

# Clinical Cardiology

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

## ABSTRACT & COMMENTARY

### Dapagliflozin Treatment Improves Life Quality for Systolic Heart Failure Patients

By *Jamie L.W. Kennedy, MD, FACC*

*Associate Professor, Division of Cardiology, Advanced Heart Failure & Transplant Cardiology, University of California, San Francisco*

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

**SYNOPSIS:** Treatment with dapagliflozin for 12 weeks resulted in improved health status, either a reduction in NT-proBNP or improvement in quality of life measures, in systolic heart failure patients with or without type 2 diabetes mellitus.

**SOURCE:** Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms and functional status in patients with heart failure with reduced ejection fraction, the DEFINE-HF trial. *Circulation* 2019;140:1463-1476.

**S**odium-glucose cotransporter-2 (SGLT2) inhibitors increase urinary excretion of glucose, thereby lowering blood sugar. Several large clinical trials of SGLT2 inhibitors in diabetic patients have shown reductions in heart failure hospitalizations. However, these trials were limited by low numbers of patients with heart failure and lack of details on their cardiac disease, such as prevalence of systolic dysfunction. Of course, heart failure remains a highly morbid and mortal disease despite currently available evidence-based interventions such as medications and devices.

Nassif et al studied the use of one SGLT2 inhibitor, dapagliflozin, in patients with established

symptomatic systolic heart failure, defined as ejection fraction  $\leq 40\%$  with New York Heart Association (NYHA) class II to III symptoms. Patients with and without type 2 diabetes mellitus were enrolled. Type 1 diabetes patients were excluded, as were patients with recent heart failure hospitalizations and chronic kidney disease stage 4 or 5. Patients were randomized to dapagliflozin or placebo for 12 weeks. The two primary endpoints were a little complex. The first endpoint is the average of six- and 12-week mean NT-proBNP. The second endpoint is a composite of the proportion of patients who achieved a meaningful improvement in health status, defined as either five-point increase in Kansas City Cardiomyopathy Questionnaire

**Financial Disclosure:** *Clinical Cardiology Alert's* Physician Editor Michael H. Crawford, MD, Peer Reviewer Susan Zhao, MD, Nurse Planner Aurelia Macabasco-O'Connell, PhD, ACNP-BC, RN, PHN, FAHA, Editor Jonathan Springston, Editor Jason Schneider, Editorial Group Manager Leslie Coplin, and Accreditations Manager Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

[INSIDE]

Value of PET Scans in  
Infective Endocarditis

page 91

Cardiac Constriction  
vs. Cardiac Restriction

page 92

Optimizing AED  
Placement Locations

page 93

Anticoagulation  
Decisions in Afib

page 94

*Clinical Cardiology Alert* (ISSN 0741-4218) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Clinical Cardiology Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

© 2019 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual.

**SUBSCRIBER INFORMATION**  
(800) 688-2421  
customerservice@reliasmedia.com  
[ReliasMedia.com](http://ReliasMedia.com)

**ACCREDITATION**  
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2.25 AMA PRA Category 1 Credit(s)<sup>™</sup>. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias 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.

(KCCQ) or a 20% decrease in the average of six- and 12-week NT-proBNP. There were a range of prespecified subgroups and secondary endpoints, too, including heart failure events as an exploratory endpoint. The 263 patients enrolled in the trial were typical of heart failure studies: 73% male, with average age 61 years; 40% were African-American. Sixty-two percent of patients had type 2 diabetes mellitus, 40% had atrial fibrillation, and 53% had ischemic cardiomyopathy. Two-thirds of patients exhibited NYHA class II symptoms, one-third class III. They were a well-managed group: 97% prescribed beta-blockers, 92% ACE/ARB/ARNI, and 61% aldosterone antagonist. Sixty-two percent presented with ICDs and 35% presented with cardiac resynchronization therapy devices. The average left ventricular ejection fraction was 26%, and the median NT-proBNP on enrollment was 1,136 pg/mL. There was no difference between the groups in the first primary endpoint, the average six- and 12-week mean NT-proBNP (1,133 pg/mL vs. 1,191 pg/mL;  $P = 0.43$ ). However, the second primary endpoint revealed a significant improvement in health status in 61.5% of patients in the treatment arm vs. 50.4% in the control arm ( $P = 0.039$ ). Both components of this composite endpoint favored dapagliflozin: 42.9% vs. 32.5% of patients with five or more point increase in KCCQ and 44.0% vs. 29.4% with 20% or more reduction in NT-proBNP. Overall, safety events were similar between groups, although there were more episodes of volume depletion in the dapagliflozin arm (12 events vs. seven events). Interestingly, there were no differences in the rates of severe hypoglycemia (one patient in each arm, both of whom were diabetics). There was no difference in response rate for diabetics vs. nondiabetics. The authors concluded that treatment with dapagliflozin for 12 weeks resulted in improved health status in systolic heart failure patients with or without type 2 diabetes mellitus.

## ■ COMMENTARY

The DEFINE-HF study was published contemporaneously with DAPA-HF, a larger study of similar population, which showed treatment with dapagliflozin reduced rates of worsening heart failure

or cardiovascular death from 21.2% to 16.3% over a median of 18.2 months of treatment ( $P < 0.001$ ).<sup>1</sup> Components of the endpoint both favored dapagliflozin as well: cardiovascular death 9.6% vs. 11.5% and worsening heart failure in 10.0% vs. 13.7%.

The mechanism(s) by which dapagliflozin and other SGLT2 inhibitors benefit patients with heart failure is unclear. Certainly, improved blood sugar control in diabetics may decrease cardiovascular morbidity and mortality, and urinary excretion of glucose may result in improved control of volume status. Studies also have shown SGLT2 inhibitors lead to reduction in left ventricular mass in patients with coronary disease and diabetes, and alterations in cardiomyocyte metabolism favoring ketone bodies and reducing intracellular sodium and calcium.

DEFINE-HF's interesting twist was its focus on quality of life. Physicians and patients always have considered quality of life when making treatment decisions, although the database to guide these discussions has, at times, been thin. However, more recently, tools to assess quality of life, such as the KCCQ, have become available and implemented in clinical trials alongside "hard" endpoints such as mortality and hospitalization. In this particular case, the quality of life data aid the patient and physician in deciding whether to add yet another medication to already-extensive regimens. Most patients in this study were taking at least six medications on enrollment: ACE/ARB/ARNI, beta-blocker, aldosterone antagonist, loop diuretic, lipid-lowering agent, and one or more medications for diabetes. The cost and complexity of these regimens certainly weigh on patients' minds and wallets. Talking with patients about mortality absolute risk reductions in the 2% range, as seen in DAPA-HF, may not be sufficient for some patients to add an additional medication, while a clinically significant improvement in quality of life may be more meaningful.

As we have seen in previous trials, the use of evidence-based heart failure therapies far exceeded that in clinical practice. The benefit of dapagliflozin may be more marked in patients unable to tolerate

other evidence-based heart failure medications. Where on the pathway from normal glucose metabolism to insulin dependence were the nondiabetics in this study? The average age and high incidence of coronary disease and dyslipidemia leads me to suspect a sizable number of nondiabetics presented with impaired glucose tolerance, which may explain some of the benefit of dapagliflozin. For example, I am less certain a benefit would be seen in lean young adults with familial cardiomyopathy. I am interested to see if SGLT2 inhibitors are helpful for patients with heart failure with preserved ejection fraction, considering the lack of evidence-based treatment options demonstrating a benefit. How will these data alter my management of systolic heart failure patients? For patients with type 2 diabetes mellitus and heart failure, dapagliflozin certainly should be part of their medication regimen, perhaps replacing less beneficial medications like sulfonylureas. For non-

diabetic patients similar to the populations studied in DEFINE-HF and DAPA-HF, we will discuss dapagliflozin as an additional therapy beyond ACE/ARB/ARNI, beta-blockers, and aldosterone antagonists. For patients significantly different from the populations studied, such as lean young adults with familial cardiomyopathy, I would like to see additional data before routinely prescribing dapagliflozin. Finally, a practical point: Coordination of care with primary care physicians and endocrinologists will be even more important in the future, as we coordinate who prescribes and monitors which medication for which patient. ■

#### REFERENCE

1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print].

## ABSTRACT & COMMENTARY

# Value of PET Scans in Infective Endocarditis

By Michael H. Crawford, MD, Editor

**SYNOPSIS:** 18F-FDG PET/CT imaging in a consecutive series of patients with proven infective endocarditis was of diagnostic value in those with prosthetic valve endocarditis (sensitivity = 83%) and of prognostic value in all cases.

**SOURCES:** San S, Ravis E, Tessonier L, et al. Prognostic value of 18 F-Fluorodeoxyglucose positron emission tomography/computed tomography in infective endocarditis. *J Am Coll Cardiol* 2019;74:1031-1040.

Rouzet F, lung B, Duval B. 18 F-FDG PET/CT in infective endocarditis: New perspectives for improving patient management. *J Am Coll Cardiol* 2019;74:1041-1043.

**P**ET plus CT scanning has been shown to be of value in the diagnosis of prosthetic valve endocarditis (PVE), but less is known about its prognostic value in PVE and native valve endocarditis (NVE). Investigators from a hospital in Marseille, France, performed 18 F-fluorodeoxyglucose (FDG) PET/CT as soon as possible after admission in consecutive patients with a definite diagnosis of left-sided PVE or NVE from 2011 to 2017.

Exclusion criteria included need for urgent cardiac surgery, hemodynamic instability, and blood glucose > 180 mg/L after a 12-hour fast before the PET study. The primary endpoint was a composite of major adverse cardiac events: death, recurrent endocarditis, heart failure, embolic events, and cardiac hospitalization. The study population included 173 patients: 109 with PVE and 64 with NVE. Guideline indications for surgery were present in 127 patients, 93 of whom eventually underwent surgery. Median time from first antibiotics to PET/CT scan was seven days. PET/CT was positive in 100 patients, more often in PVE (83%) than NVE (16%). After a mean follow-up of 225 days, the primary endpoint occurred in

54% of patients (58% PVE, 48% NVE). One-year mortality was 20% (23% PVE, 16% NVE). Recurrent endocarditis occurred in 9% of patients, embolic events in 13%. In PVE patients, but not the NVE patients, a positive PET/CT was associated with more frequent occurrence of the primary endpoint (hazard ratio [HR], 2.7; 95% confidence interval [CI], 1.1-6.7;  $P = 0.04$ ). Also, moderate or intense positivity was associated with embolic events (HR, 7.5; 95% CI, 1.24-45.2;  $P = 0.03$ ) in PVE patients and NVE patients (HR, 8.8; 95% CI, 1.1-69.5;  $P = 0.02$ ). The authors concluded that PET/CT is not only of diagnostic value in endocarditis, but is predictive of major adverse cardiac events during follow-up in PVE patients and subsequent systemic emboli in NVE patients.

#### ■ COMMENTARY

FDG PET/CT has been used for a long time for diagnosis and prognosis in oncology to detect areas of inflammation associated with tumors. Also, since echocardiography of prosthetic valves can be challenging, it has been recommended in guidelines as a diagnostic tool for PVE if the echo is not conclusive.

This study confirms the diagnostic value of PET/CT in PVE with a demonstrated sensitivity of 83%. It was not as useful for NVE (sensitivity = 16%). What this study added was information on predicting subsequent major adverse cardiac events during a one-year follow-up. Surprisingly, about half the patients experienced major events on follow-up, and a multivariate analysis showed that PET/CT was predictive of these bad outcomes in PVE patients (HR, 2.7). The only other predictor that was significant was a CRP > 100 mg/L (HR, 1.9), which makes sense. Interestingly, patients with false-negative PET/CT usually scored low CRP values. Also, PET/CT strongly predicted subsequent systemic emboli in PVE and NVE patients. Thus, this study shows that PET/CT certainly is of prognostic value, too.

Knowing a patient's prognosis is of value only if one can do something about it. In the case of endocarditis, surgery is an option. The traditional indications for surgery are hemodynamic failure, persistent infection, large mobile vegetations, and recurrent emboli. However, surgeons often are reluctant to operate on these sick patients with a poor prognosis. Perhaps a positive PET/CT would help convince them that early surgery is worth the risk. Even in NVE patients, a strongly positive PET/CT was highly predictive of subsequent emboli.

In this study, as in others, about three-quarters of emboli go to the brain. Also, a persistently positive PET/CT on antibiotic therapy may bolster the perception that the patient carries a persistent infection.

There were limitations to this study. The patient cohort was relatively small, with a low number of events — especially with NVE patients. One could consider this a study of PVE patients. There was no information offered on the effect of antibiotics on PET/CT, which could be important clinically. At this point, PET/CT certainly is worth performing in left-sided PVE. There were no data provided on right-sided or device endocarditis, but it could be useful in these patients. Also, noncardiac foci were detected in 36% of study patients, which potentially is of value to know. Some of these extra cardiac foci could be the source of the infection, which would warrant attention.

Finally, since no contrast is used, PET/CT is easy on the kidneys. On the other hand, it is a somewhat cumbersome test, with a special meal required, followed by a 12-hour fast and a documented glucose level < 180mg/L before it can be performed. The scan does involve radiation; the mean dose in this study for the whole body was 15 mSv. ■

## ABSTRACT & COMMENTARY

# Cardiac Constriction vs. Cardiac Restriction

By Michael H. Crawford, MD, Editor

**SYNOPSIS:** The five Mayo Clinic Doppler echocardiographic criteria for the diagnosis of constrictive pericarditis (CP) were tested in a group of surgically confirmed CP compared to a group of cardiac biopsy proven amyloid restrictive cardiomyopathy (RC). Interventricular septal bounce and an elevated mitral annular medial  $e'$  were found to be the most accurate criteria, especially if used together.

**SOURCE:** Qamruddin S, Alkharabsheh SK, Sato K, et al. Differentiating constriction from restriction (from the Mayo Clinic Echocardiographic Criteria). *Am J Cardiol* 2019; 124:932-938.

**T**he differentiation of cardiac constriction vs. cardiac restriction is important because constriction could be curable. The Mayo Clinic has promulgated echocardiographic criteria for this diagnostic distinction based on their experience. The purpose of this study from the Cleveland Clinic was to evaluate the diagnostic accuracy of these criteria in 107 patients with surgically proven constrictive pericarditis (CP) as distinguished from 30 patients with restrictive cardiomyopathy (RC) from biopsy-proven cardiac amyloidosis. Patients with severe mitral or tricuspid regurgitation or mitral valve prostheses were excluded, but patients with atrial fibrillation were not. Per the Mayo criteria, the following five Doppler echo variables were measured: interventricular septal shift with respiration, exaggerated respiratory variation in mitral inflow Doppler E velocity, tissue Doppler

medial mitral annular  $e'$  velocity, ratio of medial to lateral Doppler mitral annular  $e'$  velocity, and exaggerated hepatic vein diastolic forward flow reversal during expiration on pulsed Doppler.

Respiratory septal shift was more frequent in CP patients compared to RC patients (92% vs. 27%;  $P = 0.001$ ). Respiratory percent change in mitral E was higher in CP vs. RC ( $27 \pm 18\%$  vs.  $12 \pm 11\%$ ;  $P = 0.001$ ). Medial mitral  $e'$  also was higher in CP ( $11 \pm 3$  vs.  $4 \pm 1$  cm/s;  $P = 0.001$ ) as was the ratio of medial to lateral mitral  $e'$  ( $1 \pm 0.3$  vs.  $0.8 \pm 0.2$ ;  $P = 0.001$ ). Finally, hepatic vein diastolic forward flow in expiration was slower in CP ( $24 \pm 10$  vs.  $35 \pm 15$  cm/s;  $P = 0.001$ ). A multivariate analysis showed that of five variables, only medial  $e'$  velocity  $\geq 9$  cm/s (odds ratio, 8.0; 95% confidence interval, 2.4-28;

$P = 0.001$ ) was independently associated with CP. Ventricular septal respiratory shift carried the greatest sensitivity (94%), and medial  $e'$  velocity  $\geq 9$  cm/s carried the highest specificity (100%). Combining the two gave a sensitivity of 80% and a specificity of 92%. The optimal cutoff for medial  $e'$  was  $\geq 7$  cm/s (area under the curve, 0.99). The authors concluded that CP can be confused with RC, and highly accurate Doppler echo tools can help diagnose this potentially reversible condition.

#### ■ COMMENTARY

This study largely replicates the Mayo experience and validates the utility of Doppler echo to diagnose CP, with a few differences due to patient inclusion and exclusion criteria. The Cleveland Clinic study population excluded those with severe tricuspid valve regurgitation and included patients with atrial fibrillation. The key information here is the prevalence of the five Mayo Doppler echo criteria in CP, as RC from amyloidosis should be diagnosed easily through other parameters. Whether other forms of RC without thick left ventricular myocardial walls would give the same results is not discernable from this study. The results show that the most sensitive Doppler echo finding for CP is respiratory shift of the interventricular septum. This so-called septal bounce usually is the finding that prompts the consideration of CP because it is easily visible without making measurements. Unfortunately, it is not very specific and can be seen with conduction abnormalities and postcardiac surgery, which are more common conditions. However, it should grab one's attention so that one considers the other Doppler echo findings of CP.

The results of the Cleveland Clinic study suggest cardiologists look at the medical  $e'$  velocity, because if it is  $\geq 9$  cm/s and there is a septal bounce, the positive predictive value (PPV) is high (100% in this study). Also, finding that the medial  $e'$  is greater than the lateral annular  $e'$ , or so-called annulus reversus, has been considered a useful finding, because it suggests that the septal myocardium is unfettered and the lateral myocardium is tethered to the pericardium. However, in this study, this finding carried only modest sensitivity (67%) and specificity (73%). Other findings, such as late expiratory diastolic flow reversed in the hepatic veins and exaggerated respiratory variation in mitral inflow E velocity, also showed modest performance. However, combining septal shift, medial  $e'$ , and hepatic flow increased specificity to 97%, but was not that sensitive (70%).

There were some weaknesses in the study that could have affected the results. For example, high-quality hepatic vein velocity recordings were obtained in only 79% of subjects. Also, a medial  $e'$  of  $\geq 9$  cm/s can be seen in otherwise normal individuals, so this finding alone is not that useful — unless one suspects CP. The bottom line is that there are no perfect Doppler echo measurements that will diagnose CP accurately. Thus, a high index of suspicion is necessary, with a careful look at the five criteria and with an emphasis on septal bounce and medial mitral annular  $e'$  as a starting point. Suggestive findings in the other three criteria should help, but, unfortunately, are not completely reliable. Ultimately, other imaging modalities are needed to confirm the diagnosis. ■

---

## ABSTRACT & COMMENTARY

# Optimizing AED Placement Locations

By Joshua Moss, MD

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

Dr. Moss reports he is a consultant for Abbott, Boston Scientific, and Medtronic.

**SYNOPSIS:** A study of the location of out-of-hospital cardiac arrests (OHCA) compared to the location of automatic external defibrillators (AED) in Denmark showed that if the placements of AEDs more closely matched the location of OHCA, bystander defibrillation and 30-day survival would improve.

**SOURCES:** Sun CLF, Karlsson L, Torp-Pedersen C, et al. In silico trial of optimized versus actual public defibrillator locations. *J Am Coll Cardiol* 2019;74:1557-1567.

Stecker EC, Reinier K, Howell SJ. Improving resuscitation outcomes with AEDs: Location, location, location. *J Am Coll Cardiol* 2019;74:1568-1569.

**A**lthough highly effective when used for out-of-hospital cardiac arrest (OHCA), automated external defibrillators (AEDs) often are placed in areas of low risk and limited temporal availability.

Investigators from Denmark performed a retrospective study of OHCA events and AED location in Copenhagen to determine the optimal location for AEDs to maximize the coverage of

OHCAs. Emergency medical service data were used. Only OHCAs of presumed cardiac cause were included. Those due to trauma, drug overdose, or with late signs of death were excluded. OHCAs through 1994 were the training models, and those from 2007-2016 were the study period, since AED placement was registered after that point. Two models were studied: where availability was limited to a building's hours of operation (model 1) and where AEDs were available 24/7 (model 2). The primary outcome was OHCA coverage defined as an OHCA occurring within 100 m of an AED. Also, bystander defibrillator and 30-day survival were estimated.

During the study period, there were 673 public OHCAs and 1,573 AEDs in Copenhagen. Real AED placements covered 22% of the observed OHCAs. Model 1 would have covered 33%, and model 2 would have covered 43%, respectively, for relative gains of 52% and 96% ( $P < 0.001$ ). Bystander defibrillation would have increased from the actual 15% to 23% and 27% with the two models, for relative increases of 53% and 84% ( $P < 0.001$ ). Also, 30-day survival would improve from 31% to 35% for both models, for a relative increase of 11% to 13% ( $P < 0.001$ ).

The authors concluded that optimal AED placement based on the location of OHCAs in the past would increase coverage by 50% to 100% compared to real AED locations, and significantly affect predicted bystander defibrillation and 30-day survival.

#### ■ COMMENTARY

This study represents the first in silico trial of a public AED intervention, comparing AED coverage of OHCAs in real life to coverage that could be achieved using mathematical modeling (based on

prior OHCA data). Perhaps it is not surprising that placing new AEDs based on a centralized source of data about historical OHCA locations would result in better bystander accessibility. The data confirm the assumption that there are some spatial and temporal patterns to these events within a given metropolitan area that lend some degree of predictability.

The major remaining question is whether using such modeling techniques will translate into higher survival statistics that we all seek, and that the authors indeed predicted using multivariate logistic regression models. In the most optimistic scenario, one in which mathematically optimized AED locations with 24/7 availability were chosen, only 43% of cardiac arrests occurred within 100 meters of an AED, despite the passage of nine years since the first AED was placed and optimization began. Additionally, while the readily available (and functional) AED could be a critical tool for improving survival in those 43% of OHCAs, it is ultimately only one piece of many needed. The presence of a bystander who is ready, willing, and able to use the AED (as well as perform CPR when necessary), a shockable rhythm that is not refractory to defibrillation attempts, and EMS services that can transport a victim to a hospital with facilities and services to manage them are equally critical.

Overall, this study presents an intriguing method for improving public AED availability and, in turn, rapid treatment of OHCA and better chances of survival. Assuming, as the authors did, that additional AEDs will continue to be added month by month, there would seem to be little downside in using validated prediction models to help choose the locations for those AEDs, as long as privately funded devices are not discouraged. Parallel investment must be made in improving bystander education and response. ■

---

## ABSTRACT & COMMENTARY

# Anticoagulation Decisions in Atrial Fibrillation

By Michael H. Crawford, MD, Editor

**SYNOPSIS:** Using the Delphi method of arriving at a consensus among clinicians concerning to whom with atrial fibrillation to recommend oral anticoagulants, the risk of stroke, the risk of hemorrhage, and patient-specific factors emerged. Many of these factors are not included in the guidelines and should be studied further.

**SOURCE:** King PK, Fosnight SM, Bishop JR. Consensus clinical decision-making factors driving anticoagulation in atrial fibrillation. *Am J Cardiol* 2019;124:1038-1043.

**S**urveys have shown that up to 38% of high-risk-for-systemic-emboli patients with atrial fibrillation (AF) are not treated with anticoagulants. To explore the reasons for this, 27 practicing cardiologists, neurologists, internists, and clinical pharmacologists

used the modified Delphi method to rate factors important in oral anticoagulation (OAC) decisions.

The Delphi method employed three rounds of surveys conducted blindly through electronic means.

A list of potential factors for initial evaluation was derived from published literature and submitted to the participants in round 1. Each participant then rated their level of agreement of each factors' importance for decisions regarding OAC in AF. In round 2, factors with partial consensus (60-75% agreement) and full consensus (> 75% agreement) were reconsidered and assigned a score of importance from 0-50 points. All factors with a score above the median were reconsidered in round 3 and arranged in rank order.

Sixty-six factors were identified from the literature review. In round 1, 41 failed to meet consensus, and seven new factors were added. Thus, 32 factors were considered in round 2, and 16 did not meet consensus. The 16 factors in round 3 were arranged in rank order: CHA<sub>2</sub>DS<sub>2</sub>-VAsC score, ischemic stroke history, transient ischemic attack (TIA) history, any major GI bleed < 12 weeks ago, platelets < 50, nontraumatic intracranial hemorrhage > 12 weeks ago, any major bleed < 12 months ago, CHADS<sub>2</sub> score, adherence concerns, HAS-BLED score, GI bleed from a peptic ulcer < 12 weeks ago, goals of care, liver disease with international normalized ratio (INR) > 1.4, age, patient values/preferences, and overall prognosis. The authors concluded that several of these factors are not addressed in current guidelines, including hematologic indicators of bleeding risk, previous bleeding episodes by specific type, other risk factors for bleeding, and adherence concerns. Thus, more research needs to be conducted on the clinical implications of these emerging factors and the lack of consensus on other factors found in the literature.

#### ■ COMMENTARY

In patients with AF, the decision on whom to prescribe OACs is difficult because the risk of major bleeding is real. Not surprisingly, many AF patients end up on no OAC or on aspirin alone, which is no longer recommended in guidelines because the risk of bleeding outweighs the small potential benefit. Also, many patients are treated with OAC doses that are below those recommended. This study demonstrates another issue: the lack of consensus about which factors are important in making the decision to anticoagulate.

Out of 73 factors identified, there was only consensus on 16. Of these 16, the three highest-ranked factors all concerned protection from systemic emboli: CHA<sub>2</sub>DS<sub>2</sub>-VAsC score, ischemic stroke, and TIA history. CHADS<sub>2</sub> score was number 8 on the list, so it has clearly fallen out of favor. Six of the next 13 factors involved avoiding hemorrhage: major GI bleed within 12 weeks, platelet count < 50,

nontraumatic intracranial hemorrhage > 12 weeks ago, HAS-BLED score, bleeding peptic ulcer < 12 weeks ago, and liver disease with an INR > 1.4. The final factors involved patient-specific issues: adherence concerns, age, goals of care, patient values/preferences, and overall prognosis.

For several factors that would seem important, consensus could not be reached: dual antiplatelet therapy need, cognitive impairment, frailty, systolic heart failure, anemia, and transient postoperative AF. Why there was no agreement on these factors could not be determined in this study, but as the authors concluded, these could be good research targets.

Of special importance is the patient who requires dual antiplatelet therapy and has AF. Currently, several different approaches to this problem have been studied or research is ongoing. Thus, the lack of consensus here is not surprising.

There are strengths to the Delphi method as applied in this study. Since all the grading was conducted online, there was no peer-to-peer influence. Also, there was a broad group of practitioners, all of whom were knowledgeable about AF and OACs. In addition, the Delphi method studies thought processes, not prescribing patterns.

Still, there were weaknesses in this investigation. Participants were limited to physicians and clinical pharmacists. No nurse practitioners or physician assistants were included, yet such individuals often are involved in the decision to prescribe OACs. Also, all practitioners were in the United States, so the results may not apply internationally. Finally, with the Delphi method, the more participants included, the better the analysis, but > 50 is considered impractical. These investigators recruited 103 clinicians: 49 did not respond, 24 declined, and 30 agreed to participate. Three dropped out during round 1, leaving 27. This probably is enough for a robust analysis, as < 10 is considered inadequate.

This study interested me because it pointed out that an emphasis on protecting patients from emboli is the most important concern. However, factors addressing bleeding risk are important, too, and many of these are not things I normally ask about.

Patient-specific factors seem to be the least important to clinicians, but perhaps not to the patients. In the final analysis, patients may opt out of OAC therapy because of these reasons. There is no grand formula for deciding to prescribe OACs in AF, and many clinical characteristics need to be considered beyond the simple scores. ■

**PHYSICIAN EDITOR**  
**Michael H. Crawford, MD**  
Professor of Medicine  
Associate Chief for Education  
Division of Cardiology  
University of California  
San Francisco

**PEER REVIEWER**  
**Susan Zhao, MD**  
Director  
Adult Echocardiography Laboratory  
Associate Chief  
Division of Cardiology  
Department of Medicine  
Santa Clara Valley Medical Center

**NURSE PLANNER**  
**Aurelia Macabasco-O'Connell, PhD,**  
**ACNP-BC, RN, PHN, FAHA**  
Associate Professor  
Azusa Pacific University  
School of Nursing

**EDITORIAL ADVISORY BOARD**  
**Jamie L. W. Kennedy, MD, FACC**  
Associate Professor  
Division of Cardiology  
Advanced Heart Failure  
& Transplant Cardiology  
University of California  
San Francisco

**Joshua D. Moss, MD**  
Associate Professor  
of Clinical Medicine  
Cardiac Electrophysiology  
Division of Cardiology  
University of California  
San Francisco

**Jeffrey Zimmet, MD, PhD**  
Associate Professor of Medicine  
University of California  
San Francisco  
Director, Cardiac  
Catheterization Laboratory  
San Francisco VA Medical Center

**EDITOR**  
**Jonathan Springston**

**EDITOR**  
**Jason Schneider**

**EDITORIAL GROUP MANAGER**  
**Leslie Coplin**

**ACCREDITATIONS MANAGER**  
**Amy M. Johnson, MSN, RN, CPN**

## 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 **ReliasMedia.com** and click on My Account. First-time users must register on the site. Tests are taken after each issue.
3. Pass the online test 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, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

## CME/CE QUESTIONS

- 1. A mathematical model of where to place automatic external defibrillators based on the historical location of out-of-hospital cardiac arrests would result in:**
  - a. increased bystander defibrillation and survival.
  - b. increased bystander defibrillation, but no increase in survival.
  - c. neither an increase in bystander defibrillation or survival.
  - d. an increase in adverse events due to improper usage.
- 2. A recent study of dapagliflozin in systolic heart failure patients for 12 weeks showed:**
  - a. reduced NT-proBNP levels.
  - b. improved quality of life scores.
  - c. more hypoglycemia.
  - d. more hypovolemia.
- 3. A multivariate analysis of five echocardiographic criteria for constrictive pericarditis for distinguishing such patients from restrictive cardiomyopathy patients showed independent predictive value for:**
  - a. interventricular septal bounce.
  - b. medial mitral annular tissue Doppler  $e'$  > lateral  $e'$ .
  - c. medial  $e' \geq 9$  cm/s.
  - d. exaggerated respiratory variation in mitral inflow E velocity.
- 4. 18F FDG PET/CT imaging in suspected infective endocarditis is most useful for diagnosis and prognosis in patients with:**
  - a. culture-negative endocarditis.
  - b. fungal endocarditis.
  - c. native valve left heart endocarditis.
  - d. prosthetic valve left heart endocarditis.
- 5. Which factor for deciding whom with atrial fibrillation to anticoagulate long term is considered most important?**
  - a.  $CHA_2DS_2-VASc$  score
  - b. Recent major bleed
  - c. Patient adherence concerns
  - d. HAS-BLED score

## 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.

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand. Call us at (800) 688-2421 or email us at [reprints@reliamedia.com](mailto:reprints@reliamedia.com).

Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at [groups@reliamedia.com](mailto:groups@reliamedia.com) or (866) 213-0844.

To reproduce any part of Relias Media newsletters for educational purposes, please contact The Copyright Clearance Center for permission at [info@copyright.com](mailto:info@copyright.com) or (978) 750-8400.