ORIGINAL CONTRIBUTION

Incidence of and Outcomes Associated With Ventricular Tachycardia or Fibrillation in Patients Undergoing Primary Percutaneous Coronary Intervention

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Context The incidence and timing of sustained ventricular tachycardia or fibrillation (VT/VF) and its impact on outcomes in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) are poorly understood.

Objective To evaluate the association of sustained VT/VF and its timing on the outcomes of patients presenting for primary PCI—an aim not prespecified in the APEX AMI trial.

Design, Setting, and Patients We studied 5745 STEMI patients presenting for primary PCI at 296 hospitals in 17 countries between July 13, 2004, and May 11, 2006, from the APEX AMI trial. We categorized them into 4 groups: no VT/VF; VT/VF any time; early VT/VF, before the end of cardiac catheterization; and late VT/VF, after the end of cardiac catheterization.

Main Outcome Measure Ninety-day total mortality.

Results VT/VF occurred in 329 STEMI patients (5.7%) presenting for primary PCI. The majority of these occurred before the end of catheterization (n=205, 64%), and 90% occurred within 48 hours of presentation with symptoms of STEMI. Clinical outcomes were worse in patients with vs those without VT/VF (90-day mortality, 23.2% vs 3.6%; adjusted HR, 3.63; 95% CI, 2.59-5.09), and outcomes were worse if the VT/VF occurred late instead of early (90-day mortality for early VT/VF, 17.2% [adjusted HR, 2.34; 95% CI, 1.44-3.80]; for late VT/VF, 33.3% [adjusted HR, 5.59; 95% CI, 3.71-8.43]; for no VT/VF, 3.6% [referent]). In multivariate analyses, factors associated with early VT/VF included pre-PCI thrombolysis in MI (TIMI) flow grade 0 (HR, 2.94; 95% CI, 1.93-4.47), inferior infarction (HR, 2.16; 95% CI, 1.58-2.93), total baseline ST deviation (HR, 1.39; 95% CI, 1.19-1.63), creatinine clearance (HR, 0.88; 95% CI, 0.83-0.94), Killip class greater than I (HR, 1.88; 95% CI, 1.29-2.76), baseline systolic blood pressure (HR, 0.92; 95% CI, 0.87-0.98), body weight (HR, 1.16; 95% CI, 1.04-1.29), and baseline heart rate greater than 70/min (HR, 1.10; 95% CI, 1.01-1.20) (*c* index, 0.75). Factors related to late VT/VF were systolic blood pressure (HR, 0.83; 95% CI, 0.76-0.91), ST resolution less than 70% (HR, 3.17; 95% CI, 1.60-6.28), baseline heart rate greater than 70/min (HR, 1.20; 95% CI, 1.08-1.33), total baseline ST deviation (HR, 1.43; 95% CI, 1.14-1.79), post-PCI TIMI flow less than grade 3 (HR, 2.09; 95% CI, 1.24-3.52), pre-PCI TIMI flow grade 0 (HR, 2.12; 95% CI, 1.20-3.75), and β-blockers less than 24 hours (HR, 0.52; 95% CI, 0.32-0.85) (*c* index, 0.74).

Conclusions In this study, occurrence of VT/VF before or after the end of cardiac catheterization in patients presenting for primary PCI was associated with increased 90-day mortality.

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PRIOR INVESTIGATORS HAVE EVALUated the clinical and angiographic features and outcomes associated with ventricular tachycardia or fibrillation (VT/VF) in patients with ST-elevation myocardial infarction (STEMI) receiving fibrinolysis.[1-6] These studies have suggested that the occurrence of VT/VF in this cohort is associated with poor in-hospital and long-term adverse outcomes, irrespective of the timing of their occurrence: ie, early (≤48 hours) vs late (>48 hours) after their symptom onset.[1-6] Similarly, a prior study has identified the clinical and angiographic correlates and outcomes of VT/VF occurring in the cardiac catheterization laboratory among patients undergoing primary percutaneous coronary intervention (PCI).[7] However, this study analyzed low-risk patients (without renal failure or cardiogenic shock) enrolled before 1999, when stents and glycoprotein IIb/IIIa receptor antagonists were not routinely used, and focused only on VT/VF occurring in the cardiac catheterization laboratory,

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providing no information on incidence, risk factors, and outcomes of this arrhythmia beyond the procedure.

We analyzed 5745 patients with STEMI who presented for primary PCI from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX AMI) trial.[8,9] Our goals were to evaluate the association of VT/VF and its timing with the risk of death at 30 and 90 days in patients presenting for primary PCI, examine the differences in clinical and angiographic features and outcomes of VT/VF in these patients relative to the timing of its occurrence, and examine the mode of death in patients with this event.

METHODS

Study Population

Details of the rationale, designs, and results of the APEX AMI trial have been previously published.[8,9] Briefly, 5745 patients from 17 countries and 296 sites were enrolled in the trial between July 13, 2004, and May 11, 2006. Patients were eligible if they were 18 years or older and presented within 6 hours of symptoms with high-risk STEMI (defined as electrographic evidence of at least 2-mm ST elevation in 2 anterior leads or 2-mm elevation in 2 inferior leads coupled with ST depression in 2 contiguous leads for a total of 8 mm or more or new left bundle-branch block with at least 1-mm concordant ST elevation). Patients were excluded if they had isolated inferior STEMI, were pregnant, had known or suspected complement deficiency or active infection, had other serious medical problems likely to hamper their recovery, or had received fibrinolytic therapy for the treatment of their qualifying events.

Patients were randomized to receive an intravenous bolus of 2 mg per kg of pexelizumab or matching placebo given in double-blinded fashion prior to PCI over 10 minutes followed by infusion of pexelizumab, 0.05 mg per kg per hour, or placebo as a continuous intravenous drip of 20 mL per hour over the subsequent 24 hours. Study medicine was mandated to be given before balloon inflation and stent placement. Concomitant medications and subsequent cardiac procedures were left to the discretion of the attending physician but expected to be in compliance with the acute STEMI treatment guidelines established by the American College of Cardiology and American Heart Association.[10] The institutional review board of each participating hospital approved the APEX AMI protocol, and patients were required to provide written informed consent. The current analysis was performed as part of institutional review board–approved subanalyses of the APEX AMI trial.

The primary end point of the APEX AMI trial was whether pexelizumab reduced all-cause mortality through day 30. Secondary end points included the composite incidence of death, cardiogenic shock, or congestive heart failure through days 30 and 90. Congestive heart failure and cardiogenic shock were centrally adjudicated by a clinical events committee blinded to treatment assignment using prespecified standard definitions.[8,9] In contrast, occurrence of other tertiary end points (ie, recurrent MI, bleeding, stroke, sepsis) was ascertained by site investigators, again using prespecified definitions.[8,9] Renal failure was defined based on notes in the medical record made by the investigator identifying clinical renal failure, including patients who progressed to temporary or permanent renal replacement therapy. Race and ethnicity were self-reported by patients, recorded in the patient's medical record, and collected on the case report form in the following categories: white, black or African American, North American Indian or Native Alaskan, Hispanic or Latino, Asian, Native Hawaiian or other Pacific Islander, or other.

For the current analysis that was not prespecified in the APEX AMI trial, we stratified all patients enrolled in the trial into 2 groups: those with no VT/VF and those with sustained VT/VF any time after symptom onset. Additionally, to study the association of the timing of this arrhythmia, we divided patients with sustained VT/VF into those with VT/VF before the end of their cardiac catheterization (early VT/VF) and those with sustained VT/VF after this procedure (late VT/VF). Patients who had VT/VF before the start of the cardiac catheterization procedure were few (n=25) and were therefore included with those in whom VT/VF occurred during the procedure in the early VT/VF group. Sustained VT/VF was defined as that lasting longer than 30 seconds or that requiring electrical cardioversion and collected as such in the case report form.

Statistical Analysis

Summary statistics are presented as frequencies and percentages or as median values (with 25th and 75th percentiles). Comparisons between the study groups were made using the Wilcoxon rank-sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables. In all cases, denominators reflect cases reported. Multivariate Cox proportional hazard models were constructed to identify clinical predictors of any sustained VT/VF as well as early and late VT/VF. The candidate variables were selected based on availability and on prior studies of risk factors for arrhythmias, heart failure, and mortality.

The proportion of missing information for most variables was low (<4%) with the exception of creatinine clearance (9.3%), ST resolution less than 70% (10.4%), and left ventricular ejection fraction (55%). Because the value of left ventricular ejection fraction was missing in a large number of patients, this was presented only in univariate analysis. For the remaining variables, only cases with complete information were used in univariate and multivariate analyses. For any VT/VF, baseline characteristic variables were selected, including age, sex, weight, diabetes, renal insufficiency, smoking status, prior congestive heart failure, prior MI, prior PCI or coronary artery bypass surgery, heart rate, systolic blood pressure, creatinine clearance, inferior MI location, Killip class, time from symptom onset to randomization, and total baseline ST segment deviation. For

early VT/VF, preprocedural thrombolysis in MI (TIMI) flow and time to sheath insertion were considered in addition to the baseline variables. For late VT/VF, potential covariates also examined were β-blocker usage before the cardiac catheterization; peak creatine kinase MB values; and catheterization findings, including number of diseased vessels, left ventricular ejection fraction, postprocedural TIMI flow, ST resolution, and stent use.

Restricted cubic splines were applied to continuous variables to evaluate linearity assumption. When the assumption was not met, linear splines were applied where appropriate. The proportional hazards assumption was assessed in smoothing spline-based score tests. When the proportional hazards assumption was violated, graphical representations were made. After visual inspection, if it was felt that applying the assumption led to conservative estimates, then the factor was included as is, recognizing this limitation. Because the variable ST resolution less than 70% did not meet the proportional hazards assumption, after visual inspection of the Kaplan-Meier curves depicting late VT/VF in patients with and without ST resolution less than 70%, the time axis was partitioned and a piecewise Cox model was fitted to investigate the effect of ST resolution less than 70% on the occurrence of VT/VF in each time interval.[11]

Only variables with a significant ($P < .05$) association with sustained VT/VF by stepwise selection were included in the final regression models. Adjusted hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) were computed to determine the association of each variable with VT/VF in the final model. The *c* index was calculated to evaluate model discrimination. Because most sudden cardiac deaths are generally arrhythmic, we also evaluated factors independently associated with the composite end point of any VT/VF or sudden death and late VT/VF or late sudden death.

Unadjusted association of any, early, or late VT/VF with 90-day mortality was evaluated by calculating unadjusted HRs and 95% CIs. Multivariate Cox proportional modeling was performed to determine clinical correlates of 90-day mortality. For this purpose, we used baseline variables based on a previously developed model[12] and additional postprocedural variables, including ST resolution and TIMI flow grades. To this baseline model, any VT/VF (vs none) was then added as a time-dependent covariate to derive the adjusted HR and 95% CI of VT/VF for 90-day mortality. Similarly, early and late VT/VF (vs no VT/VF) were added to the baseline model as time-dependent covariates to derive adjusted HRs and 95% CIs of early and late VT/VF for 90-day mortality.

Furthermore, we also estimated the independent incremental proportional prognostic information contributed by (any and early or late) VT/VF to 90-day mortality in the full model: percentage = (χ^2 [log likelihood] for the model with [any and early or late] VT/VF) − (χ^2 [log likelihood] for the model without the corresponding VT/VF) ÷ (χ^2 [log likelihood] for the model with [any and early or late] VT/VF) × 100.[13] Cumulative VT/VF incidence curves were constructed by Kaplan-Meier method. Similarly, 90-day survival curves were constructed with stratification by the timing of VT/VF. Because not all patients with STEMI presenting for cardiac catheterization underwent primary PCI, we performed a sensitivity analysis to evaluate the incidence, timing, clinical correlates, and outcomes among patients undergoing primary PCI.

Finally, all models (ie, those for any, early, and late VT/VF as well as that for 90-day mortality) were internally validated using a bootstrap resampling technique. One hundred samples of 100% were drawn at random with replacement for this purpose. Model *c* index was derived for each sample and mean *c* index with 95% CIs were calculated. All *P* values were 2-sided and values less than .05 were considered significant. SAS version 8.0 (SAS Institute, Cary, North Carolina) was used for all analyses.

RESULTS

Patient Characteristics

Of the 5745 patients enrolled in the APEX AMI trial, VT/VF occurred in 329 patients (5.7%). The timing of this event was not available in 7 patients, 25 patients had VT/VF before cardiac catheterization, 180 had VT/VF during the procedure, and 117 had this event after cardiac catheterization. The majority of VT/VF (90%, n = 282) occurred within 48 hours. The median time to occurrence of late VT/VF from symptom onset was 28 hours (interquartile range [IQR], 6-63 hours) and from end of catheterization was 26 hours (IQR, 3-63 hours). Seventy percent of late VT/VF occurred within 48 hours.

Compared with patients without any VT/VF, those with VT/VF were older; had a higher heart rate, Killip class, and total baseline ST-segment deviation; and had lower systolic blood pressure and creatinine clearance (TABLE 1). Preprocedural TIMI flow grade 0 was more likely and postprocedural TIMI flow grade 3 less likely in patients with any VT/VF (TABLE 2). Patients with late VT/VF were less likely to have postprocedural TIMI flow grade 3 and complete ST resolution (≥70%) compared with those with early VT/VF. The lowest incidence of late VT/VF occurred among patients with postprocedural TIMI flow grade 3 and complete ST resolution (≥70%) and the highest among those with postprocedural TIMI flow grade less than 3 and incomplete ST resolution (FIGURE 1).

Many therapies, such as β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins, were used less frequently among patients with VT/VF (Table 2). In contrast, the use of antiarrhythmic agents, intra-aortic balloon pump, repeat cardiac catheterization, and dialysis and the need for transfusion were higher in patients with VT/VF. Other medical therapies and procedure use were similar between the early and late VT/VF cohorts, but repeat catheterization was 3-fold higher in patients with late VT/VF.

Clinical Events and Outcomes

Clinical events and outcomes are listed in TABLE 3 and TABLE 4. Many of these events were higher among patients with late VT/VF compared with those with early VT/VF. Mortality was significantly higher in patients with any VT/VF compared with those without it (90-day death, 23.2% vs 3.6%; unadjusted HR, 7.33; 95% CI, 5.61-9.59). The excess in mortality was for the most part confined to the first 30 days with similar low events beyond this point. Thus, while mortality at 30 days was more than 7-fold higher with any VT/VF, in patients with or without VT/VF, death was 0.7% from 30 to 90 days.

Other clinical outcomes such as cardiogenic shock, congestive heart failure, and recurrent MI were also associated with any VT/VF. Clinical outcomes were particularly worse among patients with late VT/VF, although even those with early VT/VF had a significantly higher event rate compared with those without any VT/VF (90-day mortality for early VT/VF, 17.2%; unadjusted HR, 5.28; 95% CI, 3.69-7.57; and for late VT/VF, 33.3%; unadjusted HR, 11.41; 95% CI, 8.09-16.10; vs 3.6% for patients with no VT/VF) (FIGURE 2). After adjusting for baseline factors, mortality at 90 days was higher for patients with any VT/VF (adjusted HR, 3.63; 95% CI, 2.59-5.09; referent, no VT/VF) and for early VT/VF (HR, 2.34; 95% CI, 1.44-3.80) and late VT/VF (HR, 5.59; 95% CI, 3.71-8.43) (referent, no VT/VF). Any VT/VF and early and late VT/VF accounted for 15.8% and 21.2% of prognostic information, respectively, in the multivariate 90-day mortality model. Most deaths (28/34, 82.3%) in the early group occurred after the cardiac catheterization procedure.

Among patients with VT/VF dying of cardiac cause (90.9% of deaths, n=70), 30 patients had sudden cardiac death and 40 patients had nonsudden cardiac deaths. The proportion of patients dying of sudden or nonsudden cardiac cause was not

Table 1. Baseline Characteristics

Characteristic[a]	No VT/VF (n = 5416)	VT/VF (n = 329)	*P* Value	VT/VF Before End of Catheterization (n = 205)	VT/VF Beyond CL (n = 117)	*P* Value
Age, median (IQR), y	61 (52-71)	64 (53-72)	.03	63 (53-72)	64 (53-72)	.78
Female sex, No. (%)	1247 (23.0)	78 (23.7)	.78	49 (23.9)	28 (23.9)	.99
Weight, median (IQR), kg	80 (70-91)	82 (70-91)	.51	82 (70-92)	81 (68-91)	.65
White race, No. (%)	5102 (94.2)	314 (95.4)	.38	197 (96.1)	111 (94.9)	.64
Clinical history, No. (%)						
Hypertension	2677 (49.4)	162 (49.2)	.94	102 (49.8)	56 (47.9)	.74
Diabetes mellitus	852 (15.7)	61 (18.5)	.18	35 (17.1)	25 (21.4)	.34
Current smoker	2344 (43.4)	134 (41.0)	.63	89 (43.6)	43 (37.1)	.50
Hypercholesterolemia	2049 (49.5)	131 (52.8)	.30	83 (52.2)	43 (52.4)	.97
Prior MI	648 (12.0)	46 (14.0)	.28	27 (13.2)	19 (15.4)	.58
Prior PCI	523 (9.7)	39 (11.9)	.19	27 (13.2)	12 (10.3)	.44
Prior CABG	116 (2.1)	12 (3.6)	.07	7 (3.4)	5 (4.3)	.76
Prior CHF	192 (3.5)	16 (4.9)	.21	6 (2.9)	10 (8.5)	.03
Prior stroke	203 (3.7)	13 (4.0)	.85	11 (5.4)	2 (1.7)	.14
Peripheral vascular disease	233 (4.3)	13 (4.0)	.76	7 (3.4)	6 (5.1)	.56
Dialysis	13 (0.2)	3 (0.9)	.06	2 (1.0)	1 (0.9)	.99
Presenting characteristics						
Heart rate, median (IQR), beats/min	75 (65-86)	77 (64-92)	.04	76 (62-90)	80 (67-94)	.10
SBP, median (IQR), mm Hg	133 (118-150)	127 (110-143)	<.001	128 (108-145)	125 (110-140)	.49
Inferior infarct location, No. (%)	1787 (33)	132 (40.1)	.06	99 (48.3)	33 (28.2)	<.001
Killip class, No. (%)						
I	4876 (90.1)	252 (76.6)	<.001	159 (77.6)	88 (75.2)	.16
II	439 (8.1)	50 (15.2)		26 (12.7)	23 (19.7)	
III	54 (1.0)	10 (3.0)		6 (2.9)	3 (2.6)	
IV	41 (0.8)	17 (5.2)		14 (6.8)	3 (2.6)	
Total baseline ST-segment deviation, median (IQR), mm	13.0 (9.0-18.5)	17.0 (11.0-22.5)	<.001	16.5 (11.0-22.0)	17.5 (11.0-22.5)	.90
Creatinine clearance, median (IQR), mL/min	83 (64-106)	75 (58-96)	<.001	76 (58-94)	71 (55-95)	.66

Abbreviations: CABG, coronary artery bypass grafting; CHF, congestive heart failure; CL, catheterization laboratory; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; VT/VF, ventricular tachycardia or fibrillation.
SI conversion factor: To convert creatinine clearance to mL/s/m^2, multiply by 0.0167.
[a]No. (%) represent patients with no missing information for these characteristics.

significantly different in patients with early VT/VF and late VT/VF (Table 4).

Clinical Correlates of VT/VF

Factors associated with increased risk of VT/VF are listed in TABLE 5. While certain factors were associated with both early and late VT/VF (baseline higher heart rate, lower systolic blood pressure, higher total baseline ST deviations, and preprocedural TIMI flow grade 0), important differences existed. Higher Killip class, inferior MI, lower creatinine clearance, shorter time from symptom onset to randomization, and higher weight were associated with increased risk of early VT/VF. In contrast, postprocedural TIMI flow grade less than 3, lack of β-blockers on admission, and ST resolution less than 70% were related to higher risk of late VT/VF. Among patients with 2 or fewer risk factors (n=3484, two-thirds of study population), the incidence of late VT/VF was only 1.2% (FIGURE 3). Even among patients with fewer than 3 risk factors (4726 patients, >90% of the patients), this incidence remained well under 2% (1.6%), most of it occurring in the first 48 hours (70%). Bootstrapping confirmed internal validation of

Table 2. Procedural, Angiographic, and Treatment Characteristics

Characteristic[a]	No VT/VF (n = 5416)	VT/VF (n = 329)	*P* Value	VT/VF Before End of Catheterization (n = 205)	VT/VF Beyond CL (n = 117)	*P* Value
Timeliness of procedure, median (IQR), h						
Symptom onset to enrollment	2.8 (2.0-4.0)	2.7 (1.8-3.8)	.06	2.6 (1.7-3.7)	3.0 (2.1-4.0)	.11
Symptom onset to PCI	3.3 (2.5-4.5)	3.3 (2.3-4.3)	.10	3.3 (2.2-4.3)	3.4 (2.5-4.5)	.39
Door to PCI	1.1 (0.7-1.5)	1.1 (0.7-1.5)	.56	1.1 (0.7-1.6)	1.0 (0.7-1.5)	.32
Preprocedural TIMI flow, No. (%)						
Grade 0	3325 (63.4)	263 (80.9)	<.001	168 (82.8)	90 (78.3)	.53
Grade 1	506 (9.6)	24 (7.4)		12 (5.9)	12 (10.4)	
Grade 2	759 (14.5)	25 (7.7)		15 (7.4)	10 (7.0)	
Grade 3	656 (12.5)	13 (4.0)		8 (3.9)	5 (4.3)	
Postprocedural TIMI flow, No. (%)						
Grade 0	122 (2.3)	17 (5.4)	<.001	7 (3.5)	9 (8.1)	.10
Grade 1	40 (0.8)	8 (2.5)		5 (2.5)	3 (2.7)	
Grade 2	322 (6.2)	43 (13.6)		23 (11.5)	20 (18.0)	
Grade 3	4724 (90.7)	249 (78.5)		165 (82.5)	79 (71.2)	
ST resolution <70%, No. (%)	2431 (49.8)	136 (50.7)	.77	74 (42.5)	59 (67.0)	<.001
Multivessel CAD, No. (%)	2385 (45.2)	157 (50.3)	.08	98 (50.3)	59 (53.6)	.57
Left ventricular ejection fraction, median (IQR), %	50 (40-60)	43 (33-55)	<.001	45 (39-55)	40 (25-50)	.02
Multivessel PCI, No. (%)	8 (0.1)	2 (0.6)	.11	1 (0.5)	1 (0.9)	.99
Stent usage, No. (%)	4862 (89.8)	285 (86.6)	.07	184 (89.8)	96 (82.1)	.05
Medical therapies, No. (%)						
Aspirin	5382 (99.4)	318 (98.8)	.28	202 (98.5)	116 (99.1)	.99
Thienopyridine agents	5133 (94.8)	297 (92.7)	.11	192 (93.7)	107 (91.5)	.46
β-Blockers	5089 (94.0)	287 (89.4)	<.001	186 (90.7)	101 (86.3)	.22
β-Blockers at home or at arrival	1906 (35.2)	110 (35.3)	.99	66 (32.2)	44 (37.6)	.32
β-Blockers in first 24 h	4630 (85.6)	231 (72.6)	<.001	148 (72.5)	83 (70.9)	.76
Glycoprotein IIb/IIIa inhibitors	3743 (69.1)	239 (74.5)	.04	146 (71.2)	93 (79.5)	.10
ACE inhibitors or ARB	4719 (87.1)	79.9	<.001	169 (82.4)	88 (75.2)	.12
Statins	5148 (95.1)	282 (85.7)	<.001	186 (87.8)	96 (82.1)	.16
Antiarrhythmic other than β-blockers, digoxin, and calcium antagonists	637 (11.8)	183 (55.6)	<.001	102 (49.8)	76 (65.0)	.08
Procedures, No. (%)						
Intra-aortic balloon pump	356 (6.6)	87 (26.7)	<.001	56 (27.3)	31 (26.5)	.87
Repeat cardiac catheterization	298 (5.5)	38 (11.9)	<.001	14 (6.8)	24 (20.5)	<.001
Repeat PCI, urgent	368 (6.8)	28 (8.5)	.23	14 (6.8)	14 (12.0)	.12
Cardiac surgery	188 (3.5)	16 (4.9)	.19	8 (3.9)	7 (6.0)	.39
Dialysis	18 (0.3)	9 (2.7)	<.001	3 (1.5)	6 (5.1)	.08
Transfusion	296 (5.5)	43 (13.4)	<.001	22 (10.7)	21 (17.9)	.07

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction; VT/VF, ventricular tachycardia or fibrillation.
[a]No. (%) represent patients with no missing information for these characteristics.

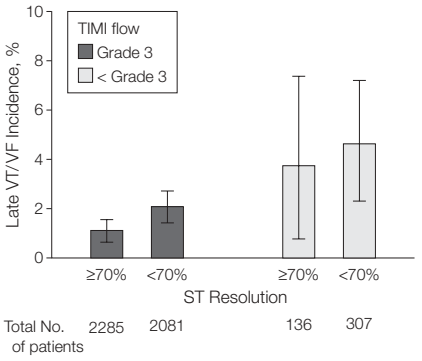
models identifying the independent correlate of any VT/VT (mean *c* index, 0.72; 95% CI, 0.67-0.73); early VT/VF (mean *c* index, 0.75; 95% CI, 0.71-0.78); and late VT/VF (mean *c* index, 0.75; 95% CI, 0.69-0.79).

Sensitivity Analyses

In the APEX AMI trial, 5373 of 5745 patients (93.5%) underwent primary PCI. In these patients, VT/VF occurred in 310 patients, accounting for 94.2% of VT/VF in the overall population (early VT/VF in 198 and late VT/VF in 107 patients, no data available on timing for 5 patients). When analyses were repeated restricting to this population, results remained unchanged compared with the findings in the overall population.

Because sudden cardiac death was more likely to be arrhythmic, we also evaluated the predictors of the composite of any VT/VF or sudden cardiac death. These factors remained the same as those for any VT/VF, although the weights of the association with the composite end point changed to some degree (TABLE 6). Similarly, when we evaluated independent factors associated with the risk of composite of late VT/VF or late sudden cardiac death (beyond the cardiac catheterization laboratory), we found that most factors associated with this composite end point were similar to that for late VT/VF alone. However, lower creatinine clearance, higher Killip class, and multivessel coronary artery disease were now independently related to increased risk of composite end point, whereas ST resolution less than 70% became nonsignificant (*P*=.13) (Table 6).

Figure 1. Postprocedural TIMI Flow and ST Resolution and Incidence of Late VT/VF



TIMI indicates thrombolysis in myocardial infarction; VT/VF, ventricular tachycardia or fibrillation. Error bars indicate 95% CIs.

COMMENT

In this study, VT/VF occurred in approximately 6% of patients with STEMI presenting for primary PCI. Two-thirds of these events occurred before the end of cardiac catheterization and 90% within 48 hours. Our data also suggest that VT/VF was not benign and was associated with substantially increased morbidity and mortality in patients undergoing primary PCI. Some of this association was related to older age, greater prevalence of comorbid conditions, and adverse presenting and post–cardiac catheterization features (ST resolution and TIMI flow) as shown by the attenuation of the risk with adjustment of these factors in a multivariate model. However, even after accounting for these variables, any VT/VF remained associated with a more than 3-fold higher risk of 90-day mortality in patients undergoing primary PCI. Up to one-fifth of prognostic information for 90-day mortality in patients undergoing primary PCI was related to the occurrence of VT/VF in multivariate modeling. The prognostic significance of late VT/VF appeared to be greater than early VT/VF with more than 5- and 2-fold higher risks of 90-day mortality, respectively. Thus, these data support the prognostic importance of (any, early, or late) VT/VF as an independent and incremental risk marker, although this does not prove a cause-and-effect relationship.

Table 3. Clinical Events[a]

Events	No. (%)			No. (%)		
	No VT/VF (n = 5416)	VT/VF (n = 329)	*P* Value	VT/VF Before End of Catheterization (n = 205)	VT/VF Beyond CL (n = 117)	*P* Value
Recurrent ischemic event	228 (4.2)	18 (6.1)	.11	8 (3.9)	10 (8.5)	.08
Atrial fibrillation or flutter	358 (6.6)	39 (12.2)	<.001	16 (7.8)	23 (19.7)	.002
Complete atrioventricular block	70 (1.3)	24 (7.6)	<.001	17 (8.3)	7 (6.0)	.45
Asystole	79 (1.5)	47 (14.6)	<.001	20 (9.8)	27 (23.1)	.001
Pericarditis	67 (1.2)	5 (1.5)	.61	1 (0.5)	4 (3.4)	.06
Cardiac tamponade	17 (0.3)	3 (0.9)	.10	1 (0.5)	2 (1.7)	.30
Acute mitral regurgitation	14 (0.3)	1 (0.3)	.59	0	1 (0.9)	.36
Acute ventricular septal rupture	6 (0.1)	4 (1.2)	.002	3 (1.5)	1 (0.9)	.99
Symptomatic hypotension	433 (8.0)	108 (33.1)	<.001	58 (28.3)	50 (42.7)	.008
Renal failure	80 (1.5)	23 (7.0)	<.001	6 (2.9)	17 (14.5)	<.001
Bleeding, moderate to severe[b]	259 (4.8)	41 (12.7)	<.001	22 (10.8)	19 (16.2)	.11

Abbreviations: CL, catheterization laboratory; VT/VF, ventricular tachycardia or fibrillation.
[a] No. (%) represent patients with no missing information for these events.
[b] Severe bleeding was defined as intracranial bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment. Moderate bleeding was defined as bleeding that resulted in need for transfusion.

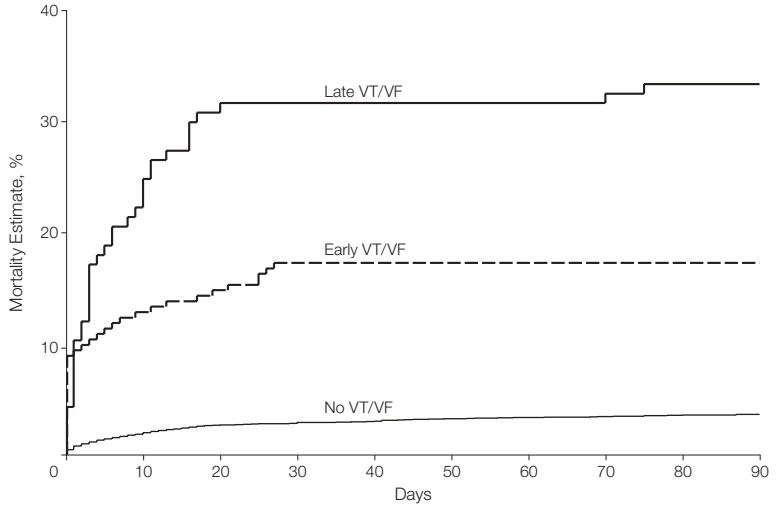
Table 4. Clinical Outcomes[a]

Outcomes	No. (%)			No. (%)		
	No VT/VF (n = 5416)	VT/VF (n = 329)	*P* Value	VT/VF Before End of Catheterization (n = 205)	VT/VF Beyond CL (n = 117)	*P* Value
Death						
At 30 d	155 (2.9)	74 (22.5)	<.001	35 (17.1)	37 (31.6)	.003
At 90 d	195 (3.6)	76 (23.2)	<.001	35 (17.2)	39 (33.3)	.001
Cause of death among patients who died						
Sudden cardiac death	80 (36.2)	30 (39.0)	.67	16 (44.4)	14 (35.9)	.45
Nonsudden cardiac death	86 (38.9)	40 (51.9)	.05	16 (44.4)	22 (56.4)	.08
Cardiogenic shock						
At 30 d	133 (2.5)	60 (18.2)	<.001	25 (12.2)	35 (29.9)	<.001
At 90 d	133 (2.5)	60 (18.2)	<.001	25 (12.2)	35 (29.9)	<.001
CHF						
At 30 d	207 (3.8)	23 (7.0)	.004	6 (2.9)	17 (14.5)	<.001
At 90 d	250 (4.6)	25 (7.6)	.01	6 (2.9)	19 (16.2)	<.001
Recurrent MI at 90 d	140 (2.6)	16 (4.9)	.01	7 (3.4)	9 (7.7)	.09
Stroke at 90 d	63 (1.2)	10 (3.0)	.008	3 (1.5)	7 (6.0)	.04
Bleeding at 14 d						
Moderate[b]	227 (4.2)	43 (10.3)	<.001	19 (9.4)	13 (11.7)	.52
Severe[b]	32 (0.6)	9 (3.0)	<.001	3 (1.6)	6 (5.8)	.07
Renal failure at 14 d	80 (1.5)	23 (7.0)	<.001	6 (2.9)	17 (14.5)	<.001
Death and/or MI at 90 d	317 (5.9)	83 (25.4)	<.001	40 (19.7)	41 (35.0)	.002
Death, shock, or CHF						
At 30 d	412 (7.6)	110 (33.4)	<.001	52 (25.4)	56 (47.9)	<.001
At 90 d	474 (8.8)	112 (34.3)	<.001	52 (25.6)	58 (49.6)	<.001

Abbreviations: CHF, congestive heart failure; CL, catheterization laboratory; MI, myocardial infarction; VT/VF, ventricular tachycardia or fibrillation.
[a] No. (%) represent patients with no missing information for these outcomes.
[b] Severe bleeding was defined as intracranial bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment. Moderate bleeding was defined as bleeding that resulted in need for transfusion.

It is noteworthy that although the majority of patients with VT/VF who died did so of a cardiac cause, sudden cardiac death was responsible for less than 50% of mortality in these patients. Additionally, this study identified important clinical correlates of VT/VF (and of the composite of VT/VF and sudden cardiac death) in patients presenting for primary PCI and suggested that these may be different based on the timing of the occurrence of this arrhythmia. Our investigation also demonstrated that postprocedural TIMI flow grade 3 and complete ST resolution (≥70%) were associated with very low incidence of late VT/VF, whereas lack of procedural success was associated with a significantly higher risk of this event. Furthermore, approximately 90% of patients presenting for primary PCI had 3 or fewer risk factors for late VT/VF. The incidence of late VT/VF in these patients was very low (1.4%). Finally, our study indicated that for all

Figure 2. Ninety-Day Mortality



No. at risk										
Late VT/VF	117	91	81	80	80	80	80	80	78	76
Early VT/VF	203	177	173	168	168	168	168	168	168	163
No VT/VF	5405	5307	5264	5254	5245	5231	5224	5219	5212	5119

During the 90-day period, the total numbers of deaths were 39 for the late VT/VF category, 35 for early VT/VF, and 195 for no VT/VF. Log-rank $P < .001$ for comparisons between no VT/VF and early VT/VF, no VT/VF and late VT/VF, and early VT/VF and late VT/VF. VT/VF indicates ventricular tachycardia or fibrillation.

patients with STEMI taken to the cardiac catheterization with the intent of performing primary PCI, the incidence and clinical correlates of VT/VF were similar whether patients received primary PCI or not. Similarly, factors associated with any VT/VF were also related to higher risk of the composite of any VT/VF or sudden death.

Few prior studies have evaluated VT/VF among patients undergoing PCI for acute MI.[7,14-16] The Primary Angioplasty in Myocardial Infarction (PAMI) investigators evaluated pooled data on more than 3000 patients from various PAMI investigations and found a 4.3% incidence of VT/VF in patients undergoing primary PCI.[7] However, mortality at 1 year did not differ significantly among patients with and without this arrhythmia. The authors concluded that VT/VF occurring in the cardiac catheterization laboratory did not influence in-hospital or 1-year outcomes when treated promptly. It is important to point out that mortality at 1 year in patients with VT/VF was significantly lower in PAMI (4.5%) compared with that observed at 90 days in our study (23.2%), suggesting that very low-risk patients were enrolled in PAMI trials. These investigators identified several of the same variables as important correlates of VT/VF in patients undergoing primary PCI as in the current study: lack of β-blockers in emergency department (odds ratio [OR], 2.34; 95% CI, 1.35-4.07), right coronary as infarct-related artery (OR, 1.93; 95% CI, 1.25-2.99), time from symptom onset to emergency department arrival less than 180 minutes (OR, 2.63; 95% CI, 1.42-4.89), and initial TIMI flow grade 0 (OR, 2.06; 95% CI, 1.23-3.47) as important correlates of VT/VF in patients undergoing primary PCI. They also identified current smoking as an additional risk factor for VT/VF (OR, 1.95; 95% CI, 1.26-3.02; model *c* index, 0.72).

Similarly, Piccini et al[14] studied more than 9000 patients with acute MI undergoing PCI within 24 hours of symptom onset from the self-reported New York State Coronary Angioplasty Reporting System database. They described the incidence of early VT/VF (ie, that occurring before PCI) to be 5.2% in these patients. Mortality for the cohort with VT/VF was 4.4-fold higher compared with those without this arrhythmia (16.3% vs 3.7%). Although successful PCI was associated with lower risk of death in patients who had VT/VF compared with those who had VT/VF but unsuccessful procedures, mortality in this cohort remained higher than that seen among patients with no VT/VF and successful PCI. They identified cardiogenic shock (OR, 4.10; 95% CI, 3.20-5.58), heart failure (OR, 2.86; 95% CI, 2.24-3.67), chronic kidney disease (OR, 2.58; 95% CI, 1.27-5.23), and early presentation (<6 hours from symptom onset; OR, 1.46; 95% CI, 1.18-1.81) to be independently associated with an increased risk of early VT/VF. In contrast, history of hypertension (OR, 0.81; 95% CI, 0.65-1.00), left circumflex as infarct artery (OR, 0.80; 95% CI, 0.65-0.99), diabetes mellitus (OR, 0.57; 95% CI, 0.42-0.78), and higher left ventricular ejection fraction (every 5% increment; OR, 0.93; 95% CI, 0.91-0.96) were found to correlate with a

Table 5. Clinical Correlates of VT/VF

Clinical Correlates of VT/VF	Wald χ^2	HR (95% CI)
At Any Time		
Creatinine clearance, mL/min[a]	23.40	0.89 (0.85-0.93)
Killip class II-IV vs I	20.72	1.95 (1.46-2.61)
Total baseline ST deviation when <20 mm[b]	42.00	1.50 (1.33-1.70)
Baseline heart rate when >70/min[a]	8.41	1.10 (1.03-1.17)
Baseline SBP, mm Hg[a]	19.95	0.90 (0.86-0.94)
Weight, kg[a]	11.32	1.16 (1.06-1.26)
Inferior MI vs other	11.37	1.50 (1.19-1.90)
c Index	0.71	
Before End of Catheterization		
Creatinine clearance, mL/min[a]	16.01	0.88 (0.83-0.94)
Killip class II-IV vs I	10.57	1.88 (1.29-2.76)
Total baseline ST deviation when <20 mm[b]	16.49	1.39 (1.19-1.63)
Baseline heart rate when >70/min[a]	5.09	1.10 (1.01-1.20)
Baseline SBP, mm Hg[a]	7.76	0.92 (0.87-0.98)
Preprocedural TIMI flow grade 0 vs TIMI flow grade 1 or higher	25.32	2.94 (1.93-4.47)
Weight, kg[a]	6.72	1.16 (1.04-1.29)
Inferior MI vs other	23.79	2.16 (1.58-2.93)
Time from symptom to randomization, h	3.06	0.91 (0.81-1.01)
c Index	0.75	
Beyond Catheterization Laboratory		
Total baseline ST deviation when <20 mm[b]	9.74	1.43 (1.14-1.79)
Baseline heart rate when >70/min[a]	10.94	1.20 (1.08-1.33)
Baseline SBP, mm Hg[a]	15.82	0.83 (0.76-0.91)
Preprocedural TIMI flow grade 0 vs TIMI flow grade 1 or higher	6.74	2.12 (1.20-3.75)
Postprocedural TIMI flow less than grade 3 vs TIMI flow grade 3	7.57	2.09 (1.24-3.52)
β-Blocker <24 h	6.70	0.52 (0.32-0.85)
ST resolution <70% early[c]	0.01	1.04 (0.54-1.97)
ST resolution <70% late[c]	11.01	3.17 (1.60-6.28)
c Index	0.74	

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure; TIMI, thrombolysis in MI; VT/VF, ventricular tachycardia or fibrillation.
[a] Increment of 10 units.
[b] Increment of 5 units.
[c] Influence of ST resolution less than 70% on VT/VF is modeled with 2 pieces (early influence, 0-24 hours, and late influence, >24 hours) within each time interval. Total baseline ST-segment deviation demonstrated 2 separate slopes with a knot at 20 mm. Hence, it was entered in the model as a continuous variable <20 mm and also as a continuous variable ≥20 mm.

lower risk of this arrhythmia (no model *c* index provided).

Majidi et al[15] performed continuous Holter monitoring on patients with anterior STEMI who had TIMI flow grade 3 following primary PCI. They demonstrated that almost all patients (99%) had ventricular arrhythmias, the majority of which were single premature beats, and most of these ventricular arrhythmias (72%) occurred within 20 minutes of reperfusion. Subjects with bursts (defined as >3 ventricular ectopic beats) had higher absolute peak ST segments and more frequent worsening of ST elevation immediately after reperfusion. Furthermore, these investigators showed that these bursts correlated with larger infarct size on SPECT (single-photon emission computed tomography) imaging and lower left ventricular ejection fraction among patients with anterior STEMI with post–primary PCI TIMI flow grade 3 and ST resolution greater than 50%.[16]

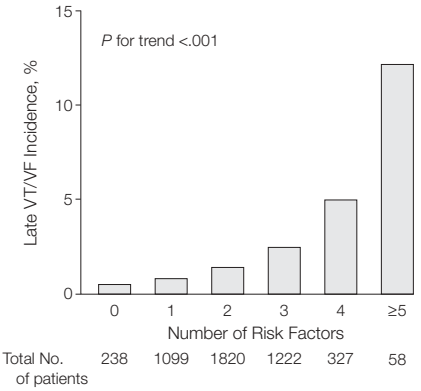
Differences in the patient populations as well as the time of the VT/VF occurrence being evaluated may explain differences observed between the present and prior studies. As highlighted earlier, a major difference between our study and PAMI was that the PAMI study focused only on VT/VF occurring in the cardiac catheterization laboratory.[7] The Piccini study included data from nearly 10 years ago and included patients with any acute MI undergoing PCI, both STEMI and non-STEMI, and only VT/VF occurring before the PCI was reported. Finally, Majidi et al[15,16] focused on a subset of patients, ie, those with anterior STEMI with TIMI flow grade 3 after primary PCI. Additionally, they defined bursts of ventricular arrhythmias as greater than 3 beats as opposed to our definition of "sustained VT/VF." In contrast with all these studies, data from APEX AMI are contemporary and include information on not only early but also late VT/VF on the largest cohort of patients undergoing primary PCI to date, allowing evaluation of the differences in the clinical correlates and outcomes of VT/VF occurring during these 2 time periods.

In contrast to limited data on VT/VF in patients undergoing primary PCI, multiple studies have evaluated the clinical significance and outcomes of VT/VF in STEMI patients receiving fibrinolysis.[1-6,15-21] The incidence of VT/VF in the largest study to examine this issue was 10.2%.[6] In spite of differences in the patient population and the method of reperfusion, VT/VF in patients receiving fibrinolysis was associated with similar adverse prognosis and was related to an increased risk of not only in-hospital mortality but also higher mortality at 1 year. Earlier studies comparing fibrinolysis with placebo suggested that the incidence of VT/VF was reduced with fibrinolytic therapy compared with placebo.[5,20] Whether primary PCI results in further reduction in the incidence of VT/VF compared with fibrinolysis remains uncertain.

Limitations

Our study is retrospective and subject to missing information. Particularly, left ventriculography was not routinely performed during the primary PCI procedures by many investigators in APEX AMI, especially those outside North America. Thus, information on

Figure 3. Incidence of Late VT/VF for All Patients According to Number of Risk Factors



Number of risk factors for late VT/VF and incidence of late VT/VF in 4764 of 5745 patients, excluding patients with early VT/VF (n=205), those for whom timing of VT/VF was unknown (n=7), those who did not survive beyond cardiac catheterization (n=8), and those for whom data were missing (n=761). VT/VF indicates ventricular tachycardia or fibrillation.

Table 6. Clinical Correlates of the Composite of VT/VF and Sudden Death

Clinical Correlates of VT/VF	Wald χ^2	HR (95% CI)
At Any Time		
Creatinine clearance, mL/min[a]	46.29	0.86 (0.83-0.90)
Killip class II-IV vs I	44.26	2.32 (1.81-2.97)
Total baseline ST deviation when <20 mm[b]	38.44	1.41 (1.26-1.57)
Baseline heart rate when >70/min[a]	15.77	1.11 (1.06-1.18)
Baseline SBP, mm Hg[a]	14.74	0.92 (0.89-0.96)
Weight, kg[a]	9.92	1.13 (1.05-1.22)
Inferior MI vs other	7.62	1.35 (1.09-1.67)
c Index	0.71	
Beyond Catheterization Laboratory		
Creatinine clearance, mL/min[a]	20.08	0.86 (0.81-0.92)
Killip class II-IV vs I	7.97	1.86 (1.21-2.86)
Total baseline ST deviation when <20 mm[b]	7.63	1.30 (1.07-1.56)
Baseline heart rate when >70/min[a]	15.11	1.20 (1.09-1.31)
Baseline SBP, mm Hg[a]	8.35	0.90 (0.84-0.97)
Preprocedural TIMI flow grade 0 vs TIMI flow grade 1 or higher	7.13	1.82 (1.17-2.82)
Postprocedural TIMI flow less than grade 3 vs TIMI flow grade 3	8.41	1.93 (1.24-3.01)
β-Blocker <24 h	4.95	0.61 (0.40-0.94)
No. of diseased coronary arteries, 2/3 vs 0/1	4.40	1.49 (1.03-2.15)
c Index	0.76	

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure; TIMI, thrombolysis in MI; VT/VF, ventricular tachycardia or fibrillation.
[a] Increment of 10 units.
[b] Increment of 5 units. Total baseline ST-segment deviation demonstrated 2 separate slopes with a knot at 20 mm. Hence, it was entered in the model as a continuous variable <20 mm and also as a continuous variable ≥20 mm.

left ventricular ejection fraction was missing for many patients. Nonetheless, when we ran the models to include only those patients who had left ventricular ejection fraction measurements, the risk factors for VT/VF did not change and left ventricular ejection fraction was not independently associated with the risk of VT/VF. This is not surprising given the colinearity between ejection fraction and other predictive variables in the model such as Killip class, creatinine clearance, TIMI flow before and after PCI, and ST resolution. These data were derived from a randomized clinical trial and subject to selection bias inherent in the inclusion of patients in clinical trials. Although we internally validated our models using bootstrapping, we were unable to validate our findings in other independent data sets of patients undergoing primary PCI for lack of information similar to that collected in our study. Moreover, splitting our own sample into test and validation data sets was limited by the modest number of events in our sample. Thus, our findings need to be confirmed in future studies. Only the occurrence of first VT/VF was captured in APEX AMI, precluding us from gauging the prognostic significance of recurrence of this arrhythmia. We are unable to gauge the effect of specific antiarrhythmic therapy on outcomes in patients with VT/VF. Because the current analysis is post hoc, the results should be interpreted with caution.

Clinical Implications

Our study, along with the few investigations described earlier, provides insight into the prognostic significance and risk factors associated with VT/VF in STEMI patients presenting for primary PCI. Whether strategies such as improving postprocedural TIMI flow grade 3 and ST resolution[22-24] and using preprocedural β-blockers[25] may help minimize VT/VF and improve outcomes of patients undergoing primary PCI requires evaluation by future investigations.

Our analysis identified patients who may benefit from closer surveillance in the intensive care or telemetry unit after the procedure because of the risk for late VT/VF (particularly those with postprocedural TIMI flow <grade 3 and ST resolution <70%, or those with ≥4 risk factors for late VT/VF). In contrast, because of very low risk for late VT/VF in patients with complete reperfusion (postprocedural TIMI flow grade 3 and complete ST resolution, or those with ≤3 risk factors), our findings suggest that close monitoring for late VT/VF may not be necessary and these patients may be candidates for early discharge. Because currently the majority of patients with STEMI worldwide are routinely monitored for longer than 72 hours, our findings have the potential to decrease resource use without compromising patient safety when a risk-based strategy of monitoring or early discharge is followed. However, this finding also needs confirmation in future studies.

CONCLUSIONS

In this study, occurrence of VT/VF before or after cardiac catheterization in patients presenting for primary PCI was associated with increased 90-day mortality. Our findings provide new insight into the incidence and timing of VT/VF in patients presenting for primary PCI and identify a high-risk subset (particularly those with TIMI flow <grade 3 and ST resolution <70%, or those with ≥4 risk factors) of patients who may require close continuous surveillance in the intensive care or telemetry unit.

Author Contributions: Dr Granger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mehta, Lopes, Granger.
Acquisition of data: Armstrong, Widimsky, Granger.
Analysis and interpretation of data: Mehta, Starr, Lopes, Hochman, Widimsky, Pieper, Armstrong, Granger.
Drafting of the manuscript: Mehta, Lopes, Hochman, Widimsky, Armstrong, Granger.
Critical revision of the manuscript for important intellectual content: Mehta, Starr, Lopes, Hochman, Widimsky, Pieper, Armstrong, Granger.
Statistical analysis: Mehta, Starr, Lopes, Pieper, Granger.
Obtained funding: Armstrong, Granger.
Administrative, technical, or material support: Mehta, Hochman, Armstrong, Granger.
Study supervision: Mehta, Pieper, Armstrong, Granger.
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