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Management if 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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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 dabigatron, 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 dabigatron 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,

or CHADS2 (**C**ongestive heart failure, **H**ypertension, **A**ge, **D**iabetes, and **S**troke) 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 dabigatron, 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

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

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

closely titrated to therapeutic range for at least 4 weeks prior to the scheduled procedure date. An alternative strategy is use of dabigatron, 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.

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 Dagres 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

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

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 dabigatron, rivaroxiban, 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 dabigatron.

Dabigatron

Dabigatron etexilate is an oral drug which is absorbed and converted to the active form of dabigatron. 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, dabigatron 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 ketoconozole. Plasma levels of dabigatron 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 dabigatron 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 dabigatron. The thrombin time (TT) is also influenced by dabigatron intake. It too is prolonged while on dabigatron but the effect is not linear and is not reflective of plasma concentrations. However, a normal TT rules out dabigatron anticoagulant effects. The Ecarin clotting time (ECT) is also affected by dabigatron intake with times felt to be dose dependent, but is not readily available in most labs

(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 dabigatron 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 dabigatron. There was also a higher incidence of GI bleed in patients taking 150 mg of dabigatron 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 dabigatron in patients with prosthetic mechanical heart valves. Evidence stemming from the phase II RE-ALIGNTM discontinued European trial showed a higher rate of blood clot formation in patients using dabigatron versus those on warfarin (Boehringer Ingelheim, 2012; United States Food and Drug Administration, 2/15/2013). Dabigatron 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 dabigatron 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

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 dabigatron 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 dabigatron 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.

Dabigatron and Catheter Ablation

Because of the advantages associated with ease of use, dabigatron 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 dabigatron 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 dabigatron 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 dabigatron (N=200) or continuous warfarin (N=200). Dabigatron 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

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), dabigatron was also deemed as safe to use. No differences in thromboembolic or bleeding rates were observed between the treatment arms. Pericardial effusions in the dabigatron arm (2/191) were treated with pericardiocentesis and did not require administration of clotting factors. In this protocol, dabigatron 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 dabigatron 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 dabigatron 110 mg twice a day. In this study, minor bleeding occurred less in the dabigatron arm ($p=.013$). 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 dabigatron 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 dabigatron 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 dabigatron 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 dabigatron to warfarin arm occurred in 3 participants due to dyspepsia (7% incidence).

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

Bleeding rates and thromboembolic events were low in the study by Kondaru and colleagues (2012) that compared dabigatron 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 dabigatron 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 dabigatron 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 dabigatron 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 dabigatron 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 dabigatron 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 dabigatron, rivaroxiban has a high degree of bioavailibilty 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, Kubitza, 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/mn. Package insert indicates that a dose of 15 mg daily can be used by individuals with a creatinine clearance ranging from 15-50 ml/mn. Rivaroxiban, like dabigatron is a substrate of the permeability glycoprotein transporter system. However, unlike dabigatron, 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

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 dabigatron, 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 dabigatron (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

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

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 dabigatron, 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

same advantages and confounders applicable to dabigatron 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, dabigatron, 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 pharmalogical 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 dabigatron 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

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

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.

References

Abhishek, F., Heist, E. K., Barrett, C., Danik, S., Blendea, D., Correnti, C., . . . Mansour, M. (2011). Effectiveness of a strategy to reduce major vascular complications from catheter ablation of atrial fibrillation. *Journal of Interventional Cardiac Electrophysiology: An International Journal of Arrhythmias and Pacing, 30*(3), 211-215. doi: 10.1007/s10840-010-9539-8; 10.1007/s10840-010-9539-8

Aldhoon, B., Wichterle, D., Peichl, P., Cihak, R., & Kautzner, J. (2013). Complications of catheter ablation for atrial fibrillation in a high-volume centre with the use of intracardiac echocardiography. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology, 15*(1), 24-32. doi: 10.1093/europace/eus304; 10.1093/europace/eus304

Asirvatham, S. J. (2007). Ablation for atrial fibrillation: Can we decrease thromboembolism without increasing the risk for bleeding? *Circulation, 116*(22), 2517-2519. doi: 10.1161/CIRCULATIONAHA.107.741454

Bassiouny, M., Saliba, W., Rickard, J., Shao, M., Sey, A., Diab, M., . . . Wazni, O. (2013). Use of dabigatran for peri-procedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. *Circulation.Arrhythmia and Electrophysiology,* doi: 10.1161/CIRCEP.113.000320

Bhave, P. D., & Knight, B. P. (2013). Optimal strategies including use of newer anticoagulants for prevention of stroke and bleeding complications before, during, and after catheter ablation of atrial fibrillation and atrial flutter. *Current Treatment Options in Cardiovascular Medicine,* doi: 10.1007/s11936-013-0242-9

Bikou, O., Thomas, D., Trappe, K., Lugenbiel, P., Kelemen, K., Koch, M., . . . Bauer, A. (2011). Connexin 43 gene therapy prevents persistent atrial fibrillation in a porcine model. *Cardiovascular Research, 92*(2), 218-225. doi: 10.1093/cvr/cvr209; 10.1093/cvr/cvr209

Boehringer Ingelheim. (2012). *Boehringer Ingelheim discontinues phase II trial in patients with artificial heart valves*. Retrieved 4/12, 2013, from http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2012/11_december_2012dabigatranetexilate1.html

Bristol-Myers Squibb Pharma Company. (2012). *Eliquis (apixaban) : Highlights of prescribing information.*. Retrieved 2/15, 2013, from http://packageinserts.bms.com/pi/pi_eliquis.pdf

Bulava, A., Slavik, L., Fiala, M., Heinc, P., Lubena, L., Lukl, J., . . . Indrak, K. (2004). Endothelial injury and activation of the coagulation cascade during radiofrequency catheter ablation. [Endotelialni poskozeni a aktivace koagulacni kaskady behem radiofrekvencni katetrove ablace] *Vnitrni Lekarstvi, 50*(4), 305-311.

Bunch, T. J., Crandall, B. G., Weiss, J. P., May, H. T., Bair, T. L., Osborn, J. S., . . . Day, J. D. (2009). Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. *Journal of Cardiovascular Electrophysiology, 20*(9), 988-993. doi: 10.1111/j.1540-8167.2009.01481.x; 10.1111/j.1540-8167.2009.01481.x

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., . . . RE-LY Steering Committee and Investigators. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine, 361*(12), 1139-1151. doi: 10.1056/NEJMoa0905561; 10.1056/NEJMoa0905561

Conway, D. S., Buggins, P., Hughes, E., & Lip, G. Y. (2004). Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. *Journal of the American College of Cardiology, 43*(11), 2075-2082. doi: 10.1016/j.jacc.2003.11.062

Dagres, N., Hindricks, G., Kottkamp, H., Sommer, P., Gaspar, T., Bode, K., . . . Piorkowski, C. (2009). Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: Still cause for concern? *Journal of Cardiovascular Electrophysiology, 20*(9), 1014-1019. doi: 10.1111/j.1540-8167.2009.01493.x; 10.1111/j.1540-8167.2009.01493.x

Di Biase, L., Burkhardt, J. D., Mohanty, P., Sanchez, J., Horton, R., Gallinghouse, G. J., . . . Natale, A. (2010). Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: The impact of periprocedural therapeutic international normalized ratio. *Circulation, 121*(23), 2550-2556. doi: 10.1161/CIRCULATIONAHA.109.921320; 10.1161/CIRCULATIONAHA.109.921320

Douketis, J. D., Spyropoulos, A. C., Spencer, F. A., Mayr, M., Jaffer, A. K., Eckman, M. H., . . . American College of Chest Physicians. (2012). Perioperative management of antithrombotic therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest, 141*(2 Suppl), e326S-50S. doi: 10.1378/chest.11-2298; 10.1378/chest.11-2298

Eerenberg, E. S., Kamphuisen, P. W., Sijpkens, M. K., Meijers, J. C., Buller, H. R., & Levi, M. (2011). Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation, 124*(14), 1573-1579. doi: 10.1161/CIRCULATIONAHA.111.029017; 10.1161/CIRCULATIONAHA.111.029017

European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., . . . ESC Committee for Practice Guidelines. (2010). Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the European society of cardiology (ESC). *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology, 12*(10), 1360-1420. doi: 10.1093/europace/euq350; 10.1093/europace/euq350

Fuster, V., Ryden, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., . . . Heart Rhythm Society. (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation, 114*(7), e257-354. doi: 10.1161/CIRCULATIONAHA.106.177292

Gage, B. F., Waterman, A. D., Shannon, W., Boechler, M., Rich, M. W., & Radford, M. J. (2001). Validation of clinical classification schemes for predicting stroke: Results from the national registry of atrial fibrillation. *JAMA : The Journal of the American Medical Association, 285*(22), 2864-2870.

Garcia, D. A. (2012). Benefits and risks of oral anticoagulation for stroke prevention in nonvalvular atrial fibrillation. *Thrombosis Research, 129*(1), 9-16. doi: 10.1016/j.thromres.2011.09.023; 10.1016/j.thromres.2011.09.023

Garwood, C. L., Hwang, J. M., & Moser, L. R. (2011). Striking a balance between the risks and benefits of anticoagulation bridge therapy in patients with atrial fibrillation: Clinical updates and remaining controversies. *Pharmacotherapy, 31*(12), 1208-1220. doi: 10.1592/phco.31.12.1208; 10.1592/phco.31.12.1208

Gaspar, K. (2009). Disorders of hemostasis. In Porth, C.M. & Matfin, G. (Ed.), *Pathophysiology: Concepts of altered health states* (8th edition ed., pp. 264-265). Philadephia, PA: Wolter Kluwer Health/Lippincott Williams & Wilkins.

Gautam, S., John, R. M., Stevenson, W. G., Jain, R., Epstein, L. M., Tedrow, U., . . . Michaud, G. F. (2011). Effect of therapeutic INR on activated clotting times, heparin dosage, and bleeding risk during ablation of atrial fibrillation. *Journal of Cardiovascular Electrophysiology, 22*(3), 248-254. doi: 10.1111/j.1540-8167.2010.01894.x; 10.1111/j.1540-8167.2010.01894.x

Go, A. S., Hylek, E. M., Phillips, K. A., Chang, Y., Henault, L. E., Selby, J. V., & Singer, D. E. (2001). Prevalence of diagnosed atrial fibrillation in adults: National implications for

rhythm management and stroke prevention: The AnTicoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA : The Journal of the American Medical Association, 285*(18), 2370-2375.

Granger, C. B., Alexander, J. H., McMurray, J. J., Lopes, R. D., Hylek, E. M., Hanna, M., . . . ARISTOTLE Committees and Investigators. (2011). Apixaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine, 365*(11), 981-992. doi: 10.1056/NEJMoa1107039; 10.1056/NEJMoa1107039

Guiot, A., Jongnarangsin, K., Chugh, A., Suwanagool, A., Latchamsetty, R., Myles, J. D., . . . Oral, H. (2012). Anticoagulant therapy and risk of cerebrovascular events after catheter ablation of atrial fibrillation in the elderly. *Journal of Cardiovascular Electrophysiology, 23*(1), 36-43. doi: 10.1111/j.1540-8167.2011.02141.x; 10.1111/j.1540-8167.2011.02141.x

Haeusler, K. G., Kirchhof, P., & Endres, M. (2012). Left atrial catheter ablation and ischemic stroke. *Stroke; a Journal of Cerebral Circulation, 43*(1), 265-270. doi: 10.1161/STROKEAHA.111.627067; 10.1161/STROKEAHA.111.627067

Hakalahti, A., Uusimaa, P., Ylitalo, K., & Raatikainen, M. J. (2011). Catheter ablation of atrial fibrillation in patients with therapeutic oral anticoagulation treatment. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology, 13*(5), 640-645. doi: 10.1093/europace/eur038; 10.1093/europace/eur038

Hankey, G. J., & Eikelboom, J. W. (2011). Dabigatran etexilate: A new oral thrombin inhibitor. *Circulation, 123*(13), 1436-1450. doi: 10.1161/CIRCULATIONAHA.110.004424; 10.1161/CIRCULATIONAHA.110.004424

Harrington, A. R., Armstrong, E. P., Nolan, P. E.,Jr, & Malone, D. C. (2013). Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke; a Journal of Cerebral Circulation,* doi: 10.1161/STROKEAHA.111.000402

Hayashi, T., Kumagai, K., Naito, S., Goto, K., Kaseno, K., Ohshima, S., . . . Isobe, M. (2013). Preprocedural therapeutic international normalized ratio influence on bleeding complications in atrial fibrillation ablation with continued anticoagulation with warfarin. *Circulation Journal : Official Journal of the Japanese Circulation Society, 77*(2), 338-344.

Hayes, C. R., & Keane, D. (2010). Safety of atrial fibrillation ablation with novel multi-electrode array catheters on uninterrupted anticoagulation-a single-center experience. *Journal of Interventional Cardiac Electrophysiology : An International Journal of Arrhythmias and Pacing, 27*(2), 117-122. doi: 10.1007/s10840-009-9457-9; 10.1007/s10840-009-9457-9

Holmes, D. R., Reddy, V. Y., Turi, Z. G., Doshi, S. K., Sievert, H., Buchbinder, M., . . . PROTECT AF Investigators. (2009). Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomised non-inferiority trial. *Lancet, 374*(9689), 534-542. doi: 10.1016/S0140-6736(09)61343-X; 10.1016/S0140-6736(09)61343-X

Hussein, A. A., Martin, D. O., Saliba, W., Patel, D., Karim, S., Batal, O., . . . Wazni, O. (2009). Radiofrequency ablation of atrial fibrillation under therapeutic international normalized ratio: A safe and efficacious periprocedural anticoagulation strategy. *Heart Rhythm : The Official Journal of the Heart Rhythm Society, 6*(10), 1425-1429. doi: 10.1016/j.hrthm.2009.07.007; 10.1016/j.hrthm.2009.07.007

Igarashi, T., Finet, J. E., Takeuchi, A., Fujino, Y., Strom, M., Greener, I. D., . . . Donahue, J. K. (2012). Connexin gene transfer preserves conduction velocity and prevents atrial fibrillation. *Circulation, 125*(2), 216-225. doi: 10.1161/CIRCULATIONAHA.111.053272; 10.1161/CIRCULATIONAHA.111.053272

Janssen Pharmaceuticals. (2013). *Xarelto (rivaroxiban): Highlights of prescribing information.*. Retrieved 4/10/2013, 2013, from http://www.janssenmedicalinformation.com/assets/pdf/products/files/Xarelto/pi/ENC-010330-11.pdf

Kaatz, S., Kouides, P. A., Garcia, D. A., Spyropolous, A. C., Crowther, M., Douketis, J. D., . . . Ansell, J. (2012). Guidance on the emergent reversal of oral thrombin and factor xa inhibitors. *American Journal of Hematology, 87 Suppl 1*, S141-5. doi: 10.1002/ajh.23202; 10.1002/ajh.23202

Kaseno, K., Naito, S., Nakamura, K., Sakamoto, T., Sasaki, T., Tsukada, N., . . . Tada, H. (2012). Efficacy and safety of periprocedural dabigatran in patients undergoing catheter ablation of atrial fibrillation. *Circulation Journal : Official Journal of the Japanese Circulation Society, 76*(10), 2337-2342.

Kim, J. S., She, F., Jongnarangsin, K., Chugh, A., Latchamsetty, R., Ghanbari, H., . . . Oral, H. (2013). Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm : The Official Journal of the Heart Rhythm Society, 10*(4), 483-489. doi: 10.1016/j.hrthm.2012.12.011; 10.1016/j.hrthm.2012.12.011

Knight, B. P. (2012). Anticoagulation for atrial fibrillation ablation: What is the optimal strategy? *Journal of the American College of Cardiology, 59*(13), 1175-1177. doi: 10.1016/j.jacc.2011.11.044; 10.1016/j.jacc.2011.11.044

Konduru, S. V., Cheema, A. A., Jones, P., Li, Y., Ramza, B., & Wimmer, A. P. (2012). Differences in intraprocedural ACTs with standardized heparin dosing during catheter ablation for atrial fibrillation in patients treated with dabigatran vs. patients on uninterrupted warfarin. *Journal of Interventional Cardiac Electrophysiology : An International Journal of Arrhythmias and Pacing, 35*(3), 277-84; discussion 284. doi: 10.1007/s10840-012-9719-9; 10.1007/s10840-012-9719-9

Koruth, J. S., Aryana, A., Dukkipati, S. R., Pak, H. N., Kim, Y. H., Sosa, E. A., . . . d'Avila, A. (2011). Unusual complications of percutaneous epicardial access and epicardial mapping and ablation of cardiac arrhythmias. *Circulation.Arrhythmia and Electrophysiology, 4*(6), 882-888. doi: 10.1161/CIRCEP.111.965731; 10.1161/CIRCEP.111.965731

Kwak, J. J., Pak, H. N., Jang, J. K., Kim, S. K., Park, J. H., Choi, J. I., . . . Kim, Y. H. (2010). Safety and convenience of continuous warfarin strategy during the periprocedural period in patients who underwent catheter ablation of atrial fibrillation. *Journal of Cardiovascular*

Electrophysiology, 21(6), 620-625. doi: 10.1111/j.1540-8167.2009.01670.x; 10.1111/j.1540-8167.2009.01670.x

Lakkireddy, D., Reddy, Y. M., Di Biase, L., Vanga, S. R., Santangeli, P., Swarup, V., . . . Natale, A. (2012). Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: Results from a multicenter prospective registry. *Journal of the American College of Cardiology, 59*(13), 1168-1174. doi: 10.1016/j.jacc.2011.12.014; 10.1016/j.jacc.2011.12.014

Latchamsetty, R., Gautam, S., Bhakta, D., Chugh, A., John, R. M., Epstein, L. M., . . . Jongnarangsin, K. (2011). Management and outcomes of cardiac tamponade during atrial fibrillation ablation in the presence of therapeutic anticoagulation with warfarin. *Heart Rhythm : The Official Journal of the Heart Rhythm Society, 8*(6), 805-808. doi: 10.1016/j.hrthm.2011.01.020; 10.1016/j.hrthm.2011.01.020

Lip, G. Y., Andreotti, F., Fauchier, L., Huber, K., Hylek, E., Knight, E., . . . European Heart Rhythm Association. (2011). Bleeding risk assessment and management in atrial fibrillation patients. Executive summary of a position document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] working group on thrombosis. *Thrombosis and Haemostasis, 106*(6), 997-1011. doi: 10.1160/TH11-10-0690; 10.1160/TH11-10-0690

Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A., & Crijns, H. J. (2010). Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel

risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest, 137*(2), 263-272. doi: 10.1378/chest.09-1584; 10.1378/chest.09-1584

Lu, G., Deguzman, F. R., Hollenbach, S. J., Karbarz, M. J., Abe, K., Lee, G., . . . Sinha, U. (2013). A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor xa. *Nature Medicine, 19*(4), 446-451. doi: 10.1038/nm.3102; 10.1038/nm.3102

McCready, J. W., Nunn, L., Lambiase, P. D., Ahsan, S. Y., Segal, O. R., Rowland, E., . . . Chow, A. W. (2010). Incidence of left atrial thrombus prior to atrial fibrillation ablation: Is pre-procedural transoesophageal echocardiography mandatory? *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology, 12*(7), 927-932. doi: 10.1093/europace/euq074; 10.1093/europace/euq074

Miyasaka, Y., Barnes, M. E., Gersh, B. J., Cha, S. S., Bailey, K. R., Abhayaratna, W. P., . . . Tsang, T. S. (2006). Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation, 114*(2), 119-125. doi: 10.1161/CIRCULATIONAHA.105.595140

Neumann, T., Kuniss, M., Conradi, G., Janin, S., Berkowitsch, A., Wojcik, M., . . . Pitschner, H. F. (2011). MEDAFI-trial (micro-embolization during ablation of atrial fibrillation): Comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular*

Electrophysiology of the European Society of Cardiology, 13(1), 37-44. doi: 10.1093/europace/euq303; 10.1093/europace/euq303

Nin, T., Sairaku, A., Yoshida, Y., Kamiya, H., Tatematsu, Y., Nanasato, M., . . . Murohara, T. (2013). A randomized controlled trial of dabigatran versus warfarin for periablation anticoagulation in patients undergoing ablation of atrial fibrillation. *Pacing and Clinical Electrophysiology : PACE, 36*(2), 172-179. doi: 10.1111/pace.12036; 10.1111/pace.12036

Oude Velthuis, B., Stevenhagen, J., van Opstal, J. M., & Scholten, M. F. (2012). Continuation of vitamin K antagonists as acceptable anticoagulation regimen in patients undergoing pulmonary vein isolation. *Netherlands Heart Journal : Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, 20*(1), 12-15. doi: 10.1007/s12471-011-0223-0; 10.1007/s12471-011-0223-0

Page, S. P., Siddiqui, M. S., Finlay, M., Hunter, R. J., Abrams, D. J., Dhinoja, M., . . . Schilling, R. J. (2011). Catheter ablation for atrial fibrillation on uninterrupted warfarin: Can it be done without echo guidance? *Journal of Cardiovascular Electrophysiology, 22*(3), 265-270. doi: 10.1111/j.1540-8167.2010.01910.x; 10.1111/j.1540-8167.2010.01910.x

Patel, M. R., Hellkamp, A. S., Lokhnygina, Y., Piccini, J. P., Zhang, Z., Mohanty, S., . . . Mahaffey, K. W. (2013). Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: Analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *Journal of the*

American College of Cardiology, 61(6), 651-658. doi: 10.1016/j.jacc.2012.09.057; 10.1016/j.jacc.2012.09.057

Patel, M. R., Mahaffey, K. W., Garg, J., Pan, G., Singer, D. E., Hacke, W., . . . ROCKET AF Investigators. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England Journal of Medicine, 365*(10), 883-891. doi: 10.1056/NEJMoa1009638; 10.1056/NEJMoa1009638

Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., & Lip, G. Y. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest, 138*(5), 1093-1100. doi: 10.1378/chest.10-0134; 10.1378/chest.10-0134

Prudente, L. A., Moorman, J. R., Lake, D., Xiao, Y., Greebaum, H., Mangrum, J. M., . . . Ferguson, J. D. (2009). Femoral vascular complications following catheter ablation of atrial fibrillation. *Journal of Interventional Cardiac Electrophysiology : An International Journal of Arrhythmias and Pacing, 26*(1), 59-64. doi: 10.1007/s10840-009-9402-y; 10.1007/s10840-009-9402-y

Reddy, V. Y., Doshi, S. K., Sievert, H., Buchbinder, M., Neuzil, P., Huber, K., . . . PROTECT AF Investigators. (2013). 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. *Circulation, 127*(6), 720-729. doi: 10.1161/CIRCULATIONAHA.112.114389; 10.1161/CIRCULATIONAHA.112.114389

ROCKET AF Study Investigators. (2010). Rivaroxaban-once daily, oral, direct factor xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET AF study. *American Heart Journal, 159*(3), 340-347.e1. doi: 10.1016/j.ahj.2009.11.025; 10.1016/j.ahj.2009.11.025

Ru San, T., Chan, M. Y., Wee Siong, T., Kok Foo, T., Kheng Siang, N., Lee, S. H., & Chi Keong, C. (2012). Stroke prevention in atrial fibrillation: Understanding the new oral anticoagulants dabigatran, rivaroxaban, and apixaban. *Thrombosis, 2012*, 108983. doi: 10.1155/2012/108983

Ruff, C. T., Giugliano, R. P., Antman, E. M., Crugnale, S. E., Bocanegra, T., Mercuri, M., . . . Braunwald, E. (2010). Evaluation of the novel factor xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the effective aNticoaGulation with factor xA next GEneration in atrial fibrillation-thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI 48). *American Heart Journal, 160*(4), 635-641. doi: 10.1016/j.ahj.2010.06.042; 10.1016/j.ahj.2010.06.042

Saad, E. B., d'Avila, A., Costa, I. P., Aryana, A., Slater, C., Costa, R. E., . . . Polanczyk, C. A. (2011). Very low risk of thromboembolic events in patients undergoing successful catheter ablation of atrial fibrillation with a CHADS2 score </=3: A long-term outcome study. *Circulation.Arrhythmia and Electrophysiology, 4*(5), 615-621. doi: 10.1161/CIRCEP.111.963231; 10.1161/CIRCEP.111.963231

Samama, M. M., Amiral, J., Guinet, C., Flem, L. L., & Seghatchian, J. (2013). Monitoring plasma levels of factor xa inhibitors: How, why and when? *Expert Review of Hematology, 6*(2), 155-164. doi: 10.1586/ehm.13.11; 10.1586/ehm.13.11

Samama, M. M., Guinet, C., Le Flem, L., Ninin, E., & Debue, J. M. (2013). Measurement of dabigatran and rivaroxaban in primary prevention of venous thromboembolism in 106 patients, who have undergone major orthopedic surgery: An observational study. *Journal of Thrombosis and Thrombolysis, 35*(2), 140-146. doi: 10.1007/s11239-012-0803-x; 10.1007/s11239-012-0803-x

Santangeli, P., Di Biase, L., Horton, R., Burkhardt, J. D., Sanchez, J., Al-Ahmad, A., . . . Natale, A. (2012). Ablation of atrial fibrillation under therapeutic warfarin reduces periprocedural complications: Evidence from a meta-analysis. *Circulation.Arrhythmia and Electrophysiology, 5*(2), 302-311. doi: 10.1161/CIRCEP.111.964916; 10.1161/CIRCEP.111.964916

Santangeli, P., Di Biase, L., Sanchez, J. E., Horton, R., & Natale, A. (2011). Atrial fibrillation ablation without interruption of anticoagulation. *Cardiology Research and Practice, 2011*, 837841. doi: 10.4061/2011/837841; 10.4061/2011/837841

Scherr, D., Sharma, K., Dalal, D., Spragg, D., Chilukuri, K., Cheng, A., . . . Marine, J. E. (2009). Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. *Journal of Cardiovascular Electrophysiology, 20*(12), 1357-1363. doi: 10.1111/j.1540-8167.2009.01540.x; 10.1111/j.1540-8167.2009.01540.x

Schmidt, M., Segerson, N. M., Marschang, H., Akoum, N., Rittger, H., Clifford, S. M., . . . Marrouche, N. F. (2009). Atrial fibrillation ablation in patients with therapeutic international normalized ratios. *Pacing and Clinical Electrophysiology : PACE, 32*(8), 995-999. doi: 10.1111/j.1540-8159.2009.02429.x; 10.1111/j.1540-8159.2009.02429.x

Snipelisky, D., Kauffman, C., Prussak, K., Johns, G., Venkatachalam, K., & Kusumoto, F. (2012). A comparison of bleeding complications post-ablation between warfarin and dabigatran. *Journal of Interventional Cardiac Electrophysiology : An International Journal of Arrhythmias and Pacing, 35*(1), 29-33. doi: 10.1007/s10840-012-9708-z; 10.1007/s10840-012-9708-z

Soucek, R., Thomas, D., Kelemen, K., Bikou, O., Seyler, C., Voss, F., . . . Bauer, A. (2012). Genetic suppression of atrial fibrillation using a dominant-negative ether-a-go-go-related gene mutant. *Heart Rhythm : The Official Journal of the Heart Rhythm Society, 9*(2), 265-272. doi: 10.1016/j.hrthm.2011.09.008; 10.1016/j.hrthm.2011.09.008

Stampfuss, J., Kubitza, D., Becka, M., & Mueck, W. (2013). The effect of food on the absorption and pharmacokinetics of rivaroxaban. *International Journal of Clinical Pharmacology and Therapeutics,* doi: 10.5414/CP201812

Tripodi, A. (2013). The laboratory and the direct oral anticoagulants. *Blood,* doi: 10.1182/blood-2012-12-453076

United States Food and Drug Aministration. (2/15/2013). *FDA drug safety communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical*

prosthetic heart valves. Retrieved 2/19, 2013, from http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm

Verma, A. K., & Brighton, T. A. (2009). The direct factor xa inhibitor rivaroxaban. *The Medical Journal of Australia, 190*(7), 379-383.

Wann, L. S., Curtis, A. B., Ellenbogen, K. A., Estes, N. A.,3rd, Ezekowitz, M. D., Jackman, W. M., . . . Yancy, C. W. (2011). 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Heart Rhythm : The Official Journal of the Heart Rhythm Society, 8*(3), e1-8. doi: 10.1016/j.hrthm.2011.01.032; 10.1016/j.hrthm.2011.01.032

Watson, T., Shantsila, E., & Lip, G. Y. (2009). Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet, 373*(9658), 155-166. doi: 10.1016/S0140-6736(09)60040-4; 10.1016/S0140-6736(09)60040-4

Wazni, O. M., Beheiry, S., Fahmy, T., Barrett, C., Hao, S., Patel, D., . . . Natale, A. (2007). Atrial fibrillation ablation in patients with therapeutic international normalized ratio: Comparison of strategies of anticoagulation management in the periprocedural period. *Circulation, 116*(22), 2531-2534. doi: 10.1161/CIRCULATIONAHA.107.727784

Weitz, J. I., Quinlan, D. J., & Eikelboom, J. W. (2012). Periprocedural management and approach to bleeding in patients taking dabigatran. *Circulation, 126*(20), 2428-2432. doi: 10.1161/CIRCULATIONAHA.112.123224; 10.1161/CIRCULATIONAHA.112.123224

Winkle, R. A., Mead, R. H., Engel, G., Kong, M. H., & Patrawala, R. A. (2012). The use of dabigatran immediately after atrial fibrillation ablation. *Journal of Cardiovascular Electrophysiology, 23*(3), 264-268. doi: 10.1111/j.1540-8167.2011.02175.x; 10.1111/j.1540-8167.2011.02175.x

Winkle, R. A., Mead, R. H., Engel, G., & Patrawala, R. A. (2011). Safety of lower activated clotting times during atrial fibrillation ablation using open irrigated tip catheters and a single transseptal puncture. *The American Journal of Cardiology, 107*(5), 704-708. doi: 10.1016/j.amjcard.2010.10.048; 10.1016/j.amjcard.2010.10.048

Wolf, P. A., Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: The framingham study. *Stroke; a Journal of Cerebral Circulation, 22*(8), 983-988.