

Comparison of the efficacy and complication rates of the hybrid maze, complete Cox-maze and catheter ablation in the treatment of atrial fibrillation

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Abstract

Introduction: Atrial fibrillation is the most common cardiac arrhythmia in the United States. It has been associated with a reduction in patient quality of life and more serious complications such as stroke and heart failure. The aim of this study was to compare the efficacy of commonly performed invasive procedures in keeping patients in normal sinus rhythm.

Methods and Results: A retrospective chart review was performed on all patients who underwent primary radiofrequency catheter ablation, the complete Cox-maze, or the hybrid maze at OSF Saint Anthony Medical Center between January 2010 and December 2013 (n=140). Immediately post-procedure, arrhythmia recurrence rates did not differ between the groups ($p = 0.28$). At all follow-up points thereafter, however, differences in procedural efficacy between surgical and catheter therapy remained highly significant ($p < 0.001$). At 2 years, 20.3% of the catheter ablation patients were in normal sinus rhythm, when compared to 57.9% of hybrid maze and 72.7% the complete Cox-maze groups. A difference in major complication rates was noted ($p = 0.04$), with the complete Cox-maze having a 17.4%, the hybrid having 22.7%, and the catheter ablation group having 5.6%.

Conclusions: This study was unable to detect differences in the efficacy rates of the surgical procedures, however they were both superior to catheter ablation. Although the hybrid approach is considered minimally invasive, complication rates were similar to those of the complete Cox-maze. Catheter ablation was the safest procedure, and since evidence of reduced mortality after the use of aggressive rhythm therapy is currently lacking, the results suggest that hybrid surgery for atrial fibrillation should be used after the failure of more conservative measures.

Introduction

As the most commonly encountered cardiac arrhythmia in the United States, atrial fibrillation is currently estimated to affect between 2 and 2.5 million people and the number suffering might rise to approximately 5.6 million by the year 2050. [1] Atrial fibrillation patients are at an increased risk of having a stroke, developing heart failure or other cardiovascular complications associated with marked reductions in quality of life. An analysis of patients in the original Framingham Study who suffered from atrial fibrillation noted that the condition is likely associated with a significant increase in patient mortality even after adjusting for other cardiac disease. [2] The condition is generally considered to be progressive in nature and involves four stages: paroxysmal, occurring in separate episodes; persistent, when it becomes constant; long standing persistent; and permanent, when the decision has been made to no longer pursue

conversion to normal sinus rhythm (NSR). Currently, there are no curative options for patients with atrial fibrillation. In fact, the annual cost of treating patients in the United States is approximately \$6.65 billion, which does not take into account additional costs incurred for stroke prevention, inpatient medications, comorbid conditions, or other inpatient expenditures. [3] Despite the profound impact on our society, the exact cause of this arrhythmia is still unknown. The pathophysiology of the disease however, depends on two major components: abnormal electrical triggers, thought to be cardiac ganglionic plexuses located at the pulmonary veins and left atrial junction, and an enlarged and often fibrotic left atrium, acting as a substrate for propagation of the abnormal signals. [4] Current invasive treatment strategies are based on these two notions and focus on the prevention of thromboembolism, which may lead to stroke or other cardio-embolic complications. [5] The condition can be asymptomatic, in which case, physicians may simply focus on anticoagulation and rate control. If symptoms are severe enough to warrant therapy, it is possible to utilize a number of antiarrhythmic medications in order to try and gain control of the abnormal rhythm. In addition to pharmacologic therapy, electrical cardioversion can be utilized to convert the patient back is also utilized with the aim of converting

Key Words

Atrial Fibrillation, Hybrid Maze, Cox Maze, PVI Catheter Ablation.

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the patient back to normal sinus rhythm. If that fails, patients may undergo more invasive ablation therapies.^[6] It is of note that the AFFIRM trial, which is a large study that compared rate versus rhythm control in the management of atrial fibrillation patients,

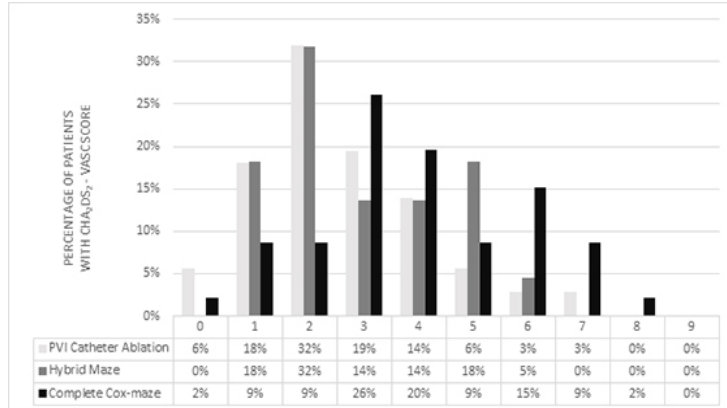


Figure 1: Percentage of Patients in each CHA₂DS₂ - VASc Score Category Stratified by Procedure

detected no decreases in overall mortality associated with either method compared to the other.^[7] Therefore, utilization of invasive approaches for rhythm management is purely for symptomatic relief with an aim of improving quality of life. Consequently, the risks of complications should carefully be weighed against the benefits of these procedures. There are three main methods of rhythm control: medical management, catheter ablation and surgical therapy. Medical management, usually being the first-line approach, involves the use of antiarrhythmics. One of the more established invasive procedures for the treatment of recurrent symptomatic patients is radiofrequency endocardial catheter ablation, in which the pulmonary veins are electrically decoupled from the left atrium with the help of a catheter that is advanced into the left atrium usually through a vein in the groin. Epicardial ablation with left atrial appendage clipping, also known as the complete Cox-maze procedure, is the most invasive surgical approach. It is an open-heart surgery which is typically performed in conjunction with surgery to correct another heart condition like coronary artery disease or valvular disease. Studies have shown outstanding efficacy rates, but due to the invasiveness of the procedure and the potential for complications, it is not recommended for all patients.^{[8]-[10]} Developed by Dr. James Cox in 1987,^{[11]-[13]} the complete Cox-maze provided a basis for other currently utilized surgical procedures. The hybrid maze combines minimally invasive surgical epicardial ablation relying on a mini-thoracotomy approach and endocardial catheter ablation. The procedure can be completed in a stepwise fashion, where the patient undergoes the minimally invasive maze and then several months later, undergoes catheter ablation. Completing both stages of the procedure at one time is also possible. This therapy combines the benefit of left atrial debulking with a minimally invasive approach, which in theory would make it a preferred choice. Current data suggests that this newer hybrid procedure may be far superior in efficacy to standard endocardial catheter ablation, with studies reporting success rates greater than 90%.^[14]

With the utilization of newer procedures and the improvement of more established techniques, patient treatment options are expanding. Yet to our knowledge, there are currently only two studies that have compared the hybrid maze to other invasive treatment modalities, and neither has examined it in the context of primary treatment, before the

Table 1: Baseline Patient Characteristics

	PVI Catheter Ablation (n=72)	Hybrid Maze (n=22)	Complete Cox-maze (n=46)
Demographics:			
§ Age, mean (SD)	61.4 (8.5)	68.1 (10.9)	69.3 (9.0)
§ Male	68.1%	72.7%	69.6%
§ Female	31.9%	27.3%	30.4%
Comorbid Conditions:			
§ Obesity (BMI > 30)+	42 (58.3%)	18 (81.8%)	22 (47.8%)
§ Mitral Valve Disease+	12 (16.7%)	8 (36.4%)	16 (34.8%)
§ Coronary Artery Disease	24 (33.3%)	7 (31.8%)	23 (50.0%)
§ Cardiomyopathy	4 (5.6%)	1 (4.5%)	1 (2.2%)
§ Hypertension	57 (79.8%)	19 (86.4%)	40 (87.0%)
§ Diabetes Mellitus Type II	25 (34.7%)	4 (18.2%)	22 (47.8%)
§ COPD	9 (12.5%)	1 (4.5%)	9 (19.6%)
§ Sleep Apnea	25 (34.7%)	8 (36.4%)	13 (28.3%)

failure of other invasive treatments.^{[15],[16]} In one trial, the control was catheter ablation, however the study included only 15 patients who underwent the maze, of which less than half followed up for more than 20 months.^[16] The other examined the differences in outcomes when adding a sequential catheter ‘touch up’ to a minimally invasive surgical ablation, essentially discussing the plausibility and potential benefits of utilizing the hybrid approach.^[15] At this time, neither the 2016 European Society of Cardiology (ESC) nor the 2014 American Heart Association (AHA) guidelines provide any recommendation as to the proper utilization of this surgical technique, despite both of them mentioning that surgical ablation may still play a role in some more highly symptomatic patients.^{[6],[17]} Because of ethical concerns regarding patient safety, a randomized controlled trial examining the hybrid maze as stand-alone treatment for atrial fibrillation is currently not feasible. Therefore, the aim of this retrospective study is to compare long-term efficacy and complication rates of the hybrid maze procedure to other more commonly utilized invasive procedures—radiofrequency endocardial catheter ablation and the complete Cox-maze.

Methods

All patients with atrial fibrillation who have undergone radiofrequency endocardial catheter ablation, the complete Cox-maze, or the hybrid maze at OSF Saint Anthony Medical Center, Rockford, IL between January 2010 and December 2013 were identified through the use of the respective CPT billing codes for each procedure – comprising 163 cases. The subjects were stratified into three groups based on the first invasive procedure they received for the treatment of their illness.

In order to provide a fair comparison between the procedures, any patient who had received prior invasive therapy to treat their condition was excluded. This included 2 patients from the hybrid maze group, 13 patients from the PVI catheter ablation group, and 8 patients from the complete maze group. The final sample size for analysis was 140 patients. Data were extracted by two independent researchers, cross-referenced and any inconsistencies or missing values were rechecked in the electronic medical record (EMR). The patients were followed up for two years post-procedure. Data on the CHADS₂ score, atrial fibrillation status, anticoagulation use (including warfarin, rivaroxaban, apixaban, dabigatran, aspirin, clopidogrel, prasugrel), antiarrhythmic use (including amiodarone,

flecainide, dronedarone, propafenone, sotalol, dofetilide, digoxin, procainamide, quinidine), major life-threatening complications and additional procedures were collected at four time points—immediately post-procedure prior to discharge from the hospital, 6 months, 12 months and 24 months post-procedure. A CHADS₂ score, which ranges from 0 to 6, where a higher number is correlated with a higher estimated risk of cerebrovascular accidents, was used

conducting the final regression analysis, the only dependent variable was procedural efficacy in keeping patients in normal sinus rhythm. The independent variables included were: age, obesity, antiarrhythmic usage, mitral valve disease, diabetes mellitus type II, and procedure utilized.

Results

Baseline demographic characteristics and co-morbid conditions stratified by procedure utilized are presented in [Table 1]. The mean age of subjects within the PVI catheter ablation group was 61.4±8.5 years, 68.1±10.9 for the hybrid maze group, and 69.3±9.0 in the complete Cox-maze group. The majority of participants in the study were males, with 68.1% in the catheter ablation group and 72.7% and 69.6% in the hybrid and complete maze groups respectively.

Discussion

Indications of the complete Cox-maze have been thoroughly studied along with its excellent long-term efficacy. However, in patients needing primary treatment solely for atrial arrhythmia, a more minimally invasive approach is preferred. Despite a clear superiority of the hybrid maze procedure when compared to pulmonary vein catheter ablation, at this time, the most appropriate indications for the procedure is yet to be identified. The current American Heart Association and European Society of Cardiology guidelines for the treatment of atrial fibrillation lack any recommendations for hybrid surgical therapy. They both do mention, however, that a standalone surgical ablation procedure can be reasonable in a symptomatic patient that is not controlled with other less invasive approaches.

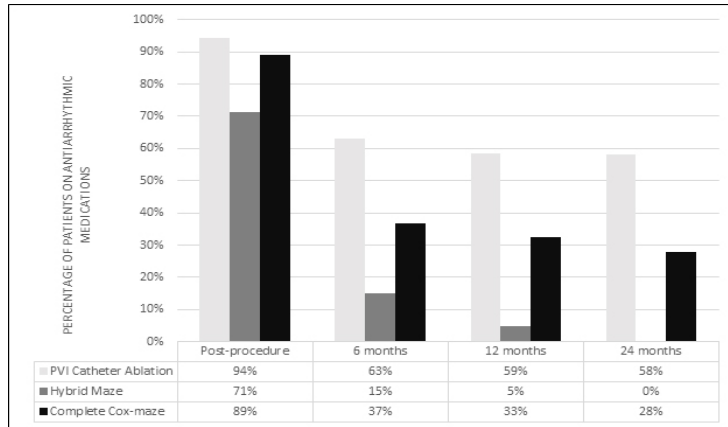


Figure 2: Usage of Antiarrhythmic Medications Stratified by Procedure Across Time Points

as a surrogate for disease severity. CHADS₂ is a risk stratification schema that includes: congestive heart failure, hypertension, age (>= 75), diabetes, and cerebrovascular accidents, including transient ischemic attacks [18]. This project was approved by the Institutional Review Boards at the University of Illinois College of Medicine at Rockford (protocol number 20150077) and OSF Saint Anthony Medical Center (protocol number #201509).

Data Analysis

The primary outcome of the study was procedural efficacy, which

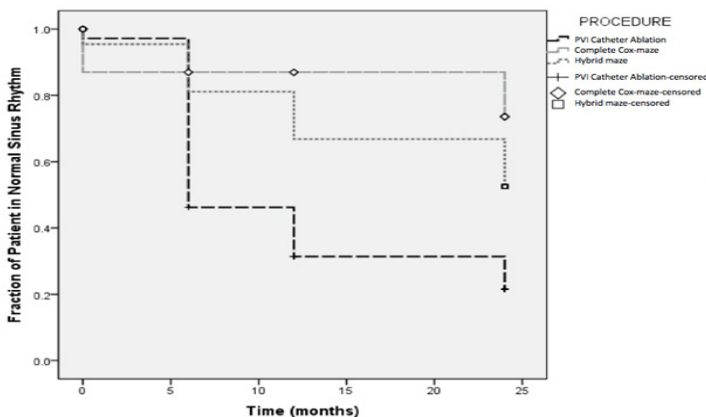


Figure 3: Kaplan-Meier Survival Plot for All Patients in the Study

was defined as absence of atrial fibrillation at four time points during the 24-month follow-up. At baseline, a one-way ANOVA was used to test for differences in mean age between the different groups and a chi-square test was used for the categorical data. Due to the small sample size within the hybrid maze procedure group, a Fisher's exact test was used where appropriate. Both a chi-square analysis and a multivariate logistic regression were used to determine if there were an association between procedure used and recurrence of atrial fibrillation at different time points. All baseline variables that were significant (p-value < 0.05) were included in the final logistic regression analysis that examined procedural efficacy. When

Table 2: Number of Complications Associated with Each Procedure during the two-year timeline

Complication	PVI Catheter Ablation (n=72)	Hybrid Maze (n=22)	Complete Cox-maze (n=46)
Major Events:			
Pneumonia	0	1	3
Acute Kidney Injury	0	0	1
Dressler's Syndrome	0	1	1
Cardioplegic Syndrome	0	0	1
Pleural Effusion	0	2	1
Acute Heart Failure	0	0	1
Stroke/Transient Ischemic Attack (TIA)	0	0	0
Pericardial Effusion/ Cardiac Tamponade	4	0	0
Procedure-related Death	0	1	1
Total number of events	4 (5.6%)	5 (22.7%)	8 (17.4%)
Minor Events:			
Pseudoaneurysm	2	0	0
Groin Hematoma/Bleed	2	0	0

The ESC states that: "Although preliminary experience with hybrid simultaneous ablation shows promise, procedural time and rates of bleeding complications are higher" [17]. Therefore, the question remains whether this procedure has a role when deciding between treatment options for patients in whom medical management has failed. Based on both the bivariate analysis and multivariate logistic regression model, it is apparent that there is a difference in atrial fibrillation recurrence at 6 months and beyond, depending on which procedure was utilized. Catheter ablation patients were much more likely to suffer from a recurrence of their atrial arrhythmia, despite the highest utilization of antiarrhythmic medication across all time

points. The study was unable to demonstrate any difference between the efficacies of the hybrid maze and the complete Cox-maze, providing further evidence that the combined minimally invasive maze and catheter ablation approach might indeed be associated with favorable efficacy rates. It is important to note that the failure of this study to prove inequality between the efficacies of the hybrid maze and the complete Cox-maze does not imply equality. In a subgroup analysis of 43 patients with longstanding persistent atrial fibrillation, the results mimicked the overall cohort, with the catheter ablation procedure having an even lower efficacy when compared to the other two procedures. Despite its promising efficacy rate, the hybrid maze procedure was associated with a significant number of complications and a possible increase in mortality. Pneumonia, Dressler's syndrome, pleural effusion, and one death were observed. In the complete Cox-maze group, acute renal failure was most common, but pleural effusion, respiratory failure, aspiration pneumonia, heart failure and Dressler's syndrome were all recorded complications. It is important to note that most complications encountered with both of the surgical treatments happened during patient recovery, and not at the time of the procedure. As catheter ablation procedures do not require long term hospitalization, patients are not as susceptible to hospital-associated adverse events. The majority of catheter ablation complications did not require any significant intervention from a physician, when compared to the other two procedures, which tended to require the involvement of a team of treating physicians in order to prevent long-term consequences or death. The most commonly encountered complication in the catheter ablation group was a pericardial effusion. At this time, it is precisely because of the high complication rates associated with surgical procedures that they are utilized as a third-line treatment, only after the failure of both medical management and catheter ablation [6],[17],[21],[22]. The FAST trial, which current guidelines are mainly based on, is the largest randomized control trial comparing minimally invasive surgical ablation and catheter ablation. It was performed by Boersma et al. in two centers, one being in Spain and the other in the Netherlands. Unfortunately, this study did not evaluate the hybrid maze, therefore surgical patients were not followed-up with a catheter procedure. Also, the patients being examined had either left atrial dilatation and hypertension or a failed prior catheter ablation, suggesting a population that is inherently resistant to treatment. Despite these differences, both complication rates (5.6% vs 3.2% in the catheter ablation group and 22.7% vs 23.0% in the minimally invasive surgical group) and efficacy rates (33.0% vs 36.5% in the catheter ablation group and 70.0% vs 65.6% in the minimally invasive surgical group) at 12 months in this study were found to be similar to those of the FAST trial, suggesting that the hybrid maze may be considered a viable option in highly symptomatic patients that have failed medical therapy [21]. There are several notable limitations to this study. Due to it being a single center retrospective analysis of electronic medical records, there is an inherent reliance on the accuracy of the records. As a result of the retrospective nature of the study, there is no way to accurately measure if the patients actually experienced any improvement of their atrial fibrillation symptoms following a procedure. Instead, the success of a procedure is based on the complete lack of recurrence of the arrhythmia. Also, because of the lack of randomization, there is no way to account for effects of other variables that were not measured at baseline. Lastly, like many other studies in this field, due to the limited utilization of surgical

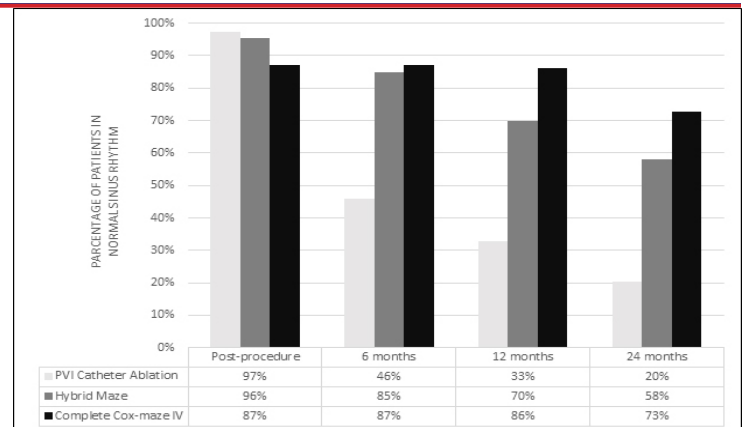


Figure 4: Percentage of Patients in Normal Sinus Rhythm at each Time Point

ablation procedures, there is a limited cohort size. Thus, as mentioned previously, the study was underpowered, and its inability to identify a difference in the efficacies of the Complete Cox-maze and the hybrid maze does not imply their equality. Adequately powered studies in patients with symptomatic longstanding persistent atrial fibrillation are still necessary to investigate whether the superior efficacy observed with surgical procedures might in fact outweigh the risk of procedural complications and ultimately provide some benefit in mortality.

Conclusions

This study was unable to detect any differences in efficacies of the two surgical procedures under investigation, however they were both found to be significantly superior to a pulmonary vein isolation catheter ablation in keeping patients in normal sinus rhythm. Although the hybrid approach utilized a minimally invasive method of gaining access to the left atrium, adverse event rates were similar to those of the complete Cox-maze. Catheter ablation had a significantly lower efficacy when compared to the surgical procedures, with most arrhythmia recurrences occurring within the first 6 months post-procedure. However, it was associated with the fewest number of potentially life threatening adverse events. Since, at this time, evidence of any long-term survival advantage after the use of aggressive rhythm therapy is lacking, the results of this study suggest that stand-alone surgical treatments for atrial fibrillation should be used as a third-line approach, only after the failure of more conservative measures. It is important to note that patients with longstanding persistent atrial fibrillation may often suffer from a substantially increased burden of disease. There is a lack of data regarding the proper utilization of the hybrid maze procedure in the treatment of this population and therefore further studies with a primary focus on these patients are necessary.

Conflict of Interests

None.

Disclosures

None.

References

- Go A S, Hylek E M, Phillips K A, Chang Y, Henault L E, Selby J V, Singer D E. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285 (18):2370–5.
- Benjamin E J, Wolf P A, D'Agostino R B, Silbershatz H, Kannel W B, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study.

- Circulation. 1998;98 (10):946–52.
3. Coyne Karin S, Paramore Clark, Grandy Susan, Mercader Marco, Reynolds Matthew, Zimetbaum Peter. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9 (5):348–56.
 4. Wazni Oussama, Wilkoff Bruce, Saliba Walid. Catheter ablation for atrial fibrillation. *N. Engl. J. Med.* 2011;365 (24):2296–304.
 5. Moukabary Talal, Gonzalez Mario D. Management of atrial fibrillation. *Med. Clin. North Am.* 2015;99 (4):781–94.
 6. January Craig T, Wann L Samuel, Alpert Joseph S, Calkins Hugh, Cigarroa Joaquin E, Cleveland Joseph C, Conti Jamie B, Ellinor Patrick T, Ezekowitz Michael D, Field Michael E, Murray Katherine T, Sacco Ralph L, Stevenson William G, Tchou Patrick J, Tracy Cynthia M, Yancy Clyde W. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130 (23):2071–104.
 7. Wyse D G, Waldo A L, DiMarco J P, Domanski M J, Rosenberg Y, Schron E B, Kellen J C, Greene H L, Mickel M C, Dalquist J E, Corley S D. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N. Engl. J. Med.* 2002;347 (23):1825–33.
 8. Weimar Timo, Bailey Marci S, Watanabe Yoshiyuki, Marin Donna, Maniar Hersh S, Schuessler Richard B, Damiano Ralph J. The Cox-maze IV procedure for lone atrial fibrillation: a single center experience in 100 consecutive patients. *J Interv Card Electrophysiol*. 2011;31 (1):47–54.
 9. Y Zhang, LZhu. Surgical ablation of atrial fibrillation. *IJC Heart and Vessels [Internet]*. 2014;0:104–108.
 10. Henn Matthew C, Lancaster Timothy S, Miller Jacob R, Sinn Laurie A, Schuessler Richard B, Moon Marc R, Melby Spencer J, Maniar Hersh S, Damiano Ralph J. Late outcomes after the Cox maze IV procedure for atrial fibrillation. *J. Thorac. Cardiovasc. Surg.* 2015;150 (5):1168–76, 1178.e1–2.
 11. Cox J L, Boineau J P, Schuessler R B, Kater K M, Ferguson T B, Cain M E, Lindsay B D, Smith J M, Corr P B, Hogue C B. Electrophysiologic basis, surgical development, and clinical results of the maze procedure for atrial flutter and atrial fibrillation. *Adv Card Surg*. 1995;6 (0):1–67.
 12. Cox J L. The surgical treatment of atrial fibrillation. IV. Surgical technique. *J. Thorac. Cardiovasc. Surg.* 1991;101 (4):584–92.
 13. Cox J L, Canavan T E, Schuessler R B, Cain M E, Lindsay B D, Stone C, Smith P K, Corr P B, Boineau J P. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. *J. Thorac. Cardiovasc. Surg.* 1991;101 (3):406–26.
 14. Kumar Prabhat, Kiser Andy C, Gehi Anil K. Hybrid treatment of atrial fibrillation. *Prog Cardiovasc Dis.* 2015;58 (2):213–20.
 15. La Meir Mark, Gelsomino Sandro, Lucà Fabiana, Pison Laurant, Parise Orlando, Colella Andrea, Gensini Gian Franco, Crijns Harry, Wellens Francis, Maessen Jos G. Minimally invasive surgical treatment of lone atrial fibrillation: early results of hybrid versus standard minimally invasive approach employing radiofrequency sources. *Int. J. Cardiol.* 2013;167 (4):1469–75.
 16. Mahapatra Srijoy, LaPar Damien J, Kamath Sandeep, Payne Jason, Bilchick Kenneth C, Mangrum James M, Ailawadi Gorav. Initial experience of sequential surgical epicardial-catheter endocardial ablation for persistent and long-standing persistent atrial fibrillation with long-term follow-up. *Ann. Thorac. Surg.* 2011;91 (6):1890–8.
 17. Kirchhof Paulus, Benussi Stefano, Kotecha Dipak, Ahlsson Anders, Atar Dan, Casadei Barbara, Castella Manuel, Diener Hans-Christoph, Heidbuchel Hein, Hendriks Jeroen, Hindricks Gerhard, Manolis Antonis S, Oldgren Jonas, Popescu Bogdan Alexandru, Schotten Ulrich, Van Putte Bart, Vardas Panagiotis, Agewall Stefan, Camm John, Baron Esquivias Gonzalo, Budts Werner, Carerj Scipione, Casselman Filip, Coca Antonio, De Caterina Raffaele, Deferetos Spiridon, Dobrev Dobromir, Ferro José M, Filippatos Gerasimos, Fitzsimons Donna, Gorenek Bulent, Guenoun Maxine, Hohnloser Stefan H, Kolh Philippe, Lip Gregory Y H, Manolis Athanasios, McMurray John, Ponikowski Piotr, Rosenhek Raphael, Ruschitzka Frank, Savelieva Irina, Sharma Sanjay, Suwalski Piotr, Tamargo Juan Luis, Taylor Clare J, Van Gelder Isabelle C, Voors Adriaan A, Windecker Stephan, Zamorano Jose Luis, Zeppenfeld Katja. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*. 2016;18 (11):1609–1678.
 18. Gage B F, Waterman A D, Shannon W, Boehler M, Rich M W, Radford M J. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285 (22):2864–70.
 19. CN Bairey Merz, LJ Shaw, SE Reis, VBittner, SFKelsey, MOlson, BDJohnson, CJPepine, SMankad, BLSharaf, WJRogers, GMPohost, ALerman, AAQuyyumi, GSopko. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Part II: Gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular cor. *J Am Coll Cardiol [Internet]*. Elsevier Masson SAS; Available from: <http://dx.doi.org/10.1016/j.jacc.2004.12.084>. 2006;47:21–29.
 20. Polk Donna M, Naqvi Tasneem Z. Cardiovascular disease in women: sex differences in presentation, risk factors, and evaluation. *Curr Cardiol Rep*. 2005;7 (3):166–72.
 21. Boersma Lucas V A, Castella Manuel, van Boven Wimjan, Berruezo Antonio, Yilmaz Alaaddin, Nadal Mercedes, Sandoval Elena, Calvo Naiara, Brugada Josep, Kelder Johannes, Wijffels Maurits, Mont Lluís. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation*. 2012;125 (1):23–30.
 22. Calkins Hugh, Brugada Josep, Packer Douglas L, Cappato Riccardo, Chen Shih-Ann, Crijns Harry J G, Damiano Ralph J, Davies D Wyn, Haines David E, Haissaguerre Michel, Iesaka Yoshito, Jackman Warren, Jais Pierre, Kottkamp Hans, Kuck Karl Heinz, Lindsay Bruce D, Marchlinski Francis E, McCarthy Patrick M, Mont J Lluís, Morady Fred, Nademanee Koonlawee, Natale Andrea, Pappone Carlo, Prystowsky Eric, Raviele Antonio, Ruskin Jeremy N, Shemin Richard J. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace*. 2007;9 (6):335–79.

