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ABSTRACT & COMMENTARY

# Is Empagliflozin Safe in Combination with a Neprilysin Inhibitor for Heart Failure?

*By Michael H. Crawford, MD, Editor*

SYNOPSIS: A prespecified subgroup analysis of heart failure patients with reduced ejection fraction who were on neprilysin inhibitors before empagliflozin was administered (vs. those not on neprilysin inhibitors) showed the reduction in mortality and hospital admissions for heart failure were not attenuated by concurrent neprilysin use.

SOURCE: Packer M, Anker SD, Butler J, et al. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial. *Eur Heart J* 2021;42:671-680.

There are little data on the effect of combining a neprilysin inhibitor with a sodium-glucose cotransporter-2 (SGLT2) inhibitor in patients with systolic heart failure. In the EMPEROR-Reduced trial of the SGLT2 empagliflozin vs. placebo in patients with heart failure and reduced ejection fraction, 20% of 3,730 randomized patients were on concomitant sacubitril/valsartan at baseline.[1] Packer et al conducted a prespecified subgroup analysis of this 20% (727 patients). These patients were New York Heart Association (NYHA) class II-IV heart failure with ejection fraction less than 40% and were on appropriate treatment for heart failure, including devices. They were randomized to empagliflozin 10 mg/day vs. placebo. The primary endpoint was the composite of adjudicated cardiovascular death or hospitalization for heart failure. The authors also assessed several secondary endpoints involving renal function, symptoms, and blood metabolic parameters.

Among baseline clinical characteristics, those treated with neprilysin inhibition recorded lower blood pressure readings, heart rate, and BNP levels, and were more likely to have a cardiac device and be from North America. Compared to placebo, empagliflozin reduced the primary endpoint by 23% in those not on neprilysin inhibition and by 36% in those on neprilysin inhibition (HR, 0.77; 95% CI, 0.66-0.90; $P$ = 0.0008 and HR, 0.64; 95% CI, 0.45-0.88; $P$ = 0.009, respectively). The heart failure hospitalization component of the primary endpoint also declined by 29% in subjects who were not on a neprilysin inhibitor and by 35% in subjects who were taking a neprilysin inhibitor (HR, 0.71; 95% CI, 0.58-0.88; $P$ = 0.002 and HR, 0.65; 95% CI,

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0.42-1.00; $P = 0.052$, respectively). Also, empagliflozin slowed the rate of decline in estimated glomerular filtration rate (eGFR) by 1.7 mL/min/1.7m$^2$/year in those not on a neprilysin inhibitor ($P < 0.0001$) and by 1.92 mL/min/1.7m$^2$/year in those on a neprilysin inhibitor ($P = 0.016$). There were no significant differences in adverse events between those on or off neprilysin inhibition treated with empagliflozin. The authors concluded the beneficial effects of empagliflozin in patients with symptomatic heart failure with reduced ejection fraction are not attenuated by concomitant neprilysin inhibition treatment, and such therapy is well tolerated.

## ■ COMMENTARY

The most recent heart failure guideline update now recommends in NYHA class II-IV patients with heart failure caused by systolic dysfunction to start an angiotensin receptor/neprilysin inhibitor (ARNI) and a beta-blocker soon after stabilization of volume status and relief of congestion. Then, in those with an eGFR > 30 mL/min and a potassium < 5 mEq/L, start a mineralocorticoid antagonist and a SGLT2 inhibitor.[2] This recommendation was given on the strength of studies such as DAPA-HF, which showed robust reductions in mortality and hospitalizations when SGLT2 inhibitors were administered on top of ACEI or ARB, beta-blocker, and mineralocorticoid inhibition.[3] However, in DAPA-HF, only 11% of patients also were on an ARNI, so the efficacy and safety of this subgroup was underpowered for firm conclusions.

Since EMPEROR-Reduced included about twice as many patients on an ARNI at baseline, it made sense to evaluate the benefit of adding an SGLT2 inhibitor in this subgroup. Not only were the beneficial effects statistically similar in this subgroup, numerically, the effects were larger. This is somewhat surprising, since the ARNI group was exceptionally well treated at baseline: 95% on beta-blockers, 70% on mineralocorticoid antagonists, 27% with an implanted cardiac defibrillator, and 10% with a cardiac resynchronization device. In addition, this combination was well tolerated. There was minimal additional blood pressure-lowering and volume depletion in the ARNI group, and other adverse effects were unusual in both groups.

What was disturbing was the aggregate of all serious adverse effects occurred in about 50% of subjects in both groups with the addition of empagliflozin. Hence, it is difficult to rationalize how the authors could state that empagliflozin was "well tolerated." This observation raises the difficult issue of patient tolerance of the ever-growing list of must-have drugs to treat heart failure, especially since clinicians are supposed to titrate the drugs to the maximum doses used in trials. Of course, trial participants are not exactly equivalent to the patients seen in practice, such that most heart failure patients are not on the optimal doses of all these drugs because of intolerance, usually caused by low blood pressure or heart rate, or metabolic derangements, such as hyperkalemia. Once again, clinicians are challenged to bring patients on board with all these lifesaving drugs.

There were limitations to this study. For this type of trial, the number of patients was relatively small. The authors did not address the reverse issue of adding an ARNI to someone already on an SGLT2 inhibitor, such as a diabetic patient. Also, the authors did not explore the timing of initiation of the recommended drugs for systolic heart failure. The sequence and timing of the administration and titration of the recommended drugs in new heart failure patients are not well studied, but perhaps the SGLT2 inhibitors should be introduced before mineralocorticoid antagonists. ■

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ABSTRACT & COMMENTARY

# Can Left Ventricular Strain Detect Early Cardiac Toxicity of Cancer Chemotherapy?

*By Michael H. Crawford, MD, Editor*

SYNOPSIS: Using left ventricular peak systolic global longitudinal strain vs. left ventricular ejection fraction to survey patients undergoing potentially cardiotoxic chemotherapy with at least one other risk factor for heart failure showed no difference in the primary endpoint of the difference in ejection fraction between the two groups at one year.

SOURCE: Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol* 2021;77:392-401.

Traditional surveillance of cardiac function during cancer chemotherapy has relied on left ventricular (LV) ejection fraction (EF) measured by echocardiography. Echocardiographic peak systolic LV global longitudinal strain (GLS) has shown promise for detecting subclinical cardiac dysfunction before LVEF is abnormal. Whether GLS would be useful for implementing cardioprotective therapy (CPT) or ceasing chemotherapy is unclear.

Thus, this analysis of the one-year follow-up results of the multicenter, multinational Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) study is of interest. The authors randomized 331 patients treated with anthracycline-based chemotherapy and another risk factor for heart failure at 28 centers on four continents between 2014 and 2019 to an EF-guided arm and a GLS-guided arm measured by 3D echocardiography every three months. Other risk factors included trastuzumab therapy in HER2+ breast cancer; use of tyrosine kinase inhibitors; doxorubicin doses of > 450 mg/m$^2$; or any traditional heart failure risk factor, such as older than age 65 years, diabetes, hypertension, or prior myocardial infarction. Exclusion criteria included a history of heart failure or an EF < 50%, moderate or more valvular heart disease, systolic blood pressure lower than 110 mmHg, and heart rate < 60 bpm.

In the EF-guided group, a symptomatic drop in EF of > 5% or an asymptomatic drop of > 10% compared to baseline was considered cancer chemotherapy-related cardiac dysfunction (CRD). In the GLS-guided arm, a decrease of > 12% in LV function from baseline was considered significant. Those with CRD started on an ACE inhibitor or an ARB, followed by a beta-blocker titrated to maximally tolerated doses. The primary outcome was the difference between baseline and one-year LVEF between the two arms.

During follow-up, 24 patients in each group did not complete the one-year follow-up, mainly because they dropped out or there were missing data. Only two patients died during the year. The remaining 307 patients were mean age 54 years, and 91% were women with breast cancer. The median dose of doxorubicin was 218 mg/m$^2$, with no significant difference between the two arms. About half the patients received left chest radiation therapy, too. At one year, 19 patients in the EF group and 29 in the GLS group could not be included because of poor images, mainly caused by breast implants or chest wall sensitivity from treatment. At baseline, there was no significant difference in EF or GLS between the two arms.

At one year, EF was lower in the EF arm compared to the GLS arm (55% vs. 57%; $P = 0.05$). After an adjustment for baseline differences in comorbid conditions and their related therapy, this difference was not significant. However, 14% of the EF arm and 6% of the GLS arm met criteria for CRD at one year (relative risk reduction, 57%; 95% CI, 10-80%), with a number needed to treat of 13 to prevent one CRD event using the GLS-guided approach to employing CPT). Also, patients who received CPT in the EF arm recorded a greater reduction in EF than those in the GLS arm who received CPT (-9% vs. -3%; $P = 0.03$). In addition, in those meeting CRD criteria during follow-up, 45% of the EF arm and 14% of the GLS arm met CRD criteria on the final visit ($P = 0.01$) for a relative risk reduction of 70% (95% CI, 26-88%) with GLS-guided CPT. The authors concluded the results endorse the use of GLS rather than EF to determine which patients with at least one risk factor for heart failure should receive CPT during potentially cardiotoxic chemotherapy.

## ■ COMMENTARY

According to the authors, this was the first randomized, controlled trial of GLS compared to EF for guiding the decision to employ CRT in patients undergoing potentially cardiotoxic chemotherapy. However, based on retrospective, observational data, the American and European Societies of Echocardiography had endorsed GLS for this purpose in 2014.[1] Indeed, our echo laboratory routinely measures GLS in chemotherapy

patients, but we have not moved to using it as the sole criterion for initiating CRT. Should we? Based on the SUCCOUR study, the question remains open. This was a well-conducted study that was multicentered and international. It focused on high-risk patients for cardiotoxicity, and the authors enrolled a reasonable number of such patients. The centers used the same echocardiographic equipment, and the results were corroborated by a core echo lab. Also, in 60% of patients, the authors used 3D echo to calculate EF. However, clinical decisions were made locally by the treating doctors, which made this a real-world study. In addition, the authors randomized the screening strategy, not the CRT. Thus, it is unknown whether those given CRT would have developed CRD if it had not been administered.

A potential weakness is the study was not blinded, so one cannot exclude some biases. Additionally, the cutpoints the authors used for deciding what was a significant change in GLS warranting CRT were not well validated. The trial did not meet the primary endpoint after adjustment for other factors that could influence the results. The final EF and the change in EF from baseline to one year was the same for both groups. In this sense, it was a negative trial.

Despite this, the authors, based on a variety of secondary endpoints, concluded GLS and not EF should be used in the surveillance for CRD. Their explanation for the negative primary endpoint was that those without CRD recorded an increase in EF at one year, which skewed the results toward null. The authors did not explain why this increase in EF occurred in some patients. Other factors may have included the fact the patients in both groups were well managed. Only one patient in each group was hospitalized for heart failure, and few cut back or ended their chemotherapy. Yet more than twice as many patients in the GLS group initiated CRT vs. the EF group. One must wonder if subjecting all these patients to the risk and expense of CRT was worth it. Unfortunately, these authors did not provide sufficient data to support the use of GLS exclusively for surveillance and, if used at all, at what value CRT is indicated. ■

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## ABSTRACT & COMMENTARY

# Intracranial Plaque Rupture and Stroke

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

SYNOPSIS: An MRI study of cerebral circulation in patients with embolic stroke of undetermined etiology showed evidence of atherosclerotic plaque in most patients, supporting the theory that unstable intracranial artery plaques play an etiologic role in embolic stroke.

SOURCE: Lin Tao MM, Li XQ, Hou XW, et al. Intracranial atherosclerotic plaque as a potential cause of embolic stroke of undetermined source. *J Am Coll Cardiol* 2021;77:680-691.

Ruptured non-stenotic intracranial atherosclerotic plaque has been suspected to cause embolic stroke of undetermined source (ESUS), but there are little data to support this hypothesis. Accordingly, Tao et al evaluated the morphology and composition of intracranial plaque in patients with ESUS and small vessel disease (SVD).

They used the 3.0 Tesla MRI to compare the ipsilateral side to the contralateral side of the stroke. Patients with acute ischemic stroke who had undergone a full evaluation for stroke etiology, including intracranial high-resolution MRI and met criteria for ESUS or SVD, were enrolled retrospectively. Patients with bilateral or posterior circulation strokes were excluded, leaving 243 with ESUS and 160 with SVD. Plaque was defined as eccentric focal wall thickening at the point of minimal lumen diameter in the major vessels in the anterior intracranial circulation. Vessel reference sites were adjacent plaque-free areas. The remodeling index (RI) was the ratio of the cross-sectional area of the vessel at the plaque site to the reference vessel area. Plaque burden (PB) was defined as the percent difference between the total vessel area and the luminal area at the plaque site. Among ESUS patients, 69% had any intracranial plaque. Among SVD patients, 40% had any intracranial plaque ($P < 0.001$ for the difference).

The prevalence of intracranial plaque was higher in the ipsilateral vs. the contralateral side in ESUS patients (64% vs. 43%; OR, 5.25; 95% CI, 2.83-9.73). In SVD patients, this difference was not found (36% vs. 31%; OR, 2.14; 95% CI, 0.87-5.26; $P = 0.13$). Also, ESUS patients exhibited larger PB and RI in the ipsilateral vs. the contralateral plaque (PB: 64% vs. 60%; $P = 0.002$ and RI: 1.17 vs. 1.09; $P < 0.001$). In addition, complicated plaque was ipsilateral more often in ESUS patients (77% vs. 60%; $P = 0.003$). None of these plaque features were associated with stroke

in SVD patients. A multivariate logistic regression analysis excluding overlapping plaque characteristics showed RI was independently associated with ESUS (OR, 2.30; 95% CI, 1.66-3.17; $P < 0.001$). Using an RI cutoff of 1.162, the area under the curve was 0.74. The authors concluded these data suggest high-risk, non-stenotic intracranial plaque represents a significant underestimated embolic source in patients with ESUS.

## ■ COMMENTARY

This is an important foundational study. ESUS represents about 20% of ischemic stroke patients,[1] and they are at a high risk of recurrence. Also, there is no established therapy to prevent recurrences. Standard stroke prevention therapies have shown mixed results. In NAVAGATE ESUS, the subgroup with non-stenotic intracranial or generalized atherosclerosis showed no difference in recurrent events between treatment with rivaroxaban or aspirin.[2] By contrast, in COMPASS patients with cryptogenic stroke, reduced recurrence rates were observed on low-dose rivaroxaban and aspirin vs. aspirin alone.[3] Neither study focused exclusively on patients with intracranial atherosclerosis. Techniques for studying intracranial arterial lesions, such as the MRI technique used in the Tao et al study, are relatively new but have shown excellent intra- and interobserver agreement. Thus, now, there are tools to study this issue more carefully. Hopefully, more effective recurrence-preventing therapies will be discovered.

It has been evident for some time that non-stenotic atherosclerotic lesions in extracardiac vessels proximal to the cerebral circulation, such as the proximal aorta, carotids, and vertebral basilar system, could produce emboli to the brain, but evidence of the potential for intracranial vessel plaques to be a source has been limited by technical issues. In the Tao et al study, positive remodeling of ipsilateral arterial plaque sites was shown to be the best independent predictor of ESUS. Thus, intracranial arteries that have enlarged because of the presence of plaque and have a larger RI seem to be the most likely sites of plaque-derived emboli. However, patients with negative remodeling were excluded because they were more likely to be stenotic. Plaque burden was less predictive of ESUS, probably because it can be overestimated thanks to curved vessels and oblique cuts. The authors interpreted images without any clinical knowledge about the patients. This, along with the cutting-edge imaging and sophisticated statistical analysis, made this a compelling investigation. Still, there were weaknesses. It was retrospective, with a small number of patients, all of whom were Chinese. There were no histologic data to support the analysis of plaque characteristics. Also, there are multiple possible sources of emboli; excluding other causes is imperfect in ESUS. However, one could argue too much attention is paid to patent foramen ovale and occult atrial fibrillation, both of which are unusual causes of ischemic strokes. Finally, the long-suspected-but-not-proven theory that cerebral vessel atherosclerosis and resultant embolization of debris from damaged plaques is getting its due. ■

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ABSTRACT & COMMENTARY

# PFO Closure for Resistant Migraines: Finding an Elusive Link


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

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SYNOPSIS: A meta-analysis of two randomized trials of patent foramen ovale closure in resistant migraine showed a significant benefit in three of four clinical endpoints.


SOURCE: Mojadidi MK, Kumar P, Mahmoud AN, et al. Pooled analysis of PFO occluder device trials in patients with PFO and migraine. *J Am Coll Cardiol* 2021;77:667-676.

There is a suspected association between right-to-left cardiac shunts and migraine. The first report of migraine improvement after patent foramen ovale (PFO) closure, based on a retrospective review of just 37 patients who had undergone a closure procedure, was published in 2000.[1] Since then, at least four small, randomized trials have been performed to assess the efficacy of PFO closure in reducing migraine

symptoms. Of those, two were recent and performed with currently available closure devices: Percutaneous Closure of PFO in Migraine with Aura (PRIMA) and Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management (PREMIUM).[2,3] Each failed to meet their primary endpoints, in part because of limited study size. However, multiple secondary endpoints were positive, with a minority of subjects reporting significant reductions in headache frequency.

In an unusual-but-thoughtful meta-analysis, Mojadidi et al obtained patient-level data from just these two studies and redefined the endpoints to re-evaluate the potential benefit to PFO closure. A total of 337 subjects were included: 176 who had undergone closure with the Amplatzer PFO occluder and 161 who were treated with medical therapy alone. Since there were different primary endpoints in PRIMA and PREMIUM, Mojadidi et al defined four endpoints for the combined data: mean reduction in monthly migraine days, mean reduction in monthly migraine attacks, responder rate, and complete migraine cessation. The responder rate matched the primary endpoint of the PREMIUM trial and was defined as a 50% reduction in migraine attacks and adverse events.

Of the four endpoints, only the responder rate did not achieve statistical significance. PFO closure patients showed a greater reduction in migraine days vs. those on medical therapy (-3.1 ± 4.5 days vs. -1.9 ± 4.2 days; $P = 0.02$). The mean reduction in migraine attacks also declined significantly among PFO closure patients (-2.0 ± 2.0 vs. -1.4 ± 1.9 days; $P = 0.01$). Fourteen of 157 PFO closure patients showed complete resolution of migraines vs. one of 146 in the control group ($P < 0.001$). Mojadidi et al also attempted to assess the gradations of response to PFO closure in migraine patients with and without aura. Subjects with migraine with aura experienced a significant reduction in migraine days after PFO closure that was not seen in those without aura. In addition, those with migraine with frequent aura (defined as aura in > 50% of migraine attacks) showed a significant change with PFO closure in all four defined endpoints, including the elusive responder rate (there also were more subjects with complete headache cessation). The authors concluded PFO closure was associated with significant reductions in monthly migraine days and attacks and led to a greater likelihood of complete migraine cessation vs. medical therapy alone.

## ■ COMMENTARY

Some migraine sufferers with PFO may benefit from closure. Each trial included in the Mojadidi et al study included significant numbers of subjects who appeared to respond to treatment, and each showed significant treatment effects in secondary outcomes. The strong suggestion of benefit here is not new.

Migraines and PFOs are common. Should clinicians start closing PFOs in all patients where the two coexist? The answer is no. The more useful piece of the Mojadidi et al study is in making some headway, albeit small, in determining which subsets of patients are most likely to benefit. Specifically, it appears patients with migraine with aura are more likely to see a response from PFO closure. Among these, those with frequent aura are most likely to respond. But this does not tell the whole story, as some patients without aura also seemed to respond to the procedure. Unfortunately, there is no clear pathophysiologic understanding of the link between PFO and migraine. More data are needed. An additional randomized study, the RELIEF trial, will use migraine responsiveness to P2Y12 inhibition as an additional criterion for entry. Investigators plan to begin enrolling later this year. The key point over time will be separating those migraine patients where PFO is causative from those where it is incidental. Only then will the rational use of PFO closure in treatment of migraine become a reality. ■

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ABSTRACT & COMMENTARY

# Low BNP Levels in Up to 16% of Heart Failure Patients

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

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SYNOPSIS: In patients with clinical heart failure and low B-type natriuretic peptide levels, the authors found these patients usually are young and obese, with higher ejection fraction and better renal function.

SOURCE: Bachmann KN, Gupta DK, Xu M, et al. Unexpectedly low natriuretic peptide levels in patients with heart failure. *JACC Heart Fail* 2021;9:192-200.

The myocardium releases natriuretic peptides in response to elevated wall stress. There are two forms: atrial natriuretic peptide (ANP) and brain, or B-type, natriuretic peptide (BNP). They exert their effects in several ways, including increasing renal sodium and water excretion, promoting vasodilation, and reducing myocardial fibrosis.

Clinical use of BNP levels started with evaluation of patients in the ED for dyspnea in the Breathing Not Properly trial.[1] They have become powerful tools for risk assessment, not only in heart failure but also patients with atrial fibrillation, pulmonary arterial hypertension, acute pulmonary embolism, and systemic hypertension. Serial BNP measurements can help track disease course over time. BNP levels are increasingly incorporated into clinical trial criteria as well to enrich the study population in patients at high risk for clinical events. For example, some heart failure therapy trials have required BNP levels above a certain threshold before enrollment. BNP has become a therapeutic target, too; sacubitril inhibits neprilysin, resulting in higher levels of natriuretic peptides.

Interestingly, there is a subset of patients with clear heart failure with normal or even low BNP values. To further evaluate this phenomenon, Bachmann et al queried a de-identified version of their institution's electronic medical record to find patients with measured BNP values and heart failure based on echo or hemodynamic criteria or hospitalized with heart failure. Echo criteria included left ventricular ejection fraction 35% or lower or left ventricular hypertrophy based on estimated left ventricular mass (> 162 g for women, > 224 g for men). BNP measurement was required within 90 days of the study. Hemodynamic criteria included left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, or right atrial pressure of 20 mmHg or greater or cardiac index less than 2 L/min/$m^2$, with BNP measurements required within one day of the procedure. Heart failure hospitalizations required at least one dose of IV diuretic and an ICD diagnosis code for heart failure, and that the BNP measurement was recorded in the 24 hours preceding admission or during the hospitalization. The authors identified 47,970 adult patients with a measured BNP value: 9,153 were associated with a heart failure hospitalization, 7,041 met echo criteria, and 363 met hemodynamic criteria (some patients fell into multiple groups). BNP levels below 50 pg/mL were present in 4.9% of patients hospitalized for heart failure, 14% of patients with abnormal echoes, and 16.3% of patients with abnormal hemodynamics.

Bachmann et al studied the characteristics of patients hospitalized with heart failure, looking for differences between patients with low (< 50 pg/mL) vs. normal or elevated BNP levels. In a multivariate analysis, higher BMI, younger age, higher ejection fraction, and lower creatinine predicted low BNP levels. Finally, the authors sequenced whole exomes for nine patients with low BNP levels (less than 10 pg/mL to 37 pg/mL). They did not find any loss of function variants in the synthetic pathway for BNP production or mutations that would prevent accurate measurement of BNP levels in lab assays. They found two loss-of-function variants in the NP clearance receptor; one would expect this to result in higher BNP levels. These findings suggest up to 16% of patients with significant hemodynamic derangements produce normal BNP values, and the data confirm the previously observed trend: lower BNPs are seen in younger patients with higher BMIs, higher ejection fraction, and lower creatinine levels.

## ■ COMMENTARY

The heart failure hospitalization criteria are the most subjective. Patients with dyspnea and low BNP levels may be erroneously diagnosed with something other than heart failure and inappropriately treated. Thus, they were not captured in this study. The timing of BNP measurement during hospitalization also is relevant. A normal BNP at admission would be surprising, while a normal BNP at discharge may be a marker of aggressive heart failure management.

The authors' analysis did not include this consideration.

The authors accepted a surprisingly wide period between BNP measurement and echo study. Unfortunately, this was a significant limitation of their study. It is not uncommon for cardiac function to change dramatically over a 90-day period. For example, an acute myocardial infarction or stress cardiomyopathy often exhibit marked improvement in left ventricular function within days of hospitalization, making interpretation of widely spaced echo and BNP results difficult at best. The hemodynamically defined patients are the most compelling. Significantly elevated filling pressures or low cardiac index closely correlated with BNP measurements.

Management of obese patients with heart failure can be challenging. Assessment of volume status by physical exam is limited: neck veins can be hard to visualize, hepatomegaly hard to appreciate, and peripheral edema from venous stasis is common. As demonstrated in this study, BNP levels can be low, too, taking away another diagnostic tool. Implantable pulmonary artery pressure sensors can be helpful, although patients with large chest circumferences are not candidates for this device. Further compounding the problem: Obese patients are more likely to be excluded from clinical trials based on low BNP levels, limiting our understanding of heart failure therapies in this significant patient population. ■

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## CME/CE QUESTIONS

1. **Adding a sodium-glucose cotransporter-2 to optimal heart failure treatment, including a neprilysin inhibitor/angiotensin receptor blocker, resulted in:**
   a. significantly more hypotension.
   b. worse renal function.
   c. a lower mortality rate.
   d. fewer heart failure hospitalizations.

2. **Low brain natriuretic peptide levels often are seen in heart failure patients with:**
   a. obesity.
   b. preserved left ventricular ejection fraction.
   c. acute kidney injury.
   d. advanced age.

3. **A meta-analysis of two recent randomized trials of patent foramen ovale closure for migraines vs. medical therapy failed to show:**
   a. fewer migraine days/month.
   b. fewer monthly migraine attacks.
   c. more patients with complete cessation of migraines.
   d. an improved responder rate (reduction in migraine attacks and adverse events).

4. **Comparing surveillance of cancer chemotherapy patients with global longitudinal strain (GLS) vs. ejection fraction (EF) for detecting cardiac damage and treating it revealed:**
   a. EF after one year was higher in the GLS group.
   b. cardiac damage developed in more EF group patients at one year.
   c. less cardiac protective therapy was used in the GLS group.
   d. fewer GLS group patients slowed or stopped chemotherapy.

5. **A sophisticated MRI study of the intracranial circulation showed atherosclerotic plaques in what percentage of patients with embolic stroke of undetermined source?**
   a. 24%
   b. 43%
   c. 69%
   d. 78%