

In-Hospital Versus Out-of-Hospital Presentation of Life-Threatening Ventricular Arrhythmias Predicts Survival

Results From the AVID Registry

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- OBJECTIVES** This study describes the outcomes of patients from the Antiarrhythmics Versus Implantable Defibrillators (AVID) Study Registry to determine how the location of ventricular arrhythmia presentation influences survival.
- BACKGROUND** Most studies of cardiac arrest report outcome following out-of-hospital resuscitation. In contrast, there are minimal data on long-term outcome following in-hospital cardiac arrest.
- METHODS** The AVID Study was a multicenter, randomized comparison of drug and defibrillator strategies to treat life-threatening ventricular arrhythmias. A Registry was maintained of all patients with sustained ventricular arrhythmias at each study site. The present study includes patients who had AVID-eligible arrhythmias, both randomized and not randomized. Patients with in-hospital and out-of-hospital presentations are compared. Data on long-term mortality were obtained through the National Death Index.
- RESULTS** The unadjusted mortality rates at one- and two-year follow-ups were 23% and 31.1% for patients with in-hospital presentations, and 10.5% and 16.8% for those with out-of-hospital presentations ($p < 0.001$), respectively. The adjusted mortality rates at one- and two-year follow-ups were 14.8% and 20.9% for patients with in-hospital presentations, and 8.4% and 14.1% for those with out-of-hospital presentations ($p < 0.001$), respectively. The adjusted long-term relative risk for in-hospital versus out-of-hospital presentation was 1.6 (95% confidence interval [CI] 1.3–1.9).
- CONCLUSIONS** Compared with patients with out-of-hospital presentations of life-threatening ventricular arrhythmias not due to a reversible cause, patients with in-hospital presentations have a worse long-term prognosis. Because location of ventricular arrhythmia presentation is an independent predictor of long-term outcome, it should be considered as an element of risk stratification and when planning clinical trials. (J Am Coll Cardiol 1999;34:1111–6) © 1999 by the American College of Cardiology

Most studies of cardiac arrest report the outcomes of patients who experience cardiac arrhythmias out-of-hospital (1–12). Furthermore, many studies limit inclusion to patients with ventricular fibrillation (VF) on arrival of para-

edics (1–3), and some describe the results only for patients with coronary artery disease (4). Thus, the immediate and the long-term outcomes of patients suffering out-of-hospital cardiac arrest and surviving to leave the hospital are well known. In contrast, outcomes following in-hospital cardiac arrest are less well studied (13–18), and there are minimal data on the long-term outcome of in-hospital cardiac arrest survivors (14,16,17). Furthermore, the relation of the location of cardiac arrest on long-term outcome is unknown.

Arguments may be made that the survivors of in-hospital resuscitation could have either better or worse prognoses than those with out-of-hospital presentations. On the one hand, prompt resuscitation of patients already in the hos-

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Abbreviations and Acronyms

AVID Study	= Antiarrhythmics Versus Implantable Defibrillators Study
ICD	= implantable cardioverter-defibrillator
VF	= ventricular fibrillation
VT	= ventricular tachycardia

pital should reduce immediate morbidity due to the cardiac arrest itself and possibly improve the chance for long-term survival. On the other hand, inpatients may have important comorbidities that negatively affect survival (15,16). Conversely, patients with out-of-hospital presentations may be expected to have worse outcomes owing to a prolonged time to the initiation of advanced cardiac life support and defibrillation (4,5,8-10). Still, those who do survive may be selected for better long-term outcomes because they lived to be admitted to the hospital.

When the Antiarrhythmics Versus Implantable Defibrillators (AVID) Study was planned, patients resuscitated from both in-hospital and out-of-hospital life-threatening ventricular arrhythmias were considered eligible for randomization if they had appropriate arrhythmias and were candidates for both implantable cardioverter-defibrillator (ICD) and antiarrhythmic drug therapy (19,20). As the trial progressed, it became evident during the assessment that a significant number of patients with in-hospital presentations of ventricular arrhythmias were being randomized. The present study describes the outcomes of patients included in the AVID Study Registry to determine how the location of ventricular arrhythmia presentation influences survival. The results may influence the choice of inclusion criteria for future secondary prevention trials to manage life-threatening ventricular arrhythmias. It may also help to risk-stratify these patients better, thus helping to determine their future treatments.

METHODS

Study design. The AVID Study was a multicenter, randomized comparison of antiarrhythmic drug treatment (mostly amiodarone) and ICD implantation to manage patients resuscitated from life-threatening ventricular arrhythmias not due to transient or reversible causes. Eligible arrhythmias included 1) VF; 2) sustained ventricular tachycardia (VT) with syncope; and 3) sustained VT with an ejection fraction of ≤ 0.40 , and symptoms suggestive of severe hemodynamic compromise. The trial design and primary end-point paper have been published (19,20). It is interesting to note that the location of index ventricular arrhythmia presentation was not a factor in eligibility for randomization. Each participating institution had approval from its Institutional Review Board for conduct of the study. All patients who underwent randomization gave written informed consent.

As part of the study design, a registry was maintained of all patients with sustained ventricular arrhythmias at each study site. It included not only patients who were randomized, but also 1) patients who were eligible for the AVID Study but did not undergo randomization because of refusal or exclusions to participation; 2) patients with arrhythmias who did not qualify for randomization in the trial because they were thought to be less serious, such as stable VT, or VT or VF with a transient or correctable cause; and 3) patients with unexplained syncope. The present study includes all patients, both randomized and not randomized, who had AVID-eligible arrhythmias (VF; sustained VT with syncope; or sustained VT with an ejection fraction of ≤ 0.40 , and symptoms suggestive of severe hemodynamic compromise).

Patients were excluded from the Registry and randomization in the AVID Study if the index arrhythmia occurred in-hospital within five days of myocardial infarction (defined by electrocardiographic changes or enzyme elevations in accordance with local standards), coronary angioplasty, coronary artery bypass grafting, or if the patient had undergone prior ICD implantation. Other exclusions included life expectancy less than one year, severe neurologic damage, chronic bacterial infection, severe neurologic impairment, class IV congestive heart failure, anticipated cardiac transplantation or the presence of an intra-aortic balloon pump, other device or drug necessary for hemodynamic support. Additional trial exclusions included coronary revascularization (either surgical or percutaneous) planned or performed since the index arrhythmia event and left ventricular ejection fraction > 0.40 ; arrhythmia or aneurysm surgery planned or performed since the index event, index event on amiodarone (or exposure to amiodarone in last six months, unless the total dose was < 10 g, exposure < 2 weeks, or level ≤ 0.2 $\mu\text{g/ml}$); contraindication to amiodarone, long QT syndrome, atrial fibrillation, or other supraventricular tachycardia requiring class I or III antiarrhythmic drug therapy; and bradycardia or heart block without an implanted pacemaker.

All Registry patients were followed through hospital discharge. Data on long-term mortality were obtained through the National Death Index as of December 31, 1996.

Statistical analyses. Univariate comparisons of the characteristics of patients presenting with out-of-hospital versus in-hospital life-threatening ventricular arrhythmias were based on *t* tests for continuous variables or chi-square tests for discrete variables. Survival rates were estimated by the Kaplan-Meier method. Survival was measured with time zero being the day of the index ventricular arrhythmia. Adjusted relative risk estimates were based on the proportional hazards survival model. Covariates included in the model were age; race; gender; arrhythmia type; history of atrial fibrillation, congestive heart failure, diabetes, syncope, coronary artery disease, revascularization, prior VT; left

Table 1. Baseline Characteristics by Location of Index Ventricular Arrhythmia Presentation

	In-Hospital Presentation (n = 806)	Out-of-Hospital Presentation (n = 1,868)	p Value
Age (yr, mean value ± SD)	65 ± 11	64 ± 12	< 0.001
White (%)	83	90	< 0.001
Female gender (%)	27	23	0.03
LV ejection fraction (mean value ± SD)	0.31 ± 0.13	0.34 ± 0.15	< 0.001
History of			
Congestive heart failure (%)	55	40	< 0.001
Atrial fibrillation (%)	33	22	< 0.001
Diabetes (%)	31	18	< 0.001
Ventricular tachycardia (%)	20	14	< 0.001
Syncope (%)	15	10	< 0.001
CABG/PTCA (%)	37	32	0.01
Coronary artery disease (%)	80	76	0.007
AAD at presentation (%)	18	13	< 0.001

AAD = antiarrhythmic drug; CABG = coronary artery bypass grafting; LV = left ventricular; PTCA = percutaneous coronary angioplasty; SD = standard deviation.

ventricular ejection fraction; antiarrhythmic drug use at the time of the index event; and discharge treatments (ICD, beta-adrenergic blocking agent, diuretics, digitalis, amiodarone, other antiarrhythmic drug and warfarin). A p value of 0.05 was used as the significance level for the multivariate analyses.

RESULTS

The study group included 2,674 patients in the AVID Registry resuscitated from primary life-threatening ventricular arrhythmias, 806 (30%) that occurred in-hospital and 1,868 (70%) that occurred out-of-hospital. All had experienced VF (n = 1,351, 51%), VT with syncope (n = 593, 22%), or hemodynamically compromising VT and a left ventricular ejection ≤0.40 (n = 730, 27%). None of these arrhythmias was due to acute myocardial infarction or a reversible cause. Twenty-one percent of the patients with in-hospital presentations had been admitted for noncardiac reasons, 12% had events within five days of an invasive procedure not related to the arrhythmia itself or to correction of ischemia and 87% were in monitored setting at the time of their arrhythmia event. Ventricular fibrillation was the index arrhythmia in 992 (53.1%) of patients with out-of-hospital presentations and 359 (44.5%) with in-hospital presentation (p < 0.001).

Baseline characteristics. Patients resuscitated from in-hospital events were older, more likely to be ethnic minorities and female and had lower left ventricular ejection fractions than did those with out-of-hospital presentations (Table 1). Patients with in-hospital presentations more frequently had histories of congestive heart failure, atrial fibrillation, diabetes, prior VT, syncope, coronary artery revascularization by either surgical or catheter-based interventions and coronary artery disease. Finally, they were more likely to be taking an antiarrhythmic drug at the time

of their index arrhythmia. There was no significant difference in their respective histories of prior VF, prior myocardial infarction, cigarette use or the incidence of nonischemic cardiomyopathy.

Discharge treatments. Patients with in-hospital arrhythmia presentations were more likely to be discharged receiving a diuretic, digoxin, amiodarone, another antiarrhythmic drug or warfarin (Table 2). Those resuscitated from an out-of-hospital arrhythmia were more likely to have received a beta-blocker or an ICD. There was no difference in the use of angiotensin-converting enzyme inhibitors, calcium channel blockers, or revascularization following the index event.

Survival. The in-hospital mortality rate for patients with in-hospital presentations was 4.6% and with out-of-hospital presentations 1.1% (p < 0.001) (Table 3). The unadjusted late mortality rates at one- and two-year follow-ups were 23.0% and 31.1% for patients with in-hospital presentations, and 10.5% and 16.8% for those with out-of-hospital presentations (p < 0.001), respectively (Fig. 1). The adjusted late mortality rates at one- and two-year follow-ups were 14.8% and 20.9% for patients with in-hospital presentations, and 8.4% and 14.1% for those with out-of-hospital presentations (p < 0.001), respectively (Fig. 2). The adjusted long-term relative risk for in-hospital versus out-of-hospital presentations was 1.6 (95% CI 1.3-1.9).

DISCUSSION

Compared with patients with out-of-hospital presentations of life-threatening ventricular arrhythmias not due to a reversible cause, patients with in-hospital presentations are sicker and have a worse long-term prognosis. It is important to note that the difference in survival remained after adjusting for all the measured baseline predictors and discharge therapies.

Table 2. Discharge Treatments by Location of Ventricular Arrhythmia Presentation

	In-Hospital Presentation (n = 806)	Out-of-Hospital Presentation (n = 1,868)	p Value
Diuretic (%)	60	46	< 0.001
Digoxin (%)	48	40	< 0.001
Beta-blocker (%)	24	29	0.005
Implantable cardioverter-defibrillator (%)	43	53	< 0.001
Amiodarone (%)	49	40	< 0.001
Other antiarrhythmic drug (%)	8	5	0.009
Warfarin (%)	32	24	< 0.001
ACE inhibitor (%)	61	61	NS
Calcium channel blocker (%)	14	14	NS
Revascularization after index event (%)	14	14	NS

AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme.

In-hospital presentation. Survival to hospital discharge is low following in-hospital cardiac arrest (13,14,16,17). However, the ability to draw conclusions from small studies is limited because they include patients suffering cardiac arrest from a variety of causes such as trauma, drug overdose and myocardial infarction (13-18). Although long-term outcome in survivors of in-hospital resuscitation is not often described, Bedell et al. (16) reported in 1983 a 14% discharge rate (41 patients) of 294 patients resuscitated in a university teaching hospital. Long-term mortality of patients who survived to hospital discharge was high (25%) at six months' follow-up. Some older studies also included patients who suffered cardiac arrest in unique locations such as the operating room and cardiac catheterization laboratory, and therefore were specially selected (14,15). In the AVID Registry, patients with certain reversible or transient causes and acute ischemia were excluded.

Out-of-hospital presentation. The 83.1% two-year survival rate for patients with out-of-hospital presentations of life-threatening ventricular arrhythmias and who were treated with antiarrhythmic drugs, ICDs, and a combination of therapies in the AVID Registry was similar to the 81.6% two-year survival rate for patients randomized to receive ICDs in the main AVID Study (20). None of these patients had evidence for acute ischemia or a reversible or transient cause of their arrhythmia. The strict eligibility criteria make a comparison to earlier studies difficult because many of these other studies included patients with VF

associated with acute myocardial infarction (1-4,6,11). In some studies (12), the actual incidence of acute myocardial infarction is not indicated, but it is stated that most patients had complaints, such as chest pain, before cardiac arrest, suggesting that ischemia was present in a large proportion.

Role of prompt resuscitation. Survival rates range from 43% in Seattle, Washington, for bystander-initiated cardiopulmonary resuscitation (21) to as low as 0.8% for African-Americans suffering cardiac arrest in Chicago (22). Variations in survival from cardiac arrest, whether occurring in-hospital or out-of-hospital, depend on myriad factors including differences in case definition and community demographics (23,24), whether or not arrest is witnessed (8,24), whether or not resuscitation is begun quickly (9,21,25,26) and whether or not first responders are trained in defibrillation, advanced life support and use of automatic defibrillators (8,26). Problems in gaining access to arrested patients in the out-of-hospital setting represents a significant impediment to survival (22). When automatic external defibrillators are used, rates of survival-to-hospital discharge as high as 49% have been reported for patients treated for VF by police and paramedics (26) and 26% for patients treated in an airline cardiac arrest program (27). One might expect that an in-hospital life-threatening ventricular arrhythmia presentation would increase the chance for early intervention, successful resuscitation and perhaps long-term survival.

Table 3. Mortality Rate by Location of Presentation

	In-Hospital Mortality Rate	Late Mortality Rate		Adjusted Relative Risk
		1 Year	2 Year	
In-Hospital Presentation (n = 806)	4.6%	23.0%	31.1%	1.6 (95% CI 1.3-1.9)
Out-of-Hospital Presentation (n = 1,868)	1.1%	10.5%	16.8%	
p Value	< 0.001	< 0.001		< 0.001

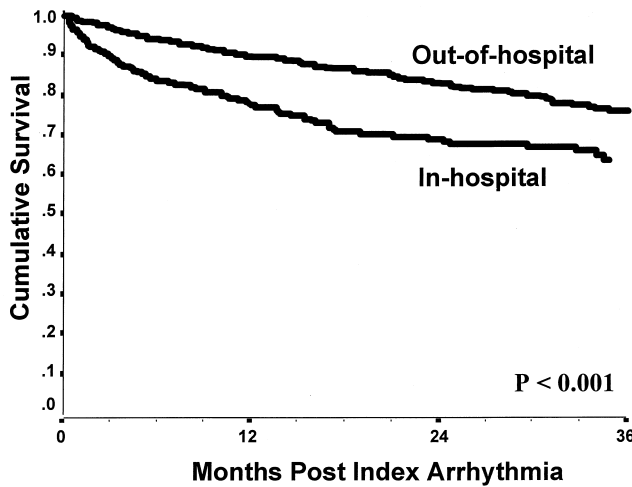


Figure 1. Unadjusted survival of patients in the AVID Registry with in-hospital versus out-of-hospital presentations of AVID-eligible ventricular arrhythmias. Time zero is the date of the index arrhythmia.

The importance of location. Early defibrillation is thought to increase the chance for resuscitation from cardiac arrests that occur out-of-hospital, and to improve long-term outcome for those who survive (21,25,28). Thus, the chance for successful resuscitation from cardiac arrests that occur in-hospital might be expected to be even greater because of the availability of prompt resuscitation. Nevertheless, a statement for health care professionals regarding in-hospital resuscitation emphasizes that, in some hospitals, cardiac arrest response teams must bring defibrillators from remote locations (29). Thus, early defibrillation may not be achieved even in the hospital setting. Furthermore, in-hospital arrhythmias can occur in nonmonitored settings where time to discovery of arrest might be quite prolonged. Of note, 87% of our in-hospital presentations occurred while the patients were being monitored. Nevertheless, patients with in-hospital presentations in the AVID Registry had a fourfold greater in-hospital mortality than did those with out-of-hospital presentations (Table 3).

Study strengths and limitations. The present study provides contemporary data regarding long-term survival after successful resuscitation from life-threatening ventricular arrhythmias. Only patients with primary arrhythmic causes were included.

Only survivors of life-threatening ventricular arrhythmias who were candidates for both drug and ICD therapy were included in this study. Patients with out-of-hospital presentations who died before reaching the hospital, or soon after hospital admission, and those who were not candidates for AVID therapies, patients who survived in-hospital presentations but were not candidates for both AVID therapies, or who died soon after their cardiac arrest and resuscitation, patients with acute myocardial infarction or ischemia and patients too ill to be included in the AVID Registry were

not followed. Thus, because the patients were highly selected, the study's strength of having a very clearly defined and specific population is similarly a weakness.

Furthermore, there may be a problem of selection bias for both groups that may be opposite: Whereas sicker patients were already in the hospital and hence had worse prognoses, healthier patients were both not hospitalized yet well enough to survive out-of-hospital resuscitation. As noted, in-hospital mortality for patients with in-hospital presentations was significantly greater than for those with out-of-hospital presentations.

Finally, although the adjusted analysis shows the persistence of a worse outcome for patients with in-hospital presentations, many unaccounted variables could explain the difference. Not only were patients with in-hospital presentations sicker than were those with out-of-hospital presentations but the relative contributions of concomitant disease, location of presentation or other unknown variables on outcome are unknown. One possibility is that outpatients had prolonged VT as their initiating arrhythmia that provided some hemodynamic stability before degeneration to VF, thereby increasing the chance for successful resuscitation.

Data on the effect of type of arrhythmia management on outcome stratified by location of presentation were not analyzed for this cohort because treatment was not randomized in all patients, and some of the nonrandomized patients received neither ICD nor drug therapy. Such an analysis for those randomized in the main study was done, and in fact showed no difference in survival. However, the groups were small, thereby limiting power of the analysis.

Implications of the present study. The present study reports long-term survival data for patients with life-threatening ventricular arrhythmias treated with contemporary drugs and devices stratified by the location of arrhyth-

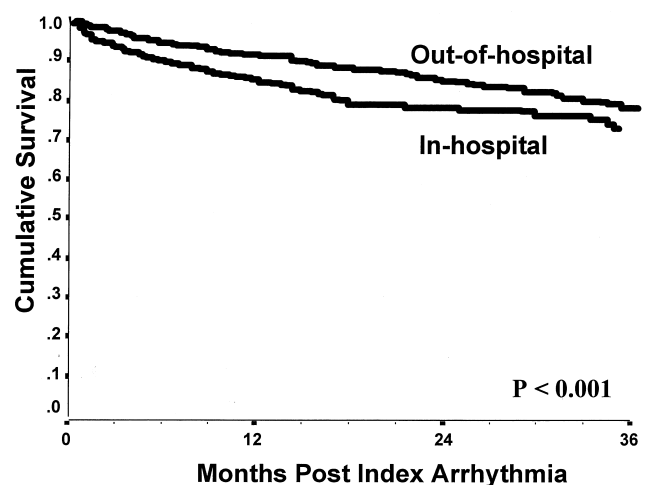


Figure 2. Adjusted survival of patients in the AVID Registry with in-hospital versus out-of-hospital presentations of AVID-eligible ventricular arrhythmias. Time zero is the date of the index arrhythmia.

mia presentation. Given the poor prognosis for survivors of in-hospital cardiac arrest previously reported (13,14,16,17), it should not be surprising that our patients with in-hospital presentations had higher long-term mortality rates compared to survivors of out-of-hospital presentations. However, patients were not entered in the AVID Registry unless they were candidates for both ICD and drug treatment and were thought to have a survival probability of at least one year. That their survival probabilities were still imperfect, even with ICD therapy, attests to the need for further work to improve survival for patients with life-threatening ventricular arrhythmias.

Patients in the present study with in-hospital presentations of life-threatening ventricular arrhythmias carried greater burdens of concomitant disease than did those with out-of-hospital presentations. Thus, improved management of ventricular arrhythmias in the hospital may not influence long-term outcome.

In addition, patients with in-hospital presentations in this study were more likely to be treated with amiodarone than with an ICD, perhaps further decreasing their chance for long-term survival. Regardless, that survival can be so influenced by location of presentation and concomitant disease emphasizes the importance of randomization in clinical trials, and that comparison with nonconcurrent, nonrandomized data may be misleading if unsuspected confounders such as location of presentation are not considered. In the main AVID Study, the results were not affected because randomization was done irrespective of location of presentation and equal numbers of patients with either presentation were included in each treatment arm. However, because location of presentation is an independent predictor of long-term outcome, it should now be considered when deciding on clinical trial inclusion and design issues in the future. Finally, the location of arrhythmia presentation could be considered for risk stratification.

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