Prevalence and clinical profile of patients with myocardial infarction with non-obstructive coronary arteries in Turkey (MINOCA-TR): A national multi-center, observational study

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Accepted Date: 09.12.2019 **Available Online Date:** 12.02.2020

DOI:10.14744/AnatolJCardiol.2019.46805

Abstract

Objective: Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is a relatively new term that is characterized by clinical evidence of MI with normal or near-normal coronary arteries on coronary angiography (QCA). To date, there have been no population-based studies on the prevalence of MINOCA in Turkey. The aim of this nationwide study was to document the prevalence and demographics of MINOCA in a Turkish population.

Methods: MINOCA-TR is national, multi-center, prospective, all-comer study that was conducted in 32 hospitals. All consecutive patients who were ≥18 years old, diagnosed with MI according to the Third Universal Definition of Myocardial Infarction, and had undergone QCA were included in the study. Patients with stable coronary artery disease, unstable angina pectoris, a history of revascularization, and type 4/5 MI were excluded.

Results: A total of 1793 patients who were diagnosed with MI and had undergone QCA were screened between March 2018 and October 2018, of whom 1626 (mean age: 61.5±12.5 years, 70.7% male) were enrolled from 32 centers. The prevalence of MINOCA was 6.7% (n=109) in the overall study population. Compared with non-MINOCA patients, those with MINOCA were younger, had a higher prevalence of the female gender, and had a history of flu. The percentages of current smokers, ST-segment elevated myocardial infarction patients, and those with a history of hypertension, diabetes mellitus, and hyperlipidemia were significantly lower in MINOCA patients ($p<0.05$, for all). Also, the median left ventricular ejection fraction as seen on echocardiography and the ratio of Killip Class I status at presentation was significantly higher in MINOCA patients than in non-MINOCA patients ($p<0.001$). Patients with MINOCA received a preload dose of P2Y12 antagonist before QCA less often than non-MINOCA patients ($p<0.001$).

Conclusion: The prevalence of MINOCA in Turkey is 6.7% in patients who were admitted with MI. Also, as compared to non-MINOCA patients, the MINOCA patients were exposed to fewer traditional risk factors of coronary artery disease. *(Anatol J Cardiol 2020; 23: 176-82)*

Keywords: myocardial infarction with non-obstructive coronary arteries, myocardial infarction, coronary angiography

Introduction

Acute myocardial infarction (MI) is a life-threatening condition that is associated with obstructive coronary artery disease (CAD) (defined as >50% stenosis) in over 90% of patients undergoing quantitative coronary angiography (QCA). Early fundamental studies have demonstrated a close relationship between the atherosclerotic process and the pathogenesis of MI. However, a significant proportion of patients with MI who are indicated for QCA do not have obstructive CAD (defined as <50% stenosis). This condition is called myocardial infarction with non-obstructive coronary arteries (MINOCA) (1, 2). Previous registries had reported a varying prevalence of MINOCA with values ranging from 2.6% to 15% (3-8). This result corresponds to the large number of patients among whom all CAD patients are considered. A recent position paper by the European Society of Cardiology (ESC) focused on the definition, clinical features, potential mechanisms, and treatment of MINOCA (2). This study emphasized that the diagnostic process of MINOCA is a working diagnosis and that non-coronary/coronary etiologies should be investigated. A wide etiologic possibility underlies MINOCA, including: myocarditis, vasospasm, thromboembolism, microvascular dysfunction, supply/demand mismatch, Takotsubo syndrome, myocarditis, acute pulmonary embolism, coronary thrombosis, and dissection. Therefore, the diagnostic process may require multiple diagnostic steps such as echocardiography, left ventriculography, intracoronary imaging, computed tomography, pulmonary angiography, and cardiac magnetic resonance imaging (CMRI). Since no algorithm has been established for diagnostic work-up to date, diagnostic tools should be selected based on the suspected etiology. Further, no clear treatment orientations have yet been established. Turkey's population is almost 82 million, and approximately 300.000 cases of acute coronary syndrome (ACS) occur annually in the population (9, 10). Therefore, it is important to determine the demographics and clinical characteristics of MINOCA patients to help establish a new strategic plan and approach for these patients in our population. In turn, we hope that these results might help us derive a new scoring system for predicting the diagnosis of MINOCA before administering QCA. The present study focused on the demographic, clinical, and etiological properties of MINOCA and aimed to clarify this issue from a national perspective.

Methods

Study population and definition

The design and rationale of the MINOCA-TR study has been published previously (11). MINOCA-TR is a national, multicenter, prospective, and observational cohort study that is being conducted in 18 universities and 4 private hospitals across 10 states in Turkey. The study protocol has been reviewed by the Dokuz Eylül University Clinical Research Ethic Committee. The MINOCA-TR study protocol was approved on February 22, 2018. This study has been registered with www.clinicaltrials.gov (NCT03364387).

All consecutive patients older than 18 years of age who were diagnosed with MI according to the Third Universal Definition of Myocardial Infarction and had undergone diagnostic coronary angiography were screened for inclusion in this study. The Acute Myocardial Infarction (AMI) criteria feature a positive cardiac biomarker and corroborative clinical evidence of an AMI, such as ischemic symptoms, new ischemic ECG changes, development of pathological Q waves, and imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.

Patients (1) younger than 18 years (2) with stable CAD, (3) unstable angina pectoris, (4) a history of revascularization [percutaneous coronary intervention (PCI) and/or coronary artery

Anatol J Cardiol 2020; 23: 176-82
DOI:10.14744/AnatolJCardiol.2019.46805

bypass grafting (CABG)], (5) MI types 3–5, and (6) those who had not provided informed consent were excluded from the study.

A total of 1793 patients were screened between March 2018 and October 2018; of these, 1626 patients were included in the study. All the included patients had previously undergone QCA and had demonstrated evidence of ischemia. As a result of the component of the definition, all patients included in the study showed elevated cTn as a marker of injury. Also, 70.4% of patients had new ischemic ECG changes (ST-segment elevation or depression) as evidence of ischemia. The remaining patients showed a pathological Q-wave, a new regional wall motion abnormality in imaging, or some ischemic symptoms.

MINOCA was diagnosed according to the current opinion paper of the ESC working group that focused on the clinical context of MINOCA (2). According to this paper, MINOCA is diagnosed immediately upon performing QCA in a patient presenting with features that were consistent with those of acute MI, as detailed by the following criteria:

1. AMI Criteria (Third Universal Definition of Myocardial Infarction) (12)
2. Non-obstructive coronary arteries on QCA
3. Absence of a clinically overt, specific cause for acute presentation

The AMI criteria required a positive cardiac biomarker and corroborative clinical evidence of an AMI, such as ischemic symptoms, new ischemic electrocardiogram changes, and imaging evidence.

The term non-obstructive coronary arteries on angiography in the definition refers to the absence of obstructive CAD on angiography (i.e., no coronary artery stenosis of ≥50%) in any possible infarct-related artery. The term includes angiographically normal coronary arteries (no stenosis >30%) and mild coronary atheromatosis (stenosis >30% but <50%).

Data collection

The baseline clinical characteristics and medical history of patients were recorded as case report forms after the coronary angiography.

Coronary angiography of patients was performed according to the protocols of the individual laboratory. Patients with angiographically normal coronary arteries (no stenosis >30%) and mild coronary atheromatosis (stenosis >30% but <50%) were identified. Digital copies of the coronary angiographies of these patients were collected and shipped to the contracted research organization office for evaluation by the MINOCA adjudication committee. The committee consisted of three invasive cardiologists who were unaware of the clinic and the patients. The committee evaluated these digital copies to check for a possible overlook of type 1 MI and Takotsubo syndrome. The diagnosis of MINOCA was confirmed by the committee for the all patients, except 2, both of whom were diagnosed as having type 1 MI.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences 20.0 software (SPSS Inc., IL, USA). Continuous variables were reported using mean and standard deviation (mean±SD) or median (25^{th}–75^{th} percentile) values, while categorical variables were reported as proportions (%) and number of cases. The nominal data were compared using the Chi-squared test or the Fisher's exact test. The distribution of the variables was assessed using the Kolmogorov-Smirnov test, and Levene's test was performed to assess variance equality. Variables with normal and non-normal distribution were compared using the Student's t-test and the Mann-Whitney U test, respectively. Differences were considered statistically significant if p was <0.05.

Results

A total of 1793 patients were screened between March 2018 and October 2018; of these, 1626 patients were enrolled from 32 centers. Table 1 lists the demographic and clinical characteristics of the study population. The mean age of the study population was 61.5±12.5 years and 1149 (70.7%) patients were male. Nearly half of the study patients (n=754, 46.4%) presented with ST-elevation myocardial infarction (STEMI) at admission. The prevalence of MINOCA was 6.7% (n=109) in the overall study population. Table 1 also presents a comparison of the demographical, clinical, and laboratory characteristics of MINOCA and non-MINOCA groups. Compared with non-MINOCA patients, MINOCA patients were younger, likely to be female, and had a history of flu during the past three weeks. Regarding cardiovascular risk factors, the ratio of current smokers (42.9% vs. 33.0%; p<0.001), history of hypertension (49% vs. 30.0%; p=0.001), history of diabetes mellitus (30.5% vs. 16.5%; p=0.002), and history of hyperlipidemia (31.5% vs. 18.3%; p=0.004) were significantly higher in the non-MINOCA group. Further, the ratio of STEMI at presentation was significantly lower in the MINOCA group than in the non-MINOCA group (5.5% vs. 49.4%; p<0.001). Most patients showed a Killip Class I status on admission, and the percentage of patients who with Killip Class I presentation was significantly higher in the MINOCA group. The prevalence of Takotsubo syndrome was 0.24% in MINOCA patients.

The median left ventricular ejection fraction (LVEF) value on echocardiography was also higher in the MINOCA group [60% (25^{th}–75^{th} percentile, 58.5%–62%) vs. 50% (40%–55%); p<0.001]. Patients with MINOCA were less likely to receive a loading dose of a P2Y12 inhibitor before QCA (68.9% vs. 94.6%; p<0.001). All the MINOCA patients were followed-up with medical treatment. Of the non-MINOCA patients, 1280 patients underwent PCI, 171 patients underwent coronary artery bypass graft, 166 patients were monitored with medical treatment, and 7 patients received other treatments.

Table 1. Baseline characteristics of the study population

Variables	MINOCA (n=109)	Non-MINOCA (n=1517)	*P*-value
Age, median years (mean±SD)	54.9±15	61.9±12.1	<0.001
BMI (kg/m^2) (mean±SD)	27.6±4.4	27.5±4.7	0.871
Systolic blood pressure (mm Hg) (mean±SD)	129±23.6	128±21.1	0.583
Diastolic blood pressure (mm Hg) (mean±SD)	77.4±14.1	77.7±11.8	0.635
Sex (female) n, (%)	49 (45.0)	428 (28.2)	<0.001
Active smoker n, (%)	36 (33.0)	651 (42.9)	
Former-smoker n, (%)	11 (10.1)	244 (16.1)	0.005
Non-smoker n, (%)	62 (56.9)	622 (41.0)	
Alcohol n, (%)	171 (11.3)	12 (11.0)	0.909
History of flu n, (%)*	25 (22.9)	150 (9.9)	<0.001
Diagnosis STEMI n, (%)	6 (5.5)	748 (49.4)	<0.001
Family history of CAD n, (%)	23 (21.1)	392 (25.9)	0.184
Hypertension n, (%)	33 (30.3)	744 (49.0)	0.001
Diabetes mellitus n, (%)	18 (16.5)	462 (30.5)	0.002
Hyperlipidemia n, (%)	20 (18.3)	477 (31.5)	0.004
Sinus rhythm at admission n, (%)	104 (95.4)	1446 (95.3)	0.935
Killip Class I/II/III/IV n, (%)	103 (97.2)/1(0.9)/ 2 (1.9)/0 (0)	1264 (84.2)/191 (12.7)/ 29 (1.9)/18 (1.2)	0.002
Fibrinolytic therapy n, (%)	1 (0.9)	38 (3.2)	0.252
P2Y12 antagonist received n, (%)	73 (68.9)	1423 (94.6)	<0.001
Oral anti-coagulant agents n, (%)	3 (2.8)	23 (1.5)	0.490
Access site (n; %)			
Femoral	99 (90.8)	1464 (96.5)	0.008
Radial	10 (9.2)	51 (3.4)	
Hs-Troponin-T (ng/mL), median (25th–75th percentile)	36.5 (3.08-555)	335.4 (4.29-937)	0.490
Hemoglobin (g/dL) (mean±SD)	13.4±2.1	13.6±1.9	0.205
Random blood glucose (mg/dL) median (25th–75th percentile)	111 (92-150)	124 (105-176)	0.005
Perform echocardiography n, (%)	104 (95.4)	1281 (84.4)	0.002
Atrial fibrillation n, (%)	4 (3.7)	47 (3.1)	0.743
Blood pressure ≥140/90 mm Hg, n (%)	29 (26.6)	569 (37.6)	0.022
Left ventricular ejection fraction (%) median (25th–75th percentile) (echocardiography at admission)	60 (58.5-62)	50 (40-55)	<0.001
Estimated glomerular filtration rate median (25th–75th percentile)	102.4 (77.5-121.7)	95.5 (73.4-120)	0.119

*Last three weeks. BMI - body mass index; CAD - coronary artery disease, eGFR- estimated glomerular filtration rate, Hs-troponin - high-sensitive troponin; MINOCA - myocardial infarction non-obstructive coronary artery; STEMI - ST-segment elevated myocardial infarction

Discussion

As a nationwide study, MINOCA-TR showed that the prevalence of MINOCA was 6.7% in patients who were diagnosed with MI, without having a history of MI and revascularization. Previous studies of unselected patients presenting with acute MI reported that the prevalence of MINOCA was 2.6–15% (3-8). Further, we determined that MINOCA patients were younger, more likely to be female, and accompanied by fewer traditional cardiovascular risk factors, all of which are in line with previous studies (1, 3, 13-15). Moreover, STEMI was lower in patients with MINOCA, which is also in line with previous stud-

Anatol J Cardiol 2020; 23: 176-82
DOI:10.14744/AnatolJCardiol.2019.46805

ies (3, 13-15). Although these characteristics had already been reported elsewhere, they had never been reviewed in a Turkish population. Our results indicate that the Turkish population has many specific characteristics as compared to European populations. Approximately 300.000 cases of ACS occur annually in the Turkish population, and the rate of young MI patients (age <50 years) is significantly higher in Turkey than in Europe (9, 10). Since MINOCA patients are relatively younger than non-MINOCA patients, this result highlights the importance of MINOCA in the Turkish population. Also, as Turkey has a well-organized ambulance/emergency medical service, most STEMI patients received primer PCI and a few patients received thrombolytic therapy. Further, nearly all patients receiving thrombolytic therapy underwent a diagnostic coronary angiogram 3–24 hours after the initial presentation. In this context, the MINOCA percentage reported in the study could be robust to the selection bias of MI patients who had not undergone diagnostic QCA for different reasons.

Nevertheless, study-population-related factors might influence the observed prevalence of MINOCA. First, not all patients presenting with non-ST-segment elevation myocardial infarction undergo QCA. Patients with the highest likelihood of obstructive CAD were found to be most likely to undergo QCA. In contrast, patients who had a high likelihood of MINOCA, such as those with low traditional cardiovascular risk factors, younger patients, and female patients, might not receive QCA. These factors might be the cause of the low frequency of MINOCA observed in some studies. Although all consecutive patients who were diagnosed with ACS and had undergone QCA were included in the present study, low-risk patients might not have received QCA or may have been referred to the cardiology department by the emergency service. The relevant ESC guidelines recommended using high-sensitivity cardiac troponin (hs-troponin) instead of standard troponin assays, resulting in increased MI detection and a corresponding decrease in the diagnosis of unstable angina (16). Therefore, the use of hs-troponin for MI diagnosis might increase the prevalence of MINOCA. All centers included in the present study use hs-troponin for MI diagnosis. Moreover, since ours was a prospective study, ventriculography was performed on all patients who were considered to have MINOCA after QCA; this had the advantage of\excluding or exposing Takotsubo etiology with more accuracy as compared to previous retrospective studies (3, 15).

MINOCA is just an initial diagnosis and may involve one or more causes with different underlying pathophysiologies (1, 2). It is important to determine the etiopathologies of patients who are initially described as having MINOCA (2). The low proportion of traditional cardiovascular risk factors and low age of MINOCA patients indicates that mechanisms other than atherosclerosis and thrombosis can potentially underlie MINOCA pathology.

Coronary pathologies have several mechanisms. The most common coronary causes of MINOCA are coronary dissection, thromboembolism, coronary artery spasm, plaque rupture or erosion, and other forms of type 2 MI (2, 3, 17-20). Plaque rupture, erosion, ulceration, and intraplaque hemorrhage may cause plaque disruption that may, in turn, cause thrombosis. Coronary artery spasm is common; it may occur due to endogenous causes and may also be provoked by exogeneous substrates (21). Since some non-coronary causes are treatable, well-planned diagnostic tools are important for final diagnosis and treatment. The current ESC Clinical and Practice Guidelines on STEMI emphasized that the failure to determine the underlying cause of MINOCA patients may result in inappropriate therapy and outcomes for these patients (22). Currently, the ESC working group position paper on MINOCA has proposed the use of non-invasive (echocardiography, CMRI, coronary CT angiography, and CT scan) and invasive (ventriculography, intravascular ultrasonography (IVUS), optical coherence tomography, ergonovine/acetylcholine test, and endomyocardial biopsy) diagnostic modalities based on the suspected diagnosis (2). Similar to previous studies, we found that MINOCA patients have a lower cardiovascular risk profile than non-MINOCA patients (1, 2). Further, MINOCA patients were younger and likelier to be female as compared to non-MNOCA patients. These results might indicate that a sex-driven hormonal influence plays a role in MINOCA; this issue needs further investigation. Similar to previous studies, we found that the LVEF of MINOCA patients was significantly higher than that of non-MINOCA patients. This might be because the degree of myocardial damage was presumed to be lower in MINOCA patients than that of non-MINOCA patients (1, 14).

In addition, the patients in our study have a significantly higher rate of flu history. A higher prevalence of flu history might be developed due to cases with no obvious symptoms or clinical signs of myocarditis.

The prognosis of MINOCA patients depends on the underlying etiology. Although most studies have reported a better prognosis for MINOCA patients, this result is not consistent across all reports (1, 2). Moreover, no long-term prognostic data is available for MINOCA patients (14). A systemic review of MINOCA trails reported a mortality rate as high as 4.7% in one year (3). Although MINOCA patients are younger and have a low rate of cardiovascular risk factors, these results highlight the importance of MINOCA. More studies are needed on the prognosis of MINOCA patients. A MINOCA-TR registry study was designed to determine the short- and medium-term prognosis of MINOCA patients. Patient follow-up in this trial is continuing at present. Further, risk scores need to be developed to predict the status of the patients before QCA and eliminate unnecessary QCA procedures.

Due to the various underlying etiologies, the treatment of MINOCA patients remains unclear. Secondary prevention therapies, whose effects have been demonstrated in patients with classical type 1 MI, have unknown effects on MINOCA patients. Recently, one study indicated the beneficial effects of long-term treatment with statins and renin-angiotensin system blockers. Moreover, beta blockers and dual antiplatelet therapy are less likely to re-

duce cardiovascular events (23). To confirm these results, proven randomized controlled trials are needed in the future.

Study limitations

The present study had several limitations. First, MI and MINOCA were defined in line with the Third Universal Definition of Myocardial Infarction. However, the Fourth Universal Definition of MI was published after the start date of this study.

Second, although patients with Takotsubo syndrome were diagnosed with left ventriculography during the QCA, the other possible causes of MINOCA were not assessed during the initial hospitalization, owing to the observational nature of the study. However, clinicians were advised to perform a diagnostic work-up to reveal the underlying etiology. Lastly, because many MINOCA patients had a lower burden of CAD risk factors, some of them might not have referred to the QCA, resulting in an underestimated prevalence of MINOCA.

Conclusion

In the present study, we showed that the prevalence of MINOCA in Turkey is 6.7% in patients who were admitted with MI. Also, as compared to non-MINOCA patients, the MINOCA patients were exposed to fewer traditional risk factors of CAD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – S.K., M.Z., U.Ö.T.; Design – S.K., M.Z., U.Ö.T.; Supervision – O.E.; Funding – S.K., G.A., A.Ç., Y.K.D., Ö.A.Ö., Y.Ç., İ.Ü., M.T., R.D., V.P., H.Ö., M.Ö., K.T., D.K., N.Ç., M.G., S.İ., F.Y.Ç., H.A., M.Z., O.E., U.Ö.T.; Materials – S.K., G.A., A.Ç., Y.K.D., Ö.A.Ö., Y.Ç., İ.Ü., M.T., R.D., V.P., H.Ö., M.Ö., K.T., D.K., N.Ç., M.G., S.İ., F.Y.Ç., H.A., M.Z., O.E., U.Ö.T.; Data collection and/or processing – S.K., G.A., A.Ç., Y.K.D., Ö.A.Ö., Y.Ç., İ.Ü., M.T., R.D., V.P., H.Ö., M.Ö., K.T., D.K., N.Ç., M.G., S.İ., F.Y.Ç., H.A., M.Z., O.E., U.Ö.T.; Analysis and/or interpretation – S.K., U.Ö.T.; Literature search – S.K., M.Z.; Writing – S.K., U.Ö.T.; Critical review – O.E.

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Anatol J Cardiol 2020; 23: 176-82
DOI:10.14744/AnatolJCardiol.2019.46805

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