Does Bepridil Create a Paradigm Shift in the Treatment of Persistent Atrial Fibrillation?

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Two therapeutic strategies exist for the treatment of persistent atrial fibrillation (AF): electrical (or pharmacological) cardioversion followed by antiarrhythmic drugs (rhythm control) or control of heart rate during AF (rate control). Both therapies are reported to be comparable in terms of mortality, whereas rhythm control may be preferable in terms of preserving the quality of life! In the ACC/AHA/ESC 2006 Guidelines describing the treatment of recurrent persistent AF, patients with symptoms favoring sinus rhythm should be treated with an antiarrhythmic drug before cardioversion, as shown in Figure 1, in which bepridil is not included in the antiarrhythmic drugs for rhythm control.

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Bepridil was introduced as an antianginal agent in the early 1980s in Europe, and the usefulness of low-dose bepridil in converting persistent AF to sinus rhythm has been reported from Japan since the early 2000s. Although most reports are consistent with regard to the effectiveness of bepridil, the results do not seem to completely validate bepridil’s dose-response effectiveness and safety because previous studies were limited with regard to patient selection, trial setting and methods of assessing the recurrence of AF after conversion to sinus rhythm.

Here in this issue of the Journal, Yamashita et al report on a clinical trial to determine the dose–response effects of bepridil, the J-BAF study, which was a multicenter, randomized, placebo-controlled and parallel group study in patients with persistent AF. According to the authors, the conversion success rate was 37.5% for a dose of 100 mg/day, and 69.0% for a dose of 200 mg/day of bepridil alone, which was high and seems to be almost equivalent to previously reported success rates, which ranged from 34% to 58% with dosages of 100–200 mg. The dose-dependent effectiveness of bepridil demonstrated in the J-BAF study has already been accepted as 1 of the main pieces of evidence in the Guidelines for the Pharmacotherapy of Atrial Fibrillation (JCS 2008) and may greatly affect physicians strategies for treating persistent AF.

However, the authors also emphasize that bepridil should be used carefully, with close monitoring, because of its adverse effects, including sudden cardiac death (1.1%). I recently experienced a case of ventricular fibrillation caused by bepridil in a 64-year-old woman with a body weight of 51.5 kg who was suffering from paroxysmal AF that had been well controlled by a daily dose of bepridil (200 mg) + verapamil (80 mg) for approximately 1 year. She collapsed suddenly during the day at a railway station, where she was resuscitated and cardioverted with an automated external defibrillator (Figure 2a). Marked QT prolongation and frequent premature ventricular complexes occasionally triggering torsades de pointes (TdP) waves were documented in the emergency room (Figure 2b). The referring physician stated that she was carefully followed in his outpatient clinic by periodic ECG recordings; however, the ECG recorded 2 weeks before the index admission revealed remarkable QT prolongation (QTc 0.53) as shown in Figure 2c.

Twenty years ago, Perelman et al compared bepridil with amiodarone in the treatment of persistent AF and reported that 3 weeks of bepridil (200–600 mg/day) was slightly more effective than 2–3 months of amiodarone (100–400 mg/day) in converting AF to sinus rhythm (9/14 vs 4/10 patients, respectively). However, they concluded that bepridil was unsuitable for the management of AF because it was associated with the development of ventricular...
lar arrhythmias in 8 of 14 patients; in 1 of 2 patients with TdP, the arrhythmia degenerated into fatal ventricular fibrillation. On the basis of the clinical data, bepridil has not been used for the treatment of AF in Europe or the USA. Because the cardiovascular mortality rate of Japanese AF patients is low (0.6–1.3%/year) the rate of sudden cardiac death observed in the J-BAF study should be emphasized. Bepridil administration was discontinued in 4 of 90 patients because the QT interval became remarkably prolonged, and, moreover, this study was performed by cardiologists with experience and knowledge of bepridil in the selected patients, most of whom were non-elderly males with preserved systolic left ventricular function. Taking this into account, the TdP occurrence rate may have increased to more than 1.1%. As stated in the ACC/AHA/ESC 2006 Guidelines, antiarrhythmic drugs are recommended before non-pharmacological therapy, mainly because they may be much safer than catheter ablation. It should be discussed whether bepridil is preferable to catheter ablation in patients with symptomatic persistent AF. In the largest clinical study of bepridil administration for AF, TdP occurred in 4 of 459 patients (0.9%). An atrioesophageal fistula after left atrial radiofrequency catheter ablation of AF, which is the main cause of procedure-related death, was reported to occur in 6 (0.029%) of 20,425 patients having undergone AF ablation resulting in a complication rate that appears to be lower than the sudden cardiac death rate related to bepridil. Yamashita et al’s study, which reveals both the high efficacy and possible high risk of bepridil for the treatment of persistent AF, will make us face a crucial and important issue: can we select bepridil as the first-line therapy for rhythm control in the non-invasive treatment of persistent AF? Because AF is not a fatal arrhythmia and we have a useful alternative, catheter ablation, and will have promising antiarrhythmic drugs such as dronedarone, bepridil may be used in low doses (≤150mg/day?) with close monitoring in selected persistent AF patients, even if its powerful ability to cardiovert AF to sinus rhythm is attenuated.

References