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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

# Hyperdynamic Left Ventricular Function: Good or Bad News?

*By Michael H. Crawford, MD, Editor*

SYNOPSIS: A large population study has shown a U-shaped relationship between left ventricular ejection fraction (EF) and mortality, with a nadir at 60-65%. The authors identified a new group at high risk for death: those with an EF ≥ 70%.

SOURCE: Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: Where does the nadir of risk lie? *Eur Heart J* 2020;41:1249-1257.

In heart failure (HF) patients, there is a well-known exponential relationship between left ventricular (LV) ejection fraction (EF) and mortality. However, the relationship of EF to mortality in large populations of patients who undergo echocardiography for a variety of clinical indications is less clear.

Wehner et al evaluated records from Geisinger Health System, which serves patients in New Jersey and Pennsylvania. Specifically, the authors investigated information collected from 1998 to 2018 regarding patients who underwent an echocardiogram. Researchers also studied similar records from the Waitemata District Health Board (New Zealand) for the sake of creating a validation cohort. As about three-quarters of the Pennsylvania echo labs recorded EF in the 4% to 5% range, all studies were categorized in 5% intervals, where the lowest and highest intervals were ≤ 20% and ≥ 70%. The derivation of the EF was described as qualitative in 59% of cases; 8% were quantitative, mostly from the biplane method. In the remaining 33%, no method was given. The primary endpoint was all-cause mortality. The authors studied several subgroups, looking for features potentially associated with increased EF or reduced EF. Also, they performed several sensitivity analyses to assess clinical factors that could affect the results, such as multiple echoes during the observation period.

Overall, 596,503 echoes from 271,201 patients were discovered in the U.S. cohort. Because of missing data, such as EF, 192,526 echoes were excluded, leaving 403,977 echoes in 203,135 patients who met inclusion criteria. Their mean age was 64 years, and 13% had a diagnosis of HF. During a median follow-up of four years (range,

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1.3-8.4), 23% of patients died. Adjusted hazard ratios (HR) for death exhibited a U-shaped relationship with EF, with the risk nadir at 60-65%. When EF was ≥ 70%, the HR was 1.71 (95% confidence interval [CI], 1.64-1.77), which was similar to the HR when EF was 35-40% (1.73, 95% CI, 1.66-1.80).

Similar results were observed in the New Zealand cohort. Also, the results were not changed significantly when restricted by age, sex, and HF as well as when adjusted for conditions associated with increased EF, such as mitral regurgitation, LV hypertrophy, and anemia. The authors concluded any deviation in EF from the 60-65% range is associated with increased adjusted all-cause mortality. These results uncovered a new high-risk group: those with EF ≥ 70%.

## ■ COMMENTARY

The most provocative finding in this study was that patients with EF ≥ 70% died at the same rate as patients with EF in the 35% to 40% range. Most HF studies have shown that once EF is > 45%, differences in mortality are not significant. However, prior HF studies usually only included patients with EF < 50%. The authors of studies of HF with preserved (p) EF used various EF cutpoints, but > 50% seems to be most strongly associated with the futility of standard HF medications. The Wehner et al study revealed increases in mortality at > 65%. This raises the issue of how cardiologists should define HFpEF.

Other studies have shown similar results. For example, the authors of the MESA population study reported an EF nadir at 60%.[1] The authors of the GRACE study of women with acute coronary syndrome reported a mortality nadir at 65% EF.[2] When the Wehner et al study was subdivided into inpatients and outpatients, the EF nadir for mortality remained at 60-65% for inpatients. However, in outpatients, the rate was 55-60%. Thus, the precise nadir may vary with the population studied.

Another interesting finding in the Wehner et al study is that end-systolic volume index < 10 mL/m$^2$ also was associated with increased mortality, suggesting that a small LV cavity size may be part of the adverse physiology of EF ≥ 70%. An analysis of the influence of body mass index (BMI) on mortality is interesting, too. BMI showed a U-shaped relationship to mortality, with a nadir at 30-35 kg/m$^2$, which confirms the obesity paradox — at least at the moderately obese level. However, the highest HR for mortality was at BMI < 18.5 kg/m$^2$, which suggests one can be too thin, especially if he or she has a small, hyperdynamic left ventricle.

[The most provocative finding in this study was that patients with ejection fraction greater than or equal to 70% died at the same rate as patients with an ejection fraction in the 35% to 40% range.]

There were limitations to the Wehner et al study other than its retrospective, observational design. Foremost is the almost exclusive use of visual estimation of EF on two-dimensional echo, although studies show that with experienced readers these estimates are reasonably accurate. Also, the authors reported no data on cause of death (but the fact the patients studied were referred for an echo suggests the authors may have suspected cardiac disease). In addition, both populations studied were largely of European ancestry.

The new information from this study is the patient with a small hyperdynamic left ventricle is at particularly high risk for mortality for reasons that are not yet clear. ■

## REFERENCES

1. National Heart, Lung, and Blood Institute. Multi-Ethnic Study of Atherosclerosis (MESA). https://bit.ly/34jdrBM
2. Global Registry of Acute Coronary Events (GRACE). https://bit.ly/3e5oinm

ABSTRACT & COMMENTARY

# Antiplatelet Agents Add to Bleeding Risk, Do Not Add Benefit in TAVR Patients Already on Oral Anticoagulation

***By Jeffrey Zimmet, MD, PhD***

*Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center*

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

SYNOPSIS: In a randomized trial of patients already on anticoagulation undergoing transcatheter aortic valve replacement, adding clopidogrel to oral anticoagulation increased the incidence of serious bleeding vs. oral anticoagulation alone, but did not improve cardiovascular outcomes.

SOURCE: Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020; Mar 29. doi: 10.1056/NEJMoa1915152. [Epub ahead of print].

The question of optimal anticoagulation regimens after transcatheter aortic valve replacement (TAVR) procedures continues to be a source of confusion and consternation. In general, there remains uncertainty about whether there is benefit to dual antiplatelet over single antiplatelet therapy. Although anticoagulants (but not antiplatelet agents) appear to be protective against imaging-defined subclinical leaflet thrombosis, the results of the recently published GALILEO trial suggested harm rather than benefit from adding rivaroxaban to a treatment strategy in post-TAVR patients without an established indication for anticoagulation.[1]

What about TAVR patients with an established indication for anticoagulation? Until now, the only data on this question have come from post-hoc analyses of older trials, some of which have suggested a benefit to antiplatelet therapy in reducing stroke in this population over the intermediate term. Current guidelines generally recommend a vitamin K antagonist for these patients, either alone or in combination with single antiplatelet therapy, and essentially ignore the direct-acting anticoagulant (DOAC) medications altogether. Until now, randomized trials have been lacking.

To bridge part of this knowledge gap, Nijenhuis et al published the results of cohort B of the POPular TAVI trial. Between December 2013 and August 2018, 326 patients on oral anticoagulation were enrolled at 17 sites in four European countries. These patients were randomly assigned to receive either clopidogrel or no clopidogrel for three months following the TAVR procedure. Ultimately, 157 patients were assigned to receive oral anticoagulation alone, and 156 to receive anticoagulation plus clopidogrel. Those in the first group were not administered a placebo control. The primary outcomes were any bleeding and non-procedure-related bleeding at 12 months.

Included patients were fairly typical of a TAVR population for this era; subjects were a mean age of 81 years, and 45% were women. As expected, the indication for anticoagulation was atrial fibrillation in approximately 95% of patients. Patients with recent percutaneous coronary intervention (and, thus, an absolute indication for $P2Y_{12}$ inhibition) were excluded. After one year, any bleeding had occurred in 21.7% of patients on anticoagulation alone, compared with 34.6% of patients receiving anticoagulation plus clopidogrel (risk ratio [RR], 0.63; 95% confidence interval [CI], 0.43-0.90; $P$ = 0.01). Because of the way the endpoints were defined, non-procedure-related bleeding was nearly identical to all bleeding.

A secondary composite endpoint including bleeding (cardiovascular death, bleeding, stroke, or myocardial infarction [MI]) showed a benefit for the anticoagulation-alone group (31.2% vs. 45.5%; RR, 0.69; 95% CI, 0.51-0.92). A separate secondary composite endpoint that did not include bleeding (cardiovascular death, stroke, or MI) was not significantly different between the groups. Importantly, stroke as an individual secondary outcome did not differ between the two groups, occurring in 5.7% and 5.8% of patients. The authors concluded that among patients on long-term anticoagulation for an accepted indication, the addition of clopidogrel led to a higher incidence of serious bleeding vs. anticoagulation alone.

## ■ COMMENTARY

This was a significant trial that focuses on the central importance of bleeding as a frequent and clinically

relevant outcome. Although this is important work that addresses, at least in part, a common clinical question about the TAVR population, it is worthwhile to spend a moment to acknowledge its flaws. The sample size was relatively small. This was an open-label trial without a placebo control. Essential details are missing or simply left out, including information about aspirin use, and whether anticoagulants were paused periprocedurally.

The authors made the unconventional choice to use the Bleeding Academic Research Consortium type 4 definition to designate procedure-related bleeding. While this does identify severe bleeding, it excludes most episodes of what common sense would dictate to be procedure-related, including bleeding from the puncture site. Supplementary materials reveal access site bleeding accounted for approximately half of all bleeding events.

While there was no sign the anticoagulant-alone group were at higher risk for stroke or MI, the small size of the trial and the wide noninferiority margins mean this is not a conclusive result. The lack of effect on stroke hazard contradicts the previously published results of a retrospective analysis of the PARTNER II trial.[2] Those researchers reported that antiplatelet therapy was associated with a significant reduction in the two-year incidence of stroke among patients with AF undergoing TAVR.

There is little doubt that bleeding is a central outcome that occurs at significant rates in post TAVR patients. As the only randomized trial published thus far in this particular group, POPular suggests withholding antiplatelet therapy as a reasonable tactic to reduce significant bleeding. Further trials will be necessary to determine whether this represents the optimal method to minimize other important outcomes, including death, stroke, and MI. ■


REFERENCES

1. Dangas GD, Tijssen JGP, Wöhrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;382:120-129.
2. Kosmidou I, Liu Y, Alu MC, et al. Antithrombotic therapy and cardiovascular outcomes after transcatheter aortic valve replacement in patients with atrial fibrillation. *J Am Coll Cardiol Intv* 2019;12:1580-1589.


ABSTRACT & COMMENTARY

# TAVR in Bicuspid Aortic Valves

***By Michael H. Crawford, MD, Editor***


SYNOPSIS: Investigators assessed the Society of Thoracic Surgeons/American College of Cardiology transcatheter aortic valve replacement (TAVR) data, with a focus on the use of newer TAVR devices in patients with bicuspid aortic valve vs. tricuspid aortic valves. They found the outcomes post-procedure and for one year are not significantly different between the two types of native valve anatomy.


SOURCE: Halim SA, Edwards FH, Dai D, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: A report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Circulation* 2020;141:1071-1079.

Early reports of transcatheter aortic valve replacement (TAVR) in patients with bicuspid aortic valves (BAV) showed reduced successful device deployment, a higher incidence of paravalvular regurgitation, and more strokes. This resulted in a lack of Food and Drug Administration approval for this use of TAVR. More recent data about third-generation devices have shown much better results. Halim et al analyzed the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy Registry (TVTR) to evaluate TAVR outcomes in patients with BAV vs. tricuspid valves (TrAV). The TVT is a compulsory database of all commercial TAVR in the United States.

For this analysis, TAVRs performed between late 2011 and late 2018 were included. The authors excluded aborted procedures, previous AV replacement, and other valve morphologies (e.g., unicuspid). Valve prostheses were stratified as early or current (SAPIEN 3 or Evolut R). Several procedural and post-procedural outcomes in hospital, at 30 days and one year, were assessed.

In 593 sites, 170,959 patients met the inclusion criteria. AV morphology was assessed by CT scans in 75%, transesophageal echo in 13%, and transthoracic echo in 12%. BAV was discovered in 5,412 patients who were significantly younger compared to TrAV patients (74 years vs. 82 years; $P < 0.001$). In 81% of patients, current-generation prosthetic valves were used. Their insertion increased the frequency of successful valve deployment (96.3% vs. 93.5%; $P = 0.001$). Also, newer valves exhibited less 2+ paravalvular leak (2.7% vs. 14%; $P < 0.001$).

There was no significant difference in BAV device success compared to TrAV (96.3% vs. 97.4%; $P = 0.07$), but there was slightly more moderate to severe aortic regurgitation with BAVs (2.7% vs. 2.1%; $P < 0.001$). In the Medicare subgroup, the adjusted one-year mortality rate was lower in the BAV group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.78-0.99), but there was no difference in stroke (HR, 1.14; 95% CI, 0.94-1.39).

The authors concluded procedural, post-procedural and one year outcomes with current TAVR prostheses were comparable in BAV and TrAV.

## ■ COMMENTARY

This study is a potential gamechanger, especially for younger patients with BAV. Current guidelines recommend a mechanical prosthesis because of its superior longevity, but it would require near lifelong warfarin therapy, on which many active young patients are not keen. Now, suppose a patient between age 35 and 40 years with symptomatic severe aortic stenosis or regurgitation could undergo TAVR. By the time this TAVR failed, perhaps this patient could be older than age 50 years and could receive a surgically placed bioprosthetic valve. There now are many options for avoiding warfarin.

The results of this large retrospective, observational registry study of TAVR for BAV are excellent and not clinically different than the results with TrAV. The in-hospital rates of major complications were low: death (2%), stroke (2%), and bleeding (6%). This study confirms the experience in smaller single-center studies of BAV patients. The major trials that permitted commercialization of TAVR all excluded patients with BAV. Even the new trials of TAVR in low-risk patients are excluding BAV patients. Thus, this registry study is important.

There were limitations. There was no external blinded adjudication of valve morphology, and only 75% of patients underwent CT angiography. Also, there was no breakdown by BAV subtypes. In 12% of subjects, the post-procedure echo was missing. In addition, the new Evolut PRO, released in 2017, was not included.

This field is a moving target, as new TAVR devices are arriving rapidly. This study is a start, as mean STS predicted risk of mortality was 3.8% in the BAV patients, which was lower than the 5.6% observed in older TrAV patients ($P < 0.001$). Expect more liberalization of TAVR use going forward, especially as more data on low-risk patients arrive. ■

ABSTRACT & COMMENTARY

# Coronary CT Angiography to Identify Plaque Stabilization

***By Michael H. Crawford, MD, Editor***

SYNOPSIS: Researchers identified subjects with no known coronary artery disease drawn from a large international, multicenter registry of coronary CT angiography. Subjects were divided into matched pairs with and without a subsequent acute coronary syndrome event. The authors demonstrated those with a high density of calcium plaques experienced the fewest events, suggesting high-density calcium plaques are stable.

SOURCE: van Rosendael AR, Narula J, Lin FY, et al. Association of high-density calcified 1K plaque with risk of acute coronary syndrome. *JAMA Cardiol* 2020; Jan 22. doi: 10.1001/jamacardio.2019.5315. [Epub ahead of print].

Coronary artery plaque characteristics are believed to be important for assessing the likelihood of plaque rupture based largely on pathology studies. Although the presence of coronary artery calcium on CT scans identifies plaques, more does not necessarily predict subsequent coronary events. Van Rosendael et al sought to determine the relationship between increasing density of calcified plaque and the risk of an acute coronary syndrome (ACS).

They developed a nested, case-controlled study called ICONIC. Using information from the CONFIRM registry, van Rosendael et al identified subjects with no known coronary artery disease (CAD), had undergone coronary CT angiography (CCTA), and had been followed for four years. Patients who experienced an ACS event were matched with those who did not, which resulted in 189 pairs. The density of coronary plaques was expressed in Hounsfield units (HU). Plaques were categorized as necrotic core, fibro-fatty, fibrous, and calcified based on HU strata: < 30, 31-130, 131-350, and > 350, respectively. The authors focused on calcified plaques, and divided those into three groups: 351-700 HU, 701-1,000 HU, and > 1,000 HU. The latter group was termed 1K plaque. The mean age of the study population was

60 years, and 65% were men. Total plaque volume was similar in the paired group. However, with each increasing calcium density stratum, calcium volume was lower in ACS subjects than in non-ACS subjects. The mean volume of 1K plaque in the ACS patients was 3.9 vs. 9.4 for the control subjects ($P = 0.02$). But for subjects > age 75 years, 1K plaque did not differ between patients and controls. Among the participants in the highest quartile of 1K plaque in both groups, there was more calcified plaque (48% vs. 25%; $P < 0.001$) and relatively less necrotic core plus fibro-fatty plaque (13% vs. 25%; $P < 0.001$) compared to the other three quartiles. The authors concluded that on a per patient basis, the measure of high density (> 1,000 HU), calcified plaque was associated with a lower risk of subsequent ACS.

## ■ COMMENTARY

The Multi-Ethnic Study of Atherosclerosis (MESA) study included subjects without known CAD. Those authors, using non-contrast, older generation CT scanners, showed that coronary artery calcium (CAC) volume and density were more predictive of the risk of CAD events than the pooled atherosclerosis risk score.[1] The MESA authors used the Agatston score to assess calcium volume, which is upwardly weighted for more density of calcium. The authors estimated calcium density from the Agatston score, which was associated with fewer CAD events.

Here, van Rosendael et al used newer multislice CT scanners. These machines provide higher HU values because of the effect of contrast, which attenuates vascular structures. These authors demonstrated that higher calcium density reduces the risk of CAD events. This suggests more calcium density equates to plaque stabilization. Thus, the best risk prediction would factor in calcium volume (more risk) and calcium density (less risk). Notably, a high calcium density (> 1,000 HU) showed a significant association with fewer ACS events. Lower values did not, demonstrating the equipoise for CAD events between calcium volume and density at lower densities. There were limitations to this study. The cohort was a subgroup derived from a larger registry study (CONFIRM), so there was selection bias and unmeasured confounders. In those > age 75 years, there was no association between calcium density and events, but this was a small group that was not as well matched. Also, subjects with total coronary artery occlusions were excluded, and the authors did not provide information on medication use. Thus, the study should be considered hypothesis-generating until a prospective, controlled study is completed. However, this study does support the results of MESA, extending the observations of those authors using newer CT scanners with contrast images of the coronary arteries.

Van Rosendael et al believe the features of atherosclerotic plaques are important for estimating prognosis in those with CAD, and that a high density of calcium represents plaque stability. Pathogenic studies have supported this concept because they have shown that ruptured plaques tend to be fibroatheromas with large necrotic cores and thin inflamed fibrosis caps. The noninvasive detection of vulnerable plaques is the Holy Grail of coronary imaging. How does this study of presumably stable high-density calcium plaques help cardiologists clinically? Based on the results of other studies, statins increase calcium volume and reduce the volume of the necrotic core in plaques. Presumably, many of these stable patients in the van Rosendael et al study were on statins. If not, would adding a statin to all those with calcium densities < 1,000 HU (but not to those > 1,000 HU) make sense? The former might, but I am not sure about the latter. This study adds support to the plaque stabilization by calcium theory and highlights the lack of value of serial CCTA imaging at this point in technologic development. Also, it emphasizes that cardiologists have moved on from the Agatston score and need to use the advanced quantitative features of current CCTA imaging. ■

## REFERENCE

1. National Heart, Lung, and Blood Institute. Multi-Ethnic Study of Atherosclerosis (MESA). https://bit.ly/34jdrBM

ABSTRACT & COMMENTARY

# Many Serious Cardiac Complications of Pregnancy Are Preventable

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

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

SYNOPSIS: Investigators determined about half of serious cardiac complications of pregnancy are preventable.

SOURCE: Pfaller B, Sathananthan G, Grewal J, et al. Preventing complications in pregnant women with cardiac disease. *J Am Coll Cardiol* 2020;75:1443-1452.

Cardiovascular disease is the leading cause of maternal mortality in the United States, accounting for more than one-third of all pregnancy-related deaths.[1] The rate of adverse fetal events also is much higher in women with heart disease, including premature birth, small for gestational age infants, and fetal death. Pfaller et al sought to characterize serious cardiac events in pregnant women with heart disease.

Pregnant women with heart disease were prospectively enrolled in the Canadian Cardiac Disease in Pregnancy (CARPREG) study. Some patients were known to have heart disease prior to conception, while others were diagnosed during pregnancy. This substudy concerned the cohort of patients followed at two centers, one in Vancouver and one in Toronto, between 2004 and 2014. Serious events during pregnancy and up to six months postpartum were recorded. Cardiac events included heart failure, cardiac death, arrest, arrhythmias requiring intensive care unit admission, myocardial infarction, aortic dissection, mechanical valve thrombosis, endocarditis, cerebrovascular events, and need for urgent cardiac intervention. At least two cardiologists reviewed serious cardiac events to determine preventability and contributing factors.

Of the 1,315 pregnancies followed in this study, 17% were complicated by cardiac events, 3.6% of them serious, including five maternal deaths and four resuscitated cardiac arrests. Patients with acquired heart disease, mechanical valves, high-risk native valve lesions, systemic ventricular dysfunction, cyanosis, and New York Heart Association class III or IV symptoms were more likely to suffer serious cardiac events. The need for urgent cardiovascular intervention was the most common serious cardiac event, occurring in 0.7% of pregnancies and including valve intervention, resection of cardiac tumor, atrial septal defect closure, and aortic root replacement. Two-thirds of events occurred during pregnancy: one-quarter postpartum, and the remaining during labor and delivery.

Of the 47 pregnancies complicated by severe cardiac events, 42 resulted in live births (45% were preterm deliveries). The overall rate of adverse fetal events in pregnancies with severe cardiac events was 62%, compared to 29% in pregnancies without cardiac events and 32% in pregnancies with nonserious cardiac events. There were 22 severe obstetric events, none fatal, most commonly severe pre-eclampsia. Overall, 5.1% of pregnancies were complicated by pre-eclampsia. Fortunately, only two pregnancies were complicated by both severe cardiac and obstetric events.

On chart review, 49% of severe cardiac events were considered definitely, probably, or possibly preventable, including two maternal deaths and three cardiac arrests. Most preventable events occurred in the antepartum period. Provider management-related factors were the largest group of preventable events (74%), including failure to identify cardiac disease, failure to recognize high-risk patients, delays in diagnosis and intervention, and inappropriate treatment. Many preventable events occurred in women who had not been diagnosed with heart disease and patients initially managed at smaller centers. Patient-related factors were identified in 17% of events, including failure to seek care, noncompliance, and lack of access to healthcare. The authors concluded that although uncommon, about half of serious cardiac complications of pregnancy are preventable.

## ■ COMMENTARY

The Centers for Disease Control and Prevention reports pregnancy-related mortality in the United States was 17.4 per 100,000 live births in 2018, up from 7.2 per 100,000 in 1987.[2,3] In Canada, the rate has been fairly stable at between 9 and 11 deaths per 100,000 live births between 2000 and 2017.[4] The reasons for the increase in the United States are many and poorly understood. More women conceiving and delivering at an older age (and more likely to do so with comorbid conditions) and improved survival to adulthood for patients with congenital heart disease are two likely contributors. Comorbid conditions in Canadian women also have increased over time without a corresponding increase in mortality, raising the possibility that the Canadian healthcare system is better equipped to care for pregnant women with heart disease.

Sadly, there are significant racial and ethnic disparities in outcomes. Black women exhibit the highest maternal mortality rate in the United States at 42.2 deaths per 100,000 live births.[2] Disadvantages that black women experience at many levels contribute to this discrepancy, including the rate of unintended pregnancy, burden of comorbid conditions, and limited healthcare access. Of note, black women are more frequently affected by peripartum cardiomyopathy for unclear reasons. The reported number of serious cardiac events in this population of pregnant women with heart

disease is not unexpected, although the high number of potentially preventable events is surprising. Regardless, there is an opportunity for improvement. Women with known heart disease are somewhat easier to target, with interventions such as preconception counseling, referral to an expert center, and close monitoring throughout pregnancy and the postpartum period by both obstetrician and cardiologist. Interpreting the many physiological changes of pregnancy can be challenging for both patient and physician. Serial biomarkers such as brain natriuretic peptide and even echocardiograms to monitor left ventricular function can be helpful.

Faster diagnosis of heart disease during pregnancy requires higher suspicion from treating physicians, primarily in obstetrics, primary care, and emergency medicine, followed by the cardiologists who receive these referrals. Dyspnea at rest, orthopnea, and severe chest pain always are abnormal and warrant full evaluation. ■

## REFERENCES

1. Petersen EE, Davis NL, Goodman D, et al. Vital Signs: Pregnancy-related deaths, United States, 2011-2015, and strategies for prevention, 13 states, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2019;68:423-429.
2. National Vital Statistics Report. Maternal mortality in the United States: Changes in coding, publication, and data release, 2018. Jan. 30, 2020. https://bit.ly/2XgMMUQ
3. Centers for Disease Control and Prevention. Pregnancy mortality surveillance system. Updated Feb. 4, 2020. https://bit.ly/39Ouk8Q
4. World Health Organization. Maternal mortality in 2000-2017, Canada. Published 2019. https://bit.ly/2JN9snM

## CME/CE QUESTIONS

**1. A population study of the relationship between left ventricular ejection fraction and mortality showed a U-shaped curve with a nadir at:**

a. 50-55%.
b. 55-60%.
c. 60-65%.
d. 65-70%.

**2. Most preventable serious cardiac events in pregnant women occur:**

a. antepartum.
b. during labor.
c. during delivery.
d. postpartum.

**3. A randomized trial of adding clopidogrel to an anticoagulant in patients with atrial fibrillation undergoing transcatheter aortic valve replacement (TAVR) resulted in:**

a. fewer strokes.
b. fewer myocardial infarctions.
c. a reduced mortality rate.
d. more bleeding.

**4. A large registry of patients treated by TAVR with bicuspid aortic valves compared to tricuspid valves has shown:**

a. better procedural success.
b. more moderate aortic regurgitation.
c. fewer strokes.
d. higher mortality.

**5. From a registry of subjects without known coronary artery disease who underwent a CT coronary angiogram, those with subsequent acute coronary syndromes were compared to those without. The former showed:**

a. more plaque volume.
b. lower plaque density.
c. less fibro-fatty plaque.
d. less necrotic core.