BRUGADA SYNDROME; CURRENT STATUS

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I INTRODUCTION AND EPIDEMIOLOGY (ESC 2022)

- **Definition:** Brugada Syndrome (BrS) (first described by Pedro and Josep Brugada in 1992) is an inherited arrhythmogenic syndrome characterized by a **coved-type ST-segment elevation (Type 1 pattern) in the right precordial leads (V1–V2)** and an increased risk of **Sudden Cardiac Death (SCD)** due to polymorphic Ventricular Tachycardia (pVT) or Ventricular Fibrillation (VF) in patients without overt structural cardiomyopathy.
- **Epidemiology:** Inherited in an autosomal dominant pattern with incomplete, age- and sex-dependent penetrance (and strong polygenic modulation). Despite equal genetic transmission between sexes, clinical phenotype expression is **8- to 10-fold higher in adult males than females** (driven by higher androgen-mediated *Ito* density in males) and peaks in the **3rd to 4th decade of life** (mean age of VF arrest ~41 years), predominantly occurring **at night during sleep or rest** (periods of heightened vagal/parasympathetic tone and bradycardia) or during **febrile illnesses** (historic nocturnal sudden unexplained death syndrome: *Bangungut* in the Philippines, *Pokkuri* in Japan, and *Lai Tai* in Thailand).

II PATHOPHYSIOLOGY AND GENETIC SUBSTRATE

- **Genetic Architecture:** Pathogenic loss-of-function variants in ***SCN5A*** (chromosome 3p22, encoding the alpha-subunit of the cardiac voltage-gated sodium channel **Nav1.5**) account for **20 to 30 percent** of diagnosed BrS probands. In 2018, the **ClinGen** expert curation panel concluded that ***SCN5A* is the only gene with definitive monogenic evidence for BrS** (the other 20 curated genes had only limited or disputed evidence), while Genome-Wide Association Studies (**GWAS**) prove that common variants at ***SCN5A, SCN10A, HEY2*, and *MAPRE2*** form a **Polygenic Risk Score** that dictates ECG penetrance.
- **Two Complementary Cellular Hypotheses:**
  - **The Repolarization Hypothesis (Antzelevitch):** Reduction in inward sodium current (***INa***) leaves the prominent **transient outward potassium current (*Ito*)** in the **RVOT epicardium** unopposed during Phase 1 of the action potential. This causes loss of the Phase 2 action potential dome selectively in RVOT epicardial cells (while endocardial cells retain the dome), creating a **transmural voltage gradient** (manifesting as coved J-point/ST elevation) and **Phase 2 re-entry** that triggers closely coupled PVCs and polymorphic VT/VF.
  - **The Depolarization / Micro-Structural Hypothesis (Wilde & Coronel / Nademanee):** Conduction delay, **interstitial micro-fibrosis**, and reduced **Connexin-43 (Cx43) gap-junction expression** localized specifically to the **anterior epicardium of the RVOT** cause delayed, fractionated activation (manifesting as late potentials and coved ST elevation) that supports anatomical re-entry—providing the direct target for **epicardial catheter ablation**.

III DIAGNOSTIC ALGORITHM, HIGH-LEAD PLACEMENT AND PROVOCATION TESTING

- **Diagnostic Type 1 (“Coved”) vs. Non-Diagnostic Type 2 (“Saddleback”) ECG:**
  - **Type 1 Brugada ECG (Only Diagnostic Morphology):** Coved J-point/ST-segment elevation **>= 2 mm (0.2 mV)** followed by a concave/straight descent into a **negative T wave** in **>= 1 right precordial lead (V1 and/or V2)** placed in the **standard 4th, 3rd, or 2nd intercostal space**.
  - **High Right Precordial Lead Placement (2nd and 3rd ICS):** Moving leads V1 and V2 superiorly to the **2nd and 3rd intercostal spaces** places the electrodes directly over the high anatomical position of the RVOT, doubling diagnostic sensitivity.
  - **Exclusion of Brugada Phenocopies:** Acute anterior/RV myocardial ischemia, pulmonary embolism, hyperkalemia, hypercalcemia, arrhythmogenic right ventricular cardiomyopathy (ARVC), pectus excavatum, and mechanical compression of the RVOT must be excluded.
  - **Pharmacological Sodium Channel Blocker Challenge (Unexplained Cardiac Arrest and Family Screening; Shanghai Score >=3.5 Required if Drug-Induced):**
  - **Agents and Dosing: Ajmaline (1 mg/kg IV over 5 to 10 minutes — highest sensitivity ~80–90% and ultra-short half-life)**, **Flecainide (2 mg/kg IV over 10 minutes, max 150 mg, or 400 mg oral)**, or **Procainamide (10 mg/kg IV over 10 minutes)** under continuous 12-lead (including high V1–V2) ECG monitoring with a defibrillator and **IV Isoproterenol + 8.4% Sodium Bicarbonate** at the bedside.
  - **Mandatory Immediate Termination Criteria:** (1) Development of a diagnostic **Type 1 Brugada ECG**; (2) Development of **frequent PVCs or ventricular arrhythmias**; (3) **QRS widening to >= 130 percent of baseline** (or additional Type 2 ST elevation >=2 mm); or (4) Completion of the full drug infusion.

Clinical / ECG Scenario	ESC 2022 Guideline Class	Recommended Management Strategy
All BrS Patients (General Measures)	**Class I**	Avoid **brugadadrugs.org** agents, cocaine, & heavy alcohol; **treat any fever immediately with antipyretics**
Aborted Cardiac Arrest or Sustained VT/VF	**Class I (Level C)**	**ICD Implantation** (Transvenous or Subcutaneous S-ICD)
Spontaneous Type 1 ECG + Arrhythmic Syncope	**Class IIa (Level C)**	**ICD Implantation** (Use **ILR [Class IIa]** if syncope is unexplained/equivocal)
Asymptomatic + Spontaneous Type 1 ECG	**Class IIb (Level B)**	**Programmed Electrical Stimulation (PES)** (up to 2 extrastimuli) may be considered; ICD if VF inducible
Electrical Storm (Acute >=3 VF in 24 h)	**Class IIa (Level C)**	**IV Isoproterenol infusion (1–2 mcg/min)** + initiate oral **Quinidine** + cool fever/correct K+
Recurrent ICD Shocks / Storm (Chronic)	**Class IIa (Level B/C)**	**Oral Quinidine** (300–600 mg q6–8h) AND/OR **Epicardial RVOT Substrate Catheter Ablation**
Asymptomatic + Drug-Induced Type 1 Only	**Class III (No ICD)**	Very low event rate (<0.1–0.3%/yr); lifestyle/fever precautions only (**PES and ICD not recommended**)

IV RISK STRATIFICATION, ELECTRICAL STORM AND EPICARDIAL ABLATION

- **Hierarchy of Annual Arrhythmic Event Rates:**
  - **Aborted SCA Survivors: ~7.7 percent per year** (FINGER registry) (**Class I ICD**).
  - **Spontaneous Type 1 ECG + Arrhythmic Syncope: ~2 to 3 percent per year** (**Class IIa ICD**).
  - **Asymptomatic Spontaneous Type 1 ECG: ~0.5 to 1.0 percent per year** (additional ECG risk markers include **fragmented QRS [fQRS]**, **prominent S wave in Lead I** [amplitude >=0.1 mV or duration >=40 ms, reflecting RVOT conduction delay], **aVR sign** [R wave >=0.3 mV in aVR], concomitant inferolateral early repolarization, and sinus node dysfunction).
  - **Asymptomatic Drug-Induced Type 1 ECG Only: <0.1 to 0.3 percent per year** (reassurance and fever/drug avoidance only).
  - **Emergency Management of Brugada Electrical Storm (>=3 VT/VF Episodes in 24 Hours):**
  - **Step 1 — ICU Admission and Trigger Eradication:** Immediately lower body temperature (**IV Paracetamol + active cooling blankets**), normalize serum **Potassium (>4.0 to 4.5 mEq/L)** and Magnesium, sedate to suppress anxiety/vagal swings, and reprogram the ICD to avoid shocks on non-sustained episodes.
  - **Step 2 — Intravenous Isoproterenol Infusion (First-Line Acute Drug — Class IIa):** Start **Isoproterenol at 1 to 2 mcg/min IV** (targeting a 20 percent increase in baseline sinus rate to 90–110 bpm), which boosts inward L-type calcium current (***ICa-L***), restores the epicardial action potential dome, and rapidly suppresses VF storm (in contrast to catecholaminergic arrhythmias like LQTS/CPVT where isoproterenol is harmful).
  - **Step 3 — Oral Quinidine Loading (Class IIa):** Administer **Hydroquinidine / Quinidine Sulfate** (blocks ***Ito***) while weaning Isoproterenol over 48 to 72 hours.
  - **Step 4 — Epicardial RVOT Substrate Catheter Ablation (ESC 2022 Class IIa):** Performed via percutaneous subxiphoid pericardial access; eliminates fractionated late potentials over the anterior RVOT epicardium, **normalizing the Type 1 ECG and keeping 96 percent of patients VF-free after one or more procedures** (**BRAVO Registry**, *Circulation* 2023) (**Class III caveat:** Catheter ablation is **not** recommended in asymptomatic BrS patients).

KEY REFERENCES

- **Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al.:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, *European Heart Journal*, 2022.
- **Nademanee K, Veerakul G, Chandanamattha P, et al.:** Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium, *Circulation*, 2011 / **BRAVO Registry**, *Circulation*, 2023.
- **Hosseini SM, Kim R, Udupa S, et al. (ClinGen Consortium):** Reappraisal of Reported Genes for Sudden Arrhythmic Death: Evidence-Based Evaluation of Gene-Disease Validity for Brugada Syndrome, *Circulation*, 2018.