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Ventricular Arrhythmias Complicating Coronary Artery Disease: Recent Trends, Risk Associated with Serum Glucose Levels, and Psychological Impact

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TITLE

VENTRICULAR ARRHYTHMIAS COMPLICATING

CORONARY ARTERY DISEASE: RECENT TRENDS, RISK ASSOCIATED

WITH SERUM GLUCOSE LEVELS, AND PSYCHOLOGICAL IMPACT

A Dissertation Presented

By

HOANG VU TRAN

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VENTRICULAR ARRHYTHMIAS COMPLICATING

CORONARY ARTERY DISEASE: RECENT TRENDS, RISK ASSOCIATED

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ABSTRACT

Introduction: Ventricular arrhythmias (VAs) are common after an acute coronary syndrome (ACS) and are associated with worse clinical outcomes. However, little is known about recent trends in their occurrence, their association with serum glucose levels, and their psychological impact in ACS setting.

Methods: We examined 25-year (1986-2011) trends in the incidence rates (IRs) and hospital case-fatality rates (CFRs) of VAs, and the association between serum glucose levels and VAs in patients with an acute myocardial infarction (AMI) in the Worcester Heart Attack Study. Lastly, we examined the relationship between in-hospital occurrence of VAs and 12-month progression of depression and anxiety among hospital survivors of an ACS in the longitudinal TRACE-CORE study.

Results: We found the IRs declined for several major VAs between 1986 and 2011while the hospital CFRs declined in both patients with and without VAs over this period. Elevated serum glucose levels at hospital admission were associated with a higher risk of developing in-hospital VAs. Occurrence of VAs, however, was not associated with worsening progression of symptoms of depression and/or anxiety over a 12-month follow-up period in patients discharged after an ACS.

Conclusions: The burden and impact of VAs in patients with an AMI has declined over time. Elevated serum glucose levels at hospital admission may serve as a predictor for in-hospital occurrence of serious cardiac arrhythmias. In-hospital occurrence of VAs may not be associated with worsening progression of symptoms of depression and anxiety in patients with an ACS.

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AMI	Acute myocardial infarction
ACS	Acute coronary syndrome
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CFRs	Case-fatality rates
GAD	Generalized Anxiety Disorder
GEE	Generalized Estimating Equations
GRACE	Global Registry of Acute Coronary Events
IRs	Incidence rates
NSTEMI	Non-ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
PHQ	Patient Health Questionnaire
PMM	Predict mean matching
STEMI	ST-elevation myocardial infarction
TRACE-CORE	Transitions, Risks, and Actions in Coronary Events - Center for Outcomes Research and Education
VAs	Ventricular arrhythmias
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHAS	Worcester Heart Attack Study

PREFACE

Some of the work presented or related to this dissertation has been published, is currently under review, or is prepared to be submitted for peer-reviewed publication.

Chapter II:

Hoang V. Tran, MD, Arlene S. Ash, Joel M. Gore, Chad E. Darling, Catarina I. Kiefe, Robert J. Goldberg. **Twenty-five year trends (1986-2011) in hospital incidence and case-fatality rates of ventricular tachycardia and ventricular fibrillation complicating acute myocardial infarction.** *American Heart Journal* (under review).

Chapter III:

Hoang V. Tran, MD, Arlene S. Ash, Joel M. Gore, Chad E. Darling, Catarina I. Kiefe, Robert J. Goldberg. **Hyperglycemia and risk of ventricular tachycardia among patients hospitalized with acute myocardial infarction**. *Nutrition, Metabolism, and Cardiovascular Disease* (under review).

Chapter IV:

Hoang V. Tran, MD, Arlene S. Ash, Joel M. Gore, Chad E. Darling, Catarina I. Kiefe, Robert J. Goldberg. **Occurrence of life-threatening arrhythmias and progression of depression and anxiety following an acute coronary syndrome.** *Journal of Psychosomatic Research* (under review).

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CHAPTER I

INTRODUCTION

Ventricular arrhythmias are common complications of acute myocardial infarction

Ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF) frequently complicate the clinical course of patients hospitalized with acute myocardial infarction (AMI), in upwards of 25% of patients.[1,2] The development of theses ventricular arrhythmias (VAs) in patients with AMI is associated with a large infarct size, ventricular wall dyskinesis, ventricular dysfunction, and extent of underlying coronary artery disease.[3] The incidence rates of VAs complicating AMI are higher in patients who develop an ST-elevation myocardial infarction (STEMI) than in those who develop an non-ST-elevation myocardial infarction (NSTEMI) or unstable angina. For instance, in the Early Glycoprotein IIb/IIIa Inhibition in non ST-elevation ACS (EARLY ACS) trial of 9,211 patients hospitalized with non-ST-elevation acute coronary syndrome, VT occurred in 0.8% of patients[4]. On the other hand, in a study of 225 patients who underwent a primary coronary intervention (PCI) for their STEMI, VT occurred in up to two thirds of this population.[5]

The occurrence of VAs is associated with worse in-hospital and long-term outcomes, especially sudden cardiac death.[6] Data from 16,842 patients with AMI in the

Gruppo Italiano per lo Studio della Soprovvivenza nell'Infarto Miocardico (GISSI-3) trial showed that VAs were associated with a 6-fold higher risk of death at 6 weeks post discharge compared with patients who did not develop VAs.[7] In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial of 6,560 patients hospitalized with a NSTE-ACS, the occurrence of VAs was associated with a 2.3-2.8 times higher risk of sudden cardiac death after 1 year in comparison to patients who did not develop VAs.

VAs primarily occur during the first 24-48 hours after acute symptom onset in patients with an AMI.[5] For instance, among 5,745 patients with a STEMI from 296 sites in 17 countries in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX AMI) trial, the vast majority (90%) of cases of VT or VF occurred within 48 hours of symptom onset.[8] In patients with a STEMI, early (within 48 hours after symptom onset) VT has been associated with a higher in-hospital and 30-day death rate but not worse long-term outcomes, whereas late (after the first 48 hours) VT usually is associated with worse in-hospital and long-term outcomes.[9-11] On the other hand, prior studies have shown that both early and late VAs have been associated with worse long-term outcomes in patients with an NSTEMI. For example, in the EARLY ACS trial, both early and late VT was associated with a higher risk of 30-day and 1-year all-cause mortality compared to patients who did not develop VT.[12]

Recent trends in ventricular arrhythmias complicating acute myocardial infarction

National data on either the incidence rates (IRs) or case-fatality rates (CFRs) of VAs complicating AMI in the U.S. are not available. In a medical records linkage study of 2,317 patients who were admitted to all hospitals in Olmsted county, Minnesota, for an acute or old MI or angina pectoris, the annual incidence rate of sustained VT remained stable at 1.8% while that of VF decreased from 7.7% in 1979 to 5.0% in 1998.[13] However, more recent trends in the IRs and CFRs of VAs complicating AMI in the U.S. have not been examined. Nevertheless, several changes in the management of AMI during recent years, including the prompt administration of percutaneous coronary intervention (PCI), or the early use of beta-blockers, may have led to a change in the magnitude and/or short-term outcomes of VT and VF after AMI.[14,15] More important, changes in treatment practices, include aggressive reperfusion therapies, may affect patients with a STEMI differently from patients with a NSTEMI. Thus, reexamination of potentially changing trends in the incidence and CFRs of VT complicating AMI during recent years is needed to understand the contemporary burden of these serious complications.

Mechanisms underlying the development of ventricular arrhythmias in acute myocardial infarction

The underlying electrophysiological mechanisms of VAs in the setting of AMI are multifactorial and complex, involving substrate, trigger, and modulating factors, each of which depend on the time course of myocardial ischemia.[16] In the very early phase (within 4 hours) of an acute coronary event, the increase in resting membrane potential,

reduction in action potential amplitude, upstroke velocity and duration, and early cellular uncoupling[17], re-entry within the ischemic myocardium, and reperfusion injury[18] contribute to the onset of VAs. In the subacute phase (between 4 hours and 72 hours) of the acute coronary event, VT is provoked by increased automaticity in surviving Purkinje cells which give rise to reentry and triggered activity.[16] In later stages, VT usually occurs due to reentry pathways that occur via isolated bundles of surviving myocytes at the border of the infarct and the larger sub-endocardial muscle mass.[19]

Several systemic changes in response to a myocardial injury are thought to contribute to electrophysiological disturbances that lead the development of VAs. The activation of sympathetic system plays an important role in the development of VAs, especially in very early and early phases.[17] Studies in animal models found catecholamines were released within 10 minutes from myocardial ischemia and was correlated with the ischemic duration.[20] Ischemia-induced catecholamine release is suggested to mediate occurrence of VAs.[21] Other studies also suggest that systemic inflammation, demonstrated by an elevation in C-reactive protein or leukocytes levels, may also contribute to the development of VAs.[22,23] Although these proposed mediating factors are in accordant with severer clinical presentation observed in patients who develop VAs, the evidence on these factors are still contradicting, perhaps due to the complex and multifactorial nature of these arrhythmic complications.[17,24]

Factors associated with the occurrence of ventricular arrhythmias

To better identify, monitor, and treat patients at higher risk of developing VAs during hospitalization for an AMI, several studies have examined factors associated with developing of VAs . Several factors, including younger age[25], female sex, lower systolic blood pressure or higher heart rate[26], higher Killip class[27], atrial fibrillation[13], heart failure, cardiogenic shock, chronic kidney disease, and presentation within 6 hours of acute symptoms[28] have been found to be associated with VAs. Data from more than 26,000 patients with NSTE ACS in the Global Use of Streptokinase and tPA for Occluded Arteries (GUSTO)-IIb, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-A, and PARAGON-B trials showed that chronic obstructive pulmonary disease, prior myocardial infarction, and ST-segment changes at presentation were associated with the in-hospital development of VAs.[6]

On electrocardiography, a QTc dispersion, or premature beat with early coupling (R on T phenomenon) has been suggested to be associated with higher odds of developing VAs after an AMI[29-32]; however, evidence is mixed[33-35]. Electrolyte abnormalities, such as hypokalemia at the time of hospital admission, has also been associated with the occurrence of VAs.[36] Early successful restoration of coronary flow with fibrinolysis or PCI has been shown to reduce the risk of VAs.[37,38] In the APEX AMI trial, Killip class greater than I, baseline systolic blood pressure, baseline heart rate greater than 70 beat/minute, pre-PCI and post-PCI TIMI flow grade 0 were associated with occurrence of VAs.[8]. However, the role of several markers for inflammation or the

stress response early during the course of AMI (e.g., white blood cell count, C-Reactive Protein (CRP), or serum glucose levels) on the development of VAs have not been well studied. These factors, which have also been found to be associated with a more extensive infarction and worse short-term outcomes, may be related to the development of this arrhythmic complication.

A limited number of studies have suggested that risk factors for early or late VAs may be different as may be their mechanisms. For example, an anterior infarction has been shown to be associated with the development of early VAs, whereas an inferior infarction has been shown to be associated with VAs occurring at a later time.[39] In addition, these factors may be different in patients who have a STEMI as with patients who suffer an NSTEMI, or in patients who receive different reperfusion treatment strategies since the underlying mechanism may be different in each of these particular patient subgroups. Thus, understanding regarding factors associated with VAs must also examine potential variation in subgroups of patients.

Potential association between serum glucose levels and ventricular arrhythmias

Early after the onset of an AMI, the sympathetic nervous system responds to physiological and emotional stress with the release of noradrenalin.[40] Serum glucose levels typically increase early after an AMI in 25-50% of patients, reflecting a preexisting insulin resistance or an acute response to physiological/emotional stress after the acute coronary event.[40,41] Elevated serum glucose levels at the time of hospital admission have

been associated with worse outcomes in the setting of AMI, including in-hospital and long-term death in both diabetic and nondiabetic patients[42].[43,44]

The hyperglycemic state can directly alter cardiac electrophysiological status, creating conditions that facilitate the occurrence of VAs.[42] In addition, hyperglycemia is associated with more extensive infarct size,[45] impaired microvascular circulation,[46] and worse left ventricular function,[47] each of which can promote electrical instability. However, few studies have examined the association between serum glucose levels at the time of hospital admission and onset of VAs after an AMI. In a study of 1,258 patients with AMI, a glucose level of >180 mg/dl at admission was associated with a higher risk of developing VAs or ventricular fibrillation after adjusting for several potentially confounding factors.[48] In a small study among 76 diabetic patients with a first AMI, serum glucose levels >225 mg/dl were associated with several myocardial electrical complications, including Vas, ventricular premature complex, atrial fibrillation, and conduction system disorders.[49] However, these studies have considered VAs together with other arrhythmias, which may not share the same underlying mechanisms, and ignored the timeline of VAs onset from the beginning of acute coronary related symptoms. Inasmuch, there is a need to reexamine the association between serum glucose levels at the time of hospital admission with the occurrence of VAs in a large sample of patients hospitalized with AMI.

Potential association between ventricular arrhythmias and depression and anxiety following an acute coronary syndrome

In patients who are diagnosed with an acute coronary syndrome (ACS), depression and anxiety are prevalent in up to 20-40%, approximately 10 times that of general population.[50-53] Of importance for long-term patient management, both depression and anxiety are usually not transient after the ACS event, but rather long-lasting.[54,55] For instance, in the Depression after Myocardial Infarction (DepreMI) study of 475 patients admitted to 4 hospitals in the Netherlands for an AMI, the prevalence of depression was approximately 25% during the 12 month follow up period. The presence of depression or anxiety further complicated the in-hospital and long-term management of patients with an ACS,[52,56,57] and untreated depression and anxiety has been associated with worse clinical outcomes among patients discharged from the hospital after an ACS, including higher all-cause death rates[58,59], recurrent coronary events, and impaired quality or life.[51,60,61] However, these conditions are often under and/or undiagnosed and under-treated in patients hospitalized for an ACS, and have been called for greater recognition and attention by the American Heart Association (AHA).[62]

On the other hand, the occurrence of VAs may increase the levels and frequency of symptoms of anxiety or depression. The symptoms of VAs, including pre-syncope (pounding or racing heartbeat, lightheadedness, feeling faint)[2,63] or actual syncope or cardiac arrest can lead to further stress and fear in patients with underlying CAD, which may worsen the symptoms of depression or anxiety. Thus, there is a need to study the impact of VAs on long-term progression of depression and anxiety among patients surviving an ACS. However, no study has investigated the association between occurrence of VAs and trajectories of depression or anxiety following an ACS.

Study aims and hypotheses

The discussion in this thesis is intended to fill the current gaps in the knowledge of VAs in the setting of an ACS by archiving the following aims.

Aim 1:

Examine 25 year trends (1986-2011) in the incidence rates and compare the in-hospital case-fatality rates of patients who developed, versus those who did not develop VAs complicating AMI in the Worcester Heart Attach Study (WHAS)

Hypothesis: The incidence rates and case-fatality rates of VAs (including VT and VF) decreased during the period under study with larger declines observed among patients with STEMI than in patients with NSTEMI.

Aim 2:

Examine the association between serum glucose levels at hospital admission with in-hospital occurrence of VAs using data from the WHAS.

Hypothesis: Patients who had higher levels of serum glucose were more likely to develop VAs during the hospitalization for an AMI.

Aim 3:

Examine association between occurrence of VAs and progression of depressive and anxiety symptoms over a 12-month period in patients discharged from the hospital after an acute coronary syndrome (ACS) in the Transitions, Risks, and Action in Coronary Events – Center for Outcomes Research and Education (TRACE-CORE) study.

Hypothesis: Patients who experienced in-hospital VAs had higher risk of developing depression or anxiety during the 12-month period following hospital discharge for an ACS compared with patients who did not develop VAs.

CHAPTER II

**TWENTY-FIVE YEAR TRENDS (1986-2011) IN HOSPITAL INCIDENCE AND
CASE-FATALITY RATES OF VENTRICULAR ARRHYTHMIAS AND
FIBRILLATION COMPLICATING ACUTE MYOCARDIAL INFARCTION**

Abstract

Background: Long-term trends in the incidence rates (IRs) and hospital case-fatality rates (CFRs) of ventricular tachycardia (VT) and ventricular fibrillation (VF) among patients hospitalized with acute myocardial infarction (AMI) have not been recently examined.

Methods: We used data from 11,825 patients hospitalized with AMI at all 11 medical centers in central Massachusetts on a biennial basis between 1986 and 2011. Multivariable logistic regression modeling was used to examine trends in hospital IRs and CFRs of VT and VF complicating AMI.

Results: The median age of study population was 71 years; 57.9% was male, and 94.7% was white. The hospital IRs declined from 14.3% in 1986/1988 to 10.5% in 2009/2011 for VT and from 8.2% to 1.7% for VF. Over the same period, in-hospital CFRs declined from 27.7% to 6.9% for VT and from 49.6% to 36.0% for VF. The IRs of both early (<48 hours) and late VT and VF declined over time, with greater declines in those of late VT and VF. The incidence of VT declined similarly for patients with either type of AMI, while for VF it declined only in those with a STEMI.

Conclusion: The hospital incidence and mortality rates of VT and VF have declined over time, likely due to changes in acute monitoring and treatment practices. Despite these encouraging trends, efforts remain needed to identify patients at risk for these serious ventricular arrhythmias and implement preventive and treatment strategies as necessary.

Introduction

Ventricular tachycardia (VT) and ventricular fibrillation (VF) frequently complicate the clinical course of patients hospitalized with an acute myocardial infarction.[1,2] The development of these serious ventricular arrhythmias in patients hospitalized with an acute myocardial infarction (AMI) is often associated with a larger infarct, ventricular wall dyskinesia and dysfunction, more extensive underlying coronary artery disease, and ST segment-elevation myocardial infarction (STEMI).[3-5,8] The development of VT and VF in patients hospitalized with AMI is associated with increased in-hospital and post discharge morbidity and mortality.[6,7]

National data on either the incidence rates (IRs) or case-fatality rates (CFRs) of VT and VF complicating AMI in the U.S. are not presently available. In a medical records linkage study of 2,280 patients who were admitted to all hospitals in Olmsted County, Minnesota, for coronary heart disease between 1979 and 1998, the annual IRs of sustained VT remained stable at 1.8%, while the IRs of VF declined from 7.7% in the initial study years to 5.0% during the most recent years under study.[13] However, this study was limited by its small sample size and by the lack of more contemporary data. A number of changes in the more optimal management of patients hospitalized with acute coronary disease during recent years may have led to favorable changes in the magnitude and/or outcomes of ventricular arrhythmias among patients hospitalized for an AMI.[14,15]

Using data from a population-based surveillance study of patients hospitalized with confirmed AMI at all central Massachusetts medical centers, we examined 25-year trends (1986-2011) in the hospital IRs and CFRs of VT and VF, and compared

differences in the in-hospital CFRs of patients who developed, with those who did not develop, VT or VF complicating their AMI.

Methods

Study design and data collection

Data from the Worcester Heart Attack Study (WHAS), an ongoing population-based investigation that is examining long-term trends in the incidence, in hospital, and post-discharge CFRs of AMI among residents of the Worcester, Massachusetts, metropolitan area were used for this investigation. The details of this study have been described previously.[64-69] In brief, the medical records of residents of central Massachusetts hospitalized for possible AMI at the 11 medical centers serving residents of this large central New England metropolitan area were individually reviewed. The diagnosis of AMI was independently validated according to criteria developed by the World Health Organization with further sub-classification into those with an ST-segment elevation AMI (STEMI) or Non-ST segment elevation AMI (NSTEMI).[70,71] This investigation was approved by the Institutional Review Board at the University of Massachusetts Medical School.

Trained nurses and physicians abstracted demographic and clinical data from the medical records of residents of the Worcester metropolitan area hospitalized with a confirmed AMI. Quality control activities were routinely conducted on all nurse and physician data abstractors. Abstracted information included patient's age, sex, medical history, physiologic factors, laboratory test results at the time of hospital admission, and

length of hospital stay. Information about the in-hospital use of important cardiac medications, coronary angiography, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery was collected. Development of several significant clinical complications (e.g., atrial fibrillation, cardiogenic shock, stroke, heart failure, survival status) during the patient's index hospitalization was defined according to standardized criteria.[71-74]

Study population

Among the 12,804 residents of the Worcester metropolitan area who were hospitalized with an independently verified AMI on an approximate biennial basis between 1986 and 2011, we excluded patients with missing data on age (n=281), race (n=476), serum potassium levels (n=212), and length of hospital stay (n=10). The final study sample consisted of 11,825 patients with an AMI.

Ventricular arrhythmias

In the present study, the occurrence of VT and VF was based on physicians' progress notes. To reduce the possible misclassification of VT and VF due to underreported occurrence of these arrhythmias in physicians' notes, the study research physicians also reviewed patients' ECG strips in their hospital medical records. Ventricular tachycardia was defined as a cardiac arrhythmia of three or more consecutive complexes originating in the ventricles at a rate of greater than 100 beats per minute (cycle length less than 600 milliseconds).[2] Information was also collected about the date of initial VT occurrence since hospital admission. Ventricular fibrillation was defined as a rapid, usually more than 300 beats per minute (cycle length 200 millisecond or less),

grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude.[2]

Following definitions used in prior investigations,[13,68,75] we further classified VT and VF as either occurring early (within 48 hours after hospital admission) or late (after the first 48 hours) and primary (occurring without concomitant heart failure or cardiogenic shock) or secondary to concurrent heart failure or cardiogenic shock. For patients who had multiple episodes of VT (582/1,731 patients, 33.6%) and VF (158/574 patients, 27.5%), only the first episode was counted. We classified the 348 patients who developed both VT and VF as having VF, since VF is more clinically serious than VT.

Statistical analysis

Patient characteristics, including demographic factors, clinical presentation, physiologic findings, and laboratory test results were compared between patients who developed VT or VF, and those who did not, using Chi-Square tests for categorical variables and the t-test or Kruskal–Wallis test for continuous variables. Changes in these characteristics between our respective comparison groups were also examined across study years using chi square tests for trends.

The hospital IRs (e.g., frequencies) of VT and VF complicating AMI were calculated as the proportion of new cases of VT and VF which occurred among all patients hospitalized with AMI.[75] In-hospital CFRs for each condition were calculated as the number of in-hospital deaths/total number of cases with a particular arrhythmia.[76] The IRs and CFRs were graphed on continuous admission date between 1986 and 2011 using locally weighted line least-square smoothing.[77]

We controlled for the effects of changes in patients' demographic characteristics, clinical presentation, and medical therapies and reperfusion practices on trends in hospital IRs and CFRs using multivariable logistic regression modelling. Study year was treated as an integer-valued variable when examining linear trends in these endpoints. Potentially confounding factors were identified based on differences in the baseline characteristics of hospitalized patients according to the presence or absence of VT or VF using a p-value of <0.05 as a cutoff. These variables were successively introduced into the multivariable logistic regression model in blocks to a full model. Since length of hospital stay may affect the possibility of capturing VT or VF during the patient's acute hospitalization, or serve as a proxy for disease severity, length of stay was also included in the fully adjusted models as a potentially confounding factor.

We also examined the overall magnitude, and changes over time therein, in the frequencies of VT and VF based on the presence of concomitant heart failure/cardiogenic shock or not. Since the occurrence of VT may differ between patients with a STEMI and NSTEMI, trends in the hospital IRs and CFRs of VT were also examined for these two groups, separately in patients admitted to all central Massachusetts hospitals between 2001 and 2011, when information about the type of AMI was collected. We also examined trends in hospital IRs of early (during the first 2 days after hospital admission) versus late VT in patients further classified by type of AMI (e.g., STEMI vs. NSTEMI).

Given the large size of this study, almost all differences that were observed were highly statistically significant. Thus, all reported differences without an explicit P-value had a p value <0.05.

Results

Baseline patient characteristics

The median age of the study population was 71 years, most patients were white (94.7%), and 57.9% were men. Patients whose clinical course was complicated by either VT (n=1,731) or VF (n=574) were several years younger than patients who did not develop these serious ventricular arrhythmias and were more likely to be male (Table 2.1). Patients who developed VT or VF were less likely to have a medical history of diabetes, hypertension, or a stroke/transient ischemic attack. On the other hand, patients in whom these arrhythmias were diagnosed were more likely to have developed important clinical complications (e.g., atrial fibrillation, heart failure, cardiogenic shock) during their acute hospitalization. Compared with patients who did not develop these ventricular arrhythmias, patients who developed VT or VF were more likely to have been treated with antiarrhythmic agents or thrombolytic therapy, but less likely to have received aspirin, Angiotensin converting enzyme inhibitor/Angiotensin II receptor blockers (ACE-I/ARBs), beta blockers, and lipid lowering agents.

Between 1986 and 2011, the prevalence of several preexisting comorbidities (e.g., heart failure, diabetes, hypertension, stroke) increased (Table 2.2), as did the prescribing of aspirin, ACE-I/ARBs, beta blockers, lipid lowering agents, PCI, and CABG surgery. During this period, there were declines in the frequency of several important in-hospital complications, including atrial fibrillation, heart failure, and cardiogenic shock. Receipt of thrombolytic therapy and the average hospital length of stay also decreased (Table 2.2).

Twenty-five year trends in hospital IRs of VT and VF

Between 1986 and 2011, VT developed in 14.6% and VF in 4.9% of all patients admitted to central Massachusetts hospitals for an AMI. During this period, the proportion of patients with AMI who developed VT declined from 14.3% in 1986/1988 to 10.5% in 2009/2011 while the proportion of patients who developed VF declined from 8.2% in 1986/1988 to 1.7% in 2009/2011 (Figure 2.1, top panel). After adjusting for changes in the demographic and clinical characteristics of our patient population over time, the proportion of patients who developed VT declined by approximately 11% (95%CI=6-17%) while the proportion of patients who developed VF declined by 37% (95%CI=30-43%) after each decade, respectively (Table 2.3). After we adjusted for changes over time in the receipt of various cardiac medications and reperfusion therapies received at the time of hospital admission during the years under study, the proportion of patients who developed VT did not change over time while adjustment for the receipt of these therapies attenuated the magnitude of the decline in IRs of VF after each decade to 20% (95%CI=7-32%).

Trends in hospital IRs of VT and VF according to concomitant heart failure or cardiogenic shock

Approximately 41% of our 11,825 study patients developed either heart failure or cardiogenic shock during their hospitalization for AMI. The development of ventricular arrhythmias in these patients was more common than in patients who did not develop either heart failure or cardiogenic shock (17.2% vs. 12.9% for VT and 7.3% vs. 3.2% for VF, respectively). The proportion of patients who developed VT among those with

concomitant heart failure or cardiogenic shock decreased from 17.7% in 1986/1988 to

13.6% in 2009/2011 while the hospital IRs for VT for those who did not develop these

hemodynamic disturbances did not significantly decline (p=0.45). The IRs of VF among

those with concomitant heart failure or cardiogenic shock decreased from 10.7% in

1986/1988 to 2.1% in 2009/2011 compared with a decrease from 6.0% in 1986/1988 to

1.6% in 2009/2011 among patients without concomitant heart failure or cardiogenic

shock (Figure 2.1, bottom panel).

Trends in hospital IRs of ventricular arrhythmias by timing of occurrence

Data on the time of occurrence of VT and VF and type of AMI were collected in

5,764 patients admitted to all greater Worcester hospitals on a biennial basis with AMI

between 2001 and 2011. During this period, VT occurred in 13.2% while VF occurred in

2.8% of these patients, respectively. The frequency of VT declined from 15.8% in

2001/2003 to 9.9% in 2009/2011 and from 3.5% to 1.6% for VF. More than two thirds of

all VT and VF episodes occurred during the first 48 hours after hospital admission. The

hospital IRs of both early and late VT declined over time, with greater declines noted for

those with late VT in both relative and absolute terms (Figure 2, top panel). Similarly, the

incidence rates of early and late VF significantly declined during the most recent decade

under study, with a larger decline observed for late VF (Figure 2.2).

Trends in hospital IRs of ventricular arrhythmias according to type of AMI

During the most recent decade (2001-2011) under study in which data were

collected on the type of AMI patients experienced, 32.0% of study patients (n=1,161)

were diagnosed with a STEMI. The occurrence of both VT and VF were more common

in patients with a STEMI than for those with an NSTEMI (17.3% vs. 11.3% for VT and

5.3% versus 1.6% for VF). Among patients with a STEMI, about 80% of episodes of VT

and VF occurred within the first 48 hours after hospital admission, compared with only

60% of such episodes for those with an NSTEMI. The hospital IRs of VT and VF

declined between 2001 and 2011 in patients with a STEMI (Figure 2.2, bottom panel).

The IRs of VT also declined in patients with an NSTEMI, whereas the IRs of VF in these

patients did not change significantly over time (p=0.25, Figure 2.2).

Twenty-five year trends in Hospital CFRs of VT and VF

The overall in-hospital CFRs were 48.3% among patients who developed VF,

13.9% in patients who developed VT, and 8.9% in patients who did not develop either of

these ventricular arrhythmias during their acute hospital stay. The in-hospital CFRs

decreased from 27.7% in our 2 initial study years (1986/1988) to 6.9% in our 2 most

recent study years of 2009/2011 for patients who developed VT, from 49.6% to 36.0%

for patients who developed VF, and from 11.5% to 4.6% for those whose hospital course

was not complicated by either VT or VF (Figure 2.3). After adjusting for changes in

patient's demographic characteristics and clinical presentation during the years under

study, the hospital CFRs decreased by 41% (95%CI=39-50%) for patients who developed

VT and by 24% (95%CI=14-32%) for those who developed VF after each study decade

(Table 2.3). However, the declining trends in the hospital CFRs of VT and VF were

markedly attenuated after adjusting for the receipt of various cardiac medications and

reperfusion treatments during the patient's index hospitalization.

Discussion

In this community-based study of approximately twelve thousand patients hospitalized with AMI at all central Massachusetts medical centers, we found that the incidence rates of both VT and VF, especially among patients with concomitant heart failure or cardiogenic shock, declined between 1986 and 2011. While the in-hospital death rates for patients whose hospital course was complicated by VT or VF have declined during the study period, mortality remained high, at approximately 40% in patients who developed VF in 2009/2011. Between 2001 and 2011, trends in the magnitude of early vs. late VT differed, while trends in the frequency of VF complicating AMI differed according to the type of AMI patients developed.

Trends in the hospital incidence rates of VT complicating AMI

We observed declining trends in the frequency of sustained and nonsustained VT among patients admitted to the hospital for an AMI between 1986 and 2011. Published data examining long-term or recent trends in the magnitude or death rates associated with VT complicating AMI are extremely limited. In a study of 2,280 patients who were admitted to all hospitals in Olmsted County, Minnesota, for an AMI between 1979 and 1998, sustained VT occurred in 1.8% of hospitalized patients.[13]

Notably, our observed declines in the frequency of VT were primarily driven by declines in VT among patients who had concomitant heart failure or cardiogenic shock. The declines we observed in the frequency of VT in patients with heart failure or cardiogenic shock might be due to increases in the use of coronary reperfusion therapies, including thrombolytic therapy and PCI, which have been shown to improve cardiac function and lower the risk of developing heart failure.[78] Indeed, in our study, the

proportion of patients who developed heart failure after AMI decreased from 44% in 1986 to 29% in 2011.

While reperfusion therapies might reduce the incidence of primary and secondary VT after AMI, reperfusion arrhythmias, including VT, might offset these benefits.[8,79] An increasing occurrence of reperfusion arrhythmias might also explain the smaller decrease in the incidence of early VT, where reperfusion VTs are more prevalent, compared with the incidence rates of late VT that were observed between 2001 and 2011.

While evidence-based treatment modalities may have an impact on preventing early onset VT, which is often induced by transient abnormalities of automaticity or triggered activity following acute myocardial ischemia, these treatments can reduce infarct size and remodeling of the arrhythmic substrate or reentry pathways, thereby reducing the risk of late VT.[16] Discontinuation of the use of prophylactic lidocaine and other antiarrhythmic agents in the mid-1990s might also have contributed to declines in the frequency of VT.[80,81] The trends we observed are consistent with these hypotheses; however, disentangling the interplay of these factors on trends in the incidence rates of VT is complex, and remains a research topic for further study.

Trends in the hospital incidence rates of VF complicating AMI

The frequency of primary VF (i.e., VF which occurs in patients without heart failure or cardiogenic shock) and secondary VF among patients with an AMI also decreased between 1986 and 2011, with a larger decrease in the frequency of secondary VF. This finding was in contrast to our prior analysis of data from this community-wide study which failed to find a significant change in the incidence rates of primary VF

complicating AMI between 1975 and 1997,[68,69] or with the results of the Rochester

Epidemiology study between 1979 and 1998.[13]

Declining trends in the magnitude of VF that we observed may be due, in part, to

the favorable effects of increased utilization of evidence-based treatments for AMI during

the years under study. In contrast with relatively stable trends in the frequency of VT

between 1986 and 2011, declines in the occurrence of primary VF might be explained by

the fact that reperfusion-induced VF occurs in a considerably smaller proportion of

treated patients compared with the frequency of VT.[82]

Trends in hospital incidence rates of VT and VF according to type of AMI

Consistent with prior reports,[6,83,84] we found that VT and VF occurred more

commonly in patients with a STEMI than in patients with an NSTEMI. Most instances of

VT and VF tended to occur early within the first 48 hours of hospitalization in patients

with a STEMI while slightly more than one half of all episodes of VF occurred during

this high-risk period among patients with an NSTEMI. The greater frequency of

ventricular arrhythmias in patients with a STEMI is possibly due to the more common

occurrence of electrical or inflammatory disturbances that result after the complete

blockage of a coronary artery compared to less common disturbances due to residual

coronary flow in patients with an NSTEMI.[85] In addition, emergent PCI is more common

in patients with a STEMI, which may result in a greater frequency of reperfusion-induced

VT as compared to patients with an NSTEMI, where a "watchful waiting" strategy is

more commonly employed. Differences in the timing of these ventricular arrhythmias

may have implications for when to discharge high risk patients with an NSTEMI.

However, later discharge and/or increased post-discharge surveillance for patients with an NSTEMI needs to be considered from a cost-benefit perspective given the fairly low incidence rates of VF (1.6%) among these patients.

Patients with either a STEMI or a NSTEMI experienced a decline in the hospital frequency of VT between 2001 and 2011. Similar trends were observed with regards to the development of VF among patients with an STEM while the incidence of VF among patients with an NSTEMI did not change. It is unclear why the frequency of VF did not decrease in patients with a NSTEMI during the study period. However, the low frequency of VF (1.6%) among these patients might have been difficult to detect in our study. Differences in the trends of VT and VF among patients with an NSTEMI may also suggest distinct underlying mechanisms and risk factors for the development of these serious arrhythmias among these patients.

Trends in hospital case-fatality rates of VT and VF complicating AMI

We observed an encouraging decline in the hospital death rates of patients who did not develop VT or VF, as well as in patients who developed either VT or VF, between 1986 and 2011. Our prior work also found a lower odds of dying among patients who developed primary VF in the late 1990s and early 2000s compared with the late 1970s.[75]

Improvements in the timing and use of in-hospital cardiopulmonary resuscitation might have contributed to the decreased in-hospital CFRs of VT and VF that we observed during the years under study. Data from 17,490 patients with in-hospital pulseless VT or VF who were studied in the Get With The Guidelines–Resuscitation registry showed that

immediate survival after resuscitation increased from 58% in 2001 to 72% in 2009.[86]

Several factors, including early recognition and rapid defibrillation, greater availability of

trained personnel, better chest compressions, and therapeutic hypothermia likely

contributed to improved survival rates.[86-89] For patients with hemodynamically stable VT,

changes in patient management, including correction of electrolyte and acid/base

abnormalities and treatment of important clinical complications during the period under

study may have further reduced the risk of deterioration into pulseless VT or VF and

death.

It is important to note that in the present study, changes in medical treatments,

namely the increased use of aspirin, ACE-I/ARBs, beta blockers, and lipid-lowering

agents, as well as increased use of PCI and CABG surgery during the period under study,

primarily accounted for the improvement in the short-term survival rates we observed

among patients who developed either VT or VF. Our findings provide encouragement for

the continued high use of effective treatments for AMI to reduce the risk of dying from

these ventricular arrhythmias.

Study strengths and limitations

The present study has several strengths. It is among the very few studies that have

provided more generalizable community-based epidemiologic data that can furnish

insights into the magnitude and impact of the major ventricular arrhythmias in patients

hospitalized with AMI. All patients admitted to the coronary care unit were telemonitored

for their entire stay, making it unlikely that episodes of asymptomatic and nonsustained

VT were missed. However, our study also has several limitations. Due to considerable

missing data on duration of prehospital delay, we were unable to systematically classify the time of onset of VT or VF according to symptom onset. However, in an analysis of 1,501 patients with available information, the classification of early from late VT or VF based on acute symptom onset agreed well with that based on the timing of hospital admission.

Conclusions

The results of this community-wide study found declining multi-decade long trends in the incidence and mortality of VT and VF following AMI. The encouraging trends that we observed are likely due to changes in hospital treatment practices during the years under study. However, efforts remain needed to identify patients at risk for these serious ventricular arrhythmias and implement effective preventive and treatment strategies as necessary.

Table 0.1: Baseline characteristics of patients admitted to the hospital for an acute myocardial infarction according to the presence of ventricular tachycardia or ventricular fibrillation

Characteristics	No VT/VF (n= 9,520)	VT (n= 1,731)	VF (n= 574)	p1	p2
Age (median [IQR], years)	72 [60-81]	70 [58-79]	68 [58-77]	**<0.001**	**<0.001**
Age (years, %)				**<0.001**	**<0.001**
<55	15.3	19.5	19.0		
55-64	18.3	18.9	20.4		
65-74	24.5	25.0	28.9		
≥75	42.0	36.6	31.7		
Men (%)	55.7	66.7	67.8	**<0.001**	**<0.001**
White (%)	94.4	96.0	95.1	**0.010**	0.49
History of disease (%)					
Coronary artery disease	36.5	36.1	35.2	0.75	0.53
Heart failure	20.8	21.1	14.8	0.83	**0.001**
Diabetes	32.8	27.8	23.9	**<0.001**	**<0.001**
Hypertension	65.2	60.2	57.5	**<0.001**	**<0.001**
Angina	21.4	20.8	17.3	0.56	**0.018**
Stroke/transient ischemic attack	12.6	10.3	8.7	**0.009**	**0.006**
Admission potassium (median [IQR], mmol/L)	4.2 [3.9-4.6]	4.2 [3.8-4.6]	4.0 [3.5-4.4]	**0.017**	**<0.001**
Length of stay (median [IQR], day)	5 [3-9]	7 [4-11]	7 [2-13]	**<0.001**	**<0.001**
In hospital complications (%)					
Atrial fibrillation	15.8	24.7	27.9	**<0.001**	**<0.001**
Heart failure	35.7	43.9	47.6	**<0.001**	**<0.001**
Pulmonary edema	12.4	17.0	20.7	**<0.001**	**<0.001**
Cardiogenic shock	4.3	9.2	26.7	**<0.001**	**<0.001**
Treatment (%)					
Aspirin	82.2	81.2	67.6	0.29	**<0.001**
ACE-I/ARBs	47.4	48.6	38.0	0.33	**<0.001**
Antiarrhythmic agents	12.9	27.8	40.6	**<0.001**	**<0.001**
Beta blockers	77.0	77.9	62.5	0.41	**<0.001**
Lipid lowering agents	40.3	39.3	24.6	0.40	**<0.001**
Thrombolytic therapy	11.3	21.4	22.0	**<0.001**	**<0.001**
PCI	25.6	27.7	28.1	0.06	0.19
CABG surgery	4.6	6.9	5.8	**<0.001**	0.19

VT: ventricular tachycardia, VF: ventricular fibrillation (with/without VT), IQR: interquartile range, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin II receptor blockers, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft

p-value from Chi-square test and Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables; p1: no VT/VF vs. VT, p2: no VT/VF vs. VF.

Table 0.2: Trends in the characteristics of patients admitted to the hospital for an acute myocardial infarction

Characteristics	1986-1990 (n=2,012)	1997-2001 (n=3,074)	2007-2011 (n=2,157)	*P for trend*
Age (median [IQR], years)	70 [60-78]	73 [61-82]	68 [57-80]	**0.12**
Age (years, %)				
<55	14.0	15.5	19.8	
55-64	21.8	16.1	21.1	
65-74	30.3	22.9	22.3	
≥75	33.9	45.5	36.9	
Men (%)	60.1	57.3	61.0	0.99
White (%)	97.6	95.4	91.7	**<0.001**
History of disease (%)				
Coronary artery disease	19.1	52.4	32.0	**<0.001**
Congestive heart failure	14.8	23.5	20.6	**<0.001**
Diabetes	25.7	32.0	38.3	**<0.001**
Hypertension	49.9	65.0	74.9	**<0.001**
Stable angina	27.6	23.3	6.6	**<0.001**
Stroke/transient ischemic attack	9.1	13.5	13.1	**<0.001**
Admission potassium (median [IQR], mmol/L)	4.1 [3.7- 4.4]	4.2 [3.9- 4.7]	4.2 [3.8- 4.6]	**<0.001**
Length of stay (median [IQR], day)	10 [7- 13]	5 [3-8]	3 [2-6]	**<0.001**
In hospital complications (%)				
Atrial fibrillation	19.3	16.9	17.2	**0.047**
Heart failure	41.5	36.1	32.4	**<0.001**
Pulmonary edema	18.3	13.3	8.2	**<0.001**
Cardiogenic shock	6.9	6.3	5.1	**<0.001**
Treatment (%)				
Aspirin	43.7	88.4	94.5	**<0.001**
ACE-I/ARBs	8.6	54.2	72.4	**<0.001**
Antiarrhythmic agents	20.3	14.6	11.1	0.11
Beta blockers	48.4	81.1	92.6	**<0.001**
Lipid lowering agents	2.9	38.2	89.2	**<0.001**
Thrombolytic therapy	17.4	16.2	0.6	**<0.001**
PCI	2.8	22.6	53.6	**<0.001**
CABG surgery	1.7	6.6	7.5	**<0.001**

Note: Years 1991-1995 and 2003-2005 were omitted for easy presentation of data.

p-values for trend were from logistic regression for categorical variables and linear regression for continuous variables with study year as a linear predictor.

IQR: interquartile range, CK: creatinine kinase, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin II receptor blockers, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

Table 0.3: Trends in hospital incidence rates and case-fatality rates of ventricular tachycardia and ventricular fibrillation for each decade among patients with acute myocardial infarction

	Ventricular tachycardia		Ventricular fibrillation	
Incidence rates	N= 11,251		N= 10,094	
In years 1986/1988	14.3		8.2	
In years 2009/2011	10.5		1.7	
Trends regression models	IRR	95%CI	IRR	95%CI
Unadjusted	**0.85**	**0.81-0.91**	**0.57**	**0.51-0.64**
Demographic factors (1)	**0.86**	**0.81-0.91**	**0.58**	**0.52-0.65**
History of disease (2) & (1)	**0.87**	**0.82-0.92**	**0.60**	**0.53-0.67**
Clinical presentation (3) & (1), (2)	**0.89**	**0.83-0.94**	**0.63**	**0.57-0.70**
In-hospital treatments (4) & (1), (2), (3)	**0.89**	**0.81-0.97**	**0.80**	**0.68-0.93**
Case-fatality rates	N= 1,731		N= 574	
In years 1986/1988	27.7		49.5	
In years 2009/2011	6.9		37.5	
Trends regression models	IRR	95%CI	IRR	95%CI
Unadjusted	**0.64**	**0.53-0.77**	**0.87**	**0.76-0.99**
Demographic (1)	**0.59**	**0.49-0.71**	**0.84**	**0.74-0.95**
History of disease (2) & (1)	**0.57**	**0.47-0.68**	**0.80**	**0.71-0.90**
Clinical presentation (3) & (1), (2)	**0.59**	**0.50-0.71**	**0.76**	**0.67-0.86**
In-hospital treatments (4) & (1), (2), (3)	1.09	0.86-1.39	1.07	0.91-1.27

IRR: incidence rate ratio, 95%CI: 95% Confidence interval

Note: each block of variables was added to precedent blocks in the successive models.

Block 1: Age, sex, race

Block 2: History of heart failure, diabetes, hypertension, and stroke/transient ischemic attack

Block 3: In-hospital serum potassium levels, complication of atrial fibrillation, heart failure, and cardiogenic shock

Block 4: In hospital treatment of aspirin, angiotensin converting enzyme inhibitors, antiarrhythmic agents, beta-blockers, lipid-lowering agents, thrombolytics, percutaneous coronary intervention, and coronary artery bypass surgery.
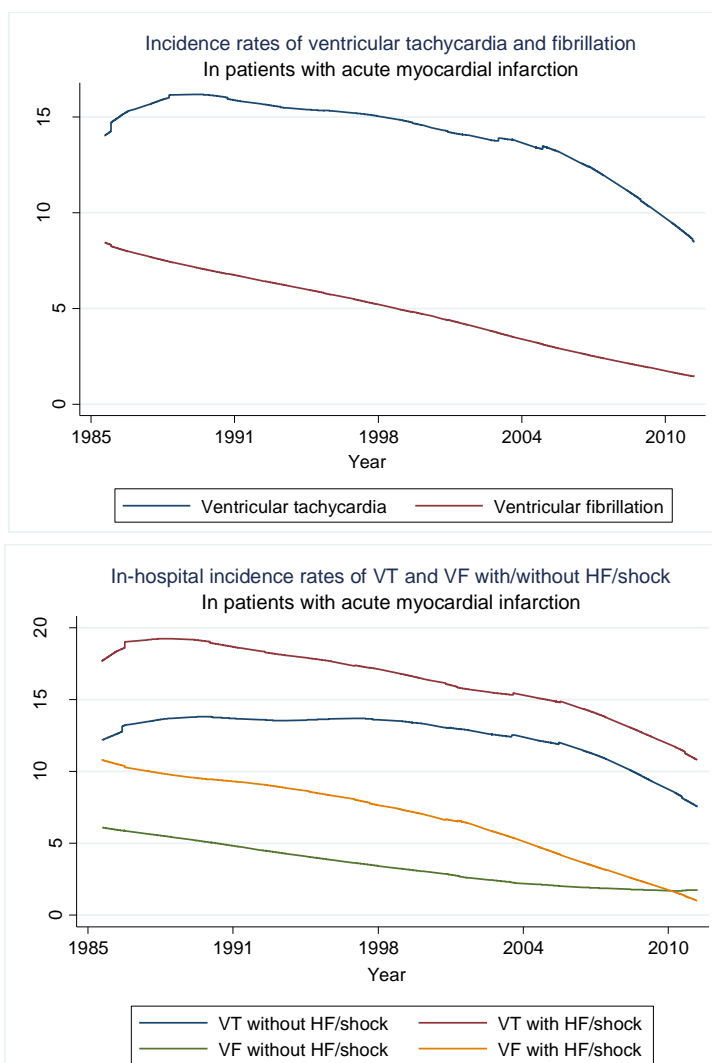
Figure 0.1: Trends in hospital incidence rates of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with acute myocardial infarction, Worcester Heart Attack Study.
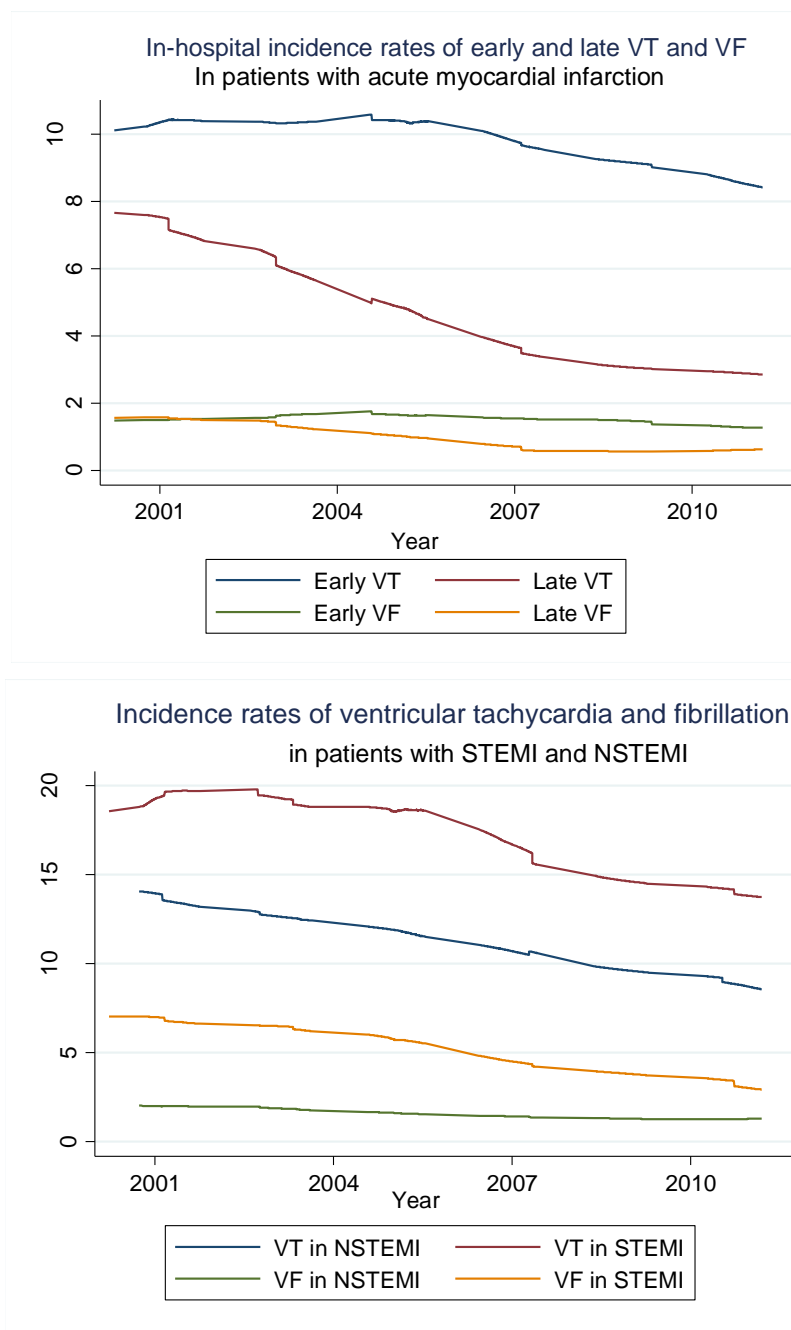
Figure 0.2: Trends in hospital incidence rates of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with ST segment-elevation myocardial infarction and non-ST segment -elevation myocardial infarction (top panel) and by timing of VT and VF (early: in the first 48 hours of hospital stay, late: after the first 48 hours of hospital stay, bottom panel).
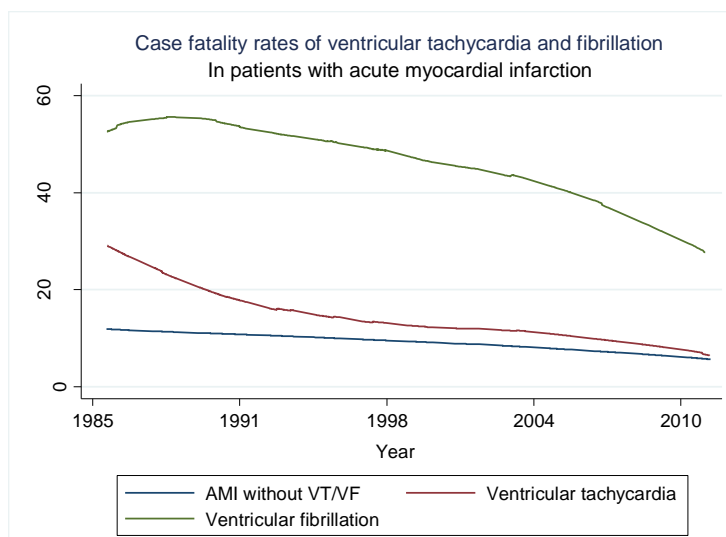
Figure 0.3: Trends in hospital case-fatality rates of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with acute myocardial infarction, Worcester Heart Attack Study.

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CHAPTER III

**ASSOCIATION BETWEEN GLYCEMIC STATE AT THE TIME OF HOSPITAL
ADMISSION AND OCCURRENCE OF VENTRICULAR ARRHYTHMIAS IN
PATIENTS SUFFERING ACUTE MYOCARDIAL INFARCTION**

Abstract

Background: While patients with hyperglycemia are at increased risk for dying in the setting of acute myocardial infarction (AMI), little is known about the association of hyperglycemia with the development of dangerous ventricular arrhythmias in patients hospitalized with AMI.

Methods: We used data from a population-based study of patients hospitalized with AMI at all central Massachusetts medical centers on a biennial basis between 2001 and 2011. Hyperglycemia was defined as a serum glucose level ≥140mg/dl at the time of hospital admission. Ventricular tachycardia (VT) and fibrillation (VF) were identified from physicians' progress notes and electrocardiographic findings. Multivariable logistic regression models were used to adjust for several potentially confounding variables.

Results: The mean age of the study population (n=4,140) was 70 years, 58.0% were men, and 92.7% were non-Hispanic white. Hyperglycemia was present in 51.9% of patients at the time of hospital admission; VT occurred in 652 patients (15.8%) and VF in 108 patients (2.6%), and two-thirds of these episodes occurred during the first 48 hours after hospital admission (early). After multivariable adjustment, hyperglycemia was associated with an increased risk of VT (adjusted OR=1.48, 95%CI=1.23-1.78). Hyperglycemia was significantly associated with early VT (multivariable adjusted OR=1.39, 95%CI=1.11-1.73) but not with late VT (adjusted OR=1.19, 95%CI=0.89-1.59). Similar associations were observed in both diabetic and nondiabetic patients, and in patients with and without ST-segment elevation AMI. Hyperglycemia was initially associated with occurrence of any VF (crude OR=1.73, 95%CI=1.16-2.59) but was not significant after multivariable adjustment (OR=1.44, 95%CI=0.92-2.25).

Conclusions: Efforts should be made to closely monitor and treat hyperglycemia, especially early after hospital admission, in patients hospitalized for AMI to reduce their risk of VT.

Introduction

Ventricular tachycardia and fibrillation frequently complicate the clinical course of patients hospitalized with acute myocardial infarction and is associated with worse in-hospital and long-term outcomes, especially sudden cardiac death.[6,7] The development of ventricular tachycardia (VT) in patients with an acute myocardial infarction (AMI) is typically associated with a larger infarct, ST segment elevation, ventricular dysfunction, and more extensive underlying coronary artery disease.[4,5]

During the early stages of AMI, the sympathetic nervous system responds to physiological and emotional stress by releasing noradrenalin, and serum glucose levels typically increase shortly in response to this sympathetic stimulation.[40] The hyperglycemic state can directly alter cardiac electrophysiological status by prolonging the QT-interval, thereby increasing the risk of VT and other serious cardiac arrhythmias.[42] In addition, hyperglycemia is associated with a larger infarct size,[45] impaired microvascular circulation,[46] and worse left ventricular function,[47] which can independently promote electrical instability. Few studies have, however, examined the association between serum glucose levels at the time of hospital admission and occurrence of VT or VF after an AMI.[48,90,91]. Moreover, these studies have been limited by their small sample size, have examined the occurrence of VT with other cardiac arrhythmias which may not share the same underlying mechanisms, or have not examined the time of onset of VT in relation to elevated blood glucose levels.[48,49,90,91]

Using data from a large population-based surveillance study of patients hospitalized with independently confirmed AMI at all 11 central Massachusetts medical

centers, we examined the association between serum glucose levels at the time of hospital admission and the development of VT and VF during the patient's acute hospitalization.

Methods

Study design and data collection

We used data from the Worcester Heart Attack Study, an ongoing population-based investigation that is examining long-term trends in the incidence, hospital, and post-discharge case-fatality rates of AMI among residents of the Worcester, Massachusetts, metropolitan area for this investigation.[65] In brief, the medical records of people hospitalized for possible AMI at the 11 medical centers serving residents of central Massachusetts were individually reviewed and the diagnosis of AMI was independently validated according to criteria developed by the World Health Organization; patients were further classified into those with an ST-segment elevation AMI (STEMI) or Non-ST segment elevation AMI (NSTEMI).[70] This investigation was approved by the Institutional Review Board at the University of Massachusetts Medical School.

Trained nurses and physicians abstracted demographic, clinical, and treatment data from the medical records of patients hospitalized with a confirmed AMI.[65] Quality control was routinely conducted with all nurse and physician data abstractors. Abstracted information included: patient's age, sex, medical history, physiologic factors, laboratory test results at the time of hospital admission, length of hospital stay, and the in-hospital use of important cardiac medications and procedures (coronary angiography,

percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery). Development of several significant clinical complications (e.g., atrial fibrillation, cardiogenic shock, stroke, heart failure) during the patient's index hospitalization was identified using standardized criteria.[72]

Ventricular arrhythmias

In the present study, the occurrence of VT and VF was based on physicians' progress notes. To reduce the possible misclassification of VT and VF due to underreported occurrence of these arrhythmias in physicians' notes, the study research physicians also reviewed patients' ECG strips in their hospital medical records. Ventricular tachycardia was defined as a cardiac arrhythmia of three or more consecutive complexes originating in the ventricles at a rate of greater than 100 beats per minute (cycle length less than 600 milliseconds).[2] Information was also collected about the date of initial VT occurrence since hospital admission. Ventricular fibrillation was defined as a rapid, usually more than 300 beats per minute (cycle length 200 millisecond or less), grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude.[2]

Patients were classified as having either early, defined as occurring within 48 hours after hospital admission, or late (occurring after 48 hours) VT. For patients who had multiple episodes of VT and VF, only the first episode was counted.

Serum glucose levels

Glucose levels were measured from blood samples drawn at the time of admission to the emergency department of all participating medical centers as part of their standard

workup of hospitalized patients. All blood tests followed a standardized protocol in the laboratories at each participating hospital.

Prior studies that have examined the prognostic impact of admission serum glucose levels have used various thresholds to define hyperglycemia.[92,93] For purposes of this study, we defined hyperglycemia as a serum glucose level ≥140 mg/dl, the cutoff suggested by the American Heart Association (AHA) for both diabetic and nondiabetic patients.[41]

Study population

There was a total of 5,783 patients hospitalized with a verified AMI at all central Massachusetts medical centers on a biennial basis between 2001 and 2011. We excluded from this pool of patients 84 patients who developed VT and VF prior to hospital admission and 18 for whom the timing of VT or VF could not be determined. We also excluded patients with missing data on age (n=263), race (n=187), heart rate (n=100), blood pressure (n=34), serum potassium (n=42), glucose (n=87), white blood cell count (n=20), troponin I (n=349), and serum calcium (n=450) findings, as well as length of hospital stay (n=9). The final study sample consisted of 4,140 patients with independently confirmed AMI.

Data Analysis

The baseline characteristics of patients who had serum glucose levels greater or less than 140mg/dl were compared using Chi-Square tests for categorical variables and the t-test or Kruskal–Wallis test for continuous variables. We used multivariable logistic regression modelling to examine the association between serum glucose levels at the time

of hospital admission with the occurrence of VT and VF, while controlling for several potentially confounding factors. We *a priori* controlled for age, sex, and race in all regression models. Other variables were then iteratively tested and variables which changed the estimates of the effects of elevated serum glucose levels on the development of VT or VF by more than 10% were retained in the final models. We also carried out subgroup analyses in which we examined the association between hyperglycemia and VT and VF in patients with STEMI in comparison to those with an NSTEMI, and according to a history of diabetes as recorded in hospital medical records. Finally, in a sensitivity analysis, we used a higher serum glucose cutoff of ≥180mg/dl to define hyperglycemia to facilitate comparisons with a prior study.[48]

Results

Baseline patient characteristics

The average age of the study population was 70 (± 13.8) years, 58.0% were men, and 92.7% were non-Hispanic whites. The mean and median [inter quartile range (IQR)] serum glucose levels at the time of hospital admission were 171.4 mg/dl and 143.0 [116.0-203.0] mg/dl, respectively. Hyperglycemia, defined as a serum glucose level ≥140mg/dl at the time of hospital admission, was present in 51.9% of hospitalized patients (Figure 3.1).

Patients with high serum glucose levels at admission were approximately 5 years older and more likely to be female than patients with glucose levels <140mg/dl (Table 3.1). Patients with hyperglycemia were more likely to have been previously diagnosed

with several important comorbidities (e.g., heart failure, chronic lung disease, chronic kidney disease, diabetes, and hypertension); these patients also had higher heart rate, serum potassium, and serum white blood cell count findings at hospital presentation than patients with glucose levels <140mg/dl (Table 3.1). They were also more likely to have developed clinically significant in-hospital complications (e.g., acute kidney injury, atrial fibrillation, heart failure, and cardiogenic shock) and were more likely to have received ACE-I/ARBs and anti-arrhythmic agents during their hospital stay compared with patients with lower serum glucose levels. On the other hand, patients with hyperglycemia had lower systolic blood pressure and serum calcium findings at hospital presentation, and were less likely to have received aspirin or lipid lowering agents or to have undergone a PCI during their acute index hospitalization.

Serum glucose levels and incidence of ventricular tachycardia

In our patient population, VT occurred in 652 patients (15.8%); for two-thirds of these patients (n=434) their first episode occurred within 48 hours of hospital admission. Overall, after adjusting for several demographic and clinical variables of prognostic importance, patients admitted with serum glucose levels ≥140mg/dl had an almost 50% higher odds of developing VT during their acute hospital stay than those with lower glucose levels (Table 3.2). This association was observed in the 434 patients who developed early VT (adjusted OR=1.39, 95%CI=1.11-1.73) whereas among the 218 patients whose VT developed at a later time (more than 48 hours after hospital admission), the association between hyperglycemia and late onset VT was weaker and not statistically significant (adjusted OR=1.19, 95%CI=0.89-1.59). Adjusting for the

hospital receipt of various cardiac interventions and medications did not materially affect the observed associations.

A history of diabetes was present in 36.1% of study patients. As expected, the mean and median [IQR] serum glucose levels were 224mg/dl and 209 [147-283]mg/dl among patients with previously diagnosed diabetes and 142mg/dl and 129 [110-157]mg/dl among patients without a history of diabetes. However, as other have found, the development of VT was similar among patients with and without a history of diabetes (14.5% vs. 16.5%, respectively, p=0.09), and most events of VT in these patient populations occurred during the first 48 hours of hospital presentation (61.6% and 69.0%, respectively, p=0.06).

In further examining the relationship between hyperglycemia and VT further stratified according to the presence of previously diagnosed diabetes, patients with elevated serum glucose levels had a 40-70% higher odds of developing any VT or early VT compared with patients with lower serum glucose levels in those with and without a history of diabetes (Table 3.3).

Serum glucose levels were essentially similar for the 1,277 patients with STEMI and for the2,863 patients with an NSTEMI. The mean and median [IQR] serum glucose levels were 168mg/dl and 144 [120-189]mg/dl, respectively, in patients with a STEMI and 173mg/dl and 143 [114-210]mg/dl, respectively, in patients who had an NSTEMI (p=0.46). However, VT developed significantly more often in patients with a STEMI than an NSTEMI (22.0% vs. 13.0%, respectively, p<0.001) and a significantly greater proportion of VT episodes occurred during the first 48 hours of hospital admission in

patients with a STEMI (78.7%) than among those with an NSTEMI (57.4%), (p<0.001).

Compared with patients who had lower serum glucose levels, patients who had elevated

serum glucose levels had an approximate 30% higher multivariable adjusted odds of

developing VT, regardless of the type of AMI (Table 3.3).

We conducted a sensitivity analysis using a cutoff for hyperglycemia at ≥180

mg/dl, a cut point that has been used in several prior studies.[48] Using this cutoff, a total of

1,309 patients were considered to be hyperglycemic. With this more stringent definition,

hyperglycemia no longer was a risk factor for developing VT at any time during the

patient's acute hospitalization (adjusted OR=1.04, 95%CI=0.87-1.25), with essentially

similar findings noted for the development of either early VT (adjusted OR=1.16,

95%CI=0.90-1.49), or late VT (adjusted OR=1.09, 95%CI=0.82-1.46), nor at any time

during the acute hospitalization for patients with a history of diabetes (adjusted OR=0.93,

95%CI=0.69-1.25).

Serum glucose levels and incidence of ventricular fibrillation

Ventricular fibrillation occurred in 108 patients (2.6%), with 67 (62.0%) occurred

within 48 hours after hospital admission. Approximately a half of patients (51.9%) who

developed VF also developed VT. A serum glucose level ≥140mg/dl was associated with

a higher risk of developing VF during hospitalization (OR=1.73, 95%CI=1.16-2.59).

However, this association was attenuated and became statistically insignificant after

adjusting for age, sex, race, history of diabetes, the development of cardiogenic shock,

and the presence of ST-segment elevation (OR=1.44, 95%CI=0.92-2.25).

Discussion

We found that patients with serum glucose levels above 140 mg/dl at the time of hospital admission for an AMI were at considerably greater risk for developing VT during their hospitalization, most notably early during their acute hospital stay, than patients with normoglycemia. This association was observed in both diabetic and nondiabetic patients and in patients with a STEMI and an NSTEMI.

Serum glucose levels and risk of developing VT

Elevated serum glucose levels at the time of hospital admission for AMI have been associated with higher death rates in both diabetic and nondiabetic patients.[94] However, evidence for an association between hyperglycemia and developing a serious cardiac arrhythmia, especially VT, is limited. In our large community-based study we found an elevated risk for developing VT among AMI patients with serum glucose levels ≥140mg/dl.

Our findings are consistent with those of a limited number of prior studies, despite their small sample sizes, non-optimal reperfusion treatment,[48,90] and failure to examine the relation between hyperglycemia and the time of onset of VT[48,91]. In a study of 1,258 consecutive patients with AMI admitted to a single coronary care unit in Valencia, Spain during a 4 year period, patients with serum glucose levels ≥180mg/dl at the time of hospital admission had more than twice the odds of developing either VT or ventricular fibrillation than patients with lower serum glucose levels.[48]

Several mechanisms have been proposed to explain the potentially proarrhythmic effects of hyperglycemia in patients hospitalized with an AMI.[41] Hyperglycemia can cause QT-interval prolongation and dispersion,[95] which can trigger ventricular

arrhythmias in those with underlying coronary artery disease.[96] Hyperglycemia has been associated with a larger infarct size, worse left ventricular function,[94,97] and increases in serum markers of inflammation [41,97] which may promote the development of secondary cardiac arrhythmias. Hyperglycemia following an ischemic injury may also be a proxy of increased sympathetic activity, which could exert its proarrhythmic effects through elevated circulatory catecholamines and free fatty acids.[98] Irrespective of the underlying mechanisms involved, the greater risk of developing VT among AMI patients with elevated glucose levels emphasizes the need for systematically assessing serum glucose levels at hospital admission and for more aggressive surveillance and treatment of patients with elevated glucose to reduce their risk of VT.

Association of elevated serum glucose levels and timing of VT

After adjusting for several potentially confounding variables, we found that patients with hyperglycemia were at increased risk for developing early VT. Early VT may be triggered by increased sympathetic activity or the inflammatory response to acute ischemic injury, each of which have been shown to be associated with elevated serum glucose levels in patients with AMI.[16] Inflammatory responses to the acute ischemic insult predominately occur during the first few days after an AMI and are associated with increased resting membrane potential and prolonged action potential duration,[41,97] which may contribute to the triggering of early VT.[17]

While reperfusion therapy may induce reperfusion-associated cardiac arrhythmias, and may have contributed to some of the cases of early VT observed in the

present investigation, adjusting for reperfusion therapy did not materially change the estimated association of hyperglycemia with the development of VT.

In addition, hyperglycemia was associated with a higher likelihood of developing late VT, a condition that usually occurs due to reentry pathways via isolated bundles of surviving myocytes at the border of the infarct.[19] Late VT may also occur secondarily to developing heart failure or cardiogenic shock,[94] which may be more prevalent in patients with a larger infarct, that is also associated with the hyperglycemic state.[99]

In the present study, the elevated risk for developing late VT in patients with hyperglycemia was modestly attenuated after adjusting for heart failure and other potentially confounding factors of prognostic importance. This suggests that hyperglycemia may act by worsening left ventricular function to promote the onset of late VT. Inasmuch, efforts to reduce infarct size and improve left ventricular function may reduce the late proarrhythmic effects of hyperglycemia.

Risk of VT in diabetic and nondiabetic patients with high serum glucose levels

At hospital admission, patients with diabetes had higher serum glucose levels than patients without this metabolic disorder. However, these higher average glucose levels did not translate into a greater risk for VT. Several prior studies have also reported that, compared to patients without diabetes, patients with diabetes had a similar risk of developing new onset ventricular arrhythmias.[48,100]

In separate analyses for patients with and without previously diagnosed diabetes, we found that glucose levels ≥140mg/dl at admission were associated with an increased risk of developing VT. In the aforementioned study in Spain, similar associations were

observed only among patients without, but not those with, a history of diabetes.[48] However, the authors of that study used a cutoff of 180mg/dl to define hyperglycemia and the risk of VT primarily increased when serum glucose levels were higher than 120mg/dl in patients with diabetes. Inasmuch, high risk patients might have been included in the 2 comparison groups.[48] In a sensitivity analysis using a ≥180mg/dl cutoff to define hyperglycemia, we similarly found an elevated risk of developing VT with hyperglycemia only in patients without previously diagnosed diabetes.

Elevated sympathetic activity and acute inflammatory processes may play a larger role in inducing VT after AMI rather than the effect of chronic high concentrations of glucose itself. This hypothesis may also help to explain the significant association that we observed between hyperglycemia and the development of early, but not late VT, when sympathetic activation and the inflammatory response may subside. It is also possible that the antidiabetic therapies that patients with a history of diabetes might have received could have prevented or mitigated the onset of VT. However, these hypotheses remain speculative and warrant further investigation.

Risk of VT in patients with STEMI and NSTEMI with high serum glucose levels

Consistent with the results of prior studies,[84] we found that VT occurred more frequently in patients with a STEMI than in those with an NSTEMI (22% vs. 13%). This may be due to the complete blockage of a coronary artery that occurs in patients with a STEMI and the subsequent development of hemodynamic disturbances and myocardial electrical instability. In the present study, when stratifying on the presence of the type of AMI, patients with hyperglycemia experienced a 30% elevated odds of developing VT

during their acute hospitalization. We are not aware of any previous study that has

examined the relationship between elevated serum glucose levels and the risk of

developing VT according to the 2 principal phenotypic expressions of AMI. The

increased risk of VT associated with hyperglycemia suggests that close monitoring and

treatment of hyperglycemia may reduce the risk of VT in patients with either a STEMI or

an NSTEMI.

Serum glucose levels and risk of developing VF

Despite an initial higher risk of developing VF in patients with hyperglycemia at

hospital admission, this risk was statistically insignificant after adjusting for important

potential confounders. Other studies which used a composite outcome of VT and VF

found an association between hyperglycemia and VAs.[48,90] It was unclear if the

association between hyperglycemia and VAs in prior studies was mainly driven by VT

since VT is more common than VF and these studies did not examine VT and VF

separately. The null association between hyperglycemia and VF in contrast with that of

VT may suggest VF have different contributing factors, as a half of VF cases in the

present study did not coexist with or develop from deteriorating VT. However, given less

than 3% of patients developed VF in the present study, it is possible that we lack the

statistical power to detect a meaningful association, and larger studies are warranted.

Study strengths and limitations

The present study has several strengths. We used data from a large, population-

based, investigation of patients hospitalized with AMI at all medical centers in central

Massachusetts, all of whom were telemonitored for their entire hospital stay, thereby

minimizing the possibility of undiagnosed asymptomatic VT. However, some limitations of our observational study must also be noted. The in-hospital management of patients with hyperglycemia may affect the development of VAs, especially late VAs; however, we were unable to examine the impact of anti-hyperglycemic treatment since we did not collect data on the use of insulin or other antidiabetic medications. We also did not collect any information on changes in serum glucose levels during hospitalization for AMI, and, therefore, could not characterize the persistence of hyperglycemia throughout a patient's acute hospitalization.

Conclusions

Hyperglycemia was associated with an increased risk for VT, especially within the first 48 hours after hospital admission, among patients hospitalized with validated AMI at all medical centers in central Massachusetts. Further studies are needed to more fully understand both the biologic mechanisms involved in the associations observed and the effects of hospital therapies that reduce serum glucose levels on the risk of developing VT following an AMI.

Table 0.1: Baseline characteristics of patients according to serum glucose levels at the time of hospital admission for an acute myocardial infarction

Characteristics	<140 mg/dl (n=1,949)	≥140 mg/dl (n= 2,191)	p-value
Age (median [IQR], years)	69 [57-81]	74 [63-82]	**<0.001**
Age (%)			**<0.001**
<55	20.7	11.9	
55-64	20.4	16.3	
65-74	20.2	23.9	
≥75	38.8	48.0	
Men (%)	62.0	54.4	**<0.001**
White (%)	93.0	92.5	0.58
Medical History (%)			
Coronary artery disease	32.6	42.9	**<0.001**
Heart failure	17.1	28.1	**<0.001**
Chronic lung disease	15.6	19.2	**0.002**
Chronic kidney disease	16.5	24.3	**<0.001**
Diabetes	16.3	53.7	**<0.001**
Hypertension	70.3	79.6	**<0.001**
Hypercholesterolemia	61.8	62.6	0.59
Stable angina	13.9	15.3	0.23
Stroke/transient ischemic attack	12.2	16.0	**<0.001**
Findings at admission			
Pulse (median [IQR], beat/min)	78 [67-92]	88 [74-104]	**<0.001**
SBP (median [IQR], mmHg)	141 [122-161]	140 [119-161]	0.18
Troponin I (median [IQR], ng/mL)	0.51 [0.10-3.50]	0.50 [0.10-3.70]	0.72
Potassium (median [IQR], mmol/L)	4.1 [3.8-4.5]	4.2 [3.9-4.7]	**<0.001**
Calcium (median [IQR], mg/dL)	9.1 [8.7-9.5]	9.0 [8.7-9.4]	**0.002**
WBCC (median [IQR], 10^9cell/L)	8.9 [7.2-11.2]	10.4 [7.9-13.4]	**<0.001**
ST segment elevation	29.8	31.8	0.16
In hospital complications (%)			
Acute kidney injury	10.4	19.3	**<0.001**
Atrial fibrillation	16.7	22.1	**<0.001**
Heart failure	25.9	45.5	**<0.001**
Cardiogenic shock	2.4	6.5	**<0.001**
Treatment during hospitalization (%)			
Aspirin	94.4	91.6	**<0.001**
ACE-I/ARBs	67.7	73.3	**<0.001**
Antiarrhythmic agents	14.6	18.9	**<0.001**
Beta blockers	92.3	90.9	0.10
Lipid lowering agents	77.2	74.1	**0.018**
Thrombolytic therapy	2.3	2.4	0.74
Percutaneous coronary intervention	51.6	42.0	**<0.001**
CABG	7.1	6.9	0.80
Length of stay (median [IQR], day)	4 [2-6]	4 [3-7]	**<0.001**

p-value from Chi-square test and Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

IQR: interquartile range, WBCC: white blood cell count, ACE-I/ARBs: angiotensin converting enzyme inhibitor/angiotensin II receptor blockers, CABG: coronary artery bypass graft surgery.

Table 0.2: Association between serum glucose levels at the time of hospital admission and development of ventricular tachycardia (VT) in patients with acute myocardial infarction (n=4,140)

		Odd ratio (95% Confidence interval)			
		Unadjusted		Adjusted	
Type of VT	**VT (IR)**	<140mg/dl	≥140mg/dl	<140mg/dl	≥140mg/dl
All VT	652 (15.7%)	Reference	**1.28 (1.08-1.51)**	Reference	**1.48[*] (1.23-1.78)**
Early VT	434 (10.5%)	Reference	1.21 (0.99-1.48)	Reference	**1.39[†] (1.11-1.73)**
Late VT	218 (5.32%)	Reference	**1.42 (1.07-1.87)**	Reference	1.19[‡] (0.89-1.59)

IR: incidence rate.

Early VT was defined as VT occurred within 48 hours after hospital admission.

[*]Adjusted for age, sex, race, and history of diabetes

[†]Adjusted for age, sex, race, history of diabetes, and AMI subtype

[‡]Adjusted for age, sex, race, and in-hospital heart failure complication

Table 0.3: Association between serum glucose levels at hospital admission and development of ventricular tachycardia (VT) in subgroups of patients with acute myocardial infarction

Population	VT/n	Odd ratio (95% Confidence interval)			
		Unadjusted		Adjusted	
		<140mg/dl	≥140mg/dl	<140mg/dl	≥140mg/dl
Diabetes status					
Diabetic	216/1,494	Reference	**1.66 (1.11-2.47)**	Reference	**1.72[ǀ] (1.15-2.57)**
Nondiabetic	436/2,646	Reference	**1.36 (1.10-1.67)**	Reference	**1.41[ǀ] (1.14-1.74)**
AMI subtype					
STEMI	281/1,277	Reference	1.17 (0.90-1.53)	Reference	**1.32[ǀ] (1.00-1.73)**
NSTEMI	371/2,863	Reference	**1.33 (1.07-1.66)**	Reference	**1.30[ǀ] (1.04-1.63)**

STEMI: ST segment-elevation myocardial infarction, NSTEMI: non-ST segment -elevation myocardial infarction, n: subsample
[ǀ]Adjusted for age, sex, and race

Table 0.4: Association between serum glucose levels at the time of hospital admission and development of ventricular fibrillation (VF) in patients with acute myocardial infarction (n=4,140)

		Odd ratio (95% Confidence interval)			
		Unadjusted		Adjusted[*]	
	VF (IR)	<140mg/dl	≥140mg/dl	<140mg/dl	≥140mg/dl
All VF	127 (3.07%)	Reference	**1.73 (1.16-2.59)**	Reference	1.44 (0.92-2.25)

IR: incidence rate.

[*]Adjusted for age, sex, race, history of diabetes, cardiogenic shock complication, and the presence of ST-segment elevation
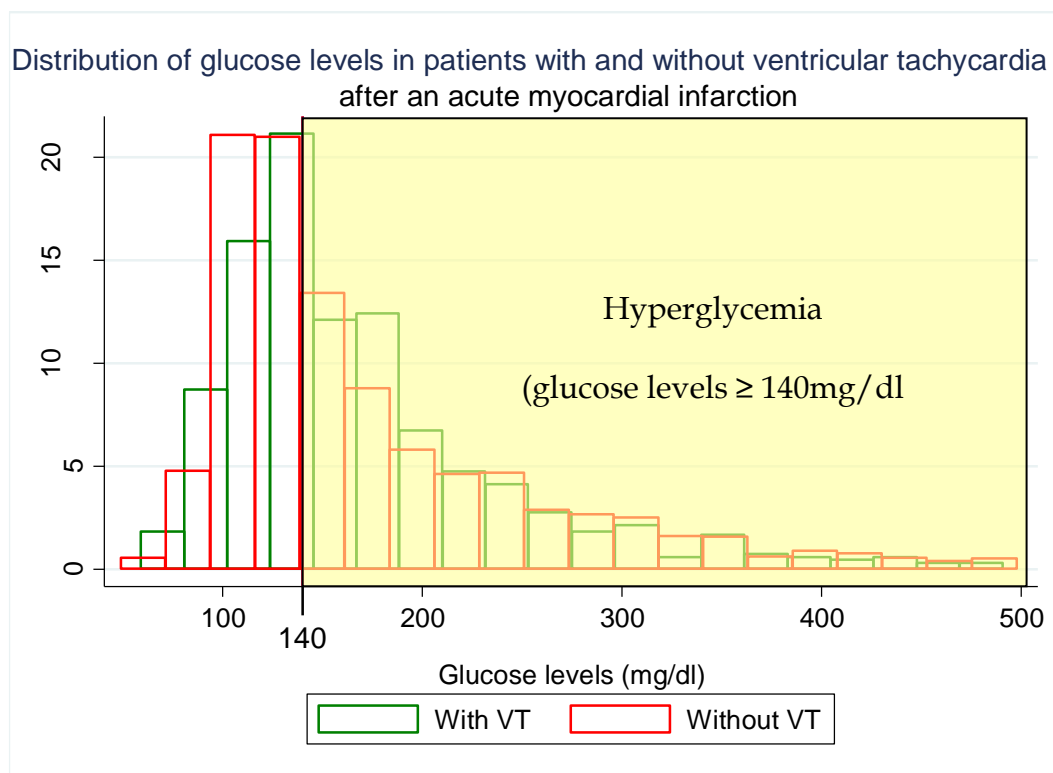
Figure 0.1: Distribution of serum glucose levels at hospital admission in patients who did and did not develop ventricular tachycardia after acute myocardial infarction
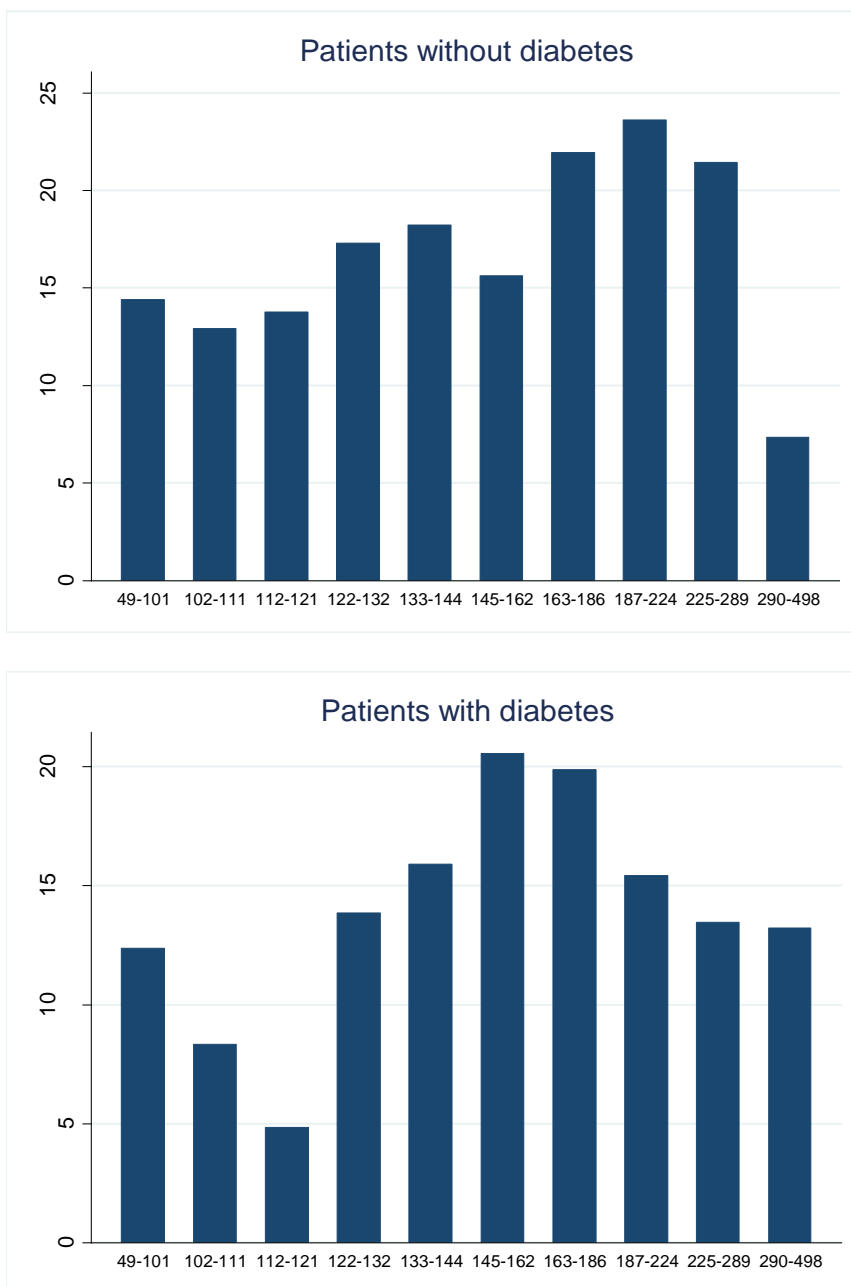
Figure 0.2: Incidence rates of ventricular tachycardia in decile groups of patients based on serum glucose levels (mg/dl) at hospital admission
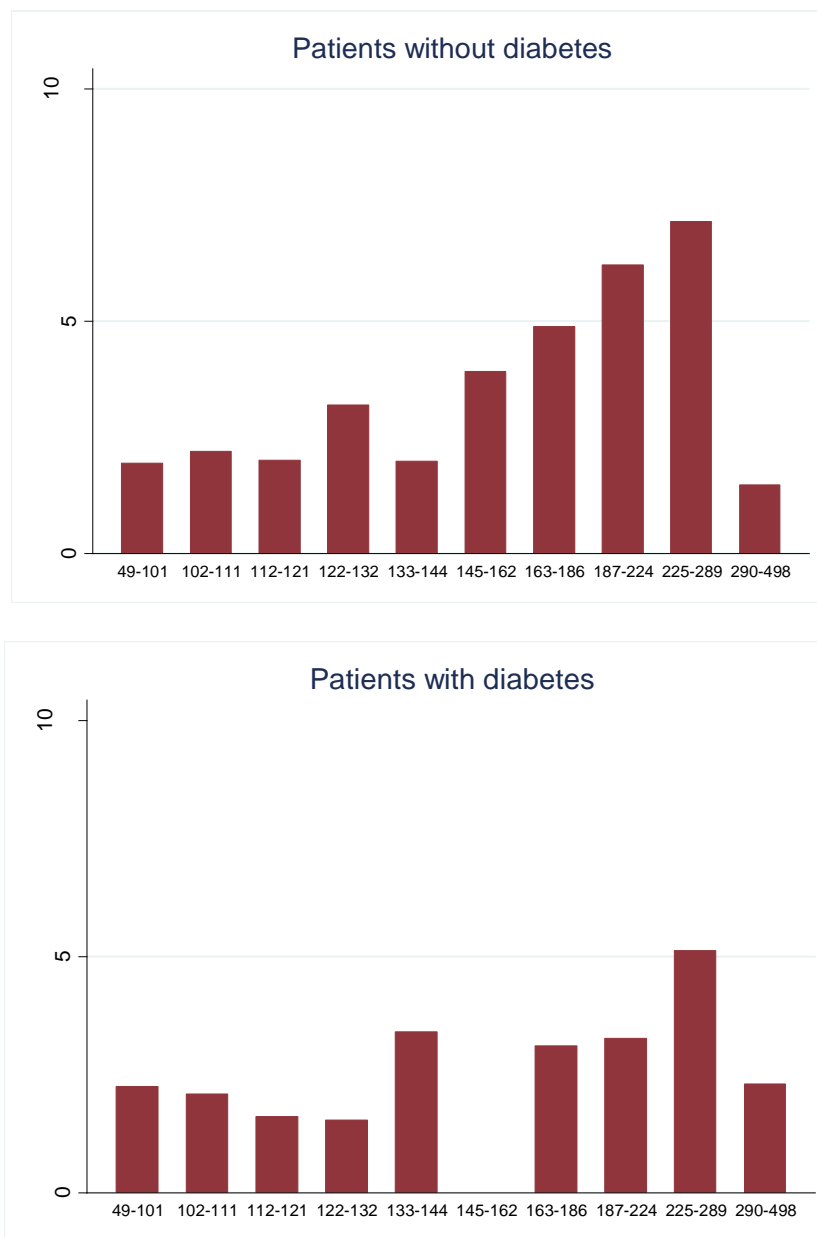
Figure 0.3: Incidence rates of ventricular fibrillation in decile groups of patients based on serum glucose levels (mg/dl) at hospital admission
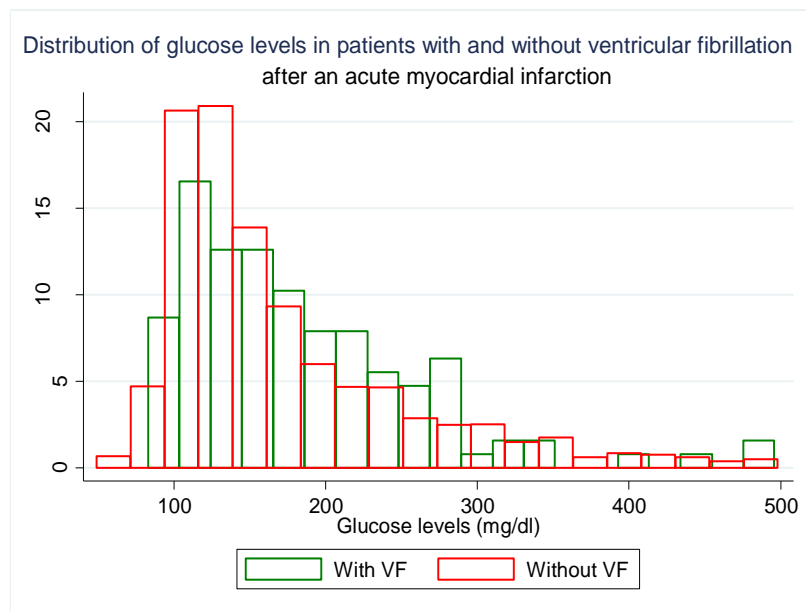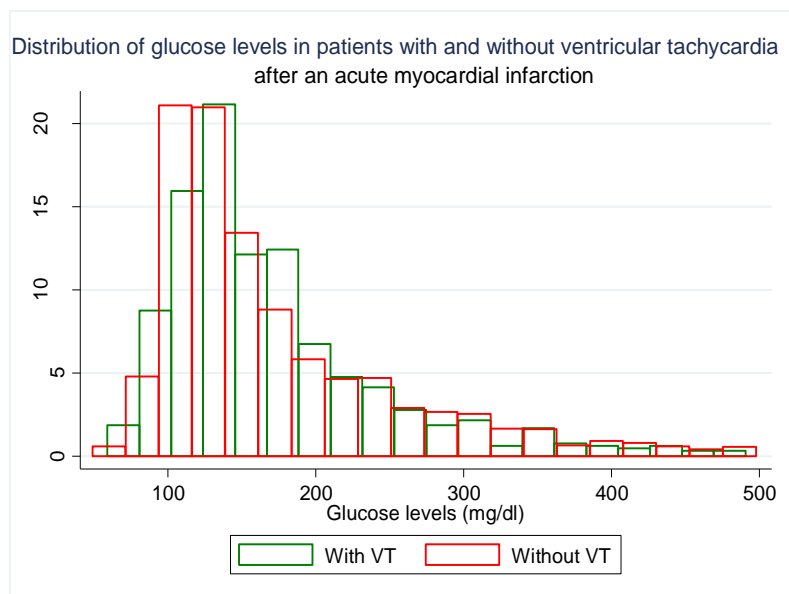
Figure 0.4: Distribution of serum glucose level at hospital admission in patients according to the presence of ventricular tachycardia (VT) or ventricular fibrillation (VF)

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CHAPTER IV

**ASSOCIATION BETWEEN OCCURRENCE OF VENTRICULAR
ARRHYTHMIAS AFTER AN ACUTE CORONARY SYNDROME AND 12-
MONTH PROGRESSION OF DEPRESSION AND ANXIETY**

Abstract

Background: Comorbid depression and anxiety are common and associated with worse clinical outcomes in patients hospitalized with an acute coronary syndrome (ACS). We investigated the association between serious ventricular arrhythmias (VAs) with progression of depression and anxiety among hospital survivors of an ACS.

Methods: Patients were interviewed in hospital, and at 1, 3, 6, and 12 months after hospital discharge. The primary outcome was the presence of moderate/severe symptoms of depression and anxiety defined as a Patient Health Questionnaire (PHQ)-9 score ≥10 and a Generalized Anxiety Disorder (GAD)-7 score ≥10 at baseline and 1 month and PHQ-2≥3 and GAD-2≥3 at 3, 6, and 12 months. We used marginal models to examine the association between VAs (ventricular tachycardia, ventricular fibrillation, cardiac arrest) and symptoms of depression or anxiety and PHQ-2 and GAD-2 scores over time.

Results: Average age of the study population (n=2,074) was 61.1 years, 33.5% were women, and 78.3% were white. VAs developed in 105 patients (5.1%). Symptoms of depression and anxiety were present in 22.2% and 23.5% of patients at baseline and declined to 14.1% and 12.6%, respectively, at 1 month post-discharge. Occurrence of VAs was not associated with progression of symptoms of depression (adjusted relative risk [aRR]=1.28, 95% Confidence interval [CI]=0.94-1.76) and anxiety (aRR=1.27, 95%CI=0.90-1.77), or with change in PHQ-2 and GAD-2 scores over time, both before and after risk adjustment.

Conclusion: The prevalence of symptoms of depression and anxiety were high after an ACS but quickly declined and were not associated with the occurrence of in-hospital VAs.

Introduction

Among patients with an acute coronary syndrome (ACS), anxiety and depression is prevalent, with upwards of one quarter to one half of patients reporting symptoms of either condition.[50,52,53] Moreover, these psychosocial disorders are highly interrelated, with coexistence in up to 80% of patients[101,102], and are usually long-lasting following an ACS.[54,103] Both depression and anxiety are associated with higher all-cause death rates, recurrent coronary events, and impaired quality of life.[52,56-61] However, these conditions are often undiagnosed and/or under-treated in patients hospitalized for an ACS, and have been called for greater recognition and attention by the American Heart Association.[62]

Serious ventricular arrhythmias following an ACS, including ventricular tachycardia (VT), ventricular fibrillation (VF), or cardiac arrest, may lead to additional stress and fear in patients, which could contribute to depression or anxiety. However, the impact of these life-threatening cardiac arrhythmias on the long-term progression of depression and anxiety among patients surviving an ACS has not been studied.

Using data from a large and sociodemographically diverse population of patients discharged from the hospital after an ACS, we describe the 12-month progression of symptoms of depression and anxiety, and the impact of the in-hospital occurrence of life-threatening ventricular arrhythmias, on the progression of symptoms of depression and anxiety during the subsequent year.

Methods

Study design and population

We used data from the Transitions, Risks, and Action in Coronary Events – Center for Outcomes Research and Education *(*TRACE-CORE) study for this investigation.[104] In brief, TRACE-CORE is a multicenter prospective cohort study of adult men and women hospitalized with an ACS at three tertiary care and community medical centers in Worcester, MA, two hospitals in Atlanta, GA, and one hospital in Macon, GA, between April 2011 and May 2013. Each validated episode of an ACS was categorized as either an ST-segment elevation acute myocardial infarction (STEMI), a Non ST-segment elevation myocardial infarction (NSTEMI), or as unstable angina (UA).[104] IRB approval was obtained from all participating sites and study subjects provided written informed consent.

Trained study staff collected a wide range of patient sociodemographic, lifestyle, and psychosocial characteristics at baseline (in-person hospital interview) and at 1, 3, 6, and 12 months after discharge (via phone interview). We also collected information about patients' clinical presentation, laboratory test results, and receipt of cardiac medications and coronary reperfusion therapy from hospital electronic medical records.[104]

Measurement of symptoms of anxiety and depression

Symptoms of anxiety and depression were assessed by the validated 7-item Generalized Anxiety Disorder (GAD)-7 questionnaire , range of scores from 0-21,[105] and 9-item Patient Health Questionnaire (PHQ)-9[106], score range [0- 29], at baseline and first month post discharge, and by shorter versions, GAD-2 (score range [0-6])[107] and PHQ-2 (score range [0-6])[108], at 3, 6, and 12 months post discharge to reduce participant burden.

Both the GAD and PHQ assess symptoms of anxiety and depression during the prior 2 weeks. The questionnaires were conducted in person during the first 2-3 days of the patient's index hospitalization (baseline interview) and by telephone interview at 1, 3, 6, and 12 months after hospital discharge. Due to its clinical significance, we chose the primary study outcome as the presence of moderate/severe symptoms of depression or anxiety, defined as scores of PHQ-9≥10 or PHQ-2≥3 for moderate/severe depression and GAD-7≥10 or GAD-2≥3 for moderate/severe anxiety. These cutoffs have been previously validated in general patient populations and in those with coronary heart disease. Each has sensitivity greater than 90% and specificity greater than 80%.[107-110] We also generated the PHQ-2 and GAD-2 from the first two questions of the PHQ-9 and GAD-7, respectively, at baseline and 1 month and used scores of PHQ-2 and GAD-2 as our secondary study outcomes at all post hospital discharge time points.

Life-threatening ventricular arrhythmias

The occurrence of VT, VF, and cardiac arrest were based on physicians' progress notes. To reduce misclassification of VT and VF due to underreporting of these arrhythmias in physicians' notes, our research physicians also reviewed patients' ECG strips in their hospital medical records. Ventricular tachycardia was defined as a cardiac arrhythmia of three or more consecutive complexes originating in the ventricles at a rate of greater than 100 beats per minute (cycle length less than 600 milliseconds).[2] Ventricular fibrillation was defined as a rapid, usually more than 300 beats per minute (cycle length 200 millisecond or less), grossly irregular, ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude.[2] Cardiac arrest was defined

as the sudden cessation of cardiac activity such that the victim became unresponsive without normal breathing or signs of circulation.[63] Patients were considered as having a life-threatening ventricular arrhythmias (VAs) if they developed any of VT, VF, or cardiac arrest during their acute index hospital stay.

Other covariates

Comorbidity burden was assessed using the Charlson comorbidity index,[111] and acute coronary event severity by the GRACE-risk score (based on age, heart rate, systolic blood pressure, Killip class, presence of renal failure, ST-segment deviation, cardiac arrest, and serum levels of creatinine and troponin.[112] Additional important comorbidities that are not used in the Charlson index, such as hypertension, depression, and anxiety, were also noted. Cognitive function was measured using the Telephone Interview for Cognitive Status (TICS).[113] Social support was measured by the 6-item Medical Outcomes Study Social Support Survey.[114] Pharmacotherapy for depression or anxiety included receipt of serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and oral benzodiazepines (lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, and chlordiazepoxide) as documented in medical records at hospital discharge. We also collected data on the hospital receipt of the following cardiac medications: aspirin, P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor, cangrelor), beta blockers, Angiotensin converting enzyme inhibitors/Angiotensin II receptor blockers (ACE-I/ARBs), and statins.

Missing data

TRACE-CORE contains 2,222 participants with a verified acute coronary syndrome (ACS). After excluded 82 patients who died within 12 months of follow up, there were Among 1,836 patients who had complete data (medical record abstraction and in-person interview) at baseline (Appendix 5.12). Among them, 297 patients (16.2%) dropped out of the study after the baseline interview. Patients who dropped out after baseline were 3 years younger, less likely to be married/lived as married, less likely to have a college degree or higher education, more likely to be uninsured or under Medicaid coverage, had higher prevalence of history of selected diseases (chronic kidney disease, congestive heart failure, or depression), had longer hospital stay, and higher scores of depression or anxiety symptoms at baseline compared with patients who remained in the study (Appendix 5.13).

Among 1,539 who remained in the study, 793 patients (51.5%) had complete data on symptoms of depression and anxiety at all time points while 746 patients had at least one missing variable of either symptoms of depression. The frequency of missing data for symptoms of depression and anxiety was lowest at first month (627 and 617, respectively) and highest at one year (742 and 741, respectively). The most common missing pattern is missing after the first month (8%) and missing at the first month (6%). Patients who had intermittent missing data were younger, more likely to being a non-white race, less likely to be married/lived as married, had lower levels of education and health insurance compared with patients who had complete data at all time points.

Patients who had intermittent data also had higher prevalence of depression and anxiety at baseline, as well as any time point during the follow-up (Appendix 5.14).

Statistical analysis

For this study, we excluded 82 patients who died within 1 year after hospital discharge and 55 patients with missing data on the symptoms of depression and anxiety at all time points. This left 2,074 patients with an independently confirmed ACS in this prospective study. Of these, 327 (15.8%) dropped out after the baseline hospital interview. Of the 1,747 patients who remained, 886 (50.7%) had missing data at one or more follow-up time points (1, 3, 6, and 12 months post discharge). We imputed 30 datasets for each missing score of the PHQ-9, PHQ-2, GAD-7, and GAD-2 using multiple imputations by the chained equations method and predictive mean matching (PMM) models.[115] The PMM took the observed score from a randomly chosen patient among 10 patients who had predictive scores that were most closely matched with the predictive score of a missing patient and then assigned that score to the missing patient.[116] These models generate imputed scores that have a similar distribution to the observed scores, especially when the scores are discrete and bounded.[116] All analyses were conducted in Stata 13.0.

We compared the distributions of sociodemographic and clinical characteristics in patients who did and did not experience VAs at baseline, and described changes over the 12-month follow up period in the prevalence of moderate/severe symptoms of depression and anxiety, as well as mean PHQ-2 and GAD-2 scores over time. We did this for all patients, and separately in patients with and without VAs, and in those without a history

of depression or anxiety. We used generalized estimating equations (GEE) with a Poisson distribution, a log link, robust variance estimation, and exchangeable correlation structure to estimate the relationship between VAs and progression of symptoms of depression and anxiety over following 12 months.[117,118] The Charlson comorbidity index, GRACE-risk scores, and study sites were *a priori* included in all regression models. Other variables were tested iteratively, with those that changed estimates by more than 10% being retained in final models. We also re-analyzed the data after excluding patients with a history of depression or anxiety, since the impact of VAs on depression or anxiety progression could differ for these patients.

Results

Baseline characteristics

The study population (n=2,074) was, on average, 61.1 years old, 33.5% were women, 78.3% were white and 15.5%, black. History of depression and anxiety was present in 255 (12.3%) and 177 (8.5%) patients, respectively, with 94 (4.5%) presented with a history of both condition. Among study patients, 105 patients (5.1%) developed at least one type of serious VAs, with 21 patients experiencing a cardiac arrest, 25 patients, VF, and 76, VT at some time during their acute hospitalization.

Compared with patients who did not develop VAs, patients with VAs were, on average, about 2 years younger, had lower comorbidity burden as measured by the Charlson comorbidity index, were more likely to have developed heart failure, cardiogenic shock, or atrial fibrillation/flutter during hospitalization, were less likely to

have been hospitalized for unstable angina, and more likely to have undergone a PCI or

coronary artery bypass graft surgery (CABG). They were also more likely to have been

treated with beta-blockers or benzodiazepines during their acute hospitalization. (Table

4.1).

Progression of symptoms of depression and anxiety over time

Depression and anxiety frequently coexisted, with 59.2% to 68.4% of patients

who reported moderate/severe symptoms of depression also reporting moderate/severe

symptoms of anxiety at the same time. At baseline, moderate/severe symptoms of

depression were present in 22.2%, and anxiety in 23.5% of patients at baseline (Figure

4.1, top panel). These prevalences rapidly declined to 14.1% and 12.6%, respectively, at

1 month and remained relatively stable at the 12-month follow-up. Although the

prevalence of moderate/severe symptoms of depression in patients with a history of

depression (44.5%) and the prevalence of anxiety in patients with a history of anxiety

(51.7%) were higher than among those without a history of depression (19.0%) or anxiety

(20.9%), each of these patient groups experienced rapid decreases in their symptoms of

these conditions during the first month post discharge, as did the overall patient

population (Figure 1, middle and bottom panels).

The prevalence of moderate/severe symptoms of depression and anxiety were

slightly, but nonsignificantly, higher in patients with VAs compared with patients without

VAs at baseline and during the first 3 months after hospital discharge; the frequencies of

these conditions were similar at 6 and 12 months post discharge (Figure 4.2).

Association between VAs and progression of symptoms of depression and anxiety

Since differences in the frequency of moderate/severe symptoms of depression and anxiety were most notable in the first 3 months after hospital discharge, we compared the risk of reporting symptoms of depression and anxiety during the first 3 months after hospital discharge between patients who did and did not develop VAs during their acute hospitalization. After adjusting for comorbidity burden, severity of the ACS episode, and study site, patients who developed in-hospital VAs at baseline had a insignificant elevated risk of developing symptoms of depression (adjusted Relative risk [aRR]= 1.28, 95% Confidence interval [CI]=0.94-1.76) and anxiety (aRR=1.27, 95%CI=0.90-1.77) during the first 3 months post discharge compared with patients who did not developed VAs (Table 2). Similar findings were found for moderate/severe symptoms of depression (aRR=1.41 95%CI=0.99-2.02) and anxiety (aRR=1.22 95%CI=0.84-1.79) in our secondary sensitivity analysis when patients with a history of depression or anxiety were excluded.

When we examined trends in symptoms of depression and anxiety, PHQ-2 and GAD-2 scores, depression and anxiety scores were similar for patients who did and did not develop VAs at all time points examined (Figure 4.3). In regression models, both before and after adjusting for several potentially confounding factors, VAs were not associated with higher scores of symptoms, depression or anxiety during the first 3 months after hospital discharge (Table 4.4).

Discussion

Comorbid depression and anxiety are common and have been shown to contribute to worse clinical outcomes in patients hospitalized for an ACS. In this study, the prevalence of moderate/severe symptoms of depression and anxiety quickly declined during the first month after hospital discharge and remained relatively stable thereafter. The occurrence of VAs had little effect on the symptoms of moderate/severe depression and anxiety in the short-term, and failed to show any significant association with the progression of symptoms of depression and anxiety over our 12-month follow-up period.

Progression of symptoms of depression and anxiety

We found that overall, the prevalence of moderate/severe symptoms of depression and anxiety rapidly declined by more than 50% in relative terms, from approximately 25% to 12%, during the first month after hospital discharge for an ACS. Prior studies that have described the natural progression of symptoms of depression or anxiety in patients with coronary artery disease were based on very small patient samples,[54,119] or were potentially biased due to complete-case analysis,[119,120] including non-ACS patients,[121] or having few reassessments of symptoms over a prolonged follow up period.[119,120] For instance, one study of 226 women admitted to 4 hospitals for acute myocardial infarction (AMI) or CABG surgery in Melbourne, Australia found that more than 80% of patients experienced a decrease in their symptoms of depression and anxiety measured by the Hospital Anxiety and Depression Scale at 2 and 4 months post discharge, which remained at these levels throughout 12 months of follow up.[121] On the other hand, a study of 287 patients discharged after an AMI from 4 hospitals in the Netherlands between 2003 and

2005 found that symptoms of depression measured by the Beck Depression Inventory were similar across the baseline, 2, and 12 months post discharge assessments.[54]

Stress and fear from an acute coronary event may contribute to the high "baseline" prevalence of moderate/severe symptoms of depression and anxiety that we observed. We found such feelings to be less common thereafter, starting at the first month post discharge. Other factors, including the in-hospital setting of the baseline interview during the patient's acute hospitalization, might have also triggered worse self-reported symptoms compared with the later time points, when patients were interviewed via telephone at home. Regardless of the underlying reasons or contributory causes, our findings suggest that a single screening for symptoms of depression and anxiety during the acute hospital stay may overestimate the continuing burden of these comorbidities in patients who have experienced an ACS. Since the prevalence of moderate/severe symptoms of depression and anxiety were stable after 1 month, screening for the symptoms of depression or anxiety in the outpatient setting may be more useful than an in-hospital assessment after an acute coronary event.

On the other hand, several studies using latent group analysis have suggested that patients with coronary artery disease may be usefully classified into several groups with distinct trajectories of depression and/or anxiety over time.[103,121-123] These studies, despite being based on relatively few patients, suggest that serial measurement of symptoms of depression and anxiety may be needed to identify high-risk patients with worsening psychosocial trajectories who are most likely to benefit from post-discharge interventions. However, when, where, and how to screen for a level of sustained

depression and anxiety following an acute coronary event that may warrant further intervention deserves further study.

As expected, patients with a history of depression or anxiety were more likely to report these problems that patients without these pre-existing conditions. However, despite baseline differences, the progression of symptoms of depression and anxiety over the subsequent several months was similar for the two groups. This suggests that acute stress or fear that patients have after the ACS may only exert an acute impact on the symptoms of depression and anxiety, but are not likely to change the chronic course of these symptoms in patients with a history of depression or anxiety. We also note that the progression of depression was similar to that of anxiety during one year of follow up. This was perhaps due to the fact that close to two-thirds of patients with moderate/severe symptoms of either depression or anxiety reported symptoms of both conditions. These findings appear to reflect the close clinical association between these two conditions, which may share long-term trajectories of progression, and suggests the value of screening for both conditions simultaneously.

Association between VAs and progression of symptoms of depression and anxiety

To our knowledge, the present study is first to examine the association between occurrence of a serious VA in the hospital and progression of symptoms of depression and anxiety among patients discharged following an ACS. Although patients with VAs were somewhat more likely to report moderate/severe symptoms of depression or anxiety during the first 3 months after hospital discharge than other patients, these differences were not statistically significant. In both unadjusted and adjusted analyses, the

development of VAs was not associated with a greater risk of having symptoms of depression or anxiety at 3 months after hospital discharge. These results were confirmed in a secondary analysis, in which we measured depression and anxiety as numerical scores. In contrast to our initial expectation, experiencing a serious VA after an ACS does not appear to increase the risk of developing moderate/severe symptoms of depression or anxiety in the first year following hospital discharge. Note that only 105 (5.1%) of our study population developed these clinically significant cardiac arrhythmias: a larger study might be able to detect differences in the symptoms of depression and anxiety associated with VAs. However, our study suggests that such differences are unlikely to be particularly large.

Study strengths and limitations

This study is first to examine the psychological impact of VAs in patients hospitalized with ACS and post-discharge trends in symptoms of depression and anxiety over time. It used a large, geographically and sociodemographically diverse patient population. Rich socioeconomic and clinical data were available, allowing us to adjust for many potentially important confounders. The study also has important limitations. While patients' perceived susceptibility might be different for sustained VT (more dangerous) than nonsustained VT (usually self-limited), we did not collect information on the type of VT that occurred during the patients' acute hospital stay. In addition, although we have addressed missing data using statistically sound methods, there were substantial amounts of missing follow-up data.

Conclusions

In this study of a large and diverse population discharged from the hospital after an ACS, prevalence of self-reported moderate/severe symptoms of depression and of anxiety were both high at the time of an in-hospital index interview, but substantially declined during the month post hospital discharge and remained stable thereafter. The occurrence of VAs was not associated with an elevated risk of moderate/severe symptoms of depression or anxiety after hospital discharge. Future studies should seek to identify an appropriate post-hospital time to screen for depression and anxiety in the setting of an ACS, and find an efficient way to identify patients at high risk, where intervention efforts might do the most good.

Table 0.1: Baseline characteristics of patients discharged from the hospital after an acute coronary syndrome according to the presence of serious ventricular arrhythmia (VAs)

	With VAs (n=105)	Without VAs (n= 1,969)	*p-value*
Age (mean, years)	58.8	61.2	**<0.001**
Women (%)	23.8	34.0	**0.031**
Race/ethnicity (%)			
White	81.8	78.1	0.64
Black	15.7	15.7	
Other	5.8	6.3	
Marital status (%)			
Married/lived as married	60.0	58.8	0.29
Separate/divorced/widowed	24.8	30.2	
Single/never married	15.2	11.1	
Educational attainment (%)			
College graduate or higher	26.7	25.2	0.68
Some technical school or college	26.7	29.0	
High school graduate	33.3	29.2	
Less than high school	13.3	16.6	
Insurance coverage (%)			
Medicare plus private insurance	15.2	18.7	0.54
Private insurance only	50.5	49.6	
Medicare only	13.3	13.2	
Medicaid	8.6	10.4	
Uninsured	12.4	8.1	
Unemployed/retired (%)	54.3	58.1	0.44
Social support (mean)	20.6	20.1	0.29
Disease impact scale (mean)	34.6	32.6	0.50
Cognitive function (mean)	32.2	31.7	0.21
Previously diagnosed (%)			
Anxiety	4.8	8.7	0.16
Depression	7.6	12.5	0.14
Hypertension	68.6	75.4	0.12
Charlson Comorbidity Index (mean)	2.7	3.3	**0.013**
Physiologic findings at admission (mean)			
Systolic blood pressure (mmHg)	135.5	142.4	**0.008**
Diastolic blood pressure (mmHg)	80.0	80.6	0.75
Heart rate (beat/min)	83.0	77.3	**0.002**
GRACE risk score	94.4	94.3	0.98
In hospital complications (%)			
Acute kidney injury	8.6	4.9	0.10
Heart failure/cardiogenic shock	8.6	2.1	**<0.001**
Atrial fibrillation/flutter	18.1	6.4	**<0.001**
ACS Type (%)			
Unstable angina	18.1	32.1	**0.003**
STEMI	27.6	17.5	
NSTEMI	54.3	50.4	
Reperfusion treatment received (%)			
Medical treatment	8.6	20.6	**0.004**
PCI	72.4	67.5	
CABG	19.0	11.8	
Medications at hospital discharge (%)			

Aspirin	97.1	96.5	0.74
P2Y12 inhibitors	89.5	84.9	0.20
ACE-I/ARBs	64.8	61.8	0.54
Beta-blockers	97.1	89.3	**0.017**
Statins	88.6	86.8	0.61
SSRI/SNRIs	15.2	16.2	0.79
Benzodiazepines	41.0	29.1	**0.010**
Length of hospital stay (days)	6.0	4.9	0.70
30-day hospital readmission (%)	12.4	11.8	0.85

NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin receptor blockers, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin and norepinephrine reuptake inhibitors.
Benzodiazepines: lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide.
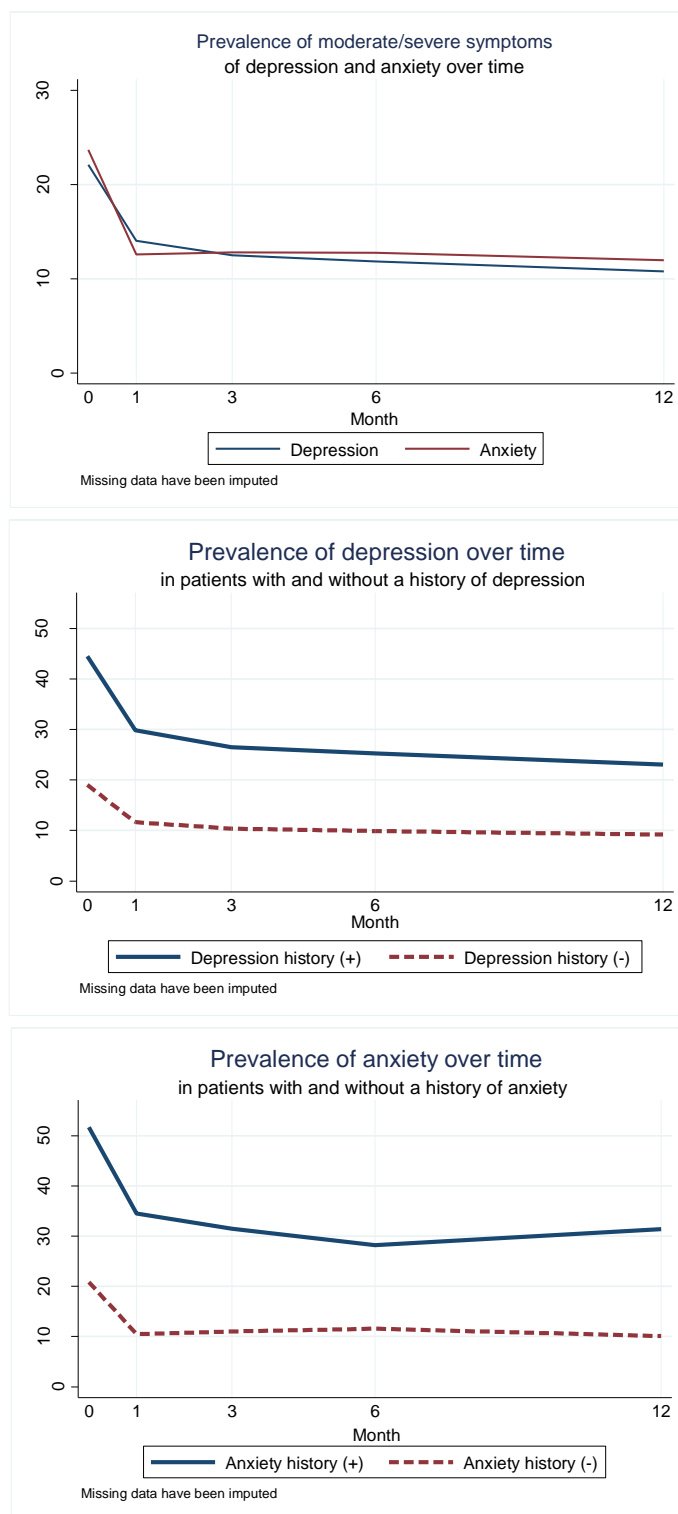
Figure 0.1: Prevalence of moderate/severe symptoms of depression and anxiety overall and by the presence of a history of these conditions among patients discharged from the hospital after an acute coronary syndrome.
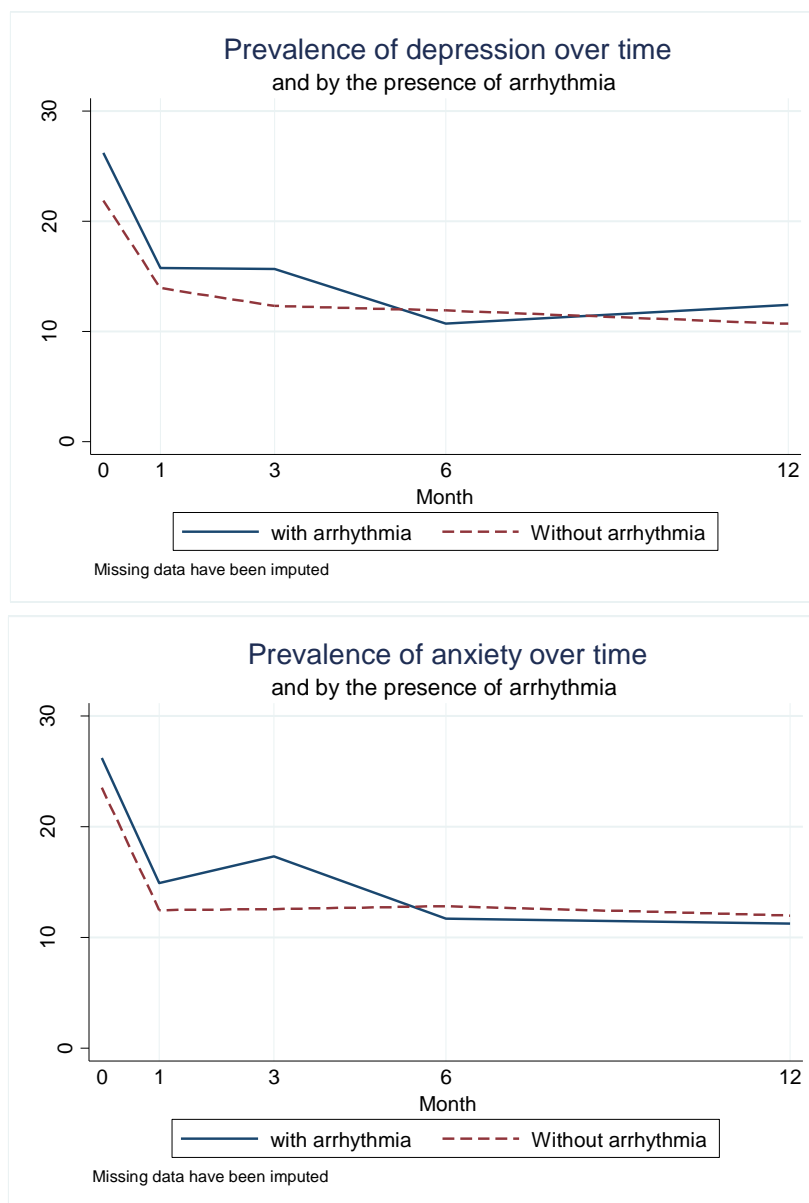
Figure 0.2: Prevalence of moderate/severe symptoms of depression and anxiety among patients discharged from the hospital after an acute coronary syndrome, with and without in-hospital serious ventricular arrhythmias at baseline. Higher scores mean worse symptoms

Table 0.2: Association (Relative risk, 95%Confidence interval) between occurrence of in-hospital serious ventricular arrhythmia and progression of moderate/severe symptoms of depression and anxiety in the first 3 months following hospital discharge in patients with an acute coronary syndrome.

	Depression		Anxiety	
	Unadjusted	Adjusted[†]	Unadjusted	Adjusted[†]
All patients				
Arrhythmia	1.18 (0.86-1.63)	1.28 (0.94-1.76)	1.17 (0.84-1.64)	1.27 (0.90-1.77)
Time (month)	**0.83 (0.79-0.87)**	**0.83 (0.79-0.87)**	**0.82 (0.78-0.86)**	**0.82 (0.78-0.86)**
Patients without a history of depression or anxiety				
Arrhythmia	1.30 (0.90-1.88)	1.41 (0.99-2.02)	1.22 (0.84-1.79)	1.22 (0.84-1.79)
Time (month)	**0.82 (0.77-0.87)**	**0.82 (0.77-0.87)**	**0.81 (0.76-0.86)**	**0.81 (0.76-0.86)**

Estimates are from generalized estimating equation marginal models with exchangeable correlation matrix.
[†]Additionally adjusted for the Charlson comorbidity index, GRACE risk score, and study site
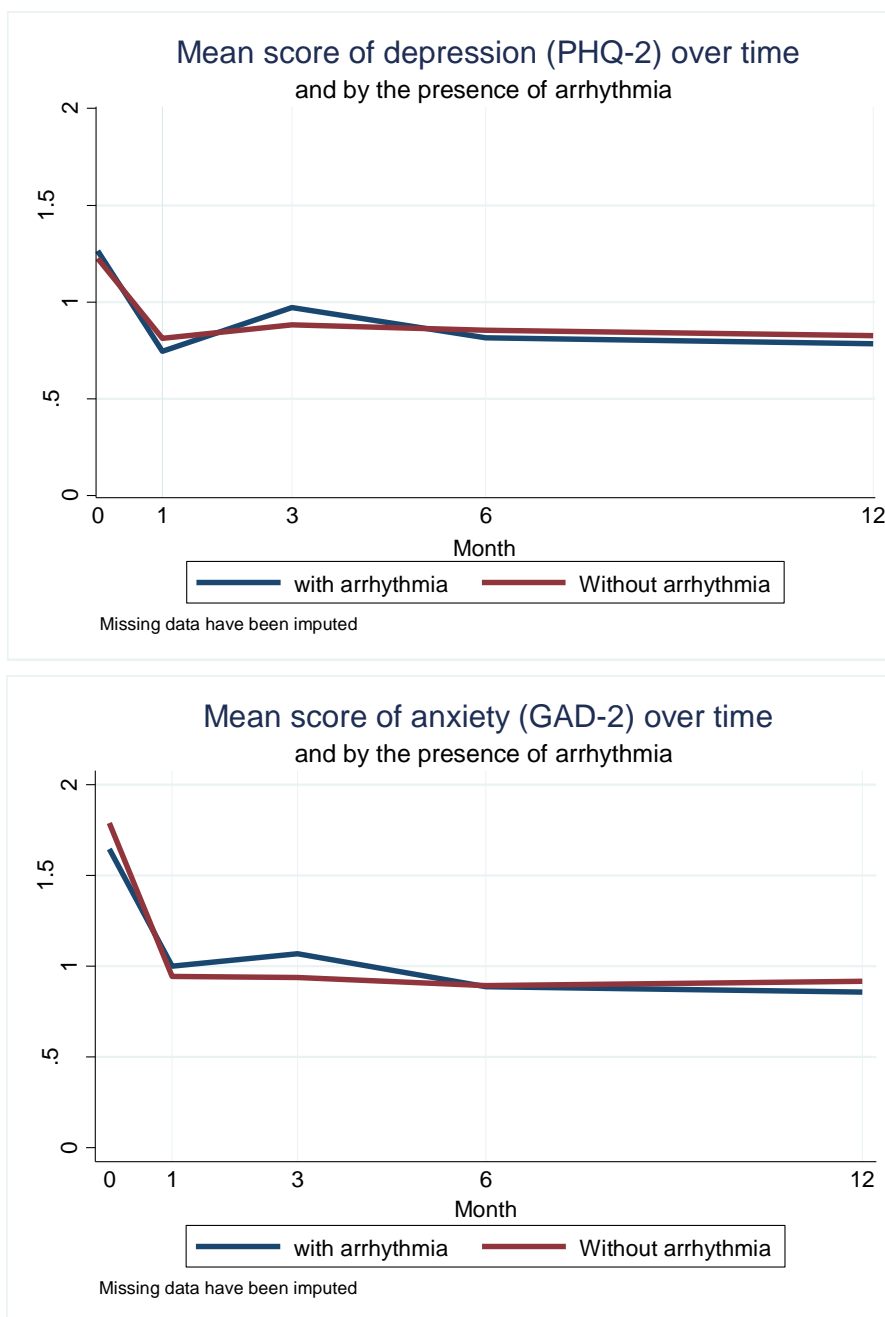
Figure 0.3: Mean scores of symptoms of depression (PHQ 2) and anxiety (GAD 2) over time, separately for those with and without serious ventricular arrhythmias in patients discharged from the hospital following an acute coronary syndrome. Higher scores mean worse symptoms

Table 0.3: Differences in mean score (95% Confidence Interval) of depression (PHQ-2) and anxiety (GAD-7) symptoms during the first 3 months following hospital discharge between patients with and without in-hospital serious ventricular arrhythmias after an acute coronary syndrome

	Depression		Anxiety	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Arrhythmia	0.04 (-0.23; 0.30)	0.14 (-0.11; 0.39)[†]	0.02 (-0.30; 0.34)	0.04 (-0.26; 0.34)[‡]
Time (month)	**-0.10 (-0.13; -0.08)**	**-0.10 (-0.13; -0.08)**[†]	**-0.25 (-0.28; -0.23)**	**-0.25 (-0.28; -0.23)**[‡]

Estimates are from generalized estimating equation marginal models with exchangeable correlation matrix. Positive or negative scores mean higher or lower symptoms, respectively.

[†]Additionally adjusted for the Charlson comorbidity index, GRACE risk score, study sites, and history of depression.

[‡]Additionally adjusted for Charlson comorbidity index, GRACE risk score, study sites, age, sex, history of depression, and the use of benzodiazepines

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APPENDICES

Chapter 2

Appendix 0-1: Raw data for Figure 1, top and middle panels: actual counts of VF and VF episodes in patients with acute myocardial infarction in each study year

Year	Number of patients	All VT VF			Primary VT/VF			Secondary VT/VF		
		None	VT only	VF	None	VT only	VF	None	VT only	VF
1986	685	525	101	59	290	49	25	235	52	34
1988	603	474	83	46	289	31	17	185	52	29
1990	724	566	117	41	328	51	13	238	66	28
1991	824	621	152	51	366	75	21	255	77	30
1993	918	674	185	59	416	97	28	258	88	31
1995	930	734	137	59	444	77	25	290	60	34
1997	946	798	94	54	526	57	20	272	37	34
1999	935	755	133	47	461	65	11	294	68	36
2001	1,193	957	185	51	580	100	20	377	85	31
2003	1,020	810	179	31	465	99	11	345	80	20
2005	890	751	110	29	463	61	8	288	49	21
2007	780	647	110	23	402	55	11	245	55	12
2009	702	608	85	9	433	51	4	175	34	5
2011	675	600	60	15	416	36	11	184	24	4
Total	11,825	9,520	1,731	574	5,879	904	225	3,641	827	349

Note: VF is with or without VT.

Appendix 0-2: Raw data for Figure 1, bottom panel: In-hospital death for patients with acute myocardial infarction complicating by ventricular tachycardia or ventricular fibrillation

		Study year												
	Status	1986	1988	1990	1991	1993	1995	1997	1999	2001	2003	2005	2007	2009	2011
	Alive	28	25	14	27	25	33	33	23	25	17	15	17	4	11
VF	Dead	31	21	27	24	34	26	21	24	26	14	14	6	5	4
	Total	59	46	41	51	59	59	54	47	51	31	29	23	9	15
	Alive	75	58	97	128	161	124	82	113	164	159	97	98	77	58
VT	Dead	26	25	20	24	24	13	12	20	21	20	13	12	8	2
	Total	101	83	117	152	185	137	94	133	185	179	110	110	85	60
	Alive	470	414	504	556	611	658	720	694	863	753	693	588	583	570
No VT/VF	Dead	55	60	62	65	63	76	78	61	94	57	58	59	25	30
	Total	525	474	566	621	674	734	798	755	957	810	751	647	608	600

VT: ventricular tachycardia, VF: ventricular fibrillation, with/without VT.

Appendix 0-3: Raw data for figure 2, top panel: frequency of early and late ventricular tachycardia and ventricular fibrillation in patients with acute myocardial infarction

Arrhythmia	**Timing**	Year						Total
		2001	2003	2005	2007	2009	2011	
	Early	67	94	58	80	45	33	377
VT	Late	62	48	25	22	22	7	186
	All	129	142	83	102	67	40	563
	Early	11	11	12	15	2	8	59
VF	Late	12	11	7	2	5	3	40
	All	23	22	19	17	7	11	99
Total patients		762	729	695	703	532	448	3,869

VT: ventricular tachycardia, VF: ventricular fibrillation, with/without ventricular tachycardia

Appendix 0-4: Raw data for figure 2, bottom panel: Frequency of ventricular tachycardia and ventricular fibrillation in patients with ST-segment elevation and non-ST-segment elevation myocardial infarction

	Arrhythmia	Year						
		2001	2003	2005	2007	2009	2011	Total
STEMI	None	198	164	151	167	98	95	873
	VT	46	72	32	36	20	22	228
	VF	13	16	12	12	0	7	60
	Total	257	252	195	215	118	124	1,161
NSTEMI	None	412	401	442	417	360	302	2,334
	VT	83	70	51	66	47	18	335
	VF	10	6	7	5	7	4	39
	Total	505	477	500	488	414	324	2,708

VT: ventricular tachycardia, VF: ventricular fibrillation, with/without VT

Appendix 0-5: Regression coefficients for trends in the incidence rates of ventricular tachycardia among patients hospitalized for an acute myocardial infarction between 1986 and 2011

	RR	Robust SE	z	P>z	95% CI	
Trends (in 10 years)	0.885	0.041	-2.620	0.009	0.808	0.970
Age (in years)						
55-64	0.846	0.059	-2.410	0.016	0.739	0.969
65-74	0.829	0.056	-2.760	0.006	0.726	0.947
>=75	0.767	0.054	-3.740	0.000	0.667	0.881
Sex	1.431	0.070	7.330	0.000	1.300	1.575
Non-white	0.780	0.087	-2.220	0.026	0.627	0.971
History of heart failure	1.153	0.068	2.410	0.016	1.027	1.295
History of diabetes	0.861	0.044	-2.910	0.004	0.779	0.953
History of hypertension	0.921	0.043	-1.780	0.075	0.841	1.008
History of stroke	0.909	0.067	-1.290	0.197	0.787	1.051
Serum potassium (in mg/dl)	0.957	0.032	-1.340	0.181	0.897	1.021
Atrial fibrillation complication	1.301	0.074	4.660	0.000	1.165	1.454
Heart failure complication	1.277	0.064	4.920	0.000	1.159	1.408
Cardiogenic shock complication	1.462	0.109	5.090	0.000	1.263	1.692
Aspirin	0.908	0.058	-1.520	0.129	0.801	1.029
ACE-I/ARBs	1.122	0.058	2.250	0.025	1.015	1.241
Antiarrhythmic agents	1.788	0.090	11.490	0.000	1.619	1.974
Beta blockers	1.079	0.064	1.290	0.198	0.961	1.211
Lipid lowering agents	1.127	0.067	2.000	0.046	1.002	1.267
Thrombolysis therapy	1.751	0.098	10.010	0.000	1.569	1.954
PCI	1.127	0.065	2.080	0.038	1.007	1.261
CABG	0.959	0.087	-0.460	0.644	0.803	1.146
Length of stay (in day)	1.013	0.002	7.090	0.000	1.010	1.017
_constant	0.122	0.020	-13.040	0.000	0.089	0.167

RR: relative risk, SE: standard error, CI: confidence interval, ACE-I/ARBs: Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery

Appendix 0-6: Regression coefficients for trends in the incidence rates of ventricular fibrillation among patients hospitalized for an acute myocardial infarction between 1986 and 2011

	RR	Robust SE	z	P>z	95% CI	
Trends (in 10 years)	0.796	0.065	-2.800	0.005	0.678	0.934
Age (in years)						
55-64	0.837	0.101	-1.470	0.140	0.661	1.060
65-74	0.872	0.106	-1.120	0.261	0.686	1.107
>=75	0.637	0.085	-3.380	0.001	0.490	0.827
Sex	1.599	0.140	5.350	0.000	1.347	1.899
Non-white	1.021	0.180	0.120	0.906	0.722	1.443
History of heart failure	0.818	0.096	-1.710	0.088	0.650	1.030
History of diabetes	0.822	0.079	-2.030	0.042	0.681	0.993
History of hypertension	1.030	0.086	0.360	0.721	0.875	1.213
History of stroke	0.869	0.124	-0.990	0.322	0.657	1.148
Serum potassium (in mg/dl)	0.646	0.049	-5.770	0.000	0.557	0.749
Atrial fibrillation complication	1.259	0.123	2.350	0.019	1.039	1.525
Heart failure complication	1.355	0.124	3.310	0.001	1.132	1.621
Cardiogenic shock complication	3.661	0.352	13.480	0.000	3.031	4.421
Aspirin	0.712	0.072	-3.340	0.001	0.583	0.869
ACE-I/ARBs	1.053	0.099	0.550	0.583	0.876	1.266
Antiarrhythmic agents	2.955	0.258	12.410	0.000	2.490	3.506
Beta blockers	0.707	0.063	-3.910	0.000	0.594	0.841
Lipid lowering agents	0.753	0.088	-2.420	0.015	0.599	0.947
Thrombolysis therapy	1.529	0.152	4.280	0.000	1.259	1.857
PCI	1.365	0.144	2.960	0.003	1.111	1.678
CABG	0.860	0.151	-0.860	0.389	0.610	1.212
Length of stay (in day)	1.007	0.002	3.280	0.001	1.003	1.011
_constant	0.706	0.225	-1.100	0.274	0.378	1.317

RR: relative risk, SE: standard error, CI: confidence interval, ACE-I/ARBs: Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery

Appendix 0-7: Regression coefficients for trends in the mortality rates of patients who had ventricular tachycardia complicating acute myocardial infarction

	RR	Robust SE	z	P>z	95% CI	
Trends (in 10 years)	1.093	0.133	0.730	0.463	0.862	1.387
Age (in years)						
55-64	1.701	0.594	1.520	0.128	0.859	3.372
65-74	2.335	0.774	2.560	0.010	1.220	4.470
>=75	3.420	1.126	3.730	0.000	1.794	6.521
Sex	0.830	0.094	-1.660	0.098	0.665	1.035
Non-white	1.848	0.456	2.490	0.013	1.139	2.998
History of heart failure	1.333	0.166	2.310	0.021	1.044	1.702
History of diabetes	0.975	0.119	-0.210	0.837	0.767	1.239
History of hypertension	1.017	0.126	0.140	0.889	0.798	1.297
History of stroke	1.107	0.180	0.620	0.533	0.805	1.523
Serum potassium (in mg/dl)	1.383	0.095	4.730	0.000	1.209	1.582
Atrial fibrillation complication	1.169	0.137	1.330	0.183	0.929	1.472
Heart failure complication	1.475	0.191	3.000	0.003	1.144	1.902
Cardiogenic shock complication	3.105	0.350	10.060	0.000	2.490	3.872
Aspirin	0.659	0.086	-3.200	0.001	0.510	0.851
ACE-I/ARBs	0.544	0.072	-4.570	0.000	0.419	0.706
Antiarrhythmic agents	1.549	0.181	3.750	0.000	1.232	1.947
Beta blockers	0.684	0.085	-3.050	0.002	0.537	0.873
Lipid lowering agents	0.612	0.119	-2.520	0.012	0.418	0.897
Thrombolysis therapy	0.970	0.178	-0.170	0.868	0.677	1.389
PCI	0.749	0.142	-1.530	0.127	0.516	1.086
CABG	0.612	0.197	-1.520	0.128	0.326	1.151
Length of stay (in day)	0.974	0.008	-3.120	0.002	0.959	0.990
_constant	0.022	0.010	-8.830	0.000	0.010	0.052

RR: relative risk, SE: standard error, CI: confidence interval, ACE-I/ARBs: Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery

Appendix 0-8: Regression coefficients for trends in the mortality rates of patients who had ventricular fibrillation complicating acute myocardial infarction

	RR	Robust SE	z	P>z	95% CI	
Trends (in 10 years)	1.075	0.090	0.870	0.386	0.913	1.266
Age (in years)						
55-64	1.418	0.268	1.850	0.064	0.979	2.054
65-74	1.567	0.288	2.450	0.014	1.094	2.245
>=75	1.970	0.349	3.820	0.000	1.392	2.789
Sex	0.839	0.059	-2.490	0.013	0.731	0.963
Non-white	1.077	0.187	0.430	0.669	0.766	1.515
History of heart failure	1.042	0.093	0.460	0.648	0.874	1.241
History of diabetes	1.257	0.091	3.150	0.002	1.090	1.449
History of hypertension	1.112	0.084	1.400	0.162	0.958	1.290
History of stroke	1.439	0.136	3.860	0.000	1.196	1.732
Serum potassium (in mg/dl)	1.080	0.047	1.740	0.081	0.990	1.177
Atrial fibrillation complication	0.994	0.084	-0.070	0.941	0.843	1.172
Heart failure complication	1.153	0.090	1.820	0.068	0.989	1.345
Cardiogenic shock complication	1.601	0.113	6.690	0.000	1.395	1.838
Aspirin	0.871	0.074	-1.630	0.103	0.738	1.028
ACE-I/ARBs	0.759	0.086	-2.440	0.015	0.608	0.947
Antiarrhythmic agents	1.256	0.097	2.950	0.003	1.079	1.461
Beta blockers	0.788	0.069	-2.740	0.006	0.664	0.935
Lipid lowering agents	0.758	0.105	-2.000	0.045	0.579	0.994
Thrombolysis therapy	0.736	0.084	-2.680	0.007	0.587	0.921
PCI	0.536	0.067	-4.960	0.000	0.418	0.686
CABG	0.728	0.227	-1.020	0.309	0.395	1.342
Length of stay (in day)	0.983	0.009	-1.920	0.054	0.966	1.000
_constant	0.281	0.074	-4.810	0.000	0.167	0.471

RR: relative risk, SE: standard error, CI: confidence interval, ACE-I/ARBs: Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery

Chapter 4

Appendix 0-9: Patterns of progression of symptoms of depression 12-month post discharge in patients with non-missing data (TRACE-CORE)

Depression 0	Depression 1	Depression 3	Depression 6	Depression 12	Frequency	Percent
0	0	0	0	0	603	73.36
0	0	0	0	1	9	1.09
0	0	0	1	0	11	1.34
0	0	0	1	1	2	0.24
0	0	1	0	0	22	2.68
0	0	1	0	1	2	0.24
0	0	1	1	0	1	0.12
0	0	1	1	1	5	0.61
0	1	0	0	0	17	2.07
0	1	0	0	1	1	0.12
0	1	0	1	1	1	0.12
0	1	1	0	0	1	0.12
0	1	1	0	1	2	0.24
0	1	1	1	0	1	0.12
0	1	1	1	1	3	0.36
1	0	0	0	0	58	7.06
1	0	0	0	1	6	0.73
1	0	0	1	0	9	1.09
1	0	0	1	1	1	0.12
1	0	1	0	0	6	0.73
1	0	1	0	1	2	0.24
1	0	1	1	0	2	0.24
1	1	0	0	0	12	1.46
1	1	0	0	1	5	0.61
1	1	0	1	0	2	0.24
1	1	0	1	1	4	0.49
1	1	1	0	0	9	1.09
1	1	1	0	1	2	0.24
1	1	1	1	0	10	1.22
1	1	1	1	1	13	1.58

Frequency Missing = 1086

Appendix 0-10: Patterns of progression of symptoms of anxiety 12-month post discharge in patients with non-missing data (TRACE-CORE)

Anxiety 0	Anxiety 1	Anxiety 3	Anxiety 6	Anxiety 12	Frequency	Percent
0	0	0	0	0	598	72.14
0	0	0	0	1	14	1.69
0	0	0	1	0	9	1.09
0	0	0	1	1	6	0.72
0	0	1	0	0	17	2.05
0	0	1	0	1	3	0.36
0	0	1	1	0	5	0.60
0	0	1	1	1	2	0.24
0	1	0	0	0	8	0.97
0	1	0	0	1	3	0.36
0	1	0	1	0	2	0.24
0	1	0	1	1	1	0.12
0	1	1	0	0	1	0.12
0	1	1	0	1	5	0.60
0	1	1	1	0	3	0.36
0	1	1	1	1	1	0.12
1	0	0	0	0	67	8.08
1	0	0	0	1	6	0.72
1	0	0	1	0	8	0.97
1	0	0	1	1	5	0.60
1	0	1	0	0	6	0.72
1	0	1	0	1	2	0.24
1	0	1	1	0	1	0.12
1	0	1	1	1	3	0.36
1	1	0	0	0	10	1.21
1	1	0	0	1	5	0.60
1	1	0	1	0	4	0.48
1	1	0	1	1	2	0.24
1	1	1	0	0	7	0.84
1	1	1	0	1	1	0.12
1	1	1	1	0	6	0.72
1	1	1	1	1	18	2.17

Frequency Missing = 1079

Appendix 0-11: Characteristics of patients discharged from the hospital after an acute coronary syndrome according to missing baseline data (TRACE-CORE)

	Missing data n=304	Complete data n=1,836	*p-value*
Age (years)	64 [56-72]	61 [53-69]	**<0.001**
Age group (%)			**<0.001**
<55	22.2	30.7	
55-64	29.1	32.0	
65-75	30.8	25.0	
≥75	18.0	12.4	
Women (%)	35.9	32.9	0.28
Race/ethnicity (%)			0.41
White	75.2	78.3	
Black	17.2	15.8	
Other	7.5	5.9	
Marital status (%)			0.28
Married/lived as married	56.7	58.7	
Separate/divorced/widowed	33.5	29.7	
Single/never married	9.7	11.7	
Educational attainment (%)			**0.001**
College graduate or higher	21.7	25.3	
Some technical school or college	28.6	28.9	
High school graduates	25.4	30.3	
Less than high school	24.3	15.5	
Insurance coverage (%)			**0.011**
Medicare plus private insurance	19.8	18.6	
Private insurance only	42.0	50.2	
Medicare only	18.9	12.6	
Medicaid	11.5	10.2	
Uninsured	7.7	8.4	
Unemployed/retired (%)	67.8	57.3	**<0.001**
Previously diagnosed (%)			
Anxiety	10.1	8.4	0.28
Chronic kidney disease	14.3	9.9	**0.011**
Congestive heart failure	18.1	12.8	**0.006**
Coronary artery disease	28.8	25.9	0.25
Depression	10.9	12.7	0.33
Diabetes	31.6	37.8	**0.022**
Hypertension	70.5	75.2	0.06
Physiologic findings at admission			
Systolic blood pressure (mmHg)	137 [119-155]	141 [125-157]	**0.007**
Diastolic blood pressure (mmHg)	74 [65-84]	80 [70-91]	**<0.001**
Heart rate (beat/min)	74 [63-85]	75 [65-88]	**0.028**
Laboratory findings at admission			
Creatinine (mg/dl)	1 [.84-1.25]	0.97 [.81-1.17]	**0.010**
Glucose (mg/dl)	132 [106-183]	126 [105-168]	0.20
GRACE risk score	102.5 [78.2-122.1]	92.2 [74.1-111.7]	**<0.001**
Potassium (mmol/l)	4.4 [4.1-6.4]	4.3 [4-7.1]	**0.034**
White blood cell count (109 cell/L)	10.8 [8.2-35.7]	10.9 [8.5-43.3]	0.17
In hospital complications (%)			
Acute kidney injury	5.7	5.4	0.81
Heart failure/cardiogenic shock	1.6	1.9	0.64

Atrial fibrillation/flutter	5.7	7.4	0.24
ACS Type (%)			**<0.001**
Unstable angina	39.8	29.6	
STEMI	12.8	18.7	
NSTEMI	47.4	51.7	
Reperfusion treatment received (%)			**<0.001**
Medical treatment	38.3	19.4	
PCI	53.1	68.1	
CABG	8.6	12.5	
Medications at hospital discharge (%)			
Aspirin	92.0	97.1	**<0.001**
P2Y12 inhibitors	79.5	85.3	**0.005**
ACE-I/ARBs	57.5	62.4	0.08
Beta-blockers	86.8	90.1	0.05
Statins	79.8	87.9	**<0.001**
SSRI/SNRI/atypical antidepressants	14.5	16.5	0.33
Benzodiazepines	32.6	29.3	0.19
Length of hospital stay (days)	2 [1-5]	3 [2-5]	**<0.001**
Depression symptoms score			
Baseline [0-27]	4 [2-8]	4 [2-9]	0.67
1 month [0-27]	3 [1-7]	2 [1-6]	0.32
3 months [0-6]	1 [0-6]	1 [0-6]	0.57
6 months [0-6]	0 [0-1]	0 [0-1]	0.63
12 months [0-6]	0 [0-1]	0 [0-1]	0.96
Anxiety symptoms			
Baseline [0-21]	5 [1-10]	4 [1-9]	0.28
1 month [0-21]	2 [0-6]	2 [1-5]	0.45
3 months [0-6]	0 [0-2]	0 [0-1]	0.27
6 months [0-6]	0 [0-1]	0 [0-1]	0.63
12 months [0-6]	0 [0-2]	0 [0-1]	0.33

Note: continuous variables were reported in median [interquartile range]

NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin receptor blockers, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin and norepinephrine reuptake inhibitors.

Atypical antidepressants included bupropion, mirtazapine, nefazodone. Benzodiazepines included lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide.

Appendix 0-12: Baseline characteristics of patients discharged from the hospital after an acute coronary syndrome according to being drop out after baseline (TRACE-CORE)

	Remaining n=1,573	Dropout n=335	*p-value*
Age (years)	61 [53-69]	59 [50-69]	**0.013**
Age group (%)			**0.003**
<55	28.29	37.61	
55-64	32.55	28.66	
65-75	26.57	20.00	
≥75	12.59	13.73	
Women (%)	32.61	33.73	0.69
Race/ethnicity (%)			0.21
White	78.58	75.82	
Black	15.38	19.10	
Other	6.04	5.07	
Marital status (%)			**0.042**
Married/lived as married	59.50	52.54	
Separate/divorced/widowed	28.93	35.52	
Single/never married	11.57	11.94	
Educational attainment (%)			**<0.001**
College graduate or higher	26.32	17.61	
Some technical school or college	29.94	23.58	
High school graduates	30.71	28.66	
Less than high school	13.03	30.15	
Insurance coverage (%)			**0.001**
Medicare plus private insurance	19.33	17.01	
Private insurance only	50.99	42.39	
Medicare only	12.52	14.93	
Medicaid	9.92	12.54	
Uninsured	7.25	13.13	
Unemployed (%)	57.34	62.69	0.07
Previously diagnosed (%)			
Anxiety	8.33	10.75	0.16
Chronic kidney disease	9.47	16.12	**<0.001**
Congestive heart failure	12.46	20.60	**<0.001**
Coronary artery disease	26.32	28.66	0.38
Depression	12.40	16.42	**0.048**
Diabetes	37.19	42.39	0.08
Hypertension	75.65	77.01	0.60
Physiologic findings at admission			
Systolic blood pressure (mmHg)	141 [125-157]	139 [121-158]	0.47
Diastolic blood pressure (mmHg)	80 [69-90]	80 [70-94]	0.22
Heart rate (beat/min)	75 [64-88]	78 [68-89]	**0.012**
Laboratory findings at admission			
Creatinine (mg/dl)	0.97 [0.81-1.16]	1.01 [0.84-1.27]	**0.003**
Glucose (mg/dl)	126 [105-167]	128 [105-176]	0.82
GRACE risk score	93.3 [75.4-111.9]	92.0 [72.6-119.1]	0.79
Potassium (mmol/l)	4 [3.7-4.3]	4 [3.7-4.3]	0.10
White blood cell count (109 cell/L)	8.5 [6.8-10.9]	8.7 [6.9-10.9]	0.79
In hospital complications (%)			
Acute kidney injury	4.58	11.64	**<0.001**

Heart failure/cardiogenic shock	1.97	2.09	0.89
Atrial fibrillation/flutter	7.82	6.87	0.55
ACS Type (%)			0.90
Unstable angina	29.82	28.66	
STEMI	18.37	18.21	
NSTEMI	51.81	53.13	
Reperfusion treatment received (%)			**0.003**
Medical treatment	18.94	26.57	
PCI	69.10	60.00	
CABG	11.95	13.43	
Medications at hospital discharge (%)			
Aspirin	96.95	97.01	0.95
P2Y12 inhibitors	85.95	81.49	**0.037**
ACE-I/ARBs	62.05	62.39	0.91
Beta-blockers	89.89	92.24	0.19
Statins	87.86	87.46	0.84
SSRI/SNRI/atypical antidepressants	15.83	21.19	**0.017**
Benzodiazepines	28.80	32.54	0.17
Length of hospital stay (days)	3 [2-5]	3 [2-6]	**0.001**
Depression symptoms			
Baseline	4 [1-8]	6 [3-11]	**<0.001**
Anxiety symptoms			
Baseline	4 [1-9]	6 [2-13]	**<0.001**

Note: continuous variables were reported in median [interquartile range]

NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin receptor blockers, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin and norepinephrine reuptake inhibitors.

Atypical antidepressants included bupropion, mirtazapine, nefazodone. Benzodiazepines included lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide.

Appendix 0-13: Characteristics of patients discharged from the hospital after an acute coronary syndrome according to missing longitudinal data on symptoms of anxiety or depression (TRACE-CORE)

	Complete data n=793	Missing data n=780	p-value
Age (years)	63 [55-70]	59 [52-67]	**<0.001**
Age group (%)			**<0.001**
<55	23.96	32.69	
55-64	29.76	35.38	
65-75	32.03	21.03	
≥75	14.25	10.90	
Women (%)	31.53	33.72	0.354
Race/ethnicity (%)			**<0.001**
White	83.73	73.33	
Black	10.09	20.77	
Other	6.18	5.90	
Marital status (%)			**<0.001**
Married/lived as married	64.31	54.62	
Separate/divorced/widowed	25.98	31.92	
Single/never married	9.71	13.46	
Educational attainment (%)			**<0.001**
College graduate or higher	31.40	21.15	
Some technical school or college	31.78	28.08	
High school graduates	29.26	32.18	
Less than high school	7.57	18.59	
Insurance coverage (%)			**<0.001**
Medicare plus private insurance	24.09	14.49	
Private insurance only	50.69	51.28	
Medicare only	12.61	12.44	
Medicaid	8.58	11.28	
Uninsured	4.04	10.51	
Unemployed (%)	58.01	56.67	0.591
Previously diagnosed (%)			
Anxiety	7.57	9.10	0.270
Chronic kidney disease	9.08	9.87	0.592
Congestive heart failure	10.21	14.74	0.007
Coronary artery disease	26.73	25.90	0.706
Depression	12.36	12.44	**0.963**
Diabetes	36.44	37.95	0.537
Hypertension	74.91	76.41	0.487
Physiologic findings at admission			
Systolic blood pressure (mmHg)	142 [125-158]	140 [125-156]	0.2691
Diastolic blood pressure (mmHg)	79 [69-90]	80 [70-90]	0.4565
Heart rate (beat/min)	74 [64-86]	76 [66-89]	**0.0287**
Laboratory findings at admission			
Creatinine (mg/dl)	0.97 [0.8-1.13]	0.97 [0.81-1.19]	**0.2952**
Glucose (mg/dl)	125 [104-167]	126 [106-169]	0.6477
GRACE risk score	95.9[77.5-112.7]	90.7 [72.6-111.2]	0.0056
Potassium (mmol/l)	4.1 [3.8-4.3]	4 [3.7-4.4]	0.1642
White blood cell count (109 cell/L)	8.5 [6.8-10.8]	8.4 [6.8-11]	0.7299
In hospital complications (%)			
Acute kidney injury	3.03	6.15	**0.003**

Heart failure/cardiogenic shock	2.40	1.54	0.221
Atrial fibrillation/flutter	8.95	6.67	0.091
ACS Type (%)			0.228
Unstable angina	29.89	29.74	
STEMI	16.77	20.00	
NSTEMI	53.34	50.26	
Reperfusion treatment received (%)			**0.131**
Medical treatment	17.02	20.90	
PCI	70.37	67.82	
CABG	12.61	11.28	
Medications at hospital discharge (%)			
Aspirin	96.85	97.05	0.814
P2Y12 inhibitors	86.76	85.13	**0.352**
ACE-I/ARBs	61.79	62.31	0.833
Beta-blockers	91.30	88.46	0.062
Statins	88.02	87.69	0.842
SSRI/SNRI/atypical antidepressants	14.25	17.44	**0.083**
Benzodiazepines	26.61	31.03	0.053
Length of hospital stay (days)	3 [2-4]	3 [2-5]	**0.1289**
Depression symptoms			
Baseline	4 [1-7]	5 [2-10]	**<0.001**
1 month	2 [1-5]	3 [1-7]	**0.0737**
3 months	0 [0-1]	0 [0-2]	**<0.001**
6 months	0 [0-1]	0 [0-2]	**<0.001**
12 months	0 [0-1]	0 [0-2]	**0.0008**
Anxiety symptoms			
Baseline	3 [1-7]	5 [1-10]	**<0.001**
1 month	0 [1-5]	2 [0-6]	**0.0173**
3 months	0 [0-1]	0 [0-2]	**0.0009**
6 months	0 [0-1]	0 [0-2]	**<0.001**
12 months	0 [0-1]	0 [0-2]	**<0.001**
Depression symptoms			
Baseline	16.65	25.51	**<0.001**
1 month	9.71	16.63	**<0.001**
3 months	9.46	14.96	**<0.001**
6 months	7.82	16.71	**<0.001**
12 months	6.94	15.32	**<0.001**
Anxiety symptoms			
Baseline	18.16	25.77	**<0.001**
1 month	8.83	14.34	**0.002**
3 months	9.33	13.62	**0.022**
6 months	8.58	16.46	**<0.001**
12 months	9.08	14.44	**0.006**

Note: continuous variables were reported in median [interquartile range]

NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin receptor blockers, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin and norepinephrine reuptake inhibitors.

Atypical antidepressants included bupropion, mirtazapine, nefazodone. Benzodiazepines included lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide.

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