

Real world management and outcomes in acute coronary syndrome: analysis of a large US cohort

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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

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**REAL WORLD MANAGEMENT AND OUTCOMES IN ACUTE CORONARY
SYNDROME: ANALYSIS OF A LARGE US COHORT**

Doctoral dissertation

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prof. Mamas A. Mamas, MD DPhil

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Keele Cardiovascular Research Group from Keele, United Kingdom.

MENTOR: prof. Mamas A. Mamas, MD DPhil

„Try not to become a man of success, but rather try to become a man of value. “

Albert Einstein

First and foremost, I would like to express strong gratitude and deepest appreciation to my mentor Professor Mamas A. Mamas for guiding my scientific research with high standards.

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1. ABBREVIATIONS

aOR – adjusted odds ratios

ATEs – average treatment effects

IHD – ischemic heart disease

MHI – median household income

95% CI – 95% confidence interval

non-OMI – non-occlusive myocardial infarction

NSTE-ACS – non-ST-elevation acute coronary syndrome

NSTEMI – non-ST-elevation myocardial infarction

OMI – occlusive myocardial infarction

PSM – propensity-score matching

SDoH – social determinants of health

STEMI – ST-elevation myocardial infarction

STROBE – STrengthening the Reporting of OBservational studies in Epidemiology

2. INTRODUCTION

2.1. Acute coronary syndrome

Acute coronary syndrome is a clinical event that is associated with acute myocardial ischemia (1). This comprehensive clinical entity comprises several clinical scenarios in the setting of acute myocardial ischemia, allowing for prompt clinical proceeding to prevent potentially severe complications. It represents a leading cause of morbidity and mortality worldwide (2), and is usually considered a clinical manifestation of the critical phase of coronary artery disease (3).

2.1.1. Classification of acute coronary syndrome

Acute coronary syndrome represents a clinical entity that is composed of ST-elevation myocardial infarction (STEMI) and non-ST-elevation acute coronary syndrome (NSTEMI), which further encompasses non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. In addition, patients with sudden cardiac death that is presumably due to acute myocardial ischemia, could also be classified as having acute coronary syndrome (4).

This modern classification depends on the diagnostic findings during clinical, electrocardiographic and laboratory assessment, and has direct implications on the clinical decision-making processes. As the name suggests, the differentiation of STEMI and NSTEMI patients includes the recognition of different electrocardiographic patterns. The greatest subset of patients with acute coronary syndrome shows evidence of acute myocardial injury as determined by the high-sensitivity troponin levels, thereby representing a population of patients with acute myocardial infarction (4). The remaining minor part of the population does not exhibit an elevation of high-sensitivity troponin levels, although having manifest clinical and electrocardiographic signs of acute myocardial ischemia. These patients are therefore considered to have unstable angina. Due to importance of laboratory analysis, patients with NSTEMI and unstable angina are hardly differentiated at initial encounter (5).

Due to potential limitations of the existing categorization, emerging studies justify the novel classification schemes that are based on the clinical assumptions of the underlying coronary occlusion. These classifications stratify patients with acute coronary syndrome into those having occlusive myocardial infarction (OMI) or non-occlusive myocardial infarction (non-OMI). The rationale includes an increased awareness about the necessity for urgent invasive management in former scenarios, compared to clinically guided utilization of invasive

management in latter cases (6). Furthermore, other pathogenesis-based multi-mechanistic approaches have been also suggested for the classification of acute coronary syndrome (1). Nevertheless, further studies are warranted to determine whether different approaches offer any clinical benefit or have only an arbitrary meaning.

2.1.2. Diagnosis of acute coronary syndrome

The diagnosis of acute coronary syndrome includes the combination of clinical factors, electrocardiographic findings, and laboratory parameters (7). Each component bears a complementary role and correct interpretation of conjoint results is of paramount importance (8). This requires a systematic and analytical approach with clinical scrutiny and utilization of different validated algorithms.

Clinical assessment warrants a physical examination with an evaluation of clinical signs and patient-reported symptoms. Patient-reported symptoms could be diverse, varying from typical chest pain (discomfort, pressure, or tightness) or its potential equivalents (dyspnoea, dyspepsia, burning sensation, epigastric pain, neck pain, mandibular pain, or left arm pain) to ominous presentations with haemodynamic and/or electrical instability (transient loss of consciousness, acute heart failure, cardiogenic shock, or cardiac arrest) (8). The symptoms are usually clustered in the association with acute myocardial ischemia. Aside from clinical assessment, multiple scoring systems are available to objectivize the patient's risk of coronary artery disease. Some risk scores determine a baseline cardiovascular risk providing an insight into the likelihood of future cardiovascular events for each patient. Selected scoring tools endorse the quality of patient-reported symptoms with relevance to coronary artery disease. Finally, several scoring tools integrate various patient characteristics and provide an estimated risk for acute coronary syndrome. The utilization of detailed clinical appraisal and risk stratification allows for calculation of pre-test probability for coronary artery disease and/or acute coronary syndrome in each individual patient (9).

Electrocardiographic assessment includes a detailed evaluation of contemporary electrocardiogram and its comparison to previous and subsequent records (8). The detection of dynamic changes represents an important clinical information. Based on the initial electrocardiographic assessment, electrocardiogram could be considered as normal; abnormal without diagnostic ST-segment elevation; and abnormal with diagnostic ST-segment elevation. Patients with electrocardiographic findings that exclude diagnostic ST-segment elevation mandate clinical consideration with respect to possible NSTEMI-ACS. Importantly, the presence

of normal electrocardiogram does not exclude acute coronary syndrome if there is a discordance with other clinical and/or laboratory determinants (10). On contrary, patients with diagnostic ST-segment elevation require urgent clinical proceeding and urgent invasive coronary angiography. Some electrocardiographic findings could be considered equivalents to diagnostic ST-segment elevation, including a novel left bundle branch block, diffuse ST depression with ST-segment elevation in augmented vector right (aVR) lead, and ST depression in septal leads with ST-segment elevation in posterior leads (11).

Laboratory analysis incorporates a biochemical detection of the acute cardiomyocyte injury by measuring fluctuation of cardiac markers (8). Modern laboratory analysis is based on high-sensitivity cardiac troponin assays which offer unique biochemical properties. Depending on the utilized assay and pre-test probability, it is possible to select among different validated diagnostic algorithms (10).

Additional diagnostic tools such as the echocardiography or cardiac magnetic resonance imaging are sometimes needed to provide more information. Imaging evidence of novel regional wall motion abnormality or loss of myocardial viability are associated with acute coronary syndrome (8).

Having in mind that acute coronary syndrome represents a new-onset coronary event with ongoing ischemia and continuing pathophysiology, the importance of accompanying dynamics in clinical, electrocardiographic and laboratory findings is strongly underscored. Overall, an assessment of patients with suspected acute coronary syndrome has several goals. In the first instance, it is mandatory to accurately detect patients with acute coronary syndrome, while excluding other mimicking conditions. Second, it is vital to detect patients with high likelihood for acute coronary occlusion, such as those with STEMI or its equivalents, who should benefit from urgent invasive strategy. Third, proper risk stratification of each individual patient is warranted to reduce the myocardial ischemia, guide further management strategies, and tailor an appropriate pharmacologic strategy. Finally, it is crucial to effectively and timely detect each patient to spare the myocardium, while avoiding excessive and unnecessary utilization of healthcare resources (“time is myocardium”) (12).

2.1.3. Risk factors and pathophysiology of acute coronary syndrome

There is plethora of risk factors for acute coronary syndrome, including non-modifiable and modifiable risk factors. Non-modifiable risk factors include older age, male sex, genetic background, and ethnicity. Modifiable risk factors could be divided into standard modifiable

risk factors and non-standard modifiable risk factors (2). Standard modifiable risk factors include smoking, dyslipidaemia, hypertension, and diabetes. Non-standard modifiable risk factors encompass various conditions, such as obesity, physical inactivity, diet, kidney disease, peripheral artery disease and others (2, 13).

The pathophysiology of acute coronary syndrome is complex and involves various concomitant events (3). However, atherosclerosis represents the central dynamic process of most coronary events, that usually onsets long before the clinical manifestation of acute coronary syndrome. This long-year process includes cholesterol accumulation and coronary wall changes with subsequent formation of adaptive intimal thickening and intimal “fatty streaks” xanthoma. Continuation of the process leads to formation of fibrous cap atheroma and the development of other advanced plaque forms. As a result, affected coronary arteries exhibit coronary remodelling, endothelial dysfunction and local pro-inflammatory state which makes them prone to subsequent vessel injury and prothrombotic milieu. These events are promoted by systemic inflammation and various neurohumoral factors, along with multiple other anatomical, mechanical, and patient risk factors. If the atherosclerotic cascade continues, multiple overlapping events may occur leading to the development of vulnerable thin fibrous cap atheroma (3, 14).

The principal underlying mechanism of an acute coronary syndrome is atherosclerotic plaque destabilization with consequent thrombus formation. A critical point is rupture, fissure or erosion of unstable atherosclerotic plaque which initiates a local cascade of pro-thrombotic events with an obstruction of coronary artery blood flow and acute myocardial ischemia. This process follows the pattern of positive feedback loop during which consequent events potentiate the antecedent elements (14).

Nevertheless, other less frequent pathophysiologic mechanisms of acute coronary syndrome include spontaneous coronary artery dissection, coronary artery spasm, or coronary microvascular dysfunction. Some patients may even develop acute coronary syndrome without evidence of obstructive coronary artery disease or other mimicking conditions (2).

2.1.4. Epidemiology of acute coronary syndrome

Ischemic heart disease (IHD) represents a leading single cause of mortality worldwide, accounting for more than 20% of mortality events (15). It is calculated that 7.2% of the adult population in United States have IHD (16). This produces a substantial global healthcare burden (15-17).

The predominant driver of these worrisome trends is acute coronary syndrome. Recent data from the *Heart Disease and Stroke Statistics* reveal that more than 3.1% of adult population in the United States have a history of acute coronary syndrome, while it is estimated that 805,000 patients develop acute myocardial infarction per year (16). Globally, it is projected that yearly incidence of acute coronary syndrome includes more than 150 patients per 100,000 inhabitants (18).

When looking at its subtypes, the incidence of NSTEMI-ACS has remained relatively stable or slightly increased, while the incidence of STEMI has significantly decreased in recent years (19, 20). This is a result of better preventive measures and improved diagnostic methods, particularly in the form of high-sensitivity troponin tests. Due to distinct utilization of the abovementioned methods across different countries, the epidemiologic trends differ between lower and higher income regions (18). Nevertheless, due to the widespread use of the high-sensitivity troponin tests, the diagnosis of unstable angina has substantially diminished on the account of increased incidence of NSTEMI (18).

2.1.5. Management of acute coronary syndrome

The management of patients with acute coronary syndrome is vital for the prevention of serious associated complications. Depending on its timing, the management of acute coronary syndrome could be differentiated into acute or chronic treatment. Furthermore, the management depends on the underlying specific condition, i.e., whether the patient suffers from STEMI or NSTEMI-ACS. Finally, the management could be divided into invasive (revascularization and medications) or conservative (only medications) management. Invasive management could be further divided into percutaneous or surgically mediated revascularization (3, 8).

The acute management of patients with STEMI involves medications (antiplatelets and other supportive therapy) with urgent invasive coronary angiography that is usually accompanied by a percutaneous coronary intervention of the culprit coronary artery. This management algorithm is justified as most patients with STEMI exhibit an underlying acute occlusion of coronary artery which demands urgent reperfusion (**Figure 1**).

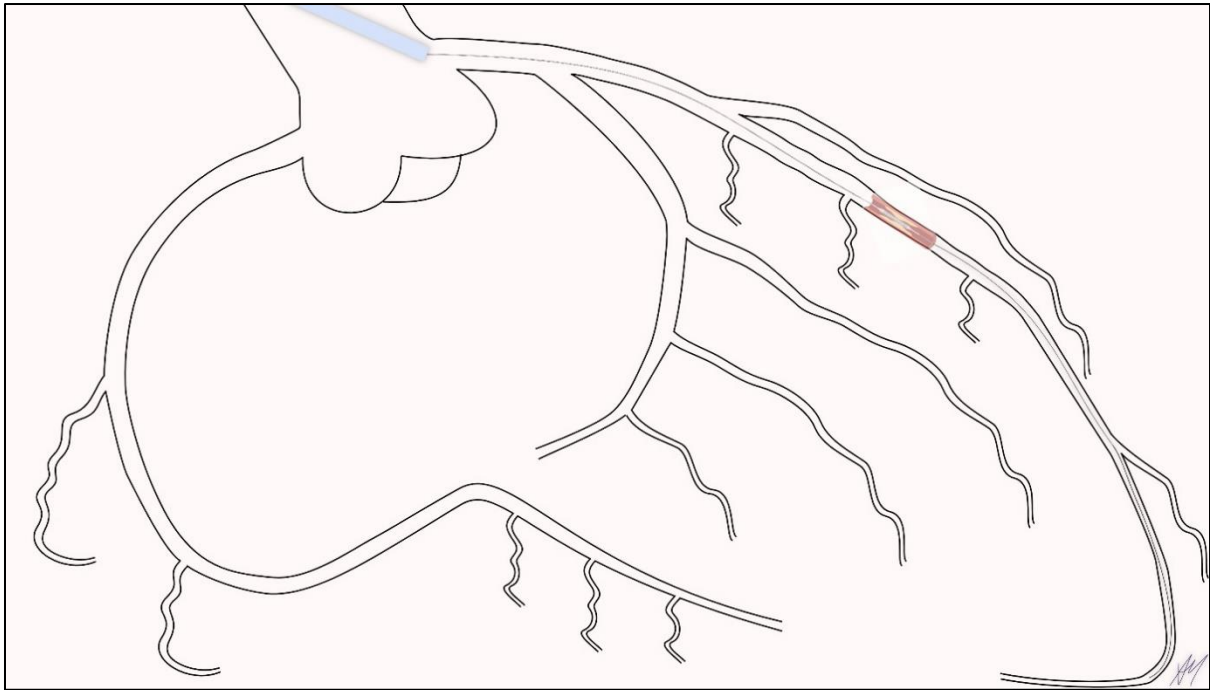


Figure 1. Illustration of the percutaneous coronary intervention in the left anterior descending coronary artery (original author's work)

It is recommended to administer the dual antiplatelet therapy in the periprocedural period and maintain it up to 12-months after the development of STEMI in most cases (11) (Figure 2).

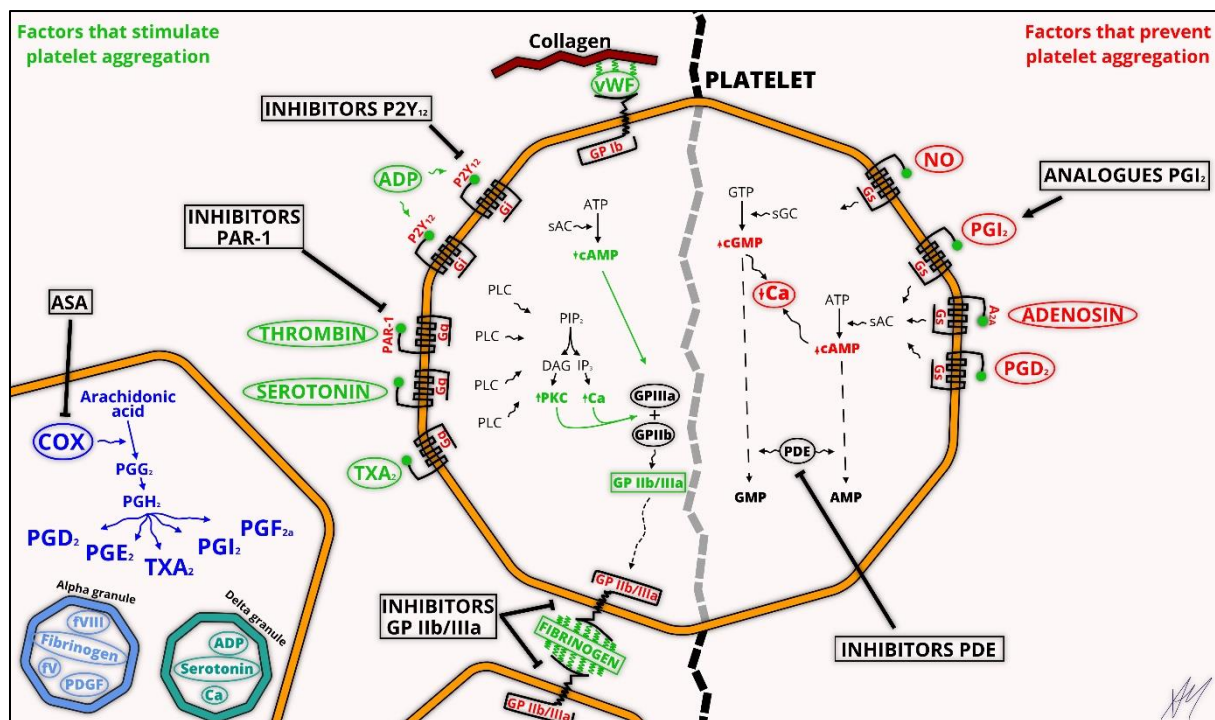


Figure 2. Mechanism of action of antiplatelet medications (original author's work)

Abbreviations: ADP – adenosine diphosphate; AMP – adenosine monophosphate; ATP – adenosine triphosphate; ASA – acetylsalicylic acid; Ca – calcium; cGMP – cyclic guanosine monophosphate; COX –

cyclooxygenase; cAMP – cyclic adenosine monophosphate; f – factor; GPIIb/IIIa – glycoprotein 2b/3a; GPIb – glycoprotein 1b; PKC – protein kinase C; GTP – guanosine triphosphate; GMP – guanylate monophosphate; NO – nitric oxide; PAR-1 – Protease-activated receptor-1; PDE – phosphodiesterase; PDGF – Platelet-derived growth factor; PGG₂ – prostaglandin G₂; PGH₂ – prostaglandin H₂; PGD₂ – prostaglandin D₂; PGE₂ – Prostaglandin H₂; PGI₂ – prostaglandin I₂; PGF_{2α} – Prostaglandin F_{2α}; PLC – phospholipase C; P2Y₁₂ – purinergic receptor type Y, subtype 12; sAC – soluble adenylyl cyclase; sGC – soluble guanylate cyclase; TXA₂ – thromboxane A₂; vWF – von Willebrand factor.

If there is a presumable delay in the necessary invasive management, an application of thrombolytic therapy is recommended to attempt pharmacologic reperfusion. These patients should be transferred to the closest centre immediately after the administration of the thrombolytic therapy. Other management options such as urgent surgical revascularization or conservative management are rarely utilized for patients with STEMI due to the abovementioned necessity for prompt reperfusion (3, 8, 11).

The acute management of patients with NSTEMI-ACS involves detailed risk stratification to guide medications (**Figure 3**) and estimate the timing of invasive coronary angiography. Depending on the findings of invasive coronary angiography, the subsequent management is determined between percutaneous coronary intervention, surgical revascularization, or continuation of only pharmacologic therapy. Some patients benefit from hybrid approaches which include staged percutaneous and surgical revascularization (3, 8, 10).

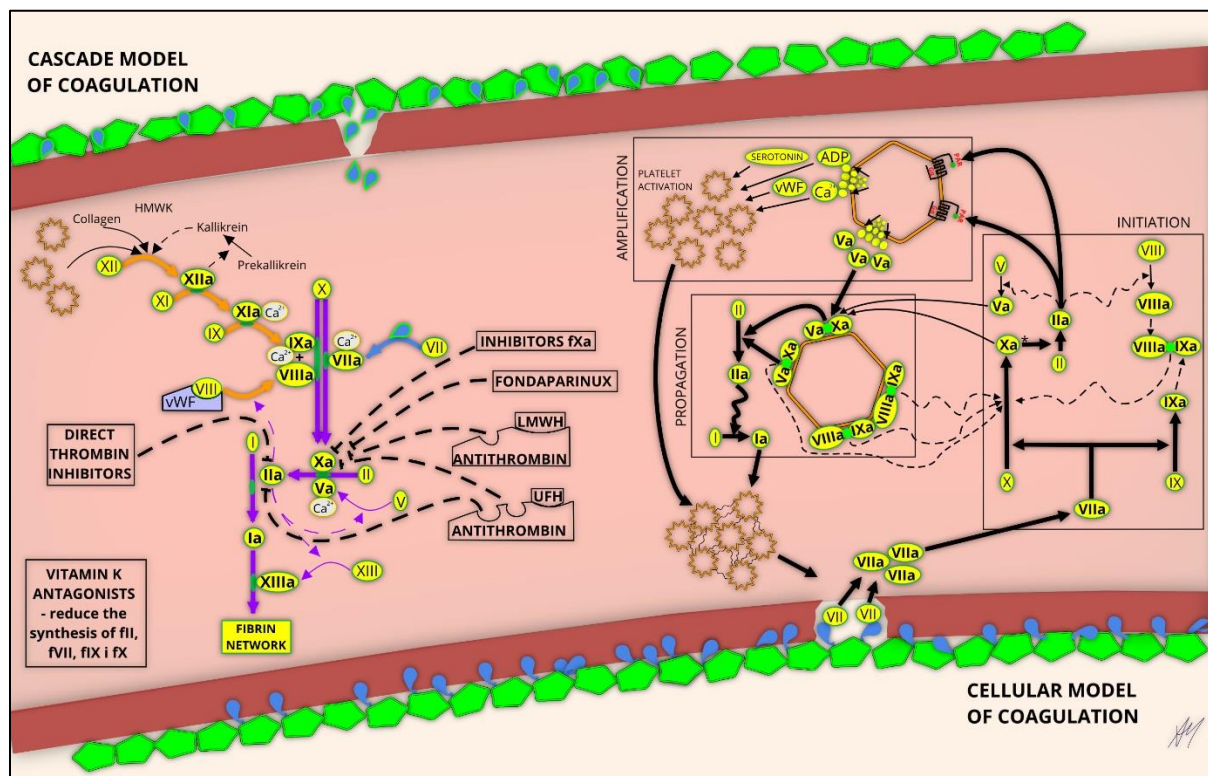


Figure 3. Mechanism of action of anticoagulant medications (original author's work)

Abbreviations: ADP – adenosine diphosphate; Ca – calcium; f – factor; HMWK – high molecular weight kallikrein; LMWH – low molecular weight heparin; UFH – unfractionated heparin; vWF – von Willebrand factor.

Chronic management of patients with acute coronary syndrome depends on the acute management strategy, but usually involves potent dual antiplatelet and lipid-lowering therapy with beta-blockers and management of concomitant comorbidities (8).

2.1.6. Prognosis of acute coronary syndrome

Due to substantial improvement in the management of these patients, particularly in the form of percutaneous coronary intervention and advanced medications, short- and long-term prognosis of this population has improved (19). Recent estimates indicate a decline of annual mortality rate for IHD by 25.2% in the period from 2009 to 2019 in United States (16). Nevertheless, it remains the most frequent single cause of mortality worldwide (11).

Estimations of 1-month mortality of overall patients with acute coronary syndrome depict a variation between 2% and 5%. Sensitivity analysis by type of acute myocardial infarction reveals a 1-month mortality rates of 2-4% for NSTEMI and 3-8% for STEMI (10, 11). When analysing the longer period, it is estimated that 1-year mortality for the overall cohort of acute coronary syndrome approaches 14% (16). These findings implicate that patients with STEMI portend worse short-term prognosis, but long-term analyses reveal a trend reversal with higher 1-year mortality in patients with NSTEMI (10, 11).

Nevertheless, survivors of acute coronary syndrome have an increased risk of future cardiovascular events or complications such as heart failure, arrhythmias, conduction disturbances, mechanical complications, or pericarditis (11).

2.2. Emerging issues in acute coronary syndrome

Acute coronary syndrome represents an ever-growing and challenging field that utilizes substantial healthcare and scientific resources (21). Recent years have revealed an emerging importance of equity and equality in the management and outcomes of this vulnerable population. However, increasing data have suggested that some populations are understudied with potential for undertreatment and worse outcomes. Essential features of this population such as their socioeconomic status, sex, hospital records (diagnostic coding priority) or trial recruitment status, have been increasingly prioritized to meet the literature demands.

Disparities, bias, and inequalities in this population have been mediated through differences in risk profile, public education, access to healthcare, clinical process, physician bias, rehabilitation phase, adherence to recommended therapy, and inadequate scientific evidence (underreport of specific population data and underrepresentation in clinical studies).

Therefore, this doctoral dissertation targeted a contemporary analysis of patients with acute coronary syndrome using the valuable real-world data from large registries. The analyses were focused on the differences between patients based on their socioeconomic status, diagnostic coding priority, trial recruitment and sex (**Figure 4**). Such initiatives are warranted to improve and equalize the quality of care and outcomes in this important population.



Figure 4. Emerging issues in acute coronary syndrome – socioeconomic status, hospital records (diagnostic coding priority), sex and trial recruitment (original author's work)

2.2.1. Socioeconomic determinants of acute coronary syndrome

Socioeconomic factors represent important social determinants of health (SDoH), along with the psychosocial and environmental aspects, that have been linked to the outcomes of patients with cardiovascular disease (22). Each SDoH is multidimensional, often with overlapping features, which further aggravates the understanding of this complex interaction.

The assessment of SDoH is additionally affected by the heterogeneity of available measuring methods leading to a lack of standardization. A recent systematic review of longitudinal studies revealed a utilization of various measures of psychosocial and environmental determinants (various indices, individual-level perceived scales, questionnaires, records of public bodies, psychometric tools, etc.) (22).

Socioeconomic status could be expressed with the different measures, including the income, educational attainment, neighbourhood status, and occupation (23). Median household income (MHI) represents an important aspect of the socioeconomic status that could be easily quantified and utilized to objectively stratify the population of interest. It has been previously confirmed as a surrogate of socioeconomic status for the purpose of health research.

In the context of acute coronary syndrome, patient differences in socioeconomic status have been consistently associated with diverse outcomes. The reasons for distinct outcomes are complex and multifactorial. Numerous underlying mechanisms have been proposed, including the social, behavioural, and biological factors. This includes impaired prevention strategies, dietary patterns, higher risk profile, limited access to healthcare, bias in clinical decision-making process, lower adherence to recommended therapy, and multiple other biological mechanisms. For example, lower socioeconomic status could promote chronic stress, inflammation, atherosclerosis, and accelerated ageing (22).

The existing studies encompassed specific or single-centre cohorts that prevented its extrapolation to wider population, warranting further studies (24-27). Other important factors, such as the distinct methodology in determining socioeconomic status across the studies, also precluded direct comparison of the findings. There was also a lack of data on temporal trends of the socioeconomic disparities in terms of management and outcomes of patients with acute coronary syndrome. Therefore, solid data from large research studies was required to further determine the presence and explore the extent of this association. There were no similar studies based on the *National Inpatient Sample* database.

2.2.2. Diagnostic coding priority of acute coronary syndrome

Diagnostic coding of conditions and procedures represents an important part of large administrative databases to ensure adequate collection of data for multiple purposes. This process includes recognition of major admission causes that should be recorded in the primary or principal diagnostic fields. However, non-negligible portion of important conditions are being coded at the secondary level leading to potential errors in future dataset analyses.

Large-scale administrative databases represent the main reference point for national healthcare systems. Data from these registries are used to inform the reformative measures and reimbursement purposes, as well as to gain insights about the real-world state of the population of interest. The coding and extraction algorithms are therefore substantially important.

Most previous studies on patients with acute coronary syndrome have utilized only primary-coded diagnosis of acute coronary syndrome (28-35). However, these algorithms could potentially introduce a substantial selection bias as administrative data may not contain correctly prioritized diagnostic codes, leading to underestimation of the true cohort and exclusion of a significant number of patients with acute coronary syndrome. Furthermore, it was not clear whether patients with primary and secondary coded acute coronary syndrome share similar risk profile and exhibit similar outcomes, which may lead to potential miscalculation of the overall prognosis of the cohort if focusing only on selected patients. Existing literature on this topic was restricted to small cohort studies over a limited period. There were no similar studies based on the *National Inpatient Sample* database.

2.2.3. Trial recruitment in acute coronary syndrome

Conventional clinical trials are usually representative of the highly selective population and their generalizability to overall population is questionable. Multiple determinants affect their wider applicability including robust exclusion criteria, biased management, and strict follow-up. Therefore, insights into the real-world data were warranted to determine whether the population of patients enrolled into clinical trials, which form the reference point for society guidelines, differs from real-world population of patients with acute coronary syndrome. While there were several literature works investigating this important topic, there were based on smaller sample sizes with restricted study period (36-39). There were no similar studies based on the *National Inpatient Sample* database.

2.2.4. Sex differences in acute coronary syndrome

There are important sex-related differences in the characteristics of acute coronary syndrome. It has been shown that acute coronary syndrome occurs from 7 to 10 years earlier in men compared to women. This could be mostly explained by biologic differences, including the protective properties of premenopausal hormonal patterns. However, other factors have a complementary role such as the genetic expression, occupation, or environmental exposure.

Aside from aforementioned differences, additional observations have emerged suggesting higher prevalence of atypical clinical symptoms and higher proportion of underdiagnoses in female population with acute coronary syndrome. Previous reports have also suggested that female patients with acute coronary syndrome receive less guideline-directed management, including the lower utilization of invasive management, which could be associated with worse outcomes (40-44).

Therefore, literature was lacking additional data to determine whether there are sex-related disparities in the real-world population. While there were numerous studies investigating the sex-related differences in acute coronary syndrome, it was difficult to draw strong conclusions because of existing limitations such as specific or highly selected cohorts, underpowered analyses, or specific geographic regions. Furthermore, multiple studies focused only on the subset of acute coronary syndrome patients such as those with STEMI or NSTEMI-ACS (45). There were no similar studies based on the *National Inpatient Sample* database.

2.3. Relevance to the literature

Real-world data from validated registries and clinical databases are warranted to provide true insights into the management and outcomes of population with acute coronary syndrome, regardless of their differences in understudied characteristics. This is important to understand deficiencies in real-world clinical practice and provide data network for global quality improvement programs.

3. AIMS OF THE CONSOLIDATED RESEARCH STUDIES

Primary aims of the research studies were:

1. To determine whether there are differences in invasive management and clinical outcomes of patients with acute coronary syndrome based on their socioeconomic status.
2. To determine whether there are differences in invasive management and clinical outcomes of patients with acute coronary syndrome based on their diagnostic coding priority.
3. To determine whether there are differences in invasive management and clinical outcomes of patients with acute coronary syndrome based on their trial recruitment status.
4. To determine whether there are differences in invasive management and clinical outcomes of patients with acute coronary syndrome based on their sex.

Secondary aims of the research studies were:

1. To determine whether there are differences in characteristics of patients with acute coronary syndrome based on their socioeconomic status, diagnostic coding priority, trial recruitment status, and sex.
2. To determine whether there are differences in comorbidities of patients with acute coronary syndrome based on their socioeconomic status, diagnostic coding priority, trial recruitment status, and sex.
3. To determine whether there are differences in total hospitalization charges and length of stay of patients with acute coronary syndrome based on their socioeconomic status, diagnostic coding priority, trial recruitment status, and sex.

4. HYPOTHESES OF THE CONSOLIDATED RESEARCH STUDIES

Hypotheses of the research studies were:

1. Patients with acute coronary syndrome that have lower household income will receive less invasive management and have worse clinical outcomes compared to their counterparts.
2. Patients with acute coronary syndrome that were coded as secondary diagnosis will receive less invasive management and have worse clinical outcomes compared to their counterparts.
3. Patients with acute coronary syndrome that are not enrolled in clinical trials will receive less invasive management and have worse clinical outcomes compared to their counterparts.
4. Female patients with acute coronary syndrome will receive less invasive management and have worse clinical outcomes compared to their counterparts.

5. MATERIALS AND METHODS

5.1. Study design

The research studies represent original research articles with an observational retrospective design. Randomization of the subjects was not performed. The researchers independently determined the structure and methodology of the research before the actual data collection and analysis. The research used primary data sources – data from the electronic registry *National Inpatient Sample* that were independently collected, extracted, and prepared for the analysis (46).

The literature search was conducted in accordance with the standard principles of scientific literature search. For the published research studies, we have searched multiple literature databases (MedLine; EMBASE; Cochrane Library) up to December 2021 without setting a limit on the type of research or the language in which the research was published. The literature search was undertaken using the keywords (acute coronary syndrome; socioeconomic status; diagnostic coding priority; trial recruitment; sex differences), their appropriate MeSH equivalents and their combinations (with the logical operator AND: „acute coronary syndrome“ AND „socioeconomic status“; „acute coronary syndrome“ AND „diagnostic coding priority“; „acute coronary syndrome“ AND „trial recruitment“; „acute coronary syndrome“ AND „sex differences“), while the search area was focused on the entire research text. Using the algorithm, we found a total of 576 scientific papers. During further screening, an additional 312 scientific papers were excluded due to insufficient matching of the topic, and an additional 130 scientific papers were excluded after a critical reading of the summaries of the remaining scientific papers (insufficient matching of the topic, methodological differences, differences in the target population). Finally, a total of 134 research articles relevant to the published research studies were included, and eventually were cited.

The studies and analyses were organized according to the recommendations of the *Agency for Healthcare Research and Quality* and the *Healthcare Cost and Utilization Project* (46). After the secure download of the datasets, further proceedings were done including the code preparation, data extraction, and cohort selection. The missing cases in relevant variables were excluded, in line with the other exclusion criteria. Detailed list of comorbidities and outcomes was then defined using the appropriate codes, followed by the remaining analyses, tabular and graphical presentations, and manuscript preparation. All the analyses and study

procedures were undertaken under the supervision of mentor Professor Mamas A. Mamas, while the further manuscript refinement followed collaborators' suggestions.

5.2. Study population

The research studies encompassed a population of patients with acute coronary syndrome that was derived from the *National Inpatient Sample* over the period from January 2004 to December 2018, depending on the sub-study. The diagnosis of acute coronary syndrome was confirmed using the discharge codes of the *International Classification of Diseases*. Exclusion criteria were age <18 years, missing cases in the relevant variables, and elective admissions (**Figure 5**).

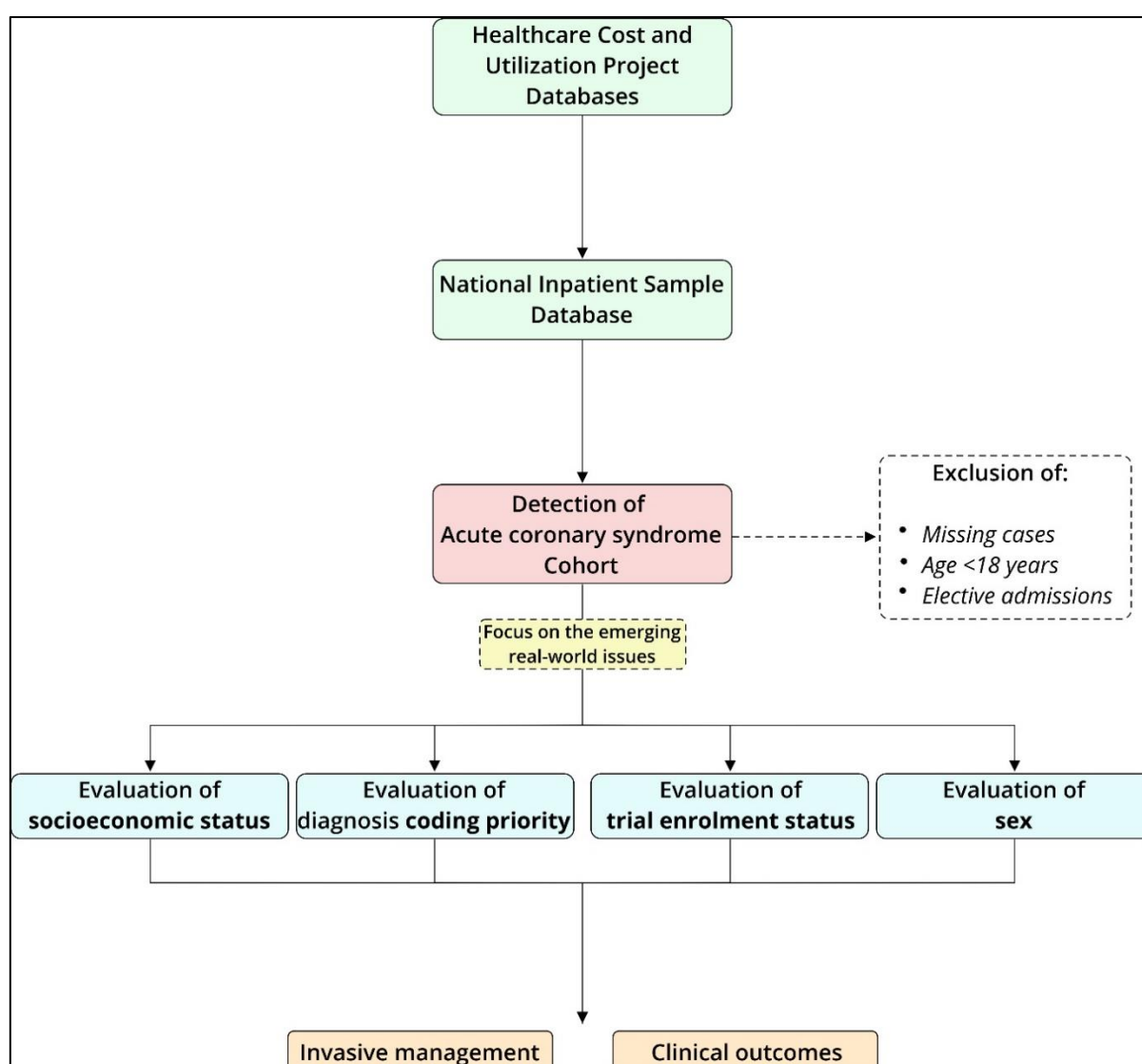


Figure 5. Flow diagram of the research studies

5.3. Database

The *National Inpatient Sample* was developed by the *Agency for Healthcare Research and Quality*, under the *Healthcare Cost and Utilization Project*. It is the largest all-payer longitudinal database of hospital inpatient discharges in the US containing anonymized discharge-level data from >7 million hospitalizations annually. It represents a 20% stratified sample of the community hospitals in United States, excluding rehabilitation and long-term acute care hospitals, and provides sampling weights to calculate national estimates representing more than 95% of the hospitalized population in United States (46).

5.4. Ethical principles

The research studies from the *National Inpatient Sample* database are exempt from institutional review board or ethics committee because all data are publicly available, de-identified and anonymised, and approved by the *Agency for Healthcare Research and Quality* for research purposes. The applicant/analyst undertook the data user training and gained the certificate prior to the study initiation as requested by the *Agency for Healthcare Research and Quality* (https://www.hcup-us.ahrq.gov/tech_assist/dua.jsp). This training emphasizes the importance of data protection, reduces the risk of inadvertent violations, and describes the individual responsibility when using the data from the *Healthcare Cost and Utilization Project*.

5.5. Outcomes of the research studies

Primary outcomes of the research studies were:

1. Invasive management in the form of coronary angiography and percutaneous coronary intervention.
2. In-hospital clinical outcomes in the form of all-cause mortality, major adverse cardiovascular and cerebrovascular events (composite of all-cause mortality, acute ischemic stroke, and cardiac complications [hemopericardium, cardiac tamponade, coronary dissection and any pericardiocentesis procedure]), acute ischemic stroke, and major bleeding.

Secondary outcomes of the research studies were:

1. Comparison of patient characteristics.
2. Comparison of patient comorbidities.
3. Comparison of healthcare utilization (hospitalization charges, length of stay).

5.6. Statistical analysis

The *Statistical Package for the Social Sciences* (SPSS) (IBM Corp, Armonk, New York; version 25) and *Stata MultiProcessor* (StataCorp, College Station, Texas, United States; version 17.0) were used for statistical analysis. Different statistical graphs were created using the corresponding statistical software, while the other graphical illustrations were prepared using the *Gravit Designer PRO* (Gravit GmbH, Berlin, Germany; version 2022.i1.1).

Data were summarized using medians (interquartile range) for continuous non-parametric data and as counts (percentages) for categorical data. Quantitative data were analysed with Mann–Whitney U tests, and categorical data with Chi-squared tests.

The research studies utilized complex adjustment models to account for the different confounding variables. One method used binomial multivariable logistic regression analysis to estimate the adjusted odds ratios (aOR) and 95% confidence interval (95% CI) of the outcomes across the studied groups. Multivariable models were adjusted for different hospital- and patient-level variables that are relevant to the outcomes. Other method utilized propensity-score matching (PSM) with the *teffects psmatch* command in Stata (logistic treatment model), which estimates the average treatment effects (ATEs) by taking the average of the difference between the observed and potential outcomes for each subject. Percentage changes ($\Delta\%$) were derived from ATEs, by multiplying ATEs with 100, to assist with interpretation of data. A detailed lists of variables used in the multivariable models and propensity matching are available in the research studies. Finally, trend analysis with a Mantel-Haenszel extension of the chi-square test of trend (linear-by-linear association) used to establish trends of invasive management over the study period.

All analyses were conducted with appropriate sampling weights provided by the *Agency for Healthcare Research and Quality* for each individual discharge. Statistical significance was defined at a level of $p < 0.05$. All the research studies were reported according to the *STrengthening the Reporting of OBservational studies in Epidemiology* (STROBE) guidelines (47).

6. SCIENTIFIC CONTRIBUTION OF THE CONSOLIDATED RESEARCH STUDIES

This doctoral dissertation is based on the published research studies about the contemporary management and outcomes of patients with acute coronary syndrome, based on their socioeconomic status, diagnostic coding priority, trial recruitment and sex (48-51). The management and prognosis of patients with acute coronary syndrome has substantially improved in the last decades, but whether this applies to all patient subgroups and whether there are discrepancies by socioeconomic factors, diagnostic coding priority, trial recruitment and sex, was not well defined. With the growing needs of this population, abovementioned novel challenges represent a particularly important consideration in their management and care.

The present doctoral thesis includes a big data analysis of ~11 million discharge records with the diagnosis of acute coronary syndrome, making it by far the largest to examine the management strategies and in-hospital clinical outcomes according to socioeconomic status, diagnostic coding priorities, trial recruitment status and sex. The provided data expand over a substantial 12-year period allowing for insights into the trends and temporal changes. This doctoral dissertation is supported by its reliance on the sufficiently powered registry data, that provide an excellent insight in the real-world contemporary state. It is strengthened by detailed literature review and international collaboration with experts in the field. The results show a substantial discrepancy in the management and clinical outcomes of acute coronary syndrome patients, warranting further incentives to equalize the quality of care and prognosis across the wide spectrum of this patient population.

To the best of our knowledge, existing literature was lacking an adequate, contemporary, and powered data on this topic, magnifying the gaps in evidence and preventing the clinicians to implement measures for disparity reduction in this high-risk population. Therefore, the scientific novelty of this work is clear, while the scientific and clinical contributions of the published studies within this doctoral dissertation are numerous. Powered analyses from large national registries provide real-world data that could guide healthcare reforms to equalize the patient care and diminish disparities. This could contribute to more equitable outcomes in patients with acute coronary syndrome irrespective of the population differences in monthly income, discharge coding, trial recruitment or sex. Increased awareness for specific patient groups could reduce the physicians' bias and improve the patient care. Furthermore, different initiatives and continued public health measures could aid screening and prevention, leading to improved outcomes in these patient groups. The findings from this doctoral dissertation also

promote different healthcare measures leading to sustainable development and improved quality of care. Additionally, future studies are encouraged in the studies from this doctoral dissertation outlining its hypothesis-generating purposes.

7. APPLICABILITY OF RESEARCH DATA TO THE REPUBLIC OF CROATIA

The generalizability of the present research findings is particularly important (48-51). However, the complexity of subject matter necessitates a thorough understanding of its multi-dimensional aspects prior to any wider application. Different determinants should be considered when translating these results to the cardiovascular field in the Republic of Croatia.

7.1. Population differences

It is important to consider the population differences and trends between the Republic of Croatia and United States of America. The data presented mostly reflect a year 2018 with the aim of easier comparison and its relevance to the research period. Overall, there are potential differences between the populations which could include a different risk profile, comorbidity burden, environmental factors, dietary factors, and others.

According to the data of the *Croatian Bureau of Statistics*, the average age of the Croatian population was 43.4 years (41.5 and 45.0 years in men and women, respectively) with the life expectancy of 78.2 years (74.9 and 81.4 years in men and women, respectively). There was a slightly higher proportion of women in the overall population (51.7%) (52). According to the data of the *Croatian health statistics yearbook* for 2018, cardiovascular diseases were the leading cause of mortality in the Republic of Croatia (mortality rate of 563.8/100,000) and leading cause of hospital admissions. The Croatian population shows a trend of progressive ageing with 20.4% of inhabitants being older than 65 years (53). The population of United States of America exhibited average age of 38.2 years, with the life expectancy of 78.6 years (54). Therefore, the Croatian population follows the global trends of increased ageing, which is more pronounced than in the United States, with the maintenance of cardiovascular diseases as the leading cause of mortality.

The abovementioned data are population estimate of the Republic of Croatia by the of the *Croatian Bureau of Statistics*: Census of Population, Households and Dwellings, birth statistics, death statistics, statistics of the internal migration of population, statistics of the international migration of population. The reported population estimates were based on the 2011 Census, natural change and net migration data (52). The *Croatian health statistics yearbook* is based on the data representative of the comprehensive national health system (53).

When looking at the comorbidities and risk factors, it is evident that the prevalence of obesity (22.6% vs. 41.9%, respectively), diabetes mellitus (6.1.% vs. 11.3%) and arterial

hypertension (37.5% vs. 47.0%) is lower in the population of Republic of Croatia compared to United States (53, 55-58). However, the adherence to dietary and lifestyle measures have been increasingly deteriorated in the Republic of Croatia, irrespectively of its Mediterranean position, which could diminish the comorbidity differences in the future (59). Therefore, Croatia represents a country with high cardiovascular risk in the recent European prevention guidelines, which is contrary to most other Mediterranean countries (60).

Although it is out of the scope of this dissertation, these condensed highlights indicate that there are potential population differences which should be accounted for. Nevertheless, the present doctoral dissertation and published research studies reported results that are adjusted for age, comorbidities, and other important confounders, thereby allowing for impact reduction and increase of data applicability.

7.2. Specificities of healthcare system

There are important bidirectional differences in the healthcare system between the Republic of Croatia and United States. First, healthcare in the Republic of Croatia represents a universal healthcare system which is contrary to the non-universal healthcare system in United States. This indicates a potentially substantial differences in the access to healthcare between the countries. Second, there is distinction in the economic power of the countries which is closely related to the healthcare development. For example, macroeconomic determinants depict a much lower gross domestic product per capita (12,704 Euros vs. 57.379 Euros) in the Republic of Croatia compared to United States (52). Third, healthcare system in United States utilizes a substantial expenditure which aggravates direct comparison to the Republic of Croatia. Specifically, the total health expenditure as a share of gross domestic product in 2020 was 7.8% in the Republic of Croatia, which is hardly comparable to United States (19.7% of gross domestic product) (52). Finally, the organization of the healthcare providers and resources is important to achieve wide accessibility. The healthcare system in the Republic of Croatia showed a better availability with 272 inhabitants per one medical doctor, which is superior to the United States (385 inhabitants per one medical doctor) (52, 61). Importantly, the infant mortality as a relevant indicator of quality of healthcare was similar in the Republic of Croatia and United States (4.2 vs. 5.7/1,000 live births, respectively) (52).

7.3. Organization of interventional network for the management of acute coronary syndrome

The access to healthcare is also reflected by the availability of centres for primary percutaneous coronary interventions. The Republic of Croatia has well-developed national network of the centres that contribute to the management of patients with acute coronary syndrome providing a non-stop access (62) (**Figure 6**).

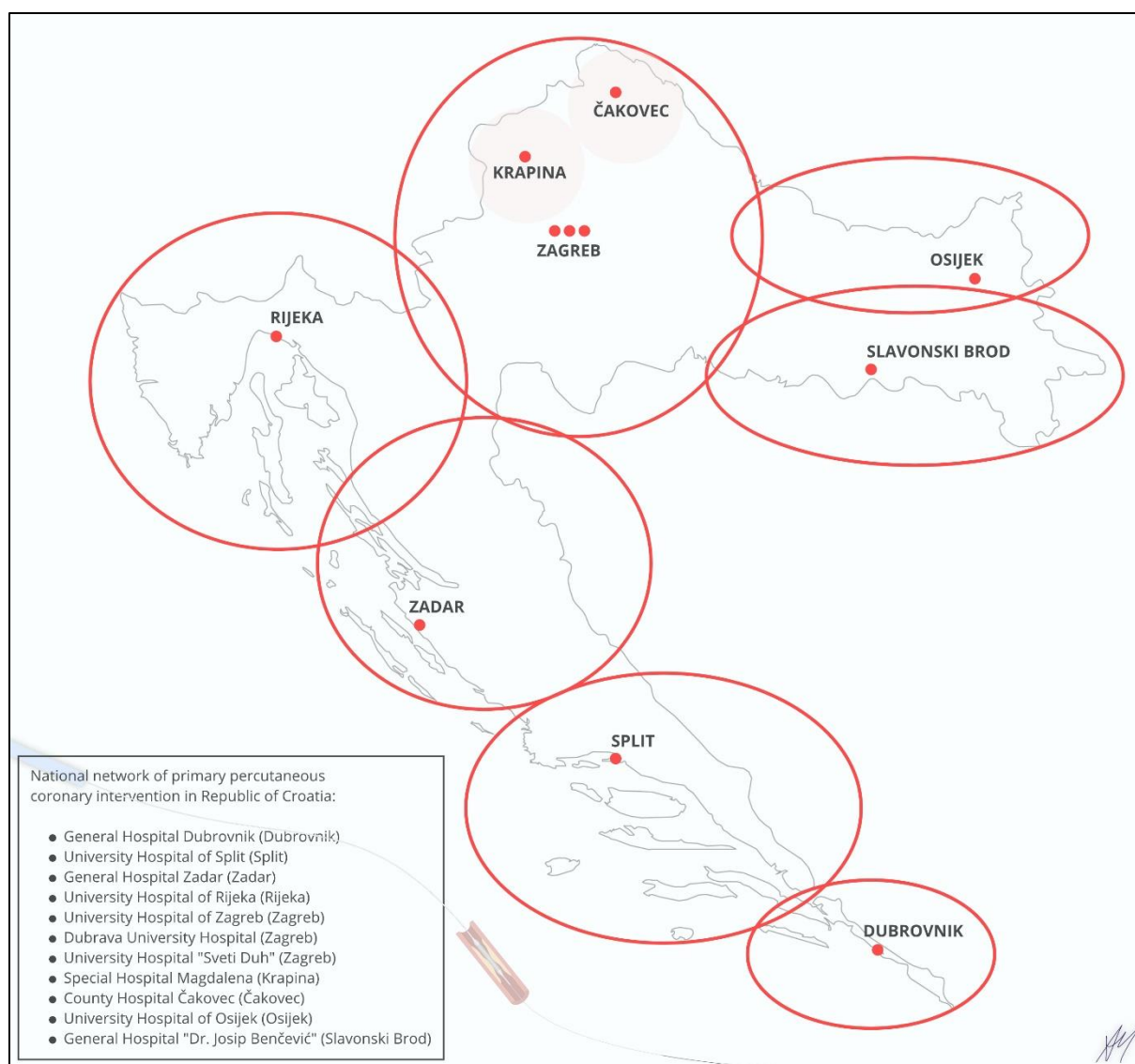


Figure 6. National network of primary percutaneous coronary intervention in the Republic of Croatia (original author's work)

Due to geographical specificities, it is hard to directly compare the access to primary percutaneous coronary interventions centres between these countries. For example, the Republic of Croatia contains multiple islands which is highly demanding for the healthcare

organization (62). Access to primary percutaneous coronary interventions centres is therefore dependent on the location and meteorologic conditions (availability of helicopter service), despite the staff organization and resource coverage. Similarly, the United States includes the different rural areas which exhibit worse access to primary percutaneous coronary interventions centres, and this was associated with impaired outcomes (63, 64).

7.4. Social deprivation and socioeconomic status

As elaborated previously, there are important differences in the economic power of the Republic of Croatia and United States. This is related to the healthcare system, but also to the economic status of the inhabitants. An average monthly net earnings per person in 2018 were 828 Euros (883 and 768 Euros in men and women, respectively) in the Republic of Croatia (52) which is substantially lower than in the United States. Although this does not provide direct insights into the social deprivation, it could be an indirect measure of the access to healthcare system.

When analysing the indicators of poverty and social exclusion in Republic of Croatia, there were 24.8% of people at risk of poverty or social exclusion, 8.6% of people severely materially deprived (lacking 4 or more necessary items), and 11.2% of people living in households with very low work intensity. Importantly, there were 7.7% of households with inability to keep home adequately warm during the coldest months. Overall Gini coefficient was 29.7 and income quintile share ratio was 5.0 (52). Although these facts are worrisome for the Republic of Croatia, the Gini index for the United States was 41.1 that even indicates a higher discrepancies in the socioeconomic status within the population (65). Therefore, it is possible that the observed differences across the income groups could be less obvious in populations with lower baseline variation in the socioeconomic status. Nevertheless, the direction of the association between the socioeconomic class and outcomes could be translated into various populations, despite potentially having different expression and effect size.

7.9. Final thoughts

Detailed understanding of multi-dimensional aspects of this complex topic is vital to ensure an adequate translation of this research data to cardiovascular field in other healthcare systems. In the context of the Republic of Croatia, the present big data analyses offer a potentially valuable contribution that could guide further focused interventions to improve the quality of care and outcomes of regional population with acute coronary syndrome.

8. LIMITATIONS

There are several limitations of this research project. The limitations could be categorized according to the underlying mechanisms, into database-related, study design-related and healthcare system-related limitations.

First, the research studies were prone to inherent limitations of the *National Inpatient Sample* database, including the potential for coding inaccuracies (mis-coding or under-coding), uncertain timing of events, and incomplete data granularity (clinical factors, coronary anatomy, procedure timing, medications, laboratory parameters, etc.). Furthermore, it is a hospitalization-based registry which does not recognize recurrent hospitalizations and captures only in-hospital events. There is no reported data on the specific cause of mortality, but rather all-cause mortality. The analysis does not account for multiple dimensions of socioeconomic determinants (education level, employment status, etc.).

Second, several limitations are justified by the study design. This includes a potential for selection bias. Also, it was not possible to fully eliminate a residual confounding bias, although this research project utilized complex adjustment analytical methods. Additionally, some findings in the research project could be influenced by an observation bias ('Hawthorne effect'). Lastly, there was no formal adjudication of captured events.

Finally, the specificity of healthcare system in United States could affect applicability and generalizability of these findings to other systems that provide 'universal healthcare' model.

9. MAIN CONCLUSIONS

This doctoral dissertation and consolidated research studies derived several essential conclusions.

First, there was an important disparity in the management and outcomes of patients with acute coronary syndrome based on their socioeconomic status, so that patients with low socioeconomic status received less invasive management and had worse in-hospital prognosis, including higher mortality, major adverse cardiovascular and cerebrovascular events, and ischemic stroke. Importantly, these findings were consistent even after the adjustment for the worse risk profile of patients with lower socioeconomic status.

Second, a substantial disparity was shown regarding the diagnostic coding priority of acute coronary syndrome, so that patients with secondary-coded acute coronary syndrome were less likely to receive invasive management and more likely to experience in-hospital adverse events. This is important as about one-third of all hospitalizations for acute coronary syndrome are not coded as a principal diagnosis.

Third, the management and outcomes of patients with acute coronary syndrome significantly differed according to their trial recruitment status, with a higher utilization of invasive management and better in-hospital outcomes in patients who were enrolled in a clinical trial.

Fourth, there were persistent sex-based differences in the management and outcomes of patients with acute coronary syndrome. Female patients were less likely to receive invasive therapies and more likely to experience adverse outcomes including mortality, major bleeding, and stroke. Importantly, this gap has narrowed over the study period.

These findings underscore the importance of a continued multilevel, collaborative approach with improved access to healthcare, particularly in low socioeconomic areas and special population. There should be an increased awareness for observed sex-based disparities, to eliminate any discrimination as soon as possible. Hospital systems should be alarmed to properly code all admission for acute coronary syndrome, while future data analyses should consider the diagnosis of acute coronary syndrome from all diagnostic fields, to accurately inform clinical decision-making and health planning. Finally, it is important to consider population differences during trial planning and recruitment, with the aim of wider inclusion criteria, adequate representation of understudied patient groups, reduction of bias by

implementing machine-based learning models, modifications of study designs (encouragement of pragmatic clinical trials) and improved data reporting. Nevertheless, the extrapolation of these findings to other healthcare systems should be done with caution.

10. TRANSCRIPTS OF THE PUBLISHED RESEARCH STUDIES

This doctoral dissertation is based on the 4 published research studies (48-51):

1. Matetic A, Bharadwaj A, Mohamed MO, Chugh Y, Chugh S, Minissian M, Amin A, Van Spall H, Fischman DL, Savage M, Volgman AS, Mamas MA. Socioeconomic Status and Differences in the Management and Outcomes of 6.6 Million US Patients With Acute Myocardial Infarction. *Am J Cardiol.* 2020;129:10-18. doi: 10.1016/j.amjcard.2020.05.025.
2. Matetic A, Doolub G, Van Spall HGC, Alkhouli M, Quan H, Butalia S, Myint PK, Bagur R, Pana TA, Mohamed MO, Mamas MA. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.
3. Matetic A, Mohamed MO, Roberts DJ, Rana JS, Alraies MC, Patel B, Sauer AJ, Diaz-Arocutipa C, Sattar Y, Van Spall HGC, Mamas MA. Real-world management and outcomes of 7 million patients with acute coronary syndrome according to clinical research trial enrollment status: A propensity matched analysis. *Eur Heart J Qual Care Clin Outcomes.* 2021:qcab098. doi: 10.1093/ehjqcco/qcab098.
4. Matetic A, Shamkhani W, Rashid M, Santos Volgman A, Van Spall HGC, Coutinho T, Mehta SL, Sharma G, Parwani P, Mohamed MO, Mamas MA. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. *CJC Open.* 2021;3(12 Suppl):S19-S27. doi: 10.1016/j.cjco.2021.06.012.

11.1. Research study 1

Socioeconomic Status and Differences in the Management and Outcomes of 6.6 Million US Patients With Acute Myocardial Infarction



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Little is known about the impact of socioeconomic status (SES) on management strategies and in-hospital clinical outcomes in patients with acute myocardial infarction (AMI) and its subtypes, and whether these trends have changed over time. All AMI hospitalizations from the National Inpatient Sample (2004 to 2014) were analyzed and stratified by zip code-based median household income (MHI) into 4 quartiles (poorest to wealthiest): 0th to 25th, 26th to 50th, 51st to 75th, and 76th to 100th. Logistic regression was performed to examine the association between MHI and AMI management strategy and in-hospital clinical outcomes. A total of 6,603,709 AMI hospitalizations were analyzed. Patients in the lowest MHI group had more co-morbidities, a worse cardiovascular risk factor profile and were more likely to be female. Differences in receipt of invasive management were observed between the lowest and highest MHI quartiles, with the lowest MHI group less likely to undergo coronary angiography (63.4% vs 64.3%, $p < 0.001$) and percutaneous coronary intervention (40.4% vs 44.3%, $p < 0.001$) compared with the highest MHI group, especially in the STEMI subgroup. In multivariable analysis, the highest MHI group experienced better outcomes including lower risk (adjusted odds ratio; 95% confidence intervals) of mortality (0.88; 0.88 to 0.89), MACCE (0.91; 0.91 to 0.92) and acute ischemic stroke (0.90; 0.88 to 0.91), but higher all-cause bleeding (1.08; 1.06 to 1.09) in comparison to the lowest MHI group. In conclusion, the provision of invasive management for AMI in patients with lower SES is less than patients with higher SES and is associated with worse in-hospital clinical outcomes. This work highlights the importance of ensuring equity of access and care across all strata SES. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;129:10–18)

Lower socioeconomic status (SES) has been previously linked to higher prevalence of traditional cardiovascular risk factors,¹ increased burden of coronary artery disease² and higher mortality.³ Of the individual components of SES, median household income (MHI) has been shown to be a surrogate of SES for the purpose of health research.^{4,5} Although previous studies have evaluated the relationship between SES and management strategy or in-hospital

outcomes in the context of acute myocardial infarction (AMI), the findings have been subject to limitations such as the inclusion of specific cohorts (e.g., ST-segment elevation myocardial infarction (STEMI) only or elderly patients),^{6–8} or were limited to single center analyses.⁹ More importantly, there is a lack of temporal data of how disparities in management and outcomes of AMI attributable to SES have changed over time. In this study we sought to evaluate the association of SES, as measured by MHI, on receipt of invasive management and subsequent in-hospital clinical outcomes in a nationwide cohort of AMI hospitalizations in the United States over an 11-year period.

Methods

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the US and is sponsored by the Agency for Healthcare Research and Quality (AHRQ).¹⁰ It includes anonymized data on discharge diagnoses and procedures from >7 million hospitalizations annually. The NIS dataset was designed to approximate a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent >95% of the US population.

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All nonelective hospitalizations of adults (≥ 18 years) discharged between 2004 and 2014 with a principal diagnosis of AMI (STEMI and non-STEMI [NSTEMI]) were extracted from the NIS using the International Classification of Diseases, Ninth revision and Clinical Classification Software codes (Supplementary Table S1). Additional co-morbidities were identified using AHRQ-Elixhauser co-morbidity measures. Charlson Comorbidity Index was extracted using the variables according to the Deyo modification of the score as previously described.¹¹ Patient characteristics and in-hospital clinical outcomes were stratified according to MHI quartiles in 4 groups: 0th to 25th, 26th to 50th, 51st to 75th, and 76th to 100th, indicating the poorest to the wealthiest groups, respectively (Supplementary Table S2). Missing records for length of stay and total charges were excluded from further analysis (Supplementary Figure S1).

We analyzed the database for receipt of in-hospital invasive management (coronary angiography, percutaneous coronary intervention (PCI) and coronary artery bypass grafting [CABG]) for AMI between different incomes groups. Subsequent in-hospital clinical outcomes including major acute cardiovascular and cerebrovascular events (MACCE), mortality, cardiac complications, and acute stroke were assessed for differences among income groups. MACCE was defined as a composite of mortality, acute stroke/transient ischemic attack and cardiac complications. Cardiac complications included hemopericardium, cardiac tamponade, coronary dissection, and any pericardiocentesis procedure.

Statistical Package for the Social Sciences statistical software (IBM Corp, Armonk, New York; version 25) was used for statistical data analysis. We assessed the normality of data distribution graphically and by the Kolmogorov-Smirnov test. Data were expressed as median (interquartile range) for continuous variables and as whole numbers (percentages) for categorical variables. Mann-Whitney *U* test and Kruskal-Wallis test have been used for comparison of quantitative nonparametric variables between the study groups. The Chi-square test was used for the comparison of categorical variables between the different groups according to MHI.

Multivariable logistic regression analysis was used to determine the adjusted odds ratios (aOR [95% confidence interval]) of in-hospital adverse outcomes and the likelihood of an invasive management strategy, according to the different MHI groups in comparison to patients with the MHI in the lowest (0th to 25th) quartile as a reference. Separate models for in-hospital clinical outcomes and invasive management were conducted. Regression models for in-hospital clinical outcomes included PCI as a predictor variable. As well, the following variables were adjusted for in regression analysis: age, sex, weekend admission, dyslipidemia, smoking, previous AMI, previous CABG, history of ischemic heart disease, previous PCI, previous cerebrovascular accident, family history of coronary artery disease, shock during hospitalization, hospital bed size, hospital region, location/teaching status of hospital, year of hospitalization and 27 AHRQ co-morbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anemias, chronic blood loss anemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver

disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, pulmonary circulation disorders, renal failure, solid tumor without metastasis, peptic ulcer disease excluding bleeding, valvular heart disease and weight loss). Using a Bonferroni's correction method, threshold of significance for the regression model has been set to $p < 0.001$. A trend analysis with a Mantel-Haenszel test of trend (linear-by-linear association) was conducted in order to establish important changes in in-hospital outcomes and receipt of invasive management over the 11-year time period. Statistical significance was defined at a level of $p < 0.05$.

Results

A total of 6,603,709 hospitalizations for AMI were included in the analysis. The distribution of patients according to MHI quartile was as follows: 0th to 25th: 28.5% ($N = 1,884,699$), 25th to 50th: 27.4% ($N = 1,806,775$), 51st to 75th: 23.7% ($N = 1,567,720$), and 76th to 100th: 20.4% ($N = 1,344,515$), indicating poorest to wealthiest, respectively (Table 1).

The median age range was similar across MHI groups (67 to 69 years), whereas in the lower MHI subgroups females comprised a higher percentage (42.0% to 37.4%, $p < 0.001$). STEMI prevalence ranged from 34.2% to 35.4% with the highest rates found in the third quartile MHI group (51st to 75th). An inverse relationship between MHI quartile and comorbidity burden was observed across the groups, as measured by Charlson Comorbidity Index score and overall comorbidity prevalence ($p < 0.001$). The lowest MHI group was more commonly treated in large hospitals than higher MHI quartiles (67.9% vs 65.7% vs 64.1% vs 62.4%, $p < 0.001$). Furthermore, only 1.1% of high MHI patients were treated in rural hospitals compared with 19.4% of lowest MHI group ($p < 0.001$; Table 1), and had significantly higher total charges of hospitalization (40,939 vs 41,208 vs 44,639 vs 47,676 USD, $p < 0.001$; Table 2).

The lowest MHI group was less likely to undergo coronary angiography (63.4% vs 64.3% to 65.7%, $p < 0.001$) and PCI (40.4% vs 42.7% to 44.8%, $p < 0.001$; Table 2, Figure 1). In contrast, the wealthiest group was less likely to undergo CABG (8.5% vs 8.9% to 9.1%, $p < 0.001$; Table 2). These differences persisted irrespective of the AMI subtype, except for the coronary angiography which was the least utilized in NSTEMI patients from the highest MHI group (57.8% vs 59.7% to 60.1%, $p < 0.001$).

After adjustment for baseline differences, the highest MHI group had greater odds of receipt of PCI (aOR 1.10 [1.10, 1.11]) in comparison to the lowest income group (Table 3), irrespective of the AMI subtype ($p < 0.001$; Table 4). On the other hand, odds of receipt of coronary angiography have been dependent on AMI subtype, showing lower odds in NSTEMI and higher odds in STEMI patients from the highest MHI group (Table 4).

The highest MHI subgroup experienced the lowest MACCE, mortality and acute stroke rates ($p < 0.001$). In contrast, all-cause bleeding and receipt of circulatory support (left-ventricle assist device and intra-aortic balloon pump) were more commonly observed in the highest MHI group. In sensitivity analysis, these differences decreased in

Table 1
Patient characteristics according to median household income (percentile)

Variables	0th-25th (n = 1884699)	26th-50th (n = 1806775)	51st-75th (n = 1567720)	76th-100th (n = 1344515)	p value
Age at admission (years), median (IQR)	67 (56, 78)	68 (57, 79)	68 (57, 79)	69 (57, 80)	<0.001
Women	42.0%	40.1%	38.8%	37.4%	<0.001
STEMI	34.2%	35.4%	35.5%	35.4%	<0.001
Charlson comorbidity index (CCI) score					<0.001
0	37.8%	40.5%	42.4%	45.9%	
1	38.4%	37.3%	36.3%	34.9%	
2	16.8%	15.7%	15.0%	13.5%	
≥3	7.0%	6.5%	6.3%	5.7%	
Dyslipidaemia	51.5%	54.1%	55.8%	56.3%	<0.001
Smoker	35.5%	35.2%	33.9%	30.4%	<0.001
Previous AMI	10.1%	10.1%	10.3%	10.3%	<0.001
Previous PCI	11.3%	11.4%	11.4%	11.5%	0.001
Previous CABG	7.6%	7.6%	7.4%	7.4%	<0.001
Previous CVA	4.0%	3.7%	3.7%	3.5%	<0.001
Atrial fibrillation	15.3%	16.4%	17.0%	17.9%	<0.001
History of IHD	75.5%	76.9%	77.7%	77.0%	<0.001
Family history of CAD	7.2%	7.6%	8.1%	8.5%	<0.001
Deficiency anemias	15.2%	14.1%	14.5%	14.4%	<0.001
Chronic blood loss anemia	1.1%	1.1%	1.1%	1.1%	0.018
Congestive heart failure	1.0%	0.9%	0.8%	0.8%	<0.001
Valvular disease	0.2%	0.3%	0.2%	0.3%	<0.001
Hypertension	67.7%	66.0%	65.9%	65.2%	<0.001
Cardiogenic shock	4.7%	4.8%	5.0%	5.1%	<0.001
Peripheral vascular disorders	11.0%	11.1%	10.8%	10.1%	<0.001
Pulmonary circulation disorders	0.1%	0.1%	0.1%	0.1%	0.001
Chronic pulmonary disease	23.2%	21.6%	19.6%	17.0%	<0.001
Coagulopathy	4.1%	4.1%	4.4%	4.6%	<0.001
Obesity	12.0%	11.9%	11.8%	10.3%	<0.001
Weight loss	2.4%	2.1%	2.1%	1.8%	<0.001
Diabetes, uncomplicated	30.8%	28.3%	27.1%	24.6%	<0.001
Diabetes with chronic complications	6.2%	5.9%	6.1%	5.7%	<0.001
Hypothyroidism	8.8%	9.7%	10.0%	10.1%	<0.001
Drug abuse	2.9%	1.8%	1.6%	1.2%	<0.001
Alcohol abuse	3.2%	2.8%	2.6%	2.3%	<0.001
AIDS	0.2%	0.1%	0.1%	0.1%	<0.001
Depression	6.3%	6.5%	6.3%	6.1%	<0.001
Peptic ulcer disease excluding bleeding	0.0%	0.0%	0.0%	0.0%	<0.001
Liver disease	1.3%	1.1%	1.1%	1.1%	<0.001
Renal failure	17.5%	16.3%	16.0%	15.6%	<0.001
Other neurological disorders	6.0%	5.7%	5.6%	5.7%	<0.001
Paralysis	1.8%	1.5%	1.6%	1.5%	<0.001
Psychoses	2.3%	2.0%	1.9%	1.7%	<0.001
Rheumatoid arthritis/collagen vascular diseases	2.0%	2.1%	2.2%	2.3%	<0.001
Solid tumor without metastasis	1.4%	1.4%	1.4%	1.5%	<0.001
Metastatic cancer	0.8%	0.8%	0.9%	1.0%	<0.001
Lymphoma	0.4%	0.5%	0.5%	0.6%	<0.001
Fluid and electrolyte disorders	19.7%	18.8%	19.0%	18.5%	<0.001
Weekend admission	26.1%	26.0%	25.9%	25.6%	<0.001
Admission type (Elective vs. Non-elective)					<0.001
Elective	8.1%	7.5%	6.3%	6.1%	
Non-elective	91.9%	92.5%	93.7%	93.9%	
Primary expected payer					<0.001
Medicare	59.1%	58.3%	56.2%	55.3%	
Medicaid	8.7%	5.9%	4.7%	3.2%	
Private Insurance	21.0%	26.4%	30.7%	35.4%	
Self-pay	7.5%	6.0%	5.2%	3.6%	
No charge	0.7%	0.6%	0.6%	0.3%	
Other	3.0%	2.8%	2.6%	2.1%	
Bed size of hospital					<0.001
Small	8.8%	11.0%	11.2%	11.0%	

(continued)

Table 1 (Continued)

Variables	0th-25th (n = 1884699)	26th-50th (n = 1806775)	51st-75th (n = 1567720)	76th-100th (n = 1344515)	p value
Medium	23.4%	23.3%	24.6%	26.6%	<0.001
Large	67.9%	65.7%	64.1%	62.4%	
Hospital region					
Northeast	12.4%	15.8%	20.7%	32.9%	
Midwest	19.2%	29.1%	26.2%	18.2%	
South	57.1%	40.0%	32.1%	24.7%	<0.001
West	11.3%	15.1%	21.1%	24.2%	
Location/teaching status of hospital					
Rural	19.4%	13.5%	4.4%	1.1%	
Urban nonteaching	34.2%	42.6%	46.7%	46.0%	
Urban teaching	46.4%	43.9%	48.9%	52.9%	

Notes: Dyslipidemia indicates disorders of lipid metabolism and was defined by code 53 of the Clinical Classification Software.

Abbreviations: AIDS = acquired immunodeficiency syndrome; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; CVA = cerebrovascular accidents; IHD = ischemic heart disease; IQR = interquartile range; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST-elevation myocardial infarction.

Table 2

Comparison of clinical outcomes and invasive management between the different Median Household Income groups

Variables	0th-25th (n = 1884699)	26th-50th (n = 1806775)	51st-75th (n = 1567720)	76th-100th (n = 1344515)	p value
Receipt of CA					
Total cohort	63.4%	64.6%	65.7%	64.3%	<0.001
NSTEMI	59.7%	60.1%	60.1%	57.8%	<0.001
STEMI	70.5%	72.7%	76.0%	76.3%	<0.001
Receipt of PCI					
Total cohort	40.4%	42.7%	44.8%	44.3%	<0.001
NSTEMI	31.3%	32.8%	33.8%	32.7%	<0.001
STEMI	58.0%	60.7%	64.8%	65.5%	<0.001
Receipt of CABG					
Total cohort	8.9%	9.1%	8.9%	8.5%	<0.001
NSTEMI	9.5%	9.7%	9.5%	9.2%	<0.001
STEMI	7.7%	7.9%	7.8%	7.4%	<0.001
Receipt of thrombolysis					
Total cohort	0.4%	0.4%	0.5%	0.6%	<0.001
NSTEMI	0.2%	0.2%	0.2%	0.3%	<0.001
STEMI	0.8%	0.8%	0.9%	1.1%	<0.001
Use of assist device or IABP					
Total cohort	4.5%	4.8%	5.1%	5.5%	<0.001
NSTEMI	2.7%	2.7%	2.8%	3.0%	<0.001
STEMI	8.1%	8.6%	9.2%	10.0%	<0.001
In-hospital MACCE					
Total cohort	8.1%	7.8%	7.7%	7.7%	<0.001
NSTEMI	6.3%	6.2%	6.2%	6.3%	<0.001
STEMI	11.4%	10.9%	10.5%	10.3%	<0.001
In-hospital mortality					
Total cohort	6.0%	5.9%	5.7%	5.7%	<0.001
NSTEMI	4.3%	4.2%	4.1%	4.2%	<0.001
STEMI	9.4%	9.0%	8.5%	8.3%	<0.001
In-hospital all-cause bleeding					
Total cohort	5.0%	5.2%	5.5%	5.7%	<0.001
NSTEMI	5.2%	5.4%	5.6%	5.6%	<0.001
STEMI	4.7%	4.9%	5.5%	5.7%	<0.001
In-hospital ischemic stroke					
Total cohort	1.8%	1.7%	1.7%	1.7%	<0.001
NSTEMI	1.9%	1.8%	1.8%	1.8%	<0.001
STEMI	1.7%	1.5%	1.5%	1.4%	<0.001
In-hospital cardiac complications					
Total cohort	0.6%	0.7%	0.7%	0.7%	<0.001
NSTEMI	0.4%	0.5%	0.5%	0.5%	<0.001

(continued)

Table 2 (Continued)

Variables	0th-25th (n = 1884699)	26th-50th (n = 1806775)	51st-75th (n = 1567720)	76th-100th (n = 1344515)	p value
STEMI	0.9%	1.0%	1.1%	1.1%	<0.001
Length of stay (days)					
Total cohort	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	<0.001
NSTEMI	4 (2, 7)	4 (2, 6)	3 (2, 6)	3 (2, 6)	<0.001
STEMI	3 (2, 6)	3 (2, 5)	3 (2, 5)	3 (2, 5)	<0.001
Total charges, US Dollars					
Total cohort	40939 (20912, 71953)	41208 (21118, 71665)	44639 (23940, 77011)	47676 (25146, 82276)	<0.001
NSTEMI	34732 (18047, 62686)	34362 (17743, 62163)	37417 (19740, 67221)	39895 (20494, 71637)	<0.001
STEMI	41298 (20812, 68627)	42798 (23486, 69763)	47265 (28323, 76956)	51545 (30615, 83956)	<0.001

Abbreviations: CA = coronary angiography; CABG = coronary artery bypass graft; IABP = intra-aortic balloon pump; MACCE = major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/ transient ischemic attack and cardiac complications); PCI = percutaneous coronary intervention.

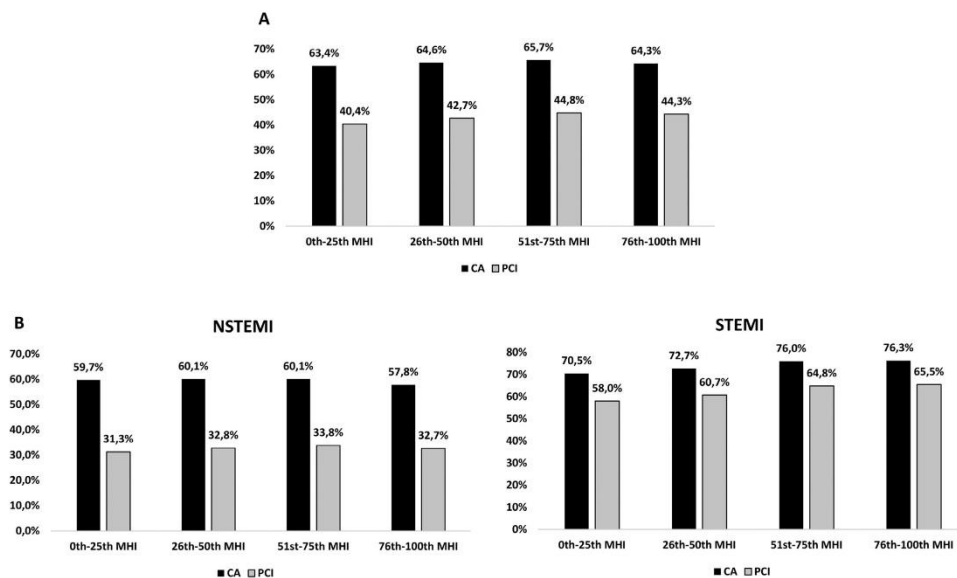


Figure 1. Receipt of CA and PCI according to the MHI: (A). In total cohort; (B). In AMI subtypes. CA = coronary angiography; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

Table 3

Adjusted odds of in-hospital treatments and outcomes according to the Median Household Income group in total cohort*

Outcome	26th-50th (n = 1806775)		51st-75th (n = 1567720)		76th-100th (n = 1344515)	
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
Treatments						
Receipt of CA	1.06 [1.06, 1.07]	<0.001	1.02 [1.02, 1.03]	<0.001	0.95 [0.95, 0.96]	<0.001
Receipt of PCI	1.09 [1.09, 1.10]	<0.001	1.14 [1.13, 1.14]	<0.001	1.10 [1.10, 1.11]	<0.001
Outcomes:						
MACCE	0.98 [0.97, 0.99]	<0.001	0.95 [0.95, 0.96]	<0.001	0.91 [0.91, 0.92]	<0.001
Mortality	0.97 [0.96, 0.98]	<0.001	0.94 [0.93, 0.95]	<0.001	0.88 [0.88, 0.89]	<0.001
Acute stroke/TIA	0.95 [0.93, 0.96]	<0.001	0.93 [0.92, 0.95]	<0.001	0.90 [0.88, 0.91]	<0.001
All-cause bleeding	1.04 [1.03, 1.05]	<0.001	1.06 [1.05, 1.07]	<0.001	1.08 [1.06, 1.09]	<0.001

* Reference group: 0th-25th (n=1884699) group.

Abbreviations: CA = coronary angiography; CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); OR = odds ratios; PCI = percutaneous coronary intervention; TIA = transitory ischemic attack.

Table 4
Adjusted odds of in-hospital outcomes according to the Median Household Income group in AMI subgroups*

Outcome	26th-50th (n = 1806775)		51st-75th (n = 1567720)		76th-100th (n = 1344515)	
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
Treatments						
Receipt of CA						
NSTEMI	1.05 [1.05, 1.06]	<0.001	0.99 [0.98, 0.99]	<0.001	0.91 [0.90, 0.91]	<0.001
STEMI	1.06 [1.05, 1.07]	<0.001	1.08 [1.07, 1.09]	<0.001	1.04 [1.03, 1.05]	<0.001
Receipt of PCI						
NSTEMI	1.08 [1.07, 1.09]	<0.001	1.09 [1.08, 1.10]	<0.001	1.04 [1.03, 1.05]	<0.001
STEMI	1.08 [1.07, 1.09]	<0.001	1.17 [1.16, 1.18]	<0.001	1.17 [1.16, 1.18]	<0.001
Outcomes						
MACCE						
NSTEMI	0.98 [0.97, 0.99]	<0.001	0.96 [0.95, 0.97]	<0.001	0.93 [0.92, 0.94]	<0.001
STEMI	0.98 [0.96, 0.99]	<0.001	0.95 [0.94, 0.97]	<0.001	0.90 [0.89, 0.91]	<0.001
Mortality						
NSTEMI	0.97 [0.96, 0.98]	<0.001	0.94 [0.92, 0.95]	<0.001	0.90 [0.88, 0.91]	<0.001
STEMI	0.97 [0.95, 0.98]	<0.001	0.94 [0.93, 0.96]	<0.001	0.88 [0.87, 0.89]	<0.001
Acute stroke/TIA						
NSTEMI	0.95 [0.93, 0.97]	<0.001	0.93 [0.91, 0.95]	<0.001	0.90 [0.88, 0.92]	<0.001
STEMI	0.95 [0.92, 0.98]	0.001	0.96 [0.93, 0.99]	0.006	0.90 [0.87, 0.93]	<0.001
All-cause bleeding						
NSTEMI	1.05 [1.04, 1.06]	<0.001	1.05 [1.04, 1.06]	<0.001	1.07 [1.05, 1.08]	<0.001
STEMI	1.02 [1.00, 1.03]	0.043	1.09 [1.07, 1.11]	<0.001	1.11 [1.09, 1.13]	<0.001

* Reference group: 0th-25th (n=1884699) group.

Abbreviations: AMI = acute myocardial infarction; CA = coronary angiography; CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); NSTEMI = non-ST-elevation myocardial infarction; OR = odds ratios; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = transitory ischemic attack.

the NSTEMI subgroup for the MACCE outcome, but remained in other outcomes irrespective of the AMI subtype. Differences were generally more pronounced in the STEMI subgroup (Table 2).

The findings persisted in multivariable analysis, in which the highest MHI group had the lowest odds of MACCE (aOR 0.91 [0.91, 0.92]), mortality (aOR 0.88 [0.88, 0.89]) and acute stroke/transient ischemic attack (aOR 0.90 [0.88, 0.91]; Table 3). This pattern was found in both STEMI and NSTEMI subgroups (Table 4).

Overall receipt of coronary angiography or PCI steadily increased over the years, irrespective of MHI (Table 5). Graphical analysis of adjusted odds for invasive management has shown a constant pattern of MHI-related disparity in coronary angiography and PCI receipt, but recent years suggest alleviation of such inequalities. This tendency has been observed for PCI in both AMI subgroups, while receipt of coronary angiography has shown a convergent trend only in STEMI patients (Figure 2, Supplementary Tables S3 to S5). Likewise, outcome inequalities among different MHI groups exist but generally tended to decrease in recent years, except for mortality which maintains a divergent trend in both AMI subgroups (Figure 3, Supplementary Tables S3 to S5). Trend analysis revealed a significant decrease in all adverse outcomes across the years, except all-cause bleeding which showed a steady increase, in all MHI groups (Table 5).

Discussion

The present study of >6.5 million hospitalizations is by far the largest to examine the trends of management

strategies and in-hospital clinical outcomes of AMI according to SES over an 11-year period. Several key findings can be noted. First, we show that SES is associated with comorbidity burden, with a lower overall co-morbidity burden found in the higher SES groups. Second, we observe a direct relationship between SES and invasive management, with higher SES patients more likely to receive coronary angiography and PCI. Patients with higher SES had better outcomes, including MACCE, mortality and acute stroke, but not bleeding. Notwithstanding, these inequalities have considerably improved over the study period, although not fully resolved.

Our analysis reveals that AMI patients with low SES generally have more co-morbidities compared with their high SES counterparts, consistent with previous reports.^{6,7,12-14} Whilst significant differences among AMI patients based on SES in terms of management and outcomes were observed, these substantially lessened over time. An improvement in mortality with an increase in bleeding rates was observed in all MHI groups over the study period. These trends could partly be attributable to higher overall use of invasive management, but other factors like potent antithrombotic therapy could presumably also affect bleeding rates.¹⁵ Previous studies that have evaluated the impact of SES on outcomes of AMI are smaller,¹⁶ included only STEMI patients⁷ or elderly patients⁸ or occurred in healthcare settings outside of the US.^{6,12} Yong et al evaluated acute coronary syndrome patients (N = 835,070) and found that low SES patients were least likely to get timely revascularization and DES.¹⁶ Agarwal et al analyzed NIS data of STEMI patients (2003 to 2011) reporting that lower SES patients had decreased timely reperfusion and increased in-hospital mortality.⁷ Rao et al

Table 5
Trend of in-hospital outcomes and invasive management from 2004 to 2014

Outcome/Year	2004-2006	2007-2009	2010-2012	2013-2014	p value (for trend)
MACCE					
0th-25th MHI	9.0%	8.2%	7.5%	7.1%	<0.001
26th-50th MHI	8.6%	8.2%	7.2%	7.1%	<0.001
51st-75th MHI	8.4%	8.1%	7.1%	7.0%	<0.001
76th-100th MHI	8.3%	7.8%	7.2%	7.1%	<0.001
Mortality					
0th-25th MHI	7.1%	6.1%	5.5%	5.1%	<0.001
26th-50th MHI	6.8%	6.0%	5.2%	4.9%	<0.001
51st-75th MHI	6.5%	5.9%	5.1%	4.8%	<0.001
76th-100th MHI	6.5%	5.6%	5.2%	5.0%	<0.001
Acute stroke/TIA					
0th-25th MHI	2.0%	1.9%	1.7%	1.6%	<0.001
26th-50th MHI	1.7%	1.8%	1.5%	1.7%	<0.001
51st-75th MHI	1.8%	1.8%	1.5%	1.6%	<0.001
76th-100th MHI	1.7%	1.7%	1.6%	1.6%	<0.001
Cardiac complications					
0th-25th MHI	0.4%	0.7%	0.7%	0.7%	<0.001
26th-50th MHI	0.5%	0.7%	0.8%	0.8%	<0.001
51st-75th MHI	0.5%	0.8%	0.8%	0.9%	<0.001
76th-100th MHI	0.5%	0.8%	0.8%	0.9%	<0.001
All-cause bleeding					
0th-25th MHI	3.9%	4.8%	5.7%	6.1%	<0.001
26th-50th MHI	4.1%	5.0%	5.9%	6.4%	<0.001
51st-75th MHI	4.6%	5.4%	6.0%	6.7%	<0.001
76th-100th MHI	5.1%	5.7%	5.8%	6.5%	<0.001
CA					
0th-25th MHI	56.5%	62.2%	66.8%	70.7%	<0.001
26th-50th MHI	59.2%	64.0%	67.2%	70.5%	<0.001
51st-75th MHI	61.4%	64.8%	68.2%	70.7%	<0.001
76th-100th MHI	61.1%	63.2%	66.5%	69.0%	<0.001
PCI					
0th-25th MHI	34.6%	39.6%	43.3%	46.2%	<0.001
26th-50th MHI	37.8%	42.1%	45.3%	47.9%	<0.001
51st-75th MHI	40.9%	44.2%	47.0%	49.1%	<0.001
76th-100th MHI	41.0%	43.7%	46.4%	48.4%	<0.001

Abbreviations: CA = coronary angiography; MACCE = major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient and cardiac complications); MHI = median household income; PCI = percutaneous coronary intervention; TIA = transitory ischemic attack.

evaluated elderly American Medicare beneficiaries in the angioplasty era concluding that there were significant disparities in management and outcomes based on SES.⁸ Interestingly, studies performed in countries offering universal healthcare systems have shown less disparity in delivery of healthcare based on SES.^{6,12,17} An Australian study of

STEMI patients (2005 to 2015) treated at 6 government funded hospitals (N = 5,665) reported that even though lower SES was associated with more co-morbidities and slightly longer reperfusion times, there was no difference in in-hospital and 1-year mortality and MACE (composite of death, AMI, and target vessel revascularization).⁶ However a Swiss

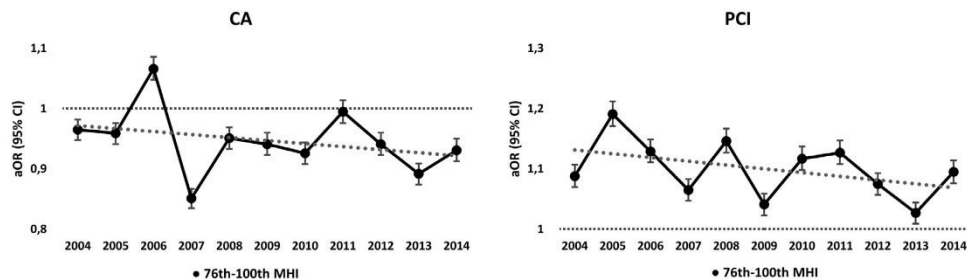


Figure 2. The trend of adjusted odds for invasive management according to the MHI from 2004 to 2014.

*Reference group: 0th-25th (n=1884699) group; $p < 0.001$ for all trends. CA = coronary angiography.

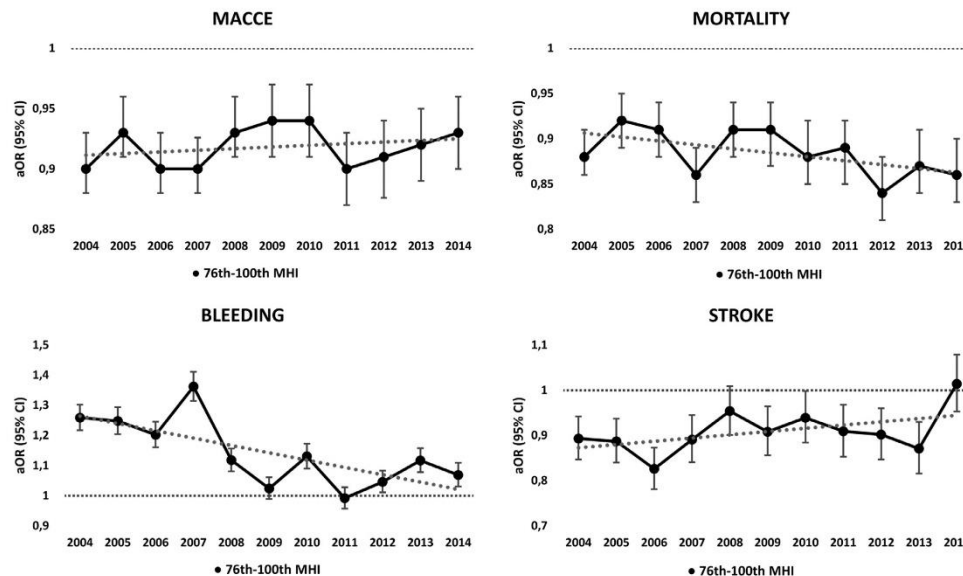


Figure 3. The trend of adjusted odds for different clinical outcomes according to the MHI from 2004 to 2014.

*Reference group: 0th-25th (n=1884699) group; $p < 0.001$ for all trends. MACCE = major adverse cardiovascular and cerebrovascular events.

study of 10,895 AMI patients (1995 to 2013) revealed that patients residing in low SES areas had worse outcomes with differences persisting even after adjusting for traditional risk factors.¹⁸

The reasons for lower adoption of evidence-based management and the poor outcomes among low SES AMI patients are complex and multifactorial. Lack of education and social awareness, poor access to transport and specialized care hospitals and lack of insurance places low SES patients at a disadvantage.⁵ Even when they do receive invasive therapy low SES patients with AMI have longer reperfusion times,⁷ and are less likely to receive DES¹⁶ and to be prescribed guideline directed medical therapy at follow-up.⁶

This is the largest study to date to analyze in-hospital outcomes of AMI patients based on SES from a national perspective. Our analysis emphasizes the importance of continued public health measures to aid screening and prevention in low SES groups. The World Health Organization's "25by25" initiative aims to reduce cardiovascular mortality by 25% by year 2025 irrespective of any socioeconomic, racial or gender-based differences.¹⁹ Universal health care, which will enable equal access to primary care services, has been recognized as a step towards sustainable development and diminishing inequalities.²⁰ In the absence of universal health care other measures such as the US Federal Government's Healthy People initiative are imperative. This initiative aims to provide data and tools to eliminate disparities in healthcare access and delivery based on sex, age, race, region, and SES. A 5-step framework for public health intervention called MAP-IT (mobilize, assess, plan, implement, and track) has been recommended as a path to the establishment of a healthy community.²¹ Additionally at a physician-level, outreach services to lower SES

communities, mass screening initiatives, and raising public awareness through media campaigns should be considered.

We acknowledge several limitations of our study, including the utilization of zip code based MHI as a surrogate for SES. Although we do not take into account other SES components such as education and employment as has been defined in expert documents,⁵ the sole utilization of zip code based income is a well-established method within healthcare systems.^{22,23} Secondly, some limitations like coding errors, hospitalization-based data, under-reporting of secondary diagnoses, and lack of formal adjudication of outcomes are inherent to the NIS database itself.¹³ The NIS also does not capture the exact cause of death, and long-term outcomes thereby limiting us to just in-hospital events. Finally, the NIS does not capture antithrombotic strategies or drug therapies that may confound our findings.

In conclusion, using zip-code based SES, patients with low SES have more cardiovascular and noncardiovascular co-morbidities than their high SES counterparts with low SES patients receiving less coronary angiography and PCI associated with higher in-hospital mortality, MACCE, and ischemic stroke, especially in the STEMI patients. Over an 11-year study period significant differences in terms of management and in-hospital clinical outcomes were observed which were largely mitigated towards the end of the study period (2013 to 2014). Our findings underscore the importance of a continued multilevel, collaborative approach with easy access to healthcare particularly in low SES zip codes.

Author Contribution

Andrija Matetic: Software, Data curation, Methodology, Formal analysis, Visualization, Writing - Reviewing and

Editing; Aditya Bharadwaj: Methodology, Writing - Original draft preparation, Writing - Reviewing and Editing, Validation; Mohamed Mohamed: Conceptualization, Methodology, Data curation, Formal analysis, Writing - Reviewing and Editing; Yashasvi Chugh: Validation, Writing - Reviewing and Editing; Sanjay Chugh: Validation, Writing - Reviewing and Editing; Margot Minissian: Validation, Writing - Reviewing and Editing; Amit Amin: Validation, Writing - Reviewing and Editing; Harriette Van Spall: Validation, Writing - Reviewing and Editing; David L. Fischman: Validation, Writing - Reviewing and Editing; Michael Savage: Validation, Writing - Reviewing and Editing; Annabelle Santos Volgman: Validation, Writing - Reviewing and Editing; Mamas A. Mamas: Supervision, Conceptualization, Methodology, Resources, Project administration, Validation, Writing - Reviewing and Editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2020.05.025>.

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Supplementary Table S1. ICD-9 and CCS search codes.

Variables	Source	Codes
Diagnoses		
STEMI	ICD-9	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x
NSTEMI	ICD-9	410.70, 410.71, 410.72
Dyslipidemia	CCS	53
Smoking Status	ICD-9	V15.82, 305.1
Atrial fibrillation	ICD-9	427.31
History of ischaemic heart disease	ICD-9	414.00-07, 414.2-9
Previous myocardial infarction	ICD-9	412
Previous primary coronary intervention	ICD-9	V45.82
Previous coronary artery bypass grafting	ICD-9	V45.81
Family history of coronary artery disease	ICD-9	V17.3
Previous CVA (TIA and Stroke)	ICD-9	V12.54
In-hospital procedures and outcomes		
Acute ischemic stroke	ICD-9	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0-1, 435.8-9, 436
Acute hemorrhagic stroke	ICD-9	431, 432.x, 430,
Bleeding requiring transfusion	ICD-9, CCS	998.11, 998.12, 285.1, 222
Shock during admission	ICD-9	785.51
Use of assist device or IABP	ICD-9	37.68, 37.61
Hemopericardium	ICD-9	423.0
Pericardiocentesis	ICD-9	37.0
Cardiac tamponade	ICD-9	423.3
Thrombolysis	CCS	46
Diagnostic cardiac catheterisation	CCS	47
Coronary artery bypass grafting	CCS	44
Primary coronary intervention	CCS	45

Abbreviations: ICD-9-CM International Classification of Diseases, Ninth Edition, Clinical Modification; CCS Clinical Classification Software.

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Supplementary Table S3. Annually adjusted odds of in-hospital outcomes according to the Median Household Income group in total cohort*.

Outcome	MHI group	Year										
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
		OR [95% CI] p-value										
Management:												
Receipt of CA	26 th -50 th	1.13 [1.11, 1.15] <0.001	1.02 [1.01, 1.04] 0.011	1.10 [1.09, 1.12] <0.001	1.04 [1.02, 1.06] <0.001	1.08 [1.06, 1.10] <0.001	1.14 [1.12, 1.16] <0.001	1.00 [0.99, 1.02] 0.728	1.06 [1.04, 1.08] <0.001	1.04 [1.02, 1.06] <0.001	1.02 [1.00, 1.04] 0.027	1.03 [1.01, 1.05] 0.001
	51 st -75 th	1.04 [1.03, 1.06] <0.001	1.00 [0.98, 1.02] 0.979	1.11 [1.09, 1.13] <0.001	0.98 [0.96, 0.99] 0.006	1.01 [0.99, 1.03] 0.446	1.02 [1.01, 1.04] 0.010	0.98 [0.96, 1.00] 0.011	1.08 [1.06, 1.10] <0.001	0.99 [0.97, 1.01] 0.231	1.00 [0.98, 1.02] 0.877	1.01 [0.99, 1.03] 0.386
	76 th -100 th	0.97 [0.95, 0.98] <0.001	0.96 [0.94, 0.98] <0.001	1.07 [1.05, 1.09] <0.001	0.85 [0.84, 0.87] <0.001	0.95 [0.93, 0.97] <0.001	0.94 [0.92, 0.96] <0.001	0.93 [0.91, 0.94] <0.001	1.00 [0.98, 1.01] 0.613	0.94 [0.92, 0.96] <0.001	0.89 [0.87, 0.91] <0.001	0.93 [0.91, 0.95] <0.001
	Receipt of PCI	26 th -50 th	1.12 [1.10, 1.13] <0.001	1.07 [1.05, 1.09] <0.001	1.13 [1.11, 1.15] <0.001	1.06 [1.04, 1.08] <0.001	1.09 [1.08, 1.11] <0.001	1.12 [1.10, 1.14] <0.001	1.07 [1.06, 1.09] <0.001	1.10 [1.09, 1.12] <0.001	1.07 [1.06, 1.09] <0.001	1.08 [1.06, 1.10] <0.001
51 st -75 th		1.14 [1.12, 1.16] <0.001	1.18 [1.16, 1.19] <0.001	1.19 [1.17, 1.21] <0.001	1.12 [1.10, 1.14] <0.001	1.14 [1.12, 1.16] <0.001	1.12 [1.10, 1.14] <0.001	1.14 [1.12, 1.16] <0.001	1.15 [1.13, 1.17] <0.001	1.08 [1.06, 1.10] <0.001	1.08 [1.06, 1.09] <0.001	1.14 [1.12, 1.16] <0.001
76 th -100 th		1.09 [1.07, 1.11] <0.001	1.19 [1.17, 1.21] <0.001	1.13 [1.11, 1.15] <0.001	1.07 [1.05, 1.08] <0.001	1.15 [1.13, 1.17] <0.001	1.04 [1.02, 1.06] <0.001	1.12 [1.10, 1.14] <0.001	1.13 [1.11, 1.15] <0.001	1.08 [1.06, 1.09] <0.001	1.03 [1.01, 1.04] 0.003	1.10 [1.08, 1.11] <0.001
Outcomes:												
MACCE	26 th -50 th	0.95 [0.92, 0.97] <0.001	1.00 [0.97, 1.02] 0.732	1.01 [0.98, 1.04] 0.529	1.00 [0.97, 1.03] 0.917	0.99 [0.96, 1.01] 0.371	1.02 [0.99, 1.04] 0.266	0.99 [0.97, 1.02] 0.605	0.94 [0.92, 0.97] <0.001	0.94 [0.91, 0.96] <0.001	0.99 [0.97, 1.03] 0.794	0.99 [0.96, 1.02] 0.458
	51 st -75 th	0.93 [0.91, 0.95] <0.001	0.97 [0.95, 0.99] 0.035	0.99 [0.96, 1.02] 0.391	1.02 [0.99, 1.05] 0.146	0.97 [0.94, 0.99] 0.025	0.98 [0.95, 1.01] 0.132	0.92 [0.89, 0.94] <0.001	0.95 [0.92, 0.97] <0.001	0.93 [0.90, 0.96] <0.001	0.92 [0.89, 0.95] <0.001	0.96 [0.93, 0.99] 0.012
	76 th -100 th	0.90 [0.88, 0.93] <0.001	0.93 [0.91, 0.96] <0.001	0.90 [0.88, 0.93] <0.001	0.90 [0.88, 0.93] <0.001	0.93 [0.91, 0.96] <0.001	0.94 [0.91, 0.97] <0.001	0.94 [0.91, 0.97] <0.001	0.90 [0.87, 0.93] <0.001	0.91 [0.88, 0.94] <0.001	0.92 [0.89, 0.95] <0.001	0.93 [0.90, 0.96] <0.001
	Mortality	26 th -50 th	0.95 [0.93, 0.98] <0.001	1.01 [0.99, 1.04] 0.363	1.02 [0.99, 1.05] 0.137	1.00 [0.97, 1.03] 0.815	0.97 [0.94, 0.99] 0.025	1.01 [0.98, 1.04] 0.603	0.97 [0.94, 1.01] 0.105	0.93 [0.90, 0.97] <0.001	0.92 [0.89, 0.95] <0.001	0.95 [0.92, 0.98] 0.002
51 st -75 th		0.92 [0.90, 0.95] <0.001	0.97 [0.94, 0.99] 0.036	0.99 [0.96, 1.03] 0.686	0.99 [0.96, 1.02] 0.404	0.95 [0.92, 0.98] 0.002	0.98 [0.95, 1.01] 0.214	0.88 [0.85, 0.91] <0.001	0.93 [0.90, 0.96] <0.001	0.91 [0.88, 0.95] <0.001	0.88 [0.84, 0.91] <0.001	0.90 [0.87, 0.93] <0.001
76 th -100 th		0.88 [0.86, 0.91] <0.001	0.92 [0.89, 0.95] <0.001	0.91 [0.88, 0.94] <0.001	0.86 [0.83, 0.89] <0.001	0.91 [0.88, 0.94] <0.001	0.91 [0.87, 0.94] <0.001	0.88 [0.85, 0.92] <0.001	0.89 [0.85, 0.92] <0.001	0.84 [0.81, 0.88] <0.001	0.87 [0.84, 0.91] <0.001	0.86 [0.83, 0.90] <0.001

Supplementary Material:

Matetic A, et al. Socioeconomic Status and Differences in the Management and Outcomes of 6.6 Million US Patients With Acute Myocardial Infarction. Am J Cardiol. 2020;129:10-18. doi: 10.1016/j.amjcard.2020.05.025.

Acute stroke/TIA	26 th -50 th	0.87 [0.83, 0.92] <0.001	0.90 [0.85, 0.94] <0.001	0.98 [0.93, 1.03] 0.445	0.90 [0.85, 0.95] <0.001	1.00 [0.95, 1.05] 0.92	0.98 [0.93, 1.03] 0.419	0.91 [0.86, 0.96] 0.001	0.91 [0.86, 0.97] 0.002	0.90 [0.85, 0.95] <0.001	1.05 [0.99, 1.11] 0.093	1.06 [1.00, 1.12] 0.038
	51 st -75 th	0.92 [0.88, 0.97] 0.002	0.94 [0.89, 0.99] 0.014	0.94 [0.89, 0.99] 0.016	0.98 [0.92, 1.03] 0.396	0.98 [0.93, 1.03] 0.429	0.87 [0.83, 0.92] <0.001	0.93 [0.88, 0.98] 0.012	0.94 [0.88, 0.99] 0.027	0.92 [0.87, 0.98] 0.009	0.94 [0.88, 1.00] 0.034	1.06 [1.00, 1.12] 0.063
	76 th -100 th	0.89 [0.85, 0.94] <0.001	0.89 [0.84, 0.94] <0.001	0.83 [0.78, 0.87] <0.001	0.89 [0.84, 0.95] <0.001	0.95 [0.90, 1.01] 0.098	0.91 [0.86, 0.96] 0.001	0.94 [0.88, 1.00] 0.044	0.91 [0.85, 0.97] 0.003	0.90 [0.85, 0.96] 0.001	0.87 [0.82, 0.93] <0.001	1.01 [0.95, 1.08] 0.660
	26 th -50 th	1.01 [0.98, 1.05] 0.412	1.05 [1.02, 1.09] 0.005	1.06 [1.03, 1.10] <0.001	1.11 [1.10, 1.15] <0.001	0.93 [0.90, 0.96] <0.001	1.05 [1.01, 1.08] 0.005	1.15 [1.11, 1.18] <0.001	1.00 [0.97, 1.03] 0.915	1.02 [0.99, 1.05] 0.284	1.12 [1.08, 1.15] <0.001	1.04 [1.01, 1.08] 0.010
All-cause bleeding	51 st -75 th	1.16 [1.12, 1.20] <0.001	1.11 [1.07, 1.15] <0.001	1.13 [1.09, 1.17] <0.001	1.21 [1.17, 1.26] <0.001	0.99 [0.96, 1.02] 0.518	1.07 [1.04, 1.11] <0.001	1.17 [1.13, 1.21] <0.001	1.06 [1.02, 1.09] 0.001	1.03 [1.00, 1.06] 0.098	1.17 [1.13, 1.21] <0.001	1.08 [1.05, 1.12] <0.001
	76 th -100 th	1.26 [1.22, 1.30] <0.001	1.25 [1.20, 1.29] <0.001	1.20 [1.16, 1.25] <0.001	1.36 [1.31, 1.41] <0.001	1.12 [1.08, 1.16] <0.001	1.02 [0.99, 1.06] 0.173	1.13 [1.09, 1.17] <0.001	0.99 [0.96, 1.03] 0.658	1.05 [1.01, 1.08] 0.010	1.12 [1.08, 1.16] <0.001	1.07 [1.03, 1.11] <0.001

*Reference group: 0th-25th (n=1884699) group.

Abbreviations: MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); TIA – transitory ischemic attack; CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention; OR – Odds Ratios; CI – Confidence Interval.

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Supplementary Table S4. Annual adjusted odds of in-hospital outcomes according to the Median Household Income group in NSTEMI patients*.

Outcome	MHI group	Year										
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
		OR [95% CI] p-value										
Management:												
Receipt of CA	26 th -50 th	1.13 [1.10, 1.15] <0.001	1.01 [0.99, 1.03] 0.290	1.09 [1.06, 1.11] <0.001	1.02 [1.00, 1.04] 0.036	1.08 [1.06, 1.10] <0.001	1.16 [1.14, 1.19] <0.001	1.01 [0.99, 1.03] 0.424	1.06 [1.04, 1.08] <0.001	1.02 [1.00, 1.04] 0.096	1.01 [0.99, 1.03] 0.139	1.03 [1.01, 1.05] 0.008
	51 st -75 th	0.99 [0.97, 1.02] 0.655	0.96 [0.94, 0.99] 0.001	1.11 [1.09, 1.14] <0.001	0.93 [0.91, 0.95] <0.001	0.96 [0.94, 0.98] <0.001	0.96 [0.94, 0.98] <0.001	0.94 [0.92, 0.96] <0.001	1.06 [1.04, 1.08] <0.001	0.94 [0.92, 0.96] <0.001	0.98 [0.96, 1.00] 0.124	1.00 [0.98, 1.02] 0.941
	76 th -100 th	0.94 [0.92, 0.96] <0.001	0.88 [0.86, 0.90] <0.001	1.02 [1.00, 1.05] 0.041	0.82 [0.80, 0.84] <0.001	0.89 [0.87, 0.91] <0.001	0.88 [0.86, 0.90] <0.001	0.85 [0.83, 0.87] <0.001	0.93 [0.91, 0.95] <0.001	0.88 [0.86, 0.90] <0.001	0.87 [0.85, 0.89] <0.001	0.92 [0.90, 0.94] <0.001
	26 th -50 th	1.07 [1.04, 1.09] <0.001	1.05 [1.03, 1.07] <0.001	1.14 [1.12, 1.17] <0.001	1.05 [1.03, 1.08] <0.001	1.09 [1.07, 1.12] <0.001	1.11 [1.09, 1.14] <0.001	1.08 [1.06, 1.11] <0.001	1.11 [1.09, 1.13] <0.001	1.05 [1.04, 1.07] <0.001	1.08 [1.06, 1.10] <0.001	1.06 [1.04, 1.08] <0.001
	51 st -75 th	1.07 [1.05, 1.10] <0.001	1.12 [1.10, 1.15] <0.001	1.19 [1.16, 1.21] <0.001	1.08 [1.06, 1.11] <0.001	1.09 [1.07, 1.11] <0.001	1.05 [1.02, 1.07] <0.001	1.09 [1.07, 1.12] <0.001	1.09 [1.07, 1.12] <0.001	1.04 [1.02, 1.06] <0.001	1.04 [1.02, 1.06] <0.001	1.12 [1.10, 1.14] <0.001
	76 th -100 th	1.01 [0.98, 1.03] 0.680	1.08 [1.06, 1.11] <0.001	1.09 [1.07, 1.12] <0.001	1.05 [1.03, 1.08] <0.001	1.10 [1.08, 1.13] <0.001	0.92 [0.90, 0.95] <0.001	1.00 [0.98, 1.03] 0.699	1.05 [1.03, 1.08] <0.001	1.02 [1.00, 1.05] 0.021	1.00 [0.98, 1.02] 0.872	1.06 [1.04, 1.09] <0.001
Outcomes:												
MACCE	26 th -50 th	0.95 [0.91, 0.98] 0.002	0.99 [0.95, 1.02] 0.440	1.03 [0.99, 1.06] 0.178	0.94 [0.91, 0.98] 0.002	1.00 [0.97, 1.04] 0.942	1.02 [0.99, 1.06] 0.226	1.02 [0.99, 1.06] 0.214	0.92 [0.88, 0.95] <0.001	0.94 [0.91, 0.98] 0.002	0.98 [0.95, 1.02] 0.421	0.99 [0.96, 1.03] 0.725
	51 st -75 th	0.94 [0.90, 0.97] 0.001	0.94 [0.90, 0.97] 0.001	1.02 [0.98, 1.06] 0.240	1.03 [1.00, 1.08] 0.073	0.96 [0.93, 1.00] 0.035	0.96 [0.93, 1.00] 0.042	0.93 [0.89, 0.97] <0.001	0.96 [0.92, 1.00] 0.032	0.94 [0.90, 0.97] 0.001	0.91 [0.88, 0.95] <0.001	0.96 [0.93, 1.00] 0.063
	76 th -100 th	0.92 [0.88, 0.95] <0.001	0.92 [0.89, 0.96] <0.001	0.94 [0.90, 0.97] 0.001	0.90 [0.87, 0.94] <0.001	0.94 [0.91, 0.98] 0.002	0.93 [0.89, 0.97] <0.001	0.96 [0.92, 1.00] 0.037	0.92 [0.88, 0.95] <0.001	0.90 [0.86, 0.93] <0.001	0.95 [0.91, 0.99] 0.008	0.98 [0.94, 1.02] 0.243
	26 th -50 th	0.98 [0.94, 1.02] 0.242	1.00 [0.96, 1.04] 0.903	1.01 [0.97, 1.06] 0.562	0.95 [0.91, 1.00] 0.036	1.00 [0.95, 1.04] 0.864	1.00 [0.96, 1.04] 0.990	0.98 [0.94, 1.03] 0.461	0.92 [0.88, 0.96] <0.001	0.96 [0.92, 1.01] 0.089	0.92 [0.88, 0.96] 0.001	0.95 [0.90, 0.99] 0.015
	51 st -75 th	0.94 [0.90, 0.98] 0.007	0.92 [0.88, 0.96] <0.001	1.00 [0.95, 1.04] 0.864	0.99 [0.94, 1.03] 0.627	0.99 [0.94, 1.03] 0.610	0.95 [0.91, 1.00] 0.048	0.87 [0.83, 0.91] <0.001	0.97 [0.93, 1.01] 0.183	0.95 [0.90, 0.99] 0.021	0.84 [0.80, 0.88] <0.001	0.90 [0.86, 0.94] <0.001
	76 th -100 th	0.92 [0.88, 0.96] <0.001	0.88 [0.84, 0.92] <0.001	0.92 [0.88, 0.97] 0.001	0.88 [0.84, 0.93] <0.001	0.95 [0.91, 1.00] 0.033	0.88 [0.84, 0.93] <0.001	0.88 [0.84, 0.93] <0.001	0.88 [0.84, 0.93] <0.001	0.83 [0.79, 0.87] <0.001	0.90 [0.86, 0.95] <0.001	0.92 [0.87, 0.97] 0.002

Supplementary Material:

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Acute stroke/TIA	26 th -50 th	0.86 [0.81, 0.92]	0.87 [0.82, 0.93]	1.03 [0.97, 1.10]	0.92 [0.87, 0.99]	1.00 [0.94, 1.06]	1.02 [0.96, 1.09]	1.01 [0.95, 1.08]	0.88 [0.82, 0.95]	0.85 [0.79, 0.91]	1.05 [0.99, 1.13]	1.04 [0.98, 1.11]
		<0.001	<0.001	0.323	0.020	0.894	0.483	0.719	<0.001	<0.001	0.112	0.184
	51 st -75 th	0.91 [0.86, 0.98]	0.91 [0.85, 0.97]	1.03 [0.96, 1.10]	1.02 [0.95, 1.09]	0.90 [0.84, 0.96]	0.91 [0.85, 0.97]	0.95 [0.89, 1.02]	0.90 [0.84, 0.97]	0.86 [0.80, 0.92]	0.93 [0.87, 1.00]	1.01 [0.95, 1.08]
		0.008	0.004	0.411	0.570	0.001	0.003	0.169	0.004	<0.001	0.055	0.721
All-cause bleeding	76 th -100 th	0.88 [0.82, 0.94]	0.90 [0.85, 0.97]	0.87 [0.81, 0.93]	0.88 [0.82, 0.95]	0.90 [0.84, 0.96]	0.97 [0.91, 1.04]	1.00 [0.93, 1.08]	0.91 [0.84, 0.98]	0.85 [0.79, 0.91]	0.86 [0.80, 0.93]	0.96 [0.89, 1.03]
		<0.001	0.004	<0.001	0.001	0.002	0.432	0.908	0.009	<0.001	<0.001	0.232
	26 th -50 th	0.98 [0.94, 1.02]	1.02 [0.97, 1.07]	1.02 [0.98, 1.06]	1.20 [1.14, 1.25]	0.99 [0.95, 1.03]	1.06 [1.02, 1.10]	1.18 [1.14, 1.23]	0.99 [0.96, 1.04]	1.06 [1.02, 1.09]	1.14 [1.11, 1.18]	1.05 [1.02, 1.09]
		0.373	0.393	0.392	<0.001	0.530	0.002	<0.001	0.973	0.002	<0.001	0.003
	51 st -75 th	1.09 [1.04, 1.14]	1.05 [1.00, 1.10]	1.02 [0.98, 1.07]	1.23 [1.17, 1.29]	1.01 [0.97, 1.05]	1.01 [0.97, 1.05]	1.07 [1.03, 1.11]	1.04 [1.00, 1.08]	1.00 [0.97, 1.04]	1.12 [1.08, 1.16]	1.08 [1.04, 1.11]
		<0.001	0.046	0.310	<0.001	0.590	0.649	0.001	0.030	0.905	<0.001	<0.001
	76 th -100 th	1.23 [1.18, 1.29]	1.17 [1.12, 1.23]	1.04 [0.99, 1.08]	1.40 [1.34, 1.47]	1.09 [1.05, 1.14]	0.93 [0.89, 0.97]	1.04 [1.00, 1.09]	0.92 [0.88, 0.96]	1.03 [1.00, 1.07]	1.07 [1.03, 1.11]	1.01 [0.97, 1.05]
		<0.001	<0.001	0.115	<0.001	<0.001	<0.001	0.052	<0.001	0.080	<0.001	0.599

*Reference group: 0th-25th (n=1884699) group.

Abbreviations: NSTEMI – non-ST-elevation Myocardial Infarction; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); TIA – transitory ischemic attack; CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention; OR – Odds Ratios; CI – Confidence Interval.

Supplementary Material:

Matetic A, et al. Socioeconomic Status and Differences in the Management and Outcomes of 6.6 Million US Patients With Acute Myocardial Infarction. Am J Cardiol. 2020;129:10-18. doi: 10.1016/j.amjcard.2020.05.025.

Supplementary Table S5. Annually adjusted odds of in-hospital outcomes according to the Median Household Income group in STEMI patients*.

Outcome	MHI group	Year										
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
		OR [95% CI] p-value										
Management:												
Receipt of CA	26 th -50 th	1.14 [1.10, 1.16] <0.001	1.03 [1.00, 1.06] 0.030	1.12 [1.09, 1.15] <0.001	1.07 [1.04, 1.10] <0.001	1.07 [1.04, 1.10] <0.001	1.06 [1.02, 1.09] 0.001	0.97 [0.93, 1.00] 0.061	1.04 [1.01, 1.08] 0.019	1.10 [1.05, 1.14] <0.001	1.01 [0.98, 1.05] 0.461	1.00 [0.96, 1.04] 0.981
	51 st -75 th	1.13 [1.10, 1.16] <0.001	1.05 [1.02, 1.08] <0.001	1.09 [1.06, 1.13] <0.001	1.09 [1.05, 1.12] <0.001	1.11 [1.08, 1.15] <0.001	1.21 [1.17, 1.26] <0.001	1.06 [1.03, 1.10] 0.001	1.09 [1.05, 1.13] <0.001	1.15 [1.11, 1.20] <0.001	1.03 [0.99, 1.08] 0.099	0.97 [0.93, 1.01] 0.128
	76 th -100 th	1.01 [0.99, 1.04] 0.306	1.11 [1.08, 1.14] <0.001	1.15 [1.11, 1.18] <0.001	0.91 [0.89, 0.94] <0.001	1.11 [1.07, 1.15] <0.001	1.09 [1.05, 1.13] <0.001	1.12 [1.08, 1.16] <0.001	1.14 [1.09, 1.18] <0.001	1.12 [1.08, 1.17] <0.001	0.96 [0.92, 1.01] 0.089	0.90 [0.86, 0.94] <0.001
	26 th -50 th	1.17 [1.14, 1.19] <0.001	1.06 [1.03, 1.08] <0.001	1.09 [1.06, 1.11] <0.001	1.07 [1.04, 1.10] <0.001	1.07 [1.05, 1.10] <0.001	1.09 [1.06, 1.12] <0.001	1.01 [0.98, 1.04] 0.620	1.06 [1.03, 1.10] <0.001	1.07 [1.04, 1.10] <0.001	1.03 [1.00, 1.07] 0.033	1.05 [1.02, 1.09] 0.002
	51 st -75 th	1.22 [1.19, 1.25] <0.001	1.22 [1.19, 1.25] <0.001	1.17 [1.14, 1.20] <0.001	1.17 [1.14, 1.20] <0.001	1.19 [1.16, 1.23] <0.001	1.23 [1.19, 1.26] <0.001	1.14 [1.10, 1.17] <0.001	1.17 [1.13, 1.20] <0.001	1.11 [1.07, 1.14] <0.001	1.12 [1.09, 1.16] <0.001	1.07 [1.04, 1.11] <0.001
	76 th -100 th	1.22 [1.19, 1.25] <0.001	1.34 [1.30, 1.37] <0.001	1.17 [1.14, 1.20] <0.001	1.06 [1.03, 1.09] <0.001	1.25 [1.21, 1.28] <0.001	1.18 [1.14, 1.21] <0.001	1.19 [1.15, 1.23] <0.001	1.16 [1.12, 1.20] <0.001	1.10 [1.06, 1.13] <0.001	1.04 [1.01, 1.08] 0.015	1.02 [0.98, 1.05] 0.343
Outcomes:												
MACCE	26 th -50 th	0.95 [0.92, 0.98] 0.002	0.99 [0.95, 1.02] 0.502	0.98 [0.95, 1.02] 0.383	1.06 [1.02, 1.11] 0.002	0.98 [0.94, 1.02] 0.279	1.01 [0.97, 1.05] 0.760	0.94 [0.90, 0.98] 0.007	0.96 [0.92, 1.01] 0.109	0.92 [0.87, 0.96] <0.001	1.00 [0.95, 1.04] 0.878	0.96 [0.92, 1.01] 0.104
	51 st -75 th	0.94 [0.90, 0.97] <0.001	1.01 [0.97, 1.05] 0.521	0.95 [0.92, 0.99] 0.018	1.01 [0.97, 1.06] 0.485	0.99 [0.95, 1.04] 0.829	1.01 [0.97, 1.05] 0.638	0.89 [0.85, 0.93] <0.001	0.92 [0.88, 0.96] <0.001	0.90 [0.86, 0.94] <0.001	0.92 [0.87, 0.96] <0.001	0.93 [0.89, 0.98] 0.004
	76 th -100 th	0.92 [0.89, 0.96] <0.001	0.96 [0.92, 1.00] 0.036	0.88 [0.84, 0.92] <0.001	0.89 [0.85, 0.93] <0.001	0.95 [0.91, 0.99] 0.029	0.93 [0.89, 0.97] 0.001	0.88 [0.84, 0.93] <0.001	0.86 [0.82, 0.90] <0.001	0.90 [0.86, 0.95] <0.001	0.87 [0.83, 0.92] <0.001	0.83 [0.78, 0.87] <0.001
	26 th -50 th	0.94 [0.90, 0.97] 0.001	1.01 [0.97, 1.05] 0.765	1.02 [0.98, 1.07] 0.282	1.04 [0.99, 1.08] 0.107	0.95 [0.91, 0.99] 0.014	1.02 [0.97, 1.07] 0.385	0.95 [0.91, 1.00] 0.057	0.94 [0.89, 0.99] 0.019	0.86 [0.82, 0.91] <0.001	0.96 [0.91, 1.01] 0.125	0.90 [0.85, 0.94] <0.001
	51 st -75 th	0.93 [0.89, 0.96] <0.001	1.02 [0.98, 1.07] 0.249	0.99 [0.95, 1.04] 0.747	1.00 [0.95, 1.05] 0.994	0.94 [0.89, 0.98] 0.006	1.03 [0.98, 1.08] 0.233	0.88 [0.84, 0.93] <0.001	0.88 [0.84, 0.93] <0.001	0.85 [0.80, 0.89] <0.001	0.92 [0.87, 0.98] 0.005	0.86 [0.81, 0.91] <0.001
	76 th -100 th	0.90 [0.86, 0.94] <0.001	0.98 [0.94, 1.03] 0.448	0.92 [0.88, 0.96] <0.001	0.83 [0.79, 0.87] <0.001	0.91 [0.86, 0.95] <0.001	0.91 [0.86, 0.96] 0.001	0.86 [0.82, 0.91] <0.001	0.87 [0.82, 0.91] <0.001	0.85 [0.80, 0.89] <0.001	0.84 [0.79, 0.89] <0.001	0.75 [0.70, 0.79] <0.001

Supplementary Material:

Matetic A, et al. Socioeconomic Status and Differences in the Management and Outcomes of 6.6 Million US Patients With Acute Myocardial Infarction. Am J Cardiol. 2020;129:10-18. doi: 10.1016/j.amjcard.2020.05.025.

Acute stroke/TIA	26 th -50 th	0.91 [0.85, 0.99]	0.97 [0.89, 1.05]	0.94 [0.86, 1.02]	0.86 [0.78, 0.94]	1.08 [0.99, 1.19]	0.91 [0.83, 1.00]	0.72 [0.65, 0.80]	1.01 [0.91, 1.13]	1.05 [0.94, 1.18]	1.05 [0.94, 1.17]	1.14 [1.02, 1.27]
		0.020	0.445	0.114	0.002	0.084	0.060	<0.001	0.807	0.353	0.389	0.021
	51 st -75 th	0.95 [0.87, 1.03]	1.02 [0.94, 1.12]	0.85 [0.78, 0.92]	0.92 [0.84, 1.01]	1.22 [1.11, 1.34]	0.80 [0.72, 0.89]	0.87 [0.78, 0.96]	1.00 [0.90, 1.12]	1.10 [0.99, 1.23]	0.96 [0.85, 1.08]	1.19 [1.07, 1.34]
		0.197	0.572	<0.001	0.099	<0.001	<0.001	0.005	0.945	0.081	0.494	0.002
	76 th -100 th	0.95 [0.87, 1.03]	0.89 [0.81, 0.98]	0.80 [0.72, 0.87]	0.93 [0.84, 1.02]	1.13 [1.02, 1.26]	0.74 [0.66, 0.82]	0.81 [0.72, 0.90]	0.87 [0.77, 0.98]	1.09 [0.97, 1.23]	0.90 [0.80, 1.02]	1.16 [1.03, 1.30]
		0.207	0.016	<0.001	0.136	0.017	<0.001	<0.001	0.019	0.143	0.114	0.017
All-cause bleeding	26 th -50 th	1.04 [0.99, 1.09]	1.03 [0.97, 1.08]	1.08 [1.03, 1.14]	0.96 [0.91, 1.01]	0.92 [0.88, 0.97]	0.96 [0.91, 1.01]	1.03 [0.97, 1.09]	1.07 [1.01, 1.13]	0.97 [0.91, 1.03]	1.07 [1.01, 1.13]	1.11 [1.05, 1.18]
		0.108	0.325	0.004	0.136	0.001	0.131	0.299	0.013	0.298	0.029	<0.001
	51 st -75 th	1.18 [1.12, 1.24]	1.05 [0.99, 1.10]	1.23 [1.16, 1.29]	1.13 [1.07, 1.19]	0.95 [0.90, 1.00]	1.06 [1.01, 1.12]	1.15 [1.09, 1.22]	1.02 [0.97, 1.08]	0.98 [0.92, 1.04]	1.21 [1.15, 1.29]	1.07 [1.01, 1.14]
		<0.001	0.101	<0.001	<0.001	0.051	0.024	<0.001	0.476	0.531	<0.001	0.032
	76 th -100 th	1.18 [1.13, 1.25]	1.15 [1.08, 1.21]	1.29 [1.22, 1.36]	1.18 [1.12, 1.25]	1.04 [0.99, 1.10]	1.04 [0.99, 1.10]	1.08 [1.02, 1.15]	0.93 [0.87, 0.99]	1.04 [0.98, 1.11]	1.03 [0.97, 1.10]	1.04 [0.98, 1.11]
		<0.001	<0.001	<0.001	<0.001	0.127	0.140	0.008	0.017	0.174	0.317	0.190

*Reference group: 0th-25th (n=1884699) group.

Abbreviations: STEMI – ST-elevation Myocardial Infarction; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); TIA – transitory ischemic attack; CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention; OR – Odds Ratios; CI – Confidence Interval.

11.2. Research study 2



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Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission

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Abstract

Background: In recent years, there has been a growing interest in outcomes of patients with acute myocardial infarction (AMI) using large administrative datasets. The present study was designed to compare the characteristics, management strategies and acute outcomes between patients with primary and secondary AMI diagnoses in a national cohort of patients.

Methods: All hospitalisations of adults (≥ 18 years) with a discharge diagnosis of AMI in the US National Inpatient Sample from January 2004 to September 2015 were included, stratified by primary or secondary AMI. The International Classification of Diseases, ninth revision and Clinical Classification Software codes were used to identify patient comorbidities, procedures and clinical outcomes.

Results: A total of 10 864 598 weighted AMI hospitalisations were analysed, of which 7 186 261 (66.1%) were primary AMIs and 3 678 337 (33.9%) were secondary AMI. Patients with primary AMI diagnoses were younger (median 68 vs 74 years, $P < .001$) and less likely to be female (39.6% vs 48.5%, $P < .001$). Secondary AMI was associated with lower odds of receipt of coronary angiography (aOR 0.19; 95%CI 0.18-0.19) and percutaneous coronary intervention (0.24; 0.23-0.24). Secondary AMI was associated with increased odds of MACCE (1.73; 1.73-1.74), mortality (1.71; 1.70-1.72), major bleeding (1.64; 1.62-1.65), cardiac complications (1.69; 1.65-1.73) and stroke (1.68; 1.67-1.70) ($P < .001$ for all).

Conclusions: Secondary AMI diagnoses account for one-third of AMI admissions. Patients with secondary AMI are older, less likely to receive invasive care and have worse outcomes than patients with a primary diagnosis code of AMI. Future studies should consider both primary and secondary AMI diagnoses codes in order to accurately inform clinical decision-making and health planning.

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1 | INTRODUCTION

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality globally accounting approximately for 366 000 deaths in the United States (US).¹ In recent years, there has been a growing interest in outcomes research in AMI patients using large administrative datasets.²⁻¹⁰ While these datasets have been previously validated for the purpose of cardiovascular outcomes research, their accuracy is reliant on both the standard of clinical coding as well as physician judgement as to what constitutes the primary discharge diagnosis for the clinical episode.^{11,12}

Previous studies examining AMI management strategies and outcomes using large administrative datasets, such as the US National Inpatient Sample and the Centers for Medicare & Medicaid Services (CMS) datasets have largely focussed on cohorts identified using the primary or principal discharge fields.^{13,14} The proportion of AMI coded as a primary vs secondary diagnosis in large national datasets is unknown. There is also a paucity of data on the differences between patients with a secondary AMI diagnosis and those with a primary AMI diagnosis with regards to the characteristics, risk profiles and clinical outcomes.

It has previously been suggested that differences in patient clinical outcomes may exist between acute coronary syndrome (ACS) events documented as primary vs secondary diagnoses.¹⁵ However, such studies are limited by relatively small patient sample sizes, and do not study temporal patterns of how primary vs secondary AMI diagnoses have changed over time or their clinical outcomes. Furthermore, previous studies have not reported patient characteristics, treatment strategies or clinical outcomes stratified by the primary/principal diagnosis for patients coded with secondary AMI diagnoses.

The present study aimed to address this knowledge gap by utilising a large contemporary nationwide dataset to compare the characteristics, management strategies and outcomes between patients with primary vs secondary AMI, and to examine the primary diagnoses of patients admitted with a secondary AMI. The overarching goal was to help guide the inclusion criteria of future studies when studying cohorts of AMI patients using administrative datasets.

2 | METHODS

2.1 | Data

The National Inpatient Sample (NIS) represents the largest publicly available all-payer longitudinal databases of hospital inpatient discharges in the US. It was developed by the Agency for Healthcare Research and Quality (AHRQ), under the Healthcare Cost and Utilization Project, with a purpose of building a multistate database for medical research and decision making. It contains anonymised discharge-level data from >7 million hospitalisations annually, which can be used for the estimation of hospital utilisation, quality and

What's known

- Previous studies examining AMI management strategies and outcomes using large administrative datasets have largely focussed on cohorts identified using the primary or principal discharge fields, while there is a paucity of data for the AMI patients coded as the secondary diagnosis.
- This study examined the characteristics, management strategies and outcomes in AMI patients based on diagnosis coding priority by utilising a large contemporary nationwide dataset.

What's new

- First study to compare characteristics and management of AMI from administrative data according to admission diagnosis priority.
- Patients with secondary AMI diagnoses were most commonly admitted for infection (21.8%), respiratory disorders (11.8%), heart failure (9.9%), disorders of coronary circulation other than AMI (6.7%) and gastrointestinal disorders (5.5%).
- Secondary AMI diagnosis patients were less likely to receive invasive management.
- Secondary AMI diagnosis patients were more likely to develop adverse in-hospital outcomes, including mortality, major adverse cardiovascular and cerebrovascular events, major bleeding, cardiac complications and stroke.

other related issues. It was designed to approximate 20% stratified sample of the US community hospitals, excluding rehabilitation and long-term acute care hospitals, and provides sampling weights to calculate national estimates that represent more than 95% of the US population.

2.2 | Study design and population

All hospitalisations of adults (≥ 18 years) with a discharge diagnosis of AMI from January 2004 to September 2015 were included, stratified by diagnosis level variables (DX) in the dataset into primary (DX1) and secondary (DX2-DX30) AMI. The International Classification of Diseases, ninth revision (ICD-9) and Clinical Classification Software (CCS) codes were used to identify patient comorbidities, procedures and clinical outcomes (Table S1). Additional comorbidities were identified using the existing 29 AHRQ Elixhauser comorbidity measures. Cases excluded because missing data represented 0.4% ($n = 68\ 183$) of the original dataset (Figure S1).

2.3 | Outcomes

In-hospital adverse outcomes included major acute cardiovascular and cerebrovascular events (MACCE), all-cause mortality, major bleeding, acute stroke and cardiac complications. MACCE was defined as a composite of all-cause mortality, acute stroke/transient ischaemic attack (TIA) and cardiac complications. Cardiac complications included hemopericardium, cardiac tamponade, coronary dissection and any pericardiocentesis procedure. Differences in treatment were analysed, comparing the receipt of invasive management, in the form of coronary angiography (CA) and percutaneous coronary intervention (PCI).

2.4 | Statistical analysis

Statistical Package for the Social Sciences (SPSS) statistical software (IBM Corp, Armonk, NY; version 25) was used for statistical analysis. Data were expressed as median (interquartile range) for continuous non-parametric data and as whole numbers (percentages) for categorical data. Quantitative data were analysed with the Mann-Whitney U test for non-normally distributed data, while the chi-squared test was used for the comparison of categorical variables between the study groups. All analyses were conducted with appropriate sampling weights provided by the AHRQ, for each individual discharge. A trend analysis was conducted by assessing the interaction between AMI diagnosis priority and time (years) on clinical outcomes in a logistic regression analysis. Multivariable logistic regression analysis was used to determine the adjusted odds ratios (aOR [95% confidence interval (CI)]) of receipt of invasive management and the likelihood of adverse outcomes in the secondary AMI diagnosis group, using the primary diagnosis group as the reference category. Variables adjusted for in the regression models are listed in Appendix A (Supplementary Material). Variables evaluating the socioeconomic characteristics of the patients such as "primary expected payer" and "median household income" were included in the multivariable logistic regression analysis to remove any confounding effects. Furthermore, hospital-related variables such as "hospital bedsize," "hospital region" and "hospital location/teaching status" have been included in the analysis because of its possible impact on the outcomes of the studied population and to eliminate any hospital-related variability in the outcomes.

3 | RESULTS

3.1 | Characteristics

From January 2004 to September 2015, a total of 10 864 598 weighted AMI hospitalisations were recorded. Of these, 7 186 261 (66.1%) were primary AMI diagnoses and 3 678 337 (33.9%) were secondary diagnoses. There was an increase in the proportion of hospitalisations with secondary AMI, from 2004 to 2015 from

28.2% to 35.7% ($P < .001$) (Figure S2). Compared with primary AMI patients those with secondary AMI diagnoses were older (median 74 years vs 68 years, $P < .001$) and more likely to be female (48.5% vs 39.6%, $P < .001$) (Table 1).

Patients with a primary AMI diagnosis were more likely to be males, with a higher prevalence of smoking history, previous MI, dyslipidaemia, hypertension and obesity, whilst patients with secondary diagnoses were more likely to have comorbidities, such as anaemia, atrial fibrillation (AF), valvular disease, congestive heart failure, peripheral vascular disorders, chronic renal failure, chronic pulmonary disease, metastatic cancer and prior CABG. Compared with patients with a secondary diagnosis of AMI, patients with a primary diagnosis were more critically unwell, with a higher prevalence of cardiogenic shock and ventricular arrhythmias. Patients with a primary AMI diagnosis were also significantly more likely to present with STEMI (28.3% vs 10.1%, $P < .001$, Table 1).

Amongst patients with secondary AMI diagnosis, the most frequent principal diagnosis was infection (21.8%), followed by respiratory disorders (11.8%), heart failure (9.9%), disorders of coronary circulation other than AMI (mainly coronary atherosclerosis of native vessels) (6.7%) and gastrointestinal disorders (5.5%) (Figure 1). Further breakdown of the "coronary circulation disorder" group reveals that this cohort of patients mainly had a coded primary diagnosis of coronary atherosclerosis of native vessels (Table S2).

3.2 | Invasive management

Patients with a primary AMI diagnosis were more likely to undergo CA (64.9% vs 18.6%, $P < .001$), PCI (43.3% vs 8.5%, $P < .001$), CABG (8.8% vs 3.4%, $P < .001$) as well as the use of assist device (9.8% vs 5.2%, $P < .001$) (Table 2, Figure 2). Following multivariable adjustment, patients with a secondary AMI diagnoses had significantly reduced odds of receipt of invasive coronary angiography (OR 0.18; 95% CI 0.18-0.18) and PCI (OR 0.24; 95% CI 0.23-0.24) in comparison to patients with a primary AMI diagnosis (Table 3 and Figure 3).

Similarly, in the STEMI subgroup, patients with a primary AMI diagnosis were more likely to undergo CA (82.1% vs 35.5%, $P < .001$) and PCI (71.3% vs 25.9%, $P < .001$) (Table S3). Following multivariable adjustment, patients with a secondary AMI diagnoses had reduced odds of receipt of invasive coronary angiography (OR 0.15; 95% CI 0.15-0.15) and PCI (OR 0.20; 95% CI 0.19-0.20) in comparison to patients with a primary AMI diagnosis (Table S4 and Figure S3).

The odds of receiving CA and PCI decreased from 2004 to 2015 amongst secondary AMI compared with primary AMI diagnosis ($P < .001$ for trend) (Figure S4).

3.3 | Outcomes

Secondary AMI diagnoses had significantly higher all-cause mortality (16.5% vs 5.8%), MACCE (23.3% vs 9.6%, $P < .001$), major

TABLE 1 Baseline characteristics of patients in the National Inpatient Sample discharged with a primary or secondary diagnosis of AMI

Characteristics	Diagnosis priority		P-value
	Primary AMI diagnosis (66.1%)	Secondary AMI diagnosis (33.9%)	
Number of weighted discharges	7 186 261	3 678 337	
Age (y), median (IQR)	68 (57, 79)	74 (63, 83)	<.001
Age groups (y), %			<.001
<60	33.2	19.9	
60-70	22.9	20.3	
71-80	21.8	26.4	
≥80	22.1	33.4	
Female sex, %	39.6	48.5	<.001
Race, %			<.001
White	76.7	76.3	
Black	9.8	11.2	
Hispanic	7.5	6.9	
Other	6.0	5.6	
STEMI, %	28.3	10.1	<.001
Elective admission, %	6.9	16.2	<.001
Weekend admission, %	26.0	23.5	<.001
Primary expected payer, %			<.001
Medicare	57.2	72.7	
Medicaid	6.2	6.3	
Private Insurance	27.6	15.7	
Self-pay	5.7	2.9	
No charge	0.6	0.3	
Other	2.7	2.0	
Median Household Income (percentile), %			<.001
0-25th	27.5	27.2	
26th-50th	27.4	26.5	
51st-75th	23.7	24.2	
76th-100th	21.4	22.0	
Cardiogenic shock, %	5.0	4.3	<.001
Cardiac arrest, %	3.1	4.9	<.001
Ventricular tachycardia, %	6.0	5.9	<.001
Ventricular fibrillation, %	2.7	1.9	<.001
Cardiac tamponade, %	0.1	0.1	<.001
Comorbidities, %			
Atrial fibrillation	16.6	26.0	<.001
Dyslipidaemia	54.9	36.6	<.001
Thrombocytopenia	3.3	6.2	<.001
Dementia	5.8	10.5	<.001
Smoking	34.9	21.6	<.001
Previous AMI	10.4	7.9	<.001
Previous PCI	11.8	11.7	<.001
Previous CABG	7.5	9.2	<.001
Previous CVA	4.0	4.8	.038

(Continues)

TABLE 1 (Continued)

Characteristics	Diagnosis priority		P-value
	Primary AMI diagnosis (66.1%)	Secondary AMI diagnosis (33.9%)	
Anaemias	15.8	26.6	<.001
Heart failure	31.3	47.6	<.001
Valvular disease	0.3	9.6	<.001
Hypertension	66.9	62.6	<.001
Peripheral vascular disorders	10.9	13.1	<.001
Pulmonary circulation disorders	0.1	5.0	<.001
Chronic pulmonary disease	20.7	27.5	<.001
Obesity	12.0	9.2	<.001
Diabetes mellitus	34.3	34.8	<.001
Hypothyroidism	9.7	11.6	<.001
Drug abuse	2.1	2.5	<.001
Alcohol abuse	2.8	3.4	<.001
Depression	6.4	8.1	<.001
Liver disease	1.2	2.4	<.001
Chronic renal failure	16.7	25.6	<.001
Paralysis	1.6	3.9	<.001
RA/collagen vascular diseases	2.2	2.7	<.001
Solid tumour without metastasis	1.4	2.5	<.001
Metastatic cancer	0.9	2.4	<.001
Lymphoma	0.5	0.9	<.001
Fluid and electrolyte disorders	19.4	41.1	<.001
Bed size of hospital, %			<.001
Small	10.7	12.8	
Medium	24.8	25.4	
Large	64.5	61.8	
Hospital Region, %			<.001
Northeast	19.3	21.2	
Midwest	23.0	23.6	
South	40.1	37.5	
West	17.6	17.8	
Location/teaching status of hospital, %			<.001
Rural	10.3	12.1	
Urban non-teaching	40.9	39.5	
Urban teaching	48.7	48.5	

Abbreviations: AIDS, acquired immunodeficiency syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVA, cerebrovascular accidents; IQR, interquartile range; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis; STEMI, ST-elevation myocardial infarction.

bleeding (7.5% vs 3.0%), as well as stroke (8.1% vs 3.6%) ($P < .001$ for all, Table 2, Figure 2). Patients with secondary AMI diagnoses had an increased length of hospital stay (6 days vs 3 days, $P < .001$) and total direct hospitalisation costs (USD 44 610 vs USD 44 099, $P < .001$) (Table 2). Similar outcomes were observed in the STEMI subgroup (Table S3).

Secondary AMI diagnosis patients had significant increased odds of MACCE (OR, 1.73; 95% CI, 1.72-1.74), all-cause mortality (OR 1.71; 95% CI, 1.70-1.72), as well as complications such as such as major bleeding (OR 1.63; 95% CI, 1.62-1.65), cardiac complications (OR 1.70; 95% CI, 1.66-1.74) and stroke (OR 1.68; 95% CI, 1.69-1.70) ($P < .001$ for all), compared with primary AMI diagnosis (Table 3,

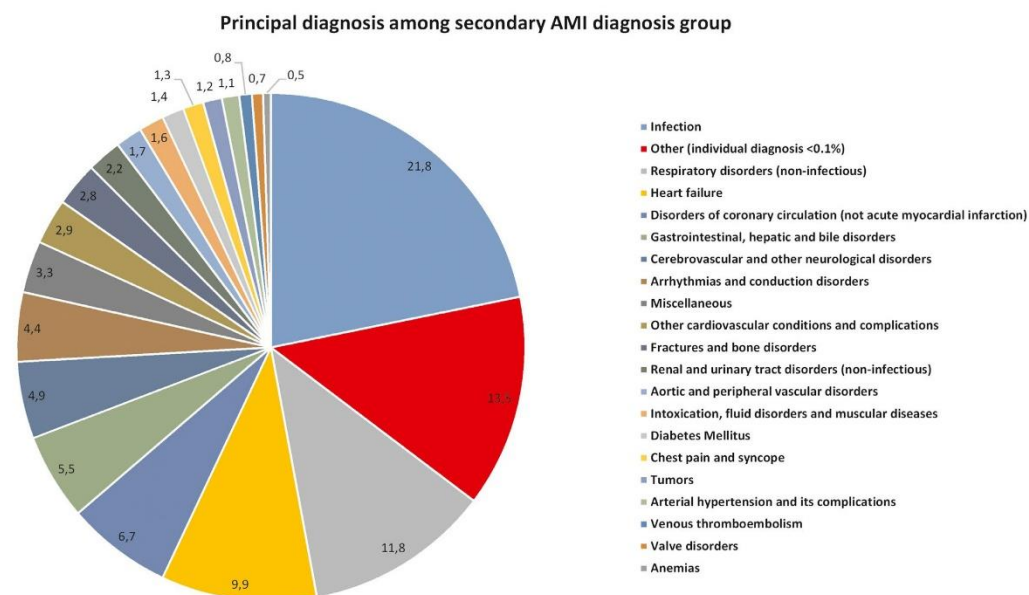


FIGURE 1 Principal diagnoses among secondary AMI diagnosis group

Variables	Diagnosis priority		P-value
	Primary AMI diagnosis (66.1%)	Secondary AMI diagnosis (33.9%)	
Treatments, %			
CA	64.9	18.6	<.001
PCI	43.3	8.5	<.001
CABG	8.8	3.4	<.001
Pericardiocentesis	0.074	0.107	<.001
Use of assist device or IABP	4.9	1.5	<.001
Outcomes, %			
MACCE	9.6	23.3	<.001
All-cause mortality	5.8	16.5	<.001
Major bleeding	3.0	7.5	<.001
Cardiac complications	0.687	0.478	<.001
Coronary dissection	0.526	0.261	<.001
Procedure-related bleeding	0.675	0.910	<0.001
Stroke	3.6	8.1	<.001
Length of stay (d), median (IQR)	3 (2, 6)	6 (3, 11)	<.001
Total charges (USD), median (IQR)	44 099 (23 946, 76 923)	44 610 (21 617, 91 133)	<.001

TABLE 2 Comparison of treatments and in-hospital adverse outcomes according to diagnosis priority

Abbreviations: CA, coronary angiography; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; IQR, interquartile range; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischaemic attack and cardiac complications); PCI, Percutaneous coronary intervention; USD, United States Dollar.

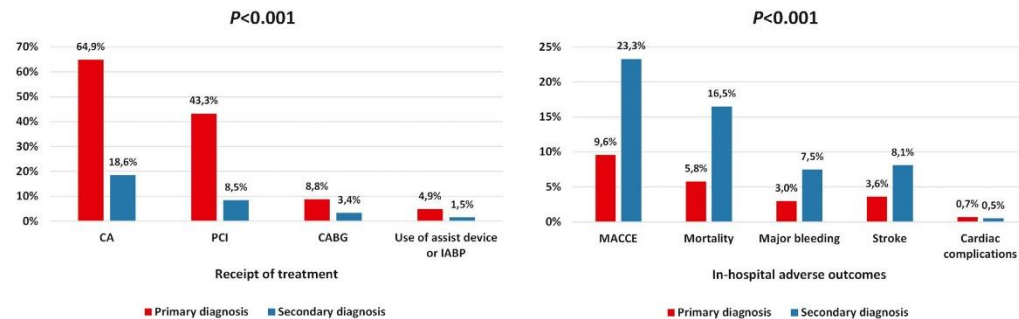


FIGURE 2 Comparison of receipt of treatments and in-hospital adverse outcomes according to primary or secondary diagnosis

Figure 3). Similar outcomes were observed in the STEMI subgroup (Table S4 and Figure S3).

Lastly, a stratification of outcomes amongst secondary AMI diagnosis by year from 2004 to 2015 shows a shift towards increased odds for MACCE, mortality, major bleeding, as well as stroke in this group (Figure S5).

3.4 | Characteristics, treatments and outcomes of secondary AMI diagnoses when stratified by the principal/primary diagnosis

Significant differences in median age were observed across the secondary AMI subgroups when stratified by the primary/principal diagnosis, with the youngest patients in the disorders of coronary circulation group (median age 65) whilst the oldest patients were observed in the heart failure and valve disorders group (median age 78) (Table S5). Similarly, there were significant differences in the prevalence of cardiovascular risk factors and co-morbid conditions across the primary/principal diagnosis of the secondary AMI subgroups summarised in Table S5.

Among the secondary AMI subgroups, patients with "disorders of coronary circulation" had the highest utilisation of CA, PCI and CABG, while the least likely patients to receive CA and PCI were in the "infection" subgroup ($P < .001$ for all) (Table S6 and Figure S6). Following adjustment for differences in covariates, patients with "disorders of coronary circulation" exhibited increased odds of receipt of invasive coronary angiography (OR 1.57; 95% CI 1.55-1.58) and PCI (OR 2.59; 95% CI 2.57-2.62) in comparison to patients with a primary AMI diagnosis, while all other subgroups were less likely to receive invasive management (Table S7).

Finally, within the secondary AMI subgroups, patients with "disorders of coronary circulation" had the lowest rates of MACCE, mortality and major bleeding, while the highest rates of MACCE and mortality exhibited "infection" subgroup ($P < .001$ for all) (Table S6 and Figure S6). The secondary AMI subgroup with the highest rate of major bleeding was "gastrointestinal, hepatic and bile disorders" subgroup ($P < .001$) (Table S6 and Figure S6). After the covariate

TABLE 3 Adjusted odds of invasive management and in-hospital adverse outcomes in secondary AMI group (N = 3 678 337)

Variables	Secondary AMI diagnosis	
	OR [95% CI]	P-value **
Invasive management:		
CA	0.18 [0.18, 0.18]	<.001
PCI	0.24 [0.23, 0.24]	<.001
Outcomes:		
MACCE	1.73 [1.72, 1.74]	<.001
All-cause mortality	1.71 [1.70, 1.72]	<.001
Major bleeding	1.63 [1.62, 1.65]	<.001
Cardiac complications	1.70 [1.66, 1.74]	<.001
Stroke	1.68 [1.69, 1.70]	<.001

Abbreviations: CA, coronary angiography; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischaemic attack and cardiac complications); OR, odds ratios; PCI, percutaneous coronary intervention.

*Reference group is primary AMI group.; **Multivariable logistic regression model adjusted for: bed size of hospital, region of hospital, location/teaching status of hospital, age, sex, race, weekend admission, primary expected payer, smoking status, previous myocardial infarction, previous coronary artery bypass graft surgery, history of ischaemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accident, atrial fibrillation, thrombocytopenia, Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, chronic blood loss anaemia, chronic pulmonary disease, coagulopathy, congestive heart failure, deficiency anaemias, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological disorders, obesity, paralysis, peptic ulcer, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, rheumatoid arthritis/collagen vascular diseases, solid tumour without metastasis, valvular heart disease, and weight loss) and receipt of PCI.

adjustments, patients with "disorders of coronary circulation" had lower odds of MACCE (OR 0.96; 95% CI 0.95-0.98), mortality (OR 0.49; 95% CI 0.48-0.50) and major bleeding (OR 0.55; 95% CI 0.53-0.57), but more cardiac complications (OR 3.39; 95% CI 3.27-3.51),

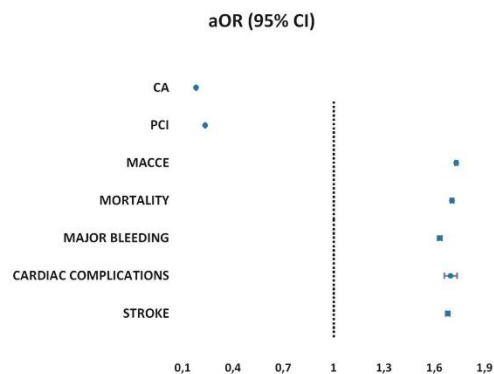


FIGURE 3 Adjusted odds ratios (OR) of invasive management and in-hospital adverse outcomes in secondary AMI group*

in comparison to patients with a primary AMI diagnosis (Table S7). Other secondary AMI subgroups had increased odds for all-cause mortality compared with primary AMI diagnosis group (Table S7).

Finally, a sensitivity analysis revealed a lower proportion of STEMI patients in the subgroup of patients with AF, irrespective of the diagnosis coding priority (Table S8).

4 | DISCUSSION

This is the first study comparing characteristics, management and outcomes of AMI according to diagnosis priority as coded within a large national dataset. Several important findings can be drawn. Firstly, up to one in three patients diagnosed with AMI nationwide have AMI coded as a secondary diagnosis. Thus, such patients would not be included in studies assessing AMI presentations, treatments and outcomes using administrative datasets when only a primary diagnosis code is considered as inclusion criterion. Secondly, there are significant differences in characteristics between patients presenting with primary and secondary AMI diagnoses, with the former group being younger, has a more predominance of males, and higher rates of previous MI and PCI, more likely to present with STEMI, and the latter group having a higher prevalence of non-cardiac comorbidities. Thirdly, patients with a secondary AMI diagnosis are less likely to undergo invasive management and were more likely to experience adverse outcomes such as all-cause mortality, MACCE, bleeding and stroke, compared with primary AMI patients, despite adjustments for baseline differences. Finally, we report that the characteristics, treatments and outcomes of patients diagnosed with a secondary AMI vary according to the principal diagnosis of this patient group, with patients with respiratory disorders and infection as the primary diagnosis least likely to receive invasive management and have worse outcomes.

Previous studies assessing AMI hospitalisations, their management and outcomes in different cohorts of patients have mainly focussed on primary AMI diagnosis.^{2-7,16,17} However, the diagnosis

priority as recorded administrative data may not necessarily reflect the acute cause of admission in these patients. Thus, failure to include patients with a secondary AMI diagnosis may result in the exclusion of a significant cohort of patients with AMI, leading to a significant underestimation of the AMI burden when evaluating in-hospital services as well as comorbid conditions and clinical outcomes associated with AMI. Furthermore, this may lead to potential miscalculation of the overall impact of AMI on health economics. This is particularly relevant when benchmarking services for the quality of care delivered in the management of AMI, where up to one-third of all AMI admissions may not be considered and so any assessment of the quality of services is likely to be inaccurate.

Our study outlines the crucial health and financial burden associated with secondary AMI, which represented one-third of all hospital admissions with AMI—findings that may require attention when considering resource allocation and strategic planning within health-care. Of the few existing studies focusing on primary and secondary AMI, Sacks et al examined trends in AMI hospitalisations, reporting an increase in secondary AMI diagnoses from 2002 to 2011, with the secondary AMI group accounting for 43% of all expenditures for hospitalisations with AMI.¹⁸ Shroff et al analysed trends in discharge claims for AMI amongst dialysis patients, reporting a considerable increase in AMI claims for secondary diagnoses, with a corresponding decline seen for primary AMI diagnoses.¹⁹

There are limited data on differences in management and outcomes of AMI between patients with primary and secondary AMI diagnoses. One recent study by Kerr et al looked at primary and secondary ACS hospitalisations, reporting that patients with secondary diagnoses were less likely to receive CA but also revascularisation in the form of PCI or CABG.¹⁵ The secondary ACS diagnosis group also experienced a higher prevalence in all-cause mortality, cardiovascular mortality, stroke and bleeding.¹⁵ Although it was unclear whether these findings reached statistical difference, they are in line with the conclusions drawn from our study. Reasons for these findings could include the fact that patients in the secondary AMI group were significantly older than their primary counterparts, and thus likely to be frailer and have complex cardiac comorbidities in the first place. Another reason would be that the primary cause of admission might be associated with relative contraindications for invasive work up and management (eg, intracranial bleeding, septic shock, etc). Our findings of higher mortality in secondary diagnoses also correlate with some studies examining diagnostic coding position on outcomes of acute heart failure admissions. For instance, Shoaib et al demonstrated that patients admitted to hospital with heart failure as a secondary rather than primary diagnosis have high mortality.²⁰ Furthermore, it has been previously shown that socioeconomic characteristics such as 'primary expected payer' status and 'median household income' are associated with worse outcomes in patients with principal discharge diagnosis of AMI through disparities in the receipt of evidence-based therapies and guideline recommended care.^{21,22} However, in order to diminish the influence of these variables, we have conducted a multivariable logistic regression analysis and adjusted for them.

There are several reasons why an AMI admission may be coded as a secondary diagnosis coded rather than a principal diagnosis code. Firstly, it is possible that patients are admitted with other medical conditions and sustain an AMI during their in-patients stay. Not considering such cases will lead to a significant underestimate of the burden of AMI in the in-hospital setting and may lead to inaccurate benchmarking of services around the quality of care, particularly when the odds of receipt of invasive management for the secondary AMI cases were significantly lower than those cases diagnosed as a primary AMI. Secondly, a secondary AMI diagnosis code may represent coding errors, although given the major differences in patients characteristics and clinical outcomes between primary and secondary diagnoses, this seems unlikely. Thirdly, a proportion of the AMI cases coded using a secondary diagnosis code, may in fact represent a type 2 MI, which is defined as myocardial necrosis caused by mismatch between oxygen supply and demand in the absence of coronary atherothrombosis, which is often precipitated by critical illness.²³ Among studies using the 2007 and 2012 Universal Definition MI, the reported prevalence of type 2 MI ranged from 2% to 58%.²⁴ Multiple mechanisms contributing to type 2 MI have been identified, and these include small vessel coronary obstruction, endothelial dysfunction, anaemia, hypotension as well as inflammation.^{25,26} AF often leads to high ventricular rates, atrial fibrosis and systemic inflammation, all of which could potentially mediate type 2 MI. Having in mind the global health burden of AF, these reports are additionally emphasised.²⁷ Interestingly, a recent study showed that patients with AF were less likely to have STEMI than non-AF patients with different coronary involvement including less right coronary artery occlusions.²⁸ Our analysis revealed consistent findings of lower proportion of STEMI patients in AF subgroup, irrespectively of the diagnosis coding priority. Other mechanisms identified in the respiratory disorder, heart failure, arrhythmia and gastrointestinal groups leading to possible type 2 MI are hypoxia, tachycardia and anaemia respectively, which all either result in reduced blood supply or increased physiological demand, leading to supply-demand mismatch.²⁹ It is therefore important to differentiate between secondary AMI diagnoses and type 2 MI where treatments would be different particularly around the utilisation of revascularisation, as would be patient outcomes.

The primary cause of admission amongst patients with secondary AMI diagnoses varied significantly, with the most common causes being infection, respiratory disorders, and heart failure. There were significant differences in patient characteristics and invasive management strategy for AMI between secondary AMI diagnosis subgroups when stratified according to primary admission diagnosis. However, these differences persisted in multivariable analysis, with respiratory and infection primary diagnoses associated with the highest odds of mortality while the gastrointestinal group was associated with an 8-fold increase in odds bleeding, suggesting that these adverse events were more likely as a result of their primary diagnosis than their secondary AMI.

4.1 | Limitations

We acknowledge some limitations of our study. First, the NIS is an administrative dataset that is subject to coding inaccuracies and underreporting of secondary diagnoses.³⁰ Although the identification of AMI diagnoses was based on the use of administrative codes, ICD-9 codes have previously been validated for the purposes of cardiovascular research.^{31,32} Furthermore, we acknowledge that an unknown proportion of secondary AMI diagnosis patients represented type 2 AMI, in the setting of acute illness such as infection, arrhythmias and respiratory disorders. Unfortunately, ICD-9 does not provide means to distinguish between type 1 and type 2 AMI, nor is it possible to assess the severity of coronary artery disease or the ability to risk-stratify AMI patients with established risk scores such as GRACE or Killip class.

Thirdly, since the NIS dataset does not record pharmacotherapy, it was not possible for us to examine the differences in antiplatelet therapy commenced between the primary and secondary diagnosis groups. The NIS also fails to capture the exact cause of death as well as long term outcomes in the primary and secondary AMI diagnosis groups, thereby limiting findings to in-hospital events. Nevertheless, we believe that our study provides insight into real world in-hospital clinical outcomes of a large cohort of patients with primary and secondary diagnosis AMI.

5 | CONCLUSION

Our comparison between primary and secondary AMI diagnoses illustrates that up to one-third of all AMI admitted to hospitals in the United States do not have AMI coded as a principal diagnosis. We find significant differences in characteristics, management strategy as well as in-hospital outcomes. Importantly this study highlights the significant healthcare burden associated with secondary AMI. It will be essential in future for studies to consider all AMI diagnoses in order to accurately inform clinical decision-making and health planning.

DISCLOSURE


The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors take full responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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APPENDIX A**MULTIVARIABLE LOGISTIC REGRESSION MODEL**

The following variables were adjusted for in multivariable logistic regression analysis because of clinical importance and possible direct relation to the clinical outcomes: hospital factors: bed size of hospital, region of hospital, location/teaching status of hospital, and patient demographics: age, sex, race, weekend admission, primary expected payer, median household income, smoking status, previous myocardial infarction (MI), previous coronary artery bypass graft (CABG) surgery, history of ischaemic heart disease (IHD), previous percutaneous

coronary intervention (PCI), previous cerebrovascular accident (CVA), atrial fibrillation (AF), thrombocytopenia, Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, chronic blood loss anaemia, chronic pulmonary disease, coagulopathy, congestive heart failure, deficiency anaemias, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological disorders, obesity, paralysis, peptic ulcer, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, rheumatoid arthritis/collagen vascular diseases, solid tumour without metastasis, valvular heart disease, and weight loss) and receipt of PCI.

Supplementary Material:

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Supplementary Table 1. Search codes.

Variable	Source	Codes
Diagnoses		
AMI	ICD-9	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.70, 410.71, 410.72, 410.8x, 410.9x
STEMI	ICD-9	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x
NSTEMI	ICD-9	410.70, 410.71, 410.72
CLD	ICD-9	571.0, 571.2, 571.3, 571.4x, 571.5, 571.6, 571.8, 571.9
Dyslipidemia	CCS	53
Smoking Status	ICD-9	V15.82, 305.1
AF	ICD-9	427.31
History of IHD	ICD-9	414.00-07, 414.2-9
Previous MI	ICD-9	412
Previous PCI	ICD-9	V45.82
Previous CABG	ICD-9	V45.81
Family history of CAD	ICD-9	V17.3
Previous CVA (TIA and Stroke)	ICD-9	V12.54
Thrombocytopenia	ICD-9	287.5, 287.49
In-hospital procedures and outcomes		
Acute ischemic stroke	ICD-9	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0-1, 435.8-9, 436
Shock during admission	ICD-9	785.51
Major bleeding	ICD-9	430, 431, 432x, 459.0, 578x, 784.7, 786.3
Use of assist device or IABP	ICD-9	37.68, 37.61
Hemopericardium	ICD-9	423.0
Pericardiocentesis	ICD-9	37.0
Cardiac tamponade	ICD-9	423.3
Coronary dissection	ICD-9	414.12
Diagnostic Cardiac catheterization	CCS	47
CABG	CCS	44
PCI	CCS	45

Abbreviations: AF – atrial fibrillation; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CLD – chronic liver disease; CVA – cerebrovascular accident; IABP – intra-aortic balloon pump; IHD – ischemic heart disease; MI – myocardial infarction; NSTEMI – non-ST-elevation myocardial infarction; PCI – percutaneous coronary intervention; STEMI – ST-elevation myocardial infarction; TIA – transient ischemic attack.

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Supplementary Table 2. Primary diagnoses in the secondary AMI diagnosis group.

	Primary diagnoses:	ICD-9 codes	%
Disorders of coronary circulation (not acute myocardial infarction)	Coronary atherosclerosis of native coronary artery	414.01	6.2%
	Coronary atherosclerosis of autologous vein bypass graft	414.02	0.2%
	Coronary atherosclerosis of unspecified type of vessel, native or graft	414.00	0.2%
	Other specified forms of chronic ischemic heart disease	414.8	0.1%
Heart failure	Congestive heart failure, unspecified	428.0	4.9%
	Acute on chronic systolic heart failure	428.23	1.9%
	Acute on chronic diastolic heart failure	428.33	1.0%
	Systolic heart failure, acute	428.21	0.7%
	Acute diastolic heart failure	428.31	0.4%
	Unspecified hypertensive heart disease with heart failure	402.91	0.2%
	Rheumatic heart failure (congestive)	398.91	0.2%
	Diastolic heart failure, unspecified	428.30	0.2%
	Acute combined systolic and diastolic heart failure	428.41	0.2%
	Systolic heart failure, unspecified	428.20	0.1%
	Chronic systolic heart failure	428.22	0.1%
Valve disorders	Aortic valve disorders	424.1	0.5%
	Mitral valve disorders	424.0	0.1%
	Mitral valve insufficiency and aortic valve stenosis	396.2	0.1%
Arrhythmias and conduction disorders	Atrial fibrillation	427.31	2.0%
	Paroxysmal ventricular tachycardia	427.1	0.7%
	Ventricular fibrillation	427.41	0.4%
	Other specified cardiac dysrhythmias	427.89	0.4%
	Atrioventricular block, complete	426.0	0.3%
	Sinoatrial node dysfunction	427.81	0.3%
	Atrial flutter	427.32	0.2%
Aortic and peripheral vascular disorders	Paroxysmal supraventricular tachycardia	427.0	0.1%
	Atherosclerosis of native arteries of the extremities with gangrene	440.24	0.3%
	Occlusion and stenosis of carotid artery without mention of cerebral infarction	433.10	0.3%
	Abdominal aneurysm without mention of rupture	441.4	0.2%
	Arterial embolism and thrombosis of lower extremity	444.22	0.2%
	Abdominal aneurysm, ruptured	441.3	0.1%
	Atherosclerosis of native arteries of the extremities with ulceration	440.23	0.1%
	Atherosclerosis of native arteries of the extremities with intermittent claudication	440.21	0.1%
	Peripheral vascular complications, not elsewhere classified	997.2	0.1%
	Atherosclerosis of native arteries of the extremities with rest pain	440.22	0.1%
	Peripheral vascular disease, unspecified	443.9	0.1%
	Dissection of aorta, thoracic	441.01	0.1%
	Other pulmonary embolism and infarction	415.19	0.7%
	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity	453.41	0.1%

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Arterial hypertension and its complications	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	404.91	0.3%
	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease	403.91	0.2%
	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease	404.93	0.1%
	Unspecified essential hypertension	401.9	0.1%
	Malignant essential hypertension	401.0	0.1%
	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage I through stage IV, or unspecified	403.00	0.1%
	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage I through stage IV, or unspecified	403.90	0.1%
	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	404.01	0.1%
	Other complications due to other cardiac device, implant, and graft	996.72	1.5%
Other cardiovascular conditions and complications	Cardiac complications, not elsewhere classified	997.1	0.5%
	Cardiac arrest	427.5	0.2%
	Other complications due to other vascular device, implant, and graft	996.74	0.2%
	Hypotension, unspecified	458.9	0.1%
	Orthostatic hypotension	458.0	0.1%
	Takotsubo syndrome	429.83	0.1%
	Postmyocardial infarction syndrome	411.0	0.1%
	Unspecified disease of pericardium	423.9	0.1%
	Other chest pain	786.59	0.7%
Chest pain and syncope	Syncope and collapse	780.2	0.3%
	Chest pain, unspecified	786.50	0.3%
	Unspecified septicemia	038.9	9.8%
Infection	Pneumonia, organism unspecified	486	3.3%
	Septicemia due to escherichia coli [E. coli]	038.42	1.2%
	Urinary tract infection, site not specified	599.0	0.8%
	Methicillin susceptible Staphylococcus aureus septicemia	038.11	0.6%
	Streptococcal septicemia	038.0	0.6%
	Other septicemia due to gram-negative organisms	038.49	0.6%
	Methicillin resistant Staphylococcus aureus septicemia	038.12	0.3%
	Intestinal infection due to Clostridium difficile	008.45	0.3%
	Infection and inflammatory reaction due to other vascular device, implant, and graft	996.62	0.3%
	Other postoperative infection	998.59	0.3%
	Other specified septicemias	038.8	0.3%
	Cellulitis and abscess of leg, except foot	682.6	0.2%
	Calculus of gallbladder with acute cholecystitis, without mention of obstruction	574.00	0.2%
	Pneumococcal septicemia [Streptococcus pneumoniae septicemia]	038.2	0.2%
	Other staphylococcal septicemia	038.19	0.2%
	Septicemia due to gram-negative organism, unspecified	038.40	0.2%

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Respiratory disorders (non-infectious)	Infection and inflammatory reaction due to indwelling urinary catheter	996.64	0.2%
	Acute and subacute bacterial endocarditis	421.0	0.2%
	Methicillin susceptible pneumonia due to <i>Staphylococcus aureus</i>	482.41	0.1%
	Pneumonia due to other gram-negative bacteria	482.83	0.1%
	Infection and inflammatory reaction due to cardiac device, implant, and graft	996.61	0.1%
	Methicillin resistant pneumonia due to <i>Staphylococcus aureus</i>	482.42	0.1%
	Septicemia due to anaerobes	038.3	0.1%
	Influenza with pneumonia	487.0	0.1%
	Pneumonia due to <i>Pseudomonas</i>	482.1	0.1%
	Bacterial pneumonia, unspecified	482.9	0.1%
	Infection due to central venous catheter	999.31	0.1%
	Staphylococcal septicemia, unspecified	038.10	0.1%
	Human immunodeficiency virus [HIV] disease	042	0.1%
	Pneumococcal pneumonia [<i>Streptococcus pneumoniae</i> pneumonia]	481	0.1%
	Bacteremia	790.7	0.1%
	Bloodstream infection due to central venous catheter	999.32	0.1%
	Infection and inflammatory reaction due to internal joint prosthesis	996.66	0.1%
	Intestinal infection due to other organism, not elsewhere classified	008.8	0.1%
	Infection (chronic) of amputation stump	997.62	0.1%
	Acute respiratory failure	518.81	5.8%
	Pneumonitis due to inhalation of food or vomitus	507.0	1.7%
	Obstructive chronic bronchitis with (acute) exacerbation	491.21	1.4%
	Acute and chronic respiratory failure	518.84	1.0%
	Acute on chronic combined systolic and diastolic heart failure	428.43	0.7%
	Obstructive chronic bronchitis with acute bronchitis	491.22	0.3%
	Chronic obstructive asthma with (acute) exacerbation	493.22	0.2%
	Unspecified pleural effusion	511.9	0.1%
	Postinflammatory pulmonary fibrosis	515	0.1%
	Acute bronchitis	466.0	0.1%
	Acute edema of lung, unspecified	518.4	0.1%
	Pulmonary insufficiency following trauma and surgery	518.5	0.1%
	Asthma, unspecified type, with (acute) exacerbation	493.92	0.1%
Gastrointestinal, hepatic and bile disorders	Hemorrhage of gastrointestinal tract, unspecified	578.9	1.0%
	Acute pancreatitis	577.0	0.4%
	Chronic or unspecified gastric ulcer with hemorrhage, without mention of obstruction	531.40	0.3%
	Blood in stool	578.1	0.3%
	Chronic or unspecified duodenal ulcer with hemorrhage, without mention of obstruction	532.40	0.3%
	Diverticulosis of colon with hemorrhage	562.12	0.3%
	Intestinal or peritoneal adhesions with obstruction (postoperative) (postinfection)	560.81	0.2%
	Diverticulitis of colon (without mention of hemorrhage)	562.11	0.2%
	Unspecified intestinal obstruction	560.9	0.2%
	Acute vascular insufficiency of intestine	557.0	0.2%
	Unspecified vascular insufficiency of intestine	557.9	0.1%
	Angiodysplasia of stomach and duodenum with hemorrhage	537.83	0.1%

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	Other and unspecified noninfectious gastroenteritis and colitis	558.9	0.1%
	Hematemesis	578.0	0.1%
	Acute cholecystitis	575.0	0.1%
	Angiodysplasia of intestine with hemorrhage	569.85	0.1%
	Paralytic ileus	560.1	0.1%
	Calculus of gallbladder with other cholecystitis, without mention of obstruction	574.10	0.1%
	Other specified gastritis, with hemorrhage	535.41	0.1%
	Esophageal reflux	530.81	0.1%
	Alcoholic cirrhosis of liver	571.2	0.1%
	Perforation of intestine	569.83	0.1%
	Hemorrhage of rectum and anus	569.3	0.1%
	Gastroesophageal laceration-hemorrhage syndrome	530.7	0.1%
	Unspecified gastritis and gastroduodenitis, with hemorrhage	535.51	0.1%
	Incisional ventral hernia with obstruction	552.21	0.1%
	Acute gastric ulcer with hemorrhage, without mention of obstruction	531.00	0.1%
	Cirrhosis of liver without mention of alcohol	571.5	0.1%
	Acute duodenal ulcer, with hemorrhage	532.00	0.1%
	Other specified intestinal obstruction	560.89	0.1%
	Ulcer of esophagus with bleeding	530.21	0.1%
Cerebrovascular and other neurological disorders	Cerebral artery occlusion, unspecified with cerebral infarction	434.91	1.9%
	Cerebral embolism with cerebral infarction	434.11	0.8%
	Intracerebral hemorrhage	431	0.4%
	Subarachnoid hemorrhage	430	0.2%
	Unspecified transient cerebral ischemia	435.9	0.2%
	Occlusion and stenosis of carotid artery with cerebral infarction	433.11	0.2%
	Other convulsions	780.39	0.1%
	Anoxic brain damage	348.1	0.1%
	Epilepsy, unspecified, without mention of intractable epilepsy	345.90	0.1%
	Subdural hemorrhage	432.1	0.1%
	Subdural hemorrhage following injury without mention of open intracranial wound, with no loss of consciousness	852.21	0.1%
	Grand mal status	345.3	0.1%
	Cerebral thrombosis with cerebral infarction	434.01	0.1%
	Hepatic encephalopathy	572.2	0.1%
	Altered mental status	780.97	0.1%
	Encephalopathy, unspecified	348.30	0.1%
	Subdural hemorrhage following injury without mention of open intracranial wound, unspecified state of consciousness	852.20	0.1%
	Alzheimer's disease	331.0	0.1%
Fractures and bone disorders	Closed fracture of intertrochanteric section of neck of femur	820.21	0.8%
	Closed fracture of unspecified part of neck of femur	820.8	0.5%
	Other closed transcervical fracture of neck of femur	820.09	0.4%
	Osteoarthritis, Localized, not specified whether primary or secondary, lower leg	715.36	0.3%
	Osteoarthritis, localized, not specified whether primary or secondary, pelvic region and thigh	715.35	0.1%
	Closed fracture of subtrochanteric section of neck of femur	820.22	0.1%
	Spinal stenosis, lumbar region, without neurogenic claudication	724.02	0.1%
	Osteoarthritis, unspecified whether generalized or localized, lower leg	715.96	0.1%

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	Pathologic fracture of vertebrae	733.13	0.1%
	Closed fracture of pubis	808.2	0.1%
	Closed fracture of lumbar vertebra without mention of spinal cord injury	805.4	0.1%
	Closed fracture of shaft of femur	821.01	0.1%
Acute renal failure and urinary tract disorders (non-infectious)	Acute kidney failure, unspecified	584.9	1.8%
	Acute kidney failure with lesion of tubular necrosis	584.5	0.2%
	Calculus of ureter	592.1	0.1%
	Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms (LUTS)	600.01	0.1%
Anemias	Acute posthemorrhagic anemia	285.1	0.2%
	Anemia, unspecified	285.9	0.1%
	Iron deficiency anemia secondary to blood loss (chronic)	280.0	0.1%
	Iron deficiency anemia, unspecified	280.9	0.1%
Diabetes Mellitus	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled	250.13	0.3%
	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled	250.80	0.3%
	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled	250.12	0.2%
	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled	250.70	0.2%
	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled	250.82	0.1%
	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled	250.72	0.1%
	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled	250.60	0.1%
	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled	250.40	0.1%
	Dehydration	276.51	0.2%
	Poisoning by; other specified central nervous system stimulants	970.8	0.2%
Intoxication, fluid disorders and muscular diseases	Poisoning by cocaine	970.81	0.1%
	Hyposmolality and/or hyponatremia	276.1	0.1%
	Rhabdomyolysis	728.88	0.1%
	Poisoning by other opiates and related narcotics	965.09	0.1%
	Poisoning by benzodiazepine-based tranquilizers	969.4	0.1%
	Metabolic encephalopathy	348.31	0.1%
	Poisoning by opium (alkaloids), unspecified	965.00	0.1%
	Hyperpotassemia	276.7	0.1%
	Volume depletion	276.5	0.1%
	Toxic encephalopathy	349.82	0.1%
	Poisoning by heroin	965.01	0.1%
	Poisoning by methadone	965.02	0.1%
	Malignant neoplasm of upper lobe, bronchus or lung	162.3	0.1%
	Malignant neoplasm of bronchus and lung, unspecified	162.9	0.1%
Tumors	Acute myeloid leukemia, without mention of having achieved remission	205.00	0.1%
	Malignant neoplasm of kidney, except pelvis	189.0	0.1%
	Malignant neoplasm of ascending colon	153.6	0.1%
	Malignant neoplasm of lower lobe, bronchus or lung	162.5	0.1%
	Malignant neoplasm of cecum	153.4	0.1%

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	Secondary malignant neoplasm of brain and spinal cord	198.3	0.1%
	Malignant neoplasm of rectum	154.1	0.1%
	Malignant neoplasm of prostate	185	0.1%
	Secondary malignant neoplasm of bone and bone marrow	198.5	0.1%
	Benign neoplasm of colon	211.3	0.1%
	Care involving other specified rehabilitation procedure	V57.8 9	2.5%
	Care involving other physical therapy	V57.1	0.2%
	Resection of vessel with replacement, upper limb vessels	384.3	0.1%
Miscellaneous	Other complications due to renal dialysis device, implant, and graft	996.73	0.1%
	Hemorrhage complicating a procedure	998.11	0.1%
	Hematoma complicating a procedure	998.12	0.1%
	Other malaise and fatigue	780.79	0.1%
	Other iatrogenic hypotension	458.29	0.1%
Other (individual diagnosis <0.1%)		/	13.6 %

Abbreviations: AMI – Acute Myocardial Infarction.

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Supplementary Table 3. Comparison of treatments and in-hospital adverse outcomes according to diagnosis priority in the STEMI subgroup.

Variables	Diagnosis priority		P-value
	Primary AMI diagnosis (66.1%)	Secondary AMI diagnosis (33.9%)	
Treatments, %			
CA	82.1	35.5	<0.001
PCI	71.3	25.9	<0.001
CABG	7.7	7.5	<0.001
Use of assist device or IABP	9.8	5.2	<0.001
Outcomes, %			
MACCE	9.9	22.6	<0.001
All-cause mortality	7.0	16.3	<0.001
Major bleeding	2.8	6.0	<0.001
Cardiac complications	1.154	1.454	<0.001
Stroke	2.3	6.8	<0.001
Length of stay (days), median (IQR)	3 (2, 5)	5 (2, 9)	<0.001
Total charges (USD), median (IQR)	54,666 (34,846, 86,796)	45,355 (20,333, 93,498)	<0.001

Abbreviations: CA – Coronary Angiography; CABG – Coronary Artery Bypass Graft; IABP – Intra-aortic Balloon Pump; IQR – Interquartile Range; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/ transient ischemic attack and cardiac complications); PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

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Supplementary Table 4. Adjusted odds of invasive management and in-hospital adverse outcomes in secondary AMI group amongst STEMI patients*.

Variables	OR [95% CI]	P-value**
CA	0.15 [0.15, 0.15]	<0.001
PCI	0.20 [0.19, 0.20]	<0.001
MACCE	1.42 [1.40, 1.44]	<0.001
All-cause mortality	1.25 [1.23, 1.27]	<0.001
Major bleeding	1.33 [1.30, 1.36]	<0.001
Stroke	1.70 [1.66, 1.74]	<0.001

*Reference group is primary AMI group.

**Multivariable logistic regression model adjusted for: bed size of hospital, region of hospital, location/teaching status of hospital, age, sex, race, weekend admission, primary expected payer, smoking status, previous myocardial infarction, previous coronary artery bypass graft surgery, history of ischaemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accident, atrial fibrillation, thrombocytopenia, Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, chronic blood loss anaemia, chronic pulmonary disease, coagulopathy, congestive heart failure, deficiency anaemias, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological disorders, obesity, paralysis, peptic ulcer, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, rheumatoid arthritis/collagen vascular diseases, solid tumor without metastasis, valvular heart disease, and weight loss) and receipt of PCI.

Abbreviations: CA – Coronary Angiography; CI – Confidence Interval; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); NSTEMI – non-ST-elevation Myocardial Infarction; OR – Odds Ratios; PCI – Percutaneous Coronary Intervention; STEMI – ST-elevation Myocardial Infarction.

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Median Household Income (percentile), %										<0.001
0-25th	27.5	25.3	28.1	28.9	27.9	25.2	27.0	26.2	27.0	
26th-50th	27.4	26.2	27.0	27.1	26.5	27.5	26.0	26.4	26.3	
51st-75th	23.7	24.5	24.1	23.7	23.1	25.5	24.7	25.6	24.4	
76th-100th	21.4	24.0	20.8	20.3	22.4	21.8	22.3	21.8	22.3	
Cardiogenic shock, %	5.0	3.4	4.3	6.2	5.3	5.3	2.6	3.0	3.4	<0.001
Cardiac arrest, %	3.1	2.3	2.5	8.4	5.1	9.6	3.6	3.5	4.6	<0.001
Cardiac tamponade, %	0.091	0.250	0.107	0.049	0.071	0.125	0.029	0.050	0.183	<0.001
Hemopericardium, %	0.041	0.103	0.034	0.011	0.015	0.063	0.005	0.025	0.053	<0.001
Comorbidities, %										
Atrial fibrillation	16.6	15.5	30.5	24.4	27.1	15.6	27.6	25.0	22.4	<0.001
Dyslipidemia	54.9	63.2	39.0	30.1	27.9	44.7	35.4	32.9	37.4	<0.001
Thrombocytopenia	3.3	4.5	4.4	5.3	9.6	4.4	6.4	7.4	5.5	<0.001
Dementia	5.8	1.8	9.6	11.0	15.7	8.5	9.3	14.7	9.5	<0.001
Smoking	34.9	34.1	20.7	27.2	16.2	23.2	19.0	15.8	21.6	<0.001
Previous AMI	10.4	8.3	9.6	7.8	6.4	10.6	8.2	7.3	7.9	<0.001
Previous PCI	11.8	24.5	12.7	7.6	5.9	14.8	13.0	8.8	13.2	<0.001
Previous CABG	7.5	5.1	12.4	7.7	7.5	12.1	10.6	9.4	9.8	<0.001
Previous CVA	4.0	3.1	4.9	4.6	5.0	5.4	5.0	5.5	4.9	<0.001
Anemias	15.8	13.5	28.5	24.6	28.6	18.8	31.8	38.6	24.0	<0.001
Chronic blood loss anemia	1.1	1.0	1.5	1.4	1.4	0.9	12.2	2.4	2.2	<0.001
Valvular disease	0.3	11.2	25.4	13.9	12.4	18.8	14.6	12.8	11.6	<0.001
Hypertension	66.9	66.6	57.3	51.4	47.4	61.0	56.2	52.9	55.0	<0.001
Peripheral vascular disorders	10.9	11.8	14.0	11.6	12.5	11.0	14.0	12.9	13.0	<0.001
Obesity	12.0	12.0	9.3	10.0	8.1	9.7	6.6	9.0	8.0	<0.001
Weight loss	2.2	1.6	4.5	9.8	14.4	3.9	10.0	11.4	8.0	<0.001
Diabetes Mellitus	34.3	35.4	42.8	34.8	34.9	31.2	32.1	41.0	31.6	<0.001
Hypothyroidism	9.7	7.5	12.5	10.7	11.5	13.0	11.2	12.1	10.7	<0.001
Liver disease	1.2	0.9	1.5	1.8	2.7	1.2	3.7	2.5	2.1	<0.001

Supplementary Material:

Matetic A. et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Chronic renal failure	16.7	11.7	32.7	24.5	28.8	21.6	24.2	45.7	21.3	<0.001
RA/collagen vascular diseases	2.2	1.6	2.3	2.4	3.1	2.5	2.8	2.4	2.6	<0.001
Solid tumor without metastasis	1.4	0.3	1.0	1.8	2.4	1.0	1.6	2.4	3.4	<0.001
Metastatic cancer	0.9	0.3	1.0	1.8	2.4	1.0	1.6	2.4	3.4	<0.001
Lymphoma	0.5	0.3	0.8	0.8	1.5	0.9	0.9	1.4	0.9	<0.001
Fluid and electrolyte disorders	19.4	12.6	29.7	44.0	49.9	26.8	37.5	62.4	31.5	<0.001
Bed size of hospital, %										<0.001
Small	10.7	8.8	14.5	13.8	14.4	12.8	13.2	13.2	11.7	
Medium	24.8	21.4	26.0	26.9	27.0	25.2	26.3	26.2	24.4	
Large	64.5	69.8	59.5	59.3	58.6	62.0	60.4	60.6	63.9	
Hospital Region, %										<0.001
Northeast	19.3	16.5	22.1	20.0	21.8	21.4	23.2	22.5	21.4	
Midwest	23.0	25.7	23.3	22.6	21.7	24.8	23.8	23.2	24.5	
South	40.1	38.5	37.9	40.9	37.3	36.9	36.3	38.2	36.5	
West	17.6	19.2	16.7	16.5	19.3	16.9	16.7	16.1	17.7	
Location/teaching status of hospital, %										<0.001
Rural	10.3	5.4	14.6	13.8	13.2	13.1	13.3	12.1	11.2	
Urban non-teaching	40.9	37.6	42.0	44.7	41.0	39.6	40.4	41.6	36.4	
Urban teaching	48.7	57.0	43.4	41.5	45.8	47.3	46.3	46.3	52.4	

Abbreviations: AMI – Acute Myocardial Infarction; CABG – coronary artery bypass grafting; CVA – cerebrovascular accident; IQR – interquartile range; PCI – percutaneous coronary intervention; RA – rheumatoid arthritis; STEMI – ST-elevation myocardial infarction.

Supplementary Material:

Matetic A. et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Table 6. Comparison of treatments and in-hospital adverse outcomes among subgroups of secondary AMI diagnosis group (based on primary diagnostic category).

Variables	Diagnosis priority									P-value
	Primary AMI diagnosis (66.1%)	Disorders of coronary circulation (not AMI) (2.3%)	Heart failure and valve disorders (3.5%)	Respiratory disorders (non-infectious) (3.8%)	Infection (7.1%)	Arrhythmias and conduction disorders (1.5%)	Gastrointes (inal, hepatic and bile disorders (1.7%)	Acute renal failure and urinary tract disorders (non-infectious) (0.7%)	Other (13.2%)	
Treatments, %										
CA	64.9	61.0	20.0	14.8	9.7	29.0	9.8	8.9	17.4	<0.001
PCI	43.3	49.8	5.2	3.6	3.0	9.0	3.1	3.1	7.8	<0.001
CABG	8.8	33.8	4.0	0.3	0.4	1.7	0.5	0.5	1.3	<0.001
Outcomes, %										
MACCE	9.6	9.2	13.8	27.2	29.4	13.9	18.4	18.5	25.7	<0.001
All-cause mortality	5.8	3.0	10.5	23.8	26.1	9.7	15.3	15.6	14.1	<0.001
Major bleeding	3.0	1.7	3.8	6.9	6.9	3.2	29.7	6.9	7.5	<0.001
Stroke	3.6	4.5	3.7	5.1	5.0	4.5	3.8	3.8	13.6	<0.001

Abbreviations: AMI Acute Myocardial Infarction; CA Coronary Angiography; MACCE Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); PCI Percutaneous Coronary Intervention.

Supplementary Material:

Matetic A. et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Table 7. Adjusted odds of invasive management and in-hospital adverse outcomes in subgroups of secondary AMI diagnosis group (based on primary diagnostic category)*.

Variables	OR [95% CI]**							
	Disorders of coronary circulation (not AMI)	Heart failure and valve disorders	Respiratory disorders (non-infectious)	Infection	Arrhythmias and conduction disorders	Gastrointestinal, hepatic and bile disorders	Acute renal failure and urinary tract disorders (non-infectious)	Other
Invasive management:								
CA	1.57 [1.55, 1.58]	0.20 [0.19, 0.20]	0.16 [0.16, 0.16]	0.11 [0.11, 0.11]	0.29 [0.29, 0.30]	0.09 [0.09, 0.09]	0.09 [0.09, 0.10]	0.14 [0.14, 0.14]
PCI	2.59 [2.57, 2.62]	0.13 [0.13, 0.13]	0.10 [0.10, 0.11]	0.10 [0.10, 0.10]	0.18 [0.18, 0.18]	0.08 [0.07, 0.08]	0.10 [0.09, 0.10]	0.17 [0.17, 0.17]
Outcomes:								
MACCE	0.96 [0.95, 0.98]	0.98 [0.97, 0.99]	2.07 [2.05, 2.08]	1.99 [1.98, 2.00]	1.07 [1.06, 1.09]	1.25 [1.23, 1.26]	1.07 [1.05, 1.10]	2.13 [2.12, 2.15]
All-cause mortality	0.49 [0.48, 0.50]	1.14 [1.12, 1.15]	2.65 [2.63, 2.68]	2.48 [2.46, 2.49]	1.15 [1.13, 1.17]	1.51 [1.49, 1.53]	1.26 [1.23, 1.29]	1.53 [1.52, 1.54]
Major bleeding	0.55 [0.53, 0.57]	0.92 [0.90, 0.94]	1.56 [1.54, 1.59]	1.41 [1.40, 1.43]	0.87 [0.84, 0.90]	7.99 [7.89, 8.10]	1.33 [1.29, 1.37]	1.84 [1.82, 1.85]
Cardiac complications	3.39 [3.27, 3.51]	0.84 [0.79, 0.90]	0.35 [0.32, 0.39]	0.38 [0.36, 0.41]	1.13 [1.04, 1.23]	0.27 [0.23, 0.32]	0.43 [0.35, 0.52]	1.48 [1.44, 1.52]
Stroke	1.42 [1.39, 1.45]	0.73 [0.71, 0.74]	1.01 [0.99, 1.02]	0.92 [0.91, 0.93]	0.95 [0.93, 0.98]	0.76 [0.74, 0.78]	0.70 [0.67, 0.73]	3.13 [3.11, 3.16]

*Reference group is primary AMI group.

**Multivariable logistic regression model adjusted for: bed size of hospital, region of hospital, location/teaching status of hospital, age, sex, race, weekend admission, primary expected payer, smoking status, previous myocardial infarction, previous coronary artery bypass graft surgery, history of ischaemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accident, atrial fibrillation, thrombocytopenia, Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, chronic blood loss anaemia, chronic pulmonary disease, coagulopathy, congestive heart failure, deficiency anaemias, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological disorders, obesity, paralysis, peptic ulcer, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, rheumatoid arthritis/collagen vascular diseases, solid tumor without metastasis, valvular heart disease, and weight loss) and receipt of PCI.

Abbreviations: AMI – Acute Myocardial Infarction; CA – Coronary Angiography; CI – Confidence Interval; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); OR – Odds Ratios; PCI – Percutaneous Coronary Intervention.

Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. Int J Clin Pract. 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Table 8. Evaluation of STEMI prevalence according to AF presence.

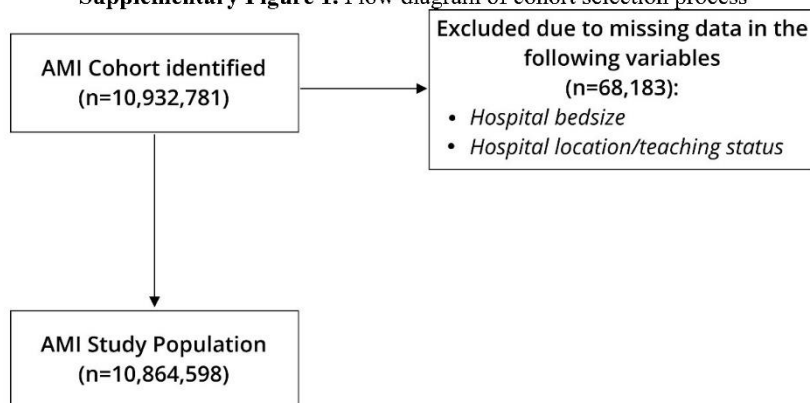
	Variables	No-AF	AF	P-value
STEMI, %	Total AMI cohort	24.0	14.4	<0.001
	Primary AMI diagnosis cohort	29.9	20.1	<0.001
	Secondary AMI diagnosis cohort	11.1	7.4	<0.001

Abbreviations: AF – atrial fibrillation; AMI – Acute Myocardial Infarction; STEMI – ST-elevation myocardial infarction.

Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. Int J Clin Pract. 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Figure 1. Flow diagram of cohort selection process

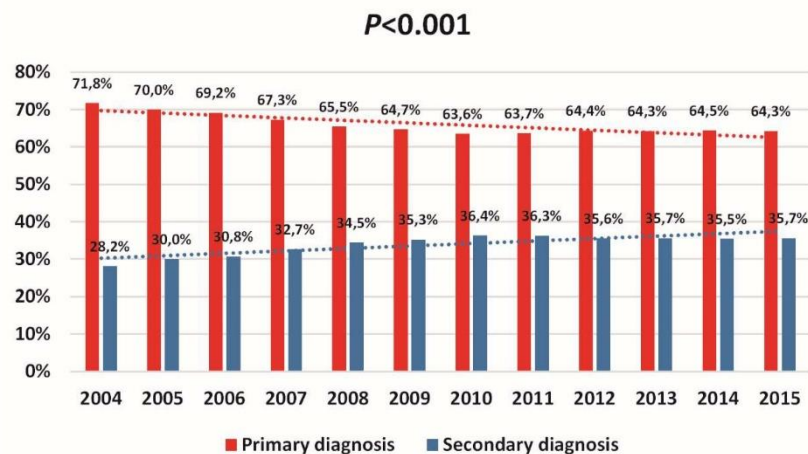


Abbreviations: AMI – Acute Myocardial Infarction.

Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Figure 2. Diagnosis priority distribution amongst AMI hospitalizations (2004-2015).

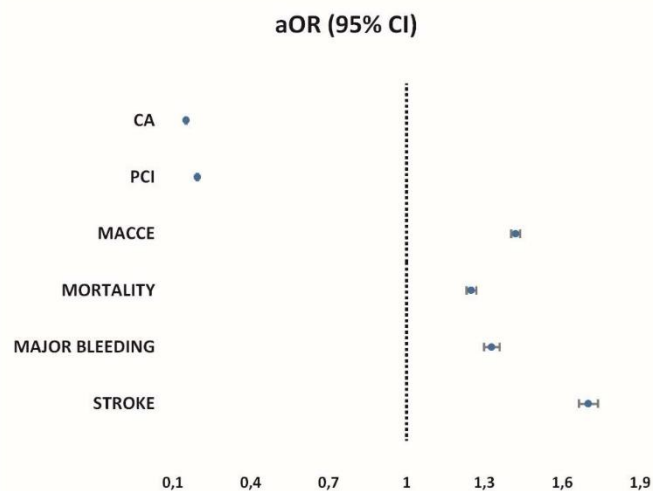


Abbreviations: AMI – Acute Myocardial Infarction.

Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. Int J Clin Pract. 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Figure 3. Adjusted odds ratios (OR) of invasive management and in-hospital adverse outcomes in secondary diagnosis group amongst STEMI patients*

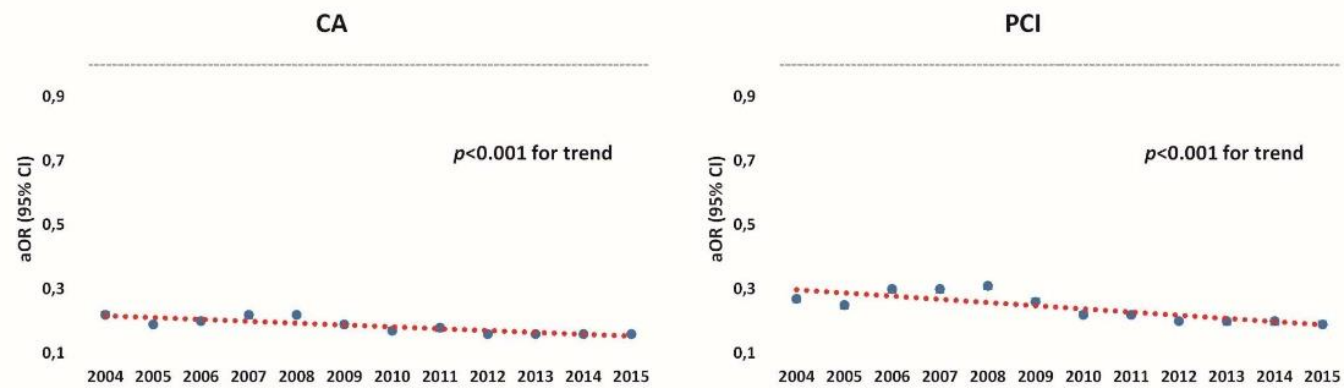


*Reference group is primary AMI diagnosis group. **Abbreviations:** CA – Coronary Angiography; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); NSTEMI – non-ST-elevation Myocardial Infarction; PCI – Percutaneous Coronary Intervention; STEMI – ST-elevation Myocardial Infarction.

Supplementary Material:

Matetic A. et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Figure 4. Trend of adjusted odds for invasive management in the secondary AMI diagnosis group from 2004 to 2015.

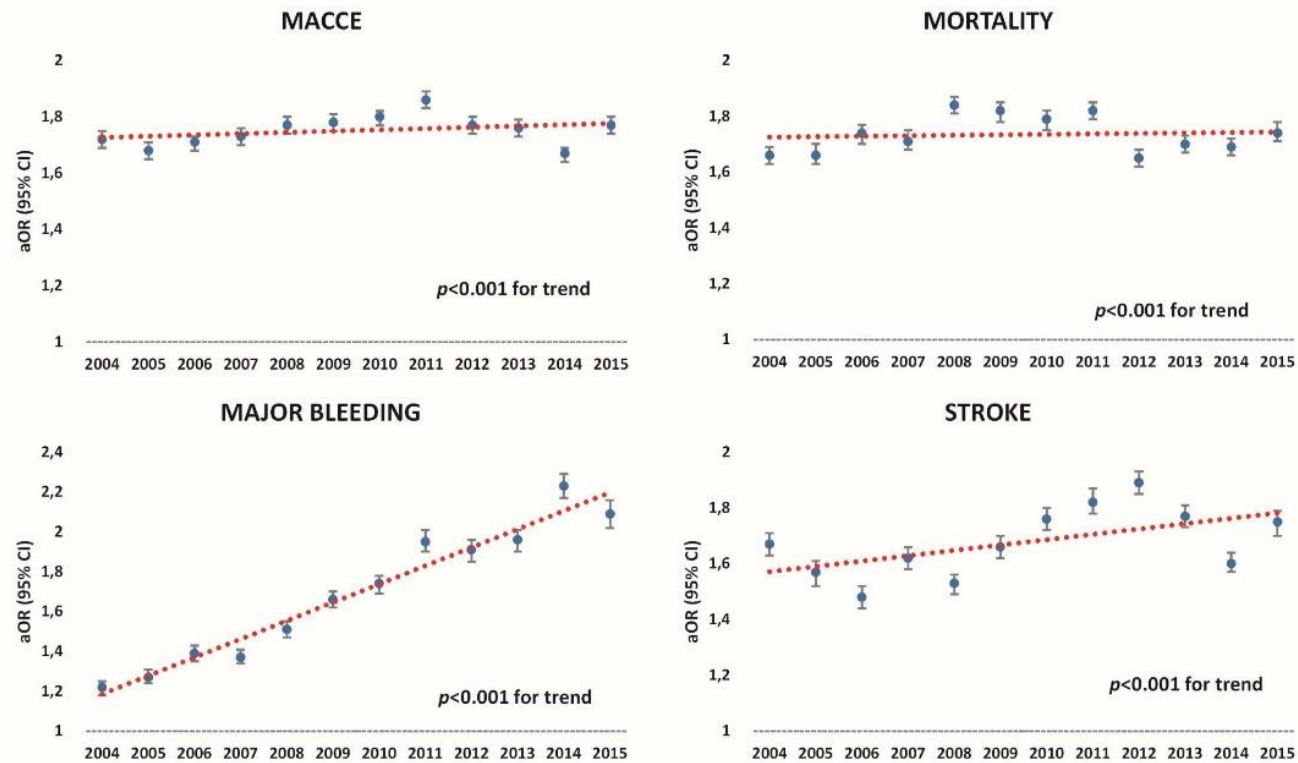


*Reference group is primary diagnosis group. **Abbreviations:** CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention.

Supplementary Material:

Matetic A. et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Figure 5. Trend of adjusted odds for in-hospital adverse outcomes in the secondary AMI diagnosis group from 2004 to 2015.



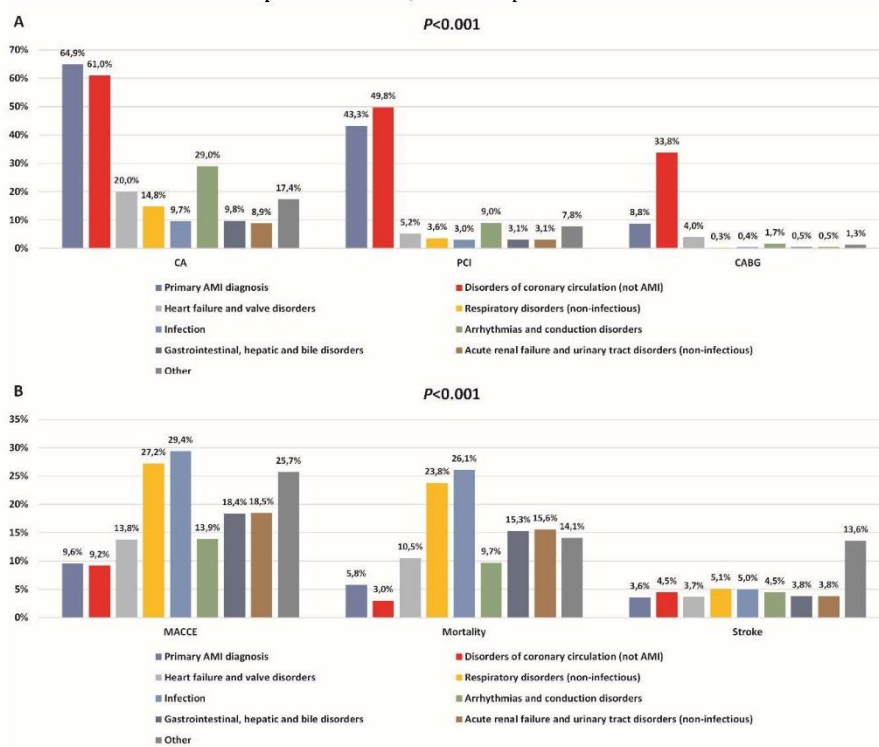
*Reference group is primary diagnosis group. **Abbreviations:** MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/ transient ischemic attack and cardiac complications).

Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Supplementary Figure 6. Comparison of treatments and in-hospital adverse outcomes among subgroups of secondary AMI diagnosis group (based on primary diagnostic category):

A. Receipt of treatment; **B.** In-hospital adverse outcomes.

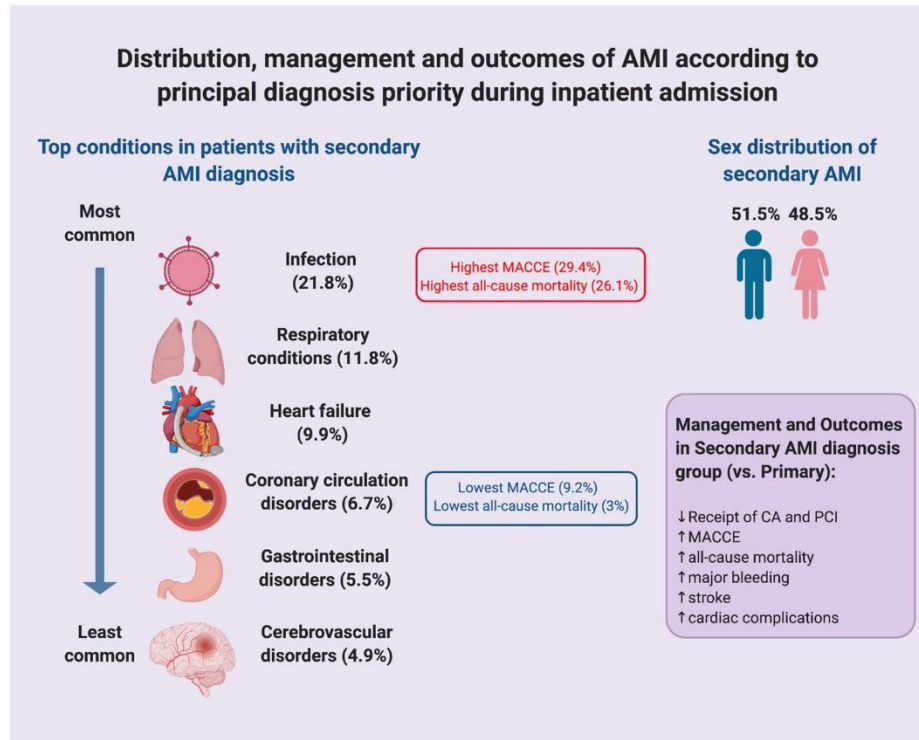


Abbreviations: CA – Coronary Angiography; CABG – Coronary Artery Bypass Grafting; IABP – Intra-aortic Balloon Pump; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/ transient ischemic attack and cardiac complications); PCI – Percutaneous Coronary Intervention.

Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. *Int J Clin Pract.* 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Visual Abstract



Supplementary Material:

Matetic A, et al. Distribution, management and outcomes of AMI according to principal diagnosis priority during inpatient admission. Int J Clin Pract. 2021;75(10):e14554. doi: 10.1111/ijcp.14554.

Appendix A. Multivariable logistic regression model

The following variables were adjusted for in multivariable logistic regression analysis due to clinical importance and possible direct relation to the clinical outcomes: hospital factors: bed size of hospital, region of hospital, location/teaching status of hospital, and patient demographics: age, sex, race, weekend admission, primary expected payer, median household income, smoking status, previous myocardial infarction (MI), previous coronary artery bypass graft (CABG) surgery, history of ischaemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accident (CVA), atrial fibrillation (AF), thrombocytopenia, Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, chronic blood loss anaemia, chronic pulmonary disease, coagulopathy, congestive heart failure, deficiency anaemias, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological disorders, obesity, paralysis, peptic ulcer, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, rheumatoid arthritis/collagen vascular diseases, solid tumor without metastasis, valvular heart disease, and weight loss) and receipt of PCI.

11.3. Research study 3

Real-world management and outcomes of 7 million patients with acute coronary syndrome according to clinical research trial enrolment status: a propensity matched analysis

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Aims

We aimed to determine whether clinical outcomes and invasive care of acute coronary syndrome (ACS) patients participating in trials differed from those of non-participants, particularly including those who were trial eligible.

Methods and results

We included all hospitalizations with a principal diagnosis of ACS in the US National Inpatient Sample between January 2004 and September 2015, stratified by trial enrolment and eligibility using the International Classification of Diseases, ninth revision. We conducted propensity score matching to investigate the following outcomes: all-cause mortality; major bleeding; stroke; composite of mortality, stroke, and cardiac complications [major adverse cardiovascular and cerebrovascular events (MACCEs)]; coronary angiography (CA); and percutaneous coronary intervention (PCI). A total of 7 091 179 weighted ACS hospitalizations were analysed, including 19 684 (0.3%) trial participants and 7 071 495 non-participants (3 485 514 of whom were trial eligible). Trial participants were more likely to receive CA ($\Delta\%$ 28.73%, 95% confidence interval (CI) 27.22–30.24, $P < 0.001$) and PCI ($\Delta\%$ 27.13%, 95% CI 24.86–29.41, $P < 0.001$), with decreased mortality ($\Delta\%$ –3.51%, 95% CI –4.72 to –2.31, $P < 0.001$), MACCEs ($\Delta\%$ –3.04%, 95% CI –4.55 to –1.53, $P < 0.001$), and bleeding ($\Delta\%$ –0.89%, 95% CI –1.59 to –0.19, $P = 0.013$) compared with non-participants. After accounting for eligibility, trial participants were more likely to undergo CA ($\Delta\%$ 22.78%, 95% CI 21.58–23.99, $P < 0.001$) and PCI ($\Delta\%$ 23.95%, 95% CI 21.77–26.13, $P < 0.001$), and had no difference in mortality ($\Delta\%$ –0.21%, 95% CI –0.65 to 0.24, $P = 0.362$).

Conclusion

Among ACS patients, trial enrolment was associated with significantly greater invasive care and lower mortality than among matched non-participants. Trial participants were more likely to be invasively managed even when compared with eligible non-participants, even though there was no difference in mortality.

Keywords

Acute coronary syndrome • Trial enrolment • Management • Outcomes

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Introduction

The management and outcomes of patients with acute coronary syndrome (ACS) have significantly improved in the last decade largely owing to evidence from randomized controlled trials.^{1,2} Patients with comorbidities that are frequently encountered in clinical practice, including cancer, end-stage renal disease or severe liver disease, and frailty, are often excluded from these trials.^{3–5} As such, patients enrolled into clinical trials or any other clinical studies are often lower risk than patients encountered in the real world and have a lower burden of important comorbidities that portend to worse outcomes.

Previous studies have investigated the association between trial enrolment and clinical outcomes among patients with ACS.^{6–9} Analysis of the GRACE registry showed that patients with acute myocardial infarction (AMI) enrolled in randomized controlled trials had lower comorbidity burden and in-hospital mortality compared with their counterparts.⁸ Similar findings were reported in the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry—Get With the Guidelines.⁹ Data from the nationwide Chest Pain–MI registry suggested that patients admitted to hospitals participating in clinical trials had better long-term outcomes.⁶ Further, analysis of the FAST-MI registry in France revealed higher receipt of guideline-directed therapy in trial participants, but this was not associated with lower 1-year mortality.⁷ The favourable outcomes of trial participants may be attributed to a lower risk profile.¹⁰ However, little is known about the management and outcomes of patients who may potentially meet trial eligibility recruitment criteria but are not enrolled into a trial. A comparison of care and outcomes between trial-eligible, but not enrolled, and trial-enrolled patients could add insight into whether trial participation is independently associated with benefit to patients.

In this retrospective study using a national database of ACS hospitalizations, we compared the management and clinical outcomes of patients enrolled in clinical trials with those who were not enrolled, including those who were trial eligible. In addition, we have compared management and clinical outcomes within non-participants based on eligibility. This is important, as groups of patients under-represented in clinical trials, such as ethnic minorities and women, may not gain the same benefits from trial participation as other sections of society.

Methods

Data

The National Inpatient Sample (NIS) was developed by the Agency for Healthcare Research and Quality (AHRQ), under the Healthcare Cost and Utilization Project. It is the largest publicly available all-payer longitudinal database of hospital inpatient discharges in the United States containing anonymized discharge-level data from >7 million hospitalizations annually. It represents a 20% stratified sample of the US community hospitals, excluding rehabilitation and long-term acute care hospitals, and provides sampling weights to calculate national estimates representing more than 95% of the US hospitalized population.¹¹ Since the NIS is a deidentified and publicly available database, institutional review board approval was not required. Finally, the study is reported according to the

STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (see Appendix A in the Supplementary Material).

Study design and population

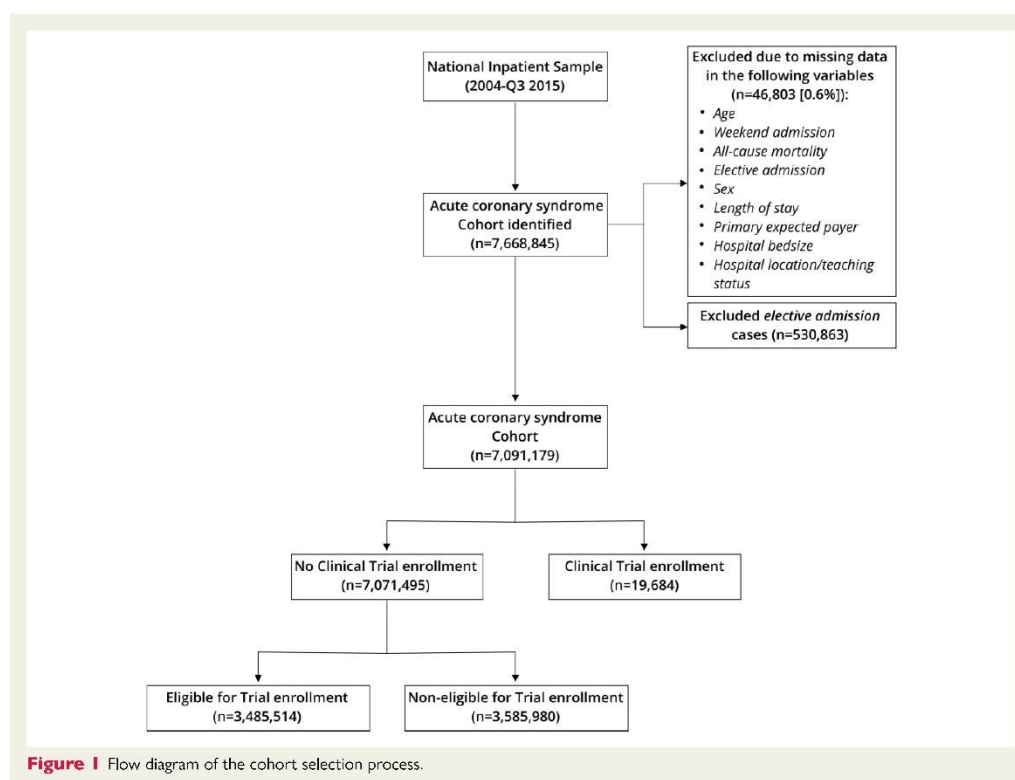
All hospitalizations of adults (≥ 18 years) with a principal discharge diagnosis of ACS between January 2004 and September 2015 were included, stratified by trial enrolment. Trial enrolment was defined according to the presence of International Classification of Diseases, ninth revision (ICD-9) discharge code V70.7, which indicates examination of a trial participant. Those not identified with this code were considered unenrolled.

For the second analysis, patients were stratified by eligibility criteria for trial enrolment. Eligibility criteria for trial enrolment were defined according to four major cardiovascular trials enrolling patients with ACS, including CURRENT-OASIS 7 (dose comparisons of clopidogrel and aspirin in ACS),¹² ISAR-REACT 5 (ticagrelor or prasugrel in patients with ACS),¹³ PLATO (ticagrelor vs. clopidogrel in patients with ACS),¹⁴ and TRITON-TIMI 38 (prasugrel vs. clopidogrel in patients with ACS).¹⁵ These trials were used due to their relevance to the field of ACS and robust clinical impact on the target study population. The list of eligibility criteria for the aforementioned clinical trials is outlined in the Supplementary material online, Table S1. In addition, patients with any life-limiting comorbidities or conditions with short life expectancy were considered ineligible (Supplementary material online, Table S2). Overall, the following conditions were among the exclusion criteria: thrombocytopenia, coagulopathy, prior cerebrovascular accident, anaemia, atrial fibrillation, end-stage renal disease and dialysis, pregnancy, cardiac arrest, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, neutropenia, peptic ulcer, diabetic retinopathy, uncontrolled hypertension, homelessness, alcohol abuse, drug abuse, dementia, psychoses, tumours, lymphoma, metastatic cancer, brain tumours, chronic liver disease including complications (liver cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, and hepatopulmonary syndrome), fibrinolysis and oral anticoagulation treatment, acquired immunodeficiency syndrome (AIDS), paralysis, and weight loss. Patients were classified as trial-eligible participants if they met none of the exclusion criteria (Supplementary material online, Table S2).

Identification of patient comorbidities, invasive care [including coronary angiography (CA) and percutaneous coronary intervention (PCI)], clinical outcomes, and healthcare utilization (length of stay, direct costs) was accomplished using the ICD-9 and Clinical Classification Software (CCS) codes (Supplementary material online, Table S1). Additional comorbidities were identified using the existing 29 AHRQ Elixhauser comorbidity measures. A total of 0.6% ($n = 46\,803$) hospitalizations were excluded from the original data set due to missing values (Supplementary material online, Figure S1).

Outcomes

Clinical outcomes included in-hospital all-cause mortality, major bleeding, acute stroke (ischaemic and haemorrhagic), and the composite of all-cause mortality, acute stroke, and cardiac complications [major adverse cardiovascular and cerebrovascular events (MACCEs)]. Cardiac complications included haemopericardium, cardiac tamponade, coronary dissection, and any pericardiocentesis procedure. In addition, invasive management (including CA and PCI) and healthcare utilization (length of stay and direct unadjusted costs) were compared between the groups. Direct total costs contain total charges during each hospitalization (excluding professional fees and non-covered charges), and reflect the expenses related to healthcare during the clinical episode. All-cause mortality was



agement over the study period. In addition, the estimated costs were direct and unadjusted for inflation. All analyses were conducted with appropriate sampling weights provided by the AHRQ, for each individual discharge.

Statistical analyses

Statistical Package for the Social Sciences (SPSS) (IBM Corp, Armonk, NY; version 25) and Stata MP version 16.0 (StataCorp, College Station, TX) were used for statistical analysis. Data were summarized using medians (interquartile range) for continuous non-parametric data and as counts (percentages) for categorical data. Quantitative data were analysed with Mann–Whitney *U* tests, and categorical data with χ^2 tests. Propensity score matching (PSM) was conducted using the *teffects psmatch* command in Stata (logistic treatment model), which estimates the average treatment effects (ATEs) by taking the average of the difference between the observed and potential outcomes for each subject. Percentage changes ($\Delta\%$) were derived from ATEs, by multiplying ATEs with 100, to assist with interpretation of data. Variables used for matching are listed in Appendix B in the Supplementary material online and under the corresponding table/figure. Matching variables were determined based on the baseline between-group differences and clinical importance of particular variables. Matching balance was assessed by tabular data comparison and graphical elements (balance plots). Trend analysis with a Mantel–Haenszel extension of the χ^2 test of trend (linear-by-linear association) used to establish trends of invasive man-

Results

Characteristics

Between January 2004 and September 2015, a total of 7 091 179 weighted ACS hospitalizations were recorded, including 19 684 (0.3%) hospitalizations coded for trial enrolment (Figure 1). Compared with non-participants, patients enrolled in clinical trials were more likely to be younger and male, with a lower prevalence of atrial fibrillation, previous cerebrovascular accident, anaemia, heart failure, diabetes mellitus, chronic pulmonary disease, dementia, and chronic renal failure ($P < 0.05$). In contrast, trial participants were more likely to be smokers and have comorbidities such as dyslipidaemia and obesity ($P < 0.05$). Trial participants had significantly lower prevalence of cardiogenic shock and cardiac arrest (3.5% vs. 4.8%, $P < 0.001$, and 1.7% vs. 3.0%, $P < 0.001$, respectively), and were also more likely to present with ST-elevation myocardial infarction (STEMI) (31.5% vs. 26.7%, $P < 0.001$, Table 1).

Table 1 Baseline patient characteristics according to clinical trial enrolment and eligibility in the National Inpatient Sample

Characteristics	Non-participants			Trial participants (0.3%)	P-value ^a	P-value ^b
	Total (99.7%)	Eligible (49.2%)	Non-eligible (50.6%)			
Number of hospitalizations	7 071 495	3 485 514	3 585 980	19 684		
Age (years), median (IQR)	67 (57, 79)	63 (54, 74)	72 (61, 82)	61 (53, 71)	<0.001	<0.001
Age groups (%)					<0.001	<0.001
18–29	0.3	0.3	0.2	0.1		
30–49	11.6	15.4	8.0	16.5		
50–79	64.2	69.1	59.5	73.1		
≥80	23.9	15.2	32.3	10.3		
Female sex (%)	40.3	37.5	43.0	30.2	<0.001	<0.001
Race/ethnicity (%)					<0.001	<0.001
White	76.2	76.7	75.5	81.3		
Black	10.1	9.1	11.4	9.2		
Hispanic	7.7	8.0	7.4	4.4		
Other	6.0	6.2	5.7	5.1		
Clinical indication (%)					<0.001	0.003
STEMI	26.7	29.2	24.3	31.5		
NSTEMI-ACS	73.3	70.8	75.7	68.5		
Weekend admission (%)	26.4	26.2	26.6	23.2	<0.001	<0.001
Primary expected payer (%)					<0.001	<0.001
Medicare	56.7	45.7	67.5	41.5		
Medicaid	6.5	6.6	6.4	4.2		
Private insurance	27.7	36.6	19.0	41.0		
Self-pay	5.8	7.3	4.4	8.7		
No charge	0.6	0.7	0.4	1.0		
Other	2.7	3.2	2.3	3.7		
Median household income (percentile) (%)					<0.001	<0.001
0–25th	29.3	28.0	29.8	22.7		
26th–50th	27.3	27.4	26.8	22.8		
51st–75th	23.6	24.1	23.6	23.6		
76th–100th	19.8	20.5	19.8	30.9		
Cardiogenic shock (%)	4.8	—	9.4	3.5	<0.001	—
Cardiac arrest (%)	3.0	—	5.8	1.7	<0.001	—
Ventricular tachycardia (%)	5.7	—	11.3	7.1	<0.001	—
Ventricular fibrillation (%)	2.6	—	5.1	2.6	0.881	—
Comorbidities (%)						
Atrial fibrillation	16.2	—	31.9	10.5	<0.001	—
Dyslipidaemia	54.7	60.1	49.5	68.4	<0.001	<0.001
Thrombocytopenia	3.2	—	6.2	2.8	0.011	—
Smoking	34.6	39.0	30.2	46.2	<0.001	<0.001
Previous AMI	10.6	9.9	11.3	10.1	0.015	0.547
History of IHD	74.1	75.9	72.4	91.0	<0.001	<0.001
Previous PCI	11.7	12.2	11.2	12.8	<0.001	0.005
Previous CABG	7.7	6.8	8.5	4.1	<0.001	<0.001
Previous CVA	4.0	—	7.9	2.7	<0.001	—
Anaemias	15.4	—	30.3	8.0	<0.001	—
Heart failure	30.0	18.1	41.6	18.0	<0.001	0.078
Valvular disease	0.2	0.1	0.4	0.1	0.018	0.007
Hypertension	67.1	65.8	68.3	67.9	0.001	<0.001
Peripheral vascular disorders	10.6	7.9	13.3	9.9	<0.001	<0.001
Diabetes mellitus	34.3	31.3	37.1	29.5	<0.001	<0.001
Hypothyroidism	9.8	8.2	11.4	7.7	<0.001	0.051

Table 1 Continued

Characteristics	Non-participants			Trial participants (0.3%)	P-value ^a	P-value ^b
	Total (99.7%)	Eligible (49.2%)	Non-eligible (50.6%)			
Chronic pulmonary disease	20.6	17.3	23.8	16.2	<0.001	<0.001
Pulmonary circulation disorders	0.095	0.0	0.2	0.102	0.753	<0.001
Coagulopathy	4.2	—	8.3	3.7	<0.001	—
Dementia	5.8	—	11.4	0.7	<0.001	—
Depression	6.6	5.9	7.4	5.6	<0.001	0.230
Psychoses	2.1	—	4.2	1.3	<0.001	—
Paralysis	1.6	—	3.1	0.5	<0.001	—
Other neurological disorders	5.8	2.8	8.7	2.2	<0.001	<0.001
Liver disease	1.2	—	2.4	1.0	0.001	—
Peptic ulcer (without bleeding)	0.035	—	0.1	0.000	0.009	—
Chronic renal failure	16.4	7.3	25.2	9.6	<0.001	<0.001
Rheumatoid arthritis/collagen vascular diseases	2.2	1.9	2.4	1.8	<0.001	0.091
AIDS	0.141	—	0.3	0.071	0.009	—
Alcohol abuse	2.9	—	5.7	2.7	0.222	—
Drug abuse	2.1	—	4.2	2.0	0.091	—
Fluid and electrolyte disorders	19.1	10.6	27.3	12.5	<0.001	<0.001
Obesity	12.1	13.3	10.9	15.7	<0.001	<0.001
Weight loss	2.1	—	4.2	1.0	<0.001	—
Solid tumour without metastasis	1.4	—	2.8	0.8	<0.001	—
Metastatic cancer	0.9	—	1.7	0.3	<0.001	—
Lymphoma	0.5	—	1.0	0.5	0.767	—
Bed size of hospital (%)					<0.001	<0.001
Small	11.1	11.2	11.0	6.2		
Medium	24.8	24.7	24.9	18.2		
Large	64.1	64.1	64.1	75.6		
Hospital region (%)					<0.001	<0.001
Northeast	20.1	20.1	20.1	22.0		
Midwest	22.7	22.7	22.6	18.5		
South	39.4	39.9	38.9	51.9		
West	17.9	17.3	18.4	7.6		
Location/teaching status of hospital (%)					<0.001	<0.001
Rural	10.8	11.5	10.2	2.8		
Urban non-teaching	41.2	41.6	40.9	30.9		
Urban teaching	48.0	46.9	48.9	66.3		

Trial enrolment was established using the International Classification of Diseases, version 9, code v70.7.

Criteria for non-eligibility: thrombocytopenia, coagulopathy, prior cerebrovascular accident, anaemia, atrial fibrillation, end-stage renal disease (grades 4 and 5) and dialysis, pregnancy, cardiac arrest, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, neutropenia, peptic ulcer, diabetic retinopathy, uncontrolled hypertension, homelessness, alcohol abuse, drug abuse, dementia, psychoses, tumours, lymphoma, metastatic cancer, brain tumours, chronic liver disease including complications (liver cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, hepatopulmonary syndrome), fibrinolysis and oral anticoagulant treatment, AIDS, paralysis, and weight loss.

AIDS, acquired immunodeficiency syndrome; AML, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CLD, chronic liver disease; CVA, cerebrovascular accidents; IHD, Ischaemic heart disease; IQR, interquartile range; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis; and STEMI, ST-elevation myocardial infarction.

^a Non-participants vs. trial participants.

^b Eligible non-participants vs. trial participants.

When comparing trial participants with eligible non-participants, trial participants were more likely to be younger and male ($P < 0.05$), but the differences narrowed in most comorbidities or even disappeared for heart failure, hypothyroidism, and depression ($P > 0.05$) (Table 1).

Propensity score matching

Adequacy of group matching is illustrated in Table 2. After PSM, the baseline differences between non-participants and trial participants have mostly disappeared, except in proportion of heart failure (21.6% vs. 22.6%, $P < 0.001$, respectively), hospital location/teaching

Table 2 Patient characteristics according to clinical trial enrolment and eligibility (propensity score matched between-group balance)

Characteristics	Non-participants	Trial participants	P-value	Eligible non-participants	Trial participants	P-value	Eligible non-participants	Non-eligible non-participants	P-value
Number of hospitalizations	15 699	15 297		14 298	13 955		136 619	138 120	
Age (years), median (IQR)	63 (54, 73)	63 (54, 73)	0.517	63 (54, 73)	62 (54, 73)	0.991	61 (52, 72)	61 (51, 72)	0.002
Female sex (%)	35.1	35.6	0.306	36.4	36.4	0.952	46.3	46.1	0.392
STEMI (%)	34.5	29.2	<0.001	39.4	29.0	<0.001	23.9	21.6	<0.001
Atrial fibrillation (%)	12.6	13.2	0.108	—	—	—	—	—	—
Dyslipidaemia (%)	64.6	64.4	0.708	63.7	63.4	0.582	58.5	59.2	0.001
Smoking (%)	44.8	45.1	0.609	46.5	46.2	0.592	48.1	48.2	0.647
Previous PCI (%)	14.1	15.0	0.020	15.4	16.0	0.192	29.0	29.3	0.101
Previous CABG (%)	4.8	5.2	0.105	5.3	5.4	0.666	21.5	21.2	0.065
Anaemias (%)	9.9	10.2	0.350	—	—	—	—	—	—
Heart failure (%)	21.6	22.6	0.032	22.8	22.8	0.976	30.2	30.6	0.027
Hypertension (%)	68.1	68.1	0.921	67.0	67.8	0.178	61.1	64.4	<0.001
Peripheral vascular disorders (%)	11.9	12.3	0.333	12.9	13.2	0.585	22.5	22.6	0.499
Diabetes mellitus (%)	32.9	33.7	0.839	28.4	29.3	0.093	43.3	42.4	<0.001
Chronic pulmonary disease (%)	18.7	20.4	<0.001	20.8	21.8	0.048	35.2	35.3	0.674
Hypothyroidism (%)	8.5	9.5	0.001	9.0	10.1	0.001	20.7	21.1	0.007
Dementia (%)	0.9	0.9	0.611	—	—	—	—	—	—
Chronic renal failure (%)	11.6	12.2	0.096	—	—	—	—	—	—
Location/teaching status of hospital (%)			<0.001			<0.001			<0.001
Rural	4.3	3.5		3.9	3.8		22.1	20.8	
Urban non-teaching	33.2	31.3		35.4	32.8		38.4	38.7	
Urban teaching	62.5	65.3		60.8	63.4		39.5	40.5	
Primary expected payer (%)			<0.001			0.742			<0.001
Medicare	46.4	46.4		45.0	44.7		35.7	35.7	
Medicaid	5.8	5.0		5.7	5.4		14.3	14.6	
Private insurance	33.8	33.4		33.5	33.5		27.7	25.8	
Self-pay	9.6	9.5		9.8	10.0		11.5	11.6	
No charge	0.9	1.2		1.2	1.3		2.5	2.8	
Other	3.6	4.5		4.8	5.1		8.3	9.5	

Criteria for non-eligibility: thrombocytopenia, coagulopathy, prior cerebrovascular accident, anaemia, atrial fibrillation, end-stage renal disease (grades 4 and 5) and dialysis, pregnancy, cardiac arrest, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, neutropenia, peptic ulcer, diabetic retinopathy, uncontrolled hypertension, homelessness, alcohol abuse, drug abuse, dementia, psychosis, tumours, lymphoma, metastatic cancer, brain tumours, chronic liver disease including complications (liver cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, hepatopulmonary syndrome), fibrinolysis and oral anticoagulant treatment, AIDS, paralysis, and weight loss. CABG, coronary artery bypass graft; IQR, interquartile range; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Table 3 Derived percentage changes ($\Delta\%$) of in-hospital process and clinical outcomes in different groups (propensity score matched cohort)

Variables	Trial participants ^a		Trial participants ^b		Non-eligible non-participants ^c	
	$\Delta\%$ (95% CI)	P-value	$\Delta\%$ (95% CI)	P-value	$\Delta\%$ (95% CI)	P-value
Management:						
CA	28.73 (27.22, 30.24)	<0.001	22.78 (21.58, 23.99)	<0.001	-4.72 (-4.89, -4.56)	<0.001
PCI	27.13 (24.86, 29.41)	<0.001	23.95 (21.77, 26.13)	<0.001	-6.57 (-6.74, -6.40)	<0.001
Outcomes:						
All-cause mortality	-3.51 (-4.72, -2.31)	<0.001	-0.21 (-0.65, 0.24)	0.362	5.58 [5.50, 5.66]	<0.001
MACCEs	-3.04 (-4.55, -1.53)	<0.001	1.11 (0.25, 2.00)	0.012	7.10 [6.99, 7.20]	<0.001
Major bleeding	-0.89 (-1.59, -0.19)	0.013	0.07 (-0.47, 0.62)	0.792	2.08 [2.03, 2.14]	<0.001
Stroke	-0.07 (-1.41, 1.27)	0.918	0.48 (-0.17, 1.14)	0.152	1.78 [1.71, 1.85]	<0.001
Cardiac complications	0.85 (0.36, 1.34)	0.001	1.14 (0.65, 1.63)	<0.001	0.25 (0.22, 0.28)	<0.001

Criteria for non-eligibility: thrombocytopenia, coagulopathy, prior cerebrovascular accident, anaemia, atrial fibrillation, end-stage renal disease (grades 4 and 5) and dialysis, pregnancy, cardiac arrest, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, neutropenia, peptic ulcer, diabetic retinopathy, uncontrolled hypertension, homelessness, alcohol abuse, drug abuse, dementia, psychosis, tumours, lymphoma, metastatic cancer, brain tumours, chronic liver disease including complications (liver cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, hepatopulmonary syndrome), fibrinolysis and oral anticoagulant treatment, AIDS, paralysis, and weight loss.

Percentage changes ($\Delta\%$) were derived from average treatment effects by multiplying average treatment effects by 100.

ATE, average treatment effect; CA, coronary angiography; CI, confidence interval; MACCEs, major adverse cardiac and cerebrovascular events (composite of mortality, stroke, and cardiac complications); and PCI, percutaneous coronary intervention.

^a Reference group are non-participants. Propensity score matching model: groups were matched on the following variables—age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus, anaemia, atrial fibrillation, arterial hypertension, peripheral vascular disease, chronic renal failure, dyslipidaemia, heart failure, smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft, chronic lung disease, dementia, and hypothyroidism.

^b Reference group are eligible non-participants. Propensity score matching model: groups were matched on the following variables—age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus (excluding diabetic retinopathy), arterial hypertension (excluding uncontrolled hypertension), peripheral vascular disease, dyslipidaemia, heart failure, smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft, chronic lung disease, and hypothyroidism.

^c Reference group are eligible non-participants. Propensity score matching model: groups were matched on the following variables—age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus (excluding diabetic retinopathy), arterial hypertension (excluding uncontrolled hypertension), peripheral vascular disease, dyslipidaemia, heart failure, smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft, chronic lung disease, and hypothyroidism.

status, and primary expected payer ($P < 0.001$) (Table 2). Similarly, the baseline differences between eligible non-participants and trial participants were eliminated, except in hypothyroidism (9.0% vs. 10.1%, $P = 0.001$, respectively) and hospital location/teaching status ($P < 0.001$) (Table 2). Finally, the baseline differences between eligible and non-eligible non-participants persisted in age, dyslipidaemia, heart failure, arterial hypertension, diabetes mellitus, hypothyroidism, hospital location/teaching status, and primary expected payer ($P < 0.05$) (Table 2). Graphical illustration of PSM is presented in the Supplementary material online, Figures S1–S3.

Non-participants vs. trial participants

Patients enrolled into clinical trials had significantly lower all-cause mortality (1.3% vs. 5.5%), MACCE (5.4% vs. 9.2%), major bleeding (1.3% vs. 2.5%), and stroke (3.0% vs. 3.7%) compared with non-participants ($P < 0.001$ for all, Supplementary material online, Table S3 and Figure S4B). However, trial-enrolled patients had higher total direct hospitalization costs (55 942 vs. 41 726 USD, $P < 0.001$) (Supplementary material online, Table S3). These associations were consistently present during the study period (38 438 vs. 28 210 USD, $P < 0.001$ in 2004; 53 726 vs. 41 502 USD, $P < 0.001$ in 2009; 101 966 vs. 58 417 USD, $P < 0.001$ in 2015).

After PSM, trial participants were less likely to experience in-hospital mortality ($\Delta\% -3.51\%$, 95% CI -4.72 to -2.31 , $P < 0.001$), MACCEs ($\Delta\% -3.04\%$, 95% CI -4.55 to -1.53 , $P < 0.001$), and

major bleeding ($\Delta\% -0.89\%$, 95% CI -1.59 to -0.19 , $P = 0.013$), although there was no difference in stroke ($P > 0.05$) (Table 3 and Figure 2A).

Trial participants were more likely to undergo CA (90.5% vs. 62.0%, $P < 0.001$) and PCI (70.8% vs. 40.5%, $P < 0.001$) (Supplementary material online, Table S3, and Supplementary material online, Figure S4A). After PSM, trial participants were consistently more likely to undergo CA ($\Delta\% 28.73\%$, 95% CI 27.22–30.24, $P < 0.001$) and PCI ($\Delta\% 27.13\%$, 95% CI 24.86–29.41, $P < 0.001$) (Table 3 and Figure 2A).

Eligible non-participants vs. trial participants

When evaluating clinical outcomes, there was no difference in all-cause mortality, major bleeding, and stroke between the matched groups ($\Delta\% -0.21\%$, 95% CI -0.65 to 0.24 , $P = 0.362$; $\Delta\% 0.07\%$, 95% CI -0.47 to 0.62 , $P = 0.792$; and $\Delta\% 0.48\%$, 95% CI -0.17 to 1.14 , $P = 0.152$, respectively), although trial patients were more likely to sustain MACCEs or cardiac complication ($\Delta\% 1.11\%$, 95% CI 0.25–2.00, $P = 0.012$; and $\Delta\% 1.14\%$, 95% CI 0.65–1.63, $P < 0.001$, respectively) (Table 3 and Figure 2B).

However, compared with eligible non-trial patients, trial participants were consistently more likely to undergo CA ($\Delta\% 22.78\%$, 95% CI 21.58–23.99, $P < 0.001$) and PCI ($\Delta\% 23.95\%$, 95% CI 21.77–26.13, $P < 0.001$) (Table 3 and Figure 2B).

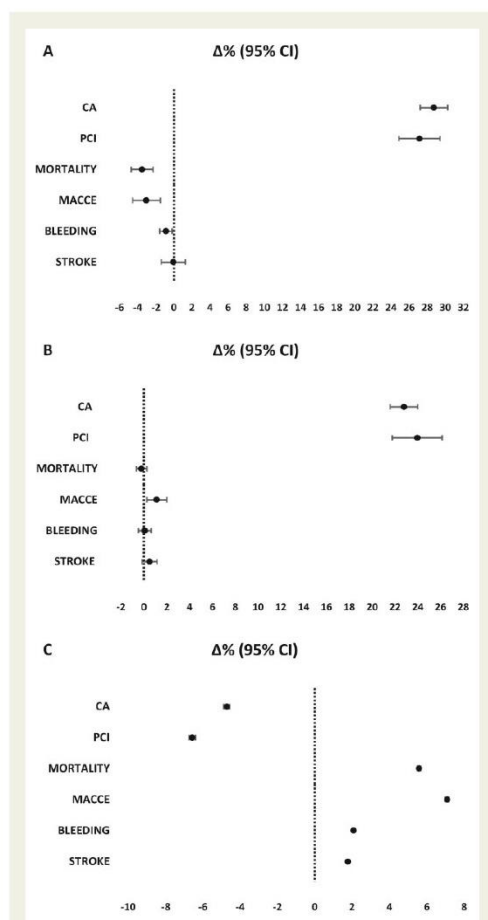


Figure 2 Average treatment effects of in-hospital process and clinical outcomes: (A) non-participants vs. trial participants¹; (B) eligible non-participants vs. trial participants²; and (C) eligible non-participants vs. non-eligible non-participants.³ Percentage changes ($\Delta\%$) were derived from average treatment effects by multiplying average treatment effects with 100. ¹Reference group are non-participants. Propensity score matching model: groups were matched on the following variables—age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus, anaemia, atrial fibrillation, arterial hypertension, peripheral vascular disease, chronic renal failure, dyslipidaemia, heart failure, smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft, chronic lung disease, dementia, and hypothyroidism. ²Reference group are eligible non-participants. Propensity score matching model: groups were matched on the following variables—age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus (excluding diabetic retinopathy), arterial hypertension (excluding uncontrolled hypertension), peripheral vascular disease, dyslipidaemia, heart failure, smoking, previous percutaneous coronary intervention, previous coronary

Figure 2 (Continued) artery bypass graft, chronic lung disease, and hypothyroidism. ³Reference group are eligible non-participants. Propensity score matching model: groups were matched on the following variables—age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus (excluding diabetic retinopathy), arterial hypertension (excluding uncontrolled hypertension), peripheral vascular disease, dyslipidaemia, heart failure, smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft, chronic lung disease, and hypothyroidism. Criteria for non-eligibility: thrombocytopenia, coagulopathy, prior cerebrovascular accident, anaemia, atrial fibrillation, end-stage renal disease (grades 4 and 5) and dialysis, pregnancy, cardiac arrest, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, neutropenia, peptic ulcer, diabetic retinopathy, uncontrolled hypertension, homelessness, alcohol abuse, drug abuse, dementia, psychoses, tumours, lymphoma, metastatic cancer, brain tumours, chronic liver disease including complications (liver cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, hepatopulmonary syndrome), fibrinolysis and oral anticoagulant treatment, AIDS, paralysis, and weight loss. CA, coronary angiography; CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; and PCI, percutaneous coronary intervention.

Eligible non-participants vs. non-eligible non-participants

When comparing clinical outcomes between eligible and non-eligible non-participants, the non-eligible group was more likely to develop all-cause mortality, MACCEs, major bleeding, stroke, and cardiac complications ($P < 0.001$) (Table 3 and Figure 2C).

In addition, non-eligible non-participants were less likely to undergo CA ($\Delta\% -4.72\%$, 95% CI -4.89 to -4.56 , $P < 0.001$) and PCI ($\Delta\% -6.57\%$, 95% CI -6.74 to -6.40 , $P < 0.001$) (Table 3 and Figure 2C).

When looking across the study period, differences in utilization of PCI between eligible non-participants and trial participants have decreased ($P < 0.001$ for all trends) (Supplementary material online, Figure S5).

Discussion

This study compared outcomes of patients with ACS enrolled into clinical trials and their counterparts after accounting for the influence of possible confounding factors. We also conducted sensitivity analyses to compare eligible non-participants with trial participants. We report several important findings. First, trial participants were younger and had lower comorbidity burden than non-participants. Second, after accounting for the baseline differences in PSM, trial participants were significantly less likely to develop all-cause mortality, MACCEs, and major bleeding compared with their counterparts. Furthermore, trial participants were more likely to undergo CA and PCI. Finally, when compared with eligible non-participants, trial participants were also consistently more likely to undergo CA and PCI, but the differences in all-cause mortality were no longer present. This may suggest that the better outcomes of trial participants are not just related to differences in the health status of

patients enrolled, but rather the quality of care received such as receipt of invasive therapies.

It has been shown that participants enrolling in ACS trials are younger and have a lower risk profile.^{7–9} It has been also reported that trial participants more frequently receive contemporary evidence-based therapy.^{7,9} Several previous studies have focused on trial enrolment-based outcomes in the ACS setting.^{6–9} However, the present study yields important additional strengths, including a national-level analysis of the large real-world cohort, over a substantially long 11-year period. This is the largest observational study to date focusing on the trial enrolment that provides an important sensitivity analysis based on eligibility criteria for trial enrolment.

The present study reveals worse in-hospital mortality in ACS patients not enrolled into clinical trials consistent with previous registry-based studies.^{8,9} Steg *et al.* observed lower crude and risk-adjusted in-hospital mortality among trial participants compared with both eligible and non-eligible non-participants.⁸ Additionally, data from the Chest Pain–MI Registry suggest that patients admitted to trial-participating hospitals have lower in-hospital and long-term mortality.⁶ In contrast, analysis of the French FAST-MI registry did not show lower 1-year mortality in trial participants, despite more optimal in-hospital management.⁷

Lower rates of clinical outcomes in trial participants, particularly all-cause mortality, could be driven by different mechanisms. First, the lower risk profile of patients enrolled into clinical trials could inherently lead to lower rates of complications and adverse outcomes.^{7–9} Several patient groups are particularly underenrolled in clinical trials, including female and elderly patients, while there is no evidence of higher refusal rates in these patient groups.^{5,16,17} In addition, socially deprived patients such as those with lower median household income have been out of the scope of most clinical trials and it is well known that sex, age, and lower socioeconomic status are associated with worse outcomes in AMI.^{18–21}

Clinical cardiovascular trials may target patients undergoing invasive management^{13,22} contributing to selection biases particularly when considering receipt of an invasive treatment strategy as an endpoint. Invasive therapy in the setting of ACS has been shown to reduce mortality but is associated with an increased risk of complications, including major bleeding, contrast-induced nephropathy, and stroke.²³ Patients with greater comorbidity burden encountered in the real world are at greater risk of sustaining these complications, and when the risks of an invasive strategy outweigh the benefits, patients are often managed medically.²⁴ This would be particularly relevant in patients not enrolled into clinical trials by virtue of their adverse comorbidity profile. Furthermore, clinicians' awareness of trial enrolment could facilitate patients' being more likely to be treated with evidence-based guidelines.^{25,26} The phenomenon of participants' behavioural changes due to clinical trial enrolment, in the form of partial Hawthorne effect, may also explain some of the benefits of trial enrolment²⁷ and has been previously detected in cardiovascular trials.^{28,29} The benefits associated with clinical trial enrolment may also reflect structural differences at the hospital level: research-active hospitals have better medical staffing levels,³⁰ and lower standardized mortality ratios for acute admissions.³¹ Patients admitted to research-active hospitals may also have better outcomes because greater research participation leads to accumulated knowledge, de-

velops infrastructure, and brings in resources that can be used to improve clinical care.³²

An important objective of our study was to evaluate ACS management and outcomes based on trial eligibility as opposed to trial enrolment, which has only been examined in a limited number of previous studies.^{8,9} This is particularly important as it challenges the notion of comorbidities driving worse outcomes in non-participants as being the only factor contributing to better outcomes in trial-enrolled patients. When looking at PSM analysis, there was no significant difference in mortality between eligible non-participants and trial participants, although we report more frequent use of invasive strategies and revascularization in the trial participants, which may reflect structural and practice differences in research-active hospitals contributing to the better delivery of care, rather than differences due to a lower risk, less comorbid population. Interestingly, previous studies by Steg *et al.* and Udell *et al.* have shown higher adjusted mortality in trial-eligible patients compared with trial-enrolled patients.^{8,9} Several potential reasons could mediate these differences. First, these studies used different definitions of trial eligibility than the current analysis, which may contribute to the differences in observed outcomes. Second, Steg *et al.* included only STEMI patients, which could account for differences in outcomes.⁸

Management of ACS patients enrolled in clinical trials in our study was consistently better, with significantly higher utilization of CA and PCI. This could be possibly explained by the fact that the younger, lower risk population more often offered an invasive management due to lower risk from periprocedural complications. These observations are in line with previous data derived from the GRACE,⁸ NCDR (National Cardiovascular Data Registry),⁹ and FAST-MI registries.⁷ However, these studies were subject to certain limitations, such as the analysis of smaller (e.g. $n = 8469$ in the GRACE registry; $n = 190\,476$ in the NCDR registry; and $n = 9414$ in the FAST-MI registry) or older procedural cohorts (e.g. 1999–2004 for the GRACE registry and 2008–11 for the NCDR registry), and therefore may be less representative of contemporary practice.^{7–9} Importantly, none of the available studies reported data on whether eligible non-participants are less likely to receive invasive treatment, which forms the mainstay of treatment for ACS management, compared with trial participants. Our current analysis shows that even when compared with a lower-risk trial-eligible cohort, trial participants receive more optimal clinical care (in the form of cardiac catheterization and revascularization), suggesting that differences in outcomes may not relate just to the better risk factor profile of the trial participants. Nevertheless, the influence of both the risk profile and undermanagement on prognosis is emphasized by the overall worse clinical outcomes of non-eligible non-participants in comparison to their eligible counterparts. Importantly, invasive trends have become more widespread in recent years, particularly since the use of more sensitive cardiac markers has entered routine clinical practice, hence why differences in the invasive approach have decreased over time.

This study has important clinical implications as it provides clinicians with insights into population differences in trial enrolment, which emphasises the need for wider inclusion of under-represented patient groups in future trial designs. Furthermore, our observations that patients recruited into trials have better treatments and clinical outcomes, even when compared with trial-eligible non-recruited

patients, have important clinical implications from a wider population perspective. Given that there are known disparities with under-recruitment of ethnic minorities and women into trials, this may contribute to disparities in treatments and outcomes reported in these patient groups, and limit the relevance of trial data to these population.

Limitations

This study has several limitations. First, the NIS is an ICD-9-code-dependent administrative data set, where there may be imprecise classifications of diagnoses or procedures. There are also insufficient data on the specific timing, type of clinical trial, and enrolment reason, due to the limited ICD-9 coding. Second, since the NIS does not capture post-discharge information, we were unable to assess long-term outcomes. Third, considering that the NIS registers each hospitalization as an independent event and that the ACS population is at high risk for readmissions, there is a possibility of multiple entries from the same patient and introduction of selection bias. Fourth, while PSM reduced the confounding bias, residual confounding effects could not be fully eliminated and these could introduce selection bias by eliminating a substantial number of non-matched patients from the analysis. Similarly, statistical analysis did not include multilevel hierarchical modelling for different hospitals. Fifth, since we have evaluated patients hospitalized during the period 2004–15, this may not reflect more contemporary practice regarding the management of ACS patients. Sixth, pharmacological management of ACS has an important impact on the outcomes but is not captured in this data set. In addition, due to the limited data on laboratory and clinical parameters, we were unable to quantitatively assess a patient's risk profile by different risk scores. Finally, this study is non-experimental and the observed results may be explained by potential study design bias or different individual patient risk profiles.

Conclusion

This national-level study reports significantly better invasive management and outcomes of ACS patients who are enrolled in a clinical trial compared with their non-trial counterparts. These differences may relate to a higher risk profile of non-participants, but even after considering trial eligibility, trial participants were more likely to be invasively managed. In addition, non-eligible non-participants experience worse clinical outcomes and receive less invasive care compared with their eligible counterparts, indicating the importance of the risk profile and comorbidities.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Funding

None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: The authors declare no conflict of interest.

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Supplementary Table 1. Full list of eligibility criteria for trial enrolment in 4 major cardiovascular trials*.

Clinical Trial	Exclusion criteria
ISAR-REACT 5	<ul style="list-style-type: none"> – Intolerance of or allergy to ticagrelor or prasugrel – History of any stroke, transient ischemic attack or intracranial bleeding – Known intracranial neoplasm, intracranial arteriovenous malformation or intracranial aneurysm – Active bleeding, clinical findings, that in the judgement of the investigator are associated with an increased risk of bleeding – Fibrin-specific fibrinolytic therapy less than 24 hours before randomization, non-fibrin-specific fibrinolytic therapy less than 48 hours before randomization – Known platelet count <100,000/μl at the time of screening – Known anaemia (hemoglobin <10 g/dl) at the time of screening – Oral anticoagulation that cannot be safely discontinued for the duration of the study – <i>International normalized ratio</i> known to be greater than 1.5 at the time of screening – Chronic renal insufficiency requiring dialysis – Moderate or severe hepatic dysfunction (child pugh B or C) – Increased risk of bradycardia events (sick sinus, AV block grade II or III, bradycardia-induced syncope) – Index event is an acute complication (<30 days) of PCI – Concomitant medical illness that in the opinion of the investigator is associated with a life expectancy <1 year – Concomitant oral or intravenous therapy with strong cytochrome P4503A inhibitors (e.g. Ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1 l/day), cytochrome P4503A substrates with narrow therapeutic indices (e.g. Cyclosporine, quinidine), or strong cytochrome P4503A inducers (e.g. Rifampin/rifampicin, phenytoin, carbamazepine, dexamethason, phenobarbital) that cannot be safely discontinued – ≥1 doses of ticagrelor or prasugrel within 5 days before randomization – No written informed consent – Participation in another investigational drug study – Previous enrolment in this study – For women of childbearing potential no negative pregnancy test and no agree to use a reliable method of birth control during the study – Pregnancy, giving birth within the last 90 days, or lactation – Inability to cooperate with protocol requirements

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	<ul style="list-style-type: none"> – Any condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence – Intolerance of or allergy to aspirin, ticlopidine, or clopidogrel – May be unable to cooperate with protocol requirements and follow-up procedures
PLATO	<ul style="list-style-type: none"> – Any contraindication against the use of clopidogrel – Fibrinolytic therapy within 24 hours before randomization – A need for oral anticoagulation therapy – An increased risk of bradycardia – Concomitant therapy with a strong cytochrome P4503A inhibitor or inducer
CURRENT-OASIS 7	<ul style="list-style-type: none"> – Age <18 years – Use of oral anticoagulants within the last 10 days with an <i>International Normalized Ratio</i> > 1.5 or planned use of such agents during the hospitalization period – Administration of clopidogrel > 75 mg within 24 hours prior to randomization – Contraindication to the use of clopidogrel and/or aspirin – History of drug allergy to thienopyridine derivatives or aspirin – History of clinically significant or persistent thrombocytopenia or neutropenia – Active bleeding or significant increased risk of bleeding, such as elderly patients receiving fibrinolytic therapy and other potent antithrombotic agents – Severe hepatic insufficiency – Current peptic ulceration – Proliferative diabetic retinopathy – History of severe systemic bleeding (e.g. gastrointestinal bleeding, gross hematuria, intraocular bleeding, hemorrhagic stroke, or intracranial hemorrhage) or other history of bleeding diathesis or coagulopathy – Uncontrolled hypertension – Previously entered in the CURRENT-OASIS 7 study – Use of an investigational treatment (drug or device) within the previous 30 days – Medical, geographic or social factors making study participation impractical or inability to provide written informed consent

*CURRENT-OASIS 7 [Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes], ISAR-REACT 5 [Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes], PLATO [Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes], and TRITON-TIMI 38 [Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes].

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Supplementary Table 2. Search codes.

Diagnoses	Source	Codes
Clinical Trial enrolment	ICD-9	V70.7
AMI	ICD-9	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.7x, 410.8x, 410.9x
STEMI	ICD-9	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x
NSTEMI	ICD-9	410.7, 410.70, 410.71, 410.72
Unstable angina	ICD-9	411.1, 413.0, 413.1, 411.81, 411.89
Dyslipidaemia	CCS	53
Smoking	ICD-9	V15.82, 305.1
History of IHD	ICD-9	414.00-07, 414.2-9
Previous MI	ICD-9	412
Previous PCI	ICD-9	V45.82
Previous CABG	ICD-9	V45.81
Family history of CAD	ICD-9	V17.3
In-hospital procedures and outcomes		
Acute ischemic stroke	ICD-9	433.x, 434.x, 436, 435.x, 362.3
Haemorrhagic stroke	ICD-9	430, 431, 432.0, 432.1, 432.9
Post procedure haemorrhage	ICD-9	998.11
Major bleeding	ICD-9	430, 431, 432x, 578x, 786.3, 786.30, 786.39
Shock during admission	ICD-9	785.51
Use of assist device or IABP	ICD-9	37.68, 37.61
Hemopericardium	ICD-9	423.0
Pericardiocentesis	ICD-9	37.0
Cardiac tamponade	ICD-9	423.3
Coronary dissection	ICD-9	414.12
Diagnostic Cardiac catheterisation	CCS	47
CABG	CCS	44
PCI	CCS	45
Exclusion criteria		

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AIDS	ICD-9	042.x-044.x
Atrial Fibrillation	ICD-9	427.31
Anaemia	ICD-9	280.0-281.9, 285.2, 285.9, 648.2
Adverse events of fibrinolysis and anticoagulants	ICD-9	E934.2, E934.4, 964.2, 964.4, 286.7
Ventricular tachycardia	ICD-9	427.1
Ventricular fibrillation	ICD-9	427.41
Cardiac arrest	ICD-9	427.5
Uncontrolled hypertension	ICD-9	401.0, 642.00-642.94, 997.91, 405.01, 405.09
Stage 4 and 5 renal disease including dialysis	ICD-9	585.4, 585.5, 585.6 V56, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, V45.1, V45.11, V45.12, 38.95, 38.42, 39.43, 39.27, 39.53, 39.95, 54.98, 792.5, 996.56, 996.68, 996.73, E87.91
Neutropenia	ICD-9	288.0-288.09
Solid tumors (without metastasis)	ICD-9	140.x-172.x, 174.x-195.x
Brain neoplasms	ICD-9	191.x, 192.x, 239.6
Metastatic cancer	ICD-9	196.x-199.x
Lymphoma	ICD-9	200.x-202.x, 203.0, 238.6
Previous CVA (TIA and Stroke)	ICD-9	V12.54
Thrombocytopenia	ICD-9	287.5, 287.49
Coagulopathy	ICD-9	286.x, 287.1, 287.3-287.5
Chronic liver disease	ICD-9	571.0, 571.2, 571.3, 571.4x, 571.5, 571.6, 571.8, 571.9, 572.8, 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, V42.7
Liver cirrhosis	ICD-9	571.2, 571.5, 571.6, 573.5, 572.2, 572.3, 572.4
Hepatic encephalopathy	ICD-9	572.2
Portal hypertension	ICD-9	572.3, 456.0, 456.1, 456.20
Hepatorenal syndrome	ICD-9	572.4
Hepatopulmonary syndrome	ICD-9	573.5
Diabetic retinopathy	ICD-9	362.0, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07
Paralysis	ICD-9	342.x-344.x, 438.2-438.5
Pregnancy	ICD-9	V22, V72.42, V61.6, V61.7, 761.4, 761.5, 630-679, 779

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Homelessness	ICD-9	V60.0
Peptic ulcer	ICD-9	531.41, 531.51, 531.61, 531.7, 531.91, 532.41, 532.51, 532.61, 532.7, 532.91, 533.41, 533.51, 533.61, 533.7, 533.91, 534.41, 534.51, 534.61, 534.7, 534.91
Alcohol abuse	ICD-9	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3
Drug abuse	ICD-9	292.x, 304.x, 305.2-305.9, V65.42
Weight loss	ICD-9	260.x-263.x, 783.2
Psychoses	ICD-9	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Dementia	ICD-9	290.x, 294.x

Legend: CABG – coronary artery bypass grafting; CVA – cerebrovascular accident; IABP – intraaortic balloon pump; IHD – ischemic heart disease; MI – myocardial infarction; NSTEMI – non ST-elevation myocardial infarction; PCI – percutaneous coronary intervention; STEMI – ST-elevation myocardial infarction; TIA – transient ischemic attack.

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Supplementary Table 3. In-hospital process and clinical outcomes in ACS patients according to clinical trial enrolment and eligibility in the *National Inpatient Sample*. Trial enrolment was established using ICD-9 code v70.7.

Characteristics	Non-participants			Trial participants (0.3%)	P-value ¹	P-value ²
	Total (99.7%)	Eligible (49.2%)	Non-eligible (50.6%)			
Process outcomes, %						
Coronary angiography	62.0	69.5	54.8	90.5	<0.001	<0.001
PCI	40.5	49.0	32.3	70.8	<0.001	<0.001
Clinical outcomes, %						
All-cause mortality	5.5	1.6	9.3	1.3	<0.001	0.003
MACCE	9.2	4.2	14.3	5.4	<0.001	<0.001
Major bleeding	2.5	1.0	4.0	1.3	<0.001	0.002
Cardiac complications	0.6	0.6	0.7	1.4	<0.001	<0.001
Procedure-related bleeding	0.6	0.4	0.8	0.9	<0.001	<0.001
Stroke	3.7	2.2	5.1	3.0	<0.001	<0.001
Length of stay (days), median (IQR)	3 (2, 6)	3 (2, 4)	4 (2, 8)	3 (2, 5)	0.007	<0.001
Total charges (USD), median (IQR)	41,726 (20,571, 74,132)	40,030 (20,026, 66,030)	44,300 (21,132, 87,050)	55,942 (35,537, 87,424)	<0.001	<0.001

¹Non-participants vs. trial participants

²Eligible non-participants vs. trial participants

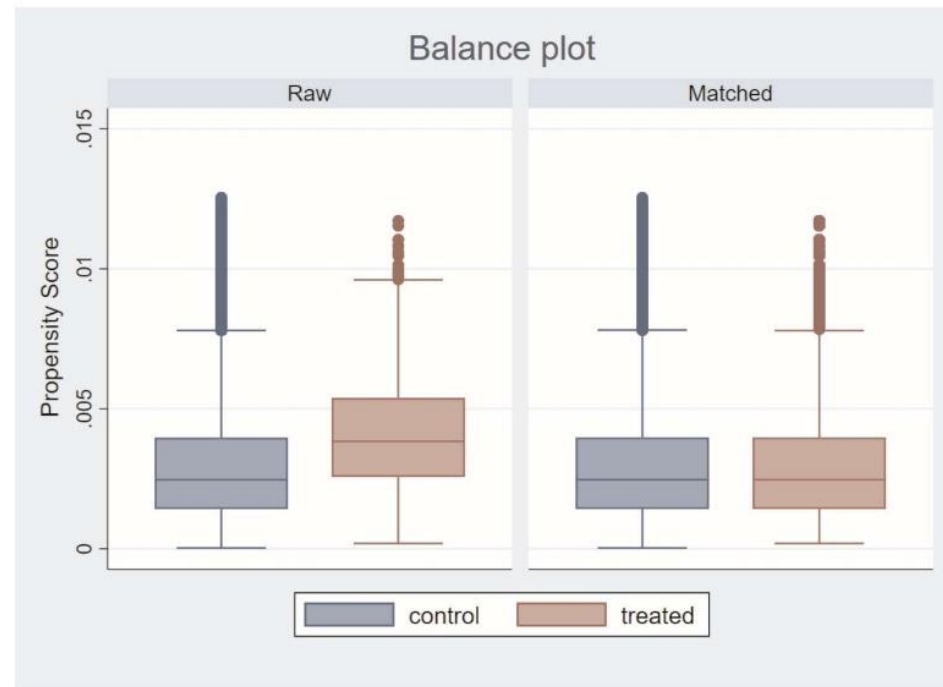
Abbreviations: IQR Interquartile Range; PCI Percutaneous Coronary Intervention; MACCE Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, stroke and cardiac complications); USD United States Dollar.

Criteria for non-eligibility: thrombocytopenia, coagulopathy, prior cerebrovascular accident, anaemia, atrial fibrillation, end-stage renal disease (grades 4 and 5) and dialysis, pregnancy, cardiac arrest, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, neutropenia, peptic ulcer, diabetic retinopathy, uncontrolled hypertension, homelessness, alcohol abuse, drug abuse, dementia, psychoses, tumors, lymphoma, metastatic cancer, brain tumors, chronic liver disease including complications (liver cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, hepatopulmonary syndrome), fibrinolysis and oral anticoagulant treatment, AIDS, paralysis and weight loss.

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Supplementary Figure 1. Analysis of adequacy of propensity score matching analysis between **non-participants** and **trial participants** (propensity-score matched between-group balance).



Note: Control group corresponds to **non-participants**, while treated group corresponds to **trial participants**.

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Supplementary Figure 2. Analysis of adequacy of propensity score matching analysis between **eligible non-participants and trial participants** (propensity-score matched between-group balance).

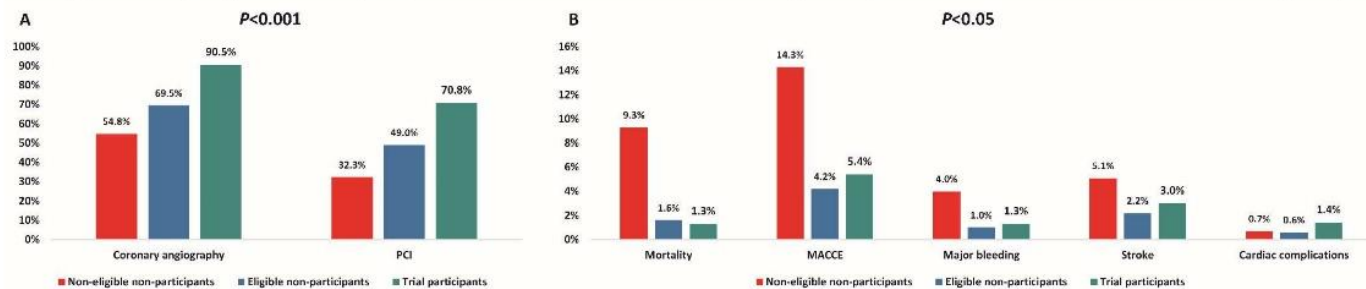


Note: Control group corresponds to **eligible non-participants**, while treated group corresponds to **trial participants**.

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Supplementary Figure 4. In-hospital process and clinical outcomes according to the presence of clinical trial enrolment and eligibility.

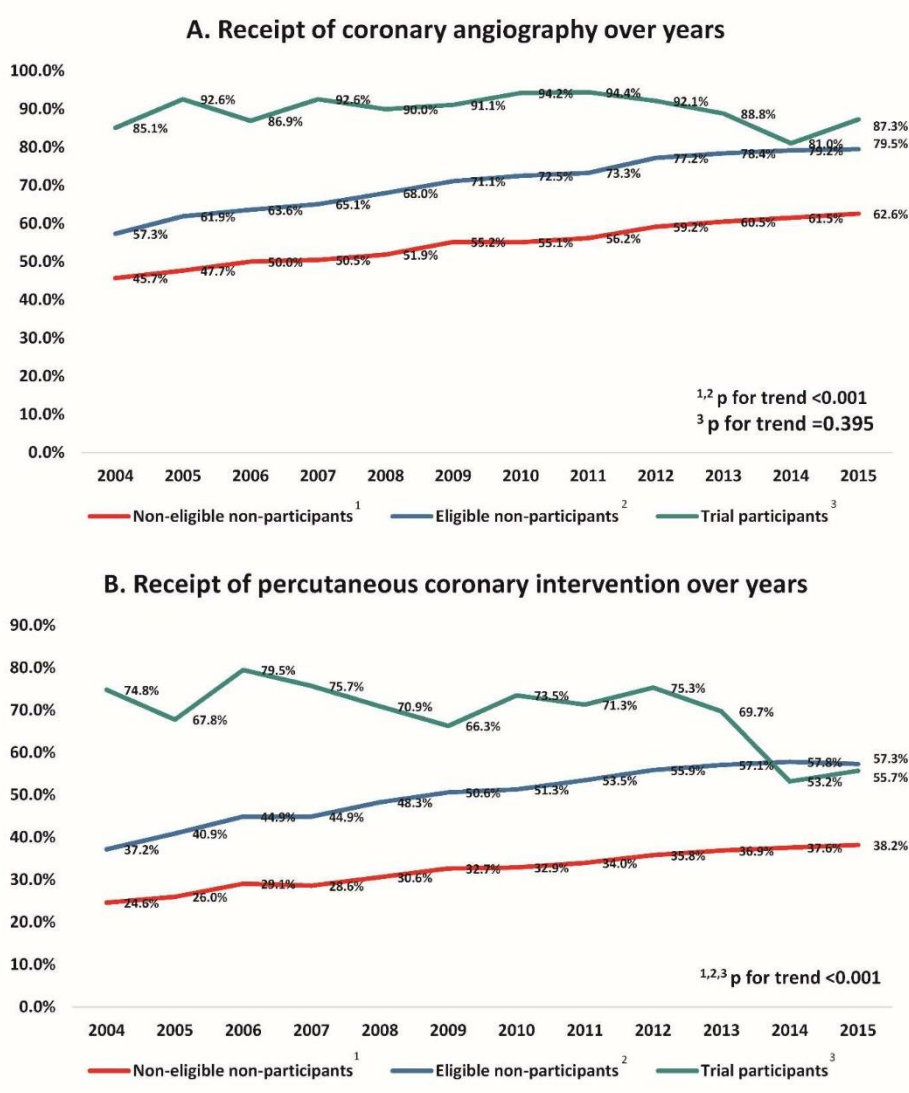


Abbreviations: CA – coronary angiography; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, stroke and cardiac complications); PCI – percutaneous coronary intervention.

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Supplementary Figure 5. Trends in the utilization of invasive management: **A.** Coronary angiography; **B.** Percutaneous coronary intervention.

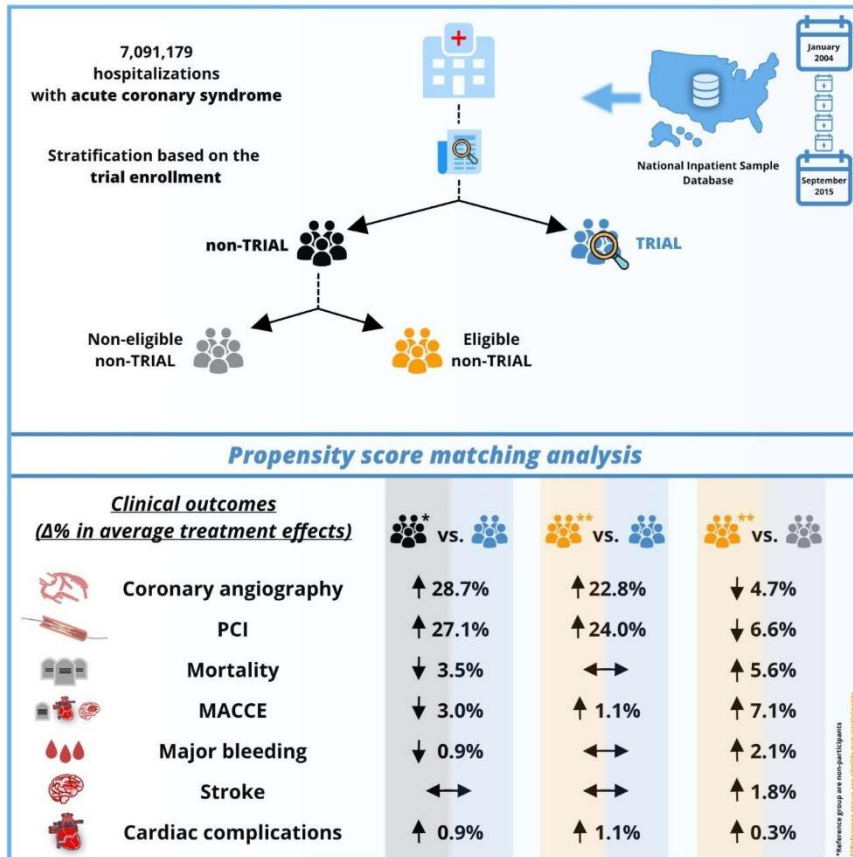


Note: Trend analysis with a Mantel-Haenszel extension of the chi-square test of trend (linear-by-linear association).

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Visual Abstract



Supplementary Material:

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Appendix B. Propensity-score matching model

Propensity-score matching was done using a statistical software Stata MP version 16.0 (StataCorp, College Station, Texas, US).

The following variables were used for matching of the non-participants and trial participants: age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus, anaemia, atrial fibrillation, arterial hypertension, peripheral vascular disease, chronic renal failure, dyslipidaemia, heart failure, smoking, previous PCI, previous CABG, chronic lung disease, dementia, hypothyroidism.

The following variables were used for matching of the eligible non-participants and trial participants, as well as the eligible non-participants and non-eligible non-participants: age, sex, hospital location/teaching status, primary expected payer, diabetes mellitus (excluding diabetic retinopathy), arterial hypertension (excluding uncontrolled hypertension), peripheral vascular disease, dyslipidaemia, heart failure, smoking, previous PCI, previous CABG, chronic lung disease, hypothyroidism.

11.4. Research study 4



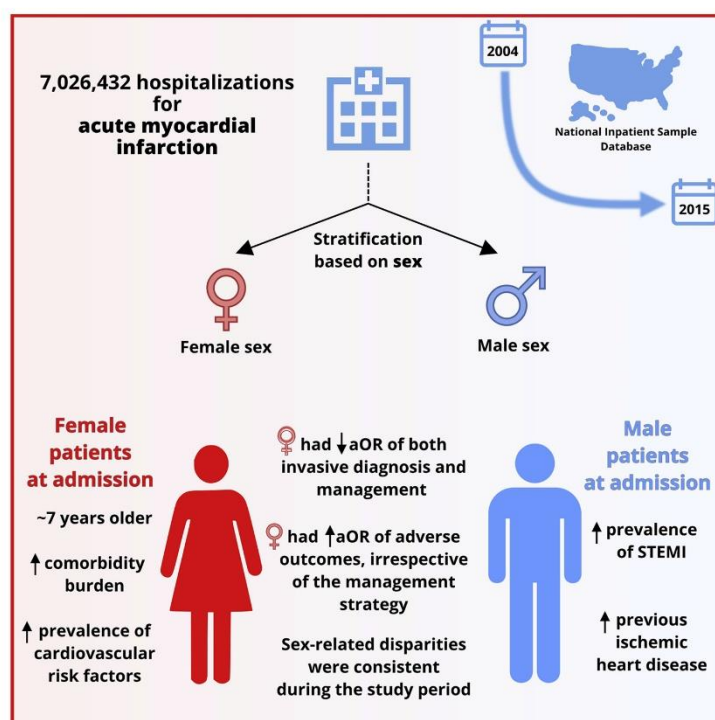
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Original Article

Trends of Sex Differences in Clinical Outcomes After Myocardial Infarction in the United States

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ABSTRACT

Background: Female patients have been shown to experience worse clinical outcomes after acute myocardial infarction (AMI) compared with male patients. However, it is unclear what trend these differences followed over time.

Methods: Data from patients hospitalized with AMI between 2004 and 2015 in the National Inpatient Sample were retrospectively analyzed, stratified according to sex. Multivariable logistic regression analyses were performed to examine the adjusted odds ratios (aORs) of invasive management and in-hospital outcomes according to sex. The Mantel-Haenszel extension of the χ^2 test was performed to examine the trend of management and in-hospital outcomes over the study period.

Results: Of 7,026,432 AMI hospitalizations, 39.7% ($n = 2,789,494$) were women. Overall, women were older (median: 77 vs 70 years), with a higher prevalence of risk factors such as diabetes, hypertension, and depression. Women were less likely to receive coronary angiography (aOR, 0.92; 95% confidence interval [CI], 0.91-0.93) and percutaneous coronary intervention (aOR, 0.82; 95% CI, 0.81-0.83) compared with men. Odds of all-cause mortality were higher in women (aOR, 1.03; 95% CI, 1.02-1.04; $P < 0.001$) and these rates have not narrowed over time (2004 vs 2015: aOR, 1.07 [95% CI, 1.04-1.09] vs 1.11 [95% CI, 1.07-1.15], with similar observations recorded for major adverse cardiovascular and cerebrovascular events.

Conclusions: In this temporal analysis of AMI hospitalizations over 12 years, we showed lower receipt of invasive therapies and higher mortality rates in women, with no change in temporal trends. There needs to be a systematic and consistent effort toward exploring these disparities to identify strategies to mitigate them.

RÉSUMÉ

Contexte : Il a été démontré que les femmes présentent de moins bons résultats cliniques après un infarctus aigu du myocarde (IAM) que les hommes. Cependant, la tendance de ces différences dans le temps n'est pas claire.

Méthodologie : Les données de la *National Inpatient Sample* sur les patients hospitalisés pour un IAM entre 2004 et 2015 ont été analysées rétrospectivement, stratifiées selon le sexe. Des analyses de régression logistique multidimensionnelles ont été effectuées pour examiner les rapports de cotes ajustés (RCA) de la prise en charge par un traitement invasif et des résultats obtenus en milieu hospitalier en fonction du sexe. Le test du χ^2 étendu de Mantel-Haenszel a été effectué pour examiner la tendance de la prise en charge et des résultats en milieu hospitalier au cours de la période d'étude.

Résultats : Sur 7 026 432 patients hospitalisés pour un IAM, 39,7 % ($n = 2 789 494$) étaient des femmes. Dans l'ensemble, les femmes étaient plus âgées (âge médian : 77 vs 70 ans), avec une plus forte prévalence de facteurs de risque comme le diabète, l'hypertension et la dépression. Les femmes étaient moins susceptibles que les hommes de subir une coronarographie (RCA : 0,92; intervalle de confiance [IC] à 95 % : 0,91-0,93) et une intervention coronarienne percutanée (RCA : 0,82; IC à 95 % : 0,81-0,83). Les probabilités de mortalité toutes causes confondues étaient plus élevées chez les femmes (RCA : 1,03; IC à 95 % : 1,02-1,04; $p < 0,001$), et ces taux n'ont pas diminué avec le temps (2004 vs 2015 : RCA : 1,07 [IC à 95 % : 1,04-1,09] vs 1,11 [IC à 95 % : 1,07-1,15], des observations similaires étant consignées pour les événements cardiovasculaires et vasculaires cérébraux majeurs.

Conclusions : Dans cette analyse temporelle des hospitalisations pour IAM sur 12 ans, nous avons montré que les femmes subissaient moins de traitements invasifs et présentaient des taux de mortalité plus élevés, sans changement dans les tendances temporelles. Il faut un effort systématique et cohérent pour explorer ces disparités afin de cibler des stratégies pour les atténuer.

Acute myocardial infarction (AMI) is the most acute presentation of ischemic heart disease and the leading cause of mortality in men and women worldwide, accounting for 17.9 million deaths globally per year (31% of all deaths).¹⁻³ Ischemic heart disease-related mortality has declined in recent years because of increased awareness of cardiovascular risk,⁴ advances in pharmacological therapy, coronary revascularization, and cardiovascular prevention.⁵ Notwithstanding, several studies have shown a higher incidence of adverse events in women after AMI,^{6,7} and have attributed worse outcomes in women to their lower rate of receipt of invasive management, in the form of coronary angiography (CA) or percutaneous coronary intervention (PCI).⁶ Furthermore, anatomical and biological factors could place

women at a greater risk of mechanical and procedural complications after AMI, such as smaller-sized arteries and differences in plaque characteristics.^{8,9}

Most of the evidence on sex differences in AMI management and outcomes to date is limited to data from highly selected cohorts (such as age younger than 55 years^{10,11} or randomized controlled trials), which might not be representative of real-world practice, certain geographical regions,¹² specific syndromes (eg, ST-elevation myocardial infarction [STEMI] only),¹³ or are of relatively small sample sizes.¹⁴ However, it is unclear whether there have been temporal changes in sex-based differences and in particular whether disparities have narrowed, especially in light of the increasing recognition of sex disparities in recent years. Older studies from the national registry of myocardial infarction in the United States (1994-2006) suggested a narrowing in the differences in outcomes between sexes, with an overall improvement in mortality outcomes.¹⁵ In contrast, a national French registry analysis of 5000 STEMI patients hospitalized between 2006 and 2011 showed significant persistent sex-based differences in management and outcomes.¹⁶ Although these findings provide us with insight into sex differences in a STEMI population, it is unclear whether these differences are

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See page S26 for disclosure information.

also observed across a broader spectrum of presentations. Moreover, their analysis was derived from a cohort from close to more than a decade ago, after which there have been many advances in AMI care and improvements in outcomes with the development of regional PCI services.

Therefore, in the present study we sought to examine the temporal trends in invasive management and in-hospital outcomes of both sexes over a period of 12 years in a national cohort of AMI hospitalizations in the United States.

Methods

Data source

The National Inpatient Sample (NIS) is a set of the largest publicly available all-payer longitudinal databases of hospital in-patient discharges in the United States. It is developed for the Agency for Healthcare Research and Quality (AHRQ), which administers the Healthcare Cost and Utilization Project.^{17,18} It contains anonymized retrospectively collected data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. Therefore, it can be used for the national and regional estimation of hospital utilization, quality, and other related issues. The NIS data set was designed to approximate a 20% stratified sample of the US community hospitals, excluding rehabilitation and long-term acute care hospitals, and provides sampling weights to calculate national estimates that represent more than 95% of the US population. Previous validation studies have shown that it has better demographic capture compared with a large multistate electronic health record data set and that it is highly comparable with other related databases.^{19,20}

Study design and population

All hospitalizations of adults (18 years of age and older) with a principal discharge diagnosis of AMI between January 2004 and September 2015 were included, stratified according to sex. International Classification of Diseases, Ninth Revision (ICD-9) and Clinical Classification Software codes were used to identify STEMI and non-STEMI (NSTEMI), patient comorbidities, procedures, and clinical outcomes (Supplemental Table S1). Additional comorbidities were identified using the existing 29 AHRQ Elixhauser comorbidity measures. Hospital-related factors including hospital bed size, region, and location/teaching status were analyzed to account for any hospital-level differences. The "Hospital bed size" variable refers to the number of short-term acute hospital beds and is specific to the hospital's location and teaching status. Missing data represented 0.4% ($n = 27,042$) of the original data set and, therefore, such cases were excluded (flow diagram: Supplemental Fig. S1).

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included major acute cardiovascular and cerebrovascular events (MACCE; composite of all-cause mortality, acute stroke/transient ischemic attack, and cardiac complications), all-cause bleeding, and acute stroke/transient ischemic attack. Cardiac complications included hemopericardium, cardiac tamponade, coronary dissection, and any

pericardiocentesis procedure. The process outcome was the receipt of invasive management for AMI, in the form of CA and/or PCI.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) statistical software version 25 (IBM Corp, Armonk, NY) was used for statistical data analysis. We assessed the normality of data distribution using the Kolmogorov-Smirnov test. Data were expressed as median (interquartile range) for continuous nonparametric data and as whole numbers (percentages) for categorical data. Quantitative nonparametric data were analyzed using the Mann-Whitney U test, whereas the χ^2 test was used for the comparison of categorical variables between the study groups. All analyses were conducted with appropriate sampling weights provided by the AHRQ for each individual discharge.

Multivariable binomial logistic regression analyses were used to determine the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of invasive management and in-hospital adverse outcomes between sexes (Appendix 1).

Trend analysis with a Mantel-Haenszel extension of the χ^2 test of trend (linear-by-linear association) was conducted to establish trends of invasive management and in-hospital adverse outcomes over 12 years.

Results

Patient characteristics

A total of 7,026,432 records of AMI hospitalizations between 2004 and 2015 were included, of which 2,789,494 (39.7%) were women. Overall, women were, on average, 7 years older than men (median, 77 vs 70 years). The 2 groups were comparable on characteristics such as household income class, hospital bed size, and weekend admission. STEMI presentation was more common in men compared with women (32.6% vs 24.3%, respectively; $P < 0.001$). The prevalence of conventional cardiovascular risk factors such as diabetes, stroke, hypertension, and chronic kidney disease was higher in women compared with men (36.7% vs 32.8%, 3.6% vs 2.7%, 69.8% vs 65.1%, and 17.7% vs 16.2%, respectively; $P < 0.001$ for each). In contrast, men had a higher prevalence of previous cardiovascular disease, as evidenced by the higher prevalence of previous AMI, PCI, coronary artery bypass grafting, and angina (9.3% vs 7.5%, 11% vs 7.8%, 6.9% vs 4.9%, and 7.8% vs 5.3%, respectively; $P < 0.001$ for each). Smoking was less prevalent in female patients (21.8% vs 32.8%, $P < 0.001$), obesity was slightly more often prevalent (12.8% vs 11.5%, $P < 0.001$), but depression and hypothyroidism were substantially more prevalent in female patients (9.2% vs 4.7%, $P < 0.001$ and 16.5% vs 5.4%, $P < 0.001$, respectively; Table 1).

In-hospital management

Overall, receipt of invasive therapies was higher in men than in women (CA, 70.1% vs 57.2% and PCI, 48.8% vs 34.8%, respectively; $P < 0.001$ for both) (Table 2, Supplemental Fig. S2). Women had significantly lower odds of receiving invasive therapy than men after adjustment for

Table 1. Patient characteristics according to sex

Characteristic	Sex		P
	Female (39.7%)	Male (60.3%)	
Number of weighted discharges	2,789,494	4,236,938	
Median age (IQR), years	77 (66-85)	70 (60-80)	< 0.001
Age group, %			< 0.001
18-29	0.2	0.3	
30-49	7.6	13.5	
50-79	57.4	68.8	
> 80	34.8	17.4	
STEMI, %	24.3	32.6	< 0.001
Elective admission, %	6.7	7.1	< 0.001
Weekend admission, %	25.9	26.0	0.003
Primary expected payer, %			< 0.001
Medicare	68.6	50.0	
Medicaid	6.3	5.9	
Private insurance	19.1	33.2	
Self-pay	4.0	6.8	
No charge	0.4	0.7	
Other	1.6	3.4	
Median household income (percentile), %			< 0.001
0-25	30.3	27.7	
26-50	27.5	27.1	
51-75	23.2	24.2	
76-100	19.0	21.0	
Cardiogenic shock, %	4.7	5.1	< 0.001
Cardiac arrest, %	1.5	1.7	< 0.001
Ventricular tachycardia, %	2.0	2.9	< 0.001
Ventricular fibrillation, %	1.9	3.2	< 0.001
Cardiac tamponade, %	0.063	0.055	< 0.001
Hemopericardium, %	0.027	0.023	< 0.001
Comorbidities, %			
Atrial fibrillation	18.4	15.5	< 0.001
Dyslipidaemia	51.0	57.7	< 0.001
Thrombocytopenia	2.1	2.6	< 0.001
Dementia	2.5	1.2	< 0.001
Smoking history	21.8	32.8	< 0.001
Previous AMI	7.5	9.3	< 0.001
History of IHD	70.2	81.2	< 0.001
Previous PCI	7.8	11.0	< 0.001
Previous CABG	4.9	6.9	< 0.001
Previous CVA	3.6	2.7	< 0.001
Family history of CAD	5.3	7.8	< 0.001
Deficiency anemias	18.9	12.0	< 0.001
Chronic blood loss anemia	1.4	0.9	< 0.001
Congestive heart failure	1.1	0.7	< 0.001
Valvular disease	0.329	0.198	< 0.001
Hypertension	69.8	65.1	< 0.001
Peripheral vascular disorders	11.5	10.6	< 0.001
Pulmonary circulation disorders	0.137	0.082	< 0.001
Chronic pulmonary disease	23.5	18.9	< 0.001
Coagulopathy	3.9	4.7	< 0.001
Obesity	12.8	11.5	< 0.001
Weight loss	2.7	1.8	< 0.001
Diabetes mellitus, uncomplicated	29.8	27.2	< 0.001
Diabetes mellitus with complications	6.9	5.6	< 0.001
Hypothyroidism	16.5	5.4	< 0.001
Drug abuse	1.3	2.5	< 0.001
Alcohol abuse	1.0	4.0	< 0.001
AIDS	0.1	0.2	< 0.001
Depression	9.2	4.7	< 0.001
Peptic ulcer disease excluding bleeding	0.034	0.031	0.068
Liver disease	1.0	1.3	< 0.001
Chronic renal failure	17.7	16.2	< 0.001
Other neurological disorders	7.2	4.9	< 0.001

Table 1. Continued.

Characteristic	Sex		P
	Female (39.7%)	Male (60.3%)	
Paralysis	1.9	1.4	< 0.001
Psychoses	2.5	1.8	< 0.001
RA/collagen vascular diseases	3.6	1.3	< 0.001
Solid tumour without metastasis	1.2	1.6	< 0.001
Metastatic cancer	0.891	0.853	< 0.001
Lymphoma	0.467	0.508	< 0.001
Fluid and electrolyte disorders	23.7	16.6	< 0.001
Bed size of hospital, %			< 0.001
Small	11.6	10.1	
Medium	25.4	24.5	
Large	65.4	63.0	
Hospital Region, %			< 0.001
Northeast	19.9	18.6	
Midwest	23.9	23.2	
South	39.8	40.0	
West	16.4	18.2	
Location/teaching status of hospital, %			< 0.001
Rural	11.5	9.4	
Urban non-teaching	41.6	40.8	
Urban teaching	47.0	49.8	

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVA, cerebrovascular accident; IHD, ischemic heart disease; IQR, interquartile range; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis; STEMI, ST-elevation myocardial infarction.

differences in baseline covariates (CA: aOR, 0.92 [95% CI, 0.91-0.93]; PCI: aOR, 0.82 [95% CI, 0.81-0.83]; $P < 0.001$ for both; [Table 3](#), [Fig. 1](#)).

Similar findings were observed in the STEMI subgroup ([Supplemental Table S2](#)). Women with STEMI were less likely to receive CA (aOR, 0.89 [95% CI, 0.88-0.90]; $P < 0.001$) or PCI (aOR, 0.85 [95% CI, 0.84-0.86]; $P < 0.001$; [Supplemental Table S3](#)).

Furthermore, although there was a gradual increase in rates of receipt of invasive therapy for both sexes over the 12 years analyzed, women had persistently lower rates of CA over the years studied ([Supplemental Table S4](#), [Fig. 2](#)). Even after adjustment for differences in baseline covariates women had persistently lower odds of receipt of CA (2004: aOR, 0.95 [95% CI, 0.93-0.96]; 2015: aOR, 0.94 [95% CI, 0.92-0.95]; P for trend < 0.001) and PCI (2004: 0.90 [95% CI, 0.89-0.92]; 2015: 0.83 [95% CI, 0.82-0.84]; P for trend < 0.001) over time ([Supplemental Table S5](#), [Supplemental Fig. S3](#)).

In-hospital clinical outcomes

Overall, crude in-hospital outcomes were worse in women than in men (mortality: 6.8% vs 5.1%; bleeding: 3.3% vs 3.0%; stroke: 2.0% vs 1.2%, respectively; $P < 0.001$ for all; [Table 2](#)). Similar findings were reported in the STEMI ([Supplemental Table S2](#)), as well as in the PCI subgroup in which women had higher rates of adverse outcomes than men (mortality: 3.8% vs 2.5%; bleeding: 3.2% vs 2.1%; stroke: 1.2% vs 0.6%, respectively; $P < 0.001$ for all; [Supplemental Table S6](#)).

The overall adjusted odds of MACCE and mortality were higher in women than in men (aOR, 1.08 [95% CI,

Table 2. Comparison of treatments and in-hospital adverse outcomes for the different sex groups

Variable	Sex		P
	Female (39.7%)	Male (60.3%)	
Treatment, %			
CA	57.2	70.1	< 0.001
PCI	34.8	48.8	< 0.001
CABG	6.3	10.5	< 0.001
Thrombolysis	1.1	1.5	< 0.001
Use of assist device or IABP	3.7	5.7	< 0.001
Outcomes, %			
MACCE	8.5	6.1	< 0.001
All-cause mortality	6.8	5.1	< 0.001
All-cause bleeding	3.3	3.0	< 0.001
Cardiac complications	0.084	0.074	< 0.001
Postprocedural hemorrhage	0.7	0.7	0.418
Stroke	2.0	1.2	< 0.001
Median length of stay (IQR), days	5 (3-8)	4 (2-8)	< 0.001
Median total charges (IQR), USD\$	41,254 (20,718-78,877)	50,151 (25,284- 95,125)	0.003

CA, coronary angiography; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; IQR, interquartile range; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); PCI, percutaneous coronary intervention.

1.07-1.09]; aOR, 1.03 [95% CI, 1.02-1.04], respectively; $P < 0.001$ for all). Women had an increased risk of stroke compared with men (aOR, 1.31 [95% CI, 1.29-1.33]; $P < 0.001$). In contrast, the odds of bleeding were lower in women than in men (aOR, 0.94 [95% CI, 0.93-0.95]; $P < 0.001$; Table 3, Fig. 1). In the STEMI subgroup analysis, women were at increased odds of all complications (MACCE, mortality, bleeding, and stroke) (Supplemental Table S3).

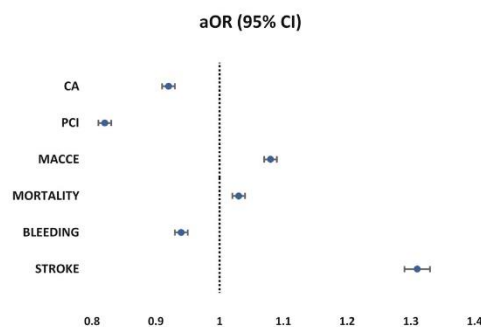
In a subgroup analysis of all patients who underwent PCI, women were associated with increased odds of all complications, including MACCE (aOR, 1.27 [95% CI, 1.26-1.29]), mortality (aOR, 1.2 [95% CI, 1.18-1.22]), bleeding (aOR, 1.20 [95% CI, 1.20-1.24]), and stroke (aOR, 1.49 [95% CI, 1.45-1.53]; $P < 0.001$ for all; Table 4).

Table 3. Adjusted odds of invasive management and in-hospital adverse outcomes in women*

Variable	Female sex, OR (95% CI)	P
Invasive management		
CA	0.92 (0.91-0.93)	< 0.001
PCI	0.82 (0.81-0.83)	< 0.001
Outcomes		
MACCE	1.08 (1.07-1.09)	< 0.001
All-cause mortality	1.03 (1.02-1.04)	< 0.001
All-cause bleeding	0.94 (0.93-0.95)	< 0.001
Cardiac complications	1.12 (1.06-1.19)	< 0.001
Stroke	1.31 (1.29-1.33)	< 0.001

CA, coronary angiography; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); OR, odds ratio; PCI, percutaneous coronary intervention.

* Reference group is men.

**Figure 1.** Adjusted odds ratios (aORs) of invasive management and in-hospital adverse outcomes in women (reference group is men). CA, coronary angiography; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications); PCI, percutaneous coronary intervention.

Over 12 years, there was a gradual decline in adverse event rates in both sexes (Fig. 3). However, in each year, the event rates of adverse outcomes were persistently higher in women compared with men (P for trend < 0.001 ; Supplemental Table S4). Throughout the years studied, women were more likely to die, or have a major adverse cardiovascular event or stroke than men; except for major bleeding complications (P for trend < 0.001). Odds for major bleeding complications were similar in women compared with men initially, although from approximately 2009, the odds for bleeding were consistently higher in women compared with men with the highest values in 2014 (aOR, 1.2 [95% CI, 1.15-1.25]; $P < 0.001$; Supplemental Table S5, Supplemental Fig. S4). Similar trends were observed in the STEMI subgroup with consistently increased risk in women compared with men in almost all outcomes in the studied years except bleeding risk (P for trend < 0.001). Initially the trends of bleeding risk suggested lower odds in women. However, this pattern reversed in 2009, in which women had 35% (95% CI, 1.27- 1.44; $P < 0.001$) increased risk compared with men, after which the odds continued to be higher (Supplemental Table S7).

Discussion

To our knowledge, our study is the largest representative study of more than 7 million AMI admissions in the United States to report trends in sex-based differences in management and adverse outcomes over 12 years. Over the last decade, we witnessed improved awareness in sex-based cardiovascular risks, wider adoption of invasive management, and significant advances in the pharmacological management of acute coronary syndromes. Yet, we report no significant changes in disparities in AMI treatments and outcomes among the sexes. Women are still less likely to receive CA or PCI, and continue to have worse adverse outcomes compared with men. Even when women were offered PCI, their outcomes remained worse than men.

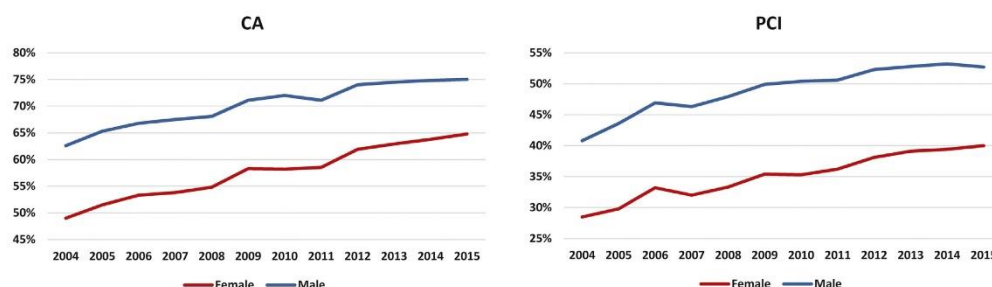


Figure 2. Receipt of invasive management according to sex from 2004 to September 31, 2015. $P < 0.001$ for all trends. CA, coronary angiography; PCI, percutaneous coronary intervention.

The 2014 American and the 2020 European society guidelines in the management of acute coronary syndromes do not differentiate between sexes, with no sex-specific differences in recommendations around the receipt of invasive management or medical therapies.²¹⁻²³ Despite this, our analysis suggests that women are 10%-20% less likely to receive invasive therapies and more likely to have worse outcomes than men. The differences in management and outcomes between sexes have not narrowed over time. Furthermore, this analysis was adjusted for hospital-level factors (bed size, region, and location/teaching status) to alleviate any hospital-related effects.

Similar findings have been reported in older studies in which trends over a relatively short period were investigated. An analysis of 78,254 patients with AMI from the Get With The Guidelines (GWTG)-coronary artery disease (CAD) registry between 2001 and 2006 showed no difference in adjusted in-hospital mortality among the sexes in the overall AMI cohort (aOR, 1.04; 95% CI, 0.99-1.10) with women only at an increased risk of mortality only in the STEMI subgroup (aOR, 1.12; 95% CI, 1.02-1.23).²⁴ In a more recent study, Stehli et al. reported on in-hospital and 30 days post-AMI outcomes of 13,451 patients between 2013 and 2016 from the Victorian Cardiac Outcomes registry and showed the worst outcomes in the STEMI subgroup in women (mortality: 8.4% vs 5.7%; bleeding: 3.5% vs 1.8%; $P < 0.001$ for both).²⁵

Differences in outcomes between sexes could very well be related to the receipt and timing of invasive treatments. Women consistently have a higher risk profile at presentation compared with men, and are commonly older,²⁶ have a greater comorbidity burden,^{27,28} and a higher prevalence of

nonconventional risk factors,^{6,29} and are therefore less likely to be managed invasively. Similarly, sex bias or patient refusal of invasive cardiac procedures could mediate lower CA utilization in female patients.^{30,31} Even in patients at highest risk of ischemic complications, a contemporary study in 137,265 patients with NSTEMI has shown that women with high Global Registry of Acute Coronary Events (GRACE) scores were less likely to receive invasive management compared with men. Even when they received an invasive strategy, it was consistently delayed compared with men.³² In the STEMI subgroup, time to primary PCI was significantly greater in women than in men, irrespective of whether they had chest pain symptoms.³³ Udell et al. evaluated differences in management in 104,817 STEMI patients from the GWTG-ACS database (2003-2008) with women 15% less likely to experience a door-to-balloon within 90 minutes than men even after adjustment for differences in baseline characteristics.³⁴ Also, Leurent et al. observed significant differences in women compared with men among 5000 STEMI cases from the French registry in time from first medical contact to balloon inflation or thrombus aspiration (100 vs 94 minutes; $P < 0.05$), use of radial access (40% vs 51%; $P < 0.001$), death (9% vs 4%; $P < 0.001$), and even use of guideline-directed medical therapy at discharge.¹⁶ Interestingly, Setoguchi et al. reported no significant sex-related differences in the management of AMI with even lower mortality in women among patients aged 75 years or older.³⁵ However, a smaller sample size (1625), a higher proportion of female patients (approximately 80%), and different time period (1999-2000) could play a role for differing findings.

However, it is important to note that several other factors could play a role in the observed sex gap in invasive management. Women, compared with men, have higher rates of AMI with nonobstructive coronary arteries (plaque erosion, coronary spasm, microvascular dysfunction, and stress-induced myocardial infarction), spontaneous coronary artery dissection,³⁶ as well as type II AMI.³⁷ Johnston et al. reported on the sex prevalence of AMI in patients with nonobstructive CAD among 95,849 patients (2005-2010) from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). The prevalence of nonobstructive CAD in the STEMI group was 7% (6% in men vs 10% in women), and 17% in the NSTEMI group (11% in men vs 28% in women).³⁸

Table 4. Adjusted odds of in-hospital adverse outcomes in females who underwent PCI*

Variables	OR (95% CI)	P
MACCE	1.27 (1.26-1.29)	< 0.001
All-cause mortality	1.20 (1.18-1.22)	< 0.001
All-cause bleeding	1.22 (1.20-1.24)	< 0.001
Stroke	1.49 (1.45-1.53)	< 0.001

OR, odds ratios; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

*Reference group is males.

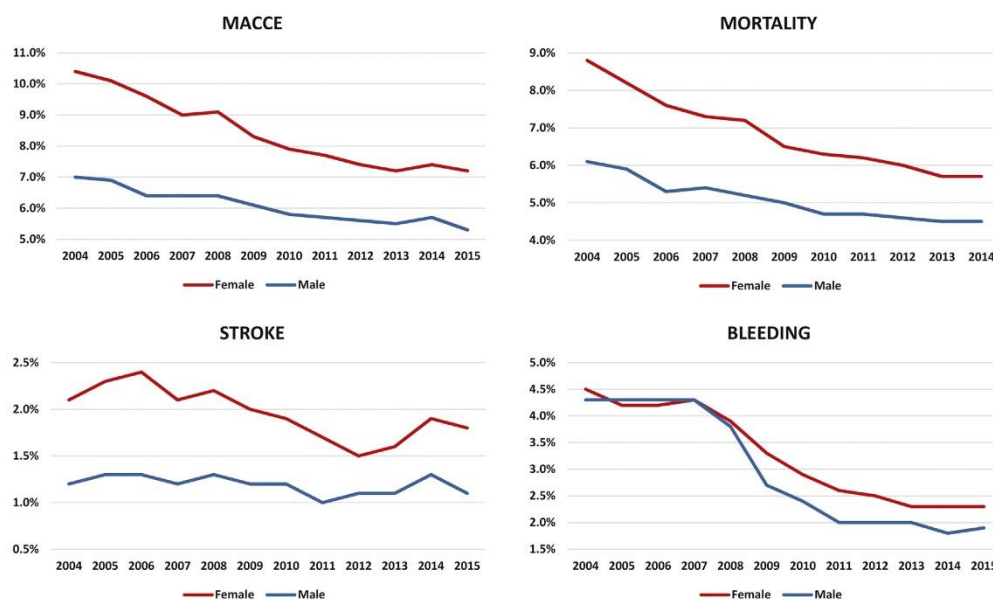


Figure 3. In-hospital adverse outcomes according to sex from 2004 to September 31, 2015. $P < 0.001$ for all trends. MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

Interestingly, we observed that the odds of bleeding were approximately 10% lower in women compared with men initially; although around 2009, the risk changed with a consistently higher risk in the order of 10%-20% observed in women. Higher bleeding risk in women compared with men could be multifactorial, with factors such as differences in response to antiplatelets,³⁹ certain medications,^{39,40} and thrombolytic therapy,⁴¹ smaller body habitus and artery sizes,^{42,43} as well as procedural factors (such as access site choice).^{44,45} Other studies have confirmed the increased risk of major bleeding in women; for example, Nanna et al. reported higher rates of bleeding complications in 3041 patients older than 75 years who were hospitalized for AMI from the Comprehensive Evaluation of Risk Factors in Older Patients with Acute Myocardial Infarction (SILVER-AMI) in women with STEMI (26.2% vs 15.6%; $P < 0.001$) but not NSTEMI (17.8% vs 15.7%; $P = 0.21$).⁴⁶

An important finding in our study is that even when women are treated with PCI, their outcomes remain worse, and this did not change over time. Although this elevated risk in women could be multifactorial, some of the factors could be avoided where possible. For example, in a recent study, Daugherty et al. investigated sex and bleeding risk associated with the use of bleeding-avoiding strategies (BAS) of bivalirudin, radial artery access, and closure devices among patients who underwent PCI, from 2008 to 2011. Among > 185,000 women who underwent PCI, the bleeding rate was reduced by 50% (12.5% vs 6.2%; $P < 0.01$) if any BAS was used. This reduction in bleeding events in women was even more significant than that observed in men (6.2% vs 3.0%; $P < 0.01$). Overall, BAS were less likely to be used in women compared

with men and fewer women had PCI using radial access compared with men.^{47,48} Additionally, superiority of potent purinergic receptor P2Y₁₂ inhibitors against thrombotic events in PCIs has been shown in trials.⁴⁹ However, studies suggested underuse in women. For example, the association between the use of different types of purinergic receptor P2Y₁₂ inhibitors and outcomes post primary PCI, was examined in > 89,000 patients from the British Cardiovascular Intervention registry. Women were more likely to receive clopidogrel and less likely to receive more potent antiplatelet treatments.⁵⁰ The worse outcomes observed after PCI in women do not appear to be related to lesion complexity. An observational retrospective study in which CAD complexities were compared in 29,265 AMI patients treated in the Netherlands showed that women had less extensive CAD, with higher rates of single-vessel disease compared with men (49.4% vs 46.9%; $P < 0.001$) and lower rates of multivessel disease (47.2% vs 50.8%; $P < 0.001$). Despite less complex disease in women, women younger than 70 years of age had higher rates of mortality (7.3% vs 5.6%; $P < 0.001$).⁵¹ Another prospective study evaluated sex-based differences in patients with 100,704 drug-eluting stents (DES) implanted between 2005 and 2009 in Germany. Women, compared with men, had lower rates of use of DES in those with NSTEMI (24.8% vs 27.3%; $P < 0.0001$) especially in women older than 75 years, although no significant differences use of DES were observed in the STEMI group.⁵²

There are several limitations to the present study. First, the data collected reflect in-patient outcomes only; longer follow-ups of adverse events would provide a more complete

understanding of sex differences in outcomes. Second, individual risk factors, details regarding coronary anatomy, and time frames such as door-to-balloon time were not available in the NIS; this could provide further insight as to whether there are any sex-related differences in the complexity of coronary lesions and procedure approaches as well as details of timing of the index procedure. Similarly, the study lacks granularity regarding the “coronary artery dissection” variable, which did not include only iatrogenic events. Furthermore, no data regarding medications, antithrombotic therapy, Killip class, left ventricular ejection fraction, and creatinine clearance is captured in the NIS. These data might reveal sex differences in the prescription of different antiplatelet regimens, utilization and optimization of guideline-directed medical therapy, and their effect on MACCE. Also, in this study we were not able to match specific cardiovascular pathophysiologic features of AMI with the outcomes, which could have an effect on prognosis. Likewise, in this study we present a sex-based analysis and we did not account for gender-related aspects, which could also have a role in management bias. Finally, because NIS is an administrative database, there is always a risk of reporting and coding errors that represent a potential bias as is the under-reporting of other comorbidities. Furthermore, the ICD-9 codes in the data set are validated for the purpose of cardiovascular research.⁵³

In conclusion, our nationwide temporal analysis shows persistent differences in the management and outcomes of AMI among the sexes over a period of 12 years, with women less likely to receive invasive therapies, and more likely to experience adverse outcomes including mortality, major bleeding, and stroke. The gap between sexes has not narrowed over time. A sex-based approach to the management of AMI, taking in to account the clinical and biological differences previously described, could possibly eliminate the persistent disparity in outcomes in the near future.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2021.06.012>.

Supplementary Material:

Matetic A, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. CJC Open. 2021;3(12 Suppl):S19-S27. doi: 10.1016/j.cjco.2021.06.012.

Supplemental Appendix S1. Variables included in multivariable binomial logistic regression models

The following variables were adjusted for in the logistic regression analysis: age, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking history, previous acute myocardial infarction, previous CABG, history of ischaemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accident, family history of coronary artery disease, cardiogenic shock or cardiac arrest during hospitalization, bed size of hospital, region of hospital, location/teaching status of hospital, thrombocytopenia, ventricular and atrial fibrillation, ventricular tachycardia, and Elixhauser comorbidities (acquired immune deficiency syndrome, anaemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes mellitus, drug abuse, hypertension, hypothyroidism, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, pulmonary circulation disorders, renal failure, solid tumour without metastasis, valvular heart disease, and weight loss). Except for the aforementioned variables, regression model for in-hospital adverse outcomes (MACCE, all-cause mortality, all-cause bleeding, stroke) included PCI as a predictor variable. Multivariable logistic regression analyses which compared different subgroups did not include the same stratification factor as predictor variable (i.e. PCI in the PCI subgroup analysis, etc.).

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Supplemental Table S1. ICD codes used to identify the cohort, comorbidities, and outcomes

Variable	Source	Codes
Diagnoses		
STEMI	ICD-9	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x
NSTEMI	ICD-9	410.70, 410.71, 410.72
Dyslipidemia	CCS	53
Smoking Status	ICD-9	V15.82, 305.1
AF	ICD-9	427.31
History of IHD	ICD-9	414.00-07, 414.2-9
Previous MI	ICD-9	412
Previous PCI	ICD-9	V45.82
Previous CABG	ICD-9	V45.81
Family history of CAD	ICD-9	V17.3
Previous CVA (TIA and Stroke)	ICD-9	V12.54
Thrombocytopenia	ICD-9	287.5, 287.49
In-hospital procedures and outcomes		
Acute ischemic stroke	ICD-9	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0-1, 435.8-9, 436
Shock during admission	ICD-9	785.51
Use of assist device or IABP	ICD-9	37.68, 37.61
Hemopericardium	ICD-9	423.0
Coronary dissection	ICD-9	414.12

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Cardiac tamponade	ICD-9	423.3
Diagnostic Cardiac catheterisation	CCS	47
CABG	CCS	44
PCI	CCS	45

Abbreviations: STEMI – ST-elevation myocardial infarction; NSTEMI – non-ST-elevation myocardial infarction; CLD – chronic liver disease; AF – atrial fibrillation; IHD – ischemic heart disease; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CVA – cerebrovascular accident; TIA – transient ischemic attack; IABP – intra-aortic balloon pump.

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Supplemental Table S2. Invasive management and in-hospital adverse outcomes in the STEMI subgroup

Variables	Sex		P-value
	Female (39.7%)	Male (60.3%)	
CA, %	74.0	84.2	<0.001
PCI, %	61.4	73.8	<0.001
MACCE, %	11.6	6.5	<0.001
All-cause mortality, %	10.1	5.6	<0.001
All-cause bleeding, %	3.8	2.9	<0.001
Stroke, %	1.9	1.0	<0.001

Abbreviations: STEMI- ST elevation myocardial infarction; CA- coronary angiogram; PCI- percutaneous coronary intervention; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

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Supplemental Table S3. Adjusted odds of invasive management and in-hospital adverse outcomes in females in the STEMI subgroup*

Variables	OR [95% CI]	P-value
CA	0.89 [0.88, 0.90]	<0.001
PCI	0.85 [0.84, 0.86]	<0.001
MACCE	1.21 [1.20, 1.23]	<0.001
All-cause mortality	1.19 [1.17, 1.20]	<0.001
All-cause bleeding	1.05 [1.03, 1.07]	<0.001
Stroke	1.38 [1.35, 1.42]	<0.001

*Reference group is males.

Abbreviations: OR – Odds Ratios; CI – Confidence Interval; STEMI- ST elevation myocardial infarction; CA- coronary angiogram; PCI- percutaneous coronary intervention MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

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Supplemental Table S4. Trend of in-hospital outcomes and treatments from 2004 to 2015*

Outcome/Year	2004-2006	2007-2009	2010-2012	2013-2015*	P-value (for trend)
MACCE, %					
Female	10.0	8.8	7.7	7.3	<0.001
Male	6.8	6.3	5.7	5.5	<0.001
All-cause mortality, %					
Female	8.2	7.0	6.2	5.7	<0.001
Male	5.7	5.2	4.7	4.4	<0.001
Stroke %					
Female	2.3	2.1	1.7	1.8	<0.001
Male	1.2	1.2	1.1	1.2	<0.001
All-cause bleeding, %					
Female	4.3	3.8	2.6	2.3	<0.001
Male	4.3	3.6	2.2	1.9	<0.001
CA, %					
Female	51.2	55.6	59.5	63.8	<0.001
Male	64.9	68.9	72.3	74.8	<0.001
PCI, %					
Female	30.4	33.6	36.5	39.5	<0.001
Male	43.8	48.1	51.1	52.9	<0.001

*September 31, 2015.

Abbreviations: MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient and cardiac complications); CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention.

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Supplemental Table S5. Adjusted odds of invasive management and in-hospital adverse outcomes in females stratified by year*

Year	Female sex					
	OR [95% CI]					
	P-value					
	CA	PCI	MACCE	Mortality	Bleeding	Stroke
2004	0.95 [0.93, 0.96]	0.90 [0.89, 0.92]	1.11 [1.09, 1.14]	1.07 [1.04, 1.09]	0.86 [0.84, 0.88]	1.37 [1.31, 1.42]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2005	0.92 [0.91, 0.94]	0.84 [0.83, 0.85]	1.07 [1.05, 1.09]	1.01 [0.98, 1.03]	0.79 [0.77, 0.81]	1.35 [1.29, 1.41]
	<0.001	<0.001	<0.001	0.600	<0.001	<0.001
2006	0.92 [0.90, 0.93]	0.86 [0.85, 0.88]	1.14 [1.12, 1.17]	1.08 [1.06, 1.11]	0.79 [0.77, 0.81]	1.41 [1.35, 1.47]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2007	0.92 [0.90, 0.93]	0.83 [0.82, 0.84]	1.03 [1.01, 1.05]	0.97 [0.94, 0.99]	0.82 [0.79, 0.84]	1.26 [1.20, 1.31]
	<0.001	<0.001	0.016	0.011	<0.001	<0.001
2008	0.94 [0.93, 0.95]	0.84 [0.83, 0.85]	1.07 [1.04, 1.09]	1.01 [0.98, 1.04]	0.87 [0.85, 0.90]	1.30 [1.24, 1.36]
	<0.001	<0.001	<0.001	0.480	<0.001	<0.001
2009	0.96 [0.94, 0.97]	0.83 [0.82, 0.84]	1.03 [1.00, 1.05]	0.96 [0.93, 0.98]	1.12 [1.08, 1.16]	1.32 [1.26, 1.38]
	<0.001	<0.001	0.020	0.002	<0.001	<0.001
2010	0.92 [0.90, 0.93]	0.81 [0.80, 0.82]	1.07 [1.04, 1.10]	1.02 [1.00, 1.05]	1.09 [1.05, 1.13]	1.26 [1.20, 1.32]
	<0.001	<0.001	<0.001	0.111	<0.001	<0.001
2011	0.93 [0.91, 0.94]	0.82 [0.81, 0.83]	1.09 [1.06, 1.11]	1.01 [0.99, 1.04]	1.12 [1.08, 1.16]	1.36 [1.29, 1.43]
	<0.001	<0.001	<0.001	0.331	<0.001	<0.001
2012	0.90 [0.89, 0.91]	0.79 [0.78, 0.80]	1.05 [1.03, 1.08]	1.02 [1.00, 1.05]	1.12 [1.08, 1.16]	1.23 [1.17, 1.29]
	<0.001	<0.001	<0.001	0.106	<0.001	<0.001
2013	0.91 [0.90, 0.92]	0.82 [0.81, 0.83]	1.07 [1.04, 1.10]	1.00 [0.97, 1.03]	1.03 [0.99, 1.07]	1.27 [1.20, 1.33]
	<0.001	<0.001	<0.001	0.948	0.201	<0.001
2014	0.92 [0.90, 0.93]	0.79 [0.78, 0.80]	1.09 [1.06, 1.12]	1.05 [1.02, 1.08]	1.20 [1.15, 1.24]	1.28 [1.22, 1.34]
	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
2015**	0.94 [0.92, 0.95]	0.83 [0.82, 0.84]	1.16 [1.13, 1.20]	1.11 [1.07, 1.15]	1.14 [1.10, 1.20]	1.36 [1.29, 1.44]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

*Reference group is males; **September 31, 2015.

Abbreviations: OR – Odds Ratios; CI – Confidence Interval; CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

Supplementary Material:

Matetic A, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. CJC Open. 2021;3(12 Suppl):S19-S27. doi: 10.1016/j.cjco.2021.06.012.

SupplementalTable S6. In-hospital adverse outcomes in the PCI subgroup

Variables	Sex		P-value
	Female (39.7%)	Male (60.3%)	
MACCE, %	4.9	3.1	<0.001
All-cause mortality, %	3.8	2.5	<0.001
All-cause bleeding, %	3.2	2.1	<0.001
Stroke, %	1.2	0.6	<0.001

Abbreviations: MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

Supplementary Material:

Matetic A, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. CJC Open. 2021;3(12 Suppl):S19-S27. doi: 10.1016/j.cjco.2021.06.012.

Supplemental Table S7. Adjusted odds of invasive management and in-hospital adverse outcomes in female STEMI patients stratified by year*

Year	Female sex					
	OR [95% CI]					
	P-value					
	CA	PCI	MACCE	Mortality	Bleeding	Stroke
2004	0.89 [0.87, 0.91]	0.92 [0.90, 0.94]	1.25 [1.21, 1.29]	1.20 [1.15, 1.24]	0.96 [0.92, 1.01]	1.62 [1.49, 1.75]
	<0.001	<0.001	<0.001	<0.001	0.084	<0.001
2005	0.91 [0.89, 0.93]	0.87 [0.85, 0.89]	1.23 [1.19, 1.28]	1.21 [1.16, 1.26]	0.86 [0.82, 0.90]	1.41 [1.30, 1.54]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2006	0.90 [0.87, 0.92]	0.92 [0.90, 0.94]	1.25 [1.20, 1.30]	1.15 [1.11, 1.20]	0.95 [0.90, 1.00]	1.75 [1.61, 1.90]
	<0.001	<0.001	<0.001	<0.001	0.032	<0.001
2007	0.92 [0.89, 0.94]	0.89 [0.87, 0.91]	1.22 [1.17, 1.27]	1.19 [1.14, 1.24]	0.86 [0.82, 0.91]	1.43 [1.31, 1.57]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2008	0.92 [0.90, 0.95]	0.86 [0.83, 0.88]	1.24 [1.19, 1.30]	1.21 [1.16, 1.27]	0.94 [0.89, 0.99]	1.42 [1.30, 1.56]
	<0.001	<0.001	<0.001	<0.001	0.016	<0.001
2009	0.91 [0.88, 0.94]	0.84 [0.81, 0.86]	1.10 [1.05, 1.15]	1.11 [1.06, 1.17]	1.35 [1.27, 1.44]	1.11 [1.00, 1.23]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2010	0.84 [0.81, 0.87]	0.84 [0.82, 0.87]	1.17 [1.11, 1.23]	1.16 [1.11, 1.23]	1.22 [1.14, 1.31]	1.23 [1.12, 1.37]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2011	0.93 [0.90, 0.97]	0.86 [0.84, 0.89]	1.18 [1.13, 1.24]	1.13 [1.07, 1.19]	1.25 [1.16, 1.35]	1.42 [1.28, 1.57]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2012	0.93 [0.89, 0.96]	0.83 [0.80, 0.85]	1.17 [1.11, 1.23]	1.17 [1.11, 1.23]	1.12 [1.04, 1.21]	1.21 [1.09, 1.35]
	<0.001	<0.001	<0.001	<0.001	0.003	<0.001
2013	0.89 [0.86, 0.92]	0.85 [0.82, 0.87]	1.12 [1.07, 1.18]	1.08 [1.02, 1.14]	1.26 [1.17, 1.37]	1.21 [1.09, 1.35]
	<0.001	<0.001	<0.001	0.005	<0.001	0.001
2014	0.89 [0.86, 0.92]	0.80 [0.78, 0.83]	1.29 [1.22, 1.35]	1.31 [1.24, 1.38]	1.42 [1.31, 1.54]	1.38 [1.25, 1.53]
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2015**	0.92 [0.88, 0.96]	0.89 [0.86, 0.92]	1.29 [1.22, 1.37]	1.32 [1.24, 1.41]	1.21 [1.10, 1.33]	1.19 [1.06, 1.35]
	<0.001	<0.001	<0.001	<0.001	<0.001	0.005

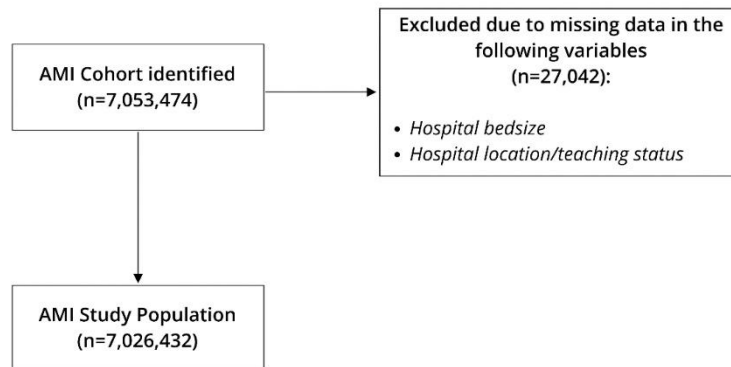
*Reference group is males; **September 31, 2015.

Abbreviations: STEMI – ST elevation myocardial infarction; OR – Odds Ratios; CI – Confidence Interval; CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

Supplementary Material:

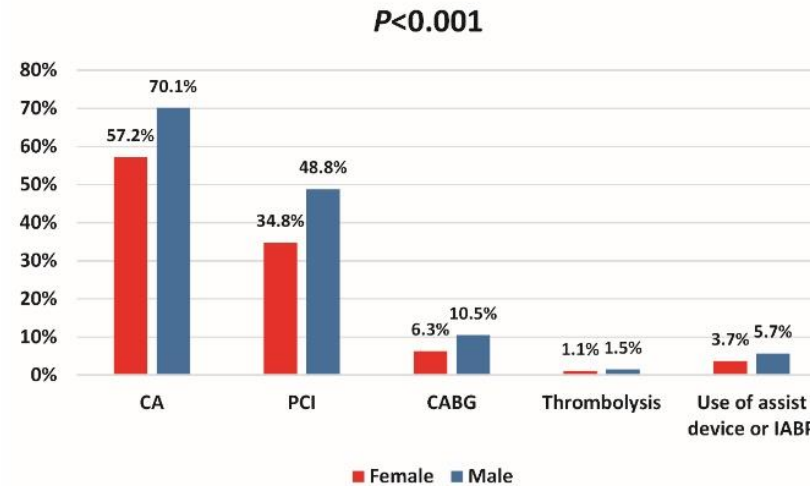
Matetic A, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. CJC Open. 2021;3(12 Suppl):S19-S27. doi: 10.1016/j.cjco.2021.06.012.

Supplemental Figure S1. Flow diagram of cohort selection process



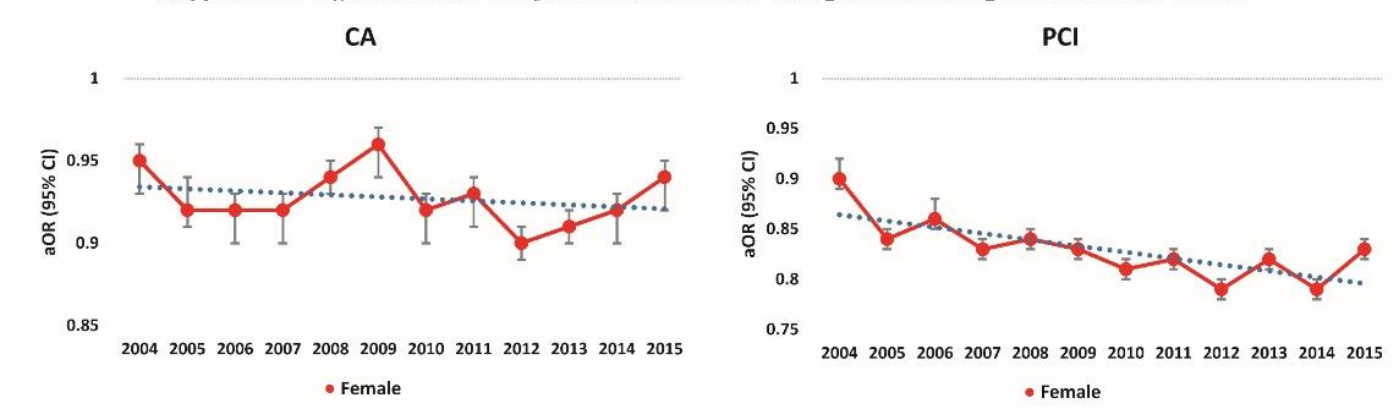
Abbreviations: AMI – Acute Myocardial Infarction.

Supplemental Figure S2. Receipt of treatments according to sex



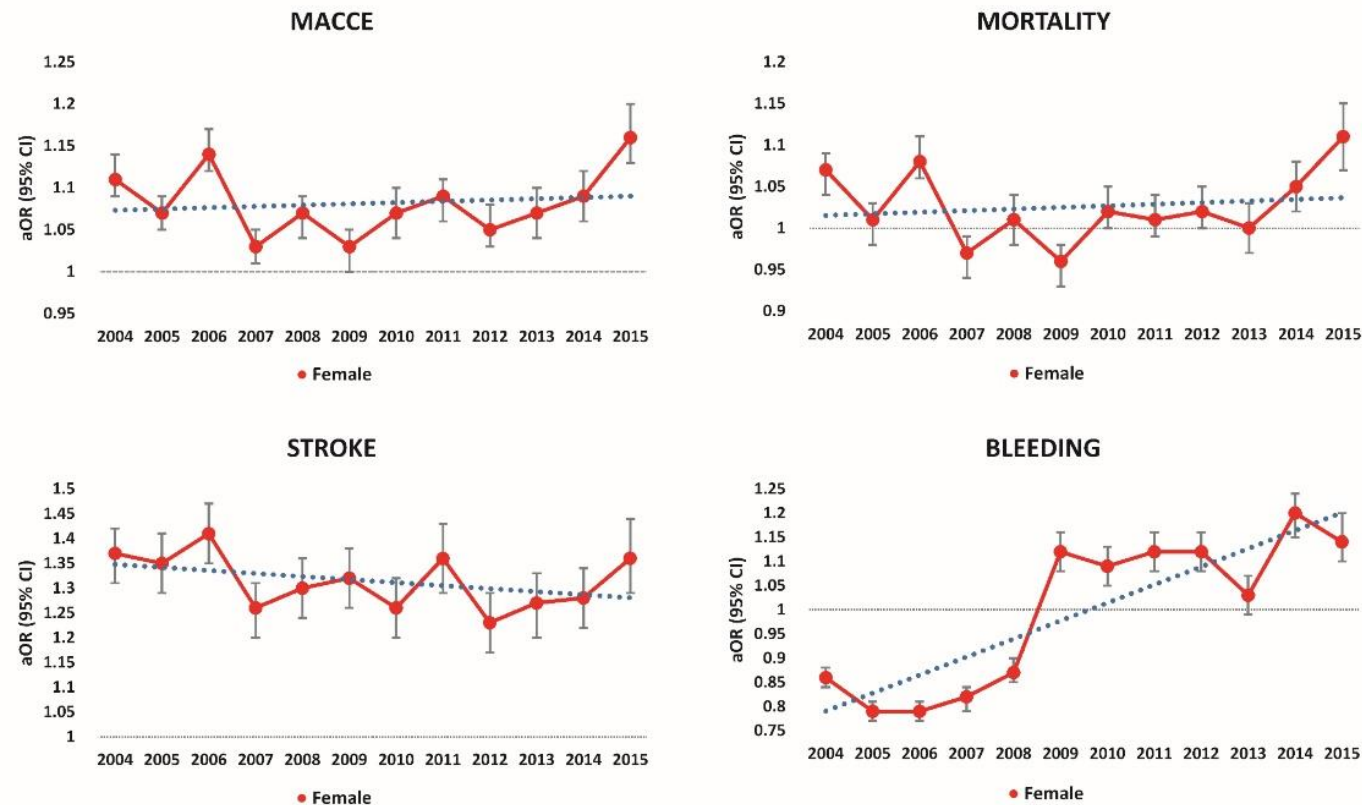
Abbreviations: CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention; CABG – Coronary Artery Bypass Graft; IABP – Intra-aortic Balloon Pump.

Supplemental Figure S3. Trend of adjusted odds for invasive management according to sex from 2004 to 2015*



*September 31, 2015; Reference group is males. **Abbreviations:** CA – Coronary Angiography; PCI – Percutaneous Coronary Intervention.

Supplemental Figure S4. Trend of adjusted odds for in-hospital adverse outcomes according to sex from 2004 to 2015*



*September 31, 2015; Reference group is males. **Abbreviations:** MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and cardiac complications).

11. ABSTRACT (ENGLISH LANGUAGE)

Doctoral dissertation title: REAL WORLD MANAGEMENT AND OUTCOMES IN ACUTE CORONARY SYNDROME: ANALYSIS OF A LARGE US COHORT.

Main objectives: The main aim of this doctoral dissertation and consolidated research studies was to compare the management and outcomes of patients with acute coronary syndrome based on their socioeconomic status, diagnostic coding priority, trial recruitment status and sex.

Materials and methods: Using the complex adjustment models, analysis of the largest national registry *National Inpatient Sample* was performed from January 2004 to December 2018, depending on the sub-study. The analysis included ~11 million discharge records of patients with acute coronary syndrome.

Main findings and scientific contribution: There were several main findings. First, patients with low socioeconomic status received less invasive management and had worse in-hospital prognosis. Second, patients with secondary-coded acute coronary syndrome were less likely to receive invasive management and more likely to experience in-hospital adverse events. Third, a higher utilization of invasive management and better in-hospital outcomes was observed in patients who were enrolled in a clinical trial. Fourth, female patients were less likely to receive invasive therapies and more likely to experience adverse outcomes. The scientific contribution of this doctoral dissertation and consolidated research studies is unequivocal. It represents a big data analysis of sufficiently powered registry with an excellent insight in the real-world contemporary state and detailed literature review. It is a result of an international collaboration with experts in the field of cardiovascular medicine. This research project warrants further incentives to equalize the quality of care and prognosis across the wide spectrum of acute coronary syndrome patients.

Conclusions: The management and outcomes of patients with acute coronary syndrome is subjected to disparity based on socioeconomic status, diagnostic coding priority, trial recruitment status and sex. Future initiatives are encouraged to eliminate the disparity gap in this vulnerable population.

12. SAŽETAK (HRVATSKI JEZIK)

Glavni ciljevi: Glavni cilj ove doktorske disertacije i objedinjenih znanstvenih istraživanja bio je usporediti liječenje i ishode bolesnika s akutnim koronarnim sindromom na temelju njihova socioekonomskog statusa, prioriteta dijagnostičkog kodiranja, uključenja u kliničko ispitivanje i spola.

Materijali i metode: Koristeći kompleksne statističke modele prilagodbe, učinjena je analiza najvećeg nacionalnog registra “*National Inpatient Sample*” iz Sjedinjenih Američkih Država za razdoblje od siječnja 2004. do prosinca 2018. godine, ovisno o pojedinom znanstvenom istraživanju. Analiza je uključila ~11 milijuna otpusnih zapisa o pacijentima s akutnim koronarnim sindromom.

Glavni nalazi i znanstveni doprinos: Utvrđeno je nekoliko glavnih nalaza. Prvo, pacijenti s niskim socioekonomskim statusom su bili rjeđe podvrgnuti invazivnom liječenju i imali su lošiju unutarbolničku prognozu. Drugo, pacijenti sa sekundarno kodiranom dijagnozom akutnog koronarnog sindroma su rjeđe dobili invazivno liječenje uz lošije unutarbolničke ishode. Treće, utvrđena je veća primjena invazivnog liječenja, kao i bolji ishodi, u pacijenata koji su bili uključeni u kliničko ispitivanje. Četvrto, pacijentice su rjeđe dobile invazivno liječenje uz veći rizik za neželjene unutarbolničke ishode. Znanstveni doprinos ove doktorske disertacije i objedinjenih znanstvenih istraživanja jest značajan, a uključuje analizu velikog registra s izvrsnim uvidom u suvremeno stanje u stvarnom svijetu i detaljnim pregledom literature. Navedeni projekt je plod međunarodne suradnje sa stručnjacima iz područja kardiovaskularne medicine. Ovaj istraživački projekt potiče ujednačenje kvalitete skrbi, liječenja i prognoze u širokom spektru bolesnika s akutnim koronarnim sindromom.

Zaključci: Liječenje i ishodi pacijenata s akutnim koronarnim sindromom podložni su razlikama na temelju socioekonomskog statusa, prioriteta dijagnostičkog kodiranja, uključenja u kliničko ispitivanje i spola. Potrebne su daljnje inicijative za smanjenjem različitosti u ovoj ranjivoj populaciji.

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