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Monomorphic Outflow Tract Ventricular Tachycardia: Unique Presenting Manifestation of Gitelman’s Syndrome

Subba Reddy Vanga, MD*, Chandra Annapureddy, MD†, Mazda Biria, MD*, Dhanunjaya Lakkireddy, MD FACC*.

*Mid America Cardiology @ University of Kansas Hospital, Kansas City, KS. † Howard University Hospitals, Washington, DC.

Introduction

Outflow Tract Ventricular Tachycardia (OTVT) is typically seen in young to middle aged people with structurally normal hearts. These arrhythmias are triggered by emotional or stress factors and that responds to medications. Electrolyte abnormalities rarely cause ventricular arrhythmia. Gitelman’s syndrome, a rare autosomal recessive renal disorder causes hypokalemia, metabolic alkalosis and hypomagnesaemia. This disorder is often benign with mild clinical symptoms and excellent long-term prognosis. We present a case of Gitelman’s syndrome with symptomatic OTVT as initial manifestation.

Case description

A 27-year old male presented for arrhythmia evaluation after multiple ER visits with symptoms of palpitations, light headedness and near syncope over a period of 2 months. Typical episodes were spontaneous in onset and were not associated with activity or exercise or caffeine intake. They lasted from few seconds to few minutes and are associated with lightheadedness. His past medical history was otherwise unremarkable. His family history is negative for coronary artery disease or sudden death. His alcohol and caffeine intake were not significant and he denied tobacco or illicit drug use. His only medication includes potassium supplements at 20 mEq per day for documented hypokalemia (Serum K+ 3.1 mEq/L; Normal: 3.5 -5.0 mEq/L) during one of his ER visits. Cardiovascular examination revealed a normotensive male with regular rhythm and rate without any murmur or clicks. A 12 lead EKG obtained during his initial office visit showed normal sinus rhythm and QT interval without any obvious pre-excitation or PR prolongation to suggest AV nodal dysfunction. Patient was sent home on a continuous looping event monitor.

Two weeks later he presented to the ER with another episode of palpitations with documented sustained VT. He was found to have hypokalemia (Serum K+ 2.8mEq/L, Normal: 3.5 – 5.0mEq/L) and hypomagnesaemia (Serum Mg++ 0.7 mEq/L; Normal: 1.3 -2.1 mEq/L) during the work up in the ER and was admitted for further evaluation. On repeat questioning, he denied diuretic or laxative abuse. Interim review of his event monitor showed significant arrhythmia burden which accounted for more than 14% of his monitored period, with bigeminy, trigeminy, non sustained and sustained VT. All of his non-sustained and majority of sustained VT were asymptomatic. ECG obtained dur-
ing an episode of VT revealed left bundle branch block morphology with transition in V2/V3 and an inferior axis suggesting the origin from ventricular outflow tract [Figure 1]. The transition in V2/V3 makes it difficult to diagnose the origin of VT without an EP study.

His biochemistry panel also showed metabolic alkalosis. In the absence of diuretic use and GI losses, it triggered further workup which demonstrated hypocaliuria. His urinary prostaglandins were normal. Plasma renin-activity, aldosterone and cortisol levels were in the upper normal range. Patient had a Thiazide test which demonstrated a blunted diuretic response to thiazide diuretic with lower than the normal (2.2%) fractional chloride clearance. These findings were suggestive of Gitelman’s syndrome. His 2D-Echocardiogram was normal and cardiac MRI ruled out arrhythmogenic right ventricular dysplasia. His arrhythmia improved with intravenous electrolyte replacement alone and hence an electrophysiology study was not undertaken. He required 80 mEq of potassium, 2 grams of magnesium supplements every day and spironolactone was added to maintain his serum potassium and magnesium levels within normal range. Patient remained asymptomatic on oral electrolyte supplementation alone and 24-Hour Holter monitor demonstrated less than 10 premature ventricular contractions without arrhythmia at one year follow up.

Discussion

Gitelman’s syndrome, also called as familial hypokalemia hypomagnesemia, is a autosomal recessive disorder resulting from a gene (SLC12A3) defect that encodes the renal thiazide-sensitive sodiumchloride co-transporter. Secondary to this defect, the biochemical abnormalities closely mimic chronic thiazide diuretic abuse characterized by hypokalemic metabolic alkalosis with significant hypomagnesemia and low urinary calcium excretion. The differential diagnosis of Gitelman’s syndrome includes Barter’s syndrome and Hereditary Magnesium loosing nephropathy. Barter’s syndrome is not associated with hypomagnesemia and hypocalcuria while the magnesium loosing nephropathy does not present with hypokalemia. The diagnosis is made on clinical symptoms and biochemical abnormalities. Although genetic testing is available, it is not recommended because of excellent long-term prognosis of this syndrome. Gitelman’s syndrome typically manifests during adolescence and adulthood with symptoms of fatigue, muscle weakness,
cramps, and tetany from hypomagnesemia. Acute fluid and electrolyte losses such as dehydration, vomiting or diarrhea can exaggerate or precipitate these symptoms. Gitelman’s Syndrome is hereditary, no other first degree relatives of this patient had electrolyte abnormalities.

The mechanism of arrhythmogenesis in Gitelman’s syndrome is not clear. Chronic hypokalemia can predispose but not sufficient to generate a symptomatic ventricular arrhythmia. Electrocardiographic abnormalities were studied in Barter’s syndrome patients who have predominantly hypokalemia. Electrocardiograms demonstrated prolongation of QT interval and frequent premature ventricular contractions were noted in 2 patients on Holter monitor. No arrhythmia was documented. Another study specifically looking at cardiac workup in Gitelman’s syndrome, found out that QT interval is often prolonged but 24 hour Holter, treadmill exercise, echocardiographic data was unchanged. Similar changes in QT interval were reported from other study without any documentation of arrhythmia. Magnesium deficiency can potentially result in torsades-de-pointes and cardiomyopathy. Similarly VT was documented in a patient with Magnesium deficiency. A rare case of exercise induced VT in Gitelman’s syndrome was that disappeared with electrolyte replacement was reported. In another case report VT in a patient with Gitelman’s syndrome did not respond to electrolyte replacement but required multiple antiarrhythmic medications and ICD therapy. Rarely this syndrome can present as sudden cardiac death. Autonomic system imbalance can cause arrhythmia and this patient did not demonstrate any signs or symptoms suggestive of such problem. It is unlikely that this patient had a concurrent idiopathic monomorphic OTVT because the arrhythmia was suppressed with simple electrolyte replacement alone. Premature ventricular contraction might have probably precipitated the arrhythmia in this patient whose substrate was modified from chronic electrolyte imbalance. Recent study supports the role of microvascular dysfunction and myocardial perfusion abnormalities as triggering factors precipitating malignant ventricular arrhythmias in the context of chronic hypokalemia usually present in Gitelman’s syndrome patients.

Conclusions
Electrolyte imbalance is an easily correctable cause that could be the potentially precipitate or exaggerate an arrhythmia. Every effort should be taken to correct hypokalemia and hypomagnesemia early in the management of an arrhythmia. Rare causes of electrolyte disorders should be kept in differential diagnosis in such cases as these problems will recur if not treated appropriately. Gitelman’s syndrome, a rare cause of hereditary hypokalemic, hypomagnesemic metabolic alkalosis is gaining recognition for its association with cardiac arrhythmia.

Key Words : Gitelman’s Syndrome, VT.

References
Level of natriuretic peptide Determines outcome in atrial fibrillation

Qi-xian Zeng MD¹, Ming-fen Wei MD², Wei Zhang MD PhD¹, Yun Zhang MD PhD¹, Jing-quan Zhong MD PhD¹.

¹ Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education and Chinese Ministry of Health, Jinan, China; Department of Cardiology, Qilu Hospital, Shandong University, Jinan, China. ² Shandong Communication Hospital, Jinan, China.

Abstract

Background : Natriuretic peptide (NP) is high in atrial fibrillation (AF) and may decrease after cardioversion to sinus rhythm and the levels of atrial NP (ANP) and brain NP (BNP) in different types of AF and whether ANP and BNP have predictive values for relapsed AF have not been determined.

Purpose : We aimed to examine the levels of ANP and BNP in AF to determine their roles in different types of AF, including a predictive value in relapsed AF.

Methods and Results : ANP and BNP were measured in 100 consecutive patients with AF and without heart dysfunction at baseline and in 20 controls. All patients had higher levels than controls (p<0.01). After cardioversion treatment with antiarrhythmic therapy, 40 patients failed to cardioversion successfully and still showed AF, whereas 60 patients were successful. ANP and BNP levels decreased significantly after cardioversion (163.55±54.27 pg/ml vs. 200.20±55.63 pg/ml; 124.15±43.00 pg/ml vs. 161.99±48.04 pg/ml, for ANP and BNP respectively, both p<0.0001). 18 of the 60 successfully cardioverted patients had AF recurred within 24 hours, who were then excluded from 500-day follow-up and the remaining 42 patients were enrolled. During 500-day follow-up period, AF relapsed in 16 patients. Comparing with the 42 patients, the 16 patients showed higher concentrations of ANP (187.72±32.79 pg/ml vs. 138.42±30.65 pg/ml, p<0.0001). Besides, both ANP and BNP were significantly higher in the relapsed patients than those remained SR during follow-up (153.38±29.61 pg/ml vs. 129.21±27.98 pg/ml for ANP, p=0.01 and 147.41±25.95 pg/ml vs. 121.87±20.53 pg/ml for BNP, p=0.001). The area under the receiver-operating characteristic curve was 0.799 for BNP and 0.706 for ANP in predicting a relapse of AF. Using the BNP optimized cut-off level of 138 pg/ml, relapsed AF can be predicted with relatively acceptable accuracy. Conclusions : ANP and BNP decrease significantly after cardioversion in patients with AF, and both can be useful predictors of relapsed AF.

Key Words : Atrial fibrillation; Cardioversion; ANP; BNP; relapse of atrial fibrillation.

Corresponding Address : Jing-quan Zhong MD, PhD, Department of Cardiology, QiLu Hospital, Shandong University, 107 West Wenhua Road, Jinan, Shandong, 250012, P.R. China.
Atrial fibrillation (AF) is one of the most common arrhythmias, the prevalence in the general populations is estimated to be 0.4% and increases with age.1-2 The risk of stroke and heart failure is associated with AF,3-4 and even more, AF can be an independent risk factor for death in people aged 55 to 64.5 Atrial natriuretic peptide (ANP) is synthesized and secreted mainly in the atrium.6 During AF, atrium enlargement and atrial pressure increase are associated with elevated plasma concentration of ANP,7,8 which may decrease greatly with a return to sinus rhythm (SR)9 and this indicates its active role in AF. Brain NP (BNP), once described as an indicator of ventricular function,10-13 has drawn much attention recently in terms of AF7, 8, 10 Although these two peptides may share some common physiological actions, including natriuresis, vasodilatation, and modulation of central and peripheral baroreflexes,14 their main origins are different, which suggests different roles in AF. In this study, we aimed to examine the levels of ANP and BNP in AF to determine whether they play a comparable role in different types of AF, including a possible predictive value in relapsed AF.

Material and Methods

Study population

The study enrolled 100 consecutive patients with AF, including paroxysmal AF (lasting < 7 days) and persistent AF (lasting ≥7 days) from our institution. The enrollment criteria were (1) clinical symptoms of AF such as palpitation and tiredness and AF revealed by 12-lead electrocardiography and (2) possible association of well-controlled mild to moderate hypertension or stable coronary heart disease. All patients underwent X-ray examination and echocardiogram to exclude severe heart dysfunction or structural heart diseases such as rheumatic heart disease or dilated cardiomyopathy, and according to the New York Heart Association (NYHA) functional classification; diabetes mellitus; hyperthyroidism; cerebrovascular disease; renal dysfunction or any other systemic diseases were also excluded. All patients were given antiarrhythmic drugs (propranolol or amiodarone) to control or eliminate AF, as well as an anticoagulant warfarin or aspirin if contraindicated to warfarin to manage the potential hypercoagulating status, maintaining the international normalized ratio between 1.6 and 2.2. Patients received an electrocardiographic monitor during hospitalization to determine if they returned to SR (successful cardioversion group) or not (permanent AF; permAF group). Successful cardioversion group was defined as patients who returned to SR; and those who maintained SR at least 24h went to SR group. If patients failed to return to SR after cardioversion attempt, they were defined as permanent AF group (permAF group). Twenty healthy people comparable to the study patients in sex and age were recruited as a control group. Patients and controls gave their informed consent to participate, and the study was approved by the ethics committees of Qilu Hospital and Shandong Communication Hospital.

Measurement of ANP and BNP

All patients underwent blood sampling before cardioversion in the morning after having fasted for 12 h and after being supine for at least 30 min; 4 ml of blood sample was drawn from the antecubital vein then distributed into 2 polyethylene tubes and mixed well with 10% EDTA 30 μl and 50 μl of aprotinins. The tubes were then centrifuged at 3,000 rpm for 15 min at 4, and plasma was stored at -70. Blood sample was obtained using the same method immediately after cardioversion within 24 h. Plasma ANP and BNP levels were measured by enzyme-linked immunosorbent assay (ELISA) with commercially available kits (BPB Biomedicals, Inc., USA), which had a sensitivity of 0.5 pg/ml for ANP and 1.0 pg/ml for BNP, and with inter-and intra-assay coefficients of variation of <6% and <13%, respectively, for ANP and <2.0% and <4.2%, respectively, for BNP. The normal reference values for plasma ANP and BNP concentrations are <120 pg/ml and <90 pg/ml, respectively.

Follow-up

Patients in the SR group who maintained SR at least 24h after cardioversion (n=42) were followed up for 500 days after discharge. During this period, patients were interviewed by telephone.
every 2 weeks or asked to come to the clinic to undergo scheduled electrocardiography every 2 weeks, when convenient. Those who complained of symptoms of AF (reAF group) or any other discomforts were told to contact their doctor as soon as possible; the exact time of onset of the relapsed AF was recorded, and patients underwent 12-lead electrocardiography to confirm the recurrence of AF and echocardiography to measure left atrial diameters. Blood samples were taken for measurement of ANP and BNP levels within 24 h after cardioversion, or at the end of the follow-up period.

Echocardiography

Transthoracic 2-D echocardiography involved use of a GE system Model 5 Color Doppler Ultrasound (PHILIPS7500, California, USA) with the changeable transducer frequency from 2.25 to 5.5 MHz, to compare the SR group and reAF group at 500-day follow-up. Left atrial diameters were measured in the left-ventricular long axial view.

Statistical analysis

Continuous values were expressed as mean±SD and compared by ANOVA with Student-New man-Keuls test. Multiple Coxes, proportional hazard regression model was used to identify determinants associated with risk of relapsed AF with 6 variables (age, left-atrium diameter, ANP and BNP concentration before or after cardioversion). ANP and BNP levels at baseline were examined by receiver-operating characteristic curve (ROC) analysis as predictors of relapsed AF in the successful cardioversion group; the areas under the curve (AUC) from the ROC curve were calculated, and the preferred cut-off values that provided the optimal test accuracy were derived from the ROC curve. The cumulative recurrence-free rates of all patients in the successful cardioversion group during follow-up were calculated by both Kaplan Meier and life table methods. A P<0.01 was considered statistically significant, and statistical analysis involved use of SAS 9.1 (SAS Inst., Cary, NC, USA).

Results

Patient characteristics

The characteristics of patients in different AF groups at baseline are shown in [Table 1]. All 100 patients were free of heart dysfunction (NYHA Class I). Groups did not differ by age or sex. Some patients in the successful cardioversion, permAF, SR, and reAF groups may have had cardiovascular risk factors (coronary heart disease or hypertension), but groups did not significantly differ in these factors. Groups were comparable in both systolic and diastolic blood pressure and heart rate.

Comparison of ANP and BNP levels in AF groups

As compared with the control group, ANP level was higher in all patients with AF, whether in the permAF group (175.53pg/ml±33.09 pg/ml vs. 110.06 pg/ml±29.82pg/ml, p<0.01) or successful cardioversion group (200.20 pg/ml±55.63 pg/ml vs. 110.06 pg/ml±29.82 pg/ml, p<0.01) than con-

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<tr>
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<td>Diastolic blood pressure (mmHg)</td>
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<td>Heart rate (beats/min)</td>
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<tr>
<td>Cardiovascular risk factors (%)</td>
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<td>Hyper tension</td>
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controls before cardioversion. The permAF group showed a relatively steady, high ANP concentration, which was significantly lower than that for the successful cardioversion group before cardioversion (175.53±33.09 pg/ml vs. 200.20±55.63 pg/ml, p<0.01). However, the ANP level became comparable after cardioversion (200.20±55.63 pg/ml vs. 163.55±54.27 pg/ml, p=NS), because the concentration of ANP in the successful cardioversion group decreased significantly after cardioversion (200.20±55.63 pg/ml vs. 163.55±54.27 pg/ml, p<0.01) [Table 2, Figure 1].

The analysis of BNP level showed almost the same characteristics as those for ANP: both the permAF and successful cardioversion group showed a higher level of BNP than the control group (158.76±33.99 pg/ml vs. 161.99±48.04 pg/ml, p<0.01) before cardioversion attempt, and the cardioversion group showed a significant decline in BNP level after cardioversion (161.99±48.04 pg/ml vs. 124.15±43.00 pg/ml, p<0.01). However, the BNP level was similar in the permAF and successful cardioversion groups before cardioversion (158.76±33.99 pg/ml vs. 161.99±48.04 pg/ml, p=NS) but differed significantly after cardioversion (158.76±33.99 pg/ml vs. 124.15±43.00 pg/ml, p<0.01) [Table 2, Figure 2].

Follow-up and predictors of relapsed AF

During the 500-day follow-up, 16 patients in the SR group (n=42) experienced AF relapse (reAF group) and the rest of the 26 patients remained SR at the end of follow-up period. ANP and BNP values before cardioversion were re-analyzed, and a lower concentration for both ANP and BNP in the SR group than in the reAF group (138.42±30.65 pg/ml vs. 187.72±32.79 pg/ml; 131.60±25.71 pg/ml vs. 179.56±24.43 pg/ml, respectively, both p<0.01) had been observed [Table 3, Figure 3].

Concentrations of ANP and BNP before cardioversion, as well as patients' age, left-atrial diameter, and concentrations of ANP and BNP after cardioversion were investigated as potential predictors of relapsed AF. Patients with (n=16) or without (n=26) recurrence of AF did not differ in age or left-atrial diameter.
The ANP and BNP levels were checked within 24 hours of relapsed AF or at the end of the follow-up period if the patient remained SR. Patients with relapsed AF showed higher levels of ANP (153.38±29.61pg/ml vs. 129.21±27.98pg/ml, p=0.0112) and BNP (147.41±25.95pg/ml vs. 121.87±20.53pg/ml, p=0.0010) than those who remained SR [Table 4].

Multiple Coxes, proportional-hazard regression analysis revealed that concentration of ANP and BNP before or after cardioversion predicted relapsed AF well by univariate analysis. On stepwise multivariate analysis, only ANP and BNP before cardioversion were independent risk factors of AF recurrence: with each unit increase in BNP, the probability of relapsed AF would increase by 3.4%, when controlling for level of ANP (β=0.00335, relative risk=1.034, 95% confidence interval (CI) 1.013–1.055). With each unit increase in ANP, the probability would increase by 2.6%, when controlling for BNP (β=0.0255, relative risk=1.026, 95% CI 1.004–1.048).

The AUC of the ROC curve for baseline ANP and BNP as predictors of relapsed AF were 0.706 and 0.799, respectively [Figure 4]. From the ROC analysis, 139 pg/ml for ANP and 138 pg/ml for BNP were calculated as cut-off values of optimal test accuracy for predicting relapsed AF. Applying the optimized cut-off value for ANP revealed a sensitivity of 68.75%, a specificity of 66.15%, a positive predictive value of 44% and a negative predictive value of 70.59%. Applying the optimized cut-off value for BNP revealed a sensitivity of 68.75%, a specificity of 70.08%, a positive predictive value of 61.11% and a negative predictive value of 79.17%, which indicates that BNP is a more effective predictor of relapsed AF.

The cumulative rates of non-recurrence of AF for all patients in the successful cardioversion group during follow-up were calculated by both the Kaplan-meier and life table methods. The 100-, 200-, 300- and 500-day AF non-recurrence rates were 95.24±3.29%, 88.1±5.0%, 78.57±6.33%, 69.05±7.13% and 61.9±7.49%, respectively. With the Kaplan-meier analysis, patients with ANP<139 pg/ml or BNP<138 pg/ml retained SR more so than...
patients with higher levels (p=0.003 and p=0.002, respectively).

Discussion

Disagreement of ANP and BNP in AF

Previous studies have demonstrated that the atrium may increase its synthesis and secretion of ANP during an AF episode in association with atrial stretching, and the level decreases immediately after successful cardioversion. In contrast, during prolonged AF, ANP level may not be increased because of failure of the atrial productive capacity with structural atrial damage. However, most of these studies included subjects with underlying structural heart disease that may have biased the results. Patrick and associates studied level of pro-ANP in patients with AF alone and found no significant increase in pro-ANP level. Since pro-ANP and active ANP are released equally, we measured ANP level among different AF groups after AF. Although both the permAF and successful cardioversion groups showed elevated levels of ANP at baseline comparing with controls, the successful cardioversion group showed a higher ANP level than the permAF group before cardioversion, which sustained a steady but relatively moderate range of ANP even after cardioversion. Van Den Berg and colleagues ascribed a sustained level of ANP to an impaired ability of the atria to produce ANP because of degenerative changes; however, unlike the authors’ patients, none of our patients had congestive heart failure. So we cannot conclude that our findings of low ANP level in the permAF group are due to degenerative atrial change resulting in lower ANP secretion. ANP level seemed more vulnerable to the fluctuation of heart rhythm, specifically, the shift from normal to abnormal or the reverse, so that when the rhythm remained steady, even in AF, a relatively low level would be obtained.

The level of ANP in AF remains controversial, as does the level of BNP. Rossi reported that BNP was not independently associated with AF and was strongly determined by left-ventricular dysfunction, for which it was an independent marker. However, Nakamura and other researchers showed BNP level elevated in AF patients. Nevertheless, when AF is restored to SR, BNP showing a significant decrease has gained wide attention. However, all of these study cohorts featured cardiac conditions associated with heart failure, which have been confirmed to be related to elevated BNP that would inevitably affect AF itself. All patients in the present study had AF alone. So in contrast to ANP level, BNP level did not differ between the permAF and successful cardioversion group at baseline, which agrees with previous findings implicating diverse reactions in the two NPs in AF. BNP may have much to do with AF itself or may be more coincidental with AF but can be an useful indicator of AF, whereas ANP represents the atrium status well; it can be an useful indicator of different types of AF and its severity. Further investigation of AF alone will help clarify the exact relations of the NPs with AF and explore their roles in this process.

Predictive value of ANP and BNP

The values of NPs in predicting relapse of AF are debated. Researchers have found NPs to be predictors of relapsed AF. A 1-year follow-up study of 71 AF patients with mild heart failure who then underwent direct-current cardioversion concluded that a high level of BNP together with a low level of ANP before cardioversion were risk factors of relapsed AF in patients with congestive heart failure. As well, poor response of ANP after exercise was a risk factor of relapsed AF after direct cardioversion. However, in all types of AF, as well as paroxysmal AF, the level of BNP might not assess severity or probability to relapse well. The diversity in findings suggests that AF has diverse intrinsic properties, so prediction is difficult. In the present study, concentrations of ANP and BNP in patients with AF alone were both significantly higher in the reAF group than in the SR group before or after cardioversion. In applying the optimized cut-off value of 138 pg/ml, the measurement of BNP provided a sensitivity of 68.75% and a specificity of 73.08% in predicting relapse of AF, which were specific than those for ANP; from Kaplan-Meier analysis, in patients with a BNP<138 pg/ml, the SR sustained rate would be higher than patients with higher BNP (p=0.002).

In conclusion, this study has revealed that the concentrations of ANP and BNP rose markedly during the onset of AF and then decreased after cardioversion but not to baseline levels. The level of ANP and BNP before and after cardioversion...
can predict the outcome of AF; a level above the cut-off value may help to confirm the probability of relapsed AF.

Clinical implication

AF is a threatening disease, with mortality 2 times higher in AF patients than those with SR.\textsuperscript{39-46} It is also a costly disease, in terms of not only money\textsuperscript{51-52} but also quality of life.\textsuperscript{43} The earlier the atrium returns to SR the better the benefit. With the simple measurements of ANP and BNP and determination of their relationship at the first cardioversion, we may assess the severity of AF and the status of the atrium. Furthermore, applying a cut-off value of BNP may help distinguish AF that could be refractory to antiarrhythmic drug therapy and help in considering early direct-current cardioversion or ablation therapy.

Study limitations

AF is associated well with age: its prevalence and severity are increased in elderly people. Therefore, assessments of ANP and BNP should be viewed in terms of age categories. In our study, patients’ ages were in a relatively small range, which may not represent all types of AF and thus prevents generalization of results to a wider population. However, the age range in the present study was typical for AF, and the results may still help in understanding the relation between NPs and AF and their roles in predicting relapsed AF. As well, our study has the limitation of any small case-series study; the reAF group especially contained only 16 patients. Thus, the results need further investigation in a larger cohort of patients for definitive conclusions.

Acknowledgements

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References

C-Reactive Protein and the risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis.

Venkata M Alla MD, Senthil Thambidorai MD, Kishlay Anand MD, MS, Aryan N Mooss MD, Richard Baltaro MD, Syed M Mohiuddin MD.

Abstract

There is increasing evidence linking C-reactive protein (CRP) and atrial fibrillation (AF). Despite the abundance of literature, confusion exists regarding this association because of inconsistent results. MEDLINE and Cochrane Controlled Trials Register databases were carefully searched through July, 2009 combining the following terms “C-reactive protein” and “atrial fibrillation”. Reference lists of selected articles and reviews were also screened to identify additional relevant studies. Of the 129 studies initially identified, 8 studies with 7507 subjects (719 with AF) were included in the meta-analysis. Analysis yielded a relative risk of 1.63 (1.43, 1.86) for occurrence of AF when CRP level was above a cut off of 3-3.5 mg/l. When 3 studies with data on a higher cut off of 4.5-5.0 mg/l were analyzed separately, the relative risk was 4.03 (3.1, 5.25). Our study suggests that elevated CRP is associated with increased risk for AF. The risk appears incremental with higher CRP levels conferring proportionately increased risk. There is an urgent need for further large scale, well designed prospective studies to assess the relationship between CRP and AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in everyday clinical practice and affects approximately 0.9% of the general population. It is associated with significant cardiovascular morbidity and mortality and also has an adverse impact on the quality of life. The prevalence of AF increases with increasing age. With the demographic curve leaning towards the elderly, the burden imposed by this disease on healthcare systems across the western world is expected to increase significantly. It is therefore imperative to devise new ways to prevent, detect and treat this condition. There is growing evidence linking inflammation to a variety of cardiovascular diseases. C-reactive protein (CRP) is an excellent marker of inflammation and has been linked to the pathogenesis and prognosis in patients with coronary artery disease, congestive heart failure, AF, myocarditis and aortic valve disease. The increasing body of evidence linking CRP and AF has opened a new door of opportunity in our understanding of AF and will potentially lead to new ways of managing this common problem. The association between CRP and AF has been demonstrated in various settings and has been previously reviewed. The aim of this study is to systematically review published data on the association between CRP and AF and study the strength of this association. We used a meta-analytic approach to estimate the relative risk of AF associated with elevated CRP.
Methods

Literature Search

MEDLINE and Cochrane Controlled Trials Register databases were carefully searched through July, 2009 combining the following terms “C-reactive protein” and “Atrial Fibrillation”. One of the authors (V.A) screened the studies for potential inclusion. Reference lists of the identified reports, reviews and letters were also screened to include potentially relevant studies. Studies were selected for further review after letters, reviews and irrelevant articles were excluded from the search results [flow sheet in Figure 1]. The manuscripts of the short listed studies were then separately reviewed by two of the authors (V.A, S.T) for inclusion in the systematic review. Studies which fulfilled the following criteria were included for systematic review. 1. Availability of baseline CRP levels. 2. Availability of duration of follow up 3. Exclusion of atrial arrhythmias other than AF. 4. AF diagnosed by a physician based on EKG or telemetry strip, or by coded diagnosis of AF (ICD-9) on discharge records. 5. Availability of the absolute number of subjects with AF in the high and low CRP groups, and CRP cut offs. 6. CRP measurement using high sensitive assay. 7. Quality score ≥ 7. The quality of the selected studies was assessed using the Newcastle-Ottawa quality assessment scale. Discrepancies were resolved by consensus after review by the third author (K.A). If more than one study from the same authors fulfilled the inclusion criteria, the larger of the two was included in the review so as to avoid duplication of data sets.

Data Extraction

Using a standardized data extraction form the two authors extracted the following data from each of the eligible studies: first author, citation, year of publication, study population, study design, ascertainment of AF, method of CRP assay, baseline CRP distribution, CRP cut off, number of subjects in the high and low CRP groups, incidence or prevalence of AF in the high and low CRP groups, relative risk for AF based on CRP level, adjusted covariates and brief results. A CRP value of 3mg/l was empirically chosen for stratification into high and low CRP groups based on the AHA statement on CRP and increased risk of cardiovascular dis-

Figure 1: Flow diagram of study identification and selection
ease. From among the studies selected for systematic review, those in which high and low CRP groups could be stratified into a combinable format (CRP cut off close to 3 mg/l) were included in the final meta-analysis. Letters were mailed to the authors regarding the above details when the same were not available in the manuscript.

**Statistical Analysis**

The absolute number of subjects who developed AF in the high and low CRP groups, and the total number of subjects in each group were obtained for each individual study and the pooled data was used to obtain the cumulative relative risk. Meta-analysis was performed adhering to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Analyses were conducted based on intention to treat principle. Each study was considered as a single stratum. We obtained the pooled relative risks with 95% confidence interval (CI) for development of AF using the random effects model of Der Simonian and Laird. Random effects model was preferred over fixed effects model because of the significant heterogeneity between the included trials. We performed an influence analysis and assessed the influence of individual studies on the summary effect estimate. A funnel plot was also done to look for any publication bias in the studies. All statistical analyses were performed using Stata 9.0 (Stata Corporation, College Station, TX).

**Results**

The literature search yielded 129 potentially relevant studies. 84 of these were excluded after scrutiny of the abstract because they were letters, replies, reviews or irrelevant. Manuscripts of the

<table>
<thead>
<tr>
<th>Author / year</th>
<th>Study group</th>
<th>N</th>
<th>Type of AF/ Ascertainment</th>
<th>CRP assay</th>
<th>Cut offs</th>
<th>RR (CI)</th>
<th>Qual. score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aviles 2003</td>
<td>Random Patients from Medicare &gt; 65 yrs.</td>
<td>5806</td>
<td>Prevalent AF / EKG or discharge diagnosis</td>
<td>ELISA</td>
<td>3.4 mg/l</td>
<td>1.31 (1.08-1.58)</td>
<td>9</td>
</tr>
<tr>
<td>Bernard Lo 2005</td>
<td>Patients of stable angina undergoing CABG.</td>
<td>152</td>
<td>Post CABG AF / EKG or Telemetry.</td>
<td>Immunonephelometry</td>
<td>3.0 mg/l</td>
<td>3.3 (1.4-7.6)</td>
<td>8</td>
</tr>
<tr>
<td>Dernellis J. 2006 §</td>
<td>Healthy subjects in sinus rhythm.</td>
<td>1011</td>
<td>Incident AF / EKG or Holter.</td>
<td>Immuno turbidometry</td>
<td>4.85 mg/l</td>
<td>1.1 (1.0-1.4)</td>
<td>9</td>
</tr>
<tr>
<td>Hogue 2006 §</td>
<td>Women &gt; 55 years undergoing open heart surgery.</td>
<td>130</td>
<td>Post Cardiac surgery AF / EKG or Telemetry.</td>
<td>Immuno nephelometry</td>
<td>19.2 mg/l</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Kotsakaou. 2006 ¶</td>
<td>1st paroxysm of Lone AF.</td>
<td>125</td>
<td>Recurrent AF / EKG</td>
<td>Immunoassay</td>
<td>4.9 mg/l</td>
<td>1.15 (1.04-1.24)</td>
<td>8</td>
</tr>
<tr>
<td>Loricchio 2007</td>
<td>Cardiverted patients of Persistent AF</td>
<td>102</td>
<td>Post cardioversion AF / EKG, Holter</td>
<td>Immunoturbidometry</td>
<td>1.9 mg/l</td>
<td>4.98 (1.75-14.26)</td>
<td>9</td>
</tr>
<tr>
<td>Watanabe 2006 ¶</td>
<td>Persistent AF successfully cardioverted</td>
<td>84</td>
<td>Post cardioversion AF / EKG or Holter.</td>
<td>Latex nephelometry</td>
<td>0.6 mg/l</td>
<td>5.3 (2.46-115)</td>
<td>7</td>
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<tr>
<td>Wazni 2005</td>
<td>Cardiverted patients of Persistent AF</td>
<td>111</td>
<td>Post cardioversion AF / EKG</td>
<td>Immunonephelometry</td>
<td>3.09 mg/l</td>
<td>2.0 (1.2-3.2)</td>
<td>8</td>
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<tr>
<td>Zarauza J 2006</td>
<td>Cardiverted patients of Persistent AF</td>
<td>37</td>
<td>Post cardioversion AF / EKG</td>
<td>ELISA</td>
<td>3 mg/l</td>
<td>45.9 (1.3-1600)</td>
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<tr>
<td>Mazza A 2009</td>
<td>Cardiverted patients of Persistent AF</td>
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<td>Post cardioversion AF / EKG</td>
<td>Immunonephelometry</td>
<td>3 mg/l</td>
<td>1.47 (1.05-2.06)</td>
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<tr>
<td>Korantzo-poulos 2008 ¶</td>
<td>Cardiverted patients of Persistent AF</td>
<td>60</td>
<td>Post cardioversion AF / EKG</td>
<td>Immunonephelometry</td>
<td>4.3mg/l</td>
<td>6.3 (3.1-12.7)</td>
<td>8</td>
</tr>
</tbody>
</table>

¶ Not included in the final meta-analysis. § Studies reporting no association between CRP and AF. RR=relative risk; CI= confidence interval; CRP=C-reactive protein; EKG=electrocardiogram; CABG=coronary artery bypass grafting; ACS=acute coronary syndrome; CAD= coronary artery disease.
remaining 45 were reviewed separately by two of the authors (V.A, S.T). 34 more were subsequently excluded as they did not meet the inclusion criteria and the remaining 11 were selected for systematic review.\textsuperscript{10,20} The concise detail of these studies is shown in [Table 1]. Of these, only 8 studies in which absolute numbers (of subjects at risk for AF and subjects with AF) for a CRP cut off of around 3 mg/l could be obtained were included in the final meta-analysis.\textsuperscript{10-13, 15, 17-19} The 8 studies included 7507 subjects of which 719 had AF. Of these, one study (n=5806) pertained to prevalent AF in patients enrolled in a Cardiovascular study registry \textsuperscript{10}, 2 studies (n=282) dealt with post cardiac surgery AF,\textsuperscript{11, 13} one (n=1011) pertained to incident AF in normal healthy adults and the remaining 4 studies (n=408) pertained to AF recurrence after successful cardioversion.\textsuperscript{15,17-19} The mean age of the study populations varied between 45-70 and males constituted 50-75%.

Meta-analysis of the 8 studies yielded a relative risk of 1.63 (1.43, 1.86) for occurrence of AF when CRP was elevated above 3-3.5 mg/l [figure 2]. In an influence analysis, none of the individual studies had an overwhelming effect on the summary effect estimate and it remained relatively stable and significant on excluding one study at a time. There was no publication bias observed on the funnel plot [figure 3] and Egger’s weighted regression method p-value was 0.20. Three of the studies selected for review were not included in the final meta-analyses as the cut off CRP used was quite dissimilar.\textsuperscript{14, 16, 20} The studies by Korantzopoulos et al\textsuperscript{20} and Kotsakaou et al\textsuperscript{14} used CRP cutoffs of 4.3 and 4.9 mg/l respectively. Secondary analysis using the data from these studies and that from Dernellis et al,\textsuperscript{12} where numbers for a similar CRP cut off (4.85 mg/l) were available, yielded a relative risk of 4.03 (3.1, 5.25) for AF [Figure 4].

**Review of studies**

Two of the 11 studies selected for systematic review accounting for 1141 subjects reported lack of independent association between CRP and AF.\textsuperscript{12,13}
In the study by Dernellis et al, elevated CRP was predictive of AF only in the presence of concomitant elevation of complement. The poor ability of CRP in predicting incident AF in this study was probably due to the low risk population studied (relatively young, exclusion of those with CAD, CHF or other heart diseases). Additionally, measuring downstream products of inflammation (complement components) could have led to underestimation of the association between CRP and AF in this study. It is known that women have more elevations in inflammatory markers at baseline. This might have been a potential reason for the poor predictive value of CRP in the study by Hogue et al, which was done in a small and select group of women (post menopausal women > 55 years of age undergoing cardiac surgery). Further studies evaluating the sex specific limitations in the utility and applications of CRP are therefore warranted.

The 5 studies that addressed recurrent AF following electrical cardioversion were limited by their observational design, lack of uniformity in the study population, follow up, and their small size. In the study by Aviles et al, elevated CRP was predictive of both prevalent and incident AF. Watanabe et al used a CRP cutoff of 0.6 mg/l (falls into low risk category by AHA definition) and demonstrated a relative risk of 5.3 for post cardioversion AF recurrence. This was included neither in the primary nor the secondary analysis because of the extremely low cut off used (which was very dissimilar to most other studies). It is well known that the median CRP level in healthy Japanese and Chinese subjects is much lower compared to their western counterparts. The high risk of AF despite relatively low CRP levels in Asian populations could be related to differences in body mass index and genetic constitution which alter inflammatory response and CRP levels.

Discussion

The pathophysiology of AF is complex and to date is not completely understood. It is now known that pulmonary veins serve a crucial role in the initiation of this arrhythmia. Once initiated, AF sets in motion a process of self-propagation through electrical, biophysical and structural remodeling of the atria. There is a strong association between AF and inflammation. Numerous serum markers of inflammation like TNF α, IL-6, leukocyte count and CRP have been shown to be elevated in AF. It is known that AF and inflammation alter myocardial energy kinetics and increase oxidative stress which can further perpetuate the arrhythmia. In addition, CRP leads to complement activation and tissue damage locally in the atrial myocardium further increasing the substrate for AF. Moreover, CRP levels progressively increase with increasing AF burden but it is unclear whether inflammation is a cause or consequence of AF. Some investigators have shown that anti-inflammatory therapy reduces recurrences of AF with parallel reductions in CRP suggesting a pos-
sible cause effect relationship. However, this remains unproven.

The present systematic review and meta-analysis supports the strong association between elevated CRP and occurrence of AF across a variety of clinical settings. Moreover, our study suggests possible incremental relationship with higher CRP levels conferring a relatively higher risk of AF. It is important to bear in mind a number of limitations while interpreting and applying results of metaanalyses. The potential for publication bias against negative studies and small studies is the foremost concern. This might have caused our study to overestimate the risk attributable to elevated CRP. Thirteen out of the 45 studies initially selected for review, showed no independent association between AF and CRP. Only 2 of these 13 studies met the inclusion criteria. On the other hand, 32 out of the 45 studies reported a significant independent association between CRP and AF and 11 of these met the inclusion criteria. It is apparent that publication bias against negative studies would not have a major impact on our study as more than a third of the reviewed studies reported no association between CRP and AF. In addition, both Beggs’s Funnel plot and Eggers test did not reveal any effect of publication bias on our results. However, a potential shortcoming of our study could be the inclusion of more studies reporting a positive result in the final analysis. Of note, a majority of the negative studies that were excluded were small and poorly designed. On the other hand, the studies that reported a positive association had to be excluded because of lack of absolute numbers in the high and low CRP groups or absolute values for CRP cut off despite better design and higher numbers. Thus, with the relatively small number of subjects in the excluded negative studies, it is unlikely that we would have erroneously detected an association between CRP and AF in the true absence of one.

Another major concern would be the issue of bias. As with any study on AF, all the studies in our analysis had a propensity for ascertainment bias because the follow up for AF was periodic and not continuous. Additionally, despite adjustment for confounding factors like coronary artery disease, hypertension, diabetes, heart failure, age and smoking status by the individual investigators, residual confounding cannot be excluded. The lack of original data from the included trials precluded our ability to perform a logistic regression analysis to independently assess the effects of these confounders. Moreover, it is both impractical and impossible to adjust for the confounding effects of the innumerable inflammatory markers and cytokines; leaving enormous scope for ‘residual confounding’. Other potential limitations of our analysis are exclusion of studies not published in English, wide variation in the study populations and the heterogeneity of CRP assay among the individual studies. All of these inherent problems adversely influence the applicability of the results and make it difficult to make general conclusions regarding the relation between CRP and AF. Finally, all the included studies utilized single measurements of CRP for stratification; whereas, it is
generally recommended that for improved specificity, CRP be measured at least 2 different times (2 weeks apart) when being used for risk assessment of cardiovascular diseases. Only a small number of patients with elevated CRP have AF and not all patients with AF have elevated CRP. Thus, the lack of specificity limits the general applicability of CRP in predicting the presence or the occurrence of AF. As in the case of coronary artery disease where CRP measurement is best used for further risk stratification of patients at intermediate risk, it is imperative to identify appropriate populations for CRP testing in the context of AF. Review of literature supports a potential role for CRP testing in the following scenarios. In patients with a prior history of AF, CRP can help discriminate between those who will and will not have a recurrence and identify patients at a higher risk for complications like embolism. CRP testing can potentially identify patients at risk for developing postoperative AF and AF following acute myocardial infarction. In addition, recent data suggests that CRP can predict recurrence of AF following the first episode of paroxysmal AF, success of cardioversion for persistent AF and recurrent AF following successful cardioversion. In our study, secondary analysis using studies that addressed postcardioversion AF recurrence [15, 17-19] yielded a relative risk of 1.49 (1.23, 1.79) for AF recurrence when CRP was >3-3.5 mg/L. This is consistent with the findings of previously published studies assessing the association between CRP and AF recurrence following cardioversion. Thus, CRP has the potential to be an invaluable tool in identifying patients who would require increased surveillance and serve as a guide to determine the intensity of treatment and follow up.

Conclusions

Overall the evidence linking elevated CRP and AF is robust and the strength of association is strong. There is fair consistency in the data supporting this association and there seems to be an incremental relationship with higher CRP levels conferring proportionately increased risk. Elevated CRP (usually above 3.0-3.5 mg/L) is associated with about 1.6 times increased risk of AF compared to CRP < 3 mg/L. The major limitation in the clinical utility of CRP is its poor specificity (as it could be elevated in multiple other disease states). The potential benefit of CRP lies in our ability to use it in selected groups of patients at risk for AF (heart failure, acute myocardial infarction) and in specific settings like post operative state, post cardioversion etc. The importance of using the mean value of CRP measurements made over time as opposed to single measurements should be emphasized and encouraged. There is therefore, a pressing need for further large and well designed prospective studies to test the association of CRP with AF and its utility in clinical practice.

References


Dabigatran, a direct thrombin inhibitor, in atrial fibrillation: Is it already time for a change in oral anticoagulation therapy?

Osmar Antonio Centurión, MD, PhD, FACC.

Division of Electrophysiology and Arrhythmias, Cardiovascular Institute, Sanatorio Migone-Battilana, Asunción, Paraguay. Departamento de Cardiología. Primera Cátedra de Clínica Médica. Universidad Nacional de Asunción.

Introduction

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence increases with aging and the severity of heart disease. AF affects more than 2 million people in the US, and more than 4 million in Europe. It is expected that the age adjusted prevalence in US will exceed 10 million people by the year 2050. In the last decade, we were able to see the light shed by several trials that dealt with AF mechanisms and the appropriate management of AF patients. Clinical studies have focused mainly on the electrophysiological properties of the substrate in the atrial muscle during sinus rhythm and on the atrial electrical responses elicited by premature stimulation method. However, many fundamental aspects of this arrhythmia have been poorly understood until quite recently, and there are several features on the mechanisms of AF that makes it difficult to manage it properly. Increasing awareness of AF as a disease with possible fatal complications rather than as an acceptable alternative to sinus rhythm has led to search for clear arguments to support a certain strategy as a golden standard.

There is no atrial contraction during AF, a situation that renders the pooled blood inside the atrium susceptible to develop thrombus formation particularly in the left atrium. AF increases the overall risk of stroke five-fold, and is associated with particularly severe strokes. About 76% of AF patients have a moderate to high risk of embolic complications, and they have also a significant risk factor for stroke recurrence. It looks very clear that all the difficulties we have to face in finding proper answer to its therapeutic management. Vitamin K antagonist drugs, such as warfarin and acenocumarol, reduce the risk of AF-related stroke by about 70%. They are the only oral anticoagulants currently recommended for the prevention of stroke in patients with a moderate to high risk of stroke. These pharmacological agents produce their anticoagulant effect by preventing the γ-carboxylation of the vitamin K-dependent coagulation factors prothrombin and Factors VII, IX, and X. Despite the good clinical results obtained with these oral anticoagulants that are far from being ideal, there are some inconvenient factors which make their conventional use difficult to implement and follow. There is a consistent suboptimal utilization of oral anticoagulation therapy. Warfarin is prescribed to only two thirds of appropriate candidates despite guidelines recommendations. The narrow therapeutic window in the anticoagulation process makes it necessary to monitor closely the prothrombin time. Insufficient
Anticoagulation may result in embolic complications, while over-anticoagulation increases the risk of bleeding. There are also other disadvantages related to the unpredictable pharmacokinetics and pharmacodynamics of these oral anticoagulants, which are affected by genetic factors, drug to drug interactions, and consumption of foods containing vitamin K. Therefore, it is paramount that a regular coagulation monitoring and dose adjustment is necessary to ensure adequate anticoagulation. This fact leads to high rates of discontinuation of therapy, and many patients remaining on therapy have also inadequate anticoagulation. Another important issue is the concern about real-world effectiveness which was found to be around 35%. It is clear to see that there is a great need of new oral anticoagulants for stroke prevention in patients with AF.

**The RE-LY trial design and outcome**

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a large, multicenter, randomized trial designed to compare two fixed doses of dabigatran (110 mg and 150 mg), each administered in a blinded manner, with openlabel use of warfarin in AF patients who were at increased risk for stroke. Patients recruited from 951 clinical centers in 44 countries were eligible if they had documented AF on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Exclusion criteria are detailed in [Table 2]. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly.

The primary study outcome was stroke or systemic embolism. The primary safety outcome was major hemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Other outcomes were myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization. The primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. A total of 18,113 patients were enrolled. The three treatment groups were well balanced with respect to baseline characteristics. The mean age of the patients was 71 years, and 64% were men. Half the patients had received long-term therapy with vitamin K antagonists. The mean CHADS2 score was 2.1. The rate of the primary outcome was significantly lower with

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of an ideal anticoagulant for long-term use in AF</th>
</tr>
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<tbody>
<tr>
<td>1. Oral administration.</td>
<td></td>
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<tr>
<td>2. Predictable pharmacokinetics.</td>
<td></td>
</tr>
<tr>
<td>3. Predictable pharmacodynamics.</td>
<td></td>
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<tr>
<td>4. Low propensity for food and drug interactions.</td>
<td></td>
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<tr>
<td>5. Administration of fixed doses.</td>
<td></td>
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<tr>
<td>6. Wide therapeutic window.</td>
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<tr>
<td>7. No necessity for regular monitoring.</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Exclusion criteria in the RE-LY trial</th>
</tr>
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<tbody>
<tr>
<td>1. Presence of a severe heart-valve disorder.</td>
<td></td>
</tr>
<tr>
<td>2. Stroke within 14 days.</td>
<td></td>
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<tr>
<td>3. Severe stroke within 6 months before screening.</td>
<td></td>
</tr>
<tr>
<td>4. A condition that increased the risk of hemorrhage.</td>
<td></td>
</tr>
<tr>
<td>5. Creatinine clearance of less than 30 ml per minute.</td>
<td></td>
</tr>
<tr>
<td>6. Active liver disease.</td>
<td></td>
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<tr>
<td>7. Pregnancy.</td>
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dabigatran at a dose of 150 mg twice daily (1.11% per year) than with either dabigatran at a dose of 110 mg twice daily (1.53% per year) or warfarin (1.69% per year). Both doses of dabigatran were noninferior to warfarin (p<0.001), and the higher dose of dabigatran was even superior to warfarin (p<0.001). The rate of non-hemorrhagic stroke was also significantly lower with 150 mg of dabigatran (0.92% per year) than with either 110 mg of dabigatran (1.34% per year) or warfarin (1.20% per year). The rates per year of hemorrhagic stroke with the 110-mg and 150-mg dabigatran doses (0.12% and 0.10%) were significantly lower than that with warfarin (0.38%). The rate of extracranial hemorrhage was similar in all three groups: 2.51% with 110 mg of dabigatran, 2.84% with 150 mg of dabigatran, and 2.67% with warfarin.

Other interesting outcomes are as follows: there was no significant difference in the rates of death from any cause, and they were 4.13% per year with warfarin, as compared with 3.75% per year with 110 mg of dabigatran and 3.64% per year with 150 mg of dabigatran. The rate of myocardial infarction was 0.53% per year with warfarin and was higher with dabigatran: 0.72% per year in the 110-mg group (relative risk, 1.35; 95% CI, 0.98 to 1.87; P = 0.07) and 0.74% per year in the 150-mg group (relative risk, 1.38, 95% CI, 1.00 to 1.91; P = 0.048). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.80; 95% CI, 0.69 to 0.93; P = 0.003) and 3.11% per year in the group that received 150 mg of dabigatran. The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia. Hepatotoxicity was investigated in detail in this trial. Elevations in the serum aspartate aminotransferase or alanine aminotransferase level of more than 3 times the upper limit of the normal range did not occur more frequently with dabigatran, at either dose, than with warfarin. Patients requiring hospitalization for a liver disorder was equivalent in the three treatment groups. However, the follow-up period in this trial was only a median of 2.0 years, so the hepatic risks of long-term use are unclear. The hepatotoxicity and safety of the long-term use of dabigatran is being investigated in a follow-up study.

A finding that needs our full attention and should be addressed in a long-term follow-up is the fact that the rate of myocardial infarction was higher with both doses of dabigatran than with warfarin. Therefore, it seems that warfarin provides better protection against coronary ischemic events than dabigatran. Although warfarin was shown to reduce the risk of myocardial infarction, when it was compared to another direct thrombin inhibitor (Ximelagatran) in AF patients, the rates of myocardial infarction were similar. The explanation for this finding of higher rates of myocardial infarction with dabigatran remains therefore uncertain.

Is it time for a change in oral anticoagulation therapy of AF?

A new oral anticoagulant for AF patients which would have similar efficacy and safety as warfarin, in addition to obviate the need for permanent monitoring of blood tests and dosing would incline the scales toward the utilization of the new oral anticoagulant. However, Dabigatran showed more than just similar efficacy compared to warfarin. Both dabigatran doses were noninferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150-mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding. Furthermore, there is no necessity for anticoagulation monitoring neither dose adjustments with dabigatran.

The RE-LY trial is the first large, multicenter, randomized trial that investigated this new oral anticoagulant agent, dabigatran, in AF patients. Therefore, despite the excellent results in efficacy and safety of dabigatran and the superiority shown over warfarin in embolic complications, a class IIB indication can only be given to the use of dabigatran in AF patients at this moment. Results of long-term follow-up and from more trials are needed in order to give dabigatran a class IA indication.

Nevertheless, we have to keep in mind certain issues with the use of dabigatran in AF patients. There was a higher rate of myocardial infarction in AF patients treated with dabigatran. Also, this
direct thrombin inhibitor is not without important drug interactions. It is known that P-glycoprotein inhibitors, such as verapamil, amiodarone, and quinidine, raise dabigatran serum concentrations considerably. This interaction may have contributed to the trend toward greater efficacy of dabigatran in the subgroup of patients taking amiodarone in the RE-LY trial, but it could elevate the risk of hemorrhage in such patients. These issues should be addressed in detail in the long-term follow-up study which is underway.

Coumarins were discovered more than 60 years ago, and for more than 50 years, they have been the sole anticoagulant drugs available to clinicians, and are currently the only oral anticoagulants available. Several new anticoagulants have been introduced, and many more are under clinical development. Dabigatran given at a dose of 150 mg twice daily prevented more strokes than warfarin, and dabigatran at a dose of 110 mg twice daily caused fewer hemorrhagic complications than warfarin. Indeed, dabigatran showed statistical significant superiority compared to warfarin. It is hard to say good-bye to a good friend after more than 50 years of friendship. However, with dabigatran, a new friend around, it may be already time for a change in oral anticoagulant therapy for atrial fibrillation.

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Introduction

Over the past several years pulmonary vein stenosis has emerged as an increasingly uncommon but important complication of pulmonary vein isolation (PVI) to treat atrial fibrillation. Patients manifest dyspnea on exertion, cough, hemoptysis and pleuritic chest pain as the typical symptoms, and it is frequently a life altering condition. Balloon and stent angioplasty have been performed with mixed results, but good long-term patency rates and symptom relief have been achieved when relatively large stents can be used. Despite an extensive body of literature on this condition, routine surveillance is not always performed, leading to delayed intervention and suboptimal outcome. This manuscript will describe the evaluation, treatment and mid to long-term outcome of patients with post ablation pulmonary vein stenosis based on a large experience accumulated in a single institution over the past decade.

Screening for pulmonary vein stenosis after pulmonary vein isolation

The incidence of clinically significant pulmonary vein stenosis has been dramatically reduced since the first patients presented with this complication in the late 1990’s, from about 20% in the early years to 0.4-2% today. Delivery of radiofrequency energy in the antrum rather than the ostium of the pulmonary vein, titration of energy application or use of alternative energy sources, use of intracardiac echocardiography to guide ablations, and image integration of multislice computer tomography performed prior to PVI with electroanatomical mapping during PVI are some of the most important technical advances contributing to the
Recognizing that there is no consensus at this time on routine screening for pulmonary vein stenosis after PVI, we follow a protocol at our institution to ensure that the small number of patients who still develop significant pulmonary vein stenosis is not missed. Imaging is performed 3 months following PVI, and repeated 3 months later only if significant stenosis is detected at the time of the first scan.

Detailed anatomy of the pulmonary veins is best defined by electrocardiographically (ECG)-gated contrast-enhanced multidetector computed tomogram (MDCT) [Figure 1]. Frequently, images are acquired with retrospectively gated helical scanning. However, despite the use of dose modulation, these protocols are associated with higher radiation exposure. Therefore, with recent advances in scanner technology, there is a trend to scanning with prospectively triggered protocols in patients with controlled heart rate. In those patients with fast and irregular heart rate, scanning with spiral non-gated imaging is a good alternative. Images are reconstructed with overlapping 1.00- to 1.25-mm slice thickness for analysis with multiplanar reconstructions, maximal intensity projections, and volume rendered imaging. Semi-automated analysis and display software supports the evaluation of the images.

Figure 1: Multidetector computer tomogram shows relatively long-segment stenosis of the left inferior pulmonary vein. See normal size right superior vein for comparison. (LA = left atrium, LIPV = left inferior pulmonary vein, RSPV = right superior pulmonary vein)

Cardiac MRI is an excellent alternative modality, and avoids exposure to ionizing radiation. It has been used in clinical care and clinical research, but is more expensive (at least in the United States) and time-consuming. Transesophageal echocardiography has been considered as a screening tool also to avoid radiation exposure, but it is not always possible to evaluate each pulmonary vein with 100% sensitivity when compared to MDCT, and it is not possible to evaluate the anatomy in detail if an interventional procedure is necessary.

It should be noted that even the most detailed noninvasive imaging modality, namely MDCT, grossly overestimates total pulmonary vein occlusion. As previously published, only 52% of the veins thought to be totally occluded by MDCT were in fact totally occluded by pulmonary artery wedge angiography, while 48% had a tiny opening that was crossed in every instance allowing intervention.

**Evaluation of the patient with pulmonary vein stenosis: When to intervene**

Referral for further evaluation and possible intervention is based on the presence of symptoms and the severity of stenosis. Clinically significant stenosis that can lead to symptoms typically requires ≥ 60% narrowing of the pulmonary vein, or an absolute stenosis diameter of 4-6 mm for a 10-15 mm vessel, the normal reference diameter of a pulmonary vein. This degree of stenosis has been found to correlate with perfusion defects on quantitative measurements of lung perfusion. It must be kept in mind that not infrequently stenotic veins are also diffusely hypoplastic, with a reference diameter well below that of a normal pulmonary vein. Therefore a 4 mm stenosis might be reported as 50% if the reference diameter is only 8 mm, but it is a clinically significant lesion. The majority of patients with significant stenosis of two or more veins are symptomatic, but patients with severe stenosis of only one pulmonary vein do not always manifest symptoms.

Onset of symptoms has been reported to occur as early as immediately after PVI to nearly a year later, with a median between 7.5 weeks and 14.5 weeks post ablation depending on the series. Nearly half of the patients (44%) with severe stenosis.
nosis of at least one pulmonary vein, defined as ≥ 70% luminal narrowing, has been reported to have no subjective symptoms at the time of diagnosis 5.2 ± 2.6 months after ablation. However, studies with longer term follow-up have found that the majority of these initially asymptomatic patients do in fact develop symptoms as late as 2 years after PVI. The presence of severe stenosis in more than one pulmonary vein is associated with a higher risk of symptoms. Nearly 100% of symptomatic patients complain of dyspnea on exertion, and patients with more than 2 severely stenotic veins may be dyspneic at rest. About half the patients develop a chronic dry cough, and about 25% have recurrent hemoptysis. Pleuritic chest pain in the area corresponding to the affected vein is experienced by about 15% of patients. A small number of patients develop significant pleural effusions, often recurring despite drainage until the pulmonary vein stenosis is relieved [Figure 2].

Figure 2: Chest roentenogram of a patient with total occlusion/complete obliteration of the right superior pulmonary vein and severe stenosis of the right inferior pulmonary vein demonstrates a large right pleural effusion and airspace consolidation. After repeated thoracenteses the right inferior pulmonary vein was stented with resolution of the effusion within 3 weeks.

In a few cases, there is a relatively abrupt presentation with fever, shortness of breath, hemoptysis, with or without a pleural effusion, mimicking the presentation of a pulmonary embolus. The pathophysiology may be similar with pulmonary infarction resulting from relatively acute pulmonary venous obstruction. Several reports of the accompanying histology of post ablation pulmonary vein stenosis have described a pattern of “venoocclusive disease”, interstitial edema and fibrosis, and hemosiderin-laden macrophages within the alveoli consistent with pulmonary hemorrhage. There is likely a varying degree of injury to the pulmonary parenchyma and pulmonary vasculature, not all of which reverses after restoration of pulmonary venous patency.

Patients with no subjective symptoms are sometimes found to have decreased exercise tolerance when tested objectively with metabolic stress testing. It must be remembered that the majority of these patients had either chronic or frequent atrial fibrillation before PVI interfering with their physical performance, and therefore their “normal” subjective baseline may be far from normal. Elimination of the atrial fibrillation results in symptomatic improvement, which may hinder their perception of symptoms arising from pulmonary vein stenosis. We would therefore recommend exercise testing when it is not clear whether or not to recommend intervention. We currently perform metabolic stress testing in all patients undergoing evaluation for possible intervention. Patients who proceed to intervention have a metabolic stress test repeated at the time of their first follow-up, 3-6 months post intervention for smaller stents, and 12 months post intervention for larger stents (see section on followup below). Preliminary data in 14 patients shows a statistically significant improvement in functional capacity with a peak oxygen consumption (VO2) of 20.8 ± 5.3 ml/kg/min before intervention increasing to 26.0 ± 5.8 ml/kg/min at follow-up (p = 0.002).

The functional significance of an anatomic narrowing can be further evaluated by measuring quantitative lung perfusion in each lung quadrant (percentage of flow to the left superior, left inferior, right superior and right inferior quadrants). Although a lung quadrant does not exactly correspond to the anatomic drainage of each pulmonary vein, and there is some degree of patient to patient variability, it is fairly representative in most patients, particularly when there is unilateral pulmonary vein stenosis [Figure 3]. When there is bilateral stenosis the results can be more difficult to interpret, since percentage of flow to any one quadrant is dependant on the amount of flow to all the other areas. However, in those with
bilateral involvement it often does help determine which veins have more functionally important stenosis.

Any symptomatic patient should be considered for intervention. Whether or not patients with no obvious symptoms but severe stenosis of at least one pulmonary vein should undergo intervention remains in question in the absence of sufficient information about their natural history. There is evidence that some of these patients will develop symptoms over the course of time, as exemplified by one patient in our experience who was symptom-free for four years after developing severe stenosis of the left superior pulmonary vein. Four years after PVI he developed intermittent fever, recurrent hemoptysis, dyspnea on exertion, and shifting infiltrates on chest roentgenogram. After extensive and unrevealing investigation for other etiologies he underwent stenting of the left superior pulmonary vein to 10 mm with complete resolution of symptoms within less than a month. Two years later he remains asymptomatic with a widely patent stent. Neumann et al describe 4 initially asymptomatic patients with severe stenosis of a single vein all developing dyspnea by 2 years of follow-up. We do not, however, know what percentage of asymptomatic patients will develop problems over time. We also do not know to what extent a severely stenotic pulmonary vein could exacerbate the clinical course of relatively common cardiopulmonary problems that may arise in previously asymptomatic patients as they age, such as chronic obstructive pulmonary disease, diastolic cardiac dysfunction, or systolic cardiac dysfunction from underlying coronary artery disease.

Another concern in conservative treatment of severe pulmonary vein stenosis is the risk of progression to total occlusion. When this occurs it is not always possible to traverse the occluded segment, precluding percutaneous intervention. There is at this time no reliable way of predicting which severely stenotic veins will totally occlude. Additionally, severely stenotic pulmonary veins have the potential to develop progressive hypoplasia of the entire vein over time with its detrimental effect on outcome should intervention then become necessary, as will be explained below. Our current practice for asymptomatic patients with significant stenosis of at least one vein is to have a frank discussion about what is known and what is yet to be learned. We then make a mutual decision that the patient and the operator feel comfortable with.

**Percutaneous intervention for pulmonary vein stenosis**

When the syndrome of post ablation pulmonary vein stenosis began to appear for the first time in the late 1990’s the only clinical model to draw from in order to guide management was primarily that of congenital pulmonary vein stenosis. Acquired, adult onset pulmonary vein stenosis is seen very rarely in a few conditions such as fibrosing mediastinitis, neoplasm, or sarcoidosis, and management has been reported sparingly, mostly in isolated case reports, with mixed results. The larger experience with congenital pulmonary vein stenosis was fairly dismal with universally high recurrence rates and high mortality with both transcatheter and surgical intervention. In particular, stenting congenitally stenotic pulmonary veins had been essentially abandoned after a handful of studies documented very poor results. With that background in mind, though realizing the pathophysiology was different, we felt we should approach this problem initially in the least invasive manner in the form of balloon angioplasty for significantly symptomatic patients. We quickly encountered high recurrence rates in the order of 70% after balloon dilation, but did observe tempo-
ráry symptom relief before restenosis occurred. We then opted to treat dilation restenosis with stent placement.

**Figure 4**: Time free from restenosis, defined as freedom from reintervention, for stented and balloon dilated veins. (Hazard ratio for balloon dilation 4.2, 95% confidence interval 2.4-7.3, P<0.001).

We continued to see restenosis after stenting, but began to observe that larger stents (≥ 9-10 mm diameter) did not develop restenosis. Unfortunately we were not able to place such large stents in all of the veins, because a significant percentage of these injured veins do not only have discrete stenosis but also diffuse hypoplasia, sometimes with reference diameters as small as 3-5 mm. (It is a known tenet of stent angioplasty work that “over-stenting” a vessel, i.e. placing a stent significantly larger than the reference vessel, leads to a proliferative reaction in the “over-stretched” vessel at the edge of the stent, resulting in edge restenosis and migration of the stenosis further into the vessel). In view of the favorable results obtained with stent placement in veins that maintained a reasonable reference diameter we began to stent primarily any vessel that admitted at least an 8 mm stent. We now have mid to long term follow-up on a large number of stented pulmonary veins, and have confirmed low restenosis rates for stents ≥10 mm, but a significant incidence of in-stent restenosis for smaller stents [Figure 6]. We therefore continue to balloon dilate very hypoplastic vessels (≤ 7 mm), knowing that the majority will develop restenosis. We have observed that after improving flow at least temporarily post dilation some of these veins increase their reference diameters, enabling placement of a larger stent at the second intervention and improving the long-term outlook.

The majority of patients undergoing pulmonary vein intervention are on warfarin at the recommendation of their electrophysiologist. Patients who are no longer having atrial fibrillation but have significant pulmonary vein stenosis are typically maintained on warfarin due to concern about sluggish flow potentially resulting in thrombosis. There is no data from which to derive recommendations, but our protocol is to continue warfarin in all patients following intervention. Patients with a newly deployed stent are started on enoxaparin the morning after the procedure at 1 mg/kg/
dose once a day for 3-4 days until a therapeutic INR (≥ 1.8) is reached. In most patients with larger stents (≥ 9-10 mm) we have discontinued warfarin after 9-12 months if there is no evidence of in-stent restenosis and no recurrence of atrial fibrillation. They are then placed on aspirin indefinitely. Patients with diffusely hypoplastic veins and/or small stents are maintained on coumadin indefinitely. We have not seen significant thrombotic complications when patients adhere to this regimen. Although it is not always possible to tell whether lumen loss is due only to in-stent restenosis or at least partially to thrombus, we have seen 3 instances of probable thrombosis of small stents combined with in-stent restenosis when warfarin has been self-discontinued. Of the 3 occluded stents 2 were successfully recanalized and redilated.

**Pulmonary vein intervention: Complications**

The benefit of any intervention has to be weighed against the inherent risks. There are obviously significant potential risks to pulmonary vein dilation or stenting. As with any technically challenging procedure, there is a learning curve. Due to the relative rarity and continuing decrease in the incidence of post ablation pulmonary vein stenosis, for which electrophysiologists should be commended, only a few specialized centers have gained a reasonable amount of experience.

In our center from a total of 98 patients with 173 stenotic pulmonary veins requiring 145 catheterizations, we have had 2 pulmonary vein perforations. Both required emergent pericardiocentesis in the catheterization laboratory, followed by surgical drainage due to ongoing bleeding. Both patients survived without neurologic or other sequelae. One patient suffered a cerebrovascular accident with complete neurologic recovery. One patient in whom the transseptal puncture was difficult had inadvertent perforation of the back wall of the left atrium. He underwent percutaneous pericardiocentesis without sequelae. One stent dislodged after placement and was successfully snared in the left atrium and withdrawn from the body, but the patient required a femoral vein cutdown to remove it. A few patients have had transient limited hemoptysis usually resolving within the first 24-72 hours. There has been no mortality.

The most serious complications, namely the two pulmonary vein perforations and one cerebrovascular accident, occurred in the first 30 patients. One of the perforations occurred during balloon dilation of a moderately severe stenosis with a large balloon in a vein with a large reference diameter. This lesion would now be treated with primary stenting using a smaller balloon than was used for balloon angioplasty, which would be safer. The patient who suffered the cerebrovascular accident was the second in our series, and since then we have been more aggressive with systemic anticoagulation during the procedure, maintaining the ACT around 300 seconds.

**Follow-up – when and how to reintervene**

The majority of patients experience symptomatic improvement after relief of pulmonary vein stenosis. Complete resolution of symptoms is usually seen when it is possible to stent the vein(s) to a normal pulmonary vein diameter. Flow to the affected lung quadrant increases significantly in most patients, but usually does not normalize. This is likely due to a varying degree of irreversible injury that the pulmonary vasculature has incurred prior to relief of the stenosis.

We typically repeat a quantitative lung perfusion scan within days of the intervention, and this can then be used in follow-up. The development of in-stent restenosis is accompanied by a gradual decrease in flow to the affected lung quadrant. In
addition to providing information about the functional significance of recurrent stenosis, a lung perfusion scan is associated with less radiation exposure when compared to MDCT. Transesophageal echocardiography has been used in some centers to follow patients after pulmonary vein intervention. Its usefulness may be limited in following smaller veins that continue to show abnormal flow patterns despite optimal intervention. In addition, TEE relies on increases in flow velocity as restenosis develops. Doppler flow measurements are flow dependent, and may not reliably increase in veins with low flow. The use of MRI to visualize stented veins is limited due to metal artifact, but magnetic resonance perfusion imaging may still be used to assess changes in lung perfusion.

Patients in whom the risk of restenosis is low (≥ 10 mm stents in all veins) are followed in one year’s time with an MDCT and quantitative lung perfusion scan. As the graph in figure 6 shows, the small number of patients who develop restenosis with large stents typically do so within the first 2 years post intervention. Neumann et al found no restenosis in 10 veins stented with ≥ 10 mm stents over 4 years of follow-up. Until recently we have followed patients on a yearly basis, but as further data is gathered it may become evident that after a few years of restenosis-free follow-up patients with large stents may be thought of as cured. We have begun to space follow-up to every 2 years in patients with more than 3-4 years of follow-up with no restenosis [Figure 7 A-C].

Patients with smaller stents require closer followup, being mindful of the amount of radiation exposure. We typically repeat a quantitative lung perfusion scan 3-6 months after intervention if a significant increase in flow was documented after the procedure, otherwise a MDCT is performed. Restenosis is typically accompanied by recurrence of symptoms, which also guides when to repeat imaging studies. If it appears that repeat catheterization is likely to be necessary we sometimes avoid repeating a MDCT, and rely on a decrease in perfusion and return of symptoms to decide when to re-intervene. As shown in figure 6, restenosis in small stents can be seen as early as 3 months post stenting, particularly for very small stents (≤ 6 mm), and there is a steady decline in the percent of stents free from restenosis in the first 2 years of follow-up. In the majority of cases this can be treated by stent redilation with a combination of cutting balloons and high pressure balloons [Figure 8 A, B]. We have previously reported that the use the cutting balloons in conjunction with standard high pressure balloons appears to decrease the risk of recurrent in-stent restenosis when compared to high pressure balloons alone, at least in intermediate term follow-up [34]. Cutting balloons are known to confer a more controlled vessel wall injury imparted by the longitudinal microsurgical blades, and therefore the proliferative response responsible for restenosis may be lessened.

In some cases of in-stent restenosis the pulmonary vein proximal to the stent has grown in size, and

Figure 7 A-C: A. Selective angiogram in the left superior pulmonary vein shows severe discrete stenosis. B. Following stenting to 10 mm. C. MDCT 4 years later shows a widely patent stent. (LSPV = left superior pulmonary vein)
it is possible to further enlarge the stent above its original size. For this reason, we believe it is important whenever possible to implant stents that allow dilation to larger sizes at any time post implantation, such as the unmounted Palmaz Genesis series of stents. We generally avoid using pre-mounted stents, which are much more limited in terms of the largest diameter that can be achieved when treating restenosis, and also have less radial strength, making it more difficult to completely relieve a resistant stenosis even with high pressure balloons.

Unfortunately patients with small stents and recurrent stenosis remain at risk for recurrence, but the risk is diminished when the stent can be made larger, which is sometimes the case. We have also observed that in some cases after 1-2 redilations of in-stent restenosis the reactivity of the vessel begins to diminish, and we begin to see long-term patency even in the smaller stents. In the small number of patients with repeated recurrences we have considered the use of covered stents, but the availability of these stents in the diameters and lengths needed for pulmonary veins is limited. We have one patient in our series in whom such stent was implanted inside a bare metal stent (iCAST covered stent, Atrium Medical Corporation, New Hampshire), and 5 years later it remains patent based on stable perfusion and lack of symptoms. It has not been possible to evaluate this stent by MDTC due to excessive metal artifact. We continue to be concerned about restenosis at the edge of a covered stent as has been reported by others, and therefore do not use them routinely. Drug eluting stents (DES) are not currently commercially available in diameters larger than 3.5 mm in the United States, but could be considered for severely hypoplastic veins. We have used a DES (CYPHER® Stent, Cordis Corporation), in one patient [Figure 5C], and it has remained patent after 18 months of follow-up. Systemic treatment with anti-proliferative agents, such as sirolimus, has been reported in two patients with no significant restenosis detected by imaging after 3-6 months of follow-up, and persistent symptom improvement after 12-18 months. More data is needed to make any recommendation, but these agents could be considered for patients with multiple recurrences and persistent symptoms, with close follow-up of potential recurrences.

Figure 8 A-B: Selective angiogram in a previously stented left superior pulmonary vein shows severe in-stenosis restenosis of a 7 mm stent. The 7 Fr catheter completely occludes the remaining lumen. B. Following dilation with an 8 mm cutting balloon followed by an 8 mm high pressure balloon. (LSPV = left superior pulmonary vein)

Figure 10: Pulmonary artery wedge angiogram in the left upper lung demonstrates total occlusion with complete obliteration of the left superior pulmonary vein on levophase. (LSPV = left superior pulmonary vein)
Importance of prompt diagnosis and timely intervention for pulmonary vein stenosis

In addition to the diameter of the stent and the reference diameter of the pulmonary vein (which determines the diameter of the stent), we have identified one more risk factor for restenosis: the time interval from pulmonary vein isolation to intervention for pulmonary vein stenosis. These factors are clearly interrelated. Pulmonary vein stenosis post PVI is known to be progressive at least in the first 6-12 months post ablation, with potential worsening of any given stenosis during this period. Of significant concern due to its impact on long-term outcome, there can also be progressive hypoplasia of the entire pulmonary vein proximal to the stenosis over time. This may be due in part to the degree of initial injury to the pulmonary vein, but as documented histologically there can be pulmonary vascular occlusive changes with intimal hyperplasia and medial thickening of both large and small pulmonary veins and arteries within the lung that are likely progressive and probably not fully reversible. These changes could result in irreversibly decreased pulmonary venous flow with secondary atrophy of the major vein. We have seen normal sized veins with reference diameters of 12 mm and severe discrete stenosis 3 months post PVI shrink down to 7 mm at the time of intervention 3 months later. There may be some degree of reversibility to this “veno-occlusive” process accounting for the observed growth in some of these veins after intervention, and the observed further increase in perfusion that we and others have seen months after intervention when restenosis does not occur. However, complete normalization of either the size or the flow from moderately hypoplastic veins does not occur in our experience.

As mentioned before, severe stenosis can also progress to total occlusion, sometimes precluding percutaneous intervention. Just as progressive stenosis can reach the point of total occlusion, total occlusion can reach the point of total obliteration or thrombosis of the entire pulmonary vein. Total occlusion is sometimes treatable percutaneously, but total obliterations that cannot be recanalized can only be treated by lung resection when warranted due to severe symptoms.

There are no established guidelines at this time recommending routine screening for pulmonary vein stenosis following PVI, but it is suggested at least for centers beginning to perform the procedure for the first time. The downside of screening all patients post PVI includes primarily cost and radiation exposure if MDTC is used, but as discussed above other imaging modalities with no or less radiation exposure are available. Waiting for symptoms to signal the presence of PVS will miss patients who despite severe stenosis are, at least subjectively, asymptomatic. Without screening, symptomatic patients may undergo extensive evaluation and unnecessary testing for their respiratory symptoms before the correct diagnosis is made. We have encountered patients who have
undergone bronchoscopy, lung biopsy, and even partial lung resection for a suspected malignancy before the diagnosis of pulmonary vein stenosis was considered. Waiting for significant symptoms, or waiting for the correct diagnosis to be made, may delay intervention and adversely affect outcome for the reasons discussed above. Further study is needed to evaluate the validity of routine screening. At our institution we believe that all patients should be screened, and referred promptly for evaluation when severe stenosis is detected. That is not to say that every patient should undergo intervention if significant stenosis is detected 3 months post PVI. In some cases ongoing remodeling of the pulmonary vein in the first few months post PVI in fact results in improvement rather than worsening of the stenosis, though significant improvement is not typically seen when the narrowing is very severe. A judgment call has to be made taking into account the degree of stenosis, the size of the reference vessel and the clinical picture.

It is imperative that all clinicians caring for patients who have undergone pulmonary vein isolation for atrial fibrillation be knowledgeable about the presentation of pulmonary vein stenosis, and maintain a high index of suspicion for this entity. Pulmonologists, to whom these patients are often referred for evaluation of dyspnea and/or hemoptysis, should always consider pulmonary vein stenosis in their differential diagnosis. Despite nearly a decade in existence, and a large body of literature about post ablation pulmonary vein stenosis, we continue to see patients who go as far as having an open lung biopsy before the diagnosis of pulmonary vein stenosis is finally made. It is in part from these unnecessary biopsies that we have learned about the histological findings of a “veno-occlusive” pattern, alveolar hemorrhage, and interstitial fibrosis as the pathophysiological processes underlying severe pulmonary vein stenosis, processes that likely continue to smolder as long the stenosis is not relieved.

Future directions
We have learned that post ablation pulmonary vein stenosis carries a better prognosis than would have been predicted from other models of pulmonary vein stenosis. With close follow-up, we are able to maintain pulmonary vein patency and improve symptoms in a large majority of patients [Table 1]. However, we continue to be challenged by high restenosis rates for either balloon dilation or stentangioplasty of small veins requiring repeated interventions. The ultimate goal is complete elimination of this complication by further technical advances in ablative techniques. In the meantime, further advances in stent technology may come to our aid. Drug-eluting stents (DES) are currently commercially available only in very small sizes (≤ 3.5 mm) to treat coronary artery stenosis. Trials in peripheral arterial disease using larger DES have not shown definite superiority over bare metal stents in that setting, but they remain untested in pulmonary veins. In light of the significant proliferative reaction associated with either balloon or stent angioplasty of the pulmonary veins, the use of DES seems to be the next logical step in improving restenosis rates for smaller vessels. Unfortunately DES larger than 3.5 mm in diameter are not currently available in the United States, either commercially or for research purposes. However, larger trials in peripheral arterial disease are planned in the near future, and may make DES available to be tried in small pulmonary veins. Research on biodegradable stents shows promise, but is still far from widespread clinical applicability. Investigation of congenital pulmonary vein stenosis at the cellular level has revealed that the proliferative reaction is caused by a relatively undifferentiated myofibroblast, a cell that is also found in certain rare neoplasms. At least one anti-proliferative agent effective against this cell type has been identified, but the toxicity profile may be prohibitive. Research into other such agents is ongoing. The lessons we have and will continue to learn from post ablation pulmonary vein stenosis will hopefully not only benefit patients with this relatively new syndrome, but also carry over to other more fulminant forms of this disease.

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Management of the Asymptomatic Patient After Catheter Ablation of Atrial Fibrillation

David S. Frankel, M.D., Edward P. Gerstenfeld, M.D.

From the Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

Abstract

Ablative therapy for atrial fibrillation is becoming more commonplace, and some minimally symptomatic or asymptomatic patients will be referred for ablative therapy. Reasons to ablate asymptomatic patients include young age and/or the presence of a tachycardia induced cardiomyopathy; in addition, some symptomatic patients may become asymptomatic after ablation. Managing these patients can be challenging. In this review, we will discuss the use of telemetric monitoring, antiarrhythmic drugs and anticoagulation after ablation in asymptomatic patients with atrial fibrillation.

Abbreviations

AAD- antiarrhythmic drugs
AF- atrial fibrillation
LVEF- left ventricular ejection fraction
TTM- transtelephonic monitor

Introduction

Ablation of atrial fibrillation (AF) has been gaining popularity since it was initially described by Haisaguerre and colleagues in 1998. While initially reserved for patients with structurally normal hearts and extremely symptomatic AF refractory to multiple antiarrhythmic drugs (AAD), the indications for ablation have continued to broaden. According to the recently published guidelines for the management of AF by the American College of Cardiology, American Heart Association and European Society of Cardiology, catheter ablation is now considered standard of care after a patient has developed recurrent AF on one AAD. Wazni and colleagues demonstrated that in patients with new onset AF, the outcome at one year with AF ablation was superior to treatment with AAD. Hsu and colleagues, as well as our laboratory, have demonstrated that the outcome of AF ablation in patients with heart failure and left ventricular dysfunction is reasonable and typically leads to improvement in left ventricular function.

Yet, one may reasonably wonder why AF ablation should ever be performed in the asymptomatic patient. The AFFIRM study found no mortality benefit to maintenance of sinus rhythm with AAD(s) compared to a strategy of ventricular rate control and anticoagulation. Studies using prolonged external monitoring after AF ablation have found a significant incidence of asymptomatic AF after ablation, and recent studies have shown that late recurrences of AF can continue to occur even...
Further, the potential long term risk of major complications from AF ablation, including a 1/1000 risk of death. So, what is the potential benefit of AF ablation in the asymptomatic patient?

For this review, we will limit our discussion to the truly asymptomatic patient. Patients with unclear symptoms who realize they feel better only after conversion to sinus rhythm are not uncommon, and are not the population presently considered. In our opinion, there are several reasons to consider AF ablation in the asymptomatic patient. The first is to achieve a potentially underestimated, long term mortality benefit in young patients with AF. The AFFIRM trial compared strategies of rate and rhythm control in patients who were either older than age 65 or had other risk factors for stroke or death. The mean follow-up of 3.5 years is certainly reasonable for a prospective, multicenter, randomized trial, but hardly reflects the long-term outlook of a 35 year old with AF who has decades of life ahead. The rhythm control strategy in AFFIRM predominantly utilized AAD rather than ablation to maintain sinus rhythm. Many AAD have side effects and may in fact increase mortality. Although patients in AFFIRM were randomized to rate or rhythm control “strategies,” only 2/3 of patients randomized to the rhythm control strategy remained in sinus rhythm at the end of the study, compared to 1/3 of patients in the rate control arm. In a post-hoc analysis of AFFIRM, patients who actually achieved and maintained sinus rhythm were compared to those who remained in AF. There was a nearly two fold higher mortality among patients who were in AF at the end of the study, and the predictors of increased mortality included the use of AAD. The authors conclude that, “if an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might improve survival.” Therefore, in a young patient with AF and few comorbidities, there is some evidence that restoring sinus rhythm may improve long term survival. In addition, restoration of sinus rhythm prevents the long term atrial dilatation and adverse electrical and mechanical remodeling that can occur with AF. Further, the potential long term risk of major bleeding (2.2 events per 100 patient-years) from anticoagulation with warfarin remains. The CABANA trial is prospectively investigating the long term effect on mortality of catheter ablation compared to medical therapy.

A second reason to ablate asymptomatic AF is to reverse a tachycardia-induced cardiomyopathy. While the onset of this condition is typically gradual, recurrent tachycardia in a patient with a prior tachycardia-mediated cardiomyopathy can lead to a precipitous decline in cardiac function, with development of heart failure and even death. Hsu and colleagues reported a 21% improvement in left ventricular ejection fraction (LVEF) following catheter ablation in patients with AF, heart failure and LVEF<45%. Gentlesk and colleagues from our laboratory reported similar improvement in LVEF following ablation, even among cardiomyopathy patients with apparent ventricular rate control in AF prior to ablation. Thus, it is reasonable to consider AF ablation to reverse a cardiomyopathy caused by AF, and to prevent recurrent cardiomyopathy in a patient in whom a prior tachycardia–mediated cardiomyopathy occurred.

Finally, management of asymptomatic AF is important because some patients who have symptomatic AF prior to ablation may become asymptomatic after ablation. For example, in a study by Hindricks and colleagues, AF ablation was performed in patients with highly symptomatic AF. In the seven day Holter recordings prior to ablation, only 5% had exclusively asymptomatic AF. When seven day Holter monitors were repeated six months following ablation, 37% had exclusively asymptomatic episodes. The mechanism whereby symptomatic AF becomes asymptomatic after ablation is unclear, but may involve modification of the autonomic nervous system with ablation. While this highlights the importance of monitoring for asymptomatic AF, it also emphasizes that dealing with patients with asymptomatic AF following ablation is not uncommon.

Post ablation monitoring

Multiple studies have documented that patients frequently have asymptomatic AF following ablation.
tion;\textsuperscript{7, 9} therefore, monitoring for recurrence should not rely on symptoms alone. Many patients undergoing ablation also have a heightened awareness of palpitations and may report symptoms of palpitations from atrial or ventricular premature beats rather than AF. Because the presence of recurrent AF has important implications for continued anticoagulation and antiarrhythmic treatment, objective telemetric monitoring of the heart rhythm is of paramount importance. It also should be recognized that patient compliance with home monitoring is greatest soon after the ablation procedure, and decreases with time.

Our practice is to demonstrate use of a transtelephonic monitor (TTM) to all patients in the hospital the day after ablation, and then to send patients home with a 30-day monitor with either continuous monitoring capability or an auto-trigger algorithm to detect asymptomatic AF in addition to symptomatic, patient triggered episodes [Figure 1]. Patients are also instructed to transmit a strip of their heart rhythm twice daily regardless of symptoms. The monitor aids in the detection of AF even during the typical 6 to 8 week “blanking period” following ablation. In patients with recurrent AF after ablation, the TTM can confirm patient symptoms, aid in the adjustment of antiarrhythmic and AV nodal blocking medications, and guide the scheduling of cardioversions. There is evidence that in patients with paroxysmal AF, early AF recurrence suggest a significantly increased risk of late AF recurrence, and therefore a lower likelihood of complete AF cure.\textsuperscript{21, 22} We perform a second 30-day monitor at 6-months after ablation or whenever the discontinuation of warfarin is considered in patients with CHADS\textsubscript{2} risk factors for stroke. Additional monitors are sent to patients if any symptoms of recurrent AF occur outside of these windows.

### Post ablation antiarrhythmic therapy

Most patients undergoing ablation have tried an

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**Figure 1:** Information recorded from transtelephonic monitor in a patient who underwent atrial fibrillation (AF) ablation. The top panel indicates the percentage of each day spent in sinus rhythm vs. atrial fibrillation according to the monitor, as well as the mean ventricular rate in AF compared to sinus rhythm. A sample rhythm strip is provided in the bottom panel, during which AF terminates, followed by a single sinus beat and then reinitiation of AF. This episode was asymptomatic.
AAD prior to the ablation procedure. The practice after ablation varies by institution and practitioner. Many physicians choose to continue antiarrhythmic therapy for 6-weeks after ablation in paroxysmal AF patients to facilitate the reverse atrial remodeling that occurs in sinus rhythm and to limit the inconvenience of recurrent AF in the early period. Others send patients home without AAD, with a plan to resume them if AF recurs.

In order to test the hypothesis that antiarrhythmic therapy after ablation reduces the need for recurrent hospitalization or cardioversion after ablation, we randomized 110 patients with paroxysmal AF to six weeks of AAD therapy plus AV nodal blocking agents versus AV nodal blocking agents alone immediately following AF ablation. The primary endpoint was a composite of clinically significant atrial arrhythmias lasting over 24 hours or requiring initiation of AAD therapy, cardioversion or hospital admission, or intolerance to an AAD requiring drug cessation. The composite endpoint was significantly reduced in the AAD compared to the no-AAD arm [19 vs. 42%; p=0.005, Figure 2]. Including only the hard endpoints of recurrent arrhythmia lasting > 24 hours and need for cardioversion or hospitalization, there remained a significant reduction in the AAD group (13 vs. 28%; p=0.05). Therefore, it is our practice to continue AAD in all patients with paroxysmal AF for 6 weeks following ablation. As most patients have been on an AAD in the past, we typically resume a previously tolerated AAD and AV nodal blockade the evening after ablation; patients can then be discharged the following day without the need for extensive inpatient monitoring. Patients are seen in the office at 6-weeks following ablation and the drug is discontinued in patients with no recurrent AF. In those with frequent recurrent episodes of AF, the AAD is continued and the patient is reevaluated at 6 months.

For patients with persistent AF, most electrophysiologists would continue the AAD after ablation to promote sinus rhythm and thereby facilitate reverse electrical and mechanical remodeling, as well as to decrease the need for early cardioversion. We typically continue antiarrhythmic agents for six months following ablation in persistent AF patients, after which the drug is discontinued for those patients maintaining sinus rhythm.

Occasionally, patients can develop a rapid organized atrial tachycardia following ablation. While the initial strategy for management of these trou-

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**Figure 2:** In the 5A study, patients who were treated with antiarrhythmic drugs (AAD) for six weeks following atrial fibrillation ablation had a lower incidence of the primary endpoint than those treated with just AV nodal blocking agents. The primary endpoint was a composite of atrial arrhythmias lasting more than 24 hours; atrial arrhythmias associated with severe symptoms requiring hospital admission, cardioversion, or initiation/change of antiarrhythmic drug therapy; and intolerance to antiarrhythmic agent requiring drug cessation. (From Roux JF et al. Circulation 2009;120:1036-1040).
blesome tachycardias includes cardioversion and use of an AAD, we have found that class IC drugs which block sodium channels and facilitate slow conduction can occasionally perpetuate these arrhythmias [Figure 3]. A trial of AAD cessation can be helpful in these patients prior to considering repeat ablation.²⁴

Post ablation anticoagulation

Discontinuation of warfarin remains the most controversial decision following AF ablation. According to the guidelines written by the American College of Cardiology, American Heart Association and European Society of Cardiology, long term anticoagulation for stroke prevention should be recommended for those with AF and CHAD₅² risk scores of 2 or greater unless contraindications are present. Warfarin should be considered for those with a score of 1 and should not be recommened for those with a score of 0. Aspirin is an alternative to warfarin in patients at low risk (CHAD₅₂≤1) or in those with contraindications to warfarin.² While these guidelines suggest that warfarin therapy following ablation should be based on the CHAD₅₂ score and not the presence or absence of AF, most patients are extremely motivated to discontinue warfarin, and instructing patients to continue warfarin when no detectable AF is present can be challenging. Furthermore, anticoagulation with warfarin increases the risk of intracranial hemorrhage two to five-fold.²²,²⁵ However, as documented by Shah and colleagues, late AF recurrences can occur, even after several years of apparent freedom from AF following ablation.⁹ Thus, the optimal anticoagulation strategy following AF ablation needs to be tailored to the individual risks and preferences of the patient. Three series have examined the safety of discontinuing warfarin following AF ablation. Oral and colleagues studied 755 patients with paroxysmal (490) or chronic (265) AF. Fifty-six percent had CHAD₅₂ risk scores of 1 or greater.²⁶ AAD were discontinued two to three months following ablation. All participants were anticoagulated with warfarin for three months following ablation, and then warfarin was discontinued in patients without symptomatic AF recurrences. Some thromboembolic events occurred early after ablation despite warfarin use, most (7 of 9) in the first two weeks. Of the 522 patients who remained in sinus rhythm during the first three months, aspirin was substituted for warfarin in 79% of those who

Figure 3: A telemetry strip recorded from a patient who developed an organized atrial tachycardia while being treated with flecainide following catheter ablation of atrial fibrillation. Flecainide was discontinued when the patient was admitted to the hospital the night before a scheduled repeat ablation procedure. During the evening, the atrial tachycardia degenerated into atrial fibrillation and then converted to sinus rhythm. We hypothesize that in some cases, slow conduction facilitated by Class IC agents may facilitate organized atrial tachycardias after ablation. We have found that on occasion, a trial of antiarrhythmic drug cessation can result in termination of these organized tachycardias.
with a CHADS$_2$ risk score of 0 and 68% of those with CHADS$_2$ risk scores of 1 or greater. None of these patients developed a thromboembolic event during mean follow-up of 25 months.

We followed 1,058 patients who underwent AF ablation at our institution between 1999 and 2005. Guidelines for the discontinuation of warfarin after ablation included a left atrial size <4.5 cm, CHADS$_2$ score of 2 or less, no prior stroke or TIA, and the absence of AF on two 30-day TTMs over a 6-month period. Warfarin was eventually discontinued in 31% of patients. Over a mean follow-up of 3.5 years, only one patient (0.3%) had an embolic stroke off warfarin; this patient was later documented to have recurrent AF.

Finally, the experiences of four centers, including our own, were combined into a large series of 2,436 patients undergoing AF ablation who discontinued warfarin. Sixty-five percent had paroxysmal AF, 16% persistent AF and 19% “permanent” AF. CHADS$_2$ risk score was 0 in 62%, 1 in 27% and 2 or greater in 11%. Warfarin was discontinued in 2,436 patients after ablation. During a mean follow-up of 31 months, only one patient had a stroke (0.04%). Therefore, discontinuation of warfarin is feasible in the appropriate patient with a good short term outcome. Longer term follow-up will be required to confirm these findings.

**Recommendations**

**Post ablation monitoring**

We recommend discharging all patients after ablation with a 7 to 30-day TTM with instructions to transmit strips twice daily and with any symptoms. A monitor with continuous telemetry or an algorithm for automatic AF detection should be used to assure detection of asymptomatic AF. Delivery of the monitor directly to the patient after ablation allows demonstration of proper use at a time when compliance with TTM use is highest. A second 7 to 30 day TTM should be used outside the “blanking period” to detect asymptomatic AF and determine procedure efficacy. Additional monitors may be sent to patients with symptomatic palpitations that cannot be easily documented with an ECG.

**Post ablation antiarrhythmic therapy**

Based on the results of the 5A study, we discharge all patients with paroxysmal AF who have previously used an AAD on the previously tolerated AAD to reduce the need for early cardioversion and hospitalization. Antiarrhythmic therapy is continued for 6 weeks. Therapy of patients with no prior AAD use is individualized. All patients with persistent AF are also discharged on AAD which is typically continued for 6 months.

**Post ablation anticoagulation with warfarin**

In conjunction with the consensus statement from the Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society, all patients are discharged after ablation on warfarin anticoagulation. While one study has suggested that aspirin may suffice in low risk patients, the risk of thromboembolism after ablation warrants warfarin use, in our opinion. Patients are either continued on warfarin through the ablation procedure, or bridged with heparin or lovenox immediately following ablation. In patients with CHADS$_2$ risk scores of 0, there is no indication for long term warfarin use in patients with no recurrence of AF after six months. This group comprises a significant proportion of patients undergoing AF ablation. CHADS$_2$ scores of 1 have the option of aspirin or warfarin therapy according to American College of Cardiology, American Heart Association and European Society of Cardiology guidelines. We give CHADS$_2$ 1 patients with no symptoms of recurrent AF and no asymptomatic AF detected on two TTMs the option of discontinuing warfarin at 6 months. The treatment of CHADS$_2$ 2 patients is controversial. CHADS$_2$ patients at lower risk of stroke (no history of stroke or transient ischemic attack (TIA), left atrial size <4.5 cm, normal left ventricular function), if there are no symptoms of recurrent AF for six months after ablation with confirmation on two 30-day auto-trigger TTMs, the option of warfarin cessation is discussed with the patient after reviewing the risks and benefits. Some patients may elect to continue on long term warfarin therapy. The option of warfarin cessation is based on the results of the three studies reviewed above, demonstrating a low risk of thromboembolic events in selected
patients and the established bleeding risk with continued warfarin therapy.\textsuperscript{25-28} All patients are instructed to take their pulse twice daily for the rest of their lives and report any palpitations or symptoms of AF. Patients with a prior stroke or TIA, left atrial dilatation, left ventricular dysfunction or a CHADS\textsubscript{2} score of 3 or greater are advised to continue anticoagulation with warfarin indefinitely. Decisions regarding warfarin cessation in higher risk patients after long term follow-up can be individualized.

References