 Coronary Heart Disease

Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries

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Background—Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a puzzling clinical entity with no previous evaluation of the literature. This systematic review aims to (1) quantify the prevalence, risk factors, and 12-month prognosis in patients with MINOCA, and (2) 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% confidence interval, 5%–7%] with a median patient age of 55 years (95% confidence interval, 51–59 years) and 40% women. However, in comparison with those with myocardial infarction associated with obstructive coronary artery disease, 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 months was lower in MINOCA (4.7%; 95% confidence interval, 2.6%–6.9%) compared with myocardial infarction associated with obstructive coronary artery disease (6.7%, 95% confidence interval, 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. (Circulation. 2015;131:861-870. DOI: 10.1161/CIRCULATIONAHA.114.011201.)

Key Words: coronary artery disease ■ coronary vasospasm ■ magnetic resonance ■ mortality ■ myocardial infarction ■ physiopathology ■ thrombophilia

Contemporary management strategies of acute ST-segment–elevation myocardial infarction (STEMI) are based on 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 used, initially with the use of thrombolytic therapy and subsequently with percutaneous coronary interventions. In contrast, early angiography in patients with non–ST-segment–elevation myocardial infarction (NSTEMI) showed an occluded vessel in fewer 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 studies1,2 demonstrated the presence of significant obstructive coronary artery disease in >97% of these MI patients, thus underscoring the importance of obstructive coronary atherosclerotic disease in this condition.

Clinical Perspective on p 870

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.\textsuperscript{3} These patients with MI with nonobstructive coronary arteries (MINOCA)\textsuperscript{4} represent a conundrum because the underlying cause of their MI is not immediately apparent. Furthermore, whether they have similar clinical features and outcomes as patients with MI with obstructive coronary artery disease (MI-CAD) 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 (1) the prevalence, clinical features, and 12-month prognosis of MINOCA patients, and (2) the major underlying pathophysiological mechanisms responsible for this disorder.

Methods

This study used 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 predetermined study end points.

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,’ ‘nonobstructive,’ and ‘angiography.’ Only original human clinical research studies published in English were considered. However, the references in recent key review articles 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 MI research studies (1033 publications) between 1966 and 2013 (inclusive), reference to nonobstructive coronary artery disease was evident in 237 publications (Figure 1). These articles were reviewed for the following prespecified inclusion and exclusion criteria by 2 of the investigators (S.P., R.T.).

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 as defined by (1) significant elevation of a cardiac biomarker and (2) at least 2 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 (ie, no epicardial vessel with a stenosis ≥50% on angiography). Those MI patients with significant obstructive coronary artery disease (at least 1 stenosis ≥50%) were designated as MI-CAD. The decision to use a ≤50% lesion threshold to delineate nonobstructive CAD from the obstructive CAD is based on the following rationale: (1) well established criteria in clinical guidelines,\textsuperscript{6} accordingly (2) it is the most frequently used definition in published angiographic studies, (3) considering the limitations of angiography, the presence of angiographic smooth vessels does not exclude the presence of significant atherosclerosis, (4) attention should be focused on why myocardial infarction/injury has occurred in the absence of a functionally obstructive lesion, and (5) the more inclusive definition allows future prognostic studies to determine whether 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 article,

3. there was no original data or the data were reproduced from a former study, and

4. isolated case report format.

Using these inclusion and exclusion criteria, 152 original MI publications had sufficient data to clearly identify those patients with MINOCA. Further analysis was dependent on the specific objectives of this study, namely (1) determining the clinical (primary objective) or (2) pathophysiological (secondary objective) attributes of MINOCA (Figure 1). The studies used in the analyses are listed in Table I in the online-only Data Supplement.

Because the primary objective requires a representative sample to quantitatively assess the clinical attributes of MINOCA, only publications that recruited (1) at least 100 patients with MI, and (2) consecutive MI patients, were included in the analysis. The specific definitions used in these studies for the various cardiovascular risk factors are listed in Table II in the online-only 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 pathophysiological mechanisms 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 (ie, within 6 weeks of MI) are also described.

Data Extraction and Analysis

The end points evaluated in the primary objective included (1) prevalence of MINOCA, (2) clinical features including age, sex, MI type (STEMI or NSTEMI), cardiovascular risk factors, and (3) prognosis (including in-hospital and 12-month all-cause mortality). Data for these end points were pooled and analyzed using random effects meta-analysis models.\textsuperscript{7} This conservative approach assumes that individual studies are estimating different treatment effects. Heterogeneity in the study estimates were assessed using I\textsuperscript{2} statistics\textsuperscript{8} with larger values indicating increasing heterogeneity between studies. In addition, for studies including both MINOCA and MI-CAD patients, the summary odds ratios (ORs) or mean difference and exact 95% confidence intervals (95% CI) were calculated. Data from the pathophysiological mechanism publications was more limited so that qualitative assessment could only be undertaken. This involved pooling of frequency data from studies with similar end points. All analyses were performed using STATA (version 12; College Station, Tex.)
Results

From the 152 MINOCA publications identified on PubMed and Embase, we embarked on (1) quantitative assessment of 28 studies to evaluate the clinical attributes of the condition and (2) qualitative evaluation of 46 studies that focused on its pathophysiologic attributes (Figure 1 and Table I in the online-only Data Supplement). 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% to 14% with an overall prevalence calculated at 6% (95% CI, 5%–7%), based on random effects analysis (Figure 2). The F statistic was estimated to be 99%.

Clinical Features

Sex

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).
Sufficient data were available in 13 studies (n=9986) to determine the pooled mean age of MINOCA patients. This was calculated to be 61.2 years (95% CI, 52.2–70.4 years) and 61.3 years (95% CI, 50.5, 68.7 years) of MINOCA studies. Results reported within this section will be confined to the comparative studies.

Age
Sufficient data were available in 13 studies (n=9986) to determine the pooled mean age of MINOCA patients. This was calculated to be 61.2 years (95% CI, 51.6–66.1 years) and 61.3 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 because 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%] versus 21% [95% CI, 6%–35%], respectively; OR, 0.63; P<0.001). However, it is noteworthy that the prevalence of hyperlipidemia among 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 mellitus, smoking, and family history of premature coronary artery disease were similar between the groups (Table 1).

Infarct ECG Findings
Ten studies (n=1998) documented the prevalence of an acute STEMI presentation among MINOCA patients.

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

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>MI-CAD % (95% CI)</th>
<th>MINOCA % (95% CI)</th>
<th>Mean difference/MI-CAD (95% CI) &amp; MINOCA P Value</th>
<th>All MINOCA Studies % (95% CI) &amp; P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.3 (52.2, 70.4)</td>
<td>58.8 (51.6, 66.1)</td>
<td>4.1 (2.9, 5.4) P&lt;0.001</td>
<td>54.7 (50.5, 58.7) P=0.785</td>
</tr>
<tr>
<td>Women</td>
<td>24% (19%, 30%)</td>
<td>43% (35%, 51%)</td>
<td>2.1 (1.7, 2.7) P&lt;0.001</td>
<td>40% (33%, 46%) P=0.333</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>32% (15%, 48%)</td>
<td>21% (6%, 35%)</td>
<td>0.6 (0.5, 0.7) P=0.001</td>
<td>33% (25%, 41%) P=0.183</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45% (30%, 59%)</td>
<td>52% (41%, 62%)</td>
<td>1.3 (0.9, 1.9) P=0.001</td>
<td>44% (38%, 50%) P=0.333</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22% (14%, 29%)</td>
<td>15% (9%, 20%)</td>
<td>0.8 (0.5, 1.3) P=0.001</td>
<td>13% (11%, 16%) P=0.183</td>
</tr>
<tr>
<td>Smoking</td>
<td>39% (26%, 52%)</td>
<td>42% (33%, 51%)</td>
<td>1.1 (0.7, 1.5) P=0.785</td>
<td>42% (36%, 48%) P=0.333</td>
</tr>
<tr>
<td>Family history</td>
<td>27% (10%, 43%)</td>
<td>21% (5%, 38%)</td>
<td>1.0 (0.7, 1.3) P=0.001</td>
<td>28% (17%, 39%) P=0.284</td>
</tr>
</tbody>
</table>

Data presented as either mean or percentage (%) with 95% confidence intervals (CI; %) where appropriate. MI-CAD indicates myocardial infarction with coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; and OR, odds ratio.
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 (ie, no lesions visible on angiography) compared with minor irregularities on angiography was assessed in 5 clinical trials with 1046 MINOCA patients (Figure I in the online-only Data Supplement). Among the MINOCA patients, the prevalence of smooth vessels on angiography was 51% (95% CI, 39%–61%). Importantly, the I^2 test confirmed the presence of significant heterogeneity among 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 reinfarction. Overall, 8 studies reported all-cause mortality in patients with MINOCA, including in-hospital (5 studies, n=9564), and 12 months (4 studies, n=1924) after 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 used three distinct approaches, including (1) assessment of structural myocardial dysfunction with CMR imaging (26 publications), (2) provocative coronary artery spasm testing (15 publications), and (3) thrombophilia screening (8 publications, including 3 of the spasm studies). The remaining 35 publications used more heterogeneous approaches investigating isolated aspects of MINOCA and were 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 hyperenhancement in only 24% of 1801 MINOCA patients studied. The most common finding in the CMR imaging studies was myocarditis, with 33% of the 1676 MINOCA patients having features of this condition. Other myocardial abnormalities reported in the MINOCA CMR imaging studies included Takotsubo cardiomyopathy (18% of 1529 patients), hypertrophic cardiomyopathy (3% of 1074 patients), dilated cardiomyopathy (2% of 625 patients), and other causes (7% of 760 patients) such as pericarditis and amyloidosis. Importantly, 26% of 1592 MINOCA patients

<table>
<thead>
<tr>
<th>Proportion (95% CI) % Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21 (0.17, 0.27)</td>
</tr>
<tr>
<td>1.00 (0.29, 1.00)</td>
</tr>
<tr>
<td>0.36 (0.31, 0.41)</td>
</tr>
<tr>
<td>0.15 (0.02, 0.45)</td>
</tr>
<tr>
<td>0.38 (0.35, 0.41)</td>
</tr>
<tr>
<td>0.07 (0.01, 0.22)</td>
</tr>
<tr>
<td>0.53 (0.35, 0.71)</td>
</tr>
<tr>
<td>0.22 (0.10, 0.39)</td>
</tr>
<tr>
<td>0.64 (0.58, 0.69)</td>
</tr>
<tr>
<td>0.00 (0.00, 0.27)</td>
</tr>
<tr>
<td>0.33 (0.22, 0.44)</td>
</tr>
</tbody>
</table>

NOTE: weights are from random effects analysis

**Figure 3. Prevalence of acute ST-segment–elevation myocardial infarction (STEMI) presentation in myocardial infarction with nonobstructive coronary arteries (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 (CI; %).**

<table>
<thead>
<tr>
<th>Comparative Studies</th>
<th>All-Cause Mortality in Patients With MINOCA or MI-CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI-CAD</td>
</tr>
<tr>
<td>All MINOCA Studies</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>In-hospital</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>(1.8%, 4.6%)</td>
</tr>
<tr>
<td>12-month</td>
<td>6.7%</td>
</tr>
<tr>
<td></td>
<td>(4.3%, 9.0%)</td>
</tr>
</tbody>
</table>

Data presented as percentage (%) and 95% confidence intervals (%) with odds ratio (OR) and P values. MI-CAD indicates myocardial infarction with coronary artery disease; and MINOCA, myocardial infarction with nonobstructive coronary arteries.
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 (Table III in the online-only Data Supplement). 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 (ie, MI ≥ 6 weeks) and spasm was provoked in 34% of patients (Table 3).

Thrombophilia Disorders
As summarized in Table 4, 8 publications examined the presence of inherited thrombotic disorders in patients with MINOCA, with most undertaken in the early postinfarction 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 (1) a 6% prevalence of all MI presentations, (2) no diagnostic distinguishing clinical presentation compared with MI-CAD, (3) a better 12-month all-cause mortality compared with MI-CAD, although its prognosis should be considered as guarded, and (4) 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 causes, it should be considered a working diagnosis that requires further evaluation of the potential underlying causes because 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
MINOCA Patients Have a Guarded Prognosis

Patients with MINOCA have a significantly reduced all-cause mortality compared with 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 with other published prognostic studies. Firstly, the Korean MI Registry evaluated 12-month all-cause mortality in 8510 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 (ie, no previous MI) and normal smooth coronary arteries on angiography have a 0.2% annual all-cause mortality, whereas those with only minor luminal irregularities have a 0.3% annual all-cause mortality. Accordingly, MINOCA patients appear to have a poorer prognosis than those with stable chest pain and nonobstructive 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 because it may have prognostic implications (eg, 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 because it is the optimal diagnostic imaging modality for delineating cardiac structural disorders in this condition.

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### 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, n (%)</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>2</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>Overall</td>
<td>41/344 (12%)</td>
<td>5/189 (2.6%)</td>
<td>4/163 (2.5%)</td>
<td>51/356 (14%)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%). APCR indicates activated protein C Resistance; MINOCA, myocardial infarction with nonobstructive coronary arteries; and NE, not examined.

*Dacosta et al (1998) was ignored from the calculations because the same patient cohort was again used in Dacosta et al (2004).
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% to 80% of MI-CAD patients. 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. First, there is no time-dependence for inducible spasm among 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. Second, there appears to be an ethnic predisposition to coronary spasm in patients with a recent myocardial infarct, particularly among Japanese patients. Fukai et al from Japan reported an 81% prevalence of inducible spasm in patients with MINOCA, whereas studies from Europe and the United States have a pooled prevalence of only 14%. Interestingly, other Asian-based studies 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.

The above findings relating to coronary spasm in MINOCA are exploratory and require further investigation because 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 because 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 spasm.

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% to 7% in Western populations but was observed in 12% of MINOCA patients. Furthermore, comparative studies with MI-CAD patients also report a higher prevalence in MINOCA (Mansourati et al: 4.5% versus 12.1%; and Van de Water et al: 4.3% versus 11.7%, respectively). Protein C & S deficiency are autosomal dominant disorders with a population prevalence of 0.1% to 1%, yet occur in 2.6% of MINOCA patients and similarly those with MI-CAD.

These associations with the genetic thrombophilia disorders are based on small studies and require confirmation with larger multicenter prospective studies. Furthermore, investigation of acquired thrombophilia disorders should be considered because 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. First, the analysis is dependent on the available published data and is thus limited by publication bias, patient selection bias, suboptimal definitions for cardiovascular risk factors, retrospective analyses, and applicability of historical publications to contemporary practice. Second, 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. Third, the second objective, which focused on pathophysiological studies, did not lend itself to quantitative meta-analysis but a qualitative evaluation of published data. This was necessary because 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 on 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.

Acknowledgments

Dr Stuart Howell, Senior Statistician, provided statistical support; Mick Draper, Librarian, assisted with the literature search; and Thomas Sullivan, Senior Statistician, provided statistical support.

Disclosures

None.

References

This article systematically summarizes the published literature concerning patients with myocardial infarction with nonobstructive coronary arteries. These patients account for 6% of all those experiencing an acute myocardial infarct. Although they have a similar prevalence for many risk factors to those with myocardial infarction associated with obstructive coronary artery disease, in comparison they tend to be younger, more often female, and less likely to have hyperlipidemia. Moreover, although their prognosis is better than those with obstructive coronary artery disease, it remains guarded with an all-cause mortality of 4.7% (95% confidence interval, 2.6%–6.9%) at 12 months. The key clinical practice implication from this study is that myocardial infarction with nonobstructive coronary arteries should be considered as a working diagnosis that necessitates further investigation for an underlying cause (ie, similar to that required for a heart failure diagnosis). Important causes include myocarditis, Tako-tsubo cardiomyopathy, vasospastic angina, and hereditary thrombophilia disorders, all of which require different management strategies. Cardiac magnetic resonance imaging is a useful initial investigation to delineate some of these causes. Assessment for coronary artery spasm and thrombophilia disorders should also be considered. The importance of identifying these causes resides with the potential to use effective therapies that otherwise may not have been considered and that may impact on prognosis (eg, calcium channel blockers for coronary spasm). Accordingly, there is the potential to reduce the guarded prognosis in these patients.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
SUPPLEMENTAL MATERIAL

Systematic Review of patients presenting with suspected Myocardial Infarction and Non-Obstructive Coronary Arteries (MINOCA)

Authors: Sivabaskari Pasupathy B.Sc (Hons), Tracy Air B.A (Hons), M.Biostatistics, Rachel P. Dreyer. B.Sc.(Hons) PhD, Rosanna Tavella B.Sc.(Hons) PhD, John F. Beltrame B.Sc, BMBS, FRACP, PhD, FESC, FACC, FAHA, FCSANZ

Supplemental Table 1: Studies Utilised in MINOCA Systematic Analysis
Supplemental Table 2: Cardiovascular Risk Factor Definitions
Supplemental Table 3: Summary of CMR Findings in MINOCA Publications
Supplemental Figure 1: Prevalence of ‘normal’ smooth coronary arteries in MINOCA
**Supplemental Table 1: Studies Utilised in MINOCA Systematic Analysis**

The publications listed below are those selected to evaluate objective A (clinical characteristics) and B (pathophysiological mechanism) in this systematic review, as summarised in Figure-1. Each study has been allocated a study number* and where they are utilised in data analysis is detailed under Figures and Tables#. 

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Reference</th>
<th>Figures &amp; Tables#</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td>Agewall S, Daniel M, Eurenius L, Ekenback C, Skeppholm M, Malmqvist K, Hofman-Bang C, Collste O, Frick M, Henareh L, Jernberg T, Tornvall P. Risk factors for myocardial infarction with normal coronary arteries and myocarditis compared with myocardial infarction with coronary artery stenosis. Angiology. 2012;63:500-503</td>
<td>Figure 2 Table 1 Appendix 3</td>
</tr>
<tr>
<td>A-2</td>
<td>Ahmar W, Lefkovits J. Acute st elevation myocardial infarction with angiographically normal coronary arteries: Causes and outcomes. International Journal of Cardiology. 2008;128:131-133</td>
<td>Figure 2 Table 1</td>
</tr>
<tr>
<td>A-6</td>
<td>Frycz-Kurek AM, Gierlotka M, Gąsior M, Wilczek K, Lekston A, Kalarus Z, Polonski L. Patients with no significant lesions in coronary arteries and st-segment elevation myocardial infarction have worse outcome than patients with non-st-segment elevation myocardial infarction: Analysis from pl-acs registry. Kardiol Pol. 2010;68:1211-1217</td>
<td>Figure 2&amp;3 Table 1&amp;2</td>
</tr>
<tr>
<td>A-7</td>
<td>Gehani AA, al-Mulla AW, Chaikhouni A, Ammar AS, Mahrous F, Tirkawi R, Ashraf A, Hajar HA. Myocardial infarction with normal coronary angiography compared with severe coronary artery disease without myocardial infarction: The crucial role of smoking. J Cardiovasc Risk. 2001;8:1-8</td>
<td>Figure 2 Table 1</td>
</tr>
<tr>
<td>A-8</td>
<td>Gehrie ER, Reynolds HR, Chen AY, Neelon BH, Roe MT, Giberl WB, Ohman EM, Newby LK, Peterson ED, Hochman JS. Characterization and outcomes of women and</td>
<td>Figure 2 Table 1&amp;2</td>
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</tbody>
</table>
men with non-st-segment elevation myocardial infarction and nonobstructive coronary artery disease: Results from the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the acc/aha guidelines (crusade) quality improvement initiative. Am Heart J. 2009;158:688-694


<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Reference</th>
<th>Figures &amp; Tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-2</td>
<td>Ahmed H, Mohammed N, Alsaileek A. The role of delayed contrast-enhanced cardiac magnetic resonance in the differential diagnosis between myocarditis and myocardial infarction. Journal of the Saudi Heart Association. 2010;22:103</td>
<td>Figure 4 Appendix 4</td>
</tr>
<tr>
<td>B-5</td>
<td>Assomull RG, Lyne JC, Keenan N, Gulati A, Bunce NH, Davies SW, Pennell DJ, Prasad SK. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. European Heart Journal. 2007;28:1242-1249</td>
<td>Figure 4 Appendix 4</td>
</tr>
<tr>
<td>B-8</td>
<td>Bellenger NG, Peebles C, Harden S, Dawkins K, Curzen N. Troponin-positive chest pain with unobstructed coronary arteries: A role for delayed enhanced cardiovascular magnetic resonance in the diagnosis of non-st elevation myocardial infarction. J Invasive Cardiol. 2006;18:594-598</td>
<td>Figure 4 Appendix 4</td>
</tr>
<tr>
<td>B-9</td>
<td>Bhatti L, Kim HW, Parker M, Macwar R, Kim RJ. Rate of acute myocardial infarction in patients with troponin-positive chest pain and unobstructed</td>
<td>Figure 4 Appendix 4</td>
</tr>
<tr>
<td>B-14</td>
<td>Chopard R, Jehl J, Dutheil J, Genon VD, Seronde MF, Kastler B, Schiele F, Meneveau N. Evolution of acute coronary syndrome with normal coronary arteries and normal cardiac magnetic resonance imaging. Archives of Cardiovascular Diseases. 2011;104:509-517</td>
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Table 4


Figure 4

Appendix 4


Table 3


Figure 4

Appendix 4


Figure 4

Appendix 4


Figure 4

Appendix 4


Table 3


Table 3


Table 3


Table 3


Table 4


B-44  Van De Water NS, French JK, Lund M, Hyde TA, White HD, Browett PJ. Prevalence of factor v leiden and prothrombin variant g20210a in patients age <50 years with no significant stenoses at angiography three to four weeks after myocardial infarction. Journal of the American College of Cardiology. 2000;36:717-722


### Supplemental Table 2: Cardiovascular Risk Factor Definitions

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Self reported Publications</th>
<th>Specific Definition Publications</th>
<th>Not specified Publications</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>A-17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total cholesterol &gt;93.6mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A-18, A-25</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A-6, A-13, A-20</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A-17</td>
<td></td>
</tr>
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</table>
Supplemental Table 3: Summary of CMR Findings in MINOCA Publications

<table>
<thead>
<tr>
<th>Study Features</th>
<th>MI (Diagnosis/Total MINOCA CMR)</th>
<th>Myocarditis (Diagnosis/Total MINOCA CMR)</th>
<th>Takotsubo (Diagnosis/Total MINOCA CMR)</th>
<th>HCM (Diagnosis/Total MINOCA CMR)</th>
<th>DCM (Diagnosis/Total MINOCA CMR)</th>
<th>Other (Diagnosis/Total MINOCA CMR)</th>
<th>No abnormality</th>
<th>No abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24% 429/1,801</td>
<td>33% 562/1,676</td>
<td>18% 277/1,529</td>
<td>3% 38/1,074</td>
<td>2% 12/625</td>
<td>7% 50/760</td>
<td>26% 415/1,592</td>
<td></td>
</tr>
<tr>
<td>Early (&lt;6 wks)</td>
<td>24% 285/1,167</td>
<td>38% 400/1,066</td>
<td>16% 171/1,083</td>
<td>3% 23/779</td>
<td>2% 8/358</td>
<td>6% 30/480</td>
<td>21% 229/1,066</td>
<td></td>
</tr>
<tr>
<td>Late (&gt;6 Wks)</td>
<td>18% 52/290</td>
<td>23% 66/290</td>
<td>27% 41/151</td>
<td>NE 1/60</td>
<td>2% NE</td>
<td>56% 130/231</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>27% 92/344</td>
<td>30% 96/320</td>
<td>22% 65/295</td>
<td>5% 15/295</td>
<td>1% 3/207</td>
<td>7% 20/280</td>
<td>19% 56/295</td>
<td></td>
</tr>
</tbody>
</table>

Data represented as % (n). MI, Acute Myocardial Infarction; HCM, Hypertrophic cardiomyopathy; DCM, Dilated cardiomyopathy; MINOCA, Myocardial Infarction with Non Obstructive Coronary Arteries; CMR, Cardiac Magnetic Resonance Imaging; NE, Not examined.
Supplemental Figure 1: Prevalence of ‘normal’ smooth coronary arteries in MINOCA

Overall (I-squared = 84.6%, p=0.000)

- Rossini, 2013: 0.47 (0.41, 0.53) 28.48%
- Agewall, 2012: 0.46 (0.17, 0.77) 10.29%
- Widimsky, 2006: 0.74 (0.57, 0.87) 20.22%
- Larsen, 2005: 0.37 (0.34, 0.41) 30.06%
- Sharifi, 1995: 0.58 (0.27, 0.85) 10.94%

Overall Proportion (95% CI): 0.51 (0.39, 0.61) 100.00%

Proportion (95% CI) % Weight

0.0 0.2 0.4 0.6 0.8 1.0
Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries
Sivabaskari Pasupathy, Tracy Air, Rachel P. Dreyer, Rosanna Tavella and John F. Beltrame

Circulation. 2015;131:861-870; originally published online January 13, 2015;
doi: 10.1161/CIRCULATIONAHA.114.011201
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/suppl/2015/01/13/CIRCULATIONAHA.114.011201.DC1.html

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