Systematic Review of Patients Presenting with Suspected Myocardial Infarction and Non-Obstructive Coronary Arteries (MINOCA)

Running title: Pasupathy et al.; Systematic review of suspected MINOCA

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Abstract

Background—Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a puzzling clinical entity with no previous evaluation of the literature. This systematic review aims to: (A) quantify the prevalence, risk factors, and 12-month prognosis in patients with MINOCA, and (B) evaluate potential pathophysiological mechanisms underlying this disorder.

Methods and Results—Quantitative assessment of 28 publications using a meta-analytic approach evaluated the prevalence, clinical features, and prognosis of MINOCA. The prevalence of MINOCA was 6% [95%CI: 5, 7%] with a median patient age of 55 years (95%CI: 51, 59 years) and 40% women. However, in comparison to those with myocardial infarction associated with obstructive coronary artery disease (MI-CAD), the patients with MINOCA were more likely to be younger and female but less likely to have hyperlipidemia, although other cardiovascular risk factors were similar. All-cause mortality at 12-month was lower in MINOCA (4.7% [95%CI: 2.6, 6.9%]) compared to MI-CAD (6.7% [95%CI: 4.3, 9.0%]). Qualitative assessment of 46 publications evaluating the underlying pathophysiology responsible for MINOCA, revealed the presence of a typical myocardial infarct on cardiac magnetic resonance imaging in only 24% of patients, with myocarditis occurring in 33% and no significant abnormality in 26%. Coronary artery spasm was inducible in 27% of MINOCA patients and thrombophilia disorders were detected in 14%.

Conclusions—MINOCA should be considered as a ‘working diagnosis’ with multiple potential causes that require evaluation so that directed therapies may improve its guarded prognosis.

Key words: myocardial infarction, coronary artery disease, coronary spasm, coagulation/thrombosis, cardiac magnetic resonance imaging, imaging, coronary artery abnormality, magnetic resonance
Introduction

Contemporary management strategies of acute ST-elevation myocardial infarction (STEMI) are based upon the pioneering early angiographic studies of DeWood and colleagues\(^1\), who demonstrated an occluded coronary artery in almost 90% of these patients. Accordingly, the ‘open artery’ management strategy was employed, initially with the use of thrombolytic therapy and subsequently with percutaneous coronary interventions. In contrast, early angiography in patients with non-ST elevation myocardial infarction (NSTEMI) showed an occluded vessel in less than a third of these patients\(^2\) so that strategies focusing on maintaining arterial patency were developed. However both of these acute myocardial infarction (MI) angiographic studies\(^1,2\) demonstrated the presence of significant obstructive coronary artery disease in more than 97% of these MI patients, thus underscoring the importance of obstructive coronary atherosclerotic disease in this condition.

With the widespread use of coronary angiography in the early clinical management of MI, multicenter MI registries have evolved and reported that as many as 10% of MI patients have no evidence of obstructive coronary artery disease\(^3\). These patients with MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries)\(^4\) represent a conundrum as the underlying cause of their MI is not immediately apparent. Furthermore, whether they have similar clinical features and outcomes as patients with MI-CAD (Myocardial Infarction with obstructive Coronary Artery Disease) is unclear. Ascertaining whether MINOCA is a distinct clinical entity with specific clinical features, outcomes and pathophysiological mechanisms is paramount to determining the appropriate management strategy for these patients, yet to-date there is no systematic review of the published literature concerning these patients. Furthermore, given the limited investigation of these patients, it is not surprising that there are no professional guidelines...
on the management of MINOCA.

Accordingly, the primary objectives of this systematic review are to detail the clinical attributes of these patients by systematically evaluating the published literature in regards to (A) the prevalence, clinical features, and 12-month prognosis of MINOCA patients, and (B) the major underlying pathophysiological mechanisms responsible for this disorder.

Methods

This study utilized a comprehensive structured systematic approach that included a methodical literature search, well-defined inclusion criteria for MINOCA, extraction of available raw data and pooling of the data to determine the frequency of each of the pre-determined study endpoints.

Published Literature Search

An unrestricted literature search was conducted using PubMed and Embase. The search terms in each of these databases and the subsequent evaluation process are summarized in Figure 1. In brief, searches were conducted in both databases focusing on the terms ‘myocardial infarction’, ‘non-obstructive’ and ‘angiography’. Only original human clinical research studies published in English were considered. However, the references in recent key review papers were also crosschecked with the database searches to ensure a comprehensive source of original papers. A search of the Cochrane database revealed no relevant systematic reviews on this topic.

Systematic Assessment of the Available Literature

Of the original human myocardial infarction research studies (1,033 publications) between 1966 and 2013 (inclusive), reference to non-obstructive coronary artery disease was evident in 237 publications (Figure 1). These manuscripts were reviewed for the following pre-specified inclusion and exclusion criteria by two of the investigators (SP, RT).
Inclusion Criteria

For consideration in this meta-analysis, it was essential for the following criteria to be documented in the protocol of the published study:

1. Evidence of an MI \(^5\) as defined by (a) significant elevation of a cardiac biomarker and (b) at least one of the following – ischemic symptoms, new ST/T changes or new left bundle branch block.

2. Qualitative coronary angiography findings to allow determination of the presence/absence of obstructive coronary artery disease.

MINOCA was defined as the presence of an MI (as per the above criteria) in the absence of obstructive coronary artery disease (i.e. no epicardial vessel with a stenosis \(\geq 50\%\) on angiography). Those MI patients with significant obstructive coronary artery disease (at least one stenosis \(\geq 50\%\)) were designated as MI-CAD. The decision to utilize a \(<50\%\) lesion threshold to delineate non-obstructive CAD from the obstructive CAD is based upon the following rationale: (a) well established criteria in clinical guidelines \(^6\), accordingly (b) it is the most frequently used definition in published angiographic studies, (c) considering the limitations of angiography, the presence of angiographic smooth vessels does not exclude the presence of significant atherosclerosis, (d) attention should be focused on why myocardial infarction/injury has occurred in the absence of a functionally obstructive lesion, and (e) the more inclusive definition allows future prognostic studies to determine if there is clinical utility in delineating those with angiographically smooth vessels from those with minor CAD.

Exclusion Criteria

Publications were excluded from further consideration if:

1. coronary angiography was not performed in the context of an MI admission,
2. tako-tsubo cardiomyopathy or myocarditis were the primary focus of the paper,
3. there was no original data or the data was reproduced from a former study, and
4. isolated case report format.

Utilizing these inclusion and exclusion criteria, 152 original MI publications had sufficient
data to clearly identify those patients with MINOCA. Further analysis was dependent upon the
specific objectives of this study, namely (A) determining the clinical (primary objective) or (B)
pathophysiologic (secondary objective) attributes of MINOCA (Figure 1). The studies utilized in
the analyses are listed in Supplemental Table 1 of the Data Supplement.

As the primary objective requires a representative sample to quantitatively assess the
clinical attributes of MINOCA, only publications that recruited (i) at least 100 patients with MI,
and (ii) consecutive MI patients, were included in the analysis. The specific definitions used in
these studies for the various cardiovascular risk factors are listed in Supplemental Table 2 of
the Data Supplement.

For the second objective, original studies fulfilling the above inclusion/exclusion criteria
were included if they performed systematic diagnostic evaluations on a group of MINOCA
patients with the intention of exploring the underlying pathophysiologic mechanism/s
responsible for the MI. These included myocardial imaging studies such as cardiac magnetic
resonance (CMR) imaging and functional studies such as provocative spasm testing and
thrombophilia screening (Figure 1). For consistency, the total frequency of each abnormal
pathophysiologic investigation was documented although it is acknowledged that the findings
may be time-dependent. Accordingly, the results of early investigations (i.e. within 6 weeks of
MI) are also described.
Data Extraction and Analysis

The endpoints evaluated in the primary objective included (a) prevalence of MINOCA, (b) clinical features including age, gender, MI type (STEMI or NSTEMI), cardiovascular risk factors, and (c) prognosis (including in-hospital and 12-month all-cause mortality). Data for these endpoints were pooled and analyzed using random effects meta-analysis models. This conservative approach assumes that individual studies are estimating different treatment effects. Heterogeneity in the study estimates were assessed using I-squared statistics with larger values indicating increasing heterogeneity between studies. In addition, for studies including both MINOCA and MI-CAD patients, the summary odds ratios (OR’s) or mean difference and exact 95% confidence intervals (95% CI) were calculated. Data from the pathophysiologic mechanistic publications was more limited so that qualitative assessment could only be undertaken. This involved pooling of frequency data from studies with similar endpoints. All analyses were performed using STATA (version 12, College Station, TX, USA).

Results

From the 152 MINOCA publications identified on PubMed and Embase, we embarked upon (A) quantitative assessment of 28 studies to evaluate the clinical attributes of the condition and (B) qualitative evaluation of 46 studies that focused on its pathophysiologic attributes (Figure 1 & Data Supplement: Supplemental Table 1). These clinical and pathophysiologic attributes of MINOCA are detailed below.

Prevalence

The prevalence of MINOCA was determined from 27 large clinical trials/registries involving 176,502 consecutive MI patients who had coronary angiography performed. These studies reported
a prevalence of MINOCA ranging from 1-14% with an overall prevalence calculated at 6% (95%CI: 5, 7%), based upon random effects analysis (Figure 2). The I-squared statistic was estimated to be 99%.

Clinical Features

In 15 publications there was sufficient detail to evaluate gender, age, cardiovascular risk factors, STEMI presentation, and angiographic characteristics of MINOCA patients. Some of these studies provided the opportunity to compare these features with those from patients with MI-CAD.

Gender

In the 15 publications reporting gender (n=11,334), pooled analyses revealed that only 40% (95%CI: 33, 46%) of MINOCA patients were women. However pooled analysis of 10 studies that recruited both MINOCA (n=5,322) and MI-CAD (n=70,253) patients, revealed an over-representation of women with MINOCA (43%; 95%CI: 35, 51%) relative to that observed with MI-CAD (24%; 95%CI: 19, 30%; Table 1).

Age

Sufficient data was available in 13 studies (n=9,986) to determine the pooled mean age of MINOCA patients. This was calculated to be approximately 55 years (95%CI: 51, 59 years) with no significant heterogeneity between studies as estimated by the I-squared statistic. In 6 publications, data on age was available for both MINOCA (n=3,927) and MI-CAD (n=48,082) patients, with the respective pooled mean ages between 58.8 (95%CI: 51.6, 66.1 years) and 61.2 years (95%CI: 52.2, 70.4 years). Analysis of these comparative studies confirmed that patients with MINOCA were younger than those with MI-CAD. This analysis may have underscored this difference since the 6 studies included in this comparison recruited MINOCA patients at the upper age spectrum of the overall MINOCA cohort (Table 1).
Cardiovascular Risk Factors

By evaluating comparative studies that included both MINOCA and MI-CAD patients, the relative frequencies of cardiovascular risk factors were determined. These are summarized in Table 1 along with the cardiovascular risk profile from all available MINOCA studies. Results reported within this section will be confined to the comparative studies. Compared with MI-CAD patients, those with MINOCA were less likely to have hyperlipidemia (32% [95%CI: 30-59%] vs. 21% [95%CI: 6-35%], respectively; OR = 0.63, P<0.001). However it is noteworthy that the prevalence of hyperlipidemia amongst MINOCA patients in these comparative studies was considerably lower than that observed for the overall MINOCA cohort (33%; 95%CI: 25-41%). Other cardiovascular risk factors including hypertension, diabetes, smoking and family history of premature coronary artery disease were similar between the groups (Table 1).

Infarct ECG Findings

Ten studies (n=1,998) documented the prevalence of an acute STEMI presentation amongst MINOCA patients. Pooled analysis revealed that 33% (95%CI 22, 44%) presented with features of STEMI (Figure 3). Accordingly, approximately two-thirds of patients were categorized with NSTEMI.

Angiographic Findings

By definition, MINOCA patients have <50% lesions on angiography. The relative frequency of smooth vessels (i.e. no lesions visible on angiography) compared with minor irregularities on angiography was assessed in 5 clinical trials with 1,046 MINOCA patients (Data Supplement: Supplemental Figure 1). Amongst the MINOCA patients, the prevalence of smooth vessels on angiography was 51% (95% CI: 39-61%). Importantly, the I² test confirmed the presence of significant heterogeneity amongst these studies.
**Prognosis**

Studies assessing prognosis in patients with MINOCA were considerably heterogeneous in their follow-up period and few reported the prevalence of cardiac mortality or re-infarction. Overall 8 studies reported all-cause mortality in patients with MINOCA, including in-hospital (5 studies, n=9,564), and 12-month (4 studies, n=1,924) following MI. Pooled meta-analysis of these studies revealed an all-cause in-hospital and 12-month mortality of 0.9% (95% CI: 0.5, 1.3%), and 4.7% (95% CI: 2.6, 6.9%), respectively. In 6 of these 8 studies, all-cause mortality was assessed in both MINOCA and MI-CAD patients, thereby allowing comparisons of the relative mortality between these forms of MI. As shown in Table 2, although the in-hospital mortality and 12-month mortality were lower in MINOCA patients, the findings remain of concern considering the limited clinical attention received by these patients.

**Potential Pathophysiological Mechanisms**

Of the 81 original publications investigating the potential mechanisms responsible for MI in MINOCA patients, 46 utilized three distinct approaches including, (i) assessment of structural myocardial dysfunction with CMR imaging (26 publications), (ii) provocative coronary artery spasm testing (15 publications), and (iii) thrombophilia screening (8 publications, including 3 of the spasm studies). The remaining 35 publications utilized more heterogeneous approaches investigating isolated aspects of MINOCA and therefore not conducive to pooled analysis.

**Structural Myocardial Dysfunction**

Pooled analyses of the 26 CMR imaging publications involving MINOCA patients, revealed features consistent with a subendocardial infarct on delayed hyper-enhancement in only 24% of 1,801 MINOCA patients studied. The most common finding in the CMR imaging studies was myocarditis, with 33% of the 1,676 MINOCA patients having features of this condition. Other
myocardial abnormalities reported in the MINOCA CMR imaging studies included, Tako-tsubo cardiomyopathy (18% of 1,529 patients), hypertrophic cardiomyopathy (3% of 1,074 patients), dilated cardiomyopathy (2% of 625 patients), and other causes (7% of 760 patients) such as pericarditis and amyloidosis. Importantly, 26% of 1,592 MINOCA patients undergoing contrast CMR imaging did not have detectable myocardial abnormalities.

Of the above investigations, 16 CMR studies were undertaken within 6 weeks of the MI (Data Supplement: Supplemental Table 3). These reported similar frequencies in abnormal CMR findings including subendocardial infarct (24%), myocarditis (38%), Tako-tsubo cardiomyopathy (16%) and no significant abnormality (21%).

**Coronary Artery Spasm**

Provocative spasm testing was undertaken in 14 studies involving MINOCA patients (Table 3). Of the 402 MINOCA patients in the pooled dataset, 28% had inducible spasm. In 8 studies (n=298), provocative testing was performed within 6 weeks of an MI and 28% had inducible spasm. In 4 studies (n=90), provocation testing was undertaken in MINOCA patients with an old myocardial infarct (i.e. MI ≥ 6 weeks) and spasm was provoked in 34% of patients (Table 3).

**Thrombophilia Disorders**

As summarized in Table 4, eight publications examined the presence of inherited thrombotic disorders in patients with MINOCA, with most undertaken in the early post-infarction period. Pooled analyses revealed the following abnormalities within the coagulation pathway: activated Protein C resistance or Factor V Leiden in 12% of 344 patients, Protein C/Protein S deficiency in 3% of 189 patients and Factor XII deficiency in 3% of 163 patients. Overall, 14% of the 378 MINOCA patients who underwent thrombophilia screening had evidence of an inherited thrombotic disorder.
Discussion

This detailed systematic review provides the first comprehensive overview of patients with MINOCA. It demonstrates that MINOCA has (a) a 6% prevalence of all MI presentations, (b) no diagnostic distinguishing clinical presentation features compared with MI-CAD, (c) a better 12-month all-cause mortality compared with MI-CAD, although its prognosis should be considered as ‘guarded’, and (d) structural dysfunction, coronary spasm and thrombotic disorders as some potential underlying causes. Given that MINOCA has similar features to MI-CAD, a guarded prognosis and multiple potential etiologies, it should be considered a ‘working diagnosis’ that requires further evaluation of the potential underlying causes since these may have important clinical implications.

MINOCA patients do not have a distinguishing clinical presentation.

Patients with MINOCA may present with STEMI or NSTEMI, with two-thirds presenting as the latter. Compared with MI-CAD patients, those with MINOCA tend to be younger, predominantly male (although women are over-represented relative to those with MI-CAD, 40% vs 25% respectively) with significant cardiovascular risk factors, although less often have hyperlipidemia (Table 1). Thus although there are statistical differences in the clinical profile of patients with MINOCA, there are no clinically distinguishing characteristics or risk factors that can easily delineate these patients from those with MI-CAD based upon a systemic review of the literature. Specific future studies examining details of the clinical history may be more discerning. Once coronary angiography is performed and defines the MINOCA patients, completely smooth (i.e. ‘normal’) coronary arteries are observed in only half of the patients, with many having minor irregularities thereby justifying the term ‘MINOCA’. The clinical importance of delineating MINOCA patients with angiographically smooth coronary arteries
from those with only mild irregularities needs to be clarified in future prognostic studies. The only published MINOCA study that has undertaken this comparison examined 12-month all-cause mortality and reported poorer outcomes in those with smooth coronaries, however sample size was small (24 deaths in total)\(^9\). If future studies demonstrate different outcomes in these angiographic subgroups, then it will be justifiable to clinically delineate them.

**MINOCA patients have a ‘guarded prognosis’**

Patients with MINOCA have a significantly reduced all-cause mortality compared to those with MI-CAD; including a 63% lower in-hospital mortality and 41% lower 12-month mortality (Table 2).

Although these findings may be reassuring, the 4.7% (95%CI: 2.6-6.9%) 12-month all-cause mortality for patients with MINOCA is of concern when compared to other published prognostic studies. Firstly, the Korean MI Registry\(^{10}\) evaluated 12-month all-cause mortality in 8,510 consecutive MI patients, reporting a 3.1% mortality in those with MINOCA, 3.2% in those with single or double vessel coronary artery disease, and 6.5% in those with triple vessel disease or a significant left main coronary artery stenosis. Secondly, patients with stable chest pain (i.e. no prior MI) and normal smooth coronaries on angiography have a 0.2% annual all-cause mortality, while those with only minor luminal irregularities have a 0.3% annual all-cause mortality\(^{11}\). Accordingly, MINOCA patients appear to have a poorer prognosis than those with stable chest pain and non-obstructive coronary artery disease, and more akin to those with an MI and single/double vessel coronary artery disease. Thus their prognosis should be considered somewhat ‘guarded’ despite being better than those with MI-CAD.

**MINOCA – A Heterogeneous ‘Working Diagnosis’ with some Treatable Causes**

Similar to the diagnosis of heart failure, MINOCA should not be considered as a specific
diagnosis but a heterogeneous ‘working diagnosis’ that requires further evaluation to elucidate potential underlying causes. Identifying the cause of MINOCA is important since it may have prognostic implications (e.g. identification of a cardiomyopathy) but even more importantly, it may require institution of specific therapies to treat the underlying cause. Important MINOCA-related diagnoses that may warrant specific targeted therapies include structural myocardial dysfunction (such as cardiomyopathies), coronary spasm and thrombophilia disorders. These are further discussed below.

**Structural Myocardial Dysfunction**

The detection of structural heart disease with CMR imaging in patients with MINOCA syndrome, can reveal cardiomyopathies such as tako-tsubo, hypertrophic or dilated cardiomyopathy (Figure 4). Although tako-tsubo cardiomyopathy is an important diagnosis considering its prognostic implications, currently there are no specific therapies for this condition. In contrast, hypertrophic and dilated cardiomyopathy (although seldom detected in MINOCA patients) have important management strategies/therapies that can influence patient outcomes. Accordingly, detection of these treatable conditions further justifies the routine use of CMR imaging in patients with MINOCA since it is the optimal diagnostic imaging modality for delineating cardiac structural disorders in this condition.

Myocarditis is an important cause of MINOCA that is optimally diagnosed by CMR imaging. It accounts for approximately a third of MINOCA cases and provides a definitive diagnosis that may have prognostic implications, although generally it requires only conservative management.

Another important MINOCA subgroup detected by CMR imaging are those with a subendocardial infarct pattern on delayed hyper-enhancement images. The infarct may arise from
transient occlusive coronary spasm or thrombosis\textsuperscript{12}.

**Coronary Spasm**

More than a quarter of patients with MINOCA undergoing provocative spasm testing have inducible spasm. Unfortunately there are no suitable studies directly comparing provocative spasm testing between MINOCA and MI-CAD patients, although several have reported inducible spasm in 20-80\% of MI-CAD patients\textsuperscript{13, 14}. Thus the relative contribution of coronary spasm to the pathophysiology of MINOCA requires further investigation.

There are several interesting observations in relation to provocative spasm testing findings in patients with MINOCA. Firstly, there is no time-dependence for inducible spasm amongst MINOCA patients (Table 3), whereas MI-CAD patients with a recent (<6 weeks) infarct are more likely to have inducible spasm than those with an old (>6 weeks) infarct. Whether the persistent inducible spasm in MINOCA patients reflects an underlying vasospastic predisposition is open to speculation. Secondly, there appears to be an ethnic predisposition to coronary spasm in patients with a recent myocardial infarct\textsuperscript{14}, particularly amongst Japanese patients\textsuperscript{15}. Fukai et al\textsuperscript{16} from Japan reported an 81\% prevalence of inducible spasm in patients with MINOCA, whereas studies from Europe\textsuperscript{17-20} and the United States\textsuperscript{21, 22} have a pooled prevalence of only 14\%. Interestingly, other Asian-based studies\textsuperscript{23, 24} also report a high prevalence of inducible spasm (Table 3). Finally, cocaine may induce coronary spasm and should be considered as a potential cause of MINOCA however a recent large registry reported that cocaine use was associated with only 0.9\% of MI cases\textsuperscript{25}.

The above findings relating to coronary spasm in MINOCA are exploratory and require further investigation since the data are heterogeneous with the studies differing in their study design, provocation stimulus and coronary spasm definition. In particular, ergonovine provocation
is less often used since it is no longer available in some countries and acetylcholine has become the preferred provocation stimulus. Despite these study differences, the importance of coronary spasm as a potential cause of MINOCA must not be overlooked as it appears to occur frequently and the use of calcium channel blockers is an independent determinant of survival in patients with coronary spasm26.

**Thrombophilia Disorders**

As summarized in Table 4, genetic thrombophilia disorders have been observed in MINOCA. Factor V Leiden is a single point mutation with a prevalence of 3-7% in Western populations27 but was observed in 12% of MINOCA patients. Furthermore, comparative studies with MI-CAD patients also report a higher prevalence in MINOCA (Mansourati et al28: 4.5% vs 12.1%; and Van de Water et al29: 4.3% vs 11.7%, respectively). Protein C & S deficiency are autosomal dominant disorders with a population prevalence of 0.1-1%27, yet occur in 2.6% of MINOCA patients and similarly those with MI-CAD30.

These associations with the genetic thrombophilia disorders are based upon small studies and require confirmation with larger multicenter prospective studies. Furthermore, investigation of acquired thrombophilia disorders should be considered as these may also occur in the context of acute MI and could exacerbate the genetic disorders. Irrespective of the prevalence of these thrombophilia disorders in MINOCA, their detection may influence subsequent management thereby justifying their routine evaluation in patients with MINOCA.

**Limitations**

The results from this structured systematic review should be interpreted in the context of several potential limitations. Firstly, the analysis is dependent on the available published data and thus limited by publication bias, patient selection bias, suboptimal definitions for cardiovascular risk...
factors, retrospective analyses, and applicability of historical publications to contemporary practice. Secondly, there is significant heterogeneity between the studies included in the meta-analysis although the random effects model approach used in this study is less influenced by this pitfall. Thirdly, the second objective, which focused upon pathophysiological studies, did not lend itself to quantitative meta-analysis but a qualitative evaluation of published data. This was necessary as there were differences in patient recruitment, methods of investigation and definitions of a positive result, for each of the respective studies involving CMR imaging, provocative spasm testing, and genetic thrombophilia disorders.

Conclusions
This systematic review provides an important reference point for further research and development of MINOCA. It demonstrates that the condition is not uncommon, has no delineating clinical presentation, a guarded 12-month prognosis, and multiple potential causes with some amenable to specific therapies. Despite this, there are no guidelines regarding the management of these patients and limited insights into the contemporary management undertaken (if any) in affected patients. Based upon the findings of this systematic review, we would propose that MINOCA be considered a ‘working diagnosis’ that requires routine evaluation for treatable underlying causes. This may include CMR imaging, provocative spasm testing, and thrombophilia assessment. Further research is required to define the optimal therapy in MINOCA patients who do not have an identifiable underlying cause. These strategies may potentially improve the guarded prognosis in these patients.

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Conflict of Interest Disclosures: None.

References:


Table 1. Cardiovascular Risk Factors in Patients with MINOCA or MI-CAD

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Comparative Studies</th>
<th>All MINOCA Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI-CAD % (95% CI)</td>
<td>MINOCA % (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>61.3 (52.2-70.4)</td>
<td>58.8 (51.6-66.1)</td>
</tr>
<tr>
<td>Women</td>
<td>24% (19, 30%)</td>
<td>43% (35, 51%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>32% (15-48%)</td>
<td>21% (6-35%)</td>
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<tr>
<td>Hypertension</td>
<td>45% (30-59%)</td>
<td>52% (41-62%)</td>
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<tr>
<td>Diabetes</td>
<td>22% (14-29%)</td>
<td>15% (9-20%)</td>
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<tr>
<td>Smoking</td>
<td>39% (26-52%)</td>
<td>42% (33-51%)</td>
</tr>
<tr>
<td>Family history</td>
<td>27% (10-43%)</td>
<td>21% (5-38%)</td>
</tr>
</tbody>
</table>

Data presented as either mean or percentage (%) with 95% confidence intervals (%) where appropriate. MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; MI-CAD, Myocardial Infarction with Coronary Artery Disease; CAD, Coronary Artery Disease; SD, Standard Deviation; CI, Confidence Interval; Pubs, Publications.

Table 2. All-Cause Mortality in Patients with MINOCA or MI-CAD

<table>
<thead>
<tr>
<th>All-cause Mortality</th>
<th>Comparative Studies</th>
<th>All MINOCA Studies</th>
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<tbody>
<tr>
<td></td>
<td>MI-CAD % (95% CI)</td>
<td>MINOCA % (95% CI)</td>
</tr>
<tr>
<td>In-Hospital</td>
<td>3.2% (1.8-4.6%)</td>
<td>1.1% (-0.1-2.2%)</td>
</tr>
<tr>
<td>12-Month</td>
<td>6.7% (4.3-9.0%)</td>
<td>3.5% (2.2-4.7%)</td>
</tr>
</tbody>
</table>

Data presented as percentage (%) and 95% confidence intervals (%) with Odds Ratio and P values. MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; MI-CAD, Myocardial Infarction with Coronary Artery Disease; OR, Odds Ratio; CI, Confidence Interval; Pubs, Publications.
**Table 3. Provocative Spasm Testing in Patients with MINOCA.**

<table>
<thead>
<tr>
<th>Publications</th>
<th>n</th>
<th>Provocation Test</th>
<th>Spasm Definition</th>
<th>Provoked/Spontaneous Spasm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Provocative Spasm Testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(within 6 weeks of acute myocardial infarction)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Bory, 1988</td>
<td>59</td>
<td>iv ergot</td>
<td>≥ 50% constriction on angio</td>
<td>2/59 (3%)</td>
</tr>
<tr>
<td>Fukai, 1993</td>
<td>21</td>
<td>iv ergot</td>
<td>≥ 75% constriction on angio</td>
<td>13/16 (81%)</td>
</tr>
<tr>
<td>Dacosta, 2001</td>
<td>91</td>
<td>iv ergot</td>
<td>≥ 70% constriction on angio</td>
<td>11/71 (15%)</td>
</tr>
<tr>
<td>Wang, 2002</td>
<td>23</td>
<td>ic ergot</td>
<td>≥ 90% constriction on angio</td>
<td>17/23 (74%)</td>
</tr>
<tr>
<td>Hung, 2003</td>
<td>19</td>
<td>ic ergot</td>
<td>≥ 70% constriction on angio</td>
<td>18/19 (95%)</td>
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<tr>
<td>Dacosta, 2001</td>
<td>82</td>
<td>iv ergot</td>
<td>≥ 70% constriction on angio</td>
<td>13/82 (16%)</td>
</tr>
<tr>
<td>Abid, 2012</td>
<td>21</td>
<td>iv ergot</td>
<td>≥ 70% constriction on angio</td>
<td>5/21 (24%)</td>
</tr>
<tr>
<td>Ong 2008</td>
<td>7</td>
<td>ic acetylcholine</td>
<td>≥ 75% constriction on angio</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td><strong>Early spasm</strong></td>
<td></td>
<td></td>
<td></td>
<td>(83/298) 28%</td>
</tr>
<tr>
<td><strong>Late Provocative Spasm Testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥ 6 weeks following myocardial infarction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legrand, 1982</td>
<td>18</td>
<td>iv ergot</td>
<td>Chest pain &amp; ST elevation</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td>Raymond, 1988</td>
<td>74</td>
<td>iv ergot</td>
<td>≥ 75% constriction on angio</td>
<td>5/16 (31%)</td>
</tr>
<tr>
<td>Ammann, 2000</td>
<td>23</td>
<td>Hyperventilate</td>
<td>ST elevation</td>
<td>0/23 (0%)</td>
</tr>
<tr>
<td>Kim, 2005</td>
<td>33</td>
<td>iv ergot</td>
<td>RWMA on echocardiography</td>
<td>20/33 (61%)</td>
</tr>
<tr>
<td><strong>Late spasm</strong></td>
<td></td>
<td></td>
<td></td>
<td>(31/90) 34%</td>
</tr>
<tr>
<td><strong>Undefined timing for Provocative Spasm Testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(relative to myocardial infarction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salem, 1985</td>
<td>10</td>
<td>iv ergot</td>
<td>Chest pain &amp; ST elevation</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>Verheugt, 1987</td>
<td>21</td>
<td>iv ergot</td>
<td>NR</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td><strong>Provocative Spasm Testing on Cocaine induced MINOCA Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Kossowsky, 1989</td>
<td>5</td>
<td>cold pressor</td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Overall pooled spasm</strong></td>
<td></td>
<td></td>
<td></td>
<td>114/402 28%</td>
</tr>
</tbody>
</table>

Data presented as n (%). MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; iv, intravenous; ic, intracoronary; ergot, Ergonovine; angio, Coronary angiography; RWMA, regional wall motion abnormality; NR, Not recorded. * Kossowsky et al., 1989 was ignored from the calculations as it represents the cohort of Cocaine abuse patients.
Table 4. Thrombophilia Screening in Patients with MINOCA.

<table>
<thead>
<tr>
<th>Publications</th>
<th>No of patients in the study</th>
<th>APCR/ Factor V Leiden</th>
<th>Protein C/S Deficiency</th>
<th>Factor XII Deficiency</th>
<th>Thrombotic disorders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brecker, 1993</td>
<td>12</td>
<td>NE</td>
<td>0</td>
<td>NE</td>
<td>(0 / 12) 0%</td>
</tr>
<tr>
<td>DaCosta, 1998*</td>
<td>22</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>(4 / 22) 18%</td>
</tr>
<tr>
<td>Lande, 1998</td>
<td>26</td>
<td>3</td>
<td>2</td>
<td>NE</td>
<td>(5 / 14) 36%</td>
</tr>
<tr>
<td>Mansourati, 2000</td>
<td>107</td>
<td>13</td>
<td>NE</td>
<td>NE</td>
<td>(13 / 107) 12%</td>
</tr>
<tr>
<td>Van de Water, 2000</td>
<td>60</td>
<td>8</td>
<td>NE</td>
<td>NE</td>
<td>(8 / 60) 13%</td>
</tr>
<tr>
<td>DaCosta, 2001</td>
<td>91</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>(9 / 73) 13%</td>
</tr>
<tr>
<td>DaCosta, 2004</td>
<td>82</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>(12 / 78) 15%</td>
</tr>
<tr>
<td>Abid, 2012</td>
<td>21</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>(4 / 12) 33%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>12%</strong></td>
<td><strong>2.6%</strong></td>
<td><strong>2.5%</strong></td>
<td><strong>14%</strong></td>
<td><strong>(41 / 344) (5 / 189) (4 / 163) (51 / 356)</strong></td>
</tr>
</tbody>
</table>

Data presented as n (%). MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; APCR, Activated Protein C Resistance; NE, Not Examined.

*Dacosta et al., 1998 was ignored from the calculations as the same patient cohort again used in Dacosta et al., 2004.

Figure Legends:

**Figure-1.** Flow diagram of study selection process. The following abbreviations are used in the above figure: Pubs - refers to number of publications in the literature search; AMI- Acute Myocardial Infarction; CAD- Coronary Artery Disease; MINOCA- Myocardial Infarction with Non Obstructive Coronary Arteries; CMR- Cardiac Magnetic Resonance Imaging; SPECT- Single Photon Emission Computed Tomography; IVUS- Intravascular ultrasound; Echo- Echocardiography.

**Figure 2.** Prevalence of MINOCA. Forest plot of published studies examining the prevalence of MINOCA using random effects meta-analysis. Data presented as percentage (%) and 95% confidence intervals (%). MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; CI, Confidence Interval.
Figure 3. Prevalence of Acute STEMI Presentation in MINOCA. Forest plot of published studies examining the frequency of STEMI presentation in patients with MINOCA, using a random effects meta-analysis. Data presented as percentage (%) and 95% confidence intervals (%). STEMI, ST Elevation Myocardial Infarction; MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; CI, Confidence Interval.

Figure 4. CMR Imaging Findings in Patients with MINOCA. Bar graph of published studies showing the diagnostic significance of CMR imaging in MINOCA patients. Data presented as percentage (%). CMR, Cardiac Magnetic Resonance; AMI, Acute Myocardial Infarction; HCM, Hypertrophic Cardiomyopathy; DCM, Dilated Cardiomyopathy; NAD, Diagnosis not available; MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries.
<table>
<thead>
<tr>
<th>PubMed® Search Terms¹</th>
<th>Embase® Search Terms¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>[[Myocardial infarction(MH)</td>
<td>OR myocardial infarct*</td>
</tr>
<tr>
<td>OR subendocardial infarct*</td>
<td>OR transmural infarct*</td>
</tr>
<tr>
<td>OR &quot;unobstructed&quot; OR &quot;unobstructive&quot; OR &quot;normal&quot; OR &quot;not significant&quot;</td>
<td>OR &quot;unobstructed&quot; OR &quot;unobstructive&quot; OR &quot;normal&quot; OR &quot;not significant&quot;</td>
</tr>
<tr>
<td>AND (angiogram* OR coronary OR stenosis* OR &quot;cardioangiogram&quot;)</td>
<td>AND (angiogram* OR coronary OR stenosis* OR &quot;cardioangiogram&quot;)</td>
</tr>
<tr>
<td>OR arteriography* OR CAD OR artery OR arteries* OR arterioles* OR vessel*</td>
<td>OR arteriography* OR CAD OR artery OR arteries* OR arterioles* OR vessel*</td>
</tr>
<tr>
<td>OR human OR humans OR man OR men OR woman OR women</td>
<td>OR human OR humans OR man OR men OR woman OR women</td>
</tr>
</tbody>
</table>

1,897 publications¹

Original English Human

CAD Exclusions:
- Post revascularization: 664
- Angiography performed: 9

Disease Publications: 237

Non AMI Exclusions:
- Angina population: 33
- Chest pain syndrome population: 8
- Exclusively Myocarditis/Cardiomyopathy population: 8
- Normal versus control patient population: 8
- Other Non AMI exclusion: 6

MINOC:
152 publications¹

Objective A (Clinical) Selection¹

- Exclusions:
  - Small sample size: 64
  - n<100: 64
  - Large n: 20
- Non consecutive recruitment: 46
- Consecutive recruitment: 42
- Selections ± Bias:
  - Definitions ± Gender ± Age: 44
  - Prevalence: 47
  - Clinical risk factors: 45
  - Prognosis: 8

Objective A cohort: 28 publications¹

Objective B (Pathophysiologic) Selection¹

- Exclusions:
  - Nonmechanistic: 1
  - Isolated pathophysiology: 8
  - Issues: 8
- Coronary spasm: 44
- Drug Related spasm: 4
- Thrombophilia: 6

Objective B cohort: 46 publications¹

Figure 1
Figure 2

Note: Weights are from random effects analysis

Proportion (95% CI) % Weight

Larsen, 2013 0.04 (0.03, 0.04) 4.07
Collste, 2013 0.28 (0.25, 0.31) 4.06
Sun, 2012 0.06 (0.06, 0.07) 3.68
Rhew, 2012 0.02 (0.00, 0.03) 3.86
Hamdan, 2012 0.08 (0.07, 0.10) 2.31
Aldrovandi, 2012 0.09 (0.04, 0.14) 4.04
Agewall, 2012 0.04 (0.03, 0.04) 2.69
Tritto, 2011 0.07 (0.03, 0.11) 2.69
Leurent, 2011 0.05 (0.04, 0.06) 3.96
Kang, 2011 0.04 (0.03, 0.05) 3.59
Uchida, 2010 0.13 (0.11, 0.16) 4.09
Hamdan, 2012 0.04 (0.04, 0.05) 2.73
Frycz-Kurek, 2010 0.08 (0.04, 0.12) 4.11
Gehrie, 2009 0.03 (0.03, 0.03) 4.11
Baccouche, 2009 0.10 (0.09, 0.10) 4.11
Ong, 2008 0.14 (0.12, 0.16) 3.71
Ahmar, 2008 0.10 (0.07, 0.13) 3.09
Larson, 2007 0.06 (0.07, 0.07) 3.79
Widimsky, 2006 0.04 (0.03, 0.05) 3.97
Strunk, 2006 0.03 (0.02, 0.04) 3.97
Patel, 2006 0.08 (0.05, 0.10) 3.43
Larsen, 2005 0.09 (0.08, 0.09) 4.11
Larsen, 2013 0.07 (0.07, 0.08) 4.08
Germing, 2005 0.06 (0.04, 0.08) 3.68
Hung, 2003 0.10 (0.06, 0.14) 2.67
Gehani, 2001 0.05 (0.04, 0.06) 3.99
Hochman, 1999 0.07 (0.06, 0.07) 4.05
Zimmerman, 1995 0.04 (0.04, 0.05) 4.10
Sharifi, 1995 0.01 (0.00, 0.02) 4.07
Overall 0.06 (0.05, 0.07) 100.00

(l-squared = 99%, p=0.000)
Overall (I-squared = 95.4%, p=0.000)

NOTE: weights are from random effects analysis

Figure 3
Diagnosis/Total

<table>
<thead>
<tr>
<th>Diagnosis/Total</th>
<th>429/1,801</th>
<th>562/1,67</th>
<th>277/1,529</th>
<th>38/1,074</th>
<th>12/625</th>
<th>50/760</th>
<th>415/1,592</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINOCA CMR</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4