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ANMCO-SIMEU consensus document: appropriate management of atrial fibrillation in the emergency department

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Atrial fibrillation (AF) accounts for 2% of the total presentations to the emergency department (ED) and represents the most frequent arrhythmic cause for hospitalization. It steadily increases the risk of thromboembolic events and is often associated with several comorbidities that negatively affect patient's quality of life and prognosis. AF has a considerable impact on healthcare resources, making the promotion of an adequate and coordinated management of this arrhythmia necessary in order to avoid clinical complications and to implement the adoption of appropriate technological and pharmacological treatment options. AF management varies across regions and hospitals and there is also heterogeneity in the use of anticoagulation and electric cardioversion, with limited use of direct oral anticoagulants. The ED represents the first access point for early management of patients with AF. The appropriate management of this arrhythmia in the acute setting has a great impact on improving patient's quality of life and outcomes as

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well as on rationalization of the financial resources related to the clinical course of AF. Therefore, physicians should provide a well-structured clinical and diagnostic pathway for patients with AF who are admitted to the ED. This should be based on a tight and propositional collaboration among several specialists, i.e. the ED physician, cardiologist, internal medicine physician, anesthesiologist. The aim of this ANMCO-SIMEU consensus document is to provide shared recommendations for promoting an integrated, accurate, and up-to-date management of patients with AF admitted to the ED or Cardiology Department, in order to make it homogeneous across the national territory.

Introduction

Atrial fibrillation (AF) represents the widest supraventricular arrhythmia worldwide as it involves about 9 million European individuals aged > 55 years old in 2010 with an estimated prevalence higher than 18 million in 2060.[1]

It has been estimated that 1 million patients aged > 65 aa suffers from AF in Italy, the prevalence estimated to double within 2060.[2]

AF represents about 2% of admittance to the Emergency Department (ED), 65% of which are managed by the physicians of the ED.[3] This is mostly related to several comorbidities of patients with AF which might obscure the identification and treatment of the arrhythmia at the time of ED access.[4]

The most worrisome issue is related to the impact of AF on the prognosis of patients: about 14% of patients who are admitted to the ED due to AF occurrence might experience all-cause death at 1-year follow-up, 42% of which were cardiovascular deaths.[3] As cerebral ischemic events might occur in 3% of them at 1-year follow-up and lead to disability,[3] physicians should be aware about the impact of this arrhythmia on the prognosis of patients and the financial burden of it on national and international health resources.[5,6] It has been calculated that the costs related to the management of AF in Italy involved about 2.5% of the total health financial budget.[7] Specifically, a mean cost of 5252€ was calculated for AF hospitalization which was similar to other European countries such as Spain and Netherlands where the mean costs for hospitalization for AF were 6360€ and 6445€, respectively.[8]

Hospitalization course (44–78%) and the use of antiarrhythmic drugs (15–20%) account for the main expenditures related to AF management.[9]

In relation to these background, the central role of the ED emerges in the management of the patients with AF in relation to the great impact that every clinical decision has on the prognosis at short, medium, and long-term follow-up.

The aim of this consensus document from the National Association of Hospital Cardiologists (ANMCO) and the Italian Society of the Emergency Medicine (SIMEU) was to provide recommendations which should be shared between the Departments of Emergency Medicine and Cardiology for the integrated and updated management of patients suffering with AF.

Epidemiology

AF is a worrisome global health problem as data from studies within the last 20 years outlined increased prevalence and incidence.[7,10,11]

Previous systematic analysis estimated a growing number of worldwide cases of AF till 33.5 million; nevertheless, most of studies referred to populations from North America or Europe. The prevalence seemed effectively related to the characteristics of the study population such as age, gender, race, geography, and period of observation.

Gender/ethnicity

The prevalence was higher in men than women (1.1% vs. 0.8%) independently from age. A further study outlined a prevalence of 6% and 5.2%, respectively.[12]

AF diagnosis seemed more frequent in Caucasian individuals as compared to Afro-American ones, above all in those > 50 years (2.2% vs. 1.5%).[13] An observational study which enrolled 14 million individuals from California between 2005 and 2009 who were admitted to the hospital tried to identify a possible relationship between the incidence of AF and race.[14] After adjusting for risk factors and demographic data, black Americans, Hispanic, and Asiatic individuals resulted at lower risk for AF development than white Caucasian.[14] These data have been recently confirmed by a recent study which demonstrated that female gender and some ethnic groups showed higher incidence in prolonged and symptomatic AF, poor quality of life, increased incidence in drug-relate adverse events, lower prevalence in anticoagulants administration, and higher risk in death.[15]

The higher A.F.-related risk of stroke in female gender might be related to several reasons such as: reduced renal function, endothelial dysfunction, pro-thrombotic conditions, hormone-replacement therapy, lower administration rate in and quality control of oral anticoagulant therapy, and poor management of the cardiovascular disease which promotes AF.[16]

Age

The distribution of AF in general population according to age should be divided into two groups: age between 18–65 years and age > 65 aa.[17–19] Indeed, some studies excluded patients with valvular cardiac disease,[12] while studies on general population are often based on data from public health records which are hardly comparable with those from the analysis of outpatient clinical

Table 1 Number of articles of the last 5 years on atrial fibrillation in relation to country of origin

Country	Population (millions)	No. publication
United States	332	12 765
China	1442	4710
Germany	84	4225
United Kingdom	56	4037
Italy	62	3320
Japan	126	3289
Canada	38	2419
Spain	47	1898
France	67	1867
Netherlands	17.5	1780

Table reported results from a research which was published on Web of Science about the number of articles which dealt with atrial fibrillation in relation to the population of the country of origin (total, 43 509 records from 154 countries). We included the first 10 countries. There was an evident disproportion between the number of articles and the population of each country.[27]

charts,[20,21] hospital clinical charts,[22,23] or data from primary facilities.[24,25]

Therefore, more accurate data should be adjusted for several variables, for example, general practitioners, specialist physicians or those from hospital wards.

Geographical distribution

According to a study of some years ago,[11] the prevalence rate of AF adjusted-per-age (per 100 000 inhabitants) was higher in North America (from 700 to 775) and lower in Japan and South Korea (from 250 to 320) as well as in China (from 325 to 400). It is likely that a significant bias might underlie these data as epidemiological studies from lower income countries are lacking; this could explain the wide range of variations in prevalence estimation—from 45.7 to 75.3 million of cases.[26]

Most of the literature about the epidemiology of AF effectively derives from studies from higher income countries such as United States, Western European countries, and Australia. It efficiently described the prevalence of the disease, health and social costs, but insufficient data were from Asia, Africa or South America. A research in Web of Science about articles on AF which have been published within the last 5 years remarked the great gap between the number of publications and the populations from different countries (*Table 1*).[27]

Data on the incidence also showed wide range of heterogeneity due to the lack of standardization: some studies reported rough data,[28,29] other data were adjusted by adopting as denominator the differences among populations,[18,24] other compared the estimation of the number of cases to the general population.[12,17,20-22,30]

Results outlined a higher prevalence of AF; it was associated to advanced age: men better demonstrated this relationship in each age slot than women. An observational study was performed in Italy in 2011 from ANMCO and General Medicine Italian Society and involved 233 general practitioners who screened 265 906 patients aged ≥ 15-year-old: they observed a prevalence in AF in Italy equal to 2.04% with no differences between Northern, Centre, and Southern Italy.[31]

Data about the prevalence of AF[32] were in line with those from the great majority of age groups derived from other European studies lead in Netherlands (Rotterdam study),[12] Portugal (SAFIRA study),[33] and Northern Italy [Progetto Veneto Anziani (Pro.V.A.)].[34] They are also in line with those from further international studies which referred to United States population,[35,36] although revealed differences as compared to other areas such as (lower prevalence) United Kingdom,[37] Portugal,[38] Iceland,[39] and Sweden (higher prevalence).[40]

In conclusion, the incidence and the prevalence of AF increase due to the ageing of the population and the proportional boost in cardiovascular risk factors prevalence, above all hypertension, heart failure, obesity, and sleep apnea.[19] The diagnosis is associated to the increase in morbidities,[41] mortality,[42] and health costs. This represents an intriguing challenge within health management in relation to its socio-economic burden.[43]

Frequencies

Reports in the temporal trends about the incidence of AF in Western countries are rarely reliable due to different criteria adopted for data collection. Most of studies outlined the increase in incidence,[17-19] others pointed out a stable condition,[22] one—derived from a European analysis—reported reduction in incidence through years.[23] A recent English study[44] described the time-trend of the pathology through the analysis of long-term temporal variations adjusted for gender, age, socio-economic features, number and characteristics of the comorbidities, and geographical regions. It combined data from primary care datasets with those from hospital activities within a 20-year period (1997–2017). Results pointed out a relevant increase in the incidence of AF cases.[44] These data were recently confirmed by a study[45] which showed the increase in incidence and mortality percentages in the United States, except two States (Columbia and Alaska). This trend involved women overall.

Hospitalization

Hospital admissions related to AF increased 2.4-fold or higher from 1985 to 1999[46] and a further 23% during the further 10 years.[47] In 2005, the annual costs for the management of AF was about 6.65 billion dollars,[43] further estimations confirmed the tendency to the increase.[48]

In order to reduce the burden of hospital admission due to AF and the related costs, dedicated interventional protocols in the ED have been implemented in some structures.[49] U.S. data revealed a high rate of hospital admission due to almost stable AF in 70% of cases in 2010.[50] Nevertheless, the impact of modifications in US health system and in the management of AF during the last years is still under investigation. A study performed between 2007 and 2014[51] found an annual hospital admission volume higher than 16% due to the increase in the number of total access to the ED due to AF, although this datum showed a slight decrease as compared to previous years. This trend and its link to a 27.7% increase in admission costs per patient contributed to the significant growth of the management costs. Registries from ANMCO demonstrated a significant reduction in Italy

Table 2 Features of patients with AF (readapted from Andrade et al 2020[61])

Medical history		
Establish the time of onset of the arrhythmia, possibly by means of ECG		
Define duration and frequency of the episodes (paroxysmal, persistent, long-term)		
Evaluate the presence of symptoms		
Search for previous episodes, previous, on air or suspended treatments		
Search for possible secondary causes or triggers		
Define the interference with daily activities (may be by the use of dedicated score)		
Examination		
Measure heart rate and arterial pressure or other vital parameters:		
temperature, oxygen saturation, consciousness, diuresis, weight (body mass index)		
search for triggers, secondary causes and/or risk factors		
Trigger	**Secondary causes**	**Modifiable risk factors**
Poison/analeptic/alcohol	Acute cardiac diseases	Hypertension
Sleep deprivation	Acute coronary syndrome	Diabetes
Stress	Valvulopaties	Smoke
Physical exercise	Myocarditis/pericarditis	Obesity
Noctural sleep	Acute pulmonary diseases	Subclinical hyperthyroidism
Digestion	Pulmonary embolism	Obstructive apnee
	Polmonitis	Chronic obstructive pulmonary disease
	Acute infections/sepsis	
	Thyrotoxicosis	
	Electrolytes imbalance	
	Anemia	
	Post-surgery	

Table 3 European heart rythm association (EHRA) symptom scale.[24] AF, Atrial Fibrillation

EHRA score	Effects on daily clinical life
Score 1	AF does not provoke any symptoms
Score 2°	Normal daily activity not affected, symptoms not troublesome to patient (mild)
Score 2b	Normal daily activity not affected but patient troubled by symptoms (moderate)
Score 3	Normal daily activity affected (severe)
Score 4	Normal daily activity discontinued (disabling)

within the last two decades in ward admission of patients who referred to the ED. The FIRE study[52]—which was lead in 2000—revealed that 61.9% of patients who were admitted to the ED were subsequently admitted to other hospital departments. After 17 years, the BLITZ AF study[53] outlined that only 27.8% of patients were finally admitted to other hospital Departments other than the ED. Indeed, this still represent a higher number of admissions which could be avoided by implementing a dedicated program (PDTA) which should be shared between Emergency and Cardiology Departments.

Clinical presentation

The commonest symptoms related to AF are dyspnea, palpitations, and fatigue; sometimes patients suffer chest pain, vertigo, or sleep disturbances.[54] Palpitations are independently related to lower risk of cardiovascular events and mortality as compared to other signs and symptoms.[55] Patients with paroxysmal AF usually have higher number of symptoms as compared to those with permanent AF (80% and 50%, respectively), although the latter often complain dyspnea, fatigue, and reduced exercise tolerance.[56] Symptoms might often be related to concomitant comorbidities which might be not specifically managed as in case of hypertension or denovo/acute decompensation of heart failure (HF).[57] It has been observed a prevalence in HF equal to 33%, 44%, and 56% in patients with paroxysmal, persistent, and permanent AF, respectively. HF with preserved ejection fraction (HFpEF) had been mostly associated to AF occurrence, while serum level in B-natriuretic peptide are often altered and help in defining the clinical situation.[58] In case of HF with reduced ejection fraction (HFrEF), AF might promote haemodynamic instability and provoke syncope, symptomatic hypotension, pulmonary edema, and even worse conditions such as myocardial ischemia and cardiogenic shock.[24] Nevertheless, 50–80% of patients is asymptomatic: asymptomatic AF is associated to the worst prognosis.[59] Finally, AF symptoms could vary in relation to the treatment, while recurrences could show poor number of symptoms.[60]

Parameters control during emergency department stay

The aims of the evaluation and monitoring of patients at admission to the ED are: (1) To identify the degree of clinical decompensation related to the presence of AF; (2) To diagnose clinical conditions which might explain

Table 4 Severity of atrial fibrillation (SAF) scale according to the Canadian cardiovascular society (CCS). AF, atrial fibrillation

CCS SAF score	Effects on daily clinical life
Class 0	Asymptomatic according to AF presence
Class 1	AF-related symptoms minimally impact on quality of life: rare episodes or single episode without syncope or signs/simptoms of heart failure
Class 2	AF-related symptoms have minor impact on quality of life: • slight consciousness about AF presence during permanent AF • rare episodes which are felt by patients with paroxysmal AF (a few episodes/year)
Class 3	AF-related symptoms have moderate impact on quality of life: • moderate consciousness about AF presence during permanent AF • episodes which are felt by patients with paroxysmal AF (some episodes/year)
Class 4	AF-related symptoms have severe impact on quality of life: • continuous and fastidious AF-related symptoms in patients with permanent AF • several, symptomatic episodes in patients with paroxysmal AF • syncope or signs/symptoms of AF related to AF

the occurrence of AF; and (3) To estimate the thrombotic and hemorrhagic risks of the patient in order to manage the correct antithrombotic strategy.[61]

Patient with unstable AF is defined in case of chest pain, pulmonary edema, persistent hypotension, shock, and altered state of consciousness.[24,62-66] These patients should undergo evaluation and monitoring of respiratory and cardiovascular function, support of respiratory and cardiovascular functions, identification and treatment of the reversible cause—such as acute coronary syndrome (ACS), pulmonary embolism, thyrotoxicosis, electrolytes imbalance, poisoning, valvular heart diseases, enamia -, and manage pf synchronized electric cardioversion (ECV).

Anamnesis

Anamnesis should point out the onset time of AF (paroxysmal, persistent, long-term, permanent), the presence of known comorbidities which might promote the occurrence of AF (cardiomyopathies, valvular heart diseases, extracardiac diseases such as altered thyroid function, hypertension, diabetes, chronic obstructive pulmonary disease), triggering factors (alcohol assumption, inflammatory diseases, pulmonary, pleural, pericardial diseases, and trauma), previous events and related treatments which had been or are administered (*Table 2*). The anamnesis should weight the impact of AF on the quality of life of patients[65-67] (*Tables 3* and *4*).

Table 5 Recommended evaluations in patients with atrial fibrillation[24,61]

Esami consigliati in tutti i pazienti
12-leads ECG
Biochemical evaluations:
Blood cells count
Coagulation
Fasting glycaemia
Serum electrolytes (calcium, magnesium)
Renal function
Liver function
Thyroid function
Acid-base balance (arterial blood gas analysis)
Echocardiography

Physical examination

Physical examination should point out the clinical imbalance and the presence of concomitants comorbidities (*Table 2*). Physicians should monitor vital parameters such as heart rate, arterial pressure, respiratory frequency, peripheral oxygen saturation, body temperature, and diuresis.

Electrocardiogram

Electrocardiogram (EKG) represents the main tool for diagnosing AF, measuring mean heart rate, and managing subsequent therapeutic options. It provides information about possible extra- or intra-cardiac abnormalities. The identification of pathological ventricular pauses in patients with transient loss of consciousness or ischemic alteration within ACS allows physicians to better address the management of the patient since the admission at the ED.

Biochemical and instrumental examinations

All patients with AF—above all in case of first AF occurrence—should undergo biochemical examinations (*Table 5*): renal function (creatinine, acid-basic balance), liver function [bilirubin, transaminases, coagulation profile such as prothrombin time test, activated partial thromboplastin time, international normalized ratio (INR), fibrinogen, platelets], and—in selected cases (i.e. patients at first AF episode, or specific clinical features, or concomitant therapies such as amiodarone) the dosage of thyroid hormones (thyroid-stimulating hormone, FT3, and FT4) as hyperthyroidism still remain the most frequent cause of AF occurrence.[68]

Troponin evaluation should be only reserved to those patients with angina-like symptoms or with instrumental alterations which suggest ACS[69] or acute myocardial injury (suspected myocarditis, cardiac contusion, and electrocution). One should remind that AF *per se* might provoke the increase in troponin plasma levels above all in case of higher heart rates.[70]

Blood gas analysis is also useful due to its fast data and interesting clinical information. It is generally available in almost all the EDs and could give information about the presence or not of respiratory failure and its physiopathological mechanisms, presence of relevant

comorbidities and/or precipitating factors such as altered glycaemia, haemoglobin concentration, perfusion of peripheral organs, acid-base imbalance, ions alterations, and poisonings.

Thrombotic and haemorrhagic risk stratification

AF is responsible for the 20–25% of all ischemic strokes, as it increases three-to-five-fold the risk for this event as compared to general population.[71] Actually, AF-related thromboembolic risk is not uniform, but rather related to various causes which affect the clinical outcome of patients in very different ways.[24,72] It is therefore mandatory to stratify to the best the probability of AF-related cardioembolic events.

Population studies validated various risk scores suitable for contextualizing and outlining the thromboembolic prognosis of the patient suffering from AF.[24,72,73] In 2001, one of the first risk scores—CHADS2 score (C: Congestive Heart Failure, H: Hypertension, A: Age > 75 years, D: Diabetes [1 point each] and S_2: Stroke history [2 points])—was validated and adopted by the most important international guidelines as a tool to categorize stroke risk in patients suffering from AF.[74] Despite its easy application in daily clinical practice, CHADS2 score does not include further stroke-associated risk factors such as gender, vascular diseases, or age ≥65 years. CHA_2DS_2-VASc score (*Table 6*) implemented thromboembolic risk stratification in AF patients. It was validated on the population of the Euro Heart Survey[75] and included in the 2012 guidelines from European Society of Cardiology (ESC) for the management of AF.[76] CHA_2DS_2-VASc score improved the prognostic stratification of thromboembolic risk as compared to CHADS2 score, above all in patients at lower risk.[77]

Although renal function is a further risk factor for the occurrence of ischemic stroke in patients with AF, any attempts for its inclusion in dedicated risk scores—as the R_2CHADS_2 which was validated from a subanalisys of the ROCKET AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)[78]—did not add any further amelioration in the stratification of thromboembolic risk. Furthermore, the original validation of this score did not consider patients whose estimated glomerular filtration rate was < 30 mL/min.[79]

In parallel to AF-related thromboembolic risk stratification, it is also mandatory to evaluate the haemorrhagic risk. Correct identification of haemorrhage probability in patients suffering from AF is essential not as much to prevent anticoagulants prescription or to decrease their dosage, but rather to correct modifiable risk factors and adjust the number of follow-up visits and monitoring the clinical conditions. The HAS-BLED score was validated in 2010 to evaluate the haemorrhagic risk.[80] HAS-BLED values included between 0 and 2 identify subjects with low-moderate haemorrhagic risk, while values > 3 identify high haemorrhagic risk individuals. Even if other risk scores such as $HEMORR_2HAGES$ and ATRIA were proposed, HAS-BLED proved better discrimination index.[81] In particular, HAS-BLED has greater sensibility as compared to $HEMORR_2HAGES$ and ATRIA (HAS-BLED vs. ATRIA: 41% vs. 23%; HAS-BLED vs. $HEMORR_2HAGES$: 53% vs. 27%), with a score performance measure evaluation better than ATRIA (HAS-BLED vs. ATRIA: 2.22% vs. 1.98%).[82]

Therefore CHA_2DS_2-VASc and HAS-BLED are the most important thromboembolic and haemorrhagic risk scores, respectively, to be applied in the process of prognostic stratification of the patient suffering from AF.[24]

Moreover, frailty evaluation should be an integral part of the haemorrhagic and thromboembolic risk stratification process of the AF afflicted elderly patient.[83]

Management of atrial fibrillation lasting < 48 h

The initial management of the patient suffering from AF has to concentrate on both the haemodynamic condition of the patient and the identification of the arrhythmic episode onset time.

The haemodynamic instability of the subject with AF (a patient afflicted by syncope, acute pulmonary oedema, acute myocardial injury, symptomatic hypotension or cardiogenic shock) suggests the need for rhythm restoration/adequate cardiac rate control.[24] The pre-treatment with beta-blockers, albeit theoretically useful for such conditions characterized by sympathetic nervous system hyperactivity, is counterindicated in patients with severe left ventricle dysfunction.[24] The same goes for Digitalis which, in patients with sympathetic nervous system hyperactivity, might not be efficient or however tolerated.[24] Guidelines recommend the use of amiodarone in this context (class of recommendation IIb, level of evidence B), paying attention to the hypotension potentially caused by the administration of this drug.[24]

The ECV, instead, remains the best therapy (class of recommendation I, level of evidence B) in case of haemodinamic instability, in association with anticoagulants administration as soon as possible.[24,84] Actually, in order to implement the defibrillation effectiveness and/or limit the possibility of a subacute relapse of the arrhythmia, it may be useful the administration of antiarrhythmic drugs such as quinidine, propafenone, flecainide, amiodarone, sotalol, ibutilide or verapamil (*Table 7*).[84]

In haemodynamically stable patients, an approach intended to control cardiac rhythm—i.e. to restore sinus rhythm—may be considered when, according to medical history, AF onset turns out to be < 48 h.[24] In this case, the stability of the clinical picture allows to choose between a pharmacological treatment and one based on an internal (in case of a patient with an ICD device) or external ECV.

Rhythm control through pharmacological therapy

2020 ESC Guidelines[24] recommend sinus rhythm restoration in order to improve the symptoms and the quality of life of patients with symptomatic AF (class of recommendation I, level of evidence A). The evaluation of the anticoagulation state must precede whichever attempt to restore sinus rhythm. Thus, two conditions may occur: (1) the patient already takes an optimal therapy with

Table 6 CHA_2DS_2-VASc score and HAS-BLED score

	Risk factors	Score		Risk factors		Score
C	Heart failure/Left ventricle dysfunction	1	H	**Hypertension**	Defined as SBP > 160 mmHg	1
H	Hypertension	1	A	**Renal dysfunction**	Chronic dialysis of renal transplantation or creatinine ≥ 2.2 mg/dL	1
A_2	Age ≥ 75 years	2	A	**Liver dysfunction**	Cirrhosis or bilirubin doubling or three-fold increase in transaminases	1
D	Diabetes	1	S	**Stroke**	Previous ischemic or hemorrhagic stroke	1
S_2	Stroke/TIA/TE	2	B	**Hemorrhages**	History of major bleeding or anemia or severe thrombocytopenia	1
V	Vascular diseseas (CAD, PAD, Aortic plaque)	1	L	**Lable INR control**	Unstable INR or TTR <60%	1
A	Age between 65–74 years	1	E	**Age ≥ 65**	Or extreme frailty	1
Sc	Female gender	1	D	**Drug abuse/ alcohol**	Concomitant use of antiplatelet or NSAID agents or alcohol	1/1
	Maximum score	**10**		**Maximum score**		**9**

NSAID, nonsteroidal anti-inflammatory drugs; CAD, coronary artery disease; INR, international normalized ratio; PAD, perpheral artery disease; SBP, systolic blood pressure; TE, thromboembolic event; TIA, transient ischemic attack; and TTR, time in therapeutic range.

Table 7 Impact of drugs on the threshold for electric cardioversion of AF and reduction in subacute recurrences after cardioversion (readapted from Brandes *et al.*[85])

Decrease threshold for cardioversion or suppress AF recurrences	Riduzione recidive subacute di F.A.
Quinidine	Quinidine
Propafenone	Propafenone
Flecainide	Flecainide
Amiodarone	Amiodarone
Sotalol	Amiodarone + Sartans
Ibutilide	Beta-blockers
Verapamil	Verapamil
Uncertain Effects	*Uncertain Effects*
Procainamide	Verapamil
Disopiramide	Diltiazem
Dofetilide	Dofetilide
Beta-blockers	
Verapamil	
Diltiazem	

A.F., atrial fibrillation.

anticoagulants, so that he can directly undergo cardioversion; (2) the patient does not take or has never taken anticoagulants, which is why prompt anticoagulant [preferably a direct oral anticoagulant (DOAC) or low molecular weight/non-fractioned heparin] administration is needed before any cardioversion attempt.

In principle, when AF onset is < 48 h pharmacological cardioversion can be carried out by using i.v. drugs such as flecainide and propafenone (which have to be avoided in patients with structural cardiac disease, substantial left ventricle hypertrophy, left ventricle dysfunction or ischemic cardiac disease), amiodarone (above all in patients with heart failure or structural cardiac diseases) (class of recommendation I, level of evidence A).[24]

The use of ibutilide i.v. can be taken into account for pharmacological cardioversion of atrial flutter.

Pharmacological cardioversion should not be performed in patients with Sick Sinus Syndrome, atrioventricular conduction disorder or QT_c > 500 ms, in order to avoid the risk of pro-arrhythmic effects and serious hypokinetic arrhythmias (class of recommendation III, level of evidence C).[24]

Table 8 summarizes the principal drugs to be used in case of need for AF cardioversion and the relative dosage and half-life.

Rhythm control through electrical cardioversion

ECV is the best option in patients with haemodynamic instability (class of recommendation I, level of evidence B) or pre-excited AF (class of recommendation I, level of evidence C).[24] It can also be taken into account in haemodynamically stable patients, even after a pre-treatment with amiodarone, flecainide, ibutilide, or propafenone in order to facilitate its success (class of recommendation IIa, level of evidence B).[24]

After verification of the patient's anticoagulation state, ECV can be performed after adequate sedation and analgesia.[85] The drug to be used has to guarantee rapid achievement of altered consciousness state, be rapidly removed from circulation and, above all, not negatively affect cardiovascular and respiratory apparatus.[86]

Benzodiazepines (midazolam) and/or propofol are the most used drugs for sedation before ECV. Midazolam (dose of 0.1 mg/kg to be halved in the elderly) in association with fentanyl (1 μg/kg) can allow optimal sedation and pain management. Even if flumazenil and naloxone are able to antagonize midazolam and fentanyl, the patient has to be strictly monitored after the procedure. Another option is the use of propofol (dose of 1 mg/kg to be halved in the elderly) with subsequent boluses of half the initial dose every 2–3 min,

Table 8 Pharmacological cardioversion of AF: drugs, modes of administration, pharmacokinetics, adverse events, and contraindications

Antiarrhythmic drug	Vaughan-Williams classification	Route of administration	Initial dose for cardioversion	Maintenance dose	Success rate and timeline for conversion	Half-life	Route of elimination	Contraindications/ precautions
Flecainide	Classe I	Oral i.v.	200-300 mg 2 mg/kg in 10 min	-	Overall rate: 59-78% (51% a 3 h, 72% a 8 h)	12-27h	95% renal/5% liver	• Do not use in case of ischemic cardiac disease and/or significant structural cardiac disease • Hypotension or atrial flutter with 1:1 condution (3.5-5% of patients) • Flecainide might enlarge the QRS • NO use in pharmacological cardioversion of atrial flutter
Propafenone	Classe I	Oral i.v.	450-600 mg 1.5-2 mg/Kg in 10 min	-	Oral: 45-55% a 3 h, 69-78% a 8 h. E.v.: 43-89% till 6h	2-10h	99% liver/1% renal	
Vernakalant	Classe III	i.v.	3 mg/Kg in 10 min	2 mg/Kg in 10 min (10-15 min after bolus)	< 1 h (50% conversion within 10 min)	3-5.5h	Glucuronidation ad renal excretion	• NO use in patients with hypothension (SBP < 100 mmHg), recent ACS (<1 month), HF, NYHA class III-IV, long QT, or severe aortic stenosis • Might cause hypotension, QT prolongation, QRS enlargement and NSVT
Amiodarone	Classe III	i.v.	5-7 mg/Kg in 1-2 h	50 mg/h (max 1.2 g in 24 g)	44% (from 8 to 12 h to several days)	From 20 h (single dose) to 50 days (long-term)	Liver and intestinal, minimally renal	• Might cause phlebitis (use large peripheral veins, < 24 h, volumetric pump) • Might cause hypothension, tachycardia/AV blocks, QT prolongation • Use in case of hyperthyroidism only in the absence of other options (thyrotoxicosis risk)

Continued

Table 8 Continued

Antiarrhythmic drug	Vaughan-Williams classification	Route of administration	Initial dose for cardioversion	Maintenance dose	Success rate and timeline for conversion	Half-life	Route of elimination	Contraindications/ precautions
Ibutilide	Classe III	i.v.	1 mg/Kg in 10 min o 0.01 mg/Kg se peso < 60 Kg	1 mg/Kg in 10 min (10-20 min after bolus)	31-51% (AF); 63-73% (atrial flutter) About 1 h	2-12h	Liver	• Useful in atrial flutter cardioversion • NO use in long QT, severe left ventricle hypertrophy, reduced LVEF • Use only in ICU due to risk of torsades des pointes • ECG monitoring during the last 4 h for arrhythmias risk

ACS, acute coronary syndrome; AV, atrioventricular; CV, cardioversion; ICU, intensive care unit; i.v., intravenous; LVEF, left ventricle ejection fraction; NSVT, non-sustained ventricular tachycardia; SBP, systolic blood pressure.

until deep sedation is achieved. However, as a respiratory depressant, propofol may lead to intubation, not to mention that it may cause low blood pressure.[86]

The sedation of the patient may be achieved also using ketamine (1–2 mg/kg), even if the duration of sedation (even 20–30 min) does not allow us to consider it as a first choice anesthetic in this context.

In many Italian institutions, ECV is already performed using sedation without the presence of the anesthesiologist, both in ED and in electrophysiology labs.[87,88] It is appropriate to acquire an adequate knowledge of the drugs used for sedation in order to involve the anesthesiologist only in complicated patients.

The electrode positioning for cardioversion is actually a matter of debate. A metanalysis from Zhang *et al.*[89] outlined that antero-posterior position shows better benefits only in case of patients with isolated AF and left atrium antero-posterior diameter ≤45 mm, without real utility in other clinical contexts. Nonetheless, a recent work from Schmidt *et al.*[90] which involved about 468 patients with AF randomized to external ECV demonstrated that antero-lateral electrodes positioning was more effective than antero-posterior for sinus rhythm restoration with biphasic current.

Even in patients with ICD it may be useful considering external ECV compared to internal. Recent clinical studies[91–94] highlighted a higher chance of sinus rhythm restoration in patients undergone to external ECV,[91,92] without significant lesions or alterations to the device caused by biphasic current.

International guidelines do not give clear and unambiguous recommendations about the electricity to be supplied for the purposes of external cardioversion. Both 2016[95] and 2020,[24] ESC Guidelines do not clarify the matter. Biphasic current supply is better than monophasic in order to successfully obtain rhythm control, keeping in mind that it allows an energetic load lower than monophasic.[96] Even in case of resistant forms of AF, the use of ascending series of thoracic biphasic electricity is better than single monophasic high intensity shock in order to restore sinus rhythm.[97]

The use of the maximum dose of energy allows higher probabilities of cardioversion than the emanation of incremental electric shocks.[98] Schmidt *et al.*,[98] indeed, recently demonstrated that the supply of fixed doses of electricity (360–360–360 J) allowed sinus rhythm restoration in 72% of patients right 1 min after the shock compared to 66% of patients undergone progressive biphasic shock (125–150–200 J) ($P < 0.001$).

Management of atrial fibrillation of >48 h duration

The patient who arrives at the Emergency Department for an episode of AF arisen for > 48 h deserves an integrated approach in order to optimize the situation by deciding for rhythm or rate control.

Again, AF characterized by haemodynamic instability needs to be immediately cardioverted in order to restore sinus rhythm and improve the clinical and prognostic picture of the patient.

On the contrary, in case of haemodynamic stability, the evaluation of the anticoagulation state is essential for

therapeutic procedures. If the patient already takes anticoagulants, it is appropriate to take into account the treatment duration and adherence, the kind of anticoagulant taken and potential interruptions. A continuous oral anticoagulation therapy for more than 3 weeks allows the clinicians to proceed with a rhythm control treatment.[24] In case of lesser duration of the anticoagulation therapy, sinus rhythm restoration may be considered only after transoesophageal echocardiogram (TOE) execution in order to exclude the presence of blood clots in the left atrium appendage.[24]

Scientific literature is not particularly diriment about the absolute need for sinus rhythm restoration compared to a cardiac rate control strategy.[99-103] AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study reported that a therapeutic strategy based on rhythm control was not so convenient for mortality reduction as compared to one based on rate control.[103] Nevertheless, a pre-specified subgroup analysis of AFFIRM study pointed out a non-substantial reduction of mortality [Hazard Ratio (HR) 0.81; $P = 0.06$] for rhythm control strategy in patients with AF aged < 65 years.[104] A subsequent metanalysis of 10 studies comparing rhythm vs. rate control strategy in patients with AF aged < 65 years outlined a significant reduction of the composite all-cause-mortality, heart failure, bleeding and thromboembolic events endpoint in the group of patients assigned to rhythm control strategy.[105]

The EAST-AFNET (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) 4 study reported that an untimely rhythm control therapy is able to reduce the risk for adverse cardiovascular events.[102] Sethi *et al.*[100] observed that cardioversion strategies actually tend to increase the risk for adverse events in patients suffering from AF, therefore they suggested the possibility to save this treatment for peculiar groups of patients like those who do not bear the arrhythmia or with haemodynamic instability. The presence of factors such as young age, first AF episode, tachycardiomyopathy, slightly dilated left atrium, reduced number of comorbidities/cardiovascular diseases, difficulty in achieving an efficient average ventricular rate control, or patient's choice may incline clinicians towards rhythm instead of rate control. Alternatively, ever since the arrival into ED, the patient can undergo a rate control treatment.[24]

Heart rate control

Heart rate control in patients with AF is an optimal therapeutic strategy as improves the quality of life of patients and reduces the perception of symptoms related to the arrhythmia. Literature does not provide clear evidence about superiority of rhythm over heart rate control in patients with AF.[99-103]

Furthermore, it is unclear what the optimal mean heart rate is in patients with AF. Higher heart rate in patients in sinus rhythm is related to increased risk for all-cause-mortality, cardiovascular mortality, heart failure, and stroke.[106-109] The reduction of heart rate in patients in sinus rhythm might improve the outcomes.[110] Nevertheless, data on AF are ambiguous. Rawles[111] demonstrated that mean heart rate of about 90 b.p.m. or, at least, inferior to 140 b.p.m. guaranteed good cardiac output and hemodynamic performances in patients with AF.[111] RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient vs. Strict Rate Control II) study outlined that lenient heart rate control (rest heart rate < 110 b.p.m.) in patients on permanent AF reduced primary endpoint (combination of cardiovascular death, hospitalization for heart failure, stroke/systemic embolism, bleeding and mortal arrhythmic events) of 16% [HR 0.84, confidence interval (CI) 95% 0.58–1.21] as compared to strict control (rest heart rate < 80 b.p.m. and < 110 b.p.m. during exercise).[112]

Patients who suffered for AF and heart rate with preserved or reduced ejection fraction did not benefit from strict reduction in mean heart rate.[113-115] Xing *et al.*[116] pointed out that lower heart rate (< 65 b.p.m.) in patients with AF and heart failure was associated to higher risk of all-cause death and heart failure re-hospitalization than lenient control (mean heart rate between 65 and 85 b.p.m.). Furthermore, lower heart rate is more dangerous in patients with left ventricle ejection fraction < 50%.

Table 9 summarized the main drugs that could be adopted for mean heart rate control, their dosages, and half-lives.

Anticoagulation therapy management

AF-related thromboembolic risk forced the need for adequate oral anticoagulation therapy since admission of patient at the ED. Choose of anticoagulation is related to the characteristics of the patient, to its thromboembolic risk, and to the onset of the arrhythmia.

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have always been considered as the first line choice in patients with AF who were admitted to the ED, independently from the therapeutic strategy (rhythm vs. rate control). Indeed, evidence about the use of LMWH in patients with AF is scarce. Siu *et al.*[117] randomized 96 patients with recent onset AF to tinzaparin (175 U/kg/die) or UHF (activated partial thromboplastin clotting time target 50–70 s) since ED admission. The study outlined higher thromboembolic protection with tinzaparin as compared to UHF within 48 h although results should be weight for the small sample size.[117] Data from the pilot study named ACUTE II (Assessment of Cardioversion Using Transesophageal Echocardiography)[118] pointed out that treatment with enoxaparin in patients who should undergo transesophageal echocardiography (TEE)-guided electrical cardioversion was equal to UFH in terms of safety and efficacy. Indeed, hospital length of stay was significantly lower in those who were treated with enoxaparin than UHF which is really interesting in term of management costs of AF.[118] Enoxapanin was not inferior to the combination of UHF + phenprocoumon in preventing thromboembolic risk, haemorrhagic complications, and all-cause-mortality in patients with AF > 48 h and ≤ 1 years.[119] A retrospective study by Khazan *et al.*[120] reported the safety and efficacy of enoxaparin (1 mg/kg bid or subcutaneously 1.5 mg/kg/die): among 213 patients none had any ischemic event when correct therapeutic dose of enoxaparin was administered. Nevertheless, patients already on anticoagulation therapies should not undergo interruption

in favour of bridge with LMWH. Data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry revealed that LMWH bridge was performed in 25% of patients and induced increased rates in haemorrhagic and adverse events.[121]

The introduction of DOAC (dabigatran—direct inhibitor of thrombin—and rivaroxaban, apixaban, and edoxaban—direct inhibitors of factor Xa) allowed overcoming the need for LMWH or UHF bridge in patients admitted to the ED with AF.[24] Both randomized trials[122-125] and 'real world' studies[126,127] demonstrated the superiority or—at least—non inferiority of DOAC over VKA in preventing thromboembolic risk in patients with non-valvular AF.

The pharmacokinetics, handling, and antidotes advent[128,129] improved the wide inclusion of DOAC in daily clinical practice 2020 ESC guidelines favoured the use of DOAC according to indications in the summary of product characteristics since the first approach to patient with non-valvular AF (class of recommendation I, evidence level A).[25] Patients with mechanic heart valve or moderate-to-severe mitral stenosis should only undergo VKA treatment.[25]

Continuation of anticoagulation therapy will depend on the thromboembolic risk stratification of the patient: 4 weeks after cardioversion in case of CHA_2DS_2-VASc score = 0 for men or = 1 for women (optional in case of AF duration < 24 h); long-term duration in case of patients with non-valvular AF and CHA_2DS_2-VASc score ≥ 2 in men and ≥ 3 in women (class of recommendation I, evidence level A).[25]

Table 10 summarized the main characteristics and dosages of anticoagulants which could be adopted in patients with AF.

Echocardiography in the emergency department

Echocardiographic approach to patients with AF who are admitted to the EF is fundamental in order to define their clinical/prognostic risk profile. Transthoracic echocardiography (TTE) represents the first line imaging technique for the evaluation of patients with AF.

The aim of TTE is to define anatomy, morphology, and function of cardiac valves and chambers in order to fast drive the diagnostic process and correctly address therapies; TTE also contributes to the evaluation of the hemodynamic status of the patient.[130]

TTE allows defining dimension and function of left ventricle, the presence of tachicardiomyopathy,[131-133] left atrium morphology and function: all of them are important features for the prediction of the success of cardioversion and recurrence risk.[134-136]

The technique is also able to identify the presence of pericardial effusion, sometimes associated to AF and valvular heart disease. Specifically, TTE might improve the diagnosis of cardiac valvular dysfunction such as moderate-to-severe mitral stenosis which contraindicates DOAC use.[24]

It is advisable the physicians working in the ED should be trained in echocardiography in order to correctly manage AF patients since the ED by fast obtaining information about the dimension of atrial and ventricular chambers, left ventricle ejection fraction, presence of pericardial effusion, valve heart disease and/or aortic pathologies.[137]

'Focused cardiac ultrasound' (FoCUS) might be used by physicians not specifically trained in standard echocardiography but rather in FoCUS, as recommended in the position statement of the European Association of Cardiovascular Imaging (EACVI).[138]

Transoesophageal echocardiography: indications and use in the setting of emergency

Transoesophageal Echocardiography (TOE) is an imaging technique that may play a pivotal role in the emergency/urgency setting in patients with AF.[139] 2020 ESC Guidelines recommend TOE in patients with AF whose temporal onset is unknown or > 48 h, with no anticoagulation therapy, or in case of accelerated cardioversion in order to exclude the presence of thrombus in atrium or left atrium appendage (class of recommendation I, evidence level B).[24] TOE should be repeated in case of thrombus identification or spontaneous echo contrast ('sludge' effect) with slow emptying velocities after adequate anticoagulation periods in order to evaluate thrombus disappearing.

AF might effectively promote the formation of thrombi in the left atrial appendage[140] as this might become emboli in case of sinus rhythm recovery.

TOE before cardioversion might be avoided in patients with AF lasting < 48 h (class of recommendation IIa, evidence level B).[24]

Training courses should be performed in order to use TOE within the ED since the first moments after patients' admission. This will promote fast therapeutic action and avoid un-necessary delays.[141] Wray *et al.*[142] demonstrated the feasibility of TOE in the emergency setting independently from the clinical reason for it. Although advanced imaging techniques—such as tree-dimensional ones[143]—might ameliorate the evaluation of left atrium during AF, standard TOE examination is *per se* able to identify the essential features of thromboembolic risk of patient and ameliorate the clinical approach to patients.

Complex clinical scenarios

AF in pregnancy

AF is one of the most frequent arrhythmias in pregnancy, whose incidence is increasing above all in case of congenital cardiomyopathies and in advanced age.[24,144,145]

It is common in the third trimester and in those who have already experienced previous episodes. The substrate is related to alterations during pregnancy: anatomic, hemodynamic, and electric (i.e. tendency to QT prolongation). AF is associated to the increased risk of all-cause death and complications to mother and foetus, in particular in case of underneath cardiac diseases. Therefore, the need for an early treatment is mandatory although physicians should cautionally consider use of drugs due to scarce evidence in pregnancy and possible pro-arrhythmic effects which might increase atrioventricular conduction and significantly impair maternal and foetus hemodynamics.

Table 9 Pharmacological control of mean ventricular rate in AF: drugs to be used, administration use, pharmacokinetics, adverse events, and contraindications

Antiarrhythmic drugs	I.V. administration	OS administration	Peak of concentration	Half-life	Elimination	Contraindications/ precautions
BETA-BLOCKERS						
Metoprolol tartrate	2.5–5 mg i.v. bolus to 4 doses	25–100 mg b.i.d.	1–2h	1–9 h	Renal (95%)	Bradycardia, cardiogenic shock, congestive heart failure. No use in pregnancy. Severe asthma. In asthma better use Beta1 antagonists.
Metoprolol succinate	/	50–400 mg o.d.	1–2h	1–9 h	Renal (95%)	
Bisoprolol	/	1.25–10 mg o.d.	1–3h	10–12 h	Renal/liver (50%/ 50%)	
Esmolol	500 mg/kg i.v. bolus in 1 min then infusion at 50–300 mg/kg/min	/	/	9 min	Renal	
Landiolol	100 mg/kg i.v. bolus in 1 min then infusion at 10–40 mg/kg/min	/	/	4 min	Renal	
Nebivolol	/	2.5–10 mg o.d.	0.5–4 h	13–56 h	Liver	
Carvedilol	/	3.125–50 mg b.i.d.	1–2 h	4–6 h	84% liver, 16% renal	
NON-DIHYDROPYRIDINE CALCIUM ANTAGONIST						
Verapamil	2.5–10 mg i.v. bolus in 5 min	40 mg b.i.d. to 480 mg (slow release) o.d.	1–2 h	5–12 h	70% renal, 16% liver	Controindicated in case of heart failure with reduced ejection fraction. Modify dosage in relation to liver and renal function.
Diltiazem	0.25 mg/kg i.v. bolus in 5 min, then infusion at 5–15 mg/h	60 mg t.i.d. to 360 mg (slow release) o.d.	1–4 h	2.1–5.9 h	Renal e liver	
DIGITALIS GLYCOSIDES						
Digossina	0.5 mg i.v. bolo (0.75–1.5 mg in 24 h in shared doses)	0.0625–0.25 mg o.d.	2–5 h	36–48 h	Renal	Higher serum concentrations increase risk of death. It is useful to evaluate renal function before the beginning of therapy in patients with chronic kidney insufficiency.
Digitossina	0.4–0.6 mg	0.05–0.1 mg o.d.	0.5–2 h	3–16 days	20% feces	Higher serum concentrations increase risk of death.
OTHERS						
Amiodarone	300 mg i.v. in 250 mL glucose solution 5% in 30–60 min (better in central vein), then 900–1200 mg i.v. in 24 h diluted in 500–1000 mL glucose solution 5% in central vein	3 × 200 mg o.d. for 4 weeks, then 200 mg o.d. (reduce dose of other drugs for controlling the heart rate)	3–7 h	15–142 days	Liver	Pay attention in case of thyroid diseases

b.i.d., bis in die; o.d., once daily; and t.i.d., ter in die.

Although pregnancy is commonly associated to enhanced coagulation status thus increasing thromboembolic risk, there are no specific studies which addressed such a subject, therefore common risk scores for the evaluation of thromboembolic risk in general population are adopted (CHA_2DS_2-VASc score).

The most appropriate anticoagulation regimen depends on the gestational trimester as LMWH are better

Table 10 Anticoagulant drugs: pharmacokinetic features, pharmacodynamics, and dosages

Drug	UFH	LMWH			Warfarin/ Acenocumarol	DOAC			
		Enoxaparine	Tinzaparine	Dalteparine		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose	Bolus 80 UI/ Kg, then infusion at 18 UI/kg/h	1 mg/kg bid o 1.5 mg/kg od; reduce to 1 mg/ kg od or pass to UFH if CrCl < 30 mL/min	175 UI/kg od; pass to UFH if CrCl < 30 mL/ min	100 UI/kg bid o 200 UI/kg od; aggiustare se CrCl < 30 mL/ min	Variable, o.d.	150 mg bid; 110 mg bid if age > 80 aa, use of Verapamil, high bleeding risk	20 mg od; 15 mg od if CrCl 15-49 mL/min	5 mg bid; 2.5 mg if at least 2 out of 3 criteria: age ≥ 80 aa, weight ≤ 60 Kg, creatinine ≥ 1.5 mg/ dL	60 mg od; 30 mg od if at least one criterium: CrCl 30-50 mg/dL, weight ≤ 60 Kg, concomitant use of verapamil, quinidine, dronedarone
Target	Factor Xa e IIa	Factor Xa >> IIa (ratio from 4:1 to 2:1)	Factor Xa >> IIa (ratio from 4:1 to 2:1)	Factor Xa >> IIa (ratio from 4:1 to 2:1)	Factors vit. K dependent	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Half-life	1 h	4.5 h	3.7 h	4 h	Warfarin 32-36 h Acenocumarol: 12 h	7-17 h	7-13 h	8-15 h	9-11 h
Renal Clearance	No	Prevalent	Prevalent	Prevalent	0%	80%	60%	25%	40%
Inhibition action onset	1 h	3 h	4-6 h	3-4 h	3-5 h	1 h	2 h	3 h	1 h
Monitoring anticoagulation status	aPTT ratio 1.5-2.5 (anti-Xa activity: 0.3-0.7 IU/mL)	Anti-Xa activity: 0.5-1.1 IU/mL	Anti-Xa activity: 0.8-1.6 IU/mL	Anti-Xa activity: 0.5-1.1 IU/mL	INR 2-3	No need	No need	No need	No need
Interactions	/	/	/	/	Multiple	P-gp	P-gp; CYP3A4	P-gp; CYP3A4	P-gp; CYP3A4
Antidote	Protamine	Partially reversed by protamine	Partially reversed by protamine	Partially reversed by protamine	Vitamin K	Idarucizumab	Andexanet alfa	Andexanet alfa	Andexanet alfa

aPTT, partial thromboplastin time; b.i.d., bis in die; CrCl, creatinine clearance; DOAC, direct oral anticoagulation inhibitors; INR, international normalized ratio; LMWH, low molecular weight heparin; o.d., once daily; UFH, unfractionated heparin; and IU, international unit.

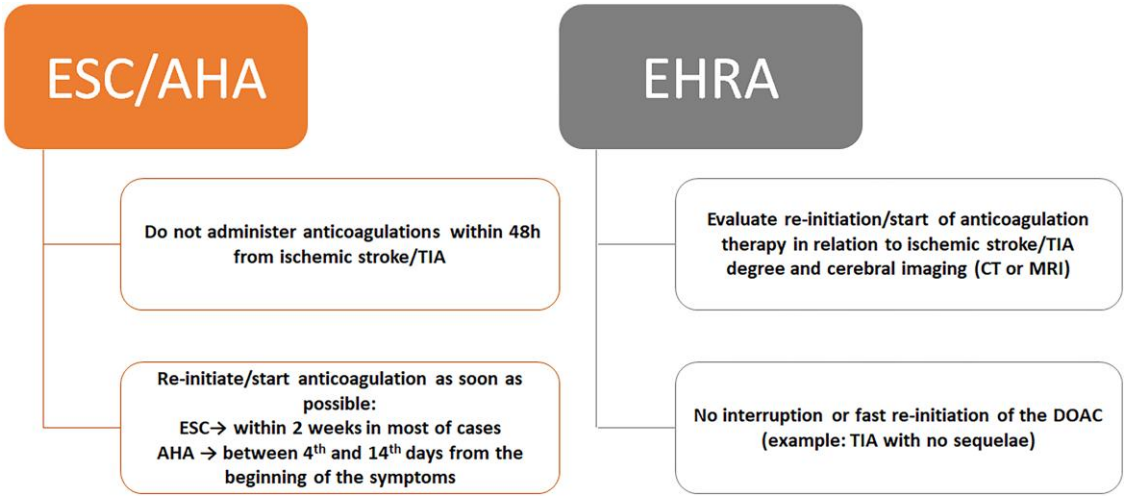

Figure 1 Management of anticoagulation therapy in patients with ischemic stroke/transient ischemic attack and atrial fibrillation in relation to the most recent guidelines. AHA, American Heart Association; DOAC, direct oral anticoagulants; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; MRI, magnetic resonance imaging; CT, computer tomography; and TIA, transient ischemic attack.

Table 11 Antiarrhythmic drugs, renal excretion, and dosages to be adopted in patients with renal insufficiency. CrCL, creatinine clearance and CKD, chronic kidney disease

Antiarrhythmic drug	Clearance	Standard dosage	Adjusted dose in CKD	Note
Flecainide	35% eliminated by kidneys	50-150 bis in die	CrCl < 35: 50 mg bis in die	Consider serum concentration measurement
Propafenone	38-50% eliminated as active metabolite	150-300 mg ter in die; slow release: 325-425 mg bis in die	No data on safety in CKD	
Amiodarone	No renal excretion	600-1200 mg once daily till 10 gr, then 100-200 mg once daily	No need to modify dose	
Dronedarone	6% eliminated by kidney	400 mg bis in die	No need to modify dose	
Dofetilide	80% eliminated by kidney not modified	500 mcg bis in die	CrCl 40-60: 250mcg bis in die CrCl 20-40: 125mcg Q12 CrCl < 20: contraindicated	Monitor ECG during the first 3 days
Ibutilide	Less than 10% eliminated by kidney not modified	1 mg ev in 10 min, then it could be repeated in 10 min	No need to modify dose	Monitor ECG for 4 h
Sotalol	70% eliminated by kidney not modified	80-160 mg bis in die	CrCl 40-60: 80 mg/day CrCl < 40: contraindicated.	Monitor ECG during the first 3 days
Disopyramide	50-60% eliminated by kidney not modified, 20% eliminated as a metabolite	400-800 mg once daily in several doses	CrCl 30-40: 100 mg per ter in die; CrCl 15-30: 100 mg Q12 CrCl < 15: 100 mg Q24	CrCl <40: avoid slow release form

recommended during the first trimester, while VKA and LMWH are indicated during the second and the third trimester.[146] Close to the delivery, UHF should be adopted in relation to its easy management and control; DOAC should be avoided during pregnancy as negative effects had been reported.

Rhythm control is the preferred strategy, while electrical cardioversion with adequate anticoagulation is the safest therapeutic choose during all pregnancy period in case of hemodynamic instability and higher risk for mother and/or foetus due to arrhythmia persistence or use of antiarrhythmic drugs.

Although the risk for foetal arrhythmias or preterm birth is low, electrical cardioversion should be safely performed by monitoring cardiac rhythm of mother and foetus and proceeding to delivery in case of needs.

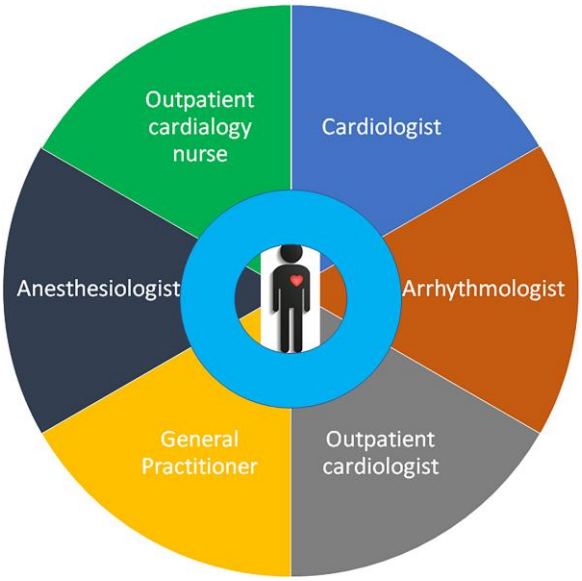

Figure 2 Integrated management of AF patients: reciprocal interaction among different professional figures for the evaluation and optimal management of patients with AF who are admitted to the emergency department.

It is recommended to control heart rate soon after electrical cardioversion.[147] Intravenous flecainide might be considered in stable patients without hemodynamic instability and structural cardiac diseases (class of recommendation IIb) for interrupting AF, but literature is scarce.[148]

Beta-blockers, such as metoprolol or bisoprolol, are safe option and recommended as first choice for the control of heart rate in the acute setting (atenolol is contraindicated). In case of failure, glycosides or verapamil might be considered. Long-term use of amiodarone is contraindicated, while its application in the acute setting might be considered in case of failure of other therapies and in relation to higher risk for mother and foetus in case of arrhythmia persistence.[149]

AF during acute ischemic cerebral event

Ischemic stroke related to AF are often fatal and disabling as they are associated to higher rate of early—between 48 h and 2 weeks from the acute event—recurrences and to higher risk for haemorrhagic transformation—which might occur even in the absence of anticoagulation therapy within ischemic stroke.[150] For this reason, the beginning of anticoagulation in the acute setting (i.e. less than 48 h from the ischemic event) might provoke brain haemorrhages which might be potentially dangerous.[151] Indeed, the risk of ischemic stroke recurrences at 90 days in patients with AF is higher than intracranial haemorrhage in those patients who receive DOAC within 4–14 days.[152] Therefore, delayed starting of DOAC (> 14 days) in AF patients with ischemic stroke and mild-to-moderate damages might be associated to higher rate of recurrences. Several randomized controlled studies which will enrol more than 9000 participants are ongoing such as ELAN (NCT03148457), OPTIMAS (EudraCT, 2018-003859-3), TIMING (NCT02961348) e START (NCT03021928). They will compare early (<1 week) vs. delayed DOAC administration. The aim of these trials is to provide indications about the optimal timing for DOAC administration in case of recent ischemic stroke and its seriousness.

DOAC are associated to a better efficacy in secondary prevention of stroke and higher safety profile in term of intracranial haemorrhage prevention than VKA. A recent meta-analysis which involved about 20 400 patients[153] demonstrated that DOAC significantly reduced risks of stroke/systemic embolism, haemorrhagic strokes, all-cause stroke, and intracranial haemorrhages.

2020 ESC guidelines on the management of AF[24] do not recommend anticoagulation therapy within 48 h from the acute ischemic event, while recommend the beginning or re-introduction of anticoagulation therapy within 2 weeks if neurological conditions allow such strategy and DOAC over VKA in case of patients' eligibility for these drugs. American guidelines[154] also support start or re-introduction of anticoagulation therapy within 4 and 14 days from the index event. European Heart Rhythm Association (EHRA) practical guide for the use of DOAC[155] suggest differential approach to re-introduction of anticoagulation therapy in relation to the type of ischemic event, despite such recommendation are not based on clinical trial data but rather on expert consensus opinion (*Figure 1*). Therefore, patients who experience transient ischemic attack (TIA) without any cerebral imaging evidences of residual damages might not stop anticoagulation therapy or rather start it or re-introduce it since the day after the index event (in relation to neurological judgement and thromboembolic risk). Anticoagulation might be re-introduced between first and third days from the index event in case of evidence of brain damages at brain imaging analysis (computer tomography or magnetic resonance). Furthermore, anticoagulation might be re-introduced after the third day from the index event in case of mild ischemic stroke after excluding haemorrhagic transformation. Finally, in case of more severe form of stroke (moderate-to-severe) and neurological deficits, it should be evaluated the possible haemorrhagic transformation and the ideal time for the management of anticoagulation therapy.[155]

AF during acute coronary syndrome

The prevalence of AF in patients with ACS varies from 2% to 23%.[156] In agreement with data from Italian registries, prevalence is higher in those with NSTE-ACS (7.2%) than those with STE-ACS (4.7%).[156] Patients with AF and concomitant ACS are at increased risk for myocardial infarction and complications, above all in case with recent onset AF.[157]

The trend is that these patients are less invasively treated in the acute setting, although this tendency is reducing; such behaviour may account for the unfavourable prognosis of patients with AF and ACS.[158]

If AF is well-tolerated and the patient is hemodynamically stable, there is no need for specific treatments other than anticoagulation therapy; electric cardioversion should be managed in case of hemodynamic instability. There are no sufficient data for choosing between rate vs. rhythm control in patients with hemodynamically stable AF and

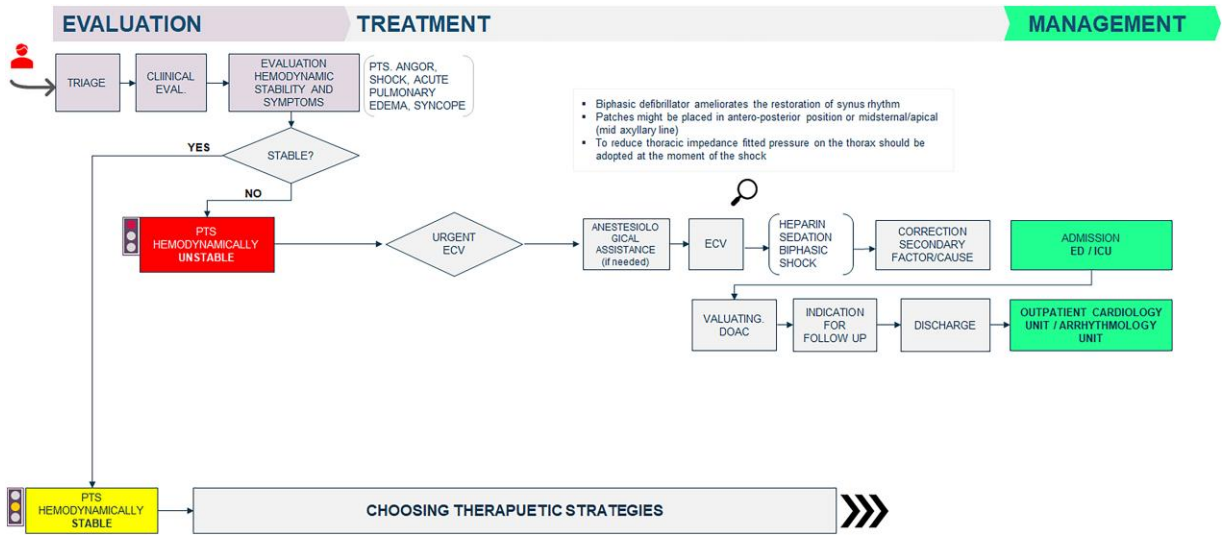

Figure 3 Summary of the clinical management of the hemodynamically unstable patients at the emergency department. ECV, electrical cardioversion; DOAC, direct oral anticoagulant; ED, emergency department; and ICU, intensive care unit.

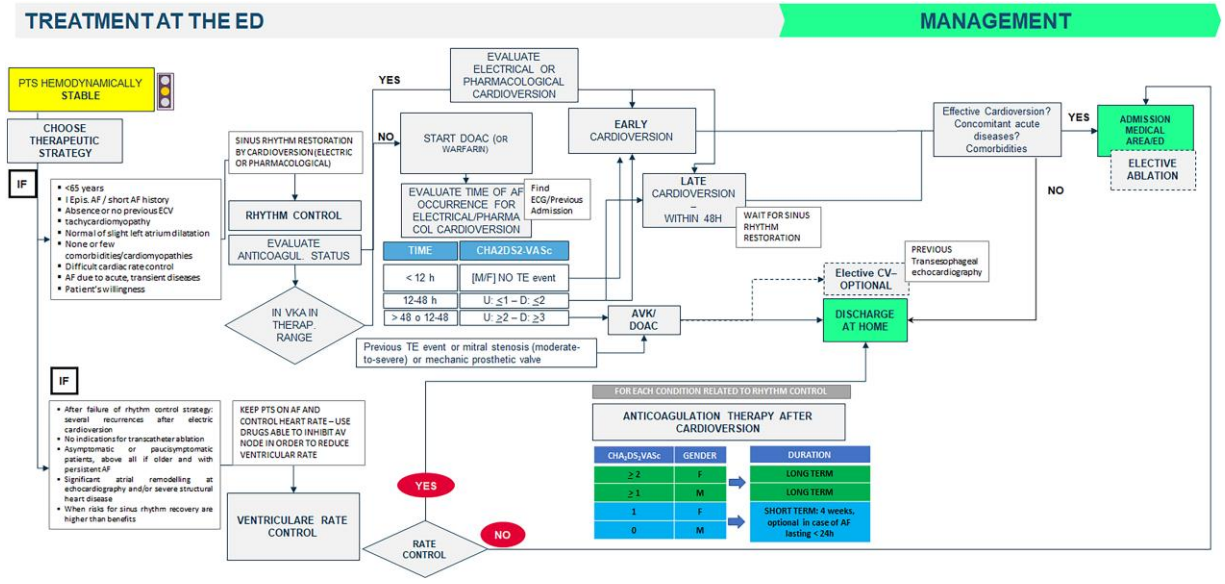

Figure 4 Summary of the clinical management of hemodynamically stable patient: from therapeutic strategy to admission in medical department/discharge from the emergency department. AF, Atrial fibrillation; AV, atrioventricular; AVK, vitamin K antagonist; CV, cardioversion; DOAC, direct oral anticoagulant; ED, emergency department; and TE, thromboembolic.

symptomatic palpitations. The only antiarrhythmic drug which could be considered in patients with AF and ischemic heart disease is amiodarone.[62] Beta-blockers are the most frequently adopted for rate control, specifically with i.v. administration.

In case of myocardial infarction and severe reduction in left ventricle ejection fraction or in case of inefficacy of beta-blockers, it is possible to consider i.v. digoxin in association with amiodarone and a tight monitoring of digoxin plasma levels. In patients with hemodynamic stability in the absence of left ventricle dysfunction and/or signs/symptoms of heart failure, the use of i.v. non-dihydropyridine calcium antagonist might be considered.[159] Patients with AF with ACS who underwent coronary angioplasty should undergo triple antithrombotic therapy [oral anticoagulant (DOAC preferred), low-dose aspirin, and $P2Y_{12}$ inhibitor] for at least 7–30 days.[12] Aspirin has been included in all randomized controlled studies in periprocedural phase in a time-interval between 1 week and 1 month; in agreement with guidelines, low-dose aspirin (≤160 mg/die) should be considered. Antiplatelet agent of choice for association with aspirin is Clopidogrel, while more powerful $P2Y_{12}$ inhibitors such as ticagrelor and prasugrel are not

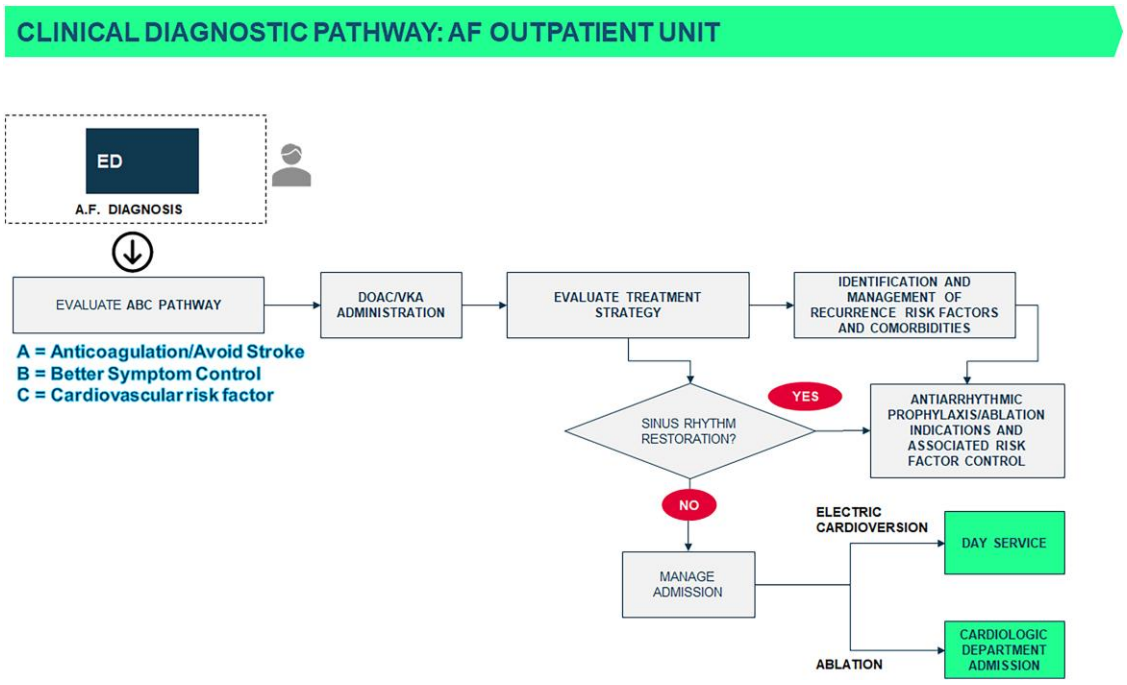

Figure 5 Summary of the clinical pathway of the AF patient after discharge. AF, atrial fibrillation; DOAC, direct oral anticoagulat; ED, Emergency Department; and VKA, vitamin K antagonist.

generally recommended.[24,158-161] Patients chronically treated with anticoagulants and who experienced ACS and subsequent angioplasty might not suspend DOAC,[162] in patients on VKA treatment, VKA should be interrupted before coronary performance and re-started after parental anticoagulant interruption. Meanwhile, there is no need for parental anticoagulation if INR is > 2.5.[161]

Therefore, parental anticoagulation therapy during coronary angioplasty should be administered independently from the latest dose of DOAC or in case of INR < 2.5.[62]

Administration of oral anticoagulants is a relative contraindication to fibrinolytic therapy in case of STE-ACS; the patient should preferentially undergo primary angioplasty after evaluating risks and benefits.[159]

Similarly to other contexts, long-term anticoagulation should be based on the evaluation of ischemic and haemorrhagic risks by means of HAS-BLED e CHA_2DS_2-VASc scores.[163]

Chronic kidney disease and AF

Studies demonstrated higher prevalence in AF in patients with chronic kidney disease (CKD), while the risk for AF development increases with the worsening of kidney function.[164,165]

There is a tight association between the two conditions: 20% of patients with CKD suffers symptomatic AD while 50% with AF suffers renal dysfunction.[166]

CKD is also associated to increased risk of haemorrhagic complications; other studies demonstrated the association between AF and thromboembolic complications.[167,168] Although rate control as compared to rhythm control has been widely studies in general population, literature is scarce about CKD patients (*Table 11*).[169]

Different drugs might be considered for rhythm control in patients with CKD. Propafenone has a lower pro-arrhythmic potential as it undergoes liver elimination. Indeed, it should not be administered in patients with structural cardiac diseases such as heart failure and significant left ventricle hypertrophy.[170] Sotalol is eliminated via the kidneys therefore caution should be paid in patients with CKD due to possible pro-arrhythmic effects. Sotalol has been associated to increased risk of torsades des pointes in patients on dialysis.[171] Amiodarone is not eliminated via kidney but liver metabolism accounts for 99% degradation; long-term adverse events reduce its use while doubts are on the effective systemic toxicity due to this drug in patients with CKD.[172] I.v. ibutilide might be used in patients with CKD; its pro-arrhythmic properties increases in case of hypokalaemia and hypomagnesemia. Dofetilide is mainly excreted via kidney; dosage should be adjusted in patients with CKD as it may increase the risk for ventricular arrhythmias.[173] Flecainide is excreted via kidney, therefore it is not recommended in patients with advanced CKD.[174]

Rate control in patients with CKD might be safely obtained by administering drugs such as beta-blockers (avoid hydro soluble agents such as atenolol, sotalol, nadolol), non-dihydropyridine calcium antagonists (paying attention to slow release formulation in order to avoid advances blocks and avoiding administration to patients with left ventricle dysfunction), and amiodarone as ultimate choice.[24]

Digoxin should be cautiously administered as it can increase the risk for toxicity due to its narrow therapeutic window, above all in patients on dialysis.[175]

The efficacy and safety of DOACs in patients with mild-to-moderate [creatinine clearance (ClCr) 30–49 mL/min] CKD is similar to that in patients with preserved renal

function as compared to VKA.[24] There is paucity of data about the superiority of DOACs vs. VKA in patients with severely impaired renal function (ClCr 15–29 mL/min) as this category of patients was excluded from the majority of trials with DOACs. Indeed, the use of factor Xa inhibitors is allowed by administering reduced dose for rivaroxaban (15 mg/die) and edoxaban (30 mg/die) in patients with ClCr 15–49 mL/min, and reduced dose of apixaban (2.5 mg bid) in case of contemporary presence of at least 2 conditions: serum creatinine $\geq$ 1.5 mg/dL, weight $<$ 60 Kg, and age $\geq$ 80 years. Evidence about the benefit of oral anticoagulant in patients with end-stage kidney disease (ClCr $\leq$15 mL/min) or in dialysis is extremely limited and somewhat controversial.[24,176]

Proposal for an integrated management through a dedicated diagnostic/therapeutic pathway

An integrated management of AF between Emergency and Cardiology Department is the main premix for ameliorating the treatment strategy of arrhythmia and avoiding inappropriate admissions which might negatively impact on the financial budget of health system and on the patient himself as he/she would be 'forced' to inadequate and un-necessary admission to wards (*Figure 2*).

A dedicated diagnostic/therapeutic pathway (PDTA) for the management of AF since the ED is useful to guarantee the best approach to these patients. First, the patient should be evaluated in order to identify the hemodynamic stability.

Hemodynamically unstable patients require immediate electric cardioversion by the physician who takes responsibility of him/her. The help of a cardiologist or anesthesiologist could be considered in relation to the hospital organization and the skills and experience of the physician who will perform the procedure (*Figure 3*).

After evaluation and treatments, hemodynamically stable patients might be directly discharged from the ED or admitted to ED ward/medical area ward/Cardiology Department also in relation to possible comorbidities.

Therapeutic strategies that could be performed in the ED are the following:

- Heart rhythm control: cardioversion and maintenance of the sinus rhythm by means of electrical cardioversion or use of antiarrhythmic drugs
- Heart rate control: consider drugs able to slow ventricular rate during AF

An early cardioversion in patients with no further comorbidities would allow the discharge of the patient with indication to anticoagulant therapy in relation to thromboembolic risk stratification; an AF lasting $>$ 48 h with acceptable mean ventricular rate allows the discharge of the patient directly at home and indication to a possible cardioversion to be programmed.

Admission to Internal Medicine or ED ward might be considered when heart rate strategy did not provide beneficial results, above all in case of patients with comorbidities; admission to the Cardiology Department will be considered in patients with clinical instability features and in those with associated comorbidities. *Figure 4* showed a flow-chart which summarized the clinical pathway for the management of patients with hemodynamically stable AF.

It is important that patients at first episode of AF who are admitted to the ED should be evaluated by a cardiologist for the further management of the patient. Therefore, shared pathways between ED and Cardiology Departments should be created in order to allow ED physicians to program within a few days after ED discharge the evaluation of patients with AF in cardiology outpatient unit or through dedicated cardiologic day service.

The management of these pathways has been already created in several hospitals by means of dedicated agenda. During the cardiologic evaluation might be evaluate indications to chronic oral anticoagulation, antiarrhythmic prophylaxis, treatment of cardiac disease which promote AF and/or risk factors which predispose to AF, indications to transcatheter ablation or percutaneous occlusion of the left atrial appendage (*Figure 5*).

Conclusions

AF still represents an arrhythmic pathology with high social-economic-health impact and one of the main causes for the need of hospital care. The pandemic widespread of AF accounts for the great number of ED admissions for the management of the arrhythmia, its complications, and diseases which may be exacerbated by AF and might condition the outcome of patients.

This forces the need for integrating interventions between ED and Cardiology Department in order to promote a one-way, homogenous management of the disease. This would allow the maximum clinical advantage to patients without provoking an overbooking of the emergency system. The control of heart rate or attempts for cardioversions in the ED would allow optimization of treatments, reduction of inappropriate admissions to wards, and improvements in national health financial status.

Those AF patients discharged from the ED should be preferentially taken in charge from Cardiology Departments. Shared protocols from different professional figures is fundamental for ameliorate the use of resources, the cooperation of colleagues from different Units, and management of patients with AF.

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Data availability

No new data were generated or analysed in support of this research.

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