

“Pill in the Pocket” Antiarrhythmic Drugs for Orally Administered Pharmacologic Cardioversion of Atrial Fibrillation



James A. Reiffel, MD^{a,*}, and Alessandro Capucci, MD^b

The therapy of atrial fibrillation often involves the use of a rhythm control strategy, in which 1 or more antiarrhythmic drugs (AAD), ablative procedures, and/or hybrid approaches involving both of these options are utilized in an attempt to restore and maintain sinus rhythm. For chronic therapy, an AAD is taken daily. However, for patients with symptomatic but infrequent, acute, but nondestabilizing episodes, the use of an AAD only at the time of an episode that can quickly restore sinus rhythm, generally as an out-patient, without the burden of a daily drug regimen, may be better. This is called “pill-in-the-pocket” therapy. This manuscript reviews the “pill-in-the-pocket” concept, traces its development from its origins using quinidine, to its expansion using class IC AADs, to the more recent investigation of ranolazine for this purpose. Who should get it, what it involves, its efficacy rates and concerns are all discussed. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;140:55–61)

In the past several years, consequent to an expansion of therapeutic options and the results of several pivotal clinical trials,¹ the management of atrial fibrillation (AF) has become progressively more complex. Trials from the early 2000s taught us there are no statistically significant survival differences between rate control and rhythm control strategies.¹ However, sub analyses of these trials and subsequently collected data have shown that for many patients, rhythm control (usually combined with rate control) provides better symptom reduction, activity tolerance, and quality of life than does rate control alone.^{1,2} Accordingly, rhythm control is a reasonable first line treatment strategy for many if not most patients with AF. Importantly, among the several rhythm control approaches, one is commonly overlooked: the “pill-in-the-pocket” (PITP) regimen. Here, rather than administering an antiarrhythmic drug (AAD) chronically (1 or more times each day) and/or performing an ablative procedure, where both approaches attempt to reduce or eliminate generally symptomatic or life style-altering paroxysmal [usually frequent] or persistent AF, the patient can take an oral regimen of medications only at the time of an AF episode with the aim of rapid termination so as to abbreviate symptomatic periods and also reduce the chance the episode will be persistent and require electrical or intravenous drug cardioversion. (Figure 1) For the overwhelming number of days each year there is no arrhythmia, no antiarrhythmic therapy is used. Risk, cost, and inconvenience with PITP should be lower than with all rhythm management alternatives so long as the patient tolerates the foreshortened AF episode.^{2,3} Major organization guidelines all note this as a reasonable option for selected patients.^{4–6}

For almost three decades we (these investigators) have had very many such patients who used the PITP approach successfully and happily and would agree with this statement. Such PITP treatment, especially with recurrent use self-administered at home improves quality of life, reduces hospital visits by up to 90%,⁷ and dramatically lowers costs.

Pill-in-the-Pocket Regimens

Paroxysmal AF (PAF), by definition, will self-terminate, so PITP regimens are only useful if they shorten the duration of the episode; or, if they prevent PAF from becoming persistent. Multiple natural history studies of PAF and placebo-control limbs of active comparator trials have shown that spontaneous termination of PAF commonly occurs within 24 to 48 hours, although it may last a week. About 50% to 75% will convert within the first day,⁸ with approximately 10% by 2 hours, 20% by 3 hours, 30% by 6 hours, 40% by 8 hours.^{2,9} Nonetheless, for the symptomatic patient, more rapid termination is commonly patient-preferred. Consequently, a PITP regimen should be relatively quick acting and quick to wash-out in case of any adverse events. Table 1 describes the features of the ideal regimen. Notably, since the regimens primarily target recurrent PAF, the drug should be one that can be administered at home once verified as effective and safe. Accordingly, whereas dofetilide, dronedarone, and amiodarone can each terminate AF, the time course of their actions is not consistent with the ideals of the PITP approach. Moreover, dofetilide must be initiated in-hospital with every new administration and has had limited efficacy with PAF versus persistent AF, and sotalolol, which can be effective in terminating atrial flutter but generally fails for AF, is also to be given in-hospital per guidelines if patients are in AF. Thus, investigations showing the PITP approach to be effective, have focused on class IA and IC AADs, and more recently, ranolazine (off-label).

^aColumbia University Medical Center, New York City, New York; and
^bMarche Polytechnic University, Ancona, Italy. Manuscript received September 2, 2020; revised manuscript received and accepted October 21, 2020.

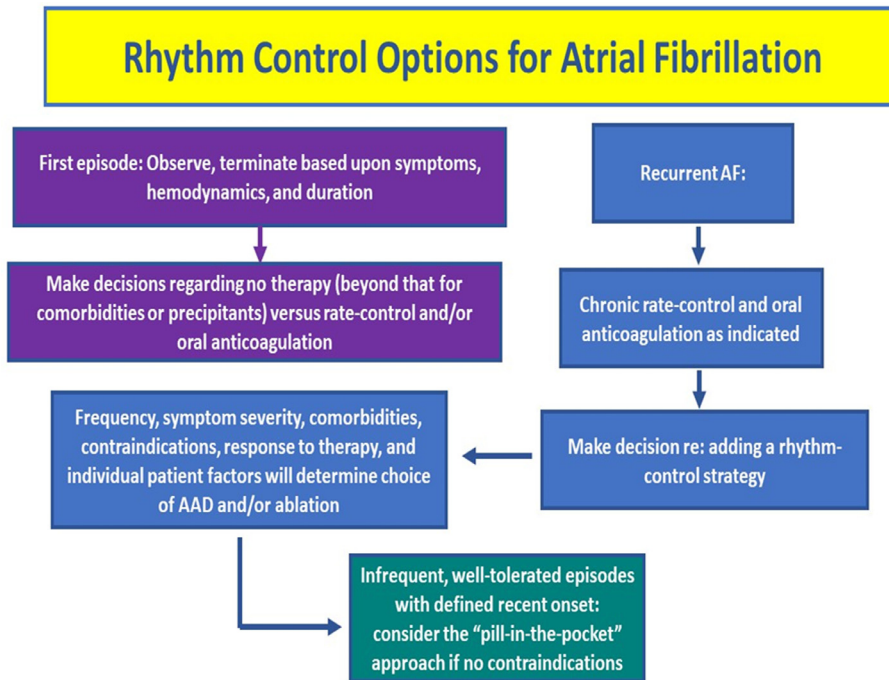
Funding: This manuscript has not received funding from any source.

See page 60 for disclosure information.

*Corresponding author: Tel.: (561)-203-2161.

E-mail address: jar2@columbia.edu (J.A. Reiffel).

TOP Left



BOTTOM Right

Figure 1. Rhythm control options for atrial fibrillation (AF).

Class IA AADs for PITP

The first AAD used for PITP therapy was quinidine. In fact, it is the only class IA AAD taken orally that has been truly assessed in this role. However, for quinidine, a consistent protocol has never been developed, the populations studied have been notably variable, and adverse effect reporting has been erratic.¹⁰⁻¹⁹

The first publication of which we are aware that deals with quinidine to produce cardioversion is by Edward Phillips and Samuel A. Levine¹⁰ in 1949 where their routine was to give 3 oral doses per day of quinidine sulfate at 4-hour intervals, starting with an initial dose of 0.2 gm and increasing each by 0.1 or 0.2 gm. In rare cases they gave 4 doses in a day and/or the inter-dose interval was 2 hours. This regimen followed a prior 1 of 3 identical doses per day with increases then made daily, which obtained reversion to sinus rhythm more slowly. The largest single incremented dose was 1.5 gm. Fourteen of 53 patients required more than 0.7 gm. Eight received individual doses of 1.0 to 1.5 gm. Subsequent protocols have included 3 different quinidine compounds:

- Quinidine sulfate* 0.3 gm every 6 hours for 4 doses¹¹; 200 mg for a maximum of 3 doses at 2-hour intervals¹³; 200 mg as a test dose, then 500 mg of a slow release preparation twice a day for 3 days¹⁴; 300 to 400 mg 3-times daily or a 300 to 600 mg loading dose¹⁶; or 200 to 400 mg every 6 hours until conversion or a maximum of 48 hrs¹⁸;
- Hydroquinidine chlorhydrate* 300 mg given 6 hours after the last dose of a digitalis load, followed by 150 mg every 3 hours for 9 hours and then 150 mg every 8 hours to a total dose of 1,350 mg¹²; 150 mg initially, followed by 300 mg 1 hour later, then 150 mg every 2 hours to a maximal total dose of 1,500 mg¹⁵; 150 mg every hour until return of sinus rhythm or a maximum of 7 doses¹⁷;
- Quinidine arabogalattan sulphate* 275 mg every 2 hours up to 8 hours maximum.¹⁹

The populations in these studies¹⁰⁻¹⁹ differed in duration and pattern of AF, causes of AF, underlying demographics, types of comparators (if any), and more. Conversion rates varied from approximately 13% to 84%, as did mean times to conversion (when reported) from approximately 4 to 11 hours. Factors favoring conversion, which were reported in only some studies, included shorter duration of AF, younger age, larger fibrillatory waves in lead V₁, and neither heart failure nor LV hypertrophy. Adverse effect reports also varied, from frequent gastrointestinal complaints ranging from mild to severe, tinnitus, a "transient pulseless state with convulsions" (which we assume was due to Torsades de pointes, [TdP]), documented TdP, sustained ventricular tachycardia and/or fibrillation, and sudden death. Female gender was associated with a higher likelihood of adverse events. Accordingly, quinidine can

Table 1

Ideal features of "Pill-in-the-Pocket" (PITP) agents

- Oral administration
- Rapid uptake
- Short time to cardiac tissue penetration
- Short half-life
- Be feasible to administer out-of-hospital and without continuous ECG monitoring
- Have a well-defined dosing algorithm for PITP use
- Have well known contraindications

work as PITP, but there is no standard for the regimen, side effects are frequent, and some can be fatal.

Class IC AADs for PITP

More recently, the class IC AADs, flecainide, and propafenone, have supplanted quinidine compounds for oral PITP therapy. Both of these agents have been given in more consistent protocols and have generally produced more rapid and higher rates of conversion and better tolerance than quinidine, sotalol, amiodarone, procainamide, and placebo.^{2,7,9,12,20–34} However, populations studied have had more specific exclusion criteria (see later) than in some of the quinidine studies. In most studies, just a single oral loading dose has been administered (Table 2). For flecainide this has usually been 300 mg, although in some cases 200 mg was used for patient weights <70 kg. For propafenone this most often has been 600 mg of the immediate release preparation, although in some cases 450 mg has been used for patient weights <70 kg. In 1 study, the loading regimen varied from 450 to 750 mg.⁹ In the multiple reported studies, with the total number of subjects exceeding 1,000 patients, conversion rates have been in the 45% to 55% range at 3 to 4 hours after dose and 70% to 85% at 8 hours after dose, in each case significantly greater than any placebo controls when compared, with the time after onset of AF being a major factor in the conversion rates. In converters, the average conversion time has been around 4 hours. In 1 report by Capucci et al³² for AF <7 days, flecainide converted 91% by 8 hours. Significant adverse effects are less frequent, less severe, and of lower risk than with quinidine (Table 3). They have included periods of atrial flutter (mostly with 2:1 atrioventricular [AV] conduction although rare episodes with 1:1 AV response and symptoms have been reported). Accordingly, pretreatment with a rate-control agent is typically employed. Sinus bradyarrhythmias (around 5% to 6%), rarely advanced AV conduction defects, and transient hypotension at the time of conversion have also been noted, mostly in patients with

possible brady-tachy syndrome or taking chronic atenolol or carvedilol, and/or with chronic renal disease.^{20–38} For studies with these class IC AADs, patients with ischemic heart disease, other significant structural heart disease, sinus node dysfunction, and/or AV conduction disturbances have generally been excluded. In some, ventricular preexcitation, hypokalemia, renal or hepatic disease, or severe hypoxia have also been exclusion criteria.

Because of the generally high response rates and reasonable tolerance, both Alboni et al^{27,31} and Botto et al²⁹ studied and documented the ability to use PITP safely at home following demonstration of tolerance and efficacy under observation for the first administration. Alboni et al reported on an out-patient regimen of either flecainide or propafenone (dose based on the 70 kg cut point), in which patients would take the dose 5 minutes after palpitations began, then rest until conversion or up to 4 hours. Of the initial 210 patients enrolled, 20% had no recurrence whereas 165 patients (79%) had 618 recurrent episodes. Of these 92% were treated at home with PITP in which 94% of the episodes (both with flecainide and propafenone) stopped in less than 6 hours; and only 5% required an emergency room visit for cardioversion. Adverse events were only a few instances of transient atrial flutter, with only 1 having a 1:1 AV response. The mean time to conversion in the out-patient setting was 113 ± 84 minutes, which was shorter than the 135 ± 79 minutes for the initial under-observation administration. Botto et al reported on 141 patients with AF <72 hours who were given propafenone as a single 450 mg or 600 mg dose. Conversion occurred in 57% within 4 hours. Conversion rates at 8 hours were not reported. No patient developed ventricular tachycardia or ventricular fibrillation or required pacemaker insertion. Eleven patients developed an atrial tachycardia or flutter, none with a 1:1 AV response. Asymptomatic sinus bradycardia with junctional escape rhythms and/or bundle branch block occurred in 6%. Both Alboni et al^{27,31} and Botto et al²⁹ suggested that in patients appropriately screened by exclusion criteria, routine admission to the hospital for PITP therapy is probably not necessary. Interestingly, 1 European study revealed that the response to a previous in hospital flecainide or propafenone iv infusion was not predictable of oral PITP possible adverse events³⁵ although in contrast, another showed reproducibility of the positive effect demonstrated with oral PITP propafenone in more than 90% of cases.²⁵

That PITP therapy with a class IC AAD might be reasonable to initiate in the out-patient setting should not be surprising. If a class IC AAD is used for the chronic reduction of AF, it is started as an out-patient in many if not most cases. In-hospital initiation is not mandated by regulatory bodies or guidelines. This, however, assumes that appropriate exclusion criteria have been used in clinical practice in selecting the patients to treat with a class IC AAD — that is, no associated ischemic or other structural heart disease, no sinus node or conduction system disease, and no Brugada syndrome. These are the same general exclusion criteria used in PITP trials. Notably, the doses used for PITP therapy are lower than the maximal daily doses recommended for chronic therapy with class IC agents. If it is reasonable to initiate or titrate class IC AADs for chronic care in doses up to the recommended maximal as an out-patient, why

Table 2

Dosing for class IC antiarrhythmic drugs and ranolazine for atrial fibrillation treatment

Dosing for Daily Maintenance Therapy

- Flecainide: 50-200 mg bid (U.S. guidelines); 50-150 mg bid (European guidelines)
- Propafenone Immediate-Release (IR): 150-300 mg tid
- Propafenone Sustained-Release (SR): 225-425 mg bid
- Approximate Propafenone IR-SR dosing equivalents:
- IR 150 mg tid approximately = SR 325 mg bid
- IR 225 mg tid approximately = SR 425 mg bid
- There is no direct equivalent for IR 300 mg bid, although the above would suggest that a total daily dose ratio between 1.25 and 1.45 of the IR dose would be needed.
- Ranolazine: There is no established daily maintenance dose for AF.

Dosing for Pill in the Pocket Therapy

- Flecainide: 300 mg single dose (consider 200 mg if weight <70 kg)
- Propafenone: 600 mg single dose immediate release formulation (consider 450 mg if weight <70 kg)
- Ranolazine: 2000 mg (given as a single dose, or two 1000 mg doses separated by no more than 4 hours)

Table 3
Risks with class IC antiarrhythmic drugs used for pill in the pocket therapy

Risk	Risk factor	Treatment choice implication
<i>Arrhythmic:</i>		
Dizziness/Syncope	Sinus Node Dysfunction AV Conduction Disorder	Avoid class IC AAD Avoid Class IC AAD
Conversion to atrial flutter	Potential for 1:1 AV response	Administer PITP only if the patient is already taking an AV nodal blocker or is given one acutely pre-PITP; and/or consider propafenone rather than flecainide. Consider 4-hr rest post dose.
Ventricular tachyarrhythmia	Structural heart disease or Brugada syndrome	Avoid class IC AAD.
<i>Hypotensive:</i>		
Dizziness/Syncope	Structural heart disease Chronic renal disease Brady-tachy syndrome Specific beta blocker/IC pk interactions	Avoid class IC AAD
<i>Nuisance Symptoms:</i>		
	No specific marker; Drug-specific	No contraindication to PITP

AAD = antiarrhythmic drug; AV = atrioventricular; PITP = pill-in-the-pocket; pk = pharmacokinetic; SN = sinus node.

would it not be just as reasonable to initiate PITP therapy in the same setting, given that the IC doses used for PITP are less than the maximal recommended doses used in the out-patient setting for chronic care and are typically given only as a single dose?

Can PITP Therapy Be Used in Patients Already Taking a Class IC AAD?

Given both the efficacy of PITP therapy with class IC AADs and the relatively common use of class IC AADs for chronic therapy in patients with more frequent or sustained AF, especially when structural heart disease is absent and/or hypertension but without severe LV hypertrophy or ischemia is present, the question arises as to superimposing PITP therapy in patients taking a class IC AAD if the daily dose is less than the maximum suggested dose for that agent. We (Drs. Reiffel and Capucci) studied this issue and presented the data in 2005 but have not previously published it in manuscript form. We assessed 45 patients taking propafenone or flecainide chronically, but at less than the recommended maximal daily dose (900 mg/d for immediate release propafenone, 850 mg/d for sustained release propafenone, 300 to 400 mg/d for flecainide)^{4,5} in whom PAF recurred whereas on chronic therapy. In these subjects, 63 episodes were treated with extra out-patient doses of propafenone immediate release or flecainide at least 3 hours after their prior drug with a dose chosen to increase their total dose of propafenone or flecainide for only that 1 day – but not to exceed the recommended total daily dose. (Table 2) For example, in a patient taking immediate release propafenone 600 mg/d, maximally a 300 mg PITP dose was given; or, in a patient taking flecainide 200 mg/d, maximally a 100 to 200 mg PITP dose was given. For patients taking sustained release propafenone, their daily dose was calculated as the immediate dose equivalent, and then the PITP dose was chosen. Chronic therapy in these patients was flecainide in 11 and propafenone in 34. After the additional single PITP dosing, conversion rates were 64% in the flecainide patients, 77% in the immediate release propafenone patients, and 62% in the sustained release propafenone patients. Four patients developed transient atrial flutter

(none with a1:1 AV response) with 3 then converting to sinus rhythm and 1 reverting back to AF. Adverse effects were mild (nausea, visual blurring, vague dizziness) and short-lived with no syncope, undue bradycardia, ventricular proarrhythmia, or signs of hypotension. These results appear quite similar to the results of PITP therapy in patients not yet on chronic AAD therapy. Importantly, however, we have not tested this approach in patients taking a different class of AAD for their chronic treatment.

Ranolazine, Another Option for PITP Therapy of AF

Ranolazine (off-label), a multichannel blocker, used alone or in combination with other agents,^{39–59} has been shown to be effective for prevention of recurrent AF, for prevention and treatment of postoperative AF, for management of multidrug refractory AF, for AF that has recurred after ablation, and for pharmacological cardioversion.^{44–59} Ranolazine is a unique agent with effects on multiple ion channels, including use-dependent blockade of the late sodium current in atrial and ventricular tissues; a modest suppressant effect on I_{Na} in the atria, but less so in the ventricles; and mild inhibition of I_{Kr} .⁶⁰ At recommended doses, about 6% of patients discontinued treatment with ranolazine because of an adverse event in controlled studies in angina patients versus about 3% on placebo – the most common causes being dizziness (1.3% vs 0.1%), nausea (1% vs 0%), asthenia, constipation, and headache (each about 0.5% vs 0%).⁶¹ Ranolazine has been used in patients with ischemic heart disease, LV hypertrophy, LV dysfunction, and diabetes with no serious toxicity. It did not suppress the sinus node or AV conduction in its placebo-controlled trials (although it did in 1 patient probably inappropriately treated clinically with the BRASH syndrome⁶²), and can improve LV compliance.^{39–58} Moreover, whereas it can lengthen the QT interval mildly (typically <10 ms), clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death.⁵⁶ Moreover, in multiple studies, ranolazine has been shown to inhibit TdP induced by other QT prolonging agents.⁶⁰

With respect to cardioversion, ranolazine has facilitated electrical cardioversion following failure without concomitant

ranolazine⁵⁷ and has enhanced the efficacy of intravenous amiodarone for cardioversion, where the combination has had higher conversion rates and shorter times to conversion than has amiodarone alone.^{53–56} Importantly herein, ranolazine has also been studied as PITP therapy, although so far in smaller numbers than quinidine or the class IC AADs.

Published experience with ranolazine used for PITP therapy includes 18 patients with new (n = 11) or paroxysmal (n = 7) AF of 3 to 48 hours duration studied by Murdock et al.⁵⁸ Seventeen had structural heart disease; each was given 2,000 mg PITP dose. Thirteen of 18 converted to sinus rhythm (72%). No proarrhythmia, hemodynamic instability, bradycardia, atrial flutter, or intolerance (other than transient constipation) were observed. A subsequent study done by Murdock, Reiffel, et al⁵⁹ included 31 patients with new (n = 16) or recurrent (n = 15) AF of 3 to 48 hours who were also given ranolazine 2,000 mg (most receiving a single 2,000 mg dose but a few receiving two 1,000 mg doses 4 hours apart). The mean age was 70; 66% were male; 80% had structural heart disease (including 33% with ischemic heart disease); mean left ventricular ejection fraction was 52% (range of 20% to 65%). Ranolazine PITP was started in-hospital (n = 22), in the office (n = 5), and at home (n = 4). Conversion to sinus rhythm occurred in 24 of 31 (77%) within 6 hours. No proarrhythmic, bradycardic, or adverse events were apparent. Whereas both of these studies were relatively small, unblinded, and not placebo-controlled, the conversion rates were in the same range as those with placebo-controlled, blinded studies with class IC AADs and quinidine. Notably, the subjects had a variety of underlying structural disorders that would have precluded use of a class IC agent in many cases. Subsequent to these studies, ranolazine as PITP therapy has been used by Dr. Reiffel in over 15 additional patients with virtually identical results. Coupled with the absence of any mandate to initiate ranolazine as an in-patient, the absence of any underlying cardiovascular disease as an exclusion to therapy (other than a long QT syndrome), plus the trials that showed ranolazine's enhancement of the efficacy of both amiodarone and electrical shock to produce cardioversion, ranolazine would seem to offer substantial promise as a PITP therapeutic agent.

The Appropriate Patient as Suggested by the Above

In our view, the patient who is a reasonable candidate for PITP therapy should meet each of the following conditions. Many have been employed in some of the published trials describing PITP studies.

1. Symptom onset should be recognized with reasonable accuracy and the episode should be acute. The efficacy of PITP is inversely related to the AF duration; it is most effective the first day, has reasonable efficacy the first 3 days, and is far less likely to work for episodes longer than 7 days.²
2. Inherently, the patient should be on oral anticoagulation (OAC) if he and/or she meets AF guidelines for such.^{4–6} In the absence of chronic (OAC), anticoagulation guidelines for new onset AF should be followed.^{4–6}

3. If a class IC AAD is chosen, the patient should be free of contraindications for its use.
4. Since some AADs can depress sinus node function and/or AV conduction, PITP should be avoided in patients with known sinus node disease or AV conduction impairment unless the drugs chosen have been used previously in the patient and shown to be safely tolerated or ranolazine is the chosen agent.
5. Because of the possibility of conversion from AF to atrial flutter with sodium channel blockers, either as a new sustained arrhythmia or as a stage during conversion, and because atrial flutter may result in faster ventricular rates due to less concealed conduction at the AV junction, it is appropriate to give a rate control agent prior to administering a class I AAD as PITP therapy, such as 80 mg of verapamil orally or an equivalent rate-slowing beta blocker an hour or so prior to giving the AAD. However, if the patient is on a rate control drug chronically, then an additional dose of a rate control drug can usually be omitted. An alternative is simply to advise the patient to stay at rest after PITP with a class IC AAD until sinus rhythm reappears or at least for the following 3 to 4 hours after dosing. Catecholamine drive has been documented to be proarrhythmic in this context and may be a factor if atrial flutter develops and a 1:1 AV response is present.
6. Ranolazine (which, when used as an AAD, is off-label) can also be effective for PITP therapy. Its efficacy and time to conversion appears similar to that of class I AADs but it does not appear to produce atrial flutter during the process. Unlike class I AADs, ranolazine can be used in the setting of structural heart disease. Efficacy rates in uncontrolled studies appear similar to that with the class IC agents.
7. Notably, the first time an agent has been administered for PITP therapy, it generally has been given under observation – as in the hospital, the emergency department, or in the clinic/office setting if resuscitative facilities are available. If effective and tolerated, subsequent episodes can be treated at home. Notably, in limited studies as noted above but also in my experience (J. Reiffel), if the patient has no structural heart disease, no sinus node or conduction disease, and is well known to the caregiver, initial administration in the out-patient setting has been used selectively with class IC agents and in general with ranolazine.

Consistent with the above, the Canadian guidelines⁶ note: Intermittent antiarrhythmic drug therapy ("pill in the pocket") may be considered in symptomatic patients with infrequent, longer-lasting episodes of AF or AFL as an alternative to daily antiarrhythmic therapy. Similarly, the European guidelines⁵ note: In selected patients with recent onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proved safe during previous testing. This approach may be used in selected, highly symptomatic patients with infrequent (e.g., between once per month and once per year) recurrences of AF. In order to implement the 'pill-in-

the pocket' technique, patients should be screened for indications and contraindications, and the efficacy and safety of oral treatment should be tested in hospital. Patients should be instructed to take flecainide or propafenone when symptoms of AF occur. In parallel, the American guidelines⁴ note: Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (*Level of Evidence: B*). Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting.

Concluding Comments

Pharmacologic cardioversion of AF using the PITP technique appears to be an underappreciated therapy that has an important role in the management of patient with AF. It can prevent hospitalization or emergent out-patient visits and shorten symptomatic episodes, thus improving quality of life of and reducing costs for symptomatic patients with infrequent events. Its risks are low and for the most part predictable and avoidable with careful patient selection. (Table 3) The frequency with which the PITP approach is appropriate is at least in part patient-specific. The PITP approach with class IC AADs or ranolazine is a valuable alternative to intravenous AAD infusions with relatively fast and usually safe results. The 1:1 flutter that may occur with class IC AADs (or quinidine) is quite infrequent in this context and may be prevented either with a simple at rest strategy for few hours after drug intake or with previous AV conduction delay concomitant therapy (US approach). PITP has reproducible efficacy and can be tested the first time in controlled conditions, which is commonly done in most patients, and always in patients not well known to the treating physician. Naturally, this therapy does not influence the anticoagulation strategy. We believe PITP should be administered more widely than has been considered to date (particularly in the US, where its use is infrequent by most physicians), and especially for recent-onset AF, before resorting to hospitalization. It can also be considered prior to the faster but more expensive and less convenient direct current cardioversion in patients whose recent onset AF is well tolerated.

Disclosures

Dr. Reiffel, during the past 12 months, has served as an investigator for Medtronic, Janssen, and Sanofi, and as a consultant for Medtronic, Sanofi, Acension, Correvio, and Amarin. Dr. Capucci, during the past 12 months, has served as a speaker sponsored by Mylan, Sanofi, Boston Scientific, Biotronick, Liva Nova, Medico, and Pfizer.

1. Reiffel JA. Atrial fibrillation: what have recent trials taught us regarding pharmacologic management of rate and rhythm control. *Pacing Clin Electrophysiol* 2011;34:247–259.
2. Marinelli A, Capucci A. Pharmacologic conversion of atrial fibrillation and atrial flutter. *Card Electrophysiol Clin* 2010;2:393–407.
3. Reiffel JA. Cardioversion for atrial fibrillation: treatment options and advances. *Pacing Clin Electrophysiol* 2009;32:1073–1084.

4. January CT, Wann S, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199–e267.
5. Camm AJ, Kirchhof P, Lip GHY, Schotten U, Savelieva I, Sabine E, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohnloser S, Kohl P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369–2429.
6. Gillis AM, Verma A, Talajic M, Nattel S, Dorian P, CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: rate and rhythm management. *Canadian J Cardiol* 2011;27:47–59.
7. Alboni P, Botto GL, Baldi N. Outpatient treatment of recurrent atrial fibrillation with the "pill-in-the-pocket" approach: practical aspects. *Ital Heart J* 2005;6(Suppl 6):335–340.
8. Naccarelli GV, Dell'Orfano JT, Wolbrette DL, Patel HM, Luck JC. Cost-effective management of acute atrial fibrillation: role of rate control, spontaneous conversion, medical and direct current cardioversion, transesophageal echocardiography, and antiembolic therapy. *Am J Cardiol* 2000;85:36D–45D.
9. Azpitarte J, Alvarez M, Baun O, Garcia R, Moreno E, Martin F, Tercedor L, Fernandez TR. Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation: results of a randomized double-blind controlled study. *Eur Heart J* 1997;18:1649–1654.
10. Phillips A, Levine SA. Auricular fibrillation without other evidence of heart disease: a cause of reversible heart failure. *Am J Med* 1949;7:478–489.
11. Rossi M, Lown B. The use of quinidine in cardioversion. *Am J Cardiol* 1967;19:234–238.
12. Capucci A, Boriani G, Rubino I, Della Casa S, Sanguinetti M, Magnani B. A controlled study on oral propafenone versus digoxin plus quinidine in converting recent onset atrial fibrillation to sinus rhythm. *International J Cardiol* 1994;43:305–313.
13. Halinen MO, Huttunen M, Paakkinen S, Tarssanen T. Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the Sotalol-Digoxin-Quinidine Trial). *Am J Cardiol* 1995;76:495–498.
14. Hohnloser SH, van de Loo A, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. *J Am Coll Cardiol* 1995;26:852–858.
15. Di Benedetto S. Quinidine versus propafenone for conversion of atrial fibrillation to sinus rhythm. *Am J Cardiol* 1997;80:518–519.
16. Kowey PR, Marinchack RA, Rials SJ, Filart RA. Acute treatment of atrial fibrillation. *Am J Cardiol* 1998;81:16C–22C.
17. Kirpizidis C, Stavratsi A, Geleris P, Boudoulas H. Safety and effectiveness of oral quinidine in cardioversion of persistent atrial fibrillation. *J Cardiol* 2001;38:351–354.
18. Schwaab B, Katalinic A, Boge U, Loh J, Blank P, Kolzow T, Poppe D, Bonnemeier H. Quinidine for pharmacological cardioversion of atrial fibrillation: a retrospective analysis in 501 consecutive patients. *Ann Noninvasive Electrocardiol* 2009;14:128–136.
19. Baroni M, Kheir A, Manfredi M, Pattarino F, Coni F. Quinidine for pharmacological cardioversion of long-lasting atrial fibrillation. *JAFIB* 2011;4:350–354.
20. Capucci A, Villani GQ, Aschieri D, Piepoli M. Safety of oral propafenone in the conversion of recent onset atrial fibrillation to sinus rhythm: a prospective parallel placebo-controlled multicentre study. *Int J Cardiol* 1999;68:187–196.
21. Capucci A, Boriani G, Botto GL, Lenzi T, Rubino I, Falcone C, Trisolino G, Della Casa S, Binetti N, Cavazza M, Sanguinetti M, Magnani B. Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. *Am J Cardiol* 1994;74:503–505.
22. Brandes A, Crijns HJGM, Rienstra M, Kirchhof P, Grove EK, Pedersen KB, Van Gelder IC. Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure. *Europace* 2020;22:1149–1161.

23. Capucci A, Villani GQ, Pirpoli MF, Aschieri D. The role of oral 1C antiarrhythmic drugs in terminating atrial fibrillation. *Curr Opin Cardiol* 1999;14:4–8.
24. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001;37:542–547.
25. Capucci A, Villani GQ, Piepoli ME. Reproducible efficacy of loading oral propafenone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation. *Am J Cardiol* 2003;92:1345–1347.
26. Crijns HJ, van Wijk LM, van Gilst WH, Kingma JH, Van Gelder IC, Lie KI. Acute conversion of atrial fibrillation to sinus rhythm: clinical efficacy of flecainide acetate. Comparison of two regimens. *Eur Heart J* 1988;9:634–638.
27. 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. *New Engl J Med* 2004;351:2384–2391.
28. Andrade JG, MacGillivray J, Macie L, Yao RJR, Bennett M, Fordyce CB, Hawkins N, Krahn A, Jus J, Ramanathan K, Tsang T, Gin K, Devell MW. Clinical effectiveness of a systematic "pill-in-the-pocket" approach for the management of paroxysmal atrial fibrillation. *Heart Rhythm* 2018;15:9–16.
29. Botto GL, Bonini W, Broffoni T, Molteni S, Lombardi R, Alfieri G, Barone P, Bernasconi G, Ferrari G. Conversion of recent onset atrial fibrillation with single loading oral dose of propafenone: is in-hospital admission absolutely necessary? *Pacing Clin Electrophysiol* 1996;19:1939–1943.
30. Er F, Aslan P, Caglayan E, Gassanov N, Nia AM, Erdmann E, Rosenkranz S. Flecainide for cardioversion in patients at elevated cardiovascular risk and persistent atrial fibrillation: a prospective observational study. *Clin Research in Cardiol* 2010;99:369–373.
31. Alboni P, Gianfranchi L, Pacchione F, Pedaci M. Antiarrhythmic drugs in patients with recurrent atrial fibrillation: where are we? *Italian Heart J* 2005;6:169–174.
32. Capucci A, Lenzi T, Boriani G, Trisolino G, Binetti N, Cavazza M, Fontana G, Magnani B. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. *Am J Cardiol* 1992;70:69–72.
33. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for management of atrial fibrillation. *Europace* 2011;13:161–173.
34. Boriani G, Biffi M, Capucci A, Botto G, Broffoni T, Ongari M, Trisolino G, Rubino I, Sanguinette M, Branzi A, Magnani B. Conversion of recent onset atrial fibrillation to sinus rhythm: effects of different drug protocols. *Pacing Clin Electrophysiol* 1998;21:2470–2474.
35. Alboni P, Botto GL, Boriani G, Russo G, Pacchione F, Lori M, Pasanisi G, Mancini M, Mariconi B, Capucci A. Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during "pill-in-the-pocket" treatment. *Heart* 2010;96:546–549.
36. Patane S, Gilippo M, DiBella G. Transient syncope, left bundle branch block, and first-degree atrioventricular block after "pill-in-the-pocket" administration. *Int J Cardiol* 2008;126:e19–e21.
37. Riccardi A, Lerza R. Controversies in the "pill in the pocket" approach to atrial fibrillation. *Intern Emerg Med* 2008;3:187–189.
38. Boriani G, Biffi M, Diemberger I, Domenichini G, Marziali G, Martignani C. Atrial fibrillation: adverse effects of "pill-in-the-pocket" treatment and propafenone-carvedilol interaction. *Int J Cardiol* 2010;140:242–244.
39. Guerra F, Romandini A, Barbarossa A, Belardinelli L, Capucci A. Ranolazine for rhythm control in atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2017;227:284–291.
40. Gong G, Zhang Z, Fragakis N, Korantzopoulos P, Letsas KP, Li G, Yan GX, Liu T. The role of ranolazine in the prevention and treatment of atrial fibrillation: a meta-analysis of randomized clinical trials. *Heart Rhythm* 2017;14:3–11.
41. White CM, Nguyen E. Novel use of ranolazine as an antiarrhythmic agent in atrial fibrillation. *Ann Pharmacother* 2017;51:245–252.
42. Dagues N, Iliodromitis EK, Lekakis JP, Simitsus P, Karatzas D, Rallidis LS, Simeonidou E, Anastasiou-nana M. Ranolazine for the prevention or treatment of atrial fibrillation: a systematic review. *J Cardiovasc Med* 2014;15:254–259.
43. Burashnikov A, Di Diego JM, Barajas-Martínez H, Hu D, Cordeiro JM, Moise S, Kornreich BG, Belardinelli L, Antzelevitch C. Ranolazine effectively suppresses atrial fibrillation in the setting of heart failure. *Circ Heart Fail* 2014;7:627–633.
44. Ghosh GC, Ghosh RK, Bandyopadhyay D, Chatterjee D, Aneja A. Ranolazine: multifaceted role beyond coronary artery disease, a recent perspective. *Heart Views* 2018;19:88–98.
45. Tsu LV, Lee S. Use of ranolazine in the prevention and treatment of postoperative atrial fibrillation in patients undergoing cardiac surgery. *Ann Pharmacother* 2014;48:633–637.
46. Trivedi C, Upadhyay A, Solanki K. Efficacy of ranolazine in preventing atrial fibrillation following cardiac surgery: results from a meta-analysis. *Arrhythm* 2017;33:161–166.
47. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olmsted A, Zareba W, Rosero S, Kowey P, the HARMONY Investigators. The HARMONY Trial: combined ranolazine and dronedarone in the management of paroxysmal atrial fibrillation: mechanistic and therapeutic synergism. *Circ Arrhythm Electrophysiol* 2015;8:1048–1056.
48. Simopoulos V, Hevas A, Hatziefthimiou A, Dipla K, Skoularis I, Tsilimigias N, Aidonis I. Amiodarone plus ranolazine for conversion of post-cardiac surgery atrial fibrillation: enhanced effectiveness in reduced versus preserved ejection fraction patients. *Cardiovasc Drugs Ther* 2018;32:559–565.
49. Sossalla S, Sohns C, Seegers J, Luthje L, Vollmann D, Zabel M. Ranolazine maintained sinus rhythm in a patient with refractory symptomatic atrial fibrillation. *Cardiovasc Ther* 2013;31:303–306.
50. Reiffel J. The power of one: a highly detailed, log-based, case example that clearly demonstrates the effective use of ranolazine for the control of progressive atrial fibrillation. *J Atr Fibrillation* 2010;3:304–306.
51. Vaishnav A, Vaishnav A, Lokhandwala Y. Refractory atrial fibrillation effectively treated with ranolazine. *Indian Heart J* 2014;66:115–118.
52. Biviano A, Goa C, Hanon S, Reiffel JA. The use of ranolazine in the management of recurrent atrial fibrillation after percutaneous radiofrequency ablation. *J Atr Fibrillation* 2012;5:562–565.
53. Tsanaxidis N, Aidonis I, Hatziefthimiou, Daskalopoulou SS, Gismouzis G, Triposkiadis F, Skoularis I. Ranolazine added to amiodarone facilitates earlier conversion of atrial fibrillation compared to amiodarone-only therapy. *Pacing Clin Electrophysiol* 2017;40:372–378.
54. Koskinas KC, Fragakis N, Katritsis D, Skeberis V, Vassilikos V. Ranolazine enhances the efficacy of amiodarone for conversion of recent-onset atrial fibrillation. *Europace* 2014;16:973–979.
55. De Vecchis R, Ariano C, Giasi A, Cioppa C. Antiarrhythmic effects of ranolazine used both alone for prevention of atrial fibrillation and as an add-on to intravenous amiodarone for its pharmacological cardioversion: a meta-analysis. *Minerva Cardioangiologica* 2018;66:349–359.
56. Fragakis N, Koskinas KC, Katritsis DG, Pagourelis ED, Zografos T, Geleris P. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. *Am J Cardiol* 2012;110:673–677.
57. Murdock DK, Kaliebe J, Larrain G. The use of ranolazine to facilitate electrical cardioversion in cardioversion-resistant patients: a case series. *Pacing Clin Electrophysiol* 2012;35:302–307.
58. Murdock DK, Kersten M, Kaliebe J, Larrain G. The use of oral ranolazine to convert new or paroxysmal atrial fibrillation: a review of experience with implications for possible "pill in the pocket" approach to atrial fibrillation. *Indian Pacing Electrophysiol J* 2009;9:260–267.
59. Murdock DK, Reiffel JA, Kaliebe J, Larrain A. The conversion of paroxysmal or initial onset atrial fibrillation with oral ranolazine: implications for a new "pill-in-the-pocket" approach in structural heart disease. *J Atrial Fibrillation* 2010;2:705–710.
60. Antzelevitch C, Burashnikov A, Sicouri S, Belardinelli L. Electrophysiological basis for the antiarrhythmic actions of ranolazine. *Heart Rhythm* 2011;8:1281–1290.
61. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021526s0291bl.pdf. Accessed August 26, 2020.
62. Zaidi SAA, Shaikh D, Saad M, Vittorio TJ. Ranolazine induced bradycardia, renal failure, and hyperkalemia: a BRASH syndrome variant. *Case Rep Med* 2019;2019:2740617. <https://doi.org/10.1155/2019/2740617>. eCollection 2019.