Short- and Long-term Myocardial Infarction Survival Rate According to the Type of Drugs Prescribed at the Time of Discharge: A Study Using Iran National Registry Data

Samaneh Mozaffarian, MSc; Niloufar Taherpour, MSc; Mohammad Sistanizad, Pharm D, PhD1-3; Mohammad Aghaali, MD, MPh, PhD4; Seyed Saeed Hashemi Nazari, MD, MPh, PhD5

1Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2Prevention of Cardiovascular Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3Department of Clinical Pharmacy, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4Department of Community Medicine, School of Medicine, Qom University of Medical Sciences, Qom, Iran
5Associate Professor of Epidemiology, Prevention of Cardiovascular Disease Research Center, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Coronary artery disease is among the first causes of death in Iran. Secondary prevention with drug therapy is recommended following acute myocardial infarction (MI) to reduce the risk of new cardiovascular events and death.

Methods: This is a retrospective cohort study on data collected from 21,181 cases of MI recorded by the MI Registry of Iran from 2013 to 2014. Ten therapies that were prescribed to patients at the time of discharge were divided into 6 groups. Survival rates were estimated using the Kaplan-Meier method and Cox regression analysis.

Results: The most common MI location was in the anterior wall (31.87%). Anticoagulants, aspirin, clopidogrel were the most common prescribed medications (94.73%). Overall, 28-day (short-term) and 3-year survival rates were 0.95 (95% CI: 0.95–0.96) and 0.82 (95% CI: 0.81–0.82). In non-ST-elevation myocardial infarction (NSTEMI) patients, the lowest short- and long-term survival rates were observed when diuretic, anticoagulants/ aspirin and clopidogrel, beta-blockers and statins medication were simultaneously taken and the highest short- and long-term survival rates were observed in patients who took anticoagulants, aspirin and clopidogrel, nitrate agent and calcium blockers, beta-blockers and statins medication. In STEMI patients, the lowest short- and long-term survival rates were observed when diuretic, anticoagulants, aspirin and clopidogrel, nitrate agent and calcium blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) were simultaneously taken. The highest short- and long-term survival rates were observed in patients who received anticoagulants, aspirin and clopidogrel, nitrate agent and calcium blockers, beta-blockers, statins, ACEIs and ARBs.

Conclusion: Prescription of the best combination of drugs, in addition to adherence to a healthy lifestyle and medication, can improve the survival rates after MI.

Keyword: Medication therapy, Myocardial Infarction, Survival rate

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Introduction

Ischemic heart disease (IHD) is one of the common causes of death in the world which accounts for a large proportion of hospital admissions. Cardiovascular diseases (CVDs), especially coronary artery diseases (CADs), are among the first causes of death in Iran.1-2

Heart failure is the most common cause of hospitalization among elderly patients.3 According to the past studies, secondary prevention drug therapy in patients with acute myocardial infarction (AMI) reduces the risk of new cardiovascular events and death.4

In-hospital myocardial infarction (MI) death rates vary from 7.7% to 19.2% worldwide.5 Overall, premature mortality in the first 30 days after AMI is approximately 30% and the survival rates, especially in patients 75 years and older, have declined dramatically.6 The survival rate of patients after AMI decreases over time. Recurrence is common after the first MI in the first six months. Thus, studying long periods after MI would be of great importance since it may show the effects of factors which influence survival.6 Survival rates can describe mortality trends, their overall changes, and their effects on decision-making about health care priorities and resource allocation. Nevertheless, there is much variability in long-term prognosis for patients with acute coronary syndrome who survive to be discharged from the hospital.7,8

Some studies have been conducted in Iran to determine the survival rate in different provinces, but none of them has been population-based, considering the whole country using MI registry data and type of drugs prescribed at the time of discharge. Therefore, this retrospective cohort study was designed to estimate short- and long-term...
survival rates in MI patients and their contributing factors and medications prescribed at the time of discharge in patients with the first attack of MI in the Islamic Republic of Iran.

Materials and Methods
This is a retrospective cohort study. The data were extracted from 21 181 cases of MI recorded by the Iranian Myocardial Infarction Registry in the 12-month period leading to 20 March 2014. The population of this study was all the patients with first MI who were hospitalized and registered in the MI Registry system in 2013. The total number of patients registered in the MI registry system in 2013 was 23 785, of whom 21 181 had a national code (to cross check with the national death registry for the date of probable death). The Iranian Myocardial Infarction Registry was set up in 2009 by the office of CVDs of the Iranian ministry of health that covers all types of hospitals (governmental, private and military hospitals) which were equipped with a coronary care unit in 31 countrywide provinces. In this registry, all medical information of CVDs patients during hospitalization is registered based on the International Classification of Disease (ICD-10) coding system. Also, patients’ data such as demographic variables, smoking status, past medical history of coronary artery diseases, hypertension, diabetes, hyperlipidaemia, signs and symptoms during an attack, post-MI complications during hospitalization, the occurrence of an arrhythmia, the location of MI, medications received, and place of residence and type of medications prescribed are recorded. Ten types of medications prescribed to the patients at the time of discharge such as, diuretics, anticoagulants, aspirin, clopidogrel, nitrate agent, calcium channel blockers, beta-blockers, statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), were categorized in six groups as follows: diuretics (group 1), anticoagulants, aspirin and clopidogrel (group 2), nitrate agent and calcium channel blockers (group 3), beta-blocking agents (group 4), statin medication (group 5), ACEIs and ARBs (group 6).

Data related to medications were collected at the time of discharge, and all the 28 possible combinations of these six groups of medications were analyzed.

Because the data were extracted from MI cases that were recorded by the Iranian Myocardial Infarction Registry, consent to participate was not applicable. Nevertheless, the study was performed in accordance with the declaration of Helsinki; this included permission to use anonymized quotations in publications and the data cannot be shared according to the ethics committee.

Follow-up Period
The follow-up of the patients began within 28 days (short-term) to three years (long-term) after the first MI and hospitalization. The last point of follow-up was the time of death for all causes or administrative right censoring.

The survival or death status was obtained 3 years after hospitalization by a cross-match of national codes of MI registry patients and the national organization for civil registration. If the patient's national code was also registered in the national organization for civil registration as a dead person, the date of death was extracted; otherwise, the patient was considered alive at the end of follow-up (30 December 2016).

Data Analysis
After data extraction, data accuracy was evaluated and data cleaning was performed. In this study, survival rates were estimated by the Kaplan-Meier method and the P values for comparison of survival rates were determined by log-rank test. Univariate and multivariable Cox model were used to investigate the relationship between the research variables and death after MI. The variables with P value ≤ 0.20 and variables whose role was important from the point of view of confounding in the univariate analysis were entered to the multivariable analysis. Adjusted hazard ratios were calculated for all variables and reported with 95% confidence intervals. In multivariable Cox regression analysis, the date of birth was entered into the model as the origin of time in setting the model in STATA Software, which controlled finely the confounding effect of age.

Evaluating the proportional hazard assumption was based on Schoenfeld residuals. The continuous variables were presented as mean ± standard deviation (SD). The categorical variables were summarized as frequencies and percentages. To compare the average age between the two genders, the independent t test was employed. The analysis was performed using STATA 14. All statistical tests were two-tailed, and P values were considered significant at less than 0.05.

Results
Totally 21 181 patients with the first attack of MI were studied in this survey. There were 15 328 (72.37%) men and 5853 (27.63%) women, where the mean age of the overall patients was 62.10 ± 13.42 years, men 60.38 ± 13.39 years and women 66.61 ± 12.38 years, in which the difference was statistically significant (P < 0.001). The most frequent age group was 55-60 years (N = 3021, 14.27%). Most of the patients were illiterate (N = 9812, 46.44%). Hypertension (N = 7656, 36.21%), diabetes (N = 4820, 22.79%) and coronary artery diseases (N = 4447, 21.01%) were the most common risk factors among the patients. The most common symptoms of MI included chest pain, which travels from left arm to neck (N = 9841, 46.60%), sweating (N = 8530, 40.37%) and shortness of breath (N = 6777, 32.07%). Totally, 6% of patients had a history of percutaneous coronary intervention or coronary artery bypass grafting (N = 1258) and 8.17% of patients underwent at least one of the mentioned interventions during hospitalization (N = 1730). The most common MI location was acute transmural MI of the anterior wall (N = 6737, 31.87%). The frequency of other locations was as follows: Acute subendocardial MI (N = 3150, 14.90%),
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Concerning MI location, the patients with acute transmural MI of the anterior wall, inferior wall, and other sites had the lowest survival rate and those with only acute transmural MI of the inferior wall had the highest survival rate. Table 1 shows the descriptive information and survival rate by gender, risk factors, and the location of MI (Table 1) The results of multivariable Cox regression model showed that the adjusted hazard ratio of underlying diseases among MI patients was 1.35 (95% CI: 1.26–1.45) for coronary artery diseases, 1.15 (95% CI: 1.08–1.23) for hypertension and 1.52 (95% CI: 1.41–1.64) for diabetes, thus significantly increasing the risk of mortality. On the other hand, history of hyperlipidemia (0.85; 95% CI: 0.78–0.93) and MI in the inferior wall (0.80; 95% CI: 0.73–0.89) statistically decreased the risk of mortality (Table 2).

Table 1. Baseline Characteristics, Survival Rate by Gender, the Location of MI and Risk Factors in Patients Hospitalized for MI

| Variables | Frequency (%) | 28-Days Survival Rate (95% CI) | 3-Years Survival Rate (95% CI) |
|-----------|--------------|--------------------------------|-------------------------------|
| Gender    |              | 0.96 (0.96–0.97) | 0.84 (0.83 – 0.85) |
| Male      | 15328 (72.37) |                   |                               |
| Female    | 5853 (27.63) | 0.93 (0.92 – 0.93) | 0.75 (0.74 – 0.76) |
| Past medical history | | | |
| Coronary artery diseases (yes) | 4447 (21.01) | 0.93 (0.92 – 0.94) | 0.73 (0.72 – 0.74) |
| Hypertension (yes) | 7656 (36.21) | 0.94 (0.91 – 0.94) | 0.76 (0.75 – 0.77) |
| Diabetes (yes) | 4820 (22.79) | 0.94 (0.93 – 0.94) | 0.76 (0.75 – 0.77) |
| Hyperlipidemia (yes) | 3818 (18.05) | 0.95 (0.94 – 0.96) | 0.81 (0.80 – 0.82) |
| Cigarette smoking (yes) | 6030 (28.50) | 0.96 (0.96 – 0.97) | 0.85 (0.84 – 0.86) |
| Location of myocardial infarction | | | |
| Acute sub endocardial myocardial infarction (NSTEMI) | 3155 (14.90) | 0.96 (0.95 – 0.96) | 0.77 (0.76 – 0.79) |
| Acute transmural myocardial infarction of other sites | 477 (2.26) | 0.96 (0.93 – 0.97) | 0.83 (0.80 – 0.86) |
| Acute transmural myocardial infarction of the inferior wall | 6094 (28.82) | 0.96 (0.95 – 0.97) | 0.86 (0.85 – 0.87) |
| Acute transmural myocardial infarction of the anterior wall | 6737 (31.87) | 0.95 (0.94 – 0.96) | 0.82 (0.81 – 0.83) |
| Acute transmural myocardial infarction of the anterior wall, inferior wall and other sites | 130 (0.61) | 0.88 (0.81 – 0.92) | 0.72 (0.64 – 0.79) |

Table 2. Results of Univariate and Multivariable Cox Regression Model Based on Gender, the Location of MI and Risk Factors in Hospitalized MI Patients

| Variables | Frequency (%) | Crude Hazard Ratio (95% CI) | P Value | Adjusted Hazard Ratio* (95% CI) | P Value |
|-----------|--------------|-----------------------------|---------|--------------------------------|---------|
| Gender    |              |                             |         |                                |         |
| Male      | 15328 (72.37) | Reference                    | –       | Reference                       | –       |
| Female    | 5853 (27.63) | 1.70 (1.59 – 1.81) | <0.001 | 1.06 (0.99 – 1.14) | 0.082 |
| Past medical history | | | | | |
| Coronary artery diseases (yes) | 4447 (21.01) | 1.78 (1.67 – 1.91) | <0.001 | 1.35 (1.26 – 1.45) | <0.001 |
| Hypertension (yes) | 7656 (36.21) | 1.72 (1.62 – 1.84) | <0.001 | 1.15 (1.08 – 1.23) | <0.001 |
| Diabetes (yes) | 4820 (22.79) | 1.54 (1.44 – 1.65) | <0.001 | 1.52 (1.41 – 1.64) | <0.001 |
| Hyperlipidemia (yes) | 3818 (18.05) | 1.08 (1.002 – 1.17) | 0.043 | 0.85 (0.78 – 0.93) | <0.001 |
| Cigarette smoking (yes) | 6030 (28.50) | 0.73 (0.68 – 0.79) | <0.001 | 0.93 (0.86 – 1.01) | 0.098 |
| Location of myocardial infarction | | | | | |
| Acute sub endocardial myocardial infarction (NSTEMI) | 3155 (14.90) | Reference                    | –       | Reference                       | –       |
| Acute transmural myocardial infarction of other sites | 477 (2.26) | 1.0001 (0.89 – 1.12) | 0.999 | 0.90 (0.72 – 1.14) | 0.389 |
| Acute transmural myocardial infarction of the inferior wall | 6094 (28.82) | 0.78 (0.73 – 0.83) | <0.001 | 0.80(0.73 – 0.89) | <0.001 |
| Acute transmural myocardial infarction of the anterior wall | 6737 (31.87) | 1.17 (1.10 – 1.24) | <0.001 | 1.05(0.95 – 1.14) | 0.333 |
| Acute transmural myocardial infarction of the anterior wall, inferior wall and other sites | 130 (0.61) | 0.93 (0.87 – 0.99) | 0.024 | 1.38 (0.99 – 1.94) | 0.060 |

*All analyses were adjusted for contextual variables (sex, education, past medical history of coronary artery diseases, Hypertension, Diabetes, Hyperlipidemia, treatment with PCI/CABG, smoking), symptoms before the heart attack, arrhythmia, complications, medication received and location of MI.
The most common medication received was group 2, with a frequency of 94.73% (N = 20045) (drug combinations of “1. anticoagulants, 2. aspirin and 3. clopidogrel”) (Table 3).

The highest drug intake was in drug combination of groups 2, 3, 4, 5, 6 (N = 6792, 32.07%), followed by drug combination of groups 2, 3, 4, 5 (N = 3635, 17.16%) and groups 2, 3, 5 (N = 1750, 8.27%) (Table 4).

Table 3. Frequency and Mortality for Types of Drugs Received at Discharge

| Groups | Type of drugs | Frequency (%) | Mortality (%) |
|--------|---------------|---------------|---------------|
| 1      | Diuretics     | 3170 (14.98)  | 20.57         |
| 2      | Anticoagulants, Aspirin and Clopidogrel | 20045 (94.73) | 10.98 |
| 3      | Nitrates and Calcium channel blockers | 18115 (85.61) | 10.96 |
| 4      | Beta-blocking agents | 15009 (70.93) | 10.03 |
| 5      | Statin medication | 17678 (81.54) | 10.96 |
| 6      | ACEs and ARBs | 11745 (55.51) | 11.13 |

Table 4. Short- and Long-term Survival Rate for All Possible Combinations of 6 Groups of Drugs Prescribed at the Time of Discharge among Patients with Different Types of MI Sites

In this study, patients who received group 1 drugs (diuretics) had the lowest short-term 92% (91%-93%) and long-term survival rate 79% (78%-81%), and the highest short- 97% (96%-97%) and long-term 90% (89%-90%) survival rates were observed in patients receiving group 4 drugs (Beta-blockers). According to Table 4, after comparing the short- and long-term survival rates among patients with different types of MI sites and drug groups, we found that in patients with any location of MI, the highest 28-day and 3-year survival rate was observed in patients who received the combination of groups 2, 4, 5 at the time of discharge, and the combination of groups 1, 2, 3, 6 had the lowest short- (80%) and long-term (49%) survival rate and the highest hazard ratio (HR: 1.43, 95% CI: 0.96–2.15, P-value: 0.082) (Table 4).

In NSTEMI patients (non-ST-segment elevation myocardial infarction acute/sub endocardial myocardial infarction), the lowest short- 83% (27%-97%) and long-term 33% (33%-67%) survival rates were observed in...

* All of the analyses were adjusted for contextual variables (sex-education-past medical history of coronary artery diseases, Hypertension, Diabetes, and Hyperlipidemia, treatment with PCI/CABG, smoking, symptoms before the heart attack, arrhythmia, complications, and location of MI.
the drug combination of groups 1, 2, 4, 5 simultaneously, and the highest short- 98% (96%–99%) and long-term 84% (80%–87%) survival rates were observed in patients who took drug combination of groups 2, 3, 4, 5. In patients with STEMI (Inferior wall MI and other site wall MI), the lowest short- 78% (36%–94%) and long-term 67% (28%–78%) survival rates were observed in concurrent use of the drug combination of groups 1, 2, 3, 6, and the highest short- 98% (97%–98%) and long-term 87% (85%–88%) survival rates were observed in patients receiving the drug combination of groups 2, 3, 4, 5, 6. Regarding the combinations of six groups of drugs which were received by patients with acute transmural MI of the anterior wall, the lowest short-term survival rates were in patients who received the drug combination of groups 1, 2, 3, 6, 73% (44%–90%) simultaneously and the highest short-term survival rates were observed in the drug combination of groups 2, 4, 5, 6, 97% (92%–98%) and/or 2, 3, 6, 97% (85%–99%) and/or 2, 3, 4, 6, 97% (92%–98%) and/or 2, 3, 4, 5, 6, 97% (96%–98%). The lowest long-term survival rate pertained to patients who received the drug combination of groups 1, 2, 3, 6, 40% (17%–63%) simultaneously and the highest long-term survival rates were observed in the combination of groups 2, 4, 95% (70%–99%).

**Discussion**

The goal behind the present study was to estimate short- and long-term survival rates in patients with MI in Iranian hospitals during 2013–2014. The results showed that in this study, 72.37% of patients were men. The average age of total patients was 62.10 years and the average age of women at the time of MI occurrence was significantly higher than men. These results are in line with other studies that reported men, compared to women, to be at higher risk of MI because of their lifestyle. Life expectancy is also lower in men than women and premature deaths are more common among men. Thus, we expect that MI occurs among women at older age and naturally, the fatality rate will be higher among them. The most common age group for MI was 55–60 years. In addition, most of MI patients were illiterate. According to a study by Roshani et al, most of MI patients who died were aged more than 65 years. Thus, improvement in primary health care and healthy lifestyles can reduce the risk of CVDs and premature deaths in middle and old ages. Also, illiterate patients are usually low-income and their health is at risk due to low awareness. Therefore, in preventive programs, special attention should be paid to these patients. Totally, the most prevalent underlying diseases among MI patients was hypertension. This is due to greater vulnerability of patients to heart attacks due to their coronary complications, which can affect the fatality rate and survival rate among them. These results are consistent with past studies. The most common MI location was acute transmural MI of the anterior wall (31.87%). According to some past studies, the most common and deadly type of MI is stroke in the anterior wall and arrhythmia in this type of MI is more common. While according to other studies, the most common MI location was acute transmural MI of the inferior wall, such that inferior wall MIs were estimated to account for 40% to 50% of all MIs in 2013. This result is inconsistent with current and other past studies.

In this study, after controlling for the confounding variables, arrhythmia, history of diabetes, history of coronary artery disease, and history of hypertension significantly increased the risk of death. According to the evidence, patients with history of CVDs are more vulnerable to heart attacks due to coronary artery problems. Moreover, diabetes has a negative effect on artery walls. Thus, these complications can increase the risk of death and decrease survival rates after MI. These results are in line with other studies. In our study, history of hyperlipidemia had a protective effect on survival after MI and about 15% decrease in risk of death. One of the main reasons for this finding can be the protective effect of lipid lowering drugs, which are usually prescribed for patients with history of hyperlipidemia after MI, and the lifestyle changes of these patients following their physicians’ recommendation. As it is clear in the drug group analysis, prescription of statins lowers the risk of death. This result was consistent with the study by Tian et al. In our study, survival rates in diabetic patients were lower than non-diabetic patients; however, some other studies showed that both diabetic and non-diabetic subjects who experience MI have the same risk for CVDs.

The short- and long-term survival rate for cigarette smoking history is longer than non-smokers though it is not significant. Although cigarette smoking is not a significant variable adjusting for other variables in this study, there are different studies that show the influence of smoking history after MI on subsequent mortality. However, there are some other studies that demonstrated no significant differences in the cardiac survival rate between smokers and non-smokers. In these cases, the reason for this observation might be that most smokers quit smoking after experiencing a MI event.

According to the results of the current study, MI in the inferior wall significantly reduces the risk of death and has a better prognosis than acute sub endocardial MI (NSTEMI). These results are consistent with past studies. However, according to some other studies, major complications such as heart block and bradycardia are more common after inferior MI compared to anterior MI and it leads to poor clinical outcomes. Thus, each site of MI has relatively specific mechanisms and the location of MI can predict the severity and prognosis of infarction.

Beta-blocker usage was accompanied with the highest long-term survival rate while prescription of diuretics after discharge from the hospital increased the risk of death. The combinations of medicines prescribed at the time of discharge along with other variables in this study, after controlling for the confounding variables, arrhythmia, history of diabetes, history of coronary artery disease, and history of hypertension significantly increased the risk of death. According to the evidence, patients with history of CVDs are more vulnerable to heart attacks due to coronary artery problems. Moreover, diabetes has a negative effect on artery walls. Thus, these complications can increase the risk of death and decrease survival rates after MI. These results are in line with other studies. In our study, history of hyperlipidemia had a protective effect on survival after MI and about 15% decrease in risk of death. One of the main reasons for this finding can be the protective effect of lipid lowering drugs, which are usually prescribed for patients with history of hyperlipidemia after MI, and the lifestyle changes of these patients following their physicians’ recommendation. As it is clear in the drug group analysis, prescription of statins lowers the risk of death. This result was consistent with the study by Tian et al. In our study, survival rates in diabetic patients were lower than non-diabetic patients; however, some other studies showed that both diabetic and non-diabetic subjects who experience MI have the same risk for CVDs.

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nitrates, calcium blockers, beta-blockers and statins (groups 2, 3, 4, 5) has the highest long-term survival rate and also the lowest hazard ratio. Other studies have also suggested that anticoagulants and beta-blockers play an important preventive role against cardiac death after MI. Nevertheless, besides the role of specialists, other medicines and lifestyle improvement in patients who have a MI event are points which should be contemplated in the interpretation of the results.

The strengths of this study include its population-based design and use of a large national database of MI patients in the country without sampling process, and studying the combination effects of cardiovascular drugs on survival rate of MI patients. In this study, there are some limitations, especially in data gathering, which should be mentioned:

1. The patients who passed away immediately after MI or on the way to the hospital were not included in this study. It could be one of the reasons that survival rates are considerably high.
2. There is a possibility that patients who were classified as having the first experience of MI, had experienced it before but they did not notice it.
3. Death, which was reported by checking the national code, is an all-cause-mortality indeed and not the deaths caused exclusively by MI.
4. People who were included as patients in this study might have different lifestyle and diets, which were not considered in the data analysis.
5. Adherence to the treatment in patients was not assessed during the study and any kind of changes in the process of treatment was not measured.

In conclusion, the pharmacological treatment of MI patients can play a preventive role against death. This study showed that multiple drug therapy with consideration of other factors such as age, sex, comorbidities, smoking and other complications can affect the survival rate of patients after MI, especially the combinations of medicines such as anticoagulants, nitrates, calcium blockers, beta-blockers and statins medications. Thus, prescription of the best combination of drugs based on physicians' order, in addition to adherence to a healthy lifestyle and medications, can improve the outcomes after MI.

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Authors' Contribution
Design and conception: SM; writing the manuscript: NT; reviewed the study: MS and MA; study supervision, analysis and interpretation: SSHN. All authors read and approved the final manuscript.

Availability of Data and Materials
The individual data are confidential and cannot be shared according to the ethic committee's decision.

Conflict of Interest Disclosures
The authors declare that they have no competing interests.

Ethics Statement
In this study, data were extracted from MI cases recorded by the Iranian Myocardial Infarction Registry. Thus, consent to participate was not applicable. Nevertheless, the study was performed in accordance with the Declaration of Helsinki; this included permission to use anonymized quotations in publications according to the ethics committee. This article is adapted from a master's thesis in Epidemiology and ethical approval was granted by Deputy for Research Affairs, Shahid-Beheshti University of Medical Sciences (SBMU), Tehran, Iran (IR.SBMU.RETECH.REC.1399.764).

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