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ABSTRACT & COMMENTARY

Importance of Atherosclerotic Disease Risk Factors in Myocardial Infarction Patients

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: ST-elevation myocardial infarction patients without standard risk factors recorded a higher all-cause mortality rate that was particularly evident in women. Using proper therapy in these patients may attenuate this risk.

SOURCE: Figtree GA, Vernon ST, Hadziosmanovic N, et al. Mortality in STEMI patients without standard modifiable risk factors: A sex-disaggregated analysis of SWEDEHEART registry data. *Lancet* 2021;397:1085-1094.

Acute ST-elevation myocardial infarction (STEMI) in patients without a history of standard modifiable cardiovascular risk factors for atherosclerosis occurs in about 10-25% of patients. Generally, clinicians believe such patients fare better short and long term compared to their counterparts with standard risk factors, but this notion has not been examined adequately. To test this hypothesis in general and by sex, Figtree et al analyzed the SWEDEHEART database. The authors identified patients with the first presentation of a STEMI and no history of coronary artery disease (CAD). Among 62,048 such patients, 33% were women, and 15% presented without a standard risk factor (17% men and 11% women; $P < 0.001$). The standard modifiable cardiovascular risk factors included hypertension (70%), elevated LDL cholesterol (higher than 135 mg/dL or total cholesterol higher than 212 mg/dL; 48%), smoking one or more cigarettes per day (33%), and diabetes (21%) — all diagnosed before their STEMI. The primary endpoint was all-cause mortality at 30 days. Secondary endpoints were major cardiac or cerebral events (MACCE) in hospital at 30 days, five years, and at the end of follow-up or death.

The primary endpoint was 11.3% in the group without risk factors vs. 7.9% in the group with risk factors ($P < 0.0001$). The HR was 1.47 (95% CI, 1.37-1.57; $P < 0.001$), which still was significant when the authors considered a multivariate adjustment for other factors known to be associated with 30-day mortality (HR, 1.24; 95% CI, 1.10-1.39; $P < 0.0003$). Mortality at 30 days in women without standard risk factors was 17.6% vs. 11.2% in women with standard risk factors. The mortality rate in men without standard risk factors

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was 9.3% vs. 6.1% in men with standard risk factors. In-hospital death and five-year cardiovascular death were higher in men without standard risk factors than in men with standard risk factors. In women, this difference was similar and persisted for 12 years. There were several significant differences in the characteristics of the two groups, but few were clinically significant. Importantly, using angiotensin-receptor blockers, beta-blockers, and statins were less frequent in the group without standard risk factors ($P < 0.0001$). The authors concluded the STEMI patients without standard risk factors record a higher all-cause mortality rate that is particularly evident in women. Further, using proper therapy in these patients may attenuate this risk.

■ COMMENTARY

Figtree et al explored other characteristics of patients without standard risk factors that would explain their higher death rate after MI. However, body mass index and triglycerides were lower, and HDL cholesterol was higher in the group without standard risk factors. C-reactive protein levels were not different, and there was no difference in door-to-balloon or thrombolysis time. Spontaneous coronary artery dissection was considered and was more common in the group without standard risk factors (1.7% vs. 0.8%), but is unlikely to explain all the differences observed. Of course, there could be multiple risk factors at just below the diagnostic or therapeutic threshold that, in aggregate, could explain the differences in outcomes. Perhaps this is why those treated with standard risk reduction therapy fared better. Also, the excess mortality was early and diminished over time, which suggests it may have been caused by arrhythmias. Renin-angiotensin-aldosterone system inhibitors and beta-blockers reduce arrhythmias and early post-MI mortality. Accordingly, Figtree et al suggested STEMI patients without risk factors be treated just as aggressively pharmacologically as those with risk factors.

There were several strengths to this study. It was large, and the follow-up period was long. Also, there were comprehensive data collected on these patients, which allowed the authors to examine many potentially meaningful clinical factors. There also were several limitations. This was an observational study, so there could have been unmeasured confounders and biases. The authors used cutpoints for who did or did not have a risk factor when it is likely that risk factors are a continuous gradient. Importantly, there were no data on family history, socioeconomic factors, or psychosocial factors. Thus, the findings must be considered hypothesis-generating. However, the findings do counter the prevalent concept that an MI usually is self-induced because of inadequate management of treatable risk factors. ■

ABSTRACT & COMMENTARY

Another Agent for Hypercholesterolemia

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: A pooled analysis of three trials of inclisiran in patients with atherosclerotic cardiovascular disease or its risk equivalent showed impressive reductions in LDL cholesterol with subcutaneous injections.

SOURCE: Wright RS, Ray KK, Raal FJ, et al. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. *J Am Coll Cardiol* 2021;77:1182-1193.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) lowers LDL cholesterol receptor levels by inhibiting their ability to be recycled to the cell surface, which hinders the removal of LDL particles from circulation. Current monoclonal antibodies targeting PCSK9 are quite effective in lowering LDL levels but require subcutaneous injections every two to four weeks. Inclisiran is a double-stranded RNA molecule that suppresses PCSK9 translation in the liver and lowers circulating concentrations of PCSK9 and LDL. Three Phase III placebo-controlled, double-blind, randomized trials of inclisiran injected subcutaneously every six months

showed the drug lowers LDL by about 50% and is well tolerated. This report provides pooled patient-level data.

The authors of ORION-9 studied patients with heterozygous familial hypercholesterolemia. The authors of ORION-10 studied patients with atherosclerotic cardiovascular disease (ASCVD) and elevated LDL levels. The authors of ORION-11 studied subjects with ASCVD or its equivalent and elevated LDL. Inclusion criteria for the three studies were elevated LDL levels > 70 mg/dL for those with ASCVD or > 100 mg/dL for the rest on maximally tolerated doses of statins, with or without other agents or documented intolerance to two statins. In all three studies, inclisiran 300 mg was injected on days 1, 90, 270, and 450. The primary endpoint was the change in LDL from baseline and compared to placebo levels. The pooled study population included 3,660 participants, and 94% of subjects completed the protocol. ASCVD was present in 85% of the subjects, and 92% were on statins. The mean LDL level at baseline was 112 mg/dL in the inclisiran group and 111 mg/dL in the placebo group.

Compared to placebo, inclisiran cut LDL levels by 51% at day 510. Injection site-related adverse events were more common in the inclisiran group (5% vs. 0.7% in the placebo group). These were predominantly mild (67%); none were severe. There were no significant changes in laboratory values for liver and kidney function nor creatine kinase values or platelet counts. The authors concluded that in subjects with familial hypercholesterolemia, ASCVD, or ASCVD equivalents, inclisiran injected twice-yearly in addition to maximally tolerated statin therapy is safe and efficacious for reducing LDL levels to target.

■ COMMENTARY

All clinicians recognize statin adherence is a challenge for many reasons: too many pills, perceived muscle symptoms, fear of liver injury, and more. The monoclonal antibodies against PCSK9 are a major advance in this regard, but an injection every two to four weeks is not acceptable to everyone. Thus, the development and early success of these inclisiran trials is encouraging. An injection every six months is likely to be better accepted and could correspond to patients' routine physician visits. The paucity of adverse effects is reassuring. Other than mild to moderate injection site symptoms, the only other adverse effect detected was an increase in bronchitis (5% vs. 2.7%), which is of uncertain significance. Of course, with this relatively small group of subjects studied for less than two years, rare adverse effects may not have been detected.

Inclisiran lowered LDL to < 100 mg/dL in 100% of subjects, to < 70 mg/dL in 68% of subjects, and to < 50 mg/dL in 52%. Also, inclisiran lowered the levels of other atherogenic lipids, such as total cholesterol, Apo-B, and non-HDL cholesterol. These robust effects should profoundly affect atherosclerosis and related major adverse cardiovascular events. Clinicians await the clinical outcome trials, but the initial data are encouraging for eventual FDA approval. ■

ABSTRACT & COMMENTARY

The Danger of ADHD Overdiagnosis

By Austin Ulrich, PharmD, BCACP

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SYNOPSIS: A growing concern about overdiagnosis of attention-deficit/hyperactivity disorder in adolescents and children demonstrates a need for a decisive answer to this concern.

SOURCE: Kazda L, Bell K, Thomas R, et al. Overdiagnosis of attention-deficit/hyperactivity disorder in children and adolescents: A systematic scoping review. *JAMA Netw Open* 2021;4:e215335.

In recent years, rates of ADHD diagnosis have risen, along with a growing concern about overdiagnosis.[1,2] Suggested reasons for increased ADHD diagnosis range from improved detection, true increases in frequency, and diagnostic inflation caused by misdiagnosis or overdiagnosis, but there is no clear consensus.

To investigate the role of diagnostic inflation, Kazda et al designed a series of definitions and questions about overdiagnosis, applied to a systematic review and meta-analysis. Studies published between Jan. 1, 1979, and Aug. 21, 2020, were included. Investigators considered only research that clearly identified diagnoses and outcomes in patients younger than age 18 years.

The authors mapped all data to five questions: Is there potential for increased diagnosis? Has the diagnosis rate actually risen? Are additional cases subclinical or low risk? Have some additional cases been treated? Might harms outweigh benefits of diagnosis and treatment? Kazda et al derived these questions from a previously identified framework for establishing

overdiagnosis. The authors evaluated 334 studies, 61 of which were primary research studies. Kazda et al reported the following information in terms of each research question: 104 studies provided evidence for a reservoir of ADHD, 45 studies indicated diagnosis of ADHD has increased, 25 studies showed the additional diagnoses of ADHD were on the mild end of the spectrum, 83 studies demonstrated pharmacological treatment of ADHD is increasing, and 151 studies reported on outcomes of diagnosis and pharmacological treatment.

The authors concluded there is convincing evidence to suggest increased overdiagnosis and overtreatment of ADHD in children and adolescents in recent years. They also identified a need for high-quality research on the long-term risks and benefits of ADHD diagnosis and treatment in youths with milder symptoms.

■ COMMENTARY

Overdiagnosis is a significant concern in healthcare because it frequently triggers a cascade of overtreatment, higher costs, and potential harm that can persist over years. Patients who receive pharmacologic treatment for ADHD often experience an improvement in symptoms, but many also might experience adverse effects of ADHD therapies. Notably, up to 30% of adults discontinue stimulants because of intolerable adverse effects or lack of symptomatic relief.[3] If a patient has only mild or borderline ADHD symptoms, the improvement in symptoms (if any) may be so minimal that treatment could result in a lack of net benefit. While the ADHD overdiagnosis observed by Kazda et al was in children and adolescents, adults can be affected, too. Two of the key criteria for diagnosis of adult ADHD is establishing a childhood history of ADHD and a family history of ADHD.[3] Thus, increases in youth ADHD diagnoses are likely to lead to more adult ADHD diagnoses and subsequent treatment. Clinicians should be aware of the potential for overdiagnosis of ADHD in youth and how this can influence ADHD diagnosis in adults.

Overall, there is a need for more research aimed at determining the harms and benefits of diagnosing and treating youth with mild or borderline ADHD symptoms. Further elucidating ADHD diagnosis patterns and implementing practice patterns to avoid harmful overdiagnosis will help optimize the treatment of ADHD in children, adolescents, and adults. ■

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ABSTRACT & COMMENTARY

Rapid Intermittent Bolus of Hypertonic Saline May Be Better Way to Correct Symptomatic Hyponatremia

By Betty Tran, MD, MSc

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SYNOPSIS: Hypertonic saline given via rapid intermittent bolus therapy was as effective and safe as slow continuous infusion, and was associated with a lower rate of recorrecting treatment and higher efficacy in achieving goal sodium within one hour.

SOURCE: Baek SH, Jo YH, Ahn S, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia. The SALSA Randomized Clinical Trial. *JAMA Intern Med* 2020;181:81-92.

Limited data are available regarding the best method to correct symptomatic hyponatremia. Baek et al sought to compare the efficacy and safety of administering 3% hypertonic saline via rapid intermittent bolus (RIB) vs. slow continuous infusion (SCI) in patients with moderate to severe symptomatic hyponatremia. SALSA was a multicenter, open-label, randomized clinical trial that enrolled adults with moderate to severe symptoms with serum sodium (sNa) levels < 125 mmol/L. Patients were enrolled through the ED and on the wards. Randomization was stratified by center and hyponatremia symptom severity. Patients in the RIB group received IV 2 mL/kg 3% saline for 20 minutes for moderate symptoms or 4 mL/kg 3% saline over 40 minutes for severe symptoms in the first 24 hours. After the initial treatment, repeat infusion of 2 mL/kg 3% saline over

20 minutes was administered every six hours up until 24 hours until the sNa level increased by 5 mmol/L to 9 mmol/L from baseline and until symptom relief. The same protocol was repeated after 24 hours until 48 hours until sNa increased by 10 mmol/L to 17 mmol/L from baseline or until sNa reached 130 mmol/L and until symptoms improved.

Patients in the SCI group received IV 3% saline at a starting rate of 0.5 mL/kg/hour for moderate symptoms or 1 mL/kg/hour for severe symptoms. The rate was adjusted every six hours up to the first 24 hours. The treatment discontinued if sNa increased by 5 mmol/L to 9 mmol/L with symptom relief. Treatment increased 0.25 mL/kg/hour if the rate of correction was less than 0.5 mmol/hour (or resumed at 0.5 mL/kg/hour if previously discontinued), and maintained if the rate of correction > 0.5 mmol/hour. The infusion rate also was adjusted every six hours depending on sNa level between 24 and 48 hours. It was discontinued if sNa increased by 10 mmol/L to 17 mmol/L or if it reached 130 mmol/L with symptom relief, it increased by 0.25 mL/kg/hour (or resumed at 0.25 mL/kg/hour if discontinued previously) if sNa increased by less than 1.5 mmol/six hours, and maintained if sNa increased by more than 1.5 mmol/six hours.

Given the low incidence of osmotic demyelination syndrome (ODS), the primary outcome chosen to be a surrogate marker of ODS was the incidence of overcorrection, defined as an increase in sNa by more than 12 mmol/L within the first 24 hours or an increase in sNa by more than 18 mmol/L within 48 hours. Multiple secondary outcomes were reported, centering around efficacy and safety. The authors checked overcorrection at every sample time point. They enacted relowering treatment if overcorrection was present: a dextrose 5% infusion of 10 mL/kg over one hour and/or an IV desmopressin of 2 mcg if sNa increase was more than 10 mmol/L within the first 24 hours or more than 18 mmol/L within 48 hours.

The authors performed statistical analyses based on both intention-to-treat (ITT) and per protocol (PP) bases, since the dropout rate was expected to be high given the complexity of the hypertonic saline infusion protocol. Overall, a total of 178 patients with a mean sNa of 118.2 mmol/L (standard deviation, 5.0) were randomized: 87 to the RIB group and 91 to the SCI group, with 72 and 73 patients, respectively, completing the study and included in the PP analysis. The causes of hyponatremia included thiazide diuretics (29.8%), syndrome of inappropriate antidiuretic hormone secretion (29.2%), adrenal insufficiency (16.3%), nonrenal sodium loss (14.0%), and increased extracellular fluid volume (10.7%). There was no significant difference in baseline characteristics between the two groups. For both the ITT and PP analyses, there was no significant difference in the primary outcome of overcorrection incidence: 17.2% in RIB vs. 24.2% in SCI group (absolute risk difference, -6.9%; 95% CI, -18.8% to 4.9%; $P = 0.26$ for the ITT analysis). In terms of secondary outcomes, the RIB group showed a decreased incidence of needing relowering treatment than the SCI group (41.4% vs. 57.1%, respectively, absolute risk difference, -15.8%; 95% CI, -30.3% to -1.3%; $P = 0.04$; number needed to treat [NNT], 6.3). Additionally, in terms of a post-hoc ITT analysis, the proportion of patients achieving target correction rate (sNa of 5 mmol/L to 9 mmol/L) within one hour was higher in the RIB group (32.2% vs. 17.6%, respectively; absolute risk difference, 14.6%; 95% CI, 2-27.2%; $P = 0.02$; NNT, 6.8). Overall, the two groups did not differ in terms of efficacy in increasing sNa after six hours or improving symptoms.

■ COMMENTARY

SALSA is the first prospective, multicenter, randomized clinical trial comparing the efficacy and safety of RIB vs. SCI of hypertonic saline in patients with moderate to severe symptomatic hyponatremia. Although both methods were similar in terms of overcorrection risk and cumulative amounts of hypertonic saline administered in 48 hours between the two groups, the trial results suggest that, not surprisingly, RIB achieved the sNa goal within one hour and with an overall reduced incidence of needing a relowering intervention for overcorrection.

Notably, Baek et al did not adjust for secondary and post-hoc outcomes, so false-positives are possible. In addition, although their reasoning in using overcorrection incidence as a surrogate marker is well-delineated, the true outcome of interest when correcting hyponatremia, ODS, was not observed in either group. As such, we cannot define which method is preferable in resolving life-threatening hyponatremic symptoms in a way to prevent ODS.

Regardless, the administration of hypertonic saline to correct symptomatic hyponatremia via RIB appears just as safe as SCI, with the possible advantages of faster efficacy and less need for relowering interventions. In addition, RIB is more user-friendly in that it does not require frequent calculations as seen with infusion rate adjustments. Finally, small, fixed boluses to correct hyponatremia are in keeping with prior American and European guidelines, which were based on smaller randomized trials, case reports, and expert opinions.[1,2] ■

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BRIEF REPORT

Ischemic Stroke in Patients with COVID-19

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor and Chair, Department of Neurology, Associate Dean for Clinical Affairs, NYP/Weill Cornell Medical College

SOURCE: Srivastava PK, Zhang S, Xian Y, et al. Acute ischemic stroke in patients with COVID-19. An analysis from Get With The Guidelines–Stroke. *Stroke* 2021;52:1826-1829.

Since the first cases of COVID-19 were reported in the United States, severe ischemic strokes also have been reported in some of these patients, some with large vessel occlusions and case reports of thrombectomy for treatment. Get With The Guidelines-Stroke is the largest national stroke registry that has been collecting data at 2,000 U.S. hospitals for many years. Srivastava et al queried the database to assess the frequency, risk factors, and severity of acute ischemic stroke (AIS) in COVID-19 patients across the country. From Feb. 4, 2020, until June 29, 2020, they identified 41,971 patients with AIS and identified 1,143 who had AIS in the setting of COVID-19 infection. They compared them with AIS patients who did not have COVID-19. Patients who had both AIS and COVID-19 were younger, or likely to be Black, Hispanic, or Asian rather than white, or more likely to have a higher National Institutes of Health Stroke Scale score, and a higher proportion had large vessel occlusions. Door-to-CT time, door-to-needle time for thrombolysis, and/or to endovascular therapy times were longer in the AIS/COVID-19 cohort compared to the control group.

In a risk-adjusted model, patients who had AIS/COVID-19 had decreased odds ratio of discharge with the modified Rankin Scale score ≤ 2 and had an increased risk of in-hospital mortality. Patients with ischemic stroke in the setting of COVID-19 were younger, had greater stroke severity, waited longer for evaluation and treatment, and experienced worse morbidity and mortality compared to those without COVID-19. ■

BRIEF REPORT

Stroke and Risk of Suicide

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor and Chair, Department of Neurology, Associate Dean for Clinical Affairs, NYP/Weill Cornell Medical College

SOURCE: Vyas MV, Wang JZ, Gao MM, Hackam DG. Association between stroke and subsequent risk of suicide: A systematic review and meta-analysis. *Stroke* 2021;52:1460-1464.

The development of depression following stroke is common, and ranges from 28% to 35% in prospective cohort studies. Depression and low mood have been associated with suicidal ideation, but factors such as cognitive impairment and physical disability also may increase the risk of suicidal ideation in survivors of stroke.

Vyas et al conducted a systematic review of the literature to perform a meta-analysis of observational studies and determine the prevalence and risk of attempted suicide in patients who survive and recover from stroke. Using key words, they systematically searched multiple literature databases and selected observational studies that reported suicide attempts or deaths by suicide in stroke survivors. Then, the authors defined a comparison group consisting of people without a history of stroke or the general population. They used a random effects meta-analysis and calculated the pooled adjusted risk ratio of suicide in stroke survivors and calculated the pooled risk ratio of suicide attempt and death by suicide.

A total of 4,093 articles were screened with 23 studies of fair quality totaling more than 2 million stroke survivors. Of those, 5,563 attempted suicide or died by suicide. Compared to the non-stroke group, the risk ratio for suicide or attempted suicide in stroke survivors was 1.73, $P = 0.03$. The risk of attempted suicide was higher than death by suicide when compared to the non-stroke population. The investigators noted that in patients who were followed in cohort studies, the risk of suicide was lower for every one year of increase in follow-up.

Stroke should be considered a risk factor for suicide. Tactics to screen and treat depression and suicidal ideation should be an important component of long-term follow-up and care for stroke patients. ■

PHARMACOLOGY UPDATE

Pegcetacoplan Injection (Empaveli)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
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The FDA has approved a new treatment for paroxysmal nocturnal hemoglobinuria (PNH), a rare, life-threatening blood disease. The previous therapeutic target for PNH treatment has been complement protein C5 (C5 inhibitors, eculizumab, and ravulizumab). Pegcetacoplan is a pegylated pentadecapeptide that targets complement C3, upstream in the complement cascade. It received fast-track, breakthrough therapy, and orphan designations, along with a priority review and accelerated approval.

INDICATION

Pegcetacoplan can be prescribed to adults with PNH.[1]

DOSAGE

The recommended dose of pegcetacoplan is 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump that includes a reservoir of at least 20 mL.[1] Pegcetacoplan is available as a single-dose vial containing 1,080 mg/20 mL. Similar to C5 inhibitors, pegcetacoplan is available only through a restricted program under a Risk Evaluation and Mitigation Strategy. Patients should be vaccinated against encapsulated bacteria (including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B) at least two weeks before initiation of therapy according to current Advisory Committee on Immunization Practices guidelines.

POTENTIAL ADVANTAGES

Pegcetacoplan provides a different mechanism of action and superior control of hemolysis vs. eculizumab.[1,2] Treatment was associated with a significant increase in hemoglobin levels.

POTENTIAL DISADVANTAGES

Injection site reactions and diarrhea are more common with pegcetacoplan compared to eculizumab (39% vs. 5%; 22% vs. 3%, respectively).[1,2] Vaccination against encapsulated bacteria lowers (but does not eliminate) risk of serious infections.[1] Pegcetacoplan interferes with laboratory tests that use silica reagents in coagulation panels, resulting in artificially prolonged activated partial thromboplastin time.[1]

COMMENTS

PNH is an acquired clonal disorder resulting in deficiency of complement regulatory proteins (CD55 and CD59), leading to complement-mediated intravascular hemolysis of susceptible red cells. Treatment with a C5 inhibitor, such as eculizumab, reduces hemolysis, cuts the need for transfusion, ameliorates anemia, lowers the risk of thrombosis, and improves quality of life. However, 25% of patients still need transfusions, some have breakthrough intravascular hemolysis and C3-related extravascular hemolysis caused by red cell opsonization by C3 fragments.[3-5]

The efficacy of pegcetacoplan was evaluated in subjects with PNH who had been treated with a stable dose of eculizumab for at least the previous three months and recorded hemoglobin levels lower than 10.5 g/dL.[1,2] The study included three phases: a four-week run-in period (pegcetacoplan + eculizumab); a 16-week randomized, controlled phase (pegcetacoplan [n = 41] or eculizumab [n = 39]); and a 32-week open-label phase (pegcetacoplan only). The primary endpoint was the change in hemoglobin from baseline to week 16. Secondary endpoints were proportion of subjects who did not require a transfusion, change in absolute reticulocyte count (ARC), and score on the Functional Assessment of Chronic illness Therapy-Fatigue (FACIT-F) scale (range, 0-52). At baseline, mean hemoglobin level was 8.7 g/dL, 55% had undergone four or more transfusions in the previous 12 months, the mean reticulocyte count was 217×10^{-9}/liter, and mean FACIT-F score was 32.

At week 16, mean change in hemoglobin from baseline was 2.37 g/dL for pegcetacoplan vs. -1.47 g/dL for eculizumab, an adjusted difference of 3.84 g/dL. Transfusion avoidance was 85% for pegcetacoplan vs. 15% for eculizumab. Mean change in ARC was -136×10^{-9} cells/L compared to 28×10^{-9} cells/L. The FACIT-F score showed a difference of 11.9 points in favor of pegcetacoplan, and 73% of subjects recorded at least a three-point score increase compared to 0% for eculizumab.

CLINICAL IMPLICATIONS

Pegcetacoplan is the first C3 inhibitor approved for PNH and provides therapeutic improvement over current C5 inhibitor therapy (e.g., eculizumab). It provides an alternative to patients inadequately controlled on eculizumab or ravulizumab, as well as an initial treatment option for treatment-naïve patients. These drugs are extremely expensive, with the annual cost of pegcetacoplan expected to be $458,000, which is similar to other drugs in this class. ■

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CME QUESTIONS

1. In an analysis of a large national database, acute myocardial infarction patients without the standard risk factors for atherosclerosis made up what percentage of the population?
a. 0%
b. 5%
c. 15%
d. 35%

2. Randomized trial data showed inclisiran injected twice a year reduces LDL cholesterol in patients on maximally tolerated statin therapy by about:
a. 10%.
b. 25%.
c. 50%.
d. 75%.

3. Which is correct about overdiagnosis of ADHD in children and adolescents?
a. ADHD is not overdiagnosed in children and adolescents.
b. Overdiagnosis of ADHD in children and adolescents does not affect adult ADHD diagnoses.
c. ADHD cases with mild or borderline ADHD symptoms are the least concerning for overdiagnosis.
d. Increased youth ADHD overdiagnosis correlates with increased pharmacologic therapy for ADHD.

4. In the SALSA trial, using rapid intermittent bolus to correct for hyponatremia compared to a slow continuous infusion resulted in:
a. a higher rate of relowering treatment.
b. a slower time to hyponatremia correction.
c. no difference in the incidence of overcorrection.
d. a lower rate of sustained symptom improvement.

5. Patients with COVID-19 and ischemic stroke have higher morbidity and mortality from their stroke.
a. True
b. False

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.