ESC European Society of Cardiology

Europace (2023) **25**, 1–8
https://doi.org/10.1093/europace/euad162

CLINICAL RESEARCH

Real-world utilization of the pill-in-the-pocket method for terminating episodes of atrial fibrillation: data from the multinational Antiarrhythmic Interventions for Managing Atrial Fibrillation (AIM-AF) survey

James A. Reiffel [1]*, Carina Blomström-Lundqvist [2,3], Giuseppe Boriani [4], Andreas Goette [5], Peter R. Kowey [6,7], Jose L. Merino [8,9], Jonathan P. Piccini [10], Sanjeev Saksena [11,12], and A. John Camm [13]

[1]Department of Medicine, Division of Cardiology, Columbia University Vagelos College of Physicians & Surgeons, c/o 202 Birkdale Lane, New York, NY 33458, USA; [2]Department of Cardiology, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [3]Department of Medical Science, Uppsala University, akademiska sjukhuset, ingang 35, 2tr 751 85 Uppsala, Sweden; [4]Division of Cardiology, Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Via Del Pozzo71, 41124 Moderna, Italy; [5]St. Vincenz Hospital, Am Busdorf 2 33098, Paderborn, Germany; [6]Sidney Kimmel Medical College at Thomas Jefferson University, 1015 Walnut Street, Philadelphia, PA 19107, USA; [7]Lankenau Heart Institute, 100 East Lancaster, Ave, Wynnewood, PA 19096, USA; [8]Chief, Arrhythmia & Robotic EP Unit, La Paz University Hospital, and Professor of Cardiology, Universidad Autonoma, IDIPAZ, Madrid, Spain; [9] La Paz University Hospital, Castellana Avenue, 261, 28046 Madrid, Spain; [10]Duke University, Duke Clinical Research Institute, 300 West Morgan Street, Durham, NC 27701, USA; [11]Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA; [12]Medical Director and Trustee, Electrophysiologiy Research Foundation, 161 Washington Valley Road, Warren, NJ 07059, USA; and [13]St George's University Hospitals, Blackshaw Road, Tooting London SW17 0QT, UK

Received 17 April 2023; accepted after revision 2 June 2023

Aims

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Episodes may stop spontaneously (paroxysmal AF); may terminate only via intervention (persistent AF); or may persist indefinitely (permanent AF) (see European and American guidelines, referenced below, for more precise definitions). Recently, there has been renewed interest in an approach to terminate AF acutely referred to as 'pill-in-the-pocket' (PITP). The PITP is recognized in both the US and European guidelines as an effective option using an oral antiarrhythmic drug for acute conversion of acute/recent-onset AF. However, how PITP is currently used has not been systematically evaluated.

Methods and results

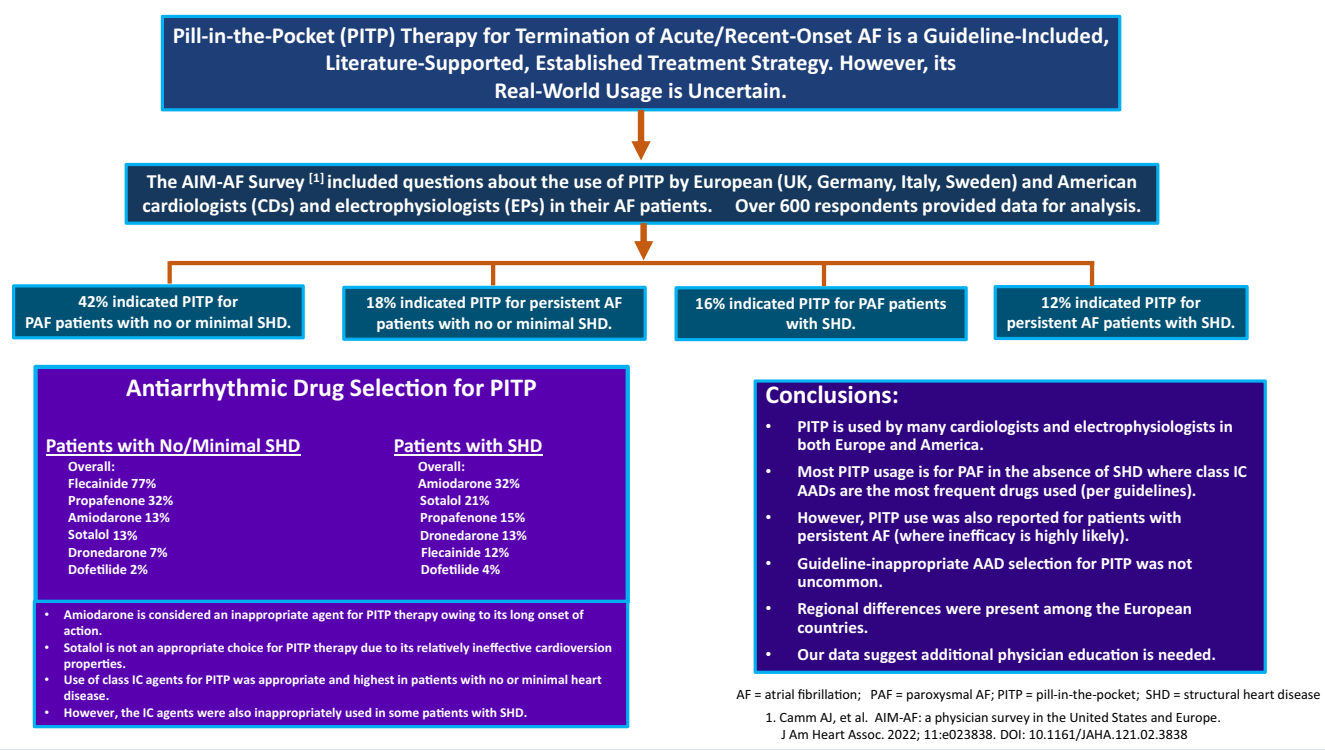
The recently published Antiarrhythmic Interventions for Managing Atrial Fibrillation (AIM-AF) survey included questions regarding current PITP usage, stratified by US vs. European countries surveyed, by representative countries within Europe, and by cardiologists vs. electrophysiologists. This manuscript presents the data from this planned sub-study. Our survey revealed that clinicians in both the USA and Europe consider PITP in about a quarter of their patients, mostly for recent-onset AF with minimal or no structural heart disease (guideline appropriate). However, significant deviations exist. See the Graphical abstract for a summary of the data.

Conclusion

Our findings highlight the frequent use of PITP and the need for further physician education about appropriate and optimal use of this strategy.

* Corresponding author. Tel: +1 561 203 2161. *E-mail address*: jar2@columbia.edu

Graphical Abstract



Keywords Atrial fibrillation • Cardioversion • Termination • Pharmacologic • Pill-in-the-pocket

What's new?

- Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Recently, there has been renewed interest in an approach to rapidly terminate acute/recent-onset AF with an oral antiarrhythmic drug regimen referred to as 'pill-in-the-pocket' (PITP). The PITP is recognized in both the US and European guidelines. However, how PITP is currently used has not been systematically evaluated.
- A multinational survey of over 600 cardiologists, stratified by USA vs. Europe, by representative countries within Europe, and by cardiologists vs. electrophysiologists was recently performed to assess current management approaches to AF: the Antiarrhythmic Interventions for Managing Atrial Fibrillation (AIM-AF) survey. This survey included questions regarding the current use of PITP.
- The herein reported AIM-AF sub-study on PITP revealed that clinicians in both the USA and Europe consider PITP in about a quarter of their AF patients. The frequency of PITP consideration was appropriately greatest in paroxysmal AF with minimal or no associated structural heart disease (SHD) (42%) vs. with SHD (16%). There was no significant difference in percentages reported between US and European practitioners; however, usage was notably higher in the USA, UK, Germany, and Italy, as compared with Sweden. The most frequently tried antiarrhythmics in the no SHD patients were guideline-consistent class IC agents.
- Nonetheless, physicians sometimes tried PITP for persistent AF, where it is not expected to work, and worrisomely also tried antiarrhythmic agents that were inappropriate for PITP therapy or were inappropriate for the type of structural heart disease present. These findings highlight the need for further physician education about appropriate and optimal use of the PITP strategy.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice.[1–3] As is more precisely defined in major guidelines,[1,2] AF may be recurrent, but stop spontaneously [paroxysmal AF (PAF)]; may terminate only via intervention (pharmacologic, electrical, and ablative) (persistent AF); or may persist indefinitely (permanent AF). Recent clinical reports emphasize the adverse-outcome reducing benefit of early rhythm control in patients with AF.[4–6] Moreover, the sooner AF stops, the lower the likelihood it will become persistent, and the briefer will be its associated symptoms.

In this context, recently, there has been renewed interest in the AF termination approach referred to as 'pill-in-the-pocket' (PITP).[7] The PITP is recognized in both the US and European guidelines[1,2] as an effective option using an oral antiarrhythmic drug (AAD) for acute conversion of recent-onset symptomatic AF that is bothersome, does not convert spontaneously, and has no associated haemodynamic instability or ischaemic symptoms—provided it employs an AAD with rapid effect and safety precautions, and standard anticoagulation guidelines are followed. However, how PITP is used in current real-world practice has not been examined. Thus, to determine the contemporary interest in and use of PITP for rapid termination of AF, questions regarding this strategy were included in the recent multinational survey of clinicians caring for patients with AF—the Antiarrhythmic Interventions for Managing Atrial Fibrillation (AIM-AF) study.[8] Our manuscript provides information regarding current PITP utilization by prescribing clinicians based upon responses in this survey.

Methods

Study design

The design, goals, and primary results of the AIM-AF study have been published previously.[8] Summarily, AIM-AF was an exploratory, online physician survey of clinical cardiologists, clinical electrophysiologists (EPs) and interventional EPs from the USA, UK, Germany, Italy, and Sweden conducted between 2 October 2020 and 12 February 2021 designed by a steering committee of nine global experts in AF. All survey participants had to have been in practice for >3 and <40 years, spend >40% of their time actively treating patients, and use both AADs and ablation (perform or refer) for AF rhythm control. Practice settings included in-hospital (both private and university) as well as primarily outpatient offices. Only 20% identified themselves as outpatient only. Ethics approval was obtained from the local ethics committee in Uppsala, Sweden, and Institutional Review Board approval was obtained from the Western Institutional Review Board. Participants provided informed consent in accordance with institutional guidelines.

Data collection and analysis

The survey was performed in compliance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct and in full accordance with the US Health Insurance Portability and Accountability Act (HIPAA) 1996. Respondents were asked to complete 96 questions[8] regarding physician demographics, patient caseload and characteristics, management of patients with different types of AF and different underlying comorbidities, and considerations regarding therapeutic choices for rhythm control with a focus on AADs and AF ablation. Among the questions asked were five specifically involving the use of PITP[8] (see Supplementary material online, *Table S1*). Data analyses were descriptive in nature and focused upon differences between US and European physicians, differences between physicians in the separate European countries surveyed, and differences between cardiologists and EPs. More detailed information regarding these analyses can be found in the manuscript reporting on the primary analyses of our study.[8]

Results

Respondent profiling and demographics

Of the 629 survey respondents: 49% were from the USA and 51% were European; 57% categorized themselves as cardiologists and 43% as EPs. For cardiologists and EPs: all said that they use AADs; cardiologists indicated that 21% of their patients were treated with ablation vs. 36.1% for EPs; 86% of EPs performed ablations.

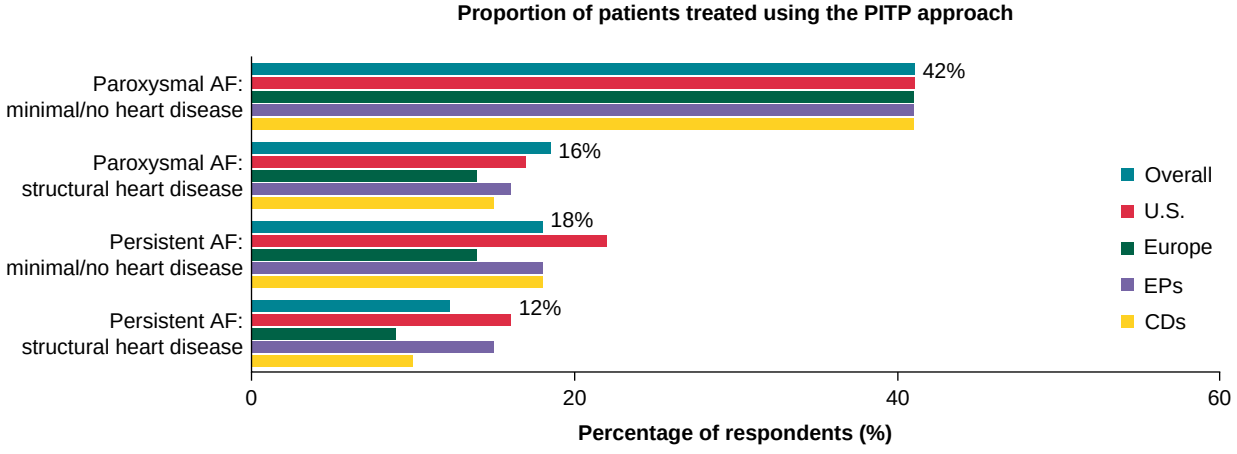
Pill-in-the-pocket use by type of atrial fibrillation and presence/absence of structural heart disease

Respondents from USA and Europe reported PITP use in 24% and 19% of their patients, respectively ($P < 0.05$), including patients with PAF or persistent AF and patients with or without associated structural heart disease (SHD) (*Figure 1* and *Table 1*). The frequency of PITP consideration was greatest in PAF with minimal or no associated SHD (42%) vs. with SHD (16%). There was no significant difference in percentages reported between US and European practitioners or between cardiologists and EPs for PAF with minimal or no associated SHD. There was no difference between US and European physicians or between cardiologists and EPs for PAF with SHD.

When examining responses by the represented European countries (the UK, Germany, Italy, and Sweden), the use of PITP for PAF with minimal or no SHD was 52, 41, 45, and 20% for these countries, respectively. For PAF with SHD, the use was 15, 14, 18, and 5%, respectively.

Although the major guidelines[1,2] only discuss PITP for AF of recent onset, the AIM-AF survey revealed that PITP was sometimes tried for persistent AF (in 19% without SHD and 13% with SHD) rather than for an acute AF episode (*Figure 1* and *Table 1*). The use of PITP was higher in the USA than in Europe for persistent AF with minimal or no SHD and for persistent AF with SHD. In persistent AF with SHD, PITP was used slightly more often by EPs than by cardiologists whereas in persistent AF with no or minimal SHD, use was the same by EPs and cardiologists (*Figure 1* and *Table 1*).

When examining responses for PITP selection in patients with persistent AF with minimal or no SHD, the frequencies for the UK, Germany, Italy, and Sweden, respectively, were 14, 13, 17, and 9%. For persistent AF with SHD, the respective responses were 11, 8, 12, and 3%.



- Overall, respondents reported using PITP in 23% (23% Europe vs. 24% U.S.) of their patients with paroxysmal or persistent AF.
- For persistent AF, PITP was higher in the U.S. than Europe (22% vs. 15%) with minimal or no SHD and 16% vs. 10% with SHD.

Figure 1 Proportion of patients treated using the PITP approach—in four patient groups: PAF without SHD; PAF with SHD; persistent AF without SHD; and persistent AF with SHD. Each group is stratified by US respondents, European respondents, cardiologists, and electrophysiologists. AF, atrial fibrillation; CDs, cardiologists; EPs, electrophysiologists; PITP, pill-in-the-pocket; SHD, structural heart disease.

Specific antiarrhythmic drugs used for pill-in-the-pocket

Our survey asked respondents which AAD or drugs they preferred for PITP treatment, stratified by the presence or absence of SHD. However, they were not asked this question separately for PAF vs. persistent AF.

For AF without SHD, class IC AADs were preferred (flecainide 77%, propafenone 32%) (*Figure 2*). In these patients, Europeans indicated flecainide (86%) more than did US physicians (66%) whereas Americans selected propafenone (41%) more than did Europeans (23%) ($P < 0.05$ for each). However, there was some use of oral amiodarone (13%) and sotalol (13%) in such patients. Both amiodarone and sotalol were chosen more by US (18% and 16%) than European respondents (8% and 10%) (each $P < 0.05$) and more by EPs than by cardiologists (20% vs. 17% and 16% vs. 17% for amiodarone and sotalol, respectively, P = ns). Dronedarone was selected in only 4–8%, and, in the USA, dofetilide (which is not available in Europe) was selected for PITP treatment in only 4%.

When examining the responses of the European respondents by country, for minimal or no SHD, amiodarone use was 2–7% (vs. 18% in the USA); flecainide use was 81–91% (vs. 66% in the USA); propafenone use was 13–23% except for Italy where it was 37% (vs. 41% in the USA); sotalol use was 10–12% except for Sweden where it was 4% (vs. 16% by the USA); and 'other' was 0–1%, except for Sweden where it was 15%.

For AF with SHD, class IC use diminished considerably (*Figure 2*) where selection was 27% by USA and 19% by European respondents and 27%, 28% by cardiologists and EPs. In contrast, the choice of amiodarone increased to 35% (Americans 32%, Europeans 36%; cardiologists 32%, EPs 31%) as did sotalol (19–21% in the USA and Europe and by cardiologists and EPs). Dronedarone selection also increased (to 13% in the USA and 9% in Europe) as did dofetilide (in the USA) to 9%.

When examining individually the responses of the European respondents to this category, amiodarone was a first choice for three of the four European countries (26–29%), which contrasted with the Italian respondents 57% but was similar to the USA, 32%. For persistent AF with SHD, dronedarone was 6–13% for the European and American respondents; flecainide was 9–13% for all except for Sweden (4%); propafenone was 7–11% for the Europeans except for Sweden (2%) (vs. 15% by the US respondents); sotalol was 21–29% for all except for Sweden (4%); and 'other' was 30%, 26%, 14%, and 58% for the UK, Germany, Italy, and Sweden, respectively (vs. 29% for the USA). No specific information as to what 'other' drugs were used is available. Nonetheless, again, it is clear that regional differences exist; the reasons for which will require future studies.

Table 1 Percentages of patients treated by PITP according to survey respondents' responses

Paroxysmal AF with no or minimal SHD			
US	42%	UK	52%
Europe	41%	Germany	41%
EPs	41%	Italy	45%
Cards	41%	Sweden	20%
Paroxysmal AF with SHD			
US	17%	UK	15%
Europe	14%	Germany	14%
EPs	16%	Italy	18%
Cards	15%	Sweden	5%
Persistent AF with no or minimal SHD			
US	22%	UK	14%
Europe	15%	Germany	13%
EPs	19%	Italy	17%
Cards	19%	Sweden	9%
Persistent AF with SHD			
US	16%	UK	11%
Europe	10%	Germany	8%
EPs	15%	Italy	12%
Cards	11%	Sweden	3%

AF, atrial fibrillation; Cards, clinical non-EP cardiologists; EPs, electrophysiologists; PITP, pill-in-the-pocket; SHD, structural heart disease; US, United States.

Concomitant rate-control drugs during pill-in-the-pocket

The PITP given with a rate-control agent was selected by 71% while 29% give PITP AADs without concomitant rate-control agents. Beta blockers were chosen more often by Europeans (95%) than Americans (87%) ($P < 0.05$) whereas Americans indicated calcium channel blockers more often than did Europeans (12% vs. 4%, $P < 0.05$). Our survey did not ask how beta blockers vs. calcium channel blockers were used in patients with vs. without SHD. Europeans gave PITP without a rate-control agent in 34% vs. Americans in 23% ($P < 0.05$). Regionally, the use of PITP without a rate-control agent was indicated by 42% in the UK, 27% by both German and Italian respondents, and 46% by Swedish respondents. When an atrioventricular (AV) nodal blocker was given with PITP, there was more uniformity with respect to beta blocker use: USA 87%, UK 99%, Germany 93%, Italy 92%, and Sweden 100%. This contrasts to calcium channel blockers, which were used by 12% in the USA vs. 0–7% by the Europeans.

Optimal arrhythmia frequency for pill-in-the-pocket

Optimal arrhythmia frequencies for PITP were felt to be monthly (13% of respondents), every 2–3 months (46%), every 4–6 months (26%), every 7–12 months (11%), and yearly or less (4%) with no meaningful differences between the US and European respondents, between cardiologists and EPs (*Figure 3*), or among the European respondents.

Discussion

The PITP strategy[7,9,10] is an alternative to intravenous AADs for the termination of acute or very recent-onset AF. Optimally, PITP employs an oral AAD with a rapid uptake and a short half-life, generally given as a single dose to acutely convert AF back to normal sinus rhythm at the time an AF event begins, or as soon thereafter as feasible (ideally within 3 days). The single dose is one which at maximum is no greater than would be the maximal total daily dose of the same agent given for chronic maintenance therapy. Due to a drop in efficacy after Day 3, PITP is unlikely to be effective in persistent AF (perhaps due to the onset of atrial remodelling effects).

If efficacy and safety are verified during the first administration (which is generally given under observation, especially if the patient is not well known to the physician), PITP can subsequently be self-administered as an outpatient.[7,10] The PITP utilization has reduced emergency room visits and hospitalizations and is thus cost effective.[7] Reported efficacy rates generally range from 70–80% for class IC AADs in PAF without significant SHD using single dose flecainide 300 mg or propafenone

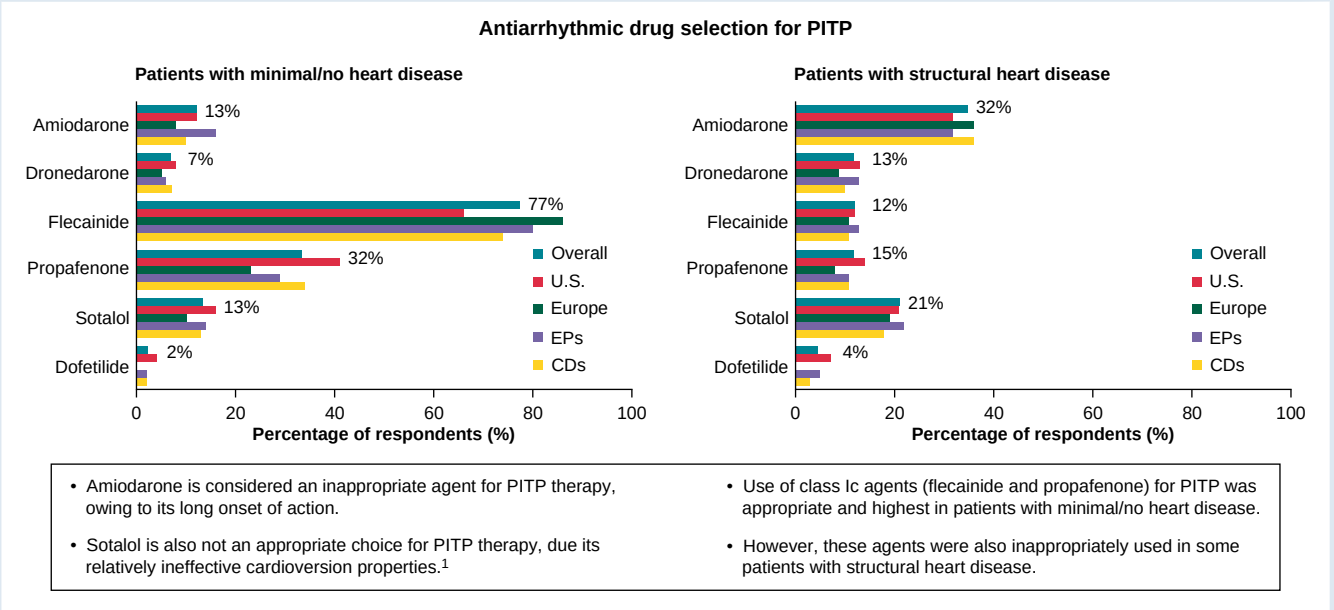


Figure 2 Antiarrhythmic drug selection in the same four patient groups as are seen in *Figure 1*. See text for discussion. AF, atrial fibrillation; CDs, cardiologists; EPs, electrophysiologists; PITP, pill-in-the-pocket; SHD, structural heart disease.

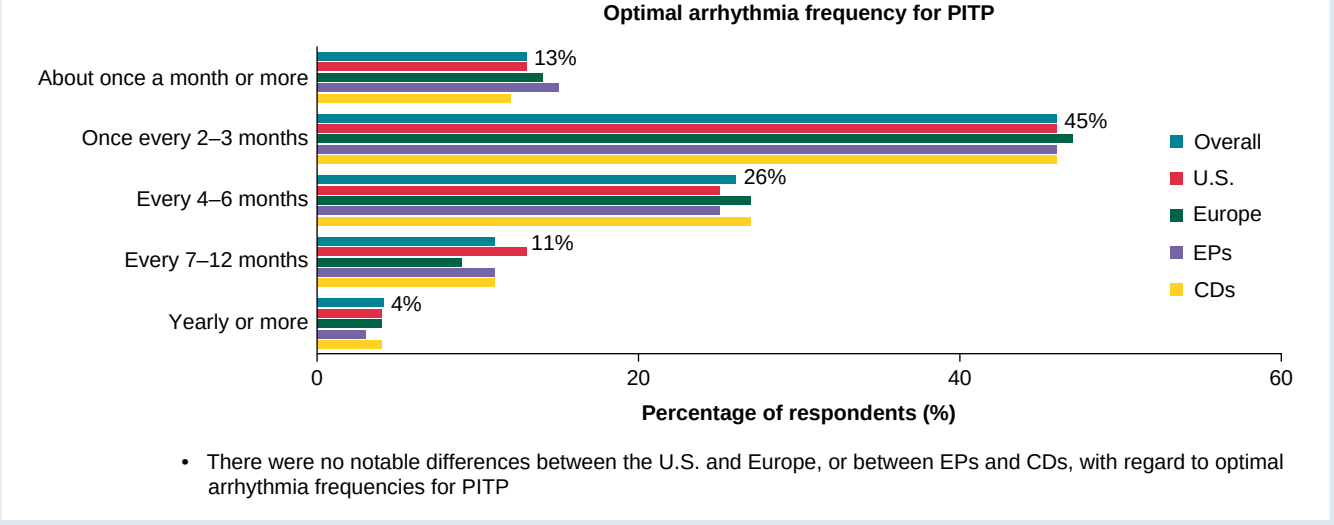


Figure 3 Frequency of atrial fibrillation episodes felt to be optimal for PITP therapy. See text for discussion. AF, atrial fibrillation; CDs, cardiologists; EPs, electrophysiologists; PITP, pill-in-the-pocket; SHD, structural heart disease.

600 mg (lower doses if low weight patients) with mean times to conversion of 4 h or less.[7] A typical protocol is shown in *Figure 4*. Most commonly, an AV node blocking agent is given as well when flecainide or propafenone is employed so as to prevent rapid rates if atrial flutter occurs (see *Figure 4*). Such agents most often are beta blockers or calcium channel blockers—the choice being made by physician preference and specific comorbidities present. They may be given acutely for this purpose unless the patient is already taking them as part of chronic therapy. Similar efficacy rates, though in a smaller number of trials, have been reported for ranolazine (2 gm) in patients with PAF with or without SHD[7] with particularly high efficacy when given concomitantly with intravenous amiodarone.[11] Additional details regarding PITP methodology, site of administration, and patient selection are beyond the scope of this manuscript but can be found in a recent thorough review.[7]

Importantly, some oral AADs, such as amiodarone or dofetilide may also terminate AF. However, the data for amiodarone are rather heterogeneous as many of the trials have used a combination of intravenous plus oral amiodarone.[12–15] In the few trials using just oral amiodarone, commonly a single oral loading dose of 30 mg/kg has been employed, with conversion rates higher than with placebo by 8 h, though still lower than with class IC agents until 24 h. During its clinical development programme, the effect of dofetilide on cardioversion of AF was examined, mainly in patients with persistent AF[16,17]

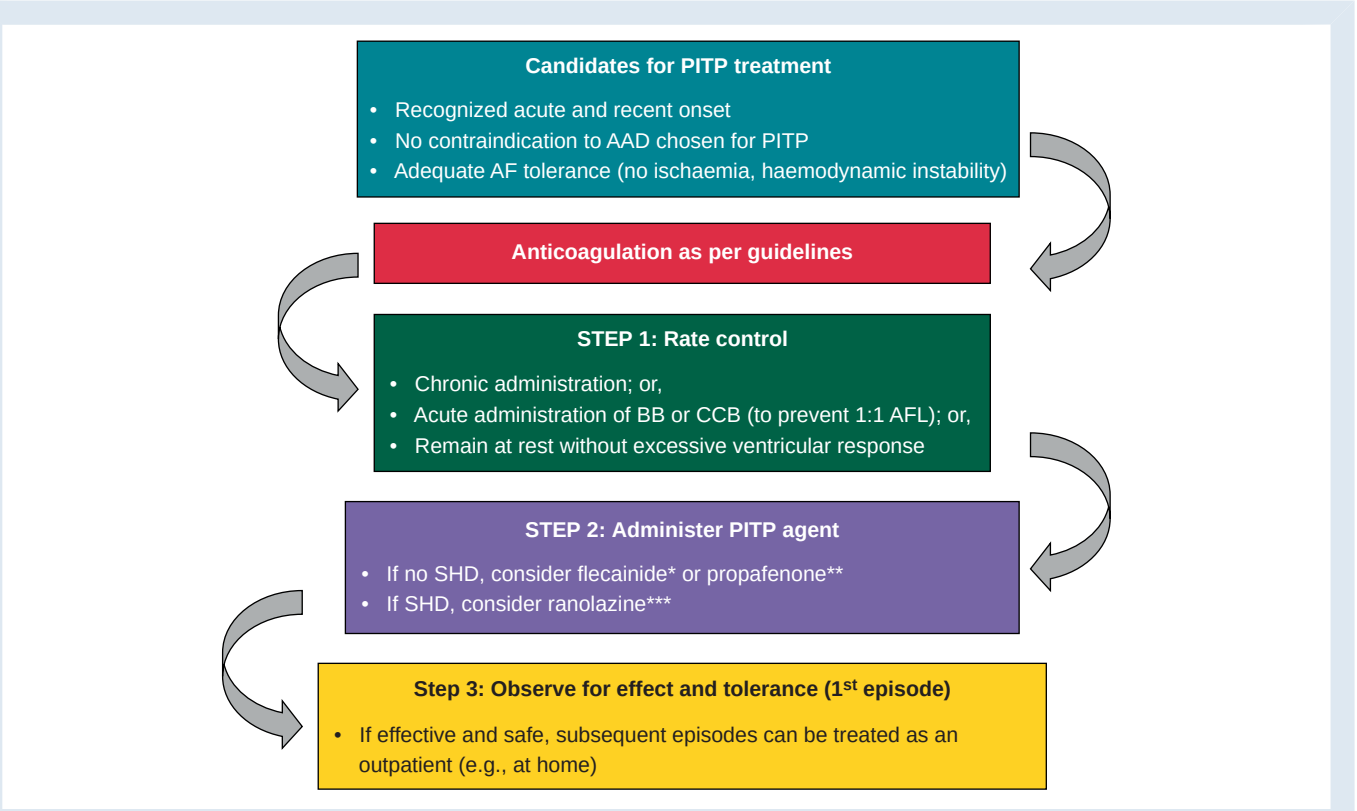


Figure 4 Typical steps involved in the administration of PITP therapy. See text and Reiffel and Capucci[7] for site and dosing of *flecainide, **propafenone, and ***ranolazine. AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; BB, beta blocker; CCB, calcium channel blocker; PITP, pill-in-the-pocket; SHD, structural heart disease.

although not compared directly against class IC AADs or amiodarone. Conversion rates of only 30% were seen, being <20% at 24 h and 30% by ~36 h.[16] Efficacy for PAF was so low that it is not a dofetilide indication. Sotalol's data are less consistent[14,18] with some showing only minimal conversion effects with oral sotalol in contrast to intravenous administration. In one direct comparison trial of oral sotalol (which provided no information on the time to conversion), sotalol's conversion rates were similar to amiodarone's but less than with flecainide.[18] Finally, dronedarone, commonly used for AF,[19–21] which was indicated by a few respondents, has not been tested for PITP use, and no significant observational datasets exist.

Given longer times to conversion ± lower rates of conversion, the abovementioned class III AADs are best not considered as true PITP agents. In both the most recent American and European AF guidelines,[1,2] the only AADs mentioned for PITP therapy as oral agents are flecainide and propafenone. While any electrophysiological effect of an AAD that can interrupt the focal automaticity and multiple reentrant loops that facilitate ongoing AF might be helpful in its termination, the atrial remodelling that occurs with longer duration AF reduces the magnitude/importance of the normal late repolarizing currents.[22,23] This effect would expectedly reduce the antiarrhythmic efficacy of class III AADs as PITP agents whereas class IC agents should still manifest their antiarrhythmic effects. However, in case of persistent or long-standing persistent AF, the progressive electro-anatomic remodelling occurring in the atria would likely reduce the effect of any AAD, regardless of drug class. Moreover, conceptually, such changes might paradoxically facilitate further atrial tachyarrhythmias, as can occur post-ablation.

Although the concept/application of PITP dates back to at least 1949,[7] its frequency of use has not been well quantitated. Accordingly, to better assess current utilization of PITP, we included questions regarding this strategy in the AIM-AF survey. The results as reported herein support the following:

First, respondents from the USA and Europe reported PITP use in 24% and 19% of their patients, respectively. The latter number is almost identical to that reported (18%) for pharmacologic cardioversion vs. electrical cardioversion in general (not just PITP) in a European survey from 2013.[24] Looking at a more granular level, PITP was indicated to be a treatment choice for PAF in the absence of SHD by 41–42% of US and European respondents and clinical cardiologists and EPs. Acute or recent-onset PAF with no or only minimal SHD is the ideal population for PITP utilization as it represents patients who are the most likely to convert and is a population in whom the class IC AADs are highly effective while also having a high tolerance and safety profile.[7,25–29]

Second, while there was rather uniform agreement about the use of PITP for such patients, regional differences were present (*Table 1*), being notably less in Sweden than elsewhere.

Third, in contrast to PAF with no or only minimal SHD, PITP was selected for only 14–18% of patients with PAF with SHD by European and American cardiologists and EPs (*Table 1*). We presume this decrease from 41–42% is consequent to contraindication considerations regarding the class IC AADs in the setting of SHD. Regional differences were much lower for this population, though Sweden was particularly low at 5%. With these two PAF population datasets pooled, it appears that PITP is used more infrequently by Swedish physicians than those elsewhere. Specific reasons for such differences cannot be assessed from the AIM-AF survey questions. However, in part, this may be due to the frequent use of beta blockers by Swedish physicians as anti-AF drugs, despite guidelines noting 'most evidence pleads against a significant role of beta blockers in preventing AF', and 'beta blockers

do not reliably terminate AF or facilitate electrical cardioversion'.[1] It may also be due in part to the fact that general physicians in Sweden are not allowed to prescribe class I or III AADs (mainly for fear of pro-arrhythmia), which may be a carryover effect to cardiologists.

Fourth, with respect to persistent AF, consideration of PITP was much lower (*Table 1*). For persistent AF with no or only minimal SHD, the indicated frequency for PITP use approximated 20% for both American and European respondents and for clinical cardiologists and EPs. For persistent AF with SHD, the reported percentages were even lower. Since PITP is unlikely to work with AF of >3–7 days duration, and since persistent AF is not a population for whom PITP is suggested in major guidelines,[1,2] these low numbers should not be surprising. Notably, here again, use in Sweden, being 9% for persistent AF with minimal or no SHD and 3% for persistent AF (*Table 1*) was less than in other geographical regions. Since other Scandinavian countries were not part of the survey, we do not know if Sweden is uniquely low in its use of PITP or if this is a more widespread regional pattern. Importantly, since we cannot eliminate the possibility that accelerated oral loading of an AAD with the goal being facilitation of electrical cardioversion or institution of antiarrhythmic treatment for avoiding post-cardioversion recurrences[30,31] might have been misinterpreted as a PITP regimen by some surveyed physicians, the true PITP numbers in this category might actually be lower.

Fifth, regarding rate-control therapy during PITP administration, AV nodal blocker use was more common in the USA (34%) than in Europe (23%); however, when drugs were used, beta blockers were overwhelmingly most common. Notably, Europeans gave PITP without a rate-control agent in 34% vs. Americans in 23% ($P < 0.05$). This was particularly high in the UK and Sweden (42–46%) vs. Germany, Italy, and USA (23–27%). Reasons for this difference are uncertain.

Sixth, in contrast to the above, there was essentially total agreement with respect to the frequency of AF events appropriate for consideration of PITP (easily seen in *Figure 3*). Not shown is that the choices were also remarkably similar among the individual European countries. Note, overall, almost three-fourths of respondents indicated that AF events occurring every 2 to 6 months were the optimal frequency for PITP. Why less frequent events, such as once a year or longer was chosen by so few (4%) is unclear and surprising, since such infrequent events would seem least likely to result in daily AAD administration or ablation. However, some practitioners may just consider the frequency of these arrhythmia events too low to be treated with antiarrhythmic medications and just consider beta blockers or other medications in this setting while awaiting spontaneous termination. Similarly, why 13% would use PITP for AF episodes occurring as often as once a month or more may also seem surprising. However, because our survey questions did not address symptom severity or duration of the episodes for which PITP would be chosen, we cannot know how such might have affected the survey choices made.

Seventh, with respect to the AADs selected for PITP, the overwhelming preference of AAD type was a class IC agent, (mostly flecainide) as is guideline appropriate for AF with no or minimal SHD. Propafenone use was second choice on both continents. In contrast, neither amiodarone, dronedarone, sotalol, and dofetilide (in the USA only) nor 'other' was indicated by more than 18%. Regional differences within Europe were small except for Sweden where the survey respondents selected amiodarone in only 2%, sotalol in only 4%, and 'other' in 15% (vs. 0–1% for 'other' everywhere else). Why the Swedish choices beyond the class IC agents varied so much vs. the other European countries and the USA again cannot be discerned from our survey.

With respect to AF with associated SHD, the choice of a class IC AAD declined as expected per guideline suggestions. No respondent country indicated more than 16% for a class IC option with a low of 2–4% for flecainide and propafenone in Sweden. For these patients, the choice of amiodarone increased, now being 32% for the USA and 26–29% for the European respondents except for an outlying 57% for the Italians. Simultaneously, the sotalol selection increased to 17–29% except for 4% in Sweden, and dronedarone, for which there has been no formal PITP study reported, remained low at 6–13%. Why the percentage range for sotalol was similar to that of the class IC AADs for AF patients with SHD and somewhat discordant from the now sotalol-discouraging guideline suggestions[1] is uncertain and cannot be determined from our survey questions. Interestingly, the choice of 'other' also increased to 14% for the Italians, 24–30% for the USA, the UK, and Germany, and an astonishing 58% for the Swedish respondents. Why the Italian choice of amiodarone and the Swedish choice of 'other' were both high and disproportionate to the selections indicated by the remaining respondents is not identifiable from our results. Thus, our survey revealed several anticipated selections, based upon the status of associated SHD, but also raised several questions regarding PITP consideration for persistent AF and individual drug class choices for which additional information will have to be gathered by additional investigation.

Limitations

Like most studies/surveys, ours has some limitations. They include: (i) questions regarding PITP were only the five referred to in our Results section. Therefore, additional considerations and areas of interest cannot be answered by our survey. (ii) We did not request nor indicate any specific definition for persistent AF vs. PAF; however, we assumed that in their practices, the investigators used definitions consistent with relevant guidelines. Also, we did not use any specific definition for SHD; and did not consider severity of concomitant SHD. Thus, we have no interpretable data as to how surveyed physicians defined persistent AF or type and magnitude of structural heart disease. (iii) We do not have data regarding the drugs that were classified as 'other.' When designing our survey, we did not anticipate the large amount of use of 'other' drugs, especially as was seen for the SHD population, so more granular data regarding this drug group were not included. (iv) While we did assess a geographically mixed population, including the US and several western European countries—themselves representing modest geographical variability—we did not survey all of Europe or worldwide. Likewise, we cannot know how physicians who did not respond to our survey request might have responded. Accordingly, we cannot know if our results may or may not be representative of PITP considerations elsewhere.

Conclusion

Our survey revealed that clinicians in both the US and European countries surveyed consider PITP in about a quarter of their AF patients, mostly for AF with minimal or no SHD (guideline appropriate). However, notable use of amiodarone and sotalol for PITP and use of class IC drugs in patients with SHD were evident—as was use of PITP for persistent AF where it is not considered to be an indicated or effective therapy. These findings highlight the need for further physician education about appropriate and optimal use of the PITP strategy.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

The AIM-AF trial was supported by Sanofi; however, no funding was provided for this manuscript except for partial support related to figure design.

Conflict of interest: J.A.R.: investigator J&J, Amarin, Sanofi, and InCarda Therapeutics, and consultant Acesion and Sanofi; speaker Sanofi, C.B.-L.: honoraria from Bayer, Boston Scientific, Correvio, Medtronic, Milestone, MSD, Sanofi, and Pfizer, A.J.C.: personal fees from Alta Thera, Sanofi, Abbott, Boston Scientific, and Medtronic, G.B.: speaker fees from Bayer,

Boehringer Ingelheim, Boston, and Medtronic, A.G.: speaker fees from Abbott, AstraZeneca, Berlin Chermie, Bayer, BMS-Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Omeicos, and Sanofi, and funding from the European Union Horizon 2020 (grant no. 965286), P.R.K.: consultant for Sanofi, J.L.M.: personal fees from Boston Scientific, Microport, and Sanofi, J.P.P.: grants for clinical research (Abbott, American Heart Association, Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, and Philips), and consultant (Abbott, AbbVie, Ablacon, AltaThera, ARCA Biopharma, BIOTRONIK, Boston Scientific, LivaNova, Medtronic, Milestone, MyoKardia, ElectroPhysiology Frontiers, Pfizer, Respicardia, Sanofi, Philips, and Up-to-Date), S.S.: consultant to Sanofi and Abbott, and research grants from Abbott and Sanofi, A.J.C.: personal fees from A.J.C.: personal fees from Sanofi, Abbott, Boston Scientific, and Medtronic; Bayer, Daiichi Sankyo, Pfizer/BMS, Anthos, Menarini, Acesion, InCarda, Milestone, Arca, and Johnson and Johnson.

Data availability

Qualified researchers may request access to data. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

References

1. Hindricks G, Potpara T, Dagres T, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC); developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr *et al.* 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:e199–267.
3. Kochav SM, Reiffel JA. Detection of previously unrecognized (subclinical) atrial fibrillation. *Am J Cardiol* 2020;**127**:169–75.
4. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–16.
5. Kim D, Yang PS, You SC, Jang E, Yu HT, Kim TH *et al.* Age and outcomes of early rhythm control in patients with atrial fibrillation: nationwide cohort study. *JACC Clin Electrophysiol* 2022;**8**:619–32.
6. Camm AJ, Naccarelli GV, Mittal S, Crijns HJGM, Hohnloser SH, Ma CS *et al.* The increasing role of rhythm control in patients with atrial fibrillation: JACC state-of-the-art review. *J Am Coll Cardiol* 2022;**79**:1932–48.
7. Reiffel JA, Capucci A. "Pill in the pocket" antiarrhythmic drugs for orally administered pharmacologic cardioversion of atrial fibrillation. *Am J Cardiol* 2021;**140**:55–61.
8. Camm AJ, Blomstrom-Lundqvist C, Boriani G, Goette A, Kowey PR, Merino JL *et al.* AIM-AF: a physician survey in the United States and Europe. *J Am Heart Assoc* 2022;**11**:e023838.
9. Brandes A, Crijns HJGM, Rienstra M, Kirchhof P, Grove EL, Pedersen KB *et al.* Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure. *Europace* 2020;**22**:1149–61.
10. Ibrahim OA, Belley-Cote EP, Um KJ, Benz AP, Dalmia S, Wang CN *et al.* Single-dose oral anti-arrhythmic drugs for cardioversion of recent-onset atrial fibrillation: a systematic review and network meta-analysis of randomized controlled trials. *Europace* 2021;**23**:1200–10.
11. deSouza IS, Tadrous M, Sexton T, Benabbas R, Carmelli G, Sinert R. Pharmacologic cardioversion of recent-onset atrial fibrillation: a systematic review and network meta-analysis. *Europace* 2020;**22**:854–69.
12. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkoran G, Touboul P. Amiodarone versus placebo and class IC drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2003;**41**:255–62.
13. Xanthos T, Bassiakou E, Vlachos IS, Bassiakos S, Michalakis K, Moutzouris DA *et al.* Intravenous and oral administration of amiodarone for the treatment of recent onset atrial fibrillation after digoxin administration. *Intern Cardiol* 2007;**121**:291–5.
14. Dell'orfano JT, Luck JC, Wollbrette DL, Patel H, Naccarelli GV. Drugs for conversion of atrial fibrillation. *Am Fam Physician* 1998;**58**:471–80.
15. Nadarasa K, Williams MJA. Single high oral dose amiodarone for cardioversion of recent onset atrial fibrillation. Heart, lung. *Circulation* 2012;**21**:444–8.
16. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M *et al.* Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation* 2000;**102**:2385–90.
17. Torp-Pedersen C, Moller M, Bloch-Thonsen PE, Kober L, Sandoe E, Egstrup K *et al.* Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *New Engl J Med* 1999;**341**:857–65.
18. Aguilar-Shea A. The safety and efficacy of sotalol in the management of acute atrial fibrillation: a retrospective case control study. *Interv Cardiol* 2016;**8**:637–42.
19. Khachatryan A, Merino JL, de Abajo FJ, Botto GL, Kirchhof P, Breithardt G *et al.* International cohort study on the effectiveness of dronedarone and other antiarrhythmic drugs for atrial fibrillation in real-world practice (EFFECT-AF). *Europace* 2022;**24**:899–909.
20. Curtis AB, Zeitler EP, Malik A, Bogard A, Bhattacharyya N, Stewart J *et al.* Efficacy and safety of dronedarone across age and sex subgroups: a post hoc analysis of the ATHENA study among patients with non-permanent atrial fibrillation/flutter. *Europace* 2022;**24**:1754–62.
21. Blomstrom-Lundqvist C, Naccarelli GV, McKindley DS, Bigot G, Wieloch M, Hohnloser SH. Effect of dronedarone vs placebo on atrial fibrillation progression: a post hoc analysis from Athena trial. *Europace* 2023;**25**:845–54.
22. Blaauw Y, Gogelein H, Tielman RG, van Hunnik A, Schotten U, Allessie MA. "Early" class III drugs for the treatment of atrial fibrillation: efficacy and atrial selectivity of AVE0118 in remodeled atrial of the goat. *Circulation* 2004;**110**:1717–24.
23. Duytschaever M, Blaauw Y, Allessie M. Consequences of atrial electrical remodeling for the antiarrhythmic actions of class IC and class III drugs. *Cardiovasc Res* 2005;**67**:69–76.
24. Hernandez-Madrid A, Svendsen JH, Lip GYH, Van Gelder IC, Dobreanu D, Blomstrom-Lundqvist C. Cardioversion for atrial fibrillation in current European practice: results of the European Heart Rhythm Association survey. *Europace* 2013;**15**:915–8.
25. Capucci A, Lenzi T, Boriani G, Trisolino G, Binetti N, Cavazza M *et al.* 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.
26. Boriani G, Biffi M, Capucci A, Botto GL, Broffoni T, Rubino I *et al.* 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**:621–5.
27. Boriani G, Biffi M, Capucci A, Botto G, Broffoni T, Ongari M *et al.* Conversion of recent-onset atrial fibrillation to sinus rhythm: effects of different drug protocols. *Pacing Clin Electrophysiol* 1998;**21**:2470–4.
28. Al-Jazairi MIH, Nguyen BO, De With RR, Smit MD, Weijs B, Hobbelt AH *et al.* Antiarrhythmic drugs in patients with early persistent atrial fibrillation and heart failure: results of the RACE 3 study. *Europace* 2021;**23**:1359–68.
29. Heijmam K, Hohnloser DH, Camm AJ. Antiarrhythmic drugs for atrial fibrillation: lessons from the past and opportunities for the future. *Europace* 2021;**23**:ii14–22.
30. Singh SN, Tang XC, Reda D, Singh BN. Systematic electrocardioversion for atrial fibrillation and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. *Heart Rhythm* 2009;**6**:152–5.
31. Um KJ, McIntyre WF, Mendoza PA, Ibrahim O, Nguyen ST, Lin SH *et al.* Pre-treatment with antiarrhythmic drugs for elective electrical cardioversion of atrial fibrillation: a systematic review and network meta-analysis. *Europace* 2022;**24**:1548–59.