

## A historical outline of quinidine

### Apunte histórico sobre la quinidina

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#### ARTICLE INFORMATION

**Key words:** Quinidine, Antiarrhythmic drug, Chronology  
**Palabras clave:** Quinidina, Fármaco antiarrítmico, Cronología

#### PROLOGUE

Quinidine, one of the first developed antiarrhythmic drugs, had a significant role in the treatment of various cardiac arrhythmias. Subsequently, concerns arose due to the increased risk of ventricular arrhythmias and increased mortality, so that its use was drastically reduced. However, recent trials have generated a renewed interest in its use: it has been used successfully in idiopathic ventricular fibrillation (IVF), by unknown mechanisms; in Brugada syndrome (BrS), by its action on potassium currents (including  $I_{to}$ ), and in short QT syndrome (SQTS), as it normalizes the ventricular refractory period. Therefore, although it is one of the oldest drugs, it has an important role in modern cardiology.

#### CHRONOLOGY

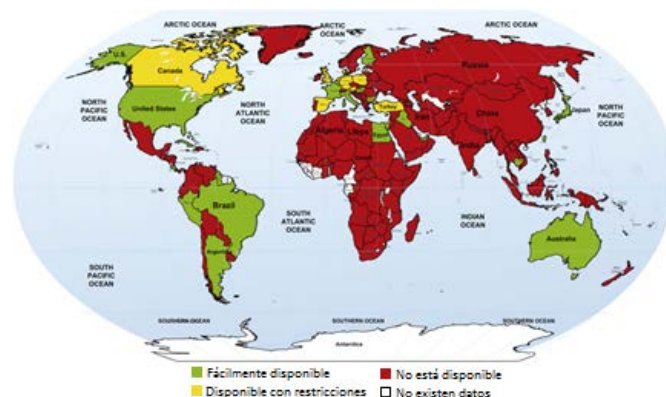
- 1400s: The Incas of Peru used cinchona bark, a precursor of quinine and its stereoisomer, quinidine, as a remedy for fevers that would later be identified as malaria<sup>1</sup>.
- 1749: Quinidine was used to treat palpitations.
- 1848: Van Heymingen described it for the first time<sup>2</sup>.
- 1853: Pasteur named it<sup>2</sup>.
- 1923: It was used in ventricular tachycardia.
- 1929: Dock reported the first case of IVF with arrhythmic storm that responded to quinidine<sup>3</sup>.
- 1950s: Quinidine syndrome was first described, as it could predispose to VF. Its use to treat AF dropped sharply.
- 1964: Selzer and Wray coined the term quinidine syncope and described the phenomenon: ventricular arrhythmias, VF, repetitive and paroxysmal events, occurring 1-3 hours after the last dose of quinidine<sup>4</sup>.
- 1987: Belhassen used it in the IVF<sup>3</sup>.
- 1990s: Coplen analyzed data from 6 trials between 1970 and 1984, and devised life estimates between control groups and after cardioversion with quinidine. AF recurrence was avoided but there was a

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- greater mortality<sup>2</sup>.
- 1990: Moosvi demonstrated the existence of increased mortality with quinidine in the treatment of cardiac arrhythmias<sup>2</sup>.
  - 1991, 1992: Data from the National Ambulatory Medical Care Survey led to a decrease in the use of quinidine for maintenance of sinus rhythm, from 5 % in 1999 to 0.0 % in 2000<sup>2</sup>.
  - 1999:
    - Southworth developed a meta-analysis expressing doubts about the safety of the use of sotalol and quinidine, comparable in their capacity to maintain sinus rhythm at 6 months follow-up. Both were higher than the controls but both had a tendency to increased long-term mortality [sotalol (2.2%), quinidine (3.0 %) and controls (1.1%)]<sup>2</sup>.
    - Belhassen used it in IVF and BrS<sup>2</sup>.
  - 2001:
    - It was suggested the role of the prominent K transient outward current ( $I_{to}$ ) in the J wave syndrome and the potential benefit of quinidine blocking this current.
    - Alings found that quinidine normalized the electrocardiogram in BrS<sup>5</sup>.
  - RuDusky wrote: “Be not the first on whom the new are tried, nor the last to lay the old aside”<sup>6</sup>.
  - 2002: It was discussed if the ICD was the only option; ultimately, the device ended the VF but did not impact recurrence.
  - 2004:
    - Belhassen suggested quinidine effectiveness in patients with high risk BrS<sup>7</sup>.
    - Quinidine was used in the SQTS.
    - Hermida used quinidine hydrochloride in BrS<sup>8</sup>.
  - 2005: Wolpert administered it in the SQTS<sup>2</sup>.
  - 2006:
    - AstraZeneca, one of the leading manufacturers, ceased production of quinidine sulfate, without informing the Heart Rhythm Society and the European Heart Rhythm Association<sup>9</sup>. Then it became difficult to get it in the world. The measure was taken due to the low demand for the product, caused by the emergence of effective antiarrhythmic drugs for AF and the use of ICD for ventricular arrhythmias. Meanwhile, its use in new diseases began to emerge, in which this medication was most effective and, sometimes, the only appropriate one. The ICD is not always available and there are recurrences and electrical storms, which should be reduced or eliminated by drug treatment. Quinidine increases the ventricular effective refractory period and may avoid VF; in the case of BrS, it suppresses phase 2 reentry.
  - Dear Pharmacist reported discontinuity in quinidine bisulfate production<sup>3</sup>.
  - Mizusawa used low dose quinidine to treat ventricular arrhythmias in BrS<sup>10</sup>.
  - 2007:
    - Cochrane Database analyzed 45 studies in order to clarify the efficacy of antiarrhythmic drugs to maintain sinus rhythm after cardioversion of AF. At one year follow-up, quinidine and disopyramide were associated with increased mortality and greater proarrhythmia, compared with controls. Quinidine showed a non-significant but clear tendency to increase mortality, and if the “lost” patients were included among the dead, it was significant<sup>2</sup>.
    - Milberg used quinidine in SQTS, which normalizes the ventricular refractory period, reduces the dispersion of repolarization and prolongs post-repolarization refractoriness, with prevention of VF<sup>3</sup>.
    - Viskin said that a valuable medication was about to disappear<sup>11</sup>.
    - Quinidine was used in the SQTS.
  - 2009:
    - Yang found that the combination of quinidine with verapamil was safe for maintenance of sinus rhythm in AF, as an alternative to the use of sotalol and amiodarone. Verapamil, in experimental and clinical studies, decreased afterdepolarizations by Class I and III antiarrhythmics that led to *torsades de pointes* and avoided ventricular high rate during arrhythmias caused by increased atrioventricular conduction (by the vagolytic effect of quinidine)<sup>2</sup>.
    - The study PAFAC (Prevention of Atrial Fibrillation After Cardioversion trial) examined the combination of quinidine and verapamil in persistent AF after electrical cardioversion, compared with sotalol and placebo<sup>2</sup>.
    - The SOPAT (Suppression Of Paroxysmal Atrial Tachyarrhythmias trial) found that the combin-

ation was effective in decreasing recurrence, similar to sotalol and superior to placebo. It showed a small but definite risk of serious side effects: more death, syncope and VT (2 with placebo, 5 with high doses of quinidine and verapamil, 4 with low doses of both drugs, and 7 with sotalol)<sup>2</sup>.

- Viskin talked about the fall and rise of quinidine<sup>3</sup>.
  - Belhassen reported again on the use of quinidine in IVF and BrS<sup>10</sup>.
  - Viskin began an empirical prospective registry of the use of quinidine in asymptomatic BrS<sup>12</sup>.
  - Haissaguerre studied the short and long term response to quinidine in IVF and early repolarization<sup>3</sup>.
- 2010: Viskin stated that an antiarrhythmic medication used in IVF, electrical storm, BrS and early repolarization, was irreplaceable and, in spite of that, it was disappearing. It was being withdrawn for commercial reasons, despite being an effective treatment and sometimes the only treatment for some diseases (lethal ventricular arrhythmias, even with ICD)<sup>13-15</sup>.
- 2012:
- Marquez highlighted the long-term efficacy of low-dose quinidine in BrS with ventricular arrhythmias and ICD (200-600 mg/day, doses less than or equal to 600 mg/day)<sup>5</sup>.
  - Belhassen wondered if quinidine was the ideal drug for BrS (ICD ends VF but does not affect its occurrence)<sup>1</sup>.
  - Empirical use of quinidine was recommended in asymptomatic BrS patients, after knowing the results of an international registry<sup>16</sup>.
  - Quinidine utility was found in a new cardiac channelopathy related to SCN5A, multifocal ectopic Purkinje-related premature contractions (MEPPC)<sup>17</sup>.
- 2013: Viskin declared that a drug that can save the lives of some patients with BrS is inaccessible in many places. The assertion was based on the opinions of 273 physicians from 131 countries (Figure)<sup>7</sup>.



**Figure.** Availability of quinidine in the world. Taken from Viskin *et al.*<sup>7</sup>, with permission from the *Journal of the American College of Cardiology*.

### EPILOGUE

Quinidine has been used in the treatment of the following conditions: IVF, SQTS, BrS, early repolarization, electrical storm and, recently, in a new cardiac channelopathy associated with SCN5A (MEPPC).

In the past three decades, the group of the Medical Center of Tel- Aviv took quinidine as a therapeutic alternative to ICD in BrS, with high effectiveness in the use of quinidine bisulfate to prevent inducibility of VF<sup>1</sup>. The usefulness of quinidine in BrS was established by: Yan and Antzelevitch (1999)<sup>18</sup>, Alings (2001)<sup>19</sup>, Belhassen (1999, 2002)<sup>20,21</sup>, Hermida (2004)<sup>22</sup>, Mok (2004)<sup>23</sup>, and Belhassen and Viskin (2004)<sup>24</sup>.

In **Tables 1 and 2** some characteristics of the drug are shown.

**Table 1.** Some *in vivo* electrophysiological characteristics of quinidine.

AVNERP	ERP-HPS	AERP	VERP	ERP-AP	
↓↔↑	↑	↑	↑	↑	
Sinus rate	PR	QRS	QT	AH	HV
↔↑	↓↔↑	↑	↑	↓↔↑	↔↑

Legend: ↑ increase, ↓ decrease, ↔ no change

**Table 2.** Some *in vitro* electrophysiological characteristics of quinidine.

Feature	Effect
Amplitude of action potential	↓
Duration of action potential	↑
Q	↓
Maximum diastolic potential	↔
Effective refractory period	↑
Conduction velocity	↓
Sinus node automaticity	↔
Phase 4	↓

Legend: ↑ increase, ↓ decrease, ↔ no change

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