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Optimal timing for cardioversion in atrial fibrillation

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Optimal timing for cardioversion in atrial fibrillation

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Abstract

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia and, in developed countries, one in four middle-aged adults are expected to develop this disease. AF is a condition associated with increased mortality and morbidity, including the occurrence of stroke, frequent hospitalizations, cognitive impairment and heart failure, and as such, it becomes essential to improve and optimize the integrated treatment of these patients. In an acute episode of AF, with less than 48 hours of duration, both pharmacological and electrical cardioversion (ECV) can be performed. However, some of these episodes can correspond to paroxysmal AF, a type of AF in which the arrhythmic episode may end spontaneously, as it happens in the vast majority of cases, and therefore, in which cardioversion would not be necessary and could be avoided. Given the uncertainty regarding the ideal timing for ECV in an acute episode of AF, a randomized clinical trial is currently on-going, the ACWAS trial, that intends to verify the non-inferiority of the wait-and-see strategy. This approach is based on submitting patients only to an early rate control strategy, while waiting for spontaneous conversion to sinus rhythm, with the possibility of cardioversion within 48 hours after onset of symptoms, if needed, in comparison to the current standard of care (urgent restoration of sinus rhythm, achieved by pharmacologic or electrical cardioversion). This review aims to provide a systematic appraisal of the evidence regarding cardioversion in an acute episode of AF, so we can try to answer the question: what is the ideal timing for cardioversion?

Materials and Methods: This review is based on pertinent articles published from 2012 to 2018 that were obtained through a selective PubMed search employing the terms ‘time to cardioversion’ and ‘acute atrial fibrillation’.

Results: In the acute care setting, the choice of the most appropriate rhythm control strategy for new onset AF varies considerably and is usually individualized and dependent of physician preferences. In a FinCV sub-study, the authors observed that an acute AF with less than 12 hours was more difficult to cardiovert electrically than one lasting 12 to 48 hours, which seems to be related to the fact that the initial trigger of AF may lead to a more difficult restoration of sinus rhythm in the first 12 hours of its onset. Another recent study showed that is more likely for a patient to remain in sinus rhythm if he is cardioverted in the first 48 hours of onset of AF than if he is cardioverted later. This can be explained not only by the continuous mechanical remodeling that occurs in the first days to weeks of AF onset, which makes the atria progressively more susceptible to AF (making recurrence more likely), but also by the irreversible structural changes that occur after a few months of AF, even in

patients undergo optimal rate control, leading to a more difficult restoration and maintenance of sinus rhythm. Overall, results suggest that performing electrical cardioversion in a patient with a duration of AF between the range of 24 hours and 48 hours may be an appropriate option, due to the fact that, on one hand, the rate of recurrence of AF is lower if it is realized after 12-24 hours of the onset of AF and, on the other hand, that, although the risk of a thromboembolic event is higher after a 24-hour duration period, it can be minimized with the correct peri and postprocedural anticoagulation in all patients. However, it would be extremely important to know the results of the ACWAS trial to understand if the wait-and-see approach is, not only, noninferior, safe and cost-effective comparing to current standard of care of AF in the emergency department, but also if this approach actually leads to a better quality in patients' life.

Conclusion: There is still no evidence of the ideal period of time in which we should perform, without any doubt, cardioversion in acute paroxysmal AF. Some data suggest that the appropriate timing to perform cardioversion is between 24 and 48 hours of AF onset. However, more studies are needed to precisely define which is the best approach for rhythm control in patients with recent-onset symptomatic AF.

Keywords: Atrial Fibrillation; rhythm control; cardioversion; optimal timing.

List of Abbreviations

AF – Atrial Fibrillation

APD – Action Potential Duration

BMI – Body Mass Index

CHA_2DS_2-VASc – Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)

CKD – Chronic Kidney Disease

DADs – Delayed Afterdepolarizations

DM – Diabetes Mellitus

EADs – Early Afterdepolarizations

ECG – Electrocardiogram

ECV – Electrical Cardioversion

EHRA – European Heart Rhythm Association

ESC – European Society of Cardiology

HF – Heart Failure

LMWH – Low Molecular Weight Heparin

NOAC – Non-vitamin K Antagonist Oral Anticoagulant

NYHA – New York Heart Association

OSAS – Obstructive Sleep Apnea Syndrome

QoL – Quality of Life

TEC – Thromboembolic Complications

UFH – Unfraccionated Heparin

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1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice and its prevalence increases with age, making it particularly frequent in patients older than 65 years.(1) It is a major risk factor for stroke and thromboembolic events, it decreases quality of life and exercise capacity, and often coexists with other comorbidities, such as heart failure (HF). Therefore, AF is not benign, since it is responsible for an increasing morbidity and mortality. The first is due to markedly increased stroke events (4-fold) and HF (6-fold).(2) In terms of mortality rate, the Framingham study has shown that it is 1.5 times higher in males and 1.9 times higher in female patients with AF, compared to healthy individuals.(1,3,4)

The duration, classification and cause of AF are crucial for the choice of treatment in the acute care setting, in terms of appropriate use of rate versus rhythm control. The current classification of AF according its duration includes paroxysmal (lasts for less than 7 days), persistent (lasts for more than 7 days) and permanent (AF for more than 1 year, that is accepted by the patient and the physician, and no rhythm strategy is implemented), with the first type being the one that most often prompts visits to the emergency department.(5,6) In this review we will be focusing our attention in patients with paroxysmal AF, trying to identify the ideal timing to perform cardioversion. In more than 50% of patients, paroxysmal AF resolves spontaneously in the first few hours, even though many patients will require interventions to control heart rate or restore sinus rhythm.(7) Therefore, it is reasonable to consider a wait-and-see strategy, in which patients are initially submitted to a rate control strategy, while waiting for a possible spontaneous cardioversion to sinus rhythm, instead of the traditional immediate cardioversion. Choosing between these two strategies may be difficult, because, on one hand, we have no data demonstrating a clear superiority of an immediate cardioversion strategy and, on the other hand, it is largely recognized that AF begets AF and that the longer the AF duration, the more difficult it becomes to convert to sinus rhythm.(8) The knowledge that AF is a progressive arrhythmia, and its tendency to become more persistent over time, even in the absence of underlying structural heart disease, favors a rhythm control strategy. The cause of this self-perpetuation of AF is the electrical, mechanical, structural and autonomic remodeling of the atria. Therefore, it is easy to understand that the longer the arrhythmia exists, the harder it gets to cardiovert, achieve and maintain sinus rhythm.(9)

But the most problematic question is ‘when’ should we cardiovert the patient, since optimal timing to restore sinus rhythm remains uncertain and not based on solid evidence. International guidelines support that patients who present with non-valvular atrial fibrillation for less than 48h should undergo cardioversion, either electrical or pharmacological, since the risk of thromboembolic events, which are a consequence of cardioversion, is very low in this group of patients. It is now known that the risk of thromboembolism increases with the duration of AF, being around 0.3% when <12h, raising to 1.1% when beyond 12h.(8) However, recent studies have shown that the thromboembolic risk associated to the restoration of sinus rhythm is not only related with the duration of the symptoms, varying greatly depending on the characteristics of the patient: the risk can go from unacceptably high (9.8%) in a patient with heart failure and diabetes, to very low (0.2%) in a patient under 60 without heart failure.(8) Even though it seems that the earlier we perform cardioversion the better, new data suggest that if restoration of sinus rhythm is performed in the first few hours of the onset of AF, more precisely before 12 hours, it may be less effective, due to recurrence of AF, probably because of the persistence of the factors that triggered AF.(9) Therefore, the management of acute onset paroxysmal AF remains a challenge even nowadays. Should we cardiovert even knowing that more than 70% of the cases will revert spontaneously to sinus rhythm in the first 24 hours of AF’s onset?(10) And if we should cardiovert, what is the optimal time to do it? Being aware of the pathophysiology of AF, the fact that each patient is different to the others, the consequences of persistent AF and the risks involving cardiovertion, it is easy to understand the complexity of this issue and why it is so difficult for specialists to reach a consensus about the best strategy to treat a patient with acute AF. With this being said, the aim of this review is to assess the pros and cons of cardioverting a patient with acute AF and, if the restoration of sinus rhythm is the chosen strategy, when should it be done.

2. Epidemiology

AF is the most prevalent cardiac arrhythmia, occurring in 1-2% of the people worldwide. In 2010, the estimated number of men with AF worldwide was 20.9 million and of women 12.6 million, with even higher incidence and prevalence rates in developed countries. By 2030, 14–17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year.(6) By 2050 the prevalence of this pathology is projected to increase to 4% of the world's population.(4)

The increasing AF prevalence can be attributed to better detection of silent AF, alongside conditions predisposing to AF and increasing age, with the latter being the most powerfull predictor of AF risk, since 10% of people older than 80 years suffer from this condition. Furthermore, 70% of patients with AF are in the range between 65 and 85 years old.(1,6)

3. Pathophysiology

The pathophysiology of AF is highly complex and it is still not completely understood. To treat a disease, it is mandatory to understand the underlying pathophysiology, so we can select the targets that we think that may be causing that condition. Therefore, the pathophysiollogy of AF will be explored in further detail. From what has been demonstrated so far, we know that AF is related to atrial remodeling, which can be electrical, mechanical, structural and autonomic.(9)

3.1 Electrical Remodeling

Electrophysiological changes involve modification of ion channels expression and function, and are seen as early as 4 hours after the initiation of AF.(9) For AF to start and be maintained, both triggers for its onset (focal ectopic firing) and a substract for its maintenance are needed. This triggered activity can be caused by secondary cardiac depolarizations initiated by prior depolarizations (early and delayed afterdepolarizations) or by enhanced automaticity.(4,11) If these secondary depolarizations reach threshold potential, they may generate action potentials during or immediately after phase 3 of the action potential. Most of the times this triggered depolarization is caused by delayed afterdepolarizations (DADs), occurring during phase 4. These DADs are exaggerated at

rapid heart rates, conditions that are associated with intracellular calcium overload, such as high-level catecholamine states. In a smaller amount of cases, this triggered activity is caused by early afterdepolarizations (EADs), occurring during phase 3 of the action potential, interrupting repolarization. (Figure 1) Inciters of EADs include QT-prolonging drugs, hypokalemia, and bradycardia.(11)

Ca^{2+}-related abnormalities are crucial to DADs and EADs, particularly when there is an activation of sympathovagal system, with vagally mediated atrial potential duration (APD) shortening and adrenergically mediated Ca^{2+} loading.(12) In AF there are rapid atrial rates, promoting an increase in intracellular Ca^{2+}, which initiates auto protective mechanisms to reduce Ca^{2+} inflow, such as Ca^{2+} current inactivation (reducing the direct entrance of Ca^{2+}) and inward rectifier K^{+} current enhancement. These ion channel dysfunctions accelerate repolarization, abbreviate atrial APD and refractoriness, facilitating reentry circuits.(9,12) Reentry is the dominant mechanism underlying the maintenance of AF and is characterized by the re-excitation of a localized region of cardiac tissue by the same impulse, requiring bifurcating conduction pathways with different velocities and refractory periods.(11)

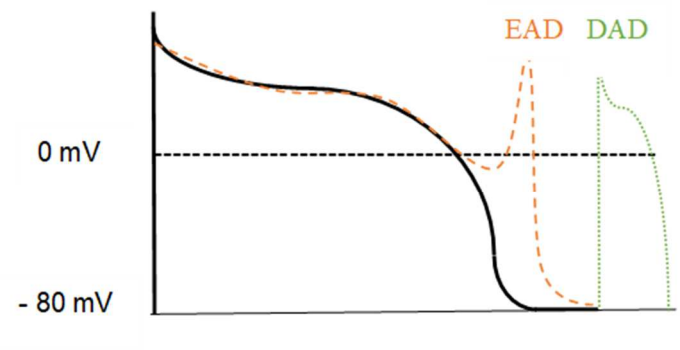


Figure 1 – Mechanism of arrhythmia onset in AF. Focal firing via triggered activity due to early or delayed afterdepolarizations (EAD and DAD, respectively) causes local ectopic activity, which can act as an AF-maintaining ectopic driver, or can trigger AF-maintaining reentry in a vulnerable substrate.

Previous experiments demonstrated that electrical remodeling is complete within hours to days, whereas the development of sustained AF usually takes more than one week, suggesting that other remodeling processes, such as structural, mechanical and autonomic, must also be present. Of interest, it is obvious that electrical changes play an essential role in the early recurrence of AF after cardioversion, as well as its tendency to progress to a more persistent state.(9)

3.2 Structural Remodeling

The term structural remodeling includes changes in atrial tissue properties, more importantly myocyte death and development of interstitial fibrosis, and has a longer course time than electrical remodeling. Atrial fibrosis can be the result of a variety of factors related to AF-inducing pathologies, or can be caused by AF itself. Fibrosis occurs as a reparative process to replace degenerative myocardial tissue, and results in the deposition of fibrillar collagen in the extracellular matrix. This process can lead to atrial arrhythmogenesis in many ways. First of all, fibrous tissue can separate atrial muscle fibers, interrupting muscle continuity and creating a physical barrier to conduction, which causes local conduction disturbances and block that induce reentry. Secondly, fibrosis is associated with proliferation of fibroblasts, which can interact with cardiomyocytes electrically, since they are inexcitable but can carry currents, and consequently slow conduction. In addition to that, because they are less polarized than cardiomyocytes, they can enhance phase 4 depolarization, leading to spontaneous firing, causing also depolarization of the cardiomyocyte resting membrane potential and shortening of atrial APD, thus favoring reentry circuits.(9,12)

3.3 Mechanical Remodeling

Mechanical remodeling includes changes in atrial size and contractility. It is known that atrial fibrillation is associated with decreased contractility and marked dilatation of the atria. Atrial fibrillation is, by itself, a condition defined by the absence of an effective atrial contraction, which is impaired after only a few minutes of experimental AF, but continues to worsen over many weeks, having its peak after 6 weeks of rapid atrial rates.(9)

3.4 Autonomic Remodeling

Altered autonomic function, meaning hyperactivity of the cardiac autonomic nervous system, plays a crucial role in the beginning and maintenance of AF and occurs in the first 24 hours after the beginning of AF.(9) This may be due to several mechanisms, such as vagally mediated atrial APD shortening, adrenergically-mediated Ca^{2+} loading and DAD promotion, and EAD induction through combined sympathoadrenal discharge.(12) It is also known that long-lasting AF causes spatially heterogeneous sympathetic hyper-innervation.

Regarding the role of cardioversion in AF remodeling, studies demonstrated that the recovery of electrical atrial changes can be complete, even if an extended time is spent in AF prior to cardioversion.(9) However, structural changes are likely to become more permanent, since experiments have shown that there is only partial structural and functional recovery after cardioversion. Since structural remodeling continues to worsen over several weeks after restoration of sinus rhythm, the recovery of atrial contractility can take weeks to months and is associated to the duration of the episode of AF. Taking this into account, it is easy to understand that if the aim is the restoration and maintenance of sinus rhythm, AF should optimally not be allowed to persist for weeks or months and a rhythm control strategy should be performed early. With that being said, and knowing that reversing these changes is possible if sinus rhythm is restored early, it seems that early cardioversion can be beneficial in preventing and reversing remodeling and, therefore, in maintaining sinus rhythm, improving outcomes in AF.(9) However, the main question remains: what is the optimal timing to perform it?

4. Risk Factors for AF and its link with Remodeling

Many cardiovascular diseases and concomitant conditions increase the risk of developing AF, recurrent AF, and AF-associated complications. The identification of such conditions, their prevention and treatment is important to prevent AF and its disease burden.(6) This wide variety of factors associated with AF can be divided into established and emerging risk factors.(3)

4.1 Established Risk Factors

- Advancing age – as mentioned previously, advanced age is related with an increased risk of developing AF, doubling the prevalence of this disease with each decade of age. This is explained by the structural remodeling of the atria that is caused by aging.(12)

- Male sex – Men have a 1.5-fold risk of developing AF compared to women. The pathophysiological mechanism for this difference is the greater expression of important repolarizing ion channel subunits (which accelerates atrial repolarization) and structural differences, such as greater atrial dimensions, that can promote AF maintenance.(12)

- Hypertension – this condition increases the risk of developing AF in 1.2-1.5-fold. The high prevalence of hypertension in the general population makes it the most significant risk factor for AF beyond age and gender. The susceptibility to AF in this case is due to structural changes, especially to the development of atrial fibrosis.(12)

- Valvular heart disease – is associated with a 1.8-fold (in men) and 3.4-fold (in women) increased risk for AF, which is due to structural changes in the heart. Any valvular pathology can be related to AF, but stenotic left-sided ones (particularly rheumatic heart disease) have the highest prevalence rates. The prevalence of AF in these patients depends on the severity of the valvular stenosis, being 9.1% in patients with mild-to-moderate stenosis and 33.7% among those with severe stenosis.(12)

- Heart failure (HF) – often coexists with AF and, similarly to patients with AF due to valvular heart disease, the prevalence of AF increases with the severity of HF symptomatology: NYHA class I <5-10%; NYHA class II-III between 10% and 26%; NYHA class IV between 40%-50%. Congestive HF produces major atrial structural changes and also causes alterations in atrial cardiomyocyte Ca^{2+} handling, promoting DAD-related triggered activity.(12)

- Diabetes Mellitus (DM) – is associated with a 1.4- to 1.6-fold increased risk of AF. They often coexist because of associations with other risk factors, such as systemic inflammation, autonomic dysfunction, obesity, obstructive sleep apnea, coronary artery disease and heart failure, leading to structural and autonomic changes in the atrial.(12)

- Obesity – overweight (BMI: 25-30 kg/m^2) and obese (BMI: ≥30 kg/m^2) individuals are at increased AF risk (1.39-1.75-fold in overweight individuals; 1.99-2.35-fold in obese individuals). This is explained by structural and mechanical changes, such as left ventricular diastolic dysfunction leading to left atrial dilation, that occur in obese people.(12)

- Obstructive sleep apnea syndrome (OSAS) – characterized by periodic reduction or cessation of breathing during sleep, is associated with a 4-fold increased risk of developing AF. OSAS exaggerates intrathoracic pressure changes, which in itself and via vagal activation can provoke shortening of the

atrial action potential and induce AF.(6) Besides that, OSAS is also associated with recurrent AF after cardioversion and ablation.(12)

- Genetic factors – a family history of AF in a first-degree relative increases AF risk 2-fold. Genetic risk factors can be separated into monogenic (rare disease-causing mutations) and polygenic (common gene variants, manifesting as single nucleotide polymorphisms). The former are associated with AF due to mutations that occur in genes encoding cardiac ion channels; the latter contribute to AF susceptibility with a much lower penetrance than monogenic causes, and therefore they predispose individuals to develop AF in association with other risk factors.(12–14)

4.2 Emerging Factors

- Prehypertension – systolic blood pressure between 130 mmHg and 139 mmHg and increased pulse pressure are also associated with increased AF risk (1.28-fold and 1.26-fold per 20 mmHg increment, respectively).(12)

- Chronic kidney disease (CKD) – AF is present in 15–20% of patients with CKD(6), increasing its risk with the severity of renal dysfunction: 1.3-1.6-fold and 1.6-3.2-fold with an estimated creatinine clearance (CrCl) rate of 30-59 mL/min and <30 mL/min, respectively.(12)

- Alcohol consumption – heavy alcohol consumption (≥36 g/d) is associated with an increased risk of 1.34 to 1.46-fold for new-onset AF (also called holiday heart syndrome). This is due to the fact that consumption of and subsequent withdrawal from alcohol result in a hyperadrenergic state, impaired vagal tone and changes in the properties of atrial conduction, predisposing to the development of AF.(12)

- Excessive endurance exercise – regular moderate physical activity decreases many cardiovascular risk factors and may also decrease the incidence of AF. However, excessive sport practices, such as endurance or high-performance athletes have an increased risk of developing AF (≈3-fold when there is a cumulative lifetime practice of more than 1500 hours). Besides, it is also a cause of AF recurrence after catheter ablation. The explanation is that long-

term endurance exercise causes structural changes and vagal enhancement. The enhancement of vagal tone causes spatially heterogeneous abbreviations in atrial refractoriness, leading to AF.(12)

- Smoking – is linked to the risk of developing AF by 1.51 to 2.05-fold, with a dose-response effect. Chronic nicotine exposure is also associated with AF recurrence after catheter ablation.(12)

- Hyperthyroidism – increases the risk of AF by 3 to 6 times, which is related not only to increased β-adrenergic tone, but also to the direct effects of thyroid hormone on pulmonary vein cardiomyocytes, leading to increased automaticity and promoting triggered activity.(12)

5. Consequences

In general, AF is related with impaired quality of life (QoL), increased mortality, thromboembolic events, left ventricular dysfunction and heart failure (HF).

5.1 Symptoms and QoL

Patients with AF experience a great variety of symptoms and signs, with the most common ones being dyspnea, lethargy, palpitations, angina pectoris, dizziness and sleeping difficulties. There is a scale (the modified EHRA scale) that is used to classify symptoms related to AF severity. This scale goes from 1 (AF does not cause any symptom) to 4 (normal daily activity discontinued because of AF) and should be used to guide symptom-orientated treatment decisions.(6) Besides the characterization of the symptoms, it is also crucial to know when the symptoms started because the chance to restore sinus rhythm is higher in patients with recent-onset AF.(12)

5.2 Mortality

People suffering from AF have a significantly greater mortality rate than patients without AF. However, it remains unclear if well-controlled AF independently predicts death because, despite the improvement in treatment strategies, AF-related mortality has remained relatively

static. To date, only anticoagulation therapy has been shown to improve patients' survival, since large-scale randomized trials did not show any benefits in mortality of rhythm-control over rate-control strategies.(12)

5.3 Stroke and Thromboembolism

This condition is associated with 3 to 5 times higher risk of stroke, accounting for approximately 20% of all strokes. The stroke risk associated with AF is variable and increases significantly with age, once it reflects clinical characteristics and comorbidities. It is also important to know that AF-related strokes are relatively more severe and often recurrent, therefore causing significantly higher resource use, long-term disability and mortality, when compared to non-AF-related strokes.(12)

5.4 Heart Failure

Although the association between AF and HF is well documented, the causative relationship between the two of them is not fully understood. On one hand we have the shorter diastolic filling time, loss of atrial contraction and elevated filling pressures caused by AF leads to a reduction in cardiac output and tachycardia-induced myocardial dysfunction. On the other hand, HF results in structural and electric remodeling, which enhances susceptibility to AF.(12)

5.5 Cognitive Impairment

AF has also been associated with a faster decline in cognitive function, not related with stroke, resulting in a 1.7 to 3.3-times higher risk of cognitive impairment and a 2.3-fold increased risk of dementia compared to patients in sinus rhythm.(12) Proposed mechanisms of cognitive impairment in atrial fibrillation include cerebral thromboembolism, cerebral hypoperfusion, and cerebral microbleeds. Anticoagulation may be protective against cognitive dysfunction in patients suffering from AF (15) and, in the absence of anticoagulation, rhythm control treatment may have this protective effect.(16) However, in both cases, further investigation is needed.

6. Diagnosis

The diagnosis of AF requires rhythm documentation using an ECG showing the typical pattern of AF: absolutely irregular RR intervals and no discernible, distinct P waves.(6) There are five types of AF, based on the presentation, duration, and spontaneous termination of AF episodes: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF. For this review, of interest is the paroxysmal one, which may last up to seven days. Current european guidelines propose five domains in the initial assessment of a patient with newly diagnosed AF:(6)

- Haemodynamic instability (which requires, necessarily, electrical cardioversion);

- Presence of precipitating factors (which must be investigated with a chest X-ray, transthoracic or transesophageal echocardiography and blood tests - including thyroid hormones - and corrected before any treatment strategy is applied)(1) and underlying cardiovascular conditions;

- Stroke risk and need for anticoagulation (given by the CHA_2DS_2-VASc score);

- Heart rate and need for rate control;

- Symptom assessment and decision for rhythm control.

As mentioned before, it is known that anticoagulation is the only treatment strategy that has shown a reduction in mortality in AF patients, due to the fact that it prevents stroke, a major consequence of AF. However, treatment of AF aims not only to reduce thromboembolic risk, but also to increase quality of life and prevent heart failure. The fact that AF is a progressive arrhythmia related to electrical, mechanical, structural and autonomic remodeling with the tendency to become more persistent over time, and therefore, resulting in significant cardiac changes, favors the option of an early rhythm control strategy. Despite this, duration of AF is the key when considering treatment options in the acute care setting,(5) because if the patient is hemodynamically stable and presents AF for more than 48 hours, an initial-rate control treatment should be preferred and being the rhythm control strategy considered after 3 weeks of effective anticoagulation. This is due to the fact that thromboembolic events are the most common complication of cardioversion. Atrial stunning (transient mechanical dysfunction of the atria and atrial appendage after cardioversion to sinus rhythm) is considered to be the primary cause of thromboembolism after cardioversion. Despite the fact

that in the presence of AF no effective atrial contractions occur, there is still some movement of blood in the left atrium and atrial appendage. Restoration of sinus rhythm by cardioversion can primarily cause a fall in blood flow in left atrial chamber and atrial appendage,(2) promoting platelet activation and thrombin generation and predisposing to embolization.(17) Therefore, the risk of occurrence of a thromboembolic complication (TEC) after cardioversion has been studied and it showed that, in patient without risk factors (CHA_2DS_2-VASc <1 in men and CHA_2DS_2-VASc <2 in women), is low when it is performed in the first 48 hours of the onset of AF; but if the duration of AF is longer than 48 hours, the risk of a TEC is too high and cannot be accepted, and so the chosen initial treatment should be the rate control one. However, there is no evidence in terms of mortality rates on the advantage of an initial rhythm versus rate control treatment and thus, in a hemodynamically stable patient with an acute-onset of non-valvular AF, there is no agreement in what should be the chosen strategy in international guidelines.(18)

7. Acute Treatment and its Complications

7.1 Electrical Cardioversion

ECV is the most effective means of terminating AF and restoring sinus rhythm, with a conversion to sinus rhythm in almost 90% of cases.(2) Success rates of cardioversion can vary, decreasing with increased AF duration, chest wall impedance and left atrial size, since a larger left atrial chamber reflects the cumulative effects of cardiac remodeling and a severe diastolic dysfunction, which, in turn, is responsible for AF recurrence.(19) This type of cardioversion requires sedation and is indicated in haemodynamically unstable patients and may also be considered in the acute phase of haemodynamically stable patients in whom AF duration is less than 48 hours. Pretreatment immediately before ECV with antiarrhythmic drugs, such as flecainide, propafenone, sotalol or amiodarone, increases the probability of restoring sinus rhythm and helps prevent the recurrence of AF. This increased efficacy of ECV using pretreatment with antiarrhythmic medications may be related to a decrease in the energy needed to achieve sinus rhythm, to a prolongation of atrial refractory periods and to a suppression of atrial ectopic foci that are responsible for early recurrence of AF.(20) In the short-term, ECV restores sinus rhythm quicker and more effectively than pharmacological cardioversion and is associated with shorter hospitalization.(6)

7.2 Pharmacological Cardioversion

Pharmacological cardioversion, on the other hand, does not require sedation but has lower rates of efficacy (restores sinus rhythm only in about 50% of patients),(6) with the highest success rates when the duration of AF is relatively short (less than 48 hours). This type of cardioversion may be considered in the acute phase of haemodinamically stable patients. The most antiarrhythmic drugs used in clinical practice are flecainide, propafenone and amiodarone. The first two are class Ic antiarrhythmics, while the last one is a class III antiarrhythmic. The most common side effect of class I antiarrhythmic drugs are: prolongation of PR and QRS duration, which can lead to ventricular proarrhythmias.(11) In what concerns class III antiarrhythmics, in the specific case of amiodarone, it can be used to treat AF in patients with structural heart disease, contrary to class I antiarrhythmics. However, amiodarone has greater toxicity than the others, with serious adverse effects that include agranulocytosis, potencially irreversible pulmonary fibrosis, optic neuropathy producing visual impairment and severe hepatic toxicity.(11)

A novel antiarrhythmic drug, Vernakalant, that has been approved for pharmacological cardioversion in Europe in 2010, is a multichannel blocking agent intended for intravenous administration and high selectivity for atrial cardiomyocytes. This drug has shown to be a quick, safe, and practical means of achieving rapid restoration of sinus rhythm (median time to conversion of 10 min) in patients with stable recent-onset AF and may be considered as an alternative to amiodarone for pharmacological conversion of AF in patients with mild HF (NYHA Class I or II).(6,21)

Therefore, the latest ESC guidelines from 2016 recommend that, in case of a haemodynamically stable patient with acute symptomatic AF, he undergoes electrical or pharmacological cardioversion and, if the latter is chosen, the choice of drug depends on the presence of structural heart disease: if present, amiodarone should be the chosen drug; if not, the chosen one should be flecainide, propafenone or vernakalant.(6)

7.3 Complications of Cardioversion

As any treatment strategy, cardioversion has its own adverse effects, which are usually self-limiting or relatively benign. However, rare but potential life-threatening complications, such as thromboembolism and arrhythmias can occur after cardioversion.(20) Systemic thromboembolism, which happens in less than 1% of the cases,(17) occurs within the first 10

days following cardioversion in 98% of the cases, with the third to fourth days after cardioversion carrying the greatest risk. Even though the first few days following cardioversion have the highest risk of TEC, this risk can persist for 30 days.(5,17,22) No difference has been found concernings the rate of thromboembolic events after electrical versus pharmacological cardioversion.(8) It was demonstrated by the large FinCV study that there was an evident 3-fold increase (23) in the risk of a thromboembolic event after 12 hour of AF duration,(24) more precisely increasing the risk of a thromboembolic event from 0.3% (if cardioverted within 12 hours of AF's onset) to 1.1% (if cardioverted after 12 hours of the onset).(8,17) Taking this into account, it appears that timing to restore sinus rhythm is an important factor related to the risk of thromboembolic events after cardioversion, and so, it seems that cardioverting as soon as possible, preferably in the first 12 hours, decreases the risk of thromboembolic events.(25) The FinCV study found that independent predictors of thromboembolic risk included age, DM, female sex and heart failure, and they also identified CHA_2DS_2-VASc score as 'highly predictive' of a thromboembolic event in the acute setting. (8) However, another study made by FinCV demonstrated that 21% of the strokes after cardioversion occurred in patients with a CHA_2DS_2-VASc score of 0-1.(23) Therefore, the most prudent and safe approach seems to be for everyone, especially those patients over 65 years, to undertake periprocedural anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) followed by 1 month of post-procedural anticoagulation with a NOAC or warfarin (since the risk of thromboembolism can persist for 30 days after cardioversion).(8,26) After this 4 week period, anticoagulation should continue lifelong in patients with CHA_2DS_2-VASc >1.(8)

Also, following both electrical and pharmacological cardioversion, arrhythmic complications can happen. In case of arrhythmic complications after ECV, they are rare and consist essentially of bradyarrhythmias, which occur in 0.9% of the electrical cardioversions. This complication is more common in older people and in female patients and is usually self-limiting, thus rarely requiring necessary a specific treatment.(27) Regarding arrhythmic complications after pharmacological cardioversion, they usually consist of ventricular arrhythmias and Torsades de Pointes (in patients treated with class III antiarrhythmics, due to the prolongation of QT interval by this class of drugs). Therefore, the selection of an antiarrhythmic drug should, not only be based on drug safety, but also be individualized, taking into consideration that each patient has his own characteristics.(21)

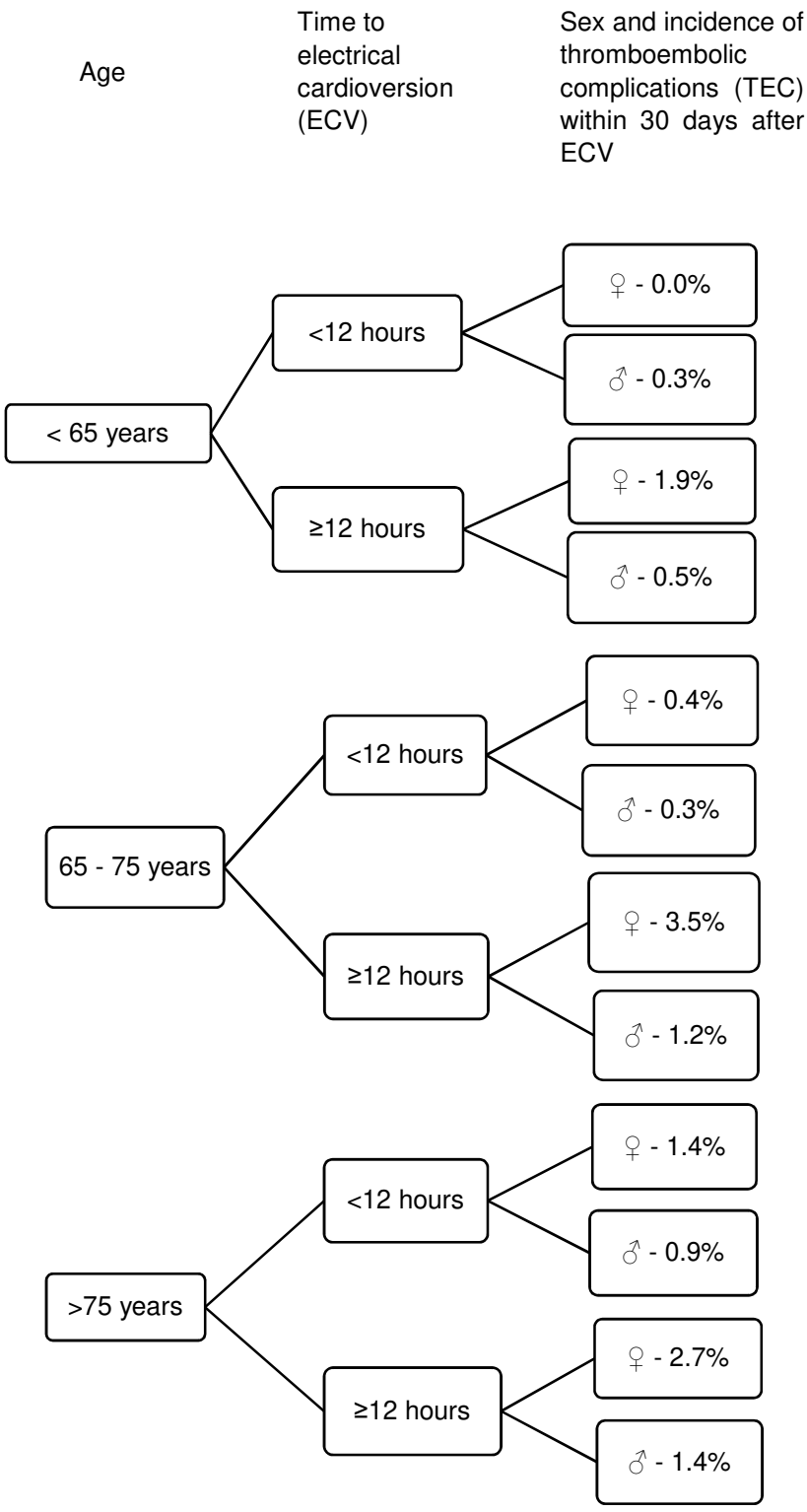
8. Results

As mentioned previously, there is no evidence that restorating sinus rhythm improves survival, neither that an early rhythm control strategy is superior to an early rate control followed by later rhythm control strategy or vice versa. Thus, in the acute care setting, the choice of the most appropriate treatment is usually individualized and dependent of physician preferences.(5) Consequently, we arrive at the question that is the aim of this review: if we decide to perform cardioversion, when, within the first 48 hours of the onset of AF, should we perform it? Should it be performed in the first 12 hours, due to the lower risk of thromboembolic events? Or should we wait and perform it between 24 to 48 hours after the onset?

To complicate things a bit more, we know that there is a high rate of spontaneous reversion to sinus rhythm for new onset AF within 48 hours:(28) by 8 hours after the onset of AF, up to 50% of patients with recent onset of AF spontaneously convert back to sinus rhythm,(5) and up to 75% of patients have been reported to spontaneously-cardiovert in acute AF.(29) Knowing this, should we cardiovert the patient or should we do a wait-and-see approach with just an acute rate control, hoping that the patient cardioverts spontaneously? To try to find an answer to this question, we focused our attention in some studies that have been performed in the last few years, related to this issue.

In a FinCV sub-study, the authors investigated the interaction between risk factors, such as female gender, old age and time to cardioversion, and the occurrence of thromboembolic events in non-anticoagulated patients. In this study, with the primary outcome of TEC in the first 30 days after electrical cardioversion, patients were divided into 3 groups according to their age (<65 years old; 65 – 75 years old; >75 years old), into two groups according to time to cardioversion (<12 hours; ≥12 hours) and divided into male or female, according to the correspondent gender. The results showed that when patients <75 years undergo ECV in the first 12 hours of AF symptoms onset, the risk of TEC was very low and there was no significant difference between the two genders. However, in the group of patients that underwent cardioversion ≥12 hours, the risk of TEC rised substancially (2 to 4-times higher), especially in women. In the age group >75 years and when cardioversion was performed after 12 hours, the risk of TEC increased substantially in both sexes. Furthermore, unsuccessful cardioversion and recurrence of AF rates were higher in women than in men. With these results, we can realize that, besides female sex and old age, also a longer duration of AF before restoration of sinus rhythm increases the risk of occurrence of a

thromboembolic event.(30) Below we show a schematic representation of the mentioned study:



In another FinCV sub-study, the authors observed that an acute AF with less than 12 hours was more difficult to cardiovert electrically than one lasting 12 to 48 hours. They also showed that the risk of failure of early ECV was higher in the ones performed due to first AF episode. This may be related to the fact that the initial trigger of AF, such as altered autonomic state with markedly increased sympathetic nervous activity, may lead to a more difficult restoration of sinus rhythm in the first 12 hours of its onset. Other risk factors for failure of ECV and early recurrence of AF were history of AF episodes within 30 days prior to cardioversion and the use of antiarrhythmic drugs. Furthermore, in this study, they realized that traditional risk factors for thromboembolic events – female sex, heart failure, DM and known vascular disease – also predicted early recurrence of AF. Thus, exposing these patients to multiple cardioversions due to the fact that they have higher recurrence rates, increases the risk of thromboembolic events even more. This way, they concluded that ECV of acute AF is an effective procedure but it is important to identify each patient's risk factors for unsuccessful cardioversion and early recurrence of AF when choosing the treatment strategy.(29)

In a recent review, Piña et al. claim (based on previous findings) that it is more likely for a patient to remain in sinus rhythm if he is cardioverted in the first 48 hours of onset of AF than if he is cardioverted after 48 hours. The explanation for this is related to the continuous mechanical remodeling that occurs in the first few days to weeks, leading to progressive atrial dilation and decreasing contractility, which makes the atria progressively more susceptible to AF, and so, making its recurrence more likely. It is also mentioned that irreversible structural changes, such as atrial fibrosis, develop after 2 to 3 months of AF, even if patients undergo optimal rate control and in the absence of congestive HF. These irreversible changes make it more difficult to restore and maintain sinus rhythm, regardless of the efforts to achieve it.(9)

In a study cohort that was gathered from databases of 3 FinCV studies, whose aim was to investigate the optimal timing to perform cardioversion in patients with AF, they divided patients into four groups, according to the duration of AF before cardioversion: <24h; 24h to 48h; 48h to 30 days and >30 days. They found that patients with AF episodes lasting between 24 to 48 hours had the lowest rate of failure of cardioversion, with a duration of the AF's episode of over 48 hours being an independent predictor of unsuccessful cardioversion. Furthermore, it demonstrated that patients with shorter AF duration (<24h and 24h-48h) had lower risk of recurrence of AF, with the recurrence rate being slightly higher in the group of patients with AF of less than 24 hours. Regarding some of the adverse outcomes of cardioversion – unsuccessful ECV, thromboembolic events and recurrence of AF - the group of patients with an index AF episode duration between 24 and 48 hours had the lowest rate,

while the risk for adverse outcomes after restoration of sinus rhythm was 2-times higher in patients with an AF episode lasting more than 48 hours. Thus, these findings suggest that cardioverting early is better than delaying it, because the longer delay from AF onset to restoration of sinus rhythm is associated with lower success rates of cardioversion and increased AF recurrence after a successful procedure. (Table I; Figure 2) (31)

Table I – Optimal timing for electrical cardioversion taking into account the percentage of unsuccessful electrical cardioversions, thromboembolic events and recurrence of atrial fibrillation (data from 3 FinCV studies databases).

Time to ECV (nº of ECV performed)	Unsuccessful ECV nº (%)	Thromboembolic events nº (%)	Recurrence of AF nº (%)
<24 h (1767)	150 (8.5%)	2 (0.1%)	481 (29.8%)
24h – 48h (516)	28 (5.4%)	0 (0.0%)	129 (26.5%)
48h – 30 days (632)	70 (11.1%)	0 (0.0%)	209 (37.3%)
>30 days (1441)	200 (13.9%)	3 (0.2%)	375 (30.0%)
Total 4356	Total 448 (10.3%)	Total 5 (0.1%)	Total 1194 (30.6%)

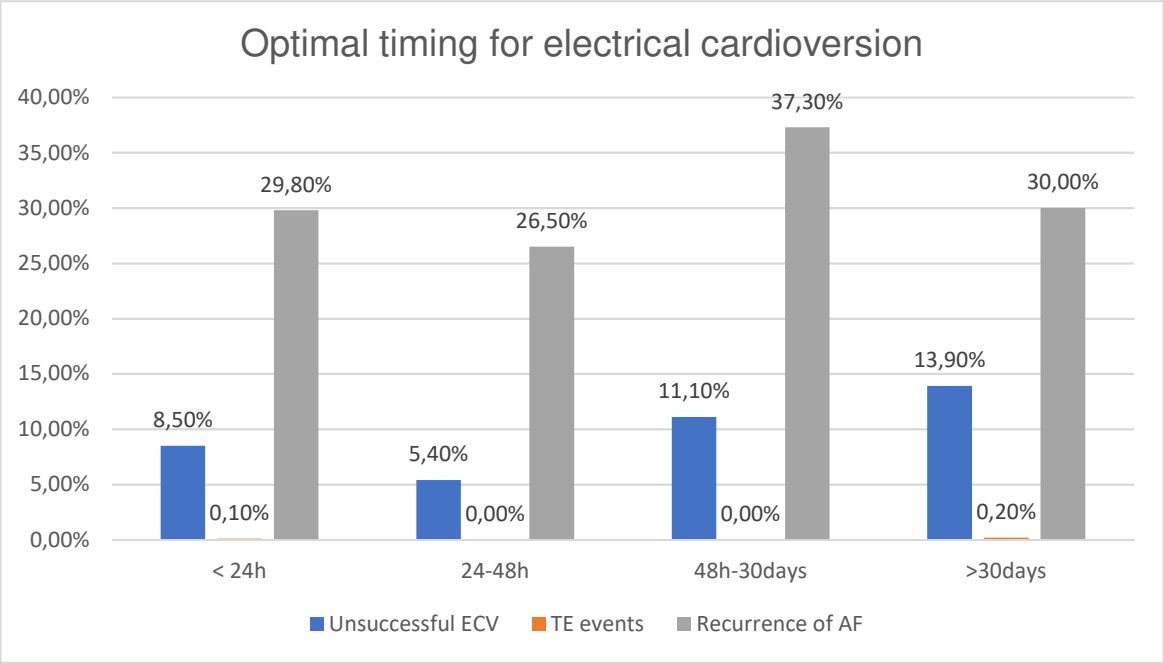


Figure 2 – Optimal timing for electrical cardioversion taking into account the percentage of unsuccessful electrical cardioversions, thromboembolic events and recurrence of atrial fibrillation (data from 3 FinCV studies databases).

The ACWAS trial compares an acute cardioversion vs a wait-and-see approach for recent-onset symptomatic atrial fibrillation in the emergency department, in a total of 437 patients. These patients will be randomized to either standard care (pharmacologic or electrical cardioversion) or the wait-and-see approach, consisting of symptom reduction through rate control medication until spontaneous conversion is achieved, since a great majority of paroxysmal AF resolves spontaneously within 24 hours. This wait-and-see approach is hypothesized to be noninferior, safe, and cost-effective as compared with current standard of care and to lead to a higher QoL.(10)

9. Discussion and Conclusion

Despite all the studies that have recently been conducted to explore what is the optimal timing for cardioversion, there is still no evidence of an ideal period of time in which we should perform, without any doubt, cardioversion in the acute management of paroxysmal AF. This probably has to do with the highly complex pathophisiology of AF, which makes this disease the common final phenotype of multiple distinct pathways. However, it seems that performing ECV in a patient with a duration of AF between the range of 24 hours and 48 hours may be an appropriate option. This is due to the fact that, on one hand, the rate of recurrence of AF is lower if it is realized after 12-24 hours of the onset of AF and, on the other hand, that, although the risk of a TEC is higher after a 24-hour duration period, with the correct peri and postprocedural anticoagulation in all patients (even in those with low CHA_2DS_2-VASc score), this risk can be minimized. By performing ECV in this period, we stop the cardiac remodeling that occurs in AF, which would lead to a progression of AF from a paroxysmal type to a persistent one, preventing the occurrence of consequences of long duration AF, such as symptoms associated with AF and, subsequently, lower QoL; high risk of stroke and TEC; HF and cognitive impairment. Even though cardioverting between 24 to 48 hours from the onset of AF seems to be an appropriate measure to minimize side effects of the process itself and to prevent the progress to persistent AF, further studies are needed. Also, the results of the ongoing ACWAS trial will be important to conclude if the early cardioversion strategy (cardioversion <48 hours) is effectively better than a wait-and-see strategy. Besides that, we must always be aware of the patient preferences and his own characteristics because, for example, females and older people have higher risk of both arrhythmic and thromboembolic complications. Therefore, when choosing the best treatment strategy for a patient, we must take into account the individual characteristics of each patient, since each person is different from another and has an unique probability of recurrence of AF and an individualized risk of complications after ECV.

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