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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

Vol. 40, Issue 7, July 2021
ReliasMedia.com

ABSTRACT & COMMENTARY

Time of the Essence with Dapagliflozin for Heart Failure

By Michael H. Crawford, MD, Editor

SYNOPSIS: By adding dapagliflozin to maximally tolerated standard therapy for heart failure with reduced left ventricular ejection fraction, researchers noted the reduction in mortality and recurrent heart failure began within one month of starting this therapy.

SOURCE: Berg DD, Jhund PS, Docherty KF, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol* 2021;6:499-507.

Hospitalization of patients with heart failure caused by reduced left ventricular ejection fraction (HFrEF) is a known adverse prognostic event. However, little is known about the relative benefits of adding treatment with dapagliflozin (dapa) to standard therapy in such patients in relation to a prior hospitalization. Investigators from the DAPA-HF trial examined the data to analyze the timing of the demonstrated clinical benefits from the onset of therapy and whether the risk of clinical events varied as function of proximity to a heart failure hospitalization.

DAPA-HF was a multinational, double-blind, placebo-controlled, randomized trial of HF patients with symptoms, EF < 40%, and elevated NT-proBNP on optimal standard medical therapy. Those enrolled were free from renal dysfunction, type 1 diabetes, and short-expected survival. Patients were excluded if they were in the hospital for HF — or, within four weeks of said hospitalization. The main trial exhibited a reduced risk of the combined primary endpoint of worsening HF and cardiovascular death (HR, 0.74; $P < 0.001$). For the Berg et al analysis, the patients were divided into three groups: no prior hospitalization (16%), a prior hospitalization more than one year ago (27%), or a prior hospitalization less than one year ago (36%). The total population included 4,744 patients, 23% of whom were women (average age was 66 years). There was an early separation of the Kaplan-Meier curves for the primary endpoint after 28 days of dapa therapy (HR, 0.51; 95% CI, 0.28-0.94; $P = 0.03$), which was driven mainly by a reduction in worsening HF. A prior HF hospitalization had occurred in 27% of patients

Financial Disclosure: None of the planners or authors for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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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.

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in < 12 months from trial onset. These patients presented with higher baseline New York Heart Association class and used more diuretics.

In the placebo arm, there was a stepwise gradient of risk of the primary outcome by timing of the most recent hospitalization: 21% with no prior hospitalization, 25% with a prior hospitalization more than one year ago, and 34% with a prior hospitalization less than one year ago ($P = 0.04$). A multivariate analysis of the primary endpoint in the placebo group showed an increase in the hospitalization more than one year ago group (HR, 1.08) and a larger increase among the prior hospitalization less than one year ago group (HR, 1.30; $P = 0.04$) vs. the no prior hospitalization group, again driven by worsening HF rather than mortality. Dapa lowered the relative risk of the primary outcome by 16% in the no prior HF hospitalization group (HR, 0.84), by 27% in the prior hospitalization more than one year ago group (HR, 0.73), and 36% in the prior hospitalization less than one year ago group (HR, 0.64; $P = 0.07$).

The authors concluded that in the DAPA-HF study population, dapa therapy produced a rapid decrease in the risk of worsening HF or death, with a sustained benefit emerging within one month of treatment onset. Also, the patients with a more recent hospitalization for HF before the trial onset were at a particularly high risk and benefitted most from the addition of dapa therapy.

■ COMMENTARY

A significant problem in the management of HFrEF, especially in the outpatient arena, is clinical inertia. The patient is doing well, so why rock the boat and risk adverse effects? We often do not have the resources to start a new drug that requires more intensive follow up. Then, there is the cost of new pharmaceuticals that are not generic yet. Finally, patients hate taking more drugs. Yet here is a new treatment that clearly not only benefits HFrEF patients, but the clinical benefit is rapidly apparent. If the patients have been hospitalized recently, this course helps prevent readmission for worsening heart failure. Thus, we may need to up our game and figure out how to efficiently put patients on dapa or one of the other sodium glucose cotransporter 2 (SGLT2) inhibitors. As the Berg et al study shows, the sooner we start, the better.

Another stumbling block for clinicians is how to sequence the many drugs now recommended for HFrEF patients. Most patients are treated with a renin-angiotensin inhibitor and a beta-blocker, but the addition of other agents has lagged for some of the reasons mentioned already. Also, physicians are loath to just slam a patient with a handful of drugs all at once and for good reasons. Yet there is unclear guidance on what to start first and what to add next in the HF patient. Recently, McMurray and Packer suggested a somewhat radical approach: start with a beta-blocker and an SGLT2 inhibitor, then add an angiotensin receptor neprilysin inhibitor, then add a mineralocorticoid receptor antagonist.[1] This is sage advice from two respected authorities in the field, but it has not been tested in a randomized trial.

The Berg et al analysis of the DAPA-HF trial was post hoc and must be considered hypothesis-generating. Another limitation is the time after hospitalization was dichotomized at one year rather than considered as a continuous variable. Also, patients in the hospital for HF or within four weeks of said hospitalization were excluded. By this trial design, the authors are not recommending starting an SGLT2 inhibitor until after the early post-discharge medication adjustments have been accomplished and renal function has stabilized. The schema proposed by McMurray and Packer would not be applicable since we apparently must wait until one month after a HF hospitalization to start an SGLT2 inhibitor. Clearly, we need more information to assimilate these new data into our treatment algorithms. ■

REFERENCE

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ABSTRACT & COMMENTARY

Age Drives Stroke Risk in Atrial Fibrillation

By Michael H. Crawford, MD, Editor

SYNOPSIS: Among patients with newly diagnosed atrial fibrillation age 66-74 years without other CHA_2DS_2-VASc risk factors for thromboembolism, the older they are in this age range, the more likely they are to experience a stroke.

SOURCE: Abdel-Qadir H, Singh SM, Pang A, et al. Evaluation of the risk of stroke without anticoagulation therapy in men and women with atrial fibrillation aged 66 to 74 years without other CHA_2DS_2-VASc factors. *JAMA Cardiol* 2021; May 19:e211232. doi: 10.1001/jamacardio.2021.1232. [Online ahead of print].

Most physicians use the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke, vascular disease, age 65-74 years, female sex) to decide which patients with atrial fibrillation (AF) to treat with anticoagulants (AC). The exact score cutpoint is controversial, especially in the group age 66-74 years with no other CHA_2DS_2-VASc risk factors.

Abdel-Qadir et al sought to determine the stroke risk in this population and the factors that influence this risk in a retrospective, population-based, cohort study using administrative databases in Ontario, Canada. They included community-dwelling individuals with newly diagnosed AF between 2007 and 2017. Patients with a prior diagnosis of AF, long-term care residents, and those on AC were excluded. The primary outcome was hospitalization with a stroke including intracerebral bleeds, but not bleeds outside the brain (e.g., subdural). Follow-up was limited to one year. Patients were censored if they were started on ACs. The subgroup who started AC within two months of AF diagnosis without an intervening stroke were the AC cohort. The occurrence of hospital-diagnosed bleeding was determined in this group.

The 16,351 individuals who met the inclusion/exclusion criteria were a mean age of 70 years. Women were 49% of the subjects, and there were 4,145 in the AC cohort. During the one-year follow-up from the onset of AF, there were 183 hospitalizations for stroke, including 19 with intracerebral bleeds, and 347 hospital-diagnosed noncerebral bleeds.

Using death as a competing risk (1,484 deaths), the risk of stroke in those not on AC was 1.1% and the risk of death without stroke was 8.1%. The stroke risk was not different between men and women, and the stroke risk in those younger than age 70 years was 0.7%.

The only baseline characteristic that was significantly associated with stroke was age. The risk of stroke more than doubled from age 66 years to age 74 years (0.7% to 1.7%, respectively). Warfarin was given to 1,936 patients, and a direct-acting oral AC was given to 2,209 patients. In the year after starting AC, there were 89 hospital-diagnosed bleeds (2.1%), which was not related to age. The authors concluded among new AF patients age 66-74 years with no other CHA_2DS_2-VASc risk factors, older patients are more likely to gain net clinical benefit from AC therapy than younger ones.

■ COMMENTARY

The CHA_2DS_2-VASc score at which AC is recommended varies from 1 to 3, depending on which societies' guidelines one considers. The biggest discordance is among patients age 66-74 years with no other CHA_2DS_2-VASc risk factors. This controversy occasioned this population study. Part of the reason for conflicting recommendations is the risk of stroke has decreased since the pre-2005 data used to develop the CHA_2DS_2-VASc score. In those early studies, the risk of stroke was approximately 4% to 6% per year. Current data suggest it is more like 2% to 3% per year. The reasons for this drop are unclear, but it is probably at least partially explained by better control of stroke risk factors.

Considering the annual bleeding risk on AC of about 2% shown in the Abdel-Qadir et al study, only the higher-risk patients are going to reap a net clinical benefit from AC therapy. What the authors clearly showed is that in the age 66-74 years group without other risk factors for AF, that age should be considered since the older patients in this group are more likely to experience a net clinical benefit from AC therapy.

Patients age 66-74 years represented 6.5% of the Abdel-Qadir et al study population with new onset AF, and there are no randomized, controlled studies for this group. Thus, this retrospective, observational study is of interest and features several strengths. It was relatively large and contemporary. The problem of the competing risk of death was considered because if one does not, the estimated stroke risk is overestimated. In this study, the competing risk of

death was substantial at about 8%. Also, there is the problem of treatment-switching, because about 38% of the subjects were started on AC. The authors addressed this by censoring those patients at this point and transforming this group into the AC cohort, which provided data on bleeding risk.

However, censoring only works if the decision to start AC was random. This raises the issue of unmeasured confounders. For example, those treated with AC may have had fewer comorbidities. Also, the types of AF were not considered (e.g., paroxysmal, permanent), nor was race or socioeconomic status. Finally, the CHA_2DS_2-VASc score usually is calculated once, and then determines lifelong AC therapy. This is an oversimplification that needs more study.

Perhaps, as these authors suggested, age should be a continuous variable rather than a categorical value, as age is included in the CHA_2DS_2-VASc score. For now, in borderline cases, I am going to consider age as an overriding factor for any decisions on AC therapy. ■

ABSTRACT & COMMENTARY

Aspirin, Clopidogrel, or Both After Coronary Interventions?

By Michael H. Crawford, MD, Editor

SYNOPSIS: A recent study of patients who had undergone a percutaneous coronary intervention and were transitioning from dual antiplatelet therapy to monotherapy showed clopidogrel was superior to aspirin for preventing further major adverse events, including bleeding.

SOURCE: Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): An investigator-initiated, prospective, randomized, open-label, multicentre trial. *Lancet* 2021; May 14:S0140-6736(21)01063-1. doi: 10.1016/S0140-6736(21)01063-1. [Online ahead of print].

Current recommendations call for six to 12 months of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI), depending on the type of stent used. Thereafter, monotherapy usually is used indefinitely. In the current era of drug-eluting stents (DES) and widespread statin use, no one has studied which drug to use for monotherapy.

Koo et al initiated a prospective, randomized, open-label, multicenter trial at 37 sites in South Korea. They enrolled 5,530 patients who were six to 18 months post-DES (second-generation in 97%) on DAPT without any intervening cardiovascular (CV) events. Patients were randomized to either aspirin 100 mg per day or clopidogrel 75 mg per day and followed up at 12 and 24 months. The primary endpoint was a composite of all-cause death, myocardial infarction, stroke, acute coronary syndrome, or an admission to hospital for a major bleeding episode. Secondary endpoints were components of the primary composite endpoint.

Follow-up was 98% complete in the 5,530 patients enrolled. Their average age was 64 years, 75% were men, and the average follow-up was 382 days. Also, 82% were on aspirin and clopidogrel before enrollment. The primary endpoint was experienced by 152 of those on clopidogrel and 207 of those on aspirin (HR, 0.73; 95% CI, 0.59-0.90; $P = 0.0035$). Mortality was 1.9% on clopidogrel vs. 1.3% on aspirin (P = not significant). A CV event was 3.7% on clopidogrel and 5.5% on aspirin (HR, 0.68; 95% CI, 0.52-0.87; $P = 0.0028$). Any significant bleeding was 2.3% on clopidogrel vs. 3.3% on aspirin (HR, 0.70; 95% CI, 0.51-0.98; $P = 0.036$). The Kaplan-Meier curves for the primary and secondary outcomes separated at about nine months. The results were not different in any of the subgroups analyzed. The authors concluded that clopidogrel monotherapy for chronic maintenance treatment after PCI with DES was superior to aspirin in preventing future CV events and significant bleeding.

■ COMMENTARY

Aspirin is an irreversible inhibitor of the cyclooxygenase pathway in platelets. It has been recommended for long-term maintenance therapy post-PCI based on older secondary prevention trials performed before the widespread use of statins and DES. The major adverse effect of aspirin is denudation of the stomach lining and upper gastrointestinal bleeding, which can be significant. Clopidogrel is an adenosine diphosphate receptor blocker and has been recommended as an alternative to aspirin for long-term maintenance therapy if the patient cannot tolerate aspirin. Recent studies of aspirin vs. clopidogrel in coronary artery disease patients with atrial fibrillation on anticoagulants

have shown clopidogrel is as effective as aspirin for preventing CV events and is associated with less bleeding. Thus, raising the issue of whether clopidogrel would be as effective as aspirin in the chronic maintenance therapy of the post-PCI patient and whether it would be associated with less major bleeding is important. In the Koo et al study, the absolute benefits were in the 1% to 2% range. However, even saving a few patients from subsequent CV events or major bleeding episodes is a worthwhile goal. Now that clopidogrel is generic, cost should not be a major issue.

There was no significant difference in all-cause mortality alone, and the authors did not report CV mortality. There was a trend for lower rates of mortality on clopidogrel vs. aspirin, which might have reached significance in a larger trial with more events.

There were weaknesses to this study. It was open-label, which may have introduced biases, but a blinded committee adjudicated all events, which would minimize this effect. The fact there were fewer events than the investigators predicted may have been caused by patient selection bias. Also, the trial design requirement for an absence of events six to 18 months before study enrollment probably resulted in the randomization of more low-risk individuals. There was no genetic testing for clopidogrel metabolism differences. It is known that at least half of East Asians carry a loss of function mutation in the CYP2C19 gene, which decreases the effectiveness of clopidogrel. However, East Asians also experience fewer thrombotic events, which has been dubbed the "East Asian paradox." Thus, this would have been interesting information, but the net clinical effect may not have been important. Also, it has been estimated about 18% of East Asians are aspirin-resistant, which further complicates interpreting the results of the Koo et al study. Finally, the follow-up period was rather short.

Considering the Koo et al study showed a significant reduction in CV events and major bleeding, I believe this study makes a strong case for substituting clopidogrel for aspirin in the long-term maintenance therapy of post-PCI patients who receive DES. ■

ABSTRACT & COMMENTARY

FFR Fails to Show Benefit in Treatment of Nonculprit Lesions After STEMI

By Jeffrey Zimmet, MD, PhD

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

SYNOPSIS: In this study of patients presenting with ST-elevation myocardial infarction and multivessel disease, nonculprit vessel percutaneous coronary intervention (PCI) guided by fractional flow reserve failed to show benefit vs. angiography-guided PCI in terms of clinical events at one year.

SOURCE: Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med* 2021; May 16. doi: 10.1056/NEJMoa2104650. [Online ahead of print].

Back in 2009, the authors of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial demonstrated that the use of fractional flow reserve (FFR) to guide coronary intervention in stable coronary disease or non-ST-elevation acute coronary syndrome results in lower rates of coronary stenting vs. angiography guidance, with a lower risk of major cardiovascular events during follow-up.[1] Since that time, several research groups have demonstrated the benefits of complete revascularization of multivessel disease following ST-elevation myocardial infarction (STEMI). Some have used angiography to guide this treatment, and some have used FFR. To date, none have compared the two decision-making techniques in STEMI patients.

The Flow Evaluation to Guide Revascularization in Multivessel ST-elevation Myocardial Infarction (FLOWER-MI) trial was designed to test the hypothesis that FFR guidance would improve outcomes in treatment of STEMI patients with multivessel disease. To this end, Puymirat et al randomized 1,171 such patients presenting to 41 centers in France who had undergone successful treatment of the infarct-related artery to guidance of complete revascularization by either FFR or by angiography. Although revascularization of nonculprit vessels during the index procedure was encouraged, only about 4% of cases were actually performed this way. The remainder were managed as staged procedures before hospital

discharge, on average two to three days after the initial presentation. In the FFR-guidance group, all lesions judged to be at least 50% severity were to be evaluated by FFR, with percutaneous coronary intervention (PCI) guided by FFR values of 0.80 or smaller, as per current guidelines. Overall, FFR was attempted in more than 95% of patients in the FFR group and was successful in the majority. PCI was performed in 388 of 586 patients in the FFR-guided group and in 560 of 577 patients in the angiography-guided group. This resulted in a lower number of stents used per patient in the FFR group. Procedure times were slightly higher in the FFR group compared with angiography (35 minutes vs. 30 minutes).

At one year, the primary outcome of all-cause death, MI, and unplanned urgent revascularization occurred in 5.5% of patients in the FFR group and in 4.2% of patients in the angiography group, which did not represent a significant difference (HR, 1.32; 95% CI, 0.78-2.23; $P = 0.31$). Rates of nonfatal MI (18 vs. 10) and any revascularization (38 vs. 26) were numerically greater in the FFR group, but these also did not reach statistical significance. The authors concluded in patients with STEMI and multivessel disease undergoing complete revascularization, FFR guidance did not show a benefit over angiography guidance in terms of the risk of death, MI, and repeat revascularization at one year.

■ COMMENTARY

The overall message of the FAME trial, and of subsequent trials, has been remarkably consistent over time. Using FFR to guide PCI outside the realm of STEMI predictably leads to lower rates of coronary stenting and better cardiovascular outcomes vs. angiography alone to guide treatment decisions. The improved outcomes presumably result from selecting lesions that are more physiologically significant for treatment, reserving PCI for those who will benefit and preventing the complications of stenting in those who will not. Part of the lesson here is PCI in patients with stable angina clearly differs from treatment of nonculprit lesions after STEMI. Generally, PCI in stable disease has not been associated with improvements in hard cardiovascular endpoints over periods of a year or less. In contrast, multiple trials have demonstrated benefit to a complete revascularization strategy after presentation with STEMI. The COMPLETE trial demonstrated improvements in rates of cardiovascular death and MI among patients with complete revascularization vs. culprit lesion-only PCI.[2] This brings up the concept that nonculprit lesions in STEMI patients are less inherently "stable," and may benefit from stenting. The authors of the COMPLETE trial reported that event curves started to visually diverge after six months, with higher rates of the primary outcome in the FFR group. It is likely some lesions left untreated in the FFR group progressed during follow-up, leading to the observed increase in event rates. The result is that less PCI is not better in the context of the post-STEMI patient. It will be interesting to see the longer-term results from this trial, once available.

Most nonculprit revascularization procedures in the FLOWER-MI trial were performed as staged procedures, several days after the STEMI presentation. The result here prevents the potential problems with interpretation of FFR in the context of ongoing STEMI, with potential confounding by arterial spasm and microvascular obstruction. However, the authors still did not demonstrate the benefits of FFR seen in more stable coronary disease. While we should be careful about applying the results to revascularization performed during the index procedure, the use of FFR early after the acute phase of a STEMI to accomplish complete revascularization would appear to be optional. ■

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ABSTRACT & COMMENTARY

Predicting Coronary Artery Disease in Breast Cancer Patients

By Michael H. Crawford, MD, Editor

SYNOPSIS: The authors applied an automated algorithm to calculate an Agatston coronary artery calcium score from non-ECG-gated planning CT scans in breast cancer patients undergoing radiation therapy. This provided a graded risk calculation that could encourage preventive measures in patients at highest risk of a cardiovascular disease event.

SOURCE: Gal R, van Velzen SGM, Hooning MJ, et al. Identification of risk of cardiovascular disease by automatic quantification of coronary artery calcification on radiotherapy planning CT scans in patients with breast cancer. *JAMA Oncol* 2021; May 6. doi: 10.1001/jamaoncol.2021.1144. [Online ahead of print].

In older women, breast cancer competes with cardiovascular (CV) disease as the leading cause of death. Most patients with breast cancer undergo a CT scan for planning purposes before starting a course of radiation therapy. Gal et al developed an automatic algorithm for measuring the coronary artery calcium score on these CT scans. Then, they conducted tests to see if these automatically produced scores would identify breast cancer patients at higher risk for CV disease.

In two centers in the Netherlands, breast cancer patients undergoing radiation therapy were included in this retrospective analysis (unless they had known metastatic disease or if their CT scan was taken more than one year before their cancer diagnosis). Clinical data were obtained from the Netherlands Cancer Registry. The CT scans were performed without ECG gating. Gal et al developed a deep learning-based algorithm to produce an Agatston score of coronary artery calcium (CAC). The authors considered five categories of CAC score: 0, 0-10, 11-100, 101-400, and > 400. The primary outcomes were fatal or non-fatal CV disease (CVD) events and all-cause mortality. Patients were followed until December 2018 unless a CVD event occurred. Also, to avoid competing risks, patients were censored for non-CVD events, breast cancer recurrence, or the development of other cancers. The risk analyses were adjusted for age, left or right breast, and concomitant anthracyclines. On average, the 15,915 patients studied were age 59 years; all were followed for an average of 57 months.

The distribution of CAC scores was: 0 in 70% of the population; 1-10 in 10%, 11-100 in 12%, 101-400 in 5%, and > 400 in 3%. A CVD-related hospitalization occurred in 8.4% of patients (0.7% died of CVD). The risk of these outcomes increased with higher calcium scores: 5% with 0 vs. 28% at > 400. The adjusted HRs for CVD risk were 1.1, 1.8, 2.4, and 3.4, respectively, in the four groups with detectable coronary calcium compared to those with a CAC score of 0. If the patient also received anthracyclines, the HR was 5.8. If they received a radiation boost, the HR was 6.1. The CAC score was particularly strong at predicting the coronary artery disease (CAD) subset of CVD (HR, 7.8). Laterality did not affect the results. The authors concluded automated CAC scoring on radiation planning CT scans may be a low-cost tool to identify breast cancer patients at higher risk of CVD. Abrogating this risk could reduce the occurrence of CVD in breast cancer patients.

■ COMMENTARY

Radiologists are paying more attention to the presence of calcium in CT scans of the chest and upper abdomen that are conducted for other reasons — specifically, when the scans show calcium in the coronary arteries. By putting this finding into their reports, radiologists hope primary care clinicians include this information into enhanced CVD prevention interventions. The Gal et al study pushed this concept to a higher level. They developed an automated algorithm by deep learning methods, which can calculate an Agatston CAC score from the non-ECG-gated CT scans used to plan radiation therapy in breast cancer patients. The derived CAC score also was excellent at detecting the subset of CVD patients with CAD. Since CVD is common in breast cancer patients and almost all received radiation therapy, this is a potentially simple, cost-effective way to identify the highest-risk patients for developing CVD.

There were other factors that augmented the CVD risk prediction. An extra radiation treatment (boost) was an obvious one. Radiation to the heart can lead to subsequent CAD, valve damage, and even cardiomyopathy. Administering concomitant anthracycline augments the risk of radiation therapy, which should not be unexpected since this chemotherapeutic agent has been associated with cardiomyopathy. There were too few patients in the Gal et al study who received trastuzumab to analyze its potential effect. Interestingly, laterality did not affect the results.

Perhaps the heart receives enough radiation through whichever breast is irradiated to cause a detrimental effect.

There were limitations to the Gal et al study. The follow-up was rather short at 4.75 years. The adverse effects of radiation therapy often are not appreciated for 10 years. There was no control group that did not receive radiation therapy, so the effects of the various insults to the heart could not be parsed. The clinical information came from administrative databases, although in this study a rather complete one (i.e., it was focused on cancer patients). There was no information on traditional risk factors and what roles they may have played. Although there were no data on the dose of radiation and its effect on the CAC score, using a boost dose later did increase the risk of CVD. Finally, we do not know if clinicians used this data to change the treatment of the patients, especially regarding CVD risk reduction. If so, did it made any difference in outcomes?

At this point, we should encourage radiologists to continue to note coronary calcium in their CT scan reports and to explore acquiring this software for calculating a CAC score soon. It is easier to make firm recommendations to patients if they are determined to be at high risk. This information from these routine CT scans would help tailor the aggressiveness of our advice to patients. ■

CME/CE QUESTIONS

1. **In breast cancer patients with a coronary artery calcium score > 400 derived from routine CT scans to plan radiation therapy, the risk of a cardiovascular disease event increases:**
   a. twofold.
   b. threefold.
   c. fivefold.
   d. eightfold.

2. **In patients age 66-74 years with new-onset atrial fibrillation and no other CHA_2DS_2-VASc risk factors, what percent experienced a stroke vs. a major bleed on oral anticoagulation therapy?**
   a. 1% and 2%
   b. 2% and 3%
   c. 3% and 4%
   d. 4% and 5%

3. **In the DAPA-HF study of the addition of dapagliflozin vs. placebo to patients with heart failure caused by reduced left ventricular ejection fraction treated with maximally tolerated standard therapy, the beneficial effects on recurrent heart failure and mortality occurred within:**
   a. one month.
   b. three months.
   c. six months.
   d. 12 months.

4. **A recent trial of chronic monotherapy after a period of dual antiplatelet therapy following a percutaneous coronary intervention showed the incidence of major adverse cardiovascular events on clopidogrel vs. aspirin was:**
   a. 2% and 3%.
   b. 3% and 4%.
   c. 4% and 6%.
   d. 6% and 8%.

5. **In which patient situation has fractional flow reserve determination resulted in better subsequent outcomes from stenting coronary lesions?**
   a. The culprit lesion in an acute STEMI
   b. Nonculprit lesions in an acute STEMI
   c. Nonculprit lesions early after STEMI
   d. Chronic stable angina