 30 days of index ED visit) was 1.7% (95% CI 0.6 – 4.3%). All were among patients admitted from ED at the index visit. The rate not related to the index ED visit was 3.1% (95% CI 1.1 – 7.4%).

Discussion

Our data shows that patients who present to ED with potential cardiac chest pain but who do not have previously known CAD, and have a non-ischaemic ECG and troponin assays below the 99th percentile are at low risk of cardiac death or MI in long-term (median 48 months) follow-up. This suggests that ED-based assessment pathways have prognostic value beyond the short term and challenges the need for routine provocative or anatomical testing in this low risk group.

Data regarding long-term follow-up after a negative ED-based ACS work-up is scarce. Reichlin et al. [7] investigated overall and cardiac-related mortality in 1124 patients evaluated for chest pain using high sensitivity troponin assays, stratified by MI diagnosis (none, small or moderate/large) with mean follow-up of 19 +/- 9 months. Cumulative 30-month mortality was 4.8% in the no MI group with cardiac mortality of 2.6%. These are both higher than found in our study. This may be due to differences in the study populations. The Reichlin study patients were older (61 vs. 52 years), there were higher rates of hypertension and smoking and most importantly 33% had prior CAD.

A small proportion of patients (1.7%) had revascularisation related to their index ED visit despite having non-diagnostic ECG and normal biomarkers in the ED. This reinforces that ECG and troponin are only tests that support clinical decision-making. Clinical acumen in identifying higher risk patients for further testing and intervention remains important.

There is a growing number of studies reporting the yield of routine testing for CAD after a negative work-up for ACS. Winchester et al. [8] report a rate of occlusive CAD of 2.5% and positive predictive value for CAD of an abnormal test of approximately 45%. Kelly et al. [9] reported that, after a negative ED-based ACS workup, the rate of MACE and revascularisation were low and that 75% of patients with these outcomes had known CAD. There was no difference in outcome between those referred for further testing and those who were not. Hermann [10] et al. in a study of ED chest pain patients without a known history of CAD who had normal ECG and biomarker assays in ED, reported that 1.5% had obstructive CAD and 0.7% had disease potentially amenable to revascularisation. In the Australian context, Paoloni et al. [11] in a study of patients referred from ED for exercise stress testing, reported that only 0.8% of patients were diagnosed with major CAD.

Computed tomography cardiac angiography (CTCA) is gaining popularity for testing for CAD in patients with a negative ACS workup. Nasis et al., [12], in a prospective study of ED chest pain patients without known CAD and with a non-diagnostic ECG, found that, on CTCA, 14% of patients had stenosis over 70%. Of these, 14% proved to be false positives, in fact having less than 40% stenosis on coronary angiography. It is unclear what proportion with stenosis over 70% on CTCA had moderate stenosis (40 – 69%) on coronary angiography. Six per cent of patients underwent coronary revascularisation, although this included some non-ST elevation MI. In long-term follow-up (median 47.4 months) there were no deaths, new MI or coronary revascularisations. Computed tomography cardiac angiography appears to have good prognostic value but whether the benefits are in balance with the costs — for example radiation exposure, generation of additional invasive tests with associated risks, impact on patient's employment and insurance status — for all patients is yet to be established.

Although, overall, patients with a negative ED-based ACS workup who do not have known CAD at the index visit are a low risk group for MACE, that does not mean that follow-up testing should be abandoned completely. Among them, there are groups of patients that are known to have higher risk for CAD, such as those of Aboriginal or Torres Strait Islander ethnicity,[13] those with diabetes [14,15] or metabolic syndromes [15] and those with a family history of early MI or cardiac death in first degree relatives, [16] who may benefit from further investigation. Research to clarify test utility in higher risk groups is needed. Additionally, as a post-hoc

analysis, our data is hypothesis generating rather than hypothesis testing. It requires confirmation in well designed prospective studies.

There are some limitations to this study which should be considered when interpreting its results. While patients were identified prospectively, some data was collected from the medical record with the inherent, associated weaknesses [17]. While mortality follow-up was complete, follow-up for MI and revascularisation was not, as a number of patients could not be contacted and did not have entries in the medical record covering the whole period after the index follow-up date. It is also possible that patients underwent revascularisation at other centres that was not identified. The choice of follow-up date was arbitrary but chosen to represent an average of approximately four years from index presentation. If the patients with incomplete follow-up had a higher rate of MI or revascularisation, the results would be different. The study was conducted at a single site so may not be generalisable to other settings. Determination of risk factors and past history was by patient self-report. No attempt was made to confirm the information provided, reflecting the 'real world' ED setting.

Conclusion

Patients who present to ED with potentially cardiac chest pain but do not have known CAD, have a non-ischaemic ECG and troponin assays below the 99th percentile are at low risk of cardiac death or MI in long-term (median 48 months) follow-up. This challenges the recommendation for routine functional or anatomic testing in this low risk group.

Competing Interests

AMK is a past co-author of the National Heart Foundation guidelines for the management of acute coronary syndromes (Australia) and their addenda.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hlc.2016.07.015.

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