Quinidine in Brugada Syndrome
Still a Long Way to Go...

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Since Brugada syndrome was identified in 1992, its therapeutic management of patients has presented a great challenge for clinicians.1

In this issue of Circulation Arrhythmia and Electrophysiology, Belhassen et al2 suggest both risk stratification of arrhythmia and therapeutic improvements using electrophysiological study (EPS) and quinidine. Although gradual progress in risk stratification at the population level has been reached through the creation of large databases,3–5 we must admit that >30 years after its first description, arrhythmic risk assessment and, therefore, the best treatment choice in a patient affected by Brugada syndrome still remain a real challenge for clinicians.

There are many factors that come into play in the treatment of Brugada syndrome. First, clinical diagnosis of Brugada syndrome is sometimes difficult and usually overestimated because it is based on the ECG aspect.6 After diagnosis, the main feature is the risk of ventricular fibrillation. However, events can be distant from each other—sometimes >20 years between 2 arrhythmic events. Moreover, although a trigger can be found in most arrhythmic diseases, it is rare in Brugada syndrome patients, making the prediction of such an event uncertain.6

In fact, the main challenge in evaluating patients affected with Brugada syndrome is the relatively low incidence of events. For instance, in the FINGER registry, patients who experienced cardiac arrest had a 7.7% event rate per year, patients with syncope had 1.9%, and asymptomatic patients experienced cardiac arrest had a 7.7% event rate per year, events. For instance, in the FINGER registry, patients who had 0.5%.3 This risk seems to be cumulative over time and reaches a 12% risk at 10 years in asymptomatic patients with Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7 This points to a spontaneous aspect of Brugada syndrome.7

In the study by the Belhassen group should be of particular interest of this work is that the treatment given to their patients was different from what is usually performed and proposed in different consensus conferences.6 Indeed, the treatment was based on an aggressive electrophysiological study to induce ventricular fibrillation, and if ventricular fibrillation was induced, the patient was then treated with quinidine to obtain a negative EPS.

In case of negative EPS, a quinidine treatment was proposed to the patient without ICD implantation even in the case of cardiac arrest. Using this approach, the authors obtained excellent results because no cardiovascular deaths occurred during the mean follow-up of 113 months.

The study raises 2 interesting questions: (1) What is the value of EPS to determine the arrhythmic risk in a patient with Brugada syndrome? and (2) Is quinidine a safe alternative to ICD to prevent sudden death?

The first question has been debated for years. Up to now, most of the studies on this topic have consisted in performing EPS and implanting an ICD if the EPS was positive. Therefore, all of these studies have a major bias in terms of the way the follow-up was performed depending on the results of the EPS. If the EPS was positive, the patient was implanted with an ICD, and he or she then benefitted from a perfect follow-up with a continuous recording of the ECG. On the contrary, if the EPS was negative, no treatment was proposed, and the patient only had yearly clinical follow-up. It is clear that the chance of detecting an arrhythmic event is not the same in these 2 situations, in particular, owing to self-limited ventricular arrhythmia that can be asymptomatic. This may, at least in part, explain the positive results of EPS in studies that did not include ICD implantation in the evaluation of the value of EPS. This is also probably the reason that the only prospective study to evaluate EPS was negative.4 This study also underlies questions about reproducibility of a positive EPS, with standard protocol, achieved in only one-third of patients.4

The study by the Belhassen group should be of particular interest to resolve this debate. However, the protocol used in the study is extremely aggressive and different from what is usually performed. Therefore, the percentage of inducible patients was extremely high (100% in aborted cardiac arrest patients, 74% in case of syncope, and 61% in asymptomatic patients). In that case, it is difficult to evaluate the value of EPS because the group with a negative EPS was too small (only 20 patients).
Regarding this study, it could be tempting to consider quinidine as a safe alternative to the implantation of an ICD. Unfortunately, it is probably not so simple!

Indeed, a large proportion of the patients included in the study were asymptomatic without a spontaneous aspect of Brugada syndrome (50 patients). This sort of patient is not usually treated at all because the risk of a cardiac event is low and the guidelines only propose annual follow-up.

For the rest of the population and more specifically the patients who experienced sudden cardiac death, it is difficult to draw a definite conclusion on the possibility of avoiding ICD implantation. The population was relatively small, and more importantly, only 2 patients were treated with a class 1 anti-arrhythmic drug alone at the end of the study with 6 of 10 patients ultimately receiving an ICD.

There are several reasons that so few patients remained on class 1 anti-arrhythmic drug only. First, many patients experienced side effects (38%) that led to the discontinuation of treatment. It is also certain that in this situation of high risk of sudden death, it would be disquieting for the patients to be without the protection of an ICD.

Finally, the question raised by this work is the following: do we really need a medical alternative to ICD implantation? The answer is certainly yes if the treatment is highly efficient and well tolerated. However, regarding the frequent side effects of quinidine, this drug is probably not the perfect candidate. Furthermore, a recent study failed to demonstrate a beneficial effect of quinidine treatment in Brugada syndrome patients.10  However, ICD technology has made significant progress over the last year in terms of battery longevity and inappropriate shocks with a dramatic reduction of their frequency using remote monitoring and good programming of the ICD. It is true that lead failure in this young and active population remains the main challenge. One can expect that the possibility now offered by subcutaneous ICD will solve this problem even if the experience with this type of device is still limited, and the frequency of inappropriate shocks a matter of concern.

In any case, Belhassen et al must be thanked for the originality and the novelty of the work presented in the journal. Quinidine is of great interest in case of an electrical storm and the novelty of the work presented in the journal is a matter of concern.

Disclosures

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References


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