Ventricular Fibrillation and Sudden Cardiac Death during Myocardial Infarction

An analysis of cardiac symptoms, risk factors, and survival

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1. THIS THESIS IS BASED ON THE FOLLOWING THREE PAPERS

Paper I (study I)

Reza Jabbari, Thomas Engstrøm, Charlotte Glinge, Bjarke Risgaard, Javad Jabbari, Bo Gregers Winkel, Christian Juhl Terkelsen, Hans-Henrik Tilsted, Lisette Okkels Jensen, Mikkel Hougaard, Stephanie E. Chiuve, Frants Pedersen, Jesper Hastrup Svendsen, Stig Haunsø, Christine M. Albert, and Jacob Tfelt-Hansen. Incidence and Risk Factors of Ventricular Fibrillation before Primary Angioplasty in Patients with First ST-Elevation Myocardial Infarction: A Nationwide Study in Denmark. J Am Heart Assoc. 2015 Jan 5;4(1).pii:e001399.doi: 10.1161/JAHA.114.001399.

Paper II (study II)

Reza Jabbari, Bjarke Risgaard, Emil L Fosbøl, Thomas Scheike, Berit Thornvig Philbert, Bo Gregers Winkel, Christine M. Albert, Charlotte Glinge, Ahtarovski KA, Stig Haunsø, Køber L, Erik Jørgensen, Frants Pedersen, Jacob Tfelt-Hansen, and Thomas Engstrøm. Factors Associated with and Outcomes following Ventricular Fibrillation before and during Primary Angioplasty among Patients with ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2015 Sep 1;116(5):678-85. doi: 10.1016/j.amjcard.2015.05.037. Epub 2015 Jun 3.

Paper III (study III)

Reza Jabbari, Bjarke Risgaard, Anders G Holst, Jonas B Nielsen, Charlotte Glinge, Thomas Engstrøm, Henning Bundgaard, Jesper H Svendsen, Stig Haunsø, Bo Gregers Winkel, and Jacob Tfelt-Hansen. Cardiac Symptoms before Sudden Cardiac Death caused by Coronary Artery Disease: A Nationwide Study among Young Danish People. Heart. 2013 Jul;99(13):938-43.

2. INTRODUCTION

Coronary artery disease and its ultimate consequence, myocardial infarction (MI), are believed to underlie 75% of the deaths of patients who experience sudden cardiac death (SCD).1,2 It is also estimated that SCD accounts for 30 to 50% of all coronary deaths.3,4 SCD is a major challenge for the clinician because most episodes occur in individuals without previously identified cardiac disease.5,6 The pathophysiology of SCD is complex. It is believed to involve an interaction between underlying disease and a transient event, such as acute myocardial ischemia, which triggers arrhythmogenic stimuli, induces electrical instability, and may cause ventricular fibrillation (VF).2 VF is fairly common and is a life-threatening complication of ST-segment elevation myocardial infarction (STEMI).7 Studies investigating ventricular arrhythmia due to MI indicate that ventricular tachycardia (VT) degenerates first to VF, following an increase in the VT rate and QRS width, and later to asystole.8,9 The most common hypothesis for a VF mechanism in the acute phase of MI is electrolyte and autonomic imbalances, low pH, and reentry. Reentry is caused by inhomogeneity and instability of electrical conduction, and it appears to be the major pathophysiological cascade responsible for VF.10

The best available knowledge regarding the incidence of VF in the primary percutaneous coronary intervention era (PPCI) is obtained from retrospective analyses of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial, which included 5,745 STEMI patients.7 In this trial, the overall incidence of VT and VF was 5.7%. However, the highest incidence of ventricular arrhythmias (i.e., VT and VF) due to MI is from the pre-PPCI era and was reported in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, which included 40,895 STEMI patients.11 The overall incidence of VT and VF in this trial was 10.2%. Nevertheless, the incidence of VF is highly likely to be underestimated because individuals who suffer SCD out-of-hospital are not included in these studies.

Clinically, it is difficult to assess the risk of VF/SCD caused by MI in the general population because most deaths occur in large, low-risk subgroups.6 Importantly, a high percentage of cardiovascular events, including SCD, occur in previously asymptomatic individuals, and VF is the first symptom noted.5,6,12 Moreover, known cardiovascular risk factors are not specific to VF/SCD and are more general predictors of MI.6 Currently, knowledge of paraclinical and clinical features that reliably identify individuals who are at risk of developing primary VF during acute MI is limited. However, large meta-analyses, retrospective analyses of several clinical trials, and observational studies have identified several risk factors associated with VF during acute MI; these

include male sex,13 younger age,14 hypokalemia on admission,14 low systolic blood pressure on admission,14 smoking,13,14 family history of sudden death,15,16 early repolarization on ECG,17,18 the presence of ST-segment elevation,7,13,14,16,19 the absence of pre-infarction angina,13,20 acute occlusion of the culprit artery,7,14,21–23 larger infarct size based on the extent of myocardial enzyme leakage,13 and atrial fibrillation.23,24

Data on the short-term and long-term prognosis of VF during STEMI in the era of PPCI are limited and inconsistent.7,21,23,25 While retrospective analyses of the Primary Angioplasty in Myocardial Infarction (PAMI) trial indicated no increase in in-hospital mortality or one-year mortality for VF,21 retrospective analyses of the APEX-AMI trial revealed an increased 90-day mortality rate.7 In line with the APEX-AMI trial results, observational case-control studies suggested an increase in in-hospital mortality for VF patients with STEMI but no increase in the long-term mortality rate for these patients compared with STEMI patients without VF.23,25 Considering these conflicting data, the current guidelines for the secondary prevention of sudden arrhythmic death in patients who survived a VF event do not recommend early treatment with implantable cardioverter-defibrillators (ICDs).26 Moreover, primary (early) VF defined as VF caused by an MI within the first 48 hours of infarction is not associated with recurrent ischemia or heart failure.7,11,16 Despite these recommendations, a more comprehensive investigation of the survival of VF patients is still needed.

In young people (i.e., those ≤49 years old), it is evident that SCD is linked to coronary artery disease (CAD).27–31 Therefore, the relatively frequent occurrence of SCD will persist as long as the prevalence of CAD remains high.27,28 In support of the claim that CAD is present even in people as young as 15 to 34 years old, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study32 demonstrated that even in individuals aged ≤19 years who died of non-cardiovascular causes, the proportion of intimal surface area (i.e., in the aorta and coronary arteries) displaying fatty acid streaks and subsequent raised lesions (i.e., fibrous plaques) was >20%. This study also demonstrated that the presence of clinically significant plaques rapidly increased between the ages of 15 and 34 years.32 However, to date, little is known about the medical history, warning signs, and prodromes of young individuals at risk. Despite the fact that young patients (i.e., those<40 years) who present to emergency departments with chest pain have a very low rate of adverse events within a year,33 it is often very difficult for physicians to identify individuals at high risk of SCD caused by MI; consequently, prevention remains challenging. The assessment of medical histories, symptoms prior to the event, and risk factors in apparently healthy individuals is crucial to improve our understanding of the mechanisms underlying SCD and may allow us to better prevent SCD/VF.

3. OBJECTIVES

The aims of this PhD thesis were to:

- Identify risk factors for VF before PPCI in the setting of STEMI (Study I).
- Assess the outcomes of VF before and during PPCI in the setting of STEMI (Study II).
- Identify and characterize symptoms, medical history, and contact with health care providers prior to SCD caused by CAD in young Danes (Study III).

4. ETHICAL CONSIDERATIONS

All studies were conducted in accordance with the ethical standards of the national ethics committee on human research and with the Helsinki Declaration. The Danish Data Protection Agency and/or the Danish National Board of Health approved all of the studies.

Study I: This study received permission from the National Committee on Health Research Ethics to include patients who were unconscious and did not have a family member available to provide informed consent (protocol number: H-3-2010-133). Informed consent in unconscious or dead patients was subsequently obtained from the next-of-kin upon arrival to the PCI center and is available for all patients enrolled in this study. Furthermore, this study was also approved by the Danish Data Protection Agency (Jr.nr. 2010-41-5688).

Study II: This study was approved by the Danish Data Protection Agency (j.nr.: 2007-58-0015).

Study III: This study was approved by the Regional Ethics Committee (KF 01272484), the Danish Data Protection Agency (2005-41-5237) and the Danish National Board of Health (7-505-29-58/1-5).

5. METHODS

Various methods have been used in this PhD thesis; therefore, a brief overview will be given followed by a short description of the methods used in each study. A thorough description of the methods for each study is provided in the original manuscripts.

5.1 GENERAL METHODS

5.1.1 The Danish Civil Registration System

All individuals with permanent residence in Denmark receive a unique and personal Civil Registration Number (CRN), which is a national identification number that links the national registers on an individual level. The CRN is used for all healthcare-related services in Denmark. We used the CRN to retrieve information on each patient's vital status (i.e., alive or date of death) from the Danish Civil Registration System, in which all individuals residing in Denmark are registered at birth or at the time of immigration. The CRN number was also used to retrieve information on prior medical history from hospital records, records from general practitioners, death certificates, and the National Patient Registry (see below).

5.1.2 The National Patient Registry (NPR)

Since 1978, the National Patient Registry contains information on all in- and outpatient activity at Danish hospitals; it includes International Classification of Diseases (ICD) diagnosis codes for each visit. ICD-8 codes were used from 1977 to 1993, and ICD-10 codes have been used since 1994.

5.1.3 The hospital PCI-registry

The Copenhagen University Hospital - Rigshospitalet is the PPCI center for all of eastern Denmark. At this center, clinical and angiographic data on consecutive patients admitted for STEMI have been stored in a local hospital registry since 1999. Furthermore, for study I, we also used data from the Western Denmark Heart Registry (WDHR), which also collects baseline characteristics and procedure information on all angiographies and coronary interventions performed in western Denmark (Odense, Aarhus, and Aalborg).

5.2 GENERAL DEFINITIONS

Sudden cardiac death was defined as "sudden, natural unexpected death of unknown or cardiac cause; in unwitnessed cases, as a person last seen alive and functioning normally <24 hours before being found dead, and in witnessed cases, as an acute change in cardiovascular status followed by death within 1 hour."27

Family history of sudden death in first-degree relatives (i.e., biological parents, brothers, or sisters) was defined as sudden, natural, unexpected death of unknown or cardiac cause in parents or siblings younger than 80 years. In witnessed cases, the family member died within 1h of an acute change in cardiovascular status, and in unwitnessed cases, the person was last seen alive and functioning normally within 24 hours before they were found dead.27

Cardiac symptoms were defined as angina pectoris, dyspnea, uncharacteristic chest pain (i.e., described as "sharp" or "stabbing"), syncope, palpitations, and fatigue.

Acute STEMI was defined as ST-segment elevation >0.1 mV in 2 adjacent electrocardiogram (ECG) leads from V4 to V6 or in limb leads II, III and aVF; as a segment elevation >0.2 mV in leads V1 to V3; or as a left bundle branch block.

VF before PPCI was defined as the occurrence of VF before guiding the catheter's insertion during a PCI procedure.

VF during PPCI was defined as VF occurring after guided catheter insertion but before the end of the procedure.

5.3 STUDY POPULATIONS

5.3.1 Study I

This study was designed as a nationwide prospective case-control study among patients with first STEMI between the ages of 18 and 80 years collected at all four PCI centers in Denmark. Patients with out-of-hospital cardiac arrest (OHCA) were included upon admission to PCI sites after resuscitation. To qualify for the study, all patients had to have cardiac symptoms lasting ≤12 hours and acute ST-segment elevation revealed by ECG. The case group was comprised of patients who experienced VF within the first 12 hours of symptoms of STEMI before PPCI (n=219), and the control group (n=441) was comprised of patients who did not have VF during this time period. A prior medical history was also collected by the research coordinators at the study sites using a predesigned standardized questionnaire that includes baseline demographics, education, smoking status, alcohol intake, and previous medications. Presenting clinical characteristics and additional clinical information at the time of STEMI were collected from medical records and the local PCI registry at each hospital.

5.3.2 Study II

This study was designed as a single-center retrospective cohort study of patients with STEMI who were aged 18 years or older. Between 1999 and 2012, 5,373 STEMI patients were included consecutively, and the clinical data were stored in Rigshospitalet's PCI registry. To qualify for the study, patients had to have cardiac symptoms lasting ≤12 hours and acute STEMI revealed by ECG. All patients underwent angiography and subsequent PPCI except when PCI was technically impossible. Of the 5,373 STEMI patients, 4,875 had STEMI without VF, 410 had VF before PPCI, and 88 had VF during PPCI. Out of 5,373 STEMI patients, 143 (15 of whom had VF before PPCI and 3 during) were excluded due to emigration, and follow-up was conducted with 5,230 STEMI patients of whom 4,750 had STEMI without VF, 395 had STEMI with VF before PPCI, and 85 had STEMI with VF during PPCI. We used the CRN to retrieve information on each patient's vital status and obtain pre-hospital reports and discharge summaries for the VF patients from the pre-hospital trauma and emergency doctors who escorted the ambulances to the hospitals. Baseline demographics, previous medical history, angiographic findings, and treatment characteristics were collected from the Rigshospitalet's PCI registry.

5.3.3 Study III

Previously, Winkel et al. conducted a nationwide retrospective study of young SCD patients in Denmark.27 Briefly, this study included all deaths (6,629) among people aged 1–35 years during 2000-06. Of these, 314 autopsied SCDs were identified, of which 13% (n=40) died due to CAD. The SCD-CAD cases (n=40) were included in the current study (study III). None of these cases had prior myocardial infarction. For comparison, the SCD-CAD case group was randomly matched 1:2 to a control group based on sex and age at time of death from 1,497 individuals who died in accidents in the same period. We used the personal CRN to collect all the available data from hospital and general practitioners' records, NPR, autopsy reports, and death certificates. Danish death certificates also include information on previous medical conditions, a description of the external examination of the body, and preliminary conclusions regarding the cause of death before autopsy. We collected medical history, cardiac symptoms, and history of relevant contacts with the healthcare system before death from all available sources mentioned above. We divided the time during which the patients had cardiac symptoms into prodromal symptoms, defined as cardiac-related symptoms occurring within one hour before death, and antecedent symptoms, defined as those occurring within a year to one hour before death.

5.4 STATISTICS

For all studies, medians or proportions of baseline and presenting characteristics were computed for cases and controls, and the significance of associations was tested using the Wilcoxon rank-sum test for continuous variables and the $\chi 2$ test or Fisher exact test (as appropriate) for categorical variables. A two-tailed P value ≤0.05 was considered statistically significant.

5.4.1 Study I

A logistic regression model was constructed to identify the risk factors that preceded STEMI and were associated with subse-

quent VF, and the adjusted odds ratios (ORs) and accompanying 95% confidence intervals (CIs) were computed to determine the association of each variable with the risk of VF. Variables previously known to be associated with VF such as age, sex, family history of sudden death, smoking, and preinfarction angina were included regardless of univariate P-value.13,14,16,19 A Hosmer-Lemeshow test of goodness-of-fit (by forming ten groups) was used to evaluate the final model, and the area under the receiver operating characteristic (ROC) curve for the logistic regression model was used to measure prediction accuracy. Tests for linear trends across alcohol intake categories were performed by assigning the median value to each category and modeling this as a continuous variable in separate logistic regression models. To test for a curvilinear association, a quadratic term (i.e., average intake squared) was added to the linear term in a separate model. We also considered a non-linear relationship between alcohol and VF risk using restricted cubic spline transformations.

5.4.2 Study II

In study II, we also used a logistic regression model to identify the risk factors that preceded STEMI and were associated with subsequent VF. An initial model was built by including any covariate that preceded STEMI (aside from the Killip class at admission) with P<0.10 in a univariate test. Age, sex, smoking, preinfarction angina, and Killip class at admission were used in the model regardless of their univariate test P-values based upon their previous associations with VF.7,13,14 Other covariates were sequentially added to the model and were retained if they were significant or if they changed the beta coefficient of a risk factor by more than 10%; covariates were excluded if they changed the standard error by more than 10%.

A Cox proportional hazard regression model was constructed to identify variables that were independently associated with all-cause mortality. For this purpose, we used all of the baseline variables and additional procedural variables including procedure time, infarct location, Killip class at admission, and thrombolysis in myocardial infarction (TIMI) flow grades. VF before PPCI and VF during PPCI were then added to this model as time-dependent variables to determine the adjusted hazard ratio (HR) and 95% CI of VF with respect to mortality within 30 days of PPCI and more than 30 days following PPCI. We also tested for interactions between VF before or during PPCI to identify mortality differences over time within the two VF groups.

Missing data for each variable are shown in Table 1 and Table 2 in the original paper II. Due to missing data, we conducted sensitivity analyses in which we compared the beta coefficients of the Cox regression analysis in complete cases with imputed data using multiple imputations by chained equations (MICE), in which the basic idea is to use complete observations to represent incomplete observations.34

Survival curves over the follow-up period were drawn using the Kaplan–Meier estimator, and the groups were compared using the log rank test. Because the survival curves diverge after 6 years, we also performed a Wilcoxon-Breslow-Gehan test of equality (i.e., in addition to the log rank test) for comparison. All patients were followed from the date of STEMI until death or until May 03, 2013, whichever came first.

6. RESULTS

For each study, only the main findings are summarized separately. The baseline characteristics for each cohort are fully described in the original manuscripts.

6.1 STUDY I

In this nationwide case-control study performed at all four PCI sites, 219 case subjects with VF and 441 control subjects without VF due to STEMI were included. The incidence of VF before PPCI was 11.6%. We identified several patient characteristics associated with significantly higher odds of experiencing VF before PPCI after adjusting for cardiovascular risk factors, infarct location, and TIMI flow. These independent risk factors include age <60 years (OR=1.75; 95% CI 1.20–2.60), family history of sudden death (OR=1.60; 95% CI 1.10–2.40), lack of preinfarction angina (OR=0.46; 95% CI 0.32–0.67), use of statins (OR=2.05; 95% CI 1.34–3.15), anterior infarction (OR=2.10; 95% CI 1.40–3.00), pre-procedural TIMI flow grade 0 (OR=1.65; 95% CI 1.14–2.40), history of atrial fibrillation (AF) (OR=2.8; 95% CI 1.10–7.30), and alcohol intake over 7 units/week. Compared with non-drinkers, patients who consumed 1–7 units, 8–14 units, or >15 units of alcohol per week had an OR=1.30 (95% CI 0.80–2.20), OR=2.30 (95% CI 1.20–4.20), or OR=3.30 (95% CI 1.80–5.90) for VF, respectively (Table 1). Finally, traditional CAD risk factors such as smoking, diabetes, hypertension, and hypercholesterolemia did not predict VF before PPCI in STEMI patients.

Analyzing the raw continuous values of alcohol intake in a restricted cubic spline model revealed a non-linear relationship between alcohol intake and VF (P for non-linear trend =0.0003). The shape of the curve is consistent, with an increased risk of VF with the consumption of more than 7 units per week and a leveling off of the curve at alcohol intakes greater than 14 units per week (Figure 1).

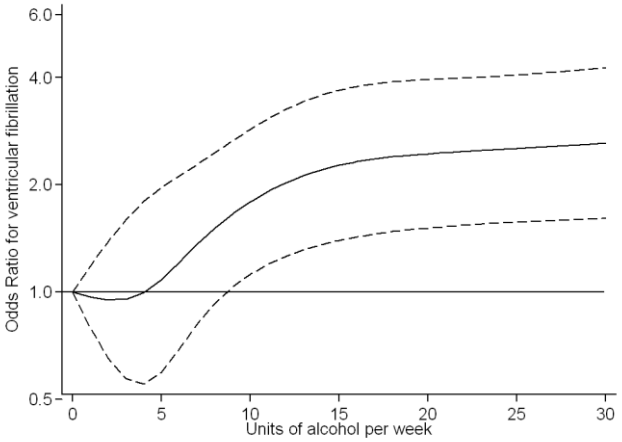

Figure 1
Restricted cubic spline for alcohol consumption.
Multivariate odds ratio of VF before PCI as a function of alcohol intake in units per week. Data are fitted by a restricted cubic spline logistic regression model and controlled for age, sex, preinfarction angina, infarct location, pre-procedural TIMI flow, atrial fibrillation, family history of sudden death, statins before STEMI, hypercholesterolemia, hypertension, and smoking. The 95% confidence intervals (CI) are indicated by dashed lines. Jabbari et al. J Am Heart Assoc. 2015 Jul;4(7). pii: e000738 with the permission of the publisher.

6.2 STUDY II

In this single-center cohort study, we consecutively enrolled 5,373 STEMI patients, of whom 410 had VF before PPCI and 88 had VF during PPCI. In total, VF before or during PPCI occurred in 498 patients (9.2%). Our study resulted in four major findings:

Table 1

Univariate and multivariate analysis of risk factors for VF

Two hundred cases and 431 controls from the four PCI centers in Denmark were included in the full multivariable model. Because the ratio of cases to controls differed among the sites, we also added the variable "study site" to the multivariable model to control for any unmeasured differences between the cases and controls enrolled at each of the four centers. OR: odds ratio; CI: confidence interval; FH: family history; TIMI: thrombolysis in myocardial infarction; PPCI: primary percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction. Jabbari et al. J Am Heart Assoc. 2015 Jul;4(7). pii: e000738 with the permission of the publisher.

		Univariate			Multivariate		
Variable	**Contrast**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Younger age	Age <60 vs. age ≥60 years	1.38	0.99-1.90	0.050	1.75	1.20-2.60	0.005
Male sex	Male vs. female	1.90	1.21-2.95	0.005	1.65	0.98-2.75	0.060
Alcohol							
1-7 units/week	Non-drinkers	1.30	0.83-2.05	0.300	1.30	0.80-2.20	0.300
8-14 units/week	Non-drinkers	1.94	1.12-3.37	0.020	2.30	1.20-4.20	0.008
≥15 units/week	Non-drinkers	3.25	1.93-5.50	<0.001	3.30	1.80-5.90	<0.001
Atrial fibrillation	Yes vs. no	2.94	1.29-6.73	0.010	2.80	1.10-7.30	0.040
Preinfarction angina	Yes vs. no	0.53	0.38-0.73	<0.001	0.46	0.32-0.67	<0.001
Family history of sudden death	Yes vs. no	1.80	1.27-2.56	0.001	1.60	1.10-2.40	0.010
Infarct location	Anterior vs. non-anterior	1.55	1.10-2.10	0.009	2.10	1.40-3.00	<0.001
TIMI flow before PPCI	TIMI flow grade 0 vs. TIMI flow grade 1-3	1.35	0.97-1.90	0.070	1.65	1.14-2.40	0.008
Statins before STEMI	Yes vs. no	2.05	1.34-3.15	0.001	2.10	1.15-4.0	0.020
Hypercholesterolemia	Yes vs. no	1.40	1.00-1.95	0.050	0.90	0.55-1.50	0.800
Hypertension	Yes vs. no	1.39	0.99-1.94	0.050	1.20	0.79-1.85	0.400
Smoking							
Past	Past vs. never	1.48	0.90-2.40	0.100	1.18	0.68-2.00	0.600
Current	Current vs. never	1.30	0.83-2.00	0.300	1.10	0.66-1.85	0.700
Study site		1.00	0.87-1.12	0.900	1.00	0.87-1.15	1.000

First, we identified several risk factors for VF before PPCI, and these factors included younger age (per 10 years of increase: OR=0.84; 95% CI 0.73–0.97), anterior infarct (OR=1.46; 95% CI 1.04–2.02), pre-procedural TIMI flow grade 0-I (OR=1.65; 95% CI 1.12–2.44), and Killip class at admission >I (OR=2.80; 95% CI 1.73–4.40).

Second, we identified several risk factors for VF during PPCI, and these factors included inferior infarct (OR=1.73; 95% CI 1.07–2.78), pre-procedural TIMI flow grade 0-I (OR=5.00; 95% CI 2.30–10.90), and Killip class at admission >I (OR=2.24; 95% CI 1.29–3.90).

Third, VF before (HR=3.40; 95% CI 1.70–6.70) and VF during PPCI (HR=4.20; 95% CI 1.30–13.30) caused by STEMI were strongly associated with a higher mortality within 30 days compared with STEMI patients without VF (Figure 2). There was no tendency toward a 30-day mortality difference between VF before PPCI and VF during PPCI VF (P=0.170).

Fourth, VF before PPCI (HR=1.04; 95% CI 0.55–2.00) and VF during PPCI (HR=1.60; 95% CI 0.65-3.95) were not associated with long-term mortality compared with STEMI patients without VF (Figure 3).

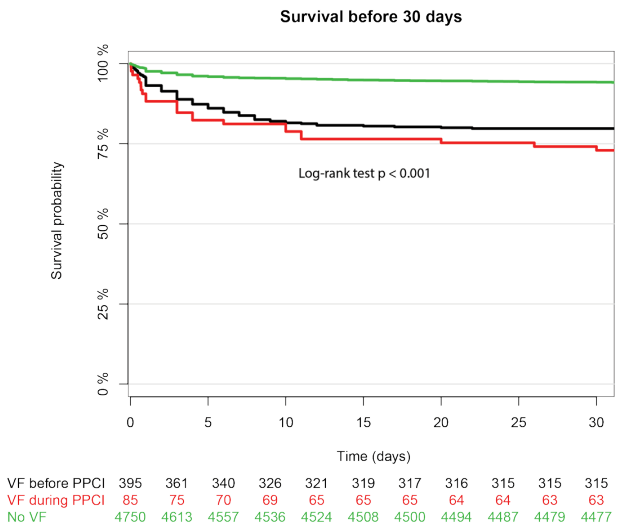

Figure 2
Kaplan-Meier curves showing the unadjusted 30-day survival of STEMI patients with and without ventricular fibrillation. Jabbari et al. Am J Cardiol. 2015 Sep 1;116(5):678-85 with the permission of the publisher.

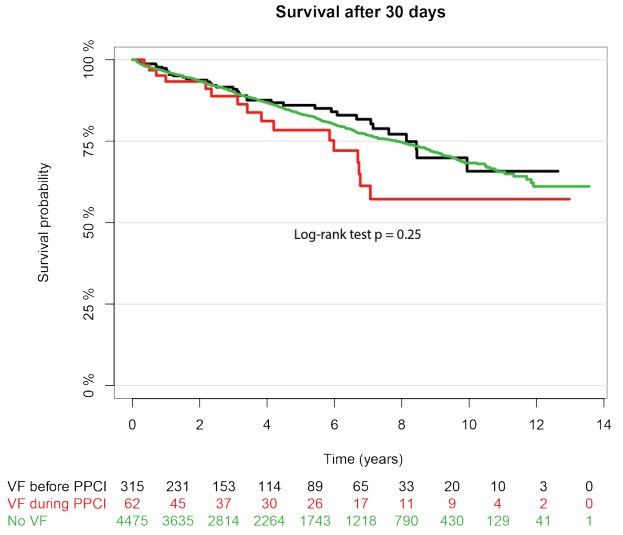

Figure 3
Kaplan-Meier curves showing the unadjusted 13-year survival of STEMI patients with and without ventricular fibrillation who survived the first 30 days. Jabbari et al. Am J Cardiol. 2015 Sep 1;116(5):678-85 with the permission of the publisher.

6.3 STUDY III

In this retrospective study of SCD caused by CAD in young Danes (n=40) aged 1–35 years, we investigated cardiac symptoms, medical history, and medical contacts before death by using all available sources, and we compared these findings with a randomly sampled control group who died in accidents (n=80). Under Danish law, a patient's records can be deleted from the registries ten years after death. This accounted for five people being excluded from the control group and one person in the case group. In the control group, it was not possible to find the death certificate for one person. Therefore, a total of one person in the case group and six people in the control group were excluded.

Compared with the controls (n=74), the SCD-CAD case (n=39) group had a significantly higher incidence of cardiac symptoms (n=31; 79%), of which angina was predominant (n=24; 62%) (Table 2). Prodromal symptoms (i.e., symptoms occurring within one hour before death) and antecedent symptoms (i.e., those occurring within a year to one hour before death) were reported in 31% and 46% of the cases, respectively (Figure 4).

In the case group, nearly half of the subjects (n=18; 46%) had one or more contact due to cardiac-related symptoms with a general practitioner and/or emergency department (ED) before death, and cardiac symptoms were suspected in only 22% of these contacts. Only one person from the control group had a cardiac symptom (syncope) and contact with the healthcare system before death (P<0.001).

In the majority of the control group, no previous disease was described, and this proportion was significantly higher in the control group than in the case group (P=0.020). Psychiatric disorders (i.e., schizophrenia and depression) were the most common diseases that exhibited no difference between the two groups (P=0.600).

Table 2
Cardiac symptoms within one year in the case and control groups. Jabbari et al. Heart. 2013 Jul;99(13):938-43 with the permission of the publisher.

Cardiac symptoms, n (%)	**Cases (n=39)**	**Controls (n=74)**	**P-value**
Overall symptoms 12 months before death	31 (79)	1 (1)	<0.001
Angina	24 (62)	1(1)	<0.001
Dyspnea	7(18)	1(1)	0.001
Uncharacteristic chest pain	6(15)	0(0)	0.001
Syncope	1(3)	0(0)	0.30
Palpitations	None	None	-
Fatigue	None	None	-

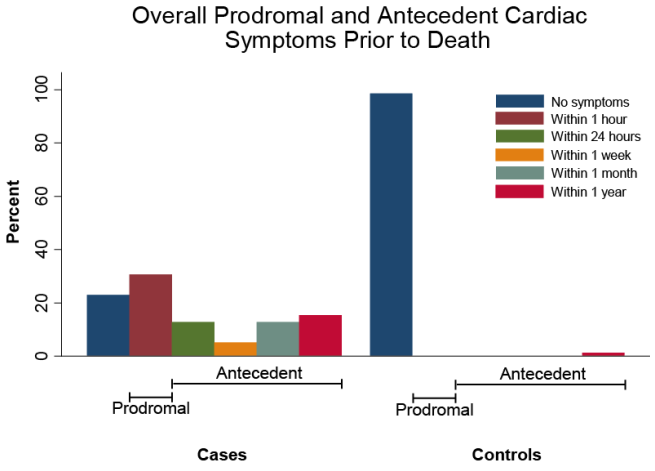

Figure 4
Overall prodromal and antecedent cardiac symptoms prior to death. Jabbari et al. Heart. 2013 Jul;99(13):938-43 with the permission of the publisher.

7. DISCUSSION

7.1 INCIDENCE AND RISK FACTORS ASSOCIATED WITH VENTRICULAR FIBRILLATION CAUSED BY STEMI

In study I,35 the incidence of VF before PPCI was 11.6%. This is higher than the incidence reported in previous studies,7,11 which may reflect better survival related to improvements in OHCA management and therapy.36 We identified several patient characteristics associated with a significantly higher risk of VF before PPCI after adjusting for common cardiovascular risk factors, infarct location, and TIMI flow. These independent risk factors include age <60 years, a family history of sudden death, the absence of preinfarction angina, statin use, a history of AF, and alcohol intake greater than 7 units/week. Traditional CAD risk factors, such as smoking, diabetes, hypertension, and hypercholesterolemia, did not predict arrhythmic risk. These results, taken together with those of previous studies,16,20,22 suggest that certain patients may be predisposed to fatal arrhythmias, vulnerable to the proarrhythmic effects of acute myocardial ischemia, and more likely to present with VF/SCD as a manifestation of CAD.

7.1.1 Association of common cardiovascular risk factors with ventricular fibrillation

In studies I and II, younger age was paradoxically associated with VF before PPCI but not with VF during PPCI (study II). This association could be caused by a higher resuscitation and/or survival rate outside of the hospital in younger individuals with VF. In line with our findings, a recent study also identified age <60 years to be significantly associated with in-hospital VF caused by MI.23 Men also tended to have a higher risk of VF before PPCI in our population, a finding that is consistent with the higher incidence of SCD among men identified in several studies;2 however, after controlling for other risk factors, the association became non-significant. In contrast, study II demonstrated that compared with women, men tended to have a lower risk of VF during PPCI (OR=0.75; 95% CI 0.46–1.23), although this association was not significant in the adjusted logistic regression model. Other common cardiovascular risk factors, such as smoking, hypertension, and hypercholesterolemia, were not associated with VF before PPCI after adjustment in our population of STEMI patients (Table 1). Smoking, hypertension, diabetes, and obesity are well known risk factors of SCD2 but according to our results these risk factors do not predict risk of VF caused by STEMI. However, because CAD is the predominant cause (≈80%) of SCD, and since there has been an age-adjusted decline in mortality from CAD including SCD in countries like the United States during the past half-century, there is rationale and indirect evidence that conventional risk factor modification reduces risk of SCD.2

In parallel with our findings, smoking and hypertension did not predict the risk of VF in the Dutch AGNES cohort consisting of STEMI patients.16 In that study, 330 survivors of primary VF presenting with first STEMI were compared with control patients who were STEMI patients without VF. In the AGNES study, however, hypercholesterolemia was associated with a lower risk of VF (OR=0.64; 95% CI 0.44–0.95). Whether high cholesterol is arrhythmogenic remains questionable. In our study, most of the patients with a known history of hypercholesterolemia were treated with statins prior to the event; thus, such an arrhythmogenic tendency may not be related to the lipid level per se but to the burden of cardiovascular disease. Also, there is no observed relationship between cholesterol concentration and the proportion of SCD caused by CAD. The actual cholesterol level at the time of acute MI may fluctuate, as cholesterols are believed to be acute-phase reactants.37,38 Therefore, acute cholesterol levels may not be suitable for predicting VF risk. This uncertainty is compounded by the fact that cholesterol levels are measured after the actual VF event.

7.1.2 Familial disposition to ventricular fibrillation

Our results suggested a possible genetic burden of VF in the Danish STEMI patients; patients with a family history of sudden death among first-degree relatives had significantly higher odds of experiencing VF before PPCI (OR=1.60). In contrast to family history of sudden death, the family history of MI among first-degree relatives did not predict the risk of VF. Previously, several studies suggested a heritable component of SCD or VF.15,16,39,40 In the observational Paris Prospective I study, 7,746 employed French men who were 43 to 52 years of age were followed for an average of 23 years. This study demonstrated that after controlling for confounding variables, parental history of sudden death was an independent risk factor for sudden death in offspring (relative risk [RR]= 1.80; 95% CI 1.11–2.88).39 If both parents suffered sudden death, the relative risk increased to 9.4. In a case-control study, primary cardiac arrest victims (n=235) were compared with population-based control subjects matched by age and sex (n=374).40 After adjusting for common cardiovascular risk factors, family history of MI or sudden death was associated with primary cardiac arrest (rate ratio [RR]=1.57; 95% CI 1.27–1.95). The authors reanalyzed their data by differentiating between family history of sudden death and family history of MI among first-degree relatives and found that family history of early onset (age <65) of sudden death was associated with a higher risk of primary cardiac arrest (OR=2.69; 95% CI 1.35–5.36).41 A Finnish study compared a series of 138 consecutive SCD (due to acute coronary events) victims who underwent autopsy with two control groups; one control group consisted of 254 consecutive acute MI survivors, and the other consisted of 470 healthy individuals. In this study, the incidence of history of SCD was significantly higher in the relatives of SCD victims compared with the incidence in AMI survivors or healthy control subjects (5.6%, 3.3%, and 1.1%, respectively).15

These initial studies did not distinguish between the different phenotypes of SCD (arrhythmic vs. non-arrhythmic), nor did they distinguish between underlying coronary artery diseases (STEMI vs. non-STEMI) to identify a discrete population with a similar pathology and phenotype. The pioneering Dutch AGNES study16 was the first study to suggest an association between a family history of sudden death and VF caused by first STEMI. This study demonstrated that a family history of sudden death in first-degree relatives was an independent risk factor for VF in this population, with an odds ratio (OR) of 2.7 (95% CI 1.8–4.0).

The genetic predisposition toward VF was further investigated in a subsequent AGNES study.42 This study reported the first genome-wide association study (GWAS) for STEMI patients with VF before PPCI. This GWAS study was conducted using 515 cases (i.e., STEMI patients with VF) and 457 controls (i.e., STEMI patients without VF), and the most significant association with VF was found at 21q21 (rs2824292, OR=1.78, 95% CI 1.47–2.13, P=3.3x10-10).42 The closest gene to this variant is CXADR, which encodes coxsackievirus and adenovirus receptor (CAR). This protein is implicated in myocarditis and is thought to be a modulator of cardiac conduction through aberrant interactions with gap junctions (Cx45) in mice.43–45 Despite this important finding, the association of single nucleotide polymorphism (SNP) rs2824292

was not detected in another small case-control study (cases=90; controls=167) of a German population46 nor in our case-control set (data not shown). Furthermore, in a meta-analysis of GWAS studies of individuals with SCD and control individuals of European ancestry from five studies (i.e., the general population), a locus at chromosome 2q24.2 (SNP rs4665058) was found to be associated with SCD (OR=1.92, 95% CI 1.57–2.34, P=1.8 x 10(-10)47); however, this SNP was not replicated in the AGNES study. These inconsistencies could be caused by heterogeneous underlying cardiac pathologies of SCD and differing phenotypes (i.e., VF vs. SCD). Therefore, it is crucial to the success of future genetic studies to integrate cohorts that have the same phenotype (VF) and pathophysiology for sudden arrest (e.g., STEMI) to achieve higher statistical power.

The finding of an association between VF and a family history of sudden death in the Danish cohort is very important because previous findings regarding an association between family history of sudden death and VF in Dutch and Finnish groups do not necessarily imply a similar pattern among the Danish cohort. Furthermore, replicating the finding of SNPs associated with SCD/VF would be an important aspect of our case-control study. Currently, VF prevention with the context of MI is based on clinical markers of VF. However, even though the genetic factors involved in this complex and multi-factorial disease are still unknown, current developments in genetic research may, in the future, add to and improve the risk assessment of VF when genetic information (i.e., risk markers) is integrated with clinical risk markers. Finally, the risk of VF associated with, e.g., a family history of sudden death could be mediated by familial aggregation of common risk factors, such as a family history of diabetes.

7.1.3 Atrial fibrillation and the risk of ventricular fibrillation

The results of study I also demonstrated a strong association between AF and VF before PPCI (OR=2.8, 95% CI 1.10–7.30). Population based studies have recently reported an association between a history of AF and SCD.48 AF at initial presentation in the context of acute MI has also been associated with an increased risk of in-hospital VF in the FAST-MI 2005 registry.23 Furthermore, a large Dutch population-based case-control study (the ARREST study) found similar increases in the risk of out-of-hospital VF arrest associated with a preceding diagnosis of AF.24 In this study, 1,397 out-of-hospital VF cases were compared with 3,474 age- and sex-matched controls from the general population (i.e., without cardiac arrest). AF was associated with a threefold increased risk of VF (OR=3.1, 95% CI 2.1–4.5). These data suggest that AF patients may have a lower threshold for VF caused by MI, which could account for the increased risk of SCD in population-based studies.

The question is whether AF by itself is proarrhythmic in the ventricles or AF is acting via another factor such as alcohol, or it is combination of both? AF has also been associated with non-sudden cardiac death suggesting that the association of AF with SCD could be mediated by shared risk factors such as CAD or heart failure (HF).48,49 For example in the Oregon-Sudden Unexpected Death Study, AF was a significant risk factor of SCD, but after adjusting for HF the AF-SCD association was no longer significant.49 In contrast to these studies there is also evidence for the proarrhythmic feature of AF, which by itself can induce VF.50 One study suggested that rapid ventricular rate during AF will reduce the ventricular refractoriness and induce ventricular tachyarrhythmia.51 Moreover, the irregular rhythm of AF may be proarrhythmic by itself and cause VF through abrupt short-to-long changes in the cycle length.52 Lastly, whether our VF patients had concealed Wolf-Parkinson-White syndrome is not known.

Heritable factors and cardiac channelopathies have been suggested as cause of VF and AF.43 For example, the SNP rs6795970 at the SCN5A/SCN10A gene locus has previously been associated with a prolonged PR interval,53 QRS interval,54 atrial fibrillation53,55 in two different studies, and with a lower risk of VF.56 SCN5A and SCN10A encode the transient sodium channel (INa) and play a pivotal role in membrane depolarization during cardiac action potentials. Therefore, further research regarding joint pathways that affect cardiac electrical function in the atrium and ventricle is necessary to further our understanding of the link between AF and VF. To support future genetic findings, it may be important to investigate the association between a family history of AF and the risk of VF.

7.1.4 Alcohol as a possible risk factor for ventricular fibrillation

Whether alcohol intake contributes to the VF risk related to MI is not clear despite supporting data on the proarrhythmic properties of alcohol.57–59 The proarrhythmic effect of alcohol intake has also been linked to incident AF,60 which in our study I also predicted VF before PPCI. Our results from study I indicate that the proarrhythmic properties of alcohol may be observed even with fairly moderate intake. Higher alcohol intake has been linearly associated with a lower risk of MI;61 in contrast, the relationship with SCD is U-shaped, with lower risks observed only with low to moderate levels of alcohol consumption (2–6 drinks per week)57,58 and higher risks observed with heavy consumption (> 6 drinks per day).59 These divergent relationships could be explained if the favorable effects of alcohol on atherosclerosis and thrombosis are offset by potential proarrhythmic effects at higher intake levels. Furthermore, in a courageous case report on a binge drinker who was resuscitated from sudden cardiac arrest, the subsequent ethanol infusion and paired ventricular stimuli led to polymorphic VT and a new episode of cardiac arrest; however, when the electrophysiological testing was later repeated without alcohol infusion, the results were normal.62 Finally, another electrophysiological study of 14 patients with a history of chronic alcohol consumption and heart disease demonstrated that after alcohol administration, the patients developed sustained and non-sustained VT, AF, and atrial flutter.63 Alcohol has also been associated with low heart rate variability in patients with CAD64 and a prolonged QT interval, which is highly associated with SCD.65 Because both the cases and the controls in our study I had STEMI, we were able to examine the relationship between alcohol and VF independent of the association with MI. Patients who reported drinking 8 to 14 units of alcohol/week had a 2.3-fold higher odds (P<0.05) of VF in the context of STEMI. This risk continued to increase, but to a lesser degree, at higher intake levels; patients who consumed >15 drinks had a 3.3-fold increased risk of VF (Figure 1).

7.1.5 Preinfarction angina and the coronary determinants of ventricular fibrillation

Our results (study I) indicated that preinfarction angina might have a protective effect against VF. In study II, a higher CCS class also exhibited an inverse association with VF before PPCI. However, this association was not significant after multivariate adjustment, possibly because of missing data for the CCS class. The association between preinfarction angina and VF was identified in a meta-analysis13 and in a prospective, consecutively enrolled case-control study of 72 AMI patients with out-of-hospital cardiac

arrest (OHCA) caused by VF (i.e., the case group); this study compared the case group with 144 AMI patients without VF (i.e., the control group)20 These studies also indicate that preinfarction angina may protect against VF, presumably as a result of ischemic preconditioning, which has recently been demonstrated to reduce the infarct size in STEMI patients.66

Angina occurs as a result of high-grade stenosis of the coronary artery, and high-grade stenosis by itself is correlated with the recruitability of collateral vessels, which supplies the infarct area with blood.67,68 The role of collateral arteries in our cohort remains to be elucidated, with the hypothesis being that STEMI patients without VF have more collateral blood supply to the infracted area, protecting them against VF.

In studies I and II, angiographic characteristics such as a completely occluded artery, defined as a pre-PCI TIMI flow grade of 0 or 0-I, were also associated with both a higher risk of VF before PPCI and with VF during PPCI. Previously, a TIMI flow grade of 0-I was demonstrated to be associated with an increased risk of VF during and after catheterization in STEMI patients in the APEX-AMI trial (HR=2.12, 95% CI 1.20–3.75)7 and in the PAMI trial (OR=2.06, 95% CI 1.23–3.47).21

We also demonstrated that anterior infarction is an independent risk factor for VF before PPCI in both study I (OR=2.10; 95% CI 1.40–3.00) and study II (OR=1.46; 95% CI 1.04–2.02). Furthermore, the results of study II demonstrated that inferior infarction (OR=1.75; 95% CI 1.13–2.95) was positively associated with VF during PPCI. Both the APEX-AMI and PAMI trials also found that inferior infarction with an occluded right coronary artery (RCA) was an independent risk factor for VF during or after catheterization, with an HR=2.16 (95% CI 1.58–2.93) and an OR=1.93 (95% CI 1.25–2.99), respectively. Previously, the GISSI-2 trial14 identified the inferoposterior infarct site to be associated with early VF, with an OR=1.45 (95% CI 1.10–1.91). The AGNES study found a non-significant trend toward increased anterior wall infarction.16 A small case-control study of 72 consecutive AMI patients with OHCA caused by VF also demonstrated that patients with acute occlusion in the LAD or LCX had higher odds of VF compared with patients with acute occlusion in the RCA, with an OR=4.82 (95% CI 2.35–9.92) and an OR=4.92 (95% CI 2.34–10.39), respectively.22 The French FAST-MI 2005 registry study, which compared AMI patients with in-hospital VF with patients without VF, also replicated the association between anterior infarct and VF (37.9% in the VF patients vs. 20.1% in the non-VF patients, P=0.001).23 Anterior MI may be a proxy for infarct size, which is difficult to accurately measure in the context of resuscitated VF arrest, and one study that adjusted for infarct size revealed a trend toward an anterior location and VF before PPCI.16 Future studies investigating the correlation of VF to creatine kinase-MB (CK-MB) levels, infarct size, area at risk (both assessed by cardiac magnetic resonance imaging), and infarct location in order to predict clinical outcome of VF is crucial.69

Alternative causes of VF during PPCI might include both sudden reperfusion per se and suboptimal reperfusion due to reperfusion injury or distal embolization of the coronary microcirculation. In fibrinolytic-treated patients, accelerated idioventricular rhythm was believed to be a marker of successful reperfusion. However, one study demonstrated that accelerated idioventricular rhythm within the course of STEMI was associated with extensive myocardial damage (based on infarct size) and delayed microvascular reperfusion.70 Because the RCA typically supplies a smaller area at risk than the LAD, we suggested that VF during PPCI may be related to factors within the artery and not the extent of ischemia per se. Extensive manipulation (i.e., catheter maneuvers) of the coronary artery could be the cause of VF during PPCI in patients with an occluded RCA, which is reflected by the longer procedure time due to a TIMI flow grade of 0–I in the group with VF during PPCI compared with patients without VF (study II). Finally, catheter maneuvers can also cause VF during PPCI due to the smaller lumen diameter and spasms of the RCA, particularly in women.71 This hypothesis was supported by results from study II, which demonstrated that the proportion of women with VF during PPCI (33%) was significantly higher than the proportion of women with VF before PPCI (18%; P=0.002). Furthermore, comparing coronary occlusion in women with VF at different times demonstrated that RCA occlusion occurred in 72% of women who had VF during PPCI and in only 24% of women who had VF before PPCI (P=0.001).

Finally, our results from study II also demonstrated that a higher Killip class at admission was highly associated with VF before PPCI and VF during PPCI. It is important to note that the Killip class is measured in the setting of the VF event and therefore, the Killip class could be the result of cardiac arrest due to VF rather than a predictor of VF. In line with our results, acute heart failure was also associated with VF in the APEX-AMI trial. In this trial, a Killip class at admission was found to be associated with early VF and sustained VT (HR=1.88, 95% CI 1.29–2.76).7

7.2 OUTCOMES OF STEMI PATIENTS WITH AND WITHOUT VENTRICULAR FIBRILLATION (STUDY II)

Ventricular arrhythmias during acute MI are typically classified based on their time of onset. This classification is usually used in the clinic because VT and VF that occur early (in ≤48 hours) have been thought to be epiphenomena of MI that do not require long-term therapy. In addition, some studies have suggested that early VT and VF are not usually associated with a worse prognosis after hospital discharge.11,14 However, because manipulations involved in guiding a catheter in the coronary artery and reperfusion may themselves induce VF, we classified the time of VF occurrence based on the time of PPCI procedure. Therefore, we defined primary VF as VF before PPCI, which occurred out-of-hospital or upon arrival to the PPCI center, and subsequent VF as VF during PPCI. Thus, we hypothesized that the risk factors and outcomes of these two VF groups may be different.

We performed the largest study in terms of the number of enrolled VF patients and had the longest available follow-up duration in the PPCI era; the complete follow-up was achieved with the use of the Danish registries. Our results demonstrated that VF before and VF during PPCI are strongly associated with a higher mortality within 30 days compared with STEMI without VF. However, VF before and VF during PPCI are not associated with long-term mortality in STEMI patients with or without VF. A novel and important message from our study with potential clinical implications for this population is that reperfusion-induced VF is not “benign,” as suggested previously;21 30-day mortality is high and is the same for patients with VF before PPCI and those with VF during PPCI.

In contrast with the existing literature,7,11,14,21,25 we enrolled cases and controls consecutively, and we chose to confine our phenotype to only patients with STEMI to provide a discrete population that allowed the selection of cases and controls with a similar pathology of underlying coronary artery disease and plaque rupture. This is in contrast with previous studies that included patients with both STEMI and non-STEMI.11,72 Furthermore, we enrolled consecutive STEMI patients with out-of hospital cardiac arrest related to VF who survived to reach the PCI

center and patients with VF during PPCI; this is in contrast with the French FAST-MI 2005 registry study, which only enrolled consecutive MI patients with in-hospital VF from intensive care units within a one-month period.23 Finally, we chose to focus on the interventional procedure itself (i.e., VF before vs. VF during), while other investigations have focused on the distinction between early (i.e., within 48 hours) and late (i.e., after 48 hours) ventricular arrhythmias.

Previous data from other studies in the era of PPCI on the short-term and long-term prognosis of VF due to STEMI are inconsistent.7,21,23,25 Retrospective analyses of the PAMI trial (3065 STEMI patients) revealed no increase in in-hospital mortality or one-year mortality for reperfusion induced-VF (VF during PPCI, n=133).21 However, the PAMI trial included only patients with VF during PPCI, and patients with cardiogenic shock were excluded; this exclusion may explain the difference in their survival data compared with ours. Retrospective analyses of the APEX-AMI trial among 5,745 STEMI patients of whom 329 had VF revealed increased 90-day mortality.7 Of the 329 STEMI patients with VF in the APEX-AMI trial, 25 had VF before PPCI, 180 had VF during PPCI, and 170 had VF after PPCI; most VF events (n=282, 86%) occurred as early VF (i.e., within the first 48 hours). Our data on short-term survival is in line with the APEX-AMI trial. Despite this similarity in the results, it is important to stress that the APEX-AMI study excluded patients with isolated inferior infarcts and those who had an onset of symptoms beyond the first 6 hours of STEMI. Finally, it is important to emphasize that patients included in randomized controlled trials (i.e., PAMI or APEX-AMI) are subject to inherent selection bias.

In line with our results, the follow-up results from the AGNES case-control study of STEMI patients with VF before PPCI suggested that patients who survived the first month after VF had prognoses similar to those of patients with STEMI without VF.25 However, in the survival analysis of the AGNES study, the patients were not enrolled consecutively, and those who died within the first month were excluded. Another observational case-control study (i.e., the FAST-MI 2005 registry), which enrolled patients consecutively, exhibited survival data similar to ours.23 This study found a higher in-hospital mortality rate for both early VF (<48 hours) and late VF (>48 hours), but VF was not associated with long-term all-cause mortality. However, this comprehensive study only included patients with in-hospital VF (i.e., both early and late VF occurring in the hospital), and patients with OHCA caused by VF were not included. Furthermore, the total number of VF patients in the follow-up cohort was fairly low (n=87).

The current guidelines do not recommend early treatment with implantable cardioverter-defibrillators (ICDs) in patients with VF in the context of MI, and the results of the survival analysis from our study are in line with and support the current guidelines.26

7.3 CORONARY ARTERY DISEASE AND SUDDEN CARDIAC DEATH IN YOUNG PATIENTS (STUDY III)

In study III,73 we reported a high incidence (79%) of cardiac symptoms in young Danes (ages 1–35 years) who suffered SCD caused by CAD. The predominant symptom in this group was angina, which occurred in 62% of the cases. Moreover, 23% of the cases had known psychiatric disorders. Furthermore, nearly half of the case group contacted health care professionals; nevertheless, SCD occurred. Although it seems that CAD was not common among the total causes of death (6,500) during the study period (2000–2006), it was responsible for nearly 13% of the SCDs in the 314 young patients on whom an autopsy was performed.27

Whether electrophysiological destabilization in the course of MI that causes VT/VF is also correlated with clinical cardiac symptoms is not known.74 Prodromes occurring several weeks or months before events have low sensitivity and are poor predictors of SCD; additionally, young patients with symptoms such as chest pain have a very low rate of adverse events within a year.33 Nevertheless, in our study, we found that cardiac symptoms occurred within the last hours before death in 31% of the cases. These results raise the possibility that symptoms that occur within a patient's last hours are more specific to SCD caused by CAD. In addition to our study, other retrospective studies in selected young populations have suggested that young patients who experience SCD have symptoms prior to death.75–80 In one study among US military personnel (n=902) with a mean age of 38 years that included all sudden unexpected death patients, a prodromal symptom was documented in 52.7% of the cohort within the week before death; the predominant symptom was chest pain (51.8%), which occurred primarily in the CAD group.76 Furthermore, a Swedish study also reported prodromal symptoms prior to death in 50% of cases.81 The same group reported ECG abnormalities, such as T wave inversion and ST changes, in 82% of the subjects.82

In study III, although half of the case group contacted the health care system because of their cardiac symptoms, death was not avoided. In general, information about the cardiovascular risk factors in our cohort was limited. Out of 39 patients with SCD caused by CAD, information on the family history of CAD was documented for 8 patients, and 7 out of 8 had a family history of CAD. Information on the family history of sudden death was only documented for one patient. Although it remains speculative, the results of study III may indicate that young SCD-CAD patients may have a genetic predisposition toward CAD and or SCD. The results may also indicate the low awareness of the burden of the disease (i.e., SCD-CAD) on young patients. Such patients are normally not considered to be at risk for SCD, especially by non-cardiologist physicians who, in most cases, examine these patients in the primary care setting or in emergency rooms.

One strength of our study is that it was conducted in a nationwide setting. It also included a systematic review of all available sources and, most importantly, included information from supplemental fields on the death certificates, which provide valuable information on antemortem prodromal symptoms. Although it is difficult to draw clinical implications from a descriptive study, taken together, our study and the literature indicate that identification and characterization of antemortem prodromal symptoms, such as sudden onset of chest pain, or dyspnea, that occur during the days or hours before cardiac arrest, may be more specific to imminent cardiac arrest when the onset of these symptoms is abrupt. This may be especially true for high-risk patients, such as those with known psychiatric disease. Previously, a history of psychiatric treatment and phobic anxieties has been associated with increased risk of fatal CAD because it increases the risk of SCD.83 Therefore, it is necessary to identify sub-groups in the general population with a high risk of sudden death, such as individuals with a familial clustering of sudden death who refer to emergency departments with cardiac symptoms.

Assessing risk factors in these retrospective postmortem studies is difficult and is associated with recall bias; this is compounded by the fact that in autopsy studies that identify the cause of death, the cause of death may not be representative of the

mechanism of death (e.g., whether it was arrhythmic or non-arrhythmic). Assessing risk factors for sudden death caused by CAD is even more complex; on one hand, we have the traditional clinical risk factors of atherosclerosis, which trigger a cascade of altered plaque characteristics with a later onset of acute MI and the development of arrhythmogenesis of SCD; on the other hand, there is personalized risk in the form of the genetic profile, which makes young patients susceptible to either rapidly progressive plaque evolution and MI84 or to arrhythmogenesis.42 Therefore, collecting prospective data from, e.g., longitudinal cohort studies that include a thorough assessment of antecedent cardiac symptoms, the family history of sudden death or MI, medical history, lifestyle risk factors, and postmortem autopsy findings, including the results of molecular autopsy,85 is essential for elucidating the associations between risk factors and SCD.86

7.4 METHODOLOGICAL CONSIDERATIONS AND THE LIMITATIONS OF THE THREE STUDIES

The limitations of each study are described in detail in each paper. However, each study requires a more detailed discussion of the strengths and limitations of the study design and the methods used in this PhD thesis. In general, the aim of epidemiological studies is to investigate the role of risk factors in the disease of interest. The common challenge in these non-experimental studies is adjusting for all possible confounders to achieve the most accurate point estimates (i.e., estimates of effect) for each risk factor. Therefore, the associations among risk factors may be operating via unobserved confounders, such as physical activity.

7.4.1 Study I

Cases and controls in study I were not enrolled consecutively. A consecutive approach to include all cases and controls at all four PCI centers within two years would have been the most unbiased and accurate way to estimate risk factors for VF due to STEMI. Furthermore, this approach would also have provided the study with higher statistical power. We only included patients who survived long enough to undergo angiography; therefore, its results may not be generalizable to STEMI patients who do not survive to reach the hospital and do not undergo angiography.

There is also the potential for recall bias, which is a limitation of any case-control study in which exposure is ascertained after the event. Although study I had a prospective design, we asked the patients about alcohol consumption, smoking and other factors after the event (i.e., the VF and/or STEMI). Therefore, the actual design of this study regarding these variables is retrospective. Furthermore, information on, e.g., symptoms prior to the event in the unconscious cases may have been less likely to be obtained, causing the proportion of those with angina in this group to be lower. A longitudinal, prospective cohort study would have been the ideal study design, although time consuming, especially for the assessment of lifestyle risk factors for VF.

In this study, we performed an unmatched case-control study and included cases and controls separately in predetermined numbers based on a power calculation before the study began, according to our protocol. We did not match the case group with the control group. In most studies, cases are matched with controls based on age and sex because one might expect that cases will come from older or younger populations, and therefore, controls might be selected because they are similar in age to a case. When matching cases with controls, it is necessary to ensure that the variables that are chosen for matching (e.g., sex or age) are strong confounders, and this information is important for an effective matching system that results in more precise coefficient estimates. In cases where the matching variable does not confound the relationship between the exposure of interest and the outcome, matching can lead to estimates with decreased precision relative to an unmatched study. Finally, we aimed to investigate whether age and sex were independent risk factors of VF in the setting of STEMI, and therefore we did not matched cases with controls, instead we adjusted for these variables.

7.4.2 Study II

This study was performed as a retrospective observational case-control study. In study II, we enrolled patients consecutively, and the completeness of the data for the angiographic findings and the presenting characteristics was high. Nevertheless, covariates that were part of the baseline characteristics were missing; additionally, crucial covariates such as lifestyle factors, socioeconomic data, and parental history of sudden death were lacking in this study. The ideal method of performing this study would have been to include data from all PCI centers in Denmark (i.e., nationwide) to improve the power of the study and to include patients from all geographical regions of the country. In this study, we did not have information on ejection fraction, glomerular filtration rate, creatinine levels, and ICD implantation. One can assume that a significant part of long-term mortality could be related to arrhythmic sudden death and ICD could have introduced a bias between the groups. Also, we did not assess the cause of death in study II in order to investigate if the patients died of arrhythmic death or not. Therefore, the patients could potentially have benefited from an ICD-treatment. Lastly, we lacked information on medical treatment prior to admission and after discharge. Potential differences regarding anti-arrhythmic medication at discharge can exist with potential impact on the outcome.

Due to missing covariates, we analyzed (using Cox analysis) only subjects with no missing data (i.e., complete case analysis), and as a consequence our study had less power and generalizability. However, there was no missing data in our primary predictor of interest (i.e., VF before or during PPCI) in the Cox regression analysis, and by using the multiple imputations by chained equations (MICE) method we confirmed the complete case analysis.

7.4.3 Study III

In the primary study by Winkel et al., the incidence of SCD in the general population was assessed using death certificates and autopsy.27 Even though this study had a retrospective design, the use of Danish death certificates and, especially, autopsy reports to assess the cause of death provided the most reliable data on the cause of SCD in young people in Denmark. In Denmark, the supplemental information field on the death certificate provides valuable information on prodromal symptoms prior to death as described by witnesses of deaths, relatives, and EMS personnel on the scene; additional information was provided in a significant number of cases by contact with the deceased's GP conducted by public health medical officers or a forensic pathologist.

One of the problems with our primary study is that not all sudden unexpected death cases were autopsied; the autopsy rate was 75% in this study. Furthermore, the ideal method would be to prospectively include and perform an autopsy on all sudden unexpected deaths in individuals who die out-of-hospital and to collect all information on previous medical history and symptoms prior to death. However, this approach would be very costly.

Autopsies can establish the "true" incidence of SCD and the underlying cause of death, especially if histology, toxicology, and molecular autopsy are also performed; however, the standardization of the autopsy procedure (as was used in our forensic autopsy cases) is crucial to the assessment of the cause of death.

8. CONCLUSION

The three studies in this PhD thesis contribute several important messages.

8.1 RISK FACTORS FOR VENTRICULAR FIBRILLATION

- The incidence of VF caused by STEMI in patients who survived to undergo angiography is 11.6%. Therefore, primary prevention for patients at risk for arrhythmic events is of the utmost importance.
- A family history of sudden death is an independent risk factor for VF in this Danish STEMI cohort and suggests that these patients have a genetic predisposition toward disease.
- Patients with AF are at significantly higher risk of VF due to STEMI, and therefore our results suggest that AF and VF may share a common pathogenesis.
- There are several factors that may help to identify high-risk patients. In the case of lifestyle factors such as alcohol, the study's findings raise the possibility that alcohol intake might affect the risk of VF.
- Absence of preinfarction angina in STEMI patients significantly increases the risk of VF and thus suggests a lack of preconditioning and/or collaterals in the VF group.
- Anterior infarction is an independent risk factor for VF before PPCI, and inferior infarction is an independent risk factor for VF during PPCI; this suggests that VF may be related to factors within the artery and not the extent or size of the infarct.
- Common cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia did not predict risk for VF in our cohort.

8.2 OUTCOMES OF VENTRICULAR FIBRILLATION

- Our data suggest an increase in the short-term (i.e., 30-day) mortality for patients with VF before and during PPCI, but VF is not associated with long-term mortality in STEMI patients.
- 30-day mortality is high and is equivalent for patients with VF before PPCI and those with VF during PPCI; this result suggests that reperfusion-induced VF (i.e., VF during PCI) is not "benign".

8.3 CORONARY ARTERY DISEASE AND SUDDEN CARDIAC DEATH IN THE YOUNG

- Prodromal and antecedent cardiac symptoms are important signs in young patients, and these occurred in 79% of the young SCD patients who died due to CAD.
- Finally, 46% of the CAD-SCD cases (n=39) contacted health care professionals, although SCD was not avoided.

Overall, these data could be useful when counseling apparently healthy younger individuals regarding the importance of CAD and lifestyle risk factor modification to prevent sudden death as a result of VF in STEMI patients.

9. PERSPECTIVES

Sudden cardiac death remains a major public health problem, and we still have a great challenge facing us. Despite tremendous research on risk stratification for predicting SCD/VF, it is still an enormous challenge for physicians to predict risk, especially in the general population.87,88 Because SCDs occur in apparently healthy individuals without prior cardiac disease, we need to move beyond identifying risk factors for SCD in high-risk patients (e.g., patients with known low EF). A recent comprehensive review87 by the world's experts in SCD suggested the use of accepted risk scores, such as Framingham and SCORE, to identify individuals without a previous history of cardiac disease who are at risk of experiencing a coronary event. These individuals would potentially benefit from lifestyle improvements and medical intervention. However, these risk scores are mainly based on common cardiovascular risk factors, such as smoking, total cholesterol level, and hypertension. The authors also acknowledge that these risk factors may not be "applicable" risk factors for the reduction of arrhythmic sudden death, as our STEMI cohort's results suggest. Therefore, several initiatives are necessary to improve the identification of CAD patients at risk for SCD. First, better estimation of the incidence of VF/SCD in various populations is necessary for the prevention of VF/SCD. This would ideally be undertaken in prospective studies of sudden unexpected death in individuals by collecting information on medical history and cardiac symptoms prior to death and by completing a standardized autopsy. Second, the use of prospective longitudinal cohort studies combined with comprehensive registries, such as the Danish registries that collect data on lifestyle factors such as physical activity, alcohol intake, psychiatric diseases, etc., to assess risk factors for VF/SCD is necessary. Third, differentiating between the pathophysiology (i.e., STEMI vs. non-STEMI) and the phenotype (i.e., arrhythmic or non-arrhythmic death) of SCD is important, especially in genetic studies. Fourth, the replication of studies to test the identified clinical risk factors and genetic markers in different cohorts is crucial.

Ideally, we would have a prediction model that allows clinicians to identify patients at risk for VF. However, it is difficult to build a robust risk prediction model with high risk prediction accuracy (i.e., c-statistic of >0.80) because prediction models require large datasets that represent the population of interest and, most importantly, a clear (homogenous) phenotype of the disease of interest. Additionally, risk stratification is usually limited by competing risks, low positive predictive values, changes in lifestyle factors, such as physical activity, and temporal changes in cardiac signs and symptoms, which are even more difficult to determine in asymptomatic patients. With these limitations in mind, Figure 5 summarizes some of the potential means of assessing risk factors for VF caused by MI to provide a future risk prediction model for VF.

10. ABBREVIATIONS

AF: Atrial fibrillation
BMI: Body mass index
CABG: Coronary artery bypass grafting
CAD: Coronary artery disease
CCS: Canadian Cardiovascular Society grading of angina pectoris
CRN: Civil Registration Number
FH: Family history
LAD: Left anterior descending coronary artery

Figure 5
Possible ways for future research to assess risk factors for ventricular fibrillation (VF) caused by myocardial infarction.

LCX: Left circumflex coronary artery
MI: Myocardial infarction
OHCA: Out-of-hospital cardiac arrest
PPCI: Primary percutaneous coronary intervention
RCA: Right coronary artery
SCD: Sudden cardiac death
SCDY: Sudden cardiac death in the young
STEMI: ST-segment elevation myocardial infarction
TIMI: Thrombolysis in myocardial infarction
VF: Ventricular fibrillation
VT: Ventricular tachycardia

11. SUMMARY

In this PhD thesis, we report that VF is still a common complication of STEMI, with an incidence of 11.6% in the population of Danish STEMI patients who survive to reach the hospital. In this STEMI population, we identified several risk factors associated with VF independent of MI. We identified and confirmed findings from several previous studies and found several risk factors, such as younger age, a family history of sudden death, a TIMI flow grade of 0, the absence of angina, anterior infarction (i.e., VF before PPCI), and inferior infarction (i.e., VF during PPCI) that were associated with VF in a Danish cohort. Furthermore, a history of atrial fibrillation and alcohol intake were identified as novel risk factors for VF.

To the best of our knowledge, this study contains data on the largest VF cohort with the longest reported follow-up published; we found that VF mortality is significantly higher within the first 30 days for patients who experience VF before and during PPCI compared with STEMI patients without VF. However, the long-term mortality rates of the three groups are the same. Importantly, our results contradict the previous understanding that VF during PPCI is “benign”; the mortality rate within the first 30 days was as high for patients with VF during PPCI as the mortality rate of patients with VF before PPCI.

Finally, although it is difficult to draw clinical implications from a descriptive study, due to the comprehensiveness of Danish death certificates, we reported a high incidence of cardiac symptoms and contact with health care professionals based on cardiac symptoms in young SCD patients who died due to CAD, although death was not avoided.

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