**Missed acute myocardial infarction: an underrecognized problem that contributes to poor patient outcomes**

Running title: Missed acute myocardial infarction

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**Abstract**

Ischemic heart disease is the number one killer in the world. Whilst improvements in the management of acute myocardial infarction (AMI) has resulted in lower mortality rates, there are still cases where AMI are missed with rates varying depending on the setting where the evaluation took place, the population sample, the definition of missed AMI and timing of evaluation. There is consistent evidence that missed AMI is associated with increased risk of complications and mortality. Many factors contribute to missed AMI which include patient factors, clinician factors and institutional factors. While many studies have been conducted to evaluated missed AMI, there is considerable heterogeneity in methodology which has resulted in variable rates of missed AMI and the factors associated with missed AMI. In this review, we provide an overview on missed AMI discussing rates reported in the literatures, why it is important, reasons why it occurs, some of the challenges in evaluating missed AMI and what could potentially be done to reduce these undesirable outcomes for patients.

**Keywords:** Acute myocardial infarction; misdiagnosis; mortality

**Introduction**

Ischemic heart disease is the number one killer in the world [1]. In the United States, approximately 805,000 patients have a myocardial infarction each year[2] and in the United Kingdom, more than 100,000 hospital admissions each year are due to heart attack [3]. Decades of research and associated improvements in clinical practice has culminated in reduced mortality in patients with acute myocardial infarction (AMI) from approximately 30% a century ago to 3.5% in the leading centers today [4]. Improved survival is the consequence of a variety of interventions including 24 hour a day 7 days a week emergency coronary revascularization with primary percutaneous coronary intervention, antithrombotic medications and secondary prevention medications which is available in many healthcare settings around the world. While the care delivered in cardiology units is based on high quality evidence, there are still patients with AMI that are missed.

*How often does missed acute myocardial infarction occur?*

Existing research report varying rates of missed AMI, with the estimates depending on the setting where the evaluation took place, the population sampled, the definition of missed AMI and the timing of the evaluation. Analysis of inpatient and emergency department (ED) data from 9 States in America found that 0.9% of 112,000 patients with AMI had visited the ED within 7 days of admission for AMI [5]. Sharp et al. evaluated misdiagnosis-related harms following missed AMI in emergency departments using a symptom-disease pair analysis of diagnosis error and found that 2,874 patients had treat-and-release ED visits in the 30-days prior to hospitalization for AMI among 44,473 AMI hospitalizations [6]. A larger study of 371,638 Medicare patients aged 65 years or greater with AMI found that 0.52% had an AMI hospital admission within 7 days of an ED discharge for a condition suggestive of cardiac ischemia [7]. In a population based cohort of men and women age 55 or older in Rotterdam, it was reported that the incidence rate of unrecognized AMI was 5.0 per 1000 person years which was higher in men compared to women (8.4 vs 3.1 per 1000 person years) [8]. A retrospective evaluation of an ED department in North Texas, reported a prevalence of missed acute coronary syndrome at 7 and 30 days after ED visit of 3.2% and 8.8%, respectively [9]. A single tertiary center study in Malaysia reported that 17% of patients had missed thrombolysis [10]. Among ED visits in Canada 7 days prior to hospitalization for AMI, the rate of missed AMI was 2.1% which varied from 0% to 29% across EDs [11]. Interestingly, high volume ED had a high odds of missed AMI compared to lower volume ED (aOR 2.0 (1.5-2.7) vs aOR 1.6 (1.1-2.3)) [11]. In a multicenter study of 1,050 patients with AMI, 20 (1.9%) were not admitted [12]. These findings suggest that the rate of missed AMI is highly variable and appears to range on average from 0.5% to as high as 17%.

*Why we should care about missed acute myocardial infarctions?*

Evidence suggests that missed AMI is associated with increased mortality and readmissions. In a Malaysian single center study, missed thrombolysis among AMI patients was associated with more than 5-fold increase in mortality (6.9% vs 1.2%) [10]. In an Australian review of 20 cases of missed AMI, the treatment delay associated with missed AMI caused half of patients to die [13]. The study by *McCarthy et al.* suggests that 1 in 4 patients with missed AMI die [12]. In an older study from ED setting, described 83% mortality associated with patients with missed [14]. In the retrospective study by *Williams et al.*, 24% of patients died in hospital with missed AMI and mortality was greatest among patients from rural hospitals (69.6%, p=0.008) [15]. The rate of 30-day readmissions was nearly increased by 10-folds (31.6% vs 3.3%, p=0.001) for patients with missed compared to patients with AMI identified at index admission [15]. Collectively, these findings suggest that patients with missed AMI are a high risk group with poor prognosis.

*Why does missed acute myocardial infarction occur?*

Patient, clinician and institutional factors all contribute to missed AMI. In terms of patient factors, healthcare professionals are reliant on patient presenting to healthcare professionals so that AMI can be identified and managed at a time where interventions are effective. There are patients who ignore symptoms of chest pain until they are severe which can contribute to failure of early detection of AMI. This is particularly a problem for patients with atypical symptoms such as the absence of chest pain, weakness, sweating, nausea, shortness of breath and cough which are associated with unrecognized myocardial infarction [16]. For clinician related factors, misdiagnosis appears to be a common theme contributing to a missed diagnosis of AMI. In a study of patients in North Texas, the most common reason for initial ED visit which led to subsequent admission for ACS was nonspecific chest pain 57.7%, atherosclerotic disease (19.5%) and heart failure (12.8%) [9]. Misdiagnosis may be related to clinician expertise as inaccurate ECG interpretation and diagnostic uncertainty/confusion have been reported to contribute to missed AMI [15,17,18]. In addition, it has been suggested that patients with undiagnosed AMI were evaluated by physicians who took less detailed histories, had less experience and who admitted fewer patients to hospital [17]. Institutional factors also play a role in missed AMI as a Canadian study found that the independent odds of missed AMI was greater among patients admitted to high volume EDs compared to low volume EDs and the authors suggest it may be related to the availability of consultants in clinical decision making [11]. However, there are other studies which suggest that higher volume centers and those with teaching or academic status are associated with fewer missed AMI [5,7]. An American study by Wilson et al suggests that above-minimum level of chest pain patient acuity was most protective of missed AMI and other protective factors include hospital with large bed number, high proportion of emergency medicine board certified clinicians, high chest pain and admission volume while rural hospitals were associated with increased risk of missed AMI [7]. Another evaluation in the United States reported that hospital teaching status, availability of cardiac catheterization, high inpatient occupancy rates and urban location were associated with fewer missed diagnoses [5]. While single factors may directly contribute to misdiagnoses of AMI, it is possible that multiple factors contribute to result in the overall undesirable outcome.

*Who are the patients that are at risk of missed acute myocardial infarction?*

Several studies have identified differences in the population with missed AMI compared to control group. Among 65 patients with undiagnosed AMI seen in ED, compared to controls patients were more likely to be younger, presented more atypically and had fewer ECG findings that were diagnostic of AMI [7]. In an American study, it was reported that missed diagnoses of AMI were associated with patients that were younger and those of black ethnicity [5]. In a case-control study of 15 missed ACS calls and 120 matched control calls of out-of-hours primary care, patients with missed ACS were more likely to use less cardiovascular medications (38.5% vs 64.1%, p=0.05) and more often experienced retrosternal chest pain (63.3% vs 24.7%, p=0.02) [19]. It has also been suggested that patients who miss reperfusion therapy, had a high proportion of patients from rural hospitals and those who presented on weekends and were less commonly transported by ambulance [13]. In addition, it has been reported that missed AMI was more likely among men (67% vs 26%, p=0.001), smokers (88% vs 39%, p<0.001), patients who have low HDL (39 mg/dl vs 59 mg/dl, p<0.001) and elevated total cholesterol (236 mg/dl vs 213 mg/dl, p=0.01) [20]. It was also reported that the Framingham risk score and Goldman risk predictors was associated with increased risk of missed AMI (OR 5.7 (1.8-18.4) and OR 7.2 (1.4-36.8), respectively) [20]. However, another study suggests that patients that missed thrombolysis were older (p=0.032) and more likely to be female (p=0.015) and that patients presenting earlier were more ill (30% with acute heart failure) compared to those who were late presenters [10]. A review of 20 cases of missed AMI in Australia found that the average age was 60 years and there were more women compared to men (60% vs 40%). Triage rate was often not at priority 2 (58%) and ECG was not correctly interpreted on 75% of occasions. Specialist cardiology support was not immediately requested and on two occasions and incorrect history was given. Time of day or week was not a factor in lack of treatment [13]. Missed AMI patients were less likely to have ECG changes and a history of AMI or nitroglycerin use than patients admitted with AMI [12]. Collectively, the factors associated with missed AMI are complex as studies evaluate a variety and different combination of factors and appear to depend on the study population.

*Should we expect all acute myocardial infarctions to be identified at first contact?*

A key consideration which regarding missed AMI is whether it was reasonable or avoidable. Chest pain is common symptom which triggers patients to seek medical and patients can present for the first time to healthcare professional in general practice, emergency departments, outpatient clinics and walk-in centers. In the ED department, it represents 5-10% of all adult visits and the vast majority no not require acute intervention [21]. While no test is 100% accurate, in current clinical practice, it is expected that correct interpretation of a 12-lead ECG and troponin tests should identify most cases of AMI. However, some healthcare professionals such as general practitioners not have rapid access to these tests so missed or delayed diagnosis of AMI may not be an unexpected outcome. Unlike emergency departments, where these tests are readily accessible and practically all patients with chest pain can have these tests, it may not be possible for a general practitioner to arrange for these test for all patients with present with chest pain so it is expected that some cases will not be identified and managed in a timely manner, particularly in rural settings and those with atypical symptoms.

There are also some cases of AMI that present atypically that may be missed by less experienced clinicians. While chest pain is the most common symptoms among patients with AMI, evidence from the SWEDEHEART registry suggest that 12.7% present without chest pain [22]. Groups that are high risk for these atypical presentations include patients that are elderly, female, diabetic and had more comorbidities [22,23]. Among elderly patients with STEMI in emergency departments, it has been reported that 58.8% had atypical reasons for admissions including faintness/fall, dyspnea, digestive symptoms/nausea, general deterioration and delirium [24]. It is possible that these patients with atypical symptoms may be missed especially by inexperienced physicians as it has been reported in the Canadian study that the lack of availability of consultants in clinical decision making in busy ED departments explained the cases of missed AMI [11]. There may be a role for better training and education about atypical presentations of AMI for frontline staff who triage patients with chest pain in settings where there are frequent cases of missed AMI.

ECG interpretation has been identified as a contributor to missed AMI. Recognition of ischemic changes on ECG is an essential skill for physicians however not all physicians review ECGs regularly so those who do not may become deskilled. In addition, it is not uncommon that the ECG is challenging to interpret. In these cases, it is essential that a second opinion should be sought and in the age of telemedicine there is no reason why remote review of ECG cannot be facilitated. The availability and timely request for specialist cardiology support was highlighted as a contributor to missed AMI in the study by Savage et al [13]. It is therefore important that clinicians who review patients with chest pain have access to ECG as well as a second opinion for its interpretation which would ideally be that from a specialist cardiology team.

*Challenges to evaluating missed acute myocardial infarction*

There are multiple considerations that makes it challenging to evaluate missed AMI. There is no formal definition for missed AMI. The failure to recognize AMI can be related to the patient not experiencing symptoms or attributing the symptoms to having an AMI. This is particularly a problem for patients who have atypical symptoms. This raises the issue that it is impossible to diagnose and treat patients with they do not present to healthcare professionals. This is further complicated by the strong association between missed AMI and sudden cardiac death as patients with out-of-hospital cardiac arrests may have died from AMI and associated complications such as ventricular arrhythmias. The effect would that estimates of missed AMI on a population level may under-capture the events. Therefore, a working definition of missed AMI should refer to a healthcare professional missing an opportunity to identify someone with AMI who presents to them which was later found a later encounter. Large database studies have also used another approach defining missed AMI as those where patients have an AMI and present to ED within 7 days for admission for AMI. This approach has the advantage that large scale patient records can be reviewed retrospectively for cases that meet this criteria. However, there are several problems as the 7 days is arbitrary and actually missing the MI could have happened many days previously. Secondly, it is important that the initial cause for ED visit was potentially related to AMI as it is possible that a patient develops AMI at any time and it happened to occur within 7 days of discharge from ED visit. This approach also has the assumption that patients will present to ED with symptoms as opposed to general practitioner or outpatient clinic. Although interventions can be done to better educate the public about chest pain and atypical symptoms of AMI, the latter definition has the advantage that it places the responsibility of identifying AMI on the healthcare professional rather than the patient to seek medical attention. This definition is a better indicator of quality of care as it is the actions of the healthcare professions that lead to the missed AMI as oppose to the patient missing the event in the community which is less avoidable.

In contemporary practice the availability and use of high sensitivity troponins has made the chance of misdiagnosis of actual AMI extremely low. These troponins which are widely available and routinely used today have excellent diagnostic accuracy for AMI [25]. This is particularly important as many of the studies of missed AMI took place before the availability of these troponin assays and these studies may only serve as a historical landmark on the problem of missed AMI. Nevertheless, even in the landscape today, it may be expected that not all patients with AMI will get these tests as there are patients with atypical symptoms such as the absence of chest pain where alternative diagnoses are given. There may also be populations in rural areas or less developed countries where these troponins may be less available and receiving timely assessment with these tests are impossible. While there are some studies from recent years, more studies investigating missed AMI in the current high sensitivity troponin era are needed.

It is important to recognize that just because a patient presented to an ED and was discharged before being readmitted for AMI does not necessarily mean that a myocardial infarction was missed. It is possible that patients had presented to ED for another non-cardiac reason and it was coincidental that the AMI occurred shortly after the episode. This is important as many of the studies considered any ED visit prior to rehospitalisation for AMI when the better methodology would have been to consider ED discharge for a condition suggestive of cardiac ischemia.[7] Even if a patient presented to ED with chest pain or features suggestive of cardiac ischaemia it does not necessitate that AMI was missed. At the initial visit to ED, a patient could have had unstable angina and not had myocardial infarction at that time. However, patients with unstable angina are a high risk population as data from PRAIS-UK suggests that in-hospital event rates have been reported to be 2% mortality, 4% progression to myocardial infarction and 3% refractory angina which increases to 7% mortality, 7% myocardial infarction and 17% refractory angina at 6 months.[26] In current hospital practice where electrocardiogram and highly sensitivity troponins are widely available and can utilised to identify patients in the ED at low risk and could be directly discharged, the important cases of missed AMI are patients who present with typical and atypical symptoms that could be associated with coronary ischaemia and these tests were not performed.

Part of the challenge of delivering high quality AMI care is the awareness that not all patients will follow the expected pathway of onset of symptoms in the community, presentation to the emergency department and diagnosis and management as an inpatient in hospital. Patients who develop AMI in the community could present to general practitioners or other healthcare professionals such as outpatient specialist clinics or rehabilitation for other health problems. In addition, patient who are already in hospital for other reasons may develop AMI. Most of the literature, define missed AMI as cases of AMI where patients had present to ED and discharge before an admission with AMI.[5,6,7,11] Defining missed AMI where patients present to non-ED setting for first evaluation before an eventual diagnosis of AMI is an area that merits future work.

*What should be done locally about missed acute myocardial infarction*

The concept of missed AMI forces clinicians to reflect on and review clinical practice and how it can be improved. Misdiagnoses is something that all clinicians want to avoid. The first step in improving clinical practice for patient with AMI is clinical audit and service evaluations combed with education when deficits are found. These evaluations have an important role in determining if there is a problem on the local level with missed cases of AMI. If rates are found to be unexpectedly high, further investigations can be conducted to determine the cause and there may even need interventions to reduce these untoward events. Interventions include development of protocols and pathways so that patients with suspected AMI can have more rapid testing, acute management and be transferred to care in the most appropriate setting as well as education and training measures for clinicians about how they should manage patients with suspected AMI. As missed AMI is associated with increased risk of death, cases of missed AMI may be discussed or identified from mortality meetings. Such meetings should be encouraged in all departments as they foster recognition of areas for improvement which can be reviewed so that changes can be made to benefit patients.

**Conclusions**

In conclusion, missed AMI is an important and underrecognized problem that is a barrier to high quality patient care. It is not uncommon depending on how it is defined and the population and has been shown consistently to be associated with increased mortality. A number of factors appears to contribute to missed AMI which include patient, clinician and institutional factors. In settings where missed AMI are identified to be a problem, interventions should be developed to better diagnose and treat patients with AMI.

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