Appropriate and Inappropriate Ventricular Therapies, Quality of Life, and Mortality Among Primary and Secondary Prevention Implantable Cardioverter Defibrillator Patients

Results From the Pacing Fast VT REduces Shock Therapies (PainFREE Rx II) Trial

Michael O. Sweeney, MD; Mark S. Wathen, MD; Kent Volosin, MD; Ismaile Abdalla, MD; Paul J. DeGroot, MS; Mary F. Otterness, MS; Alice J. Stark, RN, PhD

Background—Implantable cardioverter defibrillators (ICDs) reduce mortality in primary and secondary prevention. Quality of life, mortality, appropriate therapies for specific ventricular rhythms, and inappropriate therapies for supraventricular tachycardia (SVT) were compared among 582 patients (primary prevention=248; secondary prevention=334) in PainFREE Rx II, a 634-patient prospective, randomized study of antitachycardia pacing or shocks for fast ventricular tachycardia (FVT).

Methods and Results—ICDs were programmed identically with 3 zones (ventricular tachycardia [VT] <188 bpm; FVT=188 to 250 bpm; ventricular fibrillation [VF] >250 bpm) but randomized to antitachycardia pacing or shock as initial therapy for FVT. All treated episodes with electrograms were adjudicated. Primary prevention patients had lower ejection fractions and more coronary artery disease. β-Blocker use, antiarrhythmic drug use, and follow-up duration were similar. Over 11±3 months, 1563 treated episodes were classified as VT (n=740), FVT (n=350), VF (n=77), and SVT (n=396). The distribution of VT, FVT, and VF was not different between primary and secondary prevention patients (respectively, VT 52% versus 54%, FVT 35% versus 35%, and VF 14% versus 10%). More secondary prevention patients had appropriate therapies (26% versus 18%, \(P=0.02\)), but among these patients, the median number of episodes per patient was similar. Inappropriate therapies occurred in 15% of both groups and accounted for similar proportions of all detected and treated episodes (46% in primary prevention patients versus 34% in secondary prevention patients, \(P=0.09\)). Quality of life improved modestly in both groups, and mortality was similar.

Conclusions—Primary prevention patients are slightly less likely to have appropriate therapies than secondary prevention patients, but episode density is similar among patients with appropriate therapies. SVT resulted in more than one third of therapies in both groups, but quality of life and mortality were similar. (Circulation. 2005;111:2898-2905.)

Key Words: death, sudden ■ mortality ■ defibrillators, implantable ■ tachycardia, ventricular ■ tachycardia, supraventricular

Implantable cardioverter defibrillators (ICDs) reduce mortality among appropriately selected patients who have survived an episode of life-threatening ventricular arrhythmia (secondary prevention) or who are at risk for ventricular arrhythmia (primary prevention).1-7 An important and unresolved issue is optimal application of ICDs in different patient populations. In general, it has been postulated that secondary prevention patients have a greater frequency of spontaneous ventricular arrhythmia than primary prevention patients; however, relatively little is known about the comparable incidence of appropriate therapies for specific ventricular arrhythmias, susceptibility to inappropriate therapies due to supraventricular tachycardia (SVT), and quality of life (QoL) and mortality outcomes. Although >90% of all episodes of ventricular tachycardia (VT) can be terminated painlessly by antitachycardia pacing (ATP), painful shocks remain a significant problem. A correlation between poor-quality QoL scores and ICD shocks has been shown.8-10
compared appropriate and inappropriate ventricular therapies, QoL, and mortality according to primary or secondary prevention ICD indication in PainFREE Rx II, a prospective, randomized study of ATP or shocks for fast ventricular tachycardia (FVT).11

Methods

Study Design

The study design was a retrospective subgroup analysis derived from the Pacing Fast VT REDuces Shock Therapies (PainFREE Rx II) trial, a prospective, randomized, multicenter study that tested whether empirical ATP is as safe and effective for FVT as shocks and affords a better QoL in a general ICD population.13 Only patients believed unlikely to have substrate for stable monomorphic VT susceptible to pace termination (eg, long-QT syndrome, Brugada syndrome, or hypertrophic cardiomyopathy) were excluded. Six hundred thirty-four patients were randomized at implantation to dual-chamber ICDs. Descrimination was programmed "on" in the VT zone of all dual-chamber ICDs but was left to the discretion of the investigator for discrimination in the FVT zone defined within the ventricular fibrillation (VF) zone (FVT via VF) for a cycle length of 240 to 320 ms (250 to 188 bpm) were used. In the ATP arm, the first therapy in the FVT zone was a single burst of 8 pacing pulses; failed ATP was followed by shock at a DFT of 10 J, then by maximal energy shocks as necessary. In the shock arm, first therapy was a DFT of 10 J followed by maximal energy shocks. A VT zone with a cycle length of 320 to ≥360 ms (≥167 to 188 bpm) was programmed in all patients, and the first therapy was 3 sequences of ATP. VT discrimination was programmed "on" in the VT zone of all dual-chamber ICDs but was left to the discretion of the investigator for single-chamber ICDs.

Definition of Primary and Secondary Prevention

ICD Indications and Specification of Subgroups for Analysis

Primary prevention indication for ICD therapy was defined as (1) coronary artery disease (CAD), nonsustained ventricular tachycardia (EF <40%), and inducible sustained VT/VF; (2) CAD, prior myocardial infarction, and EF <30%; or (3) other (CAD, nonsustained VT, EF ≥40%, and inducible VT/VF). Secondary prevention indication was defined as (1) VF or cardiac arrest without transient or reversible cause; (2) spontaneous sustained VT with structural heart disease; or (3) spontaneous syncopal VT or syncope of unknown etiology and inducible sustained VT/VF.

Of 634 patients randomized, 248 had a primary prevention indication, 334 had a secondary prevention indication, and 52 had a nonstandard indication for ICD therapy. Therefore, 582 patients were the subjects of the present analysis.

Rhythm Classification and Definitions

All spontaneous episodes with stored electrograms that resulted in ventricular therapies were reviewed and classified by the principal investigator at each site and by at least 1 member of an episode review committee that consisted of 5 electrophysiologists. The present analysis was restricted to only adjudicated episodes that resulted in ventricular therapies. True ventricular detections were defined as device-detected VT/VF episodes that were confirmed to be ventricular in origin after adjudication by the episode review committee.

Quality of Life Assessment

Self-reported health-related QoL was measured at baseline and at 12 months with the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) that included 8 subscales and 2 summary measurements.13 SF-36 scores range from 0 to 100, with higher scores representing better QoL. The change in score from baseline to 12 months was compared between ICD-indication groups for each scale.

Statistical Methods

To adjust for multiple episodes per patient, the generalized estimating equations method was used in calculations of detection, therapy delivery, and cycle lengths unless otherwise noted. Baseline QoL and change in QoL over time were compared between randomization groups with a Wilcoxon test. Paired nonparametric exact methods were used to compare the change in QoL over time for each patient. Mortality and shock survival were compared between ICD indication groups by Kaplan-Meier estimation. All tests were performed at the 5% type I error level. The Hochberg method was used to adjust the testing levels for demographic comparisons, to account for multiple comparisons. Statistical analyses were performed with SAS (version 8).

Results

Description of ICD-Indication Groups and Baseline Characteristics

Primary Prevention Indication

The majority of primary prevention patients had CAD, nonsustained VT, EF <40%, and inducible sustained VT/VF (195/248, 79%). Only 17 (7%) of 248 had CAD and EF <30% but no electrophysiology study, because enrollment was largely completed before adoption of the Multicenter Automatic Defibrillator Implantation Trial II indication. A slightly larger subset (36/248, 15%) had CAD, nonsustained VT, and inducible sustained VT/VF but EF ≥40%.

Secondary Prevention Indication

The majority of secondary prevention patients had spontaneous sustained VT (with or without syncope) and EF <40% or syncope, inducible sustained VT/VF, and EF <40% (257/334, 77%). The remaining patients (77/334, 23%) were cardiac arrest survivors.

Primary prevention patients had lower EF and more CAD. Beta-blocker use, antiarrhythmic drug use, and length of follow-up were similar between groups (Table 1).

Spontaneous Ventricular Detections

Among the 3806 spontaneous episodes retrieved from ICD counters that satisfied ventricular detection criteria, 1563 (41%) had complete data that included electrograms and were analyzed. Missing data were due to ICD memory limitations, incomplete interrogation, or cleared memory. The proportion of patients with missing electrograms for spontaneous episodes was similar between primary (13%) and secondary (18%) prevention groups. After generalized estimating equation adjustment for multiple episodes in some patients, there was no difference in the number of missing episodes between primary and secondary prevention groups (22% versus 25%, P = 0.45).

Of the 1563 spontaneous episodes with stored electrograms, 396 (25%, unadjusted) were determined to be inappropriately detected SVT. The remaining 1167 (75%, unad-
justed) episodes were true ventricular arrhythmias that were detected as VT (740 episodes [47%], unadjusted), FVT (350 episodes [22%], unadjusted), and VF (77 episodes [5%], unadjusted).

Among the 191 patients with 1 or more detected VT/VF episodes (median 3, 75th percentile 9, 95th percentile 35, range 1 to 91), we found that 12 (16%) of 73 of the primary prevention patients and 32 (27%) of 118 of the secondary prevention patients had episode counts over the collective 75th percentile ($P$ = 0.09), whereas 1 (1%) of 73 of the primary prevention patients and 7 (6%) of 118 of the secondary prevention patients had episode counts above the collective 95th percentile ($P$ = 0.01). Thus, we found no evidence of a difference in proportion of patients with large episode counts between the 2 indication groups.

**Rhythm Classification by ICD-Indication Group**

The distribution of VT, FVT, and VF was similar between primary and secondary prevention groups (VT 150/315 [52%] versus 590/852 [54%], $P$ = NS; FVT 134/315 [35%] versus 216/852 [35%], $P$ = NS; VF 31/315 [14%] versus 46/852 [10%], $P$ = NS; Figure 1).

**Shocks by Rhythm Classification and ICD-Indication Group**

The rhythm classification of true ventricular detections with stored electrograms that resulted in shocks by ICD-indication group are shown in Figures 2 and 3. The proportion of true ventricular detections that resulted in shocks was similar between primary and secondary prevention groups (40% versus 32%, respectively). The proportion of inappropriate

| TABLE 1. Patient Demographics and Baseline Characteristics of Study Population |
|---------------------------------|-----------------|-----------------|-----------------|----------|
| **Baseline Characteristic**     | **Primary Prevention Group (n=248)** | **Secondary Prevention Group (n=334)** | **All Patients (n=582)** | **P** |
| Age, y                          | 70±10           | 67±11           | 68±11           | <0.01   |
| Male, n (%)                     | 207 (83)        | 253 (76)        | 460 (79)        | 0.02    |
| Cardiac substrate, n (%)*       |                 |                 |                 |         |
| CAD                             | 242 (98)        | 287 (86)        | 529 (91)        | <0.001  |
| Non-CAD                         | 6 (2)           | 47 (14)         | 53 (9)          |         |
| Previous revascularization, n (%)|                 |                 |                 |         |
| CABG*                           | 145 (58)        | 149 (45)        | 294 (51)        | 0.001   |
| PCI                             | 83 (33)         | 113 (34)        | 196 (34)        | NS      |
| Ejection fraction, %*           | 29±10           | 33±13           | 31±12           | <0.001  |
| NYHA class, n (%)               |                 |                 |                 |         |
| I                               | 18 (7)          | 30 (9)          | 48 (8)          | NS      |
| II–III*                         | 145 (58)        | 153 (46)        | 298 (51)        | <0.01   |
| IV                              | 1 (0)           | 8 (2)           | 9 (2)           | NS      |
| Prior SVT, n (%)                |                 |                 |                 |         |
| Atrial fibrillation             | 69 (28)         | 70 (21)         | 139 (24)        | NS      |
| Atrial tachycardia              | 6 (2)           | 2 (1)           | 8 (1)           | NS      |
| Other SVT                       | 16 (6)          | 9 (3)           | 25 (4)          | 0.04    |
| Spontaneous ventricular arrhythmia, n (%) | 0                      | 156 (47)             | 156 (27)             | <0.001  |
| SMVT*                           | 0               | 81 (24)         | 81 (14)         | <0.001  |
| PMVT/VF*                        | 0               | 156 (47)        | 156 (27)        | <0.001  |
| Cardiac medications, n (%)      |                 |                 |                 |         |
| β-Blockers                      | 154 (62)        | 197 (59)        | 351 (60)        | NS      |
| Calcium channel blockers        | 1 (0)           | 2 (1)           | 3 (1)           | NS      |
| Digoxin                         | 91 (37)         | 92 (28)         | 183 (32)        | 0.02    |
| Amiodarone                      | 30 (12)         | 66 (20)         | 96 (16)         | 0.02    |
| Sotalol                         | 9 (4)           | 10 (3)          | 19 (3)          | NS      |
| Class I antiarrhythmics         | 2 (1)           | 6 (2)           | 8 (1)           | NS      |
| ICD system, n (%)               |                 |                 |                 |         |
| Single chamber                  | 59 (24)         | 90 (27)         | 149 (26)        | NS      |
| Dual chamber                    | 189 (76)        | 244 (73)        | 433 (74)        |         |
| Follow-up, mo                   | 11±3            | 11±3            | 11±3            | NS      |

 PCI indicates percutaneous coronary intervention; NYHA, New York Heart Association; SMVT, sustained monomorphic VT; PMVT, polymorphic VT; and class I antiarrhythmics, procainamide, quinidine, or disopyramide.

*Difference is significantly different after adjustment for multiple comparisons.
ventricular detections due to SVT that resulted in shocks was also similar between primary and secondary prevention groups (44% versus 42%, respectively).

**Cycle Lengths of VT, FVT, and VF by ICD-Indication Group**
After adjustment for multiple episodes per patient, there were no significant differences in cycle lengths of VT, FVT, or VF between groups (Table 2).

**Relative Frequency of Appropriate and Inappropriate Ventricular Therapies by ICD-Indication Group**
The proportion of patients with at least 1 appropriate therapy was slightly higher in the secondary prevention group (Table 3), but among all patients with appropriate therapies, the median number of episodes per patient was similar between groups. Similarly, the proportion of patients with at least 1 episode that resulted in inappropriate therapy was not different. The relative proportion of inappropriate episodes that
resulted in spurious therapy was greater in the primary prevention group, but the difference was not significant.

Relative Frequency of Shocks by ICD-Indication Group

More shocks were delivered in the secondary prevention group (total shocks $n=414$, 1.24 shocks/patient) than in the primary prevention group (total shocks $n=190$, 0.77 shocks/patient); however, the proportion of true and spurious ventricular detections that resulted in shocks was not different (primary 43% versus secondary 38%; Table 4). Similarly, there was no difference between groups in the proportion of patients who received any shocks (appropriate or inappropriate).

Time to First Shock for VT/VF by ICD-Indication Group

The time from enrollment to first appropriate shock was not different between groups, nor was time to first inappropriate shock (Figure 4).

Quality of Life

Baseline or 12-month QoL surveys were missing in 156 (27%) of 582 study patients, including 55 patients who died. QoL was analyzed in the remaining 426 patients who were alive at 12 months (primary prevention 186 [44%] of 426, secondary prevention 240 [56%] of 426). There were no

![Figure 4](http://circ.ahajournals.org/content/download/18579/18579ancybox.pdf)

**Figure 4.** Top, Time to first appropriate shock by ICD indication. Bottom, Time to first inappropriate shock by ICD indication.
significant differences in baseline demographic variables between patients with or without complete QoL data.

There were no significant baseline differences in any of the 10 components of the SF-36 between groups. Both primary and secondary prevention groups experienced a significant improvement in 7 of 10 components of the SF-36 between baseline and 12 months. The improvement in physical and mental health summary scores over 12 months was similar (Figure 5).

**Total Mortality Rates**

There was no difference in total mortality rates between groups. Twenty-two (9%) of the primary prevention patients died, whereas 33 (10%) of the secondary prevention patients died within 12 months of enrollment.

**Modification to ICD Detection Programming**

**Ventricular Detection**

Because ventricular rate and duration thresholds are the primary determinants for recognition of spontaneous tachycardia, these were standardized at enrollment. Modification of detection parameters owing to changing patient conditions could result in reporting bias between comparison groups. Accordingly, changes in detection parameters were tracked during the study. VF and FVT detection parameters were modified in an equivalently small percentage of patients (9% of both primary and secondary prevention patients) during follow-up.

VT detection parameters were modified more frequently in secondary versus primary prevention groups (15% versus 9%, \( P = 0.04 \)). Twenty-two patients (9%) in the primary prevention group had at least 1 change in the VT detection interval during follow-up. Of these, the VT detection interval was decreased in 18 patients (7%) and increased in 9 (4%). Five patients (2%) had both an increase and a decrease. Forty-nine patients (15%) in the secondary group had at least 1 change in VT detection interval. Of these, the VT detection interval was decreased in 29 patients (9%) and increased in 28 (8%). Eight patients (2%) had both an increase and a decrease.

**SVT Discrimination**

There was no difference in single-chamber (24% versus 27%) or dual-chamber (76% versus 73%) ICD systems between primary versus secondary prevention groups, respectively. SVT discrimination was programmed “on” during follow-up in all dual-chamber ICD patients, in compliance with required study programming. SVT discrimination was programmed “on” at the investigator’s discretion in 16% of all single-chamber ICD patients.

**Discussion**

The 3 main findings of the present study are that (1) primary prevention patients are slightly less likely to have appropriate therapies than secondary prevention patients, (2) inappropriate detection of SVTs accounts for more than one third of therapies in both groups, and (3) QoL and mortality are similar between groups. Although primary prevention patients received statistically fewer appropriate therapies for ventricular arrhythmias within the first year of follow-up, the difference was slight (18% versus 26%). Furthermore, among patients in either group with at least 1 appropriate therapy, there was no difference in median number of episodes per patient. The absolute rate of appropriate ventricular therapies was less in primary versus secondary prevention patients, consistent with an analysis of Multicenter InSync RAndomized Clinical Evaluation ICD (MIRACLE ICD).16

The majority of true ventricular episodes in both groups were due to VT and FVT. VF accounted for only \( \approx 12\% \) of total episodes in both groups. There was no difference in the relative frequency of VT, FVT, or VF between primary and secondary prevention groups. Furthermore, there was no difference in cycle lengths of VT, FVT, VF, or SVT between groups. This is notably different from the analysis by Wilkoff et al,16 in which primary prevention patients had a significantly higher percentage of device-classified VF than secondary prevention patients (40% versus 14%). They also showed that the median cycle length of true ventricular rhythms was significantly shorter in primary versus secondary prevention patients (303±53 versus 367±54 ms). There are several possible explanations for these differences. Because an FVT zone was not used in MIRACLE ICD, it is likely that many episodes of potentially pace-terminateable rapid monomorphic VT were detected as VF. Additionally, 44% of patients in the primary prevention group had nonischemic dilated cardiomyopathy and no history of sustained VT or syncope and
hemodynamic collapse.22 primary prevention group could have been hazardous for balanced against the risk of failing to treat unanticipated VT. The zeal for reducing the probability of inappropriate cycle lengths between the primary and secondary prevention groups. The zeal for reducing the probability of inappropriate therapies in ICD patients, including prior history of SVT, atrioventricular conduction status, use of drugs that may slow atrioventricular conduction or suppress SVT, and tachycardia detection and therapy programming. Of these, the latter is probably the most important. Longer VT detection cycle lengths will increase the probability of inappropriate detections due to rapidly conducted SVTs, and the cycle lengths of inappropriately detected SVTs may be different between primary and secondary prevention patients, possibly related to mechanism of SVT.16 Additionally, some studies have reported that the cycle lengths of appropriately detected VT may be longer in secondary than in primary prevention patients16 and that the difference in cycle lengths between appropriately detected VT and inappropriately detected SVT may be greater in primary prevention patients.16,21 One possible interpretation of these data are that rate-based programming to achieve the optimal balance between VT detection and SVT rejection is different between primary and secondary prevention patients. This is not supported by the present study. We observed no difference in detected VT cycle lengths between the primary and secondary prevention groups. The zeal for reducing the probability of inappropriate therapies by eliminating a slow-VT detection zone must be balanced against the risk of failing to treat unanticipated VT. Arbitrarily choosing a shorter VT detection interval in the primary prevention group could have been hazardous for individual patients, because undetected slow VT may result in hemodynamic collapse.22

Inappropriate therapies due to misclassification of rapidly conducted SVTs occurred in 15% of both patient groups and accounted for more than one third of all therapies and ≈40% of all shocks in both groups. Although SVT discrimination was equivalently underutilized in the minority of patients with single-chamber ICDs in both groups, this is consistent with the reported rates of inappropriate therapies in other trials of secondary16,23,24 and primary16,19,21 prevention. These observations emphasize that despite increasingly sophisticated enhancements to single- and dual-chamber ICD systems that rely on rate-based detection, rejection of SVT while maintaining high sensitivity for true ventricular arrhythmias remains elusive.25–27 Because there were fewer patients with appropriate ventricular episodes in the primary prevention group, inappropriate episodes accounted for a higher proportion of all episodes than in the secondary prevention group. A similar pattern was reported by Wilkoff et al.,16 although the difference in proportion of inappropriate episodes between primary and secondary prevention groups was not significantly different in the present study.

This issue is important, because one of the principal limitations of ICD therapy is the discomfort associated with shocks. A direct correlation between poor QoL scores and shocks has been described in ICD trials of primary28 and secondary29,30 prevention; however, none of these studies compared QoL between primary and secondary prevention indication groups. We found no difference in measures of QoL between primary and secondary prevention patients. Similarly modest improvements in QoL occurred in both groups over 12 months. This may reflect the reduction in appropriate shock burden due to ATP, although further investigation is necessary to confirm this hypothesis.

Study Limitations

This was a retrospective (not prospectively defined) subgroup analysis; the study was not originally designed to evaluate differences between ICD-indication groups. Results are thus hypothesis generating rather than confirmatory in nature. Follow-up was only 1 year, perhaps not long enough to validly measure and compare the proportion of patients with appropriately detected episodes by ICD-indication group. The small sample size might account for a failure to detect important differences between groups, particularly for QoL and episode distributions.

Conclusions

Although primary prevention patients are slightly less likely to experience at least 1 appropriate detection, we detected no difference in episode density among primary and secondary prevention patients who experienced at least 1 appropriately detected episode. SVT accounts for more than one third of all therapies in both groups but a higher proportion of total therapies in primary prevention patients. Despite this, QoL improved modestly in both groups, and mortality was similar.

Disclosure

Dr Sweeney has served as a paid consultant to and participated in clinical trials for Medtronic, Inc. Dr Wathen has served as a consultant to Medtronic, Inc., and has conducted research for Medtronic, Guidant, and St. Jude Medical. Dr Volosin has conducted research and given lectures for Medtronic, Guidant, and St. Jude Medical. Mary Otterness, Dr Alice Stark, and Paul DeGroot are employed by Medtronic.

References


Disclosures


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