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Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

Role of Beta-Blockers in Heart Failure with Preserved Ejection Fraction

By Jamie L. W. Kennedy, MD, FACC

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SYNOPSIS: Discontinuation of beta-blockers in heart failure with preserved ejection fraction patients significantly improved quality of life scores and expanded exercise capacity.

SOURCE: Palau P, Seller J, Domínguez E, et al. Effect of ß-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2021;78:2042-2056.

Heart failure with preserved ejection fraction (HFpEF) is a complex syndrome of exercise intolerance and fluid retention despite normal or near-normal left ventricular systolic function. Cardiac contributions have taken center stage based on findings such as elevated left atrial pressure, impaired left ventricular diastolic function, and chronotropic incompetence. However, Houstis et al revealed the heterogenous and multiorgan system nature of HFpEF by using cardiopulmonary exercise testing (CPET) to identify the cause of exercise limitation in a series of HFpEF patients.[1] Every step of the oxygen delivery pathway, from alveolar ventilation to peripheral oxygen use, was abnormal in at least one patient. Most patients studied exhibited defects at multiple pathway points.

Patients with HFpEF often take beta-blockers for several reasons, including comorbid conditions (e.g., atrial fibrillation) and coronary artery disease, as well as less compelling indications (e.g., hypertension). Beta-blocker use has been associated with increased risk of heart failure hospitalization in a retrospective analysis of the TOPCAT study for patients with left ventricular ejection fraction (LVEF) > 50%. There was no increased risk in patients with LVEF 45% to 49%.

Palau et al assessed the effects of beta-blocker use on exercise capacity for HFpEF patients. They enrolled adults with New York Heart Association class II-IV symptoms, LVEF > 50%, left ventricular internal dimension end-diastolic < 6 cm, N-terminal-pro hormone BNP measurement of greater than

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125 pg/mL, echo evidence of HFpEF (i.e., left ventricular hypertrophy, left atrial enlargement, or diastolic dysfunction), prior heart failure hospitalization, and blunted heart rate response during CPET (defined as chronotropic index < 0.62). Patients with significant valvular heart disease, uncontrolled arrhythmias or hypertension, recent acute coronary syndrome or ischemia during CPET, significant pulmonary disease, chronic treatment with other rate control medications, resting heart rate > 75 bpm, or other life-limiting comorbid conditions were excluded.

The authors screened 250 patients, narrowing the enrollment to 52 patients (average age was 74.5 years, 60% were women, and average BMI was 31 kg/m^2). Comorbid conditions included hypertension (88%), dyslipidemia (71%), diabetes mellitus (40%), atrial fibrillation (38%), and ischemic heart disease (23%). Prescribed medications included loop diuretics (85%), ACE inhibitors or ARBs (75%), statins (67%), and mineralocorticoid antagonists (11%). Bisoprolol was by far the most common beta-blocker prescribed (88% of patients at a median dose of 2.5 mg daily).

Baseline assessment included echo, CPET, Minnesota Living with Heart Failure Questionnaire, and cognitive assessment. Patients were randomized to two groups. Group A was tapered off beta-blockers over three days, while group B continued beta-blocker at baseline dose. Complete assessment was repeated at day 15, after which group A restarted beta-blockers and group B tapered off. Complete assessment was repeated at day 30. One patient in each arm developed atrial fibrillation with rapid ventricular response and was removed from the study. One patient in group A suffered a stroke and was withdrawn. Three patients in group B withdrew consent.

Baseline CPET showed patients were fairly limited, with mean peak VO_2 at 12.4 ± 2.9 mL/kg/min, 72 ± 17.8% predicted. All enrolled patients completed a maximal baseline test with respiratory exchange ratio > 1.05. Mean resting heart rate was 64.8 ± 8.8 bpm and peak 97.2 ± 14.7 bpm for a chronotropic index of 0.41 ± 0.14. Patients in Group A improved their peak VO_2 to 14.06 ± 3.35 mL/kg/min when off beta-blocker; after re-introduction, the rate lowered to 12.26 ± 3.24 mL/kg/min ($P < 0.001$). Group B produced similar results, with continued beta-blocker use peak VO_2 12.24 ± 3.05 mL/kg/min and discontinued 14.48 ± 3.79 mL/kg/min ($P < 0.001$).

Overall, the average increase in peak VO_2 off beta-blocker was 2.1 ± 1.3 mL/kg/min. There was no evidence of period effect. Similar results were obtained when VO_2 percent predicted was analyzed (average increase of 11.7 ± 2.3%). Peak heart rate during exercise increased from 97 bpm to 127 bpm when beta-blockers were withdrawn. A mediation analysis suggested the increase in peak heart rate accounted for 36% of the improvement in peak VO_2. Quality of life scores improved with discontinuation of beta-blockers (from 27.4 to 22.3). There was no change in scores on cognitive testing when beta-blockers were discontinued.

Adverse events included atrial fibrillation and rapid ventricular response in two patients; both underwent successful cardioversions. At the 60-day follow-up visit, the beta-blocker dose decreased by at least 50% in 19 patients and completely discontinued for 27 patients. There were three cardiovascular hospitalizations for three patients at one month, and four cardiovascular hospitalizations for three patients at six months; none occurred during the beta-blocker withdrawal period. There were no deaths during six months of follow-up.

The authors demonstrated a significant improvement in exercise capacity with discontinuation of beta-blockers in HFpEF patients. Also, there was a corresponding improvement in quality of life scores, albeit over short-term follow-up. A longer-term study of morbidity and mortality is needed.

■ COMMENTARY

Palau et al did not analyze the data based on indication for beta-blocker therapy. While awaiting more data on this question, transitioning HFpEF patients with weaker indications for beta-blocker therapy (e.g., treating hypertension

with alternative agents) seems likely to result in symptomatic improvement with minimal risk of adverse events. I would be much more cautious when treating patients with atrial fibrillation or those who present with significant coronary artery disease. ■

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ABSTRACT & COMMENTARY

Pharmacotherapy for Atrial Fibrillation with Anticoagulation-Associated Intracranial Hemorrhage

By Michael H. Crawford, MD, Editor

SYNOPSIS: A study of apixaban vs. no anticoagulation in patients following an anticoagulant for atrial fibrillation-related intracerebral hemorrhage exhibited a high risk of stroke and vascular death, regardless of whether the patients were treated subsequently with apixaban.

SOURCE: Schreuder FHBM, van Nieuwenhuizen KM, Hofmeijer J, et al. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral hemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): A randomized, open-label, phase 2 trial. *Lancet Neurol* 2021;20:907-916.

Whether to restart anticoagulants after an anticoagulant-related intracerebral hemorrhage (ICH) in patients with atrial fibrillation is a current clinical dilemma. Schreuder et al conceived the apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated ICH in patients with atrial fibrillation (APACHE-AF) trial to provide pilot data (Phase II) to inform a larger Phase III randomized, clinical trial. Their aim was to test the hypothesis that apixaban treatment in patients with AF who had survived an anticoagulant-associated ICH was the best long-term alternative.

APACHE-AF was a prospective, randomized, open-label trial with a blinded endpoints assessment conducted in 16 hospitals in the Netherlands. Patients with a spontaneous ICH in the prior seven to 90 days during treatment with an anticoagulant for AF and a CHA_2DS_2-VASc score of 2 or more were included. The authors excluded patients with other reasons for anticoagulation or who presented with other potential contraindications to continuing anticoagulation (e.g., pregnancy).

Patients were randomized to apixaban at standard doses or no anticoagulation. They were stratified for intention to start an antiplatelet drug in the no anticoagulation group, age (≤ age 75 years vs. > age 75 years) and location of the ICH (lobar vs. non-lobar). The primary outcome was non-fatal stroke or vascular death. Secondary outcomes included the type of stroke, bleeding, other cardiovascular events, vascular death, and all-cause mortality. Outcomes were assessed by an adjudication committee blinded to treatment allocation. Between 2015 and 2020, 101 patients were recruited. The median age was 78 years, 54% were men, 99% were white, and the median CHA_2DS_2-VASc score was 4. Median follow-up was 1.9 years (range, one to three years). There were nine crossovers in the apixaban group and 11 in the no anticoagulation group.

The primary outcome occurred in 26% of the apixaban group and 24% of the no anticoagulant group (adjusted HR, 1.05; 95% CI, 0.48-2.31; P = 0.90). ICH occurred in 8% of the apixaban group, all of whom were taking apixaban when the event occurred, and one patient in the no anticoagulant group, who was taking rivaroxaban because of an intercurrent pulmonary embolism. Major bleeding also was more common on apixaban (12% vs. 6%). Ischemic stroke occurred in six patients in both groups, and three of each group crossed over to the other treatment. Major vascular events were similar in both groups (28% vs. 31%). The authors concluded there was a high risk of subsequent stroke or vascular death in patients with atrial fibrillation following an ICH during treatment with anticoagulants, regardless of whether they were treated with apixaban.

■ COMMENTARY

Determining the next step after an ICH in patients on anticoagulants with AF is a contentious issue. After hearing about lawsuits against cardiologists on this issue, my current practice is to consult my neurology colleagues. Often, this turns into a round

robin, as they will consult me for my opinion about this risk of vascular events if anticoagulants are withheld. Thus, this paper (albeit a pilot study) was of interest. Schreuder et al found a high rate of stroke or vascular death of about 12% per annum, regardless of whether anticoagulation was given. This is not entirely surprising since these were elderly patients (median age = 78 years) with CHA_2DS_2-VASc scores of ≥ 2 (median = 4). However, the results of prior observational studies suggested resuming anticoagulants in such patients was beneficial overall. Of course, observational studies can be biased by indication confounding. For example, patients with a high risk of vascular events but a low risk of recurrent ICH could be treated preferentially with anticoagulants. Also, most observational studies used warfarin. The APACHE-AF authors employed apixaban because of its low bleeding risk in AF populations vs. warfarin, but still saw a higher risk of major bleeding vs. those treated with no antithrombic medications or only antiplatelet drugs. Because of crossovers in both groups, the APACHE-AF investigators conducted an on-treatment analysis, which showed 13% fewer strokes or vascular deaths in those taking apixaban. Therefore, the authors concluded their study did not inform clinical practice as it does not support or deny a benefit of apixaban in this clinical situation.

The strengths of the APACHE-AF study included the exclusion of subdural hematoma patients, which does not always happen in observational studies. Also, the up to 90-day enrollment period resulted in a more stable and homogeneous population where anticoagulation resumption was a reasonable option. In addition, there was a median follow-up of almost two years, and outcomes were adjudicated blindly. The major weakness of the study was the small cohort, resulting in tiny subgroups. This makes identifying subgroups that may benefit from anticoagulation challenging. Further, since this was an open-label trial, there may have been observation biases in outcome assessment. Finally, blood pressure control could have been more aggressive. Average blood pressure was ≥ 140/80 mmHg in both groups. There is a study in progress examining tight blood pressure control in ICH patients (TRIDENT).[1]

There are seven other randomized, controlled trials on this issue in progress. The authors of only one other have reported results — the SoSTART study, which included 203 patients and revealed anticoagulants were noninferior to not starting them, but not superior, either.[2] If, like SoSTART, none of the other trials help clarify this clinical dilemma, there is hope that a meta-analysis of them will provide some clarity. ■

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ABSTRACT & COMMENTARY

Earlier Coronary Artery Bypass Grafting After Ticagrelor Discontinuation Is Safe

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 a trial that included acute coronary syndrome patients treated with ticagrelor, undergoing coronary bypass surgery within two to three days was noninferior to the guideline-recommended five to seven days regarding severe bleeding.

SOURCE: So DYF, Wells GA, Lordkipanidze M, et al. A randomized study of early vs. delayed coronary artery bypass surgery among patients with acute coronary syndromes treated with ticagrelor: The RAPID CABG study. Presented at American Heart Association Scientific Sessions, Nov. 13, 2021. https://bit.ly/3EfEoYv

Current American College of Cardiology/American Heart Association guidelines recommend instituting dual antiplatelet therapy early in the hospital course for eligible patients presenting with acute coronary syndrome (ACS).[1] This recommendation can conflict with bleeding risk in the roughly 10% of ACS patients who are referred for coronary artery bypass grafting (CABG). Perioperative bleeding is a major concern, highlighted by the higher mortality seen in the PLATO trial among patients who underwent CABG within one day of stopping ticagrelor.[2] Although

the mechanisms of action and elimination of ticagrelor are fundamentally different than that of the thienopyridines clopidogrel and prasugrel, U.S. guidelines continue to recommend a minimum waiting period of five days after cessation of ticagrelor prior to non-urgent CABG.[3] This recommendation carries a class IB designation, even though it is based on retrospective and pharmacodynamic data. The European Society of Cardiology (ESC) guidelines recommend a shorter waiting period of only three days.[4]

RAPID CABG was designed to test the safety of early vs. delayed CABG in patients presenting with ACS who have received ticagrelor. ACS patients treated with ticagrelor who were determined to require CABG after angiography were randomized in a 1:1 fashion to either early surgery (day 2-3 after ticagrelor) or delayed surgery (day 5-7). The primary outcome was the occurrence of severe or massive perioperative bleeding, according to the universal definition for perioperative bleeding (UDPB). A total of 143 patients were enrolled, of whom 72 were randomized to early surgery and 71 to late surgery. The mean age was 64 years, 57% were men, and the mean BMI was just under 30 kg/m^2. The median time to surgery was three days in the early surgery group and six days in the late group. Platelet reactivity before CABG was evaluated via the Pre-CABG VerifyNow P2Y12 (PRU) test and was found to be significantly lower in the early surgery group compared to the late group (PRU 200 vs. 251; $P < 0.001$).

The primary outcome of severe or massive bleeding occurred in 4.6% of the early CABG group and 5.2% of the delayed CABG group. This met the prespecified noninferiority margin of 8% ($P = 0.025$). Notably, all bleeding events in the trial were classified as severe, with no massive bleeding events recorded. Only one patient in the early CABG group required re-exploration, while none in the delayed group did.

Although no presurgical ischemic events were recorded in the early surgery group, six such events were reported in patients waiting for later CABG. These events included one myocardial infarction, four episodes of recurrent angina, and one occurrence of ventricular tachycardia. This difference was the main driver behind a lower six-month major adverse cardiovascular event rate in the early vs. delayed surgery group (5.6% vs. 13.0%). Hospitalization time also was significantly shorter in the early CABG group, with a median length of stay of nine days vs. 12 days in the delayed group. The authors concluded CABG two to three days after ticagrelor cessation was noninferior in incurring severe or massive perioperative bleeding vs. waiting five to seven days.

■ COMMENTARY

Relatively few randomized trials carry the potential to solve a known issue and change clinical practice, but RAPID CABG clearly falls into this category. Many cardiologists can relate to the scenario of managing an ACS patient who needs CABG for days while the P2Y12 inhibitor washes out. Current U.S. guidelines call for waiting for at least five days after cessation of ticagrelor, but the results of this trial suggest proceeding with CABG within two to three days of stopping ticagrelor is safe.

For some, this trial will confirm already-held beliefs and allow a shift toward the shorter ESC recommendation. For others, however, the small size of the trial represents an undeniable weakness. Of the 71 patients assigned to the early group, six went later and one was treated medically, leaving 65 patients treated per protocol. Of 72 patients in the late group, two refused surgery, seven went to CABG earlier than the assigned window, and four went even later than assigned, leaving only 58 patients per protocol. The total number of bleeding events was small — three in each group using the UDPB definition. The use of alternate bleeding definitions yielded even fewer events. For example, thrombolysis in myocardial infarction CABG bleeding and Bleeding Academic Research Consortium Type 4 (CABG-related) bleeding each occurred in two patients in the early group and zero patients in the late group (which were not significantly different).

Regardless, this represents the best available evidence on this issue. For the ACS patient who has been treated with ticagrelor and is awaiting CABG, earlier surgery could prevent ischemic events and shorten hospital stay, with what appears to be minimal added bleeding risk. ■

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ABSTRACT & COMMENTARY

How an Influenza Vaccine Can Affect Cardiovascular Disease

By Michael H. Crawford, MD, Editor

SYNOPSIS: A randomized, controlled trial of influenza vaccine vs. placebo in patients with acute myocardial infarction or at high risk for coronary artery disease inoculated during the index hospitalization showed a lower risk of the combined endpoint of death, myocardial infarction, or stent thrombosis at one year.

SOURCE: Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: A randomized, double-blind, placebo-controlled, multicenter trial. *Circulation* 2021;144:1476-1484.

Observational studies have shown an association between the risk of cardiovascular (CV) events and influenza, but clinical trials of influenza vaccine for preventing CV events have been inconclusive.[1,2] Fröbert et al designed the Influenza Vaccination After Myocardial Infarction (IAMI) trial to test the hypothesis that influenza vaccination in patients with high-risk coronary artery disease (CAD) or recent myocardial infarction (MI) would reduce the subsequent incidence of death, MI, or stent thrombosis.

IAMI was a randomized, double-blind, placebo-controlled study conducted in 30 centers in six European countries, Bangladesh, and Australia during their influenza seasons. From 2016 to early 2020, 2,532 patients (mean age 60 years, 18% women), were enrolled in the intention-to-treat analysis. Acute ST-elevation MI (STEMI) was present in 55% and non-STEMI in 45%. Less than 1% exhibited stable high-risk CAD. Influenza vaccine or placebo was administered within 72 hours of an invasive procedure or hospital admission. The primary composite endpoint occurred in 5.3% of the vaccine arm and 7.2% of the placebo arm (HR, 0.72; 95% CI, 0.52-0.99; $P = 0.04$). All-cause mortality was 2.9% in the influenza vaccine group and 4.9% in the placebo group (HR, 0.59; 95% CI, 0.39-0.89; $P = 0.01$). The causes of death were largely CV disease-related, and the risk of CV death alone was 2.9% vs. 4.5% (HR, 0.59; 95% CI, 0.39-0.90; $P = 0.014$). All subgroups analyzed showed the same results. When combined with the results of three smaller randomized, controlled trials in a meta-analysis, the results were similar in general, but more impressive for CV deaths (HR 0.51; 95% CI, 0.36-0.71; $P = 0.0001$). The authors concluded influenza vaccine early after MI significantly lowered the composite risk of all-cause death, MI, or stent thrombosis; the risk of all-cause mortality; and CV death.

■ COMMENTARY

The association of viral infections with a higher risk of CV events has been well established. The inflammation accompanying such infections can trigger plaque rupture and depress global myocardial function. In addition, so-called type 2 or supply/demand imbalance infarction can be precipitated by the fever, tachycardia, and hypoxia that accompanies influenza. It has been estimated that 10% to 15% of influenza patients develop CV events, which can lead to ICU admission and even death.[3] Guidelines recommend influenza vaccination for all patients with CAD.[4] However, vaccination in patients hospitalized for acute MI has not been studied extensively, and there is concern the inflammatory response to the vaccine may be deleterious. These realities make this report from the IAMI trial of interest.

Despite ending the trial early because of the onset of the COVID-19 pandemic, these results are remarkable considering vaccination was on top of excellent standard care for these patients. Also, the benefits were seen early as the time to a CV events curves separated at three months of follow up. In addition, the results were consistent in the predefined subgroups analyzed and in a meta-analysis of three smaller randomized trials. Adverse effects of the vaccine mainly were injection site reactions, which were more frequent than in the placebo group. Systemic or serious reactions were few and no different than those seen in the placebo group.

There were weaknesses in this study. Patients in Bangladesh were less likely to receive stents, which reduced the power of detecting differences in stent thrombosis. Also, there were only eight patients with high-risk stable CAD, so the conclusions may not apply to this group. Inexplicably, only 19% of subjects were women, but there did not appear to be a different result in this subgroup. Finally, the study was conducted only during flu season, alternating between hemispheres.

When added to other related data, the results of IAMI should be enough to sway the guidelines toward including influenza vaccine in the post-MI recommendations. Experience with the influenza

vaccine in all stable CAD patients as currently recommended suggests only about half of such patients are vaccinated for influenza. The key message of the IAMI trial is vaccination should happen in the hospital when patients are admitted for CV events. Not only would such a policy likely increase vaccination rates in CAD patients, but also would reduce subsequent CV morbidity and mortality. ■

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ABSTRACT & COMMENTARY

Is a New Right Bundle Branch Block a Sign of Coronary Artery Disease?

By Michael H. Crawford, MD, Editor

SYNOPSIS: For asymptomatic subjects without known cardiac or renal disease, coronary lesions by CT angiography are more frequent in those with right bundle branch block vs. those without.

SOURCE: Lee H, Jeon YJ, Kang BJ, et al. Frequency and significance of right bundle branch block and subclinical coronary atherosclerosis in asymptomatic individuals. *Am J Cardiol* 2021;158:30-36

Researchers have seen an association between right bundle branch block (RBBB) with all-cause and cardiovascular (CV) mortality in subjects without known heart disease.[1] However, such studies did not exclude subjects with symptoms that could have been caused by heart disease.

Lee et al recruited 8,103 asymptomatic subjects (mean age 54 years, 65% men) who were self-referred for a general health exam to undergo an ECG and a cardiac CT angiogram (CTA), which included a coronary calcium score (CAC). After excluding subjects with a history of CV disease, other ECG abnormalities, atrial fibrillation, or chronic renal disease, 7,205 formed the final population of whom 116 showed RBBB. Baseline characteristics of the RBBB group indicated they were older, recorded higher systolic blood pressure readings, and were more likely to have been diagnosed with diabetes. Also, their mean CAC score was 98 vs. 41 in those without RBBB (P = 0.003). Any plaque by CTA was found in 47% of RBBB subjects and 35% of those without RBBB (P = 0.007). However, when adjusted for risk factors for coronary artery disease (CAD), RBBB was not associated with CAD by CTA, as demonstrated in a propensity score analysis matching RBBB patients 5:1 with 580 subjects without RBBB (HR, 0.87; 95% CI, 0.57-1.32). The authors concluded RBBB was not associated with an increased risk of subclinical CAD in asymptomatic subjects without a history of heart or renal disease vs. those without RBBB.

■ COMMENTARY

This is somewhat of a mixed message in that RBBB was associated with subclinical CAD in asymptomatic subjects without known CAD, but not when adjusted for risk factors for CAD. RBBB as an isolated finding is not of much significance unless the individual exhibits risk factors for CAD. This is consistent with prior studies showing that RB is a risk factor for morbidity and mortality in patients with known CAD but not those without CAD, where it is generally considered benign. Consequently, if a patient with known CAD or in whom the risk of subclinical CAD is high and develops new RBBB, it may be a cause for concern. It would be reasonable to evaluate the patient further, control risk factors better, or follow closer, depending on the clinical situation. On the other hand, a new isolated RBBB without symptoms, known disease, or significant risk factors may not require any further evaluation. This study does not address this issue directly, as there are no follow-up data.

The fact this work was conducted only at a single center in Korea is a weakness. There may be a referral bias since the patients were seeking a medical

evaluation. Also, some patients showed left anterior fascicular block with RBBB, but there were too few subjects here with RBBB to analyze separately.

RBBB is rare in the general population, but becomes more common with older age. In older patients, RBBB may be just the result of an aging cardiac conduction system or a manifestation of cardiac disease. A thorough clinical evaluation should help clinicians sort this out in most patients and certainly seems appropriate, especially in older patients in whom this is a new finding. At a minimum, patients with RBBB should be told to seek medical help if they develop symptoms suggestive of complete heart block. In patients with known heart disease or at high risk for it, a new RBBB would suggest progression of the disease, which may require intensifying care or follow up depending on the situation.

The significance of RBBB must be assessed in the clinical context of the patient. It may be a benign finding or a risk factor for subsequent cardiac morbidity and mortality. ■

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CME/CE QUESTIONS

1. **Influenza vaccine administered in the hospital in acute myocardial infarction patients lowered all-cause and cardiovascular mortality rates by about what percentage at one year vs. placebo?**
   a. 20%
   b. 40%
   c. 60%
   d. 80%

2. **In patients who survive an intracranial hemorrhage on anticoagulants for atrial fibrillation, the incidence of a subsequent stroke or vascular death, regardless of whether they were restarted on apixaban, was about:**
   a. 5%.
   b. 15%.
   c. 25%.
   d. 35%.

3. **Right bundle branch block is of little or no clinical significance if the patient:**
   a. has cardiac disease.
   b. has several risk factors for coronary atherosclerosis.
   c. is symptomatic.
   d. is asymptomatic and free of cardiac disease or risk factors for it.

4. **Selected patients with HFpEF may improve their exercise capacity if what drug is discontinued?**
   a. Angiotensin receptor blocker
   b. Beta-blocker
   c. Calcium blocker
   d. Ivabradine

5. **A study of acute coronary syndrome patients treated with ticagrelor showed coronary bypass surgery within two to three days after stopping ticagrelor vs. five to seven days is associated with:**
   a. an equivalent risk of major bleeding.
   b. more major bleeding.
   c. less major bleeding.
   d. higher mortality rates.