Persistent atrial fibrillation (AF) is quite difficult to convert to sinus rhythm by spontaneous or pharmacological means. Although electrical conversion or catheter ablation may be an alternative therapy choice, some patients do not find these invasive treatments acceptable. If aiming for pharmacological sinus conversion, amiodarone has been mainly chosen despite its limited efficacy. In contrast, bepridil, which is only available as an anti-arrhythmic drug in Japan, is known to have a superior defibrillation effect against persistent AF. According to recent clinical reports, bepridil achieves more than approximately 60% of the sinus conversion rate for persistent AF. The high maintenance effect of sinus rhythm after pharmacological or electrical conversion has also been confirmed. In addition, bepridil helps prevent the recurrence of AF even after catheter ablation. A concern with bepridil is the adverse complication of QT prolongation and subsequent occurrence of torsades de pointes due to strong potassium channel blocking effects. Although scrupulous attention is always required for follow-up, bepridil could be a unique choice of drug among those drugs on the current therapeutic scene for patients with persistent AF.

**Key words:** persistent atrial fibrillation, defibrillation, torsades de pointes, bepridil

**Introduction**

Persistent atrial fibrillation (AF) is defined as AF lasting for more than 7 days and converted to a sinus rhythm by electrical or pharmacological means. If the AF lasts more than a year, it is classified as long–lasting persistent AF. It is well known that spontaneous sinus conversion is quite difficult, particularly in long–lasting type of persistent AF. Therefore, rate control therapy under appropriate anticoagulation is recommended as the initial treatment in these patients. If rhythm control is considered favorable for the patient, electrical–or pharmacological sinus conversion methods,–or catheter ablation are indicated. And if pharmacological therapy is considered, amiodarone has mainly been chosen as the most effective drug for attaining sinus conversion based on a previous study. On the other hand, bepridil hydrochloride, which is only available in Japan and is no longer used in the Western countries due to the high incidence of adverse complications, has proved effective for sinus conversion in recent clinical studies. Bepridil has a unique pharmacological mechanism that converts persistent AF to sinus rhythm, which is reflected in the current guidelines for pharmacotherapy of AF by the Japanese Cardiology Society (JCS2013). In addition, bepridil has favorably contributed to preventing AF recurrences during follow-up, even in patients who have had post-ablation procedures for persistent AF.

In this review, the author describes the overview of current antiarrhythmic drug therapy for persistent AF, with particular focus on the clinical efficacy and limitations of bepridil for treating persistent AF.

**Choice of drugs based on the guidelines**

According to the current guidelines on Pharmacotherapy for AF (JCS2013), pharmacological conversion is only indicated in patients without
organic heart disease. If the patient has organic heart disease such as left ventricular hypertrophy, a congestive or depressed functional heart, or an ischemic heart, rate control under appropriate anti-coagulation therapy is proposed from the view point of avoiding the side effects of anti-arrhythmic drugs. However, in a patient without organic heart disease, if defibrillation is required for prior to ablation therapy, there is no improvement of symptoms by rate control therapy, and/or non-pharmacological treatment is not desired, pharmacological treatment with bepridil is indicated, with careful attention to its proarrhythmic effects. Sotalol and amiodarone, which were conditionally available as drugs of choice for defibrillation purposes in the previous guidelines (JCS2008), are no longer recommended in the current guidelines.

Characteristics of bepridil

Bepridil hydrochloride is classified as a Ca\(^{2+}\) antagonist with an anti-anginal effect. It also suppresses multiple-ion channels including Na\(^+\) and K\(^+\) channels, similar to amiodarone. It is metabolized by the liver and has a long half-life about 12 hours. It is also known to be substantially excreted by the kidney. It takes about 2-3 weeks for blood level to reach steady state and drug efficacy to be observed.

In Japan, after its introduction on the commercial market the anti-arrhythmic effect of bepridil has drawn attention rather than its anti-anginal effects. In 1992, the first reimbursement was approved as drug to treat refractory ventricular arrhythmias. Thereafter, it was also approved in 2008 for treating persistent AF because of its excellent defibrillation effect in patients with persistent AF and its sinus rate maintenance effects after conversion. However, there is a concern of QT prolongation and occurrences of torsades de pointes (TdP) due to K\(^+\) channel suppression. Therefore, appropriate indications and cautious follow-up are suggested when using bepridil. The prevention of TdP due to QT prolongation is the most important issue during treatment with bepridil.

Efficacy of bepridil for persistent AF

There are few reports regarding the clinical efficacy of bepridil because it is no longer available in Western countries. As previously described, favorable defibrillation effects have been reported in Japan. In the author’s experience, 170 patients with persistent AF (average duration, 3.3 months) received bepridil and 98 patients (58%) returned to sinus rhythm within an average of 2.2 months after starting bepridil. Adding 34 cases with successful electrical defibrillation whom pharmacological defibrillation was failed, total 132 patients returned to sinus rhythm. Among them, 86 cases (78%) maintained sinus rhythm during the follow-up period, with an average follow up of 20 months. In the multicenter J-BAF (Japanese Bepridil in Patients with Persistent Atrial Fibrillation) clinical trial, 92 cases with persistent AF were randomly assigned one of 3 groups in double-blind fashion; placebo, bepridil 100 mg/day, or bepridil 200 mg/day. Patients’ clinical conditions were recorded every day and at the time of AF onset by ambulatory electrocardiograms for 12 weeks. In this trial, the sinus rhythm conversion rate, quality of life (QOL) evaluation, incidence of AF relapse, and safety were evaluated. The results showed that conversion to sinus rhythm from AF was apparently dose-dependent. Sinus conversion was observed in about 40% of cases receiving 100 mg/day group and about 70% of cases receiving 200 mg/day group within 6 weeks after starting bepridil. Although the efficacy was apparent, the rate of AF recurrences, confirmed by ambulatory electrocardiogram, was relatively high. A constant sinus rate was achieved by 21% of cases receiving bepridil 200 mg/day and 8.3% in those receiving bepridil 100 mg/day. Bepridil did not have an excellent sinus rate maintenance effect in this study. However, in many cases, even if a recurrence occurred, subjective symptoms were alleviated or disappeared. From the viewpoint of QOL, bepridil seems to be effective.

In a recent study, bepridil showed superior sinus conversion efficacy versus amiodarone. Yamase et al. compared amiodarone and bepridil in 40 consecutive patients with persistent AF in a prospective, randomized fashion. Sinus rhythm was restored in 7 of 20 patients (35%) in the amiodarone group and in 17 of 20 (85%) in the bepridil group. The bepridil group had a significantly higher sinus conversion rate compared to amiodarone (p<0.05). After pharmacological or electrical cardioversion,
sinus rhythm was maintained in 50% of patients in the amiodarone group with an average follow up of 14.7 months and in 75% of patients in the bepridil group with an average follow-up of 15.6 months. These results establish bepridil as a unique choice of drug for converting persistent AF to sinus rhythm with pharmacotherapy in Japan.

Catheter ablation of persistent AF is currently popular in clinical practice and bepridil is often used pre- or post-procedure in Japan. Miyazaki et al. retrospectively studied 82 patients with persistent AF who underwent AF ablation. The success rate of ablation was compared between those who were pretreated with bepridil (n=22) and a non-pre-treated group (n=60). In pretreated group, 15 cases were converted to sinus rhythm with bepridil before ablation and 7 failed to convert to sinus rhythm. Ablation was successfully performed in both groups, but the AF-free rate after ablation was significantly higher in the sinus converted cases than in unconverted cases. The authors concluded that conversion to sinus rhythm with bepridil might help select the optimal candidates with persistent AF for catheter ablation. Kondo et al. performed catheter ablation in 122 consecutive patients with persistent AF and administered antiarrhythmic drugs (bepridil in 46 cases, amiodarone in 20 cases, sodium channel blockers in 56 cases) after the initial ablation. AF-free survival was significantly better with bepridil than with amiodarone (p=0.012) and sodium channel blockers (p=0.018) in patients with the post-ablation procedure for persistent AF. Now bepridil is recognized as standard drug after ablation in Japan.

Adverse effects of bepridil

The most serious side effect of bepridil is QT prolongation, which may subsequently lead to TdP due to K⁺ channel suppression. In Western countries, where the maximum dosage of bepridil (600 mg/day) used was significantly higher in clinical practice, TdP was frequently reported. Therefore, bepridil was branded as a drug with dangerous side effects and taken off the market despite its superior anti-arrhythmic actions. Bepridil is still available in Japan at an appropriately lower dose (100–200 mg/day) and the evidence regarding efficacy and adverse effects, including TdP, has accumulated. Yasuda et al. investigated the incidence of side effects in a total of 459 patients treated with bepridil. QT prolongation was observed in 13 cases (2.8%) and 4 cases (0.9%) among them developed TdP. They found that the triggers for TdP were elderly age, bradycardia, excessive baseline QT prolongation, and lower serum K⁺ concentrations. Additionally, QT prolongation was also observed in patients with concomitant use of diuretics, which often induce hypokalemia. Bradycardia under general anesthesia before surgical treatment also causes QT prolongation and may induce TdP. Scrupulous attention is required to these patients.

Interstitial pneumonia is another serious adverse complication that has drawn attention, and depend on the increased use of bepridil. Vasiomanolakis et al. reported the first case of interstitial pneumonia associated with bepridil in 1993. This side effect has been described in the drug prescribing information since bepridil’s initial introduction in Japan; however, only sporadic cases are reported. The onset of interstitial pneumonia is usually 1 to 2 months, but in some cases can occur 6 months or longer after starting bepridil. If the condition is serious, steroid pulse therapy and intensive oxygen therapy might be required. Therefore, it is important to identify the early stages of interstitial pneumonia by having patients get regular clinical examinations. Once interstitial pneumonia is suspected, bepridil should be discontinued.

Usefulness of blood monitoring

Measurements of bepridil concentration levels in blood might be useful for preventing adverse effects in patients treated with bepridil. Kurita et al. indicated that all cases of TdP during bepridil therapy had a blood level of 500 ng/ml or more. Kamakura et al. reported that safe and effective bepridil blood concentration levels that were needed to improve clinical symptom were appropriately 600–1,000 ng/ml. In our experience, the blood concentration of bepridil was positively correlated to the QT interval in 41 patients with AF. In those cases, one of whom developed into TdP, the QT interval was prolonged to 0.6 sec or
more and the bepridil blood level was as high as 1,200 ng/mI. Another study also reported that QTc was over 0.5 or more if the bepridil blood concentration levels exceeded 800 ng/ml. Based on these data, a QT interval less than 0.5 sec and a bepridil blood concentration level less than 800 ng/ml would be the safe index for preventing TdP during bepridil administration. Considering that bepridil shows dose-dependent side effects, measurement of bepridil blood concentrations, which is currently reimbursed in clinical practice, should be applied as well as other anti-arrhythmic agents appropriate for use with this drug.

**Application for patients with reduced cardiac function**

In general, bepridil should not to be used in patients with reduced cardiac function because it has Ca$^{2+}$ channel blocking effects and has mild Na$^+$ channel suppressive action. On the other hand, bepridil has relatively strong K$^+$ channel suppression effects like class III drugs. In addition, a basic study demonstrated that bepridil has Ca$^{2+}$ sensitizing effects and might be cardio-protective in some situations. Used carefully, bepridil may be beneficial even in patients with reduced cardiac function. Josephson et al. reported that intravenous bepridil led to significant negative inotropic effects and reduced the left ventricular function in cases with left ventricular ejection fraction (LVEF) rates of $\leq$ 45%. Meanwhile, De Marco et al. reported that LV function was not exacerbated by administering oral bepridil in patients with impaired LV function. No evidence for oral bepridil use in patients with reduced cardiac function was observed other than in this report. Currently, there is still very limited experience regarding this patient population. At the author’s center, we administered bepridil to 22 patients with impaired cardiac function. In 481 cases with paroxysmal or persistent AF, the clinical parameters were compared between a group with LVEF $>$ 40% (n=459) and a group with LVEF $<$ 40% (n=22). There was no statistically significant difference in efficacy and, interestingly, all adverse effects were observed in the group with LVEF $>$ 40%. No complications were observed in patients with LVEF $<$ 40%. These results may suggest that physicians were aware the potential risks of bepridil use in such cases, and carefully followed up with the patients to avoid adverse complications. Therefore, we consider that bepridil can be used even in patients with reduced cardiac function if it is kept at the appropriate dose and patients are carefully followed-up with routine examinations, including electrocardiograms and blood sampling.

**Conclusion**

In this review, the author reports the current pharmacological strategies for persistent AF and focuses on the efficacy and safety of bepridil as a unique drug only available in Japan. Bepridil undoubtedly has promising sinus conversion and maintenance effects, but serious adverse complications may also occur. Therefore, the appropriate indication and careful follow-up should be mandatory.

**Conflict of interest**

The authors declare no conflict of interest associated with this manuscript.

**References**