Quinidine rehabilitated and more lessons from the PAFAC and SOPAT anti-arrhythmic drug trials for the prevention of paroxysmal atrial fibrillation

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This editorial refers to "Suppression of paroxysmal atrial tachyarrhythmias — results of the SOPAT trial" † by M. Patten et al. on page 1395

Although two recently published studies1,2 showed that rate control of persistent atrial fibrillation (AF) is not inferior to rhythm control, the maintenance of sinus rhythm and suppression of AF remain desirable in selected cases, especially in very symptomatic and often young patients.3 After successful electrical cardioversion or repeated bouts of AF, the selection, dosage and timing of an anti-arrhythmic treatment to prevent new AF recurrences, as well as the decision whether to hospitalise the patient for its initiation, constitute a series of difficult decisions in terms of efficacy, safety and cost-effectiveness. One of the oldest anti-arrhythmic drugs to prevent AF is quinidine but in the past decade its efficacy and safety was so heavily refuted that the frequency of description of this drug dropped dramatically.4 Of note, it has become clear that the diagnosis of recurrences of AF to determine the efficacy of administered treatment cannot simply rely on AF symptoms, because this arrhythmia very often emerges without symptoms in contrast to supraventricular re-entry tachycardia.5

The PAFAC and SOPAT trials published in this issue6,7 offer important innotivative findings to refresh our decision making in the prevention of AF following successful DC cardioversion or new recurrences of AF. The PAFAC trial is a large scale, double-blinded, multi-centre German–Czech study comparing the efficacy and safety of fixed dosages of sotalol (320 mg daily) with those of fixed dosages of quinidine (480 mg daily) combined with verapamil (240 mg daily) whereas a placebo group served as control. The clinical profile of the patient population (n=848) disclosed a relative short history of AF of an average of one year, mild heart failure in about 50%, valvular heart disease in 40% and ischaemic heart disease in about 30% of the patients, reflecting a population with a low cardiac sickness profile. The longstanding electrical atrial remodelling of these patients negatively affected DC cardioversion, namely 28% failure or very early AF recurrence afterwards. Daily trans-telephonic collection of electrocardiographic 1-min recordings of all included patients was applied to diagnose rhythm patterns, totalling more than 190 000 strips. The automated voice control system asked AF-specific questions allowing the comparison of ECG findings with symptoms. Although the quinidine/verapamil combination maintained the sinus rhythm better than sotalol, the one-year AF-free proportion was disappointing: 62% and 51%, respectively, and 23% on placebo. These findings are fully in line with previous studies with anti-arrhythmics after DC cardioversion. Not surprisingly, most documented recurrences occurred early after DC cardioversion and initiation of the study drugs and were frequently asymptomatic (70%). Unfortunately, quality of life was not determined in this study.

The SOPAT trial is a large scale, double-blinded, multi-centre German–Polish–Slovenian study comparing the efficacy and safety of fixed dosages of sotalol (320 mg daily), high and low fixed dosages of the combination of quinidine/verapamil (480/240 and 320/160 mg daily, respectively) versus a control group. The clinical profile of the patient population (n=1012) showed a longer history of AF of an average of 3 years with a mean of two
symptomatic AF episodes. Half of the patients had high blood pressure whereas the frequency of valvular heart disease (12%) and ischaemic heart disease (21%) was small also indicating a low cardiac sickness profile. The study treatment was administered in half of the patients after failure of class 1 and/or 3 anti-arrhythmic drugs without preceding DC cardioversion. Comparable to the PAFAC study, daily trans-telephonic collection of electrocardiographic 1-min recordings was carried out and symptoms were recorded, totally more than 180,000 strips. The efficacy of the high and low dosage quinidine/verapamil combination was highly comparable with that of sotalol but the one-year AF-free proportion was also not impressive: about 50% versus 38% on placebo. Half of the recordings showed that AF was not accompanied with symptoms whereas, if symptoms were noted, palpitations constituted the majority. Quality of life was also not determined in this study. The outcomes of both trials initiate the speculations below:

Re-appraisal of quinidine? In the last decade the popularity of this class I anti-arrhythmic drug has dropped dramatically. Fear of gastrointestinal side-effects, thrombocytopenia and specifically the unpredictable pro-arrhythmia consisting of torsades de pointes ventricular tachycardia due to prolonged repolarisation diminished its use. In addition, if AF emerges high ventricular rates can be expected to occur due to enhanced AV conduction associated with quinidine treatment, provoking even more trouble. The PAFAC and SOPAT trials strongly suggested that the current reluctance to prescribe quinidine is not fully justified. The high and low dosages of quinidine combined with verapamil showed superiority (PAFAC) or a similar efficacy (SOPAT) in suppression of AF and maintenance of sinus rhythm as compared to the daily fixed dosage of 320 mg sotalol. Additionally, frequency of adverse effects of the PAFAC trial was equal in both regimens but particularly noteworthy is that torsades de pointes ventricular tachycardia was exclusively documented in the sotalol arm. Torsades de pointes ventricular tachycardias were not observed in the SOPAT trial and only one case of sustained ventricular tachycardia in the quinidine/verapamil groups of this study. These findings do not converge with the results of a recent meta-analysis of the efficacy of seven anti-arrhythmic drugs to maintain sinus rhythm after successful DC cardioversion. Evidence of efficacy was strong for amiodarone, propafenone, disopyramide and sotalol whereas quinidine showed moderate efficacy comparable with flecainide and azimilide. This difference can be ascribed to the co-administration of verapamil, which is capable of suppressing afterdepolarisations underlying the onset of torsades de pointes ventricular tachycardia associated with class 1 and 3 anti-arrhythmic drugs. Although further studies exploring patient-tailored dosages of the quinidine/verapamil combination are needed, these findings can restore our confidence in quinidine, particularly when given in combination with verapamil.

In-hospital initiation of anti-arrhythmic drugs for AF? Whether patients should be admitted in the hospital to diminish pro-arrhythmic risks during the initiation of anti-arrhythmic drug therapy for the treatment of AF is a matter of ongoing debate. According to expert opinion, patients without structural heart disease, sinus node dysfunction, disturbed AV conduction or ventricular hypertrophy and a normal baseline QT interval do not need to be admitted in contrast to those with overt heart disease. In the PAFAC study all patients were discharged at the fourth day after successful DC cardioversion and initiation of the study anti-arrhythmic drugs. In this period 65% of all pro-arrhythmic events and life-threatening arrhythmias occurred. These findings advocate a for at least 3 days in-hospital continuous rhythm monitoring of the above mentioned risk patients after starting sotalol or quinide therapy (and possibly other anti-arrhythmic drugs), to detect and manage these serious side-effects.

On the other hand, the first dose of the study drug was only monitored at the study site in the SOPAT trial and the frequency of fatal arrhythmias was clearly lower than in the PAFAC trial. Although it remains unclear whether most arrhythmic side-effects clustered early in the SOPAT study, these findings suggest that, in younger AF patients with or no minimal structural heart disease as was the case in the SOPAT trial, outpatient initiation of AF drug treatment can be safely performed. Additional arguments for this policy can probably be offered with the results of subgroup analysis of the PAFAC study. Finally, daily automated trans-telephonic rhythm monitoring will certainly improve the safety of patients with recently installed drug treatment and this approach warrants more application in supposed high risk AF patients.

How should we assess the efficacy of anti-arrhythmic drugs? In contrast to the RACE and AFFIRM studies, all patients of the PAFAC study transmitted a 1-min single lead ECG to the automated data base daily in conjunction with answering questions about symptoms and remarks from the patient. This allowed study of the correlation of symptoms with the actual rhythm and more importantly to begin measures in case of side-effects and recurrence of AF immediately. Both trials disclosed that 50–70% of all documented AF episodes emerged without symptoms, a proportion that is in concert with the previous excellent study of Page et al. The authors of both studies correctly challenge the significance of AF symptoms as the valid tool to assess AF burden and efficacy of anti-arrhythmic drugs. These findings indicate that the use of the daily trans-telephonic patient contact constitutes a remarkably innovative and indispensable technique in the field of anti-arrhythmic drug studies. This technique can only be surpassed by implanted pacemakers and implantable defibrillators with current extensive storing facilities and automated detection of arrhythmias, time of onset, analysis of types and rates with and without patient activation of storing. In the coming years AF studies with intensive rhythm monitoring should become the standard technique and improving our insight into the type and frequency of AF recurrence and AF burden, and to quantify the efficacy of drugs and ablative procedures.

Are current AF definitions correct? In view of the large percentage of asymptomatic AF episodes of both trials, the PAFAC authors also challenge the validity of the current AF classification that eventually determines and guides all therapeutic steps. For example, daily rhythm
monitoring can demonstrate that asymptomatic paroxysmal AF alternates daily with episodes of sinus rhythm: a specific pattern that should be classified as ‘‘persistent paroxysmal AF’’. In this case the 3P classification of AF\textsuperscript{11} to quantify the frequency and intensity of this AF pattern and to guide the management appears to be unsatisfactory. In addition, the length of the interval of preserved sinus rhythm is of more importance than that of AF because in the former condition, reversed remodelling of the atrial cardiomyocytes can occur, ameliorating the electrophysiological conditions to prevent or suppress AF (‘‘sinus rhythm begets sinus rhythm’’). This concept is not all covered by the 3P classification. Thus our view on AF mechanisms, efficacy of anti-arrhythmic drugs and AF cardioversion using intensive trans-telephonic rhythm monitoring will offer much more information and therefore needs a more detailed classification system of AF.

In conclusion, the findings of both studies will undoubtedly spark a new discussion on the role of monitoring techniques to detect the true incidence of AF, and on the classification of AF as well as the efficacy of the quinidine/verapamil combination in the treatment and prevention of AF. For this contribution, the PAFAC and SOPAT investigators should be acknowledged.

References


