Electrophysiology

Prognosis among survivors of primary ventricular fibrillation in the percutaneous coronary intervention era

Jonas S. G. de Jong, MD, a Roos F. Marsman, MSc, a José P. S. Henriques, MD, PhD, a Robbert J. de Winter, MD, PhD, a Michael W. T. Tanck, PhD, b Arthur A. M. Wilde, MD, PhD, a and Lukas R. C. Dekker, MD, PhD a,c Amsterdam and Eindhoven, The Netherlands

Background Sudden cardiac death (SCD) constitutes one of the most prevalent modes of death and is mainly caused by primary ventricular fibrillation (VF), that is, VF in the acute setting of a first acute myocardial infarction (MI). Current guidelines for secondary prevention of SCD are based on data from the thrombolysis era. We analyzed follow-up data of a large group of primary VF survivors to determine prognosis and risk of SCD in patients who received contemporary MI treatment.

Methods Patients in this study were included in the ongoing Dutch multicenter primary VF study between December 1999 and April 2007. Primary VF was defined as VF during the first ST-elevation myocardial infarction (STEMI). Patients surviving the first 30 days were analyzed in this study. Data on mortality, cause of death, hospitalization, and implantable cardioverter-defibrillator (ICD) implantation were retrieved from national databases. In addition, data on left ventricular ejection fraction and medication use during follow-up were retrieved.

Results In total, 341 primary VF patients (cases) and 292 STEMI patients without VF (controls) were included in the study. Demographic and infarct characteristics were comparable between both groups. The median follow-up was 3.33 years for cases and 3.69 for controls (P = .02). The left ventricular ejection fraction post-STEMI was 45.1% versus 46.5% (P = .342). During follow-up, 19 cases died versus 24 controls. Cox regression analysis showed no significant difference in survival between cases and controls (relative risk 0.59, 95% CI 0.15-2.30). Implantable cardioverter-defibrillators were implanted in 22 cases and 2 controls (P < .001), but only 2 cases and 1 control patient received appropriate ICD shocks. ß-Blocker use during follow-up was 84.4% in cases versus 76.2% in controls (P = .049). Of cases, 2.5% were rehospitalized for acute MI versus 10.1% of controls (P < .001). The numbers of admissions for acute coronary syndromes and chest pain were not different between groups.

Conclusions In conclusion, patients who survive the first month after primary VF have a similar prognosis as patients with a STEMI without VF. This is the first study to address this question in the modern era of reperfusion therapy. Implantable cardioverter-defibrillator treatment in primary VF patients without residual ischemia or other risk factors can be safely withheld. [Am Heart J 2009;158:467-72.]

Sudden cardiac death (SCD) remains one of the most important modes of death in developed countries. The main cause of sudden death (SD) is primary ventricular fibrillation (VF), that is, VF during myocardial infarction (MI) and in the absence of heart failure.2 Because resuscitation and emergency care improve, more heart arrest victims fully recover, and the number of survivors increases.3,4 Secondary prevention of cardiac arrest includes implantable cardioverter-defibrillator (ICD) implantation. Current guidelines on the secondary prevention of SCD do not recommend ICD implantation if VF occurs within 24 to 48 hours of a transmural MI and no residual ischemia or severe left ventricular dysfunction remains.5 This recommendation is based on 2 older studies. In the 1970s, Liberthson et al6 reported on the prognosis of 42 resuscitated patients who survived to discharge. Only 35% of these patients had an MI, which, in this era, was not treated by any form of reperfusion therapy. The mean survival of patients discharged alive was a little more than 1 year. Volpi et al7 studied 435 patients who developed VF within 48 hours after onset of ST-elevation MI (STEMI), treated with thrombolysis. Because reperfusion therapy in these studies was either lacking or suboptimal, these studies may have lost external validity in the current era of...
Medical history
Location at time of arrest NA
Cardiac medication before receptor.

VF survivors receiving contemporary MI treatment.

patients are presented to determine prognosis of primary data of a large group of primary VF survivors and control

Angina
FH of SD 128 (41.0%) 76 (26.4%)

acute ST-segment elevation MI and reperfusion therapy in

that is, VF occurring between the onset of symptoms of

ischemic VF. In both studies, an unidentified number of

most SCD in the general population is caused by early

Methods
Patient population
The primary VF study is an ongoing Dutch multicenter observational case-control study of which results have been published before. Patients included between December 1999 and April 2007 represent the cohort for this long-term follow-up analysis. Cases were defined as survivors of primary VF. A random selection of STEMI patients without VF served as controls. Because VF can take minutes to hours to occur after onset of ischemia, we did not include control patients who were treated with PCI within 120 minutes. This avoided inclusion of patients with a possible predisposition to VF in the control group but in whom VF was prevented by very early reperfusion. Although focusing on long-term survival, patients who died within 30 days after the index event were excluded. Such early deaths were mostly related to severe neurologic damage or severe heart failure and occurred during the initial hospital admission. Age limits were 18 to 80 years. This study complied with the principles set out in the Declaration of Helsinki. All patients or their legal representative gave written informed consent for inclusion. The collection of long-term follow-up information was approved by the institutional ethics committee. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

Data collection
Data on risk factors and family history (FH) were acquired as described previously. Family history included SD and cardiovascular disease (CVD). Family history of SD was present when the patient reported a parent or sibling who died unexpectedly and before the age of 80 years. Hypertension, hypercholesterolemia, and diabetes were scored based on previous diagnosis and initiation of therapy. Maximal creatine kinase-MB (CK-MB) levels and time to maximal CK-MB were used as early indicators of infarct size. Creatine kinase-MB levels were measured at admission and every 4 hours thereafter until the maximal value was assessed. A lesion was considered the culprit if it appeared fresh on angiography and, in case of more than one lesion, if it corresponded with the location of ST elevation on the electrocardiogram. Echocardiography data were gathered retrospectively. Medication use during follow-up was gathered by a written 1-year follow-up questionnaire to all PCI patients in the Academic Medical Center, Amsterdam, The Netherlands, which accounted for most of the included patients.

Mortality data were obtained from the Dutch Municipality Registration databases and were available up to April 2007. Cause of death was obtained from the death certificates in the national database of Statistics Netherlands and available up to December 2005. Hospitalization data were obtained from the National Medical Registration (Landelijke Medische Registratie) and available up to December 2005. Postdischarge hospitalization

Table I. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MI with VF (n = 338)</th>
<th>MI without VF (n = 292)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>272 (80.5%)</td>
<td>240 (82.2%)</td>
<td>.581</td>
</tr>
<tr>
<td>Age at index infarction (y)</td>
<td>56.8 ± 11.3</td>
<td>55.4 ± 10.9</td>
<td>.185</td>
</tr>
<tr>
<td>Cardiovascular risk profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 3.8</td>
<td>26.8 ± 3.8</td>
<td>.047</td>
</tr>
<tr>
<td>FH of CVD</td>
<td>197 (62.3%)</td>
<td>199 (70.1%)</td>
<td>.066</td>
</tr>
<tr>
<td>Current smoker</td>
<td>203 (63.5%)</td>
<td>172 (61.2%)</td>
<td>.566</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (5.5%)</td>
<td>26 (9.7%)</td>
<td>.055</td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (29.1%)</td>
<td>90 (31.3%)</td>
<td>.612</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>77 (30.9%)</td>
<td>105 (46.5%)</td>
<td>.001</td>
</tr>
<tr>
<td>FH of SD</td>
<td>128 (41.0%)</td>
<td>76 (26.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Angina &gt;48 h before STEMI</td>
<td>124 (39.6%)</td>
<td>108 (37.4%)</td>
<td>.752</td>
</tr>
<tr>
<td>Location at time of arrest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out of hospital</td>
<td>140 (42.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulance</td>
<td>78 (23.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>108 (32.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac medication before STEMI</td>
<td>28 (8.9%)</td>
<td>30 (10.3%)</td>
<td>.552</td>
</tr>
<tr>
<td>STEMI β-Blocker</td>
<td>32 (10.3%)</td>
<td>20 (6.9%)</td>
<td>.143</td>
</tr>
<tr>
<td>Statins</td>
<td>22 (7.1%)</td>
<td>17 (5.9%)</td>
<td>.548</td>
</tr>
<tr>
<td>ACE/ARB blockers</td>
<td>26 (8.3%)</td>
<td>18 (6.2%)</td>
<td>.316</td>
</tr>
<tr>
<td>Aspirin/oral anticoagulation</td>
<td>29 (9.3%)</td>
<td>30 (10.3%)</td>
<td>.675</td>
</tr>
<tr>
<td>Medical history</td>
<td>46 (15.0%)</td>
<td>22 (8.2%)</td>
<td>.011</td>
</tr>
<tr>
<td>Other</td>
<td>56 (18.2%)</td>
<td>57 (21.3%)</td>
<td>.369</td>
</tr>
</tbody>
</table>

NA, Not applicable; ACE/ARB, angiotensin converting enzyme or angiotensin receptor.

Table II. Myocardial infarction characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MI with VF (n = 338)</th>
<th>MI without VF (n = 292)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>86.7%</td>
<td>85.7%</td>
<td>.576</td>
</tr>
<tr>
<td>CABG</td>
<td>4.2%</td>
<td>0.7%</td>
<td>.006</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>2.4%</td>
<td>2.5%</td>
<td>.971</td>
</tr>
<tr>
<td>None (spontaneous reperfusion on angiography)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between symptoms</td>
<td>159 (90)</td>
<td>180 (106)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>and PCI (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal CK-MB value</td>
<td>257 (372)</td>
<td>260 (299)</td>
<td>.552</td>
</tr>
<tr>
<td>Time to maximal CK-MB (h)</td>
<td>12 (4)</td>
<td>11 (4)</td>
<td>.265</td>
</tr>
<tr>
<td>Culprit lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>191 (60.6%)</td>
<td>145 (52.5%)</td>
<td>.087</td>
</tr>
<tr>
<td>RCX</td>
<td>44 (14.0%)</td>
<td>42 (15.2%)</td>
<td>.598</td>
</tr>
<tr>
<td>RCA</td>
<td>77 (24.4%)</td>
<td>87 (31.5%)</td>
<td>.041</td>
</tr>
<tr>
<td>LM</td>
<td>3 (1.0%)</td>
<td>2 (0.7%)</td>
<td>.078</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>75 (23.8%)</td>
<td>47 (17.7%)</td>
<td>.074</td>
</tr>
</tbody>
</table>

CABG, Coronary artery bypass graft; LAD, left anterior descending artery; RCX, ramus circumflex; RCA, right coronary artery; LM, left main.
was defined as a hospitalization more than 30 days after the first event. Hospitalizations were recoded in 6 categories according to the main reason for admission: “acute MI,” “acute coronary syndrome” (ACS), “chest pain,” “arrhythmia,” “other cardiac,” and “noncardiac.” Whether or not a patient received an ICD was determined by a query of the Dutch Pacemaker Registry (Stichting Pacemaker Registratie Nederland) database. Whether or not patients received appropriate ICD shocks was reported by their treating cardiologists.

Statistical analysis

Differences in continuous variables between study groups were tested using an independent \( t \) test when data were normally distributed or a Mann-Whitney \( U \) test otherwise. Values are presented as means ± standard deviation or median and interquartile range (IQR). The Cox proportional hazards regression model was used to evaluate the independent contribution of baseline clinical factors to the development of end points. Differences in categorical variables were compared using a Fisher exact test, and values are presented as number and percentages. All \( P \) values were 2 sided, and a \( P \) value of .05 or lower was considered significant. Analyses were performed using SPSS version 17 (SPSS Inc, Chicago, IL).

Results

Baseline and infarct characteristics

Between December 1999 and April 2007, there were 341 primary VF patients (cases) and 292 STEMI patients without VF (controls). Patient groups were comparable, except for body mass index (BMI), high cholesterol, FH of CVD, presence of a positive FH of SD, presence of multivessel disease, and time between onset of symptoms and PCI (Tables I and II). The latter was expected because of inclusion criteria.

Survival

Median follow-up was slightly shorter in cases than in controls (1,013 days [IQR 1,008 days] versus 1,055 days [IQR 938 days], \( P = .012 \)). During follow-up, 19 cases died versus 24 controls (\( P = .106 \)). Mortality status of 2 cases could not be retrieved; both were excluded from the analyses. Median follow-up was slightly shorter in cases than in controls (1,013 days [IQR 1,008 days] vs 1,055 days [IQR 938 days], \( P = .012 \)), which was caused by a small differences in inclusion rate over time between cases and controls. The Kaplan-Meier analysis is shown in Figure 1. Mortality during follow-up was not statistically significant between groups.

Left ventricular function post-MI

Median time from MI to echocardiography was 45 versus 38 days (cases vs controls, \( P = .665 \)). Average left ventricular ejection fraction (LVEF) was 44% versus 46% (cases vs controls, \( P = .086 \)). Patients in whom echocardiographic data were available did not differ from the remaining patients with respect to demographic and infarct characteristics (data not shown).
ICD implantation

Implantable cardioverter-defibrillators were implanted in 22 (6.5%) cases and 2 (0.7%) control patients \( (P < .001) \). Time between MI and implantation was not different between cases and controls \((173 \pm 290 \text{ vs } 248 \pm 306 \text{ days, } P = .736) \). Two cases and one control patient received an appropriate shock during follow-up \((P = .250)\). The indication for ICD implant in these latter patients was recurrent VF during recurrent ischemia for the 2 cases and severe left ventricular dysfunction in the control patient. The number of days with ICD protection (protected days per patient) was longer in controls \((704 \pm 540 \text{ vs } 1,631 \pm 796, P = .04)\).

Medication use during follow-up

Self-reported medication use is shown in Table III. Cases returned the questionnaire less often than controls \((70\% \text{ of } 198 \text{ vs } 84\% \text{ of } 271, P < .01)\). There was a small but significant difference in reported β-blocker use, which was higher in cases \((84.8\%) \text{ versus controls } (76.2\%, P = .049)\). Use of other drugs commonly prescribed post-MI was similar in both groups.

Cardiovascular events during follow-up

In the time window in which hospitalization data were available, 294 cases and 266 controls were included in the analysis. Of these, 276 \((94\%\) cases versus 248 \((93\%\) controls could be retrieved in the national database. Among cases, 7 \((2.5\%)\) patients were rehospitalized for acute MI versus 25 \((10.1\%)\) controls \((P \text{ for difference } < .001)\). Of all patients hospitalized for acute MI, 5 died during follow-up, all of these being controls. Of cases, 22 were hospitalized for ACS versus 19 controls \((P \text{ for difference } .895)\). In addition, 77 cases were admitted for chest pain \((\text{without MI}) \text{ versus } 71 \text{ controls } (P \text{ for difference } .853)\) (Table III).

Cox regression analysis

A Cox regression model was used, and all statistically significant different baseline characteristics were entered: BMI, high cholesterol, FH of SD, FH of CVD, history of cardiac disease. Furthermore, “time between onset of symptoms and PCI,” LVEF, and self-reported β-blocker use during follow-up were entered into the model. Univariate analysis showed that significant influence on survival was related to time to PCI \((OR 1.003 \text{ per minute, } 95\% \text{ CI } 1.000-1.006, P = .030)\) and LVEF \((OR 0.948, 95\% \text{ CI } 0.908-0.990, P = .015)\). Crude relative risk of VF on survival was 0.782 \((95\% \text{ CI } 0.428-1.429)\). After adjustment for time to PCI and LVEF, the relative risk was 0.578 \((95\% \text{ CI } 0.043-3.337)\).

A power statement indicating the detectable relative risk was calculated. With the current sample size of 338 cases and 292 controls, a 2-sided log-rank test achieves 80% power at a .05 significance level to detect a relative risk of 2.0. This assuming that the proportion of patients lost during follow-up was zero and that the hazard rates are proportional.

This study was supported by The Netherlands Heart Foundation (2001-D019) and Leducq Foundation (grant 05 CVD).

Discussion

The main finding of our study is that survivors of primary VF receiving up to date treatment of MI have an excellent prognosis. These findings are important for the increasing number of successfully resuscitated patients. Our study is unique in several aspects. Primary VF was strictly defined. By only including VF before reperfusion therapy, we focused on ischemic VF, which is presumed to account for the largest fraction of SCD cases. Furthermore, this is a prospective case-control study with a large number of VF cases. To the best of our knowledge, this is the first study analyzing prognosis of primary VF survivors in the current PCI era. This is important because this treatment has improved overall prognosis of myocardial infarct patients tremendously over the last decades.

Prognosis among VF survivors

Our results show that even after correction for possible confounders, survival of cases did not differ from controls. Accordingly, available echocardiographic data show that the main determinant of post-MI survival, ejection fraction, is similar between groups.

In the present study, we selectively included survivors of primary VF, enabling us to determine prognosis for this specific yet common cause of SCD. Previous studies in other SCD populations have shown that prognosis after VF ranges from excellent \(^9,12\) to poor, \(^13\) because prognosis of cardiac arrest survivors depends on the underlying cardiac diseases. For example, studies by Henkel et al \(^14\) and Sayer et al \(^15\) included survivors of VF in the first 48 hours after MI, which suggests that less common mechanisms of VF, such as reperfusion-induced VF, and late VF due to myocardial scar was also included. Likewise, in the Antiarrhythmics versus Implantable Defibrillators registry, 44.2% of out of hospital cardiac arrest survivors had experienced prior MI. Based on the high risk of death during follow-up in the AVIV registry population, it is likely that the risk of VF was largely determined by myocardial scarring already present during the index event. \(^15\)

Because genetic factors may determine primary VF risk, as earlier studies imply, \(^9,16\) one would expect that primary VF survivors have an increased chance of SCD during repeat ischemia. To determine this risk, we analyzed the number of hospitalizations for a second SCD during repeat ischemia. To determine this risk, we analyzed the number of hospitalizations for a second acute MI. Surprisingly, cases in our study had significantly less second infarctions compared with controls, with comparable number of admissions for ACSs and chest pain. This
may be due to a higher compliance to medication use and adherence to lifestyle advice in cases. Although the absolute difference was small, self-reported β-blocker was indeed higher among cases. Higher fear for a new infarction could lead to a comparable number of chest pain presentations.

Implantable cardioverter-defibrillator implants and current guidelines

Implantable cardioverter-defibrillators were implanted significantly more often in cases than in controls. In both groups, however, few appropriate shocks occurred. Patients who did receive appropriate shocks had additional risk factors such as a poor left ventricular function after MI. Even if ICD receivers were presumed dead, survival among cases was still much better than observed in the AVID registry. Current guidelines are based on studies from the pre-PCI era. Because we selectively included primary VF survivors treated with modern reperfusion techniques, our study results are applicable to the contemporary patient population. These results corroborate current guidelines that do not recommend ICD treatment in primary VF patients without reminiscent ischemia or other risk factors.1

Study limitations

This study was well powered to find clinically relevant effects of primary VF on prognosis. Small influences of VF could remain undetected. Nevertheless, the relative risk calculation indicates that a strong negative effect on prognosis is unlikely. The incidence of recurrent VF in cases who experienced recurrent ischemia was too low to determine whether this risk was increased in cases versus controls. However, compared with the total mortality in VF survivors, this risk of death due to recurrent VF was low. Echocardiographic follow-up data as well as medication use were not available for all patients. However, these patients did not differ with respect to demographic and infarct characteristics from patients in which these data were available.

Conclusions

Patients who survive the first month after primary VF have a prognosis that is similar to STEMI patients without VF. Patients treated with an ICD because of primary VF without additional risk factors did not receive any appropriate shocks. Our data corroborate current guidelines that were based on studies from the pre-PCI era. Implantable cardioverter-defibrillator treatment in primary VF patients without residual ischemia or other risk factors can be safely withheld. Interestingly, primary VF patients experienced less MI during follow-up possibly because of higher compliance with medication use.

Acknowledgements

We kindly acknowledge the following for providing follow-up data: M. Alings, MD, PhD, Amphia Hospital (Breda, The Netherlands); A. Arnold, MD, PhD, Medical Center Alkmaar (Alkmaar, The Netherlands); A. Elvan, MD, PhD, Isala Hospital (Zwolle, The Netherlands); A.P.M. Gorgels, MD, PhD, Maastricht University Medical Center (Maastricht, The Netherlands), and K. Sjauw, MD, Academic Medical Center (Amsterdam, The Netherlands).

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