THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation

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An increasing number of atrial fibrillation patients are being prescribed one of the new oral anticoagulants (dabigatran, rivaroxaban, or apixaban) for stroke prevention either after diagnosis or to replace warfarin. Warfarin (Coumadin) has been in routine use for over 30 years and a wealth of information is available concerning its benefits and potential for harm. Such is not the case for the new anticoagulants (NOACs). In a bid to correct this situation, the European Heart Rhythm Association recently published a set of guidelines for their use. Some highlights of these guidelines are – NOACs do not require monitoring like warfarin and INR testing is not applicable to establish the degree of anticoagulation; there are numerous known interactions with other pharmaceutical drugs including antiarrhythmics; there are currently no effective and readily available antidotes to deal with major NOAC-related bleeding; thrombolytic therapy (to deal with an ischemic stroke) is not safe for patients on NOACs and, at this time, NOACs are not recommended for cancer patients.

Also in this issue we report that a combination of vitamins C and E and fish oil is effective in preventing post-operative atrial fibrillation associated with heart surgery, that pre-existing inflammation worsens the outcome of catheter ablation, that the risk of suffering a stroke is similar in paroxysmal and persistent afibbers, that major bleeding associated with warfarin therapy is more common than originally thought and is further increased if aspirin is also prescribed and finally, that age is no barrier to having a successful catheter ablation.

If you have not yet visited the afibbers.com website I would urge you to do so. The database has just been updated and now includes the abstracts published in the 2012 issues of "The AFIB Report". You can search the entire database using the Google on-site search feature. Please give it a try! I am sure you'll like it! http://afibbers.com/atrial_fibrillation/index.htm

Last but not least, if you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to defray the cost of maintaining the web site and bulletin board. You can find the store at http://www.afibbers.org/vitamins.htm

Wishing you good health and lots of NSR,

Hans

Highlights

LETTERS TO THE EDITOR

You and I have talked via phone a couple of times over the years about afib. You recently recommended an electrophysiologist in Texas, Dr. Natale, to perform a catheter ablation. I was set to have the surgery and within two weeks of it a pulmonary specialist recommended a sleep apnea workup. Results showed a severe case of sleep apnea even though I did not typically fit the profile (overweight). I've had a CPAP machine for 3 months now and am completely free of all afib symptoms/episodes. Amazing results..... Doctor will begin eliminating meds in October if results continue. Please encourage your readers to do the same.

CS

Is there a way to search the archives with a word or phrase? I just came down with afib after a corticosteroid injection and would like to search on "corticosteroid".

DK

You can search using the word corticosteroid in the www.afibbers.com AFIB Database. The search will bring up 3 abstracts of relevant medical journal articles - all concluding that corticosteroids are effective in preventing atrial fibrillation. However, there is one article in the medical literature reporting that high-dose corticosteroid therapy (more than 7.5 mg/day of prednisone equivalents) can indeed precipitate AF in certain patients, particularly if the drug is prescribed for asthma, pulmonary disease or rheumatism. See http://archinte.jamanetwork.com/article.aspx?articleid=410283

An allergic reaction to a cortisone injection is very rare, but it is possible that a reaction can be caused by the betadine many physicians use to sterilize the injection site.

Finally, it is possible that the inflammation or other condition for which you received the injection may have been the factor precipitating the afib.

Hans

I received my results from my Exatest recently. I was normal in all areas except calcium, for which I was a little above the top of the range. I was diagnosed with Osteoporosis when I was 49 years old (I am 61 now). I took Fosamax until 2008 and then through increasing my vitamin D intake and weight lifting I got rid of the Osteoporosis without taking this medication. However, I continued to take calcium supplements at a fairly high level as a preventative. Since receiving my Exatest results I have now stopped my calcium supplementation to see if it impacts my afib.

Do you have any knowledge about high cellular calcium levels causing lone afib? Is there anything I could read on this? Are you aware of any way to reduce the cellular level of calcium other than stopping the calcium supplements? I wonder if milk would be a better source than supplements.

DB

Glad to hear that your Exatest results for magnesium and potassium were normal - that is hugely important.

One of our early LAF surveys indicated that vagal afibbers who supplemented with large amounts of calcium (1200 mg/day or more) had longer episodes. Some have found it beneficial to cut back on calcium.

In your case, with a history of osteoporosis, I would not completely eliminate calcium supplementation but perhaps limit it to 600 mg/day. You can make sure that the calcium gets into your bones rather than into your heart cells by also supplementing with vitamin K2 plus, of course, vitamin D3. A daily dosage of 90-180 mcg of vitamin K2 would suffice. For more on the importance of vitamin K2 and for general information on osteoporosis prevention see the following:

www.yourhealthbase.com/archives/ihn235.pdf
www.yourhealthbase.com/osteoporosis.htm

Hans

Thanks so much for referring me to your 12-step plan for eliminating afib (http://afibbers.org/resources/12stepplan.pdf). I chose this route instead of having an ablation. I was having an 8-10 hour episode every week. How I never had a stroke baffles the cardiologist as I was only on a daily half-dose beta-blocker and ecotrin aspirin. My cardiologist in South Africa (I live in stressful Zimbabwe) wanted to do the ablation with such a low success rate, but I told him about your article and he allowed me to try the plan on one condition – that I went on Pradaxa, a new anticoagulant.

Since following the plan I have not had an episode for 5 weeks, up until this morning when I had a mild 3-hour episode. I have changed my diet, am being treated by a chiropractor, and am doing some yoga relaxation and breathing exercises.

So I just want to thank you for the 12-step plan which is really worth trying as opposed to surgery. It DOES work!! Not sleeping on my left side is a relearning process. I also believe in the power of prayer for healing as well.

JA

Prevention of post-operative atrial fibrillation

SANTIAGO, CHILE. Oxidative stress has been implicated as a major factor in the development and promotion of atrial fibrillation (AF). The main reactive oxygen species (ROS) involved in causing oxidative stress are the superoxide anion, singlet oxygen, nitrogen dioxide (peroxynitrite) and hydroxyl radicals. They share the dubious distinction of being able to cause inflammation and inflict considerable damage in tissues, cells and individual DNA strands.

Under normal circumstances any ROS attacking the heart lining or adjacent lung tissue would quickly be rendered harmless by the body's own antioxidants or by antioxidants obtained through the diet. However, if antioxidant defenses are inadequate, the immune system is compromised, or if the autonomic nervous system is highly dysfunctional or stressed, it is likely that the ROS could get the upper hand and initiate an inflammatory response and subsequent arrhythmia.

Inflammation of the heart lining has also been linked to the development and promotion of AF and a strong association between severity of AF and the level of the inflammation biomarker CRP (C-reactive protein) has been established. There is also evidence that omega-3 polyunsaturated fatty acids (fish oils) materially reduce inflammation and CRP level.

A group of Chilean and Greek researchers now reports that pre-procedure supplementation with a combination of antioxidants (vitamins C and E) and fish oil is effective in reducing the incidence of post-operative AF in patients undergoing valve surgery or coronary artery bypass surgery. Their clinical trial involved 203 patients scheduled for on-pump cardiac surgery. The average age of the patients was 60 years, 86% were male and all were in normal sinus rhythm and had no previous history of arrhythmia.

The patients were randomized to receive placebo or supplementation with 2 grams/day of fish oil (DHA:EPA ratio of 2:1), 1 gram/day of vitamin C and 400 IU/day of vitamin E. Fish oil supplementation was initiated 7 days prior to the procedure and supplementation with vitamins C and E was started 2 days before. All supplementation was discontinued upon discharge from hospital. ECG or Holter monitoring was carried out until discharge with ECG-documented AF for at least 60 seconds being classified as post-operative atrial fibrillation (POAF). POAF occurred in 9.7% of supplement group members and in 32% of placebo group members – a statistically highly significant difference. The mean time to POAF occurrence (from completion of surgery) was 3.3 days in the supplement group and 2.9 days in the placebo group.

Oxidative stress was assessed as malondialdehyde (MDA) level in blood throughout the trial and in right atrial tissue during surgery. After 5 days of fish oil supplementation, blood levels of MDA were an average 59.6% higher than baseline level and 45.6% higher than the average level in the placebo group. However, after the addition of vitamins C and E there was no longer any difference in pre-surgery MDA levels. MDA levels, not surprisingly, increased after surgery, but to a much lesser degree in the supplement group. CRP levels also increased after surgery but significantly less so in the supplement group than in the placebo group (2.2-fold vs. 3.6-fold increase).

The researchers also noted a significantly higher activity of the endogenous antioxidant enzymes catalase, superoxide dismutase and glutathione peroxidase in the atrial tissue of supplemented patients. They conclude that supplementation with a combination of antioxidants (vitamins C and E) and fish oils reduces the incidence of post-operative AF in cardiac surgery patients by about 66%. Supplementation also increases antioxidant potential and decreases oxidative stress and inflammation. They note that using a fish oil supplement with a ratio of DHA (docosahexaenoic acid) to EPA (eicosapentaenoic acid) of 2:1 may be important in short term trials as there is evidence that DHA is incorporated more rapidly into human atrial tissue than is EPA.

Rodrigo, R, et al. A randomized controlled trial to prevent postoperative atrial fibrillation by antioxidant reinforcement. **Journal of the American College of Cardiology**, *July 8, 2013 [Epub ahead of print]*

Editor's comment: This study adds to existing evidence that vitamin C is useful in preventing postoperative atrial fibrillation in coronary artery bypass surgery[1]. There is also evidence that vitamin C prevents early recurrence following cardioversion of persistent AF and is effective in reducing levels of inflammatory markers and fibrinogen[2]. The finding that

fish oil supplementation on its own increases oxidative stress is not surprising and supports my position that fish oil should always be taken in combination with vitamins C and E.

[1] Carnes, CA, et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodelling and decreases the incidence of postoperative atrial fibrillation. Circulation Research, Vol. 89, September 14, 2001, pp. e32-e38

[2] Korantzopoulos, P, et al. Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation. International Journal of Cardiology, Vol. 102, No. 2, July 10, 2005, pp. 321-26

White blood cell count predicts post-ablation recurrence

ANKARA, TURKEY. A recent study involving participants in the Framingham Heart Study concluded that a high white blood cell (WBC) count is a risk factor for the development of atrial fibrillation (AF). Now a group of researchers from Hacettepe University of Medicine reports that a high WBC count prior to ablation is a risk factor for AF recurrence post-ablation. More specifically, they found that a high neutrophil count and an elevated neutrophil to lymphocyte ratio (NLR) predicted an increased risk of recurrence.

WBC 101

White blood cells are cells of the immune system (found in the blood stream) involved in defending the body against infections and foreign materials. A normal WBC count is between 4500 and 10000 cells per microliter.

Neutrophils are a specialized form of white blood cells that help defend against bacterial and fungal infections. They are the "first responders" to microbial infections; their activity and death in large numbers form pus. A normal neutrophil level is around 50 to 60% of WBC count.

Lymphocytes are small white blood cells. Blood contains three types – B cells (produces antibodies that bind to pathogens to target them for destruction), T cells and Natural killer cells. A normal lymphocyte level is around 30% of WBC count.

High levels of WBCs are an indication of a heightened immune system response and the accompanying inflammation.

The Turkish study involved 251 patients with symptomatic paroxysmal (80%) or persistent (20%) atrial fibrillation. The average age of the participants was 54 years, 52% were men, 41% had hypertension, 14% had diabetes, but only 11% had a history of heart disease. Prior to their scheduled ablation all patients underwent transthoracic and transesophageal echocardiography and a CT scan to determine the configuration of pulmonary veins. The ablation was carried out using a 28 mm cryoballoon catheter (*Arctic Front*). Total average procedure time was 70 minutes and average fluoroscopy time was 14 minutes. Follow-up examinations were performed at 3, 6 and 12 months after the procedure and every 6 months thereafter.

During a mean follow-up of 19 months early recurrence, defined as one or more AF episodes (lasting 30 seconds or longer) occurring during the first 3 months following the ablation (blanking period), developed in 38 patients (15.1%) and recurrence after the blanking period was observed in 60 patients (23.9%). Compared to patients who remained in sinus rhythm during follow-up, those with recurrence were older and had a higher rate of coronary artery disease, persistent AF, early recurrence, reduced left ventricular ejection fraction, increased

left atrial diameter, increased WBC count, increased neutrophil count and NLR, and elevated high-sensitivity C-reactive protein (CRP) levels.

However, on multivariate analysis, only an increased left atrial diameter, early recurrence, and an elevated NLR were associated with recurrence. A NLR above 3.15 was highly predictive of recurrence and patients with both an NLR above 3.15 and early recurrence were 19 times more likely to experience later recurrence than those with no early recurrence and a NLR below 3.15.

The researchers conclude that a pre-ablation inflammatory environment is predictive of ablation failure and suggest that treatment of this inflammation with pharmaceutical drugs may improve ablation outcome.
Canpolat, U, et al. Role of preablation neutrophil/lymphocyte ratio on outcomes of cryoballoon-based atrial fibrillation ablation. **American Journal of Cardiology**, *Vol. 112, 2013, pp. 513-19*

Editor's comment: The idea that inflammation is a cause of AF has long been debated and it is not yet entirely clear which is the cause and which is the effect. Nevertheless, going into an ablation with a normal WBC count and a low NLR would seem prudent. Of course, inflammation does not arise just out of the blue and it may be even more beneficial if the cause of the inflammation was determined and dealt with prior to ablation.

Stroke risk in paroxysmal and persistent AF

FLORENCE, ITALY. The risk of a thromboembolic event (ischemic stroke, transient ischemic attack [TIA] or systemic embolism) is elevated in atrial fibrillation (AF) patients with one or more risk factors for stroke. The degree of risk is commonly expressed in form of the $CHADS_2$ score which assigns 1 point each for the presence of heart failure, hypertension, age over 75 years, and diabetes and 2 points for prior ischemic stroke or TIA. A score of 0 is considered low risk, a score of 1 is associated with moderate risk, and a score of 2 or more is considered high risk. Atrial fibrillation is classified as paroxysmal if lasting less than 7 days and as persistent if lasting more than 7 days but amenable to termination with cardioversion.

A group of Italian researchers (GISSI-AF investigators) now report that the risk of a thromboembolic (TE) event is low in both paroxysmal and persistent AF with moderate stroke risk. Their study involved 1234 participants in the GISSI-AF trial originally designed to evaluate the efficacy of the angiotensin II receptor blocker valsartan (Diovan) in preventing AF recurrence in patients with hypertension[1,2].

The average age of the participants was 67 years, 40% were women (46% in the paroxysmal group), 62% had paroxysmal and 38% had persistent AF. The majority (85%) had hypertension, 4% had coronary artery disease, 8% had heart failure or reduced left ventricular ejection fraction, and 6% had suffered a prior TE event. Heart failure was significantly more common among persistent afibbers than among paroxysmal ones (14% vs 4%). The average $CHADS_2$ score for the total patient population was 1.41.

During a 1-year intensive follow-up period, 12 patients (0.97%) died, 12 patients (0.97%) suffered a TE event, and 10 patients (0.81%) suffered a major bleeding event (intracranial hemorrhage or major bleed requiring blood transfusion or hospitalization). There was no statistically significant difference in the incidence of TE events, major bleeding events or mortality between the paroxysmal group and the persistent group. However, the rate of TE events was significantly higher in women than in men. The incidence of TE and major bleeding events in untreated patients and in those treated with warfarin or antiplatelet agents is shown below.

	% of total group	TE event	Bleeding event
No treatment	16%	0.5%	0%
Warfarin	48%	0.84%	0.84%
Antiplatelet	34%	1.47%	0.98%
Warfarin + antiplatelet	2%	-	-

Warfarin therapy was significantly more common among persistent afibbers (87% were treated with warfarin) than among paroxysmal afibbers (25% were treated with warfarin). Warfarin therapy was underprescribed in patients with a $CHADS_2$ score of 2 or greater and overprescribed for those with a $CHADS_2$ score of 0. Thirty-five percent of patients with a zero score were still on warfarin at the end of the study period.

The GISSI investigators conclude that the incidence of TE and bleeding events was remarkably low in both paroxysmal and persistent AF despite a significant degree of over- or under-treatment with warfarin.

Disertori, M, et al. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation. **BMC Cardiovascular Disorders**, *Vol. 13, 2013, pp. 28-37*

[1] www.afibbers.com/atrial_fibrillation/risk_factors/C105c.htm
[2] www.afibbers.com/atrial_fibrillation/rhythm_control/G90d.htm

Editor's comment: This study adds to accumulating evidence that warfarin is often overprescribed and is not terribly effective except in the case of patients having suffered a previous stroke or TIA. It is also clear that the net benefit of warfarin therapy leaves much to be desired and is inappropriate in the case of lone afibbers with no risk factors for stroke[3,4].

[3] www.afibbers.com/atrial_fibrillation/stroke_prevention/N93d.htm
[4] www.afibbers.com/atrial_fibrillation/stroke_prevention/N81c.htm

Bleeding risk with warfarin therapy

TORONTO, CANADA. The initial clinical trials of warfarin for stroke prevention in atrial fibrillation (AF) patients concluded that the drug was effective in reducing the risk of ischemic stroke in patients having one or more risk factors (hypertension, diabetes, heart failure, age over 75 years, and prior stroke or TIA). The relative risk reduction was found to be about 65% when compared to placebo.

Later studies of "real world" populations found that the relative risk reduction may be substantially less – more like 40% for hypertension and 56% for prior stroke or TIA. The main reason that warfarin is less effective in a "real world" setting is that INR control is usually significantly poorer than in tightly controlled clinical trials. Too low an INR increases the risk of ischemic stroke, while an INR value above 4 materially increases the risk of a hemorrhagic stroke and major bleeding. Studies have shown that patients in "real world" settings achieve the recommended range of 2.0 to 3.0 only in about 50-60% of their INR tests.

While often ignored, warfarin therapy involves a significant risk of hemorrhagic stroke and major bleeding (bleeding requiring blood transfusions or hospital admission). This is particularly serious in older patients. A clinical trial carried out at the Boston University School of Medicine observed an overall incidence of major bleeding of 7.2% (including intracranial hemorrhage of 2.5%) in a group of patients with an average age of 77 years and one or more risk factors for stroke[1].

A team of researchers from Massachusetts General Hospital, University of California, and Kaiser Permanente of northern California carried out a 6-year study involving 13,559 patients with non-valvular AF and concluded that, when considering risk of hemorrhagic stroke, the net benefit of warfarin therapy is negative for patients with no risk factors for ischemic stroke

and zero in those with one risk factor. As a matter of fact, the risk of ischemic stroke in patients with one risk factor (except in the case of prior stroke or TIA) was only 1.2%/year – far lower than the 3-4% quoted in the original studies done to prove the efficacy of warfarin[2].

A group of Canadian researchers now confirms that hemorrhage is a serious problem with warfarin therapy. Their study included 125,195 AF patients aged 66 years or older who began warfarin therapy between 1997 and 2008. The overall rate of hemorrhage (major bleeding) was 3.8%/year. However, during the first 30 days of treatment it was 11.8% (16.7% for patients with a $CHADS_2$ score of 4 or greater). Over the 5-year follow-up, 10,840 patients visited a hospital for major bleeding and, of these, 1963 (18.1%) died in hospital or within 7 days of being discharged. The mortality was highest (42%) for patients admitted with intracranial hemorrhage (hemorrhagic stroke). The risk of major bleeding was significantly lower for patients with a $CHADS_2$ score of 0 or 1 (1.8% and 2.5% respectively).
Gomes, T, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. **Canadian Medical Association Journal**, *Vol. 185, No. 2, February 5, 2013, pp. E121-E127*
[1] www.afibbers.com/atrial_fibrillation/stroke_prevention/N81c.htm
[2] www.afibbers.com/atrial_fibrillation/stroke_prevention/N93d.htm

Editor's comment: This new Canadian study adds to the evidence that warfarin therapy carries a considerable risk of major bleeding. It also confirms that afib patients with no or only one risk factor for ischemic stroke ($CHADS_2$ score of 0 or 1) do not benefit from and may actually be harmed by warfarin therapy.

Mitral regurgitation and lone atrial fibrillation

BAKERSFIELD, CALIFORNIA. Mitral regurgitation (MR) is defined as an abnormal reversal of blood flow from the left ventricle to the left atrium. The most common causes of MR are mitral valve prolapse (MVP), rheumatic heart disease, and ischemic heart disease. A group of researchers from Bakersfield Heart Hospital now report that MR is significantly more prevalent in patients with lone atrial fibrillation (LAF) than in patients without this condition.

Their study involved 57 patients with LAF who underwent transesophageal echocardiography (TEE) prior to cardioversion and 100 patients without LAF who underwent TEE for various other reasons. All of the study participants had structurally normal mitral valves. LAF was defined as AF without concomitant heart disease, hypertension or diabetes, and age less than 60 years.

The researchers found that LAF patients were far more likely to exhibit moderate MR than were controls (66% vs 6%). Mild MR was found in 18% of LAF patients vs 31% in controls, and absence of MR was noted in 16% of LAF patients vs 63% of controls. Left ventricular ejection fraction and left atrial diameter did not differ between the two groups, but the diameter of the mitral annulus was significantly greater in the LAF group.

The researchers conclude that moderate MR may be a risk factor for the development of LAF primarily by causing mechanical stretch of the left atrium or conversely, that LAF may predispose to the development of MR over time. They also suggest the possibility that the observed MR may be a transient phenomenon that resolves once normal sinus rhythm is restored.
Sharma, S, et al. Clinically unrecognized mitral regurgitation is prevalent in lone atrial fibrillation. **World Journal of Cardiology**, *Vol. 4, May 26, 2012, pp. 183-87*

Editor's comment: The finding that mitral regurgitation and lone atrial fibrillation are somehow connected is most interesting. It is not clear from the study which is cause and which is effect, although the authors clearly lean toward the hypothesis that moderate MR is

the forerunner for LAF. Another possibility obviously has to be that MR and LAF have the same origin. If this is indeed the case, then magnesium deficiency is likely to be the common factor since both LAF and mitral valve prolapse have been found to be associated with magnesium deficiency[1,2].

[1] Khan, AM, et al. Low serum magnesium and the development of atrial fibrillation in the community. Circulation, Vol. 127, January 1, 2013, pp. 33-38
http://www.ncbi.nlm.nih.gov/pubmed/23172839
[2] Bobkowski, W, et al. The importance of magnesium status in the pathophysiology of mitral valve prolapse. Magnesium Research, Vol. 18, No. 1, March 2005, pp. 35-52
http://www.ncbi.nlm.nih.gov/pubmed/15945614

Guidelines for the use of the new anticoagulants

LEUVEN, BELGIUM. Warfarin (Coumadin) has a long history and much experience has been gained over the past 30 years to ensure safe and effective use of this drug. Recently three new oral anticoagulants – dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) – have entered the market as replacements for warfarin. The major advantage of the new anticoagulants is that, unlike warfarin, they do not require regular monitoring to ensure that their anticoagulation effect is optimal. Several clinical trials have been done to establish their benefit in preventing ischemic stroke and the risks (major bleeding and hemorrhagic stroke) associated with their use. See www.afibbers.org/resources/anticoagulants.pdf for a summary of these trials.

However, while guidelines for the use of warfarin are well established, this is not the case for the newer anticoagulants. A group of European cardiologists/electrophysiologists has now released a set of guidelines for the use of the new anticoagulants in patients with non-valvular atrial fibrillation (AF). Highlights are:

- It is recommended that patients on the new anticoagulants carry a card giving details about their treatment and other medications they may be taking. It is also recommended that patients undergo testing for liver and kidney function at least once a year and more frequently if they have reduced kidney function or have been prescribed dabigatran. Finally, patients should see their doctor at regular intervals, preferably every 3 months, for on-going review of their treatment.

- The new anticoagulants do not require routine monitoring of coagulation. The value of measuring activated partial thromboplastin time (aPTT) to provide a qualitative assessment of the presence of dabigatran, or prothrombin time (PT) to provide an assessment of the presence of rivaroxaban and apixaban is questionable, and INR monitoring is not applicable to patients on the new anticoagulants.

- It is expected that the new anticoagulants will have less interactions with foods, but interactions with other drugs will still be a problem. Not surprisingly, bleeding risk increases significantly if the new anticoagulants are taken in conjunction with other anticoagulants, platelet inhibitors or NSAIDs. Combining them with aspirin increases bleeding risk by at least 60%. Several drugs strongly potentiate the effect of the new anticoagulants and should be used with extreme caution or not at all. Among these drugs are dronedarone (Multaq), antifungal drugs such as ketoconazole and itraconazole, and HIV protease inhibitors (ritonavir). Other drugs weaken the anticoagulation effect. Most important among these are rifampicin, carbamazepine, phenytoin, phenobarbital, and the herb St. John's Wort. Some drugs potentiate the coagulation effect, but this may be countered by reducing the dose of anticoagulant. Among these drugs are verapamil and quinidine. Finally, some drugs potentiate the anticoagulant effect. But, unless two or more of these drugs are taken in combination with other potentiating drugs, anticoagulant dose does not need to be

changed. Among this category of drugs are diltiazem, amiodarone, and certain antibiotics (cyclosporine, clarithromycin, erythromycin). NOTE: For a more complete list of drug interactions see the complete article[1].

- Special precautions need to be taken when switching between different anticoagulant therapies, especially when switching from one of the new anticoagulants to warfarin[1].

- The standard dose for dabigatran is 110 or 150 mg twice a day, for rivaroxaban it is 15-20 mg once a day, and for apixaban 5 mg twice a day. NOTE: Dosages are reduced for patients with impaired kidney function. It is very important to follow the dosing schedule and to follow instructions regarding missed doses[1].

- Chronic kidney disease is a risk factor for both thromboembolic events (ischemic strokes) and bleeding in AF patients. Use of the new anticoagulants is not recommended in patients with a creatinine clearance of less than 30 mL/min or in dialysis patients.

- There are currently no specific antidotes for the new anticoagulants and no effective and readily available protocols for dealing with severe bleeding complications, although some success has been achieved with the use of dialysis and blood transfusions. The effect of an accidental overdose can sometimes be mitigated by the prompt use of activated charcoal.

- Some forms of surgery require the discontinuation of anticoagulation. The last dose should generally be taken 24 to 48 hours prior to surgery depending on the extent of the surgery and the patient's creatinine clearance level. Anticoagulation can generally be restarted 6 to 8 hours after the completion of surgery, but in some cases a wait period of 72 hours or more is required. For AF patients undergoing catheter ablation, anticoagulation with warfarin (INR between 2.0 and 3.0) would still seem to be the safest option. Patients with both AF and coronary artery disease require special consideration and different protocols may be needed depending on whether the patient has suffered a heart attack or not[1].

- In the case of AF patients whose episode has lasted more than 48 hours (or is of unknown duration), anticoagulation is required for 3 weeks before and 4 weeks after cardioversion. If there is doubt about the patient's compliance with their anticoagulation protocol, transesophageal echocardiography should be performed prior to cardioversion.

- Patients suffering an ischemic stroke should not receive thrombolytic therapy with recombinant tissue plasminogen activator or should wait for this therapy for at least 48 hours after taking the last dose of the new anticoagulants. NOTE: Thrombolytic therapy is not effective if given more than 3 hours after stroke occurred. There is no established protocol for dealing with a hemorrhagic stroke (intracranial bleeding) occurring in a patient taking one of the new anticoagulants.

- Patients with cancer are at an increased risk for thromboembolic events and some cancer therapies may increase bleeding tendency. Because of the wealth of experience in using heparin and warfarin in cancer patients and the complete lack of experience using the new anticoagulants, they are not recommended for cancer patients.

Heidbuchel, H, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. **European Heart Journal**, *Vol. 34, 2013, pp. 2094-2106*
[1] http://eurheartj.oxfordjournals.org/content/early/2013/04/25/eurheartj.eht134.full.pdf+html

Editor's comment: The guidelines for the use of the new anticoagulants in AF patients should be required reading for all afibbers prescribed dabigatran, rivaroxaban or apixaban. An excellent executive summary of the guidelines can be downloaded[1] and the full 26-page report can be found at http://europace.oxfordjournals.org/content/15/5/625.full.pdf+html Further information can also be found at the EHRA web site at www.NOACforAF.eu

Age and catheter ablation

HOUSTON, TEXAS. There is now abundant proof that catheter ablation is associated with a significantly better outcome than antiarrhythmic therapy when it comes to the treatment of atrial fibrillation (AF). There is also proof that the outcome of catheter ablation is better the sooner it is done and that trying antiarrhythmics prior to ablation may actually be counterproductive.

Despite this evidence many older AF patients are often treated solely with antiarrhythmics or rate control drugs, and thus denied the benefits of normal sinus rhythm (NSR). Two researchers from Methodist Hospital in Houston now provide evidence that the outcomes of catheter ablation in the elderly are similar to those achieved in younger patients. They cite five studies to support their contention.

- ***Corrado, et al.*** (2008) reported an average single-procedure success rate of 73% in 174 patients above the age of 75 years after a 20-month follow-up. Major and minor complications were reported in 1% and 1.5% of patients respectively.

- ***Bunch, et al.*** (2010) reported a one-year success rate (no AF or flutter without the use of antiarrhythmics) of 78% in patients 80 years or older as compared to 75% in patients younger than 80 years. There was no difference in complication rate and mortality between the two groups.

- ***Zado, et al.*** (2008) compared ablation outcome in three groups – age less than 65 years (948 patients), age between 65 and 74 years (185 patients), and age 75 years or older (32 patients). There was no significant difference between the three groups when comparing outcome and rate of major complications. Success rates in the groups were 89%, 84% and 86% respectively (no AF with or without antiarrhythmics). However, more patients in the oldest group (37%) than in the youngest group (20%) required antiarrhythmics to maintain NSR.

- ***Bhargava, et al***. (2004) demonstrated equal benefits of catheter ablation in three age groups – younger than 50 years, 51 to 60 years, and over 60 years (including patients up to 79 years of age). Success rates of the 1-year follow-up were 85%, 83% and 82% respectively.

- ***Traub, et al***. (2009) compared the outcome of pulmonary vein isolation in 15 patients over the age of 70 years and 45 patients below the age of 70, and found no difference in outcome or complication rates.

AV node ablation and pacemaker installation is another option for treating AF and is particularly favoured for elderly patients as it is relatively simple to perform. The researchers cite two studies that compared AV node ablation with pulmonary vein isolation (PVI).

- ***Khan, et al.*** (2008) compared the two techniques in 71 patients (aged between 52 and 68 years) with symptomatic AF and low left ventricular ejection fraction (40% or lower). They found that PVI resulted in better quality of life, improved physical

condition, and higher ejection fractions long-term. AV node ablation, on the other hand, was associated with AF progression and greater use of antiarrhythmic drugs. NOTE: AV node ablation also requires life-long anticoagulation.

- ***Hsieh, et al.*** (2005) compared AV node ablation with PVI in a small study of 71 elderly patients with symptomatic AF who could not be successfully treated with antiarrhythmics. Freedom from symptomatic AF was reported in 100% of the AV node ablation patients as compared to 81% in the catheter ablation (PVI) group. However, AV node ablation patients had a significantly greater incidence of heart failure (53% vs 24%), a worsening in left ventricular ejection fraction, and greater progression to persistent AF after 4 years (69% vs 8%).

The Houston researchers conclude that catheter ablation is safe and effective in elderly patients with atrial fibrillation.
Rojas, F and Valderrabano, M. Effect of age on outcomes of catheter ablation of atrial fibrillation. **Journal of Atrial Fibrillation**, *Vol. 6, No.1, June-July 2013, pp. 25-29*

Editor's comment: This study confirms that catheter ablation (PVI) is equally effective and safe in younger and older patients and will hopefully help remove any existing barriers to the use of catheter ablation in older AF patients.

Aspirin and warfarin: Should they be used together?

DURHAM, NORTH CAROLINA. Despite little evidence of benefit, millions of people around the world are taking an aspirin every day in order to ward off a first heart attack or ischemic stroke. Although the "daily aspirin ritual" is considered innocuous, it is anything but. A recent meta-analysis of 5 clinical trials comparing aspirin to placebo showed that long-term aspirin usage increases the relative risk of suffering a hemorrhagic stroke by about 40% and the risk of major gastrointestinal bleeding by 70%.

A Japanese clinical trial investigating the benefits of aspirin in low-risk atrial fibrillation (AF) patients found that there were actually more cardiovascular deaths, strokes and TIAs in the aspirin group than in the placebo group. In addition, fatal or major bleeding was found to be more frequent in the aspirin group than in the placebo group. Overall, the incidence of strokes, deaths and other adverse events was 42% greater in the aspirin group than in the placebo group. The trial was stopped early since the probability that aspirin would prove superior to placebo in stroke prevention, if it continued, was deemed to be vanishingly small.

It is well established that combining aspirin and warfarin therapy in AF patients increases the risk of major bleeding. Thus, it is surprising that a recent study found that 35% of AF patients prescribed warfarin for stroke prevention had also been prescribed aspirin. The study was part of the ORBIT-AF study and involved 7347 AF patients on oral anticoagulation with warfarin. Of the 35% of study participants prescribed both warfarin and aspirin, 39% had no atherosclerosis or other condition that would warrant prescribing aspirin in addition to warfarin. Conversely, 37% of patients with known cardiovascular disease who might benefit from added aspirin were only prescribed warfarin. Furthermore, a significant proportion of patients prescribed both warfarin and aspirin was known to have elevated bleeding risk. Not surprisingly, patients prescribed both warfarin and aspirin had a relative 50% greater risk of being hospitalized for major bleeding and a 3-fold increased risk of suffering a hemorrhagic stroke when compared to patients on warfarin only. These finding confirm earlier results from a Danish study which concluded that combining warfarin and aspirin doubles the risk of bleeding events when compared to warfarin alone.

The authors of the Duke University study conclude that physicians prescribing warfarin or one of the newer anticoagulants to AF patients need to carefully consider the benefit/risk ratio of adding aspirin.

Steinberg, BA, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation. **Circulation**, *Vol. 128, August 13, 2013, pp. 721-28*

Patrono, C and Andreotti, F. Antithrombotic therapy for patients with atrial fibrillation and atherothrombotic vascular disease. **Circulation**, *Vol. 128, August 13, 2013, pp. 684-86 (editorial)*

Editor's comment: This study adds to the proof that aspirin, whether used on its own or in combination with warfarin, is not innocuous and should be used with caution in AF patients. One of the authors of the study, Dr. Eric Peterson put it this way, "*In general, if I see a patient in my clinic who has only atrial fibrillation and no other risk factors, they should not be on aspirin because I know for sure their risk of bleeding is going to be one and a half times what it was before."*

As far as the "daily aspirin ritual" in general is concerned, the US Preventive Services Task Force has this advice, "*Patients at low risk for coronary heart disease probably do not benefit from and may even be harmed by aspirin because the risk for adverse events may exceed the benefits*."

NOTE: Discontinuing long-term use of aspirin may temporarily increase risk of stroke and TIA. For more on this see www.afibbers.com/atrial_fibrillation/stroke_prevention/N79c.htm

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