

SHORT QT SYNDROME

Definition

Short QT syndrome (SQTS) is characterized by abnormally short QT interval (<340 ms) with an increased propensity to atrial and ventricular arrhythmias and a high risk of sudden death (Table 1).¹⁻³

Epidemiology

SQTS is a rare, inherited heart disease presenting as sudden cardiac death (SCD) or aborted SCD in 34% and a family history of SCD in 15% of patients.¹ There is a striking predominance of men ($\approx 70\%$) among patients with a clinical diagnosis of SQTS, suggesting a sex-dependent penetrance.⁴

Genetics and Pathophysiology

More than 20 mutations have been linked to SQTS, with the most frequent in genes KCNQ1 (V141M mutation), KCNH2, and KCNJ2 (Table 1).¹ Gain of function mutations affecting the I_{Kr} , I_{Ks} , I_{K1} , and I_{Ca} currents are responsible for heterogenous repolarization and refractoriness that may predispose to arrhythmia (Figure 1). Rufinamide, an antiepileptic drug, has been shown to significantly shorten the QT interval, although not necessarily associated with significant clinical adverse effects.⁵ Increasing doses of bupropion have also been found to significantly decrease QTc.⁶ In the general population, an increased risk of cardiovascular disease has been observed for both very short and long QT interval.⁷

Presentation

Cardiac arrest is often the first manifestation of the disease, particularly in the first year of life (rate of cardiac arrest 4%), and between 20 to 40 years (rate of cardiac arrest is 1.3% per year).^{2,8} Patients often have permanent or paroxysmal atrial fibrillation (24%) and occasionally have depression of the PR interval. Tall, peaked T waves without flat ST segments, early repolarization patterns, and impaired rate-dependent QT shortening have been recorded (Figure 2). Most events occur during rest, sleep or ordinary activities.⁸

Diagnosis

The cut-off value of 'short' QT interval for defining SQTS remains a matter of debate as there is an overlap between healthy subjects and patients with SQTS. Short QT syndrome is usually

diagnosed in the presence of a 3436 QTc consistently below 330–340ms; while between 340 and 360 ms additional criteria are needed (Table 2).⁹ Additional ECG stigmas are peaked T-waves and/or PQ segment depression ≥ 0.05 mV (0.5 mm).¹⁰ AF and VF can be induced easily by programmed electrical stimulation in patients with SQTS.

Secondary causes of a short QT include hyperkalemia, hypercalcemia, acidosis, catecholamine's, digitalis, rufinamide (a recently FDA-approved anticonvulsant), and hyperthermia. Ischemia-induced activation of the K_{ATP} channel and parasympathetic activation of the KA-Ch channel (deceleration-dependent QT shortening) may also cause QT shortening.¹¹ A short QTc is also found in patients with the AR **primary systemic carnitine deficiency syndrome** which is characterized by hypoketotic hypoglycaemia, hyperammonaemia, liver dysfunction, hypotonia, and cardiomyopathy. It is and caused by variants in SLC22A5 and responds to carnitine supplementation.⁹

Genetic Testing

Indications for **genetic testing** are presented in Table 3 and Figure 3. However, the yield of genetic screening remains low (<25%).^{1,3}

Therapy

It is poorly defined (Table 4). The sensitivity of electrophysiology study for VF inducibility is about 50%, and noninducibility does not rule out risk of SCD. Thus, ICD is recommended in the case of documented previous cardiac arrest or sustained VT.^{3,12,13} T-wave oversensing may result in inappropriate shocks and requires careful programming. SCD may occur in young males with a Gollob score >5 ,¹⁴ but the prognostic value of this score has not been verified in other series.² Females are less prone to arrhythmic events, probably due to estrogen induced QT prolongation, but they can still suffer cardiac arrest.⁸ **Quinidine** can be efficacious in SQTS by prolonging the QT interval, normalizing the QT response to RR-interval change, and preventing cardiac events in some patients.^{15,16} It is proposed for children or patients refusing an ICD.¹⁵ I_{Kr} blockers such as sotalol may fail to normalize the QT interval in patients with SQTS. Disopyramide and amiodarone may also be helpful, and propafenone is effective in preventing AF.¹¹ It should be considered to continue quinidine therapy in women with SQTS throughout **pregnancy** and the post-partum period (ESC 2025 GL on pregnancy, IIa C). Quinidine therapy should be considered in pregnant women with SQTS and arrhythmic events during pregnancy (ESC 2025 GL on pregnancy, IIa C).¹⁷

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