CREATIVE CONCEPTS

New concepts for old drugs to maintain sinus rhythm in patients with atrial fibrillation

Paulus Kirchhof, MD,*† Günter Breithardt, MD*†

*From the *Department of Cardiology and Angiology, Hospital of the University of Münster, Münster, Germany, and †German Atrial Fibrillation Competence NETwork (AFNET).*

Atrial fibrillation (AF) is a chronic, often progressive disease. Despite the ongoing concerted effort to improve AF therapy, often there is no remedy for curing AF and preventing the deleterious effects of the arrhythmia on health. Antiarrhythmic drug therapy is likely to remain the mainstay of therapy for many patients in the foreseeable future. Available antiarrhythmic drugs are moderately effective, which is important for patients who respond, especially given the chronic and often progressive nature of the disease. This article describes emerging concepts under clinical evaluation that attempt to improve the safety of available antiarrhythmic drugs in the treatment of recurrent AF. Two concepts are reviewed: (1) combination of an antiarrhythmic drug with a calcium channel blocker to reduce proarrhythmic side effects, and (2) "intelligent" reduction of the duration of antiarrhythmic drug therapy targeted to periods of symptomatic or likely AF recurrence.

KEYWORDS Atrial fibrillation; Drug therapy; Pathophysiological concept; Proarrhythmia; Drug safety; Rhythm control

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Atrial fibrillation (AF) is the most common sustained arrhythmia.[1,2] It is a "silent killer" associated with relevant mortality.[3,4] Symptoms range from asymptomatic arrhythmia attacks (likely the majority of episodes[5,6]) to acute cardiac failure. Although no formal test has proved that maintenance of sinus rhythm ("rhythm control therapy") alleviates the burden of this disease,[7] it is generally assumed and supported by observational data and subanalyses of randomized trials that symptomatic patients benefit from rhythm control therapy[2,4,7,8] in terms of morbidity,[9,10] quality of life,[11] and left ventricular function.[4,9,10]

In controlled trials, chronic administration of antiarrhythmic drugs (mainly potassium and sodium channel blockers) approximately doubled the rate of sinus rhythm during follow-up.[5,11] This "classic" ion channel-blocking antiarrhythmic therapy remains an important therapeutic modality in rhythm control treatment strategies,[2] possibly in combination with "upstream therapy" by inhibiting the renin–angiotensin and aldosterone system.[12,13]

However, the moderate effectiveness of antiarrhythmic drugs comes at the price of rare but potentially dangerous side effects, specifically the feared and unpredictable ventricular proarrhythmia.[14–16] In addition to the development of new, safer antiarrhythmic agents and interventional procedures, an intelligent use of existing drugs may help to maintain sinus rhythm while reducing side effects. Here we describe concepts currently under clinical evaluation that aim to reduce proarrhythmia, namely, the combination of antiarrhythmic drugs with "anti-torsades" substances, and tiered antiarrhythmic drug treatment for a limited time directed at reducing the duration of therapy.

Of cocktails: A remedy for proarrhythmia by combining quinidine and verapamil?

Quinidine is one of the oldest antiarrhythmic drugs. The original substance, isolated from the *Cinchona calisaya* plant, was used as a preventive medicine against malaria, but its antiarrhythmic action was reported more than 200 years ago. Quinidine has two major effects, namely, interference with cardiac sodium and potassium currents, and vagolysis. The vagolytic effects are believed to cause the gastrointestinal side effects of quinidine.[17–19] The sodium channel-blocking effect of the drug is believed to mediate the antiarrhythmic effect of quinidine.[15–18,20]

Unlike other antiarrhythmic agents such as propafenone[21] and d,l-sotalol,[19] quinidine can increase ventricular rate when AF recurs. Given the long-standing experience with

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quinidine, quinidine was a reference drug for prevention of atrial fibrillation. In 1990, a landmark meta-analysis of eight randomized trials (808 patients) confirmed that quinidine was effective in preventing recurrent AF, but the study identified a higher mortality [2.9% vs 0.8% per year, odds ratio 2.98 (1.1–8.3), $P < .01$] in patients treated with quinidine compared with controls.[16] The higher mortality in the quinidine group was attributed to ventricular proarrhythmia (torsades de pointes). These observations were confirmed in a more recent meta-analysis and prompted stoppage of quinidine use in the treatment of AF, although proarrhythmic side effects also were found when potassium channel blockers (d,l-sotalol) were used to prevent recurrent AF.[15,22]

Verapamil is a blocker of cardiac L-type calcium channels whose antiarrhythmic effects have been known for 40 years.[23] Verapamil slows AV nodal conduction,[24] causes constipation, and may prevent excessive calcium influx into the ventricular cardiomyocyte suspected of causing early afterdepolarizations and triggering torsades de pointes.[25,26] This combination of effects is almost a mirror remedy of the problems identified with quinidine. Based on knowledge of the potential complementary effects of quinidine and verapamil and data from the spontaneous reporting system of adverse drug events, two major trials were initiated in Germany after the "Arzneimittelkommission der deutschen Ärzteschaft" issued a warning on the use of quinidine in 1996. These trials compared a fixed combination of quinidine and verapamil (160 mg quinidine and 80 mg verapamil per tablet, given two [SOPAT (Suppression of Paroxysmal Atrial Tachyarrhythmias trial)] to three times daily [PAFAC (Prevention of Atrial Fibrillation After Cardioversion trial), SOPAT]) with d,l-sotalol (160 mg per tablet given twice daily) and placebo for prevention of AF after cardioversion (PAFAC) and for suppression of atrial tachyarrhythmias in patients with paroxysmal AF (SOPAT).[5,27] All patients underwent daily transtelephonic ECG monitoring to assess the primary endpoint of recurrent AF. The trials confirmed the effectiveness of the quinidine–verapamil combination. The proarrhythmia findings were surprising. In PAFAC, 9 (2.3%) of 383 patients in the d,l-sotalol group experienced the expected rate of torsades de pointes (often nonsustained). In contrast, no patient in the quinidine–verapamil group in PAFAC experienced proarrhythmia.[5] Similar to PAFAC, no excess death or proarrhythmia occurred in the two quinidine–verapamil groups in SOPAT (518 patients total).[27] One death and one episode of ventricular tachycardia were observed in the quinidine–verapamil arm in SOPAT, comparable to a case report.[28]

Based on these data, the current guidelines for treatment of AF of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology in association with the European Heart Rhythm Association and the Heart Rhythm Society suggest that "the combination of quinidine plus verapamil appeared useful to prevent recurrent AF after cardioversion of persistent AF," whereas quinidine monotherapy is not recommended.[2] Such an "antiarrhythmic cocktail" may be a valuable addition to the range of available antiarrhythmic agents in selected patients, although larger trials and a valid adverse event reporting system are needed to address the true proarrhythmic risk of the quinidine–verapamil combination. In this context, it is noteworthy that amiodarone, an effective antiarrhythmic drug to prevent recurrent AF,[11,29] has weak calcium channel-blocking properties.[30] This might partly explain why amiodarone rarely provokes proarrhythmia.[11,31]

Of "unhappy hours": Reducing the duration of antiarrhythmic drug therapy to periods when it is most needed

Although the majority of proarrhythmic side effects occur in the first days or weeks after initiation of treatment,[5,14,27] proarrhythmia is a constant threat during antiarrhythmic drug therapy. Female gender, left ventricular hypertrophy, a prolonged basal QT interval, and abnormal prolongation of the QT interval after exposure to the potentially proarrhythmic drug can identify patients at risk,[14] but triggers such as bradycardia or hypokalemia can aggravate an inherent predisposition to such proarrhythmia at any time.[14] Furthermore, transient reductions in hepatic and renal function, abnormalities of drug metabolism (e.g., abnormal function of cytochromes), and abnormal pharmacokinetics (e.g. altered expression or function of p-glycoprotein) may markedly increase serum drug levels.[32–34] Therefore, the risk for proarrhythmia must constantly be balanced against the potential benefit—theoretically prior to ingestion of every single tablet.

Reducing the duration of antiarrhythmic drug therapy will reduce the risk of proarrhythmic events. Currently, antiarrhythmic drug therapy to prevent AF is often used as long-term (theoretically lifelong) therapy. Two emerging concepts for therapy test whether the duration of antiarrhythmic drug therapy can be reduced to periods when pharmacological cardioversion still is feasible ("pill in the pocket") or when recurrent AF is likely ("targeted reversal of electrical remodeling").

"Pill-in-the-Pocket" Treatment to Convert Recent-Onset AF. Antiarrhythmic drug therapy can be used to acutely terminate recent-onset AF in the first hours of the arrhythmia.[35] This treatment concept requires that the patient recognizes and treats recurrent AF without medical assistance. In one recent study,[35] patients took a single dose of flecainide (300 mg) or propafenone (600 mg) as soon as AF recurred without ECG documentation of the arrhythmia. During the study period (210 patients, mean follow-up 15 months), the treatment effectively terminated 94% of AF episodes, and the rate of hospitalizations for AF was markedly reduced. No ventricular proarrhythmic events were observed.

Two reasons may explain the low incidence of proarrhythmia found in the trial. (1) In the study, 14 (5%) of 268 patients were excluded because of side effects of the initial in-hospital trial treatment with flecainide or propafenone,

thereby limiting study inclusion to patients who tolerated the first exposure without problems. (2) Antiarrhythmic drug therapy duration was reduced by 99.4% compared with standard long-term therapy, from 450 day-doses per patient (follow-up 15 months) to 2.7 day-doses per patient (569 treated episodes in 210 patients). In patients who meet the inclusion criteria for the study, "pill-in-the-pocket" treatment may help to reduce proarrhythmia.

"Targeted Pharmacological Reversal of Electrical Remodeling". It has long been known that AF is most likely to recur in the first weeks after cardioversion.[2,5] The descriptions of the processes that are summarized by the term "electrical remodeling"[36,37] provide an explanation for this observation. AF shortens the atrial action potential and refractory period. These "electrically remodeled" atria are more vulnerable to recurrent AF as long as the atrial action potential and refractory period are short.[36,37] The atria "recover" from electrical remodeling in 2–4 weeks after cardioversion to sinus rhythm ("reversal" of electrical remodeling).[36,37] The main electrophysiologic effect of many antiarrhythmic drugs is prolongation of the atrial action potential. Although this effect appears reasonable to prolong the short action potential in the remodeled atrium, why therapy should be maintained once the atrial action potential has regained its normal duration is less clear. Hence, action potential-prolonging therapy aimed at preventing recurrent AF after cardioversion possibly could be limited to a few weeks after cardioversion ("targeted pharmacological reversal of electrical remodeling"). One small pilot study (approximately 60 patients per group) suggested that short-term, 8-week amiodarone treatment is not inferior to long-term antiarrhythmic treatment after cardioversion in the prevention of recurrent AF.[38] The investigator-initiated, publicly funded Flec-SL ("*Flec*ainide *S*hort-*L*ong") trial currently is testing this hypothesis.[39]

The primary endpoint of the Flec-SL trial—recurrence of persistent AF—is measured by systematic ECG recordings, comparable to the PAFAC and SAFE-T [Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T)] trials.[5,11,39] After cardioversion, patients are randomized in one of three study groups. A small control group will stop flecainide treatment after cardioversion to demonstrate the effectiveness of the study drug in preventing AF in the study population (105 patients maximally). The two main study groups (325 patients each) will receive flecainide treatment either for 4 weeks ("targeted reversal of electrical remodeling") or for the entire trial duration (6 months, standard long-term treatment). The trial is powered for noninferiority testing between the latter two groups. Short-term treatment can reduce therapy duration by 66%–92% assuming a mean time from cardioversion to recurrence of 3–12 months.

In summary, the time course of reversal of electrical remodeling may provide a rationale to reduce the duration of antiarrhythmic drug therapy and thereby limit proarrhythmic side effects while maintaining the efficacy of therapy.

References

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham heart study. Circulation 2004;110:1042–1046.
2. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006;8:651–745.
3. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–364.
4. Elesber AA, Rosales AG, Herges RM, Shen WK, Moon BS, Malouf JF, Ammash NM, Somers V, Hodge DO, Gersh BJ, Hammill SC, Friedman PA. Relapse and mortality following cardioversion of new-onset vs. recurrent atrial fibrillation and atrial flutter in the elderly. Eur Heart J 2006;27:854–860.
5. Fetsch T, Bauer P, Engberding R, Koch HP, Lukl J, Meinertz T, Oeff M, Seipel L, Trappe HJ, Treese N, Breithardt G. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. Eur Heart J 2004;25:1385–1394.
6. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol 2004;43:47–52.
7. Testa L, Biondi-Zoccai GG, Dello Russo A, Bellocci F, Andreotti F, Crea F. Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis. Eur Heart J 2005;26:2000–2006.
8. Zimetbaum P. Is rate control or rhythm control preferable in patients with atrial fibrillation? An argument for maintenance of sinus rhythm in patients with atrial fibrillation. Circulation 2005;111:3150–3156.
9. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Scavee C, Bordachar P, Clementy J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373–2383.
10. Hagens VE, Van Veldhuisen DJ, Kamp O, Rienstra M, Bosker HA, Veeger NJ, Tijssen JGP, Crijns HJ, Van Gelder I. Effect of rate and rhythm control on left ventricular function and cardiac dimensions in patients with persistent atrial fibrillation: Results from the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study. Heart Rhythm 2005;2:19–24.
11. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD Jr, Raisch DW, Ezekowitz MD. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861–1872.
12. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005;45:1832–1839.
13. Lozano HF, Conde CA, Florin T, Lamas GA. Treatment and prevention of atrial fibrillation with non-antiarrhythmic pharmacologic therapy. Heart Rhythm 2005;2:1000–1007.
14. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. Eur Heart J 2000;21:1216–1231.
15. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. Arch Intern Med 2006;166:719–728.
16. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation 1990;82:1106–1116.
17. Sodermark T, Jonsson B, Olsson A, Oro L, Wallin H, Edhag O, Sjogren A, Danielsson M, Rosenhamer G. Effect of quinidine on maintaining sinus rhythm after conversion of atrial fibrillation or flutter. A multicentre study from Stockholm. Br Heart J 1975;37:486–492.
18. Normand JP, Legendre M, Kahn JC, Bourdarias JP, Mathivat A. Comparative efficacy of short-acting and long-acting quinidine for maintenance of sinus

rhythm after electrical conversion of atrial fibrillation. Br Heart J 1976;38:381–387.
19. Juul-Moller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. Circulation 1990;82:1932–1939.
20. Rossi M, Lown B. The use of quinidine in cardioversion. Am J Cardiol 1967; 19:234–238.
21. Lee SH, Chen SA, Chiang CE, Tai CT, Wen ZC, Wang SP, Chang MS. Comparisons of oral propafenone and quinidine as an initial treatment option in patients with symptomatic paroxysmal atrial fibrillation: a double-blind, randomized trial. J Intern Med 1996;239:253–260.
22. de Paola AA, Veloso HH. Efficacy and safety of sotalol versus quinidine for the maintenance of sinus rhythm after conversion of atrial fibrillation. SOCESP Investigators. The Cardiology Society of Sao Paulo. Am J Cardiol 1999;84: 1033–1037.
23. Bender F, Kojima N, Reploh HD, Oelmann G. [Treatment of tachycardiac disorders of the heart rhythm by beta-receptor block of the atrioventricular tissue]. Med Welt 1966;20:1120–1123.
24. Seipel L, Both A, Breithardt G, Gleichmann U, Loogen F. Action of antiarrhythmic drugs on His bundle electrogram and sinus node function. Acta Cardiol 1974;Suppl 18:251–267.
25. Milberg P, Reinsch N, Osada N, Wasmer K, Monnig G, Stypmann J, Breithardt G, Haverkamp W, Eckardt L. Verapamil prevents torsade de pointes by reduction of transmural dispersion of repolarization and suppression of early afterdepolarizations in an intact heart model of LQT3. Basic Res Cardiol 2005;100:365–371.
26. Kirchhof P, Fabritz L, Begrow F, Kilic A, Breithardt G, Kuhn M. Ventricular arrhythmias, increased cardiac calmodulin kinase II expression, and altered repolarization kinetics in ANP-receptor deficient mice. J Mol Cell Cardiol 2004;36:691–700.
27. Patten M, Maas R, Bauer P, Luderitz B, Sonntag F, Dluzniewski M, Hatala R, Opolski G, Muller HW, Meinertz T. Suppression of paroxysmal atrial tachyarrhythmias—results of the SOPAT trial. Eur Heart J 2004;25:1395–1404.
28. Karch M, Schmitt C, Plewan A, Schmidt G, Schomig A. [Torsade de pointes tachycardia during administration of quinidine and verapamil in atrial fibrillation]. Herz 1997;22:51–56.
29. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000;342:913–920.
30. Himmel HM, Dobrev D, Grossmann M, Ravens U. N-desethylamiodarone modulates intracellular calcium concentration in endothelial cells. Naunyn Schmiedebergs Arch Pharmacol 2000;362:489–496.
31. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. Circulation 1999;100:2025–2034.
32. Darbar D, Roden DM. Pharmacogenetics of antiarrhythmic therapy. Expert Opin Pharmacother 2006;7:1583–1590.
33. Grube M, Meyer zu Schwabedissen HE, Prager D, Haney J, Moritz KU, Meissner K, Rosskopf D, Eckel L, Bohm M, Jedlitschky G, Kroemer HK. Uptake of cardiovascular drugs into the human heart: expression, regulation, and function of the carnitine transporter OCTN2 (SLC22A5). Circulation 2006;113: 1114–1122.
34. Yasui-Furukari N, Kaneko S. Digitalis intoxication induced by paroxetine coadministration. Lancet 2006;367:788.
35. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med 2004;351:2384–2391.
36. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–1968.
37. Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002;415:219–226.
38. Channer KS, Birchall A, Steeds RP, Walters SJ, Yeo WW, West JN, Muthusamy R, Rhoden WE, Saeed BT, Batin P, Brooksby WP, Wilson I, Grant S. A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation. Eur Heart J 2004;25:144–150.
39. Kirchhof P, Fetsch T, Hanrath P, Meinertz T, Steinbeck G, Lehmacher W, Breithardt G. Targeted pharmacological reversal of electrical remodeling after cardioversion—rationale and design of the Flecainide Short-Long (Flec-SL) trial. Am Heart J 2005;150:899.