

## Atrial fibrillation management: Issues of concern

(APRIL 2011)

**TO THE EDITOR:** I read with interest the article by Drs. Callahan and Baranowski<sup>1</sup> in your April 2011 issue about managing newly diagnosed atrial fibrillation. I believe several issues merit further discussion.

First of all, as mentioned in the article, pulmonary vein isolation, or radiofrequency catheter ablation of the left atrium, can cure paroxysmal atrial fibrillation. Callahan and Baranowski described the optimal indication for this procedure, but they failed to mention the potential adverse effects, that is, esophageal ulcer and atrio-esophageal fistula.<sup>2</sup> Owing to the proximity of the esophagus and the accompanying vagus nerve to the posterior wall of the left atrium, it is estimated that 47% of patients develop thermal mucosal injury and 18% develop esophageal ulcer after ablation, while 0.5% develop atrio-esophageal fistula.<sup>3</sup> Gastric hypomotility and pyloric spasm are reported as well. It would therefore be prudent to inform patients of such risks if a persistently symptomatic young patient demands this procedure, since the damage might be long-lasting.

In addition, in deciding on long-term anticoagulation for patients with atrial fibrillation, the CHADS<sub>2</sub> score is often utilized (1 point each for congestive heart failure, hypertension, age 75 or older, and diabetes mellitus; 2 points for prior stroke or transient ischemic attack). Although it is validated and widely applicable, the CHADS<sub>2</sub> score carries the disadvantages of oversimplification and of overclassifying atrial fibrillation patients into the intermediate-risk category.<sup>4</sup> Lip et al,<sup>5</sup> in a seminal article surveying a large group of patients who had nonvalvular atrial fibrillation, proposed using a new and also simple risk stratification scheme, the 2009 Birmingham scheme. This scheme uses the acronym CHA<sub>2</sub>DS<sub>2</sub>-VASc and differs from the CHADS<sub>2</sub> score in that patients age 75 or older get 2 points, those age 65 to 74 get 1 point, those with vascular disease get 1 point, and women get 1 point. They show that this new scheme fares marginally better than the original CHADS<sub>2</sub> score, with fewer

patients wrongly assigned to the intermediate-risk category. That means a lower percentage of patients will receive unnecessary anticoagulation and suffer from unneeded anguish. Subsequent studies also prove that this newer scoring index possesses higher sensitivity and predicts thromboembolic events more accurately than the CHADS<sub>2</sub> score. Thus, I believe this should also be factored into the decision process when initiating warfarin in atrial fibrillation patients, especially in light of the fact that scanty evidence exists for the use of newer anticoagulants based on the CHADS<sub>2</sub> score.

CHIA-TER CHAO, MD  
Division of Nephrology  
Department of Internal Medicine  
National Taiwan University Hospital  
College of Medicine  
National Taiwan University  
Taipei, Taiwan

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**IN REPLY:** Dr. Chao raises several important points regarding our manuscript on the management of newly diagnosed atrial fibrillation.<sup>1</sup>

Dr. Chao mentions some of the complications of pulmonary vein antrum isolation. A review of catheter ablation for atrial fibrillation was outside the scope of our manuscript, so the details of the procedure and potential complications were not covered. Dr. Chao does mention some of the important potential complications. However, the complication rates he cites are not generally supported by the available medical literature. Thermal mucosal injury of the esophagus was reported at rates as low as 4% in

the same studies cited by Dr. Chao in patients undergoing pulmonary vein antrum isolation with conscious sedation. The rate of 47% was seen in patients undergoing the procedure with general anesthesia. The rate of atrio-esophageal fistula is not well known. As of 2010, about 49 cases were reported in the literature.<sup>2</sup> Rates have been described ranging from 0.01% to 0.2%,<sup>3-9</sup> far lower than the rate mentioned by Dr. Chao. A careful review with the patient of the risks, benefits, and alternatives is standard practice before any elective, invasive procedure.

Multiple anticoagulation schemes have been proposed, including the Birmingham 2009 scheme.<sup>10</sup> We included the CHADS<sub>2</sub> score in our paper because it is widely accepted and well validated. The Birmingham 2009 scheme acknowledges other potential risk factors such as female sex, history of vascular disease, and age between 65 and 75 years. It will be interesting to see if it will ever supplant the CHADS<sub>2</sub> score. However, no risk stratification scheme should replace sound clinical judgment. Individual patient factors must be considered when deciding whether anticoagulation is appropriate for an individual patient.

THOMAS CALLAHAN, MD  
Department of Cardiovascular Medicine  
Cleveland Clinic

BRIAN BARANOWSKI, MD  
Department of Cardiovascular Medicine  
Cleveland Clinic

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## Angioedema due to the renin inhibitor aliskiren

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**TO THE EDITOR:** The interesting report by Korniyenko and colleagues of the delayed diagnosis of visceral angioedema due to angiotensin-converting enzyme (ACE) inhibitor therapy<sup>1</sup> should alert readers that a long duration of use of ACE inhibitors should not rule out the diagnosis of ACE inhibitor-induced angioedema, as symptoms can be delayed for up to a decade.

Risk factors for angioedema for patients on ACE inhibitor therapy that have been identified so far include black race, the XPNPEP2 C-2399A polymorphism in men (which leads to decreased aminopeptidase P activity),<sup>2</sup> and concomitant use of the mTOR inhibitors sirolimus (Rapamune) or everolimus (Afinitor) in renal transplant recipients.<sup>3</sup> All of these factors further decrease metabolism of the vasoactive peptide bradykinin. However, the effect of cofactors such as use of nonsteroidal anti-inflammatory drugs, aspirin, simvastatin, estrogen, or a tendency for angioedema (such as in patients with recurrent or episodic idiopathic angioedema) on lowering the threshold for angioedema or increasing the severity of the angioedema episode or episodes after starting ACE inhibitor therapy remains unknown.

Physicians should also be aware of angioedema as a significant side effect of the new renin inhibitor aliskiren (marketed by Novartis Pharmaceuticals as Rasilez in the United Kingdom and as Tekturna in the United States) for treatment of essential hypertension.<sup>4</sup> A pooled analysis of 31 studies in 12,188 patients showed the incidence of angioedema associated with aliskiren monotherapy to be 0.4%, similar to that with ACE inhibitors: relative risk 0.31, 95% confidence interval 0.07–1.47 for 150 mg; relative risk 0.57, 95% confidence interval 0.17–1.89 for 300 mg.<sup>5</sup> However, no patients were hospitalized with a serious angioedema event.

Although the mechanism of action of

aliskiren via renin inhibition would suggest that bradykinin may not be the causative agent of angioedema, physicians should ensure that patients who report significant angioedema episodes or those who present with angioedema have their medication history thoroughly reviewed to prevent a serious untoward event.

DR. S. KHAN  
Department of Immunology  
Frimley Park Hospital  
NHS Foundation Trust  
Frimley, UK

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**IN REPLY:** We agree with Dr. Khan that the duration of ACE inhibitor therapy should never be used to rule out ACE inhibitor-associated angioedema. In an Italian study of 85 cases of angioedema with ACE inhibitor therapy, the mean ACE inhibitor exposure was a full 12 months before angioedema was diagnosed.<sup>1</sup> More disturbing was the fact that another 12 months elapsed before the ACE inhibitor actually was discontinued. This would indicate that neither the patient nor the physician related the angioedema to ACE inhibitor therapy. In patients with visceral angioedema, since the diagnosis is unusually challenging, even a further delay can be expected.

Angioedema has been reported with aliskiren, but the 0.04% incidence reported by White et al<sup>2</sup> may reflect very simply that physicians are more alert and on the lookout now more than they ever were when ACE inhibitors were first available. Obviously, greater awareness will lead to more frequent diagnosis. As Dr. Khan points out, there is no known mechanism by which aliskiren should cause angioedema, whereas there is fairly solid evidence that ACE inhibitor-associated angioedema is mediated by bradykinin.<sup>3,4</sup>

ALEKSANDR KORNIYENKO, MD  
St. Luke's-Roosevelt Hospital Center  
Columbia University College  
of Physicians and Surgeons  
New York, NY

FRANZ H. MESSERLI, MD  
Director, Hypertension Program  
Professor of Clinical Medicine  
Columbia University College  
of Physicians and Surgeons  
Division of Cardiology  
St. Luke's -Roosevelt Hospital Center  
New York, NY

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