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Use of Multinational Registries to Assess and Compare Outcomes of Patients with an Acute Coronary Syndrome: A Dissertation

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**USE OF MULTINATIONAL REGISTRIES TO ASSESS AND COMPARE
OUTCOMES OF PATIENTS WITH AN ACUTE CORONARY SYNDROME**

A Dissertation Presented

By

Hamza Awad, M.D., M.S.

Submitted to the Faculty of the
University of Massachusetts Graduate School of Biomedical Sciences, Worcester
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

JULY 25th, 2011

MAJOR SUBJECT

Clinical and Population Health Research

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OUTCOMES OF PATIENTS WITH AN ACUTE CORONARY SYNDROME**

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Dean of the Graduate School of Biomedical Sciences
Clinical and Population Health Research Program
July 25th, 2011

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**USE OF MULTINATIONAL REGISTRIES TO ASSESS AND COMPARE
OUTCOMES OF PATIENTS WITH AN ACUTE CORONARY SYNDROME A**
Dissertation Presented

By

Hamza Awad, M.D., M.S.

Abstract

Background

Acute coronary syndromes (ACS) are a major cause of mortality and morbidity in the developed world. By 2020, ACS will be the leading cause of morbidity and mortality worldwide, largely due to substantial increases in ACS burden in developing countries. The developing world has been under-represented in international ACS registries. The Arabian Gulf area is a part of the developing world where little is known about the epidemiology of ACS. The first aim of the dissertation is to compare ACS patient characteristics, current practice patterns, and in-hospital outcomes in the Arabian Gulf area to a large multinational sample.

Patients with an ACS suffer numerous clinical complications that worsen their prognosis. Cardiogenic shock (CS) is the most serious complication of ACS and the leading cause of in-hospital death. Despite advances in therapies; CS hospital mortality rates continue to exceed 50%. The second aim of the dissertation is to describe the characteristics of patients presenting with ACS complicated by cardiogenic shock, their management, and outcomes in a large multinational sample.

In recent years, ACS has been increasingly affecting younger patients. While marked age-related differences have been observed in the risk of developing as well as the

prognosis of ACS, few studies however examined time trends in the epidemiology of ACS in young adult patients. The third aim of the dissertation is to examine trends in frequency rates, patient characteristics, treatment practices, and outcomes in young adults hospitalized with an ACS.

Methods

Data from two large multinational registries of patients hospitalized with an ACS were used for this investigation. Nearly 65,000 patients were enrolled in the Global Registry of Acute Coronary Events (GRACE) between 2000 and 2007, while 6,700 patients participated in the Gulf Registry of Acute Coronary Events (Gulf RACE) in 2007.

Results

Aim1: Patients in Gulf RACE were significantly younger and were more likely to be male, diabetic, and smoke Compared to GRACE. Patients in Gulf RACE were less likely to receive evidence based therapies. Short-term mortality rates were comparable between the two patient cohorts.

Aim2: Compared to patients with no CS, patients with CS were more likely to be older, female, have a history of diabetes, and heart failure. Patients with CS were less likely to receive effective cardiac catheterization and adjunctive cardiac medications. In-hospital case-fatality rate of patients with CS were 59.4%. While in-hospital mortality declines over the study period, incidence rates only showed minor declines.

Aim2: Baseline characteristics of patients < 55 years of age did not significantly change, while the use of evidence based therapies increased significantly during the years under

study. Rates of short-term adverse outcomes and mortality significantly declined over time.

Conclusions

We observed marked regional differences in the risk profile, clinical management, and outcomes of patients with an ACS internationally compared to the Arab Middle East.

Despite the encouraging trends in the use of evidence based therapies which have likely contributed to the improving trends in the prognosis of ACS, rates of development of ACS, as well as mortality due to ACS complications, remain high.

Table of Contents

List of Tables	x
List of Figures	xi
List of Acronyms	i
1. CHAPTER I	1
Introduction.....	1
1.1 Specific Aims	1
1.2 Background and Significance.....	4
1.2.1 Scope of the Problem of ACS/AMI	4
1.2.2 Multinational ACS Survey Efforts.....	5
1.2.3 Management and Outcomes of ACS.....	6
1.2.4 ACS in Comparatively Young Adults	7
1.2.5 Cardiogenic Shock as A Major Complication of ACS.....	8
1.2.6 ACS Survey Efforts in the Gulf Countries.....	9
1.3 Significance of Proposed Study	10
1.4 Research Design and Methods.....	10
1.4.1 Study Designs and Patient Populations.....	11
1.4.2 Measures and Statistical Analyses	20
2. CHAPTER II.....	33
Comparison of Characteristics, Management Practices, and Outcomes of Patients Between the Global Registry and the Gulf Registry of Acute Coronary Events	
2.1 Introduction	37
2.2 Methods.....	37
2.3 Results	39
2.4 Discussion and Conclusions.....	43
3. CHAPTER III	55
Cardiogenic Shock Complicating Acute Coronary Syndromes: The Global Registry of Acute Coronary Events	
3.1 Introduction	58
3.2 Methods.....	59
3.3 Results	62
3.4 Discussion	65
3.5 Conclusions	71
4. CHAPTER IV	77
Clinical Features, Treatment Practices, and Short-term Outcomes of patients <55 Years of Age Hospitalized with an Acute Coronary Syndrome: The Global Registry of Acute Coronary Events	77
4.1 Introduction	79
4.2 Methods.....	79
4.3 Results	81
4.4 Discussions.....	84
4.5 Conclusions	89
5. CHAPTER V	96

Conclusions.....	96
5.1 Summary of Findings.....	96
5.2 Strengths and Limitations.....	98
5.3 Implications and Future Research Directions	99
References.....	101

List of Tables

Table 1.1 Characteristics of the Global Registry of Acute Coronary Events (GRACE) Population Over Time	16
Table 1.2 Characteristics of the Gulf Registry of Acute Coronary Events (Gulf RACE) Population	19
Table 2.1 Baseline Characteristics of Patients hospitalized with an Acute Coronary Syndrome (ACS)	48
Table 2.2 Clinical Presentation of Patients Hospitalized with an Acute Coronary Syndrome (ACS)	50
Table 2.3 In-hospital Complications of Patients Hospitalized with an Acute Coronary syndrome (ACS)	53
Table 3.1 Characteristics of Patients Hospitalized with an Acute Coronary Syndrome Complicated by Cardiogenic Shock.....	72
Table 3.2 Treatment of Patients Hospitalized with an Acute Coronary Syndrome Complicated by Cardiogenic Shock	73
Table 3.3 Univariate Predictors of Hospital Survival for Patients with an Acute Coronary Syndrome Complicated by Cardiogenic Shock	74
Table 4.1. Baseline Characteristics of Young Patients with Acute Coronary Syndrome Overall and According to Time Period of Hospitalization	91
Table 4.2 In-hospital Therapies of Young Patients with Acute Coronary Syndrome Overall and According to Time Period of Hospitalization.....	92
Table 4.3 Risk of Selected Clinical Complications in Patients Hospitalized With an Acute Coronary Syndrome	93
Table 4.4 Short-Term Death Rates in Patients Hospitalized With an Acute Coronary Syndrome.....	94
Table 4.5 Odds of Dying in Younger Patients Hospitalized with an Acute Coronary Syndrome.....	95

List of Figures

Figure 2.1.A Use of in-hospital Medications (first 24 hours) in All Patients with an Acute Coronary Syndrome (ACS)	52
Figure 2.1.B Use of in-hospital Medications (first 24 hours) in Patients with an ST-elevation Myocardial Infarction	53
Figure 2.2 Receipt of Reperfusion Therapy in Eligible Patients with ST-elevation Myocardial Infarction	Error! Bookmark not defined.
Figure 3.1 Time Trends in Crude Hospital Incidence Rates of Cardiogenic Shock Among Patients with Acute Coronary Syndromes	75
Figure 3.2 Time Trends in Crude Hospital Case-fatality Rates for Acute Coronary Syndrome Patients with and without Cardiogenic Shock	76

List of Acronyms

Acronym	Definition
CHD	Coronary heart disease
ACS	Acute coronary syndrome
AMI	Acute myocardial Infarction
STEMI	ST segment elevation acute myocardial infarction
NSTEMI	Non-ST segment elevation acute myocardial infarction
UA	Unstable angina
WHAS	Worcester heart attack study
GRACE	Global registry of acute coronary events
Gulf RACE	Gulf registry of acute coronary events
ACE inhibitors	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft surgery
LDL	Low-density lipoprotein
GFR	Glomerular filtration rate
OR	Odds ratio
HR	Hazard ratio
CI	Confidence interval
IQR	Inter quartile range

CHAPTER I

Introduction

1.1 Specific Aims

Acute coronary syndromes (ACS), which include ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), are a major cause of mortality and morbidity in the developed world¹. Each year, approximately 6.3 million people worldwide suffer an acute myocardial infarction (AMI), of whom 25% die as a result². By 2020, ACS will be the leading cause of morbidity and mortality worldwide, largely due to substantial expected increases in the incidence of ACS in developing countries. Despite the importance of ACS as a global public health problem, little reliable data are available about changing trends in the prevalence and “real-world” management of patients with an ACS.

Further investigation is needed to more fully understand the use of various management practices in patients hospitalized with an ACS as well as the natural history and long-term outcomes of these high risk patients and changing trends therein. Relatively few studies on ACS patients have collected post-discharge data. Furthermore, few data are available regarding contemporary and changing trends in post-discharge outcomes in patients with ACS.

Patients with an ACS suffer numerous clinical complications that worsen their prognosis. Cardiogenic shock carries the worse prognosis among all clinical complications being the most common cause of in-hospital death in patients with ACS. Reported

incidence rates range from remained relatively constant over the past decade. Despite advances in medical treatment, revascularization techniques and mechanical support; cardiogenic shock continues to have devastating outcomes with hospital mortality rates exceeding 50%.

Population-based registries are a valuable tool for providing information on disease burden, clinical practices, and outcomes. A number of coronary heart disease registries around the world have helped identify optimal therapeutic strategies in an attempt to improve the outcomes of patients hospitalized with an ACS. The GRACE (Global Registry of Acute Coronary Events) is the largest multinational, prospective study of clinical management practices and patient outcomes across the full spectrum of ACS. The GRACE registry provides insights into the therapeutic options used and the relationship between processes of care and the clinical decision-making process with various hospital and post discharge outcomes. GRACE includes representative hospitals in North America, South America, Europe, Asia, Australia and New Zealand. It is one of the few registries that have followed patients after hospital discharge for an ACS, further contributing to our understanding of long-term outcomes of ACS patients.

Although developing countries will likely be the major contributors to the increasing burden of CHD over the next several decades, they have been poorly represented in multinational studies of CHD to date. The Arabian Gulf area (also known as the Persian Gulf) in particular and the Middle East in general, is a great example of developing countries that have seen limited CHD survey efforts. Little is known about the magnitude and forms of ACS that exist in the Arabian Gulf area. Additionally, there is a

lack of knowledge concerning the ACS related clinical practices and outcomes in that unique population. Recent evidence indicates an increased risk of ACS among the Gulf population with a high prevalence of diabetes, obesity, and smoking. The Gulf RACE (Gulf Registry of Acute Coronary Events) is the first completed registry designed to assess the actual incidence of ACS in the Arabian Gulf area and related clinical practices in an uncontrolled real-life setting.

The aims of my proposed project are compare the disease characteristics of ACS in the Arabian Gulf area to a multinational sample, to investigate the characteristics, management and outcomes of patients with cardiogenic shock, and to report on time trends in frequency, management and outcome of young adult patients presenting with an ACS. For purposes of this dissertation, I will utilize data from two multinational ACS studies: GRACE and Gulf RACE.

Aim 1: is to compare ACS patients in the Arabian Gulf area (Gulf RACE) to a sample of ACS patients from a large multinational study (GRACE) in terms of patient demographics, clinical characteristics, current practice patterns, and in-hospital outcomes. The secondary objective is to compare in-hospital mortality rates and identify factors associated with mortality that may differ in the 2 hospitalized cohorts.

Aim 2: is to describe the demographic and clinical characteristics of patients presenting with ACS complicated by cardiogenic shock, their management, and outcomes in a large multinational sample (GRACE). The secondary objective is to identify factors associated

with increased mortality among patients with ACS complicated by cardiogenic shock. Cardiogenic shock remains the main cause of in-hospital mortality among ACS patients and despite advances in diagnosis and management continues to have high mortality rates exceeding 50%.

Aim 3: is to examine trends in frequency rates, patient characteristics, hospital treatment practices, and short-term outcomes in comparatively young adults (<55 years old) who had been hospitalized with an ACS.

1.2 Background and Significance

1.2.1 Scope of the Problem of ACS

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in the United States and developing countries³. By 2020, it is projected that mortality from CHD will more than double the present mortality from this disease and CHD will be the single largest global cause of morbidity and mortality. Developing countries will be a major contributor to this increase². These increases are taking place despite aggressive campaigns for prevention, advances in drug therapy, and increasing application of coronary reperfusion and revascularization approaches. Given the aging of the world's population, and the ongoing epidemics of diabetes and obesity, these ongoing changes will further expand the healthcare burden of atherosclerosis, both in developing countries as well as globally⁴.

Acute coronary syndrome (ACS) is a common manifestation of underlying CHD. ACS is defined as a set of symptoms and signs compatible with acute myocardial ischemia which results from coronary artery disease. It is an umbrella term that encompasses unstable angina in addition to the two subtypes of acute myocardial infarction (AMI), ST-segment elevation myocardial infarction and non ST-segment elevation myocardial infarction.

1.2.2 Multinational ACS Survey Efforts

Management of ACS is complicated involving a series of diagnostic and therapeutic decisions, invasive and noninvasive interventions^{5,6}. In the past 30 years, significant progress has been made in the development of effective treatment strategies for patients diagnosed with an ACS. Before the 1990s relatively little reliable data were available about the prevalence of ACS, routine management of ACS, and the extent to which advanced treatments and strategies are used in daily clinical practice. Most of the data available during this period were derived from clinical trials. It is hard to extrapolate data from clinical trials to the 'real-world' due to their highly controlled environment, highly selected populations with little representation of the elderly and patients with comorbidities. The lack of information in "real world" settings has given rise to the development of ACS registries to allow better interpretation of the results of clinical trials and the effectiveness of treatments and procedures^{7,8}. Several multinational ACS registry studies have been conducted in patients with unstable angina and AMI. Among the large

multinational registries were the Multinational MONItoring of trends and determinants in Cardiovascular disease(MONICA)1 project, the Organisation to Assess Strategies for Ischemic Syndromes (OASIS registry)⁹, and The European Network for Acute Coronary Treatment (ENACT) study¹⁰. None of these registries, however, have provided insights into the relationship between processes of care and patient outcomes, or the clinical decision-making process. The Global Registry of Acute Coronary Events (GRACE) registry is the largest multinational study that covers the full spectrum of patients hospitalized with an ACS. It is also one of the few registries that studies post-discharge outcomes^{11, 12}. Results from the GRACE study have enhanced the understanding of patient management and outcomes in the ‘real-world’ which has helped to improve patient outcomes around the globe¹³⁻¹⁷.

1.2.3 Management and Outcomes of ACS

Patients with ACS present with diverse demographic and clinical characteristics and experience a wide range of serious cardiovascular outcomes^{11, 18}. Relatively limited multinational data are available on the post-discharge management and outcomes of ACS patients. The post-discharge period is a particularly critical period considering the proportion of ACS patients that develop adverse outcomes^{12, 19}. Six-month case-fatality rates range to upwards of 7% depending on severity, comorbidities, and management¹². Identifying patients at higher risk for unfavorable outcomes is important in guiding patient triage and use of effective management approaches. Studies have shown that missed opportunities of reperfusion together with under-prescription of effective treatments play

an important role in the high post-discharge rates of unfavorable outcomes²⁰. Targeting high risk populations and increasing the use of evidence based therapies is crucial to improving post-discharge outcomes in patients with an ACS²¹⁻²⁴.

Several studies examining factors associated with the receipt of evidence-based medications and procedures among persons with ACS/AMI have found that admission to teaching/academic hospitals and treatment by cardiologists are associated with higher utilization rates of evidence-based medications and procedures. On the other hand, being from a lower SES, not having medical insurance, history of heart failure, diabetes, hypertension, kidney disease, PCI, or CABG, prolonged pre-hospital delay, and development of hospital complications were associated with lower rates of utilization of evidence-based cardiac medications and interventional procedures.

1.2.4 Acute Coronary Syndromes in Comparatively Young Adults

Acute coronary syndromes are more common among middle aged and older individuals. The average age of patients with an ACS in GRACE was 65 years. Most of our current knowledge of the pathology underlying ACS is based on studies of patients of middle age or older, and some studies of patients with CHD used to exclude individuals < 40 years old. While marked age-related differences have been observed in the risk of developing as well as the prognosis of ACS, few studies however examined time trends in the epidemiology of ACS in comparatively younger patients. This is exceedingly important in light of increasing trends in obesity, diabetes, and hyperlipidemia worldwide among young adults. In recent years, ACS has been increasingly affecting younger patients, which

is a matter of concern due to the resulting premature morbidity and mortality as well as the psychological and social burden for individuals during the most productive period of their lives.

1.2.5 Cardiogenic Shock as a Major Complication of ACS

Cardiogenic shock is the primary cause of death among patients hospitalized with ACS^{25,26}. In spite of significant advances over the past 30 years in diagnosing cardiogenic shock, and in the care of patients who develop this serious complication of AMI, cardiogenic shock remains a devastating complication with an incidence of upwards of 8% among AMI patients and a 30-day mortality rate close to 50%^{26,27}. It is believed that prompt diagnosis of cardiogenic shock and rapid initiation of therapy are key factors in improving the prognosis of patients with this clinical complication. . Multinational registries offer a great tool to expand our knowledge base with regards to identifying the optimal treatment strategies of cardiogenic shock patients, the extent to which early revascularization is adopted in the ‘real world’ as the treatment strategy of choice, and changes in patients’ outcomes over time²⁸. This knowledge is necessary to inform clinical practice guidelines and improve patient survival²⁹.

1.2.6 ACS Survey Efforts in the Gulf Countries

Although developing countries will be the major contributors to the increasing burden of CHD, they have been poorly represented in multinational studies of CHD to date³⁰. The Arabian Gulf area (also known as the Persian Gulf) in particular and the Middle East in general, is a great example of developing countries that have seen limited CHD survey efforts. There is a considerable lack of knowledge regarding the magnitude and forms of CHD that exist in the Gulf area. Recent data suggest that the prevalence of major CHD risk factors is on the rise among the Gulf population³¹. Studies have shown high prevalence rates of type 2 diabetes among the Gulf population reaching up to 18%³²,³³. The prevalence of obesity has also been increasing over time in several Gulf countries^{34, 35}. Rates of smoking remain among the highest worldwide. For example, 34% of adult men in Kuwait were found to be regular smokers^{36, 37}. Other major CHD risk factors are not well studied. Furthermore, little is known about ACS clinical practices in the Gulf area. Data from isolated studies suggest an underutilization of effective treatments and procedures in the Gulf area³⁸⁻⁴¹. Comparing the characteristics of patients, clinical practice patterns of ACS, and patient outcomes in the Gulf countries to the rest of the world and to standard guidelines would enhance efforts of primary and secondary prevention in those countries.

1.3 Significance of Proposed Study

In summary, ACS is a significant and growing public health and clinical concern. Despite improving trends in short-term outcomes after an ACS, important gaps between countries and regions as well as between individuals of different ages may persist. Therefore, there is a need for contemporary epidemiologic research that systematically describes differences in extent of patients' characteristics, receipt of hospital treatments and outcomes, including mortality and complications, and to determine whether differences in these endpoints have changed over time. The findings of this proposed research will provide useful current information regarding inter-regional differences as well as changes over time in patient characteristics, hospital management practices, and hospital outcomes that can inform the design of appropriate public health interventions and clinical guidelines to improve the prognosis of patients with an ACS.

1.4 Research Design and Methods

This dissertation consists of secondary data analyses of patients enrolled in the GRACE and Gulf RACE project. The purpose of the proposed study was to examine differences in the patient characteristics, the receipt of evidence-based treatments, and in hospital complications and CFRs between different regions of the world as well as describing special subpopulations of patients with ACS including patients developing cardiogenic shock and patients developing ACS at a comparatively young age. A particular strength of this study is the use of contemporary data from two large multinational registries of ACS.

1.4.1 Study Designs and Patient Populations

1.4.1.1 The Global Registry of Acute Coronary Events (GRACE)

The GRACE study is a large, multinational, observational study of patients hospitalized with ACS in 14 countries in North and South America, Europe, Australia, and New Zealand between 1999 and 2008. The objectives of GRACE are to improve the hospital and long-term outcomes of patients with ACS⁴².

Participating Centers and Sampling Methods

Study hospitals were located in 18 cluster sites of 14 countries. Data collection activities began in April 1999 with the goal of collecting data on approximately 10,000 patients hospitalized with ACS on an annual basis. A total of four sites were included in the United States (Massachusetts, Michigan, North Carolina, and California), whereas an additional 16 sites were included from Canada, Europe, Australia, and New Zealand. The two geographic clusters in South America have recruited relatively more study hospitals than other clusters to provide a more descriptive overview of national practices in the management and outcomes of patients with ACS.

These geographic clusters were chosen to represent populations with varying demographic, clinical, and treatment characteristics as well as hospital systems of different sizes and treatment and diagnostic capabilities. A total of 46 hospitals were included at these population sites, representing hospitals of varying size, characteristics, and diagnostic and treatment capabilities. At the study clusters in which a population-based site (where ACS patients from geographically defined catchment areas) was considered either not feasible or not cost effective, a sample of hospitals representative of those from that region

or country was selected and cases of ACS were included irrespective of the patient's geographic origin. A total of 47 hospitals were included at these study clusters. Where required, hospitals received approval from their local hospital's ethics or institutional review board, and signed, informed consent for follow-up contact was obtained from the patients at enrollment. For those sites using active surveillance for case identification, verbal or written consent was obtained from patients to review information contained in their medical charts.

Patients who died early during their index hospitalization were thereby excluded from study consideration at the sites where active case ascertainment was carried out. The impact of this and other exclusionary factors needed to be considered in interpreting hospital outcomes and the descriptive characteristics and treatment practices used in the respective study samples.

Patient Identification Approaches

To facilitate the review of medical records in a systematic manner, and accommodate the varying ways in which the data were collected, prospective ("warm" or active pursuit) and retrospective ("cold" or passive pursuit) surveillance approaches for identifying cases of ACS, similar to the MONICA Project²³ were adopted. In hospitals that used warm pursuit, eligible patients were identified during the index admission and medical records were reviewed on an ongoing basis after appropriate consent has been obtained, if necessary. In study sites that used the cold pursuit method of approach to case identification, hospital listings of persons discharged from participating hospitals were

reviewed to identify potentially eligible cases with use of the International Classification of Diseases, Ninth Revision (ICD-9), codes 410 or 411 or corresponding codes in ICD-10. These charts were subsequently reviewed after the patient has been discharged from the hospital. The majority of study centers adopted warm pursuit whereas a limited number of centers used cold pursuit to identify cases of ACS.

Patients hospitalized with a discharge diagnosis of ACS constitute the primary sample of interest at the clusters where passive or cold pursuit surveillance was adopted. At the centers where warm pursuit surveillance approaches were used, patients with an admission diagnosis of ACS were studied irrespective of whether their final discharge diagnosis is ACS, another cardiac diagnosis, or non-cardiac disease. The medical records of patients with a primary or secondary discharge diagnosis of AMI (ICD-9 code 410) or unstable angina (ICD-9 code 411) were reviewed in their entirety at the study sites using passive surveillance. Previous surveillance studies have shown a relatively low yield of confirmed cases of ACS, particularly AMI, from other possible coronary disease diagnostic categories (eg, ICD-9 codes 412-414, 786.5). Thus, the medical records of patients with a discharge diagnosis of these latter diagnostic codes were not reviewed. As previously mentioned, at the study sites where active or warm pursuit surveillance was used, hospitalized patients with a suspected diagnosis of ACS were identified on a regular basis and charts were concurrently reviewed. Given the varying sizes of the populations under study and the number of patients hospitalized with a suspected or a discharge diagnosis of ACS, a sampling scheme was used to select possible cases of ACS for

subsequent review. Each study site selected a final annual sample of approximately 600 cases of ACS from each study cluster spread out over the entire year.

GRACE inclusion/Exclusion criteria

- Must have one of the ACS as a presumptive diagnosis.
- Must be ≥ 18 years old.
- Must be alive at the time of hospital presentation.
- The qualifying ACS must not have been precipitated or accompanied by a significant comorbidity such as a motor vehicle crash, trauma, severe gastrointestinal bleeding, operation, or procedure. In-patients who were already hospitalized, for any reason, when ACS symptoms develop were not eligible for enrollment.
- Patients transferred into or out of a registry hospital could be enrolled regardless of the time spent at the transferring hospital.
- For patients transferred out of a registry hospital, data collection for the initial case report form ended with the transfer and indication of purpose of transfer.
- Patients could be re-enrolled in GRACE provided that 6 months or more passed since the prior enrollment. When a patient was re-enrolled, a new patient number must be assigned.
- The criteria for ACS must be met, with one exception: patients hospitalized for < 1 day who died and did not meet the criteria could be enrolled provided that the cause of death was confirmed to be due to ACS.

Data Abstraction

A standardized data abstraction form was developed for study-wide use. The team of investigators developed the initial case report form, which was subsequently finalized for field use after pilot testing at each of the participating hospitals. Information was collected on patient demographic characteristics, medical history, duration of pre-hospital delay from the time of onset of acute symptoms to seeking medical care, presenting symptoms, electrocardiographic findings, clinical characteristics, use of cardiac medications and interventional procedures, and hospital-associated outcomes. Standardized definitions for patient-related variables and clinical diagnoses were used. All cases of confirmed ACS were assigned to 1 of the following categories: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). Patients were diagnosed with STEMI when they had new or presumed new ST-segment elevation ≥ 1 mm seen in any location, or new left bundle branch block on the index or subsequent electrocardiogram with at least one positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent electrocardiogram had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in each hospital's laboratory were within the normal range. Full definitions can be found on the GRACE web site at www.outcomes.org/grace

Characteristics of the GRACE Population Over Time

Table 1.2 presents changing characteristics of the GRACE population over time. The mean age and sex distribution of study sample have been unchanged over time. There has been a lower proportion of patients presenting to GRACE hospitals with a history of angina, heart failure and renal disease, but a greater proportion of patients presenting with a history of diabetes. The proportion of patients presenting with a history of MI and stroke have unchanged. In term of clinical complications and death, the proportions of patients developing clinical complications and dying during hospitalization have declined over time. Pre-hospital delay (median) has remained unchanged whereas the length of hospital stay has declined in the most recent study years.

***Table 1.1 Characteristics of the Global Registry of Acute Coronary Events (GRACE)
Population Over Time***

Characteristic	1999/2001 (n=16,951)	2002/03 (n=13,417)	2004/2005 (n=11,726)	2006/2007 (n=8,002)
Age (median, yrs)	67.0	66.9	67.4	66.7
Male (%)	66.0	66.4	66.7	67.4
Medical history (%)				
Angina	63.6	51.6	46.7	45.4
Diabetes	24.3	24.9	25.5	25.7
Heart failure	11.6	10.9	10.5	9.5
MI	31.0	30.1	30.7	31.7
Renal disease	8.1	7.1	8.1	7.8
Stroke	8.7	8.5	8.5	8.4
Clinical complications (%)				
Atrial fibrillation	9.1	8.4	7.2	6.4
Heart failure	17.2	13.7	10.7	9.3

Stroke	0.9	0.7	0.7	0.5
Shock	4.6	3.9	3.9	3.7
Hospital mortality (CFRs) (%)	6.0	5.7	5.0	4.6
Median (mean) of pre-hospital delay, hours	3 (76)	3 (94)	3 (24)	3 (31)
Mean of Length of stay, days	8.2	7.4	6.9	6.8

1.4.1.2 The Gulf Registry of Acute Coronary Events (Gulf RACE)

The Gulf RACE is a prospective, multinational, multicenter survey of patients hospitalized with an ACS in six Arabian Gulf countries - Bahrain, Kuwait, Qatar, Oman, United Arab Emirates (UAE) and Yemen. Gulf RACE was funded by Sanofi Aventis. The main goal of this registry was to study clinical practice patterns in the management of ACS and to assess the gap between the practice and available evidence and guidelines, and to then try to improve the quality of cardiac care provided to the population of the Gulf countries

Study Design

Since one of the main goals of the registry was to capture incidence rates of ACS, the study attempted to include the majority of consecutive ACS patients in the six countries involved. In Bahrain, Kuwait and Qatar, all hospitals that admit patients with ACS participated, while in Oman, UAE and Yemen, most hospitals (covering at least 85% of the population) participated. Patients were followed up for the duration of their hospital stay. A total of 6706 ACS patients were enrolled from 65 participating hospitals and

medical centers. Diagnosis of the different types of ACS and definitions of data variables were based on the American College of Cardiology (ACC) clinical data standards.⁴²

Study Population

The Gulf RACE included all patients with a discharge diagnosis of ACS. The majority of patients were enrolled using warm pursuit surveillance. In addition to patients with an initial diagnosis of ACS, the registry also included patients who were admitted with different diagnoses who were then diagnosed with ACS during the hospital stay. There were no age limitations or other exclusion criteria. For patients to be eligible for enrollment, patients had to be diagnosed with MI or UA. Cases were validated through the review of their medical records. The Gulf RACE included both citizens and expatriates working in the Gulf countries. Expatriates constituted nearly 44% of the study population.

Definition of MI: typical rise and gradual fall (troponin), or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

- Ischemic symptoms
- Development of pathological Q waves on ECG
- ECG changes indicative of ischemia (ST elevation or depression)
- Coronary artery intervention

Definition of UA: at least one of the following has to be present:

- Angina that occurred at rest and was prolonged, lasting more than 20 min

- New-onset angina of at least Canadian Cardiovascular Society (CCS) classification III severity

Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least 3 CCS class

Data Collection and Management

Standard case record forms (CRF) were filled out, prospectively, at the time of admission for each patient with suspected ACS (by whom and what quality control measures were employed??). The different elements of the form were filled out during the patients stay in the hospital until hospital discharge. For individuals whose initial admission was not ACS but were subsequently diagnosed with ACS, the registry form was filled out, retrospectively. All countries enrolled used the same CRF except for Yemen in which an additional question on using “Khat” (a plant that is legally consumed in Yemen and has an-amphetamine like stimulant effect) was added.

CRFs were filled out by centrally trained professionals, and data were electronically entered into computers after being reviewed.

Characteristics of the Gulf RACE Population

Table 1.2 presents the characteristics of the Gulf RACE population.

Table 1.2 Characteristics of the Gulf Registry of Acute Coronary Events (GRACE)

<i>Population</i>	
Characteristic	(n=6,706)
Age (median, yrs)	56.0
Male (%)	76.0
Medical history (%)	

Angina	42.0
Diabetes	41.0
Hypertension	51.0
MI	25.0
Hyperlipidemia	32.0
Current smoking	41.0
Clinical complications (%)	
Cardiogenic Shock	5.0
Recurrent ischemia	9.0
Infarction	2.0
Stroke	0.7
Hospital mortality (CFRs) (%)	3.8
Mean of Length of stay, days	5.6

1.4.2 Measures and Statistical analyses

1.4.2.1 Aim 1: Comparison between GRACE and Gulf RACE Patients and Outcomes

Aim 1 of this proposal is to compare ACS patients in the Arabian Gulf area (Gulf RACE) to a sample of ACS patients from a large multinational study (GRACE) in terms of patient demographics, clinical characteristics, current practice patterns and in-hospital outcomes. The secondary objective is to compare in-hospital mortality rates between the two cohorts and identify factors associated with differences in mortality rates.

Study sample/design:

The comparative analyses will be carried out between the complete cohort of Gulf RACE and the 2007 cohort of GRACE (to limit the potential confounding effect of time). Only in-hospital data will be used for the analyses as Gulf RACE did not include a follow-up component.

Measures:

The two cohorts will be compared in terms of patient characteristics, in-hospital management practices, complications and outcomes. Patient characteristics will include demographics (eg, age, gender, BMI), past medical history (eg, angina, MI, PCI, Diabetes, hypertension, hyperlipidemia, smoking, family history of CAD, PCI, CABG), comorbidities (eg, stroke, peripheral vascular disease, kidney disease), and presentation (eg, cardiac arrest, heart rate, BP, Killip class, heart rhythm, STEMI, NSTEMI, UA).

In-hospital management will include medications prescribed during hospitalization and on discharge (eg, ASA, heparin, Beta blockers, Glycoprotein IIb/IIIa inhibitor, calcium channel blocker, diuretics) in addition to procedures (eg, Catheterization, PCI, CABG, thrombolytics). Complications and in-hospital outcomes will include recurrent ischemia, infarction, mechanical ventilation, cardiogenic shock, atrial fibrillation major bleeding, stroke and death.

Definitions of variables in both the GRACE protocol and the Gulf RACE protocol were based on the American College of Cardiology (ACC) guidelines. In examining factors related to differences in mortality rates between the two registries, in-hospital mortality is the main outcome of interest. The registry variable (GRACE or Gulf RACE)

will be the main independent variable. Potential confounding variables include: patient demographics, medical history, clinical variables, and duration of hospital stay.

Statistical plan:

The GRACE and Gulf RACE data sets will be merged into one data set containing a variable indicating the registry to which each individual belongs. A comparison between GRACE and Gulf RACE in participant's demographics, medical history, comorbidities, clinical presentation and length of hospital stay will first be carried out to examine differences and determine potential confounders that need to be accounted for in modeling outcomes of interest. A second comparison between the two registries will be carried out to examine differences in in-hospital clinical practices including prescribed medications and procedures. Both analyses will be age stratified to explore the interaction (effect modification) between age and other variables. Age categories used in comparisons will be decided according to the distribution of the age variable in both registries. Gender specific analyses will be considered if gender shows to be an effect modifier in exploratory analyses. To determine statistically significant differences between the two registries, the Chi square test will be used to compare categorical variables while Wilcoxon rank-sum test will be used for continuous variables.

To determine if differences between the two registries explain the difference in in-hospital mortality rates, a survival analysis approach will be used. The survival analysis approach was chosen to account for the confounding effect of length of hospital stay (previous research has shown that mortality rates are related to length of hospital stay and

preliminary analyses of our data showed difference in the length of hospital stay between the two registries).

Univariate analyses will be carried out to examine the potential confounders of the association between mortality and registry using log-rank tests. Survival curves for GRACE and Gulf RACE will be created using the Kaplan-Meier method. The Cox Proportional Hazards (PH) model will be used to examine the association of interest adjusting for potential confounders. A similar selection process of potential confounders described previously in aim 1 will be applied. Variables of the GRACE risk score will be forced on the model (age, HR, SBP, Creatinine, Killip class, cardiac arrest, ST- segment deviation and elevated cardiac enzymes). An adjusted Cox PH curve will be created to check the PH assumption.

Cox PH model: $\log[h(t)/h_0(t)] = \beta_{1,2}\text{Registry}_{1,2} + \beta_{3-n}(\text{confounders}) + \beta_{n-m}(\text{interaction terms})$

1.4.2.2 Aim 2: Outcomes of Patients with an ACS Complicated by Cardiogenic Shock (GRACE)

Aim 2 of this proposal is to describe the demographic and clinical characteristics of patients presenting with AMI complicated by cardiogenic shock, their management, and outcomes. The secondary study objective is to determine factors associated with increased mortality among patients with ACS complicated by cardiogenic shock. Cardiogenic shock remains the most frequent cause of in-hospital death as a complication of ACS.

Study sample/design:

Analyses will be carried out on all ACS patients in GRACE who were diagnosed with cardiogenic shock at admission or during hospital stay. Nearly 3,000 patients in GRACE were diagnosed with cardiogenic shock. Reported incidence rates range between 5-10% and despite therapeutic advances; it continues to have devastating outcomes with mortality rates of over 50%.

Measures:

The primary outcome of interest in study aim 2 is mortality (hospital mortality + 6-month mortality). Type of ACS and time of development of cardiogenic shock (at admission vs. during hospitalization) are the main independent variables. Potential confounders include: patient demographic, medical history, clinical variables in addition to influence of effective cardiac medications and coronary interventional approaches.

Operational definitions are as follows:

Cardiogenic shock: a state of global tissue hypoperfusion due to failure of the cardiac ventricles to perform effectively. Cardiogenic shock is diagnosed by the criteria similar to Killip class IV: pulmonary edema and hypo perfusion characterized by systolic blood pressure < 80 mmHg. Data on Cardiogenic shock was collected during the period of in-hospital stay and classified according to time of diagnosis into two categories: at hospital presentation or during hospital stay. No data on occurrence of cardiogenic shock was collected in the follow-up CRFs.

Type of ACS: All cases of confirmed ACS were assigned to 1 of the following categories: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). Patients were diagnosed with STEMI when they had new or presumed new ST-segment elevation ≥ 1 mm seen in any location, or new left bundle branch block on the index or subsequent electrocardiogram with at least one positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent electrocardiogram had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in each hospital's laboratory were within the normal range.

Mortality: during the index hospitalization. Exact date of death was recorded in addition to the main cause of death.

Definitions of other in-hospital adverse outcomes followed the ACC definitions of key variables.

Statistical plan:

For, all statistical plans, examination of the distributions of all dependent and independent variables will be carried out to determine the appropriateness of model distributional assumptions for dependent variables (outcomes) and variability of independent variables (predictors). The distribution of the predictors will help assess the informational content and inform the process of variable categorization if needed.

Descriptive and graphical analyses of the characteristics of hospital survivors, as compared to decedents, among ACS patients stratified by type of ACS will be carried out.

Differences in the distribution of patient characteristics between the primary comparison groups (STEMI, NSTEMI, and UA) will be examined using chi-square tests of statistical significance for categorical variables and the Kruskal-Wallis test for continuous variables. Functional associations between different variables will be examined as well as between covariates and the outcome of interest (assumptions of linearity will be checked for continuous and ordinal variables). Assumptions of proportional hazards will be checked for Cox proportional hazards models.

First, an analysis of differences in the distribution of patient characteristics between ACS patients with cardiogenic shock vs. ACS patients who did not develop cardiogenic shock during their index hospitalization will be carried out. A repeat of the previous analysis will be carried out stratified by type of ACS (STEMI, NSTEMI, and UA). Differences between groups will be examined using chi-square tests of statistical significance for categorical variables and the Kruskal-Wallis test for continuous variables. Second, an analysis will be carried out to compare the characteristics of cardiogenic shock patients enrolled in the last 2 years of GRACE to those enrolled over the complete study period will be carried out to determine if any changes in the characteristics of patients or their presentation has taken place over the 9 year period of the study. Third, similar analyses will be carried out to describe the clinical management including medications and procedures used for cardiogenic shock patients stratified by type of ACS and by time of diagnosis of cardiogenic shock (at admission vs. during hospitalization) will be performed.

Two approaches will be used to examine the association between mortality and type of ACS as well as between mortality and time of development of cardiogenic shock (at presentation vs. during hospitalization). The first will be a logistic regression while the second will be a Cox-proportional hazards approach. In each approach, univariate analyses will be carried out to examine potential confounders (eg. demographic, medical history, clinical variables and others) of the association between the outcomes of interest and types of ACS. Variables with p values <0.1 will be considered for inclusion in the multivariable models.

In the multivariable models, CS will be forced into the models first and then potential confounding variables selected from the univariate analyses will be added one by one in a forward selection fashion. Potential confounders will be included in the models if they are statistically significant ($p < 0.05$) or change the point estimates of ACS type variable by at least 10%. Variables that fail to pass the screening in the univariate analyses will be re-considered in the final models.

To examine whether the association between CS and outcomes of interest has changed over time, an interaction term between CS and study year will be included in the models previously built. Likelihood ratio tests comparing models with and without interaction terms will be used to examine whether the interaction terms are statistically significant.

Logistic model: $\text{logit}(E(Y|x)) = \beta_0 + \beta_{1,2}CS_{1,2} + \beta_{4-n}(\text{confounders}) + \beta_{n-m}\text{interaction terms}$

For the first approach, model fitting will be examined using Hosmer-Lemeshow Goodness of fit test for logistic regression.

For the second approach, a life-table will be used to examine differences in 6 outcomes between types of patients with and without CS including patients with varying lengths of follow-up. The reported outcomes rates will be calculated from these life-table analyses. Incidence rates of outcomes of interest over the study period will be analyzed. A proportional hazards regression approach will be used to examine differences between the comparison groups with regard to outcomes of interest while controlling for potentially confounding demographic, medical history, and clinical variables. Similar univariate analyses followed by multivariable regression modeling as described previously for logistic regression will be applied. Univariate analyses will be carried out to examine the potential confounders of this association using log-rank tests and survival curves be created using the Kaplan-Meier method. A similar selection process of potential confounders described previously for logistic regression will be applied. Time dependent variables will be included if needed. An adjusted Cox proportional hazards curve will be created. In examining whether associations of interest have changed over time, similar approaches described for logistic regression will be used.

Cox PH model: $\log[h(t)/h_0(t)] = \beta_{0,1}CS_{0,1} + \beta_{4-n}(\text{confounders}) + \beta_{n-m}\text{interaction terms}$

Separate regression analyses (separate models for each type of ACS: STEMI, NSTEMI and UA) will be performed to examine baseline demographics, medical history, and clinical factors associated with occurrence of death in patients with STEMI, NSTEMI, and unstable UA. Goodness of fit of our final models will be assessed and C statistics will be examined.

**1.4.2.3 Aim 3: Acute coronary syndromes in comparatively young adults
(≤55 years)**

Aim 3 of the study is to examine trends in frequency rates, patient characteristics, hospital treatment practices, and short-term outcomes in comparatively young adults (<55 years old) who had been hospitalized with an ACS.

Study sample/design:

Analyses will be carried out on all ACS patients in GRACE who were ≤55 years. Nearly 15,000 patients in GRACE were enrolled in GRACE between 1999 and 2007 and were ≤55 years of age, representing around 23% of the total study population.

Measures:

The outcomes of interest in study aim 3 are patients characteristics, treatments, adverse outcomes, and mortality (hospital mortality + 30-day mortality). The study period (3 categories) is the main independent variable. Potential confounders include: patient demographic, medical history, clinical variables in addition to influence of effective cardiac medications and coronary interventional approaches.

Operational definitions are as follows:

Young patients: the cutoff age used to define young patients in previously published literature on ACS patients has been 10 years less than the average age. Since the

average age of patients enrolled in GRACE is 65 years, we chose the age of 55 years as the cutoff point to identify young patients.

Time periods: the GRACE study period extending between 1999 and 2007 (a total period of 9 years) will be divided into three equal time periods, 1999 to 2001, 2002 to 2004, and 2005 to 2007. The three time periods will be used to examine near decade time trends, and as a mean to simplify the presentation of the results.

Type of ACS: All cases of confirmed ACS were assigned to 1 of the following categories: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). Patients were diagnosed with STEMI when they had new or presumed new ST-segment elevation ≥ 1 mm seen in any location, or new left bundle branch block on the index or subsequent electrocardiogram with at least one positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent electrocardiogram had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in each hospital's laboratory were within the normal range.

Mortality: in-hospital and death during the 30 days following admission. Exact date of death was recorded in addition to the main cause of death.

Definitions of other in-hospital adverse outcomes followed the ACC definitions for key variables.

Statistical plan:

For, all statistical plans, examination of the distributions of all dependent and independent variables will be carried out to determine the appropriateness of model distributional assumptions for dependent variables (outcomes) and variability of independent variables (predictors). The distribution of the predictors will help assess the informational content and inform the process of variable categorization if needed. Descriptive and graphical analyses of the characteristics patients, treatments received, in-hospital outcomes, and mortality will be compared according to the study period they fall under. Differences in the distribution of patient characteristics between the primary comparison groups will be examined using chi-square tests of statistical significance for categorical variables and the Kruskal-Wallis test for continuous variables. Functional associations between different variables will be examined as well as between covariates and the outcome of interest (assumptions of linearity will be checked for continuous and ordinal variables). Assumptions of statistical models will be checked.

Chi-square tests for categorical variables and ANOVA for continuous variables will be used to examine potentially changing trends in various demographic and clinical factors. The short-term outcomes in each period will be examined by calculating in-hospital and 30-day case-fatality rates and trends in these endpoints will be examined through the use of chi-square tests for trends. Logistic regression modeling will be used to assess the significance of a near decade trends in short-term death rates while controlling for several potentially confounding demographic, medical history, and clinical characteristics of prognostic importance.

For purpose of building the logistic regression model, univariate analyses will be carried out to examine potential confounders (eg. demographic, medical history, clinical variables and others) of the association between the outcomes of interest and the study period. Variables with p values <0.1 will be considered for inclusion in the multivariable models.

In the multivariable models, the study period will be forced into the models first and then potential confounding variables selected from the univariate analyses will be added one by one in a forward selection fashion. Potential confounders will be included in the models if they are statistically significant ($p < 0.05$) or change the point estimates of ACS type variable by at least 10%. Variables that fail to pass the screening in the univariate analyses will be re-considered in the final models.

Logistic model: $\text{logit}(E(Y|x)) = \beta_0 + \beta_{1,2}CS_{1,2} + \beta_{4-n}(\text{confounders}) + \beta_{n-m}\text{interaction terms}$

Model fitting will be examined using Hosmer-Lemeshow Goodness of fit test for logistic regression.

CHAPTER II

Comparison of Characteristics, Management Practices, and Outcomes of Patients Between the Global Registry and the Gulf Registry of Acute Coronary Events

Short Title: Acute Coronary Syndrome Registries

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Abstract

The Arab Middle East is a unique region of the developing world where little is known about the outcomes of patients hospitalized with an acute coronary syndrome (ACS), despite playing an important role in the global burden of cardiovascular disease. The primary objectives of this observational study were to compare patients with ACS hospitalized in the Arab Middle East to patients enrolled in a multinational non-Arabian ACS registry. The study cohort consisted of patients hospitalized in 2007 with an ACS, including 4,445 from the Global Registry of Acute Coronary Events (GRACE) and 6,706 from the Gulf Registry of Acute Coronary Events (Gulf RACE). The average age of patients in Gulf RACE was nearly a decade younger than GRACE (56 vs 66 years). Patients in Gulf RACE were more likely to be male, smoke, and diabetic, while they were less likely to be hypertensive compared with GRACE patients. Patients in Gulf RACE had a higher odds of receiving aspirin, and lower likelihood of receiving ACE inhibitors/ARBs, β -blockers and clopidogrel during their index hospitalization. While the majority of eligible patients with ST- elevation myocardial infarction in Gulf RACE received thrombolytics, the majority of their counterparts in GRACE underwent a primary PCI. Multivariable adjusted in-hospital case-fatality rates were not significantly different between Gulf RACE and GRACE patients. In conclusion, despite differences in patient characteristics and treatment practices, short-term mortality rates were comparable between ACS patients enrolled in these two registries. Future studies should explore the effects of these differences on long-term prognosis and other pertinent patient outcomes.

Keywords: acute coronary syndromes, Middle East, coronary disease registries

2.1 Introduction

The primary objectives of this observational study were to compare the characteristics, management, and short-term outcomes of patients hospitalized with an acute coronary syndrome (ACS) in the Arab Middle East with a large multinational sample of patients with ACS using patient level data from two large ACS registries.^{1,2}

2.2 Methods

Full details of the Global Registry of Acute Coronary Events (GRACE) and Gulf Registry of Acute Coronary Events (Gulf RACE) projects have been previously published.¹⁻⁴

Gulf RACE is a prospective registry of all patients hospitalized with an ACS in 65 centers in 6 Arab Middle Eastern countries (Kuwait, Oman, United Arab Emirates, Yemen, Qatar, and Bahrain). Patients were enrolled in this observational study from January to June, 2007. All hospitals that care for patients with ACS in Kuwait, Bahrain, and Qatar participated, as did the majority of hospitals in Yemen, United Arab Emirates, and Oman^{2,4}.

GRACE is the largest multinational prospective registry designed to reflect an unselected population of patients hospitalized with an ACS. A total of 123 hospitals

located in 14 countries in North and South America, Europe, Australia, and New Zealand have contributed data to this registry between 1999 and 2007. For purposes of the present analyses, we used contemporaneous individual patient data of ACS patients enrolled in both registries during calendar year 2007.^{1,3}

All patients with a clinical history of ACS accompanied by at least one of the following were included in the respective study samples: electrocardiographic (ECG) changes consistent with ACS, serial increases in cardiac biomarkers of necrosis, or documented coronary artery disease. Patients were diagnosed with ST-elevation myocardial infarction (STEMI), non ST- elevation myocardial infarction (NSTEMI) or unstable angina (UA) using standardized criteria based on clinical presentation, ECG findings, and cardiac biomarkers.^{5,6} In both patient registries, the diagnosis of ACS and definitions of key study variables and clinical complications were similar and were based on the American College of Cardiology key data elements.⁷ Information about the use of coronary artery bypass surgery (CABG) was not collected in Gulf RACE.

For ease of interpretation, patients with an STEMI and patients with left bundle branch block (LBBB) were considered as one category (STEMI) while NSTEMI and UA patients were combined into a single category (NSTE-ACS).

Univariate comparisons of patient characteristics, clinical presentation, management practices, and outcome data were carried out using Wilcoxon rank sum or χ^2 tests. Short-term hospital survival rates were estimated using the Kaplan-Meier method. Cox

proportional hazards models were employed to compare the hazards of in-hospital death between patients enrolled in the two registries while controlling for potentially confounding variables of prognostic importance. Two multivariable adjusted models were built; in the first, we adjusted for age and sex only, while in the second we additionally controlled for all baseline characteristics and clinical presentation variables that were significantly associated with in-hospital mortality in the univariate analyses. Logistic regression modeling was used to more systematically examine differences in the risk of adverse in-hospital outcomes, other than death, between patients enrolled in the two registries while controlling for potential confounding demographic and clinical characteristics. We did not control for the use of hospital treatments due to the non-randomized nature of this study and potential for confounding by indication.

2.3 Results

A total of 11,151 patients (4,445 from GRACE and 6,706 from Gulf RACE) with a confirmed diagnosis of ACS admitted in 2007 comprised our study population. Of the patients in Gulf RACE, 39% had an STEMI; of the patients enrolled in GRACE, 34% developed an STEMI.

Patients in Gulf RACE were, on average, nearly a decade younger than patients enrolled in GRACE. The proportion of patients less than 55 years old in Gulf RACE was approximately twice that in GRACE while the proportion of patients 75 years and older in Gulf RACE was less than one third that of GRACE (Table 1).

Patients in Gulf RACE were more likely to be male, diabetic, currently smoke, and have renal impairment than patients enrolled in GRACE; on the other hand, these patients were less likely to be hypertensive or have previously undergone coronary revascularization. These differences remained when we examined the distribution of these characteristics between the two registry populations according to ACS type (Table 1).

Patients developing an STEMI in Gulf RACE were more likely to experience longer pre-hospital delays in seeking medical care compared to patients included in GRACE. Among 2,540 patients with STEMI in Gulf RACE who presented within 24 hours of acute symptom onset, 784 (31%) presented >12 hours after symptom onset; in GRACE, 1,381 STEMI patients presented within 24 hours of symptom onset, of which 139 (10%) presented >12 hours after acute symptom onset. The average hospital stay was significantly shorter for ACS patients included in Gulf RACE by nearly one day (Table 1).

In terms of clinical presentation, patients in Gulf RACE were more likely to present with higher heart rate and initial glucose values, and in a higher Killip class, compared to patients enrolled in GRACE. These differences persisted when comparing the respective study populations across type of ACS (Table 2).

While Gulf RACE patients were more likely to have been prescribed aspirin, nitrates, and statins, they were less likely to have received β -blockers, angiotensin-converting enzyme (ACE) inhibitors / angiotensin receptor blockers (ARB), calcium

channel blockers, clopidogrel, or glycoprotein IIb/IIIa antagonists compared to patients enrolled in GRACE during the first 24 hours of hospital admission. Gulf RACE patients were more likely to have been managed with intravenous heparin compared to patients enrolled in GRACE, who were more likely to have been managed with low molecular weight heparin. Similar patterns were observed when comparing patients with an STEMI between the two registries (Figures 1.A. and 1.B.). Nearly 75% of GRACE hospitals had on-site catheterization facilities compared with only 20% of Gulf RACE hospitals. In addition, nearly all hospitals in GRACE had coronary care units compared to less than 65% of hospitals in Gulf RACE.

Cardiac catheterization was performed nearly 4 times as frequently in GRACE compared to Gulf RACE in both STEMI patients (81.1% vs. 18.0%), and in NSTEMI-ACS patients (59.4% vs 13.1%). Thrombolysis was the reperfusion strategy of choice among STEMI patients enrolled in Gulf RACE compared to GRACE. Patients who developed an STEMI in GRACE were more likely to receive primary percutaneous coronary intervention (PCI). A total of 1,242 patients with STEMI in GRACE presented within 12 hours of symptom onset, of whom 163 (13%) received thrombolytics, 805 (65%) received primary PCI, 13 (1%) underwent CABG, and 261 (21%) did not receive any reperfusion modality. In Gulf RACE, 1,756 patients with STEMI presented within 12 hours of symptom onset, of whom 1,364 (78%) received thrombolytics, 227 (13%) received primary PCI, and 165 (9%) did not receive any form of coronary reperfusion therapy (Figure 2).

While patients in Gulf RACE, irrespective of their ACS diagnosis, were at higher risk for developing heart failure during their index hospitalization, only STEMI patients in Gulf RACE had a significantly higher risk of developing cardiogenic shock compared to patients included in GRACE. On the other hand, patients in Gulf RACE had a significantly lower risk of developing major bleeding during their hospitalization (Table 3). Gulf RACE patients experienced higher in-hospital case-fatality rates (CFR) compared with GRACE patients (1.3% vs 1.9%; 1.9% vs 3.5%; 3.7% vs 5.4%; and 7.7% vs 10.8%) in each of the age strata examined (<55, 55-64, 65-74, and ≥ 75 years) respectively (all p values ≤ 0.05 except for the <55 years group) .

Using survival modeling to account for differences in hospital length of stay, and controlling for age and sex, Gulf RACE patients had a higher risk of dying in-hospital (HR=1.41, CI= 1.23, 1.67). After controlling for additional characteristics of prognostic importance, there were no statistically significant differences in the risk of dying in-hospital between patients enrolled in the two registries (Table 3).

Multivariable adjusted odds ratios (OR) showed that Gulf RACE patients were at significantly greater risk for developing heart failure, cardiogenic shock, and stroke, while being at lower risk for developing major bleeding during their index hospitalization (Table 3).

2.4 Discussion and Conclusions

The present study is the first to compare the characteristics, management practices, and hospital outcomes of patients with ACS in the Arab Middle East to a large multinational and predominantly “Western” population hospitalized with ACS. Our study shows that ACS patients in the Arab Middle East were younger, more likely to have diabetes, and currently smoke cigarettes. They were more likely to present to participating hospitals after prolonged delay after the onset of acute coronary symptoms and were less likely to receive evidence-based cardiac therapies. Patients with ACS in the Arab Middle East had comparable in-hospital death rates to their counterparts in GRACE but had higher rates of in-hospital clinical complications.

Prior work has suggested that patients with ACS in the Gulf region are more likely to develop ACS at an earlier age and have a higher prevalence of diabetes and smoking^{2,8,9}; similar findings were observed in the present study. The average age of patients in Gulf RACE was nearly a decade younger than that of patients enrolled in GRACE. This striking difference might have resulted from differences in the coronary risk factor profile between the two cohorts leading to earlier development of ACS or acceleration of underlying coronary atherosclerosis among subjects in the Arab Middle East. The markedly high prevalence of diabetes observed among Gulf RACE patients, despite their younger age, may partially reflect shifts in diet and lifestyle practices towards a more westernized one.¹⁰ Similarly, the high cigarette smoking rates reported in Gulf RACE

likely reflect the late adoption of smoking awareness campaigns and the lack of public smoking bans in most Gulf countries.

More than 30% of patients with STEMI in Gulf RACE presented after 12 hours of acute symptom onset compared to 10% of those enrolled in GRACE. Prolonged delays in seeking acute medical care have been associated with the sub-optimal initiation of evidence-based management strategies and unfavorable hospital outcomes.¹¹ Future studies should explore the factors and reasons associated with late hospital presentation among ACS patients residing in the Gulf region.

Patients in Gulf RACE were more likely to present to participating hospitals with an STEMI and in a higher Killip class, suggesting a more severe form of the disease or late presentation compared to patients enrolled in GRACE. The risk profile of patients hospitalized with an ACS in the Arab Middle East and their late presentation seems to place them at higher odds for unfavorable cardiac outcomes despite their younger age.

Regional variations in ACS management practices throughout the world have been previously reported¹²⁻¹⁴ and have been partially explained by differences in health care models and rapidity of adopting evidence-based medicine guidelines. The observed differences in the types of hospitals and their facilities between the two registries might have affected the clinical management strategies used.

There were fundamental differences between the two patient registries in the use of interventional cardiology procedures as well as medical treatments; these differences were particularly noted in STEMI patients in need of urgent intervention. Despite differences in reperfusion modalities, the overall reperfusion rate in eligible STEMI patients was higher in Gulf RACE compared to GRACE (91% vs. 78%, respectively), and the reperfusion shortfall rate observed in Gulf RACE (9%) was lower than what has been previously reported from other ACS registries^{15,16}. These differences appear to be driven by local practice and availability of services and trained interventionalists rather than by patient characteristics or perceived risk. Similar inter-regional differences have been reported by previous studies showing that physicians in the U.S. and Europe adopted more aggressive coronary reperfusion strategies earlier than the rest of the world.^{14,17,18}

While patients in Gulf RACE were at higher odds for receiving aspirin, nitrates, and statins, they were less likely to receive other cardiac medications associated with better outcomes. These differences could have resulted from the striking differences in the use of cardiac catheterization and reperfusion modalities between the two cohorts. They could also be related to different clinical practices, insurance systems, and types of hospitals included.

Regional as well as inter-country differences in the short-term clinical outcomes of patients hospitalized with an ACS have been previously observed.^{13,14,19,20} Patients in Gulf RACE were more likely to have developed heart failure and cardiogenic shock during their

index hospitalization than patients enrolled in GRACE. This could be due to differences in hospital management strategies between the respective patient populations, including the use of invasive procedures as evidenced by a higher risk of major bleeding episodes for GRACE patients. In addition, it is possible that other unaccounted for factors could have led to the observed differences in these clinical outcomes.

Despite the younger age of Gulf RACE patients, there was no significant difference in crude in-hospital CFRs between the two study cohorts. Comparison of in-hospital CFRs between the two cohorts, adjusted for age and sex differences, suggested a higher risk of dying during hospitalization for Gulf RACE compared to GRACE patients. Multivariable analyses further adjusted for differences in baseline characteristics and clinical presentation revealed no short-term survival advantage for one cohort over the other despite significant differences in treatment strategies between the 2 registries. The higher risk of dying for Gulf RACE patients compared to their counterparts from GRACE of a similar age and sex might be partially explained by the higher rates of coronary disease risk factors and more prolonged delays in seeking medical care. Higher primary PCI/thrombolysis ratio and greater use of evidence-based medications for GRACE patients did not translate into a short-term survival advantage. The very low reperfusion shortfall rate for eligible patients in Gulf RACE might partially explain the observed lack of differences in short-term mortality rates. On the other hand, GRACE patients had a lower risk of important short-term complications including heart failure, cardiogenic shock, and stroke. Potential

explanations for the higher rates of short-term complications in Gulf RACE include differences in the receipt of different treatment modalities and more prolonged delays in seeking medical care.²¹

Similar findings to our study were observed in a meta-analysis based on data from the Gulf region which found that the majority of patients with an STEMI were managed by thrombolytics and had favorable outcomes.²² A study comparing patients enrolled in the U.S. to their Canadian counterparts in the GUSTO-I trial reported that, despite the higher utilization of invasive cardiac procedures in the U.S., favorable outcomes were only observed when comparing long-term mortality rates while short-term mortality rates were comparable.^{23,24}

Acknowledgement: We greatly appreciate the contributions and support of Dr. Gordon FitzGerald. This work was supported by an unrestricted educational grant from Sanofi Aventis

Table 2.1 Baseline Characteristics of Patients hospitalized with an Acute Coronary Syndrome (ACS)

Characteristic	All ACS			STEMI			NSTEMI-ACS		
	GRACE 07 4,445	Gulf RACE 6,706	P- value	GRACE 07 1,504(34%)	Gulf RACE 2,619(39%)	P- value	GRACE 07 2,941(66%)	Gulf RACE 4,087(61%)	P- value
Age (Years), mean (SD)	65.5(13)	56.4(13)	<0.01	63.8(14)	54.4(13)	<0.01	67.3(13)	57.3(13)	<.01
Age (Years)									
<55	1,039(23%)	3,099(46%)		428(28%)	1,399(53%)		611(21%)	1,700(42%)	
55 - 64	1,136(26%)	1,830(27%)		389(26%)	656(25%)		747(25%)	1,174(29%)	
65 - 74	1,061(24%)	1,232(18%)		331(22%)	395(15%)		730(25%)	837(21%)	
≥75	1,209(27%)	545(8%)	<0.01	356(24%)	169(7%)	<0.01	853(29%)	376(9%)	<0.01
Male	3,072(69%)	5,071(76%)	<0.01	1,099(73%)	2,250(86%)	<0.01	1,973(67%)	2,821(69%)	0.08

BMI, Mean(SD)	28.1(5.7)	27.6(5.4)	<0.01	27.5(5.0)	26.8(4.8)	<0.01	28.4(6.0)	28.1(5.6)	0.030
Diabetes Mellitus	1,181(27%)	2,745(41%)	<0.01	328(22%)	841(32%)	<0.01	853(29%)	1,904(47%)	<0.01
Hypertension	2,929(66%)	3,364(50%)	<0.01	851(57%)	890(34%)	<0.01	2,078(71%)	2,474(61%)	<0.01
Prior PCI or CABG	1,227(28%)	1,049(16%)	<0.01	217(15%)	173(7%)	<0.01	1,010(35%)	876(22%)	<0.01
Current smoker	1,217(28%)	2,452(37%)	<0.01	536(36%)	1,318(50%)	<0.01	681(23%)	1,134(28%)	<0.01
Renal Impairment	691 (16%)	1,170(18%)	0.01	188(13%)	459(18%)	<0.01	503(17%)	711(18%)	0.40
Length of Stay(mean, days)	6.6(6.8)	5.6(4.6)	<0.01	6.6(6.9)	6.1(4.3)	<0.01	6.6(6.8)	5.2(4.7)	<0.01

Table 2.2 Clinical Presentation of Patients Hospitalized with an Acute Coronary Syndrome (ACS)

Characteristic	All ACS			STEMI			NSTEMI-ACS		
	GRACE 07 4,445	Gulf RACE 6,706	P- value	GRACE 07 1,504(34)	Gulf RACE 2,619(39)	P- value	GRACE 07 2,941(66)	Gulf RACE 4,087(61)	P- value
Heart Rate , mean(SD) (bpm)	79.0(21)	86.0(23)	<0.01	79.0(22)	85.1(23)	<0.01	79.0(21)	87.0(23)	<0.01
Systolic BP , mean(SD) (mm Hg)	140.0(29)	140.0(31)	0.70	136.0(30)	134.0(31)	0.30	142.0(29)	143.0(30)	0.30
Initial Glucose, mean(SD) (mg/dl)	158.0(267)	196.0(193)	<0.01	168.0(155)	200.0(154)	<0.01	153(310)	193(214)	<0.01
Initial Creatinine, mean(SD) (mg/dl)	1.21(0.9)	1.22(1.1)	0.50	1.17(0.8)	1.2(0.9)	0.30	1.24(0.9)	1.24(1.2)	0.80
Killip Class									
I	3756(85%)	5219(78%)	<0.01	1251(83%)	2068(79%)	<0.01	2505(85%)	3151(77%)	<0.01
II	416 (9%)	874(13%)	<0.01	152(10%)	322(12%)	0.030	264(9%)	552(14%)	<0.01
III	167 (3.8%)	460(6.9%)	<0.01	56(3.8%)	139(5.3%)	0.020	111(3.8%)	321(7.9%)	<0.01
IV	46(1.1%)	137(2.1%)	<0.01	24(1.6%)	86(3.3%)	<0.01	22(0.8%)	51(1.3%)	0.040
Cardiac Arrest	161(3.7%)	168(2.5%)	<0.01	75(5.0%)	125(4.8%)	0.70	86(3.0%)	43(1.1%)	<0.01

Table 2.3 In-hospital Complications of Patients Hospitalized with an Acute Coronary syndrome (ACS)

In-hospital Outcome	All ACS				STEMI				NSTEMI-ACS			
	GRACE0 7 4,445	Gulf 6,706	P- valu e	Adjusted OR (CI)	GRACE0 7 1,504(34)	Gulf 2,619(39)	P- valu e	Adjusted OR (CI)	GRACE0 7 2,941(66)	Gulf 4,087(61)	P- valu e	Adjusted OR (CI)
Cardiogenic Shock	142(3.2%)	347(5.2%)	<0.0 1	1.39(1.06,1.83)	83(5.5%)	252(9.6%)	<0.0 1	1.69(1.42,1.93)	59(2.0%)	95(2.3%)	0.37	1.26(1.09,1.48)
Heart Failure	384(9%)	1,099(16%))	<0.0 1	2.23(1.91,2.56)	177(12%)	454(17%)	<0.0 1	1.92(1.54,2.39)	207(7%)	645(16%)	<0.0 1	2.81(2.33,3.39)
Echocardiography Done	2,634(60%)	4,146(62%)	0.03		1,098(74%)	1,845(71%)	0.04		1,536(53%)	2,301(56%)	<0.0 1	
LVEF≤40%	709(16%)	1,283(19%)	<0.0 1		322(21%)	620(24%)	<0.0 1		387(13%)	663(16%)	<0.0 1	
Major Bleeding	89(2.0%)	52(0.8%)	<0.0 1	0.37(0.25,0.54)	36(2.4%)	31(1.2%)	<0.0 1	0.49(0.30,0.81)	53(1.8%)	21(0.5%)	<0.0 1	0.27,(0.16,0.44)
Stroke	21(0.5%)	49(0.7%)	0.09	2.45(1.25,4.82)	9(0.6%)	32(1.2%)	0.05 4	3.32(1.28,8.63)	12(0.4%)	17(0.4%)	0.96	1.59(0.66,3.83)
Death	167(3.8%)	247(3.7%)	0.84	1.09(0.84,1.41)	93(6.2%)	172(6.6%)	0.63	1.29(0.92,1.79)	74(2.5%)	75(1.8%)	0.06	0.77(0.53,1.13)

Figure 2.1.A Use of in-hospital Medications (first 24 hours) in All Patients with an Acute Coronary Syndrome (ACS)

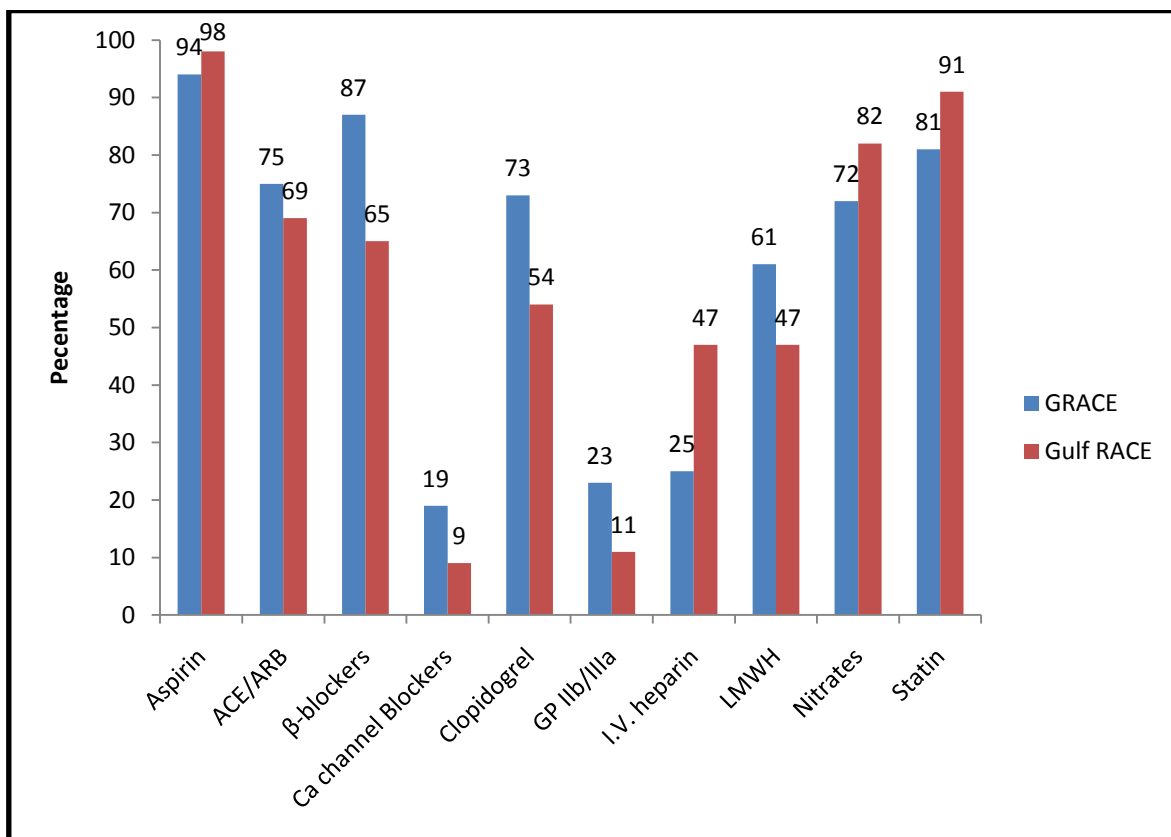


Figure 2.1.B Use of in-hospital Medications (first 24 hours) in Patients with an ST-elevation Myocardial Infarction

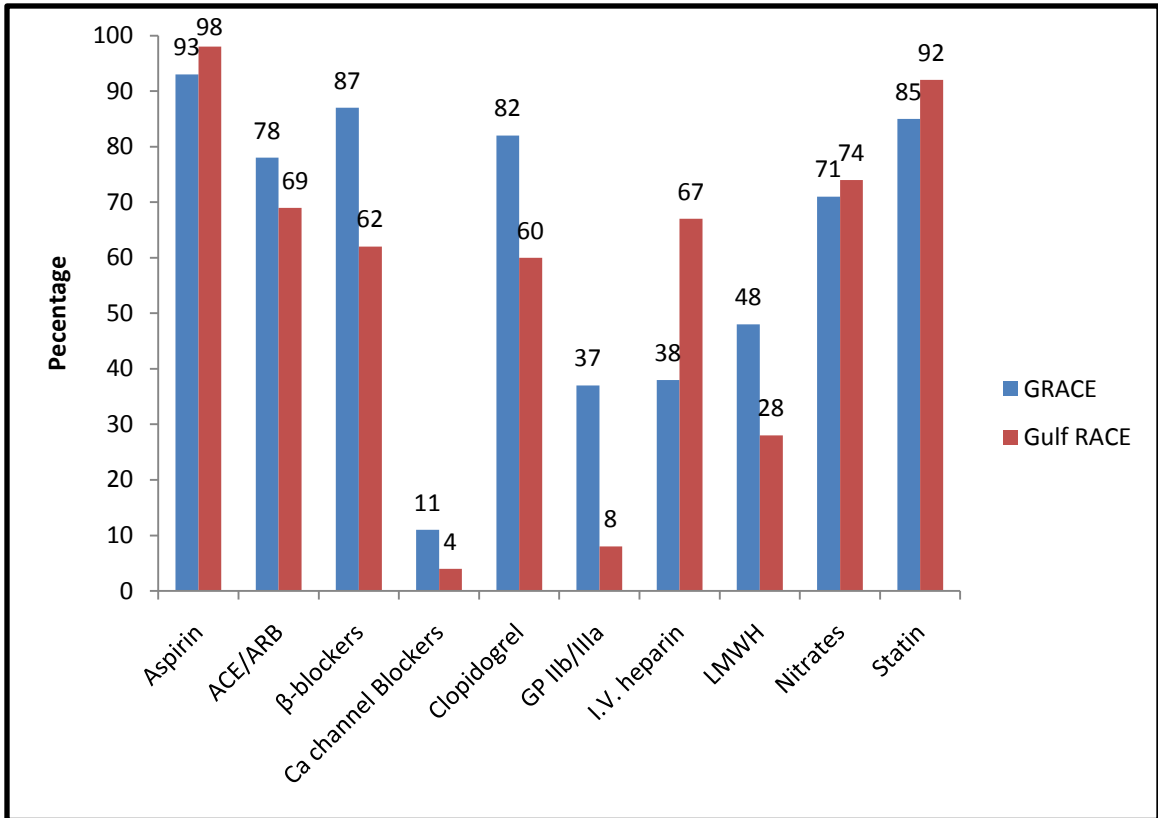
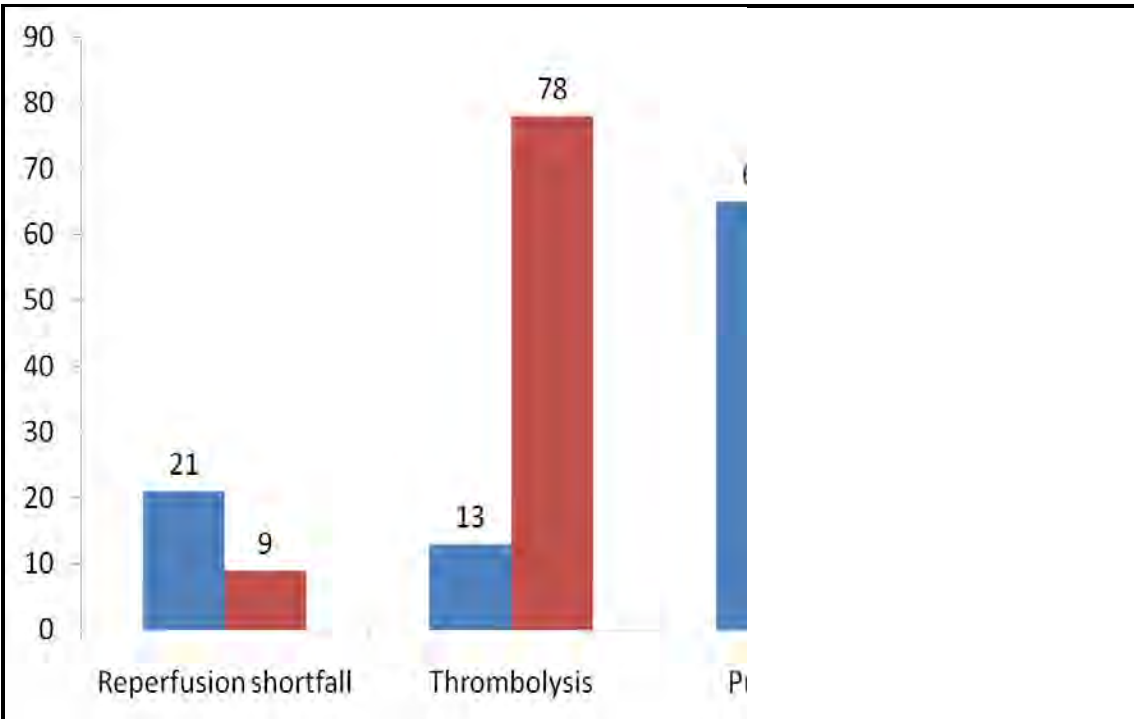


Figure 2.2 Receipt of Reperfusion Therapy in Eligible Patients with ST-elevation Myocardial Infarction



CHAPTER III
Cardiogenic Shock Complicating Acute Coronary Syndromes: the
Global Registry of Acute Coronary Events (GRACE)

Short Title: Cardiogenic Shock Complicating Acute Coronary Syndromes

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Abstract

Introduction

Cardiogenic shock (CS) is the leading cause of death for patients with an acute coronary syndrome (ACS). Despite impressive advances in the management of ACS, the frequency of cardiogenic shock among patients hospitalized with an ACS has remained relatively constant over the past several decades, and mortality remains unduly high in these high risk patients.

Objectives

To describe the characteristics, clinical management, and hospital outcomes of patients with an ACS complicated by CS. Our secondary objective was to describe decade long trends in the incidence and hospital case-fatality rates (CFRs) of CS, and predictors of increased hospital mortality in these patients.

Methods

The study sample consisted of all patients enrolled in the Global Registry of Acute Coronary Events (GRACE) between 1999 and 2007 with a confirmed ACS.

Results

Of all patients with ACS enrolled in GRACE, 2,992 (4.6%) developed CS. Compared to patients who did not develop CS, patients with CS were more likely to be older (mean age 71 vs. 65 years), female, have a history of diabetes, and heart failure, and present with ST-segment elevation. Cardiac catheterization was performed on 1,706 (57%) and in-hospital revascularization on 1,408(47%) patients with CS. Patients with CS were less likely to receive effective adjunctive cardiac medications as ACE inhibitors, aspirin and

β -blockers compared to patients who did not develop CS. The in-hospital CFR of patients with CS was 59.4% compared to 2.3% in those who did not develop CS. Hospital CFR was lower for patients who underwent revascularization compared with those in whom a conservative medical approach was adopted (45% vs. 72%). Factors associated with an increased risk of in-hospital death in CS patients included advanced age, history of diabetes mellitus, heart failure, renal insufficiency. Adjusted incidence rates of CS showed slight declines over the study period (OR= 0.97 per year, CI= 0.95 - 0.98) as well as in hospital CFRs (OR= 0.94 per year, CI= 0.90 - 0.99), while In-hospital revascularization rates increased (OR= 1.09 per year, CI= 1.06 - 1.12).

Conclusion

Despite the increasing use of evidence-based therapies, the overall hospital CFR of CS remains high (59%) and incidence showed only slight declines between 1999 and 2007.

Key words: Acute coronary syndrome, cardiogenic shock & outcomes

3.1 Introduction

Cardiogenic shock (CS) remains the most serious complication and the leading cause of death for patients hospitalized with an acute coronary syndrome^{1, 2} (ACS). Although cardiogenic shock is more commonly encountered with ST-elevation myocardial infarction (STEMI), it may also develop in patients with a non ST-elevation acute coronary syndrome (NSTE-ACS).

Despite recent studies suggesting possible declines in the risk of dying during hospitalization for patients with CS, which has been linked to advances in medical treatment, revascularization techniques, and mechanical support, in-hospital case-fatality rates associated with CS remain high exceeding 50% (55%-80%)³. Moreover, despite the clinical importance of this serious clinical complication, the incidence rates of CS in patients with an ACS have remained relatively constant over the past 30 years averaging approximately 7% (5%-10%).³⁻⁵ Utilizing data from a large multinational coronary disease registry, we describe the demographic and clinical characteristics of patients presenting with an ACS complicated by CS, the management of these high risk patients, and their short-term outcomes compared with patients who did not develop CS. A secondary study objective was to describe nearly decade long (1999-2007) trends in the incidence and case-fatality rates of CS complicating ACS and factors associated with an increased risk of dying in patients with CS.

3.2 Methods

The full details of the methods used in the Global Registry of Acute Coronary Events (GRACE) study have been previously published⁶.

This multinational prospective study was designed to reflect an unselected population of patients with an ACS, irrespective of geographic region. A total of 123 hospitals located in 14 countries in North and South America, Europe, Australia, and New Zealand have contributed data to this study. Adult patients (18 years of age) admitted with a presumptive diagnosis of ACS were potentially eligible. Patients with non-cardiovascular causes for their clinical presentation were excluded. Patients were followed up at approximately 6 months after hospital discharge by telephone, clinic visits, or through calls to their primary care physician to ascertain the occurrence of long-term outcomes.

Patient population:

Prospective (warm pursuit) and retrospective (cold pursuit) surveillance approaches for identifying cases of ACS were utilized. When required, study investigators received approval from their local hospital ethics or institutional review board. For sites using active surveillance for case identification, verbal or written consent was obtained from patients to review information contained in their medical charts. Standardized definitions of all patient-related variables, clinical diagnoses, and selected hospital complications and outcomes were based on the American College of Cardiology

key data elements and definitions for measuring the clinical management and outcomes of patients hospitalized with ACS (Cannon 2001).

Patients were defined as having an ACS if they had symptoms typical of ACS accompanied by at least 1 of the following: electrocardiographic changes consistent with ACS, serial increases in biochemical markers of cardiac necrosis (creatinine kinase-MB fraction, creatine phosphokinase, or troponin), and documented coronary artery disease. Patients who died within 24 hours of hospitalization were enrolled in the study provided that the cause of death was related to ACS.

Cardiogenic shock was defined as a systolic blood pressure of < 80 mm Hg and congestive heart failure (Killip class IV) occurring at any time during the acute hospitalization. The specific timing of shock onset was not collected, but patients presenting to the hospital with CS were differentiated from those developing shock in-hospital by Killip class IV on hospital presentation. Coronary revascularization was defined as the receipt of a PCI or CABG at any time during the index hospitalization.

Data collection:

Hospital records of patients with validated ACS were abstracted for demographic and clinical data, complications during hospitalization, electrocardiographic findings, and use of diagnostic procedures and therapeutic approaches. All medication usage was coded as present if it began either before or during the time of the index hospitalization. Data were stored and analyzed at the Center for Outcomes Research of the University of Massachusetts Medical School, Worcester, Massachusetts.

Data analysis:

Continuous variables were summarized by their means and standard deviations (SD) or medians as appropriate. Categorical variables were summarized by counts and percentages. Univariate comparisons of patient characteristics, presentation, treatments and outcomes data between patients with and without CS were carried out using the Wilcoxon rank sum or χ^2 tests.

Short-term survival rates were estimated using the Kaplan–Meier method and log-rank tests were used for between group (CS present versus absent) comparisons.

The short term prognosis in each year was examined by calculating in-hospital and 30 day post admission case-fatality rates (CFRs). A logistic multivariable regression analysis was used to examine changes over time in the incidence rates of CS and in-hospital CFRs, while controlling for potentially confounding demographic (e.g., age, sex) and clinical (e.g., prior comorbidities, ACS type) prognostic factors. These variables were considered as potential confounders based on univariate analyses and the findings of previous research. The Hosmer-Lemeshow goodness-of-fit test was used to examine the adequacy of our logistic regression models.

Unadjusted and multivariable adjusted Cox proportional hazards models were employed to determine factors associated with an increased risk of dying in the hospital among patients who developed CS while controlling for potentially confounding prognostic characteristics including demographics, medical history, and clinical presentation. Given the nonrandomized nature of the present study, and the caveats and difficulties involved in the interpretation of any multivariable-adjusted estimates of

association, we did not control for the hospital use of cardiac treatment approaches in our regression analyses in which hospital survival status was the key outcome. All analyses were performed with STATA version 11.0 (Stata Corporation, College Station, TX, USA).

3.3 Results

Baseline Characteristics

The study population consisted of 65,119 patients with an ACS enrolled in GRACE between 1999 and 2007, of whom 4.6% (n=2,992) developed CS during their index hospitalization for an ACS. Compared to patients without CS, patients with shock were more likely to be older (6 years on average), to be women, and to have a prior history of diabetes, chronic heart failure, renal insufficiency, and stroke. Patients with CS were more likely to have a higher pulse rate, an STEMI, cardiac arrest, and lower systolic blood pressure compared to patients without CS at the time of hospital admission (Table 3.1).

Treatment of Patients with Cardiogenic Shock

Cardiac catheterization was used in 57.3% and hospital revascularization was used in 47.4% of all patients with ACS complicated by shock. Revascularization was only used in 36.6% of elderly patients ≥ 75 years old compared to 55.3% of non-elderly patients with shock ($p < 0.001$).

While ACS patients presenting with CS were less likely to undergo cardiac catheterization, once they were catheterized, they were more likely to undergo PCI or

CABG compared to patients without shock. Stent use was significantly lower in patients with shock who underwent PCI compared to patients who did not develop shock (88.0% vs. 93.2%, $p < 0.001$) (Table 3.2).

Pulmonary artery catheterization, intra-aortic balloon pumps, as well as cardiac supportive drugs, including inotropes/pressors, were used significantly more often in patients with CS compared to patients without shock (32.0%, 29.0% and 79.8% vs. 3.7%, 1.5% and 11.5% respectively, $p < 0.001$) (Table 3.2)

Thrombolytic therapy was administered more frequently to patients with shock compared to patients without shock (21.2% vs. 13%). Patients with CS were less likely to have received ACE inhibitors, aspirin, β -blockers, Ca-channel blockers, LMW heparin, and nitrates than patients without CS. Of note, only Glycoprotein IIb/IIIa and unfractionated heparin were used more frequently among ACS cases complicated by shock compared to patients without shock (30.4 and 55.7% vs. 25.7% and 46.6% respectively).

In-hospital case-fatality rates

The crude in-hospital CFR for patients with CS was 59.4% compared to 2.3% in patients without shock. Hospital mortality was markedly lower for patients who underwent coronary revascularization compared with those in whom a more conservative approach was adopted (45.3% vs. 72.0%, $p < 0.001$). Patients developing CS during their acute hospitalization were at significantly higher risk for dying in-hospital compared to patients presenting to the hospital in shock (62.6% vs. 48.4%, $p < 0.001$).

In examining differences in possible prognostic factors, in patients who died, as compared with those who survived CS, older patients, those with a history of selected comorbid conditions, , and those presenting with cardiac arrest were more likely to die after developing CS than respective comparison groups (Table 3.3).

Multivariable-adjusted survival regression models showed that older age, and a history of either myocardial infarction or diabetes mellitus were associated with an increased risk of dying among patients who developed CS. Models that included time of development of shock and in-hospital procedures showed that patients with CS who survived their acute hospitalization were significantly younger, presented with shock, and underwent PCI or CABG during hospitalization.

The crude 30-day CFR for patients with ACS complicated by cardiogenic shock was 59%. Significant univariate as well as multivariable adjusted predictors of an increased risk of dying during the 30 days following development of ACS for patients with CS were identical to the predictors of in-hospital mortality.

Time trends in the incidence rates of CS

The crude hospital incidence rates of cardiogenic shock among patients with ACS decreased from 5.1% in 1999 to 3.6% in 2007 (Figure 3.1). Cardiogenic shock incidence rates adjusted for age, gender, medical history, clinical presentation, and length

of hospital stay showed significant declines over the study years (annual OR= 0.97, CI= 0.95 , 0.98).

Time trends in hospital case-fatality rates

The crude in-hospital CFRs among patients with CS declined from 62% in 1999 to 54% in 2006, with an increase in these death rates in 2007 (Figure 3.2). In-hospital CFRs of shock patients adjusted for age, gender, medical history, clinical presentation, length of hospital stay, and study site showed significant declines during the years under study (annual OR= 0.94, CI= 0.90, 0.99).

3.4 Discussion

The results of our large multinational observational study provide insights into the magnitude, management, short-term mortality rates, and the characteristics of patients with an ACS likely to develop and survive CS. While our study showed declining short-term mortality rates related to CS, the incidence rates of CS remained relatively constant during the years under study.

Baseline Characteristics

Identifying patients at increased risk for developing CS and providing these high risk patients with urgent medical care is essential to decrease the risk of developing this serious complication among patients with an ACS. Proper monitoring, risk stratification,

and aggressive intervention have been associated with improved survival among patients developing CS.⁶⁻⁹ Our study demonstrated that patients with ACS at high risk for developing CS were older, more likely to be female, diabetic, suffering from chronic heart failure, and were more likely to present to the hospital with ST-elevation myocardial infarction and cardiac arrest. Less than one quarter of all patients with CS presented to the hospital with CS, while the remainder experienced shock at a later time during their acute hospitalization.

Our results are similar to previously published findings from studies carried out in different settings including the Worcester Heart attack Study (WHAS), the GUSTO, and SHOCK trials^{6, 10, 11}.

Treatment of Patients with Cardiogenic Shock

Previously published results from clinical trials and observational studies have demonstrated that early mechanical revascularization in patients with CS was associated with lower mortality compared with initial medical stabilization (including intra-aortic balloon pump [IABP] counterpulsation and fibrinolytic therapy) followed by late or no revascularization^{7, 12}. Based on these findings, the American College of Cardiology (ACC) and the American Heart Association (AHA) have elevated early mechanical revascularization for CS to a class I recommendation for patients younger than 75 years¹³, and a class IIA recommendation for those older than 75 years who are suitable candidates¹⁴. However, the availability of clinical practice guidelines does not necessarily translate to changes in “real world” practice¹⁵. The results of our study showing that more

than 40% of patients with CS were >75 years old is consistent with the previously published literature^{4, 6}. Management of this high risk group, and appropriately selecting patients eligible for invasive management, remains an important clinical challenge.

While patients with CS were less likely to undergo cardiac catheterization, once they were catheterized, they were more likely to receive PCI or CABG. This can likely be explained by the presence of larger myocardial infarctions, a greater frequency of multi-vessel disease in these individuals, and because of their clinically unstable conditions. Patients with shock were also more likely to receive thrombolytics compared to patients who did not develop CS. Although the benefits of thrombolysis in patients with CS are less established compared to patients with AMI, this reperfusion approach has been demonstrated to reduce the risk of subsequent development of shock¹⁶ which is of significant importance considering that most patients develop CS after hospital presentation (>6 hours)^{6, 17}. Patients with CS were less likely to receive evidence -based medications compared to patients without CS. Although these medications are associated with better outcomes in patients with ACS, most of them might aggravate hypotension in patients with CS; hence their lower utilization and they are often withheld until the patient is stabilized¹⁸. Patients with CS may benefit from selective β -blockers that improve cardiac contractility and increase cardiac output without noticeably affecting the heart rate or vascular resistance. Due to the lack of information on the exact timing of development of CS in our study, we were unable to determine the relationship between time of onset of Cs and the prescription of in-hospital medications or procedures. As expected, patients developing CS were more likely to receive cardiac supportive care in

the form of inotropic agents, vasopressors and intra aortic balloon pumps (IABP). Future studies should continue to monitor the use of various treatment approaches in this high risk patient population and identify patient groups less likely to be treated with evidence based treatments.

In-hospital and 30-day case-fatality rates

Cardiogenic shock remains the most frequent cause of in-hospital death among patients with an ACS. Historic case-fatality rates reported by previous studies have ranged from 50-80%^{4, 7, 12, 19}. However, and despite the persistently high death rates associated with CS, the prognosis for patients hospitalized with CS has improved considerably over the past four decades. Declines in mortality rates have been associated with advances in supportive care and a more aggressive approach to coronary revascularization^{7, 12}.

As expected, and in agreement with the previous literature, patients with CS were significantly more likely to die in-hospital than patients who did not develop this complex hemodynamic complication (59.4% vs 2.3%).

A number of nonrandomized studies suggest that PCI improves short-term survival in patients with CS with survival contingent on the successful establishment of coronary reperfusion. Uncontrolled studies of coronary artery bypass grafting show that this revascularization approach improves short-term survival among patients with CS when they are treated soon after shock has developed¹⁰. However, we were unable to assess the role of these interventional procedures because we could not determine

whether shock preceded or followed the use of these treatment strategies or to determine other reasons why certain patients received these therapeutic regimens and others did not (confounding by indication).

Consistent with the findings from previously published studies, older age, diabetes mellitus, history of myocardial infarction, and renal insufficiency were associated with an increased risk of in-hospital mortality among patients developing CS. However, developing CS during hospitalization and following hospital presentation remains associated with a highest risk of in-hospital mortality among patients with CS.

Future studies should further explore factors associated with better monitoring of hemodynamic status at the time of hospital presentation and the accompanying risk of developing CS during hospitalization in this high risk population.

Time trends in the incidence and in-hospital case-fatality rates of CS

It is difficult to compare the actual incidence rates of CS in published studies due to varying population characteristics, definitions of CS, and whether patients developing shock in the pre-hospital setting were included^{4,20}. The incidence of cardiogenic shock reported from previous studies has ranged from 3- 15%^{21,22} depending on the study population characteristics. The overall incidence of CS reported in our study (4.6%) falls within this range. Moreover, we demonstrated that the incidence rates of CS declined slightly over the period under study, consistent with findings from previous studies examining trends in CS incidence rates during the 2000s^{10,23}. Potential contributors to declines in the incidence rates of CS include the increased adoption of early

revascularization of patients with AMI, increasing use of effective cardiac medications over time, and enhanced patient monitoring efforts.

Results from our study show a clear declining trend in short-term mortality rates of CS between 1999 and 2006 with an increase in these death rates in 2007. While the reasons for this increase in short-term CFRs during our most recent study year remains unexplained, it needs to be noted that our encouraging declines in the hospital death rates of patients with CS declined during the years under study when other covariates of prognostic importance were adjusted for. It might be considered surprising that global hospital mortality rates for shock have not decreased more significantly in a time period otherwise notable for increased use of improved techniques for PCI^{8, 24} (Refs) although global variations in use of these technologies and pharmacologies have been previously noted¹⁷.

Study strengths and limitations

Our study strengths include using high quality data and a large study sample to report on this very high risk population. Limitations of our study include the observational nature of the data and lack of information on the timing of development of cardiogenic shock as well as racial and socioeconomic data.

3.5 Conclusions

The results of this study provide insights into the characteristics, management practices, and short-term mortality of patients with ACS complicated by CS. Although the magnitude of CS appears to be slowly declining, it still develops at a relatively high rate after ACS. The hospital death rate among patients with this complication remains high despite advances in management and declining rates over time. It remains of considerable importance to examine contemporary trends in the magnitude and short-term outcomes associated with CS and to improve monitoring and risk stratification systems for identifying patients most likely to develop this devastating complication.

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Table 3.1 Characteristics of Patients with an Acute Coronary Syndrome Complicated by Cardiogenic Shock

Characteristic	Patients with CS n(%)	Patients without CS n(%)	p-value
	2,993(4.6)	62,134(95.4)	
Age, Mean (SD) yrs	71.01(12.5)	65.42(13.2)	<0.001
Age Group			
18-54	368(12.4)	14685(23.8)	
55-64	529(17.8)	14,760(23.8)	
65-75	817(27.5)	16,102(26.0)	
≥75	1,262(42.4)	16,367(26.5)	<0.001
Female	1,143(38.3)	20,100(32.5)	<0.001
History			
Angina	1,346(45.4)	32,608(52.7)	<0.001
History of CAD	665(22.8)	19,098(31.3)	<0.001
Myocardial Infarction	837(28.3)	18,710(30.3)	0.022
PCI	309(10.5)	11,045(17.9)	<0.001
CABG	272(9.2)	7,746(12.5)	<0.001
Current Smoking	1,475(50.1)	35,762(57.8)	<0.001
Diabetes Mellitus	916(31.0)	15,388(24.9)	<0.001
Chronic Heart Failure	516(17.5)	6,090(9.9)	<0.001
Hypertension	1,768(59.9)	38,386(62.1)	0.013
Renal Insufficiency	325(11.0)	4,600(7.4)	<0.001
Stroke/TIA	324(11.0)	5,070(8.2)	<0.001
Clinical Presentation			
Pulse, mean(SD)	87.1(28.3)	79.1(20.8)	<0.001
Systolic Blood Pressure	117.1(37.9)	142.5(29.0)	<0.001
Cardiac Arrest	368(12.5)	933(1.5)	<0.001
STEMI	1,909(63.8)	21,809(35.1)	<0.001
NSTEMI	701(23.4)	20,690(33.3)	<0.001

Table 3.2 Treatment of Patients with an Acute Coronary Syndrome Complicated by Cardiogenic Shock

Treatment	Patients with CS n(%) 2,993(4.6)	Patients without CS n(%) 62,134(95.4)	p-value
Procedures			
Cardiac catheterization	1,706(57.3)	37,823(61.4)	<0.001
Any Coronary	1,408(47.4)	26,471(42.9)	<0.001
Revascularization			
PCI	1,190(40.1)	23,622(38.3)	0.053
of patients undergone PCI (%stent)	977(88.0)	21,309(93.2)	<0.001
CABG	272(9.2)	3,107(5.1)	<0.001
Medications			
GP IIb/IIIa	894(30.4)	15,798(25.7)	<0.001
Intra-aortic balloon pump	852(29.0)	892(1.5)	<0.001
Pulmonary artery catheter	945(32.0)	2,285(3.7)	<0.001
Pressors/inotropes	2,368(79.8)	7,030(11.5)	<0.001
Thrombolysis	627(21.2)	8,003(13.0)	<0.001
Adjunctive hospital medications			
ACE inhibitors	1,595(53.9)	40,497(65.7)	<0.001
Aspirin	2,512(84.4)	58,130(93.7)	<0.001
β -blockers	1,656(56.1)	52,625(85.2)	<0.001
Ca channel blockers	368(12.6)	14,439(23.6)	<0.001
LMW Heparin	1,437(49.0)	36,156(58.9)	<0.001
Unfractionated Heparin	1,634(55.7)	28,544(46.6)	<0.001
Nitrates	1,916(64.7)	49,875(80.8)	<0.001

Table 3.3 Univariate Predictors of Hospital Survival for Patients with an Acute Coronary Syndrome Complicated by Cardiogenic Shock

Characteristic	Dead n(%)	Survived n(%)	p-value
Age, Mean (SD) yrs	73.9(11.6)	66.8(12.7)	<0.01
Age Group			
18-44	23(1.3)	54(4.5)	
45-54	116(6.6)	175(14.5)	
55-64	239(13.5)	289(24)	
65-75	460(26)	355(29.5)	
75-84	644(36.5)	246(20.4)	
≥85	285(16.1)	85(7.1)	<0.01
Female	733(41.5)	409(33.9)	<0.01
Medical History			
Angina	872(49.7)	472(39.0)	<0.01
CAD	419(24.2)	244(20.6)	0.024
PCI	177(11.0)	132(10.2)	0.48
CABG	170(9.7)	102(8.5)	0.24
Current Smoking	763(43.9)	709(58.9)	<0.01
Diabetes Mellitus	591(33.8)	324(26.9)	<0.01
Heart Failure	356(20.4)	160(13.3)	<0.01
Hypertension	1,090(62.5)	675(56.0)	<0.01
Renal Insufficiency	225(12.8)	100(8.3)	<0.01
Stroke/TIA	230(13.2)	94(7.8)	
Clinical Presentation			
Presented with a Shock	322(18.7)	344(29.0)	<0.01
Cardiac Arrest	228(13.0)	140(11.7)	0.282
ST-segment Elevation	1,094(61.7)	814(67.1)	<0.01
Non-ST-segment Elevation	412(23.2)	288(23.7)	0.17

Figure 3.1 Time Trends in Crude Hospital Incidence Rates of Cardiogenic Shock Among Patients with Acute Coronary Syndromes

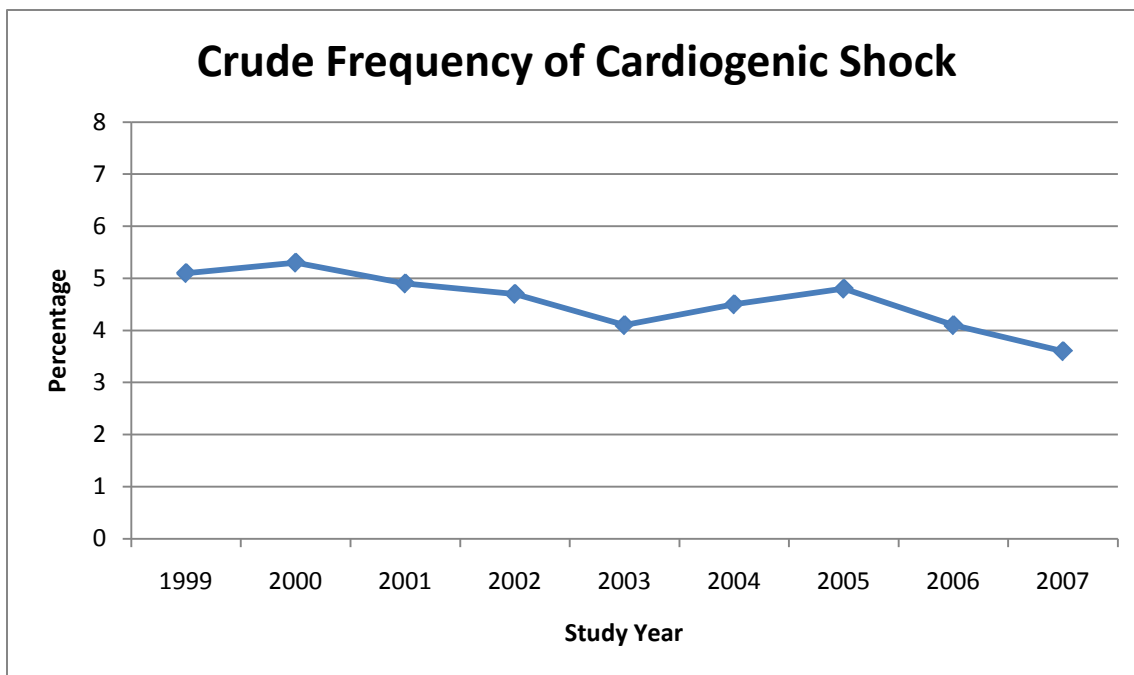
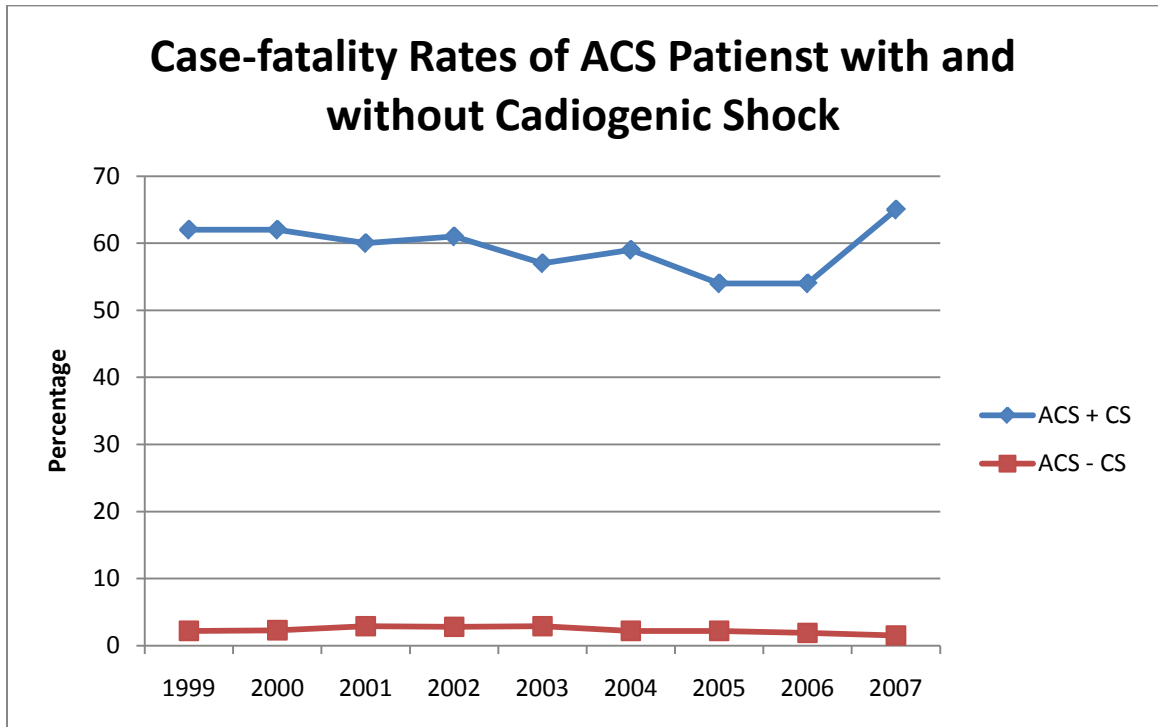


Figure 3.2 Time Trends in Crude Hospital Case-fatality Rates for Acute Coronary Syndrome Patients with and without Cardiogenic Shock



CHAPTER IV

Clinical Features, Treatment Practices, and Short-term Outcomes of Patients < 55 Years of Age Hospitalized with an Acute Coronary Syndrome: The Global Registry of Acute Coronary Events

Short Title: Cardiogenic Shock Complicating Acute Coronary Syndromes

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Abstract

Limited data are available describing the magnitude, clinical features, treatment practices, and short-term outcomes of comparatively young adults hospitalized with acute coronary syndromes (ACS). The objectives of this large multinational observational study were to describe trends in these endpoints among adults less than 55 years old who were hospitalized with an ACS between 1999 and 2007 (n=15,052). The overall proportion of young adult patients in our study population was 23% and the proportion remained relatively constant over the study period. Baseline demographic and clinical characteristics of our study sample did not change significantly during the years under study, whereas, the length of hospital stay declined by more than a day on average over the years under study. The overall in-hospital and 30-day multivariable adjusted In-hospital and 30-day death rates declined by more than 30% (OR= 0.66, 95% CI= 0.60, 0.74) during the years under study. The use of evidence based therapies proven to improve outcomes of patients with an ACS significantly increased over the study years. In conclusion, the results of this multinational study provide insights into the magnitude, changing characteristics, and short-term outcomes of comparatively young patients hospitalized with an ACS. Improving trends in short-term outcomes of comparatively young patients with an ACS during the near decade under study likely reflect enhanced primary and secondary prevention and treatment efforts.

Keywords: acute coronary syndrome, young adults, time trends

4.1 Introduction

Acute coronary syndromes (ACS) are a major cause of morbidity and mortality around the world.¹ By 2020, ACS will be the leading cause of mortality worldwide². While marked age-related differences have been observed in the risk of developing as well as the prognosis of ACS, few studies however examined the epidemiology of ACS in comparatively younger patients. This is exceedingly important in light of increasing trends in obesity, diabetes, and hyperlipidemia worldwide among young adults.³ The global registry of acute coronary events (GRACE) is the largest multinational prospective study designed to examine the characteristics, clinical management practices and outcomes of patients across the full spectrum of acute coronary syndromes⁴ (ACS). Using data from that study, we examined trends (1999-2007) in frequency rates, patient characteristics, hospital treatment practices, and short-term outcomes in comparatively young adults who had been hospitalized with an ACS. In light of global data of increasing prevalence of obesity and diabetes among young adults, we examined the trends in the proportion, treatment practices, and short-term outcomes of patients <55 years old presenting with an ACS.

4.2 Methods

The study population consisted of patients <55 years of age who were hospitalized with a final diagnosis of ACS and enrolled in GRACE between 1999 and 2007. GRACE is designed to reflect an unselected population of patients with ACS, irrespective of

geographic region. A total of 113 hospitals located in 14 countries in North and South America, Europe, Australia and New Zealand have contributed data to this study. Full details of the GRACE methods have been published elsewhere.^{5,6}

Adult patients (>18 years old) admitted with a presumptive diagnosis of ACS at participating hospitals were potentially eligible for this study. Eligibility criteria were a clinical history of ACS accompanied by at least one of the following: electrocardiographic changes consistent with ACS, serial increases in biochemical markers of cardiac necrosis (creatinine kinase-MB, creatine phosphokinase or troponin) and documented coronary artery disease. Patients with non-cardiovascular causes for the ACS clinical presentation, such as trauma or surgery, were excluded. The patients were followed-up at approximately 6 months by telephone, clinic visits or through calls to their primary care physician to ascertain the occurrence of several long-term outcomes. Where required, study investigators received approval from their local hospital ethics or institutional review board for the conduct of this study. Data were collected by trained study coordinators using standardized case report forms. Demographic characteristics, medical history, presenting symptoms, duration of pre-hospital delay, biochemical and electrocardiographic findings, treatment practices and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables, clinical diagnoses and hospital complications and outcomes were used. All the cases were assigned to one of the following categories: ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina. Data from the patients enrolled between April 1999 and December 2007 were used in this analysis.

The GRACE study period extending between 1999 and 2007 (a total period of 9 years) will be divided into three equal time periods, 1999 to 2001, 2002 to 2004, and 2005 to 2007. The three time periods will be used to examine near decade time trends, and as a mean to simplify the presentation of the results.

Chi-square tests for categorical variables and ANOVA for continuous variables were used to examine potentially changing trends in various demographic and clinical factors. The short-term outcomes in each period were examined by calculating in-hospital and 30-day case-fatality rates (CFRs) and trends in these endpoints were examined through the use of chi-square tests for trends. Logistic regression modeling was used to assess the significance of a near decade trends in short-term death rates while controlling for several potentially confounding demographic, medical history, and clinical characteristics of prognostic importance. Since length-of-stay declined over the study period, we included duration of hospital stay in our regression models.

4.3 Results

The demographic, clinical, and treatment characteristics of the study sample were shown in (Table 4.1). Approximately, one fourth of all patients enrolled in the study with a confirmed diagnosis of ACS between 1999 and 2007 was under 55 years of age. The proportion of patients <55 years presenting with ACS did not significantly change over the years under study (Figure 4.1).

For ease of analysis and interpretation, we aggregated the individual study years into three groups [1999, 2000 & 2001 (earliest), 2002, 2003 & 2004 (middle), and 2005, 2006 & 2007 (most recent)] for purposes of examining changing trends in the characteristics of patients hospitalized with an ACS (Table 4.1). In examining changing trends in baseline characteristics, the proportion of patients presenting with angina pectoris during the most recent years under study decreased markedly in the most recent years (57.0% vs. 35.5%) (p for trend <0.05). Patients in the most recent years under study were significantly more likely to present with a history of hypertension (49.3% vs. 44.6%, p<0.05), and were less likely to have a history of myocardial infarction (22.3% vs. 24.6%, p<0.05), or heart failure (3.0% vs. 3.7%) compared to patients hospitalized during the earliest years under study (all p for trend <0.05). The length of hospital stay declined significantly over the years under study (7.3 days vs. 4.5 days, p<0.05) (Table 4.1).

There was a marked and steady increase in the use of effective medical therapies and revascularization procedures during the years under study (all p<0.01) (Table 4.2). The proportion of young patients hospitalized with an ACS and prescribed ACE inhibitors, B-blockers, statins, glycoprotein IIa/IIIb, or clopidogrel during hospitalization increased significantly during the years under study. Over time, the proportion of patients prescribed aspirin remained relatively constant while the proportion of patients prescribed calcium channel blockers decreased significantly. While use of cardiac catheterization and PCI for revascularization steadily increased over the years under study (78.5% vs.

61.3%) and (55.3% vs. 37.9%) respectively, the use of thrombolysis and CABG steadily decreased (13.3% vs. 23.5%) and (3.7% vs. 4.7%) respectively (p for all <0.01) (Table 4.2).

Approximately one in every five patients <55 years of age hospitalized with an ACS developed a major cardiovascular complication during hospitalization. The incidence rates of atrial fibrillation, heart failure, cardiogenic shock, cardiac arrest, stroke, and major bleeding declined significantly between 1999 and 2007 among young patients hospitalized with an ACS (p for trend <0.01) (Table 4.3).

Crude in-hospital and 30-day mortality among young patients admitted with an ACS declined significantly over the study period between 1999 and 2006 followed by rise in 2007 (Table 4.4).

To more systematically examine trends in short-term death rates, we carried out a series of multivariable-adjusted regression analyses while simultaneously controlling for several potentially confounding prognostic factors (Table 4.5). The results of this analysis were consistent with the results of our univariate analyses, showing marked declines in

hospital and 30-day post-admission death rates over the study period by approximately a third.

4.4 Discussion

In this large multinational study of patients < 55 years old who were hospitalized with an ACS between 1999 and 2007, the proportion of young adult patients remained constant over the near decade study period. These trends were observed concomitant with an increase in the frequency of previously diagnosed hypertension and a decrease in the frequencies of previously diagnosed angina pectoris, myocardial infarction, or heart failure over time, as well as in the presence of a persistently high rate of cigarette smoking. The complications and short-term death rates after ACS declined over the years under study, even after adjustment for factors known to affect these endpoints concomitant with the increasing use of evidence based therapies.

Magnitude of Acute Coronary Syndromes in Young Patients

The overall proportion of young adult patients hospitalized with an ACS observed in our study is consistent with the relatively limited data available from observational studies examining ACS in young adults.¹ Given the increasing prevalence of several cardiovascular risk factors among young adults around the world including obesity, hypercholesterolemia, and diabetes¹⁻³ we wanted to examine trends in the proportion of young adults <55 years old presenting with an ACS in our multinational

study over time. Although we observed high rates of current smoking, and an increase in the proportion of hospitalized patients with a history of hypertension during the years under study, we observed declines in rates of medical history of angina pectoris, myocardial infarction, and heart failure, all while the incidence proportion of ACS did not significantly change over the years under study.

In our study, we observed stable trends in the proportion of young adult patients presenting with ACS despite the increasing prevalence of cardiovascular risk factors. Increasing use of evidence based medications prior to admission that have been shown to reduce the likelihood of developing cardiovascular events in high-risk patients has been previously reported, including aspirin, ACE inhibitors/beta-blockers, and statin drugs.^{4,5} Despite the non-randomized nature of our study that precludes any assumption of causality, we can with caution extrapolate that the increased outpatient prescribing of these medications may have exerted a positive effect on the overall incidence of developing ACS among young adults and potentially counter-balanced an increased risk factor burden among this population⁶.

Baseline Characteristics of Young Patients with an ACS

Previous studies have demonstrated that young patients with an ACS tend to be predominantly male, smokers, and hyperlipidemic⁷⁻¹²; we confirmed a male predominance among young patients hospitalized with an ACS. Although the rates of smoking observed in our study are high relative to contemporary studies involving patients of all ages, they are consistent with smoking rates reported in other investigations

involving comparatively young patients with an ACS.^{13,14} Our findings emphasize the strong pathophysiologic association between smoking, increased risk for coronary thrombosis, and the development of ACS in patients < 55 years of age.¹⁵⁻¹⁷ Due to missing data on hyperlipidemia in our study; we did not examine prevalence or trends in this cardiovascular risk factor.

We observed a steady increase in the prevalence of hypertension in our study sample. This finding has been previously demonstrated in comparatively young patients with AMI from the Worcester heart attack study. Although the increasing proportion of patients diagnosed with hypertension may be related to enhanced surveillance, the increasing prevalence of hypertension may be related to the high and ever increasing population burden of obesity.¹⁸

Changing Trends in Hospital Therapies

Our findings confirm expected increases in the utilization of effective in-hospital treatments that have become the standard of care for patients hospitalized with an ACS during the recent decades.^{10, 11} Similar findings have been previously demonstrated by clinical studies examining patients with an ACS. Our findings also suggest a steady incorporation of guideline-supported primary and secondary prevention therapies into everyday clinical practice.^{19,20}

Changing Trends in Hospital Complications

Twenty percent of patients < 55 years of age and hospitalized with an ACS developed a major cardiovascular complication during their index hospitalization. Although rates of major cardiovascular complications associated with ACS reported in our cohort were lower than rates that have been previously noted in populations including older patients, they paralleled those reported in other contemporary community-based studies examining young adult patient.^{12, 13} Declining rates of cardiovascular complications after ACS, especially when viewed in the context of increased use of early coronary revascularization strategies and evidence based medication, suggest that the early institution of effective inpatient therapies over time, and/or previously reported increasing baseline use of beneficial cardiac medications, may have contributed to the declining trends and lower rates of in-hospital cardiovascular complications observed in our patient population.²⁷

Short-term Mortality

Relatively young patients presenting with an ACS to the GRACE hospitals had a favorable short-term prognosis. Our short-term death rates were consistent with those reported in prior population-based studies but slightly higher than the rates that have been observed in clinical studies involving patients < 50 years old with AMI.²⁸ This is likely due to differences in age as well as variations in the socio-demographic and clinical

characteristics of patients participating in community-based studies relative to persons included in randomized clinical trials.

Crude short-term mortality in our study sample declined steadily between 1999 and 2006. The increase in crude mortality rates seen in 2007 has been previously reported by previous publications from GRACE and has been linked to the dropping of a number of medical centers in the final year of the study. However, short term mortality rates adjusted for potentially confounding prognostic factors demonstrated that rates declined by approximately one third compared to the early years under study. Improved public health awareness and increasing use of efficacious therapies for ACS have likely contributed to the decline in mortality observed.²⁹⁻³¹ However, since the reported prevalence of hypertension, obesity, and diabetes has increased, and smoking rates remain high, an increasing burden of cardiovascular risk factors and comorbid disease among young patients hospitalized with an ACS may be responsible for the constant proportion of young adult patients presenting with an ACS over the years under study which calls into question whether or not changing demographics and clinical characteristics, such as increasing body mass, have contributed to the observed trends.

Study Strengths and Limitations

The strengths of the present study include its multinational nature, its relatively large sample, its high quality, and its near decade long perspective. Our study also has several limitations. The non-randomized nature of our design precluded adjustment for differences in treatment practices over time and prevented us from establishing causality associations. Since the study design approach was not population based, we could not calculate population incidence rates. Lastly, because data on body mass index, and serum cholesterol levels were not complete, we could not examine trends in these modifiable risk factors. Lastly, lack of data on ethnicity and socioeconomic factors prevented us from examining their associations to the development and prognosis of ACS among comparatively young adults.

4.5 Conclusions

As expected, comparatively young patients with an ACS were predominantly males and smokers. Encouraging trends in hospital complications and short-term mortality were observed concomitant with increasing use of evidence based therapies.

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interpretation of data, in the writing of this report, and in the decision to submit the paper for publication.

Table 4.1. Baseline Characteristics of Young Patients with Acute Coronary Syndrome Overall and According to Time Period of Hospitalization

Characteristic [†]	Time Period			
	Total Population (n=15,052)	1999-2001 (n=4,955)	2002-2004 (n=6,033)	2005-2007 (n=4,059)
Age (mean, yrs)	47.8 (5.7)	47.7 (5.8)	47.8 (5.7)	47.7 (5.8)
Age (years)				
<40	10.2 %	10.5 %	10.2 %	9.7 %
40-44	12.7 %	13.5 %	11.7 %	13.3 %
45-50	26.7 %	25.3%	27.7 %	27.1 %
50-54	50.4 %	50.6 %	50.4 %	49.9 %
Men	78.7%	77.9 %	79.1 %	79.0 %
Medical History				
Angina pectoris	44.5 %	57.0 %	40.4 %	35.5 %
Myocardial infarction	23.1%	24.6%	22.3%	22.3%
Diabetes mellitus	17.0 %	17.0 %	16.7 %	17.6 %
Hypertension	46.6 %	44.6 %	46.5 %	49.3 %
Stroke	2.8 %	2.8 %	2.7 %	3.0 %
Heart failure	3.3 %	3.7 %	3.2 %	3.0 %
Current smoker	76.0%	76.5%	76.3%	74.7 %
Prehospital delay (median, hrs)*	2.5	2.5	2.5	2.4
Length of stay (mean, days)	6.4 (6.6)	7.3 (7.2)	6.3 (6.4)	5.6 (6.1)
STEMI	57.3%	57.5%	56.9 %	57.5 %

[†] mean values (SD)

* For patients reporting to the hospital within 48 hours of symptom onset

Table 4.2 In-hospital Therapies of Young Patients with Acute Coronary Syndrome Overall and According to Time Period of Hospitalization

In-Hospital Therapies	Time Period			
	<u>Total Population</u> (n=15,052)	<u>1999-2001</u> (n=4,955)	<u>2002-2004</u> (n=6,033)	<u>2005-2007</u> (n=4,059)
ACE/ARBs	64.2%	55.2	66.8 %	71.5 %
Aspirin	95.7%	95.7 %	96.0 %	95.5 %
Beta Blockers	89.7%	87.9 %	90.4 %	90.8 %
Calcium channel blockers	16.6%	20.7%	15.9 %	12.7 %
Statins	73.4%	56.0%	79.5 %	85.6 %
Glycoprotein IIb/IIIa	33.1%	26.7%	37.1%	35.0%
Clopidogril	61.2%	23.8%	63.9%	77.0%
Thrombolytics	18.9%	23.5%	18.8 %	13.3 %
Cardiac Catheterization	71.2 %	61.3 %	74.3 %	78.5 %
PCI	48.1%	37.9	51.4 %	55.3 %
Coronary artery bypass Graft surgery	4.5 %	4.7 %	4.8 %	3.7 %

Table 4.3 Risk of Selected Clinical Complications in Patients Hospitalized With an Acute Coronary Syndrome

Clinical Complication	Time Period			
	<u>Total Population</u> (n=15,052)	<u>1999-2001</u> (n=4,955)	<u>2002-2004</u> (n=6,033)	<u>2005-2007</u> (n=4,059)
Atrial fibrillation	2.40%	2.56%	2.42%	2.15%
Heart failure	6.1%	7.4%	6.3%	4.4%
Cardiogenic shock	2.10%	2.49%	2.02%	1.75%
Cardiac Arrest	2.25%	2.17%	1.95%	2.78%
Stroke	0.26%	0.37%	0.25%	0.15%
Major bleeding	1.34%	1.72%	1.28%	0.97%

Table 4.4 Short-Term Death Rates in Patients Hospitalized With an Acute Coronary Syndrome

Study Year	In-Hospital Death Rates	30-Day Death Rates
1999	2.12%	2.37%
2000	1.63%	1.95 %
2001	1.92%	2.19%
2002	1.41%	1.75%
2003	1.41%	1.69 %
2004	1.52%	1.74 %
2005	1.13%	1.32%
2006	0.63%	0.84%
2007	1.25%	1.73%

Table 4.5 Odds of Dying in Younger Patients Hospitalized with an Acute Coronary Syndrome

Study Period	Crude Odds of In-Hospital Death	Multivariable Adjusted Odds of In-Hospital Death*	Crude Odds of 30-day Death	Multivariable Adjusted Odds of 30-day Death*
1999-2001 ^o	1.0	1.0	1.0	1.0
2002-2004	0.89 (0.82-0.97)	0.83 (0.76-0.91)	0.93 (0.86-1.0)	0.83 (0.76-0.90)
2005-2007	0.74 (0.67-0.81)	0.66 (0.60-0.74)	0.74 (0.68-0.81)	0.62 (0.57-0.69)

*Adjusted for age, sex, length of stay, and history of angina, myocardial infarction, diabetes mellitus, hypertension, stroke, heart failure, or renal failure

^oreferent period

CHAPTER V

Conclusions

5.1 Summary of Findings

The main objective of this dissertation was to use the access to two well known international registries of ACS to answer three clinically important questions examining regional differences in disease management and outcomes, changing trends in ACS burden and complications, as well as identifying patients at higher risk of developing adverse clinical outcomes.

In comparing regional differences in patient characteristics, disease management, and outcomes between the patients in the Arabian Gulf Area (Gulf RACE) to a large multinational unbiased sample (GRACE), we found that the average age of patients in Gulf RACE was strikingly a decade younger than GRACE. Patients in Gulf RACE were more likely to be male, with very high prevalence of smoking and diabetes, which might explain the early development of ACS. Patients in Gulf RACE were less likely to be treated with evidence based therapies compared to GRACE patients. Despite differences in patient characteristics and treatment practices, short-term mortality rates were comparable between ACS patients enrolled in these two registries, while higher rates short-term complications were observed among Gulf RACE patients.

In examining cardiogenic shock as a serious clinical complication and the main cause of death in patients with an ACS, we found that 5% of patients in GRACE developed the serious hemodynamic complication. Patients developing CS were more likely to be older, female, have a history of diabetes, and heart failure, and present with ST-segment elevation. Patients with CS were less likely to receive revascularization and effective cardiac therapies. Despite declines over the study period in hospital mortality for patients with CS, case fatality rates remain really high at 59.4% compared to 2.3% in patients without CS. Although the magnitude of CS appears to be slowly declining, it still develops at a relatively high rate after ACS.

In examining nearly decade changing trends in frequency rates, patient characteristics, hospital treatment practices, and short-term outcomes of comparatively young adults who had been hospitalized with an ACS in GRACE, we found that the overall proportion of young adult patients was 23% and the proportion remained relatively constant over the study period. Baseline demographic and clinical characteristics of our study sample did not change significantly during the years under study, whereas, the length of hospital stay declined by more than a day on average over time. The overall in-hospital and 30-day multivariable adjusted In-hospital and 30-day death rates significantly declined during the years under study. The use of evidence based therapies proven to improve outcomes of patients with an ACS significantly increased over the study years. Improving trends in short-term outcomes of comparatively young patients with an ACS during the near decade under study likely reflected enhanced primary and secondary prevention and treatment efforts.

Generally, we observed marked regional differences in ACS risk profiles, clinical management, and outcomes of patients with an ACS between the developing world represented by Arabian Gulf region, and multinational sample represented by GRACE. This finding is consistent with a large body of literature highlighting the continued need for international monitoring of ACS as a major cause of morbidity and mortality worldwide. We observed encouraging trends in the use of evidence based therapies which have likely contributed to the improving trends in the prognosis of ACS evidences by declines in mortality rates and rates of clinical complications associated with ACS. There remains a large room for improving primary and secondary prevention efforts.

5.2 Strengths and Limitations

A particular strength of the dissertation was the use of data from two large multinational registries of ACS, which provided contemporary data on patients hospitalized with an ACS. The two registries used similar approaches to collect data on management practices and patient outcomes using similar standardized definition. Both studies used the American college of cardiology definitions of key variables, which represented a particular strength to our study when comparing the two patient populations. On the other hand, as with all observational studies, the GRACE and Gulf RACE project are subject to certain inherent limitations and potential biases.

The GRACE study is the largest multinational registry to include the complete spectrum of patients hospitalized with an ACS. The Gulf RACE study represents the first

survey attempt in that region – otherwise under-represented in multinational studies of ACS- to include all patients hospitalized with an ACS in recent years. In both studies, standardized criteria were employed for defining ACS and hospital outcomes and rigorous quality control and audit measures were employed. "Real-life" observational studies provide data on a heterogeneous population of patients that includes groups who are often under-represented in randomized trials. On the other hand, as observational studies, they are subject to certain inherent limitations and potential biases that must be kept in mind in interpreting the study results. Treatments were given according to individual physicians' decisions and not through the use of standardized treatment protocols. While currently recommended criteria were utilized to characterize patients who were eligible for the receipt of the cardiac medications examined, due to our reliance on data obtained from medical records, questions might be raised about our ability to characterize patient's eligibility status. Furthermore, we did not have information available on several patient associated characteristics (e.g., socioeconomic status, patient preferences) which may have confounded some of the observed associations.

5.3 Implications and Future Research Directions

Our results reinforce the need for the continued monitoring of ACS epidemiology with better representation of the developing world, being the major contributor to the projected future increase in ACS burden globally. Moreover, our results highlight the need for studies and programs with then primary focus of understanding causes leading to early development as well as triggers of ACS. Future studies should focus on the

development of dependable risk stratification systems for the early identification of patients at higher risk of developing adverse outcomes since the prompt receipt of proper therapies has been associated with better prognosis, and decreased rates of complications and mortality.

In addressing some of limitations mentioned earlier in our study, future registries should collect more data on adherence to medication to enable more accurate analyses of associations between medications and patients outcomes. A population-based approach should be adopted whenever possible in designing new studies to fill out the gaps in our knowledge about population incidence rates and outcomes rates.

Additionally, long-term follow up periods are required to detect benefits as well as adverse effects of therapies that develop over long periods of time and to assess long-term outcomes. Future Studies should deploy systems for assessment of quality of life and patient satisfaction. Furthermore, and as our results showed relatively stable time trends when examining incidence rates of ACS development, better understanding is needed of the reasons behind these trends and the main coronary risk factors playing a role in the observed trends. More attention should be focused on monitoring modifiable risk factors to be able to design programs and intervention aiming at decreasing the burden on ACS around the world.

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