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A Comparative Study of Cryoballoon, Radiofrequency, and Laser Ablations for the Treatment of Atrial Fibrillation

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Abstract
Atrial fibrillation (AF) is both a prevalent and life debilitating arrhythmia. It presents in the form of chronic fatigue, strokes, palpitations, and tachycardia. There is currently a wide variety of treatment options including antiarrhythmic drugs and procedures such as cardioversions. Unfortunately, the medical field offers few long-term solutions. Catheter ablations, however, are promising technology whose technological advancement is shedding light on a real AF solution. This study explores the safety and efficacy of three major ablation techniques: cryoballoon, radiofrequency, and laser ablation. This comparative study investigates the occurrence rates of complications such as groin hematomas, thromboembolic events, and phrenic nerve paralysis in the setting of first time catheter ablation patients.

Aim
The aim of this study is to provide an introduction into the comparison of radiofrequency, cryoballoon, and laser ablation techniques. This study is limited. It was conducted based on data obtained through secondary sources and formulated into one cohesive document. The purpose of this study is to encourage further investigation into the safety, efficacy, and outcomes of these ablation techniques as well as others not explored in this study.

Introduction

Heart disease is an all too common and deadly condition found in the United States. Topics often associated with heart disease include myocardial infarctions, stents, and bypass surgeries; the common killer being coronary artery disease (CAD). CAD is the occlusion of the arteries of the heart by plaque. While CAD makes-up a vast majority of heart disease cases, there are other heart abnormalities that are less known to the public (Center for Disease Control and Prevention, 2017). These other cardiac illnesses can, too, result in debilitating or life-threatening complications. One such group of these complications is cardiac arrhythmias (American Heart Association, 2016).

Cardiac arrhythmias are a fault, or interruptive circuit, in the electrophysiological control of cardiac tissue. The normal electrical signals that control the heart follow a specific pathway. This pathway allows for the systole (contraction) and diastole (relaxation) during a heart-beat that pushes the blood through the heart and out to the body. Abnormalities occur when a group of normally conductive tissue in the pathway becomes unable to conduct, or a group of tissue that is not-normally conductive, outside of the usual pathway, begins to conduct current. These differences in conduction result in diseases like bundle branch blocks, supraventricular tachycardia, and ventricular tachycardia (American Heart Association, 2016). The atria specifically, have some commonly expressed arrhythmias. Some of these include: atrial tachycardia, which results in an increased heart rate; atrial flutter, a circuit that occurs around the tricuspid valve that connects the right atria to right ventricle and atrial fibrillation, a circuit that predominately originates around the pulmonary veins in the left atrium (American Heart Association, 2016).

Atrial fibrillation (AF) is one such arrhythmia that can cause life-debilitating complications. It is estimated that well over three million people in the United States are converting in and out of AF

(National Center for Chronic Disease Prevention and Health, 2017). Conversion refers to the action of the heart by which is switches from one rhythm to another, either with or without outside intervention. AF itself is not a life-threatening arrhythmia. However, the symptoms of AF can be a great burden on the lives of patients. These symptoms can include progressive fatigue, fluid retention, and frequent palpitations (American Heart Association, 2018).

A serious complication associated with AF is the increased risk for thromboembolic events (blood clots) originating from the left atrium (Coll Cardiol, 2011). These blood clots can travel to the brain and lead to life-altering deficits or death by means of stroke. Approximately 10-40 percent of all new strokes lead to the diagnosis of atrial fibrillation (Daniel J. Cantillon, 2018). Because of this significant risk, patients who present for atrial fibrillation are placed on a blood thinner (Coll Cardiol, 2011). The level of risk for these events is calculated quantitatively by a system called a CHA2DS2-VASc score. In this system each risk factor is accounted for with a point, or two points, depending on the severity of the risk. These include congestive heart failure (one point), hypertension (one point), age (one point for 65 years of age or two points for 75 years of age or older), diabetes mellitus (one point), previous stroke (two points), vascular disease (one point), and sex (females one point). With an increased CHA2DS-VASc score patients are placed on one of several options of blood thinners (American Heart Association, American College of Cardiology, Heart Rhythm Society, 2014). Some examples of blood thinners include Xarelto, Coumadin, Pradaxa, and Eliquis. While the decreased risk of stroke is a necessity for patients, the side-effects associated with chronic blood thinner usage is quite burdensome. Less seriously, there is chronic bruising for patients and frequent blood work-ups. More seriously, there is an increased risk of severe, potentially lethal, bleeding complications (Gulloy, 1999).

Whether it be life-disrupting symptoms, an increased risk of stroke, or the desire to discontinue medications, patients often seek a temporary or permanent cure for their AF. Current options for patients include: anticoagulation (as discussed above to prevent stroke), medications to slow down heart rate, medications to keep the body in sinus rhythm, procedures to convert to sinus rhythm, and procedures to stay in sinus rhythm (American Heart Association, September 2016).

AF can cause tachycardia and rapid ventricular rates (RVR). RVR can be noticeable to patients causing dizziness and anxiety. However, a more serious effect of long-term RVR is atrial cardiomyopathy (Daniel J. Cantillon, 2018). To ease the pace of the heart, patients are prescribed beta blockers. Beta blockers are a widely used class of drug, but they can also cause life-altering side-effects including severe fatigue, depression, and lethargy (Daniel J. Cantillon, 2018).

Antiarrhythmic medications are another option for patients in helping to maintain sinus rhythm. While these medications can be quite successful in decreasing the burden of AF in some patients, they too come with a great deal of side-effects (Daniel J. Cantillon, 2018). Some of the available medications include Amiodarone, Flecainide, and Sotalol. Some medications require hospital admission to administer the medications due to their instance of causing other life-threating arrhythmias (typically associated with prolonged QT intervals) (Roden, Kannankeril, & Darbar, 2007). The commonly prescribed antiarrhythmic Amiodarone comes with its own long history of

complications including: tremors, weakness, and long-term skin discoloration, amongst others (Mayo Clinic, 2018).

One procedure that can convert patients to sinus rhythm, at least for a temporary time period, is a cardioversion (American Heart Association, July 2016). Cardioversions are often preformed along with a transesophageal echocardiogram (TEE) to evaluate for pre-existing blood clots. The procedure may dislodge clots, causing a thromboembolic event, thus a TEE is used to decrease this risk (American Heart Association, July 2016). In a cardioversion pads are placed on the patient, similarly to an AED, and an electrical shock is given. The patient may be sedated prior to the procedure for comfort. The shock essentially converts the heart to sinus rhythm by restarting the signal (American Heart Association, July 2016). While this procedure can be highly effective for some patients, it is difficult to say how long the conversion will last. Increased length of a patient being in AF, such as patients who are chronically in the arrhythmia versus patients who have paroxysmal AF, are more likely to convert back to the arrhythmia quickly (Institute for Quality and Efficiency in Heath Care, 2013). Cardioversions may last years, months, or simply minutes.

There are several more invasive approaches to manage AF. One more invasive approach is that of AF ablations. In an ablation, an electrophysiologist (EP) inserts a catheter into a vein in the groin and travels up to the heart. The EP enters into the right atrium and punctures a small hole in the interatrial septum, into the left atrium (Mayo Clinic, 2018). Once in the left atrium the EP delivers energy to the entrance of the pulmonary veins to cauterize the circuit causing AF and prevents the current from conducting (Haissaguerre, 2005). This may offer a long-term solution for patients with AF.

There are several forms of ablation deliverance and techniques. This study will explore the use of three types of ablation techniques: radiofrequency, cryoballoon, and laser ablation. Each delivers a different form of energy from the tip of the catheter and is associated with its own risks and benefits (Katritsis & Calkins, 2012).

Radiofrequency (RF) ablations offer a single point energy deliverance in cauterizing tissue. RF may be more time consuming, as it requires point-by-point deliverance. However, RF is not anatomically restricted because of this. Meaning that the size, nor shape, of the pulmonary veins restrict the use of RF. RF delivers a burning radiation (Thakur, et al., 2017). While RF is used in first-time ablations, it may also be used in re-do ablations to pin-point a spot of missed conducting tissue.

Cryoballoon (CB) ablation use for pulmonary vein isolation is also possible. CB uses a spherical balloon that freezes to offer a multi-contact approach to ablations. The balloon expands at the entrance of the pulmonary veins to contact the full circumference of the vein in one burn (Altmann, et al., 2012). CB may be a faster approach to an ablation but may not be compatible with the anatomy of every patient. Some veins are more oval than round and the balloon may not contact all part of the vein circumference, allowing AF to continue via the undisrupted tissue.

Laser ablation (LA) is another technique used for AF ablation. Laser ablation is a newer technique than RF and CB, but is beginning to show promise in the treatment of AF. LAs are

conducted like CB ablations and RF ablations, however they utilize a camera to allow for real-time visualization of the atrial tissue being ablated (Cardiofocus, 2019). This technique uses burning radiation and delivers it via a flexible balloon (Cardiofocus, 2019). While the device may be slightly restricted by anatomy, the flexible balloon allows for a wider variety of pulmonary veins shapes.

In deciding how to treat AF, similar to other medical decision making, the risks and benefits must be strictly considered. Ablations may offer a potential life-long solution to AF, but risks are inevitable. This question then becomes what the risks are and are they worth taking for the risky outcome. This study will focus on these ideas for CB, RF, and LA ablations. It is important to consider which of these techniques will truly provide sustained results and if any technique exhibits higher surgical complications than the others. This study will focus on three different types of complications as well as the incidence of recurrence. A lower risk complication, incidence of groin hematoma, was selected given that the complication is painful and can prolong the hospital stay of a patient but is unlikely to be lethal. Higher risk complications, including phrenic nerve paralysis and major bleeding, were selected for both the consideration that the type of energy delivered may increase or decrease the risk of this complication occurring peri-operatively and for its ability to occur and have the patient recover. Lastly, incidence of thromboembolic events/strokes was selected as it is a high-risk complication that may result in life-long deficits and/or death. Recurrence was also taken into consideration for this study with the understanding that a high rate of recurrence would render the procedure futile. Patients and physicians are unlikely to take risks for a procedure that will not sustain sinus rhythm.

There is research available for comparison of ablation techniques. However, upon extensive search, there is currently not one comprehensive study comparing RF, CB, and laser ablations. This study will investigate outcomes and recurrence rates for each ablation technique.

Methods

Data was collected from several online journals. Sources used for quantitative data were *Europace, Revista Espanola de Cardiologia, Cardiofocus*, and the *Journal of Atrial Fibrillation*.

These journals were selected based on the type of sample population as well as the complications and/or types of outcomes they reported. Literature considered for this study included patients, both male and female, undergoing their first atrial fibrillation ablation; the information collected in the study also needed to be primary data (literature reviews were not selected). The ablation must have been conducted via catheter ablation with the radiofrequency, cryoballoon, or laser approach. The size and make of catheter was not considered in this study. Outcomes of interest for this report include recurrence during a 10-month 12-month period and/or a report on groin hematoma, incidence of embolism, or phrenic nerve paralysis. The study did not need to include reports on every outcome but did need to include at least one.

After selection of eligible literature, the raw report from each study on the specified outcomes was noted and compiled into a comprehensive table (see Table 1a). All of the outcomes were then converted to a percentage of occurrence within their specific study.

While several sources noted the number of male versus female patients, none reported segregated outcomes. It is noted that incidence of thromboembolic events was combined for males and females despite the increased risk of coagulation in females. This was likely omitted given pre-ablation and peri-ablation anticoagulation protocols set forth by the American Heart Association, American College of Cardiology, and the Heart Rhythm Society (2014).

In some instances, such as with the occurrence of phrenic nerve paralysis, two studies reported an outcome for cryoballoon ablation. In these instances, both reports were used. Each reported outcome was first converted to a percentage out of 100 of cases in its individual study. Using the same example of phrenic nerve paralysis: there were 7 cases in 311 patients. As a percentage, this is 2.25% of the overall patients in the study with reported phrenic nerve paralysis (both peri-ablation and/or post-ablation). The second study had an instance of 4% phrenic nerve paralysis. An average was taken of the two reports (3.31%) to use for comparison to RF and LA. This study was otherwise largely qualitative.

Results/Discussion

Results were compiled into comprehensive tables. Table 1A describes the results obtained directly from the primary literature. Again, the data is subdivided into the four studies from which is was obtained. The same seven categorized were analyzed for each group. It is clear in this table that each study did not cover the same seven categories (listed in the far-left column) nor the same ablation techniques. It is also clear that each study was conducted separately with a different number of subjects analyzed. The orange study was by far the largest (for both CB and RF techniques). The yellow study was the smallest per subject group, but not the smallest overall (when compared to the blue study).

Technique versus Study	**Orange Study**	**Green Study**	**Blue Study**	**Yellow Study**
Cryoballoon				
# of Patients	311.00			50.00
Recurrence at 10 months	86.00			
Recurrence at 1 year				27.00
Thromboembolic event	1.00			
Groin hematoma				2.00
Major bleeding	7.00			
Phrenic nerve Paralysis	7.00			2.00
Radiofrequency				
# of Patients	376.00			56.00
Recurrence at 10 months	171.00			
Recurrence at 1 year				19.00
Thromboembolic event	1.00			
Groin hematoma				1.00
Major bleeding	12.00			
Phrenic nerve Paralysis	1.00			0.00
Laser				
# of Patients		167.00	71.00	

Recurrence at 10 months				
Recurrence at 1 year		61.00		
Thromboembolic event		2.00	0.00	
Groin hematoma			3.00	
Major bleeding		0.00	1.00	
Phrenic nerve Paralysis		6.00	4.00	

Table 1a- Instances reported directly by the four studies. Studies are sectioned into four colors to simplify viewing and to help eliminate bias while directly comparing. Study-color correlation can be found in *Appendix 1*.

Table 1b was formulated to give a better representation of the incidents of occurrence within the specific study. Given that each study had a unique number of participants to subject one to the same scrutiny as the other may be ungrounded. For example, based on Table 1a the orange study appears to have more incidents of phrenic nerve paralysis. However, given the larger sample size, as demonstrated by Table 1b, the percentage of phrenic nerve paralysis in the orange study was less, 2.25 percent, as compared to the yellow study at 4 percent.

Raw Data	**Orange Study**	**Green Study**	**Blue Study**	**Yellow Study**
Cryoballoon				
Recurrence at 10 months	27.65			
Recurrence at 1 year				54.00
Thromboembolic event	0.32			
Groin hematoma				4.00
Major bleeding	2.25			
Phrenic nerve Paralysis	2.25			4.00
RF				
Recurrence at 10 months	45.48			
Recurrence at 1 year				66.07
Thromboembolic event	0.27			
Groin hematoma				1.79
Major bleeding	3.19			
Phrenic nerve Paralysis	0.27			0.00
Laser				
Recurrence at 10 months				
Recurrence at 1 year		36.53		
Thromboembolic event		1.20	0.00	
Groin hematoma			4.23	
Major bleeding		0.00	1.41	
Phrenic nerve Paralysis		3.59	5.63	

Table 1b- Comparison of recurrence and complications in each study expressed as a percentage of total subjects. Data collected from **Table 1a** was used to complete this table. This table represents the instances of occurrence as a percentage of total subjects in study. See **Table 1a** for further explanation of study labeling.

Table 2 is the most direct comparison of the three ablation techniques. This table acts as an easy reference to the outcomes from techniques, rather than studies. Here, LA is shown to have the

lowest rate of recurrence at 12 months (36.53 percent). The second lowest being CB at 54 percent and the highest being RF at 66.07 percent.

Thromboembolic events (including cerebral vascular accidents/strokes, deep vein thrombosis, and other unspecific blood clots) were reported the least often in LA. In the selected studies, only two participants were reported to have a thromboembolic event. The second lowest was that with RF (0.27 percent) and highest being with CB (0.32 percent). To reiterate, each study reports incidence in less than 1 percent of patients.

Groin hematomas, meaning significant bleeding that causes attention (either due to discomfort of need for further intervention) occurred least frequently in RF ablations (reported in 1.79 percent of patients). LA experienced the most frequent complications were groin hematomas occurring in 4.23 percent of cases. CB followed behind with 4.0 percent occurrence.

Major bleeding, is defined as bleeding that requires extended hospital stay, significant monitoring, or intervention. Values were similar between studies, but LA demonstrated the least occurrence with 1.41% of patients requiring attention. RF reported 3.19% and CB reported 2.25%.

Phrenic nerve paralysis was taken into consideration given its potential long-term side effects. The smallest occurrence was documented at 0.14% in RF ablations. CB and LA were quite a bit higher at 3.13% and 4.62% respectively. It is noted that in most cases documented by all studies, the paralysis was temporary, and the patient gained most, if not all, function of the diaphragm.

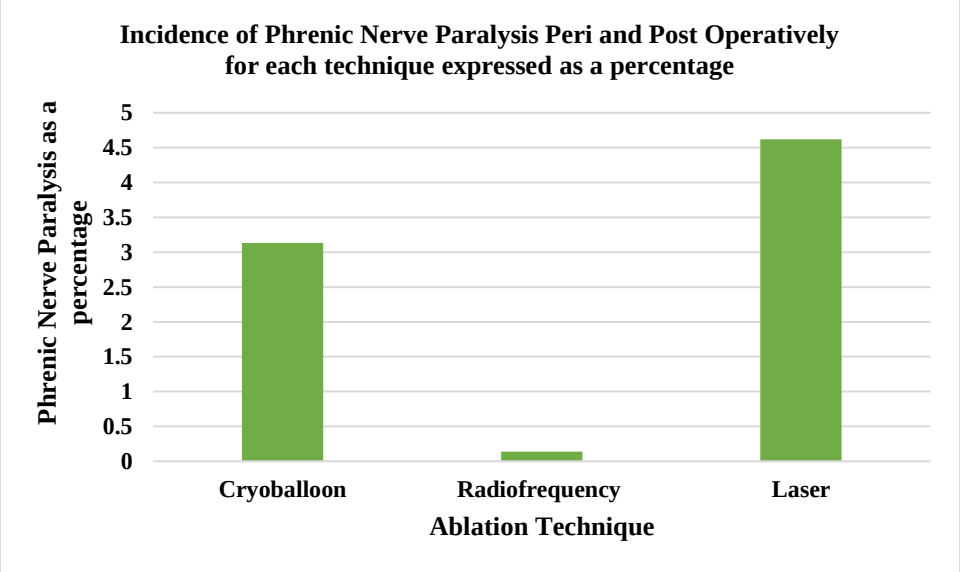

Figure 1- Incidence of Phrenic nerve paralysis (as a percentage of the number of cases for each separate technique) as given by **Table 2**. As discussed in the *Methods section* of this report, the percentage of cryoballoon phrenic nerve paralysis cases is a mean derived from two independent studies.

Comparative CA v. RF v. LA	**Cryoballoon**	**Radiofrequency**	**Laser**
Recurrence at 12 months	54.00	66.07	36.53

Thromboembolic event	0.32	0.27	0.00
Groin hematoma	4.00	1.79	4.23
Major bleeding	2.25	3.19	1.41
Phrenic nerve Paralysis	3.13	0.14	4.62

Table 2- Direct comparison of Cryoballoon, Radiofrequency, and Laser Ablations as expressed in percentage of incidences in overall study. A comprehensive comparison of CB, RB, and laser ablation recurrence and complications for each technique, expressed as a percentage out of 100.

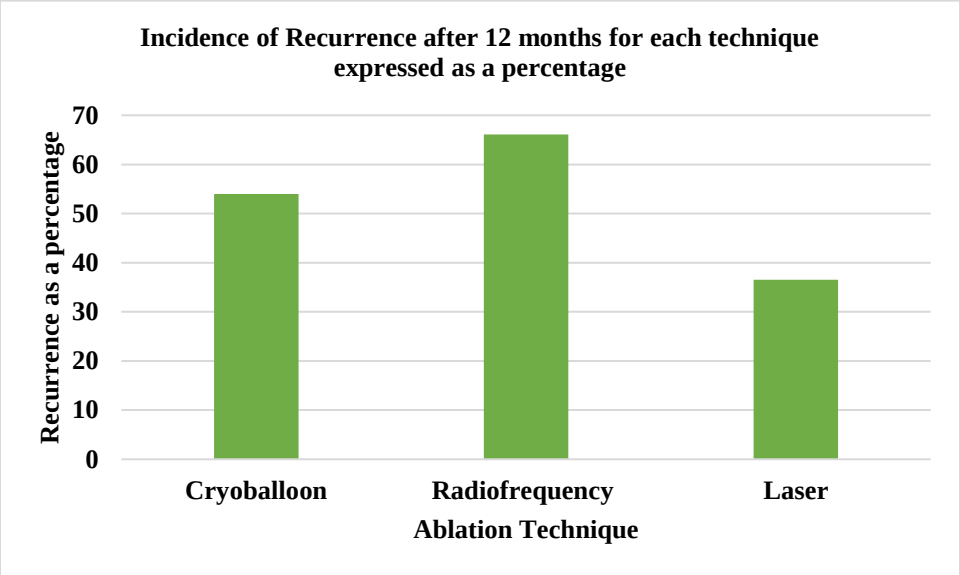

Figure 2- Incidence of recurrence (as a percentage of the number of cases for each separate technique) as represented by the combined total in **Table 2**.

While individual CB and RF studies documented incidence of recurrence in several increments (9 months, 10 months, 12 months) 12 months was chosen for comparison. 12 months is both after the 3 month blanking periods and was addressed by at least one study for each of the techniques. The highest recurrence was seen with RF at 66.07%, meaning that only 33.93% of patients saw permanent results after their first ablation. CB demonstrated a recurrence of 54% and LA demonstrated the least recurrence at 36.53%.

Conclusions

It remains unclear if one ablation technique is truly “superior” to the others, though evidence does suggest that LA techniques may result in the least incidence of recurrence. LA, too, resulted in the highest incidence of phrenic nerve paralysis and groin hematoma. It is important to note that groin hematomas were present with all techniques but is also a lower risk complication. LA noted only 2 patients who experienced the most severe complication, a thromboembolic event.

RF and CB ablations demonstrated less bleeding complications and less cases of phrenic nerve paralysis, but again, had higher recurrence rates than that of LA. Radiofrequency had the highest rate of recurrence revealing 66.07% recurrence rate after one year. That means that only a striking 34.93% of patients had relief of their atrial fibrillation after one years’ time.

Limitations of this Study

This study is, again, an introduction to the topic of laser ablations compared to more traditional catheter ablations. There are numerous limitations to consider when evaluating this information. First, this study was largely qualitative. Calculating statistical significance was omitted in this study due to the large error between different sampling techniques and the lack of clear procedural guidelines.

Additionally, like data regarding any procedure, each Electrophysiologist will have individual statistics that differ from their peers. These individual statistics should be considered by a patient making the decision to proceed with any elective surgery, specifically one like an ablation.

It is also important to consider that with each ablation technique, there are multiple sizes and makes of catheters as well as procedure differences including amount of time and frequency of the cauterization. Further investigation would need to be conducted to determine the optimal manipulation of each of these factors.

This study does not specifically take into account comorbidities that may contribute to the overall risks of such procedures including coronary artery disease, hypertension, diabetes mellitus, and prior history of embolisms. While many of the studies used their own methods of eliminating comorbidities from their results, this was not a criterion in selecting studies for this investigation.

Looking to the Future

Going forward, an investigation should be completed that encompasses radiofrequency, cryoballoon, and laser ablation techniques, ideally, at one institution. Reducing the number of institutions assures that the standards for how the procedure is carried out are similar. This includes more than just the physician, but also the operating room staff, the post-surgical care team, and even the pre-surgical patient education. Each of these factors varies from institution to institution and could create a wider variance in type and severity of outcomes. For example, if operating staff at one institution are particularly bad at sterilization, they may experience more post-operative infections. This institution may increase the average infection rates for the procedure, which may not accurately reflect the risk of infection elsewhere. If the goal of the study is to determine which institution preforms the procedures best, then multiple studies at several institutions would be beneficial.

It may be beneficial to conduct an economic cost-benefit analysis of integrating this new technology into an institution. While data can conclude that one technique is safer, the cost to institutions and to patients may limit the accessibility of the product.

The study should also be conducted with a large number of operating Electrophysiologists to reduce discrepancy between physicians. Given that this large group is ideally operating under the same institution protocols, the differences between operators should be minimal. While each physician will have different outcomes specifically, including a mass number of physicians should ideally eliminate physician-to-physician discrepancies.

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Appendix I

Explanation of Color Coded Studies

The color coordinating of the individual studies used for comparison was done for two reasons. One, color coding was done to simplify the viewing and comparison of data, both for the researcher and the reader. Color coding was also completed to help eliminate any viewer bias while comparing information. Critical review of sources is important but may over complicate viewing of data during the results section of this study. For further explanation on how sources were selected, please see the *Methods*. The colors and coding were selected arbitrarily.

Yellow Study:

Malmborg, H., Lonnerholm, S., Blomstrom, P., & Blomstrom-Lundqvist, C. (2013). Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. *Europace*, 1567-1573.

Green Study:

Dukkipati, S., Cuoco, F., Kutinsky, I., Aryana, A., Bahnson, T., Lakkireddy , D., . . . Reddy, V. (2015). Pulmonary Vein Isolation Using Visually Guided Laser Balloon. *Journal of the American College of Cardiology, 66*(12), 1350-1360.

Blue Study:

Osca, J., Andres, A., Cano, O., Alonso, P., Jose Sancho Tello, M., Olague, J., . . . Salvador, A. (2016, February 2). Electrical Isolation of Pulmonary Veins Using Laser Catheter in the Treatment of Paroxysmal and Persistent Atrial Fibrillation. One-year Results. *Revista Espanola de Cardiologia, 69*(5), 488-493.

Orange Study:

Khoueiry, Z., Albenque, J. P., Providencia, R., Combes, S., Combes, N., Jourda, F., . . . Boveda, S. (2016). Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. *Europace*, 1343-1351.