Type-II Myocardial Infarction – Patient Characteristics, Management and Outcomes

Gideon Y. Stein¹, Gabriel Herscovici¹, Roman Korenfeld¹, Shlomi Matetzky², Shmuel Gottlieb³,4, Danny Alon¹, Natalie Gevriev-Yusim², Zaza Iakobishvili³, Shmuel Fuchs¹*

¹Internal Medicine “B”, Beilinson Hospital, Rabin Medical Center, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, ²Cardiology Institute, Chaim Sheba Medical Center, Tel-Hashomer, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, ³Neufeld Heart Research Institute, Chaim Sheba Medical Center, Tel-Hashomer, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, ⁴Cardiology Department, Bikur Cholim Hospital, Jerusalem, Israel, ⁵Cardiology Department, Beilinson Hospital, Rabin Medical Center, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel

Abstract

Background: Type-II MI is defined as myocardial infarction (MI) secondary to ischemia due to either increased oxygen demand or decreased supply. This categorization has been used for the last five years, yet, little is known about patient characteristics and clinical outcomes. In the current work we assessed the epidemiology, causes, management and outcomes of type II MI patients.

Methods: A comparative analysis was performed between patients with type-I and type-II MI who participated in two prospective national Acute Coronary Syndrome Israeli Surveys (ACSIS) performed in 2008 and 2010.

Results: The surveys included 2818 patients with acute MI of whom 127 (4.5%) had type-II MI. The main causes of type-II MI were anemia (31%), sepsis (24%), and arrhythmia (17%). Patients with type-II MI tended to be older (75.6±12 vs. 63.8±13, p<0.0001), female majority (43.3% vs. 22.3%, p<0.0001), had more frequently impaired functional level (45.7% vs. 17%, p<0.0001) and a higher GRACE risk score (150±32 vs. 110±35, p<0.0001). Patients with type-II MI were significantly less often referred for coronary interventions (36% vs. 89%, p<0.0001) and less frequently prescribed guideline-directed medical therapy. Mortality rates were substantially higher among patients with type-II MI both at thirty-day (13.6% vs. 4.9%, p<0.0001) and at one-year (23.9% vs. 8.6%, p<0.0001) follow-ups.

Conclusions: Patients with type-II compared to type-I MI have distinct demographics, increased prevalence of multiple comorbidities, a high-risk cardiovascular profile and an overall worse outcome. The complex medical condition of this cohort imposes a great therapeutic challenge and specific guidelines with recommended medical treatment and invasive strategies are warranted.

Introduction

In 2007, a joint Task Force of the American College of Cardiology, American Heart Association, European Society of Cardiology and the World Heart Federation published a redefinition of myocardial infarction (MI). [1] Type-II MI was defined as MI secondary to ischemia due to either increased oxygen demand or decreased supply caused by conditions as coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension. [1] In many of these clinical situations, including sepsis and post-operative state, cardiac troponin is frequently elevated. [2–5] The underlying mechanism for this troponin elevation is multifactorial and often indicates myocardial necrosis rather than myocardial ischemia. [3] The incidence of type-II MI among all patients is currently unknown and a rate of 4% was reported among patients who experienced recurrent MI [6–8]. However, patient characteristics, clinical presentation, underlying contributing factors, management and outcomes, have not been elucidated.

The Acute Coronary Syndrome Israeli Survey (ACSIS) is a prospective nation-wide consecutive collection of data of acute coronary syndrome patients in Israel. The survey is conducted biennially over a 2-month period and data on all acute coronary syndrome patients in 26 public hospitals in Israel are provided by each participating center by means of the pre-specified case report forms. The Israel Heart Society is responsible for the collection of all case report forms and for maintaining the survey database. [9] Since 2008, the survey has implemented the universal definition of MI. Accordingly, we have performed a comparative analysis between patients with type-I and type-II MI who were enrolled in two consecutive national ACSIS.
Patients and Methods

Patient Population

During the 2-month period in 2008 and 2010, detailed data was collected in all 26 ICU and cardiology wards in all public hospitals in Israel, on patients admitted with the diagnosis of ACS. In addition, data from a representative sample of 37 Internal Medicine wards was collected by the Israel Society of Internal Medicine.

The study population consisted of 2,818 patients with myocardial infarction, of which 2,691 experienced type-I and 127 experienced type-II MI, who were included in the ACSIS registry in 2008 and 2010. Complications of coronary angiography and intervention were documented only in ACSIS 2010.

In-hospital and 30-day outcomes were available for all patients. Mortality at one-year follow-up was available for 93% of the patients. Demographic, historical and clinical data, admission ECG parameters, presence of Q-waves at discharge, medical therapies in-hospital and at discharge, invasive procedures, in-hospital complications and follow-up data were recorded on predefined forms by dedicated physicians. Patients’ functional level was categorized as: normal, mildly impaired or significantly impaired. The existence of anemia was defined at the discretion of the treating physician, based on normal laboratory range in each participating medical center.

Diagnosis and Definitions of Myocardial Infarction

The diagnosis of type-I and type-II MI were at the discretion of the treating physician, according to the 2nd universal definition of MI. [1] To assure compliance with this definition a retrospective validation of the diagnosis of all type-II MI was performed, independently, by two expert physicians. [1] Patients for whom a specific valid cause for the type-II MI was not established were re-classified as type-I MI. Global Registry of Acute Coronary Events (GRACE) risk score was calculated for each admitted patient [10,11].

Ethics Statement

This register-based analysis of pre-existing data was conducted according to the principles expressed in the Declaration of Helsinki. The ACSIS was approved by all the ethical committees in each of the participating medical centers (File S1). Informed consent was specifically waived by the ethical committees of all participating medical centers.

Statistical Analysis

Statistical analysis was performed using SAS statistical software (version 8.2, SAS Institute, Cary, NC). Categorical variables were expressed as percentage, and continuous variables were expressed as mean ± SD. Comparisons of variables were performed by Chi-Square and Fisher’s exact test for categorical variables and by unpaired t-test for continuous variables. All tests were two-sided and p value <0.05 was considered statistically significant.

Results

Patient Characteristics and Clinical Presentation

Type-II MI was diagnosed in 178 of 2818 patients, of whom, 51 were re-classified as type-I MI because a specific valid cause for the type-II MI was not established. The final cohort of type II MI comprised 127 (4.5%) patients. Compared with type-I, patients with type-II MI were older by an average of 11.5 years and the percentage of females was 2-fold higher (Table 1). Patients with type-II MI more often have a history of coronary revascularization, cardiovascular related comorbidities, and substantially higher rates of chronic renal failure and reduced functional level (Table 1). GRACE risk score was substantially higher among type II MI patients (150±32 vs. 110±35, p<0.0001), reflecting higher scores both among patients with STEMI (133±54 vs. 96±31, p<0.0001) and NSTEMI (154±50 vs. 123±33, p<0.0001). Clinical presentation varied between the two patient cohorts and patients with type-II were presented more often with atypical symptoms including dyspnea and arrhythmia, diagnosed more often with non-ST elevation MI and were more frequently admitted to an internal medicine ward and less to a cardiology department (Table 2).

Causes of Type II MI

Table 3 specifies the main causes for type-II MI. Twenty six percent of the patients had more than one cause (Table 3). The main causes were anemia, followed by sepsis, arrhythmia and post-operation. Sepsis as a cause of type-II MI was more common among patients presenting with STEMI compared with those presenting with NSTEMI (40.7% vs. 19.2%, p=0.02). Other causes did not differ between STEMI and NSTEMI patients.

| Table 1. Patient characteristics. |
|----------------------------------|
| Patient Characteristics | Type-I | Type-II | p |
| (n=2691) | (n=127) |  |
| Age | 63.8±13 | 75±12 | <0.0001 |
| Female (%) | 22.3 | 43.4 | <0.0001 |
| BMI | 27.6±4.7 | 25.8±4 | 0.0009 |
| Current smoker (%) | 40.7 | 15.8 | <0.0001 |
| Functionality Level (%) | | | |
| Normal | 83 | 54.3 | <0.0001 |
| Mildly impaired | 12.3 | 30 | |
| Significantly impaired | 4.7 | 15.7 | |
| GRACE Score | 110±35 | 150±32 | <0.0001 |
| Comorbidities (%) | | | |
| Prior MI | 28.1 | 44.4 | 0.0001 |
| Prior Angina Pectoris | 32 | 39.7 | NS |
| Prior PCI | 28.1 | 37.1 | 0.03 |
| Prior CABG | 8.3 | 14.2 | 0.02 |
| Heart failure | 9.2 | 25.6 | <0.0001 |
| Peripheral vascular disease | 8.5 | 17.3 | 0.0007 |
| Dyslipidemia | 71.5 | 73.2 | NS |
| Diabetes | 35.1 | 48 | 0.003 |
| Hypertension | 60.6 | 84.9 | <0.0001 |
| Chronic renal failure | 12.2 | 35.7 | <0.0001 |
| Past CVA/TIA | 8 | 17.3 | 0.0002 |
| COPD | 7.2 | 14.8 | 0.01 |

BMI – body mass index.
PCI – per-cutaneous intervention.
CABG – coronary artery bypass grafting.
CVA – cerebrovascular event.
TIA – transient ischemic attack.
COPD – chronic obstructive pulmonary disease.

[1] doi:10.1371/journal.pone.0084285}
In-hospital Management

Utilization of revascularization varied between groups (Table 4). Type-II MI patients were less often referred for primary and non-primary angiography and of those who underwent coronary angiography, 50% had undergone PCI. In both groups, the utilization of an invasive strategy showed an inverse relationship to patient’s risk, as assessed by GRACE risk score (Table 5).

In and Out of Hospital Outcomes

Patients with type-II MI had higher rates of in-hospital complications including post-MI angina and heart failure (Figure 1) and extended hospitalizations (7.5±6.3 vs. 6±5.3 days, p = 0.0002). In-hospital and 30-day mortality rates were almost three times higher among patients with type-II compared to type-I MI (11.8% vs. 4.2%, p = 0.0005 and 13.6% vs. 4.9%, p = 0.0005, respectively). Thirty-day major adverse cardiac event rates defined as a composite of death, re-MI, CVA or urgent revascularization, were also significantly higher among patients with type-II MI (18.9% vs. 8.8%, p = 0.0001). Kaplan-Meier survival analysis shows significant differences between groups with overall reduced one-year survival rates among patients with type-II MI (76.1% vs. 91.4%, p < 0.0001) (Figure 2). Out-of-hospital to one-year mortality rates were also higher among patients who experienced type-II compared to type-I MI (18.9% vs. 8.8%, p = 0.0001). Kaplan-Meier survival analysis shows significant differences between groups with overall reduced one-year survival rates among patients with type-II MI (76.1% vs. 91.4%, p < 0.0001) (Figure 2). Out-of-hospital to one-year mortality rates were also higher among patients who experienced type-II compared to type-I MI (18.9% vs. 8.8%, p = 0.0001). Interestingly, patients with type-II MI who had two or more identifiable causes of their MI, compared to those with a single cause, had substantially higher 30-day mortality (30.4% vs. 9.8%, p = 0.0009).

Patients with type-II MI less often received guideline-directed medical therapy. These differences were mostly distinctive for clopidogrel but were also significant for four other groups of medications, such as: aspirin, beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and HMG-CoA reductase inhibitors (Table 6).

Discussion

The current national prospective survey analysis of close to 3000 patients with MI, demonstrates a near three-fold increase in short- and intermediate-term mortality among patients with type-II compared with type-I MI. This study, the first to characterize patients with type-II MI, shows that these patients, compared to type-I MI, are: 1) older and more frequently female, 2) have higher

| Table 2. Presentation of myocardial infarction. |
| Characteristic | Type-I (n = 2691) | Type-II (n = 127) | p       |
| First arrival to (%) | 88.4 | 87.4 | <0.0001 |
| Emergency room | 72.4 | 37.4 | <0.0001 |
| Cardiology department* | 17.6 | 12.6 | NS     |
| Hospitalization (%) | 85.2 | 61.7 | <0.0001 |
| Presenting symptom (%) | 84.5 | 54.3 | <0.0001 |
| Typical angina | 7.5 | 20.5 | <0.0001 |
| Syncope | 4.1 | 5.5 | NS     |
| Arrhythmia | 4.7 | 14.2 | <0.0001 |
| Dyspnea | 3.9 | 11.8 | <0.0001 |
| MI type at presentation (%) | 52.5 | 19.7 | <0.0001 |
| ST elevation | 44.2 | 70.1 | <0.0001 |
| Non ST elevation | 3.3 | 10.2 | NS     |
| MI location (%) | 34.2 | 19.7 | <0.0001 |
| Anterior | 34.7 | 25.2 | <0.0001 |
| Inferior | 6.9 | 12.6 | NS     |
| Lateral | 1 | 0.8 | NS     |
| Posterior | 0.1 | 41.7 | <0.0001 |
| Right ventricle | 23.2 | 41.7 | <0.0001 |
| Vital signs (mean±SD) | 141±29 | 143±33 | NS     |
| Systolic blood pressure | 82±17 | 79±19 | NS     |
| Diastolic blood pressure | 80±20 | 95±25 | <0.0001 |
| Heart rate | 85 | 62.2 | <0.0001 |
| KILLIP class on admission (%) | 82.4 | 37.4 | <0.0001 |
| IV | 5.1 | 11 | <0.0001 |
| LV Ejection fraction (%) | 74.3 | 65.9 | NS     |
| Blood tests (mean±SD) | 13.8±0.9 | 1.6±1.2 | NS     |
| Creatinin (mg/dL) | 13.8±1.8 | 11.4±2.2 | <0.0001 |

*Intensive or intermediate cardiac care units.

| Table 3. Cause of type-II MI. |
| Cause | % patients (N = 127) |
| Anemia | 31 |
| Sepsis | 24 |
| Arrhythmia | 17 |
| Post-operative | 14 |
| Hypoxia | 14 |
| Heart failure | 11 |
| Valvular* | 10 |
| Stress** | 3 |
| Drugs* | 2 |
| Others* | 4 |
| Two causes | 18 |
| Three causes | 6 |
| Four causes | 2 |

*Decompensated aortic stenosis.

**Takatsubo, intense pain and suffocation.

Methylphenidate and tadalafil (Cialis).

Vasospasm, extreme hypertension and thyrotoxicosis.

doi:10.1371/journal.pone.0084285.t003
patients with type-II MI and especially type II NSTEMI will
sensitive troponin assays, it is quite possible the population of
functional status. Risk factors for type-II MI in specific clinical
revascularization, chronic renal failure, diabetes and lower
often women, they more frequently have a history of coronary
presented with atypical symptoms and diagnosed with NSTEMI.
NSTEMI. These data are in concordance with previous studies
patients and constituted 7% among patients admitted with
STEMI 89.5 52.9 <0.0001
NSTEMI 71.8 48.2 <0.0001
Culprit Vessel (%)
LMCA 1.2 0 NS
LAD 40.3 35.3
LCX 22.8 26.5
RCA 34 35.3
Graft 2.3 2.9
Complications of PCI (%)
Closure of side branch 2.8 6.3 NS
Dissection 3.9 6.3 N5
Perforation 0.3 0 NS
No reflow 3.3 6.3 NS
CPR during procedure 1.1 12.5 <0.0001
Urgent CABG 0.5 6.3 0.002
PCI - percutaneous intervention.
LMCA - left main coronary artery.
LAD - left anterior descending coronary artery.
LCX - left circumflex coronary artery.
RCA - right coronary artery.
CABG - coronary artery bypass graft.
*Percentage of all patients who had undergone angiography.
doi:10.1371/journal.pone.0084285.t004
rates of multiple cardiac and non-cardiac comorbidities with a
significantly higher GRACE risk score, 3) more frequently
presented with atypical symptoms and diagnosed with NSTEMI,
and 4) less frequently referred to coronary interventions and
received fewer guideline-directed medications.
In our cohort, type-II MI was diagnosed in 4.5% of all AMI
patients and constituted 7% among patients admitted with
NSTEMI. These data are in concordance with previous studies
assessing the frequency of type II MI in selected populations with
previous MI. [6,7,12,13] Nevertheless, following implementation
of the 3rd universal definition of MI along with utilization of high-
sensitive troponin assays, it is quite possible the population of
patients with type-II MI and specially type II NSTEMI will
increase [14,15].
We observed substantial differences in baseline characteristics
between patients admitted with type-II compared to type-I MI.
Notably, patients with type-II MI are considerably older, more
often women, they more frequently have a history of coronary
revascularization, chronic renal failure, diabetes and lower
functional status. Risk factors for type-II MI in specific clinical
situations such as post-operative have been reported and
comprised several variables including increased age, dependent
functional status and renal failure. [16] It is conceivable, that
erly patients with multiple comorbidities and an underlying
coronary disease would be more susceptible to clinical changes
that may interfere with the delicate balance of myocardial supply
and demand, ensuing in type-II MI.
Therapeutic strategy in the current study was at the discretion
of the local medical team. Anemia and sepsis were identified as
causes for MI in over 50% of the patients. These clinical
conditions, along with frequent presence of chronic renal failure
and significantly impaired functional capacity on one hand and
the high cardiovascular risk score on the other imposed a great
therapeutic decision-making challenge. Hence, additional data are
needed in order to draw specific recommendations tailored to the
various clinical conditions associated with type II MI. Considering
the high cardiovascular risk score of patients with type II MI,
recognition of subsets of cohorts, such as those experiencing post-
operative MI, may allow to implement invasive strategy [2,11,17–
19]. On the other hand, many of these patients may require initial
stabilization of the cause of the MI. This obligatory time lag may
dictate conservative approach with utilization of delayed invasive
strategy only in selective patients. [20] Whether, in selected patient
populations, a more invasive approach would benefit patients with
type II MI has not been studied. Similarly, whether current
recommended medical treatments would advantage patients with
type II MI is at present unknown. Considering the complexity of
this cohort, a potential important implication of our study is the
need for dedicated studies to assess comprehensive therapeutic
strategies in this growing patient population.
Short-term and intermediate outcomes differ between patients
with type-II and type-I MI. In-hospital complications were
substantially more frequent and short-term and intermediate
mortality rates were near three-fold higher, reaching 13.6% and
23.9% at 30 days and 1-year, respectively. Similar 30-day
mortality rates were previously noted in patients with perioperative
MI. [2] Thus, our data further extends the relatively high
mortality rates to a broader type-II patient population.

Limitations
The current study carries several limitations. In this national
survey, patients admitted to non-cardiac intensive care units were
not included. Thus, both the true frequency of type-II MI and the
observed mortality rates, which are usually substantial among
medical intensive-care patients, may be higher. Invasive strategy
was at the discretion of the treating physicians and overall, only a
minority of type-II MI patients were referred to coronary
angiography. Specific reasons for such decisions were not gathered
and accordingly, no recommendation regarding patient selection
can be made. The relatively small number of type-II MI patients

| Type-I | Type-II | p |
|-------|--------|---|
| (n = 2691) | (n = 127) |   |
| Primary reperfusion (%) | 69.2 | 32 | <0.0001 |
| PCI | 93 | 87.5 | NS |
| Thrombolysis | 6.4 | 12.5 | NS |
| CABG | 0.6 | 0 | NS |

Table 5. Differences in GRACE score by MI type and PCI status.

| Type-I | Type-II | p (Type-I vs. Type-II) |
|-------|--------|----------------------|
| N | Mean ± SD | N | Mean ± SD |
| No-PCI | 661 | 138 ± 35 | 89 | 157 ± 28 | <0.0001 |
| PCI | 1699 | 99 ± 29 | 17 | 116 ± 27 | 0.016 |
| PCI (PCI vs. no-PCI) | <0.0001 | <0.0001 |

doi:10.1371/journal.pone.0084285.t005

PLOS ONE | www.plosone.org | 4 | January 2014 | Volume 9 | Issue 1 | e84285
limits the power of our study and preclude multivariate analysis to identify predictors for and risk-stratification of type-II MI. Importantly, re-classification of patients with type II to type I MI was performed in 28% of our cohort. Precise distinction between type II and type I MI in daily practice may be perplexing as many of the causes of type II MI may actually be a complication

Figure 1. In-hospital complications. In-hospital complications of patients with type-I compared to patients with type-II MI. (** denotes significant difference with p<0.001). Pul. edema - pulmonary edema Re-MI - recurrent myocardial infarction AF - atrial fibrillation TIA - transient ischemic attack ARF - acute renal failure. doi:10.1371/journal.pone.0084285.g001

Figure 2. Kaplan-Meier Survival Analysis, Type-I vs. Type-II Myocardial Infarction. Kaplan-Meier survival analysis shows significant differences between groups with overall reduced one-year survival rates among patients with type-II MI (76.1% vs. 91.4%, p<0.0001). doi:10.1371/journal.pone.0084285.g002
of type I MI (i.e. arrhythmia, heart failure) and other, such as surgery or inflammatory state may, by themselves, lead to plaque rupture.

**References**

1. Thygesen K, Alpert JS, White HD (2007) Universal definition of myocardial infarction. Eur Heart J 28: 2525–2538.
2. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigouin A, et al. (2011) Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 154: 523–528.
3. Agewall S, Giannitsis E, Jernberg T, Katus H (2011) Troponin elevation in non-coronary disease. Eur Heart J 32: 404–411.
4. De Gennaro L, Brunetti ND, Cuculio A, Pellegro PL, Izzo P, et al. (2008) Increased troponin levels in nonischemic cardiac conditions and noncardiac diseases. J Interv Cardiol 21: 129–139.
5. Kelley WE, Januzzi JL, Christenson RH (2009) Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. Clin Chem 55: 2098–2112.
6. White HD, Reynolds HR, Carvalho AG, Pearte CA, Liu L, et al. (2012) Reinfarction after percutaneous coronary intervention or medical management using the universal definition in patients with total occlusion after myocardial infarction: Results from long-term follow-up of the Occluded Artery Trial (OAT) cohort. Am Heart J 163: 563–571.
7. Bonaca MP, Wiviott SD, Braunwald E, Murphy SA, Riff CT, et al. (2012) American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation Classification System from the universal definition of myocardial infarction: Circulation 125: 577–583.
8. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, et al. (2009) Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. Circulation 119: 2758–2764.
9. Behar S, Banter A, Forath A, Leor J, Grossman E, et al. (2003) A prospective national survey of management and clinical outcome of acute myocardial infarction in Israel. Isr Med Assoc J 5: 249–254.
10. Eagle KA, Lin MJ, Dabbous OH, Peppe KS, Goldberg RJ, et al. (2004) A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. Jama 291: 2727–2733.
11. de Araujo Goncalves P, Ferreira J, Aguiar C, Searba-Gomes R (2005) TIMI PURSUIT and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 26: 865–872.
12. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, et al. (2011) ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 32: 2999–3055.
13. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, et al. (2011) Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 123: e18–e209.
14. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chairman BR, et al. (2012) Third universal definition of myocardial infarction. J Am Coll Cardiol 60: 1501–1508.
15. Bahrami S, Heppner HJ, Christ M, Bertsch T, Sieber C (2012) Early detection of non-ST-elevation myocardial infarction in geriatric patients by a new highsensitive cardiac troponin T assay. Aging Clin Exp Res 24: 290–294.
16. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, et al. (2011) Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 124: 381–387.
17. Bankahemt B, Goodman SG, Yan RT, Welsh RC, Mehta SR, et al. (2009) Underutilization of clopidogrel and glycoprotein IIb/IIIa inhibitors in non-ST-elevation acute coronary syndrome patients: the Canadian global registry of acute coronary events (GRACE) experience. Am Heart J 153: 917–924.
18. Jedrzkiewicz S, Goodman SG, Yan RT, Welsh RC, Kordaer J, et al. (2009) Temporal trends in the use of invasive cardiac procedures for non-ST-segment elevation acute coronary syndromes according to initial risk stratification. Can J Cardiol 25: e370–376.
19. Fox KA, Anderson FA, Jr., Dabbous OH, Steg PG, Lopez-Sendon J, et al. (2007) Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE) experience. Heart 93: 177–182.
20. Hochman JS, Lamas GA, Bueller CE, Dzavik V, Reynolds HR, et al. (2006) Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 355: 2395–2407.

**Table 6.** Guideline-directed medications at discharge.

| Medications                      | Type-I (n = 2691) | Type-II (n = 127) | p     |
|---------------------------------|------------------|------------------|-------|
| Aspirin                         | 97               | 86               | <0.0001 |
| Clopidogrel                     | 86               | 50               | <0.0001 |
| Beta blockers                   | 83               | 72               | 0.001  |
| ACE-I/ARB                       | 79               | 69               | 0.006  |
| HMG-CoA reductase inhibitors    | 94               | 87               | 0.003  |

ACE-I - angiotensin converting enzyme inhibitors.
ARB - angiotensin receptor blocker.

doi:10.1371/journal.pone.0084285.t006

Conclusions

Type-II MI is not infrequent, especially among patients with NSTEMI. Compared to type-I MI, it is more frequent among the elderly with multiple comorbidities, high ACS risk score and associated with increased short and intermediate-term mortality. The implementation of current ACS guidelines to patients with type-II MI is challenging and more evidence-based patient-tailored therapeutic strategies are warranted.

**Supporting Information**

File S1  Participating medical centers in the ACSIS registry.

(DOCX)

**Author Contributions**

Conceived and designed the experiments: GYS SF. Performed the experiments: GYS GH. Analyzed the data: GYS GH NG. Contributed reagents/materials/analysis tools: SM SG. Wrote the paper: GYS SG SF. Critical review of manuscript: RK SM DA ZI.