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Sustained Ventricular Arrhythmias Among Patients With Acute Coronary Syndromes With No ST-Segment Elevation

Incidence, Predictors, and Outcomes

Sana M. Al-Khatib, MD, MHS; Christopher B. Granger, MD; Yao Huang, MS; Kerry L. Lee, PhD; Robert M. Califf, MD; Maarten L. Simoons, MD; Paul W. Armstrong, MD; Frans Van de Werf, MD; Harvey D. White, DSc; R. John Simes, MD; David J. Moliterno, MD; Eric J. Topol, MD; Robert A. Harrington, MD

Background—The prognosis of ventricular arrhythmias among patients with non–ST-elevation acute coronary syndromes is unknown. We studied the incidence, predictors, and outcomes of sustained ventricular arrhythmias in 4 large randomized trials of such patients.

Methods and Results—We pooled the datasets of the Global Use of Streptokinase and tPA for Occluded Arteries (GUSTO)-IIb, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-A, and PARAGON-B trials (n=26 416). We identified independent predictors of ventricular fibrillation (VF) and ventricular tachycardia (VT) and compared the 30-day and 6-month mortality rates of patients who did (n=552) and did not (n=25 864) develop these arrhythmias during the index hospitalization. Independent predictors of in-hospital VF included prior hypertension, chronic obstructive pulmonary disease, prior myocardial infarction, and ST-segment changes at presentation. Except for hypertension, these variables also independently predicted in-hospital VT. In Cox proportional-hazards modeling, in-hospital VF and VT were independently associated with 30-day mortality (hazard ratio [HR], 23.2 [95% CI, 18.1 to 29.8] for VF and HR, 7.6 [95% CI, 5.5 to 10.4] for VT) and 6-month mortality (HR, 14.8 [95% CI, 12.1 to 18.3] for VF and HR, 5.0 [95% CI, 3.8 to 6.5] for VT). These differences remained significant after excluding patients with heart failure or cardiogenic shock and those who died <24 hours after enrollment.

Conclusions—Despite the use of effective therapies for non–ST-elevation acute coronary syndromes, ventricular arrhythmias in this setting are associated with increased 30-day and 6-month mortality. More effective therapies are needed to improve the survival of patients with these arrhythmias. **(*Circulation*. 2002;106:309-312.)**

Key Words: coronary disease ■ tachycardia ■ fibrillation ■ prognosis ■ mortality

Many studies have investigated the prognostic significance of ventricular arrhythmias in patients with acute ST-segment elevation myocardial infarction (MI). The larger studies done in the thrombolytic era showed that ventricular arrhythmias complicating ST-segment elevation MI portend higher risks of short- and long-term mortality[1] (Sana M. Al-Khatib, MD, unpublished data, March 2002). In patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS), data on ventricular arrhythmias are scant. Thus, it is unknown whether ventricular arrhythmias in this patient population increase the risk of mortality. The purpose of this study was to examine the incidence, predictors, and outcomes of ventricular arrhythmias among patients with NSTE-ACS.

Methods

Study Population

For this study, we used a combined database of the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes

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From the Duke Clinical Research Institute (S.M.A., C.B.G., Y.H., K.L.L., R.M.C., R.A.H.), Durham, NC; University of Rotterdam (M.L.S.), Rotterdam, the Netherlands; University of Alberta (P.W.A.), Alberta, Edmonton, Canada; Gasthuisberg University Hospital (F.V.d.W.), Leuven, Belgium; Green Lane Hospital (H.D.W.), Auckland, New Zealand; University of Sydney (R.J.S.), New South Wales, Australia; and the Cleveland Clinic Foundation (D.J.M., E.J.T), Cleveland, Ohio.

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Correspondence to Sana M. Al-Khatib, MD, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail alkha001@mc.duke.edu

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(GUSTO-IIb),[2] Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT),[3] and the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-A[4] and -B[5] studies, 4 randomized clinical trials of platelet IIb/IIIa inhibitors in non–ST-segment elevation ACS. Details of these trials have been reported. In brief, these were randomized, double-blind, multicenter trials that enrolled patients with ischemic chest pain within 12 to 24 hours of presentation with transient ST-segment elevation or transient or persistent ST-segment depression or T-wave inversion. PURSUIT and PARAGON-B enrolled patients without these electrocardiographic (ECG) changes if they had elevated troponin or creatine kinase (CK)-MB levels. GUSTO-IIb also enrolled patients with persistent ST-segment elevation; these patients were excluded from the current analysis. Exclusion criteria were very similar among the trials and included active bleeding, known coagulopathy, recent surgery or ischemic stroke, prior intracranial hemorrhage, poorly controlled hypertension, and renal failure.

Treatment

Patients were randomized to receive placebo or a platelet glycoprotein IIb/IIIa inhibitor (PURSUIT and PARAGON-A and -B) or hirudin (GUSTO-IIb). The use of anti-ischemic medications, including β-blockers, and antiarrhythmic drugs was left to the discretion of the treating physicians. Prophylactic lidocaine was not routinely used.

Definitions

Ventricular fibrillation (VF) was defined as irregular undulations of varying shape and amplitude on the ECG without discrete QRS or T waves that resulted in prompt hemodynamic compromise requiring direct-current (DC) cardioversion. Sustained ventricular tachycardia (VT) was defined as a regular, wide complex tachycardia of ventricular origin lasting $\geq$30 seconds or accompanied by hemodynamic instability requiring DC cardioversion. Investigators prospectively captured the occurrence of these arrhythmias and reported them to the data coordinating center for the trial.

End Points

The end points of this analysis were mortality within 30 days and within 6 months.

Statistical Analysis

All analyses were performed using SAS software. Continuous variables were summarized as medians with 25th and 75th percentiles, and categorical variables were summarized as frequencies. Continuous variables were compared using the Kruskal-Wallis test and categorical variables were compared using the χ^2 test. Stepwise logistic multiple regression models were used to identify sets of factors that together were significantly associated with the occurrence of VF and VT. Odds ratios (OR) and 95% CIs are reported for significant predictors of ventricular arrhythmias. Results were considered significant at $P<0.05$.

The Cox proportional-hazards model was used to examine the association between ventricular arrhythmias and 30-day and 6-month mortality.[6] These analyses were performed with the arrhythmia as a time-dependent covariate. This method credits the survival time of patients who develop a ventricular arrhythmia to the group without ventricular arrhythmia until the arrhythmia actually occurs. Associations with outcomes were established univariably and multivariably. Adjusted hazard ratios (HR) and 95% CIs are reported for predictors of 30-day and 6-month mortality. Two models have been developed from the PURSUIT database; one predicts death within 30 days and one predicts death from 30 days to 6 months.[7] We adjusted for the significant predictors of mortality in these models in Cox modeling used to analyze ventricular arrhythmias.

Results

Patient Characteristics

Of 26 436 patients in the combined database, 20 were excluded from this analysis because of missing information about the timing of VF or VT. Of the remaining 26 416 patients, 552 (2.1%) developed ventricular arrhythmias during the index hospitalization. The median time to ventricular arrhythmia was 78.24 hours (25th, 75th percentiles; 16.32, 168.72 hours). The median length of stay in the hospital was 192 hours (25th, 75th percentiles; 120 hours, 288 hours). In all, 253 patients developed VF alone, 208 developed VT alone, and 91 developed both VF and VT. Baseline characteristics of these patients are shown in Table 1.

Predictors of Ventricular Arrhythmias

After adjustment for other baseline characteristics, variables that were significantly associated with VF were prior hypertension, chronic obstructive pulmonary disease, prior myocardial infarction, and the presence of ST-segment changes at presentation. Except for hypertension, these clinical variables also significantly predicted VT (Table 2).

In-Hospital and Discharge Medications

Compared with patients without VF or VT, patients who developed these arrhythmias were less likely to be treated with β-blockers. The use of antiarrhythmic medications was low in all 4 studies. Data on specific antiarrhythmic medications were not available in 2 of the 4 combined clinical trials. In the 2 clinical trials that collected data on specific antiarrhythmic medications, amiodarone and sotalol were the most commonly prescribed antiarrhythmic medications. Few patients were treated with class I antiarrhythmic medications (Table 3).

Outcomes

The unadjusted 30-day and 6-month mortality rates were higher in patients with ventricular arrhythmias (Table 4; Figure), and this pattern persisted after adjustment for other prognostic variables. Differences in 30-day mortality and 6-month mortality associated with VF or VT remained significant after excluding patients with congestive heart failure or cardiogenic shock and those who died within 24 hours after enrollment (30-day mortality: HR 18.0, 95% CI 12.3 to 26.3 for VF; HR 4.4, 95% CI 2.6 to 7.6 for VT; HR 78.0, 95% CI 49.2 to 123.6 for VT and VF; 6-month mortality: HR 10.6, 95% CI 8.0 to 14.2 for VF; HR 3.0, 95% CI 1.9 to 4.4 for VT; HR 25.0, 95% CI 16.5 to 38.0 for VT and VF). The effect of the study drug on the survival of patients with VT and VF within each study was examined and was found to be insignificant.

Discussion

Among patients with NSTE-ACS, the prognosis of sustained ventricular arrhythmias has been largely uncertain. Our study is the largest to explore this issue. It suggests that the in-hospital occurrence of sustained ventricular arrhythmias in this setting is associated with a significantly increased risk of mortality. Patients with these arrhythmias had 5- to 15- fold higher mortality within 6 months. Notably, most of the deaths occurred during the first 30 days. Thus, to improve the prognosis of these patients, potentially effective therapies for NSTE-ACS will have to be started early after admission.

TABLE 1. Baseline Characteristics by In-Hospital Ventricular Arrhythmia Based on Unadjusted Univariate Analyses

	VT Only (n=208)	VF Only (n=253)	VT and VF (n=91)	Neither (n=25,864)	P
Age, y	67 (60, 74)	66 (58, 74)	68 (55, 73)	65 (55, 72)	<0.001
Male	67	74	73	66	0.02
Diabetes mellitus	23	24	38	21	0.001
Hypertension	58	58	64	53	0.02
Prior infarction	46	38	45	32	0.001
Prior bypass surgery	18	14	16	12	0.02
Prior angioplasty	15	11	15	12	0.4
Systolic BP, mm Hg	130 (114, 149)	130 (120, 145)	130 (114, 144)	135 (120, 150)	<0.001
Pulse, bpm	77 (66, 89)	73 (64, 84)	76 (66, 92)	73 (64, 84)	0.009
Killip class					
I	75	78	86	89	0.001
II	20	21	10	9	0.001
III	4	1	4	1	0.001
IV	<1	0	0	<1	0.3
Peak CK ratio, IU	2 (1, 6)	1 (1, 4)	2 (0, 5)	1 (0, 2)	<0.001
Peak CK-MB ratio, % of control	3 (1, 9)	3 (1, 9)	4 (1, 14)	1 (1, 4)	<0.001
Symptom onset to study treatment, h	8 (4, 12)	8 (4, 13)	7 (4, 12)	8 (5, 13)	0.2

BP indicates blood pressure; CK, creatine kinase. Peak CK ratio is the highest CK value divided by upper limit of normal in a particular hospital and peak CK-MB ratio is the highest CK-MB value divided by the upper limit of normal in a particular hospital. Data shown are median (25th, 75th percentiles) or percent of group.

These findings are in agreement with the results of analyses of the GUSTO-I and GUSTO-III databases (Sana M. Al-Khatib, MD, unpublished data, March 2002).[1] Although the incidence of ventricular arrhythmias among patients with NSTE-ACS is lower (2.1%) than that among patients with ST-segment elevation (up to 10%), these arrhythmias are associated with significantly increased mortality in either setting. Notably, in the present study, the absence of congestive heart failure did not eliminate the enormous harmful effect of these arrhythmias on survival. The best therapy for patients with these arrhythmias is uncertain, but clearly these patients require therapies that can improve survival. Importantly, guidelines for implantation of cardioverter-defibrillators consider ventricular arrhythmias in acute MI a contraindication to defibrillator therapy, because such arrhythmias are not believed to affect long-term survival.[8] In light of our findings, these guidelines may need to be reconsidered.

Patients with ventricular arrhythmias were less likely to receive β-blockers during and after hospitalization in this study. This may have influenced our findings, given that β-blockers have been shown to reduce mortality after MI.[9,10] The association between ventricular arrhythmias and increased mortality in this study, however, is substantial and is unlikely to become insignificant after adjusting for this difference.

Some could argue that ventricular arrhythmias are simply a marker of an increased risk of death and by themselves do not increase mortality. In this study, adjustment for other factors known to affect mortality did not eliminate the relationship of

TABLE 2. Independent Predictors of In-Hospital Ventricular Arrhythmias in Multivariable Logistic Regression Modeling*

	OR (95% CI) for VT	OR (95% CI) for VF
Prior chronic obstructive pulmonary disease	2.5 (1.6–4.1)	1.9 (1.1–3.1)
Prior myocardial infarction	1.8 (1.3–2.3)	1.5 (1.1–1.9)
ST depression at presentation	2.5 (1.8–3.3)	1.8 (1.4–2.4)
ST elevation at presentation	1.6 (1.1–2.3)	1.6 (1.2–2.2)
Prior hypertension	...	1.4 (1.1–1.8)

*The full model for VT also included peak CK ratio, peak CK-MB ratio, age, and systolic blood pressure, which were significant predictors (with ORs close to 1) and weight and pulse, which were not. The full model for VF also included peak CK ratio, peak CK-MB ratio, and systolic blood pressure, which were significant predictors (with ORs close to 1).

TABLE 3. In-Hospital and Discharge Therapy by Ventricular Arrhythmia*

	VT only (n=169)	VF only (n=208)	VT and VF (n=74)	Neither (n=20 743)
Oral β-blockers				
In-hospital	53	56	45	64
Discharged on	44	51	46	60
Angiotensin-converting enzyme inhibitors				
In-hospital	48	37	38	30
Discharged on	39	26	50	27
Antiarrhythmic medications				
In-hospital	42	33	45	6
Discharged on	22	12	15	4

Data shown are percent of group.
Data not available for PARAGON-B.

TABLE 4. Mortality by Ventricular Arrhythmia

	VT Only vs Neither		VF Only vs Neither		VF and VT vs Neither	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
30-Day mortality	11 (8–15)	8 (5–10)	26 (21–33)	23 (18–30)	68 (52–89)	85 (64–114)
6-Month mortality	7 (6–10)	5 (4–7)	15 (12–18)	15 (12–18)	38 (29–49)	37 (29–49)

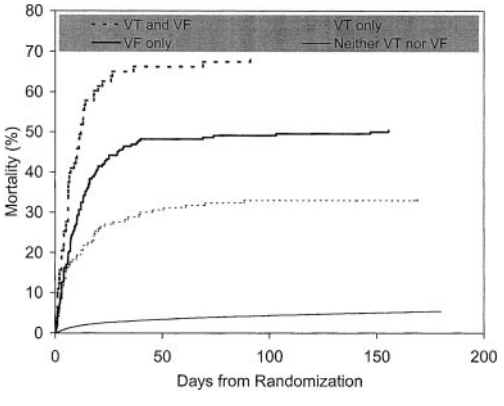
Data are shown as HR (95% CI).

ventricular arrhythmias with higher mortality, suggesting that these arrhythmias may lead to increased risk.

Predicting the occurrence of these ventricular arrhythmias is of vast importance. To our knowledge, our study is the first to identify predictors of such ventricular arrhythmias in this population. Significant independent predictors of VF were history of hypertension, history of chronic obstructive pulmonary disease, prior myocardial infarction, and ST-segment changes at presentation. Except for hypertension, these clinical variables also were significant predictors of VT. It is not surprising that ST-segment changes at presentation strongly predict ventricular arrhythmias, given that these changes may correlate with a greater degree of ischemia. It is unclear why chronic obstructive lung disease is a strong predictor of VF and VT, but chronic hypoxia or acidosis combined with ischemia could predispose patients to ventricular arrhythmias. Thus, patients who have these clinical characteristics may benefit from earlier, more aggressive interventions.

Limitations

The main limitation of this study is that because detailed information about the postdischarge procedures and medications was unavailable, we could not explore their relationships with outcomes.



Kaplan-Meier curves of mortality by ventricular arrhythmia.

Implications

Mortality of patients with NSTE-ACS and sustained ventricular arrhythmias is significantly higher than that of NSTE-ACS patients without these arrhythmias. Therefore, every effort should be made to identify therapies that would most improve the outcome of these patients. This would best be accomplished by randomized clinical trials of the available antiarrhythmic therapies, including implantable cardioverter-defibrillators.

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