

# Relationship Between Early and Late Nonsustained Ventricular Tachycardia and Cardiovascular Death in Patients With Acute Coronary Syndrome in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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**Background**—Nonsustained ventricular tachycardia (NSVT) is common after acute coronary syndrome (ACS) and a marker of increased risk of arrhythmogenic death. However, the prognostic significance of NSVT when evaluated with other contemporary risk markers and at later time points after ACS remains uncertain.

**Methods and Results**—In the Platelet Inhibition and Patient Outcomes (PLATO) trial, continuous ECGs were performed during the first 7 days after ACS (n=2866) and repeated for another 7 days at day 30 (n=1991). Median follow-up was 1 year. There was a time-varying interaction between NSVT and cardiovascular death such that NSVT was significantly associated with increased risk within the first 30 days after randomization (22/999 [2.2%] versus 16/1825 [0.9%]; adjusted hazard ratio, 2.84; 95% confidence interval, 1.39–5.79;  $P=0.004$ ) but not after 30 days (28/929 [3.0%] versus 42/1734 [2.4%];  $P=0.71$ ). Detection of NSVT during the convalescent phase (n=428/1991; 21.5%) was also associated with an increased risk of cardiovascular death, and was most marked within the first 2 months after detection (1.9% versus 0.3%; adjusted hazard ratio, 5.48; 95% confidence interval, 1.07–28.20;  $P=0.01$ ), and then decreasing over time such that the relationship was no longer significant by  $\approx 5$  months after ACS.

**Conclusions**—NSVT occurred frequently during the acute and convalescent phases of ACS. The risk of cardiovascular death associated with NSVT was the greatest during the first 30 days after presentation; however, patients with NSVT detected during the convalescent phase were also at a significantly increased risk of cardiovascular death that persisted for an additional several months after the index event.

**Clinical Trial Registration**—<http://www.clinicaltrials.gov>. Unique identifier: NCT00391872.

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**Key Words:** acute coronary syndrome ■ cardiovascular death ■ electrocardiography ■ sudden cardiac death ■ tachycardia, ventricular

Ventricular arrhythmias are common in patients with acute coronary syndrome (ACS) and are a marker of electric instability that identifies subjects at increased risk of arrhythmogenic death.<sup>1–4</sup> Previous studies primarily investigated the association between sustained ventricular tachycardia (VT) and mortality; however, the majority of these studies were conducted before the advent of rapid revascularization and contemporary pharmacological therapy.<sup>1,2,5</sup> The incidence of ventricular arrhythmias during the days and weeks after ACS and the relationship between the timing of VT after hospital admission and prognosis remain uncertain as extended continuous ECG (cECG) monitoring is not typically performed.

One contemporary study found a relationship between non-sustained VT (NSVT) and sudden cardiac death (SCD) after non-ST-segment-elevation ACS (NSTEMI).<sup>6</sup> However, the current clinical implications of NSVT across the spectrum of ACS from unstable angina to ST-segment-elevation myocardial infarction (STEMI), along with the incidence and the relationship between NSVT and cardiovascular outcomes during the convalescent phase after ACS, are not well described.

The Platelet Inhibition and Patient Outcomes (PLATO) trial randomized patients across the spectrum of ACS to either the novel antiplatelet agent ticagrelor or clopidogrel for the prevention of vascular events and death. The

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### WHAT IS KNOWN

- Ventricular arrhythmias are common in patients with acute coronary syndrome (ACS) and are a marker of electric instability that identifies subjects at increased risk of arrhythmogenic death.
- The current clinical implications of nonsustained ventricular tachycardia across the spectrum of ACS from unstable angina to ST-segment–elevation myocardial infarction, along with the incidence and the relationship between nonsustained ventricular tachycardia and cardiovascular outcomes during the convalescent phase after ACS, are not well described.

### WHAT THE STUDY ADDS

- The occurrence of nonsustained ventricular tachycardia on extended continuous ECG recordings after ACS was independently associated with an increased risk of cardiovascular death.
- In the acute phase, the risk of cardiovascular death was the greatest during the first 4 weeks after ACS. The presence of nonsustained ventricular tachycardia 30 days after ACS, during the convalescent phase, identified additional patients at extended risk of cardiovascular death that persisted several months after the index event.
- These observations in a broad ACS population have important implications for the timing of risk stratification and provide relevant clinical data when considering the appropriate strategies for identifying vulnerable individuals with persistent substrate for ventricular arrhythmia after ACS.

objective of this analysis was to evaluate the incidence and prognostic implications of NSVT in a cohort of patients in the PLATO trial.

## Methods

### Study Design

The details of the PLATO study design ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), NCT00391872) have been published previously.<sup>7,8</sup> The study included a broad range of patients with ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours, and who were hospitalized for either ST-segment–elevation ACS planned for primary percutaneous coronary intervention or NSTEMI/ACS with moderate to high risk. Treatment with ticagrelor or clopidogrel was continued for  $\leq 1$  year, with a median follow-up of 277 days. This study was approved by the appropriate national and institutional regulatory authorities, and all participants provided written informed consent.

### cECG Assessment

cECG recordings (digital, 3-lead recording on a memory chip; Lifecard CF, DelMar Reynolds/Spacelabs Healthcare, Issaquah, WA) were initiated in 2866 patients at or shortly after the administration of first dose of study drug and continued for  $\leq 7$  days after randomization (week 1 assessment). A second cECG assessment was performed in 1991 of these patients at day 30 after randomization (day 30 assessment), lasting  $\leq 7$  days. The cECG assessment was part of a safety analysis to compare the incidence of ventricular pauses and clinical bradycardia events between ticagrelor and clopidogrel.<sup>9</sup>

All cECG recordings were analyzed at the Thrombolysis in Myocardial Infarction (TIMI) Electrocardiographic Core Laboratory (Boston, MA). Arrhythmias were identified using a commercially available arrhythmia software program (Pathfinder, Spacelabs Healthcare, Snoqualmie, WA) that uses a combined automated and interactive detection technique. NSVT was defined as at least 4 consecutive ventricular ectopic beats  $>100$  beats per minute.<sup>6</sup> Sustained VT events ( $>30$  s) were excluded. All other ventricular ectopic beats and none were defined as no NSVT.

### End Points

The primary clinical end point was cardiovascular death. Cardiovascular death was defined as death from cardiovascular causes or cerebrovascular causes and any death without clear documented nonvascular cause. Cardiovascular causes were also further subclassified, including a category of SCD.<sup>10</sup> All events were adjudicated by a Clinical Events Committee blinded to treatment allocation.

### Statistical Analysis

All arrhythmia analyses were based on patients with evaluable cECG data. A total of 2866 patients were included in the cECG analysis at week 1, and 1991 of these patients were included at 1 month. Cardiovascular death is presented as Kaplan–Meier failure rates at 30 days and 12 months. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with a Cox proportional hazards regression model adjusted for TIMI risk score, previous MI, previous heart failure, and estimated creatinine clearance (Cockcroft–Gault). Left ventricular ejection fraction (LVEF) was recorded by the local investigator in 791 patients (27.6%). N-terminal pro–brain natriuretic peptide (NT-proBNP) was collected in 2714 patients (94.7%). NT-proBNP was determined with sandwich immunoassays on the Cobas Analytics e601 and c501 Immunoanalyzer (Roche Diagnostics) according to the instructions of the manufacturer. When examining the relationship between NSVT detected at 30 days and cardiovascular death, we found that NSVT violated the proportional hazard assumption, indicating that the relationship between NSVT and cardiovascular death changed over time. NSVT detected on the 30-day cECG monitoring was, therefore, re-evaluated using piece-wise constant time-varying coefficient model to examine the change in the associated relative risk of cardiovascular death and 30-day NSVT between days 30 and 360. The analyses were done with R (<http://www.R-project.org/>) and SAS software (Statistical Analysis System, SAS Institute Inc, Cary, NC). All analyses were performed independent of the sponsor by the TIMI study group.

## Results

The median duration of cECG monitoring was 6.2 days at week 1 (acute phase) after randomization and 6.8 days at 30 days (convalescent phase).

### Week 1 (Acute Phase) cECG Assessment

Ventricular arrhythmias detected on cECG during the acute phase after ACS were frequent. Overall, 1023 patients (35.7%) experienced at least 1 episode of NSVT. Baseline characteristics of patients included in the cECG assessment according to whether they did or did not experience NSVT are presented in Table. Overall, there were no significant differences between groups in terms of age, history of heart failure, history of MI, the use of statin, or randomization groups. Individuals who had NSVT at week 1 were more likely to be men, be a current smoker, and have undergone revascularization during the index hospitalization. NSVT was more common in patients presenting with STEMI ( $n=436/856$ ; 50.9%) than in those presenting with NSTEMI/ACS ( $n=563/1935$ ; 29.1%). Individuals who had NSVT were also less likely to be on  $\beta$ -blocker or

**Table. Baseline Characteristics of All Patients in Platelet Inhibition and Patient Outcomes Trial Continuous ECG Assessment**

Characteristics	No NSVT, n=1843	NSVT, n=1023	P Value
Age, y	62.9±11.5	63.2±11.4	0.55
Weight, kg	80.6±17.1	81.9±16.0	0.01
Men, %	70.1	79.9	<0.0001
Smoker, %	33.4	40.0	0.001
Hypertension, %	64.8	59.8	0.01
Dyslipidemia, %	51.3	47.2	0.04
Diabetes mellitus, %	26.5	21.9	0.01
History of congestive heart failure, %	5.1	6.5	0.13
History of myocardial infarction, %	21.6	21.8	0.90
Index diagnosis, %			
UA	17.8	10.2	<0.0001
NSTEMI	56.7	44.9	
STEMI	22.8	42.6	
Other index event	2.7	2.4	
Medications, %			
β-Blocker	81.3	75.7	0.0004
Statin	79.9	79.1	0.62
ACEI/ARB	64.6	58.5	0.001
Revascularization during index hospitalization	62.2	69.7	<0.0001
Ejection fraction, %			
≤40%	3.4	5.1	0.06*;
>40%	24.3	22.5	0.02†
Missing	72.4	72.4	
Randomization groups, %			
Ticagrelor	50.5	50.8	0.87
Clopidogrel	49.5	49.2	

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; NSTEMI, non-ST-segment-elevation myocardial infarction; NSVT, nonsustained ventricular tachycardia; STEMI, ST-segment-elevation myocardial infarction; and UA, unstable angina.

\*All ejection fraction data including missing data.

†All ejection fraction data excluding missing data.

angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy. Of the portion of patients with LVEF measurements, only 114 patients (14.4%) had EF ≤40%.

### Baseline NSVT and Cardiovascular Death

Patients with NSVT detected on cECG recording during the acute phase were at significantly increased risk of cardiovascular death compared with patients with no NSVT, even after adjusting for baseline clinical risk characteristics. There was, however, a time-varying interaction between NSVT and cardiovascular death such that the risk was significantly elevated within the first 30 days after randomization (2.2% versus 0.9%; HR<sub>adj</sub>, 2.84; 95% CI, 1.39–5.79; *P*=0.004) but was not present when using a landmark analysis that began at day 30 after randomization (3.0% versus 2.4%; HR<sub>adj</sub>, 1.11; 95% CI, 0.63–1.84; *P*=0.71; Figure 1). When NT-proBNP was added to the clinical model, the corresponding risk associated

with NSVT remained present during the first 30 days after randomization (HR<sub>adj</sub>, 2.68; 95% CI, 1.28–5.58; *P*=0.008). Of the 108 cardiovascular deaths in this cohort, 41 (38%) were classified as acute MI, 8 (7%) were classified as heart failure or cardiogenic shock, and 25 (23%) were classified as SCDs. NSVT during the acute phase was not significantly associated with SCD (1.1% versus 0.8%; HR<sub>adj</sub>, 1.09; 95% CI, 0.45–2.63; *P*=0.86).

### Risk of Baseline NSVT in Different Subgroups

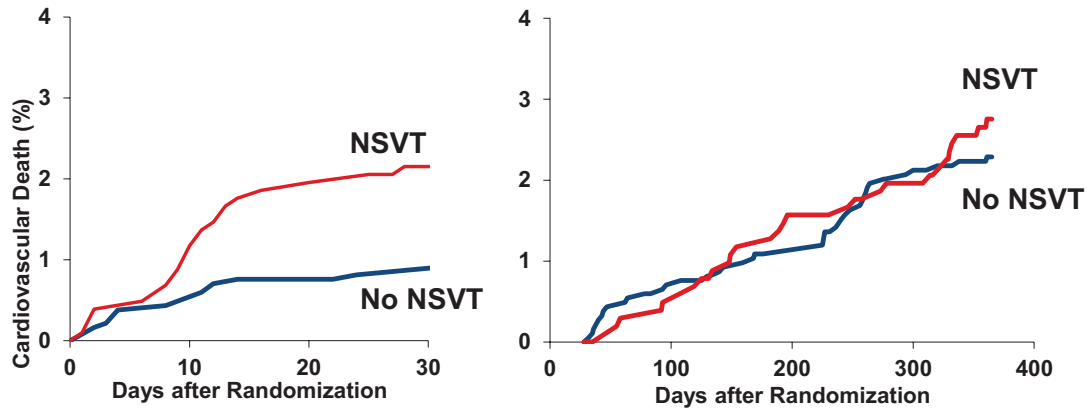
The risk of cardiovascular death in the first 30 days after randomization was assessed in various subgroups, including by index diagnosis, randomization allocation, ejection fraction, levels of NT-proBNP, history of previous MI, the use of β-blocker, and whether revascularization was performed during the index event. Overall, the absolute incidence of NSVT and cardiovascular death was higher in patients who would be considered at the highest risk, such as individuals who presented with STEMI, with depressed LVEF (≤40%), and with elevated NT-proBNP level (NT-proBNP≥median). However, the relationship between NSVT and cardiovascular death was similar in both the high- and low-risk populations (Figure 2). Even among the low-risk groups (eg, presented with unstable angina/non-STEMI, NT-proBNP≤median, and no previous history of MI), the presence of NSVT was associated with an increased risk of cardiovascular death.

### Timing of NSVT at Presentation

The association of NSVT and the risk of cardiovascular death varied in relation to the timing of the ventricular arrhythmia. Compared with patients with no NSVT, patients with NSVT occurring within 48 hours of admission did not have an increased risk of cardiovascular death (3.4% versus 3.5%; HR, 0.98; 95% CI, 0.24–4.0; *P*=0.97); however, the risk of cardiovascular death was significantly higher when NSVT occurred >48 hours after admission (6.5% versus 3.5%; HR, 1.87; 95% CI, 1.09–3.20; *P*=0.02; Figure 3).

### NSVT at 30 Days (Convalescent Phase)

On the 30-day cECG collected during the convalescent phase after ACS, a total 428 patients (21.5%) experienced at least 1 episode of NSVT (Table I in the Data Supplement). Similar to the baseline data, NSVT was more common in patients with an initial presentation of STEMI (n=146/591; 24.7%) compared with patients presenting NSTEACS (n=222/1078; 20.6%). During this convalescent phase, patients who experienced at least 1 episode of NSVT at 30 days were at significantly increased risk of cardiovascular death, and the associated risk was attenuated over time (Figure 4). The elevated risk of cardiovascular death associated with NSVT was the highest within the 2 months after detection at day 30 (day 30–90: 1.9% versus 0.3%; HR<sub>adj</sub>, 5.48; 95% CI, 1.07–28.20; *P*=0.01) but then decreased over time such that the relationship between NSVT and cardiovascular death was no longer significant by ≈5 months after the index ACS event (day 90–150: 2.6% versus 0.5%; HR<sub>adj</sub>, 4.84; 95% CI, 1.60–14.64 and day 150–210: 2.8% versus 0.9%; HR<sub>adj</sub>, 2.02; 95% CI, 0.64–6.43; Figure 4).



**Figure 1.** Risk of cardiovascular death in patients with nonsustained ventricular tachycardia (NSVT) within the first 7 days after randomization for acute coronary syndrome. Kaplan–Meier estimates from days 0 to 30 (**left**; 2.2% vs 0.9%; adjusted hazard ratio [HR<sub>adj</sub>], 2.84; 95% confidence interval [CI], 1.39–5.79; *P*=0.004) and from day 30 to 1 year (**right**; 2.8% vs 2.3%; HR<sub>adj</sub>, 1.08; 95% CI, 0.63–1.84; *P*=0.79).

**Prevalence of NSVT at Baseline and at 30 Days and Cardiovascular Death**

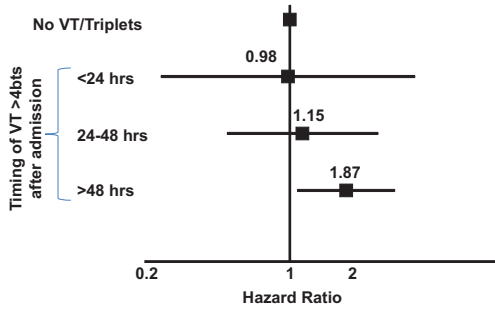
After ACS, nearly half of the patients had at least 1 episode of NSVT recorded during either the acute phase or the convalescent phase (46.1%). These were predominantly incidental isolated asymptomatic findings on the cECG monitors and were not associated with clinically evident events. Of those who had data in both phases (n=1949; Figure 5), a total of 24.5% (n=478) of patients had NSVT during the acute phase but not during the convalescent phase, compared with 9.9% (n=192) who had NSVT during the convalescent phase but not during the acute phase. Approximately 11.8% (n=229) had NSVT both during the acute and the convalescent phase, and it was these patients who had the highest rates of cardiovascular death.

**Discussion**

In this study of ≈3000 patients admitted with ACS who underwent extensive cECG monitoring, NSVT was commonly detected in both the acute and convalescent phases of ACS and was significantly associated with an increased risk of cardiovascular death. In both settings, the greatest risk of cardiovascular death was temporally closest to the detection of NSVT, although the relative time frames differed. In the immediate post-ACS phase, the highest risk of cardiovascular death associated with NSVT was in the first 30 days, whereas in the convalescent phase, the risk of death associated with NSVT remained elevated for ≈5 months, precisely during the time when there are few therapies directed to minimize the consequences of arrhythmias. These observations in a broad

Subgroup	Cardiovascular Death		
	No NSVT (%)	NSVT (%)	HR (95%CI)
UA/NSTEMI	0.6	1.6	3.26 (1.18 - 9.03)
STEMI	1.7	2.8	1.96 (0.71 - 5.38)
Ticagrelor	1.1	1.7	2.24 (0.76 - 6.59)
Clopidogrel	0.9	3.0	3.36 (1.25 - 9.00)
EF≤40%	1.6	1.9	1.39 (0.05 -36.60)
EF>50%	0.5	1.7	2.45 (0.40 -15.18)
NT-proBNP ≤median	0.2	1.4	5.85 (1.18 -29.10)
NT-proBNP>median	1.4	2.6	2.24 (0.96 - 5.23)
No prior MI	0.8	2.3	2.76 (1.28 - 5.99)
Prior MI	1.0	1.8	2.68 (0.41 -17.64)
B-Blocker	1.2	1.6	2.88 (0.54 -15.44)
No B-blocker	0.8	2.3	2.96 (1.34 - 6.54)
Revascularization	1.2	3.9	5.50 (1.82 -16.63)
No Revascularization	0.7	1.4	1.84 (0.70-4.86)

**Figure 2.** Risk of cardiovascular death in the first 30 days after admission in patients with nonsustained ventricular tachycardia (NSVT) in various subgroups. CI indicates confidence interval; EF, ejection fraction; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; NT-proBNP, N-terminal pro–brain natriuretic peptide; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.



**Figure 3.** Risk of cardiovascular death according to the time of last nonsustained ventricular tachycardia (NSVT) in relation to hospital admission.

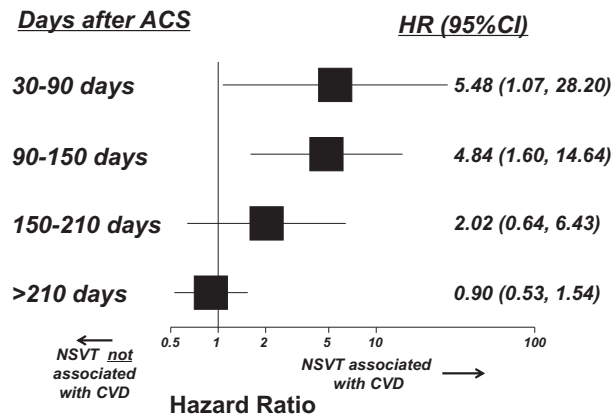
ACS population provide relevant clinical data when considering the appropriate strategies and therapies for identifying vulnerable individuals with persistent substrate for ventricular arrhythmia after ACS and serve as the basis for future studies to reduce this risk.

Previous studies of patients with STEMI offer conflicting conclusions on the relationship between VT and adverse cardiovascular events, with some demonstrating an independent relationship between VT and cardiovascular events,<sup>1,5,11,12</sup> whereas others did not find VT to be an independent prognostic indicator of subsequent adverse events.<sup>4,13</sup> In a pooled analysis of >26 000 patients with NSTEACS, Al-Khatib et al<sup>14</sup> demonstrated that sustained VT and ventricular fibrillation were independently associated with increased 30-day and 6-month mortality, but the relationship between NSVT and outcomes was not examined. Mäkikallio et al<sup>15</sup> performed an observational study of 2130 patients with STEMI and non-STEMI and found that NSVT was associated with SCD; however, the cECG recordings only lasted for 24 hours and were performed ≤4 weeks after the index event. A study of >6300 patients with NSTEACS from the Metabolic Efficiency With Ranolazine

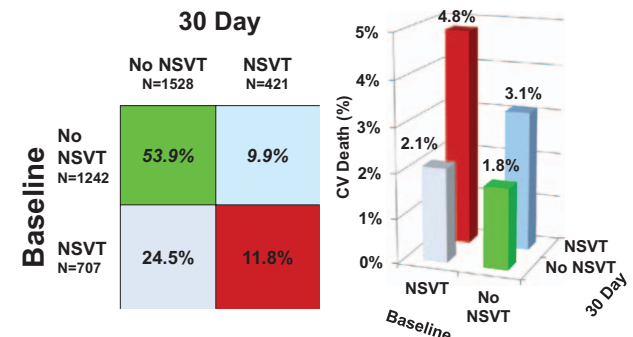
for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome (MERLIN)-TIMI 36 trial demonstrated an independent association between NSVT detected within the first 7 days of presentation and SCD.<sup>6</sup> This study differs from previous studies because it includes the entire spectrum of ACS, incorporates contemporary markers of risk stratification, such as NT-proBNP, and obtained 1-week cECG assessments in the acute phase of ACS, as well as follow-up assessments in over two thirds of these patients at 30 days.

The observation that the greatest risk of cardiovascular death is during the first 30 days after ACS, and attenuated thereafter, has important implications for the timing of potential therapeutic interventions during this vulnerable period. However, to date, there are no specific therapies proven to reduce arrhythmic death with the exception of revascularization and β-blockers.<sup>16</sup> Neither antiarrhythmic therapy<sup>17-19</sup> nor implantable cardioverter defibrillators<sup>20,21</sup> have demonstrated any improvement in mortality in the acute ACS scenario, despite the fact that mortality rate is the highest in the early post-MI period. The current approach for patients with NSVT and moderate to severe LV dysfunction (EF≤40%) is to perform an electrophysiological study to help improve risk stratification and guide decision making for implantable cardioverter defibrillator implantation.<sup>22</sup> However, the prognostic significance and recommended approach in patients with NSVT and mildly reduced or preserved EF remain unclear.

Moreover, the observation that only NSVT occurring >48 hours after hospital admission was associated with an increased risk of cardiovascular death further challenges current guidelines that do not recommend ECG monitoring beyond 24 to 48 hours of hospitalization. Although early NSVT (within the first week post ACS) predicts early mortality, it is the subacute NSVTs (occurring after 48 hours) that are most prognostic of adverse cardiovascular events. Many of the episodes of NSVT detected during the 7 days of cECG would have been missed by current standards of practice. Extending the use of cECG >1 week after the presentation of ACS could identify patients at higher risk, especially those presenting with STEMI, and thus improve risk stratification. The extended cECG recordings in the PLATO trial were done as investigational safety assessments and were not used in real time to guide clinical care, during either the early acute phase, convalescent phase, or longer term from 30 days to 1 year after the ACS event.



**Figure 4.** Time-varying effects of 30-day nonsustained ventricular tachycardia (NSVT) on cardiovascular death. Model was adjusted for Thrombolysis in Myocardial Infarction (TIMI) risk score, previous myocardial infarction, previous heart failure, creatinine clearance, and revascularization during index hospitalization. Overall *P* value of 0.013 indicates at least 1-log hazard ratio (HR; β-coefficient) across the intervals is significantly different from 0. ACS indicates acute coronary syndrome; and CI, confidence interval.



**Figure 5.** Prevalence of nonsustained ventricular tachycardia (NSVT) at baseline and 30 days and associated risk of cardiovascular (CV) death.

### Risk Associated With NSVT in Specific Subgroups

Risk stratification according to high-risk features has always been important in identifying patients at the greatest likelihood of cardiovascular events. Overall, Figure 2 demonstrates that there was a nominally increased risk of death associated with NSVT observed in all of the various subgroups. Although the PLATO trial demonstrated that, in patients with ACS, treatment with ticagrelor when compared with clopidogrel significantly reduced the rate of death from vascular causes, MI, or stroke,<sup>7</sup> the presence of NSVT was associated with an increased risk of cardiovascular death regardless of the treatment arms. Not surprisingly, the absolute incidence of cardiovascular death was higher in patients who would be considered at the highest risk (eg, individuals who presented with STEMI, with elevated NT-proBNP level, and with depressed LVEF). Of note, the relative risk of NSVT was in fact higher in patients with low NT-proBNP levels. This might indicate that in the low-risk population (NT-proBNP levels  $\leq$  median), the presence of NSVT might serve as an important predictor of increased risk of cardiovascular events. On the other hand, in high-risk patients with elevated BNP levels, the effect of NSVT might be attenuated because of the presence of other comorbidities. It is important to note that the majority of episodes of SCD in the community setting actually occur in patients with low to intermediate risk factors, in individuals without known risk factors, and in patients with normal left ventricular function. The highest risk subgroups actually constitute only a small proportion of the total number of deaths annually.<sup>23</sup> Therefore, the prevalence of NSVT in lower risk individuals might serve as an important prognostic tool to identify individuals at increased likelihood of adverse cardiovascular events who might otherwise not be targeted as high risk.

### 30-Day cECG Assessment and Outcomes

Few studies have performed extensive follow-up cECG monitoring in the weeks after ACS. Surprisingly, NSVT was frequently detected during the convalescent phase cECG recordings (22% of patients). Patients with either recurrent or new NSVT were at substantially increased risk of cardiovascular death, in particular in the first 4 months after detection. The relatively high incidence of NSVT 1 month after ACS and the associated risk of death provide relevant clinical observation when considering the appropriate strategies to identify vulnerable individuals with persistent substrate for ventricular arrhythmia after ACS. These are predominantly isolated asymptomatic NSVT episodes recorded on 1-week cECG monitors, without associated clinical events. Further studies are needed to assess whether the presence of NSVT during these periods post ACS could add incremental prognostic value when used in conjunction with other noninvasive markers of arrhythmic substrate, such as T-wave alternans, heart rate turbulence, and assessment of inducible VT during the electrophysiological study to improve risk stratification of patients at risk of SCD. Moreover, the use of additional risk stratification should be tailored according to existing data, such as left ventricular function. Most cases of post-ACS death occur in patients with only mildly reduced or normal left ventricular function, and it is this population in whom better risk stratifications tools are most needed.

### Limitations

Because of the nature of the PLATO trial as a study of antiplatelet therapy, the primary end point was cardiovascular death rather than SCD. Of the 108 adjudicated cardiovascular deaths in this study cohort, there were only 25 events adjudicated as SCD; thus, data for this particular end point were underpowered. Although the presence of NSVT after ACS was associated with a significantly increased risk of cardiovascular death, it is important to note that the event rate is relatively low. As in all outcome studies without implanted long-term monitors, we are unable to determine the number of deaths that were caused by a lethal arrhythmia. LVEF, which is the most common risk stratification metric for SCD, was only available for a portion of the patients. If this was available in the majority of patients, addition to the clinical model could have attenuated the prognostic effect of NSVT. Patients with NSVT were more likely to have undergone revascularization during the index hospitalization, which, if anything, would have biased the results toward a null relationship. Patients with NSVT were less likely to be on  $\beta$ -blocker during the index hospitalization. This difference could have in part affected the prevalence of NSVT during the acute phase after ACS and the associated risk of cardiovascular death seen between the 2 groups. However, the relationship between NSVT and cardiovascular death was similar regardless of baseline  $\beta$ -blocker use (Figure 2). We did not assess episodes of ventricular ectopic beats lasting  $<4$  beats, longer runs of ventricular ectopic beats at a rate of  $<100$  beats per minute, or the frequency of ventricular ectopy, which limits the ability to examine the overall burden of ventricular ectopic beats or the clinical significance of these episodes.

### Conclusions

The occurrence of NSVT on extended cECG recordings was common in the acute and convalescent phases after ACS, in particular in patients with STEMI, and was independently associated with an increased risk of cardiovascular death. In the acute phase, the risk of cardiovascular death was the greatest during the first 4 weeks after ACS. The presence of NSVT 30 days after ACS, during the convalescent phase, identified additional patients at extended risk of cardiovascular death that persisted several months after the index event. These observations in a broad ACS population have important implications for the timing of risk stratification, provide relevant clinical data when considering the appropriate strategies for identifying vulnerable individuals with persistent substrate for ventricular arrhythmia after ACS, and serve as the basis for future studies of potential therapeutic interventions.

### Appendix

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## Relationship Between Early and Late Nonsustained Ventricular Tachycardia and Cardiovascular Death in Patients With Acute Coronary Syndrome in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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## **SUPPLEMENTAL MATERIAL**

**Supplementary Table 1: Baseline Characteristics of Patients at Convalescent Phase (n=1991)**

<b>Characteristics</b>	<b>No NSVT (n=1563)</b>	<b>NSVT≥4 beats (n=428)</b>	<b>P-value</b>
Age (yrs)	62.4 ± 11.3	64.4 ± 11.1	0.001
Weight (kg)	80.6 ± 16.8	83.4 ± 16.1	0.0003
Men (%)	73.5%	77.3%	0.11
Smoker (%)	35.3%	37.9%	0.33
Hypertension (%)	62.1%	66.4%	0.11
Dyslipidemia (%)	50.8%	47.4%	0.22
Diabetes mellitus (%)	24.3%	25.0%	0.75
History of Congestive Heart Failure (%)	4.3%	9.4%	<0.0001
History of Myocardial Infarction (%)	20.9%	27.8%	0.003
<b>Index Diagnosis:</b>			0.12
UA (%)	15.0%	12.9%	
NSTEMI (%)	28.5%	34.1%	
STEMI (%)	54.8%	51.9%	
Other index event (%)	1.7%	1.2%	
<b>Mediations:</b>			
Beta-blockers (%)	80.2%	77.8%	0.27
Statin (%)	79.7%	78.3%	0.51
ACEI/ARB (%)	60.5%	68.2%	0.004
Revascularization during index hospitalization (%)	67.7%	61.7%	0.02
Ejection Fraction <40% (%)	11.7%	24.8%	0.001
<b>Randomization Groups:</b>			0.94
Clopidogrel (%)	50.5%	50.7%	
Ticagrelor (%)	49.5%	49.3%	