Short-Term Variability of the QT Interval Can Be Used for the Prediction of Imminent Ventricular Arrhythmias in Patients With Primary Prophylactic Implantable Cardioverter Defibrillators

Agnieszka Smoczyńska, MD; Vera Loen, MD; David J. Sprenkeler, MD, PhD; Anton E. Tuinenburg, MD, PhD; Henk J. Ritsma van Eck, MD, PhD; Marek Malik, PhD, MD; Georg Schmidt, MD, PhD; Mathias Meine, MD, PhD; Marc A. Vos, PhD

BACKGROUND: Short-term variability of the QT interval (STVQT) has been proposed as a novel electrophysiological marker for the prediction of imminent ventricular arrhythmias in animal models. Our aim is to study whether STVQT can predict imminent ventricular arrhythmias in patients.

METHODS AND RESULTS: In 2331 patients with primary prophylactic implantable cardioverter defibrillators, 24-hour ECG Holter recordings were obtained as part of the EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators) study. ECG Holter recordings showing ventricular arrhythmias of >4 consecutive complexes were selected for the arrhythmic groups (n=170), whereas a control group was randomly selected from the remaining Holter recordings (n=37). STVQT was determined from 31 beats with fiducial segment averaging and calculated as $\sum |D_{n+1} - D_n| / (30 \times \sqrt{2})$, where $D_n$ represents the QT interval. STVQT was determined before the ventricular arrhythmia or 8:00 AM in the control group and between 1:30 and 4:30 AM as baseline. STVQT at baseline was 0.84±0.47 ms and increased to 1.18±0.74 ms ($P<0.05$) before the ventricular arrhythmia, whereas the STVQT in the control group remained unchanged. The arrhythmic patients were divided into three groups based on the severity of the arrhythmia: (1) nonsustained ventricular arrhythmia (n=32), (2) nonsustained ventricular tachycardia (n=134), (3) sustained ventricular tachycardia (n=4). STVQT increased before nonsustained ventricular arrhythmia, nonsustained ventricular tachycardia, and sustained ventricular tachycardia from 0.80±0.43 ms to 1.18±0.78 ms ($P<0.05$), from 0.90±0.49 ms to 1.14±0.70 ms ($P<0.05$), and from 1.05±0.22 ms to 2.33±1.25 ms ($P<0.05$). This rise in STVQT was significantly higher in sustained ventricular tachycardia compared with nonsustained ventricular arrhythmia (+1.28±1.05 ms versus +0.24±0.57 ms [$P<0.05$]) and compared with nonsustained ventricular arrhythmia (+0.34±0.87 ms [$P<0.05$]).

CONCLUSIONS: STVQT increases before imminent ventricular arrhythmias in patients, and the extent of the increase is associated with the severity of the ventricular arrhythmia.

Key Words: short-term variability of repolarization ■ ventricular arrhythmia ■ ventricular tachycardia

T

Treatment of ventricular arrhythmias and prevention of sudden cardiac death (SCD) rapidly evolved in the past century, and innovations continuously contribute to further improvement. Introduction of the implantable cardioverter defibrillator (ICD) reduced the mortality rate in patients with a high risk for SCD.1–3 Nevertheless, SCD remains an important healthcare concern, and research about underlying mechanisms

Correspondence to: Marc A. Vos, PhD, Alexander Numan Building 4th Floor, Yalelaan 50, 3584 CM, Utrecht, The Netherlands. E-mail: m.a.vos@umcutrecht.nl

For Sources of Funding and Disclosures, see page 8.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha
Temporal dispersion of repolarization, quantified as short-term variability (STV), has been identified as a promising marker for arrhythmic risk monitoring. In animal models, STV at baseline discriminated between subjects that developed ventricular arrhythmias or SCD in the long term. Similar results were obtained in patients with acquired or congenital long-QT syndrome, patients with nonischemic heart failure, and patients with structural heart disease, where an elevated STV at baseline was associated with patients with a history of ventricular arrhythmias or the occurrence of ventricular arrhythmias during follow-up. A novel application of STV, being the ability to predict imminent ventricular arrhythmias, has also been studied preclinically. In animal studies, STV increases abruptly before ventricular arrhythmias, whereas it remains stable in the absence of arrhythmic events. Moreover, STV is a suitable parameter to guide preventive therapy to avert the immediate (re)occurrence of ventricular arrhythmias. We aim to investigate whether STV of the QT interval (STV_{QT}) also increases before ventricular arrhythmias in patients and could therefore be used to predict imminent ventricular arrhythmias in a clinical setting.

**METHODS**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Study Design**

The EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators) is a prospective multicenter, observational study. It aims to assess the current clinical value of the ICD in patients with primary prophylaxis and the electrocardiographic parameters at baseline for long-term prediction of all-cause mortality and appropriate ICD shocks. Patients with ischemic and nonischemic cardiomyopathy fulfilling the international treatment guidelines for primary prophylactic ICD implantation were included. The protocol was approved by the institutional review board or ethics committee at each participating hospital and was in compliance with the Declaration of Helsinki. All patients provided written informed consent. A 12-lead Holter ECG (CM 3000-12 BT; Getemed, Teltow, Germany) was recorded at 1 kHz sampling frequency for 24 hours in hospitalized patients before the ICD implantation. Holter recordings showing ventricular arrhythmias of >4 consecutive complexes were selected. A control group was randomly selected from the remaining Holter recordings not fulfilling this criterion.

**Measurement of STV_{QT} and other electrophysiological parameters**

Precordial lead V2 or V3 was selected in each patient based on the morphology of the T-wave. The preordial lead with the highest amplitude and slope at the end of the T-wave was used for the determination of ventricular arrhythmias or SCD in the long term. Similar results were obtained in patients with acquired or congenital long-QT syndrome, patients with nonischemic heart failure, and patients with structural heart disease, where an elevated STV at baseline was associated with patients with a history of ventricular arrhythmias or the occurrence of ventricular arrhythmias during follow-up. A novel application of STV, being the ability to predict imminent ventricular arrhythmias, has also been studied preclinically. In animal studies, STV increases abruptly before ventricular arrhythmias, whereas it remains stable in the absence of arrhythmic events. Moreover, STV is a suitable parameter to guide preventive therapy to avert the immediate (re)occurrence of ventricular arrhythmias. We aim to investigate whether STV of the QT interval (STV_{QT}) also increases before ventricular arrhythmias in patients and could therefore be used to predict imminent ventricular arrhythmias in a clinical setting.

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Description |
|--------------|-------------|
| ∆STV_{QT}    | STV_{QT} before ventricular arrhythmia minus STV_{QT} at baseline |
| EU-CERT-ICD  | European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators |
| nsVA         | nonsustained ventricular arrhythmia |
| nsVT         | nonsustained ventricular tachycardia |
| SCD          | sudden cardiac death |
| STV          | short-term variability |
| STV_{QT}     | short-term variability of the QT interval |
as $\Delta STV_{QT} = STV_{QT}$ of the last 31 complexes before ventricular arrhythmia – $STV_{QT}$ baseline. All electrophysiological parameters were determined at baseline and before the longest ventricular arrhythmia exhibited by a patient or at 8:00 AM in the control group. The latter time point was chosen because the circadian pattern of $STV_{QT}$ shows the highest peak at 8:00 AM, especially in patients with a high burden of ventricular ectopy and nonsustained ventricular tachycardia (nsVT). Baseline measurements were performed at 3:00 AM unless a ventricular arrhythmia occurred, then baseline was determined at a time point at least 1.5 hours away from the ventricular arrhythmia but between 1:30 and 4:30 AM (Figure 1A). In addition to the STV of the final 31 complexes preceding the ventricular arrhythmia, STV was also determined on the 32 to 62 and 63 to 93 prior complexes to follow the behavior of STV before the arrhythmic event (Figure 1B). Ventricular and atrial premature complexes together with the preceding and following post–extrasyostolic beat were excluded from analysis. We used the method of fiducial segment averaging for the measurement of the QT interval and calculation of $STV_{QT}$. First, all complexes were aligned around a trigger point, in this case the R-peak of the QRS complex by cross-correlating each individual complex with the average of the remainder complexes and then shifting the complex until maximum correlation was obtained (Figure 1C). Next, the same alignment process was repeated for the 2 other fiducial points, QRS onset and the end of the T-wave, respectively (Figure 1CII and III). Correct alignment was checked visually and adjusted manually where necessary.

**Statistical Analysis**

Numeric data are expressed as mean±SD unless specified otherwise. One-way analysis of variance (ANOVA) with Tukey correction for multiple comparisons was used for group analyses, and for the comparisons to baseline within a group, 1-way repeated-measures ANOVA with Tukey correction was applied. Group comparisons with both within-subject and between-subject variables were performed with a

![Figure 1. Study methodology.](http://ahajournals.org)
2-way ANOVA with Tukey correction for multiple comparisons. Categorical variables were analyzed with a \( \chi^2 \) test. Calculations were performed using SPSS (version 26; IBM, Armonk, NY) and Prism (version 8.0; GraphPad Software Inc., La Jolla, CA). \( P<0.05 \) was considered as statistically significant.

RESULTS

Study Population

The EU-CERT-ICD study enrolled 2292 patients from May 2014 until August 2018. For this substudy, we screened all the Holter ECG recordings, and 455 patients showed ventricular arrhythmias of >4 consecutive complexes (Figure 2). A total of 285 Holter ECG recordings were excluded from analysis, for example, because of atrial arrhythmias (n=106), excessive noise (n=30), a flat T-wave (n=40), or excessive ectopy resulting in <31 consecutive beats (n=24). The remaining 170 Holter ECG recordings were suitable for analysis. A variety of ventricular arrhythmias occurred in the study population; therefore, the patients were divided into 3 groups based on the severity of the arrhythmia. The first group consisted of short-lasting (<30 seconds) ventricular arrhythmias of <100 beats per minute (bpm) defined as nonsustained ventricular arrhythmia (nsVA) (n=32). The second group showed short-lasting ventricular tachy-arrhythmias of ≥100 bpm defined as nsVT (n=134). The third group were longer lasting (≥30 seconds) ventricular tachy-arrhythmias of ≥100 bpm defined as sustained ventricular tachycardia (VT) (n=4). The control group consisted of 37 patients.

Table 1 shows clinical baseline characteristics of the patients included in the analysis. The VT group was excluded from statistical analysis as a subgroup because of the missing values in an already low number of patients. There were no statistical differences in baseline characteristics between the overall group with ventricular arrhythmias and the control group, nor were there statistical differences between patients with nsVA and nsVT. The mean age of patients with ventricular arrhythmias was 63±11 years and 60±12 years in the control group. The study population was predominantly male, and the majority of the patients had ischemic cardiomyopathy as the leading cardiac disease, with 57% in the overall group with ventricular arrhythmias and 70% in the control group. Medication use was similar in the overall group with ventricular arrhythmias and the control group. In the group with a VT, 33% used β-blockers.

Arrhythmia Characteristics

Ventricular arrhythmias occurred throughout the day, as illustrated in Figure 3. nsVA tended to occur from late afternoon (5:00 PM) until early morning (7:00 AM), whereas nsVTs were distributed throughout the entire day.
day with a peak at 10:00 PM. The VTs occurred in the morning between 6:00 and 7:00 AM, and in the early evening between 5:00 and 7:00 PM. The mean heart rate of all ventricular arrhythmias was 127±30 bpm, 82±12 bpm during nsVA, 136±22 bpm during nsVT, and 177±26 during VT. The duration of ventricular arrhythmias overall was 5±6 seconds, nsVA lasted for 5±4 seconds, nsVT lasted for 4±3 seconds, and VT lasted for 39±2 seconds. The number of complexes during the ventricular arrhythmia was 12±18 in general, nsVA lasted for 8±5 complexes, nsVT lasted for 10±6 complexes, and VT lasted for 116±12 complexes.

**Electrophysiological Parameters**

Table 2 summarizes the electrophysiological parameters at baseline and before the ventricular arrhythmia. At baseline, no significant differences were observed between the groups for the RR, QT, and QTc intervals and STV_QT. Overall, the heart rate before the ventricular arrhythmias was significantly higher than the heart rate...
in baseline, with the exception of patients exhibiting nsVA. The QT and QTc intervals were shorter before nsVT and VT compared with baseline, but were the same before nsVA and their respective baseline values. In the control group there were no differences in the RR, QT, and QTc intervals between 3:00 AM and 8:00 AM.

**STV\textsubscript{QT} Increases Before Ventricular Arrhythmias**

The behavior of STV\textsubscript{QT} before a ventricular arrhythmia compared with baseline is shown in Figure 4. STV\textsubscript{QT} did not change in the control group between 3:00 AM and 8:00 AM, from 0.75±0.23 ms to 0.82±0.26 ms, respectively. STV\textsubscript{QT} increased significantly before nsVA and nsVT, from 0.80±0.43 ms at baseline to 1.18±0.78 ms in the last 31 complexes before nsVA and from 0.90±0.49 ms at baseline to 1.14±0.70 ms in the last 31 complexes before nsVT. The increase in STV\textsubscript{QT} was most pronounced in patients with VT, from 1.05±0.22 ms at baseline to 2.32±1.25 ms in the last 31 complexes before VT. This observation was confirmed by comparing the ∆STV\textsubscript{QT} between the groups, whereby ∆STV\textsubscript{QT} was significantly higher in VT compared with nsVT (+1.28±1.05 ms versus +0.24±0.57 ms), compared with nsVA (+0.34±0.87 ms), and compared with the control group (+0.07±0.18 ms). The STV\textsubscript{QT} increased progressively during the segments preceding the ventricular arrhythmia, as portrayed in Figure 4c. Compared with baseline, STV\textsubscript{QT} was increased in the segment of 62 to 32 beats onward before ventricular

---

**Table 2. Electrophysiological Parameters**

|                | Control, n=37 | Overall VA, n=170 | nsVA, n=32 | nsVT, n=134 | VT, n=4 |
|----------------|---------------|-------------------|------------|-------------|--------|
| **Baseline**   |               |                   |            |             |        |
| RR interval    | 1013±129      | 979±166           | 1009±155   | 972±170     | 972.0±128.6 |
| QT interval    | 441±45        | 427±44            | 426±42     | 427±44      | 412±32  |
| QTc interval   | 439±39        | 446±46            | 424±32     | 432±34      | 414±39  |
| STV\textsubscript{QT} | 0.75±0.23    | 0.84±0.47         | 0.80±0.43  | 0.90±0.49   | 1.05±0.22 |
| **Before VA (last 31 complexes)** | | | | | |
| RR interval    | 967±141       | 929±152*          | 1008±132   | 914±150*‡   | 769±137*‡ |
| QT interval    | 429±51        | 412±49*           | 427±40     | 409±51*     | 384±36*  |
| QTc interval   | 434±42        | 429±43*           | 425±30     | 422±44*     | 415±16   |
| STV\textsubscript{QT} | 0.82±0.26     | 1.16±0.74*,†      | 1.18±0.78*,† | 1.14±0.70*,† | 2.33±1.25*,† |

Data are expressed as mean±SD in milliseconds. nsVA indicates nonsustained ventricular arrhythmia; nsVT, nonsustained ventricular tachycardia; STV\textsubscript{QT}, short-term variability of the QT interval; VA, ventricular arrhythmia; and VT, sustained ventricular tachycardia.

*P<0.05 compared with baseline within the group.
†P<0.05 compared with control group.
‡P<0.05 compared with nsVA.

---

**Figure 4. Behavior of STV\textsubscript{QT} before ventricular arrhythmia.**

A. STV\textsubscript{QT} of the last 31 complexes increases before a ventricular arrhythmia. Data are expressed as mean±SD. B. ∆STV\textsubscript{QT} is higher before VT than nsVA and nsVT. Data are expressed as mean±SD. C. STV\textsubscript{QT} is increased from the segment 62 to 32 complexes before a ventricular arrhythmia and onward. Data are expressed as mean±SEM. *P<0.05 within-group comparison; †P<0.05 between-group comparison. ∆STV\textsubscript{QT} indicates STV\textsubscript{QT} before ventricular arrhythmia minus STV\textsubscript{QT} at baseline; nsVA, nonsustained ventricular arrhythmia; nsVT, nonsustained ventricular tachycardia; STV\textsubscript{QT}, short-term variability of the QT interval; and VT, sustained ventricular tachycardia.
arrhythmia. This translates to approximately 60 to 30 seconds before the ventricular arrhythmia based on the mean heart rate of 65 bpm (RR interval of 929±152; Table 2). STV$_{QT}$ was stable in the segments around 8:00 AM in the control group and continuously lower than the overall group with ventricular arrhythmias.

**DISCUSSION**

The results of the current study in patients with primary prophylactic ICD can be summarized as follows: (1) temporal dispersion of repolarization quantified as STV$_{QT}$ increases before ventricular arrhythmias compared with baseline conditions; (2) in the absence of ventricular arrhythmias, STV$_{QT}$ remains stable between baseline conditions at 3:00 AM and at 8:00 AM; (3) the increase in STV$_{QT}$ progresses during the minutes preceding a ventricular arrhythmia and is significantly higher from the segment of 62 to 32 beats before the ventricular arrhythmia and onward; and (4) STV$_{QT}$ increases more before VT compared with nsVA and nsVT, when it is expressed as $\Delta$STV$_{QT}$.

**Increase in Temporal Dispersion of Repolarization Reflects a Compromised Repolarization Reserve**

To our knowledge, this is the first study showing that an increased temporal dispersion of repolarization, quantified as STV$_{QT}$, precedes the imminent occurrence of ventricular arrhythmias in patients with primary prophylactic ICD. In animal models, the importance of temporal dispersion of repolarization in arrhythmogenesis has been studied extensively.$^{6,12,19}$ Ventricular remodeling attributed to volume overload in the canine model of complete chronic atrioventricular block includes electrical (downregulation of the slowly (I$_{Ks}$) and rapidly (I$_{Kr}$) activating delayed rectifier potassium channels),$^{20}$ contractile (altered calcium handling),$^{21-24}$ and structural remodeling.$^{25}$ Electrical remodeling results in a diminished repolarization reserve, which renders the heart unable to withstand stressors on repolarization.$^{25}$ This repolarization liability manifests itself as a prolongation of repolarization duration and an increased temporal dispersion of repolarization.$^{6,12}$ When repolarization is challenged further by, for example, an I$_{Kr}$-blocking drug, this can act as a final hit on the repolarization reserve.$^{26}$ In combination with the altered calcium handling this gives rise to early afterdepolarizations in vitro$^{22,23}$ and ventricular ectopy and Torsade de Pointes arrhythmias in vivo.$^{12,27}$ These arrhythmias are preceded by an increase in STV, whereas STV remains low in nonsusceptible subjects.$^{12,13}$ Moreover, the severity of the arrhythmic outcome in the chronic atrioventricular block dog is also correlated to the $\Delta$STV, as in this patient population.$^{28}$ The current study suggests that a reduced repolarization reserve and triggered activity play a role in arrhythmogenesis in a broad patient population with both ischemic and nonischemic cardiomyopathy.

**Proarrhythmic Component of STV$_{QT}$ That Is Independent of the QT-Interval Duration**

Although STV$_{QT}$ is based on QT-interval measurements, these parameters show a different circadian rhythm and behave differently before ventricular arrhythmias. The circadian rhythm of the QT interval has a cosine curve with a longer QT interval at night around 3 AM and a shorter QT interval in the afternoon around 2:00 PM.$^{29}$ This has been attributed to diurnal changes in potassium ion channel function.$^{30}$ Similarly, the QT interval of our current study was the longest at baseline, between 1:30 and 4:30 AM. STV$_{QT}$ also exhibits a circadian pattern in patients with a higher burden of ventricular ectopy and nsVT, whereby there is a peak in STV$_{QT}$ at 8:00 AM and 6:00 PM.$^{17}$ These peaks coincide with the circadian distribution of SCD$^{31}$ and are consistent with the occurrence of VT in our study population. It has been hypothesized that the circadian pattern of STV$_{QT}$ relies on the autonomic nervous system.$^{17,32}$ Interestingly, both peaks of STV$_{QT}$ coincide with the maximum slope in the diurnal cosine curve of the QT interval, suggesting that these are 2 different, yet potentially related, parameters.

Moreover, our finding that STV$_{QT}$ increases before ventricular arrhythmias without prolongation of the QT interval contributes to the hypothesis that there is an independent proarrhythmic component responsible for an increase in STV$_{QT}$. The QT interval is a well-known and broadly applied electrophysiological parameter for proarrhythmic assessment. However, preclinical studies in different animal models indicate that STV is superior to the repolarization duration in predicting the development of imminent ventricular arrhythmias and assessing the efficacy of antiarrhythmic interventions.$^{19,33}$ In the chronic atrioventricular block dog model, repolarization duration prolonged upon a challenge of the repolarization irrespective of the arrhythmic outcome, whereas STV only increased in subjects that were susceptible for ventricular arrhythmias.$^{5,12}$

**Clinical Implications**

Preclinical studies have demonstrated that STV can be used to monitor the risk for imminent ventricular arrhythmias and initiate a preventive treatment.$^{14,34}$ This study shows that STV has a similar behavior before ventricular arrhythmias in patients with a primary prophylactic indication for ICD therapy. Currently, patients at risk for ventricular arrhythmias and SCD are implanted with an ICD. Although the ICD can successfully terminate ventricular arrhythmias with anti-tachy
pacing or a defibrillation shock, the ICD is not able yet to prevent the arrhythmias from occurring. The detrimental effects of ventricular arrhythmias and the reduced quality of life as a result of anxiety for shock therapy give cause to seek further improvement of the ICD.\textsuperscript{35} STV can be derived reliably from electrogram signals that are continuously recorded by the ICD.\textsuperscript{13} Therefore, the ICD could be used for continuous monitoring of arrhythmic risk by measuring STV on intracardiac signals. A preventive therapy has also been explored in the chronic atrioventricular block dog model in the form of temporary accelerated pacing, where the pacing rate was gradually increased from 60 to 100 bpm in 20 seconds, and successfully prevented an electrical storm from occurring in 70\% of the cases.\textsuperscript{14} Our study shows that the increase in STV\textsubscript{QT} in patients is present in the segment 60 to 30 seconds before the ventricular arrhythmia, which provides sufficient time to initiate the preventive therapy. To implement this methodology, STV should be determined automatically by the device and the pacing regimen initiated once a certain threshold of STV is reached.

**Strengths and Limitations**

STV determination requires accurate measurement of the QT interval because of the unit of the variation. This requirement was addressed in two ways. First, the 24-hour ECG Holter recordings had a high resolution of 1 kHz. Second, measurement of the QT interval was done with a validated semiautomated program to minimize errors in measurement.\textsuperscript{17}

The present study also has limitations. The number of patients with a VT is limited because ECG Holter recordings were recorded for only 24 hours in patients without a history of VT. The results in the VT group should therefore be interpreted with caution. More patients with VT can be studied when STV is monitored continuously with an implanted device for a longer period of time. It is also evident that STV cannot be measured reliably in patients with an irregular heart rate attributed to, for example, atrial fibrillation. Furthermore, STV measurements are influenced by the quality of the signals; therefore, many patients were excluded because of noise. When the intracardiac electrogram can be used for STV analysis, reasons for exclusion in the current study, such as noise and a flat T-wave, would be minor issues, and approximately three quarters of the patients would be eligible for STV analysis.

**CONCLUSIONS**

This is the first clinical work to demonstrate that STV\textsubscript{QT} increases before imminent ventricular arrhythmias in patients with a primary prophylactic ICD indication and that the extent of the increase is associated with the severity of the ventricular arrhythmia. These data set a precedent that STV\textsubscript{QT} can be used for imminent ventricular arrhythmia risk monitoring.

**ARTICLE INFORMATION**

Received June 27, 2020; accepted October 7, 2020.

**Affiliations**

From the Department of Medical Physiology (A.S., V.L., D.J.S., M.A.V.) and Department of Cardiology (A.E.T., M.Meine), University Medical Center Utrecht, Utrecht, The Netherlands; Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands (H.J.R.v.; National Heart and Lung Institute, Imperial College London, London, United Kingdom (M.Malik); and Medical Klinik und Poliklinik I, Technische Universität München, Klinikum rechts der Isar, München, Germany (G.S.).

**Sources of Funding**

The EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators) has received funding from the European Community’s Seventh Framework Programme FP7/2007-2013 under Grant 602299.

**Disclosures**

None.

**REFERENCES**

1. Connoly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boccor S, Domanski M, Follmann D, et al.; on behalf of the investigators of the AVID, CASH and CIDS studies. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. *J Heart J.* 2000;21:2071–2078.

2. Moss AJ, Hall WJ, Cannon DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL. Wilber D, et al.; for the MADIT Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med.* 1996;335:1933–1940.

3. Zabel M, Willems R, Lubinski A, Bauer A, Brugada J, Conen D, Flevari P, Hasenfuß G, Swetsosak M, Hukuri HV, et al. Clinical effectiveness of primary prevention implantable cardioverter defibrillators: results of the EU-CERT-ICD non-randomised, controlled, multicentre study. *J Heart J.* 2020;41:3437–3447.

4. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation.* 2012;125:620–637.

5. Thomesen MB, Trau M, van Opstal JM, Beckmann HDM, Volders PGA, Stengl M, Vos MA. Sudden cardiac death in dogs with remodelled hearts is associated with larger beat-to-beat variability of repolarization. *Basic Res Cardiol.* 2005;100:279–287.

6. Thomesen MB, Oros A, Schoenmaker M, van Opstal JM, Maas JN, Beckman HDM, Vos MA. Proarrhythmic electrical remodelling is associated with increased beat-to-beat variability of repolarization. *Cardiovasc Res.* 2007;73:521–530.

7. Floré V, Claus P, Antoons G, Oosterhof P, Holemans P, Vos MA, Sipido KR, Willems R. Microvolt T-wave alternans and beat-to-beat variability of repolarization during early postischemic remodeling in a pig heart. *Heart Rhythm.* 2011;8:1050–1057.

8. Hintzersee M, Themsen MB, Beckmann BM, Pfeifer A, Schimpf R, Wichmann HE, Steinbeck G, Vos MA, Kläb S. Beat-to-beat variability of QT intervals is increased in patients with drug-induced long-QT syndrome: a case control pilot study. *Eur Heart J.* 2008;29:185–190.

9. Hintzersee M, Beckmann BM, Themsen MB, Pfeifer A, Pozza RD, Leoff M, Nrt H, Steinbeck G, Vos MA, Kläb S. Relation of increased short-term variability of QT interval to congenital long QT syndrome. *Am J Cardiol.* 2009;103:1244–1248.

10. Hintzersee M, Beckmann BM, Themsen MB, Pfeifer A, Ulbrich M, Sinner MF, Perz S, Wichmann HE, Lengyel C, Schimpf R, et al. Usefulness of short-term variability of QT intervals as a predictor for...
electrical remodeling and proarrrhythmia in patients with nonischemic heart failure. Am J Cardiol. 2010;106:216–220.

11. Oosterhof P, Tereschenko LG, Van der Heyden MAG, Ghanem RN, Fetics BJ, Berger RD, Vos MA. Short-term variability of repolarization predicts ventricular tachycardia and sudden cardiac death in patients with structural heart disease: a comparison with QT variability index. Heart Rhythm. 2011;8:1584–1590.

12. Thomsen MB, Verduyn SC, StengI M, Beekman HDM, de Pater G, van Opstal J, Volders PGA, Vos MA. Increased short-term variability of repolarization predicts d-sotalol-induced Torsade de Pointes in dogs. Circulation. 2004;110:2453–2459.

13. Wijes SC, Sprenkeler DJ, Bossu A, Duninnk A, Beekman HDM, Varkevisser R, Hernandez AA, Meine M, Vos MA. Beat-to-beat variations in activation-recovery interval derived from the right ventricular electrogram can monitor arrhythmic risk under anesthetic and awake conditions in the canine chronic atrioventricular block model. Heart Rhythm. 2018;15:422–448.

14. Wijes SC, Bossu A, Duninnk A, Beekman HDM, Varkevisser R, Hernandez AA, Meine M, Vos MA. Electrophysiological measurements that can explain and guide temporary accelerated pacing to avert (re)occurrence of Torsades de Pointes arrhythmias in the canine chronic atrioventricular block model. Heart Rhythm. 2017;14:749–756.

15. Zabel M, Sticherling C, Willems R, Lubinski A, Bauer A, Bergau L, Braunschweig F, Brugada J, Brusich S, Conen D, et al. for the EU-CERT-ICD Study Investigators. Rationale and design of the EU-CERT-ICD prospective study: comparative effectiveness of prophylactic ICD implantation. J Cardiovasc Electrophysiol. 2011;6:182–193.

16. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Zabel M, Sticherling C, Willems R, Lubinski A, Bauer A, Bergau L, Wijes SC, Bossu A, Dunnink A, Beekman HDM, Varkevisser R, Tattoo M, van den Hoogen GJ, Hoijkens CE, et al. Enhanced susceptibility for acquired torsade de pointes arrhythmias in dogs with chronic complete AV block is related to cardiac hypertrophy and electrical remodeling. Circulation. 1998;98:1125–1135.

17. Bredberg L, Hemmingsson C, Longfellow G, Eriksson M, Willich SN, Edler L, et al. Effect of d-sotalol on the QT interval and the incidence of Torsade de Pointes in dogs with chronic complete atrioventricular block. J Cardiovasc Electrophysiol. 2018;9:1086.

18. Voss MA, Vos MA, Van Veen TAB. Analysis of 24-h rhythm in ventricular repolarization identifies QT diurnality as a novel clinical parameter associated with previous ventricular arrhythmias in heart failure patients. Front Physiol. 2017;8:590.

19. Schroder EA, Burgess DE, Zhang X, Lefta M, Smith JL, Patwardhan A, Bartos DC, Elayi CS, Esser KA, Delise BP. The cardiomyocyte molecular clock regulates the circadian expression of Kcnh2 and contributes to ventricular repolarization. Heart Rhythm. 2015;12:1306–1314.

20. Willich SN, Levy D, Rocco MB, Tobber GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart study population. Am J Cardiol. 1987;60:801–806.

21. Sprenkeler DJ, Beekman HDM, Bossu A, Duninnk A, Vos MA. Proarrhythmic remodeling is associated with increased respiratory and low-frequency oscillations of monophasic action potential duration in the chronic atrioventricular block dog model. J Cardiovasc Electrophysiol. 2019;10:1086.

22. Voss MA, Vos MA, Van Veen TAB. Analysis of 24-h rhythm in ventricular repolarization identifies QT diurnality as a novel clinical parameter associated with previous ventricular arrhythmias in heart failure patients. Front Physiol. 2017;8:590.

23. Schroder EA, Burgess DE, Zhang X, Lefta M, Smith JL, Patwardhan A, Bartos DC, Elayi CS, Esser KA, Delise BP. The cardiomyocyte molecular clock regulates the circadian expression of Kcnh2 and contributes to ventricular repolarization. Heart Rhythm. 2015;12:1306–1314.

24. Willich SN, Levy D, Rocco MB, Tobber GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart study population. Am J Cardiol. 1987;60:801–806.

25. Schroder EA, Burgess DE, Zhang X, Lefta M, Smith JL, Patwardhan A, Bartos DC, Elayi CS, Esser KA, Delise BP. The cardiomyocyte molecular clock regulates the circadian expression of Kcnh2 and contributes to ventricular repolarization. Heart Rhythm. 2015;12:1306–1314.