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Incidence, prognosis, and factors associated with cardiac arrest in patients hospitalized with acute coronary syndromes (the GRACE Registry): A master's thesis

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Incidence, prognosis, and factors associated with cardiac arrest in patients hospitalized with acute coronary syndromes (the GRACE Registry)

By

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A Masters Thesis Presented

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Dedication

I would like to dedicate this thesis work to my wife Diana and my two daughters, Elyse and Vivian. Without their love and support, this work would not have been possible.

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I would like to acknowledge and thank the members of my Thesis Advisory Committee (Dr. Ira Ockene, Dr. Jeroan Allison, Dr. Joel Gore, Dr. Robert Goldberg) for the substantive editorial comments and guidance they provided. I would also like to acknowledge the analytic support provided to me by Ms. Wei Huang. I would also like to express my gratitude to Dr. Fred Anderson and the physicians and nurses participating in the GRACE study. GRACE was supported by an unrestricted educational grant from Sanofi Aventis to the Center for Outcomes Research, University of Massachusetts Medical School. Sanofi Aventis had no involvement in the collection, analysis, and interpretation of data; in the writing of this work.

Abstract

Objectives: Contemporary data are lacking with respect to the incidence rates of, factors associated with, and impact of cardiac arrest from ventricular fibrillation or tachycardia (VF-CA) on hospital survival in patients admitted with an acute coronary syndrome (ACS). The objectives of this multinational study were to characterize trends in the magnitude of in-hospital VF-CA complicating an ACS and describe its impact over time on hospital prognosis.

Methods: The study population consisted of 59,161 patients enrolled in the Global Registry of Acute Coronary Events Study between 2000 and 2007. Overall, 3,618 patients (6.2%) developed VF-CA during their hospitalization for an ACS. Incidence rates of VF-CA declined over time, albeit in an inconsistent manner. Patients who experienced VF-CA were on average older and had a greater burden of cardiovascular disease, yet were less likely to receive evidence-based cardiac therapies than patients in whom VF-CA did not occur. Hospital death rates were 55.3% and 1.5% in patients with and without VF-CA, respectively. There was a greater than 50% decline in the hospital death rates associated with VF-CA during the years under study. Patients with a VF-CA occurring after 48 hours were at especially high risk for dying during hospitalization (82.8%).

Conclusions: Despite reductions in the magnitude of, and short-term mortality from, VF-CA between 2000 and 2007, VF-CA continues to exert a significant adverse effect on survival among patients hospitalized with an ACS. Opportunities exist to improve the identification and treatment of ACS patients at risk for VF-CA to reduce the incidence of, and mortality from, this serious arrhythmic disturbance.

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CA = Cardiac Arrest; VF = Ventricular Fibrillation; VF-CA = Cardiac Arrest Due to Ventricular Fibrillation; ACS = Acute Coronary Syndrome; STEMI = ST-segment elevation myocardial infarction; NSTEMI = Non-ST-segment myocardial infarction

PREFACE

Data from the GRACE (Global Registry of Acute Coronary Events) Study, a large multinational sample of patients hospitalized with an ACS between 2000 and 2007, was used to perform the analyses outlined herein.

Dr. McManus wrote and designed the analyses outlined in this thesis. Wei Huang MS provided assistance with respect to performance of analyses and GRACE data management. Farhan Aslam MD, Parag Goyal MD, Joel Gore, MD, and Robert J. Goldberg PhD provided editorial assistance.

CHAPTER I

INTRODUCTION

Cardiac arrest (VF-CA) is the leading cause of death in patients with coronary artery disease, and 450,000 deaths have been attributed to this arrhythmic disturbance annually in the U.S [1]. Despite marked improvements in the monitoring and treatment of patients hospitalized with an acute coronary syndrome (ACS), this patient population remains at especially high risk for the development of serious ventricular arrhythmias and VF-CA [2-5].

Although the characteristics and treatment of patients hospitalized with an ACS have changed markedly during recent decades [2], contemporary data describing recent trends in the magnitude and impact of VF-CA in the setting of an ACS are lacking. Specifically, the increasing use of evidence-based medications and coronary revascularization procedures may have decreased the incidence of, and prognosis from, VF-CA in patients hospitalized with an ACS.[2]

Prior studies suggest that timing of VF-CA may also have prognostic importance. As such, data are needed with respect to factors associated with the development of VF-CA and impact of the timing of VF-CA on hospital survival [3]. Data from the GRACE (Global Registry of Acute Coronary Events) Study were utilized to describe these and additional endpoints in a large multinational sample of patients hospitalized with an ACS between 2000 and 2007 [4,5].

CHAPTER II

STUDY METHODS

Details of the GRACE project and its data collection methods have been previously described [4,6,7]. In brief, this large multinational observational study was designed to reflect a representative patient population 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 contributed data to this study.

Adult patients (>18 years old) admitted with a presumptive diagnosis of ACS at participating hospitals were potentially eligible for study inclusion. Eligibility criteria included a clinical history of ACS accompanied by at least 1 of the following: electrocardiographic changes consistent with ACS, serial increases in biochemical markers of cardiac necrosis (CK-MB, creatine phosphokinase, or troponin), and documented coronary artery disease. Patients with non-cardiovascular causes for their clinical presentation were excluded. Where required, study investigators received approval from their local hospital ethics or institutional review boards for the conduct of this study.

Patients were identified through the use of active and passive disease surveillance at participating study sites. Patient medical records were reviewed for pertinent information in a retrospective manner by trained study coordinators using standardized case report forms. Demographic characteristics, medical

history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices, and hospital outcome data were collected. Standardized definitions of all patient-related variables, clinical diagnoses, and hospital complications and outcomes were used. A GRACE risk score was calculated based on an 8-variable model previously developed and validated [6,10,11].

All ACS cases were assigned to 1 of the following categories using standardized definitions: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA) [8,9]. The STEMI category included patients with at least 1 positive cardiac biochemical marker of necrosis (including troponin measurements) and new or presumed new ST-segment elevation ≥1 mm seen in any location, or new left bundle branch block on the index or subsequent ECG. Patients were considered to have a NSTEMI if they had at least 1 positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent ECG. Unstable angina was considered to be present when serum biochemical markers indicative of myocardial necrosis were within the normal range. Complete definitions of these variables and other factors can be found on the GRACE web site at www.outcomes.org/grace.

Cardiac arrest from ventricular fibrillation or tachycardia was defined as any episode of ventricular tachycardia or fibrillation requiring resuscitation (external cardiac massage or direct current cardioversion or both). Early VF-CA was defined as that occurring on presentation or within the first 48 hours of

hospitalization, whereas late VF-CA occurred after this time; these cutpoints have been previously utilized in the published literature [3]. Patients with more than 1 episode of VF-CA were categorized on the basis of their initial episode.

Data Analysis

Differences in the characteristics and hospital outcomes of patients who developed VF-CA compared to those who did not were compared using chi square tests or Fisher's exact test of statistical significance for discrete variables. Continuous variables were analyzed using t tests and the Wilcoxon rank-sum test. Differences in the characteristics and hospital outcomes of patients who developed early VF-CA compared to those who developed this arrhythmia after 48 hours of hospitalization were compared in a similar fashion.

Variables considered for inclusion in our regression models were baseline demographic characteristics (age, sex), medical history (angina, myocardial infarction, heart failure, percutaneous coronary intervention, coronary artery bypass graft surgery, diabetes, hypertension, and hyperlipidemia)**,** and hospital presentation characteristics (blood pressure, pulse, Killip class, ST-segment deviation, initial cardiac markers, initial serum creatinine). Our hospital endpoints included adverse cardiac events, including recurrent ischemic/anginal symptoms, heart failure, non-cardiac adverse events (renal failure, stroke, major bleeding), and survival status at the time of hospital discharge.

CHAPTER III

STUDY FINDINGS

A total of 59,261 patients were enrolled in this coronary disease registry between 2000 and 2007 and constituted the sample of the present report. The mean age of study participants was 65.7 years, 67.3% were men, 29.9% had a history of prior myocardial infarction, and 36.7% presented with a STEMI.

Incidence Rates of Cardiac Arrest

Between 2000 and 2007, a total of 3,618 patients (6.2%) developed VF-CA during their index hospitalization for an ACS. The incidence rates of VF-CA varied significantly by ACS type, with 10.5% of patients with STEMI, 4.3% of patients with NSTEMI, and 2.9% of patients with UA developing this arrhythmic complication ($p < 0.001$). The incidence rates of VF-CA declined during the years under study, albeit in an inconsistent manner (**Figure 3.1**). The greatest decline in VF-CA occurred between 2000 (6.8%) and 2002 (5.7%).

Baseline Characteristics of Study Sample

Patients who developed VF-CA were on average older and were more likely to have higher average GRACE risk and Killip class scores, a higher maximum troponin level, a lower ejection fraction, a longer hospital stay, a history of heart failure, and present with a STEMI at the time of hospital admission in

comparison to patients who did not develop VF-CA during their acute hospitalization (**Table 3.1**).

On the other hand, ACS patients who did not develop VF-CA had a higher body mass index, higher blood pressure, and lower initial heart rate on presentation, and were more likely to have a history of smoking, hypertension, dyslipidemia, or prior coronary artery disease than ACS patients who experienced a VF-CA. Patients in whom VF-CA did not occur were also more likely to have previously undergone a percutaneous coronary intervention and coronary artery bypass graft surgery. The proportion of patients with implantable cardioverter-defibrillators did not differ between the respective comparison groups.

Outpatient and Hospital Treatment Practices

Patients who experienced a VF-CA were significantly less likely than those who did not experience a VF-CA to report outpatient use of aspirin, beta-blockers, statins, and angiotensin converting enzyme (ACE) inhibitors (**Table 3.2).** Patients who developed VF-CA during hospitalization were slightly more likely to be prescribed amiodarone as an outpatient than were patients who did not develop this ventricular arrhythmia.

Patients with VF-CA were also less likely than patients without this arrhythmic complication to have received evidence-based cardiac treatments during their hospitalization, including aspirin, beta-blockers, statins, and ACE

inhibitors (**Table 3.2**). Utilization of percutaneous coronary intervention did not differ between our 2 primary comparison groups whereas the in-hospital prescription of thrombolytics, amiodarone, and inotropes was more common among patients with VF-CA. Patients with VF-CA were more likely to have undergone coronary artery bypass surgery and intra-aortic balloon pump placement during their hospital stay as compared to those who did not develop VF-CA.

Hospital Complications

Patients who experienced a VF-CA were more likely than patients who did not develop this arrhythmic complication to have developed recurrent cardiac ischemia, cardiogenic shock, atrial fibrillation/flutter, heart failure, renal failure, stroke, and major bleeding during their hospitalization (**Table 3**). A multiple logistic regression analysis was carried out to examine the association of VF-CA with each of these in-hospital complications while controlling for a variety of factors known to affect the development of these endpoints in patients hospitalized with an ACS. The odds of developing recurrent cardiac ischemia, cardiogenic shock, heart failure, stroke, renal failure, and major bleeding remained substantially higher among patients with VF-CA after adjustment for several potentially confounding factors (**Table 3.3**).

In-Hospital Mortality

As expected, the in-hospital case-fatality rate (55.3%) and multivariable adjusted odds of dying during hospitalization for an ACS were markedly higher among patients with an ACS complicated by VF-CA than it was among patients who did not develop VF-CA (Odds Ratio 75.5, 95% Confidence Interval 66.2-86.0). Death rates among patients with in-hospital VF-CA were significantly higher than would have been expected (8.4%) on the basis of their GRACE Risk score (175), whereas in-hospital death rates among participants without VF-CA (1.5%) were similar to those predicted on the basis of their GRACE Risk Score (1.9%, 130). Mortality rates from VF-CA showed an inverse relation with ACS severity, as 66.4% of patients with UA, 59.8% of patients with NSTEMI, and 51.1% of patients with STEMI died during their hospitalization. During the period that in-hospital mortality decreased only slightly among patients without VF-CA, in-hospital mortality declined markedly among patients with VF-CA (from 70.8% in 2000 to 41.1% in 2007, p <0.001, **Figure 3.2**) [10]."

Impact of Timing of Cardiac Arrest on Hospital Prognosis

To explore the impact of timing of VF-CA on short-term prognosis, a separate analysis was carried out using data from 2,167 patients for whom timing of VF-CA was recorded (60% of patients with VF-CA, **Table 3.4**). Patients with late VF-CA (n=527) were on average older and more likely to have a history of cardiovascular disease and its risk factors than patients who suffered a VF-CA early during their hospitalization (n=1,640). Patients with NSTEMI were more

likely than those with STEMI to experience a VF-CA at a later time during their hospitalization (33.3% vs. 20.9% of VF-CA, p <0.001). On the other hand, patients with late VF-CA were less likely to currently smoke cigarettes and had a slightly lower average GRACE Risk Score as well as body mass index.

Patients with late VF-CA experienced, on average, a longer hospital stay and were more likely to have developed clinically significant in-hospital complications including recurrent angina, myocardial infarction, heart failure, cardiogenic shock, atrial fibrillation, renal failure, and major bleeding episodes than patients who developed VF-CA early during their acute hospital admission (**Table 3.5).** A significantly greater proportion of patients with late VF-CA died during hospitalization compared with patients who experienced VF-CA during the first 48 hours of hospitalization (83% vs. 39%, p <0.001).

Figure 3.1. Trends in the Incidence Rates of Cardiac Arrest (GRACE)

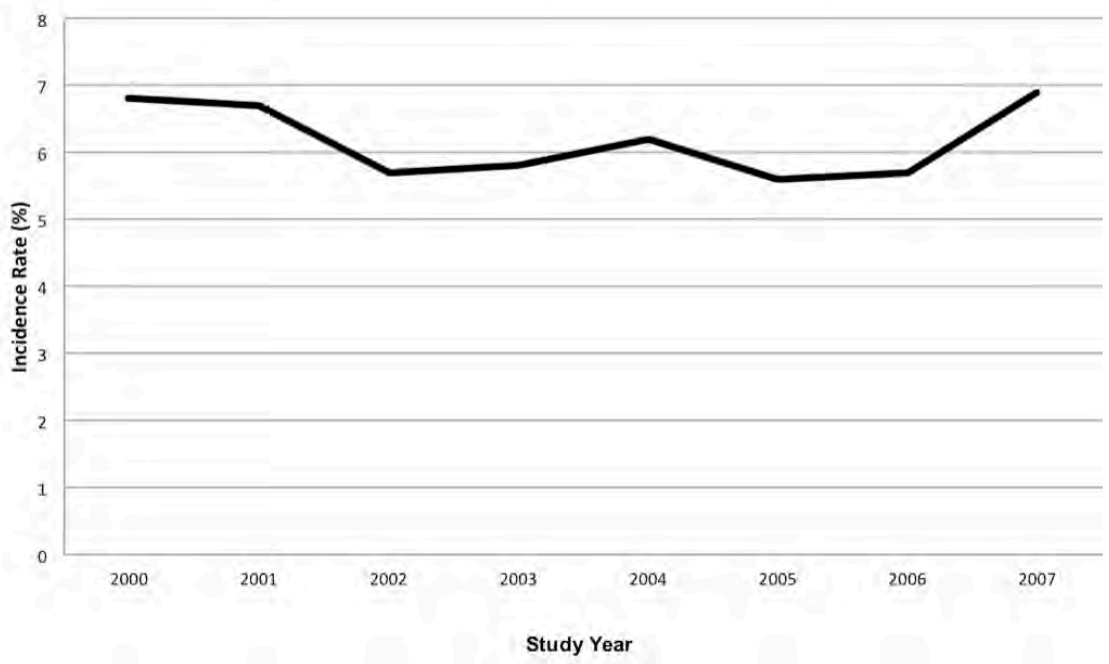

Figure 3.1 Legend. Incidence rates of VF-CA between 2000 and 2007 in the GRACE study.

Table 3.1. Baseline Characteristics of GRACE Participants with and without Cardiac Arrest

Variable*	Cardiac Arrest Present(+) (n=3,618)	Cardiac Arrest Absent (-) (n=55,149)	p-value
Age (years)	68.8 (13.6)	65.5 (13.2)	<0.001
Male	2340 (65%)	37067 (68%)	0.002
Body Mass index (kg/m^2)	26.9 (5.3)	27.7 (5.4)	<0.001
Systolic BP (mmHg)	124.7 (37.0)	142.4 (29.0)	<0.001
Diastolic BP (mmHg)	73.2 (23.0)	80.4 (17.6)	<0.001
Pulse (bpm)	84.5 (27.4)	79.1 (20.8)	<0.001
GRACE Risk Score	175.2 (44.8)	129.5 (35.6)	<0.001
Killip class III and IV	696 (20%)	2073 (3.8%)	<0.001
Length of stay (days)	8.2 (10.2)	7.2 (7.3)	<0.001
Medical History			
Smoking	1917 (54%)	31695 (58%)	<0.001
Diabetes	942 (26%)	13785 (25%)	0.11
Hypertension	2113 (59%)	34241 (62%)	<0.001
Dyslipidemia	1338 (38%)	27039 (49%)	<0.001
Angina	1550 (44%)	28161 (53%)	<0.001
AF	4110 (7.5%)	3562 (9.3%)	<0.001
MI	941 (26%)	16551 (30%)	<0.001
PCI	368 (10%)	10091 (18%)	<0.001
CABG	325 (9.1%)	6893 (13%)	<0.001
Heart Failure	508 (14%)	5348 (9.8%)	<0.001
ICD	15 (0.7%)	257 (0.8%)	0.78
AMI Type			
ST elevation MI	2256 (62%)	19317 (35%)	<0.001
Non ST elevation MI	849 (23%)	18880 (34%)	<0001
Unstable angina	513 (14%)	16952 (31%)	
Laboratory			
Creatinine (mg/dL)	1.4 (1.1)	1.2 (0.8)	<0.001
Total cholesterol (mg/dL)	184.4 (54.6)	190.7 (49.4)	<0.001
Troponin**	45.6 (99.3)	21.6 (63.6)	<0.001
Baseline EF (%)***	41.2 (15.7)	50.8 (14.3)	<0.001
LBBB	251 (6.9%)	2576 (4.5%)	<0.001

Table 3.1 Legend

* Mean (± SD), laboratory values obtained from admission

** Maximum value within first 24 hours. Upper limit of normal troponin did not vary between groups (median 0.1, interquartile range 0.1-0.4).

*** Ejection fraction was measured in 43% of patients with VF-CA and 48% of patients without VF-CA

BP = blood pressure; AF = atrial fibrillation; MI = myocardial infarction; PCI = Percutaneous coronary intervention; CABG = coronary artery bypass graft; ICD = implantable cardioverter defibrillator; CAD = coronary artery disease; EF = ejection fraction; LBBB = left bundle branch block

Table 3.2 Outpatient and In-Hospital Treatments in GRACE Participants

Stratified by Development of In-Hospital Cardiac Arrest

Treatment*	Cardiac Arrest Present (+) (n=3,618)	Cardiac Arrest Absent (-) (n=55,149)	p-value
Chronic			
Aspirin	1044 (29%)	22354 (40.6)	<0.001
Beta-blocker	877 (24.4%)	18369 (33.5%)	<0.001
ACE inhibitor	890(24.9%)	15573 (28.4%)	<0.001
Statin	657 (17.5%)	15685 (28.6%)	<0.001
Omega-3 FA	9 (0.4%)	217 (0.6%)	0.21
Amiodarone	85 (2.4%)	997 (1.8%)	0.02
In-hospital			
Aspirin	3049 (85%)	51806 (94%)	<0.001
Beta-blocker	2370 (66%)	47032 (86%)	<0.001
ACE inhibitor	2080 (58%)	36452 (67%)	<0.001
Statin	1794 (50%)	38841 (71%)	<0.001
Amiodarone**	681 (19.1%)	2027 (3.7%)	<0.001
Inotrope**	1247 (34.9%)	1600 (3.0%)	<0.001
Procedures			
PCI	1395 (38.8%)	21559 (39.4%)	0.51
Thrombolytics	796 (22.2%)	6822 (12.5%)	<0.001
CABG	225 (6.3%)	2766 (5.1%)	0.002
IABP	505 (14.3%)	1064 (2.0%)	<0.001

Table 3.2 Legend

* Mean (± SD)

** Within the first 24 hours of hospitalization

ACE= Angiotensin converting enzyme; FA = Fatty acid; PCI = Percutaneous intervention; CABG = coronary artery bypass surgery; IABP = intra-aortic balloon pump

Table 3.3 Hospital Complications According to the Presence of Cardiac Arrest

Complication*	Cardiac Arrest Present (+) (n=3,618)	Cardiac Arrest Absent (-) (n=55,149)	Adjusted** Odds of Complication
Recurrent Ischemic Symptoms (Angina)	1090 (31%)	12412 (23%)	1.7 (1.5-1.8)
Heart Failure	1431 (40%)	6326 (12%)	2.9 (2.7-3.2)
Cardiogenic Shock	1373 (38%)	969 (1.8%)	16.8 (15-18.8)
Atrial Fibrillation/Flutter	662 (19%)	3826 (7.0%)	2.0 (1.8-2.3)
Renal Failure	641 (18%)	1642 (3.0%)	4.6 (4.0-5.2)
Stroke	97 (2.7%)	327 (0.6%)	2.9 (2.2-3.9)
Major Bleeding	232 (6.6%)	1122 (2.1%)	2.3 (1.9-2.7)

Table 3.3 Legend

* Unless otherwise indicated, new-onset complications

****** Adjusted for 8 independent variables used to calculate GRACE risk score, history of angina, myocardial infarction, heart failure, percutaneous coronary intervention, CABG, diabetes, hypertension, and hyperlipidemia.

Table 3.4 Characteristics of GRACE Participants* Experiencing a Cardiac Arrest within as Compared to after 48 hours of Hospitalization

Variable**	Early Cardiac Arrest (n=1640)	Late Cardiac Arrest (n=527)	p-value
Age (years)	66.7 (13.9)	74.1 (11.3)	<0.001
Male	1114 (68%)	340 (65%)	0.18
Body Mass index (kg/m2)	27.1 (5.0)	26.5 (4.9)	0.03
Systolic BP (mmHg)	122.7 (36.7)	129.6 (31.0)	<0.001
Diastolic BP (mmHg)	72.9 (22.6)	74.3 (20.6)	0.87
GRACE Risk Score	177 (46.8)	171 (37.8)	0.04
Killip class III and IV HF	322 (20%)	90 (17%)	<0.001
Length of stay (days)	6.7 (8.8)	12.4 (12.2)	<0.001
Medical History			
Smoking	894 (55%)	250 (48%)	0.004
Diabetes	380 (23%)	178 (34%)	<0.001
Hypertension	941 (58%)	359 (69%)	<0.001
Dyslipidemia	624 (38%)	235 (45%)	0.008
Angina	555 (34%)	254 (48%)	<0.001
AF			
MI	359 (22%)	179 (34%)	<0.001
PCI	188 (12%)	63 (12%)	0.79
CABG	130 (8.0%)	76 (15%)	<0.001
Heart Failure	150 (9.3%)	122 (23%)	<0.001
ICD	9 (0.6%)	6 (1.2%)	0.22
AMI Type			
ST elevation MI	1069 (65%)	283 (54%)	<0.001
Non ST elevation MI	353 (22%)	176 (33%)	
Unstable angina	218 (13%)	68 (13%)	
Laboratory			
Creatinine (mg/dL)	1.4 (1.0)	1.5 (1.1)	<0.001
Total cholesterol (mg/dL)	180.0 (51.7)	175.7 (57.0)	0.11
Troponin***	45.4 (95.9)	46.2 (109.4)	0.07
Baseline EF (%)	42.6 (15.9)	38.7 (15.0)	<0.001
LBBB	89 (5.4%)	45 (8.5%)	0.01

Table 3.4 Legend. * Information on timing of cardiac arrest available on 2,167 GRACE participants (60% of participants with VF-CA)

** Mean (± SD), laboratory values obtained from admission

*** Maximum value within first 24 hours. Upper limit of normal troponin did not vary between groups (median 0.1, interquartile range 0.1-0.4).

BP = blood pressure; AF = atrial fibrillation; MI = myocardial infarction; PCI = Percutaneous coronary intervention; CABG = coronary artery bypass graft; ICD = implantable cardioverter defibrillator; CAD = coronary artery disease; EF = ejection fraction

Table 3.5 In-Hospital Complications Among Grace Participants Stratified by Early (within 48 hours) vs. Late (after 48 hours) Cardiac Arrest

Variable	Early Cardiac Arrest (n=1640)	Late Cardiac Arrest (n=527)	p-value
Recurrent Ischemic Symptoms (Angina)	449 (28%)	286 (55%)	<0.001
Heart Failure	463 (29%)	298 (57%)	<0.001
Cardiogenic Shock	493 (30%)	258 (50%)	<0.001
Atrial Fibrillation/Flutter	232 (14%)	145 (28%)	<0.001
Renal Failure	173 (11%)	185 (36%)	<0.001
Stroke	37 (2.3%)	18 (3.5%)	0.13
Major Bleeding	61 (4.0%)	55 (9.5%)	<0.001
Death	644 (39%)	434 (83%)	<0.001

CHAPTER IV

DISCUSSION

The results of this large, multinational study demonstrate that VF-CA is an infrequent, but often fatal, complication of an ACS. The incidence of, and mortality from, VF-CA declined over the period under study, likely due to increased monitoring and better treatment of patients with an ACS as well as VF-CA. Opportunities exist, however, for the enhanced prevention of VF-CA and its complications.

Incidence of Cardiac Arrest

Over a relatively recent study period, VF-CA developed in approximately 1 in every 14 patients hospitalized with an ACS in our multinational coronary disease registry. The incidence rates of VF-CA observed in our study were significantly lower than those reported in a community-based study of individuals hospitalized with AMI between 1975 and 1984, in which 21% of patients developed VF-CA [11]. Reasons for the differences between our study and this prior study may include the more contemporary nature of the present investigation, higher utilization of chronic and in-hospital therapies known to reduce the odds of VF-CA, a greater proportion of patients with early VF-CA, and inclusion of patients with less severe forms of ACS in our study. These hypotheses were supported by our observation that patients with MI were more

likely than those with UA to develop VF-CA in our study. In addition, a recent analysis examining the incidence rates of VF in a population-based study of central Massachusetts residents hospitalized with AMI reported declining rates of VF between 1995 and 2005, reaching levels (4.2%) more consistent with our findings (6.2%) and those of the National Registry of Myocardial Infarction-2 (4.8%) [11-14].

Consistent with the published literature, clinical characteristics associated with poorer baseline cardiovascular health, larger infarct size, and worse disease-specific clinical status were associated with the development of VF-CA in the present investigation [13]. Interestingly, however, a history of several traditional cardiovascular risk factors, including hypertension, smoking, diabetes, and dyslipidemia, was not associated with an increased risk for VF-CA. These findings suggest that ACS severity places patients at higher risk for developing VF-CA, irrespective of the presence of established cardiovascular risk factors.

Outpatient and Hospital Treatment Practices

Outpatient and in-hospital use of effective cardiac medications known to reduce the risk of ventricular arrhythmias and improve prognosis from ACS, including aspirin, statins, ACE inhibitors, and beta-blockers, were less frequently utilized in ACS patients with VF-CA in comparison to patients who did not develop VF-CA. Use of thrombolytic medications was higher in the VF-CA group, perhaps due to the fact that patients with VF-CA were more likely to present with

a STEMI or because these agents were administered as part of advanced cardiac life support efforts [15]. Chronic use of amiodarone was paradoxically higher among patients who experienced VF-CA compared to patients who did not experience VF-CA. Use of amiodarone to suppress non-sustained ventricular arrhythmias, or use of amiodarone to maintain sinus rhythm among patients with atrial fibrillation, a disease associated with a poor prognosis after an ACS, may partially explain this observation [16].

Caution in interpreting our findings is warranted, however, since the under-utilization of evidence-based therapies among hospitalized patients with VF-CA may have been partially due to the fact that patients with VF-CA were hemodynamically unstable or had experienced complications that serve as contraindications to ACS treatments. In-hospital contraindications, however, do not explain outpatient prescription patterns nor do they discount the fact that an opportunity exists for enhanced primary prevention of VF-CA through application of evidence-based ACS treatments, such as beta-blockers, among patients hospitalized with an ACS based on the results of our large descriptive study.

Hospital Complications

Patients who experienced a VF-CA during hospitalization for an ACS were at increased risk not only for developing recurrent cardiac ischemia, cardiogenic shock, and heart failure during their index hospitalization, but also renal failure and major bleeding episodes. Both major bleeding and renal dysfunction

complicating AMI have been associated with increased mortality, perhaps through the observed association with malignant ventricular arrhythmias and VF-CA [17,18]. These findings, as well as those from other studies, suggest that close attention should be directed to monitoring for, and appropriately treating, kidney injury, electrolyte abnormalities, and anemia in additional to traditional hemodynamic perturbations (e.g., tachycardia and hypotension) in hospitalized patients with an ACS.

The incidence rates of VF-CA declined in our hospitalized patient population between 2000 and 2007, concomitant with the greater and timelier application of effective ACS treatments in this population [19-22]. Although our study design precludes an assumption of causality, early intervention with evidence-based cardiac medications and coronary revascularization in patients with myocardial injury has been shown to limit infarct size and reduce the risk of ventricular arrhythmias [23]; inasmuch, the increased use of these therapies may have exerted a beneficial effect on the occurrence of VF-CA in our study population over time [20-24]. In addition, increased cardiac monitoring and prophylactic treatment of ventricular arrhythmias with anti-arrhythmic medications may have reduced the incidence rates of VF-CA observed in the present study [25,26].

Hospital Mortality in Patients with Cardiac Arrest

Previously reported in-hospital case-fatality rates for VF-CA complicating ACS vary widely, ranging from 24% to 78% [11-14,27]. The observed case-fatality rate among hospitalized patients with VF-CA complicating ACS in our study (55%) is slightly higher than that previously reported in a large clinical investigation that included nearly 41,000 patients who were treated with thrombolytic therapy [26]. Use of more restrictive inclusion criteria in the context of a randomized controlled trial, as well as varying case definitions, partially accounted for differences in these findings, a theory supported by the fact that the hospital mortality rates observed in our study are much lower than those reported in 2 observational studies involving patients with AMI (78% and 71%) [11,13].

Although in-hospital death rates remained significantly elevated in patients experiencing VF-CA during the most recent years under study, improvements in hospital survival among patients with VF-CA were observed between 2000 and 2007. Our observation that mortality rates declined by 51% during this period is notable in light of a 50% decline in death rates reported between 1993 and 2005 in a separate study of patients with ventricular fibrillation complicating their hospitalization for AMI [14]. The present findings likely reflect the enhanced treatment of patients hospitalized with an ACS as well as improved, and timelier, treatment of VF-CA over time in our cohort [22,28].

Impact of Timing of Cardiac Arrest on Short-Term Prognosis

Consistent with an emerging literature, VF-CA occurring within 48 hours of hospitalization for an ACS was associated with a more favorable prognosis than VF-CA occurring later during hospitalization, despite adjustment for potential confounders of prognostic importance [3,13,27,29]. Since patients with early and late VF-CA differed with respect to a number of factors known to affect in-hospital survival, we hypothesize that the etiology of, and prognosis after, VF-CA may differ between these groups. Our findings suggest that whereas transitory electrical instability due to myocardial ischemia, coronary reperfusion, electrolyte abnormalities, neurohormonal activation, and sympathetic nervous system up-regulation may play a large role in the development of early VF-CA, extension of myocardial injury, ventricular scar formation, generation of sustained and refractory ventricular arrhythmias, sustained hemodynamic instability, and acute kidney injury may contribute to a larger extent in the development and impact of late VF-CA, thus placing patients with late VF-CA at greater risk for dying [30-36]. Cardiac arrest occurring later during a patient's hospital stay may also reflect a failure of hemodynamic stabilization and/or coronary reperfusion, so-called "secondary" cardiac arrest. Last, patients who experienced VF-CA later during their hospitalization may have been less intensively monitored (e.g., out of the intensive care unit or off of cardiac telemetry), thereby delaying the institution of effective cardiac treatments. This hypothesis is supported by the very high mortality rate among patients with late VF-CA (83%). These results suggest that clinicians should continue their current aggressive coronary revascularization

efforts in patients with an ACS in an effort to limit infarct extension and prevent pump failure, as well as be diligent in monitoring and treating patients who develop VF-CA at a later time during their hospitalization for an ACS.

Study Strengths and Limitations

The strengths of the present study include its multi-national design, large sample of patients hospitalized with independently validated ACS, and its relatively contemporary and changing perspective into the clinical epidemiology of ACS and VF-CA. As a nonrandomized observational study, however, GRACE is subject to inherent limitations, including missing or incomplete information, and potential confounding by drug indication or other unmeasured covariates. Although they represented a minority of enrolled individuals (2%), patients with CA on presentation (including potential cases of pulseless electrical activity or asystole) were included in the present study due to limitations in our data abstraction methods. Patients who died before reaching participating study hospitals were excluded, left ventricular ejection fraction was measured in less than one half of study patients, data on non-sustained ventricular tachycardia were not collected, use of anti-arrhythmic drugs, such as lidocaine, was not recorded, and timing of VF-CA development in relation to the receipt of coronary reperfusion or other cardiac therapies was not collected.

CHAPTER V

CONCLUSIONS

In this large multinational study, we have demonstrated that VF-CA is a relatively uncommon but frequently fatal complication in patients hospitalized with an ACS. Encouragingly, we observed declining incidence and case-fatality rates of VF-CA in our patient population, likely reflecting enhanced monitoring and treatment efforts over a recent 8-year period. Nevertheless, VF-CA remains associated with renal, cardiovascular, and hematologic complications as well as reduced in-hospital survival. Continued primary and secondary prevention efforts remain warranted in all patients hospitalized with an ACS, particularly in several high-risk groups that were identified in the present investigation.

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