Original article

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Drug management of atrial fibrillation in light of guidelines and current evidence: an Italian Survey on behalf of Italian Association of Arrhythmology and Cardiac Pacing

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Aim Atrial fibrillation is a multifaceted disease requiring personalized treatment, in accordance with current ESC guidelines. Despite a wide range of literature, we still have various aspects dividing the opinion of the experts in rate control, rhythm control and thromboembolic prophylaxis. The aim of this survey was to provide a country-wide picture of current practice regarding atrial fibrillation pharmacological management according to a patient's characteristics.

Methods Data were collected using an in-person survey that was administered to members of the Italian Association of Arrhythmology and Cardiac Pacing.

Results We collected data from 106 physicians, working in 72 Italian hospitals from 15 of 21 regions. Our work evidenced a high inhomogeneity in atrial fibrillation management regarding rhythm control, rate control and thromboembolic prophylaxis in both acute and chronic patients. This element was more pronounced in settings in which literature shows a lack of evidence and, consequently, the indications provided by the guidelines are weak or absent.

Conclusion This National survey evidenced a high inhomogeneity in current approaches adopted for atrial fibrillation management by a sample of Italian cardiologist experts in arrhythmia management. Further studies are needed to explore if these divergences are associated with different long-term outcomes.

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Keywords: antiarrhythmic drugs, atrial fibrillation, catheter ablation, rate control, rhythm control

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Introduction

Atrial fibrillation is the most common sustained arrhythmia in clinical practice with a prevalence of about 1–2% in Western countries[1,2] and is associated with significantly increased morbidity, mortality and several adverse events including a five-fold increased risk for stroke.[3,4]

In addition, it must be considered that the prevalence and incidence of atrial fibrillation are increasing rapidly and that future projections estimate six million affected patients in 2050.[5]

This will lead to an increase in access to the emergency room for symptoms related to atrial fibrillation or for its complications such as heart failure and thromboembolic events.[6]

It is a different care setting as compared with the usual ward or outpatient reality and often the therapeutic choices can be complex for the clinician.

The aim of this survey was to provide a country-wide picture of current practice regarding the most debatable aspects of atrial fibrillation pharmacological management after the publication of the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation.[7]

Methods

Data collection

Data were collected using a paper survey that was administered to members of the Italian Association of Arrhythmology and Cardiac Pacing (AIAC) between September and November 2020, the period immediately following the publication of the last ESC guidelines for the diagnosis and management of atrial fibrillation (August 2020).

We received responses from 106 physicians (about one-fifth of the electrophysiologists actively associated with

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AIAC during that period); the majority (54.7%) were under the age of 40 and only 19.8% over the age of 55.

Respondents came from 72 Italian hospitals and from 15 different Italian regions and about a third came from a center performing on site all the treatment for atrial fibrillation.

Statistical analysis

Data are presented as categorical variables, expressed in terms of fractions and percentages. Discrete variables were expressed as frequencies and percentages. Statistical calculations were prepared with SPSS Version 23.0.0 (Statistical Package for Social Sciences Inc.).

Results and discussion

Acute management (<36 h from the onset) of uncomplicated symptomatic atrial fibrillation

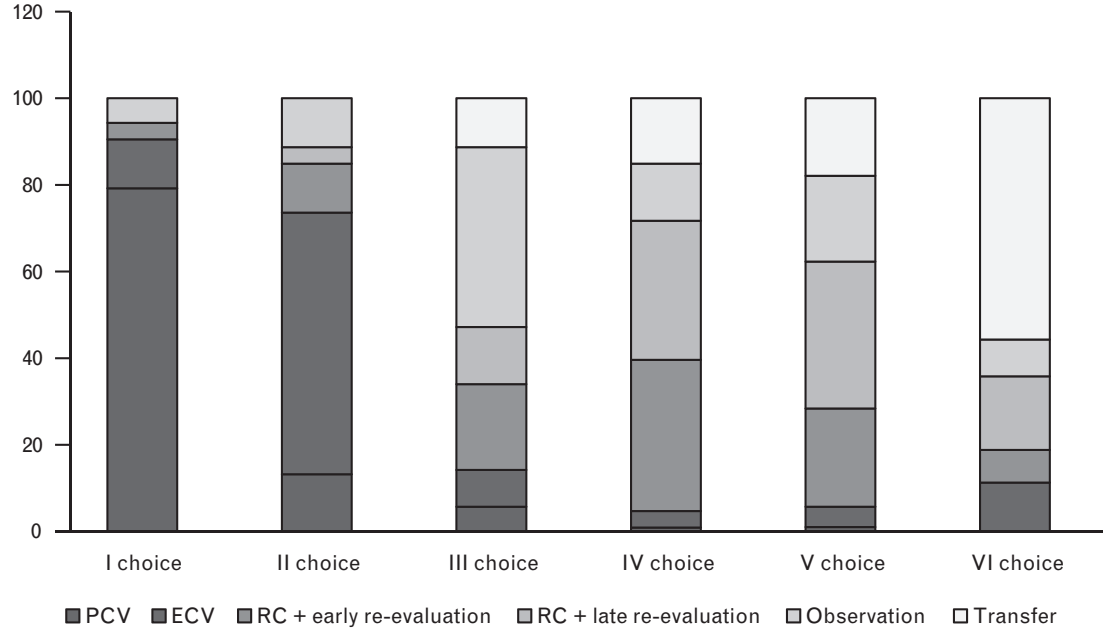
Figure 1 reports six different approaches sorted by first to last choice. The interviewed clinicians showed a clear preference for cardioversion (being the first option for 90.5% of them), especially pharmacological (79.2 vs. 11.3%), while rate control followed by early (<3 days) re-assessment by a cardiologist and observation in the emergency room ward was preferred only by a minority (respectively 3.8 and 5.7%). Early rate control followed by delayed cardiological reassessment (>5 days) and direct transfer to a cardiology ward were considered only as third options.

The quest for a quick stabilization of the patient by restoring sinus rhythm, leading to an early discharge is broadly in line with the 2020 European guidelines on atrial fibrillation,[7] supporting sinus rhythm (SR) restoration as the first option in all patients with symptoms when atrial fibrillation cannot be ruled out as a cause. However, it has to be noted that factors predisposing to arrhythmic relapse (e.g. advanced age, comorbidities, and structural heart disease) make spontaneous cardioversion less likely,[8] while in the absence of these conditions, spontaneous conversion to SR can occur in greater than 75% within 48 h.[9] This is in accordance with the results of the 'Rate Control Versus Electrical Cardioversion Trial 7–Acute Cardioversion Versus Wait and See' (RACE 7 ACWAS)[10] showing that a strategy of rate control with cardioversion deferred at 4 weeks (when required) is noninferior to early SR restoration with possible positive effects: reduction of cardioversion-related complications and pro-arrhythmia due to antiarrhythmic drugs.[11]

However, it must be considered that electrical cardioversion has a very high success rate, which can be increased by a personalized configuration of the patches,[12] and that the choice for early pharmacologic cardioversion can be helpful for planning subsequent management while unmasking pro-arrhythmia.

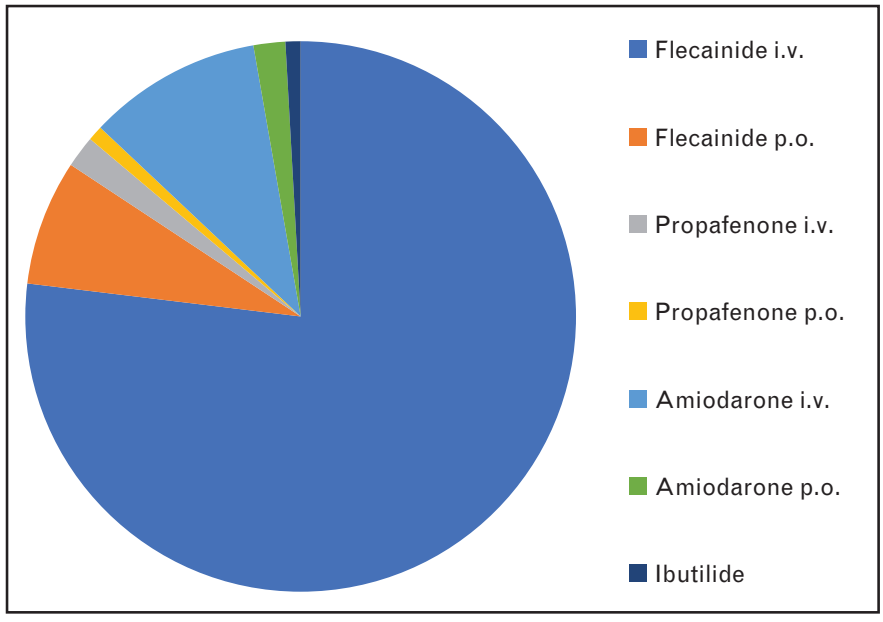
In this regard, we asked the preferred agent for pharmacologic cardioversion in this setting (Fig. 2). Interestingly, more than three-quarters of respondents chose class IC

Fig. 1



A patient admitted to an emergency room for hemodynamically stable atrial fibrillation (hazard ratio 110–130 bpm); symptoms began less than 36 h earlier and showed no signs of ischemia or heart failure. The patient has been fasting for 8 h. Which strategy would you choose? ECV, electrical cardioversion; PCV, pharmacological cardioversion; RC, rate control.

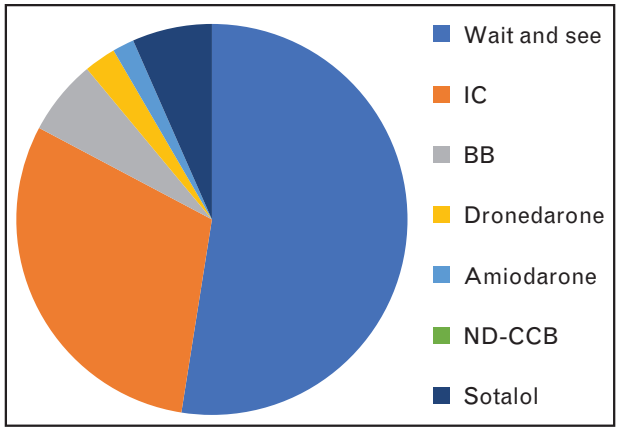
Fig. 2



What drug would you choose for pharmacological cardioversion in the same patient as Question 1? i.v., intravenous administration; p.o., per os administration.

antiarrhythmic drugs (mainly flecainide) and they, especially preferred intravenous administration. Although the intravenous approach may slightly reduce time to SR restoration and seems more practical in the acute setting, a single oral dose of a class IC antiarrhythmic drug is effective and well tolerated for cardioversion of recent-onset atrial fibrillation,[13] it allows the opportunity to test a pill-in-the-pocket strategy,[14] and its effectiveness is useful in predicting long-term maintenance of SR.[15]

Fig. 3



What prophylaxis of relapses would you use in a patient under 70 years of age with newly detected AF? BB, beta blocker; IC, antiarrhytmic drugs class IC; ND-CCB, nondihydropyridine calcium channel blocker.

Acute management (<36 h from the onset) of uncomplicated symptomatic atrial fibrillation according to different clinical conditions

When asked to re-consider their first choice according to different clinical conditions, physicians confirmed their preference for an early cardioversion strategy except in patients at very high periprocedural thromboembolic risk (e.g. elderly patients, with previous cerebral thromboembolism or with active cancer). Moreover, these patients present a high probability of arrhythmia relapse and risk of intolerance to anticoagulant therapy in the postcardioversion period (Table 1).

Fewer respondents preferred cardioversion in patients with previous bleeding (80.2%), maybe misled by the unproved feeling that this can reduce the thromboembolic risk in case of subsequent suspension of anticoagulation, or in patients suffering from chronic kidney disease (68.8%) despite several data showing poor outcomes of this strategy in such patients.[16]

Prophylaxis of relapses in patients younger than 70 years with newly detected atrial fibrillation

As shown in Fig. 3, 55.7% of respondents chose a wait-and-see strategy or use of a beta blocker (6.6%), whereas only 36.8% preferred a rhythm control strategy (32.1% with class IC antiarrhythmic drugs, 2.8% with dronedarone, and 1.9% with amiodarone).

Table 1 Which strategy would you choose between rate control, electrical cardioversion and pharmacological cardioversion in a patient similar to the previous (i.e. from Question 1), but with one of the following additional clinical elements?

	Onset of symptoms <6 h	Onset of symptoms >12 h	Female sex	Previous bleeding	Age >70 years	CHA_2DS_2-VASc <2 in M or <3 in F
RC (%)	1.9	9.4	5.7	19.8	40.6	9.4
ECV (%)	11.3	41.5	13.2	32.1	19.8	11.3
PCV (%)	86.8	49.1	81.1	48.1	39.6	79.3

	GFR <50 ml/min	Active cancer	Previous TIA/stroke	Previous PTCA	EF <40%	Symptoms other than palpitations
RC (%)	17.9	49.1	59.4	19.8	17.0	21.7
ECV (%)	50.9	14.2	10.4	46.2	57.5	56.6
PCV (%)	31.2	36.7	30.2	34.0	25.5	21.7

ECV, electrical cardioversion; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; PCV, pharmacological cardioversion; PTCA, percutaneous transluminal coronary angioplasty; RC, rate control; TIA, transient ischemic attack.

This choice, albeit in line with ESC guidelines,[7] raises some doubt in view of the possible progression of atrial fibrillation.[17,18] In this regard, the recently published 'Early Treatment of Atrial Fibrillation for Stroke Prevention Trial' (EAST-AFNET 4)[19] was the first study showing fewer cardiovascular events with an early rhythm control strategy while including more than one-third of patients at their first episode of atrial fibrillation.

However, it is important to emphasize that the clinical benefit of early, systematic rhythm control therapy was achieved using not only variable treatment patterns of antiarrhythmic drugs applied within guideline recommendations but also atrial fibrillation ablation.[20] Recently, several trials have demonstrated that an initial treatment strategy of cryoballoon catheter ablation significantly improves arrhythmia outcomes[21] and this benefit seems to be maintained in all atrial fibrillation type subgroups.[22]

Long-term antiarrhythmic drug therapy for rhythm control

Focusing on the preferred antiarrhythmic drug for long-term prophylaxis of atrial fibrillation in a middle-aged patient without any relevant structural heart disease at the second/third episode of atrial fibrillation, we found a general agreement with current guidelines for class IC as the first option.[7,23] The last three options seem more questionable being sotalol preferred to amiodarone, despite the higher risk of pro-arrhythmia,[24,25] and dronedarone being the last considered option by most of the physicians.

At this regard, despite being less effective than amiodarone, dronedarone presents fewer adverse effects,[26] which makes this agent a well tolerated choice, especially for patients not eligible for class IC drugs (because of ischemic heart disease or with history of atrial flutter)[27] as documented by a metanalysis on available trials and real-life studies.[28]

However, the available literature shows that in a real-world population, including both patients with and without structural heart disease, nonadherence to guidelines is frequently observed[29] and the use of amiodarone is predominant at the expense of a limited use of class 1c antiarrhythmic () drugs.[30]

Duration of antiarrhythmic drug prophylaxis for atrial fibrillation relapses

Beyond the choice of the antiarrhythmic agent for atrial fibrillation prophylaxis, we asked the usual duration of such treatment. As shown in Table 3, most of the interviewed physicians would continue the treatment indefinitely in all patients at increased risk of relapses, thromboembolic and/or hemorrhagic events (despite no evidence supporting the last two options). Conversely, after the first atrial fibrillation episode, there is the preference for short-term prophylaxis. In the remaining scenarios, including patients both at low risk of relapses and side effects, the opinions are more heterogeneous.

These uncertainties also stem from the absence of clear indications in the ESC guidelines on atrial fibrillation on the duration of antiarrhythmic prophylaxis of atrial fibrillation relapses.[7] However, the factors predicting the maintenance of SR are known.[31]

Of note, the only study focused on this topic, the 'Flecainide Short-Long trial' (Flec-SL),[32] which enrolled patients with persistent atrial fibrillation undergoing

Table 2 Which drug would you choose for the prophylaxis of relapses in a patient without structural heart disease at the second/third episode of atrial fibrillation?

	Amiodarone	Dronedarone	Flecainide	Propafenone	Sotalol
First choice	0.9%	1.9%	93.4%	2.8%	0.9%
Second choice	6.6%	1.9%	3.8%	85.8%	1.9%
Third choice	22.6%	32.1%	1.9%	4.7%	39.6%
Fourth choice	38.7%	33%	0.9%	3.8%	24.5%
Fifth choice	31.1%	31.1%	0%	2.8%	33%

Table 3 How long would you continue antiarrhythmic drug prophylaxis for atrial fibrillation relapses in the following scenarios?

	≤30 days	3–6 months	12 months	Chronic
First episode of AF	43.4%	34%	12.3%	10.4%
Subsequent relapses	3.8%	11.3%	19.8%	65.1%
Female sex	17.9%	30.2%	20.8%	31.1%
Absence of heart disease	24.5%	23.6%	26.4%	25.5%
Age <65 years	21.7%	25.5%	29.2%	23.6%
Previous TIA/stroke	3.8%	5.7%	15.1%	75.5%
Previous PTCA	9.4%	15.1%	26.4%	49.1%
EF <40%	2.8%	6.6%	19.8%	70.8%
GFR <50 ml/min	9.4%	9.4%	28.3%	52.8%
History of bleeding in the last 1–2 years	7.5%	9.4%	15.1%	67.9%
History of neoplasm in the last 2 years	5.7%	19.8%	18.9%	55.7%

AF, atrial fibrillation; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

planned cardioversion, showed that a 6-month treatment with flecainide nonsignificantly reduced a composite end point of time to persistent atrial fibrillation or death as compared with 4 weeks of treatment. However, at 4 weeks of follow-up, flecainide treatment as compared with no prophylaxis has been shown to be effective in reducing the primary end point (29.8 vs. 47.5%; $P = 0.01$).

Choice of drugs for rate control

We also investigated which drugs were preferred, alone or in combination, in a patient with atrial fibrillation and rapid ventricular conduction (e.g. 150–170 bpm) in different settings. The answers are summarized in Table 4.

From these data, a clear preference for beta blockers for all the proposed categories is evident despite the 2020 ESC guidelines recommending beta blockers or nondihydropyridine calcium channel blockers (ND-CCBs) as the first choice for rate control in patients with left ventricular ejection fraction at least 40% (class I, level of evidence B). This broad consensus is particularly surprising considering data suggesting a superiority of ND-CCBs in terms of rate-control efficacy, relief of a-retrial fibrillation-related symptoms and prevention of atrial fibrillation progression.[33,34] On the contrary, it is confirmation of the preference expressed for beta blockers in case of heart failure with reduced ejection fraction, despite the recent less enthusiastic data on the survival benefit in this setting.[35]

Figure 4 shows a more interesting finding: a relevant number of physicians consider the association of a beta blocker and a ND-CCB in many subsets of patients, being about half in patients without major cardiopathy and/or comorbidities. However, we lack specific trials investigating this option.

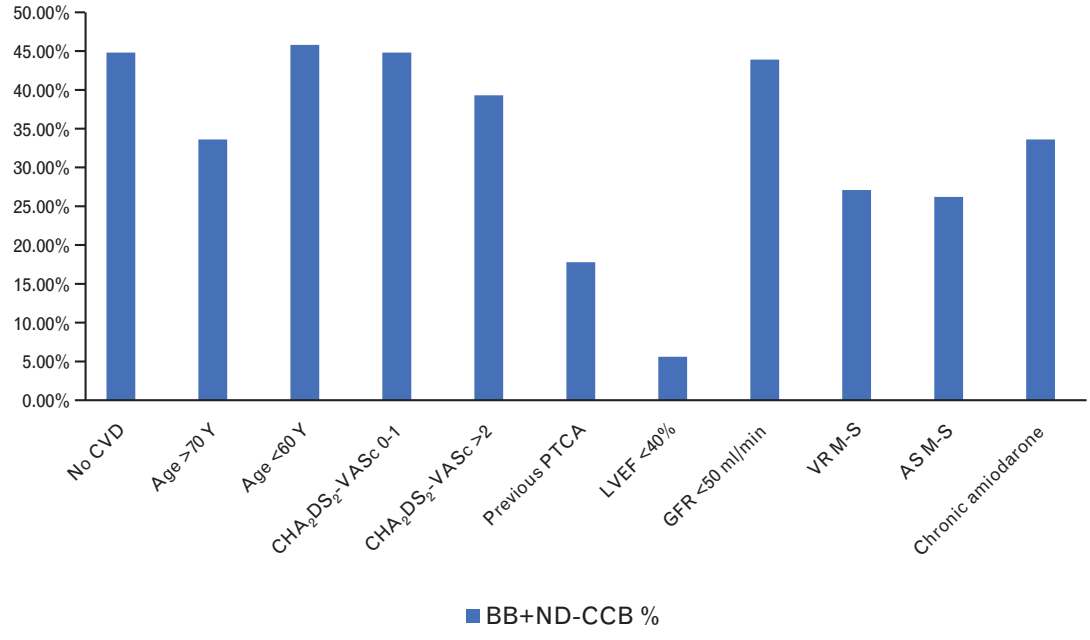
Table 4 Which drug would you use as your first choice for rate control in a patient with high-responsive atrial fibrillation (hazard ratio 150–170 bpm) in the following settings and what drug would you add if the first one was not enough to reach the therapeutic target?

		No CVD	Age >70 years	Age <60 years	CHA_2DS_2-VASc score 0–1	CHA_2DS_2-VASc score ≥2
1st C (%)	BB	80	81	77	77	84
	DZ	13	13	16	15	13
	VER	5	3	6	3	2
	DIG	2	3	1	2	1
	Amiodarone	0	0	0	3	0
2nd C (%)	BB	17	16	19	21	16
	DZ	32	25	30	31	27
	VER	23	12	22	18	18
	DIG	25	41	23	23	24
	Amiodarone	4	7	7	8	15

		EF <40%	GFR <50 ml/min	Valvular regurgitation M-S	Aortic stenosis M-S	Previous PTCA
1st C (%)	BB	83	84	82	78	94
	DZ	1	11	7	8	1
	VER	13	3	5	4	1
	DIG	3	2	4	3	2
	Amiodarone	0	0	3	8	2
2nd C (%)	BB	11	14	14	21	4
	DZ	6	34	21	19	17
	VER	3	15	11	15	9
	DIG	66	17	33	30	54

1st C, first choice; 2nd C, second choice; BB, beta blocker; CVD, cardiovascular disease; DIG, digoxin; DZ, diltiazem; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; M-S, moderate or severe; PTCA, percutaneous transluminal coronary angioplasty; VER, verapamil.

Fig. 4



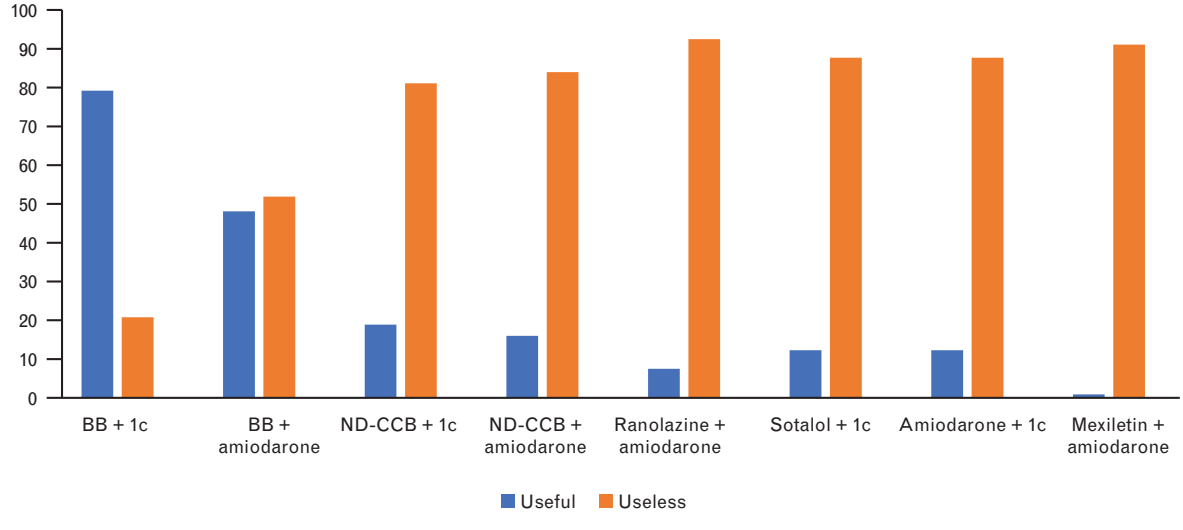
Percentage of choice of the association between beta blockers and calcium channel blockers in different settings. AS M-S, aortic stenosis moderate or severe; BB, beta blocker; CVD, cardiovascular disease; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; ND-CCB, nondihydropyridine calcium channel blocker; PTCA, percutaneous transluminal coronary angioplasty; VR M-S, valvular regurgitation moderate or severe.

On the contrary, digoxin and amiodarone very rarely represented a first choice and were more frequently selected as a second choice in combination with a negative chronotropic drug in patients at risk of acute heart failure.[36,37] This is almost in line with ESC guidelines in view of the possible side effects of amiodarone and strict therapeutic window of digoxin.[7]

Postablation pharmacological management of atrial fibrillation

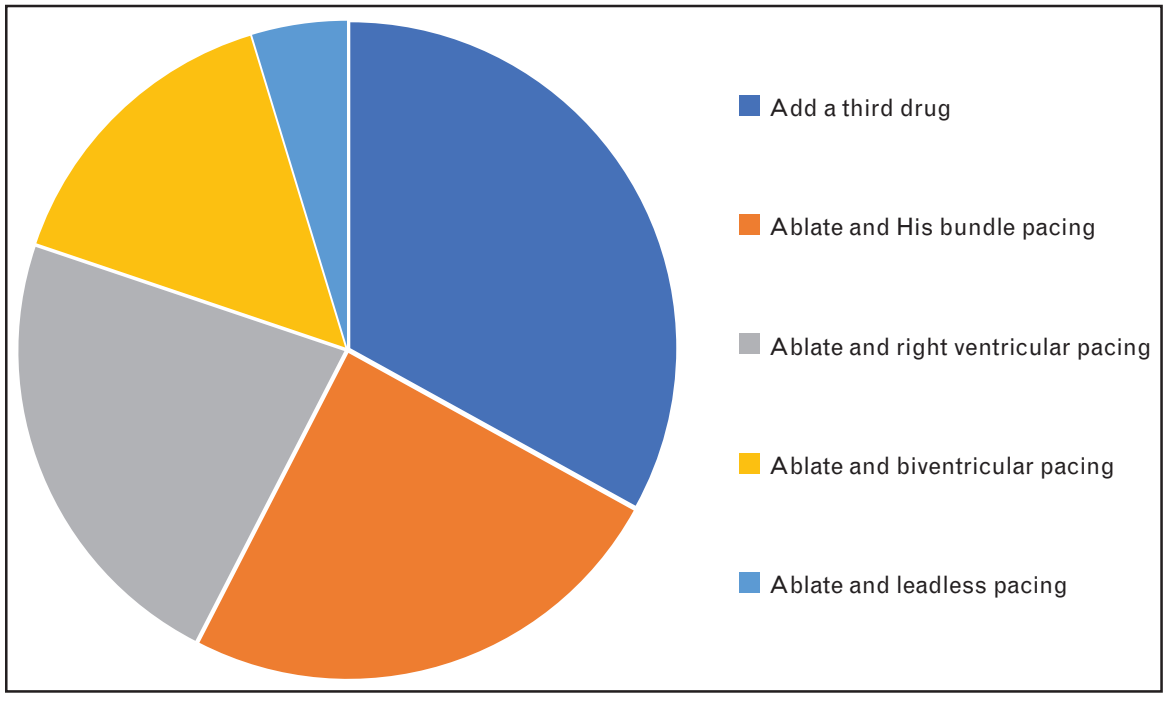
Physicians were then asked what combinations of drugs they would use for postablation pharmacological management of atrial fibrillation in case of multiple symptomatic relapses in absence of structural heart disease.

Fig. 5



What combinations of drugs do you consider useful in a patient without structural heart disease and with multiple symptomatic relapses of atrial fibrillation after transcatheter ablation? BB, beta blocker; IC, class IC antiarrhythmic drugs; ND-CCB, nondihydropyridine calcium channel blocker.

Fig. 6



What would you do in a patient without structural heart disease after failure of rhythm control therapy (including ablation) and with ineffective rate control despite using two drugs?

In the first instance, it is necessary to specify that no randomized trials have demonstrated the efficacy of these combinations in a population of patients undergoing atrial fibrillation ablation. However, only 1.9% of the physicians answered 'none' to the questionnaire. As shown by Fig. 5, the associations of a beta blocker and a class IC antiarrhythmic drug (79,2%) or amiodarone (48.1%) were the most selected. Noteworthy, the first association is supported by a postcardioversion randomized trial,[38] while for the second option, there is only a randomized trial on postsurgical patients.[39]

On the contrary, the associations of a ND-CCB and a class IC antiarrhythmic drug (18.1%) or amiodarone (16%) were less chosen, confirming the tendency to prefer beta blockers over ND-CCBs. However, 'VErapamil Plus Antiarrhythmic drugs Reduce Atrial Fibrillation relapses after an electrical cardioversion' (VEPARAF Study)[40] showed that also the addition of verapamil to class IC, or III antiarrhythmic drugs can significantly reduce atrial fibrillation relapses.

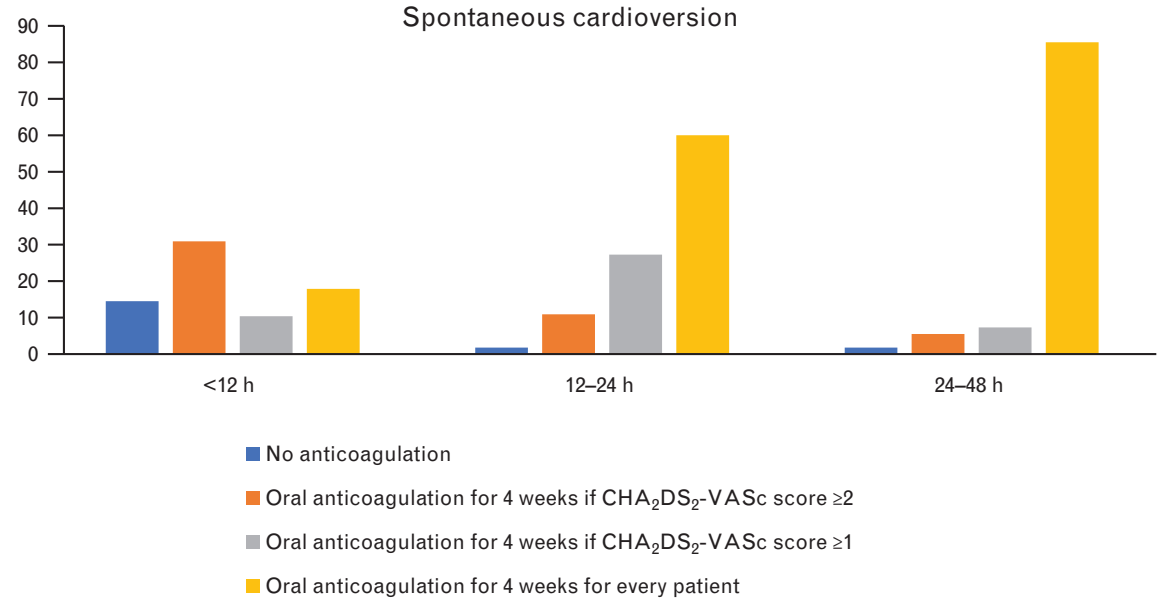
Interestingly, about one-fourth of the physicians would choose a combination between class I and class III antiarrhythmic drugs, but despite some electrophysiological basis on this association, we lack relevant studies supporting this option, especially in terms of safety.[41]

Finally, an association between amiodarone and ranolazine was considered useful by 7.5% of cardiologists. Ranolazine use seems to be well tolerated and given orally in association with amiodarone showed the property to significantly quicken the conversion of atrial fibrillation compared with amiodarone alone. Furthermore, in patients in sinus rhythm, ranolazine alone proved to reduce the frequency of relapses.[42]

Treatment of a patient with ineffective rhythm control and ineffective rate control despite combinations of two drugs

In this specific context, the preferred option was ablate-and-pace, which is in line with most of the current literature. However, Fig. 6 shows an extreme heterogeneity of the options to approach this strategy, with similar preference among right ventricular, biventricular and His bundle pacing. Notably, in this context, the available evidence is all in favor of biventricular pacing (chosen only by 15.1% of those interviewed) when compared with right ventricular pacing or rate control with up to two agents[43,44] but this has not been stressed in current guidelines.[7] On the contrary, conduction system stimulation turned out to be the preferred pacing option despite possible safety concerns in case of increasing pacing threshold[45] and in the

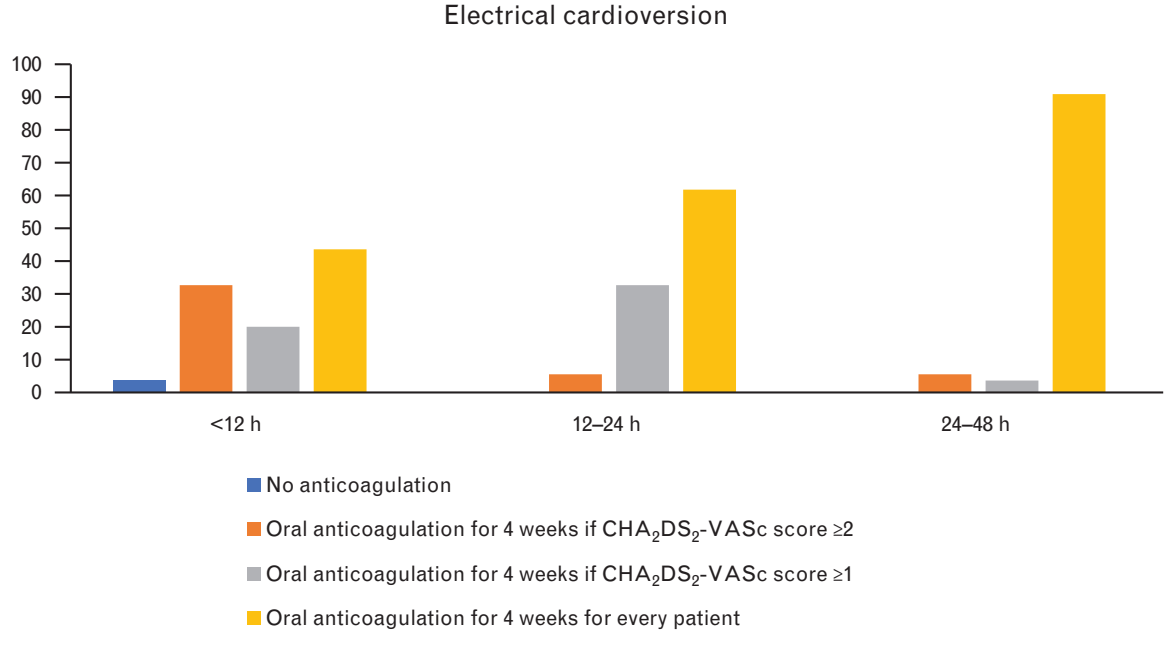
Fig. 7



How would you manage a patient's anticoagulation after spontaneous cardioversion had occurred in the following time ranges?

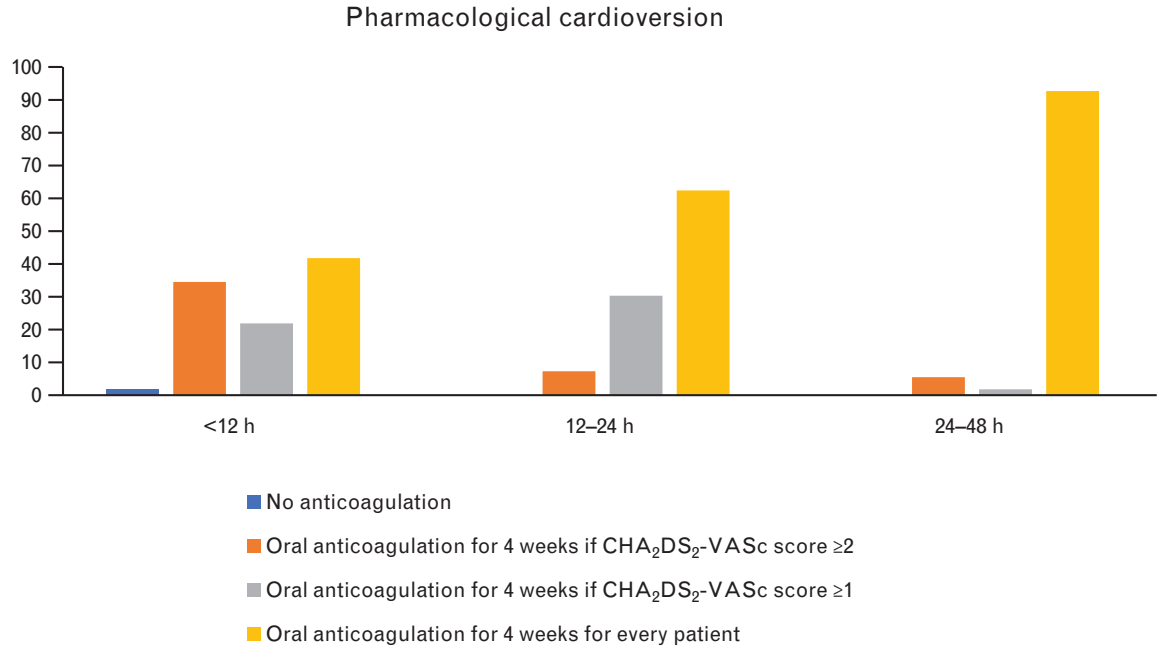
absence of any study on its application after AV node ablation. Interestingly, about one-third of the physicians would chance triple rate-control therapy before considering AV node ablation. Albeit this option has never been tested in any trial, and we also lack study combining beta blockers and ND-CCBs for this purpose, this preference may reflect the consequences of the rising issue of infection of cardiac implantable devices. Indeed, pacemaker dependency is a risk factor for this complication, and it increases the complexity of the management after device

Fig. 8



How would you manage a patient's anticoagulation after electrical cardioversion had occurred in the following time ranges?

Fig. 9



How would you manage a patient's anticoagulation after pharmacological cardioversion had occurred in the following time ranges?

extraction and postextraction complications.[46] In past ESC and American College of Cardiology (ACC) guidelines (as well as in its focused update published in 2019),[47–49] combinations of beta blockers and ND-CCBs were not allowed, while in the NHS 2016 guidelines and current ESC guidelines,[50] it was considered and only the last one overtly reports the triple therapy approach.[7]

Anticoagulation in case of restoration of sinus rhythm within 48 h

In our survey, clinicians were asked how they would manage anticoagulant therapy depending on the type of cardioversion, the time elapsed since the onset of symptoms and the patient's thromboembolic risk profile.

The results are reported in the following histograms (Figs. 7–9).

These data are surprising for two reasons:

(1) The tendency to carry out postcardioversion anticoagulant therapy in all patients who have experienced spontaneous cardioversion after 24–48 h independently of the CHA_2DS_2-VASc score;
(2) The choice of a group of colleagues to not administer anticoagulation regardless of the CHA_2DS_2-VASc score in case of cardioversion that occurred less than 12 h after the onset of symptoms (14.5% in spontaneous cardioversion, 3.6% in electrical cardioversion, 1.8% in pharmacological cardioversion).

Although the choice of not administering anticoagulant therapy regardless of thromboembolic risk is not supported by the 2020 ESC guidelines on the management of atrial fibrillation, it is more difficult to define which is the most correct therapeutic strategy in a patient with low thromboembolic risk and who has experienced spontaneous cardioversion, which seems a context similar to atrial high-rate episodes (AHREs) recorded by an implantable device. Indeed, guidelines do not express specific recommendations on anticoagulant therapy in those who have experienced spontaneous cardioversion. This certainly reflects the lack of evidence in this area.[7,51]

Conclusion

The present survey evidenced a high inhomogeneity in the pharmacological approaches adopted for atrial fibrillation management by a sample of Italian cardiologists. Further studies are needed to explore if these divergences are associated with different long-term outcomes.

Conflicts of interest

I.D. reported speaker's fees of a small amount from Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Philips outside the submitted work. G.B. reported speaker's fees of a small amount from Bayer, Boston Scientific, Boehringer, Bristol Myers Squibb, Daiichi Sankyo, Janssen and Sanofi, outside the submitted work.

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