AHC Media
A RELIAS LEARNING COMPANY

Internal Medicine [ALERT]

Evidence-based summaries of the latest research in internal medicine

Vol. 39, Issue 23, December 15, 2017
AHCMedia.com

ABSTRACT & COMMENTARY

Can Medical Therapy Improve Functional Mitral Regurgitation?

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco, Cardiology Division, Advanced Heart Failure Section

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

SYNOPSIS: Among patients who presented with heart failure with reduced ejection fraction and severe functional mitral regurgitation, mitral regurgitation improved in 38% of patients with medical management. Improvement in mitral regurgitation was associated with increased survival.

SOURCE: Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *JACC Heart Fail* 2017;5:652-659.

In heart failure with reduced ejection fraction (HFrEF), functional mitral regurgitation (FMR) develops because of left ventricular (LV) dilation and dysfunction. The resulting tethering of the structurally normal mitral leaflets causes failure to coapt. Development of FMR is associated with worse prognosis. Medical therapy for HFrEF, including ACE inhibitors and beta-blockers, improves outcomes and is associated with improvements in LV remodeling. Whether medical management of HFrEF can reduce the severity of FMR and improve prognosis has not been well studied. Nasser et al studied 163 patients with HFrEF treated at an academic medical center in Belgium. About half the patients had ischemic cardiomyopathy. MR severity was assessed by echocardiography at baseline and follow-up. All patients were treated with maximally tolerated doses of standard medical therapy for HFrEF (ACE inhibitors, beta-blockers, and aldosterone antagonists). Median follow-up was 50 months. Improvement in FMR was defined as a reduction from severe to nonsevere MR, and worsening MR was defined as an increase from nonsevere to

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott Diabetes, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cempra, Janssen, Lilly, Merck, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Contributing Editor Louis Kuritzky, MD, is a retained consultant for and on the speakers bureau of Allergan, Daiichi Sankyo, Lilly, and Lundbeck. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Executive Editor Leslie Coplin; and AHC Media Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

Internal Medicine Alert,
ISSN 0195-315X, is published twice a month by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to AHC Media P.O. Box 74008694, Chicago, IL 60674-8694

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments
Please call Editor Jonathan Springston at (404) 262-5416 or email at jspringston@reliaslearning.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.

Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Relias Learning designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins Jan. 1, 2017. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 1 AAFP Prescribed credit.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

severe MR. The primary endpoint was a composite of all-cause death, heart transplant, or hospitalization for HF or arrhythmia.

At baseline, 31% of patients demonstrated severe FMR. Patients with severe FMR were older and exhibited larger LV volumes and lower EF. During the study period, 38% of patients with severe FMR improved to nonsevere FMR, while 18% of those with nonsevere FMR at baseline progressed to severe FMR. Patients with sustained severe FMR or those who progressed to severe FMR received a significantly worse prognosis compared to those who improved or remained nonsevere ($P < 0.0001$). In multivariate models, the presence of severe FMR at follow-up was the single strongest predictor of both the primary endpoint and mortality (odds ratio, 2.5). On the other hand, severity of FMR at baseline was not associated with worse prognosis.

Patients with severe FMR at follow-up exhibited more LV enlargement and were more likely to demonstrate a restrictive LV filling pattern compared to those with nonsevere FMR. The authors concluded that severe FMR can be treated successfully with medical therapy in nearly 40% of patients, with associated improvements in LV remodeling and prognosis.

■ COMMENTARY

In multiple studies of HFrEF, FMR is associated with an increased risk of adverse outcomes, including death. The negative effect of FMR often is attributed to progressive LV remodeling because of the increased volume overload caused by MR. This creates a vicious cycle whereby the worsening LV remodeling leads to increased FMR and more LV volume overload. There is growing interest in repair of FMR, whether surgically or percutaneously. However, current medical therapy for HFrEF can improve LV remodeling and theoretically reduce the severity of FMR. Understanding the effect of medical therapy on FMR and identifying which patients will improve with medical therapy alone is crucial for appropriate patient selection for surgical or percutaneous treatment of FMR. Nasser et al showed that in a subset of patients with HFrEF and severe FMR, the degree of MR can improve with aggressive medical therapy for heart failure. Patients in whom FMR improves are less likely to show increasing LV volumes. Perhaps most importantly, patients in whom FMR improved during the study period showed significantly better survival and lower rates of the composite endpoint compared to those in whom FMR remained severe. These findings suggest an initial course of aggressive medical therapy may be indicated for most, if not all, patients with HFrEF and FMR before considering invasive valve repair.

The authors highlighted the importance of targeting volume status to prevent the progression of FMR. Patients with improvement in FMR severity during the study period were more likely to show improvement in the LV filling pattern, reflecting improvement in volume status. In the study population, diuretics were up-titrated aggressively as needed to keep patients euvolemic, and extensive education regarding dietary sodium and fluid restriction was provided. Although this association does not prove more aggressive, diuretic use can improve FMR. Given the proposed pathophysiology of FMR, it would make sense that reducing LV volume overload would help improve FMR severity.

This was a relatively small, single-center study. Only 50 patients presented with severe FMR at baseline, so, ideally, the findings should be replicated in a larger cohort to confirm the observed rate of improvement, and, hopefully, identify clinical predictors of FMR improvement. The study by Nasser et al provides helpful insight into the clinical course of patients with HFrEF and FMR who are managed medically. However, many important questions remained unanswered. First, how can clinicians identify those patients with FMR who will improve with medical therapy alone? Second, how should clinicians manage those patients who will not improve with medical therapy alone, or those in whom severe FMR persists despite maximally tolerated therapy? Percutaneous mitral valve repair has gained significant interest in recent years, but its utility in FMR is unproven. The creators of the Cardiovascular Outcomes Assessment of the Mitra-Clip Percutaneous

Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial randomized patients with severe FMR to MitraClip vs. medical therapy. The results are expected in late 2018. Until then, clinicians should use maximally tolerated medical therapy for HFrEF, including use of diuretics and salt restriction, to optimize each patient's volume status. ■

ABSTRACT & COMMENTARY

Is a Dabigatran Reversal Agent Effective?

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

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

SYNOPSIS: A pragmatic clinical study of idarucizumab for counteracting the effects of the oral anticoagulant dabigatran showed rapid and complete reversal of its effects in patients with major bleeding or urgent surgery, without any adverse safety concerns.

SOURCE: Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med* 2017;377: 431-441.

One advantage of dabigatran therapy for stroke prevention in atrial fibrillation (AF) patients is the existence of an antidote, but how well does it work? Investigators performed a multicenter, international, prospective, open-label study of idarucizumab 5 mg IV in 503 patients on dabigatran needing anticoagulant reversal, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study. The authors studied two groups of patients. Group A had life-threatening bleeding (n = 301). Group B required surgery and couldn't wait eight hours for hemostasis to return after stopping dabigatran (n = 202). The primary endpoint was the maximum percent reversal of anticoagulation four hours after completion of the infusion of idarucizumab as measured by either the thrombin time or the ecarin clotting time. Serial blood samples for pharmacologic studies were performed over the first 24 hours after the infusion of idarucizumab. A second dose of idarucizumab was permitted for recurrent or continued bleeding or objective evidence of residual anticoagulant effect. Clinical outcomes were secondary endpoints. Adverse effects were attributed to idarucizumab if they occurred within five days. More than 95% of the patients were receiving dabigatran for stroke prevention in AF. The mean age was 78 years. The median percent reversed at four hours was 100%. Dabigatran concentrations fell from around 100 mg/mL to near zero within minutes of the infusion of idarucizumab and remained < 20 mg/mL for 24 hours. A second dose of idarucizumab was administered to only eight patients.

In group A, 46% experienced gastrointestinal bleeding, and 33% experienced intracranial bleeding. The median time to cessation of bleeding was 2.5 hours after idarucizumab was administered. In group B, the planned surgery commenced at a median time of 1.6 hours. Perisurgical hemostasis was normal in 93%. At 90 days, about 7% of patients experienced a thrombotic event and 19% died. There were no serious safety issues with idarucizumab administration. The authors concluded that idarucizumab was shown to rapidly reverse the anticoagulation caused by dabigatran without any serious safety issues.

■ COMMENTARY

Although idarucizumab worked well in animals and normal volunteers to reverse the effects of dabigatran, it is always useful to see how such agents work in real-world patients. Thus, this uncontrolled, pragmatically designed, open-label study is of interest. Clearly, idarucizumab rapidly drops dabigatran blood levels to near zero for at least 12 hours. Between 12 and 24 hours, some anticoagulant effect (dabigatran levels < 20 mg/mL) returned in about 20% of patients. The authors attributed this to the redistribution of dabigatran from extravascular spaces into the vasculature. This was associated with bleeding in only 10 patients. A second dose of dabigatran was administered to seven of these patients. Overall, only one dose of 5 mg of idarucizumab was given to 98% of patients. Anti-idarucizumab antibodies were detected in about 6% of patients, but at low titers. Three patients demonstrated possible hypersensitivity events: one with a rash who also started tramadol; one with vomiting and loss of consciousness who had intracerebral hemorrhage; and one with possible anaphylaxis who was started on amoxicillin. Other potential adverse events were observed in about one-quarter of patients, but all could be ascribed to worsening of the index event or the underlying condition of the patients.

In group B, the surgeons reported 95% of patients appeared to exhibit normal or mildly impaired hemostasis at a median start time of 1.6 hours after idarucizumab was administered. Considering these data

and the safety of idarucizumab, surgery probably could start as soon as the idarucizumab is administered. In group A, the efficacy of idarucizumab is more difficult to determine. These were sick patients with a high mortality rate (7% at five days, 13% at 30 days). Also, there were many factors affecting hemostasis. Often, blood transfusions occurred and other products were administered. In addition, many received antiplatelet agents at a mean of four days, and most restarted anticoagulants at a mean of 13 days. Investigators started such agents within 72 hours in 23% of group A patients. Further, the authors noted that mortality reported in patients undergoing surgery or experiencing a major spontaneous bleeding event on warfarin is about 30%, which is higher than the 19% observed in this study. Finally, thrombotic events are to be expected if one rapidly reverses anticoagulation, but the 7% observed in this study is lower than that reported with warfarin. No procoagulant effect of idarucizumab has been observed in animals or normal human volunteers. Since there is no effective alternative to idarucizumab for reversing the effects of dabigatran, there was no comparison group, and the investigators believed that it was unethical to create a control group given the strength of the pre-clinical data. The FDA has approved idarucizumab at the doses used in this study. This makes dabigatran an attractive oral anticoagulant for patients who demonstrate indications for oral anticoagulation but are at high risk of bleeding. ■

BRIEF REPORT

Fecal Microbiota Testing

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

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

SOURCES: Saey TH. Here's the poop on getting your gut microbiome analyzed. *Science News*, June 17, 2014.
Rabin RC. Can I test the health of my gut microbiota? *The New York Times*, July 7, 2017.

Google "gut microbiota testing" and see the array of possible "gut report" kits out there for purchase. Send in a sample and pay a fee — usually $100 or more — and you will receive a profile of your gut microbiome, with lots of detailed information and colorful graphics on the dominant species populating your gut. Your fecal microbiota will be compared to the "normal" profiles of other Americans or people in other parts of the world, vegetarians, or those who follow different diets. The problem is that little is known about the typical genomic profile of the gut or what is "normal." There's obviously tremendous diversity, even in healthy people. Researchers have determined that persons with diabetes or inflammatory bowel disease — or people who have received recent antibacterial therapy — may exhibit very different microbiota profiles. Unfortunately, no one really knows what these differences mean in terms of your overall health.

Different methodologies also may offer differing results. Saey submitted stool samples to two companies for testing and received wildly different results.

Increasingly, we see outfits that offer molecular testing of blood, stool, or other specimens, but with little credibility or science behind it. Yet, patients looking for an explanation for their symptoms or an illness will latch on to anything. A young Stanford graduate student who felt "fuzzy-headed" for more than a year recently spent $1,000 on specialized "molecular" testing of his blood and stool, only to be disappointed when I explained the results were basically uninterpretable. ■

PHARMACOLOGY UPDATE

Zoster Vaccine Recombinant Adjuvanted (Shingrix)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a second zoster vaccine for the prevention of shingles in adults. In contrast to the first vaccine (Zostavax), which is a live attenuated vaccine (ZVL), zoster vaccine recombinant adjuvanted is non-live and comprised of the surface glycoprotein E antigen component (HZ/su). This vaccine is marketed as Shingrix.

INDICATIONS

HZ/su is indicated for the prevention of herpes zoster (shingles) (HZ) in adults ≥ 50 years of age.[1]

DOSAGE

The recommended dose is 0.5 mL given intramuscularly at zero and two to six months.[1] HZ/su is available as a single-dose vial of lyophilized varicella zoster virus glycoprotein E antigen component to be reconstituted with the accompanying vial of AS01B adjuvant suspension component.

POTENTIAL ADVANTAGES

HZ/su is more effective than ZVL in vaccine efficacy.

POTENTIAL DISADVANTAGES

HZ/su requires two injections, compared to a single dose for ZVL. There is potential for reduced adherence with the second dose.

COMMENTS

Efficacy was evaluated in two randomized, placebo-controlled, observer-blind clinical studies.[1,2] Study 1 included subjects ≥ 50 years of age. Study 2 included subjects ≥ 70 years of age. In study 1, subjects were randomized to HZ/su or placebo and stratified by age: 50-59, 60-69, 70-79, and ≥ 80 years. The researchers excluded immunocompromised subjects, those with a history of previous herpes zoster, or those who were vaccinated against varicella or HZ. Subjects were followed for a median of 3.1 years. The primary endpoint was confirmed cases of HZ. In an analysis population of 14,759 subjects, HZ/su reduced the risk of developing HZ by 97.2%, with no clear differences among the age stratum. No cases of postherpetic neuralgia (PHN) were reported in the vaccine group, compared to 18 in the placebo group. Study 2 randomized subjects 70-79 and ≥ 80 years to HZ/su or placebo with a median follow-up of 3.9 years. In an analysis cohort of 13,163 subjects, vaccine efficacy was 89.8%. Pooled data from the two studies showed vaccine efficacy of 91.3% for those ≥ 70 years of age. There were four cases of PHN in the vaccine group vs. 36 in the placebo group. The efficacy of HZ/su is more effective than reported with ZVL. A review of three large retrospective, nested, case-control studies totaling approximately 2.4 million mainly immunocompetent subjects showed a real-world effectiveness of ZVL of 48-55% in reducing the incidence of HZ and 59-62% in reducing post-herpetic neuralgia.

In an open-label study, there was no interference reported between HZ/su and a quadrivalent influenza vaccine (Fluarix).[1] In patients with a prior history of herpes zoster, HZ/su has been shown to induce immune response of 90% (95% confidence interval, 82-96%) based on anti-glycoprotein E antibodies one month after the second dose.[5] In adults previously vaccinated with ZVL, immune response to HZ/su was noninferior to those previously not vaccinated.[6] Most common adverse reactions associated with HZ/su are pain, redness, and swelling at the injection site. Others include muscle pain, tiredness, headache, shivering, fever, and upset stomach.[1]

CLINICAL IMPLICATIONS

Shingles is caused by the reactivation of dormant varicella zoster virus. Older individuals are at higher risk because of the reduced ability of the immune system to prevent activation. The disease usually occurs between ages 50-79 years, with an overall incidence of 2.0-4.6 cases per 1,000 person-years and increases to 10-12.8 per 1,000 person-years in those ≥ 80 years of age.[2,7] Postherpetic neuralgia is a complication of shingles that occurs in 20% of cases in individuals between 60-65 years of age and approximately 30% in those > 80 years of age.[7] HZ/su offers a more effective vaccine and is recommended by the Advisory Committee on Immunization Practices for the prevention of herpes zoster and related complications for immunocompetent adults ≥ 50 years of age, for adults who previously received Zostavax,

and is preferred over Zostavax.[8] The cost for Shingrix is $280 for two doses. ■

REFERENCES

1. Shingrix Prescribing Information. GlaxoSmithKline Biologicals, October 2017.
2. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med* 2016;375: 1019-1032.
3. Ansaldi F, Trucchi C, Alicino C, et al. Real-world effectiveness and safety of a live-attenuated herpes zoster vaccine: A comprehensive review. *Adv Ther* 2016;33:1094-1104.
4. Zostavax Prescribing Information. Merck & Co., Inc, May 2017.
5. Godeaux O, Kovac M, Shu D, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults ≥ 50 years of age with a prior history of herpes zoster: A phase III, non-randomized, open-label clinical trial. *Hum Vaccin Immunother* 2017;13:1051-1058.
6. Grupping K, Campora L, Douha M, et al. Immunogenicity and safety of the HZ/su adjuvanted herpes zoster subunit vaccine in adults previously vaccinated with a live-attenuated herpes zoster vaccine. *J Infect Dis* 2017 Sep 26. doi: 10.1093/infdis/jix482. [Epub ahead of print].
7. Fashner J, Bell AL. Herpes zoster and postherpetic neuralgia: Prevention and management. *Am Fam Physician* 2011;83:1432-1437.
8. American Academy of Family Physicians. ACIP Recommends New Herpes Zoster Subunit Vaccine, Oct. 31, 2017. Available at: http://bit.ly/2hIRPrb. Accessed Nov. 22, 2017.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log on to **AHCMedia.com** and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on their mailing label, invoice, or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. **Intense medical therapy for systolic heart failure in patients with severe functional mitral regurgitation (MR) can:**
   a. reduce MR in almost all patients.
   b. eliminate MR in most patients.
   c. reduce MR in one-third or more of patients.
   d. eliminate MR in one-third or more of patients.

2. **In patients on dabigatran who received idarucizumab (a reversal agent), dabigatran blood levels fell to near zero within:**
   a. seconds.
   b. minutes.
   c. two hours.
   d. four hours.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Cardiac Stenting No Better Than Aggressive Medical Management for Stable Angina and Single Vessel Disease

Procalcitonin to Guide Initiation or Discontinuation of Antibiotic Therapy for Acute Respiratory Infections

Migraine With Aura, Stroke Risk, and Biomarkers

Clinical Briefs

By Louis Kuritzky, MD

New Pharmacologic Direction for Parkinson's Disease

SOURCE: Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: A randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390: 1664-1675

Most clinicians are used to thinking about dopamine modulation when considering treatments for Parkinson's disease. Unfortunately, none of the current treatments can be designated as disease-modifying, even though such treatment provides transient symptomatic relief.

Current use of a glucagon-like peptide-1 receptor agonist (GLP-1RA) is limited to the management of type 2 diabetes. From where did the idea emerge that GLP-1RA might benefit Parkinson's patients?

The authors of studies about Parkinson's based on animal models have noted that a GLP-1RA not only crosses the blood-brain barrier, but produces sufficient neuroprotective and neurorestorative effects to improve motor function and memory. Investigators who conducted a subsequent open-label, one-year pilot trial of exenatide in humans with Parkinson's disease found favorable effects that endured for an additional 12 months post-treatment.

Based on these early successes, Athauda et al performed a randomized, double-blind, placebo-controlled trial of exenatide administered in weekly, subcutaneous, 2 mg doses (n = 62) for 48 weeks added to whatever current regimen study participants were receiving. The primary outcome was the motor performance subscale of a Parkinson's disease rating scale, measured 12 weeks after discontinuing exenatide treatment. Motor function improvements were demonstrated in exenatide-treated patients, whereas investigators noted deterioration in placebo patients. Larger, longer-term studies will be needed before GLP-1RA treatment could be confirmed as an appropriate consideration for Parkinson's patients. ■

CV Benefits of GLP-1RA Treatment in Type 2 Diabetes

SOURCE: Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228-1239.

Only in the last several years have randomized, clinical trials confirmed a cardiovascular (CV) benefit from glycemic control. To date, sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin, empagliflozin), glucagon-like peptide-1 receptor agonist (GLP-1RA; liraglutide, semaglutide), and bromocriptine have demonstrated CV risk reduction convincingly.

Among the SGLT-2 inhibitor and GLP-1RA classes of pharmacotherapy, there appears to be much more similarity than not. Should clinicians consider these salubrious CV effects a class effect? That is, should all members of the class be anticipated to experience similarly favorable CV outcomes?

The authors of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial randomized type 2 diabetics (n = 14,752) to either 2 mg of the GLP-1RA exenatide or placebo added to whatever ongoing diabetes regimen they already were receiving. The mean baseline A1c was 8.0%, and > 70% of participants presented with pre-existing CV disease.

After 3.2 years (mean) of intervention, exenatide failed to demonstrate a statistically significant improvement in the composite CV endpoint vs. placebo. Although all the answers are not known, the EXSCEL trial suggests there might be important differences among the class of GLP-1RA in reference to cardiovascular outcomes. Is it a class effect? Maybe not. ■

Morphine in Dyspneic Acute Heart Failure

SOURCE: Miró Ò, Gil V, Martín-Sánchez FJ, et al. Morphine use in the ED and outcomes of patients with acute heart failure: A propensity score-matching analysis based on the EAHFE Registry. *Chest* 2017;152:821-832.

Patients who experience acute heart failure (aHF) often are burdened with distressing dyspnea and its concomitant heightening of anxiety. Historically, clinicians have used morphine in these situations.

These decisions have been based on physiologic effects, such as preload and afterload reduction, as well as putative central nervous system effects, including reduced anxiety, breathlessness, and pain.

Unfortunately, morphine use in such settings is neither adequately supported nor refuted by clinical trial data.

Miró et al reviewed the data on a large population of aHF patients between 2011 and 2014 (n = 6,516). Investigators compared persons who received IV morphine within three hours of admission to an emergency department to those who did not. From this larger population of aHF patients, a subgroup who could be matched for a wide variety of other variables was selected for analysis (n = 550). Patients treated with morphine demonstrated a hazard ratio for 30-day mortality of 1.66.

The authors suggested that based on these data, clinicians should avoid morphine use in aHF patients. ■

Internal Medicine [ALERT]

ECG Review

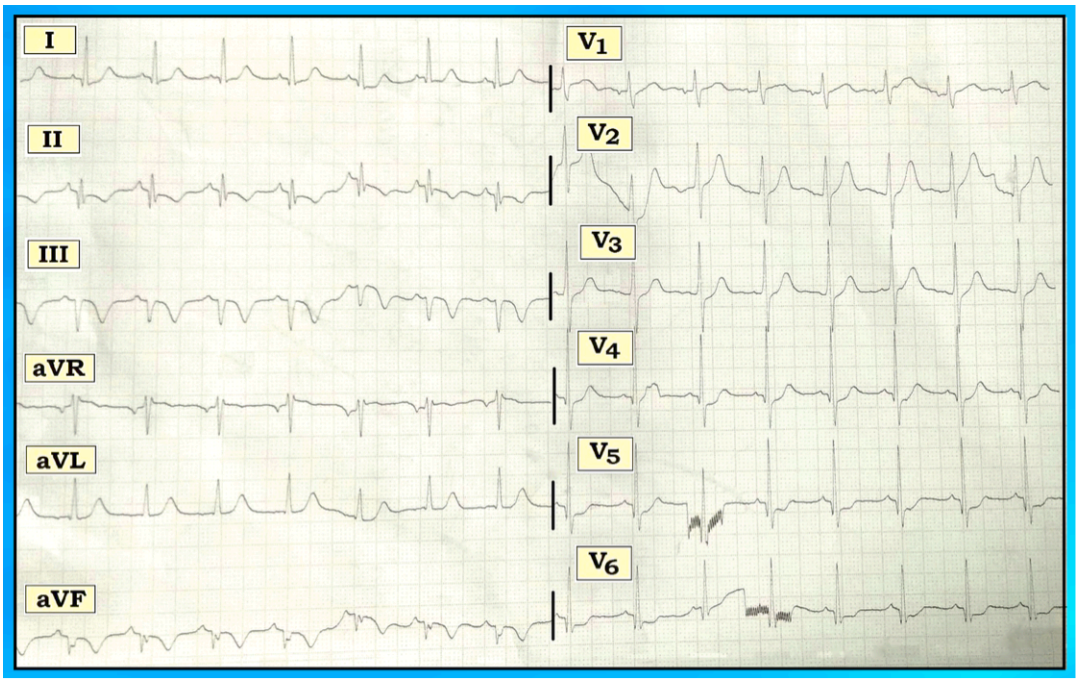
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

How Would You 'Date' This Infarct?

The ECG in the figure below was obtained from a 48-year-old man who presented to the ED with a three-day history of chest discomfort. It clearly shows evidence of infarction. How would you "date" the infarct?



The rhythm is fairly regular at 85-90 beats/minute. Upright sinus P waves are seen in lead II. The PR, QRS, and QT intervals are normal. The axis is leftward, but not by enough to qualify as left anterior hemiblock (i.e., the net QRS deflection in lead II is not predominantly negative). There is no chamber enlargement.

Q waves are present in multiple leads. Small, narrow (probably septal) q waves are seen in leads I and aVL. The Q wave in lead II is narrow but deep. Although there may be a tiny initial positive deflection (r wave) in at least some of the beats in lead III, the QRS complex is notched (fragmented), and clearly all negative in lead aVF. This defines the QRS in lead aVF as a QS complex. Thus, the overall appearance of the QRS in the inferior leads strongly suggests there has been inferior infarction. Finally, there are Q waves in leads V4, V5, and V6. Although narrow, the Q waves in leads V5 and V6 are somewhat deeper than expected to be simple "septal" q waves.

R wave progression is not normal in the chest leads. Normally, there should be a predominant negative deflection (S wave) in lead V1, with the area of "transition" (where R wave amplitude supersedes S wave depth) not occurring until after V2 or V3. Instead, R wave amplitude in lead V1 already equals S wave depth in this lead, with prominent R waves seen by lead V2. Although a number of entities may produce a disproportionately tall R wave in lead V1, recent posterior infarction should be at the top of this list. ST-T waves show numerous abnormalities. Although ST segments are not elevated, there is ST segment coving with fairly deep T wave inversion in each of the inferior leads. Additionally, there is 1-2 mm of ST depression in leads V3-V6, with more subtle ST-T wave abnormalities in leads I and aVL. Finally, the T wave in lead V2 looks prominent, and appears to be disproportionately tall. ST-T wave changes of "reperfusion" typically manifest the appearance seen here; that is, with no more than minimal residual ST segment elevation, and with deep T wave inversion in lead groups that overlie the area of infarction. Since anterior leads (i.e., leads V1, V2, V3) provide a mirror-image perspective of posterior events, the prominent T waves we see in leads V2 and V3 most likely reflect recent posterior reperfusion. This is consistent with the presence of a disproportionately tall R wave in lead V1. Thus, although the process of "dating" an infarction often is not straightforward, in view of the history of chest discomfort for three days, the overall appearance of this 12-lead tracing is consistent with recent infarction, perhaps with onset at the time symptoms began.

For more information about and further discussion on this case, please visit: http://bit.ly/2iqm1YV.