Is the History of Erectile Dysfunction a Reliable Risk Factor for New Onset Acute Myocardial Infarction? A Systematic Review and Meta-Analysis

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Key Words
Erectile dysfunction • ST-elevation myocardial infarction • Acute myocardial infarction • Coronary artery disease • Cardiovascular disease • Acute coronary syndrome • Non-ST-elevation myocardial infarction

Abstract
Acute myocardial infarction (AMI) occurs as a manifestation of coronary atherosclerotic disease. The occurrence of erectile dysfunction (ED) following AMI is well documented and this association and pathophysiology is often interrelated. Few studies have objectively assessed the diagnostic value of ED as a risk factor for AMI, in general. In this review, we aimed to better outline the diagnostic predictability of ED as a precursor for ‘first/new onset’ AMI. This review was performed using selective search terms, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. The Cochrane, Embase, PubMed, Scopus and Web of Science databases were searched (September 2018). Selected studies were further assessed for relevance and quality (Critical Appraisal Skills Program tool-Oxford). Four studies [573 participants; mean 143 (SD ± 76.3604) and median 141 participants] were eligible for analysis. Meta-analysis of the studies resulted in a pooled sensitivity of 51.36% (95% CI: 47.37–55.33%). For the single study which reported true negative and false positive cases, a specificity of 76.53% (95% CI: 68.57–83.00%) was calculated. The results of this systematic review and meta-analysis suggest that a history of ED should be used as a risk factor for new onset AMI.

Introduction
Acute myocardial infarction (AMI) is an urgent cardiovascular emergency that affects 40% of men above the age of 40 [1]. AMI accounted for 11% of Australia’s expenditure during the period of 2004–2005 [1]. Globally, it is estimated that up to 3 million people suffer from ST-elevation myocardial infarction (STEMI), while a further 4 million suffer from non-ST-elevation myocardial infarction (NSTEMI) per calendar year [2–4]. The rate of AMI (STEMI and NSTEMI) has increased in developing countries as well. Despite the global increase in AMI rates, registries have recorded a decrease in the mortality of AMI [4]. If timeous interventions are not performed, AMI may result in arrhythmia/s, thrombosis, embolus, pericarditis, heart failure, cardiogenic shock and/or death [1, 2, 4].
In the assessment of AMI, medical practitioners have reported the use of cardiac screening tools, specialized equipment and diagnostic signs to aid in the diagnosis of AMI. These include the Framingham score, electrocardiograms, stress electrocardiograms, and measurement of cardiac enzymes [2, 5].

The occurrence of erectile dysfunction (ED) following AMI is well documented due to the commonly associated pathophysiological process of underlying endothelial dysfunction [6]. Various studies have objectively described the diagnostic value of ED in relation to AMI in general [7–11]. There is, however, a need to explore the literature regarding the presence of ED specifically as a risk factor to ‘new onset’ AMI.

To better define the role, validity, clinical applicability and statistical significance of ED as a risk factor for new onset AMI, a comprehensive literature review and meta-analysis was performed using a Preferred Reporting Items for Systematic Reviews and Meta-analysis format [12] meta-analysis, on the current body of literature.

### Materials and Methods

**Search Strategy**

A search strategy was developed and performed using an electronic database search. The following databases were searched (September 2018): Cochrane Database of Systematic Reviews, Embase, PubMed, Scopus and Web of Science. The following search terms were used: ‘Erectile dysfunction AND coronary heart disease OR CHD OR coronary artery disease OR CAD OR acute coronary syndrome OR ACS OR acute myocardial infarction OR AMI OR myocardial infarction OR MI OR acute myocardial ischemia OR myocardial ischemia OR ST-elevation myocardial infarction OR STEMI OR non-ST elevation myocardial infarction OR NSTEMI OR unstable angina OR UA’. The citations of the papers generated by the search were also reviewed for any additional articles. Language restriction was not applied.

**Study Selection**

Articles included in the review met the following criteria: (i) the studies were clinical publications; (ii) studies reported the sensitivity and specificity or provided details on positive versus negative findings of ED as a risk factor to new onset AMI and (iii) the full text of the studies were available. All published studies relating to the topic, were eligible for inclusion, however, single case studies and non-human studies were excluded from the review process.

**Review Study Definition of ED as a Risk Factor to New Onset AMI**

In this systematic review, a positive history of ED as a risk factor to new onset AMI, was defined as the presence of ED prior to an AMI, with no history of an AMI. A negative history of ED as a risk factor to new onset AMI was defined as the presence of ED prior to AMI, with a positive history of previous AMI. This was performed to isolate the role of ED as a precursor/risk factor, in ‘new onset’ AMI only.

**Data Extraction and Methodological Evaluation**

The Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [12] were applied to guide the electronic database search. Eligible articles were screened by the authors, based on the inclusion criteria stipulated above. The selected studies [7–10] were ranked using the Critical Appraisal Skills Program (table 1) [13], where each author compiled a descriptive narrative of each study. The points of interest in each study were tabulated.

These included study design, study aim, sample size, sample characteristics, sensitivity, specificity, other risk factors investigated, ED validation tool and conclusion (table 2). Conflicting entries, differences and disagreements were resolved by consensus among all the authors.

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**Table 1. Details of CASP [13] tool used to assess the studies included for review**

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Did the study address a clearly focussed issue?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 Was the cohort recruited in an acceptable way?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>CT</td>
</tr>
<tr>
<td>3 Was the exposure accurately measured to minimize bias?</td>
<td>CT</td>
<td>Yes</td>
<td>No</td>
<td>CT</td>
</tr>
<tr>
<td>4 Was the outcome accurately measured to minimize bias?</td>
<td>CT</td>
<td>CT</td>
<td>Yes</td>
<td>CT</td>
</tr>
<tr>
<td>5a Have the authors listed all confounding factors?</td>
<td>Yes</td>
<td>Yes</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>5b Have the authors taken account of all the confounding factors?</td>
<td>Yes</td>
<td>Yes</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>6a Was the follow-up complete enough?</td>
<td>CT</td>
<td>Yes</td>
<td>No</td>
<td>CT</td>
</tr>
<tr>
<td>6b Was the follow-up long enough?</td>
<td>CT</td>
<td>Yes</td>
<td>No</td>
<td>CT</td>
</tr>
<tr>
<td>7 Do you believe the results?</td>
<td>Yes</td>
<td>Yes</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>8 Can the results be applied to a local population?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>CT</td>
</tr>
<tr>
<td>9 Do the results of the study fit with other available evidence?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**CT** = Cannot tell.
<table>
<thead>
<tr>
<th>Manuscript title</th>
<th>Author (ref), Region</th>
<th>Year</th>
<th>Study design</th>
<th>Study aim</th>
<th>Total sample size</th>
<th>Sample age range/mean, sex</th>
<th>Subjects with history of ED</th>
<th>Subjects with new onset AMI</th>
<th>Sens.</th>
<th>Spec.</th>
<th>Other risk factors investigated</th>
<th>ED validation tool</th>
<th>Respective authors’ conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is erectile dysfunction really a clinically useful predictor of cardiovascular disease?</td>
<td>Ströberg [7], Sweden</td>
<td>2005</td>
<td>R</td>
<td>evaluate the connection between ED and CVD, namely MI</td>
<td>229</td>
<td>35-69 yrs, M</td>
<td>64</td>
<td>100</td>
<td>34% (95% CI: 24.82-44.15%)*</td>
<td>76.74% (95% CI: 68.49-83.73%)*</td>
<td>diabetes, hypertension and smoking</td>
<td>unvalidated questionnaire</td>
<td>the association between CVD and ED was confirmed, however, lack of rise in prevalence of ED prior to MI does not support the idea that ED is a clinically useful predictor of MI</td>
</tr>
<tr>
<td>Is there a relationship between severity of coronary artery disease and severity of erectile dysfunction?</td>
<td>Canat [8], Turkey</td>
<td>2013</td>
<td>R</td>
<td>evaluate the association between the number of occluded coronary arteries in MI patients with the severity of ED and investigate the influence of related risk factors</td>
<td>183</td>
<td>55.2 yrs, M</td>
<td>100</td>
<td>183</td>
<td>54.64% (95% CI: 47.13-62%)*</td>
<td>NA</td>
<td>age, diabetes, cigarette smoking, waist circumference, hypertension, cholesterol levels and prescription medications</td>
<td>IIEF (&lt; 26: ED)</td>
<td>severity of ED correlated with the number of occluded vessels in male patients with AMI. The presence of hypertension had an influence on erectile function only in patients with three-vessel occlusion</td>
</tr>
<tr>
<td>The prevalence of sexual dysfunction before myocardial infarction in population of Polish men: a retrospective pilot study</td>
<td>Puchalski [9], Poland</td>
<td>2013</td>
<td>R</td>
<td>assess the presence of sexual dysfunction in men before MI</td>
<td>62</td>
<td>40-75 yrs, M</td>
<td>32</td>
<td>62</td>
<td>51.61% (95% CI: 38.56-64.50%)*</td>
<td>NA</td>
<td>body mass index, education, marital status, sleepiness, stress, hypertension, diabetes, cholesterol and renal function</td>
<td>IIEF (&lt; 25: ED)</td>
<td>ED was present in more than half the men before MI and it may be the first symptom of CAD</td>
</tr>
<tr>
<td>Relationship between erectile dysfunction and coronary anatomy in patients with ischemic heart disease debut</td>
<td>Garcia-Cruz [10], Spain</td>
<td>2013</td>
<td>P</td>
<td>evaluate the relationship between the ED and the coronary anatomy in a group of patients undergoing coronary angiography for an ischemic heart disease debut</td>
<td>99</td>
<td>62 yrs, M</td>
<td>56</td>
<td>99</td>
<td>56.57% (95% CI: 46.23-66.50%)*</td>
<td>NA</td>
<td>NS</td>
<td>EHS (&lt; 4: ED)</td>
<td>presence of ED is not significantly related to the presence or severity of SCD in men; in context of ischemic heart disease debut</td>
</tr>
</tbody>
</table>

R = Retrospective; P = prospective; CVD = cardiovascular disease; MI = myocardial infarction; M = Male; yrs = years; ACS = acute coronary syndrome; SCD = significant coronary artery disease; GFR = glomerular filtration rate; NA = not available; * = extrapolated.
Data Synthesis and Statistical Analysis

The number of, true and false, positive and negative cases in each study is used to calculate the sensitivity and specificity parameters. Where there were zero cases for a parameter, 0.5 was added to each parameter to prevent algebraic errors.

Results

Search

The electronic search yielded 8,454 articles with the following breakdown: Cochrane Database of Systematic Reviews (n = 90), Embase (n = 192), PubMed (n = 2,711), Scopus (n = 290) and Web of Science (n = 2,560). The articles were screened for duplicates and content. No further articles were identified from the citations provided by the selected papers (fig. 1).

A total of 381 duplicate entries, 19 animal studies, and another 7,215 entries were removed as they were unrelated to the topic. The remaining 839 articles had full text available and were independently reviewed by the researchers. All systematic review articles (n = 45), review articles (n = 303) and related but not applicable articles (n = 486) were excluded. Five articles were finally selected, of which only four were included in the review.

Details of these 4 studies are described below and are summarized in table 2 [7–10]. There were 2 studies conducted by the same author, which made use of the same study population [8, 11]. This is why the more recent published paper (2015) was excluded [11].

Region of Study Origin

All relevant selected studies were performed in Europe. One each originated from Sweden, Turkey, Poland and Spain [7–10].
Three of the included studies were retrospective reviews [7–9], the remaining study was a prospective cohort study [10].

The studies included in the review all described ED and its relation to AMI, however, the aims of the studies differed slightly; ED and its association with new onset AMI was investigated in 2 articles [7, 9], and the degree of coronary artery vessel damage as well as number of occluded vessels was described by authors in 2 studies [8, 10].

A total of 573 participants were included in the meta-analysis, the mean 143 (SD ± 76.3604) and median 141 participants. The smallest and largest studies ranged from 62 [9] to 229 [7] participants.

Three of the studies described other risk factors for AMI. These included diabetes, smoking, hypertension, age, waist circumference, prescription medication use, body mass index, stress and renal function [7–9].

For the single study which reported true negative and false positive cases, we calculated the specificity at 76.74% (95% CI: 68.49– 83.73%) [7]. The estimated positive likelihood ratio was 1.46 (95% CI: 0.96–2.20), negative likelihood ratio 0.86 (95% CI: 0.73–1.02) and diagnostic odds ratio was 1.69 (95% CI: 0.95–3.06). None of these parameters were statistically significant.

However, too few studies reported true negative and false positive cases in order to calculate a pooled value for specificity. Consequently, likelihood ratios could not be determined. Data analysis was conducted in R [14] using a number of meta-analysis packages [15–18].

Table 3. Meta-analysis table

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total sample size, n</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ströberg [7]</td>
<td>2005</td>
<td>229</td>
<td>34</td>
<td>99</td>
<td>30</td>
<td>66</td>
<td>34% (95% CI: 24.82–44.15%)</td>
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<td>66</td>
<td>54.64% (95% CI: 47.13–62%)</td>
<td>NA</td>
</tr>
<tr>
<td>Puchalski [9]</td>
<td>2013</td>
<td>62</td>
<td>32</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>51.61% (95% CI: 38.56–64.50%)</td>
<td>NA</td>
</tr>
<tr>
<td>Garcia-Cruz [10]</td>
<td>2013</td>
<td>99</td>
<td>56</td>
<td>43</td>
<td>30</td>
<td>66</td>
<td>56.57% (95% CI: 46.23–66.50%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

TP = True positive; TN = true negative; FP = false positive; FN = false negative; NA = not available.

Design of Included Studies

Overall and Systematic Review Sample Size

A log odds ratio summary effect could not be estimated due to the sparsity of the data from the included studies. A pooled sensitivity measure was computed and presented here.

Meta-Analysis

Only studies with enough data that were either reported or could be extrapolated were subjected to meta-analysis. The pooled sensitivity of ED as a risk factor to new onset AMI was calculated as 51.36% (95% CI: 47.37–55.33%). Individual sensitivities (and the single specificity) are outlined in table 2 and 3. The individual sensitivities have been depicted in the forest plot (fig. 2). The reported sensitivity ranged from 34% (95% CI: 24.82–44.15%) [7] to 56.57% (95% CI: 46.23–66.50%) [10]. The forest plot indicates that there was good agreement between studies as to the sensitivity of this factor and it is likely that the true sensitivity is less than 60%.

Discussion

ED is the continued inability to achieve and sustain an erection satisfactory enough for sexual intercourse [19, 20]. Causes of ED can be divided into organic and psychogenic causes. Organic causes can be further subdivided into vasculogenic, neurogenic, anatomic and endocrinologic causes. It is believed that the most common cause for ED involves a combination of both organic and psychogenic causes [21]. Vasculogenic ED is associated with atherosclerosis and it is found to occur concurrently with coronary atherosclerotic disease (CAD) [21].

Atherosclerosis, the deposition of lipid containing plaque along the walls of blood vessels, is a generalized systemic disease involving large and medium vessels of the arterial system [22, 23]. Due to the systemic nature of atherosclerosis, the manifestation of plaques could result in early symptomology due to differences in artery size.
artery size hypothesis demonstrates the different presentations of the same pathology and why ED could be a risk factor for other disease (specifically CAD) [19, 24–26].

The prevalence of ED has been reported to be 52% in men aged 40–70 years [27]. Furthermore, prevalence and incidence are said to be on the rise worldwide [28]. In the assessment of ED, patients are often reluctant to disclose sexual dysfunction themselves, however, they are comfortable if the issue is raised by clinicians [29]. Patients are also more willing to disclose sexual function if the matter is discussed in the third person [29].

There are multiple screening tools available for the assessment of ED. The International Index of Erectile Function (IIEF) and Erection Hardness Score (EHS) are validated and commonly used by healthcare providers in order to quantify the degree of ED [30, 31]. In this systematic review, it was noted that 3 articles made use of the IIEF [8, 9, 11]. It must be noted, though, the studies each had different scores for the ‘study’ definition of ED. This defined true ED, ranging from the highest (IIEF score ≤ 25) [8] to the lowest (IIEF score ≤ 21) [11]. Puchalski et al. [9] defined true ED as an IIEF score ≤ 24. One article made use of the EHS [10] and Ströberg et al. [7] used an unvalidated questionnaire.

Common risk factors for ED include increasing age, obesity, cigarette smoking, diabetes mellitus, dyslipidemia, hypertension, sedentary lifestyle, stress, renal dysfunction and the use of various medications [7–11, 26, 32, 33]. Most of these risk factors are also associated with the development of atherosclerosis and AMI [33, 34]. Thus, isolating ED specifically as a risk factor in new onset AMI becomes more intricate, more so in retrospective designed studies.

In the assessment of CAD risk, many healthcare providers make use of the Framingham score [5]. The tool explores and identifies common risk factors associated with CAD. These risk factors are like those stated previously (ED). It is suggested that the assessment of erectile function on history become a standard part of the work up in all adult male patients, so that the precise predictability of ED in relation to AMI, can be better quantified.

The annual mortality from AMI has been described as 16.6% globally [35]. According to Garcia-Cruz et al. [10], ED as a risk factor to new onset AMI reported a sensitivity of 56.57%. Due to the potential life-threatening nature of AMI, ED could be useful in alerting men to the possibility and likelihood of first/new onset AMI.

The results of this systematic review suggest that a history of ED is not enough to determine whether there is an increased risk of AMI. Nor is the absence of ED an indication of a decreased risk of AMI, however this estimate of specificity was based on a single and small study. Further studies with more robust designs may show some diagnostic value in this specific predictive measure.

**Fig. 2.** Forest plot of sensitivity estimates.
This systematic review and meta-analysis included four relevant related studies [7–10]. Certain hallmark related studies could not be included in the review, as they were non-specific in their methodology and findings. Montorsi et al. [19] and Kumar et al. [36] noted the relationship of ED as a risk factor for CAD, however, the study included new onset of AMI as well as patients with established CAD. Banks et al. [37] investigated the relationship between ED and systemic cardiovascular disease and reported on a non-specific relationship between ED and new onset ischemic heart disease.

Vlachopoulos et al. [38] investigated whether aortic pulse wave velocity predicted major adverse cardiovascular events in patients with ED. The authors mentioned AMI as a major adverse cardiovascular events consequence, but the results did not specify AMI results.

ED as a risk factor to new onset AMI (in isolation) has rarely been studied; however, it has been recorded as a complication following AMI. Future studies should include ED as a part of cardiovascular system risk assessments, history, and investigations in the adult male population. These future studies should be prospective and have a large sample size and are to be performed in various regions across the globe. Only then will we be confident enough to extrapolate and utilize the presence of ED as a calculated predictor for new onset AMI.

There were limited datasets available in the current literature assessed, with only one study isolated which provided enough data for both sensitivity and specificity to be extrapolated [7]. Thus, there was insufficient data for a forest plot and to test the true likelihood of ED as a reliable risk factor for new onset AMI.

Another limitation to mention in this systematic review, is that the ED assessment tools were not standardized amongst the studies included in the systematic review [7–10]. Certain studies looked at other risk factors which further predispose patients to the development of AMI along with ED [7–9]. Only 2 studies isolated in this systematic review concluded that ED had a significant role as a risk factor for new onset AMI, and also noted that ED should warrant further investigation for CAD and subsequent AMI [8, 9].

Conclusion

The results of this systematic review and meta-analysis suggest that ED should be used as a risk factor for new onset AMI. The presence of ED should warrant healthcare providers into doing further investigations, in patients that are at risk, for the prevention of potential new onset AMI. It is suggested that the assessment of erectile function, on history, become a standard part of the work up in all adult male patients to assess and quantify the precise predictability of this commonly overlooked symptom complaint as a risk factor for new onset AMI in future studies.

References


ED as a Risk Factor for New Onset Acute Myocardial Infarction


