Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and the occurrence of AF increases with age. The morbidity and mortality associated with AF are relatively high and AF adversely affects the quality of life. Therefore, treatment of AF is very important in clinical settings. Non-pharmacological treatment of AF with catheter-based pulmonary vein ablation or isolation has considerably progressed and it may be successfully used in younger and symptomatic patients with refractory paroxysmal AF. In addition, introduction of novel anticoagulants such as dabigatran may have a great impact on the treatment of AF. Many large-scale clinical trials comparing rate control with rhythm control have not yet indicated that rhythm control is any better than rate control in decreasing morbidity and mortality rate of AF patients. One possible explanation for the ineffectiveness of rhythm control is that proarrhythmic risk and toxic effects associated with currently available antiarrhythmic drugs adversely affect outcomes. Antiarrhythmic drugs currently used for AF treatment sometimes prolong QT interval and produce conduction disturbance. Many efforts have been made to discover an ideal antiarrhythmic drug that can effectively and safely terminate AF and prevent AF recurrence. One of ideal candidates may be an antiarrhythmic drug with selective affinity for the ion channels through which atria-specific K⁺ currents flow. Dronedarone is a multichannel blocker having a chemical structure similar to amiodarone. The drug acutely inhibits $I_{Na}$, $I_{Ca}$ and $I_{Kr}$, as shown in Figure 1. The drug also potently inhibits the atria-specific K⁺ current $I_{K.ACh}$. A large-scale clinical trial indicated that dronedarone significantly reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF as compared to placebo. However, it has been reported that the drug may increase early mortality in patients with severe heart failure and left ventricular systolic dysfunction. Vernakalant (RSD1235) is atria-specific K⁺ channel through which $I_{Kur}$ flows. The drug inhibits not only $I_{Kur}$, but also $I_{to}$, $I_{Kr}$ and $I_{Na}$ in similar concentrations (Figure 1). It was reported that the new atrial-selective antiarrhythmic drug was efficacious and safe for converting recent onset
AF to sinus rhythm after intravenous administration.\(^{11}\) Taking the electropharmacological effects into consideration, however, we would have to be careful in monitoring prolongation of QT interval and QRS complex in ECG after administration of vernakalant.

More recently a highly selective acetylcholine-receptor operated K\(^+\) channel blocker, NTC-801, has been developed as an atrial-selective antiarrhythmic drug in Japan.\(^{12}\) The drug selectively inhibits \(I_{K.ACh}\) and does not affect other ionic currents such as \(I_{Na}, I_{Kr}, I_{Ks}, I_{to}\) or \(I_{K1}\) (Figure 1). The drug has been shown to convert AF to sinus rhythm in various AF models of experimental animals.\(^{12}\) Paroxysmal AF occurring at night, at rest, and/or after meals or alcohol may be triggered at least partly by activation of \(I_{K.ACh}\). Atrial cells from patients with chronic AF are reported to show constitutively active \(K_{ACh}\) channel current.\(^{13}\) It has been reported that NTC-801 can decrease AF inducibility in an AF model with electrical remodeling. Therefore, NTC-801 may become a unique anti-AF drug without electrophysiological side effects in the ventricle.

Several oral anticoagulants with novel mechanisms have been developed and are being clinically available in the near future. Therefore, rate control strategy will become the first choice for the treatment of AF, especially persistent AF. However, if an effective atrial-selective antiarrhythmic drug without serious side effects is developed, rhythm control may become another choice of AF therapy.

References

Figure 1 Effects of novel antiarrhythmic drugs, dronedarone, vernakalant and NTC-801, on ionic currents involved in atrial action potential.

Ionic currents indicated by shaded circle are assumed to be atria-specific.