ORIGINAL ARTICLE

Rationale and design of the Myocardial Infarction with Non-obstructive Coronary Arteries in Turkish Population (MINOCA-TR) study

Türk Toplumunda Non-obstüktif Koroner Arterlerle Birlikte Miyokart Enfarktüsü çalışması: MINOCA-TR çalışma dizaynı

Uğur Önsel Türk, M.D.,[1] Mehdi Zoghi, M.D.,[2] Emin Alioglu, M.D.,[1] Oktay Ergene, M.D.[3]

[1]Department of Cardiology, KardiyoRitm Heart Center, İzmir, Turkey; [2]Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey; [3]Department of Cardiology, Dokuz Eylul University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Objective: Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is a new term to define the syndrome of clinical evidence of MI occurring in the absence obstructive coronary artery disease. Given that there is believed to be a large number of MINOCA cases, effective diagnostic and therapeutic strategies are needed. Documentation of the demographic parameters and diagnostic methods used in existing cases is a first step. The purpose of this study is documentation of the prevalence, demographic details, and possible etiological causes, as well as inpatient and 1-year prognosis data of MINOCA patients in the Turkish population.

Methods: The MINOCA-TR Study is a national, multi-center, prospective, observational study. A sample of 1028 consecutive MI patients who undergo diagnostic angiography will be enrolled. This is a cohort study that will include patients from 32 different centers. After an initial screening/enrollment visit, follow-up will be performed at the time of hospital discharge for the overall MI study population. Patients diagnosed as MINOCA will be followed up with 3 prospective office or telephone visits as part of the Prospective MINOCA Registry.

Conclusion: Demographic information, clinical characteristics, management strategies, and inpatient prognostic indicators will be documented in the cross-sectional portion of the registry. Additional diagnostic data, therapeutic strategies, and prognostic relevance will be recorded in the 12 months of the prospective research. The results are expected to inform future diagnostic and therapeutic strategies and enhance understanding of the condition by highlighting the national burden of the disease from a medical and a public health perspective, as well as stimulate future research focusing on the MINOCA population.

ÖZET

Amaç: Non-obstrüktif koroner arterlerle birlikte miyokart enfarktüsü (MINOCA) göreceli olarak yeni bir terim olup, tıkayıcı koroner arter hastalığı olmaksızın gelişen miyokart enfarktüsü (Mİ) tablosunu tanımlamaktadır. MINOCA olgularının olası yüksek sayısı göz önünde bulundurulduğunda etkin tanısal ve terapötik stratejiler ortaya konmalıdır. MINOCA demografiklerinin ve hâlihazırda kullanılmakta olan tanısal yöntemlerin ortaya konması bu süreçte ilk basamaktır. MINOCA-TR çalışmasının asıl amacı ülkemiz popülasyonunda MINOCA prevalansının, demografiklerinin, etiyolojik nedenlerin, hastane içi ve bir yıllık izlem prognozlarının belirlenmesidir.

Yöntemler: Çalışma, ulusal, çok merkezli, gözlemsel kohort çalışmadır. Üçüncü evrensel miyokart enfarktüsü tanımlamasına göre Mİ tanısı konan ve koroner anjiyografi uygulanan 1028 olgu çalışmaya alınacaktır. Bu, 32 farklı merkezden hastaları içerecek bir kohort çalışmasıdır. Tarama ve dâhil edilme viziti sonrasında taburculuk vizitleri tüm Mİ popülasyonunda gerçekleştirilecektir. MINOCA tanısı konan olgular ise, MINOCA-TR veri tabanı kaydının bir parçası olarak 3 ayrı prospektif vizit ile bir yıl süre ile takip edilecektir.

Sonuç: Bu çalışmanın kesitsel bölümü ile MINOCA olgularının demografikleri, klinik özellikleri, yönetim şekilleri ve hastane içi prognozları belirlenecektir. Oniki aylık prospektif bölüm ile de ek tanısal, prognostik ve terapötik stratejiler ortaya konacaktır. Sonuçlar görece sık rastlanan bu klinik antitenin daha detaylı anlaşılmasına, tanısal ve tedavi stratejilerinin ortaya konmasına yardımcı olacaktır. Ayrıca ilgili klinik tablonun hastalık yükü toplum perspektifi açısından değerlendirilecektir. Bu verilerin ilgili popülasyona odaklanmış gelecek çalışmalara ışık tutması ve tetiklemesi beklenmektedir.

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Correspondence: Dr. Uğur Önsel Türk. 288/4 Sokak, No:16 Mansuroğlu Mah., Kat: 1, Daire 2-3, Park Office, Bayraklı, İzmir, Turkey.
Tel: +90 232 - 502 15 14 e-mail: droturk@yahoo.com

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is a relatively new term to define the syndrome of clinical evidence of MI occurring in the absence of obstructive coronary artery disease (≥50% diameter stenosis in a major epicardial coronary) observed on angiography.[1] Based on registry data, it has been reported that nearly 10% of acute MI (AMI) patients had no significant coronary artery disease (CAD).[2–4] The prevalence of AMI in the general population suggests a considerable absolute number of patients with MINOCA, yet there is still insufficient research or evidence examining this population. A European Society of Cardiology (ESC) working group focused on this clinical context and issued a definition, a description of clinical features, and mechanisms and treatment to be used in a position paper.[5] According to the paper, a MINOCA diagnosis can be made immediately upon coronary angiography in a patient presenting with features consistent with an AMI, as detailed by the following criteria:

1. AMI criteria (Third Universal Definition of Myocardial Infarction).[6]

2. Non-obstructive coronary arteries on angiography.

3. Absence of clinically overt specific cause for the acute presentation.

The AMI criteria include a positive cardiac biomarker and corroborative clinical evidence of an AMI, such as ischemic symptoms, new ischemic electrocardiographic changes, imaging evidence, etc. The definition of non-obstructive coronary arteries on angiography is the absence of obstructive CAD as observed with angiography, (i.e., no coronary artery stenosis ≥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%). According to the ESC paper, MINOCA is to be considered a working diagnosis that prompts further investigation of coronary/non-coronary etiologies. Overt clinical diagnoses, such as acute myocarditis and acute pulmonary embolism, should be excluded before making the diagnosis of MINOCA. The diagnostic process may require left ventriculography, echocardiography, cardiac magnetic resonance (CMR) imaging, intracoronary imaging, and computed tomography pulmonary angiography.

Coronary plaque rupture or erosion (MI type 1), coronary artery spasm, thromboembolism, coronary dissection, takotsubo cardiomyopathy, unrecognized myocarditis, and other clinical entities of MI type 2 are the most common underlying causes of MINOCA.

Abbreviations:

ACS	*Acute coronary syndrome*
AMI	*Acute myocardial infarction*
CAD	*Coronary artery disease*
CMR	*Cardiac magnetic resonance*
CRO	*Contracted research organization*
ESC	*European Society of Cardiology*
MI	*Myocardial infarction*
MINOCA	*Myocardial infarction with non-obstructive coronary arteries*
NSTEMI	*Non- ST segment elevation MI*
STEMI	*ST segment elevation MI*

The prevalence of MINOCA is thought to be 6% to 8% in the overall MI population.[7,8] Patients with MINOCA are generally younger than those with obstructive CAD. The prevalence is higher in women than men, and in patients presenting with ST segment elevation MI (STEMI) compared with non-ST segment elevation MI (NSTEMI). The occurrence of MINOCA is similar between these 2 ST presentations for women, but there are fewer men among those with an NSTEMI presentation.[9]

To date there are no demographic, clinical, or prognostic data specific to MINOCA in the Turkish population. Since the size of the MINOCA population in our country could be significant, effective diagnostic and therapeutic data are needed. Documentation of demographic details and current diagnostic methods that have already been used is the first step in this process. The Myocardial Infarction with Non-obstructive Coronary Arteries in Turkish Population (MINOCA-TR) study was designed to address this need. The MINOCA-TR Study is linked to the MINOCA Prospective Registry, which together form the cross-sectional and prospective portions of the MINOCA-TR Registry.

The project was sponsored by the Cardiovascular Academy Society.

METHODS

Rationale, aim, risk-benefit assessment

There are currently no data available in Turkey with regard to the specific demographics, clinical characteristics, etiopathogenetic factors, and prognosis of MINOCA patients. Furthermore, at present there is no clear evidence on the prognosis of these patients. The primary purpose of this study is to document the

prevalence, demographics, and possible etiological causes of MINOCA in MI patients who undergo diagnostic coronary angiography. In addition, the research will document the inpatient prognosis of patients with de novo MI and the prevalence of atrial fibrillation in the de novo MI population. As in all observational studies, the risk-benefit assessment of MI patients, the administration of medical treatment, and the management of disease and treatment-related clinical events is the responsibility of the clinician who treats the patient. Since the scope of work includes only questionnaire-based data collection, participation in this research will not involve any additional risk to the patient. The compilation of real-world data is expected to yield valuable information about the demographics and prognosis of MINOCA patients.

Study design

The MINOCA-TR Study is national, multi-center, prospective, observational cohort study that will be conducted in 18 university, 10 state, and 4 private hospitals. Consecutive patients from 32 different centers with MI who undergo a diagnostic coronary angiography will be screened and invited to participate. The goal of the study is to provide real-life data and factors that could lead to bias were avoided as much as possible in the design. A detailed chart and visit calendar are shown in Table 1.

The MINOCA-TR Study protocol was reviewed and approved by the local ethics committee on February 22, 2018. The MINOCA-TR Study is also registered with www.clinicaltrials.gov (NCT03364387). The study timeline graph is presented in Figure 1.

Data to be collected and study outcomes

The data to be collected are summarized in Table 1. The primary outcome from the information to be analyzed is a determination of the prevalence of MINOCA in Turkey. Secondary outcomes are prognostic indicators of MINOCA, inpatient prognostic indicators of MI, and the prevalence of atrial fibrillation in the de novo MI population.

Definition of the study population

Consecutive consenting patients older than 18 years of age who are diagnosed as MI according to the Third Universal Definition of Myocardial Infarction[6] and undergo a diagnostic coronary angiography will be included in the study. The choice of management strategy is solely the discretion of the participating physicians. This means that participation in the study presents no additional risks to patients. No medical procedures are required beyond those that the patient would receive if not enrolled. To avoid potential bias and projection, the exclusion criteria are limited.

Table 1. Detailed chart of the MINOCA-TR Study data collection and visit calendar

Data	Baseline/screening visit (enrollment)	Inpatient visit	Visit 1[4] (1 month±10 days)	Visit 2[4] (6±1 months)	Visit 3[4] (12±2 months)
Informed consent	X				
Eligibility	X				
Demographics	X				
CAD risk factors	X				
Coronary angiography data	X				
Cardiac imaging data (if present)	X	X	X		
Medical history, co-morbidities	X				
Antithrombotic treatment	X[1]	X[2]	X[2]	X[2]	X[2]
Clinical events[3]	X	X	X	X	X
Serious adverse events	X	X	X	X	X
Adverse drug reactions	X	X	X	X	X
Vital signs and findings	X				

[1]Antithrombotic treatment strategies on admission and during coronary angiography. [2]Current antithrombotic treatment(s). [3]Clinical events are defined in another section. These data are to be recorded during visits 1, 2, and 3. [4]Visits 1, 2 and 3 will apply only to patients diagnosed as MINOCA. These visits may be conducted by phone or office interview. CAD: Coronary artery disease; MINOCA-TR: Myocardial infarction with non-obstructive coronary arteries-Turkey.

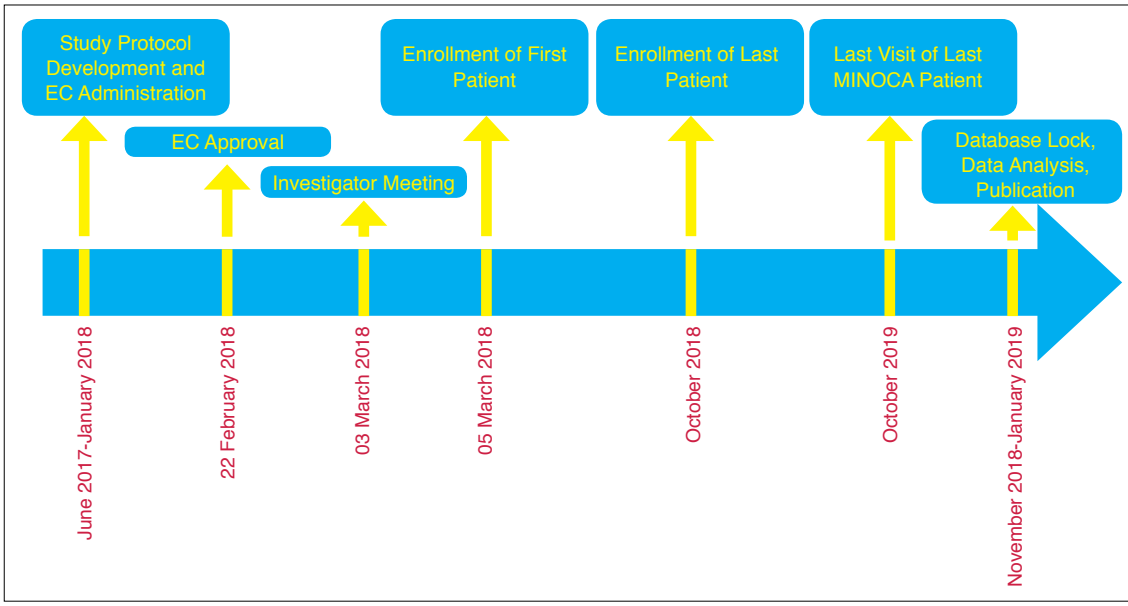

Figure 1. MINOCA-TR study timeline. EC: Ethics committee; MINOCA-TR: Myocardial infarction with non-obstructive coronary arteries-Turkey.

Potential participants are invited to participate in the study and informed consent is to be obtained after a coronary angiography (or after percutaneous coronary intervention if needed) procedure. The inclusion criteria are patients older than 18 years at the date of coronary angiography, patients diagnosed as MI according to the Third Universal Definition,[6] MI patients who underwent coronary angiography, and patients who provided written, informed consent. The exclusion criteria summarized in Table 2.

Coronary angiography

Coronary angiography will be performed according to the procedures of the individual laboratory. Patients with angiographically normal coronary arteries (no stenosis >30%) and mild coronary atheromatosis (stenosis >30% but <50%) will be allocated to the study. A digital copy of the coronary angiography of these patients will be collected and shipped to a contracted research organization (CRO) office for evaluation by the MINOCA adjudication committee consisting of 3 invasive cardiologists. The committee will evaluate digital copies of coronary angiographies for overlooked type 1 MI and possible takotsubo syndrome.

Table 2. Exclusion criteria for the MINOCA-TR Study

Exclusion criteria
• Patients with stable coronary artery disease
• Patients with unstable angina pectoris
• Patients with a history of revascularization (PCI or CABG)
• Patients with type 4 or type 5 myocardial infarction[1]
• Patients younger than 18 years of age
• Patients who do not provide written, informed consent

[1]According to the Third Universal Definition of Myocardial Infarction.[6]
CABG: Coronary artery bypass grafting; MINOCA-TR: Myocardial infarction with non-obstructive coronary arteries-Turkey; PCI: Percutaneous coronary intervention.

Study procedures

Due to the observational nature of the study, beyond questionnaire-based data collection, no additional medical procedures are required. After the initial screening/enrollment visit, the overall MI study population will be interviewed on the day of hospital discharge. In the event of inpatient mortality, data will be recorded on the day of death. Patients diagnosed as MINOCA will be followed-up with 3 prospective office or telephone visits as a part of the MINOCA Prospective Registry project at approximately 1 month, 6 months, and 1 year after the angiography procedure (Table 1). Possible etiological and prognostic data, as well as treatment/management characteristics of the MINOCA population will be recorded. CMR imaging will be recommended for patients initially diagnosed

as MINOCA according to the ESC consensus paper to clarify possible etiological factors.[5]

Study outcomes

Demographic, clinical, and management characteristics of MI patients (overall population) will be saved in the screening/enrollment visit, and MINOCA patients will be followed-up in greater detail.

The main aim of the MINOCA-TR Study is documentation of the prevalence, demographic details, and possible etiological causes of MINOCA in patients with MI who underwent a diagnostic coronary angiography.

The clinical events listed below, will be evaluated as outcomes:

• MINOCA prevalence: The ratio of patients diagnosed as MINOCA to the overall MI population during the enrollment period.

• Prognostic indicators of MINOCA: Death, cardiogenic shock, heart failure, stroke, major bleeding, major arrhythmia, re-infarction, and revascularization.

• Inpatient prognostic indicators of MI: Death, cardiogenic shock, heart failure, stroke, bleeding (major and minor), major arrhythmia, re-infarction, and revascularization.

• Atrial fibrillation prevalence: The ratio of patients who have atrial fibrillation as indicated by the admission electrocardiogram to the overall MI population during the enrollment period.

Definition of clinical events

Acute myocardial infarction: Positive cardiac biomarker (preferably cardiac troponin), defined as a rise and/or fall in serial levels, with at least 1 value above the 99th percentile upper reference limit and corroborative clinical evidence of infarction evidenced by at least 1 of the following: (i) symptoms of ischemia, (ii) new or presumed-new significant ST-T changes or new left bundle branch block, (iii) development of pathological Q waves, (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, (v) intracoronary thrombus evident on angiography or at autopsy.[6]

Heart failure: A clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural/functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressure at rest or during exercise.[10]

Cardiogenic shock: Hypotension (systolic blood pressure <90 mmHg) despite adequate filling status with signs of hypoperfusion.[10]

Major arrhythmia: Sustained ventricular tachycardia, ventricular fibrillation, asystole, second and third degree atrioventricular block.

Major bleeding: Fatal bleeding, and/or bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial bleeding, or intramuscular bleeding with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to a transfusion of 2 or more units of whole blood or red cells.[11]

Stroke: New, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause, such as a tumor or seizure.

Re-infarction: Acute MI that occurs within 28 days of an MI incident or recurrent MI.[12]

Reporting of adverse and serious adverse events

Adverse events and serious adverse events will be recorded on a designated report form appended to the case report form. This adverse event form will be used to document the seriousness, duration, actions taken, outcomes, and relationship to current management (iatrogenic events) for each adverse event.

Statistical methods

Statistical analyses will be descriptive, exploratory, and generally limited to frequency tables or summary statistics (e.g., mean±SD or median±quartiles). All values will be presented with a corresponding 95% confidence interval. $P<0.05$ will be accepted as the level of significance. Patient demographic information will be summarized using descriptive statistics (n, mean, SD, minimum, maximum, median, difference between percentiles) or frequency distribution (n and %), according to the type of data. The Student's t-test will be used for continuous variables, analysis of variance will be used for categorical variables, and Pearson's chi-square test will be used for binominal variables. Binary logistic regression will be per-

formed to determine factors related to MINOCA in each enrollment visit. Each outcome will be evaluated separately with a binary logistic regression model. In addition to binary logistic regression, the generalized least squares method will be used as a repeat measure of binary data obtained during the study for each clinic outcome, if appropriate.

Calculation of sample size

The sample size was determined using the known prevalence of MINOCA, estimated to be 6% to 8% among patients diagnosed with MI.[7,8] TUMAR study (Turkiye Akut Miyokard Infarktusu Arastirmasi) findings showed that 220,000 MI patients were hospitalized yearly in Turkey.[13] TEKHARF (Turkish Adult Risk Factor Study) data estimated that there are approximately 300,000 acute coronary syndrome (ACS) cases per year around the country.[14] According to these data, the prevalence of ACS in Turkish citizens older than 18 years of age can be calculated as follows:

ACS prevalence = Number of ACS Cases/Number of population at risk

ACS Prevalence=300000/55319222=0.00543[15]

Based on 80% response rate, 1% margin of error, and 95% CI, the necessary sample size for the present study was calculated as follows:

$$n_0 = \frac{Nt^2pq}{d^2(N-1)+t^2pq} = \frac{300000(2.57)^2 0.5*0.5}{0.04^2(300000-1)+(2.57)^2*0.5*0.5} \cong 1028$$

n_0: Sample size

N: The number of cases in the universe (country)

p: occurrence probability of eligible cases

q: non-occurrence probability of eligible cases

t: t table value

d: standard deviation

Data integrity and quality

All outcome variables and covariates will be recorded on a standardized case report form. Selection bias will be minimized by requiring investigators to document consecutive MI patients with no omissions. A CRO (Aegean CRO AS, İzmir, Turkey) will collect the related study documents from investigators weekly during the study period. All of the data will be locked in the database of the CRO. A digital copy of the data will be generated daily and secured automatically as a separate file in the database.

DISCUSSION

The MINOCA-TR Registry will be the result of the first national, prospective, observational study involving de novo MI patients who undergo coronary angiography. The registry will consist of 2 parts: the MINOCA-TR study data and the MINOCA-TR Prospective Registry. The principal objective of this nationwide cohort study will be to estimate the prevalence of MINOCA in patients with de novo MI. Demographics, clinical characteristics, management strategies, and inpatient prognostic indicators will be documented in the cross-sectional part of the registry. The 12-month prospective portion of the research will provide additional data regarding diagnostic details, therapeutic strategies, and prognostic relevance. The results will inform future diagnostic and therapeutic decision-making and enhance understanding of the public health aspects of this prevalent condition.

The prognosis of MINOCA has not yet been clearly documented. However, given the diverse nature of the underlying etiologies, it's likely to be heterogeneous.[5] Earlier AMI registries suggested that MINOCA patients had a more favorable prognosis than patients with obstructive CAD.[3,7] However, there are no long-term prognostic data about MINOCA patients.[8] A pooled analysis of MINOCA trials revealed a mortality rate at 1 year of 4.7%.[8] Since the MINOCA population is typically relatively young, this figure highlights the importance of the issue from both a medical and a public health perspective. This should not be disregarded as a trivial clinical condition. Based on these figures, it is clear that documentation of the demographic, clinical, and prognostic factors of this population is important. Furthermore, additional research, particularly multicenter studies that are translational in nature and offer diagnostic and therapeutic approaches targeting an improved prognosis for this young patient population, should be accelerated.

Conclusion

The MINOCA-TR Study and the MINOCA-TR Prospective Registry will provide an initial measurement of the demographics, clinical characteristics, management strategies, inpatient and 1-year prognostic indicators. These data will highlight the national

burden of this disease from both a medical and a public health perspective, and are expected to stimulate further research focusing on the MINOCA population.

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Ethics Committee Approval: The MINOCA-TR Study protocol was reviewed and approved by the local ethics committee on February 22, 2018.

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Keywords: Demographics; myocardial infarction; non-obstructive coronaries; prognosis.

Anahtar sözcükler: Demografi; miyokardiyal enfarktüs; non-obstrüktif koronerler; prognoz.