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# Drug Therapy Vs. Ablation Therapy for Patients with Atrial Fibrillation

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Drug Therapy Vs. Ablation Therapy for Patients with Atrial Fibrillation

By

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Paper submitted in partial fulfillment

of the Requirement for the Degree

of Master of Science

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**Abstract:** The prevalence of atrial fibrillation is 6.5 percent in the adult population in the United States, in an attempt to treat this patient population, there are numerous options and this study attempts to find the optimal treatment plan that has the least Atrial fibrillation(AF) reoccurrence, best quality of life and is the most effective. This is a Systematic Review comparing catheter ablation therapy vs. drug therapy in treating patients with atrial fibrillation. The search engines used in this analysis include PubMed, UpToDate, Google Scholar and Academic Search Premier. A total of 19 articles were analyzed and data was extracted, and conclusions were made. This review came to three conclusions, Anti-arrhythmic drugs (AAD) had no statistical significance over rate control <sup>2,7,19</sup> but specifically amiodarone had poorer side effects and more hospitalizations <sup>3,7,19</sup>. Secondly, catheter ablation therapy was more effective than drug therapy, specifically with multiple procedures and concomitant AAD use in reducing AF reoccurrence and improving quality of life <sup>12,13</sup>. Thirdly, catheter ablation therapy was associated with serious adverse effects such as cardiac tamponade and a 4.7 % increased risk for stroke<sup>9</sup>. Keeping this in mind, Amiodarone showed to have an increased risk of stroke by 1.8-fold <sup>2,3</sup>, and an increased mortality  $p=0.008$ <sup>2,19</sup>. AAD therapy has limited use because of the toxic side effects, therefore catheter ablation therapy serves as a promising long-term solution. There should be continued improved efforts towards advancing and optimizing the ablation therapy technique. Patients who fit the characteristics of more likely to succeed should be offered ablation therapy as first line treatment, and additional procedures should be offered until complete cessation of AF.

**Introduction:**

Atrial fibrillation is one of the most common types of cardiac arrhythmias diagnosed in patients, it is defined as the absence of the p wave with an irregular baseline in an EKG. The prevalence of atrial fibrillation ranges from 2.4-6.1 million in the United States<sup>1</sup>. The most common symptoms include palpitations, shortness of breath, chest discomfort and dizziness. Age is the highest predisposed risk factor for developing atrial fibrillation, but other risk factors include smoking, alcohol abuse, lung disease, hyperthyroidism, obesity, diabetes, acute cardiac illnesses and overuse of stimulants<sup>4</sup>, with these risk factors considered, it puts a big portion of the general population at risk for developing atrial fibrillation. The management is robust, it contains 3 folds, antiarrhythmic, rate control and prevention of stroke. Antiarrhythmic control can either be drug based or surgery based in which catheter ablation therapy is used. Some antiarrhythmic medications include Amiodarone, Sotalol, Procainamide, Flecainide and Dronedarone. The rate control medications include beta blockers, calcium channel blockers, digoxin and amiodarone. When a heart is in atrial fibrillation it quivers, this increases the likelihood of a clot forming and mobilizing through the vasculature into the brain causing a stroke. Anticoagulants are used to help reduce risk of stroke but will not be discussed in this paper<sup>11</sup>.

Patients can be divided based on how long standing their atrial fibrillation lasts. There is paroxysmal, persistent and permanent atrial fibrillation. If a patient's AF lasts longer than 7 days, it is considered persistent and requires synchronized cardioversion and anticoagulants. Cardioversion is used for rhythm control and is required in order to shock the heart out of an abnormal rhythm if they failed to go into normal sinus rhythm (NSR) with (AAD). Antiarrhythmic medications can also be used to keep the heart in NSR. Uncontrolled rhythm can

lead to heart failure, therefore cardiac ablation therapy has become more popular in establishing normal sinus rhythm. If a person is hemodynamically unstable such as in acute heart failure or shock, they require un-synchronized cardioversion. Rate control medications are also used to improve quality of life and assist with exercise capacity, left ventricular function and cardiac output.

This paper intends to dive deeper into the effectiveness and safety of drug therapy vs ablation therapy in paroxysmal and persistent atrial fibrillation. Patients who do not gain rate and rhythm control often go into heart failure, therefore aggressive treatment is important and required in order to improve quality of life and mortality. The question of importance is how ablation therapy compares to drug therapy in regard to reoccurrence, efficacy and safety.

#### **Methods:**

A literature search was conducted using PubMed, Google Scholar, UpToDate, and Academic Search Premier to identify studies comparing drug therapy (rate and rhythm control) with catheter ablation therapy in patients with atrial fibrillation. Key words that were used in the search include “atrial fibrillation”, “catheter ablation therapy”, drug therapy for atrial fibrillation”, “rate vs rhythm control”, “heart failure and atrial fibrillation” and “antiarrhythmic drugs”. There were 6 articles that specifically analyzed drug therapy options, 6 articles that specifically analyzed catheter ablation therapy and 7 articles that analyzed drug therapy vs. ablation therapy. For all of these search options, only randomized control studies were utilized in this systematic review, reference lists were utilized to find relevant studies that would add to this study. All Studies were no older than 10 years (2008) except for one study<sup>18</sup> which was deemed necessary because of its contribution to the topic historically. The major inclusion criteria were clinical trials that were peer reviewed, all participants were diagnosed with atrial fibrillation

(paroxysmal, persistent or permanent), all clinical trials either used drug therapy or catheter therapy or compared drug therapy vs catheter ablation therapy. The exclusion criteria included participants less than 18 years old, pregnant women, no consent, publications focusing on anticoagulation and clinical trials that analyzed treatment options with valvular heart disease. All data was investigated by the author of this systematic view, each article was analyzed individually, and data was extracted. The quality of each study was assessed by evaluating the type of design and if any there was any conflict of interest.

**Background:****Drug Therapy:**

Atrial fibrillation(AF) is a complicated heart arrhythmia and although there has been a lot research and energy put towards optimizing a treatment plan for AF, there is still a lot of work to be done. Two drug therapy options can be considered, either cardioversion and rhythmic medication or staying in AF and using rate control. To be complete, both of these strategies would also require anticoagulation, but that portion will not be discussed in this paper. Patients who are hemodynamically unstable would require immediate evaluation, including cardioversion. Stable patients will not be treated as emergently, therefore physicians can decide depending on how long the AF is presenting whether rate or rhythm control is indicated <sup>2</sup>.

A randomized control study conducted by Ulimoen et al., analyzed four rate control therapies in treating persistent atrial fibrillation(AF). The study tested two beta blockers (Carvedilol 25 mg/day and Metoprolol 100mg/day) and two calcium channel blockers (Verapamil 240mg/day and Diltiazem 100mg/day). Medication success was measured by symptom frequency and severity. The baseline frequency and severity scores were 13 and 8 respectively. Frequency was scored 0-64 with 64 being the worst and severity scored 0-48 with

48 being the worst. Diltiazem reduced symptom frequency to 10.5 and severity dropped to 6. Metoprolol and Carvedilol showed no improvement in frequency or severity of symptoms. The outcomes supported the use of calcium channel blockers over beta blockers. A limitation that may have affected the results were the dosages were not equivalent of each other which may have affected their efficacy. All of these patients also had permanent AF, rate control may work differently in paroxysmal or persistent AF<sup>17</sup>.

Although there is debate between rhythm and rate control in treating atrial fibrillation, Gwag et al., focused on antiarrhythmic drugs to find which medication was best to give to patients after cardioverting them to keep them in NSR. Cardioversion is a strategy of converting to NSR but has a high recurrence rate, antiarrhythmic medications are used as maintenance therapy. This retrospective study analyzed 265 patients, 33 patients were taking 50 mg of Flecainide, 64 patients took 300 mg of propafenone, 128 patients took 200 mg of amiodarone and 40 patients took 400 mg of dronedarone. The study found that 198 out of the 265 patients had reoccurrence of AF within one year. Some participants were concomitantly on beta blockers and calcium channel blockers. Half of the recurrences occurred during the first month of trial. Amiodarone showed to have the least reoccurrence ( $p=0.095$ ), propafenone came in second place and Dronedarone was shown to be least effective. Overall the study found that amiodarone should be held from being used as first line, it should be reserved for patients with heart failure because of its toxic side effect profile. The findings conclude that antiarrhythmic medications have shown to be moderately effective in reducing reoccurrence but in no sense is it curative<sup>7</sup>.

Chen et al. conducted a cohort study that found a link between amiodarone use and increased risk of stroke. There were two groups involved, the amiodarone group was found to have a 1.8-fold increase of developing a stroke. They also found a 1.68-fold increase in ischemic



stroke with digoxin, therefore this study recommends that digoxin and amiodarone are not used concomitantly because of a cumulative increased stroke risk, although the mechanism is unclear it is hypothesized that the increased intracellular calcium increases platelet activation<sup>3</sup>.

Amiodarone is often prescribed by physicians over other AAD's, it is important to consider the patient as a whole, looking at their comorbidities, medication list, social and family history.

Camm et al., conducted a prospective longitudinal study whose primary goal was to determine therapeutic and clinical success of rate vs. rhythm drugs. By maintaining rhythm, it allows the heart to beat in a synchronized state. Maintaining rate allows the heart to conduct blood efficiently without overworking itself; reducing symptoms. All patients involved in the study were recently diagnosed with paroxysmal AF. Therapeutic Success was defined as resting heart rate of 80 beats/minute or Normal sinus rhythm on an EKG after 12 months of therapy.

This study found that participants less than 75 years old, rhythm control strategy, absence of Coronary artery disease, absence of heart failure and no history of stroke forecasted improved therapeutic outcomes. The clinical outcomes were similar in both groups, this study did not find statistically significant results for providing data that one strategy is better than the other.

Although the outcome was similar, the rate group experienced less therapeutic success (47%) compared to the rhythm group (60%). Moreover, the rhythm group had a statistically significant therapeutic success according to a multivariable analysis. This study concluded that comorbidities had an overarching influence on cardiovascular health rather than rate or rhythm strategy but, the rhythm strategy less likelihood to progress into permanent AF.

Wyse et al., conducted a study similar to Camm et al., that analyzed rate vs rhythm but with a population group with a higher median age and more comorbidities. This study found no significant difference between rate vs rhythm. There was a tendency for increased mortality with

rhythm strategy ( $p=0.008$ ). Participants in the rhythm group were more likely to be hospitalized from adverse drug effects compared to the rate group. This is important to consider when selecting an economically viable treatment plan. These results should be considered in older patients and avoided in younger patients with paroxysmal AF and no risk factors for stroke <sup>19</sup>.

### **Catheter Ablation Therapy:**

In the last two decades, there has been profound advancements in cardiac ablation therapy. The pulmonary vein isolation treatment (PVI) has become the keystone, although it has been successful in ceasing AF, there is still relapse and continued research efforts. In the general population the reoccurrence rate post-ablation ranges from 30-70 percent depending on the patient's comorbidities.

Two studies assessed the reoccurrence rate associated with ablation therapy in younger populations. Mesquita et al., followed 253 patients through an observation study, the results found that during the mean 5 years (ranging 2-9 years) of follow up observation, 144 patients or 57 percent had an AF relapse. The cox regression multivariate analysis found three specific characteristics that were associated with relapse, they included females ( $p=0.032$ ), non-paroxysmal AF ( $p<0.050$ ) and a larger left atrium ( $p=0.008$ ). There was a 31 percent relapse that occurred during the first year, with an annual 7 % recurrence<sup>13</sup>. A cross sectional study conducted by Gerede et al., calculated a 31.3 % recurrence rate within the first three months of a cross section study. The average left atrium diameter in the reoccurrence group was 4.1 cm compared to 3.4 cm in the non-reoccurrence group. Gerede et al. utilized the Left Atrium appendage emptying peak flow velocity (LAAV) as measure of ablation therapy success, the median velocity for the reoccurrence group was 25.00 cm/s and the non-reoccurrence group LAAV was 56 cm/s. A receiver operating curve was utilized to assess the association of LAAV

and reoccurrence of A-fib and found that an LAAV  $>30$  cm/s predicted success with ablation therapy with 85 % sensitivity and 95 specificities. These results indicate that when considering ablation therapy, having a trans thoracic echocardiogram (TTE) ordered is useful to help detect if the CA therapy will be successful <sup>6</sup>.

One study conducted by Machino-ohuska et al., assessed reoccurrence after ablation therapy in patients with preserved ejection fraction ( $>50\%$ ) heart failure (HFPEF). All 72 participants suffered from heart failure symptoms such as pulmonary edema, lower leg edema, dyspnea on exertion and fatigue. There was a 27% and 45 % success rate of single and multiple procedure respectively. The participants who became AF free after one year had a LVEF increase from 67 to 69 %. The participants who remained on AAD and had multiple procedures had a 73 % success rate. Mesquita et al., found similar findings, patients who remained on antiarrhythmic drugs post-surgery had a significant long-term reduction in AF while staying on AAD's ( $p<0.004$ ). These participants also had a higher population of preserved ejection fraction. Wokhlu et al. found differently, this study found a moderately significant correlation between improved AF symptoms and ablation therapy without AAD follow up use. In fact, 72 percent of the participants became AF free without AAD follow up, 15 became AF free with AAD use and 13 % remained in AF. Further, these results agree with the growing evidence that continuing AAD after ablation therapy is beneficial.

When AAD and rate control fail, patients often lean towards ablation therapy with the hope to reduce symptoms and increase quality of life. By ablating the ectopic foci in the heart, the aim is to allow for an organized rhythm and efficient heart. When a heart is beating in a normal rhythm, the cardiac output improves; symptoms resolve <sup>1</sup>. Patients with AF could have hundreds of ectopic beats an hour, in fact in a study conducted by Haissaguerre et al., all patients

had as least 700 per every 24 hours. Therefore, it is important for patients to know whether this procedure will increase their quality of life.

Wokhlu et al., used a MAFSI scoring system for tracking symptoms, it ranged from greater to least number of symptoms (15 to -20). The group using continued AAD had an ending MAFSI score of 5.6 compared to the group without using AAD with a score of -9.5. These results indicate less symptoms were found in the group without using AAD. Quality of life was also measured in this study using a short form survey (SF-36), 0-100 scored worst to best health. When comparing baseline SF-36 scores to 3 months after the last ablation, scores increased from 63.9 to 80.6 and preserved its score to 24 months ( $p < 0.001$ ). The quality of life markedly increased and symptoms improved for most participants in this study. Not only was there improvement in quality of life but the findings extended beyond 24 months, this supports the dispute that ablation therapy assists symptomatic AF. There were factors that impaired patients in this study from improving their quality of life, including obesity and warfarin use<sup>18</sup>.

Although ablation therapy has been successful research has found specific populations and risk factors to consider. In a study conducted by Mesquita et al., after a 3-month blanking period, patients had a Holter monitor placed to detect heart arrhythmias. The cox regression multivariate analysis found three specific characteristics that were associated with relapse, they included females ( $p=0.032$ ), non-paroxysmal AF ( $p=0.050$ ) and a larger left atrium ( $p=0.008$ )<sup>13</sup>. A multivariate cox regression showed that lack of hypertension and any AF type besides permanent AF were independently associated with maintenance of sinus rhythm ( $P=0.04$ )<sup>12</sup>. Gerede et al., also found an association with recurrence and a larger left atrium and smaller Left atrium appendage emptying peak flow velocity (LAAV).

**Ablation Therapy Vs. Drug therapy:**

This paper's goal is to determine whether catheter ablation therapy has better outcomes than drug therapy, it can be agreed that AF requires a longer-term solution, AAD have shown to have many side effects<sup>18</sup> but ablation therapy also has been associated with severe adverse events<sup>9</sup>. Three randomized controlled studies were conducted on patients with paroxysmal AF. The first, conducted by Raatikainen et al., explored new grounds with 294 symptomatic paroxysmal AF patients for 24 months. Although drug therapy is usually indicated as first line treatment for paroxysmal AF, this study assessed the efficacy of radio frequency ablation (RFA) as first line. These participants were required to be AAD naïve, three groups were created with one cross over group. The AAD group were assigned either 200 mg of Flecainide or 600 mg of Propafenone. The ADD group also had 54 participants also received RFA and were considered the cross over group. Analysis of AF burden was recorded using the Mann-Whitney test. The results showed that RFA maintained its efficacy throughout the 24 months. RFA and AAD groups had lower AF burden than the cross over group. At 24 months 89 % of the RFA group were AF free compared to 74 % of the AAD group and 73 % from cross over group. These results were significant ( $p < 0.006$ )<sup>15</sup>.

The second, conducted by Pappone et al., prospectively compared 198 participants, 99 were assigned RFA and 99 to AAD's in which 44 crossed over to RFA group. quality of life and reoccurrence were tracked during a 4-year period. The AAD group tolerated 300 mg of Flecainide twice a day, 320 mg of sotalol or 600 mg of amiodarone. All participants who underwent RFA, continued AAD 6 weeks after the procedure during a blanking period. Excluding cross overs, 12 % from the AAD group and 72.7 % became AF free after four years ( $p < 0.001$ ). There were 27 participants who received redo RFA and the freedom from AF

improved to 90.9 %. There were 87 participants who crossed over to RFA therapy because of symptomatic episodes, 71.3 % reach normal sinus rhythm at 48 months. The predicting factors for recurrence in the AAD group included Left Atrium Dimension of (41 mm), diabetes, hypertension and valvular disease. The complications from AAD therapy included 68 participants who discontinued their dose because of lack of efficacy, several participants who used the median dose 400 mg/d of amiodarone had drug-induced subclinical thyrotoxicosis in 19 participants and hepatitis in one <sup>14</sup>.

THE RFA group had no serious adverse complications except 1 TIA, 1 pericardial effusion and 3 femoral hematomas which none required long term treatment. There were 325 cardiovascular event related admissions in the AAD group compared to 61 in the RFA group. Quality of life was assessed using the SF-26 score, there were significant statistics to support higher scores in participants who had RFA compared to cross over participants<sup>14</sup>.

Reynold et al. conducted a propensity matched analysis and found supporting data that Catheter ablation therapy reduced stroke and heart failure risk long term. These participants were concomitantly on rate and rhythm control while receiving ablation therapy. There were 801 pairs of participants, the results showed an overall rate of stroke risk within 3 years was 3.4 % each year compared to 5.5 % per year in the non-ablation group ( $p < 0.005$ )<sup>16</sup>. The rate of new hospitalization for heart failure episodes was 1.5 % per year in the ablation group and 2.2 % per year in the non-ablation group, although the overall percent risk was higher in the ablation group it wasn't statistically significant ( $p < 0.155$ )<sup>16</sup>.

Since heart failure and AF often coincide, it is important to determine specifically which treatment option is best in this population considering 42 percent of people with AF have heart failure <sup>3</sup>. Two studies considered the heart failure population and found similar outcomes. One

study assessed rate<sup>10</sup> and the other assessed rhythm<sup>5</sup> medications and they were compared to catheter ablation therapy. Di-Biase et al. conducted a randomized control study for 24 months comparing rhythm control vs catheter ablation therapy, it contains 203 participants- 102 were assigned to the CA group and 101 were assigned to the amiodarone group. All participants had a LVEF <40% within the last 6 months. Participants who received CA, had a 3-month blank period, this served as a grace period for any arrhythmias where if they re-entered atrial fibrillation, another CA surgery could be performed. Any arrhythmia after 3 months of surgery was considered a reoccurrence and failure of treatment. The CA participants were given 200 mg of amiodarone daily and discontinued after the blank period. Participants who were in the amiodarone group received a loading dose of 400 mg twice day for 2 weeks followed by 400 mg once day for the next two weeks and then titrated as needed. By the end of the study, 71 (69 %) patients in the CA ablation group were reoccurrence free with an average of 1.4+/- .6 procedures compared to 34 patients' (33 %) reoccurrences free in the amiodarone group. This study concluded that patients receiving only amiodarone were more likely to fail treatment with a P (< .001)<sup>5</sup>.

A randomized control study conducted by Hunter et al., assessed catheter ablation therapy vs rate control and found similar findings to Di-Biase et al. In this study, A group of 26 participants with heart failure were assigned catheter ablation therapy and 24 participants were assigned rate control. All patients needed to have symptomatic heart failure (HF) and persistent atrial fibrillation. Heart failure was defined as a Left ventricular ejection fraction < 50%. All CA treatments were confirmed using the pulmonary vein mapping catheter and this study also had a 3-month blanking period. The findings showed a single procedure success rate of freedom from AF was 38% and increased to 81% after the last ablation procedure. The primary end point of

this study was to assess LV EF which showed to be statistically significant. The CA group had an 8.1 % increase in a 6-month period compared to a -3.6% decline in the rate control group ( $p < 0.001$ ). The quality of life survey also found that the CA group has statistically significant improvements in quality of life, at baseline their physical function was at 71% compare to the rate group which was at 49.1% ( $p = 0.007$ ). The success rate of becoming AF free was at 81 % at 6 months but declined to 73 % at one year in the CA participants. Although this study showed CA to be superior in patients with heart failure, longer term research is suggested to follow patients to assess adverse effects and success rate of becoming AF free <sup>10</sup>.

The prevalence of patients with symptomatic AF has increased over the years, catheter ablation therapy has become one of the mainstays of treating symptomatic patients, but there is hesitancy with specific populations due to the risks that comes along with the procedure<sup>4</sup> Hoyt et al., conducted an analysis of major complications that occurred during ablation therapy. Data was collected from 2001 to 2010, 1190 procedures were completed on 931 patients, the complications rate was 4.7%, although there were no deaths the complications included pericardial tamponade, cerebrovascular accident (9 strokes and 3 TIA's). The complication rate decreased over time, in 2002 it was 11.1 % and decreased to 1.6% in 2010. This decrease in rate of complications is most likely attributed to the new and improved technology and enhanced training and institutions<sup>9</sup>. This study computed an analysis of the top predicting factors of a complication to occur during the procedure and they included; female gender ( $P = 0.01$ ), CHAD2 score greater than or equal to 2 ( $P = 0.002$ ) and age ( $p = 0.04$ ). There were only 6 participants who had permanent deficit. A randomized control study calculated a 19 % complication risk in a group receiving cardiac ablation therapy compared to 8% in the AAD group. This markedly increased risk took into account complications outside of the procedure such as cancer and



myocardial infarctions. The complications that occurred included cardiac tamponade, bleeding complications and atrial flutter. This study had three deaths in the RFA group and 1 death in the AAD group ( $P=0.55$ ). A trend was detected with increased serious adverse events with RFA compared to AAD but did not show to be statistically significant<sup>15</sup>. Another randomized control study found supportive data, by the end of the study, the adverse event risk rate was 7.7 % per patient<sup>10</sup>.

While the majority of search has shown to support the advantage of catheter ablation therapy over AAD, A randomized control study conducted by Alhede et al. found AAD to be superior to Cardiac ablation therapy. Long term research is limited; therefore, this study assessed AF burden within 24 months of starting initial treatment for symptomatic AF participants. There were 132 patients randomly assigned to the AAD group and 128 patients assigned to the CA group. 93 % of the AAD group took 200 mg of Flecainide, 3 % took 200 mg of Amiodarone and 2 % took 600 mg of Propafenone. AF burden was categorized into low (0-25 ectopic beats/day), moderate (25-100) and high (>100). The results were calculated using the Wilcoxon Rank. The results of this study indicated that AAD had favorable results over CA, AAD had an average reduction in AF burden from baseline by 73 percent compared to a 52 percent reduction in CA group. The AAD had an initial drop in supra ventricular ectopic complex (SVEC)/day which then stabilized within 3 months. CA participants with low SVEC risk had a statistically significant initial increase in SVEC/day ( $p=0.02$ ) which then stabilized within 3 months. Overall, if a person had an initial low SVEC burden, they had lower AF burden compared to higher risk participants. In conclusion this study suggests that AAD have more favorable results in reducing SVEC compared to CA therapy. In fact, they hypothesize that Flecainide may have the ability to stabilize electrical impulses from areas beside the pulmonary vein. The majority 94 % of ectopic

beats originate from the pulmonary vein in the left atrium but Flecainide has the ability to target non-pulmonary vein sites which may have explained the superiority of AAD in this study<sup>1</sup>.

**Discussion:**

This paper sought to compare and contrast different approaches to treating patients with atrial fibrillation, specifically drug therapy was compared to ablation therapy in regard to safety, efficacy and reoccurrence. This paper came to three conclusions, firstly, AAD had no statistical significance in efficacy over rate control<sup>2,7,19</sup> but specifically amiodarone had poorer side effects and more hospitalizations<sup>3,7,19</sup>. Secondly, catheter ablation therapy showed to be more effective in reducing reoccurrence and improving quality, in fact there was improved effectiveness with multiple procedures<sup>12,13</sup> and some evidence supported simultaneous AAD use. Thirdly, studies suggest there are serious adverse effects that must be considered when offering catheter ablation therapy, some studies suggest it outweighs the complications from drug therapy while others ask physicians to reconsider offering the procedure<sup>5,9,10,14,15,19</sup>. Overall, the effect of catheter ablation therapy was consistent with paroxysmal AF and heart failure patients.

When rate control was compared to rhythm control, one did not have substantial efficacy over the other. calcium channel blockers particularly verapamil and diltiazem had a weak evidence of having more efficacy and decreasing severity compared to beta blockers in one study<sup>17</sup>, but two other studies found no statistical difference between rate and rhythm control. Therefore, physicians should consider a patient's comorbidities, when deciding which drug therapy to choose. Amiodarone has been one of the more superior drug choice in converting to normal sinus rhythm and control and maintaining rate and rhythm in atrial fibrillation patients. Its mechanism is to block potassium, sodium and calcium channels. However, it is important to keep in mind the cardiac and non-cardiac complications of this medicine choice<sup>3</sup>. Specifically, Amiodarone showed to have increased risk of stroke by 1.8-fold<sup>2,3</sup>, and an increased mortality

$p=0.008$ <sup>2,19</sup>. In one study Amiodarone had the least reoccurrence but because of its side effect profile, it was recommended to only be used in patients with severe symptoms<sup>7</sup>. In another study there was an increased prevalence of subclinical thyrotoxicosis and hepatitis with amiodarone use<sup>14</sup>.

Overall, there was a trend towards AAD over rate control, but the results made it evident that AAD use is limited because of its side effect profile and modest reduction in reoccurrence rate, therefore ablation therapy was considered in patients who were looking for a longer-term solution. Participants who are young and have paroxysmal A fib and no risk factors for stroke should avoid amiodarone use if they fail to return into NSR after cardioversion, ablation therapy should be considered because of its increased efficacy<sup>19</sup>. One study followed patients for 24 months and used ablation therapy as first line therapy which is usually not indicated, the results found that 89 percent became AF burden free<sup>15</sup>. A similar study followed patients for four years and found supportive data, 72.7 percent became AF free compared to 12 percent of the AAD group. After multiple procedures, the success of becoming AF free became 90.9 % after four years of follow up ( $p=0.001$ )<sup>14</sup>. These two similar studies support the use of ablation therapy as first line treatment, this data could be used to advocate the dismissal of jumping to first line amiodarone, it seems the benefits of ablation therapy outweigh the complications and side effects of AAD's.

In the studies that analyzed drug therapy options, there were specific characteristics that had a decreased chance of going into NSR and staying in permanent AF, they included being older than 75 years old, having a history of AF that is not paroxysmal and having heart failure. Therefore, it's important to keep this in mind when choosing a treatment option, although drug

therapy is easier and has less acute risk, patients with this profile should consider ablation therapy because of its lower reoccurrence and decreased side effects<sup>2</sup>.

In determining the effectiveness of ablation therapy, there was a trend of a specific population who had reduced effectiveness post-procedure. The majority of the articles analyzed, included a 3-month blank period, this was a period where AF reoccurrence was not recorded and was either treated with drugs or additional ablation therapy. The main procedure utilized is pulmonary vein isolation, when patients had a larger left atrium or a small left atrium appendage emptying peak flow velocity they had an increased rate of reoccurrence<sup>6,13</sup>. One study found an increased reoccurrence with females<sup>13</sup> and another study with obesity and warfarin use<sup>18</sup>. Another study found worse outcomes with a larger left atrium dimension, diabetes, hypertension and valvular disease<sup>14</sup>. It can be recommended after compiling data that all patients who undergo ablation therapy, they should receive a TEE in order to get a baseline systolic and diastolic function and to help determine a patient's probability of going into NSR<sup>6,13</sup>.

The average reoccurrence rate was 30 percent within the first year after receiving an ablation procedure<sup>6,13</sup>. There was trend of increased effectiveness when AAD was used concomitantly with ablation procedures, in fact the effectiveness rate reached 73 percent with multiple procedures<sup>12,13</sup>. However, two studies disagreed and found data which showed only a moderate improvement with the use of AAD and ablation therapy<sup>14,18</sup>. There was also strong evidence to suggest that repeated procedures had high efficacy in becoming AF burden free. Three studies showed statistically significant results to support this statement<sup>5,10,15</sup>. Furthermore, it can be recommended that multiple procedures<sup>14</sup> and the use of AAD therapy in combination would decrease the rate of reoccurrence and improve quality of life. The downside of this recommendation, is the side effects from AAD and the expense of multiple procedures.

Considering most people with AF have multiple comorbidities, this recommendation could financially not be an option for many patients. One study contradicted the mainstream trend of supporting ablation therapy, it supported the use of AAD, this study used mostly flecainide which was different than the majority of the studies<sup>1</sup>. One must question maybe more studies need to be conducted to assess if flecainide is superior to ablation therapy in reducing ectopic electrical signals outside of the pulmonary vein.

Conventionally with any procedure there will always be risk, collectively the data shows that there is a higher adverse event risk with ablation therapy, but the long-term complication rate is low<sup>9</sup>. Some complications that can occur include stroke, TIA, cardiac tamponade, hospitalization and death. One study found a very high rate of 19 %<sup>15</sup>, while another found a 4.7% risk<sup>9</sup> and another 7.7%<sup>10</sup>. According to Hoyt, adverse events decrease with institutional experience, this study found that institutions that had performed greater than 100 procedures have less complications. This information is important to acknowledge when choosing a patient for this procedure, if a patient is hemodynamically unstable or is at risk for infection or stroke, ablation therapy should be avoided because of the risk of complications that could be fatal. This may be a time where AAD therapy would be chosen.

As mentioned before, heart failure and AF often overlap, the findings are similar to data on non-HF patients, the statistics supports the use of ablation therapy over AAD and rate control. Patients with heart failure were more likely to fail with amiodarone use<sup>5</sup> and rate control<sup>10</sup>. There were also similar results to support applying multiple procedures to decrease rate of reoccurrence. When rate control was used, there was a decrease in ejection fraction compared to an improved ejection fraction and quality of life with catheter ablation therapy<sup>10</sup>. Nonetheless,

ablation therapy remains superior in its efficacy compared to antiarrhythmic drugs and rate control.

According to the American Heart Association, a guideline was created in 2014 for treating AF patients, the guidelines specify that catheter ablation therapy can be utilized on patients who are refractory to at least one drug from class I or III, this was categorized as Level-A evidence. The majority of studies on atrial fibrillation followed this guideline, but new research is breaking innovative grounds and pushing for the use of catheter ablation therapy as first line treatment for symptomatic paroxysmal AF as well as continue being used in persistent and permanent AF patients although their chances of fully recovering are lower<sup>12</sup>. The 2014 guidelines have a recommendation that is supported by this research, it states that catheter ablation therapy can be used in recurrent symptomatic paroxysmal AF before the use of antiarrhythmic drug therapy, but this is Level-B evidence<sup>1</sup>. Thus, future studies should continue to attempt catheter ablation as first line and physicians should consider this when creating a treatment plan.

The 2014 guideline also insists on the use of antiarrhythmic drugs as it is Level- A evidence to use any of the following drugs as first line treatment to maintain normal sinus rhythm; Amiodarone, Dronedarone, Flecainide, Propafenone and Sotalol. This paper challenges this recommendation because of the evidence of catheter ablations superiority to antiarrhythmic drugs. Following this Level-A guideline, the guideline includes possibility of several risks and downfalls associated with Antiarrhythmic drugs<sup>11</sup>. There is a risk of proarrhythmia including QT-prolongation torsade's de pointes, especially with Amiodarone<sup>4</sup>. These statements are also supported by this paper. This all reiterates the validity and significance of the findings of this paper.

This literature review has several potential limitations. The first of them being the majority of the studies were limited to 24 months, this research topic requires extended follow up in order to record the rate of reoccurrence, efficacy determine if there is improved quality of life. There are a lot of toxic side effects and arrhythmias that can be induced from AAD, therefore a longer study would help guide physicians in making the best clinical decision. Some studies only included specific population for example heart failure or paroxysmal AF, therefore it is hard to make a general statement about an approach to AF treatment from research that is more specific.

When comparing different articles that analyzed AAD and rate control, each study used different dosages, therefore it made it difficult to come to conclusion as to which dosage was optimal in reducing reoccurrence and limiting side effects. Holter monitors were utilized to detect AF, this device is very sensitive and often can be influenced by sound and skin contact, recording false AF, this may have overestimated reoccurrence<sup>1</sup>. These Holter monitors were only used for a short period of time, it is impossible to detect AF that is asymptomatic, therefore it makes it difficult to confidently discern if a participant is truly AF free without keep a constant EKG recording. Also, each study had different inclusive requirements (HF, Ischemic heart disease etc.), most studies excluded valvular disease or past ischemic events, therefore this systematic review does not add information towards those populations<sup>17</sup>. Another limitation was that heart failure was defined differently, which effected which participants were allowed to be involved and the final outcome<sup>5,10</sup>. Because of the nature of reoccurrence immediately post ablation therapy, most studied utilized the 3-month blanking period, some studies utilized drugs to attempt to convert into NSR and some used additional ablation therapy, those decisions were not included in the studies and may have affected the end results. Some studies accounted significant statistics that were greater than 0.001, suggesting weaker evidence<sup>7,17</sup>.

After overlooking all of the current research, future studies may want to keep in mind certain aspects when designing a study which may strengthen their data and optimize their results. The ideal study would include at least 500 patients, participants should be a mix of paroxysmal, persistent and permanent atrial fibrillation, they would be recruited from the emergency department or cardiology centers and those who have persistent AF would more likely be refractory to antiarrhythmic and rate control drugs. The primary outcome of interest would be reoccurrence rate, and quality of life. A downfall to most studies is they often track participants for up to 24 months, an ideal study would be for 5 years, this would show more realistic results and allow time to track any long-term complications that could occur from their treatment option. Participants would be divided into two groups with similar comorbidity characteristics, one group would be assigned AAD specifically flecainide or amiodarone and the other group would be assigned catheter ablation therapy using pulmonary vein isolation technique. All participants would get a 3-month blanking period, if they go out of NSR, they would be given either drug therapy or ablation therapy depending on their assigned group. It would be recommended to exclude participants with valvular heart disease and chronic lung disease. All participant should undergo a TEE in order to determine if catheter ablation therapy is optimal. Participants would follow up on a monthly basis the first year and then every 6 months following that. A Holter monitor would be placed every 6 months and patients would be given a journal to keep track of their symptoms on a daily basis which would be collected by the physician. All of these recommendations would help produce better results.



**Conclusion:**

The current data utilized by physicians to make clinical decisions about atrial fibrillation supports the use of catheter ablation therapy technique, this review aimed to understand how significant the success in ceasing reoccurrence was and attempted to analyze the efficacy and safety of this procedure over using conventional drug therapy. The supposition of this paper demonstrated that rate control and antiarrhythmic drugs had no statistical significance in efficacy over the other, but due to the complications and side effects, antiarrhythmic drugs have a limited role in treating patients. Due to these complications it can be concluded that catheter ablation is the solution for longer term treatment and has a more promising trajectory in improving quality of life and its efficacy in reducing reoccurrence.

In terms of patients with heart failure, atrial fibrillation often exacerbates heart failure symptoms, the data commends catheter ablation over rate and rhythm control, but continued studies are warranted to strength the clinical efficacy of this procedure on this specific population. The ultimate goal for these patients is to go into NSR and maintain or improve their left ventricular ejection fraction.

These conclusions have significant application in the world of cardiology, this systematic review reiterates the superiority of ablation therapy over the use of drugs in converting atrial fibrillation into normal sinus rhythm. There should be continued improved efforts towards advancing and optimizing the ablation therapy technique. Patients who fit the characteristics of more likely to succeed should be offered ablation therapy as first line treatment, and additional procedures should be offered until complete cessation of AF. This paper demonstrates the power of leading technology, ablation therapy began in early 2000's, and after years of trial and error

there has been tremendous success<sup>9</sup>. Despite the fact that there is not a 100 percent conversion into NSR, the data insists only thriving statistics moving forward.

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**Appendix D: Masters Paper Grade Summary Report**

**Student**

**Advisor:**

**Topic:**

**Assignment: Final Paper**

<b>Quality of Content( 40 points)</b>	
<b>Clarity of Expression (40 points)</b>	
<b>Formatting (10 points)</b>	
<b>Proper Grammar and Spelling (10 points)</b>	
<b>Total (maximum 100)</b>	

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