Clinical effectiveness of a systematic "pill-in-the-pocket" approach for the management of paroxysmal atrial fibrillation

Jason G. Andrade, MD, FHRS,* Jenny MacGillivray, BScPharm,† Laurent Macle, MD, FHRS,‡ Ren Jie Robert Yao, BSc,§ Matthew Bennett, MD, FHRS,* Christopher B. Fordyce, MD, MHS, MSc,* Nathaniel Hawkins, MD,* Andrew Krahn, MD,* John Jue, MD,* Krishnan Ramanathan, MD,* Teresa Tsang, MD,* Ken Gin, MD,* Marc W. Deyell, MD, MS, FHRS*

*From the *Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, Canada, †Lower Mainland Pharmacy Services, Vancouver General Hospital, Vancouver, Canada, ‡Montréal Heart Institute, Department of Medicine, Université de Montréal, Montréal, Canada, and §University of British Columbia, Vancouver, Canada.*

BACKGROUND For patients with symptomatic, sustained atrial fibrillation (AF), a "pill-in-the-pocket" antiarrhythmic drug (PIP-AAD) strategy has been proposed to reduce emergency department (ED) use.

OBJECTIVE To assess the clinical utility of a protocolled PIP-AAD approach within contemporary practice.

METHODS Consecutive patients who hemodynamically tolerated symptomatic, sustained AF were prospectively managed with the PIP-AAD strategy. All patients were given an atrioventricular nodal blocker 30 minutes prior to a single oral dose of a class Ic antiarrhythmic drug. If the initial PIP-AAD in the ED was efficacious and tolerated, PIP-AADs were given out of hospital for subsequent sustained AF episodes. Usage and complications were systematically recorded.

RESULTS During a median follow-up period of 565 days, 43 of 80 patients presented to the ED for initial PIP-AAD. Sinus rhythm was restored without complication in 30 of 43 patients. The reasons for initial PIP-AAD failure were inefficacy (6 patients), significant hypotension (4 patients), conversion to flutter necessitating cardioversion (2 patients), and syncopal conversion pause (1 patient). For the 30 patients with successful initial PIP-AAD, 159 out-of-hospital PIP-AAD treatments occurred (mean 5.3 ± SD 1.3 per patient). Compared with ED visits in the period prior to PIP-AAD initiation, there was a significant reduction in visits (2.6 ± 3.0 vs. 0.4±0.9 ED visits per patient, $P < .001$) and the need for cardioversion (2.3 ± 3.1 vs. 0.0 ± 0.2 treatments per patient, $P < .001$). Adverse events associated with out-of-hospital PIP-AAD include presyncope (3 of 30 patients), syncope necessitating pacemaker implantation (1 patient), and conversion to flutter (1 patient).

CONCLUSION Out-of-hospital PIP-AAD can be an effective for highly selected patients; however, the rates of treatment failure and adverse events are clinically relevant, which limits the widespread application of a PIP-AAD approach.

KEYWORDS Atrial fibrillation; Antiarrhythmic; Cardioversion; Flecainide; Propafenone

(Heart Rhythm 2018;15:9–16)

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia observed in clinical practice, affecting 1%–2% of the general population and accounting for 1.0%–2.7% of total annual health care expenditures.[1,2] It has been estimated that patients with AF have health care costs that are 5 times greater than those of individuals without AF, with more than 50% of these expenses attributed to direct costs associated with emergency department (ED) visits and acute care hospitalization.[2–6] As such, strategies directed at preventing ED consultation and hospitalization are highly desirable. One approach for patients who have infrequent episodes of sustained symptomatic AF is the use of a "pill-in-the-pocket" antiarrhythmic drug (PIP-AAD) strategy.[7] Instead of taking long-term oral prophylactic medications, the patient using the PIP-AAD approach takes

Conflict of interest: None to declare. **Address reprint requests and correspondence:** Dr Jason Andrade, 2775 Laurel St, Vancouver, BC V5Z 1M9, Canada. E-mail address: Jason.guy.andrade@umontreal.ca.

1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2017.10.002

a single AAD dose at the onset of sustained palpitations to convert the AF into sinus rhythm. This approach addresses the complementary patient priorities of minimizing drug burden (avoiding the need for daily AAD administration, reducing medication costs, and minimizing the risk of adverse effects), as well as empowering patients to self-manage their episodes of sustained AF, thereby reducing the need to visit the ED or be hospitalized.

Since the initial evaluation of the PIP-AAD strategy, there has been a lack of contemporary data regarding the safety and efficacy of this treatment approach.[7] Moreover, despite the major-society guidelines advocating for an initial conversion trial being performed in a monitored setting, a minimum duration of inpatient monitoring has not been determined.[8–10] We sought to describe the utility of a protocolled PIP-AAD treatment approach within contemporary clinical practice.

Methods

We prospectively evaluated consecutive patients with symptomatic paroxysmal AF who attended our dedicated multidisciplinary AF clinic and were prescribed a PIP-AAD strategy between January 2013 and December 2016. All patients underwent extensive initial evaluation including medical history and physical examination, 12-lead electrocardiogram (ECG), 24-hour ambulatory ECG monitoring, routine biochemical laboratory tests (including thyroid hormone, renal function, liver function, and electrolytes), and echocardiography. Exercise stress testing was performed when clinically indicated. The study was approved by the institutional review board of the University of British Columbia.

Criteria for the use of an outpatient PIP-AAD strategy included symptomatic patients (i.e., the patient is able to recognize AF onset); sustained AF episodes (usually lasting $\geq$2 hours); AF episodes that occur less frequently than once per month; absence of severe or disabling symptoms during an AF episode (e.g., fainting, severe chest pain, breathlessness); ability to comply with instructions; and proper medication use and comprehension. Patients were excluded from a PIP-AAD approach if any of the following were present: significant structural heart disease (e.g., left ventricular systolic dysfunction [left ventricular ejection fraction $<$50%], active ischemic heart disease, severe left ventricular hypertrophy); abnormal conduction parameters at baseline (e.g., QRS duration $>$120 ms, PR interval $>$200 ms; or evidence of pre-excitation); clinical or electrocardiographic evidence of sinus node dysfunction/bradycardia or advanced AV block; hypotension (systolic blood pressure $<$100 mm Hg); or prior intolerance of any of the PIP-AAD medications. Patients underwent systematic anticoagulation treatment with a vitamin K antagonist or a non–vitamin K antagonist oral anticoagulant based on their baseline stroke risk and in accordance with contemporary guidelines.[11,12]

PIP-AAD initiation—education

Prior to PIP-AAD initiation, patients received multidisciplinary teaching regarding the proper use of the PIP-AAD medications from the AF clinic physician and pharmacist. Patients were instructed that the first dose of the PIP-AAD medications must be given in the ED of their local hospital to ensure safety. All patients were provided an educational handout (Appendix 1) that served the dual purpose of patient education and prescriptive guideline for the treating ED physician.

In-hospital PIP-AAD administration and monitoring

Patients received their first PIP-AAD treatment in the ED (or another comparable cardiac-monitored environment). For conversion of AF to sinus rhythm, patients were given an immediate release oral atrioventricular (AV) nodal blocker (1 dose of diltiazem 30-60 mg, verapamil 30-60 mg, or metoprolol tartrate 25–50 mg) 30 minutes prior to the administration of a class Ic AAD to prevent 1:1 conduction of atypical flutter. The class Ic AAD was administered in a single oral dose according to the weight of the patient: 300 mg of flecainide or 600 mg of propafenone if the patient's weight was $\geq$70 kg; 200 mg of flecainide or 450 mg of propafenone if patient's weight was $<$70 kg. The choice of AV nodal agent and AAD was at the discretion of the treating physician.

Following AAD administration, patients were monitored with telemetry for $\geq$6 hours (to monitor for episodes of ventricular tachycardia (VT), conversion to atrial flutter or tachycardia, or postconversion pauses or bradycardia), with blood pressure monitoring every 30 minutes (to monitor for drug-induced hypotension) and 12-lead ECG monitoring every 2 hours (to monitor for drug toxicity). The treatment was considered successful if the interval between administration of the drug and conversion to sinus rhythm was $\leq$6 hours and there were no significant adverse effects.

The PIP-AAD strategy was deemed a failure in an a priori fashion if any of the following events occurred: AF persisted for $>$6 hours after PIP-AAD administration, AF required electrical cardioversion for termination, or there was a significant adverse event. Adverse events included symptomatic hypotension (systolic blood pressure $\leq$90 mm Hg); symptomatic conversion pauses ($>$5 seconds) or symptomatic bradycardia after sinus rhythm restoration; conversion to atrial flutter or tachycardia; episodes of sustained or nonsustained ventricular tachycardia; severe symptoms (dyspnea, presyncope, syncope); or a $>$50% increase in QRS interval duration from baseline. Instructions were provided to the treating physician to consider the intravenous (IV) administration of sodium bicarbonate in the event of acute toxicity.

Patients were instructed to contact the AF clinic following an ED visit for directive care. In the event of PIP-AAD failure, patients were transitioned to an alternate treatment. If the in-hospital PIP-AAD was successful in restoring sinus rhythm without adverse event, then a prescription for the same AV nodal agent and a class Ic AAD (propafenone or flecainide) was provided for out-of-hospital treatment.

Out-of-hospital treatment

For subsequent sustained AF episodes, patients were instructed to take the AV nodal agent 30 minutes after the perceived arrhythmia onset, followed by the class Ic AAD 30 minutes after the AV nodal agent administration. Following AAD administration, patients were instructed to rest in a supine or seated position for the next 4 hours or until the episode resolved. Patients were instructed to present to the ED in the event that the AF episode did not terminate within 6–8 hours, they felt unwell after taking the medication at home (e.g., a subjective worsening of the arrhythmia following AAD ingestion, or the development of new or severe symptoms such as dyspnea, presyncope, or syncope), >1 episode occurred in a 24-hour period (patients were advised not to take a second PIP-AAD dose within 24 hours), or the AF episode was associated with severe symptoms at baseline (e.g., significant dyspnea, chest pain, presyncope, or symptoms of stroke), even in the absence of PIP-AAD use.

Follow-up

Patients were followed in the AF clinic for a minimum of 1 year. At each clinical encounter, the patients were questioned regarding PIP administrations (e.g., the number and duration of arrhythmic episodes, AAD administrations, and adverse effects). At each visit, the provincial prescription database was interrogated (this clinical database provides information regarding all drug prescriptions in British Columbia). Records regarding hospitalization were obtained and reviewed.

Statistical analysis

Continuous variables are expressed as the mean plus or minus standard deviation or median (interquartile range [IQR]) and were compared using Student *t* tests or Wilcoxon rank-sum tests for continuous variables. Categorical variables are expressed as frequency and percentage and were compared by χ^2 test or the Fisher exact test. All tests were 2 sided. A P value $< .05$ was considered statistically significant. To evaluate the persistence with PIP-AAD approach, survival curves over the follow-up period were estimated using the Kaplan-Meier estimation. All analyses were performed using SPSS 24 (IBM, Armonk, NY). The authors had full access to, and take full responsibility for the integrity of, the data. All authors have read and agree with the written manuscript.

Results

A total of 80 consecutive patients were included (Figure 1). Baseline characteristics are presented in Table 1.

The median time from initial AF diagnosis to study inclusion was 18.5 months (IQR 6–51 months). The mean number and standard deviation of ED visits for AF prior to PIP-AAD treatment initiation was 2.6 ± 2.3 visits (total 207 visits), with 2.3 ± 2.5 cardioversions prior to PIP-AAD treatment initiation (total 180 cardioversions, 127 electrical and 53 intravenous pharmacologic). Prior to study inclusion, 4 patients had experienced treatment failure and a further 3 patients had experienced complications with IV chemical cardioversion (all hypotension). No failure of electrical cardioversion was experienced prior to study inclusion.

Metoprolol was the preferred AV nodal agent (71% of patients; diltiazem 15%, bisoprolol 9%, verapamil 3%, nothing 3%), and propafenone was the preferred AAD (63% of patients). The median follow-up period (study inclusion to earliest of PIP-AAD treatment failure or last clinical follow-up) was 394.5 days (IQR 189–767 days).

Initial PIP-AAD administration in the ED

Of the 80 patients included in the study, 43 (54%) presented to the ED for first PIP-AAD administration, at a median of 46 days (range 13–200 days). The median time from symptom onset to ED administration of the PIP-AAD was 3 hours (range 1–21 hours). Of these, the first PIP-AAD administration was successful in restoring sinus rhythm, without complication, in 30 of 43 patients (70%). The median time from PIP-AAD administration to sinus rhythm restoration was 138 minutes (range 55–310 minutes).

Of the 13 for whom first PIP-AAD administration in the ED failed, the reason for PIP-AAD failure was inefficacy (persistence of AF 6 hours post PIP-AAD administration, necessitating electrical cardioversion) in 6 patients (14%), or adverse event in 7 patients (16%; conversion to atypical flutter necessitating cardioversion in 2 patients, hypotension necessitating fluid resuscitation or IV vasopressors in 4 patients, syncope secondary to a prolonged conversion pause in 1 patient). The mean time from PIP-AAD administration to hypotension or syncope onset was 152 ± 61 minutes (range 80–210 minutes), with a median difference between sinus rhythm restoration and adverse event of 58 minutes (range from 133 minutes before to 125 minutes after sinus rhythm restoration). In the 2 patients who experienced conversion from AF to atrial flutter, this conversion occurred at 65 and 204 minutes after PIP-AAD administration. The characteristics of the patients who experienced as in-hospital adverse event are presented in Table 2.

Follow-up period

The 30 patients with successful PIP-AAD administration were discharged and provided a prescription for the successful PIP-AAD regimen for ambulatory treatment of recurrent AF (flecainide in 10 patients, propafenone in 20 patients). Over the follow-up period, a further 159 PIP-AAD administrations occurred in 19 patients (63%), with a mean of 5.3 ± 1.3 out-of-hospital administrations per patient. PIP-AAD administration was successful in restoring sinus rhythm in 97% of treated episodes.

In those patients with a successful first PIP-AAD administration, the out-of-hospital PIP-AAD treatment strategy resulted in a significant reduction in ED visits (decreasing from 78 before to 11 after PIP-AAD initiation, or 2.6 ± 3.0 vs. 0.4 ± 0.9 visits per patient), and a significant reduction in electrical or IV cardioversions (decreasing from 70

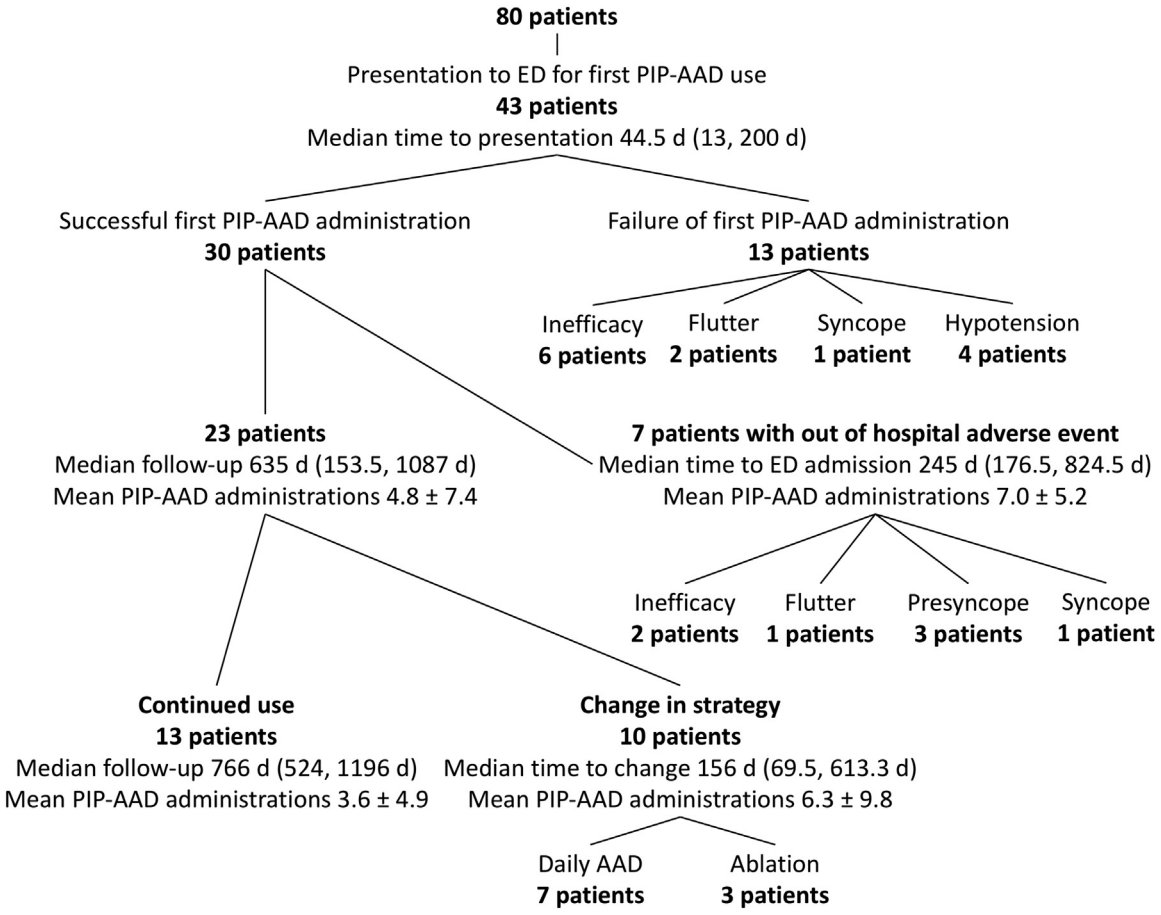

Figure 1 Patient flow diagram. Data reported as median (interquartile range), and mean ± standard deviation. AAD = antiarrhythmic drugs, ED = emergency department, PIP-AAD = "pill-in-the-pocket" antiarrhythmic drug.

cardioversions before to 7 after PIP-AAD initiation, or 2.3 ± 3.1 vs. 0.0 ± 0.2 cardioversions per patient) (Figure 2).

Hospitalizations occurred in 7 patients (1 patient with 4 visits, 1 with 2 visits, and the remaining 5 with 1 visit each) due to adverse events (presyncope in 3 patients, syncope requiring pacemaker implantation in 1 patient, and conversion to atypical flutter in 1 patient) (Table 2) or treatment inefficacy (2 patients, 4 and 2 visits, respectively). All patients had undergone a successful in-hospital treatment, and had successfully used the out-of-hospital PIP-AAD 7.0 ± 5.2 times prior to the out-of-hospital adverse event or emergency room admission. Time from first successful PIP-AAD administration to the combined endpoint of subsequent ED admission for treatment-related complication or PIP-AAD failure was 245 days (IQR 176.5–824.5) (Figure 3). Of these 7 patients, 1 transitioned to an alternative PIP-AAD, 3 transitioned to daily AAD therapy, and 3 transitioned to ablation.

A further 10 patients discontinued the PIP-AAD treatment during the follow-up period for reasons other than inefficacy or adverse event. Seven patients transitioned to daily AAD, and 3 patients transitioned to ablation. Median time to PIP-AAD discontinuation was 156 days (IQR 69.5–613.3 days). Prior to treatment discontinuation, the patients had successfully used the out-of-hospital PIP-AAD a mean and standard deviation of 6.3 ± 9.8 times.

The remaining 13 patients continued to use the PIP-AAD strategy a mean and standard deviation of 3.6 ± 4.9 times each, at a median follow-up period of 766 days (IQR 524–1996 days).

Discussion

This study demonstrates 4 key findings. In highly selected patients with symptomatic paroxysmal AF, a PIP-AAD treatment strategy is associated with a significant reduction in health care utilization (ED visits, cardioversions). The initiation of a PIP-AAD treatment strategy is associated with a significant rate of treatment failure or adverse events, thus reinforcing the need for vigilant monitoring during the index in-hospital initiation. Despite safe and successful initial PIP-AAD treatment, a significant minority of patients experience a subsequent PIP-AAD–related adverse event, emphasizing the need for careful patient selection. Long-term persistence with PIP-AAD treatment is limited and limits the widespread application of this approach as a sole treatment strategy, with most patient progressing to regular AAD therapy or an invasive ablation procedure.

Table 1 Baseline patient characteristics

Characteristic	
Age, y, mean ± SD	53.0 ± 12.6
Male sex, n (%)	53 (66)
Valvular AF, n (%)*	2 (2.5)
$CHADS_2$ score ≥2, n (%)	7 (9)
- Hypertension, n (%)	16 (20)
- Diabetes, n (%)	8 (10)
- Stroke, n (%)	2 (2.5)
Coronary artery disease (CAD), n (%)	4 (5)
- Asymptomatic CAD incidentally discovered on chest CT imaging	1
- Remote ACS with PCI-S; no inducible ischemia on MPI	2
- Nonobstructive CAD on invasive angiogram, nonsignificant FFR	1
Asthma, n (%)	3 (4)
Ablation, n (%)	9 (11)
- SVT/PVI/CTI, n	1/5/4
Pacemaker, n (%)	2 (2.5)
Left atrium	
- Dimension, mm, mean ± SD	37.6 ± 4.4
- Volume, mL/m^2, mean ± SD	34.9 ± 9.1
Electrocardiography	
- Heart rate, beats per minute	63.5 (55–73)
- PR interval, ms	158 (149–172.5)
- QRS duration, ms	94 (88–102)
- QTc interval, ms	412 (398–432.3)
Median AF duration prior to PIP-AAD prescription, mo, median (IQR)	18.5 (6–51)
Emergency room visits prior to PIP-AAD initiation, mean ± SD (total)	2.6 ± 2.3 (207)
Number of cardioversions prior to PIP-AAD initiation, mean ± SD (total)	2.3 ± 2.5 (180)
- Electrical/IV pharmacologic	127/53
Complications with IV pharmacologic cardioversion	
- Hypotension, n (%)	3 (4)
- Failure to restore sinus rhythm, n (%)	4 (5)

ACS = acute coronary syndrome; AF = atrial fibrillation; CTI = cavotricuspid isthmus ablation for typical atrial flutter; FFR = fractional flow reserve; IQR = interquartile range; IV = intravenous; MPI = myocardial perfusion imaging; PCI-S = percutaneous coronary intervention with stenting; PIP-AAD = pill-in-the-pocket antiarrhythmic drug; PVI = pulmonary vein isolation; SVT = supraventricular tachycardia.

*1 patient with moderate mitral stenosis, and another with a previous mechanical mitral valve replacement.

Benefits of a PIP-AAD treatment strategy

The contemporary costs of managing AF have been estimated to be 1.0%–2.7% of total annual health care expenditures, with a sizable proportion of these expenses attributed to direct costs associated with hospitalization and acute care.[2,4] ED patients in the United States with a primary diagnosis of AF had a hospital stay of average and standard deviation of 3.9 ± 5.2 days, with an average and standard deviation of the cost of hospitalization of $6692 ± $4928 per patient.[5] Among patients with paroxysmal AF, frequency of recurrences is strongly linked to higher resource utilization, with each recurrence averaging an additional $1600 per year.[6]

It is here where the out-of-hospital PIP-AAD approach has its greatest demonstrable impact. Specifically, the out-of-hospital PIP-AAD treatment strategy results in a substantial reduction in ED visits, as well as a substantial reduction in the need for electrical or IV pharmacologic cardioversions. However, despite the reduction in health care utilization, the number of outpatient PIP-AAD administrations for sustained AF remained substantial (159 outpatient PIP-AAD administrations, mean and standard deviation 5.3 ± 1.3 administrations per patient), suggesting that the burden of disease was unchanged but it was the strategy itself that was effective at decreasing health care utilization. However, it is important to recognize that candidacy for an outpatient PIP-AAD may be as low as 12% of patients who present to the emergency room with AF, because of a multitude of reasons including inefficacy and adverse events.[7]

Adverse outcomes associated with PIP-AAD treatment initiation

Our study reinforces the importance of administering the first dose of PIP-AAD therapy in a monitored setting to ensure the safety and efficacy of the approach. We observed an adverse event in 16% of initial PIP-AAD administrations (hypotension, proarrhythmic response, or bradycardia due to sinus or AV node dysfunction), with a total of 19% of the first PIP-AAD treatments failing to restore sinus rhythm within 6 hours. These rates are significant, but they are not out of keeping with what would be expected based on previous controlled trials of oral class Ic AAD administration, with a failure rate for cardioversion of 17%–42% and an adverse event rate of 5%–13%.[7,13–17] It is possible that the rate of adverse hypotensive and bradyarrhythmic events observed in our series may have been exacerbated by the coadministration of AV nodal blockers, which were not routinely employed in these past studies of oral class 1c AAD cardioversion.[7,13–18]

Our recommendations regarding the duration of inpatient monitoring after initial PIP-AAD administration were based on previous studies, guideline documents, and product monographs, as well as consultation with local ED physicians. Unfortunately, although they are uniform in their advocacy for an initial conversion trial be performed in a monitored setting, none of the American, Canadian, or European AF guidelines specify a minimum duration of inpatient monitoring.[8–10] Similarly, neither the flecainide nor propafenone product monograph provides a recommendation regarding monitoring after cardioversion, as this is an "off-label" use of these medications.

In contrast to previous studies, which recommended an 8-hour period of continuous electrocardiographic monitoring, we chose to decrease this period to 6 hours.[7] This change was based on the knowledge that beyond this time, the conversion rate for oral class Ic agents is similar to that of placebo, thus electrical cardioversion should be performed.[7,13–17,19,20] Moreover, given the issues with ED overcrowding and overutilization,[21,22] we believe that a period of 6 hours is more acceptable from a clinical point of view. Our data support this shortened (6-hour) observation

Table 2 Characteristics of patients experiencing in-hospital, and out-of-hospital adverse event.

In-hospital adverse event associated with initial PIP-AAD use

Age, y	Sex	Weight, kg	AF duration, mo	Prior CV (DCCV/PCV)	AVN agent	PIP- AAD	Heart rate, bpm	PR, ms	QRS, ms	QTc, ms	Adverse event
49.7	M	69	48	2/0	Mt	P	73	154	84	387	Atypical flutter requiring DCCV
56.7	M	87	3	0/1	Mt	P	45	140	96	416	Atypical flutter requiring DCCV
61.0	M	74	8	0/0	Mt	P	55	180	94	396	Hypotension requiring IVF Bradycardia requiring atropine
59.2	F	123	120	1/2	D	Fl	75	154	94	451	Hypotension requiring IVF, and epinephrine
62.9	F	57	3	2/0	Mt	P	58	152	78	408	Witnessed syncope due to conversion pause
61.0	F	81	26	2/1	D	P	64	158	90	416	Hypotension requiring IVF
64.6	M	85	108	2/0	Mt	Fl	58	172	90	420	Hypotension requiring IVF and norepinephrine

Out-of-hospital adverse event

Age, y	Sex	Weight, kg	AF duration, mo	Prior CV (DCCV/PCV)	AVN agent	PIP- AAD	Heart rate, bpm	PR, ms	QRS, ms	QTc, ms	Adverse event
68.4	F	82	0/2	3	Mt	P	73	142	84	469	Presyncope
54.3	F	66	1/0	9	Mt	Fl	56	152	90	422	Syncope requiring pacemaker
65.6	M	92	1/2	3	Mt	Fl	62	176	106	385	Atypical flutter requiring DCCV
66.6	M	70	16/0	10	Mt	P	80	142	86	410	Presyncope
40.9	M	82	1/1	2	Mt	P	61	170	98	432	Presyncope

All patients had a normal left ventricular ejection fraction and left atrial dimension. No patient had a history of coronary artery disease, asthma, or preceding pacemaker implant. None of the patients had experienced an adverse event related to prior to direct current or intravenous pharmacologic cardioversion.

AF = atrial fibrillation; AVN = atrioventricular node; CV = cardioversion; D = diltiazem; DCCV = direct current cardioversion; F = female; Fl = flecainide; IVF = intravenous fluid resuscitation; M = male; Mt = metoprolol; P = propafenone; PCV = intravenous pharmacologic cardioversion; PIP-AAD = pill in pocket antiarrhythmic drug; PR = PR interval in ms; QRS = QRS duration in ms; QTc = corrected QT interval.

period, as all conversions happened within 109–310 minutes (mean 155 minutes) and all adverse events occurred within 91–210 minutes (mean 152 minutes). However, we observed adverse events $\leq$125 minutes after sinus rhythm restoration, emphasizing the continued need for vigilant observation following pharmacologic cardioversion.

Adverse outcomes associated with out-of-hospital PIP-AAD use

Over the follow-up period, 5 patients experienced complications related to PIP-AAD usage: 1 with flutter, and 4 with syncope or presyncope. Although this rate is higher than that reported in previous series (17% vs. 7%), the duration of follow-up in our series was longer (21 vs. 15 months mean follow-up). Moreover, it is important to recognize that each of these events occurred in patients with a successful in-hospital treatment as well as multiple successful out-of-hospital PIP-AAD administrations, meaning that previous successful use does not necessarily exclude future adverse events. As such, it reinforces the importance of patient education regarding rest in a supine or seated position for the 4 hours following PIP-AAD administration or until the episode resolves. As no predictive factors for out-of-hospital adverse event were identified, the intermittent use of outpatient electrocardiographic monitoring (e.g., transtelephonic or mobile cardiac outpatient telemetry) would be useful to screen for adverse events (e.g., conversion pauses, proarrhythmia) during the outpatient treatment phase.

Limitations

The AF clinic at our institution functions first and foremost as a rapid-access clinic for patients presenting from the emergency room at our tertiary care center. As such, the decision to pursue rhythm control with PIP-AAD or regular

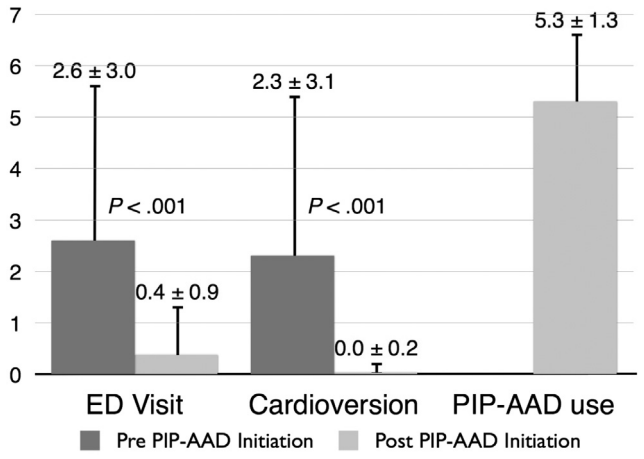

Figure 2 Emergency room visits, cardioversions, and "pill-in-the-pocket" antiarrhythmic drug (PIP-AAD) use prior to and following treatment initiation. Median duration from atrial fibrillation diagnosis to PIP-AAD treatment initiation was 990 days (interquartile range 360–1440 days), with a median follow-up duration from PIP-AAD treatment initiation of 579.5 days (interquartile range 170.3–1008.5 days). Values in the figure are expressed as mean plus or minus standard deviation.

AAD therapy is often made at the time of first consultation, based on discussion with the patient and review of the preconsultation investigations (which include an ECG, echocardiogram, and a 24-hour Holter monitor). It is possible that a longer therapeutic relationship may have provided greater insight into a propensity toward adverse events. In addition, the arrhythmic episodes and need for drug treatment during the follow-up period were determined solely on the basis of symptoms. It is possible that some of the episodes of sustained palpitations were the result of arrhythmias other than AF. Whereas the ability to accurately document the arrhythmic cause of the patient's symptomatology and provide real-time feedback (e.g., prior to PIP-AAD treatment) was deemed impractical at the study onset, the intermittent use of ambulatory ECG monitoring techniques during the outpatient phase would be beneficial to ensure appropriate PIP-AAD use (e.g., confirmation of AF episodes) and to screen for potential adverse events (e.g., conversion pauses, proarrhythmia). Lastly, the protocol necessitated the initial use of PIP-AAD in a monitored environment, and as such it may apply only to other settings where access and collaboration with multiple stakeholders is possible. We were unable to identify factors that may predict which patients it was safe to avoid the initial in-hospital PIP-AAD administration because of limited numbers.

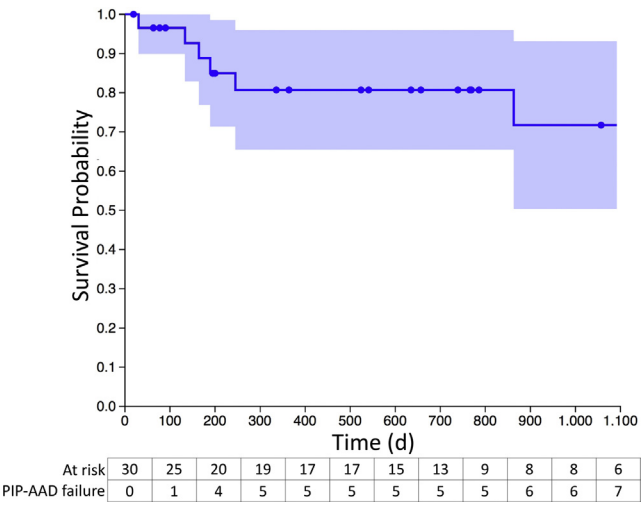

Figure 3 Time to pill-in-the-pocket antiarrhythmic drug (PIP-AAD) treatment failure in those with first successful emergency department pill-in-the-pocket antiarrhythmic drug administration.

Conclusions

An out-of-hospital PIP-AAD treatment strategy can be effective for highly selected patients with symptomatic paroxysmal AF. However, the rate of treatment failure and adverse events are clinically relevant, which limits its widespread application.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2017.10.002.

References

1. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 2014;114(9):1453–1468.
2. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 2004;90(3):286–292.
3. Wu EQ, Birnbaum HG, Mareva M, Tuttle E, Castor AR, Jackman W, Ruskin J. Economic burden and co-morbidities of atrial fibrillation in a privately insured population. Curr Med Res Opin 2005;21(10):1693–1699.
4. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. Value Health 2006;9(5):348–356.
5. Dell'Orfano JT, Patel H, Wolbrette DL, Luck JC, Naccarelli GV. Acute treatment of atrial fibrillation: spontaneous conversion rates and cost of care. Am J Cardiol 1999;83(5). 788–790, A710.
6. Reynolds MR, Essebag V, Zimetbaum P, Cohen DJ. Healthcare resource utilization and costs associated with recurrent episodes of atrial fibrillation: the FRACTAL registry. J Cardiovasc Electrophysiol 2007;18(6):628–633.
7. 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(23):2384–2391.
8. Gillis AM, Verma A, Talajic M, Nattel S, Dorian P. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: rate and rhythm management. Can J Cardiol 2011;27(1):47–59.
9. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation 2014;130(23):e199–e267.
10. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12(10):1360–1420.
11. Macle L, Cairns JA, Andrade JG, Mitchell LB, Nattel S, Verma A. Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. The 2014 Atrial Fibrillation Guidelines companion: a practical approach to the use of the Canadian Cardiovascular Society guidelines. Can J Cardiol 2015;31(10):1207–1218.
12. Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol 2011;27(1):74–90.

13. Boriani G, Biffi M, Capucci A, Botto GL, Broffoni T, Rubino I, Della Casa S, Sanguinetti M, Magnani B. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease. A randomized, controlled trial. Ann Intern Med 1997;126(8):621–625.
14. Conde D, Costabel JP, Caro M, Ferro A, Lambardi F, Corrales Barboza A, Lavalle Cobo A, Trivi M. Flecainide versus vernakalant for conversion of recent-onset atrial fibrillation. Int J Cardiol 2013;168(3):2423–2425.
15. Azpitarte J, Alvarez M, Baun O, Garcia R, Moreno E, Martin F, Tercedor L, Fernandez R. 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(10):1649–1654.
16. Botto GL, Capucci A, Bonini W, Boriani G, Broffoni T, Barone P, Espureo M, Lombardi R, Molteni S, Ferrari G. Conversion of recent onset atrial fibrillation to sinus rhythm using a single oral loading dose of propafenone: comparison of two regimens. Int J Cardiol 1997;58(1):55–61.
17. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. J Am Coll Cardiol 2001; 37(2):542–547.
18. 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(2):187–196.
19. Botto GL, Bonini W, Broffoni T, Espureo M, Cappelletti G, Lombardi R, Molteni S, Pedraglio E, Ferrari G. Randomized, crossover, controlled comparison of oral loading versus intravenous infusion of propafenone in recent-onset atrial fibrillation. Pacing Clin Electrophysiol 1998;21(11 pt 2):2480–2484.
20. Capucci A, Boriani G, Marchesini B, Strocchi E, Tomasi L, Balducelli M, Frabetti L, Ambrosioni E, Magnani B. Minimal effective concentration values of propafenone and 5-hydroxy-propafenone in acute and chronic therapy. Cardiovascular Drugs Ther 1990;4(1):281–287.
21. Miró O, Antonio MT, Jimenez S, De Dios A, Sanchez M, Borras A, Milla J. Decreased health care quality associated with emergency department overcrowding. Eur J Emerg Med 1999;6(2):105–107.
22. Trzeciak S, Rivers EP. Emergency department overcrowding in the United States: an emerging threat to patient safety and public health. Emerg Med J 2003; 20(5):402–405.