Defibrillator Versus β-Blockers for Unexplained Death in Thailand (DEBUT)

A Randomized Clinical Trial

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Background—Sudden Unexplained Death Syndrome (SUDS) is the leading cause of death in young, healthy, Southeast Asian men. The role of an implantable cardioverter defibrillator (ICD) for mortality reduction in these patients remains unclear.

Methods and Results—The Defibrillator Versus β-Blockers for Unexplained Death in Thailand (DEBUT) study is a randomized, clinical trial conducted in 2 phases (pilot study followed by the main trial) to compare the annual all-cause mortality rates among SUDS patients treated with β-blockers versus that among those treated with an ICD. A total of 86 patients who were SUDS survivors and probable SUDS survivors were randomized to receive an ICD or propranolol (20 patients were in the pilot study and 66 were in the main trial). The primary end point was death from all causes. The secondary end point was recurrent ventricular tachycardia/ventricular fibrillation (VF) or cardiac arrest. During the 3-year follow-up period of the main trial, there were 4 deaths; all occurred in the β-blocker group ($P=0.02$). Seven subjects in the ICD arm had recurrent VF, and all were effectively treated by the ICD. On the basis of the main trial results, the Data Safety Monitoring Board stopped the study. In total (both from the Pilot study and the main trial), there were 7 deaths (18%) in the β-blocker group and no deaths in the ICD group, but there were a total of 12 ICD patients receiving ICD discharges due to recurrent VF.

Conclusions—ICD treatment provides full protection from death related to primary VF in a SUDS population and is superior to β-blockade treatment. **(*Circulation*. 2003;107:2221-2226.)**

Key Words: fibrillation ■ defibrillators, implantable ■ death, sudden ■ propranolol

The Centers for Disease Control (CDC) observed an unusually high death rate among young male Laotian and Cambodian refugees in the United States after the end of the Vietnam War in 1976.[1] Subsequently, the CDC coined the name Sudden Unexplained Death Syndrome (SUDS) because any unexplained death usually occurred at night during the sleep of an apparently healthy Southeast Asian refugee whose post mortem examination did not reveal the cause of death.[1] SUDS attracted widespread attention in Thailand when 230 young Thai workers died in Singapore between 1982 and 1990.[2] Subsequently, an epidemiological study showed that the condition had been prevalent in Thailand for >50 years, where it had been named "lai tai."[3] A similar condition was described in the Philippines in 1915 as "bangungut"[4] and in Japan in 1959 as "pokkuri".[5,6]

Electrophysiological studies conducted on SUDS survivors uniformly revealed inducible polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).[3] In addition, the majority of these patients had unique ECG abnormalities, namely an ST elevation over the right precordial leads (V_1 to V_3) with a right bundle-branch block (RBBB)–like pattern, similar to that described by Brugada and Brugada[7] and by Antzelevitch et al.[8]

Although SUDS survivors and patients who experience SUDS-like symptoms face an inordinate risk of sudden death, there have been no guidelines developed for effective treatment of the syndrome. It was postulated that an implantable cardioverter defibrillator (ICD) might prevent death in these patients. Thus, the Defibrillator versus β-blocker for Unexplained Death in Thailand (DEBUT) study was developed; it aimed to compare the annual mortality rates among SUDS patients randomized to treatment with β-blockers versus that among those randomized to receive an ICD.

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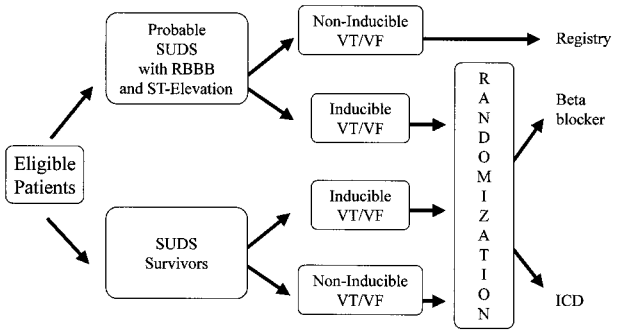

Figure 1. DEBUT study protocol.

Methods

Study Design

The DEBUT study was conducted in two phases. For Phase I, a pilot study was performed between January 1995 and April 1997 to determine the feasibility of conducting a randomized trial. For Phase II, a multicenter, randomized, clinical trial was conducted between May 1997 and December 2000. Study protocols were similar for both the pilot and the main trials.

Study Population

The target population included patients who were either SUDS survivors or probable SUDS patients. A SUDS survivor was defined as a healthy subject without structural heart disease who had survived unexpected VF or cardiac arrest after successful resuscitation. A probable SUDS survivor was defined as a subject without structural heart disease who experienced symptoms indicative of the clinical presentation of SUDS, especially during sleep, including agonal respiration, transient episodes of stress, abnormal respiration associated with grasping and groaning, syncope, or seizure-like symptoms.

All participants signed the informed consent form approved by the Institutional Review Board of the Ministry of Health of Thailand and underwent a complete history and physical examination and cardiac testing, including cardiac catheterization. Eligible patients were free of structural heart disease. However, inclusion criteria for the probable SUDS survivors were ECG abnormalities showing a RBBB-like pattern with ST elevation in the right precordial leads (V_1 to V_3) and inducible VT/VF in the electrophysiology laboratory before randomization (Figure 1). Programmed ventricular stimulation up to 3 extrastimuli and 3 cycle length driving trains (S1S1) were performed, first at the right ventricular apex and then at the right ventricular outflow tract (if VT was not inducible at the apex).

Study Protocol

Eligible patients were randomized to receive either a transvenous ICD (donated by Guidant Corporation, St Paul, Minn) or β-blockade within strata defined by SUDS survivor versus probable SUDS survivor. Patients randomized to β-blockade received long-acting propranolol (40 mg/d to up to 160 mg/d). Other β-blocking agents or amiodarone were permitted if patients developed intolerable side effects with propranolol. Patients could be treated with a β-blocker or amiodarone if frequent shocks from recurrent VF developed.

The primary end point was death from all causes. The secondary end point was recurrent VT/VF or cardiac arrest. All patients were followed after the first month and at 3-month intervals thereafter for a maximum of 3 years after randomization.

Statistical Considerations

For the pilot study, 10 patients were randomized to 1 of the 2 treatment arms. From that data, it was estimated that a total of 114 patients needed to be randomized to 1 of the 2 treatment arms in the main trial. Sample size calculations were based on an expected annual mortality rate of 20% for the SUDS population. Assuming that the annual mortality rate would be reduced 10-fold (ie, to 2%) in the ICD arm, then 57 patients per treatment arm were required to produce the expected difference at 80% power and at the 0.05 2-sided significance level.

For the main trial, 2 interim statistical analyses were proposed. The first interim analysis occurred after half (n=57) of the patients had been randomized; the second analysis occurred after three-fourths of the patients had been randomized. On the basis of the analysis of the primary end point, survival, an O'Brien/Fleming/Harrington stopping rule[9] was used to accommodate multiple looks at the data. The trial was to have been stopped after the first interim look if the probability value associated with the survival analysis was <0.005 and after the second look if the probability value was <0.006. The final statistical analysis was to be conducted at the 0.048 level of significance.

Statistical Analyses

For the intent-to-treat analysis, the randomized groups were compared for differences in baseline characteristics using standard parametric and nonparametric procedures. Factors found to be significantly different between groups were used as covariates in subsequent analyses. The intent-to-treat analysis contrasted mortality rates between the 2 treatment arms and used Kaplan-Meier methods for calculating survival curves, the log-rank method for comparing survival curves, and Cox regression methods for comparing survival curves adjusting for covariates found to be different between treatment arms.

Results

Phase I: Pilot Study

Twenty patients were randomized in the pilot study: 10 to ICD and 10 to β-blockade. One patient in the β-blockade group died before the main trial. There were no differences in any of the baseline or electrophysiological characteristics between the 2 groups (Tables 1 and 2). During follow-up, there were a total of 3 deaths in the β-blocker arm and no deaths in the ICD group ($P=0.07$). Two of the deaths were in SUDS survivors and the other occurred in a probable SUDS survivor. The deaths occurred at 5.4, 11.8, and 24.6 months after randomization. Five patients in the ICD groups had multiple VF episodes, and all were successfully treated by ICD. The first recurrent VF episodes occurred at 3.4, 9.5, 11.6, and 20.7 months.

Phase II: Main Trial

A total of 155 patients were screened for DEBUT, and 66 were randomized, 37 to ICD and 29 to β-blockade therapy (Figure 2). One additional subject was recruited but refused ICD implant after randomization; one subject was randomized at the time the Data Safety Monitoring Board (DSMB) discontinued the trial. The remaining 87 patients were not randomized for the various reasons shown in the Figure 2.

There were no differences in baseline characteristics or index arrhythmic events between patients in the two treatment arms (Table 1). None had structural heart disease.

Although 46 patients had received cardiopulmonary resuscitation (CPR), only 35 patients received defibrillation, with 20 of these having documented VF and 4 having polymorphic VT on the ECG recording. The discrepancy between the number of patients receiving defibrillation and CPR is explained by the fact that many patients lived in remote areas and there is a lack of public ambulatory service in Thailand

TABLE 1. Baseline Characteristics and Index Arrhythmic Events for Pilot Study and DEBUT Trial

	Phase I: Pilot Study			Phase II: DEBUT Trial		
	ICD (n=10)	β-Blocker (n=10)	*P*	ICD (n=37)	β-Blocker (n=29)	*P*
Total No. of subjects randomized	10	10	0.63	37	29	0.43
SUDS survivors	8	6		22	20	
Probable SUDS survivors	2	4		15	9	
Age, y	44±11	48±15	0.63	40±11	40±14	0.95
Female gender, n (%)	0 (0)	0 (0)	...	2 (5)	0 (0)	0.5
NYHA class I, n (%)	10 (100)	10 (100)	...	37 (100)	28 (100)	...
LV ejection fraction, %	67±12	69±6	0.66	66±10	67±7	0.55
RV ejection fraction, %	60±8	58±8	0.76	62±13	60±8	0.60
Approximate time of the index event, n			0.50			0.32
6 AM to noon	0	1		6	10	
Noon to 6 PM	3	4		5	3	
6 PM to midnight	3	3		13	11	
Midnight to 6 am	4	1		12	5	
Unknown	0	0		1	0	
Received CPR	9	6	0.30	26	20	0.92
Received defibrillation	8	5	0.35	17	18	0.17
Symptoms during the index event, n						
Loss of consciousness, intervention	8	6	0.63	26	21	0.85
Loss of consciousness, spontaneous recovery	2	3	0.99	5	4	0.99
Near syncope	0	1	0.99	2	1	0.99
Agonal respiration during sleep	0	0	...	3	3	0.99
Seizure	0	0	...	0	5	0.01
Difficult to arouse with signs of distress	0	0	...	2	4	0.67
Rhythm at time of recording, n			0.10			0.74
VF	7	6		9	11	
VT	0	0		2	2	
Unknown or not documented	0	4		26	16	

Values are mean±SEM or number of patients (percent).

able to reach them in a timely manner. Therefore, ECG documentation of index events was missing in these patients.

The number of patients surviving the episode by receiving CPR without defibrillation may raise the question of whether these patients had true VF episodes. However, spontaneous termination of VF episodes is well known in this patient population; thus, it is entirely possible that these patients experienced such spontaneous termination during CPR.[10]

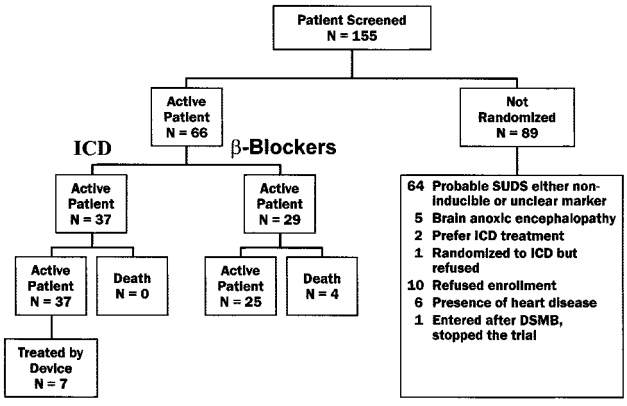

Figure 2. DEBUT study profile.

ECG and Electrophysiological Abnormalities

ECG abnormalities manifesting as RBBB and ST elevation at the precordial lead (V_1 to V_3) were observed in 39 of the 66 patients (59%), 23 in the ICD group (62%) and 16 in the β-blocker group (55%). Fifteen SUDS survivors had RBBB with ST elevation pattern. There were no differences in the ECG intervals, baseline heart rates, conduction intervals, or incidence of induced arrhythmia between the 2 groups (Table 2).

Three-Year Primary and Secondary End Point Analyses

Figure 3 presents the Kaplan-Meier survival curves for both treatment arms. During the 3-year follow-up period, there were a total of 4 deaths, all of which occurred in the β-blocker group (14% versus 0%, $P=0.02$). The annual death rate in this treatment arm was ≈10%, half of that used in the

TABLE 2. Baseline ECG and Electrophysiological Study Findings in Pilot Study and DEBUT Trial

	Phase I: Pilot Study			Phase II: DEBUT Trial		
	ICD (n=10)	β-Blocker (n=10)	*P*	ICD (n=37)	β-Blocker (n=29)	*P*
Heart rate, bpm	67±12	64±7	0.43	64±11	66±12	0.48
PR interval, ms	166±26	169±30	0.84	180±98	163±27	0.48
QRS interval, ms	98±29	92±12	0.60	99±30	95±16	0.43
QT interval, ms	396±51	387±31	0.64	404±43	394±31	0.33
Induced VF (≥300 bpm), n (%)	1 (13)	1 (10)	0.49	8 (22)	8 (30)	0.70
Induced polymorphic VT(≤300 bpm), n (%)	4 (50)	8 (80)		15 (40)	11 (41)	
Noninducible VF/VT, n (%)	3 (37)	1 (10)		14 (38)	8 (30)	
EPS was not done	2	0		0	2	
AH, ms	94±10	94±12	0.93	100±22	96±22	0.58
HV, ms	58±18	54±3	0.55	51±8	49±11	0.47
SAECG performed, n (%)	5	8	0.57	29	21	0.74
Positive	4 (80)	4 (50)		11 (38)	7 (33)	
Negative	1 (20)	4 (50)		18 (62)	14 (67)	

Values are mean±SEM or number of patients (percent). EPS indicates electrophysiological study; AH, atrio-HIS conduction time; HV, HIS-Purkinje conduction time; and SAECG, signal-averaging electrocardiogram.

sample size calculations (20%). Deaths occurred at 1, 12, 15, and 28 months, respectively. The mean (±SEM) survival time was 26.2±1.4 months.

Seven subjects in the ICD arm had recurrent VF, and all were effectively treated by the ICD. First recurrent VF episodes occurred at 1.2 months (n=1), 3 months (n=2), 6 months (n=2), 12 months (n=1), 15 months (n=1), and 18 months (n=1).

Although the primary analysis during the first interim look did not reach a level of statistical significance defined by the stopping rules, the DSMB unanimously recommended termination of the DEBUT trial. The DSMB based their decision on the cumulative weight of all evidence gained from the data supporting the conclusion that ICD therapy is superior to β-blocker treatment. The trial was terminated on December 15, 2000, and all patients from the β-blocker arm were offered ICD treatment free of charge.

VF Episodes and Effects of β-Blockade

Combining the data from the pilot study and the main trial revealed that 4 main trial patients (14%) and 3 pilot patients (30%) experienced sudden death and that all were in the β-blocker treatment group. In contrast, although there were no deaths among ICD patients, a Kaplan-Meier survival curve (Figure 4) of a composite of the primary and secondary end points (sudden death or VF episodes) of the combined pilot and main trial data showed relatively higher event rates in the ICD patients at the annual rate of 20% compared with only a 10% sudden death rate in the β-blocker treatment group. A total of 12 ICD patients, including 7 (19%) from the main trial and 5 (50%) from the pilot study, had multiple VF episodes and defibrillation shocks. Figure 5 shows an example of a patient who had multiple recurrent VF episodes during sleep. Eight of these 12 ICD patients (67%) with frequent defibrillation discharges were treated with propranolol to minimize the frequency of defibrillation discharges. Propranolol prevented recurrent VF episodes in 3 patients and drastically suppressed the VF episodes in 3 patients. The drug failed to substantially suppress VF episodes in 2 patients, thus necessitating amiodarone treatment. The remaining 4 patients (2 in the pilot and 2 in the main trial) did not experience unpleasant symptoms from the shocks (all occurred during sleep) and were not treated with β-blockers. These shocks were well tolerated, although the patients continued to have occasional recurrent episodes of VF.

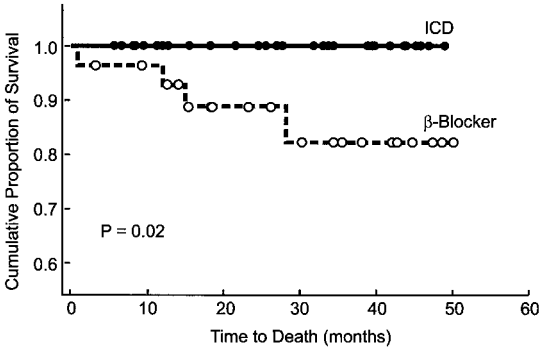

Figure 3. Kaplan-Meier survival curves for the 2 treatment arms. The primary end point was mortality.

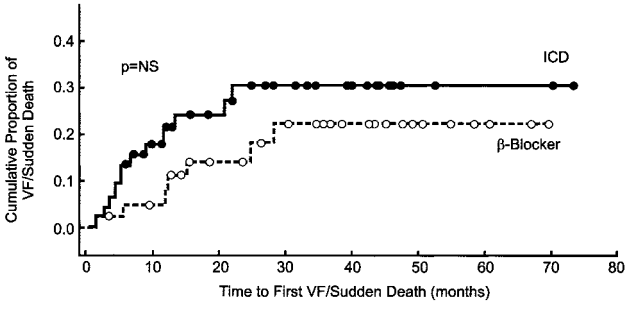

Figure 4. Cumulative proportion of the VF/death occurrence using the composite end points of recurrent VT/VF or cardiac arrest from which the patient was resuscitated or death.

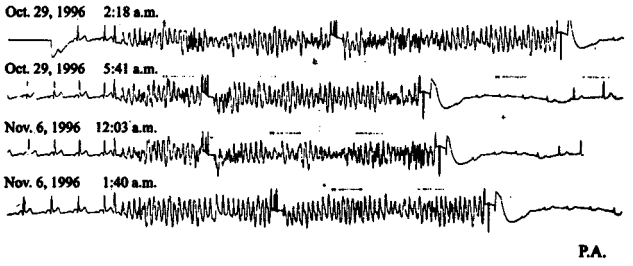

Figure 5. An example of VF episodes retrieved from the shock-E gram of the ICD from one of the SUDS survivors.

ICD Complications

Although there was no operative mortality, unwanted effects of the ICD occurred in 11 of the 37 (30%) ICD-treated patients in the main trial and 2 of the 10 ICD-treated patients (20%) in the pilot study. Most of the complications were minor; they included defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia (n=7 and 1 in the main trial and the pilot, respectively) and T-wave oversensing (3 patients in the main trial). All of the complications were corrected by reprogramming the devices without major intervention. However, 1 patient in the main trial had pocket erosion with infection that required removal of the ICD, and 1 patient in the pilot study needed to have his ICD lead replaced because of an insulation break.

Medication compliance for patients randomized to propranolol was 98%. Only 4 patients (14%) randomized to the β-blocker arm reported side effects; these included impotence/decrease in libido (1 patient), fatigue (1 patient), profound bradycardia (1 patient), and hypotension plus a central nervous system side effect (1 patient). None of the β-blocker patients changed therapy.

Discussion

The data unequivocally showed that the ICD device was effective in terminating VF episodes. Seven of 37 ICD-treated patients (19%) in the main trial and 5 of 10 (50%) in the pilot study had multiple VF episodes that were effectively terminated by the device, and no deaths occurred. In contrast, there was 10% annual mortality in the β-blocker arm of the study (4 deaths in the main trial and 3 deaths in the pilot study).

Although the zero mortality in the ICD group is distinctive, it raises a critical question: does β-blockade increase mortality in SUDS, resulting in a significantly poorer outcome compared with ICD? β-Blockade was chosen because it is the only antiarrhythmic compound with a sudden death reduction benefit and because it is devoid of proarrhythmic activity. However, after the trial commenced, Kasanuki et al[11] showed that short-term β-blockade could enhance VT/VF induction in SUDS patients, and Miyazaki et al[12] showed that isoproterenol could normalize the ECG marker (RBBB pattern with ST elevation in V_1 to V_3). The issue was presented to the DSMB, who recommended continuation of β-blockade.

Although Kasanuki et al[11] cautioned against the use of short-term β-blockade in their patients, our data clearly showed that long-term β-blockade is not contraindicated in SUDS patients. Propranolol has some beneficial effects in preventing VF recurrence, as evidenced by the fact that there was a lower incidence of the composite end points of either death or first VF episode in the β-blocker group versus the ICD group. Indeed, if it was assumed that ICD did not prevent death caused by VF episodes, the annual mortality rate in the ICD patients who were not receiving β-blockade would have been the 20% predicted and used for the sample size calculation compared with the 10% annual mortality in the β-blockade group. Our data also indicate that propranolol is effective in reducing the incidence of recurrent VF and in minimizing the number of defibrillation shocks. Thus, although ICD is superior to β-blockade in preventing deaths, both treatments are effective in reducing VF morbidity and mortality. This observation is one of the unique features of the DEBUT study.

Other unique aspects of the study are primarily that it is the first ICD study involving subjects without structural heart disease and, therefore, the first prospective, randomized trial to show the benefit of ICD in young, otherwise healthy SUDS patients. Second, the study is the first ICD trial with no deaths in the ICD arm. This observation highlights the differences of the DEBUT trial from other important ICD trials, such the Antiarrhythmics versus Implantable Defibrillators (AVID) study,[13] Multicenter Automatic Defibrillator Implantation Trial (MADIT),[14] and Multicenter Unsustained Tachycardia Trial (MUSTT).[15] Although these trials showed that ICD saved lives, there were many deaths in the ICD-treated groups. The main reason for these differences is that the majority of AVID, MADIT, and MUSTT patients had depressed ejection fractions and severe coronary heart disease, mainly with previous myocardial infarction.[13–15] ICD may have been effective in terminating VF in these trials, but nonarrhythmic causes such as ischemia and heart failure were present and may have contributed to death, despite ICD treatment. In the DEBUT study, patients had no contributing factors other than VF, allowing us to conclude that ICD fully prevented death.

However, our study patients may be heterogeneous because their enrollment into the study relied partly on the subjective symptoms of SUDS and did not require ECG documentation of VT/VF. Thus, some of our patients whose symptoms may not be related to ventricular arrhythmias might have a relatively low risk of sudden death. Nevertheless, all patients were selected and randomized based on the classic symptoms of SUDS previously described by the CDC. Therefore, it is extremely unlikely this potential heterogeneity of our study patients could have affected the overall outcome.

The finding also underscores the most important function of the ICD: terminating VF and restoring normal sinus rhythm. In DEBUT, ICD achieved 100% success in rescuing patients from VF. Advances in ICD technology permit a zero operative mortality that can be achieved even in Thailand, where ICD implantation is not common. With even one or two deaths due to surgical complications or device malfunction, the study may have failed to show the superiority of ICD versus β-blockade statistically.

Unwanted effects of ICD, however, did occur in the patients. The most common was inappropriate defibrillation shocks from either T-wave sensing or supraventricular

tachycardia. Insulation break and infection occurred rarely. Side effects seen in the β-blocker group were not common, but there may be concern about long-term drug regimen compliance in these young patients. Although noncompliance was not detected among the β-blockade patients, as evidenced by their lower heart rates, it could not be entirely excluded that noncompliance may have occurred among patients on β-blockade who died.

The SUDS patients had a similar marker as that seen in Brugada syndrome but with one peculiar characteristic: the sudden death or VF episodes usually occurred at night. It is noteworthy that the some Brugada syndrome and SUDS patients are known to have a *SCN5a* sodium channel gene mutation.[16,17] This *SCN5a* gene is also the culprit gene in Long-QT syndrome, which is associated with the highest incidence of sudden cardiac death compared with other long-QT syndrome genotypes. More importantly, most deaths in long-QT 3 also occur at night.[18,19] Whether nighttime VF episodes are part of the electrophysiological abnormality associated with this gene remains unclear and deserves further study.

It is clear, however, that the study patients are similar to those described by the CDC in the 1980s and are best treated with ICD. The findings should also apply to patients with symptomatic Brugada syndrome, in whom ICD should be the first choice of therapy. However, the data do not infer that asymptomatic patients with the Brugada ECG pattern characterized as RBBB and ST elevation in the precordial leads should be treated similarly. Optimal treatment for asymptomatic patients requires further study.

Appendix

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