RELIAS
Formerly AHC Media

Clinical Cardiology

Critical analysis of the latest clinical research in cardiovascular medicine [ALERT]

Vol. 37, Issue 3, March 2018
AHCMedia.com

ABSTRACT & COMMENTARY

CASTLE-AF Supports Catheter Ablation for Atrial Fibrillation in Patients with Heart Failure

By Joshua D. Moss, MD

Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco

Dr. Moss reports no financial relationships relevant to this field of study.

SYNOPSIS: Catheter ablation for atrial fibrillation in relatively young men with cardiomyopathy and heart failure is associated with a substantial reduction in arrhythmia burden, improvement in ejection fraction, and reduction in heart failure hospitalizations and mortality compared to medical therapy.

SOURCE: Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;378:417-427.

(Editor's Note: Late-breaking results of the landmark CASTLE-AF trial were presented at the European Society of Cardiology Congress in August 2017, with full details published in February in *The New England Journal of Medicine*.)

This prospective, randomized, open-label study at 33 sites in Europe, Australia, and the United States enrolled 398 patients with left ventricular (LV) ejection fraction (EF) ≤ 35%, heart failure, paroxysmal or persistent atrial fibrillation (AF), and "absence of response to, unacceptable side effects from, or unwillingness to take antiarrhythmic drugs." After a five-week run-in phase to adjust administration of heart failure medications according to guidelines, 363 patients who remained in the trial were randomized to catheter ablation for AF (n = 179) or medical therapy (n = 184), with a composite primary endpoint of death or hospitalization for worsening heart failure.

Catheter ablation was performed by experienced operators and consisted of pulmonary vein isolation (PVI) alone in 48% of patients or PVI plus additional

Financial Disclosure: *Clinical Cardiology Alert*'s Physician Editor Michael H. Crawford, MD, Peer Reviewer Susan Zhao, MD, Nurse Planner Amy Johnson, MSN, RN, Editor Jonathan Springston, Executive Editor Leslie Coplin, and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

[INSIDE]

Measuring Aortic Stenosis page 19
Diagnosing Aortic Dissection page 20
Physical Activity in CAD Patients page 21
Stroke Risk in Atrial Fibrillation page 23

Clinical Cardiology [ALERT]
Critical analysis of the latest clinical research in cardiovascular medicine

Clinical Cardiology Alert,
ISSN 0741-4218, is published 12 times annually by AHC Media, a Relias Learning company, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

GST Registration Number: R128870672. Periodicals Postage Paid at Cary, NC, and additional mailing offices.

POSTMASTER: Send all address changes to *Clinical Cardiology Alert*, Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments:
Please contact Editor **Jonathan Springston** at jspringston@relias.com

Subscription Prices
United States
Print: 1 year with ***free*** *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only, single user: with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Relias Learning designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Relias Learning LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [2.25] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.25 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

lesions (at the discretion of the operator) in 52% of patients during the initial procedure. Some patients (15.6%) did not undergo any ablation for several reasons and crossed over to medical therapy. After a standard 12-week post-ablation blanking period, 22.5% of patients underwent one additional ablation procedure and 2% underwent two additional procedures. Twenty-three patients were lost to follow-up for the primary endpoint.

Medical therapy was administered based on the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines. Although rhythm control was encouraged, about 70% of patients were treated using a rate-control strategy, targeting goal heart rates of 60-80 beats per minute at rest and 90-115 beats during moderate exercise. Eighteen patients crossed over to catheter ablation, and 10 were lost to follow-up.

Median age at enrollment was 64 years and median EF was about 32%, with nearly all patients (86%) male and the majority exhibiting New York Heart Association (NYHA) Class II or III heart failure symptoms. Most patients had an implantable cardioverter defibrillator (ICD) implanted before enrollment, and arrhythmia burden was assessed via ICD remote monitoring. Researchers ended the trial early (after 133 primary endpoint events had occurred) when it became apparent that the target of 195 events would not be reached in a reasonable time frame. A modified intention-to-treat analysis was performed, excluding patients who died or were withdrawn during the run-in period, endpoint events during the run-in period, and non-death events during the 12-week post-ablation blanking period (and an equivalent 12-week period after baseline in the medical-therapy group).

Death or hospitalization for heart failure occurred in 28.5% of ablation patients vs. 44.6% in the medical therapy group. Also significantly reduced in the ablation group were death from any cause (13.4% vs. 25.0%), cardiovascular death (11.2% vs. 22.3%), heart failure hospitalization (20.7% vs. 35.9%), and cardiovascular hospitalization (35.8% vs. 48.4%). There was a trend toward reduction in stroke (2.8% vs. 6.0%; $P = 0.15$). The burden of AF based on memory from the implanted devices was substantially lower in the ablation group; 63.1% of those patients were in sinus rhythm at the five-year follow-up visit with no recurrence since the four-year follow-up visit compared with 21.7% in the medical therapy group. Additionally, median absolute increase in EF was 8.0% in the ablation group compared with 0.2% in the medical therapy group. Serious complication rates were low in the ablation group. Three patients experienced pericardial effusion, one of whom required pericardiocentesis, and three demonstrated bleeding severe enough to require transfusion. There were no phrenic nerve injuries, strokes, or deaths related to the procedure. The authors concluded that catheter ablation for AF should be strongly considered early in the management of patients with heart failure.

■ COMMENTARY

The CASTLE-AF trial has quickly generated debate in the cardiology and electrophysiology community. Some point to the impressive improvements in outcomes after ablation (including a 50% relative reduction in death) as confirmation of anecdotal experience; some see an expected extension of results from other trials of catheter ablation for AF in heart failure (including CAMERA-MRI and AATAC); and some consider it a call to arms. Others have urged caution based on the relatively small number of patients, the statistical methods employed and unblinded nature of the trial, a differential loss to follow-up between the groups, and results that simply seem "too good to be true."

Regardless of the effect size (which was largely unchanged with several alternate analyses presented in the supplementary appendix), it is difficult to argue convincingly that this population of patients did not benefit from the very plausible reduction in AF burden afforded by catheter ablation. At no time did the authors contend that catheter ablation for AF is a "cure," and their arrhythmia results are in line with clinical experience and prior trials of ablation for AF. After all, of 151 patients in the ablation group who underwent ablation, 75 experienced an adjudicated recurrence of AF during up to five years

of follow-up. However, mean burden per patient was 27% of the time at five years in the ablation group vs. 64% of the time in the medical therapy group (median burden 0% vs. 99% of the time). Improvements in heart failure and mortality clearly are plausible biologically with such a significant reduction in arrhythmia burden when not achieved with additional toxic antiarrhythmic drugs. The results also are difficult to "blame" on differential effects of antiarrhythmic drugs, since at the last follow-up with documented medication use, 25% of patients in the ablation group were taking amiodarone compared with 31% in the medical therapy group. The CASTLE-AF trial is not an invitation to sign up every patient with heart failure and AF for an ablation procedure. These results alone cannot necessarily be extrapolated to older patients or even to women. Additionally, it is worth noting that there were more patients with non-ischemic cardiomyopathy in the ablation group (59%) than in the medical therapy group (49%), and a subgroup analysis suggested no benefit of ablation in more severe cardiomyopathy (EF < 25%) or heart failure (NYHA Class III). However, there also was no subgroup in which medical therapy was superior, and rates of serious complications from catheter ablation were low. Thus, the potential benefits of ablation for AF should be strongly considered early in the management of patients with heart failure. ■

ABSTRACT & COMMENTARY

What's the Best Technique to Measure Low-flow, Low-gradient Aortic Stenosis?

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco Cardiology Division, Advanced Heart Failure Section

Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: In patients with low-flow, low-gradient aortic stenosis, current guideline-based criteria for identifying true severe aortic stenosis did not predict aortic stenosis severity or survival. Calculation of the projected aortic valve area at a normal transvalvular flow rate more accurately identifies true severe aortic stenosis and is a stronger predictor of outcomes.

SOURCE: Annabi MS, Touboul E, Dahou A, et al. Dobutamine stress echocardiography for management of low-flow, low-gradient aortic Stenosis. *J Am Coll Cardiol* 2018;71:475-485.

Current guidelines define low-flow, low-gradient aortic stenosis (LF-LG AS) as the combination of left ventricular ejection fraction (LVEF) < 50%, aortic valve area (AVA) ≤ 1.0 cm^2, and a mean gradient (MG) < 40 mmHg. Dobutamine stress echocardiography (DSE) is recommended in patients with LF-LG AS to identify those with true severe aortic stenosis (TSAS) from pseudo-severe aortic stenosis (PSAS). TSAS is diagnosed when the AVA is ≤ 1.0 cm^2 with MG ≥ 40 mmHg during DSE. However, these criteria have not been well validated.

The creators of The Multicenter Prospective Study of Low-Flow Low-Gradient Aortic Stenosis (TOPAS) enrolled 186 patients with LVEF ≤ 40%, aortic valve MG ≤ 40 mmHg, and indexed AVA ≤ 0.6 cm^2/m^2. All patients underwent DSE. AS severity was confirmed either by macroscopic evaluation of the valve by a surgeon at the time of aortic valve replacement (AVR) using predefined criteria or by quantification of aortic valve calcification using multidetector computed tomography (MDCT). In addition to standard parameters obtained during DSE, the authors calculated the projected aortic valve area (AVA_{proj}) at a normal transvalvular flow rate (250 mL/min).

The recommended combination of peak stress MG and peak stress AVA correctly classified AS severity in only 47% of patients. AVA_{proj} ≤ 1.0 cm^2 correctly classified 70% of patients, better than any other marker evaluated ($P < 0.0007$). In an adjusted analysis of medically managed patients who did not undergo AVR, AVA_{proj} ≤ 1.0 cm^2 was a strong predictor of survival (hazard ratio, 3.65; $P = 0.0003$). Neither AVA or MG at peak stress predicted survival in medically managed patients. The authors concluded that in patients with low LVEF LF-LG AS, the current guideline-recommended criteria of peak stress MG ≥ 40 mmHg and AVA ≤1 cm^2 carry limited value for predicting actual stenosis severity and outcomes. The AVA_{proj} may be superior.

■ COMMENTARY

Although they only comprise a small minority of AS patients, those with LF-LG AS often present a diagnostic and therapeutic challenge. It is critical to identify patients with PSAS, where the calculated AVA

is low because the heart cannot generate enough flow to open the aortic valve leaflets, even in the absence of severe disease. Guidelines from the American College of Cardiology/American Heart Association recommend DSE to discriminate PSAS from TSAS, and even give a Class IIa recommendation for AVR in patients with LF-LG AS who meet criteria for TSAS (MG ≥ 40 mmHg and AVA ≤ 1.0 cm^2 during DSE). However, Annabi et al provided strong evidence that these criteria are neither sensitive nor specific for identifying TSAS. Furthermore, because these parameters do not predict survival in medically treated patients, they are not ideal tools for identifying candidates for AVR.

Both MG and AVA are flow-dependent parameters, and dobutamine is administered with the goal of increasing transvalvular flow to normal levels. However, in the Annabi et al study, approximately one-half of patients did not demonstrate normal flow during DSE. Both subnormal and supranormal flow rates would limit the reliability of both AVA ad MG significantly.

On the other hand, the AVA_{proj} is standardized for a transvalvular flow rate that is fixed for all patients. The formula used by the authors to calculate AVA_{proj} was as follows:

$$AVA_{proj} = AVA_{rest} + \frac{AVA_{peak} - AVA_{rest}}{Q_{peak} - Q_{rest}} \times (250 - Q_{rest})$$

Q represents flow; peak values are the maximum obtained during DSE and rest are values obtained during the resting echocardiogram. The AVA_{proj} is independent of LV function and flow. The authors showed strong evidence that AV_{proj}, using a cutoff of 1 cm^2, identifies TSAS and predicts survival in LF-LG AS much better than AVA, MG, or a combination of the two. There are several limitations to mention. Medically treated patients were thought to have either nonsevere AS or significant comorbidities, and this may introduce selection bias. The gold standard used in this study for diagnosing severe AS was assessment of the valve by the surgeon at the time of AVR. This is not a rigorous, well-defined metric for grading AS severity. The AVA_{proj} will require further validation in other AS cohorts before its widespread use can be recommended. However, in the meantime, we now have an additional metric for discriminating TSAS vs. PSAS among patients with LF-LG AS. It is worth calculating AVA_{proj} for all DSE performed to evaluate LF-LG AS. It may be particularly helpful when standard parameters for differentiating TSAS from PSAS remain discordant despite DSE. ■

ABSTRACT & COMMENTARY

Accurately Diagnosing Aortic Dissection

By Michael H. Crawford, MD, Editor

SYNOPSIS: A prospective study of patients with suspected acute aortic syndromes showed that a clinical risk score plus D-dimer testing carried a positive predictive value of 99.7% and a 0.3% incidence of false-negative studies. The authors recommended that this approach become the standard method for triage to imaging in patients with suspected acute aortic syndromes.

SOURCE: Nazerian P, Mueller C, Soeiro AM, et al. Diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes. *Circulation* 2018;137:250-258.

Aortic dissection, intramural hematoma, and penetrating ulcer are life-threatening acute aortic syndromes (AAS), with a concerning misdiagnosis rate of up to 40%. Although CT angiography can diagnose AAS accurately, < 3% of such studies conducted in patients suspected of experiencing AAS were positive in an ED-based study. Clearly, clinicians need something to increase the accuracy of diagnosis and reduce unnecessary testing.

Thus, this prospective observational study conducted in six centers in three countries in Europe and one in Brazil that tested an AAS risk score (RS) plus D-dimer testing (DD) is of interest. Adult patients presenting to the ED in whom AAS was in the differential diagnosis were assessed. Only those who refused participation or experienced significant trauma were excluded. The RS included 12 risk markers and has been published previously.[1] Confirmation of AAS was by CT angiography, MR angiography, transesophageal echocardiography, surgery, or autopsy. If these tests were not performed, researchers confirmed using a 14-day follow-up observation period. The primary outcome was the failure rate of two diagnostic strategies for excluding AAS: 1) RS = 0 and DD negative (< 500 ng/mL); and 2) RS < 1 and DD negative.

Over three years, researchers enrolled 1,850 patients in the study. Of these, 24% demonstrated RS = 0 and 58% exhibited RS = 1; thus, 82% were classified as low risk for AAS. DD was positive in 44%, 33% with RS = 0 and 41% with RS = 1. Therefore, the DD was

positive in 39% of patients with RS < 1 and in 67% with RS > 1. A conclusive diagnosis of AAS was made in 13% of the patients. A positive DD had a sensitivity of 97% and a specificity of 64% for the diagnosis of AAS. In the 294 patients with an RS = 0 and who were DD-negative, only one case of AAS was observed for a failure rate of 0.3%. The authors concluded that either RS = 0 or < 1 plus DD negative should be adopted as the standard to exclude the diagnosis of AAS.

■ COMMENTARY

This risk score for AAS was evaluated against the International Registry of Acute Aortic Dissection (IRAD) database from 1996 to 2009, which included 2,538 patients with confirmed AAS. The score is based on identifying risk markers from three groups. If one or more are discovered from a group, that equals 1 point; one or more from another group is another point and so on for a total possible score of 3. The three groups are pain features, such as abrupt, severe, or tearing; predisposition features, such as known aneurysm or aortic valve disease; and physical examination features, such as a new aortic regurgitation murmur or pulse deficits. In the IRAD database of confirmed AAS cases, 88% exhibited more than one pain feature; 28% more than one predisposition feature; and 51% one or more exam features. This resulted in a sensitivity of 96% and a false-negative rate of 4%. Given that only 1/10,000 ED visits are confirmed AAS, this is a rare condition that precludes performing a prospective study, according to the authors. Thus, the authors did not know the specificity or false-positive rates. Accordingly, the RS-DD muliticenter study is of interest, since it is prospective and includes the DD test, which is reported to carry a very high negative predictive value. The main findings of this study were that the RS-DD combination carried a very high positive predictive value of 99.7% and a failure rate of 0.3% (false-negatives). If those with a negative DD but a RS > 1 were examined, 4% had an AAS, which is similar to the false-negative rate of RS alone in the older study. Clearly, this false-negative rate is unacceptable for this condition, and the RS-DD doesn't work well in those at clinically high risk, even in those with a negative DD. Thus, these patients should undergo imaging despite the negative DD. A high clinical suspicion trumps DD.

There are limitations to this study. The clinical entry criteria were prespecified but determined by each provider. This is hard to standardize. The study was conducted in urban teaching hospitals and may not be generalizable. It was non-blinded, which likely affected the decision to perform imaging, but would it have been ethical to blind the study? Finally, about half the subjects did not undergo imaging, surgery, or autopsy, but received an AAS confirmation or denial by a two-week follow-up period under the assumption that untreated AAS would lead to early adverse events. This approach identified seven patients with AAS (0.4% of all patients), but may have missed some mild cases. These were probably not type A dissections, but could have been type B, intramural hematoma or penetrating ulcers that healed on their own.

At this point, the RS plus DD evaluation is the best tool at our disposal for the initial triage of suspected AAS cases. Those with a RS > 1 should go right to imaging. Those with RS < 1 should undergo a DD and imaging only if it is positive. ■

REFERENCE

1. Rogers AM1, Hermann LK, Booher AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. *Circulation* 2011;123:2213-2218.

ABSTRACT & COMMENTARY

Physical Activity and Death in CAD Patients

By Michael H. Crawford, MD, Editor

SYNOPSIS: An observational study of leisure time physical activity (LTPA) assessed at baseline and two years later in stable coronary artery disease patients, who then were followed for about five more years, showed that LTPA at baseline, at two years, and if it went from zero at baseline to some at two years was associated with lower rates of cardiac death compared to inactive patients.

SOURCE: Lahtinen M, Toukola T, Junttila MJ, et al. Effect of changes in physical activity on risk for cardiac death in patients with coronary artery disease. *Am J Cardiol* 2018;121:143-148.

Leisure time physical activity (LTPA) is recommended for secondary prevention in patients with stable coronary artery disease (CAD), yet studies of its beneficial effects have produced mixed results. One explanation is that most researchers assess LTPA once and do not know if it changes over the observation period. Investigators from Finland assessed LTPA over two years in CAD patients and associated it with cardiac mortality over up to seven years of observation. The study population was derived from patients

in the Innovation to Reduce Cardiovascular Complication of Diabetes at the Intersection study database of 1,946 patients with stable angiographically verified CAD and type 2 diabetes. Patients with serious, life-threating comorbidities such as Class IV heart failure and end-stage renal disease were excluded. Also excluded were those with less than two years follow-up. During the initial follow-up, information about LTPA was collected at baseline and two years. Based on these data, four groups were identified: no LPTA, irregular light LPTA, regular moderate intensity LTPA, and moderate- to high-intensity LTPA for at least 30 minutes three times a week. Also, subjects were divided by their activity at baseline compared to two years into four other groups: Active-Active or greater than or equal to irregular at both time periods, Inactive-Active, Active-Inactive, and Inactive-Inactive. The main follow-up started at the two-year point, and the primary endpoint was cardiac death.

During a median follow-up of 54 months, there were 68 cardiac deaths. Baseline LTPA was associated with cardiac death in multivariate analyses: irregularly active hazard ratio (HR) = 1.4 (95% confidence interval {CI], 0.6-3.2) and inactive HR = 4.7 (95% CI, 2.1-10.6; $P < 0.05$) compared to the active groups. The LTPA at two years was associated with cardiac death: inactive HR = 8.0 (95% CI, 2.8-22.4; $P < 0.05$), irregularly active HR = 1.7 (95% CI, 0.6-5.3), and moderate regular HR = 1.9 (95% CI, 0.6-5.7) compared to the highly active group. In addition, the change in LTPA over the two years was associated with cardiac death: Inactive-Inactive HR = 7.6 (95% CI, 4.2-13.6; $P < 0.05$), Active-Inactive HR = 3.7 (95% CI, 2.1-6.7; $P < 0.05$), and Inactive-Active HR = 1.6 (95% CI, 0.4-6.7). The authors concluded that LTPA is of prognostic value in stable CAD patients, and even small changes in activity over two years were related to the risk of cardiac death over a median of 4.5 years.

■ COMMENTARY

Current acute coronary syndrome guidelines recommend referral to cardiac rehabilitation. One of the goals of cardiac rehab is to convert patients to a long-term exercise habit. This study clearly demonstrates why this is important: Regular physical activity is associated with longevity in CAD patients. The study also reinforces that it doesn't take much activity to demonstrate this difference: The highly active group performed moderate- to high-intensity LTPA for a minimum of 30 minutes three times a week. Even the irregular light activity and regular moderate activity groups were not statistically different from the highly active groups. Only the completely inactive group demonstrated a statistically significant increase in cardiac death compared to all three active groups. Thus, we can tell our patients that any degree of LTPA carries some survival value.

The unique contribution of this study is the two-year survey of the patient's activity history before the follow-up period began. The two-year data largely mirrored the baseline activity data in the prediction of cardiac death. It is interesting that more patients became inactive at two years than became active. This pattern was associated with an increase in cardiac death compared to those who remained active. Also, those who did go from inactive at baseline to active at two years reduced their risk of cardiac death. Thus, efforts to get CAD patients active and keep them active are worthwhile.

There are limitations to this study. Since it was not a randomized trial, there may have been a patient self-selection bias where the healthiest were more likely to be active. This potential issue was observed when the baseline exercise capacity was factored into the multivariate model and the association between LTPA and cardiac death was attenuated. Unfortunately, exercise capacity was not remeasured at two years. There are minimal details on LTPA, and it was a subjective assessment. Also, very few patients went from inactive to active, so this limits conclusions about its effects on mortality.

On the positive side, we know that strenuous physical activity in CAD patients can precipitate acute coronary events, but this was not observed with LTPA in this study. Thus, it appears generally safe to recommend regular LTPA for stable CAD patients. ■

ABSTRACT & COMMENTARY

Stroke Risk in Atrial Fibrillation: A Moving Target?

By Michael H. Crawford, MD, Editor

SYNOPSIS: An investigation of patients in a national database with atrial fibrillation, no comorbidities, and not on aspirin or anticoagulants showed that the clinical features that make up the CHA_2DS_2-VASc score change over time and can increase a patient's risk for stroke, which could affect therapy decisions. Thus, the CHA_2DS_2-VASc score should be reassessed periodically and appropriate therapeutic actions taken promptly.

SOURCES: Chao TF, Lip GYH, Liu CJ, et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;71:122-132.

Gage BF. Stroke prediction rules in atrial fibrillation. *J Am Coll Cardiol* 2018;71:133-134.

Previous studies of stroke risk in patients with atrial fibrillation (AF) have assessed the risk factors imbedded in the CHA_2DS_2-VASc score at baseline and then observed the patients during years of follow up. However, as these patients age, comorbidities that affect their risk often change.

Investigators from Taiwan hypothesized that changes in the CHA_2DS_2-VASc score would carry greater predictive value than the baseline score. From the Taiwan National Health Insurance database, 31,039 patients with AF who were not on antiplatelet or anticoagulant drugs and did not exhibit any features in the CHA_2DS_2-VASc scheme (except age and sex) were identified from 1996-2009. In this group, 4,103 experienced a stroke during follow-up. The follow-up CHA_2DS_2-VASc score was the highest measured before the occurrence of stroke, mortality, or the end of 2009. The difference between the baseline and follow-up CHA_2DS_2-VASc score (delta) and the slope of the score change were calculated. During follow-up, the mean age increased from 64 to 68 years and the delta CHA_2DS_2-VASc was 1.02. The baseline, follow-up, and delta CHA_2DS_2-VASc scores were higher in those who experienced a stroke. About 52% of patients acquired a new comorbidity that affected the CHA_2DS_2-VASc score, most commonly hypertension (37%), heart failure (27%), and diabetes (13%). CHA_2DS_2-VASc remained unchanged in only 41% of patients. The delta CHA_2DS_2-VASc score predicted stroke (hazard ratio, 1.52; 95% confidence interval, 1.48-1.56; $P < 0.001$) and performed better than baseline or follow-up CHA_2DS_2-VASc. The area under the receiver operating curve (AUC) was 0.74 for delta CHA_2DS_2-VASc, compared to 0.58 for baseline and 0.73 for follow-up. Also, the slope of the delta CHA_2DS_2-VASc was higher in those with stroke compared to those without (0.58 vs. 0.42; $P < 0.001$). The authors concluded that the CHA_2DS_2-VASc score is not static over time and most patients with AF develop one or more new comorbidities that affect the CHA_2DS_2-VASc score in addition to aging. This increment in the CHA_2DS_2-VASc score also was highly predictive of stroke.

■ COMMENTARY

In some ways, the results of this study are obvious. If one acquires risk factors for stroke over time, the risk of stroke increases. Since this has not been investigated or proven, this study is of interest. The main finding of the study is that the AUC of the follow-up CHA_2DS_2-VASc score is significantly higher than that of the baseline score (0.74 vs. 0.58). However, considering that at baseline all the patients included in this study exhibited no comorbidities and registered CHA_2DS_2-VASc scores of 0 for men and 1 for women, this, too, is unsurprising. One would expect that as patients with AF age they would pick up comorbidities that affect the CHA_2DS_2-VASc score, as most subjects in this study did. What is perhaps the most interesting finding in this study is that soon after an increase in the CHA_2DS_2-VASc score, the risk of stroke is higher than later. The editorialist for this article suggested that this is because new comorbidities may not be well controlled early after diagnosis. He noted that the risk of stroke is high early after a transient ischemic attack but decreases over time. The same may be true for newly diagnosed hypertension, heart failure, or diabetes.

There are limitation to this study. It was an insurance database study, and all diagnoses were made by the patient's own physicians. However, the authors noted that the accuracy of this approach has been validated previously in the Taiwan database. There are no laboratory data available, so the influence of biomarkers cannot be ascertained. Although they assessed the value of changes in the CHA_2DS_2-VASc score, the authors explicitly stated that they are not proposing a new measure of delta CHA_2DS_2-VASc. The authors only showed these data to bolster their point that changes in the CHA_2DS_2-VASc over time must be considered and therapeutic changes made as appropriate to reduce the rising risk of stroke. ■

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log on to **AHCMedia.com** and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME/CE QUESTIONS

1. **The current best method for triaging patients with possible acute aortic syndromes to imaging studies is:**

   a. the D-dimer test (DD).

   b. a clinical characteristics risk score (RS).

   c. a combined RS-DD approach.

   d. None of the above

2. **A recent randomized trial of catheter ablation vs. medical therapy for patients with atrial fibrillation and heart failure showed that catheter ablation:**

   a. reduced cardiovascular death.

   b. reduced heart failure hospitalizations.

   c. increased left ventricular ejection fraction.

   d. All of the above

3. **A study of leisure time physical activity in stable coronary artery disease patients showed that which of the following was associated with cardiac death?**

   a. Regular high-intensity exercise

   b. Complete inactivity

   c. Irregular mild leisure activity

   d. Going from inactive to active over two years

4. **Distinguishing true from pseudo-severe aortic stenosis in patients with low-flow/low-gradient and a calculated valve area < 1.0 cm^2 is best assessed during dobutamine echo using:**

   a. mean gradient > 40 mmHg.

   b. valve area < 1.0 cm^2.

   c. the projected valve area at a flow rate of 250 mL/min.

   d. None of the above

5. **Which of the following is most correct concerning the use of the CHA_2DS_2-VASc score in patients with atrial fibrillation?**

   a. It is guideline-recommended for determining antithrombic therapy in atrial fibrillation.

   b. It should be remeasured if comorbidities change.

   c. New comorbidities should be controlled quickly.

   d. All of the above

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications, of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.