



4-2013

Management of Anticoagulation in Patients undergoing Catheter Ablation of Atrial Fibrillation

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MANAGEMENT OF ANTICOAGULATION IN PATIENTS UNDERGOING CATHETER
ABLATION OF ATRIAL FIBRILLATION

by

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Bachelor of Science in Nursing, Bemidji State University, 1987

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, ND

April

2013

PERMISSION

Title Management of Anticoagulation in Patients Undergoing Catheter Ablation of
Atrial Fibrillation

Department Nursing

Degree Master of Science

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Management of Anticoagulation in Patients Undergoing Catheter Ablation of Atrial
Fibrillation

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No conflicts of interest.

Number of tables/figures: 4

Abstract

Background

Atrial fibrillation (AF) is a heart rhythm abnormality frequently encountered in many health care settings. Stroke is a life-threatening complication linked to AF. Oral anticoagulation with warfarin, a vitamin K antagonist (VKA), has been used to successfully prevent and treat thromboembolism. Anticoagulation therapy, however, is not devoid of risks. The increasing population of individuals affected by AF has generated greater interest in therapy options. Catheter ablation offers safe treatment for AF. Stroke risk estimation and effective anticoagulation remain a priority preceding, during, and following catheter ablation. Knowledge of current evidence based anticoagulation strategies in patients undergoing catheter ablation is of utility to providers who care for these individuals.

Purpose

This review outlines issues associated with anticoagulation therapy in the face of catheter ablation including risk of bleeding and stroke, recaps the historical course of anticoagulation management during this period, and summarizes the weight of current evidence pertaining to anticoagulation strategies during catheter ablation. A discussion on what is known about new agents such as dabigatran, rivaroxiban, and apixaban is included. The review concludes with a reflection on new research with potential to impact future trends in practice.

Conclusions

Current evidence supports performance of catheter ablation for atrial fibrillation on uninterrupted VKA therapy targeting INR's at a range greater than 2.0 seconds. This strategy has been shown to diminish the risk of stroke without increasing bleeding complications. Large scale

trials are needed to provide evidence about the predictive ability of new OAC agents to diminish stroke risk without increasing risk of bleeding during catheter ablation.

Clinical Implications

Understanding rationale for anticoagulation treatment in the setting of catheter ablation as well as inherent risks is critically important. Ongoing research and development will result in greater understanding of effective treatment methods and lead to improved outcomes and increased patient satisfaction.

Key Words: Atrial fibrillation, catheter ablation, anticoagulation

Atrial fibrillation (AF) is a common heart rhythm abnormality encountered by practitioners across a broad spectrum of health care settings. By the year 2050, it has been projected that over 10 million individuals will have AF (Miyasaka et al., 2006). Epidemiological studies demonstrate that the prevalence of AF increases with age from 0.1% in individuals under the age of 55 to 9.0% in those over age 80 years (Go et al., 2001). The Framingham study generated landmark data linking AF with stroke. This study also showed that the stroke risk in individuals with AF increases with advanced age (Wolf, Abbott, & Kannel, 1991). Oral anticoagulation with vitamin K antagonists (VKA) has been shown to reduce the risk of stroke, particularly as age increases. However, anticoagulation therapy is not entirely devoid of risk and is associated with a higher likelihood of bleeding in specific populations (Lip et al., 2011). New oral anticoagulation agents such as dabigatran, rivaroxaban, and apixaban are promising treatment alternatives, but are subject to similar considerations.

The projected rise in the number of individuals affected by AF and resulting economic burden on the health care system has resulted in a heightened interest in evidence based AF management strategies. Catheter ablation has emerged as a safe therapeutic option in the treatment of AF (Cappato et al., 2005). Updated guidelines released by the European Society of Cardiology (ESAC), the American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and Heart Rhythm Society (HRS), and an expert consensus statement endorsed by the HRS provide evidence based grading as to the benefits of catheter ablation in specific populations (Calkins et al., 2012; European Heart Rhythm Association et al., 2010; Wann et al., 2011)

Anticoagulation Therapy in the Setting of Catheter Ablation

Stroke risk estimation and management of anticoagulation therapy remains a critical priority in the period preceding, during, and following catheter ablation for AF. Safe outcomes are contingent on the ability to minimize risk of embolism formation while also preventing occurrence of untoward bleeding. Procedural goals center on the provision of efficacious therapy coupled with reduction of procedural based complications. These objectives; improved outcomes, diminished risk, increased patient satisfaction, and cost containment, provide a platform upon which to base clinical investigation. As a result, the body of evidence addressing anticoagulation strategy in the setting of catheter ablation has grown and continues to evolve. Recent queries concern the safety and utility of anticoagulation bridge therapy versus uninterrupted VKA therapy (Garwood, Hwang, & Moser, 2011) and the safe use of alternative oral anticoagulation (OAC) agents pre and post procedure (Lakkireddy et al., 2012). The purpose of this paper is to present a review of the current published evidence addressing the use of uninterrupted warfarin during catheter ablation as compared to bridging therapy. An examination of the evidence pertaining to use of new OAC agents during catheter ablation is also included.

A comprehensive search of the literature was conducted for this review utilizing EBSCO host data bases including *Medline*, *CINAHL*, and *Dynamed*. The *Sciverse/SCOPUS* database was also accessed. A MeSH search conducted on PubMed using the combined terms *catheter ablation*, *atrial fibrillation*, and *anticoagulation* yielded 244 publications. This search was subsequently limited to clinical trials, meta-analysis, practice published guidelines, randomized controlled trials, case reports, multicenter and comparative studies, and abstracts. Publications were limited to a time frame from 2006 to present. The *SCOPUS* search using the same

combined terms and time frame yielded 191 documents. These were compared with results from PubMed and other search findings. Of the 21 publications identified, 13 pertained to the comparison of catheter ablation for atrial fibrillation performed on uninterrupted warfarin therapy versus a traditional approach using bridging therapy with heparin. The 13 studies were comprised of 7 prospective and 4 retrospective publications, 1 case control with an unclear cohort, and 1 meta-analysis. A summary of the studies comparing outcomes of ablation performed on uninterrupted warfarin as compared to traditional bridging therapy is included (Table 1). The sample populations in the majority of studies were sequential consecutive patients undergoing catheter ablation for atrial fibrillation.

An additional 8 publications concerned the use of dabigatran as compared to uninterrupted warfarin in the setting of catheter ablation. This group consisted of 4 retrospective and 4 prospective studies. A summary of these investigations is included (Table 2). Expert consensus statements previously referred to, namely Catheter and Surgical Ablation of Atrial Fibrillation and The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (2010) provide important recommendations which are extremely germane to this evidence based analysis.

Balancing Bleeding and Stroke: The Surgical Perspective

Anticoagulation therapy with VKA in the patient undergoing an invasive or surgical procedure has risks and benefits that present important considerations when initiating therapy. The risk of procedural bleeding must be balanced with the risk of developing a thromboembolic event should anticoagulation therapy be withheld. Risk estimation is a prediction as to the likelihood of developing thrombus when the VKA is discontinued; higher for example, in the patient with a prosthetic mitral or aortic valve, recent venous thromboembolism (VTE), stroke,

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or CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, and Stroke) score of 5 or greater. The CHADS2 scoring system, used to gauge risk of thromboembolic event in patients with AF, has been well validated (Gage et al., 2001). Points are assigned to factors including age greater than 75 years, congestive heart failure, hypertension, diabetes, and history of stroke or transient ischemic attack. A higher weighted score correlates with increased risk of embolic event. This is discussed in detail in sections to follow. In individuals deemed to be at greater risk for thrombus formation, bridging strategies using unfractionated (UFH) or low molecular weight heparin (LMWH) are usually employed during cessation of VKA therapy. The risk estimation (high, moderate or low risk) typically centers on the indication for anticoagulation and confounding medical problems. The nature of the surgery or intervention is taken into consideration. As such, individual patient history and presentation influence the approach utilized for peri-procedural anticoagulation. This clinical dilemma has been additionally compounded by the influx of new OAC and antiplatelet agents available on the market. In guidelines developed by the American College of Chest Physicians (ACCP), risk stratification is defined. High risk conditions identified in this document include any mitral valve prosthesis, any caged ball or tilting disc aortic valve prosthesis, recent stroke or TIA within 3 months, CHADS2 score > 5, recent VTE in 3 months, and severe thrombophilia. Low risk conditions include bileaflet aortic valve prosthesis without atrial fibrillation and with no other risks for stroke, CHADS2 score of 0-2 with no prior history of stroke or TIA, or VTE > 12 months prior. Individuals at moderate risk have characteristics which fall in between these two categories, an example being a CHADS2 score of 3 or 4 (Douketis et al., 2012)

The risk of bleeding must also be addressed. This includes risks associated with the given procedure as well as the effects of type and duration of anticoagulation therapy. The practice

guidelines identify surgeries and procedures with higher risk of bleeding. Cardiac surgeries are included in this list. Of note, several bleeding risk stratifications have been proposed for patients on anticoagulants due to atrial fibrillation. While these offer guidance pertaining to initiation and continuation of anticoagulation therapy, bleeding in the perioperative period is also influenced by procedural factors (Lip et al., 2011).

Historically, the AACP standards have served as the traditional guide for anticoagulation management in the perioperative period. New ACCP recommendations state that VKA should be stopped 5 days before surgery and restarted at least 12 to 24 hours after operative completion provided no bleeding issues exist (Douketis et al., 2012). Bridging therapy is recommended for high risk patients in whom VKA is stopped preoperatively. If a patient with atrial fibrillation, a mechanical valve, or VTE falls into the low risk category they need not be bridged. For those in an intermediate category, decisions about bridging are based on the individual patient presentation and nature of the procedure. For those patients undergoing bridging, guidelines suggest discontinuation of LMWH 24 hours prior to and UFH 4-6 hours before surgery (Douketis et al., 2012). It is of interest that bridging therapy itself is not rigidly defined but typically consists of administration of UFH or LMWH in one of three dosing regimens. A high dose (therapeutic dose) bridging regimen is administered in the same manner as that used for acute VTE or acute coronary syndrome and per guidelines most widely used in practice. Examples of therapeutic bridging regimens as suggested in this document are presented in Table 3 (Douketis et al., 2012). The guideline notes that trials to determine perioperative recommendations for agents such as dabigatran, rivaroxiban, and apixiban are ongoing.

Challenges in Ablation Practice

Appropriate anticoagulation in the setting of catheter ablation for atrial fibrillation is imperative. The ramifications of failed or improper treatment are significant. The risk of a thromboembolic event during ablation has been documented to occur between 1-5 % (Di Biase et al., 2010). Consequences of a thromboembolic event can include loss of individual productivity, increased economic burden, decreased quality of life, and patient death. Several aspects of catheter ablation inherently lend themselves to the formation of clot. While the mechanisms contributing to thromboembolism formation in AF aren't entirely clear, there is general agreement that a number of pathologic processes promote the prothrombotic state. These include the failure of synchronous atrial contraction which results in blood stasis, and endocardial tissue changes that manifest as fibrosis and inflammation. Stasis leads to accumulation of clotting factors and platelets; consequently a hypercoagulable condition arises. Inflammatory markers, notably increased during AF, are linked to thrombogenesis (Conway, Buggins, Hughes, & Lip, 2004; Watson, Shantsila, & Lip, 2009). In the periprocedural period, there is a tendency toward the development of thrombus on catheters and long sheaths placed within the vascular bed and endocardial cavity, particularly if anticoagulation agents have not been administered at therapeutic levels. Unfortunately, despite adequate anticoagulation thrombus can also form in long sheaths utilized for access to the left atrium, necessitating meticulous attention to proper flushing techniques. Instrumentation within the left atrium can result in travel of the thrombotic material downstream to vital organs including the brain. A thrombogenic state is thought to result from the destruction of endothelial tissue such as takes place with energy application within the atrial cavity. Studies have demonstrated increased level of von Willebrand (VWF) factor during AF ablation, a marker for endothelial destruction. VWF is a glycoprotein important in hemostasis and known to cause adhesion of platelets to collagen fibers (Bulava et al., 2004;

Watson et al., 2009). The formation of coagulum, or heat denatured fibrinogen, at the catheter tip during heating can result in thrombus. Soft thrombus present in the endocardial cavity pre ablation can be dislodged by catheter movement or conversion to normal sinus rhythm. In the post ablation period, impaired atrial contractility or “stunning” has been described, once again contributing to blood stasis. Conversely, anticoagulation in combination with procedural factors can result in bleeding. Vascular access including transseptal catheterization and manipulation of instruments within the endocardial space can result in trauma to the vessels or perforation of the myocardium with subsequent bleeding into the pericardial space or thorax. In one series of 1192 consecutive patients undergoing ablation at a large center, the most common complication observed was that of vascular injury occurring at a rate of 2.3% (Aldhoon, Wichterle, Peichl, Cihak, & Kautzner, 2013). Other complications reported in this study included three (0.25%) cases of cardiac tamponade, and five (0.42%) cerebrovascular events. As such, interest in pre, peri, and post procedural anticoagulation is significant. Approaches to minimize the risk of clot formation with consideration for bleeding can be systematically analyzed in light of these time frames within the procedural course.

Historical Course of Anticoagulation Management

Historically, for those patients who have been maintained on VKA, anticoagulation in the setting of catheter ablation has been guided by the recommended AACP bridging strategies. McCready and colleagues identified a 1.9% incidence of pre-procedure thrombus by transesophageal echocardiography (TEE) following therapeutic anticoagulation with VKA and bridging therapy with dalteparin (McCready et al., 2010). Univariate analysis categorized risk predictors for thrombus including age > 75 years, persistent AF, hypertension and cardiomyopathy. Despite relatively low rates of thrombus formation, questions about the safety

and economy of this method have been raised. Bridging therapy with low molecular weight heparin can be expensive for the patient, inconvenient, and often painful. It has been linked with an increase in vascular complications during the post procedure period (Abhishek et al., 2011; Prudente et al., 2009; Wazni et al., 2007).. Recently there has been much interest in the use of the alternative OAC agents. While they offer convenience, they can be costly. In addition, reversibility is lacking for some of the available preparations generating concerns should bleeding occur. Safe use in the setting of ablation is under investigation.

Current Evidence for Anticoagulation

In 2007, Wazni and colleagues reported initial data comparing ablation performed using traditional bridging therapy to that of procedures completed on uninterrupted warfarin. The impetus for this strategy was the elimination of periods of sub-therapeutic anticoagulation during the course of ablation (pre, peri, post-procedure); a factor contributing to stroke risk. Outcomes were compared between groups of patients on therapeutic doses of warfarin with INR's ranging between 2.0 and 3.5 versus bridging strategies using two different dosing regimens of enoxaparin. End points included major bleeds, minor bleeds, and thromboembolic events. Minor bleeding was defined as a vascular hematoma that did not require further intervention. Major bleeding was defined as cardiac tamponade, hematoma requiring intervention, or bleeding that required transfusion. The incidence of major and minor bleeding was higher in the bridged patients and was statistically significant. In addition, 3 out of 205 patients bridged with enoxaparin suffered from ischemic stroke in the post procedure period as compared to 0 out of 150 in the group on uninterrupted warfarin. While this observational study was not sufficiently powered to predict thromboembolic risk, results did demonstrate that ablation could be safely performed on continued warfarin therapy. Similar investigations followed which replicated these

findings. Of these studies, three confirmed a significant increase in the incidence of minor bleeding in the population undergoing ablation with interruption of warfarin therapy (Di Biase et al., 2010; Gautam et al., 2011; Page et al., 2011). Santangeli et al. (2012) published a meta-analysis confirming the safety of catheter ablation performed on uninterrupted therapeutic warfarin. The population studied totaled 27,402 patients. Rigorous analysis of the data demonstrated the superiority of uninterrupted warfarin in the reduction of thromboembolic events. No statistically significant differences occurred between groups in the rate of major bleeding complications. The risk of minor bleeding appeared to be largely attributed to pre-procedural bridging with heparin. A subgroup analysis supported the use of procedural intracardiac echocardiography (ICE). Bleeding complications due to cardiac tamponade were not increased on uninterrupted warfarin when this modality was utilized. However, uninterrupted warfarin tended to increase the risk of a major bleeding when ICE imaging was not employed.

One critique of the meta-analysis includes the lack of data acquired from randomized clinical trials. However, to date no randomized trials have been published. If such a trial was undertaken, the sample population would need to be exceedingly large in order to be powered to predict risk of thromboembolism. This seems unlikely given the results of the observation studies. Based on the current evidence, the HRS, EHRA & ECAS expert consensus statement endorses performance of ablation on uninterrupted warfarin. The results of the published trials are summarized in Table 1.

While ablation in conjunction with therapeutic doses of warfarin has gained acceptance and is fully endorsed in current ablation guidelines, this therapy is not without caveats (Knight, 2012). Concerns include difficulty regulating warfarin dosages to achieve and maintain therapeutic INR's as well as interactions with food and other medications. Management of

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procedural bleeding complications requires consideration, particularly those complications which are rare, but have the potential to be lethal. Alternative approaches to ablation such as those involving access to the pericardial space, which in addition to the more common complication of pericardial effusion carries a small risk of hepatic injury and intra abdominal bleeding (Koruth et al., 2011), have not been well studied in patients on uninterrupted warfarin. Operator and facility experience with ablation procedures has bearing as there is a learning curve associated with catheter manipulation, equipment operation and ablation specific emergency management such as pericardial tap. It should be pointed out that data pooled in the meta-analysis published by Santangeli et al. (2012) was taken from centers with large procedural volumes.

Anticoagulation Pre, Peri, and Post Catheter Ablation

It is important to understand that a subset of patients referred for ablation may not be placed on VKA or alternative acceptable anticoagulants prior to the procedure (Calkins et al., 2012). Initiation of anticoagulant therapy is based on risk. The CHADS2 scoring schematic has been widely used to gauge risk of thromboembolic event in patients with AF and is simple to use (Gage et al., 2001). A point is assigned for age greater than 75 years, diabetes mellitus, heart failure, and hypertension. Two points are assigned in the patient with a prior history of stroke or TIA. Scores of three or higher are classified as high risk and warrant initiation of anticoagulation, 1-2 equal intermediate risk, and a score of 0 equates with low risk for thromboembolic event. The 2006 guidelines on the management of atrial fibrillation issued by the ACC/AHA/HRS recommend aspirin for patients with a score of 0 and use of either aspirin or warfarin for patients who score either 1 or 2 (Fuster et al., 2006). However, a large number of individuals fall into the intermediate risk group; thus, the HRS, EHRA & ECAS expert consensus statement for catheter ablation address stroke risk calculation supporting use of the

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CHA₂DS₂-VASc scoring schematic. This tool has been demonstrated to provide an improved predictive value for stroke risk, particularly in those patients falling in a moderate range (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010). Two points are assigned for TIA or prior stroke and age greater than 75 years. A point is allotted for age 65-74 years, hypertension, diabetes, heart failure, vascular disease, and female sex. Using this scoring tool, patients with a score of 2 or more are considered for anticoagulation, patients with a score of 1 could be managed with either oral anticoagulation or aspirin and patients with no risks managed with aspirin.

As previously mentioned, the use of VKA to prevent stroke in the AF population must be balanced with the risk of bleeding. Pisters (2010) and colleagues developed a tool to estimate the 1 year risk of major bleeding for patients with AF. The HAS-BLED score is a well validated bleeding risk predictor for use in the AF population. This tool calculates a risk score based on the presence of factors such as hypertension, renal and liver function, prior bleed history, stroke, age, drug and alcohol use, and INR stability. It was found to have consistent predictive accuracy. As such, these tools influence the state of anticoagulation in the pre-procedural period.

The HRS, EHRA & ECAS expert consensus statement summarizes pre-ablation anticoagulation strategies. They are similar to guidelines utilized when considering cardioversion in the same patient population. In the patient who has been in AF longer than 48 hours and the duration of AF is unknown, recommendations include the institution of anticoagulation at therapeutic doses for a minimum of 3 weeks. If this is not completed, experts suggest obtaining a TEE to exclude thrombus prior to commencing with ablation. The pre-ablation strategy in patients who have remained in sinus rhythm and are at low risk for stroke is not as well defined. Institution protocol often dictates approach. In many practice settings, all patients undergoing ablative therapy are started on warfarin up to two months before the procedure with INR's

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closely titrated to therapeutic range for at least 4 weeks prior to the scheduled procedure date. An alternative strategy is use of dabigatran, rivaroxiban, or apixaban in patients with nonvalvular AF for the recommended time period. At some institutions, TEEs are performed on all patients prior to procedure regardless of the history, stroke risk, or presentation of arrhythmia.

Conversely, a protocol may allow the option to forego a TEE for the individual who remains in normal sinus rhythm and has no risk for stroke using CHA₂DS₂-VASc scoring despite failure to anticoagulate in the pre-procedure period. The consensus statement places emphasis on the use of clinical judgment when determining a pre-procedure anticoagulation strategy. Several factors should be taken into account, amongst them AF classification and risk factors for stroke. It bears consideration that with the exception of a single study, all patients included in the meta-analysis demonstrating the superiority of continuous warfarin for stroke reduction were anticoagulated with warfarin for extended periods of time. Santangeli and colleagues (2012) point out that due to the long half-life of warfarin, the full benefit from anticoagulant effects may not manifest for up to 5 days. This anticoagulation effect results from inhibition of clotting factors dependent on vitamin K synthesis; thus the antithrombotic activity only occurs when normal clotting factors are cleared. Santangeli et al. (2012) also call attention to the swift degradation in protein C that occurs after warfarin administration. Protein C deficiency has been linked to an increased state of thrombosis as well as warfarin skin necrosis. It is especially critical to observe for thromboembolic potential in the initiation period when warfarin's anticoagulation effects are not fully achieved. This a primary reason for concomitant heparin administration until a therapeutic INR is attained. This merits consideration as institutions consider pre-protocol anticoagulation strategies.

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In the intra-procedural period, following completion of vascular access and prior to or during transseptal catheterization, anticoagulation with heparin is initiated to maintain activated clotting times (ACT) between 300-400 seconds. This strategy is taken to prevent the formation of soft thrombus on the catheters and sheaths. If inadvertent perforation or vascular trauma occurs, heightened anticoagulation may result in bleeding. In a case series conducted by Dagues and colleagues (2009), cardiac tamponade was one of the more common complications of ablation occurring at a rate of 1.3%. Data published by Di Biase and colleagues (2010) showed that the occurrence of this complication did not differ between patient groups undergoing ablation on continued warfarin therapy as compared to bridged patients. What differed in this study was the reversal of anticoagulation with the addition of fresh frozen plasma in the group anticoagulated with warfarin as opposed to protamine alone. A similar study by Latchamsetty and colleagues (2011) duplicated these findings. Warfarin was reversed with fresh frozen plasma or recombinant activated Factor VII (rVIIa). Resumption of anticoagulation therapy during the procedure may take place despite occurrence of this complication and is based on the nature of the perforation and cessation of bleeding in the pericardial space. What remains unknown are the thrombotic effects of warfarin reversal under these circumstances and how re-anticoagulation in this critical post procedure period impacts stroke risk (Asirvatham, 2007).

Even during therapeutic anticoagulation in the ablative period, there is still potential for stroke due to the development of coagulum. Coagulum can form as result of heat denatured fibrinogen with direct conversion to fibrin. This typically occurs from overheating at the catheter electrode/tissue interface. The coagulant that forms has the ability to embolize. Strategies to minimize coagulation formation include use of irrigated tip catheters and careful observation utilizing imaging modalities such as ICE. Research investigating methods to prevent this

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problem are ongoing (Asirvatham, 2007). It is important to understand that coagulum differs from the formation of a thrombus which requires the presence of thrombin. Thrombin converts fibrinogen to fibrin, the substance which stabilizes the clot. Heparin works by increasing the ability of an enzyme, antibody III, to inactivate thrombin, factor Xa and other clotting factors. This in turn suppresses formation of fibrin. Warfarin decreases prothrombin and procoagulant activity by altering the ability of Vitamin K to synthesize clotting factors in the liver. Neither heparin nor warfarin effects the formation of coagulum.

In contrast to pre-procedure recommendations, the HRS, EHRA & ECAS expert consensus statement denotes that at minimum even the patient at low risk for thromboembolism should be anticoagulated for a minimal period of 2 months post procedure. The immediate period following ablation is one of transition. Unfractionated heparin administered during the procedure is either reversed or allowed to drift to levels acceptable for removal of vascular sheaths. This is typically guided by ACT values with an ACT of 200-250 seconds common. Resumption of OAC, unfractionated heparin, or LMWH, depending on the pre-procedure strategy, varies but is usually contingent on obtaining adequate hemostasis at the puncture site. This may be altered if other complications associated with bleeding are identified. As previously noted, the post procedure period is a time of enhanced risk for thrombus formation. The destruction of endothelial tissue during ablation produces a heightened state of thrombogenicity. Transient stunning of the atrium resulting in diminished mechanical function, similar to that seen post cardioversion, may occur. If present, there is potential for stasis of blood thus enhancing clot formation. Anticoagulation may not be at therapeutic levels depending on the pre-procedure strategy employed. If subtherapeutic, bridging therapy must be instituted as a means of thrombus prevention until therapeutic INR levels are achieved. Alternatively, one of the new OAC agents

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may be resumed or initiated post procedure. A single study by Bunch and colleagues (2009) suggested that patients with a low CHADS2 score undergoing ablation with an irrigated tip catheter and aggressive procedural heparin administration could be safely discharged on aspirin therapy alone. Larger trials are necessary to provide insight as to the need and appropriate duration of post procedure anticoagulation in the individual lacking major risk factors for stroke.

Alternative Oral Anticoagulants in the Setting of Catheter Ablation

Newly developed oral anticoagulation agents with indications for stroke and systemic embolization reduction in patients with non-valvular atrial fibrillation have received a great deal of attention. Three products have been approved for use by the Food and Drug Administration (FDA). These include dabigatran, rivaroxaban, and apixaban. A fourth agent, edoxaban is in phase III of clinical trials. All have been viewed as feasible option for use in the setting of catheter ablation. Their appeal lies in the simplicity and ease of use, particularly in the pre and post ablation periods. They are being increasingly used in practice settings. Clinicians are subsequently faced with decision on how to manage patients when ablation therapy is a viable option. To date, the only research publications concerning anticoagulation in the setting of catheter ablation have involved use of dabigatran.

Dabigatran

Dabigatran etexilate is an oral drug which is absorbed and converted to the active form of dabigatran. It is a potent direct thrombin inhibitor, preventing the conversion of fibrinogen into fibrin. It comes in capsule form. As absorption is enhanced when the pH of the stomach is low, the pellets within the capsule contain a tartaric acid core. This is thought to contribute to the degree of dyspepsia associated with use of the medication (Connolly et al., 2009). Use of a proton pump inhibitor is generally not felt to impact efficacy even though absorption is reduced

(Samama, Guinet, Le Flem, Ninin, & Debue, 2013). The bioavailability is approximately 6.5%. The elimination half-life ranges from approximately 12-17 hours with the administration of more than a single dose. Plasma concentrations peak in approximately 0.5-2 hours after ingestion and reach steady state after approximately 3 days. Dosing is twice daily. Since the primary mechanism of excretion is via the kidneys, the half life is increased to >24 hours in patients with a creatinine clearance less than 30 ml/minute. Standard dosing approved for use in the US is 150 mg twice a day at 12 hour intervals. For patients with a creatinine clearance of 15-30 ml/minute, the prescribed dose is 75 mg twice daily at 12 hour intervals. Conversion to active product and metabolism occur in the liver. The drug is not affected by the cytochrome (CYP) enzyme metabolic process. Rather, dabigatran is a substrate of the permeability glycoprotein transporter (P-gp) system. Interaction may occur with other potent drugs having the same substrate such as quinidine, verapamil, amiodarone or ketoconazole. Plasma levels of dabigatran can increase in the presence of these derivatives. In contrast, the drugs rifampin and St. John's wort can decrease plasma drug levels (Hankey & Eikelboom, 2011). No antidote is available to reverse the effects of the drug. Weitz, Quinlan, and Eikelboom (2012) published an algorithm detailing approach to bleeding for patients taking dabigatran in the general peri-procedural setting. In cases of severe, life threatening bleeding, dialysis is suggested as a possible option to clear the plasma. No INR monitoring is required as it offers no reflection as to plasma levels. The activated partial thromboplastin time (aPTT) is prolonged following administration of dabigatran. The thrombin time (TT) is also influenced by dabigatran intake. It too is prolonged while on dabigatran but the effect is not linear and is not reflective of plasma concentrations. However, a normal TT rules out dabigatran anticoagulant effects. The Ecarin clotting time (ECT) is also affected by dabigatran intake with times felt to be dose dependent, but is not readily available in most labs

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(Tripodi, 2013). Renal function must be evaluated prior to use given the route of drug elimination. Care must be taken when used in populations with impaired or diminished ability to metabolize and excrete drugs such as the elderly. Serious adverse events include bleeding and hypersensitivity. The more common reaction is that of GI upset.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated the non-inferiority of dabigatran as compared to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Connolly et al., 2009). At doses of 150 mg twice daily, a lower rate of stroke was observed compared to treatment with warfarin. Overall bleeding rates were similar. The rate of myocardial infarction was higher in patients taking dabigatran. There was also a higher incidence of GI bleed in patients taking 150 mg of dabigatran twice daily. Bleeding and gastrointestinal upset were the most common reported side effects. In a recent update, the Food and Drug Administration (FDA) issued a safety notification related to use of dabigatran in patients with prosthetic mechanical heart valves. Evidence stemming from the phase II RE-ALIGN™ discontinued European trial showed a higher rate of blood clot formation in patients using dabigatran versus those on warfarin (Boehringer Ingelheim, 2012; United States Food and Drug Administration, 2/15/2013). Dabigatran therapy is not to be used in patients with atrial fibrillation who have a prosthetic heart valve. In fact, patients with severe valvular heart disease were excluded from participation in the RE-LY trial.

In addition to stroke reduction, a number of other advantages to dabigatran therapy exist including ease of use facilitated by limited interactions with food and other medications. As no blood testing is currently readily available to monitor levels, frequent follow-up as required with warfarin is not needed. A major disadvantage of the drug is the lack of reversibility. Twice

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versus once daily dosing may be seen as an obstacle. A final disadvantage includes expense with an estimated retail price of a 1 month supply of dabigatran costing \$245.99 as compared to 30 tablets of warfarin (5 mg tablets) for \$13.99. This topic has been hotly debated with proponents of dabigatran noting that warfarin monitoring and effect on lifestyle add additional cost to a relatively inexpensive drug. In this regard, it is critical to address lifestyle, desires, and risk/benefit ratio for a given individual prior to therapy initiation.

Dabigatran and Catheter Ablation

Because of the advantages associated with ease of use, dabigatran has seen an increase in utilization. Accordingly, this impacts patients eligible for catheter ablation and the providers of these services. Eight studies were found that compared the use of dabigatran to continuous warfarin in the setting of ablation. Data from a single large observational trial (Lakkireddy et al., 2012) showed a slight increase in bleeding complications in the dabigatran arm. In this series, ablation occurred with drug discontinuation for only 1.5 half lives (held the morning of the procedure only). This factor was postulated to contribute to the greater incidence of bleeding. There were no significant differences in embolic events. In contrast, results from a study performed by Bassiouny and colleagues (2012) did not show differences in the rate of bleeding complications or thromboembolism in 400 participants undergoing ablation taking either dabigatran (N=200) or continuous warfarin (N=200). Dabigatran was held only the morning of the procedure in 116 individuals assigned to this arm of treatment. It was resumed almost immediately after completion of the procedure in all but those undergoing general anesthesia. It is unclear what might account for these differences in findings. The demographic population in the Lakkireddy et al. (2012) publication did include a higher inclusion of individuals age 75

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years or older. As pointed out by Bassiouny et al., (2012) procedure risk in this age group is compounded.

In participants undergoing ablation (Kim et al. 2012), dabigatran was also deemed as safe to use. No differences in thromboembolic or bleeding rates were observed between the treatment arms. Pericardial effusions in the dabigatran arm (2/191) were treated with pericardiocentesis and did not require administration of clotting factors. In this protocol, dabigatran was held for 24 hours prior to the procedure and resumed 4 hours after hemostasis was obtained. A small study by Snipelisky et al. (2011) also found that use of dabigatran was safe in the setting of ablation. A single randomized trial was performed by Nin and colleagues (2013) comparing ablation on continuous warfarin to that performed while taking dabigatran 110 mg twice a day. In this study, minor bleeding occurred less in the dabigatran arm ($p=0.013$). D-dimer levels, used as markers reflective of a procoagulant state, were monitored at set points during the ablation process. They were found to be lower in the group of participants taking dabigatran while undergoing pre-procedure TEE and 48 hours following procedure completion ($p=0.011$, $p=0.017$ respectively). The pre-procedure TEE's were performed after three weeks of dabigatran therapy or three weeks of warfarin with a therapeutic INR. Confounding variables in this trial include the lower acceptable therapeutic INR per Japanese guidelines (1.6-3.0) and use of dabigatran 110 mg twice a day. This dosage is not currently approved for use by the FDA in the US despite inclusion in the RE-LY trial data. Participants enrolled were largely low risk; prior use of OAC and age > 75 years were but two of several excluding factors. The majority of subjects randomized to the two arms carried a CHAD2 score of 0-1 (82%, 80%). Crossover from the dabigatran to warfarin arm occurred in 3 participants due to dyspepsia (7% incidence).

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A single subject crossed over from warfarin to dabigatran due to difficulty attaining a therapeutic INR.

Bleeding rates and thromboembolic events were low in the study by Kondaru and colleagues (2012) that compared dabigatran and uninterrupted warfarin during catheter ablation. The primary thrust of this study however was examination of ACT values during the intra-procedural period. While the study design lacked clarity in regards to standardized pre-anticoagulation strategies, results showed that participants on dabigatran required higher doses of heparin to achieve target ACT values and took longer to achieve the desired range. The implication is that delays to therapeutic levels of anticoagulation in the peri-procedural period could result in thrombus formation.

Bleeding was not problematic in the descriptive study carried out by Winkle and colleagues (2012). However, in this case, the drug was discontinued 36 hours prior to procedure. In addition, ACT's during the periprocedural period of ablation were below those targeted in many laboratory settings, a factor on which this group has published data (Winkle, Mead, Engel, & Patrawala, 2011).

Finally, the publication by Kaseno et al. (2012) was the only one to find a statistically significant increase in total bleeding events in the warfarin arm ($p < 0.05$). Protocol included administration of 10,000 units of unfractionated heparin in both groups post procedure for 24 hours. No thromboembolic complications were observed in either group. Of interest in this particular study was the use of cerebral MRI post procedure in 60 study participants. Silent cerebral thromboembolic lesions were found in a single subject in each arm of the study group. Neither of these individuals presented with neurological manifestations. While clinical stroke may not be evident, there is potential that such findings contribute to impairment of memory or

future cognitive decline. Cerebral microembolization occurring during the course of ablation has been implicated as a cause of such lesions. In the aforementioned study, it is unclear whether a pre-procedure MRI was also completed for comparison. However, other studies (Neumann et al., 2011) have confirmed the validity of this phenomenon. The long term ramifications remain unclear and merit further consideration.

In summary, the use of dabigatran during the period of ablation appears to be generally considered safe but certainly requires additional study, especially given the slight increase in bleeding observed in one study. The limited data presented in these reviewed publications suggest that it is optimal to administer dabigatran up to the period of ablation. While withholding only a single dose may have resulted in additional bleeding in one study, it was not validated in a second study with a greater number of participants. Discontinuation 24 hours prior to therapy is safe, but may be disadvantageous as a period of suboptimal anticoagulation exists. The studies presented in this review also suggest that safe resumption of dabigatran in the early post procedure period can be completed, again avoiding periods of subtherapeutic anticoagulation. It is important to point out that none of the trials published to date are powered to determine stroke reduction during ablation. Many questions still remain about dabigatran use in this setting including the optimal pre-procedure duration, management of bleeding complications, use in the elderly or in those with some degree of renal impairment, and ability to assess medication compliance. A final commentary pertains to gender and ethnicity. Women account for approximately 20-30 % of the study population in the reviewed trials, not surprising as fewer women undergo ablation procedures in general. Nin et al. (2013) refer to the disparity between Japanese and Western INR guidelines as based on "racial differences in the hemorrhagic or thromboembolic risk" (p.178). These factors are deserving of consideration in future studies.

Rivaroxiban

Rivaroxiban is a direct factor Xa inhibitor approved by the FDA for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. It has also been approved in the US for prevention of VTE in patients undergoing select orthopedic surgeries. Factor Xa (free activated factor X) is a critical component in the coagulation cascade, linking extrinsic and intrinsic systems to the terminal steps for both. Inhibition of factor Xa reduces the conversion of prothrombin to thrombin, ultimately limiting fibrin formation which is an essential component of clot (Gaspar, 2009; Verma & Brighton, 2009). In contrast to dabigatran, rivaroxiban has a high degree of bioavailability at 80%. The time to peak plasma concentration ranges from 2-4 hours and the plasma half life from 9-13 hours. It comes in tablets of 10, 15, and 20 mg. It is recommended that the 15 and 20 mg strength tablets be ingested with food (Janssen Pharmaceuticals, 2013; Stampfuss, Kubitzka, Becka, & Mueck, 2013). For non-valvular atrial fibrillation, rivaroxiban is administered as a once daily dose of 20 mg, to be taken with the evening meal (individuals with normal renal function). This daily dosing regime was found to be effective in clinical trial and is based on observations that rivaroxiban's anticoagulant effect sustains for up to 24 hours (Patel et al., 2011; Ru San et al., 2012). In clinical trial, a dose of 15 mg daily was administered to participants with a creatinine clearance of 30-49 ml/min. Package insert indicates that a dose of 15 mg daily can be used by individuals with a creatinine clearance ranging from 15-50 ml/min. Rivaroxiban, like dabigatran is a substrate of the permeability glycoprotein transporter system. However, unlike dabigatran, metabolism is also affected by liver enzymes CYP3A4/5 and CYP 2J2. It is eliminated primarily by the kidneys but some elimination occurs through biliary excretion in the feces. Rivaroxiban appears to be relatively well tolerated with few reported side effects. While the most common adverse effect is bleeding

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other less reported side effects include backache (3.7%) and pruritis (2.1%). Because the metabolism of rivaroxiban is influenced by the CYP enzymatic pathway, it has been shown to interact with potent inhibitors of CYP450 and CYP3A4 which includes the macrolide antibiotics, azole antifungals, and protease inhibitors. There does not seem to be interactions with more common agent such as NSAIDS, digoxin, or antacids. Package inserts recommend avoidance of strong combination CYP-P-gp products (Janssen Pharmaceuticals, 2013; Verma & Brighton, 2009).

Like dabigatran, the reversal of rivaroxiban is a concerning problem. A small trial involving the use of 4 factor prothrombin complex concentrate (PCC) was completed in 12 healthy males who received either rivaroxiban (N=6) or dabigatran (N=6). The measured protime (PT) was significantly prolonged after administration of rivaroxiban. This prolongation was reversed with 4 factor PCC (Eerenberg et al., 2011). However, the utility and efficacy of this approach in a critical situation has yet to be recommended or demonstrated (Kaatz, et al., 2012). Ongoing investigations examining rivaroxiban reversal continue with some success observed in animal models (Lu et al., 2013).

Rivaroxiban was shown to be as effective as warfarin in the prevention of stroke in the ROCKET AF trial (Patel et al., 2011). The primary endpoint of this trial was stroke or systemic embolism. There was no statistically significant difference in the risk of bleeding between the two arms of therapy, warfarin or rivaroxiban. While the occurrence of fatal bleeding and intracranial bleeds were less in the rivaroxiban arm, bleeding at other sites such as the GI tract was found to be increased. A critique of the trial is that subjects in the warfarin arm remained in therapeutic range, as based on recorded INR's, only 55% of the time. A subsequent analysis of data from the trial revealed an increase incidence of stroke and embolism in participants who

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temporarily or permanently discontinued therapy in the rivaroxiban arm as compared to warfarin at study conclusion (Patel et al., 2013). The manufacturers recommend institution of another anticoagulant if rivaroxiban must be discontinued. When transitioning from warfarin to rivaroxiban, it is recommended that dosing begin as soon as the INR is less than 3.0. Because rivaroxiban can affect the INR, the transition from rivaroxiban to warfarin is less clear. Similar to when warfarin levels become subtherapeutic, the use of unfractionated heparin may be required to bridge until warfarin levels are considered adequate (Janssen Pharmaceuticals, 2013).

Institutions are reporting the administration of rivaroxiban in the time period encompassing catheter ablation (Bhave & Knight, 2013). However, there have been no published trials, limiting evidence to evaluate use.

Apixaban

Apixaban, like rivaroxiban, is another direct factor Xa inhibitor approved for use in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The bioavailability of this drug is 50% with peak concentrations occurring 3-4 hours after ingestion. Absorption is not influenced by food. While apixaban has a short clearance half life of six hours, with repeated dosing (twice daily), it extends to 12 hours. This is due to the prolonged absorption of the drug in the GI tract. Up to 55% of absorption takes place in the small bowel and ascending colon. Apixaban is metabolized primarily via the CYP3A/4 pathway. It is eliminated in urine and feces with renal elimination accounting for 27% of excretion. Tablets come in 2.5 and 5 mg strength. The manufacturer's recommended dose is 5 mg twice daily. A dose of 2.5 mg daily is indicated if any of the following two criteria are present: age greater than or equal to 80 years, creatinine level greater than or equal to 1.5 mg/dl, or body weight less than or equal to 60 kg. Drug interactions are similar to those of rivaroxiban such that potent CYP3A/4 and P-gp

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inhibitors and inducers can alter clinical effects of the drug. Like rivaroxiban, apixaban carries a black box warning related to an increased rate of stroke following drug discontinuation. For this reason, the manufacturer recommends anticoagulation with another agent if apixaban use is terminated. Recommendations also include discontinuation at least 48 hours prior to elective surgeries or procedures with a higher risk of bleeding and 24 hours before those considered to be of lower risk. Apixaban can affect lab values such as the PT, INR and APTT. However, these changes cannot be used to guide drug dosing as they are not stable indicators of drug plasma levels (Bristol-Myers Squibb Pharma Company, 2012; Ru San et al., 2012). Anti-FXa assay tests can detect plasma levels of the direct Xa inhibitor medications. These tests are quite specialized and not available in all labs (Samama, Amiral, Guinet, Flem, & Seghatchian, 2013). Like rivaroxiban and dabigatran, there is no reversal agent for apixaban. While not tested in clinical trial, in an emergent situation if drug has been recently ingested, administration of oral activated charcoal may effectively absorb the drug (Kaatz et al., 2012).

In the clinical trial Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation, (ARISTOTLE), a randomized double blind study, apixaban was found superior to warfarin in prevention of stroke and thromboembolism, caused less bleeding, and was associated with a lower mortality (Granger et al., 2011). Unlike findings revealed in the clinical trial of rivaroxiban, apixaban as compared to warfarin resulted in a lower incidence of GI bleeding.

Given the outcomes of the ARISTOTLE trial and recent FDA approval for use in individuals with non-valvular atrial fibrillation, apixaban is likely to see increased use. The reduction of all forms of bleeding as compared to warfarin as well as superiority in regards to stroke prevention make apixaban a favorable choice for therapy. As with all of the OAC agents, great vigilance is required in the management of individuals to reduce problematic bleeding. The

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same advantages and confounders applicable to dabigatran and rivaroxiban hold true for apixaban. And, while economics remains of great concern, especially given the current state of health care, in a recent analysis performed by Harrington and colleagues (2013), apixaban was found to be cost effective compared to warfarin, dabigatran, and rivaroxiban when multiple parameters such as quality of life and years of use were factored in. One cannot overemphasize the need to tailor individual therapy.

As with rivaroxiban, administration in the setting of catheter ablation has been reported, but no published clinical trials exist, thus limiting evidence for use.

Edoxaban

Edoxaban, like rivaroxiban and apixaban is a direct factor Xa inhibitor still undergoing late stage clinical development. It is similar to apixaban and rivaroxiban in pharmacological makeup. Time to peak concentration following oral intake is 1-2 hours. The mean elimination half life ranges from 6 -10 hours. Edoxaban is excreted by the kidneys, thus lower doses of medication are required in patients with decreased creatinine clearance. Like dabigatran and rivaroxiban, edoxaban is a substrate of the permeability glycoprotein transporter system (P-gp). Plasma concentrations of drug can be affected by concomitant administration of medications that are P-gp inhibitors (Camm & Bounameaux, 2011). The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation –Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48) is an ongoing phase III randomized double blind study comparing high and low dose edoxapan (60-30 mg) and warfarin for the prevention of stroke in nonvalvular atrial fibrillation (Ruff et al., 2010). The trial is one of the largest involving novel anticoagulants with preliminary results expected to be released in the very near future.

Future Trends

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Atrial fibrillation is a problem of great magnitude. Stroke is a major complication with multiple ramifications for both individuals and society. Advances in technology and recent pharmaceutical developments aim to improve procedural outcomes and reduce complications thus improving individual quality of life

The introduction of new OAC agents to reduce stroke in atrial fibrillation for the first time since institution of warfarin is a tremendous step forward. The development of multiple agents of different pharmacological make-up, all demonstrating efficacy in the reduction of thromboembolic events with a diminished risk for bleeding, is advantageous. Competition fuels the drive for improved quality and lower cost. Clinical trials must continue with focus on affordable effective options to meet the needs across a broad spectrum of the population.

New catheter technologies continue to evolve with designs geared to improve results and reduce risk. Ongoing clinical investigations have already resulted in superior outcomes for ablation as discussed in this review. The move to perform ablation on uninterrupted warfarin has been shown to decrease the risk of thromboembolic events. Investigation into the use of novel OAC agents in the setting of ablation only looks to better current results while improving patient satisfaction and outcomes. A number of ablation technologies are being investigated. They employ different delivery systems such as robotic navigation, utilize varied energy sources such as cryoablation, encompass improved image quality and enhancements, and incorporate a variety of mapping capabilities.

Nonpharmacologic techniques to prevent thrombus embolization are undergoing investigation and show promise. Devices to close, ligate, or occlude the left atrial appendage (LAA), a source of thrombotic debris, are in clinical trial. The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF)

trial (Holmes et al., 2009) demonstrated that percutaneous closure of the LAA was non-inferior to warfarin for the prevention of stroke. The results revealed a higher rate of adverse events in the group receiving the closure device. This however, was largely due to peri-procedural complications. Investigators of The Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients With Atrial Fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) Trial (Reddy et al., 2013) reported 2.3 years of follow-up data accumulated from participants in the PROTECT AF trial. While recognizing the up-front procedural complications in the device intervention arm, over time, closure of the LAA proved to be superior to treatment with anticoagulation. The functional outcomes of those suffering from adverse events in the LAA closure group had less long term effects than those of the control group. The trial lends support to alternative treatment strategies designed to reduce the impact of stroke in the population suffering from AF.

Genetic therapy is also evolving. Promising studies have been conducted in porcine models investigating the role of gene therapy with connexin 43 and 40 to prevent AF and with the dominant-negative ether-a-go-go-related gene mutant (Bikou et al., 2011; Igarashi et al., 2012; Soucek et al., 2012). Much of our current understanding of AF has been derived from basic science. The results of endeavors such as these provide hope for future generations.

Most importantly, clinical investigation has produced evidence upon which to base practice in a manner that provides safe and effective options for treatment. In order to be of value to the broad population this evidence must be readily disseminated to practitioners and applied. Additionally, it must be tempered with the understanding that individual values and preference are important factors which influence choice of therapy. Many variables including educational

level, access to information via internet, and broader consumer marketing tactics impact a person's perception and understanding. As such, education and the presentation of risk/benefit ratio related to procedural outcomes, thrombus formation, and bleeding is of extreme importance.

Conclusion

The number of individuals affected by AF continues to grow significantly. Catheter ablation is a procedure recognized as a class IA indication in individuals with symptomatic AF who have failed or are intolerant to at least one attempt at therapy with an antiarrhythmic medication. Stroke has been associated with atrial fibrillation and is a complication that may occur as a result of catheter ablation. Anticoagulation therapy reduces this risk. This evidence based review analyzes the question of anticoagulation therapy pre, peri, and post AF ablation. Current evidence based data supports performance of catheter ablation for atrial fibrillation during uninterrupted VKA therapy targeting INR's at a range greater than 2.0 seconds. This has been demonstrated by meta-analysis to be superior to the bridging techniques that have been the standard for a significant period of time in reducing the risk of thromboembolic complications. At present, guidelines suggest continuation of anticoagulation in the post procedure period for a minimum period of two months. The future holds great promise with advances in both pharmacology and procedural technology. New OAC agents have been safely administered in the setting of ablation as demonstrated by the findings of recent observational studies. Large scale trials will provide more evidence as to the predictive ability of the new oral agents to diminish stroke risk without increasing the risk of bleeding complications. Understanding rationale for anticoagulation treatment in the setting of catheter ablation as well as inherent risks is critically important. It is hoped that the review of current evidence will lead to improvements

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in patient management, enhanced satisfaction, a reduction in procedurally related complications, and to the creation of clinically oriented research proposals ultimately geared to promote best outcomes.

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Appendix

Table 1: Published trials comparing catheter ablation performed on uninterrupted warfarin versus interrupted warfarin and bridging therapy.

Author (Year)	Purpose	Study Design	Sample	Data Collection/Methods	Analysis	Findings	Strengths/Limitations
Page et al. (2011)	Catheter ablation on uninterrupted warfarin versus interrupted warfarin.	Prospective nonrandomized controlled study. Non equivalent control group with intervention based on date. 109 participants in group 1 before 1/18/2010 and 89 participants in group 2 after 1/18/2010	Consecutive sampling of 198 participants undergoing ablation Group 1-109 interrupted warfarin, subsequent 89 uninterrupted.	Intervention: Continuation of warfarin therapy to maintain therapeutic INR Control Group: Interruption of VKA therapy and bridging with LMWH Primary outcome: Bleeding complications, thromboembolic event Post-op day 1 exam and telephone questionnaire at 4-6 weeks. Cost effectiveness examined.	Chi-square test used to compare nominal (categorical data) Student's <i>t</i> -test for continuous data. Analysis completed with commercial software. Chi square computed by comparing observed frequency of complications.	Catheter ablation on uninterrupted warfarin is associated with fewer bleeding complications ($p = .001$) Equivocal cost savings.	Not powered to detect differences in thromboembolic events. Estimated power of the sample size medium to low.
Kwak et al. (2009)	Catheter ablation on uninterrupted Warfarin versus interrupted warfarin	Prospective nonrandomized control study.	Sample population = 104 participants. Study does not describe enrollment methods. Participants were divided by the type of peri-procedural AC. CW = 49 pts, interrupted warfarin = 55 pts.	Intervention=CW therapy to maintain therapeutic range Control Group: Interruption of VKA therapy and bridging with LMWH Follow-up Hospital and OP clinic visits 1, 3, 6,9,12 months. Outcomes Bleeding complications, Pre-Post INR	Chi-square or Fisher's exact test for categorical variables (Bleeding complications) . Student <i>t</i> test and Mann-Whitney U test for continuous variables. SPSS 13.0 used for analysis. P value <0.05 statistically	INR values in therapeutic range post procedure. ($p < .001$) Participants in the CW group required less procedural unfx heparin. ($p < .001$) No difference in bleeding between groups.	Small sample size.

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				values, heparin requirements. Proportion of optimal INR post-procedure.	significant.		
Schmidt et al. (2009).	Catheter ablation on uninterrupted Warfarin versus interrupted warfarin	Case control Nonrandomized observational study.	Sample 194 consecutive participants. 87 pts. with therapeutic INR versus 107 with normal INR pre-procedure (control). Warfarin either continued or started three days before procedure. Only exclusion noted pre INR > 3.5 = postponement of procedure.	Intervention = pts with therapeutic INR versus pre procedure normal INR (control). Endpoints = Safety events – major and minor including vascular injury and bleeding	Shapiro-Wilk test used to assess data normality. Continuous variables two sample unique variance <i>t</i> -test. Proportions analyzed with Chi-Square and Fisher exact test. Logistic regression analysis to examine relationships between outcomes and pt characteristics. An accepted <i>p</i> value was not noted. Data analyzed using SAS	No significant differences in complications were noted between groups.	Not powered to detect differences in thromboembolic events. All patients given Coumadin for three days prior to the procedure – study design, definitions not clear.
Kakalahti et al. (2011).	Catheter ablation on uninterrupted Warfarin versus interrupted warfarin	Prospective nonrandomized observational study.	Sample 193 consecutive participants. Grouped based on pre-procedure INR <2.0 (103) and therapeutic INR or greater than 2.0 (125). No exclusions. INR >3.5 = procedure postponement. LA thrombus by TEE = postponement	Intervention = pts with therapeutic INR versus pre normal INR (control). Safety endpoints evaluated include major and minor bleeding and thromboembolic events. 3 month follow-up Hospital exam post procedure. No reported loss to follow-up.	Fisher's exact test and Chi-square used for nominal variables. Ordinal variables presented as mean +/- sd and compared with Wilcoxon rank sum test. Continuous variables <i>t</i> -test. <i>P</i> value <0.05 statistically significant.	No differences between major (<i>p</i> =1.00) and minor (<i>p</i> =0.56) bleeding between groups.	Sample numbers not powered to detect stroke differences. Similar findings to other studies. CHA2DS2VASc score utilized. Anticoagulation protocol pre-procedure/design not as clear. No ACT guided heparin dosing or ICE during procedure. The group with an INR >2.0 had a higher percentage of

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							thromboembolic events. The group with an INR < 2.0 had more vascular disease (p= .03).
Wazni et al. (2007).	Catheter ablation on uninterrupted warfarin versus interrupted warfarin	Prospective nonrandomized (sequential) observational study.	Sample included 355 consecutive participants undergoing ablation for AF. Three groups were examined. Group 1 = Normal INR Enoxaparin 1 mg/kg post procedure for bridge (N=105) Group 2 = Normal INR Enoxaparin 0.5 mg/kg for bridge post procedure (Q12h). (N=100). Group 3 = therapeutic INR (N= 150 patients).	Follow-up includes hospital evaluation post procedure, weekly phone calls for three months. Participants followed up at 3-4 month time period for evaluation. Safety endpoints evaluated : Major and minor bleeding, pericardial effusion, and thromboembolism	Continuous variables of the 3 groups compared with 1-way ANOVA. Categorical variables expressed as % and compared with the Fisher-Freeman-Halton test.	No significant differences observed for thromboembolism. A statistically significant difference was observed with bleeding in the LMWH bridged group compare to the CW group. (p< .001) Continuation of warfarin did not increase bleeding risk.	One of the initial studies confirming use of therapeutic warfarin during ablation. Results duplicated. Not powered for thromboembolism . All enoxaparin administered pre-procedure discontinued 12 hours prior to ablation.
Di Biase et al. (2010).	Evaluate the prevalence of periprocedural stroke and assess whether anticoagulation strategy and use of open irrigation catheter have resulted in reduction of complications.	Large prospective multicenter nonrandomized observational study	Data collected from 9 centers and consisted of 6454 consecutive participants divided into three groups. Group 1 = ablation with 8mm catheter off warfarin (n=2488) Group 2= open tip catheter off warfarin (n= 1348) Group 3 = open tip catheter on therapeutic warfarin (n= 2618 January 2002-Jan 2009 data collection	Comparison of three groups as described. Neurological evaluation q4h post Endpoints = safety events – divided into hemorrhagic versus thromboembolic. F/U scheduled 3,6,9,12 months. No mention of participants lost to f/u.	Student t-test, 1 way analysis of variance, Chi-square and Fisher exact test was used to compare differences. Multivariate logistic regression was used to identify significant predictors of stroke. Post-hoc analysis performed with Tukey-Kramer multiple comparison method. Analysis of	A statistically significant difference was observed between number of strokes that occurred in group 1 and 2 combined group 3. Minor bleeding was observed more in the off warfarin groups and was statistically significant.	Large population. Powered to enable prediction. ACT's during procedure >350. All participants on warfarin for 4 weeks pre with therapeutic INR's for 4 weeks. Warfarin stopped 3 days pre in group 1 &2. All off Warfarin participants bridged pre-procedure with enoxaparin 1 mg/kg. This was stopped 12 hours before the procedure. No TEE group 3 Covariate:

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			Group 3 participants had to have a therapeutic INR on the day of procedure. Those without therapeutic INR excluded.		variance inflation factor was used to examine multicollinearity of the covariates. The odds ratio and 95% confidence interval of periprocedural stroke were computed. P value <0.05 was considered statistically significant.		Neurological exam post procedure and every 4 hours after ablation. Post procedure, predischage completed by physician, otherwise by RN.
Hayes & Keane (2009)	Safety of AF ablation on uninterrupted warfarin using a novel multi-electrode catheter	Retrospective analysis	Sample = 81 participants. Selection = All undergoing AF ablation with novel catheter in a two year period. No exclusion criteria listed or details on participants meeting criteria for the use of this catheter. Group 1: Uninterrupted warfarin. N=49 Group 2: Participants at low risk for stroke – no warfarin pre or post procedure. Uninterrupted ASA 75 mg N=32	Comparison of two groups: Follow up: Discharge day 2 after procedure. Office visit at 2,6,12 months post procedure. End points: Review for complications including major and minor bleeding, thromboembolic events.	Descriptive statistics.	Warfarin group = 1 major bleed, 1 minor bleed. No bleeding complications in the group not receiving warfarin. Study states that no other complications occurred.	Several variables in this study adding to difficulty in interpreting results. Limited demographic information or comparison of group populations. No ACT's were obtained during the ablation procedure in either group. Warfarin group also received clopidogrel and ASA post.
Hussain et al. (2009)	Safety of AF ablation on uninterrupted warfarin	Prospective, descriptive study in a large population	Population = 3052 consecutive participants undergoing ablation between 2005-	Safety endpoints evaluated include major and minor bleeding and thromboembolic events.	Student t-test used to compare continuous variables. Categorical variables	Findings: Performing ablation with uninterrupted warfarin is safe. Overall,	Large descriptive study. Low hemorrhagic complication rate. Population with paroxysmal and persistent AF.

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			2008 with a therapeutic INR (>1.8) Exclusion criteria = INR < 1.8 on the day of ablation	Follow up: Overnight observation, Clinic F/U 3-4 month +telephone transmission on a weekly basis for three months with symptom assessment.	expressed as a percentage	bleeding 1.11% Ischemic stroke rate 0.098%	All subjects started on Coumadin 2 months before procedure with weekly INR's
elthuis et al. (2012)	Safety of AF ablation on uninterrupted warfarin	Retrospective Descriptive	151 consecutive participants undergoing procedure between Jan 2010-March 2011	Bleeding and thromboembolic events up to three months post procedure. Post follow-up = overnight observation - 4 visits: 6weeks, and three more within 3 month window. All participants on warfarin post for 3 months.	Categorical variables - expressed as frequencies or percentages. Continuous variables by mean/SD	No ischemic strokes/TIA/CVA. Minor vascular complication = 10(6.6%) Major Vascular complication = 1 (0.7%) Safe to perform procedures with therapeutic warfarin	20 subjects subtherapeutic PT on day of procedure. No bridging is employed. Smaller population, short follow-up duration.
Saad et al. (2011)	Catheter ablation on uninterrupted warfarin versus interrupted warfarin	Prospective nonrandomized observational control study.	Sample 140 consecutive participants with persistent or permanent AF Jan 2008 to August 2010. Physician procedural preference for study arm. Group 1(Control): warfarin stopped x 5 days - enoxaparin bridge 1/mg/kg BID. Last dose 24 hours before procedure. N=70 Group 2: Continued warfarin. If INR	Safety endpoints = bleeding (major, minor) thromboembolic events, cardiac mortality. Mean F/U 16 +/- 8 months. No loss to F/U. Follow-up 30, 90, 180 days at clinic visit. Daily pulse checks. OAC post for three months minimum.	Independent samples :Inferential variables - student t-test Categorical variables analyzed using Fisher's exact and Pearson's Chi-square tests. Significance value = p< 0.05	No significant differences in the complication rate between groups. No thromboembolic events.	Not powered for thromboembolism . Unsure of effect of physician selection to study arm.

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			not in desired range procedure postponed.				
Gautam et al. (2010)	Effect of INR on intra-procedural anticoagulation. Therapeutic INR associated with lower rate of bleeding complications	Retrospective observational design	Sample: 427 consecutive participants placed in 2 groups. Group 1: INR < 2.0 N=246 Group 2: INR >= 2.0 N=181 Pre-procedure AC protocol outlined for each group. Group 1 Warfarin held 3 days pre-procedure. Bridge with enoxaparin. Last dose 12 hours before procedure. Group 2 Warfarin continued with INR >= 2.0 Exclusion: Incomplete data on pre-procedural INR or intra-procedural ACT and heparin dosing.	Comparison between study groups: Intra-procedural ACT, Intra-procedural Heparin requirements, Procedural Complications: Thromboembolic and Bleeding, Analysis of procedural records.	Continuous variables = mean+/- SD. Categorical variables reported as numbered %. Compared using the chi-square test and Fisher's exact test. Continuous variables compared using 2-tailed Student's t test at 5% significance level. Multivariate regression analysis used to adjust for baseline variables that were different between groups. ACT values compared using t-test and multiple analyses of variance.	Mean ACT values significantly higher in group 2 (>350 sec). Mean requirements for heparin significantly different between groups – both total dosing and dosing required to achieve target ACT values (More heparin required in group 1). Significant difference in incidence of groin hematomas (> group 1). No difference for pericardial effusion or tamponade.	Outcomes well defined. Study variables listed. Baseline demographics similar with significant differences reported and adjusted for during analysis. Not powered for stroke prediction.
Hayashi, T. et al. (2013)	Safety of ablation in conditions of therapeutic INR, influence of INR on bleeding complications.	Retrospective design.	Sample: 150 consecutive participants undergoing RF ablation. INR > 1.8 pre-procedure. Group 1: Periprocedural BC N=22 Group 2: No periprocedural BC N= 128	Comparison of clinical characteristics between group 1 and 2 including demographic variables, heparin dosing, pre and post procedure INR, pre and post procedure APTT, pre and post procedure D-	Continuous variables compared with Student's T test. Categorical variables: chi-squared and Fisher's exact test. 2-tailed P-value <0.05 statistically significant.	Presence of absence of BC is not related to pre-procedural INR level.	No heparin administered pre-procedure in any participant. Pre-procedure INR < 2.0 in 50 participants who required more unfractionated heparin during procedure. Continuous heparin infusion restarted post

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				dimer.	Multivariable analysis for items that showed P-value smaller than 0.1 by univariable analysis.		procedure on subjects return to the ward and administered for 24 hours based on the pre-procedure INR including INR's greater than 2.5. Many study variables.
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Table legend: VKA-Vitamin K Antagonist, INR – international ratio, LMWH – low molecular weight heparin, CW – continuous warfarin, unfx – unfractionated, LA – left atrium, TEE – transesophageal echocardiogram, sd – standard deviation, q4h – every 4 hours, PT – prothrombin time, BC – bleeding complications, APTT – activated partial thromboplastin time, F/U – follow up

Table 2: *Studies comparing the use of dabigatran to continuous warfarin in the setting of catheter ablation for atrial fibrillation.*

Author (Year)	Purpose	Study Design	Sample	Data Collection/ Methods	Analysis	Findings	Strengths/ Limitations
Winkle et al., (2011)	Safe use of dabigatran for anticoagulation purposes post AF ablation	Retrospective Quantitative, Descriptive Observational Incidence Study Variables – Independent: Dabigatran Outcome: Thromboembolism, Bleeding	Nonprobability Consecutive Sampling N=123 Protocol: Discontinuation of dabigatran 36-48 hours pre-procedure based on renal function, 22 hour delay post-procedure to dabigatran initiation. Post procedure 2 doses LMWH (enoxaparin 0.5 mg/kg) first 12 hours. Pre-procedure warfarin users D/C 5 days before procedure and undergo 3 days of bridging with LMWH (enoxaparin) Algorithm published.	Observation, Self report Event sampling used for data collection. Follow-up evaluation at 30 days post procedure. Participants call to report side effects, concerns.	Descriptive study. The statistical methods not discussed. Sample size 123 Estimated effect with a sample of this size is small (.25) given a significance criterion of .05 and power of .8.	Dabigatran is safe. No thromboembolic events, no bleeding.	Small number of participants. Protocol Intra-procedural ACT 237+/- 32. Implication of this discussed in the publication.
Kim et al. (2012)	Evaluate safety of periprocedural dabigatran during AF ablation compared to continuous	Case control analysis. Prospective cohort.	Consecutive sampling 763 participants undergoing ablation. Uninterrupted warfarin N=572,	Intervention Group: Use of Dabigatran etexilate 150 mg BID started 4 weeks prior to procedure. Last	Chi-square test and Fisher's exact test used to compare categorical data. Student's t-test and	Dabigatran safe to use in the setting of ablation. No significant statistical differences in bleeding or	Nonrandomized controlled study. Endpoints defined. Lower dabigatran population =

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warfarin (CW)		Dabigatran N= 191 Demographics: Warfarin group with higher proportion of TIA or CVA in study population.	dose 24 hours before procedure. Resumption 4 hours post-procedure. Control Group: Uninterrupted warfarin. Started 4 weeks prior to procedure. Therapeutic INR (Goal 2.0-3.0) Primary outcome: Bleeding complications (major and minor), Thromboembolic events. Observation and self report. Overnight hospitalization, 3 month follow up, available clinical coordinator for questions.	Wilcoxon's sum rank for continuous data. Multivariate logistic regression analysis for predictors of complications. Univariate parameters suggestive of complication included in stepwise regression analysis. Data analyzed using SPSS software	thrombo-embolic events.	Underpowered to detect thromboembolism protection.
Mipelisky et al. (2012)	Catheter ablation on uninterrupted Warfarin versus Dabigatran	Retrospective observational study.	Sample population: N = 156 consecutive participants undergoing ablation. Dabigatran 150 mg BID N = 31, Continued warfarin N= 125. Exclusion criteria listed: Incomplete med record, failure or lack of f/u documentation, change or D/C of AC in week 1 following RFCA, INR falls out of therapeutic range (between 2.0-3.0) in the	Control = CW therapy to maintain therapeutic range Intervention Group: Dabigatran 150 mg BID Data collection from EMR, all documentation occurring in a 1 week period post RFA. Outcomes: Major and minor bleeding complications at 48 hours and 1 week.	Fisher's exact test for categorical variables	No significant statistical differences in bleeding in the first 48 hours and at 1 week. No thrombo-embolic events. Small sample size in dabigatran arm.

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			30 days preceding RFCA.				
akireddy et al. (2012)	Evaluate safety of periprocedural Dabigatron during AF ablation compared to continuous warfarin (CW)	Prospective registry multicenter nonrandomized controlled observational study.	Total sample N=290 consecutive participants undergoing AF ablation. N=145 participants taking pre-procedural dabigatron for at least 30 days matched with same number on warfarin.	Intervention group = Dabigatron Control = CW Prospectively organized registries collecting data. Events collected for 30 days. Primary safety endpoints bleeding and thromboembolic events.	Chi-square and Fisher exact test for categorical variables. Student t-test for continuous variables. Multivariate logistic model was used to identify significant predictors of complications. Odds ratio and confidence interval of bleeding and thromboembolic complications computed.	Statistically significant higher occurrence of bleeding taking place in the dabigatron group. The difference in embolic events between groups was not statistically significant.	The difference in embolic events between groups was not statistically significant. Larger patient population tested (although still powered small). Outcome definitions clear.
aseno et al. (2012)	Evaluate safety of periprocedural dabigatron during AF ablation compared to continuous warfarin (CW)	Retrospective observation study.	Sample population: N=211 consecutive participants undergoing ablation for atrial fibrillation. Intervention Group: dabigatron 110 mg BID N=110, Control Group: CW N=101	Dabigatron discontinued on the morning of ablation (last dose 12 hours prior) and restarted the morning after the procedure. Warfarin continued with target INR 2-3. Post procedure unfractionated heparin 10,000 units given for 24 hours in both groups. Measured variables: Neurological evaluation pre-procedure, 2 hours post and	Continuous variables compared using Student's t-test. Categorical variables compared using chi-square or Fisher's exact test.	No deaths or thromboembolic events. Statistically significant increase in bleeding events in the warfarin group.	Study design not well clarified (varying pre-procedure duration of dabigatron).

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				<p>prior to hospital D/C. TTE on all pts day 1 post and at f/u 2-4 weeks.</p> <p>Outcomes: Death, thromboembolic event, serious bleed, minor bleeding, study withdrawal (intolerable side effects or INR > 4.5 on 2 occasions) up to 2 months following RFA.</p>			
<p>Kondaru et al. (2012)</p>	<p>Compare the heparin anticoagulation in patients treated with dabigatran vs. patients on uninterrupted warfarin during ablation of atrial fibrillation.</p>	<p>Retrospective observation</p>	<p>Sample population: N=76 consecutive participants undergoing ablation of atrial fibrillation from Jan 1 – August 31, 2011 subjected to standard intra-procedural heparin. Control: N=52 Continuous warfarin (CW) Independent: N= 24 Dabigatran dose assumed (not published)</p>	<p>First 11 cases – uninterrupted dabigatran. Last 13 cases dabigatran held for 2 doses prior to procedure. Continued on the evening following the procedure. Warfarin continued without interruption with target INR range 2-3. Standardized intra-procedure heparin protocol. Testing of ACT q 20 minutes.</p> <p>Outcomes: Heparin bolus administration, heparin mean drip rate, time to reach ACT > =300 sec, time to ACT > = 350 sec, mean Act and peak ACT.</p>	<p>Categorical variables analyzed using the chi-square test. Continuous variables analyzed using the t-test. Independent association of variables examined using multivariable linear regression. Cox proportional hazard regression also performed. Bias adjusted for using propensity score adjustment. Secondary analysis performed using longitudinal random-effect multivariable models.</p>	<p>Statistically significant difference in heparin administered by bolus, mean heparin drip rates, and total heparin administered (higher in the dabigatran group). Statistically significant lower peak and mean ACT's in dabigatran group.</p>	<p>Confounding variables include a change in anticoagulation protocol. Definitions and design/pre-procedure AC protocol lacks clarity.</p>
<p>Bassiouny</p>	<p>Evaluate safety</p>	<p>Prospective</p>	<p>Sample</p>	<p>Outcomes:</p>	<p>Continuous</p>	<p>No difference in</p>	<p>Not powered to</p>

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<p>et al. (2012)</p>	<p>of periprocedural dabigatran during AF ablation compared to continuous warfarin (CW)</p>	<p>nonrandomized controlled observational study</p>	<p>population: N= 400 consecutive patients undergoing RFA for AF. Control: Subjects on continuous warfarin with a therapeutic INR (≥ 1.8) N= 200 Intervention: 200 subjects on dabigatran 150 mg BID. N= 200 Dabigatran held for one dose (on the morning of the procedure – last dose 12 hours pre-procedure) in 116 patients and for 2 doses in 84 subjects prior to the procedure. Administration of dabigatran 150 mg and ASA 325 mg in lab at procedure conclusion after sheaths removed. Those undergoing general anesthesia received dabigatran with transfer to the floor.</p>	<p>Comparison of incidence of thromboembolic and hemorrhagic complications in the initial 30 days, intra-procedural ACT and heparin requirements. Follow-up: Overnight hospital stay, serial neurologic, vascular access assessment. Echocardiography as needed. CW group: INR day of procedure and then followed by primary provider for AC management. Weekly f/u calls during the 1st three months. Transtelephonic ECG transmissions with symptoms first three months. F/U visit 3 months</p>	<p>data: Mean +/- SD. % If categorical. Student t-test, 1 way ANOVA, chi-square and Fisher's exact test used to compare differences across groups. Posthoc analysis – Bonferroni multiple comparison method. Tests 2 sided P <0.05</p>	<p>the total hemorrhagic and thromboembolic complications between the two groups. There was a statistically significant difference in the mean dose of unfractionated heparin required in the group taking dabigatran compared to CW (higher doses required) There was a statistically significant difference in mean ACT values in subjects who held dabigatran for two doses vs. 1 dose and compared to those who were on CW. (lower values) There was a statistically significant difference in the time to achieve ACT >350 msec (earlier in the warfarin group).</p>	<p>predict stroke risk.</p>
<p>Lin et al. (2013)</p>	<p>Feasibility of using dabigatran during ablation of atrial</p>	<p>Prospective randomized controlled study.</p>	<p>Sample population: Consecutive participants scheduled to</p>	<p>Dabigatran 110 mg twice daily. Warfarin = 3 weeks therapeutic INR</p>	<p>Continuous data: Mean +/- SD. % Categorical: Fisher's exact</p>	<p>There was a statistically significant lower incidence difference of</p>	<p>Dabigatran dosage not FDA approved in US. Small population.</p>

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fibrillation; comparison with continued warfarin.		undergo AF ablation randomized at a 1:1 ratio to receive dabigatron (N=45) or warfarin (N=45). Enrollment date 4/2011 to 5/2012. Eligibility: Symptomatic AF, no prior AC agents	(1.6-3.0). TEE for all pts pre: if spontaneous contrast or thrombi, continued AC for additional 3 weeks and TEE repeated. Dabigatron and warfarin held the AM of procedure. Anticoagulation resumes 4 hours after hemostasis. No bridging. D-dimer measurements at specific times compared. Endpoints: Compare bleeding, D-dimer levels, time from AC initiation to ablation, adverse events leading to medication change	test. Comparison of continuous variables paired, unpaired Student's t-test. Univariate logistic regression analysis	minor bleeding in subjects taking dabigatron. There was a statistically significant reduction in D-dimer levels was significantly before and after ablation in dabigatron patients compared to warfarin.	
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Table legend: AF – atrial fibrillation, INR – international ratio, LMWH – low molecular weight heparin, CW – continuous warfarin, TTE – transthoracic echocardiogram, sd – standard deviation, BC – bleeding complications, APTT – activated partial thromboplastin time, BID – twice a day, RFCA – radiofrequency catheter ablation, D/C – discharge, EMR – emergency room, msec – milliseconds, ECG – electrocardiogram, ASA – aspirin, FDA – Food and Drug Administration, AC – anticoagulation, AM – morning, F/U – follow up

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Table 3 *Examples of therapeutic bridging regimens (Adapted from Douketis et al., 2012)*

Medication	Dosage
enoxaparin	1 mg/kg bid or 1.5 mg/kg qd
dalteparin	100 International units/kg bid or 200 International units/kg daily
tinzaparin	175 International units/kg daily
IV UFH	Titrate to attain activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times the control APTT

What's New?

Findings	Implications for Practice
<p>*Performance of catheter ablation for atrial fibrillation on continuous VKA therapy targeting INR's at a range greater than 2.0 seconds reduces the risk of stroke without increasing the risk of bleeding as compared to interrupted VKA and bridging therapy.</p>	<p>For individuals on VKA prior to ablation, insure maintenance of the INR in therapeutic range (2.0-3.0) for 4 weeks prior to performance of catheter ablation. Commence with procedure on continuous VKA maintaining INR > 2.0 versus discontinuation of VKA and use of bridging therapy.</p>
<p>* While dabigatron has been safely used in the setting of catheter ablation in 7 published studies, a single large scale investigation showed a significant increase in bleeding in individuals undergoing ablation on dabigatron as compared to those on continuous warfarin.</p>	<p>There is insufficient evidence to state that use of dabigatron versus continuous warfarin in the setting of catheter ablation for atrial fibrillation reduces the risk of stroke. Further large trials are required. Additional research findings are required to add to the body of evidence supporting a lack of difference in bleeding risks between dabigatron and continuous warfarin during ablation. The use of dabigatron in this setting merits careful consideration keeping in mind individual risk and preference as well as pharmacologic properties of the agent.</p>
<p>* While use of rivaroxiban and apixaban in the setting of catheter ablation has been reported in the literature, no published trials exist to date.</p>	<p>Trials are required to demonstrate safety of use in the setting of catheter ablation.</p>

Journal of Cardiovascular Nursing Manuscript Checklist

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Manuscript Contents

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- Title page including (1) title of the article, (2) author names (with highest academic degrees) and affiliations (including titles, departments, and name and location of institutions of primary employment), (3) **corresponding author's name and complete address including email, phone and FAX numbers**, (4) any acknowledgments, credits, or disclaimers, including funding sources and conflicts of interest, and (5) number of tables and figures.
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Doe JS, Lister FG, Lise JK, Kellert JL. Allied medical education. *JAMA*. 1975; 23(3):170-184.

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Doe JS, Justin MN, Gum KL, et al. Drug use during high school. *Am J Public Health*. 1976;64(1):12-22.

Reference to an Entire Book: Author, book title, place of publication, publisher, year.

Farber SD, Ball WD. *Neurorehabilitation: A Multisensory Approach*. Philadelphia, Pa: Saunders; 1982.

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