[Year]

For atrial fibrillation patients, how effective is the use of cardiac ablation compared to antiarrhythmic drugs

DISSERTATION

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Abstract

Objectives--- to compare the effectiveness of cardiac ablation and antiarrhythmic drugs of atrial fibrillation (AF) patients for AF recurrence. The secondary outcomes are to compare cardiac ablation and antiarrhythmic drugs of AF patients for the quality of life and left ventricle ejection fraction.

Background--- Atrial fibrillation is the most prevalent type of cardiovascular arrythmia worldwide. Most individuals with AF are treated with anti-arrhythmic drugs (AADs) to achieve rhythm control. However, adverse effects and the limited efficacy of available AADs make this method less than ideal for maintaining sinus rhythm. When AADs cannot restore and sustain sinus rhythm (SR), catheter ablation (CA) is usually performed.

Design---Systematic review.

Methods and Results--- Four databases were searched. The searched was limited to English language only. The Cochrane library was a tool for risk of bias assessment and quality for included studies. There were 17 RCTs met the inclusion criteria. Two of the studies were high risk for random sequence generation. All the studies favoured the ablation group. The risk ratio was 0.58, meaning the AF recurrence rate in the ablation group is 42% lower than in the drug group (95% CI 0.51 to 0.65, $p< 0.00001$).

Conclusion--- The current evidence demonstrated that cardiac ablation is significantly lower than antiarrhythmic drugs for AF recurrence rate. Cardiac ablation is better than antiarrhythmic treatment for preventing AF recurrence.

1.0 Introduction

According to the global burden of atrial fibrillation (AF), there were approximately 33.5 million people with AF globally, including 20.9 million men and 12.6 million women, with increased prevalence and incidence rates in most developed countries (Zulkifly et al., 2018). Nearly 10 out of every 100 people over the age of 80 are affected by AF, which occurs in about 1 in 100 people in the general population. In Māori and Pacific people, AF occurs at a younger age than in the rest of New Zealanders (Ministry of Health, 2006).

Atrial fibrillation and heart failure share the same cardiovascular risk factors, and their treatment and prognosis are often complicated by coexisting and acting synergistically. For example, individuals with atrial fibrillation have a reduction in cardiac output due to a lack of atrial contraction, followed by an impairment in diastolic filling, increasing the negative hemodynamic effects that already exist in patients with heart failure. Most individuals with AF are treated with anti-arrhythmic drugs (AADs) to achieve rhythm control. However, adverse effects and the limited efficacy of available AADs in heart failure patients make this method less than ideal for maintaining sinus rhythm (Briceño et al., 2018). When AADs cannot restore and sustain sinus rhythm (SR), catheter ablation (CA) or combination therapy is usually performed. Despite the fact that trials comparing rhythm control to rate control have shown no benefits, many health practitioners believe that rhythm control therapy may reduce the risk of severe cardiovascular events. All present international AF study guidelines recommend Cardiac ablation as the initial treatment to prevent recurrent AF and improve symptoms in selected individuals with paroxysmal AF (January et al., 2019; Kirchhof et al., 2016); however, AADs remain the first-line therapy for persistent AF patients (Chen et al., 2018). Therefore, to enhance the current evidence, we did an updated systematic review and meta-analysis of randomised control trials to evaluate and compare cardiac ablation and medical treatments in AF patients for AF recurrence, quality of life and improving left ventricle function.

2.0 Background

2.1 What is atrial fibrillation?

Atrial fibrillation (AF) is the most prevalent type of cardiovascular arrythmia worldwide. In AF, the cardiac rhythm is irregular and could be very fast as the typical timer in the heart is failed. Multiple random electrical signals are generated from the heart's atria instead of a regular electrical signal. When the atria fibrillate this way, they cannot effectively pump blood into the ventricles. Blood flow to the body may be reduced because the 'booster pump' does not work, particularly if the heart rate is exceptionally high. There are two types of atrial fibrillation: intermittent (paroxysmal atrial fibrillation) and chronic (permanent or persistent atrial fibrillation) (Ministry of Health, 2006).

2.2 Pathophysiology

Atrial fibrosis can be recognized as the primary pathophysiological factor for the complications, AF recurrence, and resistance to medicines. Many mechanisms have been suggested to contribute to AF development for electrical and structural modification of cardiac tissue. Moreover, fibrosis played a significant role in this process. Fibrosis is caused by the over-proliferation of fibroblasts in regard to the pathological system, leading to the accumulation of extracellular proteins in the interstitial tissues of the heart. Fibroblast cells support the structure and maintain the homogeneity of cardiac tissues. The fibrotic process leads to the differentiation of fibroblasts into myofibroblasts, which reduces cardiac conduction velocity and enhances arrhythmogenic activity (Spencer et al., 2017). Fibrosis could be divided into two groups: reparative and interstitial fibrosis. Reparative fibrosis occurs when fibrotic tissues replace necrotic cardiac cells. Interstitial fibrosis can be classified into two categories: Reactive fibrosis occurs when there is no replacement of the dead cells, increasing the extracellular matrix in the interstitial space; infiltrative interstitial fibrosis occurs when the deposition of non-absorbable proteins or glycosphingolipids in the interstitial space (Burstein & Nattel, 2008; Nattel, 2017).

Many cellular subtypes contribute to the fibrotic process and the development of atrial fibrillation. Moreover, fibroblasts are recognized as the primary cellular effectors of atrial fibrosis. Ten to fifteen% of cardiac tissue cells are fibroblasts, which are small and spindle-shaped. They can regulate the synthesis and change of the extracellular matrix and maintain the building structure of the cardiac tissues. There are multiple signal pathways between

fibroblasts and cardiomyocytes, and they can change the current electrophysiological functions. Under different pathological situations and stress factors, fibroblasts can transform into alpha-smooth muscle actin expressing myofibroblasts. Many profibrotic stress stimuli can activate and differentiate local cardiac fibroblast. The biochemical signals can lead to fibroblast differentiation; transforming growth factor-beta (TGFβ) is essential for canonical and non-canonical pathways and can activate myofibroblast gene transcription (Davis et al., 2012). In addition, angiotensin II and endothelin one bind to the G protein receptors on the cardiac fibroblast cells, releasing fibrotic mediators to activate the transcription of fibrotic genes. Furthermore, adding mechanical forces can assist the differentiation and activation of fibroblasts to generate a more rigid and stretched matrix (Davis & Molkentin, 2014). Recent research has shown the importance of mitochondrial, metabolic, and cellular factors that enhance the formation of myofibroblasts (Gibb et al., 2020). Mitochondria regulate the fibroblast activation by decreasing calcium uptake with the profibrotic signals, which promote cytosolic calcium signalling (Sagris et al., 2022). Moreover, profibrotic stressors cause the mitochondria to produce reactive oxygen species (ROS), which activates factors, including ERK1/2 (extracellular signal regulated kinase one and two) and p38, to promote fibrotic gene expression. Recently, it has been found that different metabolic functions play an important role in the formation of myofibroblasts. A significant part of the activation of fibroblasts depends on a higher rate of glutaminolysis, while changes in glycolysis follow a rise in lactate production to develop a myofibroblast differentiation mechanism (Lu et al., 2014). Myofibroblast can activate inflammatory cells, enhance wound healing, and produce large amounts of collagen, periostin, and fibronectin, leading to fibrosis (Pellman et al., 2016; Theofilis et al., 2021).

It has been demonstrated that multiple inflammatory cells may be involved in the pro-fibrotic system for fibroblasts. Several studies have indicated that macrophages can regulate fibrosis. Macrophages originate from yolk sac-derived EMP (erythromyeloid progenitors), live in the healthy myocardium, and maintain its homeostasis. When a cardiac event occurs, monocytes from the blood infiltrate the myocardium and differentiate into macrophages. Moreover, they express large heterogeneity and have different functions, such as producing many pro-fibrotic growth factors, cytokines, and proteases that help to restructure the matrix (Kim et al., 2018). Afterward, T cells migrated to the cardiac tissues due to cytokines release. Then, T cells are converted to T-helper CD4+ (TH1 and TH2) or cytotoxic T cells (CD8+), which start the immune system. During the immediate response, T helper one and cytotoxic T cells are the

primary lymphocytes in the myocardium. They can release mediators to stop the pro-fibrotic actions. Furthermore, the production of IL4 and IL3 is affected by the interference of INF-y and T helper two cells. When the chronic injury occurs, TH2 cells will replace TH1 cells to play the leading role in the heart tissue. In the end, TH2 cells stop the activity of pro-fibrosis. It acts by releasing IL four and IL thirteen, which can stimulate collagen secretion and activate more monocytes in the injury site (Zaidi et al., 2021).

Another main component of the immune system is mast cells, which act as regulators for the process of cardiac fibrosis. Some evidence has shown that mast cells undergo proliferation during myocardial ischemia and pressure overload and release pre-existing inflammatory and fibrotic mediators. Mast cells in the heart tissue perform the connective tissue characteristics, consisting of both tryptase and chymase. Numerous articles have supported the pro-fibrotic impact of elevated chymase activity in cardiac remodelling through its facilitation of angiotensin II formation (Ahmad et al., 2011; Balcells et al., 1997; Shimizu et al., 2006). Previous research has indicated that rising concentrations of tryptase in the heart with fibrosis cause fibroblasts to multiply and change into myofibroblasts. Fibroblasts can be differentiated into myofibroblasts by stimulating the protease-activated receptor 2 in fibroblasts, which phosphorylates extracellular signal-regulated protein kinases one and two (McLarty et al., 2011). Finally, the significance of histamines generated by mast cells in cardiac fibrosis has been found through extensive research. In an animal experiment, a lack of histamine triggered a response in H2 receptor-deficient mice and decreased myocardial apoptosis and fibrosis (Zeng et al., 2014). However, the degranulation outcomes of mast cells include several anti-inflammatory and anti-fibrotic mediators, which has led to debates on the specific function of mast cells in tissue rebuilding (Sagris et al., 2022).

2.3 Risk factors for AF

Hospital admissions for atrial fibrillation are increasing worldwide due to the rising prevalence of AF and a related increase in chronic cardiovascular disease. Most of these chronic conditions are known as risk factors for AF (Patel et al., 2014). Many cardiovascular risk factors have been recognized as independent predictions of atrial fibrillation development. Research of more than two decades also determined hypertension, ischaemic heart disease, heart failure, heart valve disease, aging, and diabetes as independent risk factors (Benjamin et al., 1994). Recent studies identified more risk factors, including obesity,

left ventricular hypertrophy, male gender, obstructive sleep apnea, excessive alcohol use (Jamaly et al., 2016; Lau et al., 2017).

2.4 Complications and risks

Adults with atrial fibrillation are at higher risk of developing stroke, pulmonary embolism, and heart failure. Those complications are significantly related to high mortality rates, frequent admissions, and poorer quality of life (Lip et al., 2014). Strokes are five times more likely to occur in patients with atrial fibrillation. Individuals ages 50-59 are at 4.6% risk of ischemic stroke, while those ages 80-89 are at 20.2% (Björck et al., 2013).

According to the Virchow triad for thrombus formation theory, AF can cause stroke in several ways: extra blood remaining in the left atrium leads to abnormal blood flow; heart and vascular disease such as mitral stenosis, which fulfils the abnormal vessel walls; unusual fibrinolysis and coagulation (Watson et al., 2009). Heart failure, hypertension, diabetes, age, and past stroke are the most common risk factors linked to stroke; they were initially established based on data from randomized control trials performed many years ago, especially from the non-VKA cohorts (Lip et al., 2014).

Several measurement tools have been created to help patients with atrial fibrillation understand their risk of stroke based on the various factors that bring them at risk. The two most popular scoring systems are the CHADS2 and CHA2DS2-VASc scores. The CHADS2 score assigns one point to the following conditions: congestive heart failure, hypertension, age 75 or more, diabetes mellitus, and two points for stroke history, with a higher score indicating a greater risk. All of the risk assessment plans based on physical risk factors are ineffective at identifying individuals at high risk of AF. Nevertheless, the CHA2DS2-VASc system effectively determines low-risk people who do not need anticoagulant treatment. Therefore, more updated guidelines initially depend on identifying low-risk patients because they do not require anticoagulation instead of identifying high-risk patients (Senoo et al., 2014).

The CHADS2 tool was developed and initially assessed in a list of individuals admitted to the hospital with atrial fibrillation. The CHADS2 score is a simple instrument used to determine people at high risk (score more than two), while intermediate risk is primarily referred to as a number ranging from one to two, and *low risk* is defined as a score of zero (Gage et al.,

2001). The CHADS2 rating system displayed several flaws, as it failed to incorporate numerous widely recognized stroke risks, such as individuals aged 65-74 years, presence of vascular disease, female gender, asymptomatic left ventricular diastolic dysfunction, and others. In addition, the primary validation report stated that people who had had a stroke before and had no other risk factors would only score two and be in the moderate risk category, even though they were in the highest risk group (Karthikeyan et al., 2010).

The CHA2DS2-VASc score was first examined in the group of people who participated in the Euro-Heart study. This number considered several risk factors not part of CHADS2, such as age between 65 and 74, being female, and having vascular disease. As compared to the CHADS2 scoring system, the inclusion of the letter "c" in the CHA2DS2-VASc system represents congestive heart failure that includes moderate to severe dysfunction of left ventricles with an ejection fraction (EF) below 40%, as well as current decompensated heart failure regardless of ejection fraction (Senoo et al., 2014). Adults with cardiomyopathy, including restrictive or hypertrophic cardiomyopathy, could possibly fall under the c criteria in the last category. However, it is essential to mention that there needs to be more complete information available on this topic. The validity of the CHA2DS2-VASc system has been proven in multiple cohort studies, which have included people from non-Western regions (Siu et al., 2014; Zhu et al., 2015). In the context of those studies, it showed that the CHA2DS2-VASc score significantly predicts stroke (Siu et al., 2014). Most studies indicate that CHA2DS2-VASc is the best tool to recognize people who are considered "truly low-risk," with an annual absolute risk of stroke or systemic embolism below 1%. Furthermore, CHA2DS2-VASc predicts high-risk patients more accurately than the previous CHADS2 score (Zhu et al., 2015).

The CHADS2 and CHA2DS2-VASc are based on the risk factors that are encountered frequently in clinical settings associated with patients with atrial fibrillation. However, the CHA2DS2-VASc score does not include additional uncommon factors that have been linked to stroke or systemic embolism in atrial fibrillation, such as amyloid heart disease and end-stage renal failure. Observational studies have explained the impact of severe renal impairment on the risk of strokes and bleeding in patients with AF (Lip et al., 2011). Nevertheless, renal impairment does not contribute additional predictive value to well-established scoring systems such as CHA2DS2-VASc (Friberg et al., 2015). Patients with atrial fibrillation should also be assessed for bleeding risk, particularly when considering

thromboprophylaxis. Although several bleeding risk stratification techniques have been suggested, their use is limited due to their complexity and potential overlap with stroke risk assessment (Lip & Lane, 2015).

2.5 Antiarrhythmic drugs

Management of atrial fibrillation requires a complex strategy that involves identifying and treating underlying risk factors, comorbidities, stroke risk, and arrhythmia control (ESC Scientific Document Group, 2020). In spite of the growing significance of cardiac ablation for rhythm control, antiarrhythmic therapy remains crucial to managing atrial fibrillation (Heijman et al., 2021). The RealiseAF research, which included a population of 10,523 atrial fibrillation patients from twenty-six different countries, found that over 80% of the patients were prescribed antiarrhythmic drugs (AADs). Furthermore, approximately 50% of the patients were given AADs, which are frequently used for rhythm-control therapy (Chiang et al., 2013).

Antiarrhythmic medications have a long history. The use of cinchona extract, derived from the cinchona plant and containing quinine, was documented in 1749 by Jean Baptiste de Sénac as an intervention for palpitations prior to the discovery of atrial fibrillation as the cause (Karagueuzian et al., 2017). Afterward, the experimental findings led to many supplementary compounds with antiarrhythmic properties. Pharmacological principles were used to synthesize more advantageous derivatives, resulting in the development of substances such as procainamide, lidocaine, bretylium, and disopyramide. This was followed by the creation of amiodarone, flecainide, and propafenone. During the initial years of the 1970s, a classification system was established for a set of antiarrhythmic agents, which were divided into three different groups according to their functional and electrophysiological effects. Class I drugs were found to decrease myocardial activity, Class II drugs (commonly known as Beta-blockers) exhibited sympatholytic effects, and Class III drugs were observed to increase the repolarization period (Karagueuzian et al., 2017). A further understanding of the impacts of Class I drugs demonstrated that their effects were caused mainly by the blockage of cardiac sodium channels. On the other hand, the longer duration of repolarization was related to the inhibition of repolarizing potassium channels, specifically the highly activating delayed-rectifier K+ current. The Identification of verapamil, a calcium channel blocker with possible antiarrhythmic properties, led to the future development of Class IV antiarrhythmic drugs (Heijman et al., 2021).

The possible adverse effects of antiarrhythmic drugs were already recognized prior to the development of the Vaughan-Williams classification. In 1964, the incidence of life-threatening arrhythmias was linked to "quinidine syncope" (Selzer & Wray, 1964). However, during the early 1990s, two major clinical studies significantly changed the progress of antiarrhythmic drugs. The outcomes from the Cardiac Arrhythmia Suppression Trial (CAST) and the Survival with Oral D-Sotalol (SWORD) studies demonstrated a higher mortality rate among people who had experienced a myocardial infarction and received specific Class I or Class III AADs (Camm, 2017; Valembois et al., 2019). It caused the occurrence of drug-induced ventricular pro-arrhythmia. Drug-induced ventricular pro-arrhythmia is one of the significant reasons limiting the use of AADs in clinical practice because atrial fibrillation is not an immediate life-threatening disease (Camm, 2017). According to the guidelines of the Heart Foundation of Australia and Cardiac Society of New Zealand (Brieger et al., 2018), flecainide could be an option for prompt restoration of sinus rhythm for AF hemodynamic stable patients, given either intravenously or orally, in individuals who do not have dysfunction of left ventricles, moderate left ventricular hypertrophy, or a history of coronary artery disease (CAD). Amiodarone could be considered a second-line option for maintaining sinus rhythm in individuals with left ventricular systolic failure, moderate left ventricular hypertrophy, or CAD. However, it is crucial to assess the risk of thromboembolism before starting those courses of therapy (Brieger et al., 2018).

2.6 Cardiac ablation

Catheter ablation is one of the treatments for symptomatic atrial fibrillation. The procedure is also recommended for people with paroxysmal or chronic AF who could be resistant to antiarrhythmic medications. In some circumstances, the procedure could be considered a first step for asymptomatic patients. The available information from extensive research suggests that cardiac ablation may have an opportunity to decrease mortality rates and reduce the risks associated with heart failure and stroke. However, the findings from RCTs present a more diverse and inconclusive picture (Parameswaran et al., 2021).

Catheter ablation has become a practical therapeutic procedure for people who are experiencing symptoms related to AF. Generally, catheter ablation is recommended as a safe approach with low complication rates during the post-procedure period; however, several factors may contribute to higher complication rates or lower success rates in certain

patients. Those factors are obstructive sleep apnea, obesity, heart disease, the size of the left atrium, the age and frailty of the patient, and different types of atrial fibrillation (Gupta et al., 2013). According to current guidelines, catheter ablation is recommended as a second option for individuals with symptomatic paroxysmal atrial fibrillation with a class I recommendation or persistent atrial fibrillation with a class IIa recommendation when previous antiarrhythmic treatment is failed. Additionally, catheter ablation is indicated as a class IIb recommendation for people who have long-standing PAF (Packer et al., 2013). Moreover, regarding symptom control, multiple studies have demonstrated that cardiac ablation is more successful than antiarrhythmic drugs in preventing AF recurrence and maintaining sinus rhythm (Packer et al., 2013; Packer et al., 2019; Wilber et al., 2010).

Cardiac ablation is an effective strategy to isolate the pulmonary veins. It has changed significantly over the past twenty years, from segmental ostial pulmonary vein ablation to applying 3D imaging to guide ablation to wide area circumferential procedure with confirmation of conduction block (Arentz et al., 2007). Pulmonary vein antral isolation has gained broad support as a fundamental approach to treating atrial fibrillation (AF). It is highly recommended to be performed in all AF ablation procedures. In people with paroxysmal atrial fibrillation, pulmonary vein isolation has the freedom rate of AF recurrence from 60% to 70% (Takigawa et al., 2015; Straube et al., 2016). Furthermore, the long-term rate of freedom for AF recurrence may increase to 77 percent (Vogt et al., 2013). Lastly, catheter ablation is an initial treatment choice for individuals in specific careers, including military service staff, aircraft pilots, and athletes, who may have medication restrictions, leading to poor performance.

2.7 AF recurrence

The occurrence of return into atrial fibrillation after undergoing cardioversion and ablation is a frequent and complex therapeutic challenge. Evidence showed that 50-60% of patients who received electrical cardioversion (EC) and 25-50% following catheter ablation have AF recurrence (Climent et al., 2009). Moreover, atrial fibrillation (AF) is widely recognized as the primary complication and rhythm disturbance following cardiac surgery, presenting an incidence rate of about 27% to 40%. The increasing prevalence of atrial fibrillation, its high recurrence rates, and the associated risk of stroke, heart failure, cognitive impairment, and lower quality of life lead to a significant public health concern (Wu et al., 2013). The complex mechanism of the aetiology and recurrence of atrial fibrillation remains unresolved.

Extensive research has found a relationship between the risk of AF and the presence of a systemic inflammatory state, which is characterized by elevated levels of C-reactive protein (CRP) in the serum (Yao et al., 2009). Wu et al. (2013) have found a strong relationship between CRP and the risk of AF. The CRP protein indicates inflammation in the body's acute phase. C-reactive Protein binds to phosphatidylcholine on the membranes of cardiac cells in a particular way. In sarcolemma vesicles, acylcarnitines and lysophosphatidylcholines, derived from phosphatidylcholine, can prevent sodium and calcium ions from exchanging, which can cause AF. Along with contributing to the electrophysiological mechanism, C-reactive protein may also participate in structural remodelling. It has been suggested that CRP may trigger apoptotic loss of atrial myocytes due to the build-up of calcium within these cells during atrial fibrillation (Nattel, 2002).

2.8 Quality of life

Atrial fibrillation is not directly life-threatening, but the distress experienced by symptoms can be considerable and substantially impact the quality of life (QoL). Several factors contribute to this, including palpitations, chest discomfort, dizziness, and symptoms of heart failure. Symptoms such as weakness, light-headedness, and shortness of breath may happen as a result of an underlying cardiac condition. Moreover, the consequences of addressing atrial fibrillation, including the adverse effects of medications, treatments, and particularly hospitalization, produce a negative relationship to quality of life (Lip et al., 2011). According to the World Health Organisation (WHO), health encompasses more than just the absence of sickness and infirmity. Well-being and quality of life (QoL) are also included (Testa & Simonson, 1996). The majority of research conducted till now has investigated the health-related quality of life in people who have symptoms and are unresponsive to antiarrhythmic medication or those who have undergone ablation treatment. How AF affects the daily lives of those with mild symptoms or those who are asymptomatic remains unclear. Furthermore, the evaluation of health-related quality of life has been limited in previous studies due to small samples and the absence of control groups (Aliot et al., 2014).

2.9 Left ventricular ejection fraction

In recent years, there has been a significant rise in the availability of comprehensive data concerning individuals with atrial fibrillation and heart failure with reduced left ventricle ejection fraction. These data suggest significant advantages related to catheter ablation compared to medical treatment, as evidenced by several measurable outcomes. The

findings from those studies provide strong evidence that catheter ablation of atrial fibrillation is more effective than pharmacological rhythm control therapy or rate control treatments in terms of improving exercise capability, health quality, and left ventricular ejection fraction (Parameswaran et al., 2021).

Objective

The primary outcome is to compare the effectiveness of cardiac ablation and antiarrhythmic drugs of atrial fibrillation (AF) patients for AF recurrence. The secondary outcomes are to compare cardiac ablation and antiarrhythmic drugs of AF patients for the quality of life and left ventricle ejection fraction.

3.0 Methods

3.1 Types of studies

The study will include only randomised controlled trials or trials described as randomised controlled trials.

3.2 Types of participants

Participants aged 18 or over are with atrial fibrillation (AF), persistent AF, or paroxysmal AF, as defined or diagnosed by the included study. AF is a prevalent supraventricular arrhythmia that involves disorganised atrial contraction. The diagnosis of atrial fibrillation requires an electrocardiogram (ECG). AF episodes are any arrhythmias that display the characteristic ECG for atrial fibrillation. Atrial fibrillation occurs recurrently and lasts longer than two minutes, and less than seven days is defined as paroxysmal AF. A self-existing episode under 48 hours also falls into this category. AF that persists for more than seven days is considered chronic. If AF lasts more than 48 hours but less than seven days, it is recognised as recent onset AF (Lévy, 2000).

3.3 Types of interventions

Any trials of AF patients that compared cardiac ablation and anti-arrhythmic drugs. Any types of ablation were included, such as pulmonary vein isolation, cryoballnoon ablation, and radiofrequency ablation (Parameswaran et al., 2021). Any types of AAD were included.

3.4 Types of outcomes

The primary outcome was AF recurrence. The secondary outcomes were the quality of life measured using any health-related quality of life instrument and left ventricle ejection fraction as determined by the included study.

3.5 Search strategy

Search will be conducted on the following databases using a randomised control trial filter:

- Cochrane Library
- Medline
- Embase
- CINAHL

Used key words to search: Atrial fibrillation, AF, arrhythmia, cardiac, cardiac ablation, catheter ablation, anti-arrhythmia agents, antiarrhythmic drugs, AF recurrence.
Only English language will be applied, no dates restriction.

3.6 Other searches

The reference lists in the included studies will be searched for additional relevant studies.

3.8 Data collection and analysis

3.8 (1) Selection of studies

The EndNote reference manager was used to aggregate all the citations of studies for review and to remove duplicate citations. Titles and abstracts were screened to determine if they meet inclusion criteria. If any uncertainty was present, the study was acquired for further evaluation. After review of titles and abstracts, full text articles of the remaining studies were obtained for further screening.

3.8 (2) Data extraction and management

A standardised extraction form in Excel (version number) was created to collect the data. The data extraction form included article citations, year, country, study ID, study designs, random allocation, allocation concealments, participants blinded, investigator blinded, outcome assessor blinded, length of intervention follow up, age range, number of participants, number of completed, drop out, inclusion and exclusion criteria, intervention description, AF recurrence, quality of life, left ventricle ejection fraction, risk of bias assessments.

3.8 (3) Assessment of risk of bias

Each individual included studies study was assessed for the quality and risk of bias using the Cochrane risk of bias tool (version 1) and the guidelines from the Cochrane Handbook for systematic review of interventions. The assessment criteria are selection bias-random sequence generation, selection bias-allocation concealment, participants blinded, investigator blinded, outcome assessor-blinded, performance bias, detection bias, attribution bias, reporting bias, and other bias. Each category was assessed low risk, high risk or unclear risk of bias (lack of information or uncertainty), based on the presence or absence of available description reported in the study.

3.9 Data Synthesis

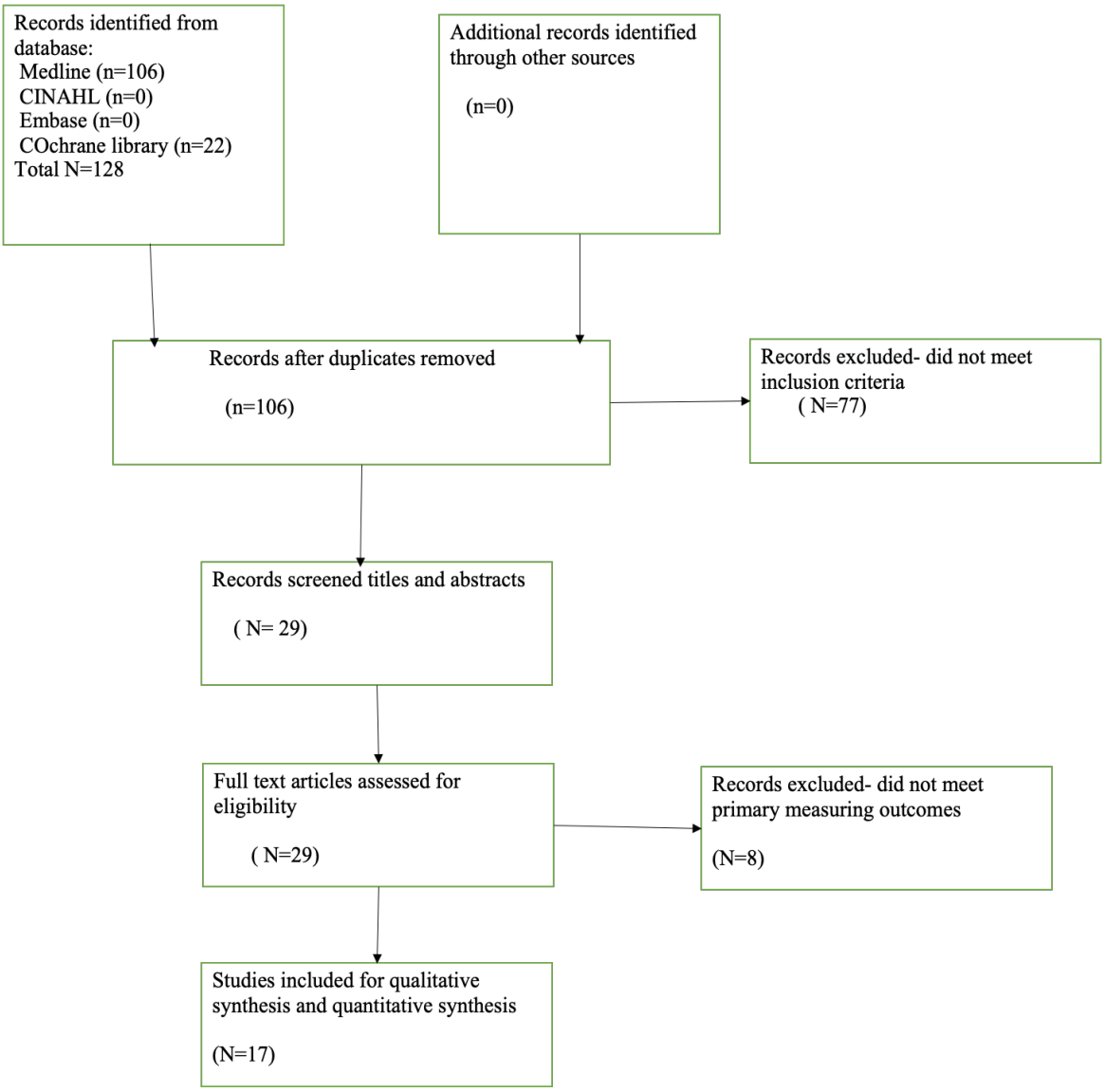
RevMan 5.4 was review manager was used to produce the meta-analysis. First, risk ratios were used for the dichotomous data, while mean difference and standardised mean difference were used for the continuous data, Ninety-five % confidence intervals for each metric were reported. Moreover, we used an intention-to-treat analysis for those data. The random-effect models were performed in the analysis. Differences were considered significant when p-values were less than 0.05, except for tests of heterogeneity where p-values less than 0.1 were considered significant heterogeneity (Higgins et al., 2022). Chi-squared test and the I^2 test were performed to analyse heterogeneity. The I^2 probability of 25%, 50%, and 75% represent low, medium, and high heterogeneity.

4.0 Results

4.1 Description of included studies

During the search, there were 128 results found (figure 1). After removing duplicates, 106 remained. After screening titles and abstracts, 29 studies with full text remained. The other 77

articles are not randomized control trials, and they do not compare those two groups' cardiac ablation and antiarrhythmic drugs. After reading and screening 29 articles, only 17 studies were left for the studies analysis. Those excluded 12 articles did not meet inclusion criteria for the primary outcome.



(Mother et al., 2009)

Figure 1. Flow diagram

4.2 Risk of Bias

Random sequence generation

Six randomized control trials were low risk of bias for random sequence generation, which used computer-generated methods (Di Base et al., 2016; Packer et al., 2019; Cosedis Nielsen et al., 2012; Andrade et al., 2021; Morillo et al., 2014; Hunter et al., 2014). Only two studies

were high risk for random sequence generation, as randomization generated by validated database systems (Blomstrom-Lundqvist et al., 2019 & Kuck et al., 2021). The rest of other studies were unclear risk for random sequence generation as there were no description of any methods.

Allocation concealment

Two studies were low risk for bias of allocation concealment (Andrade et al., 2021; Hunter et al., 2014). For the remained studies, random sequence generation did not describe, which means they were unclear risk for allocation concealment.

Performance Bias and Detection Bias

Only three studies were low risk of bias for performance bias (Mont et al., 2013; Morillo et al., 2014; Hunter et al., 2014); the rest of the RCTs did not describe blinding participants. However, most of studies were outcome assessor blinded, excluding two studies which have unclear risk for detection bias (Di Base et al., 2016 & Poole et al., 2020).

Attribution Bias

Only one study did not describe incomplete outcome data (Poole et al., 2020), the rest of studies were low risk for attribution bias.

Reporting Bias

All the studies were low risk for reporting bias.

Other Bias

All the studies are low risk for other bias, excluding one study which did not mention some of the secondary measuring outcomes (Packer et al., 2019).

4.3 Main results

AF recurrence

All the studies favoured the ablation group (Figure 2). The risk ratio was 0.58, meaning the AF recurrence rate in the ablation group is 42% lower than in the drug group (95% CI 0.51 to 0.65, $p < 0.00001$). It indicated that the finding was statistically significant. Packer 2019 has the most significant weight (12.2%) in the studies, meaning he has the largest sample size. Conversely, Andrade 2023 (0.9% weight) has the smallest sample size comparing those

studies. Moreover, the heterogeneity is statistically significant as the P-value is 0.0004, with moderate inconsistency above the level of chance (I^2 =62%).

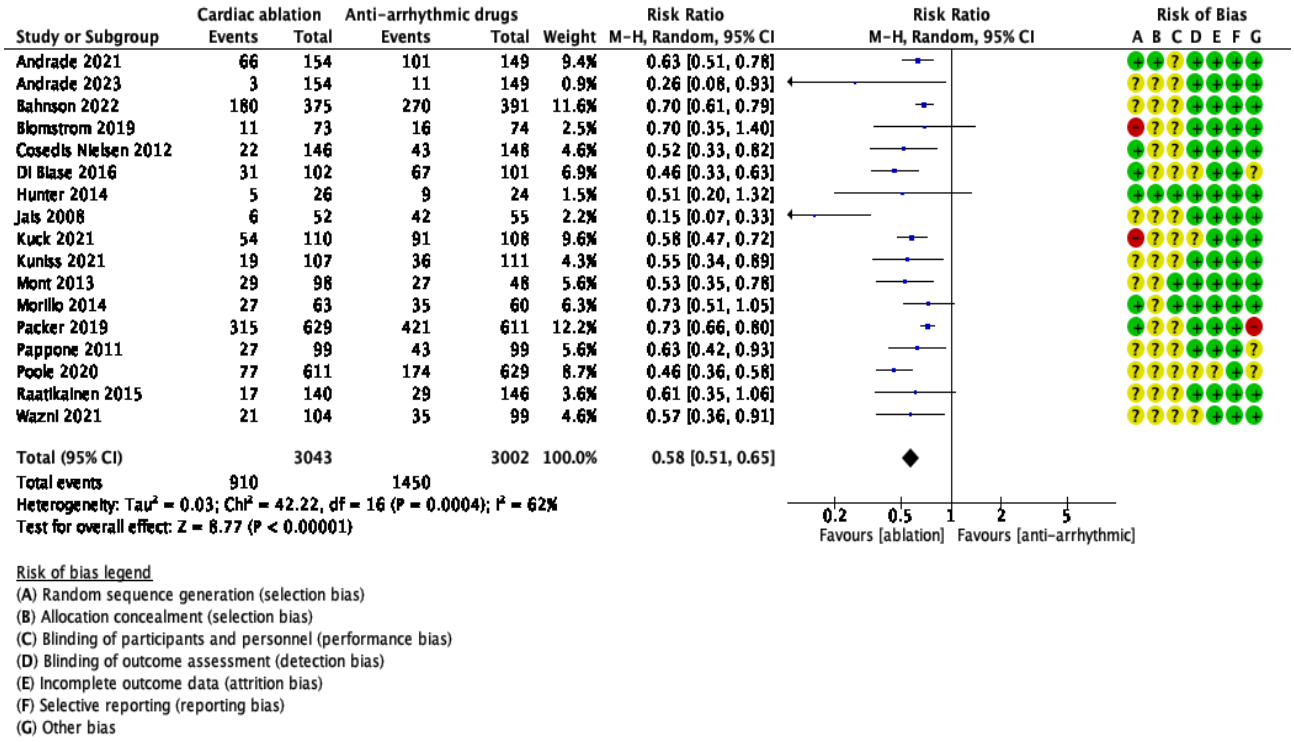


Figure 2. AF recurrence rates in ablation and anti-arrhythmic drugs

Quality of life

While some studies favored ablation, three studies crossed the vertical line of no effect, which means they are not statistically significant (Andrade 2021, Pappone 2011, Raatikainen 2015). However, the diamond shape did cross the vertical line, which means the total effect is not statistically significant (P =0.12). The standardized mean difference was 0.36 (95%CI -0.10 to 0.81) in favor of ablation, but the effect was not statistically significant. The heterogeneity was statistically significant as P<0.00001. With an I^2 of 95% indicating considerable heterogeneity above the level of chance. This heterogeneity may have been caused by the quality of the studies or the range of tools that were used, but we could only evaluate quality of the studies.

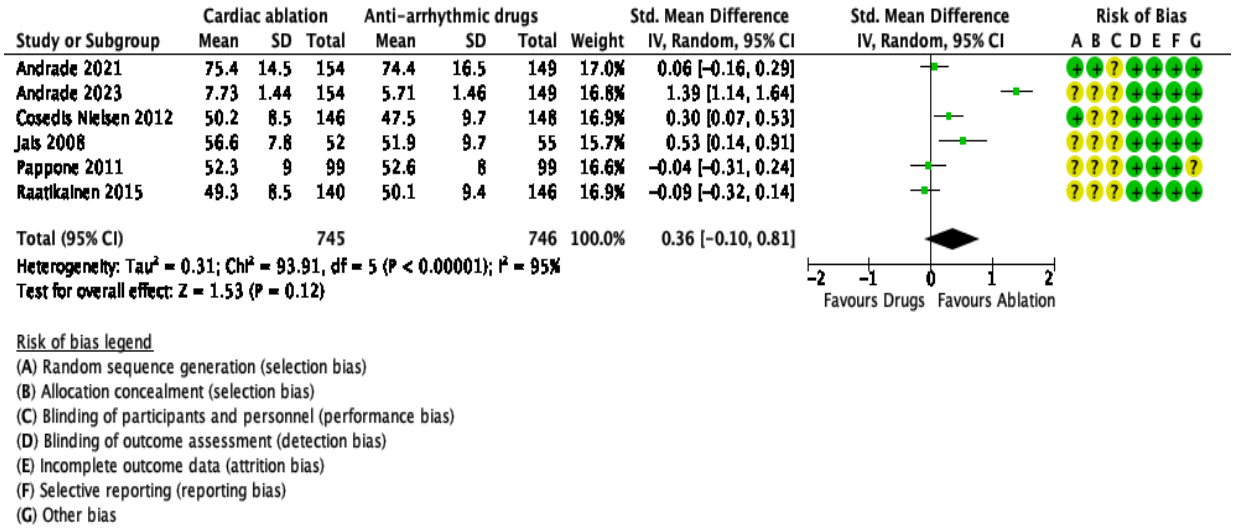


Figure 3. Quality of life in Cardiac ablation and Antiarrhythmic drugs

Left ventricular ejection fraction

Only three studies reported LVEF. All the studies crossed the vertical line, only one study did not cross the line which showed the result is statistically significant (Hunter et al., 2014). Moreover, the diamond shape did cross the vertical line, which means the total effect is not statistically significant (P =0.27). The mean difference is 1.67 which sits within -1.27 to 4.6 95% confidence interval. The heterogeneity is statically significant as P=0.06. However, I^2 is 64% which means it was moderate heterogeneity.

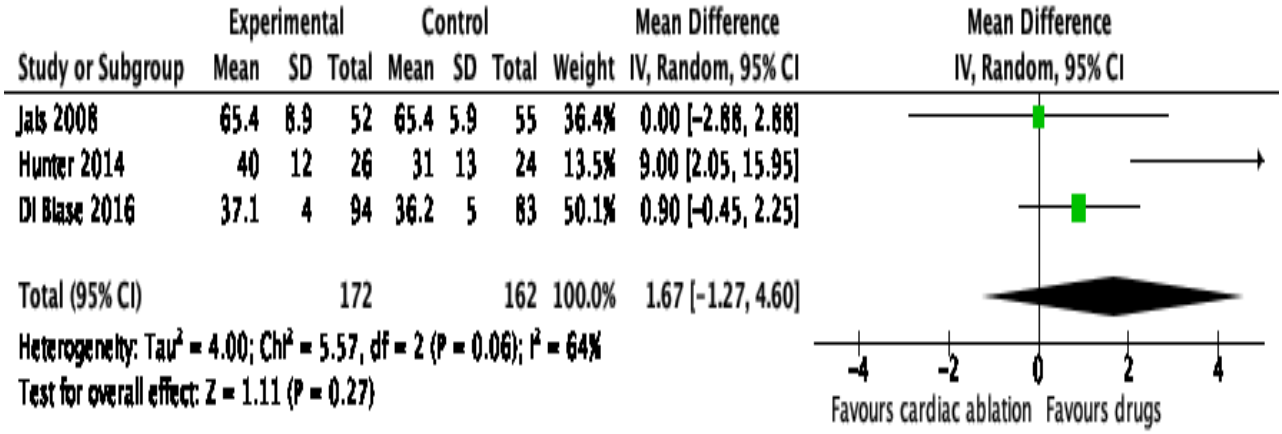


Figure 4. Left ventricle ejection fraction in cardiac ablation and antiarrhythmic drugs

When removed all the high risk and unclear selection bias studies, only six studies remained for low risk of random sequence generation selection bias. Within those quality studies in AF

recurrence, the total effect is still statistically significant (p-value <0.00001), favoring in cardiac ablation than antiarrhythmic group. The risk ratio is 0.63, meaning the AF recurrence rate in the ablation group is 37% lower than in the drug group (95% CI 0.53 to 0.74). The heterogeneity is statically significant as P=0.07. However, I^2 is 51% which means it was moderate heterogeneity.

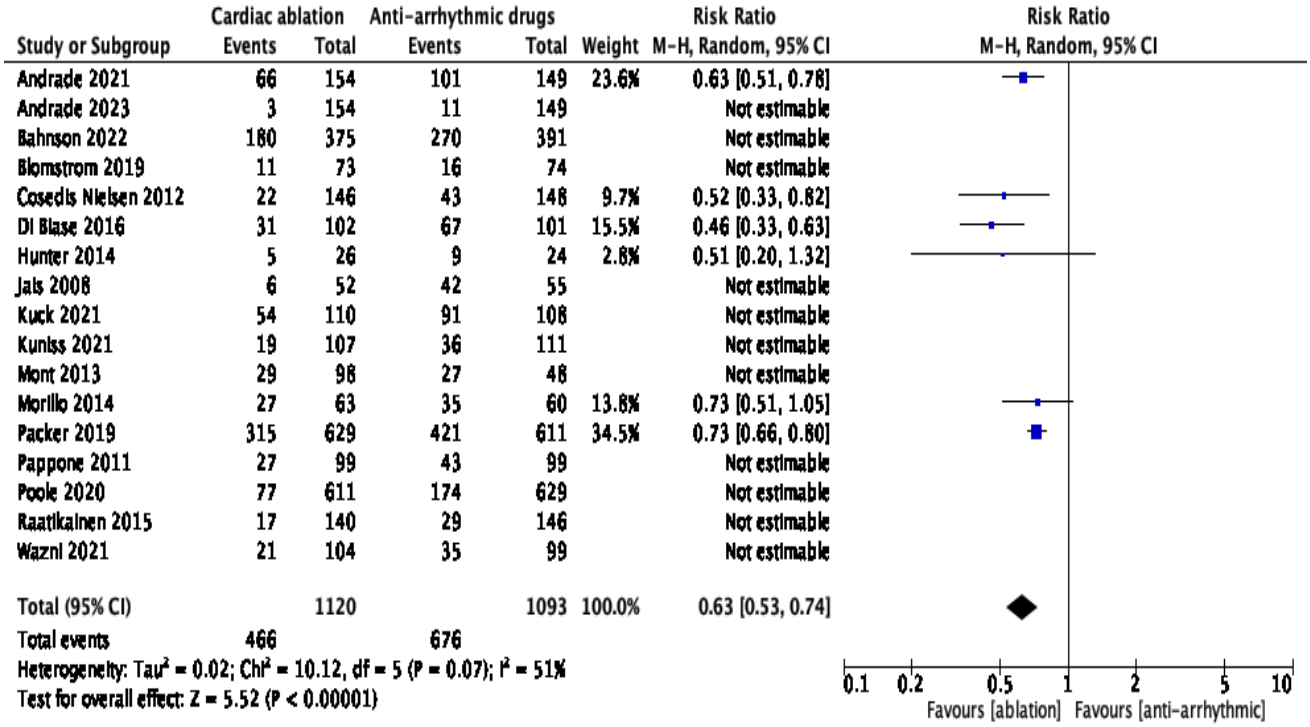


Figure 5 Quality studies of AF recurrence rates in cardiac ablation and anti-arrhythmic drugs

5.0 Discussion

5.1 Key messages

Cardiac ablation is better than anti-arrhythmic drugs for preventing AF recurrence. However, both interventions improved the quality of life from the baseline outcomes, resulting in difference between the interventions. Furthermore, there were significant differences between the treatments for effects on left ventricular ejection fraction. However, this latter finding was based just three small studies.

5.2 Comparison with previous studies (similarities)

AF recurrence

Compared with previous systematic reviews, one similarity would be comparing AF recurrence between cardiac ablations and antiarrhythmic drugs. It is critical to prevent AF recurrence in atrial fibrillation patients. The impact of AF recurrence on both mortality rates and morbidity is crucial, particularly the socioeconomic implications associated with hospitalization rates, managing chronic diseases, and the development of disabilities. It is vital to understand the importance of atrial fibrillation recurrence in order to appropriately allocate resources and implement an increasing number of treatments that attempt to reduce the burden of AF on a growing population (Chugh et al., 2001). Approximately 33.5 million people have atrial fibrillation globally, including 20.9 million men and 12.6 million women, with increased prevalence and incidence rates in most developed countries (Zulkifly et al., 2018). It means that a large population must experience the symptoms of AF recurrence most of the time worldwide; the consequence is critical. The potential causes for the negative effect of AF on mortality are likely diverse and involve multiple factors. An irregular ventricular rhythm has negative impacts on the hemodynamics of the body, perhaps leading to long-term pump failure. Repolarization abnormalities in congestive heart failure have been extensively reported and are recognized to increase the chance of life-threatening arrhythmogenesis in human and animal experiments. Further, multiple comprehensive studies have demonstrated a higher probability of arrhythmia in individuals with congestive heart failure. This finding may be attributed to the significant alteration of the effects of antiarrhythmic medications in relation to heart failure (Chugh et al., 2001).

The most severe consequence associated with atrial fibrillation recurrence is embolic stroke, with an average yearly rate of 4.4% in those diagnosed with AF. Atrial fibrillation recurrence

is also linked to a higher risk of heart failure, myocardial infarction, dementia, chronic kidney failure, and elevated death rates. Atrial fibrillation recurrence significantly raises the likelihood of stroke about five times. However, the level of the related risk, which represents the number of strokes that could be prevented by reducing AF recurrence, fluctuates substantially based on age. In particular, the risk fluctuates between 4.6% in people aged 50-59 years and over 20% in those over 80-89 years (Björck et al., 2013). The prognosis of stroke is worse for people with AF than for those with sinus rhythm. At first, epidemiological studies conducted in North American and European populations reported worse results, with a mortality rate in people with atrial fibrillation at least 1.7 times higher than those without AF (Marini et al., 2005; Lin et al., 1996). Moreover, the recurrence of atrial fibrillation in individuals who have recently experienced a stroke is linked to a longer length of hospital stay, increased incidences of ongoing disability, and increased costs related to healthcare (Rahman et al., 2014).

This review also found the similar evidence as the previous systematic reviews: cardiac ablation is superior to anti-arrhythmic drugs for preventing AF recurrence. The risk ratio of this review is 0.58, meaning the AF recurrence rate in the ablation group is 42% lower than in the drug group (95% CI 0.51 to 0.65, p< 0.00001). The risk ratio of Khan et al. (2014) is 0.40, which means the AF recurrence rate in the ablation group is 60% lower than in the anti-arrhythmic drugs group (95% confidence interval 0.31 to 0.52, *P*=0.00001). According to another review, cardiac ablation was found to be more effective than anti-arrhythmic therapy in obtaining freedom from AF recurrence (relative risk 2.08, 95% confidence interval 1.67 to 2.58, P < 0.00001) (Chen et al., 2018). In addition, the previous review found that the catheter ablation (CA) arm showed a statistically significant reduction in the risk of AF recurrence when compared to the antiarrhythmic drug arm; the odds ratio is 0.25 (95% CI 0.18-0.36 and p < 0.001) (Deshpande et al., 2022).

Cardiac ablation could be used as a first-line treatment for some patients with severe PAF before they try antiarrhythmic therapy. In a meta-analysis review with three randomized control trials that included a total number of 491 symptomatic AF patients, 98.7% of participants who had PAF had a significantly lower AF recurrence rate after catheter ablation (Hakalahti et al., 2015). Multiple studies have shown that effective ablation procedures can remove reversion pauses and prevent the requirement of permanent pacemaker placement for people with tachycardia-bradycardia syndrome.

In this situation, the existence of reversion pauses can be a limitation for most antiarrhythmic medications; therefore, cardiac ablation becomes the first-line treatment. (Hocini et al., 2003).

Quality of life

Compared with previous systematic reviews, another major similarity would be to compare the quality of life in cardiac ablation and anti-arrhythmic medications in AF patients. People with atrial fibrillation may experience symptoms such as shortness of breath, palpitations, chest tightness, dizziness, and fatigue, which affect their quality of life. Atrial fibrillation significantly increases the chance of experiencing serious adverse outcomes, including stroke and mortality. However, AF also gives rise to frequent symptoms, negatively affecting patients' daily activity and decreasing their overall quality of life (Freeman et al., 2015). Therefore, it is important to assess the level of quality of life in AF patients.

The health-related quality of life has a strong relationship with an individual's health status and symptoms since it measures the overall influence of health concerns on their well-being. Health-Related Quality of Life has been specifically described as measuring how an individual's typical or expected physical, emotional, and social well-being are influenced by a medical condition or the interventions taken to address it. Studies have found that measuring health-related quality of life depends on effective communication between health professionals and patients and is restricted by insufficient standard protocols (Rumsfeld et al., 2013). The measurement of quality of life could be challenging due to limitations in time availability and differences between examinations performed by physicians as well as health situations reported by patients. In the case of chronic conditions like AF, the symptoms that follow the condition might not represent an immediate risk to life. However, they can limit the patient's capacity to perform routine tasks and activities. Additional consequences linked to atrial fibrillation, such as episodes of fainting and incidence of strokes, are considerably more severe and can potentially result in significant harm to a person's health-related quality of life. Health quality of life is critical for elderly AF individuals, who are more likely to have chronic AF and multiple comorbidities and risk factors requiring lifelong care and medication. Assessing elderly patients' health status would not only depend on management of symptoms or preventive measures. Health-related quality of life is a significant tool for evaluating the consequences of disease and treatment in people with AF. It proves to be a helpful instrument in guiding decision-making and monitoring the progression of patients (Lane & Lip, 2009). As a result, it can be recognized that the Health-Related Quality of Life

is regularly impacted by factors such as illness, injury, medical treatment, and the health system. The evaluation of a patient's functional ability and health-related quality of life has become a crucial component in assessing patient outcomes and treatments in modern clinical practice (Rumsfeld et al., 2013).

Left ventricular ejection fraction

Lastly, compared with the previous review, another similar area would be comparing left ventricle ejection fraction in cardiac ablation and antiarrhythmic therapy for AF patients (Elgendy et al., 2018). Atrial fibrillation has been reported to be linked with a higher probability of several serious health complications, including all-cause mortality, cardiovascular deaths, severe adverse cardiac events, long-term renal failure, and congestive heart failure. However, heart failure presents the most significant risk among individuals with AF. The pathophysiological mechanisms in heart failure and atrial fibrillation could have strong relationships. The development of cardiomyopathy caused by tachycardia due to prolonged uncontrolled atrial fibrillation leads to a significant decrease in ejection fraction and a rise in heart failure exacerbations (Odutayo et al., 2016).Therefore, measuring the left ventricle ejection fraction in AF patients is essential to prevent developing heart failure.

5.3 Comparison with previous studies (differences)

This is a recent review that evaluate and compare cardiac ablation and anti-arrhythmic therapy in AF patients for AF recurrence, quality of life and left ventricle ejection fraction altogether. However, previous systematic reviews not only focused on AF recurrence; they also preferred to compare hospital admissions, mortality rates, and complications in AF patients after cardiac ablation or antiarrhythmic drugs.

Findings in other reviews not reported in this review

One of the previous meta-analysis reviews included 16 RCTs with a large population of 4822 participants. In the cardiac ablation group, there were 2417 clients, whereas in the antiarrhythmic group, there were 2405 clients. Of these participants, 3190 (66.2%) were men and 1632 (33.8%) were women. Eight RCTs of the review provided data on the result of all-cause mortality. The incidence rates for this particular outcome were relatively low, with the most extensive study, CABANA, accounting for 74% of the total weight of the results. In the

cardiac ablation group, 74 events (4.08%) were reported in 1813 patients. On the other hand, in the group receiving anti-arrhythmic drugs, there were 99 events (5.31%) of 1862 patients. The risk of all-cause mortality did not show a statistically significant difference between the AAD and CA groups (odds ratio 0.75; 95% confidence interval, 0.55–1.03; p = 0.072). While excluding the CABANA study from their analysis, it was shown that catheter ablation has a statistically significant mortality benefit compared to antiarrhythmic drugs (odds ratio 0.52; 95% confidence interval, 0.28–0.97; p = 0.04). For cardiovascular deaths, the review showed 4/458 (0.87%) events in the CA group and 7/527 (1.32%) events in the AAD group, which means there was no statistically significant difference between those two intervention groups (Deshpande et al., 2022).

Khan et al. (2014) reported the total number of adverse events was 70 out of 785 (9%) individuals who underwent cardiac ablation and 77 out of 696 (11%) who took antiarrhythmic drugs. Moreover, 5% of adverse severe events were in the CA arm and 2% in the AAD arm. There was a statistically significant difference in the number of severe adverse events compared to cardiac ablation and antiarrhythmic drugs (relative risk=2.04; 95% confidence interval 1.10-3.77; p value=0.02). Earlier studies demonstrated a higher number of severe adverse events (relative risk 3.35; 95% CI =1.15–9.75; P value 0.03) in comparison to later studies (RR = 1.51; 95% CI = 0.55–4.15; P value 0.42). Another review with a total of nine RCTs, which involved a large sample size of 3576 participants, provided data on all-cause mortality during the follow-up period. There were 96/1808 (5.3%) events in the CA group and 140/1768 (7.95%) events in the AAD group. Based on that nine studies analysis, it proved that cardiac ablation had a statistically significant decrease in all-cause mortality compared to antiarrhythmic drugs in AF patients with low heterogeneity (Relative risk 0.69; 95% CI 0.54-0.88; P=0.003; I^2=0%) (Asad et al., 2019). Hospital admissions, mortality rates, and complications after cardiac ablation or antiarrhythmic drugs are important areas for atrial fibrillation. However, those aspects required lots of resources and a longer time to complete the research project. Since there was only one person to do the current systematic review, those topics were challenged due to limited time and resources.

Another different area is when comparing cardiac ablation and anti-arrhythmic drugs for quality of life, they did not have any significant differences in the current review (mean difference is 0.36; 95% CI -0.10 to 0.81; P value=0.12). According to Reynolds et al. (2010), the quality of life in SF-36 scales was statistically significantly higher in the cardiac ablation

group than in the antiarrhythmic drugs group (52.0+_7.8 vs. 47.1+_10.6; p-value=0.01). Another review found significant increases in the physical component scores in quality of life with a standardized mean difference of (0.58; 95% CI 0.39-0.78; P<0.00001; I^2=6%), preferring cardiac ablation to antiarrhythmic drugs (Allan et al., 2020).

5.4 Strength and Limitation

One of the advantages of this review is no publication date restriction. The current evidence also showed the same results as the previous studies. Despite removing all studies with high-risk bias, the results remained the same. Furthermore, it is a large sample size systematic review, including seventeen randomized control trials with 6045 participants. Moreover, quantitative research involves the measurement of data. Due to the typically significant size of the samples and their representativeness of the population, the findings showed a broad and accurate perspective for the whole population. Some more benefits of quantitative research include work in a natural clinical environment, large-scale study, can be done in a complex system, and simple data collection and analysis by statistical methods (Queirós et al., 2017).

This review's first disadvantage is limited to the English language only. This is because only one person can do the systematic review, leading to inadequate time and limited resources for translation. Only one person screened studies and collected data, but it was a student project. In addition, two RCTs with a high risk of random sequence generation were found, and nine studies with unclear risk of random sequence generation. Fifteen out of seventeen studies did not mention allocation concealment. Fourteen out of seventeen studies had unclear risk of performance bias. Last but not least, all the studies occurred in countries with highly developed economies.

5.5 Clinical research and recommendation

In the cardiac inpatient ward of public hospitals, antiarrhythmic drugs often are the first-line treatment for AF patients. According to the evidence found in this review, cardiac ablation should be recommended as first-line treatment in the clinical setting because it is better than antiarrhythmic drugs for preventing AF recurrence. Moreover, it can promote the quality of life for AF patients, reduce hospital admissions, and lower healthcare costs. In the future,

more high-quality and low-risk bias randomized control trials should be created; it can assist in developing more high-quality and effective quantitative research.

6.0 Conclusion

In summary, the current evidence demonstrated that cardiac ablation is significantly lower than antiarrhythmic drugs for AF recurrence rate. Cardiac ablation is better than antiarrhythmic treatment for preventing AF recurrence. The current evidence also matched the previous findings. Hopefully, more health professionals will consider cardiac ablation first in the future.

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Appendices

Appendix A Draft protocol

For atrial fibrillation patients, how effective is the use of cardiac ablation compared to antiarrhythmic drugs

1.0 Background

1.1 Description of the condition

Atrial fibrillation (AF) is the most prevalent type of cardiovascular arrythmia worldwide. In AF, the cardiac rhythm is irregular and could be very fast as the typical timer in the heart is failed. Multiple random electrical signals are generated from the heart's atria instead of a regular electrical signal. When the atria fibrillate this way, they cannot effectively pump blood into the ventricles. Blood flow to the body may be reduced because the 'booster pump' does not work, particularly if the heart rate is exceptionally high. There are two types of atrial fibrillation: intermittent (paroxysmal atrial fibrillation) and chronic (permanent or persistent atrial fibrillation) (Ministry of Health, 2006).

According to the Global Burden of AF, there were approximately 33.5 million people with AF globally, including 20.9 million men and 12.6 million women, with increased prevalence and incidence rates in most developed countries (Zulkifly et al., 2018). Nearly 10 out of every 100 people over the age of 80 are affected by AF, which occurs in about 1 in 100 people in the general population. In Māori and Pacific people, AF occurs at a younger age than in the rest of New Zealanders (Ministry of Health, 2006).

1.2 why it is important to do this review.

AF and heart failure share the same cardiovascular risk factors, and their treatment and prognosis are often complicated by coexisting and acting synergistically. For example, individuals with atrial fibrillation have a reduction in cardiac output due to a lack of atrial contraction, followed by an impairment in diastolic filling, increasing the negative hemodynamic effects that already exist in patients with heart failure. Most individuals with AF are treated with anti-arrhythmic drugs (AADs) to achieve rhythm control. However, considerable adverse effects and the limited efficacy of available AADs in heart failure patients make this method less than ideal for maintaining sinus rhythm (Briceño et al., 2018). When AADs cannot restore and sustain sinus rhythm (SR), catheter ablation (CA) or combination therapy is usually performed. Despite the fact that trials comparing rhythm

control to rate control have shown no benefits, many health practitioners believe that rhythm control therapy may reduce the risk of severe cardiovascular events. All present international AF study guidelines recommend Cardiac ablation as the initial treatment to prevent recurrent AF and improve symptoms in selected individuals with paroxysmal AF; however, AADs remain the first-line therapy for persistent AF patients (Chen et al., 2018). Therefore, to enhance the current evidence, we did an updated systematic review and meta-analysis of randomised control trials to evaluate and compare cardiac ablation and medical treatments in AF patients for improving left ventricle function, AF recurrence and quality of life.

2.0 Objective

To evaluate and compare the effects of cardiac ablation and anti-arrhythmic drugs in AF patients.

3.0 Search Strategy

3.1 Online searches

Search will be conducted on the following databases using a randomised control trial filter:

- Cochrane Library
- Medline
- Embase
- CINAHL

4.0 Selection criteria

4.1 Types of studies

The study will include only randomised controlled trials or trials described as randomised controlled trials. A pseudo-randomisation trial or a method that does not use a truly random allocation of participants will not be considered.

4.2 Types of participants

Participants aged 18 or over with atrial fibrillation (AF), persistent AF or paroxysmal AF, including both males and females.

4.3 Types of intervention

Any randomised control trials of AF patients for comparing cardiac ablation and anti-arrhythmic drugs.

4.4 Types of outcome measures

The primary outcome is to compare the effectiveness of cardiac ablation and antiarrhythmic drugs of atrial fibrillation (AF) patients for AF recurrence. The secondary outcomes are to compare cardiac ablation and antiarrhythmic drugs of AF patients for the quality of life and left ventricle ejection fraction.

5.0 Data collection

5.1 Selection of studies

Only English language studies will be included, and publication dates will not be limited. The titles and abstracts will be reviewed to ensure that they meet the inclusion criteria. For articles with uncertainties, further screening will be conducted.

During each stage of the selection process, citations from the source library are exported into a candidate library, a retrieved paper library, and a final library that includes all the studies.

5.2 Data extraction and management

To collect data from the included studies, I will create and apply a standardised extraction form; data will be extracted using Excel. The data extraction form will include article citations, year, country, study ID, trials designs, methods, number of participants, inclusion and exclusion criteria, intervention description, bias assessments.

6.0 Data synthesis

Meta-analysis will be used for this review.

Appendix B Data collection

B. 1	Citation	Andrade, J. G., Deyell, M. W., Macle, L., Wells, G. A., Bennett, M., Essebag, V., Champagne, J., Roux, J. F., Yung, D., Skanes, A., Khaykin, Y., Morillo, C., Jolly, U., Novak, P., Lockwood, E., Amit, G., Angaran, P., Sapp, J., Wardell, S., Lauck, S., Cadrin-Tourigny, J., Kochhauser, S., Verma, A., EARLY-AF Investigators (2023). Progression of atrial fibrillation after cryoablation or drug therapy. *New England Journal of Medicine*, *388*(2), 105-116. https://doi.org/10.1056/NEJMoa2212540
	Study ID	1
	Year	2023
	Country	Canada
	Study design	RCT's
	Random allocation	Described as randomised
	allocation concealment	not clear
	Participants blinded	No
	Investigators blinded	No
	outcome accessor blinded	Yes
	length of Intervention follow up	91 days, 12 months, follow up 36months after initial treatment
	Drop outs	2
	Number of participants	303
	Number of completed	301
	Age range	<18 years old
	Intervention mean age	
	AF recurrence (Ablation) 3 months	3/154 (1.9%)
	AF recurrence (Ablation) one year	66/154 (42.9%)

	AF recurrence (Ablation) three year	87/154 (56.5%)
	AF recurrence (anti-arrhythmic drugs) 3 months	11/149 (7.4%)
	AF recurrence (anti-arrhythmic drugs) one year	101/149 (67.8%)
	AF recurrence (anti-arrhythmic drugs) three year	115/149 (77.2%）
AFEQT (AF effect on quality of life) score	Quality of life (cardiac ablation) mean +_SD	26.9+_ 1.9 (12 months), 28.1+_ 2.0 (36 months)
	Quality of life (antiarrhythmic drug) mean +_SD	22.9+_2.0 (12months), 24.8 +_2.0 (36 months)
EQ-5D (European Quality of life 5 dimensions) score	Quality of life (ablation) mean +_SD	0.06+_0.01 (12 months), 0.06+_0.02 (36months)
	Quality of life (antiarrhythmic drug) mean +_SD	0.01+_0.01 (12 months), 0.01+_0.02 (36 months)
EQ-VAS (European Quality of life- Visual Analogue Scale) score	Quality of life (cardiac ablation) mean +_ SD	7.73+_1.44 (12 months), 7.64+_1.59 (36 months)
	Quality of life (antiarrhythmic drug) mean +_SD	5.71+_1.46(12months), 6.15 +_1.63(36 months)
	Ejection fraction	

Intervention	Inclusion criteria	Adults>18 years old had symptomatic paroxysmal atrail fibrillation and had at least one documented ECG of one episode of AF within 24 months
	Exclusion criteria	patients who had a history of daily use of a class I or class III antiarrhythmic drug at therapeutic doses
	Intervention description	This report concerns paroxysmal, untreated atrial fibrillation patients who were randomly assigned to receive cryoballoon ablation or antiarrhythmic drug therapy and were followed for three years. As part of the trial, implantable loop recorders were placed on all patients for evaluation every six months. Data have been collected regarding the onset of persistent atrial fibrillation, recurrent atrial tachyarrhythmia (defined as atrial fibrillation, flutter, or tachycardia lasting >=30 seconds), the burden of atrial fibrillation, quality-of-life measurements, health care implementation, and safety
Bias	Selection Bias-random sequence generation	unclear risk- did not describe
	selection Bias-allocation concealment	unclear risk-did not describe
	Performance Bias	unclear risk
	Detection Bias	low risk- Quote: "randomised trial with blinded end-point adjudication at 18 centres…"
	Attrition Bias	low risk
	Reporting Bias	low risk
	Other Bias	low risk
	Comments	

B. 2	citation	Di Biase, L., Mohanty, P., Mohanty, S., Santangeli, P., Trivedi, C., Lakkireddy, D., Reddy, M., Jais, P., Themistoclakis, S., Dello Russo, A., Casella, M., Pelargonio, G., Narducci, M. L., Schweikert, R., Neuzil, P., Sanchez, J., Horton, R., Beheiry, S., Hongo, R., Hao, S., Rossillo, A., Forleo, G., Tondo, C., Burkhardt, J. D., Haissaguerre, M., Natale, A. (2016). Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the aatac multicenter randomized trial. *Circulation*, *133*(17), 1637-44. https://doi.org/10.1161/CIRCULATIONAHA.115.019406
	Study ID	2

	Year	2016
	Country	America
	study design	RCT's
	Random allocation	Yes
	allocation concealment	not clear
	participants blinded	No
	investigator blinded	No
	outcome assessor blinded	not clear
	length of intervention follow up	24 months
	Drop out	0
	Number of participants	203
	Number of completed	203
	Age range	> 18 years
	Intervention mean age	62
	AF recurrence (Ablation) 24 months	31/102 （30%）
	AF recurrence (antiarrhythmic drugs) 24 months	67/101 （64%）
MLHFQ	Quality of life (ablation) mean +_ standard deviation	52+_24
	Quality of life (antiarrhythmic drugs) mean +_ standard deviation	50+_27

LVEF % (left ventricular ejection fracrion) mean +_ standard deviation	Ablation	29+_5
	antiarrhythmic drugs	30+_8
Intervention	Inclusion criteria	Patients with a dual-chamber ICD or CRTD (with an existing functional atrial lead) with remote monitoring capabilities and an EF = 40% as determined by echocardiogram, nuclear imaging, MRI, or cardiac catheterization within the previous three months were eligible for this study.Persistent or chronic symptomatic atrial fibrillation that is resistant to antiarrhythmic medication other than Amiodarone. At least three weeks of therapeutic anticoagulation must occur before the initiation of therapy. Capability to pass a six-minute walk test. age > or=18 years old. All patients with CHF were optimally treated with beta-blockers, ACE inhibitors, or angiotensin receptor blockers.
	exclusion criteria	Patients were excluded if they had reversible AF, valvular or coronary heart disease resulting in surgical intervention, early postoperative AF (within three months of surgery), or a life expectancy of less than two years. In addition, patients with a prolonged QT interval, hypothyroidism, a history of severe pulmonary disease, or hepatic failure were excluded.
	Intervention description	Determine whether catheter-based atrial fibrillation (AF) ablation is preferable to Amiodarone treatment for persistent/permanent AF in ICD/CRTD patients with impaired left ventricular function.
Bias	Selection Bias-random sequence generation	low risk- Quote: "A computerized central randomization scheme was generated using block randomization, and sets of randomly selected blocks were provided to the investigating sites."
	selection Bias-allocation concealment	unclear risk
	Performance Bias	unclear risk
	Detection Bias	unclear risk
	Attribution Bias	low risk
	Reporting Bias	low risk
	Other Bias	low risk

B. 3	citation	Packer, D. L., Mark, D. B., Robb, R. A., Monahan, K. H., Bahnson, T. D., Poole, J. E., Noseworthy, P. A., Rosenberg, Y. D., Jeffries, N., Mitchell, L. B., Flaker, G. C., Pokushalov, E., Romanov, A., Bunch, T. J., Noelker, G., Ardashev, A., Revishvili, A., Wilber, D. J., Cappato, R., Kuck, K. H., Hindricks, G., Davies, D. W., Kowey, P. R., Naccarelli, G. V., Reiffel, J. A., Piccini, J. P., Silverstein, A. P., Al-Khalidi, H. R., Lee, K. L., CABANA Investigators (2019). Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the cabana randomized clinical trial. *JAMA, 321*(13), 1261-1274. https://doi.org/10.1001/jama.2019.0693
	Study ID	3
	Year	2019
	Country	America
	Study design	RCT's
	Random allocation	yes
	allocation concealment	not clear
	participants blinded	No
	investigator blinded	yes
	outcome assessor blinded	yes
	length of intervention follow up	4 years
	Drop out	106
	Number of participants	2204
	Number of completed	2098
	Age range	>18 years old, >= 65 years or <65 years
	Intervention mean age	68
	AF recurrence (ablation) 36 months	315/629 （50%）

	AF recurrence (antiarrhythmic drugs) 36 months	421/611 （69.5%）
	Quality of life	
	LVEF	
	Inclusion criteria	Eligible patients were 65 years of age or older, or younger than 65 years with 1 or more risk factors for stroke (hypertension, heart failure, history of stroke, diabetes, or other heart problems), 2 or more episodes of paroxysmal AF or 1 episode of persistent AF in the previous 6 months, and were suitable for catheter-based treatment or rhythm and/or rate control drug therapy.
	Exclusion criteria	Exclusion criteria included prior left atrial catheter ablation for atrial fibrillation (AF) or failure of two or more antiarrhythmic medications.
	Intervention description	The catheter ablation group underwent pulmonary vein isolation, with additional ablative procedures at the discretion of site investigators. The drug therapy group received standard rhythm and/or rate control drugs guided by contemporaneous guidelines.
Bias	Selection Bias-random sequence generation	low risk- Quote:" Randomization will be accomplished by telephone or internet using a centralized, interactive voice and web randomization system (IXRS). The enrolment scheme is based on permuted block randomization with stratification by clinical site."
	selection Bias-allocation concealment	not clear
	Performance Bias	unclear risk
	Detection Bias	low risk
	Attribution Bias	low risk
	Reporting Bias	low risk
	Other Bias	high risk- some of the secondary measurement outcomes did not mention

B. 4	citation	Poole, J. E., Bahnson, T. D., Monahan, K. H., Johnson, G., Rostami, H., Silverstein, A. P., Al-Khalidi, H. R., Rosenberg, Y., Mark, D. B., Lee, K. L., Packer, D. L., CABANA Investigators and ECG Rhythm Core Lab (2020). Recurrence of atrial fibrillation after catheter ablation or antiarrhythmic drug therapy in the cabana trial. *Journal of the American College of Cardiology, 75*(25), 3105-3118. https://doi.org/10.1016/j.jacc.2020.04.065	
	Study ID	4	
	Year	2020	
	Country	America	
	study design	RCT's	
	Random allocation	not clear	
	Allocation concealment	not clear	
	participants blinded	no	
	investigator blinded	not clear	
	outcome assessor blinded	not clear	
	Length of intervention follow up	5 years	
	Drop out	964	
	number of participants	2204	
	number of completed	1240	
	Age range	>=18 years	
	Intervention mean age	68	
	AF recurrence (Ablation)	77/611 12.6% (12months)	113/611 18.4% (60 months)
	AF recurrence (antiarrhythmic drugs)	174/629 27.5% (12 months)	145/629 23.1% (60 months)
	Quality of life		

	LVEF			
	Inclusion criteria	Paroxysmal, persistent, and long standing persistent AF. All enrolled patients using CABANA ECG core lab monitoring protocol.		
	Exclusion criteria	Of the 2204 enrolled patients, who did not have post 90 day blanking data were excluded from the study.		
	Intervention description	To use a ECG recording monitor for CABANA patients to assess recurrence AF compared with cardiac ablation and drug therapy.		
Bias	Selection Bias-random sequence generation	not clear		
	selection Bias-allocation concealment	not clear		
	Performance Bias	not clear		
	Detection Bias	not clear		
	Attribution Bias	not clear		
	Reporting Bias	low risk		
	Other Bias	unclear		

B. 5	Citation	Cosedis Nielsen, J., Johannessen, A., Raatikainen, P., Hindricks, G., Walfridsson, H., Kongstad, O., Pehrson, S., Englund, A., Hartikainen, J., Mortensen, L. S., Hansen, P. S. (2012). Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *New England Journal of Medicine, 367*(17), 1587-95. https://doi.org/10.1056/NEJMoa1113566		
	Study ID	7		
	Year	2012		
	Country	Denmark		
	Study design	RCT's		
	Random allocation	Yes		

	Allocation concelament	not clear		
	participants blinded	not clear		
	investigator blinded	Not clear		
	outcome assessor blinded	Yes		
	Length of intervetion follow up	24 months		
	Drop out	0		
	Number of participants	296		
	Number of completed	296		
	Age range	>18 and <70 years old		
	Intervention mean age	55		
	AF recurrence (cardiac abaltion)	22/146 15% (24 months)		
	Af recurrence (antiarrhythmic drugs)	43/148 29% (24 months)		
SF-36 (short term health survey	Quality of life (mean+_ SD)- Cardiac ablation	50.2+_8.5 (12 months)	50.0+_8.8 (24 months)	
	Quality of life (mean+_ SD)- Antiarrhythmic drugs	47.5+_9.7 (12 months)	47.9+_8.9 (24 months)	
	LVEF			

	Inclusion criteria	At least two episodes of symptomatic atrial fibrillation within the previous six months, but no episode lasting longer than seven days.		
	exclusion criteria	Age greater than 70, previous or ongoing treatment with antiarrhythmic medications of classes IC or III, contraindication to both classes IC and III agents		
	Interventio n description	A sutdy compared radiofrequency abaltion with antiarrythmic drugs therapy as first line treaments in patients with AF.		
	Selection Bias- random sequence generation	low risk- Quote" Block randomization was performed with the use of an automated telephone randomization system."		
	selction Bias- allocation concelame nt	Not clear		
	Performan ce Bias	not clear		
	Detection Bias	low risk		
	Attribution Bias	low risk		
	Reporting Bias	low risk		
	Other Bias	low risk		

B. 6	Citation	Raatikainen, M. J., Hakalahti, A., Uusimaa, P., Nielsen, J. C., Johannessen, A., Hindricks, G., Walfridsson, H., Pehrson, S., Englund, A., Hartikainen, J., Kongstad, O., Mortensen, L. S., Hansen, P. S., MANTRA-PAF investigators (2015). Radiofrequency catheter ablation maintains its efficacy better than antiarrhythmic medication in patients with paroxysmal atrial fibrillation: on-treatment analysis of the randomized controlled mantra-paf trial. International Journal of Cardiology, 198, 108-14. https://doi.org/10.1016/j.ijcard.2015.06.160		
	Study ID	11		
	Year	2015		
	Country	Denmark		
	Study design	RCT's		

	Random allocation	Not clear		
	Allocation concealment	Not clear		
	participants blinded	No		
	investigator blinded	Not clear		
	outcome assessor blinded	yes		
	Length of intervention follow up	24 months		
	Drop out	8		
	Number of participants	294		
	Number of completed	286		
	Age range	>18 years		
	Intervention mean age	56		
	AF recurrence (cardiac ablation)	17/140 12% (12 months)	16/140 11% (24 months)	
	AF recurrence (antiarrhythmic drugs)	29/146 20% (12 months)	39/146 27% (24 months)	
SF-36	Quality of life (Cardiac ablation) mean +_ SD	49.3+_8.5 (12months)	49.5+_8.7 (24 months)	
	Quality of life (antiarrhythmic drugs) mean +_SD	50.1+_9.4 (12 months)	49.6+_9.2 (24 months)	
	LVEF			
	Inclusion criteria	People with paroxysmal atrial fibrillation,		
	Exclusion criteria	patients who from the on-treatment analysis that did not receive the index treatment are not included		

	Intervention description	The aim of this study was to compare radiofrequency catheter ablation with antiarrhythmic drugs as the first-line treatment for paroxysmal atrial fibrillation.		
	Selection Bias-random sequence generation	Not clear		
	selection Bias-allocation concealment	Not clear		
	Performance Bias	unclear risk		
	Detection Bias	low risk		
	Attribution Bias	low risk		
	Reporting Bias	low risk		
	Other Bias	low risk		

B. 7	Citation	Andrade, J. G., Wells, G. A., Deyell, M. W., Bennett, M., Essebag, V., Champagne, J., Roux, J. F., Yung, D., Skanes, A., Khaykin, Y., Morillo, C., Jolly, U., Novak, P., Lockwood, E., Amit, G., Angaran, P., Sapp, J., Wardell, S., Lauck, S., Macle, L., Verma, A., EARLY-AF Investigators (2021). Cryoablation or drug therapy for initial treatment of atrial fibrillation. *New England Journal of Medicine, 384*(4), 305-315. https://doi.org/10.1056/NEJMoa2029980
	Study ID	12
	Year	2021
	Country	Canada
	Study design	RCT's
	Random allocation	Yes
	Allocation concealment	yes
	Participants blinded	No
	Investigator blinded	No
	Outcome assessor blinded	Yes

	Length of intervention follow up	12 months
	Drop out	0
	Number of participants	303
	number of completed	303
	Age range	>18 years old
	Intervention mean age	
	AF recurrence (cardiac ablation)	66/154 42.9% (12 months)
	AF recurrence (antiarrhythmic drugs)	101/149 67.8% (12 months)
AFEQT (AF effect on quality of life) score	Quality of life (cardiac ablation) mean +_SD	61.4+_19.7
	Quality of life (antiarrhythmic drug) mean +_SD	57.4+_20.6
EQ-5D (European Quality of life 5 dimensions) score	Quality of life (cardiac ablation) mean +_SD	0.77+_0.26
	Quality of life (antiarrhythmic drug) mean +_SD	0.75+_0.26
EQ-VAS (European Quality of life- Visual Analogue Scale) score	Quality of life (cardiac ablation) mean +_SD	75.4+_14.5

	Quality of life (antiarrhythmic drug) mean +_SD	74.4+_16.5
	LVEF	
	Inclusion criteria	Acute atrial fibrillation detected on electrocardiography within 24 months prior to randomization must be present in patients over the age of 18 with symptomatic atrial fibrillation.
	Exclusion criteria	Patients who took antiarrhythmic drugs regularly at therapeutic doses in class I or class III were excluded from the study.
	Intervention description	Three hundred and three patients with symptomatic, paroxysmal, untreated atrial fibrillation were randomly assigned to undergo catheter ablation with a cryotherapy balloon or antiarrhythmic pharmacological therapy for initial rhythm control.
	Selection Bias-random sequence generation	Low risk- Quote:" Randomization was performed with concealed allocation, according to a computer-generated allocation sequence, with permuted blocks of four and eight."
	selection Bias-allocation concealment	Low risk-Quote:" Randomization was stratified according to centre with the use of web-based software."
	Performance Bias	unclear risk
	Detection Bias	Low risk
	Attribution Bias	Low risk
	Reporting Bias	Low risk
	Other Bias	Low risk

B. 8	Citation	Kuniss, M., Pavlovic, N., Velagic, V., Hermida, J. S., Healey, S., Arena, G., Badenco, N., Meyer, C., Chen, J., Iacopino, S., Anselme, F., Packer, D. L., Pitschner, H. F., Asmundis, C., Willems, S., Di Piazza, F., Becker, D., Chierchia, G. B., Cryo-FIRST Investigators (2021). Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. *Europace, 23*(7), 1033-1041. https://doi.org/10.1093/europace/euab029
	Study ID	13
	Year	2021

	Country	Europe
	Study design	RCT's
	Random allocation	not clear
	Allocation concealment	not clear
	Participants blinded	No
	Investigator blinded	not clear
	Outcome assessor blinded	Yes
	Length of intervention follow up	12 months
	Drop out	31
	Number of participants	218
	Number of completed	187
	Age range	between 18 to 75 years old
	Intervention mean age	50.5
	AF recurrence (cardiac ablation)	19/107 17.8% (12 months)
	AF recurrence (antiarrhythmic drugs)	36/111 32.4% (12 months)
	Quality of life	
	LVEF	
	Inclusion Criteria	patients 18 to 75 years old with a normal ECG, structrually normal cardiac LVEF>=50% and recurrrent symtopmatic PAF who did not take antiarrhythmic drugs before.
	Exclusion Criteria	PAF patients who took antiarryhthmic drugs before will be excluded.

	Intervention description	In this study, cardiac ablation was compared with antiarrhythmic drug therapy for the prevention of atrial arrhythmia recurrence in rhythm control-naive patients with paroxysmal atrial fibrillation (AF).
	Selection Bias-random sequence generation	Unclear risk
	selection Bias-allocation concealment	Unclear risk
	Performance Bias	Unclear risk
	Detection Bias	Low risk
	Attribution Bias	Low risk
	Reporting Bias	Low risk
	Other Bias	Low risk

B. 9	Citation	Mont, L., Bisbal, F., Hernandez-Madrid, A., Perez-Castellano, N., Vinolas, X., Arenal, A., Arribas, F., Fernandez-Lozano, I., Bodegas, A., Cobos, A., Matia, R., Perez-Villacastin, J., Guerra, J. M., Avila, P., Lopez-Gil, M., Castro, V., Arana, J. I., Brugada, J., SARA investigators (2014). Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (sara study). *European Heart Journal, 35*(8), 501-7. https://doi.org/10.1093/eurheartj/eht457		
	Study ID	17		
	Year	2013		
	Country	Spain		
	Study design	RCT's		
	Random allocation	unclear		

	Allocation concealment	unclear		
	Participants blinded	No.		
	Investigator blinded	not clear		
	Outcome assessor blinded	Yes		
	Length of intervention follow up	12 months		
	Drop out	0		
	Number of participants	146		
	Number of completed	146		
	Age range	>18 and <70 years old		
	Intervention mean age	55		
	AF recurrence (Cardiac ablation)	29/98 29.6% (3 months)	39/98 39.8% (12 months)	
	AF recurrence (antiarrhythmic drugs)	27/48 56.3% (3 months)	34/48 70.8% (12 months)	
	Quality of life			
	LVEF			
	Inclusion criteria	Recruitment included patients with symptomatic persistent atrial fibrillation lasting more than seven days or less than seven days and refractory to at least one class I or class III antiarrhythmic drug.		
	Exclusion criteria	Exclusion criteria included age <18 or >70, long-standing persistent AF, the first episode of AF, hyper or hypothyroidism, hypertrophic cardiomyopathy, pacemaker or defibrillator implant, moderate or severe mitral disease or mitral prosthesis, LVEF less than 30%, and left atrial diameter more than 50mm.		

	Intervention description	Patients with persistent AF were randomly assigned to cardiac ablation or antiarrhythmic drugs in a 12-month follow-up study. After a three-month blanking period, the primary outcome is any episode of atrial flutter or AF lasting longer than 24 hours. The secondary outcomes included hospitalisation and cardioversion, as well as any type of atrial tachyarrhythmia lasting more than 30 seconds.		
	Selection Bias-random sequence generation	unclear		
	selection Bias-allocation concealment	unclear		
	Performance Bias	low risk		
	Detection Bias	low risk		
	Attribution Bias	low risk		
	Reporting Bias	low risk		
	Other Bias	low risk		

B. 10	citation	Blomstrom-Lundqvist, C., Gizurarson, S., Schwieler, J., Jensen, S. M., Bergfeldt, L., Kenneback, G., Rubulis, A., Malmborg, H., Raatikainen, P., Lonnerholm, S., Hoglund, N., Mortsell, D. (2019). Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the captaf randomized clinical trial. JAMA, 321(11), 1059-1068. https://doi.org/10.1001/jama.2019.0335		
	Study ID	18		
	Year	2019		
	Country	Sweden		
	Study design	RCT's		

	Random allocation	Not clear		
	Allocation concealment	No		
	Participants blinded	No		
	Investigator blinded	No		
	Outcome assessor blinded	Yes		
	Length of intervention follow up	4 years		
	Drop out	8		
	Number of participants	155		
	Number of completed	147		
	Age range	30-70		
	Intervention mean age	56.1		
	AF recurrence (Cardiac ablation)	11/73 15.1% (12months)		
	AF recurrence (antiarrhythmic drugs)	16/74 21.6% (12 months)		
SF-36 short form health survey	Quality of life (cardiac ablation)	61.8 points (baseline)	73.9 points (12 months)	
	Quality of life (antiarrhythmic drug)	62.7 points (baseline)	65.4 points (12 months)	
	LVEF			

	Inclusion criteria	A participant's age range is 30 to 70 years, with a history of symptomatic atrial fibrillation for at least six months and a symptomatic atrial rhythm confirmed by an ECG. Additionally, the participant must have had either one paroxysmal episode of atrial fibrillation in the previous two months or two persistent episodes of atrial fibrillation that were converted to sinus rhythm in the past 12 months. Alternatively, the participant can be included if they have intolerance to no more than one antiarrhythmic drug, including β-blockers.		
	Exclusion criteria	The exclusion criteria included New York Heart Association class III to IV, LVEF(left ventricular ejection fraction) less than 35%, left atrial diameter > 60 mm, atrial fibrillation related to previous ablation, and dependence on ventricular pacing.		
	Intervention description	Patients with atrial fibrillation are compared with antiarrhythmic medication and catheter ablation over a 12-month period to assess their quality of life.		
	Selection Bias-random sequence generation	high risk-Quote: “ allocation sequence was generated using permuted block randomization 4 and 1:1 allocation stratified by centre and type of atrial fibrillation. The randomization code was generated by a validated database system.”		
	selection Bias-allocation concealment	unclear		
	Performance Bias	unclear		
	Detection Bias	low risk		
	Attribution Bias	low risk		
	Reporting Bias	low risk		
	Other Bias	low risk		

B. 11	Citation	Kuck, K. H., Lebedev, D. S., Mikhaylov, E. N., Romanov, A., Geller, L., Kalejs, O., Neumann, T., Davtyan, K., On, Y. K., Popov, S., Bongiorni, M. G., Schluter, M., Willems, S., Ouyang, F. (2021). Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (attest). *Europace*, *23*(3), 362-369. https://doi.org/10.1093/europace/euaa298
	Study ID	19
	Year	2021
	Country	England
	Study design	RCT's
	Random allocation	not clear
	Allocation concealment	not clear
	Participants blinded	not clear.
	Investigator blinded	not clear.
	Outcome assessor blinded	not clear.
	Length of intervention follow up	3 years
	Drop out	37
	Number of participants	255
	Number of completed	218
	Age range	>=60 years old
	Intervention mean age	67.7
	AF recurrence (cardiac ablation)	54/110 49.1% (3 years)
	AF recurrence (antiarrhythmic drugs)	91/108 84.3% (3 years)
	Quality of life	
	LVEF	

	Inclusion criteria	In this investigation, 60-year-old patients with paroxysmal atrial fibrillation (AF) for more than two years and two episodes in the six months before enrollment.
	Exclusion criteria	A history of reversible atrial fibrillation, persistent or permanent atrial fibrillation (AF) or atrial tachycardia (AT), cardioversion >48 hours after onset of AF/AT, and recent cardiovascular events were excluded.
	Intervention description	This study examines whether radiofrequency (RF) catheter ablation delays the development of atrial fibrillation (AF) when compared to antiarrhythmic drug (AAD) treatment, as prescribed by current AF management guidelines.
	Selection Bias-random sequence generation	high risk- Quote:" Eligible patients had failed treatment with 1-2 ADDs, had a HATCH score between 1 and 4, and were randomized (1:1 stratified by gender and study site) to pulmonary vein isolation via radiofrequency ablation or AAD therapy."
	selection Bias-allocation concealment	Not clear
	Performance Bias	unclear
	Detection Bias	unclear
	Attribution Bias	low risk
	Reporting Bias	low risk
	Other Bias	low risk

B. 12	Citation	Morillo, C. A., Verma, A., Connolly, S. J., Kuck, K. H., Nair, G. M., Champagne, J., Sterns, L. D., Beresh, H., Healey, J. S., Natale, A., RAAFT-2 Investigators (2014). Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (raaft-2): a randomized trial. *JAMA*, *311*(7), 692-700. https://doi.org/10.1001/jama.2014.467		
	Study ID	21		
	year	2014		
	Country	England		

	Study design	RCT's		
	Random allocation	Yes		
	Allocation concealment	Not clear		
	Participants Blinded	unclear		
	Investigator Blinded	unclear		
	Outcome assessor Blinded	Yes		
	Length of intervention follow up	24 months		
	Drop out	4		
	Number of participants	127		
	Number of completed	123		
	Age range	>18 and <75		
	Intervention mean age	55		
	AF recurrence (Cardiac ablation)	41% (27/63)		
	AF recurrence (antiarrhythmic drugs)	57% (35/60)		
EQ5D	Quality of life (cardiac ablation)	0.86 (baseline)	1 (12 months)	
	Quality of life (antiarrhythmic drugs)	0.84 (baseline)	1 (12 months)	
	LVEF			
	Inclusion criteria	To be eligible, a person must have symptomatic recurrent paroxysmal AF lasting at least 30 seconds and at least four episodes within the past six months, and also at least more than one episode documented by an ECG within that time frame, and		

		must not be taking an antiarrhythmic drug.		
	Exclusion criteria	Left ventricular ejection fraction of less than 40%, left atrial width of more than 5.5 cm, left ventricular wall thickness of more than 1.5 cm, coronary artery disease, valvular disease or cardiac surgery in the last 6 months, previous left heart ablation, or an inability to take heparin or warfarin.		
	Intervention description	As a first-line treatment for paroxysmal AF, radiofrequency ablation is compared with antiarrhythmic drugs.		
	Selection Bias-random sequence generation	Low risk- Quote:" The randomization schedule was computer generated and stratified by site with variable block size."		
	selction Bias-allocation concelament	unclear risk		
	Performance Bias	Low risk		
	Detection Bias	Low risk		
	Attribution Bias	Low risk		
	Reporting Bias	Low risk		
	Other Bias	Low risk		

B. 13	citation	Wazni, O. M., Dandamudi, G., Sood, N., Hoyt, R., Tyler, J., Durrani, S., Niebauer, M., Makati, K., Halperin, B., Gauri, A., Morales, G., Shao, M., Cerkvenik, J., Kaplon, R. E., Nissen, S. E., STOP AF First Trial Investigators (2021). Cryoballoon ablation as initial therapy for atrial fibrillation. *New England Journal of Medicine*, *384*(4), 316-324. https://doi.org/10.1056/NEJMoa2029554
	Study ID	22
	Year	2021
	Country	America
	Study design	RCT's

	Random allocation	Not clear
	Allocation concealment	Not clear
	Participant blinded	No
	Investigator blinded	Not clear
	Outcome assessor blinded	not clear
	Length of intervention follow up	12 months
	Drop out	10
	Number of participants	203
	Number of completed	193
	Age range	18-80 years old
	Intervention mean age	60.4
	AF recurrence (cardiac ablation)	21/104 (20.2%) (3months)
	AF recurrence (antiarrhythmic drug)	35/99 (35.4%) (3 months)
	Quality of life	
	LVEF	
	Inclusion criteria	People who were 18 to 80 years of age and had recurrent symptomatic paroxysmal atrial fibrillation.
	Exclusion criteria	Treatments with antiarrhythmic medications for seven days or more, enlarged left atrial diameter of more than 5 cm, or previous left atrial ablation or surgery were excluded.
	Intervention description	A multicentre randomised trial examined patients who were between 18 and 80 years old and with paroxysmal atrial fibrillation to receive either cryoballoon ablation or antiarrhythmic drug treatment.

	Selection Bias-random sequence generation	Unclear risk
	selection Bias-allocation concealment	Unclear risk
	Performance Bias	Unclear risk
	Detection Bias	Unclear risk
	Attribution Bias	Low risk
	Reporting Bias	Low risk
	Other Bias	Low risk

B. 14	Citation	Pappone, C., Vicedomini, G., Augello, G., Manguso, F., Saviano, M., Baldi, M., Petretta, A., Giannelli, L., Calovic, Z., Guluta, V., Tavazzi, L., Santinelli, V. (2011). Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the apaf study. Circulation: Arrhythmia and Electrophysiology, 4(6), 808-14. https://doi.org/10.1161/CIRCEP.111.966408		
	Study ID	24		
	year	2011		
	country	Italy		
	Study design	RCT's		
	Random allocation	Not clear		
	Allocation concealment	Not clear		
	Participants blinded	Not clear		
	Investigator blinded	Not clear		
	Outcome assessor blinded	Yes		
	Length of intervention follow up	4 years		

	Drop out	0		
	Number of participants	198		
	Number of completed	198		
	Age range	>18 or <70 years		
	Intervention mean age	56		
	AF recurrence (cardiac ablation)	27/99 27.3% (4 years)		
	AF recurrence (antiarrhythmic drugs)	43/99 43.5% (4 years)		
SF-36	Quality of life(mean+_SD) Cardiac ablation	44..4+_9 (baseline)	52.3+_9 (4 years)	
	Quality of life(mean+_SD) Antiarrhythmic drugs	45.7+_9 (baseline)	52.6+_8 (4 years)	
	LVEF			
	Inclusion criteria	In the last six months, patients with AF burden more than two episodes per month and an AF history of more than six months were assessed by trans-telephonic monitoring.		
	Exclusion criteria	Those with persistent atrial fibrillation, left atrial diameter greater than 65mm, LVEF less than 35%, heart failure symptoms, and New York Heart Association functional class II were not included.		
	Intervention description	In a 4-year follow-up period, they evaluated the efficacy of Radiofrequency catheter ablation or Antiarrhythmic drugs.		
	Selection Bias-random sequence generation	Unclear risk		
	selection Bias-allocation concealment	Unclear risk		
	Performance Bias	Unclear risk		
	Detection Bias	Low risk		

	Attribution Bias	Low risk		
	Reporting Bias	Low risk		
	Other Bias	Low risk		

B. 15	Citation	Jais, P., Cauchemez, B., Macle, L., Daoud, E., Khairy, P., Subbiah, R., Hocini, M., Extramiana, F., Sacher, F., Bordachar, P., Klein, G., Weerasooriya, R., Clementy, J., Haissaguerre, M. (2008). Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the a4 study. *Circulation*, *118*(24), 2498-505. https://doi.org/10.1161/CIRCULATIONAHA.108.772582		
	Study ID	25		
	Year	2008		
	Country	France		
	Study design	RCT's		
	Random allocation	unclear		
	Allocation concealment	unclear		
	Participants blinded	unclear		
	Investigator blinded	unclear		
	Outcome assessor blinded	unclear		
	Length of intervention follow up	12 months		
	Drop out	4		
	Number of participants	112		
	Number of completed	108		
	Age range	> 18 years old		
	Intervention mean age	51.1		

	AF recurrence (cardiac ablation)	11.5% 6/52 (12 months)		
	AF recurrence (antiarrhythmic drugs)	76.4% 42/55 (12 months)		
SF-36	Quality of life Cardiac ablation (mean)	44.8 (baseline)	56.6+_7.8 (12 months)	
	Quality of life Antiarrhythmic drugs (mean)	43 (baseline)	51.9+_9.7(12 months)	
	LVEF (cardiac ablation) mean+_SD	65.4+_8.9%		
	LVEF (antiarrhythmic drugs) mean +_ SD	65.4+_5.9%		
	Inclusion criteria	More than two episodes of paroxysmal AF within six months were present in patients over 18 years old.		
	Exclusion criteria	Before AF ablation, patients with contraindications to > two antiarrhythmic drugs in different classes or oral anticoagulants, or with an intracardiac thrombus, AF associated with a potentially reversible cause, pregnancy, or stopping oral anticoagulants.		
	Intervention description	For atrial fibrillation, an experiment was carried out comparing catheter ablation to antiarrhythmic drugs.		
	Selection Bias-random sequence generation	unclear risk		
	selection Bias-allocation concealment	unclear risk		
	Performance Bias	unclear risk		

	Detection Bias	Low risk		
	Attribution Bias	Low risk		
	Reporting Bias	Low risk		
	Other Bias	Low risk		

B. 16	Citation	Hunter, R. J., Berriman, T. J., Diab, I., Kamdar, R., Richmond, L., Baker, V., Goromonzi, F., Sawhney, V., Duncan, E., Page, S. P., Ullah, W., Unsworth, B., Mayet, J., Dhinoja, M., Earley, M. J., Sporton, S., Schilling, R. J. (2014). A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the camtaf trial).. Circulation: Arrhythmia and Electrophysiology, 7(1), 31-8. https://doi.org/10.1161/CIRCEP.113.000806		
	Study ID	26		
	Year	2014		
	Country	England		
	Study design	RCT's		
	Random allocation	yes		
	Allocation concealment	yes		
	Participants blinded	No		
	Investigator blinded	Yes		
	Outcome assessor blinded	Yes		
	Length of intervention follow up	12 months		
	Drop out	5		
	Number of participants	55		

	Number of completed	50		
	Age range	>18 years		
	Intervention mean age	55		
	AF recurrence (cardiac ablation)	5/26 19% (6 months)	7/26 27% (12 months)	
	AF recurrence (antiarrhythmic drugs)	9/24 38% (6 months)	10/24 42% (12 months)	
	Quality of life			
	LVEF (cardiac ablation)	32+_8% (baseline)	40+_12% (6months)	
	LVEF (antiarrhythmic drugs)	34+_12% (baseline)	31+_13% (6 months)	
	Inclusion criteria	Inclusion criteria were persistent AF, symptomatic heart failure, LV ejection fraction less than 50%, and age >18 years old.		
	Exclusion criteria	A history of heart failure with a reversible cause, a prior left atrial ablation, contraindications to catheter ablation, paroxysmal atrial fibrillation, and any recent event that could affect left ventricle function.		
	Intervention description	The study aimed to compare the effects of catheter ablation and antiarrhythmic medication treatment on patients with persistent AF and HF.		
	Selection Bias-random sequence generation	Low risk- Quote: " Randomization involved a random number generator, with sealed envelopes."		
	selection Bias-allocation concealment	Low risk- Quote: " Randomization involved a random number generator, with sealed envelopes."		
	Performance Bias	Low risk		
	Detection Bias	Low risk		

	Attribution Bias	Low risk		
	Reporting Bias	Low risk		
	Other Bias	Low risk		

B. 17	Citation	Bahnson, T. D., Giczewska, A., Mark, D. B., Russo, A. M., Monahan, K. H., Al-Khalidi, H. R., Silverstein, A. P., Poole, J. E., Lee, K. L., Packer, D. L., CABANA Investigators (2022). Association between age and outcomes of catheter ablation versus medical therapy for atrial fibrillation: results from the cabana trial. *Circulation*, *145*(11), 796-804. https://doi.org/10.1161/CIRCULATIONAHA.121.055297	
	Study ID	27	
	Year	2022	
	Country	America	
	Study design	RCT's	
	Random allocation	Not clear	
	Allocation concealment	Not clear	
	Participants Blinded	Not clear	
	Investigator blinded	Not clear	
	Outcome assessor blinded	Not clear	
	Length of intervention follow up	4 years	
	Drop out	0	
	Number of participants	2204	

	Number of completed	2204	
	Age range	<65 years old, or 65-74 years old, or >= 75 years old	
	Intervention mean age		
	AF recurrence (< 65 years old age group)	180/375 48% (cardiac ablation)	270/391 69% (antiarrhythmic drugs)
	AF recurrence (65 to 74 age group)	329/577 57% (cardiac ablation)	398/553 72% (antiarrhythmic drugs)
	AF recurrence (>=75 years old age group)	81/156 52% (cardiac ablation)	119/152 78% (antiarrhythmic drugs)
	Quality of life		
	LVEF		
	Inclusion criteria	Any individual over 18 years of age with untreated or undertreated AF.	
	Exclusion criteria	People were not included if less than one active antiarrhythmic medicine prescribed for them had failed.	
	Intervention description	A study aims to compare the relationship between age and outcomes of Catheter ablation versus medical therapy for atrial fibrillation.	
	Selection Bias-random sequence generation	Unclear risk	
	selection Bias-allocation concealment	Unclear risk	
	Performance Bias	Unclear risk	
	Detection Bias	Low risk	

	Attribution Bias	Low risk	
	Reporting Bias	Low risk	
	Other Bias	Low risk	