

Brugada Syndrome Report of the Second Consensus Conference

*Endorsed by the Heart Rhythm Society and the European Heart
Rhythm Association*

Charles Antzelevitch, PhD; Pedro Brugada, MD, PhD; Martin Borggrefe, MD, PhD;
Josep Brugada, MD; Ramon Brugada, MD; Domenico Corrado, MD, PhD; Ihor Gussak, MD, PhD;
Herve LeMarec, MD; Koonlawee Nademane, MD; Andres Ricardo Perez Riera, MD;
Wataru Shimizu, MD, PhD; Eric Schulze-Bahr, MD; Hanno Tan, MD, PhD; Arthur Wilde, MD, PhD

Abstract—Since its introduction as a clinical entity in 1992, the Brugada syndrome has progressed from being a rare disease to one that is second only to automobile accidents as a cause of death among young adults in some countries. Electrocardiographically characterized by a distinct ST-segment elevation in the right precordial leads, the syndrome is associated with a high risk for sudden cardiac death in young and otherwise healthy adults, and less frequently in infants and children. Patients with a spontaneously appearing Brugada ECG have a high risk for sudden arrhythmic death secondary to ventricular tachycardia/fibrillation. The ECG manifestations of Brugada syndrome are often dynamic or concealed and may be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hypo- and hyperkalemia, hypercalcemia, and alcohol and cocaine toxicity. In recent years, an exponential rise in the number of reported cases and a striking proliferation of articles defining the clinical, genetic, cellular, ionic, and molecular aspects of the disease have occurred. The report of the first consensus conference, published in 2002, focused on diagnostic criteria. The present report, which emanated from the second consensus conference held in September 2003, elaborates further on the diagnostic criteria and examines risk stratification schemes and device and pharmacological approaches to therapy on the basis of the available clinical and basic science data. (*Circulation*. 2005; 111:659-670.)

Key Words: arrhythmia ■ death, sudden ■ electrocardiography ■ diagnosis

Since its introduction as a clinical entity in 1992,¹ the Brugada syndrome has attracted great interest because of its high incidence in many parts of the world and its association with high risk for sudden death in young and otherwise healthy adults and, less frequently, in infants and children. In recent years, an exponential rise in the number of reported cases and a striking proliferation of articles defining the clinical, genetic, cellular, ionic, and molecular aspects of the disease have occurred.² A consensus report published in 2002 focused on diagnostic criteria for the syndrome.^{3,4} The present report, emanating from the second consensus conference held in September 2003, elaborates further on the diagnostic criteria and examines risk stratification schemes

and device and pharmacological approaches to therapy. The recommendations herein are based on available clinical and basic science data and should be considered a work in progress that will require modification as additional data from molecular and clinical studies and prospective trials become available.

Clinical Characteristics and Epidemiology

The Brugada syndrome is characterized by an ST-segment elevation in the right precordial ECG leads (so-called type 1 ECG; Figures 1 to 3) and a high incidence of sudden death in patients with structurally normal hearts. The syndrome typically manifests during adulthood, with a mean age of sudden

From the Masonic Medical Research Laboratory, Utica, NY (C.A., R.B.); Cardiovascular Center, Cardiovascular Research and Teaching Institute, Aalst, Belgium (P.B.); University of Heidelberg, University Hospital of Mannheim, Mannheim, Germany (M.B.); Cardiovascular Institute, Clinical Hospital, University of Barcelona, Barcelona, Spain (J.B.); Divisione di Cardiologia, Università di Padova, Padova, Italy (D.C.); eResearch Technology, Inc, Bridgewater, NJ (I.G.); Chu de Nantes, Nantes, France (H.L.); Pacific Rim Electrophysiology Research Institute, Inglewood, Calif (K.N.); ABC's Faculty of Medicine, ABC Foundation, Santo André, São Paulo, Brazil (A.R.P.R.); National Cardiovascular Center, Suita, Japan (W.S.); Department of Cardiology, University of Münster, and Institute for Arteriosclerosis Research, Münster, Germany (E.S.-B.); and Experimental and Molecular Cardiology Group, Academic Medical Center, Amsterdam, and the Interuniversity Cardiology Institute, Utrecht, the Netherlands (H.T., A.W.).

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Correspondence to Dr Charles Antzelevitch, Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker St, Utica, NY 13501. E-mail ca@mmrl.edu

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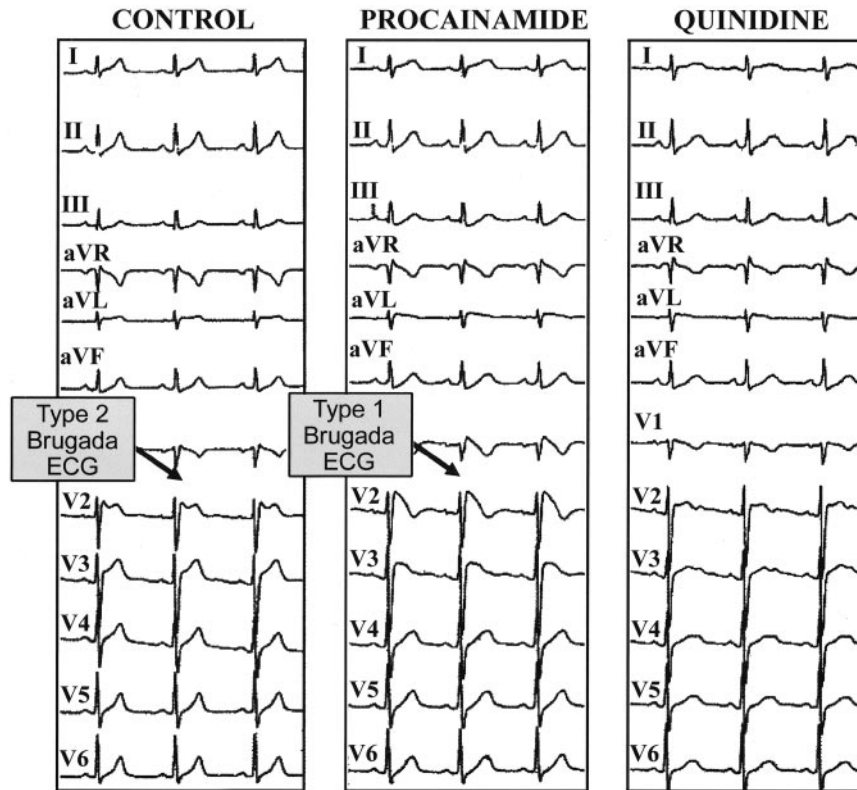


Figure 1. Twelve-lead ECG tracings in an asymptomatic 26-year-old man with Brugada syndrome. Left, Baseline: type 2 ECG (not diagnostic) displaying a saddleback-type ST-segment elevation is observed in V_2 . Center, After intravenous administration of 750 mg procainamide, the type 2 ECG is converted to the diagnostic type 1 ECG, which consists of a coved-type ST-segment elevation. Right, A few days after oral administration of quinidine bisulfate (1500 mg/d, serum quinidine level 2.6 mg/L), ST-segment elevation is attenuated displaying a non-specific abnormal pattern in the right precordial leads. VF could be induced during control and procainamide infusion but not after quinidine. Reprinted with permission from Belhassen et al.¹¹⁰ Copyright 2002, Blackwell Publishing.

death of 41 ± 15 years. The youngest patient clinically diagnosed with the syndrome is 2 days old and the oldest is 84 years old. The syndrome is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts. The prevalence of the disease is estimated to be 5/10 000 inhabitants and, apart from accidents, is the leading cause of death in men <40 years old, particularly in countries in which the syndrome is endemic.⁵ Because the ECG pattern can be dynamic and is often concealed, it is difficult to estimate the true prevalence of the disease in the general population.⁶ In a recent Japanese study, a Brugada syndrome ECG (type 1) was observed in 12/10 000 inhabitants; type 2 and 3 ECGs, which are not diagnostic of Brugada syndrome, were much more prevalent, appearing in 58/10 000 inhabitants.⁷ The prevalence of the Brugada syndrome among the general population in Europe and the United States is thought to be much lower,^{8,9} although among Southeast Asian immigrants it may be as high as it is in Southeast Asia itself.¹⁰

Sudden unexplained nocturnal death syndrome (SUNDS; also known as SUDS) and Brugada syndrome have recently been shown to be phenotypically, genetically, and functionally the same disorder.¹¹

Approximately 20% of patients with Brugada syndrome develop supraventricular arrhythmias.¹² Atrial fibrillation is associated in 10% to 20% of cases. Atrioventricular (AV) nodal reentrant tachycardia and Wolff-Parkinson-White syndrome also have been described.¹³ Prolonged sinus node recovery time and sinoatrial conduction time,¹⁴ as well as slowed atrial conduction and atrial standstill, have been reported in association with the syndrome.¹⁵ A recent study

reported that ventricular inducibility is positively correlated with a history of atrial arrhythmias.¹⁶ In patients with an indication for an implantable cardioverter defibrillator (ICD), the incidence of atrial arrhythmias was 27% versus 13% in patients without an indication for an ICD ($P < 0.05$), which suggests a more advanced disease process in patients with Brugada syndrome and spontaneous atrial arrhythmias. Inappropriate shocks from atrial arrhythmia episodes were observed in 14% of cases, highlighting the need for careful programming of the ICD.¹⁵

Diagnostic Criteria and Recommendations

Three ECG repolarization patterns in the right precordial leads are recognized.^{3,4} Type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave (Figure 1). Brugada syndrome is definitively diagnosed when a type 1 ST-segment elevation is observed in >1 right precordial lead (V_1 to V_3) in the presence or absence of a sodium channel-blocking agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration. The ECG manifestations of the Brugada syndrome, when concealed, can be unmasked primarily by sodium channel blockers but also during a febrile state or with vagotonic agents.^{17–20} Drug challenge generally is not performed in asymptomatic patients displaying the type 1 ECG under baseline conditions because the additional diagnostic value is considered to be limited, the added prognostic value is not

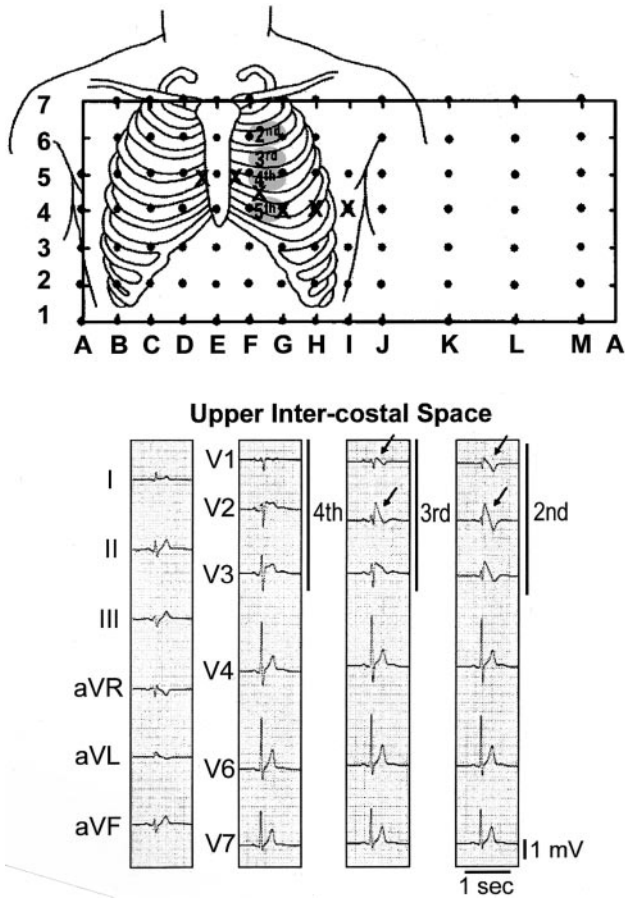


Figure 2. Shift of right precordial leads to 2nd and 3rd intercostal spaces unmasks a type 1 Brugada ECG. Top, Plot of 87 unipolar electrode sites (●) and of 6 precordial ECGs (X). Eighty-seven lead points are arranged in a lattice-like pattern (13×7 matrix), except for 4 lead points on both midaxillary lines, and covered the entire thoracic surface. V₁ and V₂ leads of the ECG are located between D₅ and E₅ and between E₅ and F₅, respectively, whereas V₄, V₅, and V₆ are coincident with G₄, H₄, and I₄, respectively. Bottom, Twelve-lead ECGs in a patient with Brugada syndrome. Type 2 saddleback-type ST-segment elevation was observed in V₁ and V₂ of the standard 12-lead ECG (4th intercostal space), whereas typical type 1 covered-type ST-segment elevation was apparent in V₁ and V₂ recorded from the 2nd and 3rd intercostal spaces (←).

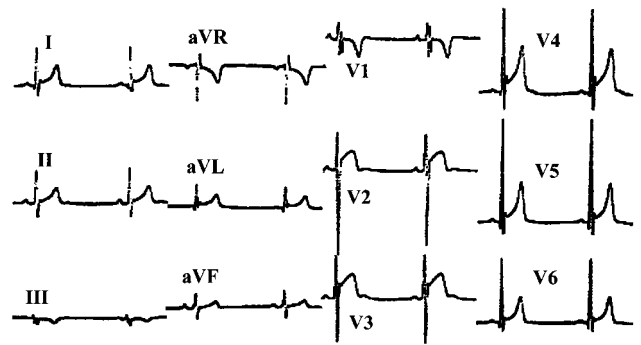


Figure 4. ECG of a well-trained, asymptomatic 24-year-old soccer player. ST-segment elevation is observed in V₂ to V₆ but with characteristics totally different from those seen in Brugada syndrome. A covered-type ST-segment elevation is not observed. A rounded or upsloping ST elevation is seen in V₂ and V₃, whereas V₄ to V₅ show a pattern resembling that commonly encountered in early repolarization syndrome.

clear, and the test is not without risk for provoking arrhythmic events.

Importantly, confounding factor or factors that could account for the ECG abnormality or syncope should be carefully excluded, including atypical right bundle-branch block, left ventricular hypertrophy, early repolarization, acute pericarditis, acute myocardial ischemia or infarction, pulmonary embolism, Prinzmetal angina,²¹ dissecting aortic aneurysm,²² various central and autonomic nervous system abnormalities,^{23,24} Duchenne muscular dystrophy,²⁵ thiamin deficiency,²⁶ hyperkalemia,^{22,27,28} hypercalcemia,^{29,30} arrhythmogenic right ventricular dysplasia/cardiomyopathy,^{31,32} pectus excavatum,³³ hypothermia,^{34,35} and mechanical compression of the right ventricular outflow tract (RVOT) as occurs in mediastinal tumor³⁶ or hemopericardium.³⁷

Of note, a Brugada-like ECG can occasionally appear for a brief period or for a period of several hours after direct-current cardioversion; it is not known whether these patients are gene carriers for Brugada syndrome.^{38–40}

Another prominent confounding factor is the type of ST-segment elevation encountered in well-trained athletes (Figure 4), which is distinguished by an upslope rather than a

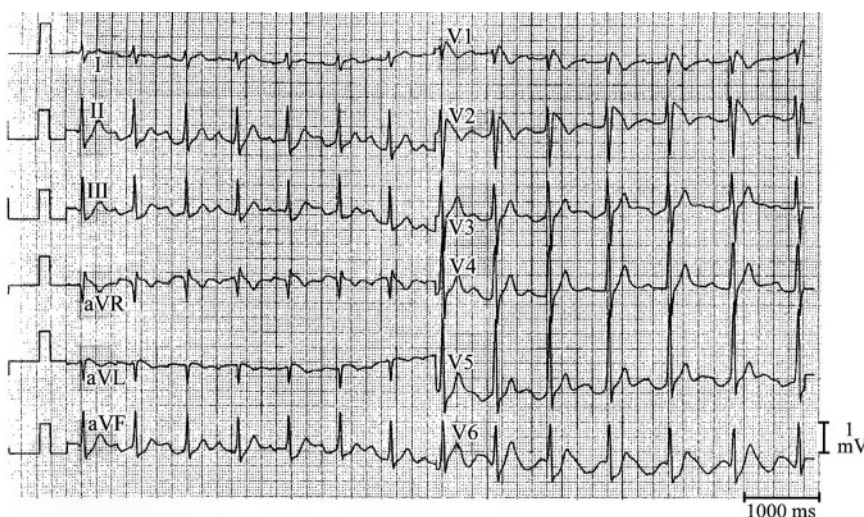


Figure 3. 12-lead ECG of a 40-year-old resuscitated man. The type 1 ECG shows typical repolarization as well as depolarization abnormalities. The former consists of ST-segment elevation in leads V₁ and V₂ (covered type, type 1). Depolarization abnormalities are present as PQ prolongation (270 ms), prolonged QRS width (120 ms), and S waves in leads I, II, and III. P wave duration is also wide.

TABLE 1. Drug-Induced Brugada-Like ECG Patterns

I. Antiarrhythmic drugs	
1. Na ⁺ channel blockers	
Class IC drugs (flecainide, ^{18,51,65,117,118} pilsicainide, ^{119,120} propafenone ¹²¹)	
Class IA drugs (ajmaline, ^{18,122} procainamide, ^{18,19} disopyramide, ^{4,19} cibenzoline ¹²³)	
2. Ca ²⁺ channel blockers	
Verapamil	
3. β -Blockers	
Propranolol, etc	
II. Antianginal drugs	
1. Ca ²⁺ channel blockers	
Nifedipine, diltiazem	
2. Nitrate	
Isosorbide dinitrate, nitroglycerine ¹²⁴	
3. K ⁺ channel openers	
Nicorandil	
III. Psychotropic drugs	
1. Tricyclic antidepressants	
Amitriptyline, ^{125,126} nortriptyline, ⁷⁷ desipramine, ⁷⁵ clomipramine ⁷⁶	
2. Tetracyclic antidepressants	
Maprotiline ¹²⁵	
3. Phenothiazine	
Perphenazine, ¹²⁵ cyamemazine ¹²⁷	
4. Selective serotonin reuptake inhibitors	
Fluoxetine ¹²⁶	
IV. Other drugs	
1. Dimenhydrinate ⁷⁸	
2. Cocaine intoxication ^{79,128}	
3. Alcohol intoxication	

downslope and by remaining largely unaffected by challenge with a sodium channel blocker. In addition, a variety of drugs have been reported to produce a Brugada-like ST-segment elevation (Table 1), although it is not yet clear whether or to what extent a genetic predisposition may be involved. The inclusion of drug categories in Table 1 should not be interpreted to imply that other members of the same "class" necessarily produce similar effects.

Although most cases of Brugada syndrome display right precordial ST-segment elevation, isolated cases of inferior lead⁴¹ or left precordial lead⁴² ST-segment elevation have been reported in Brugada-like syndromes; in some cases they have been associated with *SCN5A* mutations.⁴³

The type 2 ST-segment elevation has a saddleback appearance with a high takeoff ST-segment elevation of ≥ 2 mm, a trough displaying ≥ 1 mm ST elevation, and then either a positive or biphasic T wave (Figure 1). Type 3 has either a saddleback or coved appearance with an ST-segment elevation of < 1 mm. Type 2 and type 3 ECG are not diagnostic of the Brugada syndrome. These 3 patterns may be observed spontaneously in serial ECG tracings from the same patient or after the introduction of specific drugs. The diagnosis of Brugada syndrome is also considered positive when a type 2

TABLE 2. Drugs Used to Unmask Brugada Syndrome

Drug	Dosage and Administration
Ajmaline	1 mg/kg over 5 min, IV
Flecainide	2 mg/kg over 10 min, IV (400 mg, PO)
Procainamide	10 mg/kg over 10 min, IV
Pilsicainide	1 mg/kg over 10 min, IV

(saddleback pattern) or type 3 ST-segment elevation is observed in > 1 right precordial lead under baseline conditions and conversion to the diagnostic type 1 pattern occurs after sodium channel blocker administration (ST-segment elevation should be ≥ 2 mm). One or more of the clinical criteria described above also should be present. Drug-induced conversion of type 3 to type 2 ST-segment elevation is considered inconclusive for a diagnosis of Brugada syndrome.

Placement of the right precordial leads in a superior position (up to the second intercostal space above normal) can increase the sensitivity of the ECG for detecting the Brugada phenotype in some patients, both in the presence or absence of a drug challenge (Figure 2).^{44,45} Although previous reports suggested that none of the control patients displayed type 1 ST elevation when the V₁ to V₃ leads were displaced upward,^{44,45} a prospective study with a larger number of controls will be required to exclude the possibility of false-positive results via this method.

A slight prolongation of the QT interval is sometimes observed in association with ST-segment elevation in Brugada syndrome.^{46–48} The QT interval is prolonged more in the right precordial leads than it is in the left precordial leads, presumably because of a preferential prolongation of action potential duration in right ventricular epicardium secondary to accentuation of the action potential notch.⁴⁹ Depolarization abnormalities (Figure 3), including prolongation of P wave duration and PR and QRS intervals, are frequently observed, particularly in patients linked to *SCN5A* mutations.⁵⁰ PR prolongation likely reflects HV conduction delay.⁴⁶

In addition to Brugada syndrome, ST-segment elevation is associated with a wide variety of benign as well as malignant pathophysiological conditions. A differential diagnosis is at times difficult, particularly when the degree of ST-segment elevation is relatively small and the specificity of sodium channel blockers such as flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide^{18,48,51} to identify patients at risk is uncertain. The recommended dosages are listed in Table 2. The test should be monitored with a continuous ECG recording (a speed of 10 mm/s can be used throughout the test period, interposed with recordings at 25 or 50 mm/s) and should be terminated when the diagnostic type 1 Brugada ECG develops, the ST segment in type 2 ECG increases by ≥ 2 mm, premature ventricular beats or other arrhythmias develop, or QRS widens to $\geq 130\%$ of baseline. Intravenous sodium channel blockers always should be administered with great caution and infused slowly (as recommended in Table 1), closely monitored, and performed in a setting that is fully equipped for resuscitation. Particular caution should be exercised in patients with a preexisting

atrial or ventricular conduction (or both) disturbance (eg, suspected cases of Lev or Lenègre disease) or in the presence of wide QRS, wide P waves, or prolonged PR intervals (ie, infranodal conduction disease) to avoid the risk of precipitating complete AV block. Mechanoelectrical dissociation has been encountered in isolated cases. Isoproterenol and sodium lactate may be effective antidotes in this setting.

Patients at high risk for drug-induced AV block, such as older adults with syncope, should be administered sodium channel blockers in an electrophysiological study (EPS) environment after the insertion of a temporary pacing electrode. For other individuals, especially younger patients, sodium blocker challenge can be safely performed as a bedside test, provided the drug is discontinued as soon as excessive ST-segment elevation, QRS widening, or ventricular ectopy is observed.

Differentiation From ARVC and Other Structural Heart Diseases

A subpopulation of arrhythmogenic right ventricular cardiomyopathy (ARVC) patients have been found to display an ST-segment elevation and polymorphic VT that is characteristic of Brugada syndrome.³² In addition, a case has been reported in which a patient with a Brugada syndrome phenotype required heart transplantation because of untreatable arrhythmias⁵² and in whom severe fibrosis of the right ventricle was subsequently reported. These facts notwithstanding, the vast majority of patients with Brugada syndrome possess a structurally normal heart, which is consistent with the notion that this is a primary electrical heart disease.⁵³ It is not unreasonable to speculate that fibrosis and myocarditis, however mild, may occur and may exacerbate or indeed trigger events in patients with Brugada syndrome, although definitive evidence in support of this hypothesis is lacking. It is worth noting that recent studies suggest that some *SCN5A* defects may be capable of causing fibrosis in the conduction system and ventricular myocardium.⁵⁴

ARVC and Brugada syndrome are distinct clinical entities both with regard to clinical presentation and genetic predisposition.⁴ The only gene thus far linked to Brugada syndrome is *SCN5A*, the gene that encodes for the α subunit of the cardiac sodium channel, whereas ARVC has been linked to 10 different chromosomal loci and 3 putative genes independent of those responsible for Brugada syndrome.^{55,56} Only the ARVC5 locus has been mapped to a region that overlaps with the second locus for Brugada syndrome, but no gene has been identified as yet.^{57,58} Imaging techniques such as ECG, angiography, MRI, and radionuclide scintigraphy show no evidence of overt structural heart disease in patients with Brugada syndrome, whereas ARVC patients characteristically display right ventricular morphological and functional changes (eg, global dilatation, bulgings/aneurysms, and wall motion abnormalities). Ventricular arrhythmias in ARVC are most commonly monomorphic VT (left bundle-branch block type), which is often precipitated by catecholamines or exercise and accounts for sudden death in young competitive athletes.⁵⁹ In contrast, ST-segment elevation and arrhythmias in patients with Brugada syndrome are enhanced by vagotonic agents or β -adrenergic blockers, and polymorphic VT

occurs most commonly during rest or sleep.⁶⁰ In contrast to those in Brugada syndrome, the ECG abnormalities in ARVC are not dynamic and display a constant T-wave inversion, epsilon waves, and, in the progressive stage, reduction of the R amplitude. These are largely unaffected by sodium channel blocker administration.⁴

Electron beam computed tomography has uncovered wall motion abnormalities in a series of patients with Brugada syndrome.⁶¹ Although these contractile abnormalities are commonly considered pathognomonic of structural disease, recent studies^{62,63} suggest that such contractile dysfunction can result from loss of the action potential dome in regions of the right ventricular epicardium and thus may be unrelated to any type of morphological defect. Loss of the dome leads to contractile dysfunction because the entry of calcium into the cells is greatly diminished and sarcoplasmic reticulum calcium stores are depleted. Signal-averaged ECG recordings have demonstrated late potentials in patients with Brugada syndrome, especially in the anterior wall of the RVOT,^{64,65} and recordings from the epicardial surface of the anterior wall of the RVOT have revealed delayed potentials.⁶⁶ Although these types of potentials are commonly considered to be representative of the delayed activation of the myocardium secondary to structural defects, recent studies suggest that in the case of Brugada syndrome these late and delayed potentials may represent the delayed second upstroke of the epicardial action potential or local phase 2 reentry.⁶³ Late potentials also may reflect intraventricular conduction delays associated with *SCN5A* defects. Delayed contractile activation of the right ventricle in patients with Brugada syndrome⁶⁷ likewise may reflect delayed impulse propagation or, alternatively, a delayed second upstroke and action potential dome in the right ventricular epicardium.

Genetic Factors Underlying Brugada Syndrome

Inheritance of Brugada syndrome occurs via an autosomal dominant mode of transmission. The first and only gene to be linked to Brugada syndrome is *SCN5A*, the gene that encodes for the α subunit of the cardiac sodium channel gene.⁶⁸ More than 80 mutations in *SCN5A* have been linked to the syndrome since 2001.^{69–73} About 2 dozen of these mutations have been studied in expression systems and shown to result in loss of function because of failure of the sodium channel to express; a shift in the voltage and time dependence of sodium channel current (I_{Na}) activation, inactivation, or reactivation; entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly; or accelerated inactivation of the sodium channel. A second locus on chromosome 3, close to but apart from the *SCN5A* locus, was linked recently to Brugada syndrome⁵⁷ in a large pedigree in which the syndrome is autosomal dominant inherited and associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively benign prognosis. *SCN5A* mutations account for \approx 18% to 30% of Brugada syndrome cases. A higher incidence of *SCN5A* mutations has been reported in familial than in sporadic cases.⁷⁴ Of note, negative *SCN5A* results do not rule out causal gene mutations because, in general, the promoter region, cryptic splicing

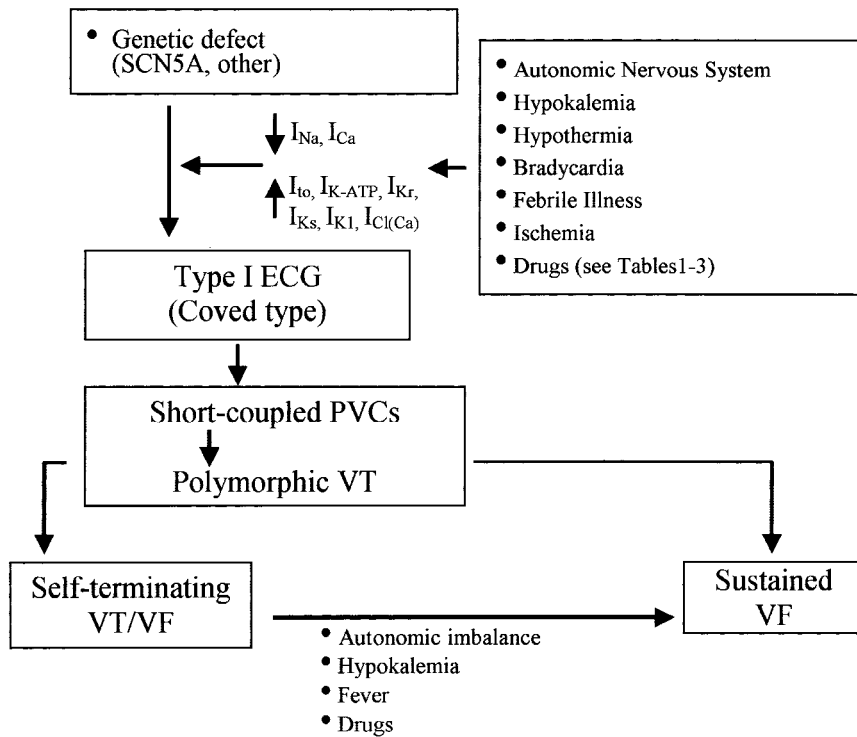


Figure 5. Factors predisposing to the ECG and arrhythmic manifestations of Brugada syndrome.

mutations, or the presence of gross rearrangements is not investigated.

At present, knowledge of a specific mutation may not provide guidance in formulating a diagnosis or determining a prognosis. Genetic testing is recommended, however, to support the clinical diagnosis, for early detection of relatives at potential risk, and to advance through research our understanding of the genotype–phenotype relationship.

Modulating and Precipitating Factors

The ECG manifestations of congenital Brugada syndrome are often concealed but can be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and alcohol and cocaine toxicity (Figure 5).^{17–19,75–81} These agents may also induce acquired forms of Brugada syndrome (Table 1). Until a definitive list of drugs to avoid in Brugada syndrome is formulated, the list of agents in Table 1 may provide some guidance.

Acute myocardial infarction or ischemia from vasospasm involving the RVOT mimics ST-segment elevation similar to that in Brugada syndrome. This effect is likely the result of a depression of calcium channel current (I_{Ca}) and the activation of ATP-sensitive potassium channel current (I_{K-ATP}) during ischemia, and it suggests that patients with congenital and possibly acquired forms of Brugada syndrome may be at a higher risk for ischemia-related sudden cardiac death.⁸²

VF and sudden death in Brugada syndrome usually occur at rest and at night. Figure 6 shows the circadian pattern of 64 VF episodes in 19 SUNDs patients treated with ICD. Circadian variation of sympathovagal balance, hormones, and

other metabolic factors are likely to contribute to this circadian pattern. Bradycardia resulting from altered autonomic balance or other factors may contribute to the initiation of arrhythmia.^{83–85}

Wichter et al demonstrated an abnormal ¹²³I-*m*-iodobenzylguanidine (¹²³I-MIBG) uptake in 8 (47%) of 17 patients with Brugada syndrome, but 0 in the control group.⁸⁶ Segmental reduction of ¹²³I-MIBG occurred in the inferior and the septal left ventricular walls, indicating presynaptic sympathetic dysfunction. It is noteworthy that imaging of the right ventricle, particularly the RVOT, is difficult with this

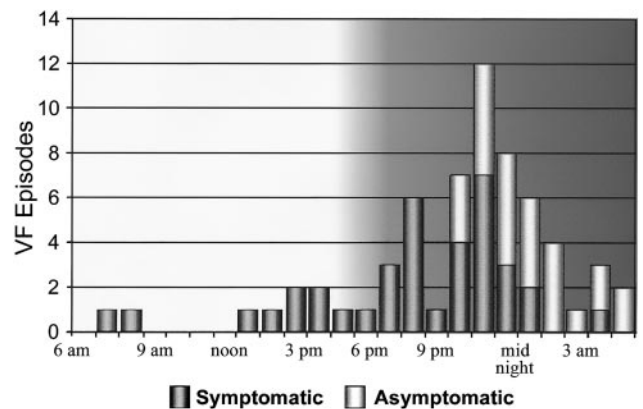


Figure 6. Circadian pattern of VF episodes in patients with Brugada syndrome. A nocturnal increase of VF episodes was found in 19 Thai-SUNDs patients with Brugada syndrome who received an ICD. All VF episodes were detected and documented by ICD interrogation. Interestingly, a significant number of VF episodes were asymptomatic because these episodes occurred while the patients were asleep (between 10 PM and early-morning hours) and they did not experience ICD discharges.

technique, so insufficient information is available about sympathetic function in the regions known to harbor the arrhythmogenic substrate. Moreover, it remains unclear what role the reduced uptake function plays in the arrhythmogenesis of Brugada syndrome. If the RVOT is similarly affected, then this defect may indeed alter the sympathovagal balance in favor of the development of an arrhythmogenic substrate.^{87,88}

Hypokalemia has been implicated as a contributing cause of the prevalence of SUNDS in northeastern Thailand, where potassium deficiency is endemic.^{81,89} Serum potassium in this northeastern population is significantly lower than that of the population in Bangkok, which lies in the central part of Thailand, where potassium is abundant in food.

The 1990 report of the Thai Ministry of Public Health found an association between a large meal of glutinous (“sticky”) rice or carbohydrates ingested on the night of death in patients with SUNDS.⁸⁹ Consistent with this observation, a recent study by Nogami et al found that glucose and insulin could unmask the Brugada ECG.⁸⁰

Dumaine et al first demonstrated that premature inactivation of the sodium channel in *SCN5A* mutations associated with Brugada syndrome is a function of temperature⁹⁰ and suggested that a febrile state may unmask Brugada syndrome. Indeed, several case reports have emerged recently demonstrating that febrile illness could unmask Brugada syndrome and precipitate VF.^{20,91–95} Anecdotal data point to hot baths as a possible precipitating factor. Of note, northeastern Thailand, where Brugada syndrome is most prevalent, is known for its hot climate.

Risk Stratification and Current Recommendations

Risk stratification aimed at the identification of patients at risk for sudden death is an important goal of research teams worldwide.^{71,96–98} Brugada et al⁹⁶ found that patients initially presenting with aborted sudden death are at the highest risk for a recurrence (69% at 54±54 months of follow-up), whereas patients presenting with syncope and a spontaneously appearing type 1 ECG have a recurrence rate of 19% at 26±36 months of follow-up. An 8% occurrence of cardiac events was observed in initially asymptomatic patients. This adverse prognosis was not observed in a population of similar size by Priori et al,⁷⁰ although the diagnostic criteria applied in the 2 studies may have been different in that the report by Priori et al does not specify a requirement for a coved-type ECG (type 1) in ≥1 precordial leads as a means to diagnose Brugada syndrome. Among asymptomatic patients, those at highest risk displayed the type 1 ECG spontaneously; patients in whom ST-segment elevation appeared only after provocation with sodium channel blockers appeared to be at minimal or no risk for arrhythmic events. Taken together, the data indicate that asymptomatic Brugada patients at highest risk are men with inducible VT/VF and a spontaneously elevated ST segment (type 1 ECG).⁹⁶

Recent studies have suggested that combined ECG markers may be helpful in risk stratification. Atarashi et al used the width of the S wave and the ST-segment elevation magnitude, whereas Morita et al combined ST-segment elevation and the

presence of late potentials.^{99,100} The value of these combined markers remains to be tested in a prospective study.

Brugada et al⁹⁶ suggested that among asymptomatic patients, the inducibility of VT/VF during EPS may forecast risk. Studies by Priori et al,⁷⁰ Kanda et al,⁹⁷ and Eckardt et al,⁹⁸ however, failed to find an association between inducibility and recurrence of VT/VF among both asymptomatic and symptomatic patients with Brugada syndrome. These discrepancies may result from differences in patient characteristics and the use of nonstandardized or noncomparable stimulation protocols.¹³ The adverse prognosis and higher predictive value of inducibility by Brugada et al may, at least in part, be due to more demanding criteria for diagnosing patients with Brugada syndrome.

It is noteworthy that programmed electrical stimulation–induced VF is observed in 6% to 9% of apparently healthy individuals and may represent a false-positive and nonspecific response, particularly when aggressive stimulation protocols are used.¹⁰¹

A protocol involving up to 3 extrastimuli applied to the right ventricular apex at cycle lengths ≥200 ms is recommended. If not inducible from the right ventricular apex, then stimulation may be applied to the RVOT. The predictive value of EPS is based largely on right ventricular apex stimulation; the value of RVOT pacing for risk stratification is not known. Although inducibility in experimental models is most readily achieved with epicardial stimulation,^{88,102} clinical data involving this approach are limited.¹⁰³ Clearly, additional studies are needed to define further the risk stratification strategy for asymptomatic patients.

A recent study by Brugada et al¹⁰⁴ reported on 547 individuals diagnosed with Brugada syndrome who had had no previous cardiac arrest. In 124 patients, the abnormal ECG was identified after ≥1 episode of syncope, and in 423 individuals, the abnormal ECG was identified during routine ECG screening or during study because they were family members of patients with the syndrome. Structural disease was ruled out in all patients. This study, which evaluated the clinical outcome of the largest population of patients with Brugada syndrome thus far reported, reached the following conclusions:

1. Patients have a relatively high risk for sudden arrhythmic death, even in the absence of a history of cardiac arrest: 8.2% experienced sudden death or at least one documented episode of VF during a mean follow-up of 24±33 months. Individuals with a spontaneously abnormal type 1 ECG carried a 7.7-fold higher risk of developing an arrhythmic event during a lifetime as compared with individuals in whom the ECG diagnostic of Brugada syndrome was evident only after sodium channel blocker challenge.
2. Male gender is another risk factor for sudden death. Men had a 5.5-fold higher risk of sudden death than did women.
3. Programmed electrical stimulation that induces a sustained ventricular arrhythmia is the strongest marker of risk, associated with an 8-fold higher risk of (aborted) sudden death than in noninducible patients.
4. Familial forms of the disease are not associated with a worse prognosis than are sporadic cases because a positive

TABLE 3. Device and Pharmacological Considerations for Therapy in Brugada Syndrome

Devices	
✓	ICD—only established effective therapy
?	Ablation or cryosurgery
?	Pacemaker
Drugs	
×	Amiodarone: does not protect ¹⁰⁸
×	β-Blockers: do not protect ¹⁰⁸
✓	β-Adrenergic agonists (isoproterenol ^{19,44})
✓	Phosphodiesterase inhibitors (cilostazol ¹¹⁶)
×	Class IC antiarrhythmics (flecainide, propafenone): contraindicated
Class IA antiarrhythmics	
×	Procainamide: contraindicated
?	Disopyramide ¹²⁹
✓	Quinidine ^{88,110,111,130}
?	Tedisamil
✓	I _{to} blockers: cardioselective and ion channel-specific

family history of Brugada syndrome did not predict outcome.

Therapeutic Recommendations for Brugada Syndrome

The important strides in the identification and characterization of Brugada syndrome during the past decade notwithstanding, progress relative to therapy has been less impressive. The various device and pharmacological therapies tested clinically or suggested on the basis of experimental evidence are listed in Table 3. Currently, an ICD is the only proven effective treatment for the disease.^{105,106} Of 690 patients with Brugada syndrome included in a multicenter registry, 258 received an ICD because of a suspected high risk of sudden arrhythmic death. The stored electrograms were reviewed to assess the efficacy of the device by analyzing the number of patients that had an appropriate defibrillation of at least one episode of VF. The patients' mean age at implantation was 42±13.5 years, and 210 (81.3%) of these were men. A total of 160 (62%) patients were symptomatic before establishing the diagnosis; 120 patients (48.4%) had a family history of sudden death, a familial Brugada ECG pattern, or both. A sustained ventricular arrhythmia was induced during the EPS in 198 patients (76.7%). During a mean follow-up of 2.5 years (median 2), 1 patient died during an electrical storm, but 69 (26.7%) patients had at least one appropriate defibrillation. The cumulative efficacy of the device was 18%, 24%, 32%, 36%, and 38% at 1, 2, 3, 4, and 5 years of follow-up, respectively (Figure 7).

Recommendations for ICD implantation are summarized in Figure 8. Symptomatic patients displaying the type 1 Brugada ECG (either spontaneously or after sodium channel blockade) who present with aborted sudden death should receive an ICD without additional need for EPS. Similar patients presenting with related symptoms such as syncope, seizure, or nocturnal agonal respiration also should undergo ICD implantation

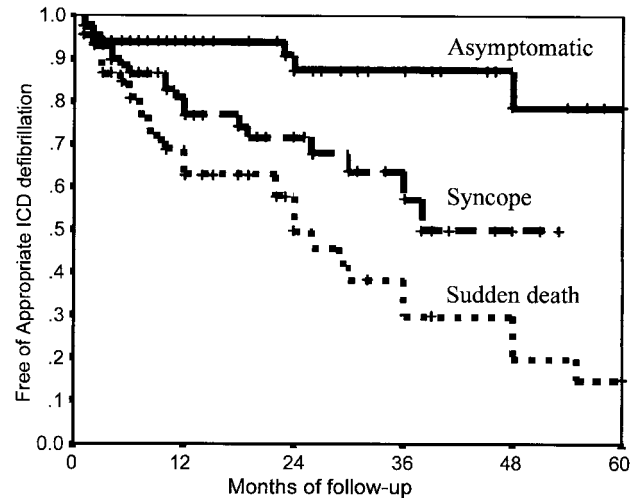


Figure 7. Kaplan-Meier curve of effectiveness of the ICD in 258 patients with ECG pattern of Brugada syndrome according to symptoms. Data are from the multicenter registry of 690 patients with Brugada syndrome.

after noncardiac causes of these symptoms have been carefully ruled out. EPS is recommended in symptomatic patients only for the assessment of supraventricular arrhythmias. Asymptomatic patients displaying a type 1 Brugada ECG (either spontaneously or after sodium channel blockade) should undergo EPS if a family history of sudden cardiac death is suspected to be the result of Brugada syndrome. EPS is justified when the family history is negative for sudden cardiac death if the type 1 ECG occurs spontaneously. If inducible for ventricular arrhythmia, then the patient should receive an ICD. Asymptomatic patients who have no family history and who develop a type 1 ECG only after sodium channel blockade should be closely followed up.

As additional data become available, these recommendations will require further refinement. Until more specific data are available, our recommendation with regard to patients who manifest a spontaneous type 1 ECG only after placement of the right precordial leads in superior positions is to treat them no differently from patients exhibiting a spontaneous type 1 ECG with the leads in the standard positions.

ICD implantation may not be an adequate solution for infants and young children or for patients who reside in regions of the world where an ICD is cost prohibitive. Although, in general, arrhythmias and sudden cardiac death occur during sleep or at rest and have been associated with slow heart rates, a potential therapeutic role for cardiac pacing remains largely unexplored. Data relative to a cryosurgical approach or the use of ablation therapy are limited. A recent report by Haissaguerre and coworkers¹⁰⁷ points to focal radiofrequency ablation as a potentially valuable tool in controlling arrhythmogenesis by focal ablation of the ventricular premature beats that trigger VT/VF in Brugada syndrome.

The pharmacological approach to therapy, based on experimental data, has been tailored to a rebalancing of currents that are active during the early phases of the epicardial action potential in the right ventricle to reduce the magnitude of the

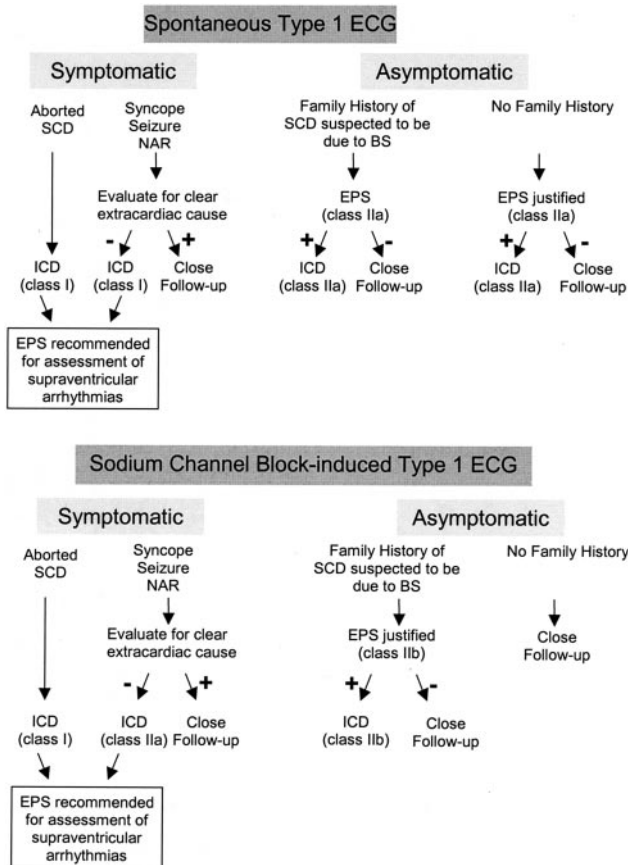


Figure 8. Indications for ICD implantation in patients with Brugada syndrome. Class I designation indicates clear evidence that the procedure or treatment is useful or effective; Class II, conflicting evidence about usefulness or efficacy; Class IIa, weight of evidence is in favor of usefulness or efficacy; and Class IIb, usefulness or efficacy is less well established. BS indicates Brugada syndrome; NAR, nocturnal agonal respiration; and SCD, sudden cardiac death.

action potential notch, restore the action potential dome, or both (Table 3). Antiarrhythmic agents such as amiodarone and β -blockers have been shown to be ineffective.¹⁰⁸ Class IC antiarrhythmic drugs (eg, flecainide and propafenone) and class IA agents (eg, procainamide) are contraindicated for reasons enumerated previously. Specific class IA agents such as quinidine and tedisamil, however, may exert a therapeutic action because of their I_{to} -blocking properties. Because the presence of a prominent transient outward current, I_{to} , in the right ventricle is at the heart of the mechanism underlying Brugada syndrome, any agent that inhibits this current may be protective. Cardioselective and I_{to} -specific blockers are not available. The only agent on the US market with significant I_{to} -blocking properties is quinidine. It is for this reason that it was suggested that this agent may be of therapeutic value in Brugada syndrome.¹⁰⁹ Studies have shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing phase 2 reentry and polymorphic VT in experimental models of Brugada syndrome.⁸⁷ Clinical evidence of the effectiveness of quinidine in normalizing ST-segment elevation in patients with Brugada syndrome has been reported (see Figure

1),^{110,111} although clinical trials designed to assess the efficacy of this agent are limited.¹¹² Relatively high doses of quinidine are recommended (1200 to 1500 mg/d). Agents that boost the L-type calcium current, such as isoproterenol, may be useful as well.^{69,87} Both types of agents (I_{to} blocker and agents that augment I_{Ca}) have been shown to be effective in normalizing ST-segment elevation in patients with Brugada syndrome and in controlling "electrical storms," particularly in children.^{44,110,111,113,114} Other than the studies by Belhassen and coworkers involving quinidine, none have as yet demonstrated long-term efficacy in the prevention of sudden cardiac death.^{110,115} The most recent addition to the pharmacological armamentarium is a phosphodiesterase III inhibitor, cilostazol,¹¹⁶ which normalizes the ST segment most likely by augmenting the calcium current (I_{Ca}), as well as by reducing I_{to} secondary to an increase in heart rate. Finally, an experimental antiarrhythmic agent, tedisamil, with potent action to block I_{to} among other outward currents has been suggested as a therapeutic candidate.⁶⁹ Tedisamil may be more potent than quinidine because it lacks the relatively strong inward current-blocking actions of quinidine. The development of a cardioselective and I_{to} -specific blocker would be a most welcome addition to the limited therapeutic armamentarium available to combat this disease. Appropriate clinical trials are needed to establish the effectiveness of all of the above pharmacological agents as well as the possible role of pacemakers in some forms of the disease.¹¹⁷⁻¹³⁰

Disclosures

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