Prevalence and prognostic implications of non-sustained ventricular tachycardia in ST-segment elevation myocardial infarction after revascularization with either fibrinolysis or primary angioplasty

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Received 6 July 2006; revised 19 December 2006; accepted 21 December 2006; online publish-ahead-of-print 16 January 2007

Aims We compared the prevalence and prognostic implications of non-sustained ventricular tachycardia (nsVT) detected early after ST-segment elevation myocardial infarction (STEMI) in patients randomized to either fibrinolysis or primary angioplasty in the DANAMI-2 trial.

Methods and results Holter recordings were available in 1017 patients (fibrinolysis: n = 501; primary angioplasty: n = 516). Primary endpoint was all-cause mortality. The prevalence of nsVT was 8.8% in fibrinolysis-treated, and 8.1% in primary angioplasty-treated patients (P = 0.71). During 4519 patient-years of follow-up (median 4.3 years), 116 patients died [fibrinolysis vs. angioplasty: HR = 1.1 (95% CI, 0.8–1.6), P = 0.47]. In univariate analysis, nsVT patients treated with fibrinolysis, had significantly higher mortality when compared with those without nsVT (P < 0.001). However, after adjustment for other relevant prespecified risk factors, the association between nsVT and mortality did not remain statistically significant. In patients treated with primary angioplasty, nsVT was not associated with mortality in either univariate or multivariate analyses.

Conclusion Immediate revascularization with primary angioplasty for STEMI does not affect the subsequent prevalence of nsVT when compared with fibrinolysis. After adjustment for other relevant risk factors, the prognostic value of nsVT detected early after STEMI is limited, regardless of the chosen reperfusion strategy.

KEYWORDS Myocardial infarction; Angioplasty; Risk factors; Arrhythmia; Electrocardiography

Introduction

Episodes of non-sustained ventricular tachycardia (nsVT) were established as a prognostic marker after acute myocardial infarction (AMI) in the pre-fibrinolytic era, and is generally considered a marker of arrhythmic propensity. However, following the advent of fibrinolysis, the prognostic value of this marker has been questioned. In a study from the Italian Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (the GISSI-2 study), where Holter monitoring was performed in 8676 patients with a recent fibrinolytic-treated AMI, nsVT was not an independent predictor of neither arrhythmic nor all-cause mortality, and the results of more recent studies have been conflicting. However, using the presence of nsVT on Holter monitoring, left ventricular (LV) ejection fraction (EF) (LVEF) ≤ 35%, and inducible, non-suppressible ventricular tachyarrhythmia on electrophysiological study as the main selection criteria, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) demonstrated improved survival with an implantable cardioverter-defibrillator (ICD) strategy as opposed to conventional antiarrhythmic therapy in the survivors of AMI. As a result, Holter monitoring is by many considered an important clinical examination in AMI survivors with an LVEF ≤ 35%. The clinical implications of nsVT in patients with an LVEF > 35% remain more disputed, although recent data have suggested that several Holter-derived markers of arrhythmic propensity, including nsVT, are of independent prognostic value in such patients.

Over the last decade, primary angioplasty has evolved as a superior alternative to fibrinolysis for the treatment of acute ST-segment elevation myocardial infarction (STEMI), as a greater reduction of major cardiovascular events is achieved with this approach. Therefore, primary angioplasty has in many centres become the treatment of choice for patients with acute STEMI. The impact of primary angioplasty on the subsequent prevalence and clinical significance of nsVT is presently unknown. Although some recent studies have included patients treated with primary...
angioplasty,

none of these were designed for a direct comparison with fibrinolysis. Our primary objective was therefore to compare the prevalence and prognostic implications of nsVT in patients with acute STEMI, randomized to treatment with either primary angioplasty or fibrinolysis in the Danish Multicenter Randomized Study on Fibrinolytic Therapy vs. Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2).

Methods

The design and results of the DANAMI-2 main study has previously been reported.\textsuperscript{14,15} DANAMI-2 is a Danish multi-centre study with 29 participating centres (24 referral; five invasive). The main inclusion criteria were an age of 18 years or more, symptoms characteristic of AMI for at least 30 min but <12 h, and cumulative ST-segment elevation of at least 4 mm in at least two contiguous leads. Patients with contraindications to either fibrinolysis or primary angioplasty and patients with left bundle branch block on leads. Patients with contraindications to either fibrinolysis or primary angioplasty and patients with left bundle branch block on leads were also excluded. Patients randomized to primary angioplasty at the regional invasive centre. If patients were randomized to fibrinolysis indicated a time-dependent effect of LVEF on mortality, we assessed accounting for the contribution of each LV segment to systolic function. WMI was calculated by adding the score of each segment and dividing by the number of segments. From the resulting WMI score, LVEF was estimated using a previously validated method.\textsuperscript{18} All echocardiograms were blindly read by two established echocardiographic readers.

Coronary angiograms

Coronary angiograms obtained during the primary revascularization procedure in patients randomized to primary angioplasty were evaluated by an independent core laboratory (Cardiallysis, Rotterdam, the Netherlands) where the number of diseased vessels (i.e. vessels with \( \geq 50\% \) stenosis) and post-angioplasty coronary flow grade was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) classification.\textsuperscript{19}

Follow-up and endpoints

Physicians responsible for the follow-up and treatment of patients were kept unaware of the results of Holter monitoring throughout the study. Patients were followed in an outpatient clinic at the randomizing centre and visited 30 days after discharge, and thereafter once yearly for 3 years. Survival status of all patients was obtained from the Danish Civil Registration System, where all deaths in the country are recorded within 2 weeks. This was done 3 years after inclusion of the last patient, yielding a follow-up period ranging from 3 to 7 years resulting in 4519 patient-years of follow-up. Causes of death were classified by the DANAMI-2 main study endpoint committee based on medical records and information available from death certificates. The primary endpoint of this study was all-cause mortality. A secondary endpoint was arrhythmic morbidity during the first 3 years of follow-up. Arrhythmic morbidity was defined as arrhythmic death, resuscitated ventricular fibrillation, or documented episodes of sustained ventricular tachycardia (at a heart rate >120 b.p.m., and lasting for >30 s). Death was considered arrhythmic if it occurred suddenly or within 1 h of symptoms, in a clinically stable patient without a history of progressive heart failure or angina pectoris. Unwitnessed death, including death during sleep, was also considered arrhythmic if no other cause of death was suspected from preceding symptoms or was documented by autopsy. The fixed follow-up time for the secondary endpoint was chosen because data regarding non-fatal endpoints were not available after the end of the clinical follow-up period of 3 years.

Statistics

Analyses were conducted with STATA/SE 9.2 (StataCorp LP, TX, USA). Results were analysed according to the intention-to-treat principle. Continuous variables are reported as mean \( \pm \) SD and prevalence as percentage. Comparison of patient characteristics and the prevalence of predefined Holter measurements was performed with Student’s t-test (unpaired, two-tailed) for continuous variables, whereas categorical variables were compared using a \( \chi^2 \) test or Fisher’s exact test when appropriate. Interaction between randomized treatment and differences in clinical characteristics associated with nsVT, was tested using logistic regression. Hazard ratios were estimated using Cox proportionate hazards regression analysis. The prespecified Holter variables were split into separate variables for each of the two treatment groups and adjusted for the following variables, chosen prior to the inspection of data: age, sex, diabetes, previous MI, anterior index MI, and LVEF. Proportionality of hazards was tested graphically based on visual inspection of log-log survival curves, and by performing a formal test of proportionality based on Schoenfeld residuals for each variable in the model. Furthermore, for age and LVEF, linearity of hazards was tested by adding squared values of the variables to the model. Because these analyses indicated a time-dependent effect of LVEF on mortality, we used a final Cox model stratified by LVEF dichotomized at \( \geq 35\% \) (reported multivariable coefficients equal across strata but with
baseline hazard unique to each stratum of LVEF). Assumptions of proportionality and linearity of hazards was met for all other included variables. A two-sided value of $P < 0.05$ was considered statistically significant in all analyses.

Results

Patient characteristics

A study flowchart is shown in Figure 1. From a total of 1462 patients discharged alive from index infarction, Holter monitoring was performed in 1159 patients at a median of 6 days (IQR: 5–8 days) after randomization. Patients in whom Holter recording was not performed ($n = 303$) were significantly older ($64.7 \pm 13.8$ vs. $61.7 \pm 11.8$ years; $P < 0.001$) and experienced a significantly higher mortality rate during follow-up (HR, 2.1; 95% CI, 1.4–3.0). The decision of not to perform a Holter recording was made at the discretion of the treating physician in all cases. In addition, 142 recordings were excluded, due to technically inadequate quality of the recording, thus leaving a total of 1017 recordings available for the study. Baseline characteristics for these patients are summarized in Table 1.

Prevalence of nsVT and VPBs

In the fibrinolysis-treated group, nsVT was found in 44 (8.8%) patients when compared with 42 (8.1%) in the angioplasty group ($P = 0.71$). If applying a more restrictive definition of nsVT, including only episodes with an RR interval $<500$ ms ($>120$ b.p.m.), the prevalence of nsVT was 7.4% in the fibrinolysis group, and 6.2% in the angioplasty group ($P = 0.45$).

A VPB frequency $\geq 10$/h was found in 78 (15.6%) patients in the fibrinolysis group, when compared with 62 (12.0%) in the angioplasty group ($P = 0.10$).

Echocardiography was performed in 979 (96.3%) patients at a median of 5 days (IQR: 4–7 days) after randomization, and showed an LVEF $\leq 35\%$ in 178 (18.2%) patients (fibrinolysis: 18.8%; primary angioplasty 17.6%; $P = 0.61$). The combination of LVEF $\leq 35\%$ and at least one episode of nsVT was present in 12 (2.5%) patients treated with fibrinolysis, and in 11 (2.2%) patients treated with primary angioplasty ($P = 0.75$).

Clinical characteristics by presence or absence of nsVT

Patients with nsVT in the two treatment groups are shown in Table 2. Mean LVEF was lower in patients with nsVT, suggesting an association between severity of myocardial damage and the risk of developing nsVT. In addition, age was higher among patients with nsVT, although this association was less pronounced among patients in the angioplasty group.

The prevalence of other characteristics such as male sex, diabetes, anterior index infarction, and mean heart rate during Holter recording, were not significantly different in patients with nsVT when compared with the remaining study population. In the angioplasty group, where angiographic data were available, the prevalence of nsVT was unrelated to the number of diseased vessels and post-angioplasty TIMI flow grade in the assumed culprit lesion.

Prognostic implications of nsVT

During a median follow-up period of 4.3 years (IQR: 3.7–5.3 years), 116 patients died [fibrinolysis vs. angioplasty: HR = 1.1 (95% CI 0.8–1.6), $P = 0.47$]. In a univariable model, nsVT was associated with increased mortality in the total study population [HR = 2.1 (95% CI 1.3–3.5), $P = 0.003$, Figure 2A]. When the two treatment groups were analysed separately, nsVT was associated with mortality in the fibrinolysis group [HR = 2.9 (95% CI 1.5–5.5), $P = 0.001$, Figure 2B] but not in the group treated with primary angioplasty [HR = 1.4 (95% CI 0.6–3.3), $P = 0.42$, Figure 2C]. However, interaction between treatment group and the prognostic value of nsVT was not statistically significant ($P_{interaction} = 0.17$).

The secondary endpoint of arrhythmic morbidity was observed in 23 cases (fibrinolysis: $n = 14$; angioplasty: $n = 9$; log-rank $P = 0.26$). Arrhythmic morbidity was seen more frequently among patients with nsVT [HR = 3.1 (95% CI 1.2–8.4), $P = 0.02$, Figure 4A]. The absolute number of arrhythmic events in patients with nsVT was however very low (fibrinolysis: $n = 2$; angioplasty: $n = 3$), and the additional risk of nsVT was not significantly different in the two treatment groups ($P_{interaction} = 0.28$).

During the first 3 years of follow-up, seven patients were treated with an implantable cardioverter-defibrillator. Of these, nsVT had been present on Holter monitoring in one patient in the angioplasty group, and none in the fibrinolysis group.

Prognostic implications of frequent VPBs

A VPB frequency $\geq 10$/h was associated with increased mortality in the total study population [HR = 2.6 (95% CI 1.8–3.9), $P < 0.001$, Figure 3A]. There was no significant interaction between randomized treatment and prognostic importance of frequent VPBs ($P_{interaction} = 0.28$). The secondary endpoint of arrhythmic morbidity also occurred more frequently in patients with $\geq 10$ VPBs/h [HR = 2.8 (95% CI 1.1–6.8), $P = 0.02$, Figure 4B].

Multivariable analysis

Cox proportionate hazards regression analysis was performed using age, sex, diabetes, previous myocardial infarction, anterior index infarction, beta-blocker treatment at discharge, nsVT, and $\geq 10$ VPBs/h as covariates, and stratifying by LVEF $\geq 35\%$. Age was entered as a continuous variable. In this model, after adjustment for other significant risk factors, neither nsVT nor frequent VPBs were independently associated with increased mortality in either of the two treatment groups (Table 3). Given the few cases of arrhythmic morbidity in patients with nsVT, multivariable analysis was not performed for this secondary endpoint.

Discussion

This is the first randomized study to compare the prevalence and prognostic significance of ventricular arrhythmias after primary angioplasty and fibrinolysis, respectively. Primary angioplasty did not decrease incident nsVT when compared with fibrinolysis treatment. While, unlike in the angioplasty group, a univariate association between nsVT and all-cause mortality was observed in the fibrinolysis group, in multivariable
regression analysis, nsVT did not independently predict mortality in either of the two treatment groups, and there was no statistical evidence of interaction between randomized treatment, and the prognostic implications of nsVT. The hypothesis of less ventricular arrhythmia in patients treated with primary angioplasty due to faster and more complete revascularization of the infarct related area was not substantiated in our study. Our findings are similar to a previous study of 400 consecutive STEMI patients all treated with primary angioplasty, with a 10% rate of nsVT, as well as rates of 6.8–9.0% in previous studies, including fibrinolysis-treated patients. Survival of more critically ill patients with AMI made possible by primary angioplasty has been suggested as an explanation for the similar prevalence of ventricular arrhythmias observed among patients treated with primary angioplasty when compared with fibrinolysis. This was not evident in our study, as other risk factors such as age and impaired LV systolic function were equally distributed among the two treatment groups. In accordance with this

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Table 1  Baseline characteristics of angioplasty and fibrinolysis-treated patients (n = 1017)

<table>
<thead>
<tr>
<th></th>
<th>Fibrinolysis (n = 501)</th>
<th>Primary angioplasty (n = 516)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>61.7 ± 12.0</td>
<td>61.6 ± 11.5</td>
<td>0.88</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>378 (75.5)</td>
<td>389 (75.4)</td>
<td>0.98</td>
</tr>
<tr>
<td>Treated hypertension, n (%)</td>
<td>104 (20.8)</td>
<td>100 (19.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>52 (10.4)</td>
<td>54 (10.5)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>31 (6.2)</td>
<td>34 (6.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Smoking a</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Never, n (%)</td>
<td>91 (18.2)</td>
<td>87 (16.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Former, n (%)</td>
<td>105 (21.0)</td>
<td>113 (21.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>300 (59.9)</td>
<td>314 (60.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Anterior index MI, n (%)</td>
<td>250 (49.9)</td>
<td>262 (50.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>Heart rate, b.p.m. (mean ± SD)</td>
<td>67.0 ± 10.7</td>
<td>68.0 ± 11.7</td>
<td>0.15</td>
</tr>
<tr>
<td>LVEF, % (mean ± SD)</td>
<td>46.2 ± 11.3</td>
<td>46.7 ± 11.1</td>
<td>0.48</td>
</tr>
<tr>
<td>LVEF ≤ 35%, n (%)</td>
<td>90 (18.8)</td>
<td>88 (17.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>Angiographic features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stenotic vessels, n (%)</td>
<td>19 (3.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Single-vessel disease, n (%)</td>
<td>153 (30.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Double-vessel disease, n (%)</td>
<td>159 (32.0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Triple-vessel disease, n (%)</td>
<td>166 (33.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Medication at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>487 (97.2)</td>
<td>498 (96.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>436 (87.0)</td>
<td>456 (89.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Other antiarrhythmics, n (%)</td>
<td>15 (3.0)</td>
<td>19 (3.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Calcium antagonists, n (%)</td>
<td>39 (7.8)</td>
<td>30 (5.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>30 (6.0)</td>
<td>19 (3.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>ACE-inhibitors, n (%)</td>
<td>188 (37.5)</td>
<td>168 (32.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>257 (51.3)</td>
<td>256 (49.6)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

aSmoking cessation within last 6 months was considered current smoking.

bPercentages are relative to the number of patients where LVEF was available (n = 979).

cOther antiarrhythmics used were amiodarone (n = 18), sotalol (n = 14), and propafenone (n = 2).
Finding, long-term mortality rates were also similar in the two treatment groups. This is most likely attributable to the fact, that in our study selection to either fibrinolysis or primary angioplasty was determined by randomization, whereas in everyday practice, patients are selected for either treatment depending on the dominant myocardial territory. The examination of the two study groups showed no difference. (Table 2, Figure 2).
clinical practice, the risk profile of patients selected for primary angioplasty may differ from that of patients selected for fibrinolysis, and accordingly, so may the subsequent prevalence of several risk factors including markers of arrhythmic propensity.

**Prognostic implications of nsVT**

The GISSI-2 Holter substudy is probably the largest post-infarction study investigating the prognostic implications of nsVT detected early after STEMI. Similar to our study, Holter monitoring of 8676 fibrinolysis-treated patients, showed a univariate association between nsVT and mortality, which did not remain after adjustment for relevant clinical risk factors and this emphasizes the correlation between nsVT and other risk factors. Also similar to our study, a recent study of 400 STEMI primary angioplasty-treated patients showed that nsVT did not predict mortality in either univariate or multivariate analyses. It is important to note that our study did show a significant association between nsVT and arrhythmic morbidity. However, the end-point event-rate was much lower than anticipated, and multivariable analysis was therefore not feasible. Among the 86 patients with documented nsVT, arrhythmic events were only observed in five (5.8%) cases. It is therefore likely that any statistical association between nsVT and arrhythmic morbidity could be clinically insignificant.

**Timing of Holter recording**

The prevalence and prognostic implications of nsVT have in previous studies been variable, depending on the timing of Holter recording. In the present study, recordings were performed on the day of discharge. In the second Danish Verapamil Infarction Trial (DAVIT II), before the widespread use of primary angioplasty, serial Holter recordings were performed at 1 week, 1 month, and 16 months following AMI. In that study, nsVT was an independent predictor of outcome when detected late (16 months) but not early (1 week and 1 month) after AMI. In the MADIT trial, more than 75% of all patients were included later than 6 months after their last AMI, and patients with episodes of nsVT documented during admission for AMI were not eligible. Therefore, very few of the qualifying episodes of nsVT in the MADIT trial, were recorded as early as in the present study. One could speculate that markers of arrhythmic propensity detected early after AMI, in some patients are attributable to benign and potentially reversible electrophysiological instability and ‘myocardial stunning’, which may resolve over the following months, depending on the degree of reperfusion and ventricular myocardial remodelling. It is therefore also possible, that the rate of nsVT would differ between the two treatment groups, if Holter monitoring was performed several months after AMI. However, in another study nsVT detected within the very first days of admission for AMI was a significant risk factor for subsequent mortality. Studies assessing the ideal time for detecting clinically relevant markers of arrhythmic propensity after primary angioplasty are therefore warranted.

**Study limitations**

The timing of Holter recording may in some part have affected our study results. We chose to perform Holter monitoring on the day of discharge, causing some variation in the number of days from index infarction. However, this was chosen in order to obtain more homogeneity in the clinical state, and degree of physical activity of patients at the time of recording, than would have been found if a fixed time-point had been chosen. Another limitation of the study relates to the

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Figure 3 Cumulative survival probability for patients with ≥10 VPBs/h, compared to those with <10 VPBs/h in the total study population (A) and in the two treatment groups, respectively (B,C).
general risk profile of the investigated cohort. Because of the exclusion criteria of the DANAMI-2 study, and the fact that Holter monitoring was performed at discharge, thus excluding all patients who died before the Holter was performed, our cohort were generally a low-risk population. In particular, the rate of arrhythmic events was surprisingly low in this study. Holter monitoring was, by choice of the treating physician, not performed in 303 patients. These patients were older, and experienced higher mortality rates than the investigated cohort. It is therefore possible that the prevalence and prognostic implications of the investigated variables differ from what would be found in an unselected population with STEMI. On the other hand, this study lends additional support to what was also observed in the Prevention of Events with ACE inhibition (PEACE) trial,\(^{20}\) the fact that the treatment of STEMI is now so effective that once patients are discharged, they are at quite low cardiovascular risk making at least some risk predictors superfluities.

**Conclusions**

Our study does not suggest that rapid revascularization using primary angioplasty reduces the subsequent prevalence of nsVT after STEMI when compared with fibrinolysis. Furthermore, the prognostic value of nsVT in our study was limited, and did not appear to be affected by the choice of reperfusion strategy.

**Acknowledgements**

The authors gratefully acknowledge all the DANAMI-2 investigators and study nurses for their efforts throughout the DANAMI-2 study, as well as the members of the DANAMI-2 steering committee for their support. The authors are also grateful to Professor Werner Vach from the Department of Statistics, University of Southern Denmark for expert statistical support. The DANAMI-2 trial was supported by grants from the Danish Heart Foundation, the Danish Medical Research Council, AstraZeneca, Bristol-Myers Squibb, Cordis, Pfizer, Pharmacia–Upjohn, Boehringer Ingelheim, and Guerbet. The DANAMI-2 Holter substudy was supported by grants from the Danish Heart Foundation (Høfsten) and the Beckett Foundation.

**Conflict of interest**: none declared.

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