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Pharmacological Cardioversion of Acute Atrial Fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia, and its prevalcence is rapidly rising worldwide, constituting a challenge of both medical and economical significance.

One cornerstone in treating AF is treating atrial fibrillation managing the risk of complications, especially thromboembolisim, through use of anticoagulation. Another is focused on reducing harm caused by AF while maintaining quality of life through either rate control – slowing down the arrhythmia to a managable pace – or rhythm control – striving to maintain normal sinus rhythm through medication and/or cardioversion, i.e. attempting to restore sinus rhythm either by electrical cardioversion or by the use of antiarrhythmic drugs.

This paper outlines the general course of AF, some of the risk factors and treatments with a particular focus on eight antiarrhythmic drugs used in pharmacological cardioversion as well as a glance at the data on pharmacological cardioversions from the FinCV study.

Keywords: atrial fibrillation, cardioversion, pharmacological cardioversion, FinCV

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1 Introduction

Atrial fibrillation (AF) is the most commonly occurring persistent arrhythmia, and the prevalence of AF is rapidly increasing.[1,2] This has been attributed to multiple factors including aging of the population structure as a consequence of increased longevity[2], the worldwide increase in the prevalence of obesity and sleep apnea[3] among others, as well as increased awareness and improving diagnostics[4]. From a public health and cost perspective; it is thus an important issue.

The aim of this paper is to review the literature providing a broad overview of the epidemiology, mechanism, and treatment of AF, subsequently developing a deeper focus on pharmacological cardioversion and finally a brief analysis of the first FinCV dataset with regards to factors influencing the success rate of pharmacological cardioversion.

1.1 Epidemiology and classification

AF is a supraventricular arrhythmia characterized by unorganized electrical and mechanical activity.[5] AF prevalence increases clearly with age, with the risk roughly doubling with every lived decade[6]. In a 2014 review of AF epidemiology in Europe, the European AF prevalence was 0.12%–0.16% in people under 50, increasing to 3.7%–4.2% in people aged 60–70 and eventually 10%–17% in people over 80.[2] Population prevalence estimates range from 1.9% to 2.9% in different European countries[2], and 1-5% in various other countries[7]. The lifetime prevalence of AF has been estimated to roughly 25%.[6,7]

Whether there is an ongoing increase in AF incidence is not as clear. One study noted no or only small increases in incidence[2], while analysis of data from the long-running Framingham Heart Study cohort attributed the increased incidence to better reporting and enhanced surveillance[4]. From a Finnish perspective, an estimated European incidence of 0.23-0.41 new AF cases[2] per 1,000 person/years equates to roughly 1,300 to 2,300 new cases of AF each year in the Finnish population.

In a clinical setting, AF is often primarily classified according to duration. The Finnish Current Care Guidelines distinguish between “acute AF” (<48h since onset) and “persisting AF” (>48h

since onset).[5] *The* European Society of Cardiology (ESC) outlines the following classification and terminology in the 2016 guidelines (Table 1). These definitions are subsequently used in this paper.

AF Pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. AF duration of up to 7 days. This includes AF that is cardioverted within this time.
Persistent AF	AF that lasts longer than 7 days, but less than one year. This includes AF that is cardioverted within this time.
Long-standing persistent AF	Continuous AF > 1 year, but eventually managed with a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). By definition, rhythm control is consequently relinquished.

Table 1 - ESC classification by AF pattern, phrasing slightly simplified.[8]

Over the course of the disease, typically over many years, AF progresses from undiagnosed/symptom-free through paroxysmal AF and persistent AF into chronic/permanent AF[9,10], shifting back and forth between sinus rhythm (SR) and atrial fibrillation either spontaneously or through cardioversion as the disease progresses. However, the initial classification is often a misclassification[8] and the distinction between persistent and permanent AF is sometimes down to the choice of treatment. Thus this classification gives an incomplete picture of disease severity and AF burden.[11]

AF burden, i.e. the share of time the patient on spends in AF compared to SR, is a predictor of stroke risk, and it is becoming more evident that also short bursts of AF pose significant risk. Using cardiac implanted electrical devices, it has been shown that as little as 5 minutes of AF per day increases stroke risk, also in subclinical patients.[12-14]

However, neither ESC class nor AF burden reflects the symptomatic picture particularly well. The modified European Heart and Rhythm Association (EHRA/mEHRA) score[8,15] is a better measure the partly subjective symptoms of AF. Higher EHRA score is, perhaps not surprisingly, associated with both lower quality of life and increased risk of hospitalization, but not with mortality.[16] Several other scoring systems exist, but their utility is uncertain[17], and they are outside the scope of this paper.

Modified EHRA score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF.
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by the symptoms.
3	Severe	Normal daily activity affected by symptoms related to AF.
4	Disabling	Normal daily activity discontinued.

Table 2 - The modified EHRA score[15]

1.2 Pathophysiology and activation mechanism

AF can also be classified according to its initiation mechanism. AF typically starts as a consequence of repeated atrial extrasystole, often originating close to the pulmonary veins.[9] As the atria are heavily innervated by both sympathetic and parasympathetic ganglia, it is not surprising that dysregulation of the autonomic nervous system can contribute to increased AF occurrence through several complex mechanisms.[18] Increased sympathetic tone, caused by e.g. acute stress or exercise, causes increased heart rate and cardiac load, reducing atrial refractoriness and initiating AF. It has been shown in several animal models that it is possible to inhibit this effect by disrupting the sympathetic innervation or providing low-level parasympathetic stimulation.[18-20] Conversely, in vagal AF, increased parasympathetic tone during rest, sleep or postprandially also leads to reduced atrial refractoriness.[18] This is common in younger AF patients, where onset of AF occurs during sleep and often resolves a few hours later in the morning.[21] In animal models, increased AF caused by increased vagal tone has been demonstrated in experiments involving both endurance exercise and sleep apnea models.[18,22,23]. This seems to be a significant part of the mechanism through which aging endurance athletes tend to develop persistent or permanent AF.

The occurrence of atrial fibrosis has been repeatedly histologically demonstrated in animal models of AF, and the consequent changes in endocardial conductivity seem to be playing an increasingly significant role. Using increasingly sophisticated electrophysiological mapping "baskets", with 64-252 electrodes and progressively improving algorithms this can now be mapped in humans in vivo, as fibrotic areas display reduced electric conductivity and lines lacking electric conductivity. This has increasingly demonstrated two different sustaining mechanisms in AF: areas of rotating activation ("rotors") and ectopic focal activation ("foci").[9] Increased duration of AF has been linked to an increased number of rotors and foci, as well as differences in the distribution of these areas. This progressively more detailed picture of the

electrophysiological mechanisms in AF has been utilized in the development of more effective ablation techniques, but the results are still somewhat contradictory.[9,24,25]

2 Management of AF

The clinical management of AF can grossly be divided into three parts:

- Management of risk factors - prevention of occurrence or recurrence of AF.
- Management of risk of sequelae – anticoagulation
- Management of the arrhythmia - rhythm and/or rate control.

2.1 Manageable risk factors

Many of the risk factors for AF are not manageable, e.g. age, sex and familial/genetic factors, and age and sex are the strongest predictors of AF, as every decade roughly doubles the risk of developing AF, and males have a 50% higher lifetime risk[6]. Variants in both ion-channel and non-ion-channel genes have been linked to AF, otherwise mostly considered a sporadic, non-genetic disorder.[26]

However, many risk factors for AF are very manageable. These are often closely related to lifestyle, including obesity, hypertension, diabetes, sleep apnea, sustained endurance exercise and the consumption of alcohol and tobacco. The following points denote some of the key features of these risk factors. It is prudent to note that this is not an exhaustive list of established risk factors, and evidence for others is continuously accumulating.

- Obesity increases AF through increased cardiac load as well as several of the factors listed below. It is associated with a hazard ratio of 1.39-1.75 already at BMI 25-30 and 1.99-2.35 at BMI over 30.[6] At every step BMI increases, the risk of AF increases by 3-7%, depending on duration.[27] A weight reduction of >10% was associated with a 6-fold increase in arrhythmia-free survival compared to lesser weight loss in one study.[28]
- Diabetes is associated with risk ratio of 1.4-1.6 for AF.[6] While many risk factors are shared, diabetes is an independent risk factor for AF, where longer disease duration and worse glycemic control increase the risk of AF.[29]

- Hypertension is a well-documented, common but relatively modest risk factor for AF, with a risk ratio of 1.2-1.5.[6,30] This risk seems to be reversible, as one study designed to lower blood pressure through renal sympathetic denervation demonstrated the reversibility of fibrosis, reduced ventricular mass as well as improved atrial conduction. It is however unclear whether part of this effect was due to direct effects of the renal denervation.[31]
- Extensive endurance training is a known risk factor particularly in lone AF, i.e. the occurrence of AF without significant comorbidity. One study found a threshold of a cumulative 1,500 hours of sport practice[32], a surprisingly low number considering that it entails a significant risk of developing AF (HR = 2.87). A study of exercise habits in the elderly found that moderate but not vigorous exercise decreased incidence of AF by 28% compared to no exercise.[33]
- Obstructive sleep apnea (OSA) and AF share many risk factors (obesity, alcohol overconsumption, autonomic dysregulation, diabetes) but OSA is an independent risk factor for AF, with an approximately 4-fold risk of developing AF.[6,34] Along with weight loss, CPAP remains the gold standard treatment for OSA, and has additionally been shown to decrease AF recurrence after catheter ablation.[35]
- While heavy drinking is a well-documented risk factor for atrial fibrillation, with a HR of 1.34 to 1.46 for new-onset AF[6,36], there seems to be considerable individual variability in the arrhythmogenic effect of alcohol. Moderate consumption seems to have very little effect on AF, while heavy consumption is associated with increased AF at least in men. “Holiday heart”, i.e. AF associated with binge drinking and/or withdrawal has been speculated to be due to increased noradrenergic activation as well as decreased vagal activation.[6] Sobering up often restores sinus rhythm without (other) intervention.
- Tobacco consumption is associated with a significant increase in AF risk. Specifically, a smoker has a hazard ratio of 1.51–2.05 compared to a never-smoker, and a former smoker somewhat less. The risk seems to be dose-dependent.[6,37,38]

2.2 Anticoagulation treatment

Oral anticoagulation (OAC) is the keystone treatment for managing the risk of thromboembolic complications (TEC), as AF is present in at least 20-25% of stroke patients

and stroke risk in AF patients is twice that of those in sinus rhythm.[5] Several significant changes have occurred in OAC in the recent years, among others the widespread use of new oral anticoagulants (NOAC) and the increased awareness of periprocedural TEC risk in cardioversion.

The 2017 Finnish Current Care Guidelines (CCG) recommend The CHA_2DS_2-VASc score for evaluating the risk of TEC; albeit with a slight modification - female sex adds one point only over the age of 75 in the Finnish version of the score. Thus the scoring system and cut-offs differ from the ESC guidelines, as the Finnish guidelines use the same cut-offs for both sexes.[5,8]

Factor		Score
C	Congestive heart failure (signs/symptoms or reduced LVEF)	1
H	Hypertension: RR >140/90 mmHg at rest repeatedly (or medication)	1
A_2	Age ≥75years	2
D	Diabetes (fasting glucose >7 mmol/L or medication)	1
S_2	Stroke or TIA or other thromboembolism	2
V	Vascular disease (ASO, MCC, vascular dementia etc.)	1
A	Age, 65–74 years	1
Sc	Sex category (female, counts only if age over 75)	1

Table 3 – Modified CHA_2DS_2-VASc score recommended by the Finnish CCG[5]

The Finnish CCG recommends OAC for patients with high risk for TEC, i.e. CHA_2DS_2-VASc ≥ 2, with an NNT of < 85, or even < 15 at CHA_2DS_2-VASc scores of 3 or higher.[5] For patients with CHA_2DS_2-VASc = 1, the CCG recommends individual assessment of the risks and benefits of OAC, including bleeding risk and thromboembolism risk factors not included in the CHA_2DS_2-VASc, e.g. smoking[39], dyslipidemia[5] and renal dysfunction[40,41]. For patients with CHA_2DS_2-VASc = 0, no anticoagulation is recommended. Acetyl salicylic acid is not recommended for stroke prevention in AF at any risk level, as it inefficient in stroke prevention but increases bleeding risk significantly, at levels comparable to warfarin.[5,8]

The HAS-BLED score, published in 2010[42], is a useful predictor of bleeding risk, see table 4. Patients with a high HAS-BLED score, particularly if they score higher on HAS-BLED than CHA_2DS_2-VASc, require a careful evaluation of the risks and benefits of oral anticoagulation.[5] However, most of the risk factors for bleeding, can be managed and reduced, and seldom pose a greater risk than the lack of anticoagulation, even in the elderly and frail.[5,43]

Factor		Score
H	Hypertension, i.e. >160 mmHg systolic blood pressure	1
A	Abnormal renal function, severe OR Abnormal liver function, severe	1 + 1
S	Stroke	1
B	Bleeding risk, e.g. anemia, thrombocytopenia, bleeding history, cancer	1
L	Labile INR, i.e. TTR < 60%	1
E	Elderly, i.e. age over 65 years	1
D	Drug or alcohol usage history (≥ 8 drinks/week) OR Medication predisposing to bleeding (NSAID etc.)	1 + 1

Table 4 – The HAS-BLED bleeding risk scale[42]

Anticoagulation is well supported in cardioversion (CV) of AF with duration >48 h, requiring NOAC or warfarin at therapeutic levels for 3 weeks before elective CV, and continuing for at least one month after CV.[5] However, the 2010 (and the 2012 update) ESC guidelines still considered cardioversion of acute AF (duration <48h) without previous anticoagulation acceptably safe in all patients, using only unfractionated or low molecular weight heparin perioperatively.[44,45] Post-CV OAC was considered based on CHA_2DS_2-VASc score, as outlined previously. However, in 2013 the FinCV study demonstrated a heightened stroke risk after CV of acute AF, with a 0,7% rate of TEC within 30 days after CV. The vast majority of the 38 TEC were TIA (n=4) or stroke (n=31). The median and mean interval between CV and TEC were 2 and 4.6 days respectively, pointing at a clearly increased risk in the days following CV, particularly in several identified subgroups. The difference in risk between electrical and pharmacological cardioversion was insignificant (p=0.32).[46] The FinCV study also demonstrated that CV without anticoagulation within 12 hours of onset of AF is significantly safer than CV in the 12-24 and 24-48 hour windows, with OR of 4.0 and 3.3 respectively.[47]

The Finnish CCG points to using the CHA_2DS_2-VASc score for evaluating TEC risk in CV of acute AF, suggesting that in low and medium risk patients (CHA_2DS_2-VASc 0-1) no pre- or post-CV anticoagulation is necessary, while in high-risk patients (CHA_2DS_2-VASc ≥ 2) NOAC or warfarin + LMWH should be started before CV.[5] The 2016 ESC guidelines have very little to say about the anticoagulation of acute AF, noting the need for further research whether there is a "safe" window for CV.[8] The 2019 update to the American Heart Association's recommendation for AF similarly points this out that the evidence for the safety of CV of acute AF without anticoagulation is limited.[48]

A decent treatise of NOACs is outside the scope of this paper, but in brief: dabigatran, rivaroxaban, edoxaban and apixaban have progressively revolutionized anticoagulation, and are as safe as or safer than warfarin, despite several of these lacking direct antidotes, and as efficient or better in preventing TEC.[8,49]

2.3 Management of arrhythmia - rhythm vs. rate control

Six key points for long-term pharmacological treatment of AF were outlined in the 2010 ESC guidelines: Treatment should aim to reduce symptoms and success may mean to reduce rather than eliminate recurrence of paroxysmal AF, efficacy of antiarrhythmic drugs (AAD) is limited, and if one fails another may be more successful. Pro-arrhythmic side-effects are common and safety should be considered the primary guiding factor, rather than efficacy alone.[8,44] These are still relevant to pharmacological treatment pursuing both rhythm and rate control, and largely applicable to short-term treatment and pharmacological CV.

Rate control, i.e. accepting AF and focusing therapy on minimizing the negative effects and risks of AF, aims to maintain left ventricular function, cardiac output and quality of life while reducing symptoms and tachycardiomyopathic effects. Rate control should be considered the primary strategy for the elderly and asymptomatic patients, as it has been shown to be non-inferior.[8,50]

Rhythm control is a broad concept. It includes pursuing sinus rhythm by medication, CV and electrophysiological or surgical intervention. Counterintuitively, there is no convincing evidence to suggest that active rhythm control would improve long term outcomes.[8] Preliminary results from the recent CABANA trial seem to close another open question, indicating that catheter ablation offers no significant advantages over optimal medication, i.e. no reduction in risk of death, disabling stroke, serious bleeding, or cardiac arrest.[51,52]

However, rhythm control is still suggested in the following patient groups: [8,15,50]

1) Symptomatic patients, i.e. a modified EHRA score of 2b or higher.
2) Patients with heart failure where AF increases symptoms
3) Young patients, at least as an initial approach when invasive treatment has not been ruled out, as prolonged AF before ablation may reduce chances of ablation success.
4) Secondary AF, e.g. in hyperparathyroidism and ischemia.

2.4 Classification and mechanisms of antiarrhythmic drugs

Miles Vaughan Williams originally proposed a four-part classification of antiarrhythmic drugs in 1970 and added the subdivision of class 1 into 3 subclasses in 1984.[53] While newer systems of classification have been proposed[54], the Vaughan Williams classification is still stands at the core of it, and as such is worth a short consideration regarding the antiarrhythmic drugs available in Finland.

However, as our understanding of the molecular mechanisms of the action potential and plethora of variants that exist among ion channels has increased dramatically since the days of Vaughan Williams, this short treatise is bound to be a simplification, as delving into the details of the various receptor affinities of each drug is outside the scope of this text. The comprehensively updated and expanded classification proposed by Lei et al in 2018 is worth looking into for further details and references.[54]

Class 1 consists of drugs inhibiting voltage gated sodium ion channels, reducing maximum rate of depolarization. Based on their differing dissociation rates, these drugs are further subdivided into classes 1a (intermediate dissociation kinetics), 1b (fast dissociation kinetics) and 1c (slow dissociation kinetics), which partly account for their different profiles.

Class 1a drugs include quinidine and disopyramide, both of which are still available by special permission ("erityislupavalmiste"). While these had some utility in the prevention of recurrence of AF[8,55], increased mortality (up to twofold in quinidine[56]) in patients with coronary heart disease and heart failure, significant pro-arrhythmic effects (Torsades de Pointes) and the availability of safer options have all but eliminated their usage significantly in the last decade.

Class 1b is best known for lidocaine, which indeed has a place alongside amiodarone in the management of acute ventricular arrhythmias. However, it lacks any significant efficacy in cardioverting AF, as in one study none of twenty AF patients administered lidocaine converted to sinus rhythm (CI 0-14%)[57].

Class 1c is the newest group, of which flecainide and propafenone are available in Finland, although propafenone only by special permission. Flecainide is commonly used both for pharmacological CV and rhythm control, and propafenone is pharmacodynamically rather similar but with a greater variability in pharmacokinetics. Both have significant

proarrhythmic effects due to a paradoxical increase in ventricular rate due to faster AV nodal conduction and/or conversion to 1:1 flutter, and both are contraindicated in patients with previous ischemic heart disease, myocardial infarction and/or heart failure. [5,56]

Class 2 consists of drugs affecting the sympathetic nervous system, in newer classifications on both the sympathetic and parasympathetic side[54], some of which are under development. In practice, the drugs that are currently clinically available in Finland are beta blockers with their varying pharmacodynamics- and kinetics, metoprolol and bisoprolol being the most commonly used[58].

Class 3 consists of drugs prolonging repolarization by blocking voltage gated potassium ion channels, and these are rather diverse. Dofetilide is the rare example of a "pure" potassium channel blocker, but not available in Europe, however, the closely related drug ibutilide is occasionally used for pharmacological CV or drug-assisted ECV in AF resistant to ECV. Amiodarone, useful for both CV and maintaining sinus rhythm, possesses traits from all of classes 1-4. Dronedarone is an amiodarone analogue, but does not contain iodine and has a somewhat different profile. Sotalol, a beta blocker, also exhibits class 3 effects at higher doses and is sometimes classified as class 3.[8,54]

Class 4 consists of the non-dihydropyridine calcium ion channel blockers, in Finland diltiazem and verapamil. While these have some utility in rate control, neither verapamil nor diltiazem have been shown to be efficient in pharmacological CV or enhancing electrical cardioversion (ECV) probability.[8,59,60]

Additionally, several drugs do not conform clearly to any of the classical classes, as they have different mechanisms: digoxin and vernakalant are two that are relevant in AF and are discussed separately in the next section.

Adenosine, mostly utilized in CV of non-AF supraventricular tachycardia, activates G-protein coupled receptors, which through K-channel activation shortens the action potential, causes hyperpolarization and reduces automaticity, thus often terminating the tachycardia.[56] While adenosine may have a place during electrophysiological examinations, there seems to be no indication that adenosine would be effective in CV of AF.

3 Electrical cardioversion

Synchronized biphasic ECV with anterior-posterior electrode placement is the gold standard of comparison for restoration of sinus rhythm in acute AF[8], with a success rate typically in excess of 90 %, in one study 94% when including all AF durations (n=88)[61]. It is the only useful method of CV in persistent or permanent AF, as pharmacological CV quickly loses its efficacy as AF is prolonged.[5,8] While immediate cardioversion is indicated in hemodynamically unstable AF patients in order to restore cardiac output, regardless of the conventional contraindications previously outlined[8,50], ECV in stable patients should only be undertaken without anticoagulation if a thrombus can be ruled out by transesophageal echocardiography[62,63]. If ECV is performed on non-acute AF without anticoagulation, the risk for thromboembolism is significant, 5-7%[5,64,65].

The major drawback for elective ECV is the requirement of anesthesia, and thus also an anesthesiologist or other physician sufficiently proficient in anesthesia. Thus, CVs are concentrated to hospital settings for patient safety. Additionally, a 4 hour period of fasting is required before anesthesia, although ECV can be performed following rapid sequence induction and intubation if hemodynamically necessary. Anesthesia is commonly performed with propofol, although midazolam and others may also be used. With propofol, the two most common anesthesia complications are apnea, requiring ventilation, and hypotension, occasionally requiring vasoactive agents such as etilefrine.[66] Significant electrical burns are very rare, but mild burns occasionally occur.

Non-transient asystole and/or bradycardia is rare, 0,9% in the FinCV study, but may require resuscitation, chronotropic medication and/or external pacing, and is often indicative of a problem in the sinoatrial node, with slightly less than half of these patients eventually getting a pacemaker.[67]

4 Pharmacological cardioversion

Pharmacological CV, by definition, is the restoration of sinus rhythm by the use of antiarrhythmic drugs, i.e. a form of acute rhythm control. The obvious advantage is the lack of need for anesthesia and pre-intervention fasting, thus allowing for a greater availability and flexibility of use outside of hospital settings. The clearest limitation, on the other hand, is the

somewhat lower efficacy of pharmacological CV compared to ECV, as well as the contraindications and side effects of the drugs used. As with the treatment of all AF, electrolyte levels should be checked before CV, and adequate hydration levels ensured to avoid unnecessary complications.

The following sections will outline the efficacy, benefits, indications and contraindications of the antiarrhythmic drugs used for rhythm control of AF in Finland.

4.1 Beta blockers

In primary and first aid/emergency care settings, beta blockers tend to be the first drug administered to patients with acute AF, often in the form of intravenous metoprolol, or sometimes oral bisoprolol or metoprolol, since these are well tolerated with few side effects.

While there are significant variations across patients regarding the negative inotropic and chronotropic effects of beta blockers, sharp declines in maximum cardiac output is rare at therapeutic doses. However, significant decompensation is a contraindication, as additional reduction in cardiac output can cause hemodynamic crashing.[56,68] On the other hand, tachycardic patients with relatively mild hypotension usually tolerate beta blockers well, in part due to the fact that at reduced heart rate improves ventricular ejection fraction.

Bradycardia, advanced peripheral artery disease and conduction abnormalities (e.g. atrioventricular block gr. II and III, sick sinus syndrome) are stricter contraindications, as beta blockers may exacerbate these conditions. Asthma and diabetes similarly warrant awareness of the potential side effects, but significant adverse events are rare.[68]

While beta blockers do have the advantage of slowing the AF to a pace that is more economical, there is no evidence that beta blockers would possess any significant efficacy as pharmacological CV drugs or ECV enhancers compared to placebo.[8,69] However, as beta blockers are so commonly administered and a significant portion of AF cases self-terminate, a misappropriation of clear causality seems to be quite common, both among patients utilizing a pill-in-the-pocket beta blocker approach as well as some physicians.

Ultrashort-acting beta blockers have, however, been suggested for CV. In a Japanese review, a CV success rate of 50-75% with landiolol was noted.[70] This was, however in an ICU setting, and does not offer any clear conclusions for usage outside the ICU.

Sotalol, a beta blocker, is often grouped among class 3, as it exhibits group 3 properties at higher doses. Curiously, sotalol is racemic mixture of two stereoisomers, of which l-sotalol is mainly responsible for the beta-blocking while d-sotalol provides the class III properties. Among beta blockers, sotalol has the rare property of being pro-arrhythmic, with TdP incidence commonly cited at 2-4%. However, a recent review points out that TdP becomes significantly rarer as long as prolonged QT-interval and EF < 35% is considered as contraindications, citing incidences as low as 0,1%.[71] In another systematic review, sotalol was found to be as effective as class 1a, 1c and amiodarone in CV of AF, and only high dose ibutilide to be more effective.[72] With a linear pharmacokinetic profile, rapid onset, and good efficacy, sotalol could provide a viable alternative both for CV as well as use in other niches such as AF prevention after coronary bypass.[71]

4.2 Digoxin

Cardiac glycosides had been utilized for several centuries before in 1785, William Withering published his findings regarding digitalis and its usefulness in dropsy, i.e. peripheral edema seen in heart failure. By trial and observation, Withering learned to dose digitalis to obtain diuresis but avoid excessive toxicity.[73]

The pharmacodynamics- and kinetics of modern digoxin, the active ingredient of *Digitalis lanata*, are complex. Digoxin acts as both an inhibitor of myocardial Na+/K+ ATPase, which leads to an increased level of intracellular calcium, causing a positive inotropic effect[56], giving it its unique position as the only inotrope currently in outpatient usage, a valuable tool for treating heart failure.

Additionally digoxin increases parasympathetic activity on several levels, among these activating CNS vagal centers and by increasing baroreceptor sensitivity. The overall effect is negatively chronotropic through hyperpolarization and increased refractory of myocytes as well as slowed AV-node conduction.[54,56] These effects give digoxin it useful properties for rate control, although it should be noted that AV-block may also occur, and 2° and 3° AV-block is a contraindication, as is hypertrophic obstructive cardiomyopathy and Wolff-Parkinson-White syndrome.[68]

As oral digoxin reaches its steady state concentrations slowly over approximately a week, digitalization per os is slow. In an acute situation, rapid digitalization can be achieved in a few

hours using intravenous administration, with individualized starting doses of 250-1000ug. Follow-up and digoxin concentration monitoring is essential, as digoxin toxicity increases rapidly at plasma concentrations above 1,5 ng/ml, not much above the therapeutic upper limit. Symptoms include general malaise and a variety of arrhythmias, and renal insufficiency and hypokalemia are among the most common risk factors.[56,68] Besides cessation of medication, treatment may include iv potassium, magnesium, atropine or lidocaine for arrhythmias as well as specific antibodies.[56,68]

While digoxin is commonly used as the second drug of choice in primary care, as it is readily available, it is suitable for use only when the primary goal is not immediate CV, as digoxin has not been shown to be useful in pharmacological CV or in enhancing ECV success likelihood.[8,74]

4.3 Flecainide

Flecainide is, despite its contraindications and side effects, well suited for CV, particularly as it is available and effective not only intravenously but also orally.

When choosing which AAD to ordinate, the essential question eventually becomes, which drug is the best one in which situation? A 2012 meta-analysis by Bash et al, analyzing 2433 patients[75] can begin to shed light on this, as this analysis compared the efficacy of several AAD:s for CV of acute AF (<48h) within two timeframes: 0-2 hours and cumulatively 8-24 hours after drug administration:

Treatment	n	CV rate by 2 h	CV rate 8-24 h
Placebo	583	11.8 %	48.2 %
Flecainide - oral	40	67.5 %	80.6 %
Flecainide - IV	234	63.7 %	69.9 %
Propafenone - Oral	326	21.2 %	78.7 %
Propafenone - IV	301	50.8 %	81.9 %
Amiodarone - Oral	43	9.3 %	87.1 %
Amiodarone - IV	266	16.2 %	61.2 %
Vernakalant - IV	365	51.8 %	N/A

Table 5 – Acute AF CV rates from 2433 patients[75]

Table 5 contains many worthwhile observations, the first of which is that the placebo CV rate by 24 hours is a stunning 48 % (n=583), but only 12 % by the 2 hour mark, raising an

interesting question in whether CV should be attempted at all before the 24-hour mark, in order to avoid unnecessary interventions in stable patients with acute AF? Then again, the increased risk of TEC after the 12 hour mark indicates that sooner seems to be better than later.[47]

Along this line of reasoning, short time to CV is one hallmark of a good CV drug, and flecainide certainly makes the mark, with 64% (iv) and 68 % (oral) CV rates respectively within the 2 hour window, making it significantly faster, with very credible OR of 9.63 (95% CrI 2.38–36.26) and 11.43 (95% CrI, 1.29–99.12) respectively. Oral flecainide achieves significance also at 8-24 hours with OR 6.53 (95% CrI 1.24–39.58), while IV flecainide does not. Similar results have been noted in another review.[76]

Although efficacy definitely backs flecainide as a good choice for pharmacological CV, previous myocardial infarction is a strict contraindications due to increased mortality demonstrated in long-term use[77], however, in mild ischemic heart disease the use of flecainide is considered acceptable[56]. Heart failure is another contraindication, as proarrhythmia tends to manifest mostly in patients with structural heart disease[56], although besides this a mild negative inotropic effect has also been demonstrated in healthy patients[78]. As flecainide may paradoxically increase ventricular rate due to faster AV nodal conduction and/or conversion to 1:1 flutter, pre-administration with a beta blocker is highly recommended and atrial flutter is naturally a contraindication. As flecainide sometimes causes post-CV bradycardia, 2° and 3° AV-block, abnormal sinus node function and widened QRS complex, whether due branch blocks or otherwise, are also contraindications.[5,56] However, it is possible to use flecainide to treat acute AF associated with WPW, as flecainide slows conduction through accessory pathways as well.[5] Care is required in patients with severe hepatic or renal insufficiency.[68]

Flecainide is an effective way to prevent recurrent AF, but regular ECG monitoring for signs of TdP is recommended at baseline and daily during days 1-3 of flecainide use. This protocol is recommended for propafenone and sotalol as well.[8] Once safety has been established, flecainide can be used for pill-in-the-pocket patient-controlled CV. One study found that this approach had a success rate of 94% and very limited adverse events, concluding that this method of CV is acceptably safe.[79]

Finally, when all else is equal, flecainide has the benefit of being cheap – a single dose of 300mg flecainide currently costs less than 2€, while another popular method for CV, IV

vernakalant, which currently costs 510€ per dose.[68] The difference will inescapably add up over time.

4.4 Propafenone

While the CV efficacy of propafenone is at least on the same level as flecainide, albeit perhaps a bit slower[75] – see table 5 above - propafenone offers few if any clear advantages over flecainide, except for being another option to try in case flecainide causes deal breaking non-cardiac side effects.

On the downside, propafenone comes with all the challenges and contraindications of flecainide, with the addition of more variation in pharmacokintetics[56], and the need to reduce doses already in mild and moderate hepatic insufficiency. To top it off, propafenone is no longer available without special permission.[68] All in all, flecainide is the go-to class 1c drug, and propafenone a second option.

4.5 Amiodarone

Amiodarone is usually classified as a class III AAD, and can be more specifically described as a non-selective blocker of voltage dependent potassium channels, prolonging refractory time, action potential recovery time and decreasing re-entrant tendency, as well as other effects mimicking the other AAD classes.[54] While Amiodarone comes with clear drawbacks in other areas, its main advantage is that it may be used also in unstable patients with significant structural or ischemic heart disease including acute myocardial infarction[8], even when ejection fraction is severely reduced, although most studies tend to exclude patients with severe heart failure.[8,80] Amiodarone has almost no negative inotropic effect, a clear advantage compared to class 1c drugs,[56] although cases of worsening heart failure have also been reported with amiodarone as well. CV success rate varies, coming in at 34-95% depending on dose, treatment regimen (iv bolus vs infusion) and patient subgroup.[81]

Due to its slower pharmacokinetics, in comparison to flecainide, amiodarone infusion is slower and the efficacy of amiodarone is inferior up to 8 hours after initiation of treatment, but similar at 24 hours after initiation of treatment.[75,82] Lengthening of QTc is a quite frequent side effect, but subsequent proarrhythmic adverse events are quite rare.[5,68]

Long-term use of amiodarone comes with significant risks of extracardiac complications, and although these are rare in short-term usage for CV[56], acute complications do occasionally occur also in as little as 24 hours[68]. As amiodarone is potentially highly pneumotoxic, initial chest x-ray is mandatory and spirometry highly recommended if time allows. If the patient displays respiratory symptoms during or after amiodarone usage, repeat X-ray or computed tomography, spirometry and diffusion capacity testing are warranted, as well as cessation of amiodarone. Resulting interstitial pneumonitis is often reversible, but fatal cases have also occurred. Similarly, amiodarone is hepatotoxic, and monitoring of transaminase levels is warranted. Acute liver toxicity within 24 hours of starting amiodarone infusion has been reported, and adequate initial follow-up is required. Amiodarone occasionally causes iatrogenic thyreotoxicosis, wherefore initial evaluation and follow-up of TSH, T4v and T3v is needed.[5,8,68]

Outpatient follow-up of ECG, ALAT, ASAT, AFOS, bilirubin, TSH, T4v, T3v, Na, K and creatinine / GFR, is recommended at 3, 6 and 12 months after initiation and annually thereafter, and spirometry and chest x-ray if needed.[56] Amiodarone also has significant interactions with many drugs, including warfarin, dabigatran, class 1a, 1c other class III and class IV AADs, several antipsychotics, antidepressants, antibiotics and antimalarial drugs.[68] Although beta blockers may cause additional negative inotropic balance, a small dose of beta blockers is generally recommended alongside amiodarone for prevention of pro-arrhtythmia.[56]

Due to its plethora of possible adverse effects and interactions, long-time treatment with amiodarone is not a first-line treatment but practically the drug of choice where class 1c is contraindicated and beta- and calcium channel blockers insufficient.[80] Whenever possible, after a steady state dose and effect has been established, it is prudent to strive to use as low a dose as possible. As noted previously, sotalol may in light of a recent review be a worthwhile alternative[71], although some studies have found sotalol to be an inferior alternative to amiodarone for CV and recurrence prevention[8,83].

4.6 Dronedarone

To the best of my knowledge, data on the efficacy of dronedarone used as a pharmacological CV drug have not been published, nor has any conclusive data on whether dronedarone might

enhance ECV success rates. However, as an amiodarone analogue, it is worth a brief consideration for its role in AF recurrence prevention.

Like amiodarone, its several decades newer sibling dronedarone possesses traits from all AAD classes, but displays several important differences. One mixed treatment comparison indicates that in long term use, although not quite as good as amiodarone for sinus rhythm retention, dronedarone is associated with to fewer serious adverse and proarrhythmic events than other AADs including amiodarone.[84]

As dronedarone, unlike amiodarone, does not contain iodine, it has significantly less thyroid complications than amiodarone. However, dronedarone is contraindicated in heart failure (increases mortality) and permanent AF (increases mortality), and thus its usage more limited than that of amiodarone. Additionally, toxic reactions to the liver or lungs from amiodarone also constitute contraindications. Liver toxicity seems to be more common than in amiodarone, and monthly transaminase monitoring is warranted during the first 6 months of use, and at regular intervals after that.[5,8,68]

In summary, careful patient selection and proper monitoring by a cardiologist is key to commencing dronedarone successfully, and dronedarone reduces AF-related hospital visits[8]. However, if and when AF becomes chronic, dronedarone should be terminated.[5,68]

4.7 Ibutilide

The capabilities of ibutilide, a quite pure potassium ion channel blocker, are well documented both when used as a CV drug and as an ECV enhancer.[85-88], It is a particularly effective drug when it comes to atrial flutter, which otherwise tends to be more treatment-resistant than AF. CV success rates have been reported at 31-61.5% in AF and 63-90% in atrial flutter. [85-87]

The most common side effect is proarrhythmia, which relegates ibutilide to be used by specialists well familiar with it. TdP occurs quite frequently, cited as high as 4-8% of CVs in one evidence review, along with other arrhythmias as well, occasionally persisting long enough to warrant electric CV[87]. Cardioversion with ibutilide is generally very fast, with a mean time to sinus rhythm at 27 min (n=266), and pro-arrhythmic complications tend to develop within a similar timeframe.[86] If CV does not succeed within 1 hour of ibutilide administration, ECV may be performed.[68]

Ibutilide can also be used to aid ECV if ECV at maximum energy fails, and the infusion can be performed under the same anesthesia. This is particularly helpful in case of ECV resistant atrial flutter.

While it is effective, it should be noted that ibutilide is contraindicated in 2° and 3° AV block, sick sinus syndrome, even marginally prolonged QTc (>440ms) and bradycardia below 50/min.[5,8,68]

It is worth noting that ibutilide is currently the most expensive drug reviewed, as a single adult dose currently costs 598€, and two doses may be used if the first fails to produce sinus rhythm within 10 minutes.[68]

4.8 Vernakalant

Vernakalant is the most recently released AAD on the Finnish market, released close to 10 years ago. When it was released, it was marketed as a fast, safe replacement for ECV, and has admittedly lived up to its promises quite well. The efficacy in short-duration AF (<72h) is good, with CV occurring in 61% of patients in one trial, and 53% retaining normal rhythm at 60 minutes after administration the first dose of vernakalant infusion.[89]

Efficacy decreases clearly the longer the AF duration is, as was clearly shown in one study demonstrating a 52% vernakalant CV efficacy with AF of 3 hour to 7 day duration (n=145) and 11% efficacy with 8 to 45 day AF duration (n=75).[90] One Finnish study found vernakalant to be more effective than iv flecainide at 120 min post-administration (63% vs 47% PCV rate, n=200, p=0,00IV[91], although as has been noted earlier, oral flecainide seems to display a higher efficacy. Unfortunately, vernakalant is no better than placebo for atrial flutter.[92]

Pharmacodynamically vernakalant is different from most other AADs, as its effect seems to be primarily based on blocking ultrarapid potassium ion channels, which are primarily expressed in the atria but not in the ventricles. This, along with several other effects of vernakalant, increases in action potential recovery time and refractory period while reducing reentrant tendency.[8,54,56]

Vernakalant has few side effects. By 2014, the only documented vernakalant-related case of TdP occurred in a patient that accidentally received both ibutilide and vernakalant[92], suggesting that vernakalant does not cause TdP. Side effects of vernakalant include temporary

disturbances of taste, sneezing, bradycardia and hypotension, the latter two of which are also contraindications. Other contraindications are moderate to severe heart failure, (NYHA III-IV), 2° and 3° AV block, severe aortic stenosis, QTc >440 ms, acute coronary syndromes within 30 days and previous administration of class 1 or 3 AADs within at least 4 hours.[8,56,68]

5 The FinCV Study

5.1 Methods

The Finnish Cardioversion - FinCV - study (ClinicalTrials.gov Identifier: NCT0138057[93]) is a multicenter retrospective study primarily investigating the incidence of thromboembolic complications within 31 days of cardioversion. All adults diagnosed with AF or atrial flutter in two university hospitals and one secondary hospital between 2003 and 2010 were included. Extensive data was gathered on each included patient, including CHA_2DS_2-VASc and HAS-BLED scores. The usage of a multitude of AADs and anticoagulants at CV as well as when the patient was discharged were recorded. In total, 7728 events were recorded from a total of 3181 patients.

From a pharmacological CV perspective, this dataset is problematic, as it did not record whether CV was primarily intended to be pharmacological or whether it was always intended to be electrical, and thus it is not possible to draw clear conclusions regarding the efficacy of AADs, as an attempted CV that does not produce sinus rhythm within a few hours in the emergency room easily turns into an ECV due to either medical or logistical reasons, and is thus recorded as an ECV. Conversely, the same drug may also be part of the patient's regular medication thus recorded as medication used at ECV, or the patient may return to sinus rhythm spontaneously without any extra doses of AADs.

Naturally, AADs used only for CV such as ibutilide and vernakalant would be clear-cut cases, however, neither of these were included in the dataset. As this is a clear methodological limitation, no further analysis attempting to ascertain whether there are significant differences in pharmacological and electrical CV efficacy in this dataset will be attempted, but some descriptive statistics may still provide insight.

Analysis was performed with SAS JMP 13.1. and Excel 2010 for Windows.

5.2 Results and discussion

In this dataset, just 753 CVs, (9,7%) were recorded as non-electrical, i.e. pharmacological. Of these, the most commonly recorded drug was flecainide, mostly with a beta blocker or as monotherapy, followed by beta blocker monotherapy and no medication, which is essentially just spontaneous termination of AF. Arguably, in the light of the literature, the same can be said of the patients with no medication noted. All other AADs had frequencies under 10, propafenone, a well-established AAD effective in CV had as little as two cases. Recorded CV success rates in the data set ranged from 91-100%, clearly indicating a selection bias.

	n	**Share of Pharmacological CV events**
Flecainide total	527	69,72 %
Flecainide and BB	*408*	*54,18 %*
Flecainide only	*72*	*9,56 %*
Beta blocker only	114	15,14 %
No medication noted	79	10,49 %
Amiodarone total	20	2,66 %
Amiodarone and BB	*15*	*1,99 %*
Others	13	1,99 %
Total	**753**	**100%**

Table 6: Frequency table of select PCV drugs

One can attempt to assume that if an AAD is used at CV but not at patient discharge, it was intended for pharmacological CV. Under this assumption we can observe a 60% CV success rate using flecainide, a result comparable to the literature mentioned in section 5.3., though it should be noted that this assumes that all ECVs done in the presence of flecainide are failed CVs, which probably an overestimation.

	n (% total)	**ECV failure**	**ECV success**	**PCV failure**	**PCV success**
Flecainide at CV only	778 (10,16%)	34 (4,37%)	266 (34,19%)	9 (1,16%)	469 (60,28%)
Propafenone at CV only	14 (0,14%)	4 (28,57%)	9 (64,29%)	1 (5,26%)	0 (0%)
Amiodarone at CV only	65 (0,85%)	18 (27,69%)	34 (52,31%)	1 (1,54%)	12 (18,46%)
Digoxin at CV only	282 (3,68)	12 (4,26%)	237 (84,04%)	0 (0%)	33 (11,70%)
Sotalol at CV only	42 (0,55%)	1 (2,38%)	38 (90,48%)	0 (0%)	3 (7,14%)
Other BB at CV only	596 (7,77%)	7 (1,17%)	476 (79,87%)	5 (0,84%)	108 (18,12%)

Table 7: Frequency of PCV success using AADs at cardioversion but not at patient discharge

However, as seen in table 7 for propafenone, amiodarone, digoxin and the beta blockers, this assumption seems not to pan out. Considering the clinical usage profile of these drugs, this is no surprise. Given all options, amiodarone is seldom used to attempt pharmacological CV, except in patients with pre-existing significant heart disease. It is also quite possible that some cases recorded as used at CV only simply reflects that the patient's regular amiodarone medication was terminated during the treatment episode. As beta blockers and digoxin are not used to attempt CV in a hospital setting, as they are not effective at it, it is similarly not surprising to see that these drugs are heavily weighted towards ECV. Propafenone usage is minimal, owing to flecainide being the favored class 1c drug, and similarly other alternatives are preferred over sotalol for attempting pharmacological CV. It is possible that data for vernakalant and ibutilide, if available, would display a similar distribution to that observed for flecainide, as they are used primarily for attempting CV.

All in all, this dataset offers little opportunity to evaluate the efficacy of AADs for CV, due to the nature of the data collection methodology.

6 Summary

To summarize, AF is rapidly becoming more prevalent due to several factors, including the aging western population structure and our increasingly sedentary lifestyle. Many risk factors are preventable by either lifestyle choices and/or treatment of the specific risk factors. AF tends to progress over time from intermittent to permanent, but the risk of recurrence can be minimized by treating risk factors, using pharmacological treatment, i.e. rhythm control medication, electrophysiological intervention or as a last resort, surgery. Proper anticoagulation is paramount in reducing the risk of thromboembolic complications.

So far, no treatment has been shown to be superior to rate control, although striving to maintain sinus rhythm is preferential in some situations. In the acute phase this is done by CV, often performed by anesthesia and synchronized defibrillation, but several pharmacological options are available. While beta blockers primarily improve rate control, sotalol may have some efficacy for CV owing to its class 3 properties. Digoxin lacks efficacy in CV, and so far there is no evidence supporting that dronedarone would be superior to placebo.

Amiodarone on the other hand, though slow and harrowed by the risk of toxicity, reaches an efficacy of 62-87% after 24 hours. Flecainide on the other hand, reaches a similar efficacy already after a few hours, and propafenone, although much less used, is rather similar, and both have the benefit of being suitable for a pill-in-the-pocket approach once safety has been established. In an ER/ICU setting, ibutilide excels at cardioverting atrial flutter, either as pharmacological CV or infused between ECV attempts, but carries significant TdP risk. The most recent AAD, vernakalant, comes with few side effects and swift action, and is similar in efficacy to amiodarone, flecainide.

The FinCV study has provided several new findings regarding the need for anticoagulation during CV of acute AF, and the existence of stratified risk also within the first 48 hours. While the study design cannot say much about the efficacy of the different AADs in CV, flecainide seems have a CV efficacy of at least 60% in this dataset, while ECV remains the gold standard with an overall 94% efficacy in this dataset.

7 Bibliography

1. Wyndham CRC. Atrial Fibrillation: The Most Common Arrhythmia. *Tex Heart Inst J*. 2000;27(3):257-267.

2. Zoni-Berisso M, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol*. 2014;6:213-220.

3. Sidhu K, Tang A. Modifiable Risk Factors in Atrial Fibrillation: The Role of Alcohol, Obesity, and Sleep Apnea. *Can J Cardiol*. 2017;33(7):947-949.

4. Schnabel RB, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386(9989):154-162.

5. Atrial Fibrillation. Current Care Guideline. Working group appointed by the Finnish Medical Society Duodecim and the Finnish Cardiac Society. Helsinki: Finnish Medical Society Duodecim, 2017 (referenced 26.1.2019). Available online: www.kaypahoito.fi. .

6. Andrade J, et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res*. 2014;114(9):1453-1468.

7. Zulkifly H, et al. Epidemiology of atrial fibrillation. *Int J Clin Pract*. 2018;72(3):e13070.

8. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962.

9. Lau DH, et al. Pathophysiology of Paroxysmal and Persistent Atrial Fibrillation: Rotors, Foci and Fibrosis. *Heart Lung Circ*. 2017;26(9):887-893.

10. Padfield GJ, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm*. 2017;14(6):801-807.

11. Charitos EI, et al. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *Journal of the American College of Cardiology*. 2014;63(25 Pt A):2840. doi: 10.1016/j.jacc.2014.04.019.

12. Boriani G, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke prevention Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J*. 2014;35(8):508-516.

13. Healey JS, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366(2):120-129.

14. Boriani G, Pettorelli D. Atrial fibrillation burden and atrial fibrillation type: Clinical significance and impact on the risk of stroke and decision making for long-term anticoagulation. *Vascul Pharmacol*. 2016;83:26-35.

15. Wynn GJ, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace*. 2014;16(7):965-972.

16. Freeman JV, et al. Association Between Atrial Fibrillation Symptoms, Quality of Life, and Patient Outcomes: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes*. 2015;8(4):393-402.

17. Lubitz SA, et al. Challenges in the classification of atrial fibrillation. *Nat Rev Cardiol*. 2010;7(8):451-460.

18. Lau DH, et al. Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications. *Eur Heart J*. 2016;37(20):1573-1581.

19. Sheng X, et al. Prevention and Reversal of Atrial Fibrillation Inducibility and Autonomic Remodeling by Low-Level Vagosympathetic Nerve Stimulation. *JACC (Journal of the American College of Cardiology)*. 2011;57(5):563-571.

20. Lu Z, et al. Atrial Fibrillation Begets Atrial Fibrillation: Autonomic Mechanism for Atrial Electrical Remodeling Induced by Short-Term Rapid Atrial Pacing. *Circulation: Arrhythmia and Electrophysiology*. 2008;1(3):184-192.

21. Altunbas G, et al. Atrial Fibrillation Triggered By Drug-Induced Bradycardia. *Journal of atrial fibrillation*. 2016;9(3):1428.

22. Guasch E, et al. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *Journal of the American College of Cardiology*. 2013;62(1):68-77.

23. Linz D, et al. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm*. 2011;8(9):1436-1443.

24. Narayan SM, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). *Journal of the American College of Cardiology*. 2014;63(17):1761-68.

25. Buch E, et al. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. *Heart Rhythm*. 2016;13(3):636-641.

26. Andalib A, et al. Atrial fibrillation: evidence for genetically determined disease. *Current Opinion in Cardiology*. 2008;23(3):176-183.

27. Dublin S, et al. Risk of New-Onset Atrial Fibrillation in Relation to Body Mass Index. *Archives of Internal Medicine*. 2006;166(21):2322-2328.

28. Pathak RK, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *Journal of the American College of Cardiology*. 2015;65(20):2159-69.

29. Dublin S, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. *J Gen Intern Med*. 2010;25(8):853-858.

30. Kannel WB, et al. Epidemiologic Features of Chronic Atrial Fibrillation. *New England Journal of Medicine*. 1982;306(17):1018-1022.

31. McLellan AJA, et al. Reverse cardiac remodeling after renal denervation: Atrial electrophysiologic and structural changes associated with blood pressure lowering. *Heart Rhythm*. 2015;12(5):982-990.

32. Elosua R, et al. Sport practice and the risk of lone atrial fibrillation: A case–control study. *International Journal of Cardiology*. 2006;108(3):332-337.

33. Mozaffarian D, et al. Physical Activity and Incidence of Atrial Fibrillation in Older Adults: The Cardiovascular Health Study. *Circulation*. 2008;118(8):800-807.

34. Goudis CA, Ketikoglou DG. Obstructive sleep and atrial fibrillation: Pathophysiological mechanisms and therapeutic implications. *International Journal of Cardiology*. 2016;230:293-300.

35. Pathak RK, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *Journal of the American College of Cardiology*. 2014;64(21):2222.

36. Djoussé L, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol*. 2004;93(6):710-713.

37. Chamberlain AM, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. *Heart Rhythm*. 2011;8(8):1160-1166.

38. Heeringa J, et al. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. *Am Heart J*. 2008;156(6):1163-1169.

39. Albertsen IE, et al. The Impact of Smoking on Thromboembolism and Mortality in Patients With Incident Atrial Fibrillation. *Chest*. 2014;145(3):559-566.

40. Friberg L, et al. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J*. 2015;36(5):297-306.

41. Roldán V, et al. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). *The American journal of cardiology*. 2013;111(8):1159.

42. Pisters R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093.

43. Donzé J, et al. Risk of Falls and Major Bleeds in Patients on Oral Anticoagulation Therapy. *American Journal of Medicine, The*. 2012;125(8):773-778.

44. Camm AJ, et al. Guidelines for the management of atrial fibrillation The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace*. 2010;12(10):1360-1420.

45. Camm AJ, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillationAn update of the 2010 ESC Guidelines for the management of atrial fibrillationDeveloped with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33(21):2719-2747.

46. Airaksinen KEJ, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *Journal of the American College of Cardiology*. 2013;62(13):1187.

47. Nuotio I, et al. Time to Cardioversion for Acute Atrial Fibrillation and Thromboembolic Complications. *JAMA*. 2014;312(6):647-649.

48. January CT, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*. 2019.

49. Steffel J, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;39(16):1330-1393.

50. Costantino G, et al. Guidelines on the management of atrial fibrillation in the emergency department: a critical appraisal. *Intern Emerg Med*. 2017;12(5):693-703.

51. Kuck K. CABANA: after all, a positive trial. *Eur Heart J*. 2018;39(30):2771-2771.

52. Packer M. The CABANA Trial: an honourable view. *Eur Heart J*. 2018;39(30):2770-2770.

53. Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol*. 1984;24(4):129-147.

54. Lei M, et al. Modernized Classification of Cardiac Antiarrhythmic Drugs (corrected 26.3.2019). *Circulation*. 2018;138(17):1879-1896.

55. Karlson BW, et al. Disopyramide in the maintenance of sinus rhythm after electroconversion of atrial fibrillation. A placebo-controlled one-year follow-up study. *Eur Heart J*. 1988;9(3):284-290.

56. Ruskoaho H, Huikuri H. *Lääketieteellinen farmakologia ja toksikologia.* Duodecim; 2018.

57. Marrouche NF, et al. High-dose bolus lidocaine for chemical cardioversion of atrial fibrillation: A prospective, randomized, double-blind crossover trial. *American Heart Journal*. 2000;139(6):E-E11.

58. *Suomen lääketilasto 2017 : Finnish statistics on medicines 2017.* 3rd ed. Lääkealan turvallisuus- ja kehittämiskeskus Fimea; 2019:195.

59. Villani GQ, et al. Effects of diltiazem pretreatment on direct-current cardioversion in patients with persistent atrial fibrillation: A single-blind, randomized, controlled study. *American Heart Journal*. 2000;140(3):437-443.

60. Hemels MEW, et al. Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion for the Improvement of Rhythm Control for Persistent Atrial Fibrillation. *Journal of the American College of Cardiology*. 2006;48(5):1001-1009.

61. Mittal S, et al. Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. *Circulation*. 2000;101(11):1282-1287.

62. Klein AL, et al. Use of Transesophageal Echocardiography to Guide Cardioversion in Patients with Atrial Fibrillation. *The New England Journal of Medicine*. 2001;344(19):1411-1420.

63. Kubota Y, et al. Television Watching as Sedentary Behavior and Atrial Fibrillation: The Atherosclerosis Risk in Communities Study. *J Phys Act Health*. 2018:1-5.

64. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. *The American Journal of Cardiology*. 1969;23(2):208-216.

65. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. *Journal of the American College of Cardiology*. 1992;19(4):851-855.

66. Stoneham MD. Anaesthesia for cardioversion. *Anaesthesia*. 1996;51(6):565-570.

67. Grönberg T, et al. Arrhythmic complications after electrical cardioversion of acute atrial fibrillation: the FinCV study. *Europace*. 2013;15(10):1432-1435.

68. Lääketietokeskus Oy. Pharmaca Fennica, the following entries: Seloken 1mg/ml injektioneste, Digoxin 0,25mg/ml injektioneste, Flecainide Orion 100mg depotkaps, Rytmonorm 150mg tabl, Amiodaron Hameln 50mg/ml inj/inf konsentr, Multaq 400mg tabl, Corvert 87 ug/ml inf liuos, Brinavess 20mg/ml inf konsentr. https://www.terveysportti.fi/terveysportti/dlr_laake.koti. Updated 2019. Accessed 28.7., 2019.

69. Nergårdh AK, et al. Maintenance of sinus rhythm with metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation: a randomized double-blind placebo-controlled study. *Eur Heart J*. 2007;28(11):1351-1357.

70. Rehberg S, et al. Landiolol for managing atrial fibrillation in intensive care. *European Heart Journal Supplements*. 2018;20(suppl_A):A1-A18.

71. Nicholas Z Kerin. Intravenous Sotalol: An Under Used Treatment Strategy. *Cardiology*. 2018;140(3):143-145. doi: 10.1159/000490759.

72. Milan DJ, et al. Efficacy of Intravenous and Oral Sotalol in Pharmacologic Conversion of Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Cardiology*. 2017;136(1):52-60.

73. Wilkins MR, et al. William Withering and digitalis. *British Medical Journal (Clinical research ed.)*. 1985;290(6464):324.

74. Hornestam B, et al. Intravenous digoxin in acute atrial fibrillationResults of a randomized, placebo-controlled multicentre trial in 239 patients. *Eur Heart J*. 1997;18(4):649-654.

75. Bash L, et al. Systematic Review and Meta-analysis of the Efficacy of Cardioversion by Vernakalant and Comparators in Patients with Atrial Fibrillation. *Cardiovasc Drugs Ther*. 2012;26(2):167-179.

76. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. *International Journal of Cardiology*. 2003;87(2):121-128.

77. Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression after Myocardial Infarction. *The New England Journal of Medicine*. 1989;321(6):406-412.

78. Santinelli V, et al. Effects of Flecainide and Propafenone on Systolic Performance in Subjects with Normal Cardiac Function. *CHEST*. 1993;103(4):1068-1073.

79. Alboni P, et al. Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach. *The New England Journal of Medicine*. 2004;351(23):2384-2391.

80. Chevalier P, et al. Amiodarone versus placebo and class ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *Journal of the American College of Cardiology*. 2003;41(2):255-262.

81. Khan IA, et al. Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation. *International Journal of Cardiology*. 2003;89(2):239-248.

82. Bonora A, et al. Efficacy and safety in pharmacological cardioversion of recent-onset atrial fibrillation: a propensity score matching to compare amiodarone vs class IC antiarrhythmic drugs. *Intern Emerg Med*. 2017;12(6):853-859.

83. Roy D, et al. Amiodarone to Prevent Recurrence of Atrial Fibrillation. *The New England Journal of Medicine*. 2000;342(13):913-920.

84. Freemantle N, et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace*. 2011;13(3):329-345.

85. Vinson DR, et al. Ibutilide Effectiveness and Safety in the Cardioversion of Atrial Fibrillation and Flutter in the Community Emergency Department. *Annals of Emergency Medicine*. 2018;71(1):9-108.e2.

86. Stambler BS, et al. Efficacy and Safety of Repeated Intravenous Doses of Ibutilide for Rapid Conversion of Atrial Flutter or Fibrillation. *Circulation*. 1996;94(7):1613-1621.

87. Raatikainen P. Käypä hoito näytönastekatsaus: Ibutilidi eteisvärinän hoidossa. https://www.kaypahoito.fi/nak04920. Updated 2017.

88. Mountantonakis SE, et al. Ibutilide to expedite ED therapy for recent-onset atrial fibrillation flutter. *The American Journal of Emergency Medicine*. 2006;24(4):407-412.

89. Roy D, et al. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *Journal of the American College of Cardiology*. 2004;44(12):2355-2361.

90. Roy D, et al. Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation: A Phase 3, Randomized, Placebo-Controlled Trial. *Circulation*. 2008;117(12):1518-1525.

91. Pohjantähti-Maaroos H, et al. Intravenous vernakalant in comparison with intravenous flecainide in the cardioversion of recent-onset atrial fibrillation. *European Heart Journal: Acute Cardiovascular Care*. 2019;8(2):114-120.

92. A. John Camm MD. The Vernakalant Story: How Did It Come to Approval in Europe and What is the Delay in the U.S.A? *Current Cardiology Reviews*. 2014;10(4):309-314.

93. Safety of Cardioversion of Acute Atrial Fibrillation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01380574. Accessed Aug 2, 2019.

8 Abbreviations used

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
CCG	Current Care Guideline
CV	Cardioversion
ECV	Electric cardioversion
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
TdP	Torsades de Pointes
TEC	Thromboembolic complication
WPW	Wolff-Parkinson-White syndrome