

YEAR IN REVIEW 2018



Original Perspectives
on the Year's Most Important
Clinical Topics in General Medicine
from the Editors of NEJM Journal Watch



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Dear Reader,

In our annual review of the year's most important clinical research, the editors of NEJM Journal Watch try to balance relevance to general medicine and recognition of landmark studies. This year, our mix of topics differs a bit from previous years: Of the 15 topics, 6 address potentially practice-changing trials in critical care medicine, and 3 address major studies of primary prevention of cardiovascular disease.

— Allan S. Brett, MD
Editor-in-Chief

NEJM Journal Watch General Medicine

Year in Review 2018

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Aspirin for Primary Cardiovascular Prevention?

Three large trials demonstrated no net benefit.

Although many people take aspirin for primary prevention of adverse cardiovascular (CV) events, previous data suggest that the benefit–harm tradeoff is close. In 2018, three studies that were conducted in patients with no cardiovascular history pushed the pendulum away from primary aspirin prophylaxis. In each trial, a 100-mg daily dose of aspirin was compared with placebo.

- ARRIVE involved 12,000 nondiabetic middle-aged and older patients (mean age, 64) with at least two CV risk factors. At 5 years, the incidence of a composite CV endpoint (including myocardial infarction and stroke) was the same in the aspirin and placebo groups (4%), but gastrointestinal bleeding was slightly more common with aspirin ([NEJM JW Gen Med](#) Oct 1 and [Lancet](#) Sep 22; 392:1036).
- ASCEND involved 15,000 diabetic patients (mean age, 63), many of whom were taking statins and blood pressure medications. At 7 years, the incidence of adverse CV events was one percentage point lower with aspirin than with placebo, but the incidence of major bleeding was one percentage point higher ([NEJM JW Gen Med](#) Oct 1 and [N Engl J Med](#) Oct 18; 379:1529).
- In ASPREE, researchers enrolled 19,000 older patients (median age, 74) without regard to other risk factors. ASPREE's primary endpoint — disability-free survival — occurred with equal frequency in the aspirin and placebo groups (10%), but major hemorrhage and mortality each were roughly one percentage point higher with aspirin. No CV benefits were noted ([NEJM JW Gen Med](#) Oct 15 and [N Engl J Med](#) Oct 18; 379:1499, 1509, 1519).

These largely negative results should be shared with patients who are taking aspirin for primary CV prevention, but two caveats should be noted: First, some data suggest that daily aspirin might lower the incidence or growth of certain cancers — particularly colorectal cancer. No such effect was described in these new trials, but longer-duration treatment probably would be necessary to show that effect. Second, a recent analysis of older primary prevention trials suggested that low-dose aspirin (i.e., 75–100 mg daily) might be insufficient to confer CV protection for people who weigh >70 kg ([NEJM JW Gen Med](#) Aug 15 and [Lancet](#) Aug 4; 392:387). However, other research suggests that higher doses confer higher risk for bleeding, so the jury is out on whether weight-based dosing would improve the overall benefit–harm calculus.

— Allan S. Brett, MD

No Value for Routine Vitamin D Supplementation

A randomized trial, a meta-analysis, and a guideline all point in the same direction.

Enthusiasm for recommending vitamin D supplementation to prevent a wide range of skeletal and extraskeletal disorders was diminished considerably by three publications in 2018.

In VITAL (Vitamin D and Omega-3 Trial), researchers randomized nearly 26,000 middle-aged and older adults with no history of cardiovascular (CV) disease, cancer, or other serious disorders to receive vitamin D₃ (2000 IU daily) or placebo. Mean serum 25-hydroxyvitamin D level increased in vitamin D₃ recipients only. During median follow-up of 5 years, major adverse CV events and invasive cancer occurred with equal frequencies in the two groups (*NEJM JW Gen Med* Dec 15 and *N Engl J Med* Nov 10; [e-pub]). The VITAL researchers are expected to report eventually on other outcomes, including fractures.

In a meta-analysis of 33 randomized trials, effects of supplementation with calcium, vitamin D, or both on fracture rates were investigated in older community-dwelling adults (age, ≥50). There was no reduction in risk for hip fracture or vertebral, nonvertebral, and total fractures for any supplementation intervention. The results applied to subgroups with 25-hydroxyvitamin D levels lower than 20 ng/mL or with previous fractures (*NEJM JW Gen Med* Feb 15 and *JAMA* 2017 Dec 26; 318:2466).

Finally, the U.S. Preventive Services Task Force (USPSTF) updated previous guidelines addressing vitamin D supplementation. The Task Force found adequate evidence to recommend against vitamin D supplementation to prevent falls and found insufficient evidence to recommend supplementation to prevent fractures in men and premenopausal women. For postmenopausal women, they recommend against low-dose supplementation, but evidence was insufficient to determine whether higher doses prevent fractures. The USPSTF emphasized that these recommendations apply only to community-dwelling older adults who are not known to have osteoporosis or vitamin D deficiency (*NEJM JW Gen Med* May 15 and *JAMA* Apr 17; 319:1592).

The VITAL study joins many others in which disease associations with low vitamin D levels do not necessarily translate to benefit from supplementation. However, given widespread routine measurement of vitamin D levels by clinicians (a practice for which there is no supportive evidence currently) and over-the-counter availability of supplements, vitamin D use is unlikely to decline.

— Thomas L. Schwenk, MD

Omega-3 Fatty Acid Supplementation for Primary Cardiovascular Prevention?

Supplementation was ineffective in patients without known cardiovascular disease.

Many people without known cardiovascular (CV) disease take omega-3 (ω -3) fatty acid supplements (“fish oil”) to prevent adverse CV events. However, recent studies cast doubt on this practice.

In the VITAL study, about 26,000 people (mean age, 67) without CV disease were randomized to 1-g capsules of fish oil (eicosapentaenoic acid plus docosahexaenoic acid) or placebo. During a mean follow-up of 5.3 years, risks for the primary endpoint (nonfatal myocardial infarction [MI], stroke, or CV-related death) and all-cause death were similar in the two groups. Although the incidence of MI was significantly lower in the ω -3 group than in the placebo group, the absolute difference was small: 1.1% vs. 1.5% during 5 years of treatment (*NEJM JW Gen Med* Dec 15 and *N Engl J Med* Nov 10; [e-pub]).

In the ASCEND trial, more than 15,000 people (mean age, 63) with diabetes but without CV disease were randomized to 1-g fish-oil capsules (eicosapentaenoic acid plus docosahexaenoic acid) or placebo. During mean follow-up of 7.4 years, risks for the primary endpoint (nonfatal MI, stroke, transient ischemic attack, or CV-related death) or all-cause death were similar in the two groups (*NEJM JW Gen Med* Oct 1 and *N Engl J Med* Oct 18; 379:1540).

A meta-analysis of 10 randomized trials (78,000 total patients) showed no significant differences between ω -3 recipients and controls in risks for coronary heart disease–related death, nonfatal MI, any coronary heart disease event, or major adverse CV events overall. Subgroup analyses among participants with known coronary heart disease or diabetes yielded similar findings (*JAMA Cardiol* Mar; 3:225).

The two new randomized trials do not support the use of ω -3 fatty acid supplements for preventing adverse CV events in patients with no history of CV disease. Although the meta-analysis showed no evidence of benefit for secondary prevention, a recently published trial (REDUCE-IT) showed that a different ω -3, icosapent ethyl, lowered risk for adverse CV events in patients with established CV disease and elevated triglycerides; those results are summarized elsewhere (see [New Adjunctive Therapies for Coronary Artery Disease?](#) in this issue, p.13)

— Paul S. Mueller, MD, MPH, FACP

Limiting Use of Antipsychotics in Intensive Care Patients

Antipsychotics did not prevent delirium or affect its clinical course.

Antipsychotics traditionally have been used to manage agitation in delirious patients at risk for injurious behavior. Recently, their use has expanded to include prophylaxis in patients at risk for delirium, as well as treating disorganized thinking in patients with hypoactive symptoms. Two 2018 studies should halt any enthusiasm for this trend.

The REDUCE trial involved 1800 intensive care unit (ICU) patients in the Netherlands who were at risk for delirium. Patients were randomized to receive haloperidol (1 mg or 2 mg thrice daily) or placebo. The 1-mg haloperidol arm was stopped early due to futility. Mortality at 28 days and 90 days did not differ between the 2-mg haloperidol and placebo groups. Incidence of delirium (33%), duration of ICU and hospital stays, and duration of mechanical ventilation were similar in both groups ([NEJM JW Gen Med](#) Apr 1 and [JAMA](#) Feb 20; 319:680).

In another randomized trial, >500 critically ill patients with delirium (75% in medical ICU; nearly all receiving mechanical ventilation; ≈90% hypoactive) at 16 U.S. hospitals received either haloperidol, ziprasidone, or placebo for as long as 14 days. Researchers found no differences in delirium-free days, duration of mechanical ventilation, length of ICU stay, or 14-day mortality among treatment groups, regardless of whether delirium was hypoactive or hyperactive ([NEJM JW Gen Med](#) Dec 1 and [N Engl J Med](#) Oct 22; [e-pub]).

These two randomized trials demonstrate that antipsychotics have no role in ICU delirium prophylaxis and should not be used to treat patients with hypoactive ICU delirium. Antipsychotics might still have a role in managing patients with hyperactive delirium who are at imminent risk for self-harm (e.g., pulling out their endotracheal tubes). However, antipsychotic use should be discontinued at first opportunity given their associated risk for harms, such as QT prolongation and aspiration pneumonia ([NEJM JW Gen Med](#) Mar 1 and [J Am Geriatr Soc](#) 2017 Dec; 65:2580).

— Neil H. Winawer, MD, SFHM, *NEJM Journal Watch Hospital Medicine*

Stress Ulcer Bleeding Prophylaxis in the Intensive Care Unit

A large randomized trial showed no mortality benefit.

The incidence of clinically important stress ulcer gastrointestinal (GI) bleeding in the intensive care unit (ICU) is decreasing. Concerns about tradeoffs between potential benefits and harms of prophylaxis with proton-pump inhibitors (PPIs) were addressed in a large randomized trial that was published in 2018. About 3300 critically ill, at-risk patients (i.e., >24 hours mechanical ventilation, shock, coagulopathy or use of anticoagulants, chronic renal replacement therapy, or chronic liver disease) received either pantoprazole prophylaxis or placebo. Nearly 60% of patients received enteral feeding on ICU day 1, and >80% received feeding by ICU day 3. GI bleeding occurred in 4.2% of patients who received PPIs versus 2.5% who received placebo (number needed to treat [NNT], 59). No differences were seen in 90-day mortality or 90-day adverse events (i.e., pneumonia, *Clostridium difficile* infection, or myocardial ischemia; [NEJM JW Gen Med](#) Dec 15 and [N Engl J Med](#) Dec 6; 379:2199).

Earlier in 2018, a network meta-analysis of 57 randomized controlled trials of stress ulcer prophylaxis was published. PPIs more effectively prevented GI bleeding than did placebo (absolute risk reduction, 1.6%; NNT, 63), histamine (H₂)-receptor blockers, or sucralfate. However, pneumonia risk also was higher with PPIs (absolute risk increase, 3.1%; number needed to harm, 33). No mortality difference was seen among groups ([Intensive Care Med](#) Jan; 44:1).

What are the take-home points on stress ulcer prophylaxis? First, stress ulcer–induced GI bleeding in the ICU is uncommon, especially with enteral nutrition, and even without pharmacologic prophylaxis. Second, ICU patients without risk factors probably should not receive pharmacologic prophylaxis. And, third, in ICU patients with risk factors, PPI prophylaxis marginally lowers GI bleeding risk but does not lower in-hospital mortality.

— Daniel D. Dressler, MD, MSc, SFHM, FACP

Steroids for Septic Shock

Taken together, two trials suggested that benefits probably outweigh harms for selected patients.

For nearly 20 years, clinicians have debated about whether to treat septic shock patients with corticosteroids. In 2018, two large trials added to the debate, because they yielded slightly different results. In one trial (APROCCHSS), 90-day mortality was significantly lower in patients who were treated with both the glucocorticoid hydrocortisone (50 mg every 6 hours for 1 week) and the mineralocorticoid fludrocortisone (50 μ g daily) than in placebo recipients (43% vs. 49%). Active-treatment patients also were liberated significantly more quickly from mechanical ventilation and vasopressors (*NEJM JW Gen Med* Apr 15 and *N Engl J Med* Mar 1; 378:809).

In contrast, the other trial (ADRENAL) was a comparison of hydrocortisone alone versus placebo; mortality was virtually the same in both groups — about 28%. Time alive and free from the intensive care unit (ICU) or free from mechanical ventilation did not differ in the two groups; however, similar to APROCCHSS' results, duration of septic shock was shorter in the steroid group (*NEJM JW Gen Med* Mar 1 and *N Engl J Med* Mar 1; 378:797). Steroid-related side effects were minimal in both studies.

The jury is still out on whether steroids lower mortality in septic shock patients, but multiple trials now have shown that steroids shorten duration of septic shock. If this effect shortens the length of ICU stays (as it did in ADRENAL), steroid use might translate to cost savings and less-challenging hospitalizations for some patients and their families — even if the mortality benefit is marginal. I will continue to use glucocorticoids for patients with refractory septic shock who require multiple vasopressors or rapidly escalating doses. The dose of fludrocortisone given in APROCCHSS was so low that some have questioned its physiological effect in the setting of such high glucocorticoid dosing. Nevertheless, fludrocortisone is inexpensive, and its addition likely imparts no harm, so using the treatment protocol from APROCCHSS makes sense to me.

— Patricia Kritek, MD

Fluid Choice: Balanced Crystalloid Instead of Saline

Two studies demonstrated less renal injury when patients were given lactated Ringer's instead of saline.

The choice of crystalloid fluid for volume resuscitation is debated often. With rising concern about the effect of hyperchloremic metabolic acidosis associated with normal saline, clinicians more commonly are opting for balanced crystalloids, such as lactated Ringer's solution or Plasma-Lyte. In two parallel trials, investigators from Vanderbilt randomized patients to receive either normal saline or balanced crystalloid (generally, lactated Ringer's). One trial was performed in the emergency department (ED); one was done in the intensive care units (ICUs). The computer order-entry system directed providers to use the assigned fluid.

In the ICU trial, patients who received balanced crystalloids had fewer adverse kidney events, a composite outcome that included death, renal replacement therapy, or a doubling of creatinine at discharge (*NEJM JW Gen Med* Apr 15 and *N Engl J Med* Mar 1; 378:819). The ED trial, which included all-comers admitted from the ED to acute care, yielded similar results. The effect of balanced fluids was more pronounced in patients with sepsis and in those who received large volume resuscitation (*NEJM JW Gen Med* Apr 15 and *N Engl J Med* Mar 1; 378:829).

These two trials were conducted at a single center but enrolled more than 28,000 patients between them. Based on these results — which are consistent with a trend that probably preceded the trials — many intensivists now default to lactated Ringer's except in specific patient populations (e.g., saline is preferable for patients with traumatic brain injury, because its higher osmolarity might improve brain edema). Two ongoing large multicenter trials of fluid choice hopefully will provide more-definitive guidance. But, in the meantime, I have transitioned to reaching for lactated Ringer's — particularly for septic patients who require larger volume resuscitation.

— *Patricia Kritek, MD*

Renal Replacement Therapy in the ICU

Studies suggested no benefit for early RRT, and bicarbonate infusion might help avoid RRT altogether.

Critical care providers continue to struggle with finding the right time to start renal replacement therapy (RRT) for intensive care unit (ICU) patients. A growing body of literature offers conflicting results. In 2018, investigations focused on specific patient populations to assess whether a more-targeted approach to RRT could provide definitive guidance.

In a previously published trial, ICU patients with acute kidney injury (AKI stage 3, defined by serum creatinine and urine output criteria) who required mechanical ventilation or pressors were randomized to receive either early or delayed RRT, with specific criteria for initiation of delayed RRT (*NEJM JW Gen Med* Jul 15 2016 and *N Engl J Med* 2016 Jul 14; 375:122). Now, in a 2018 post hoc analysis of that trial, researchers focused specifically on patients with septic shock or acute respiratory distress syndrome (ARDS). Within both of these cohorts, no difference was found between early and delayed RRT in mechanical ventilation–free days, length of hospital stay, or 60-day mortality (*NEJM JW Gen Med* Aug 15 and *Am J Respir Crit Care Med* Jul 1; 198:58). These results were similar to findings in the previously reported overall cohort.

In a new 2018 trial, 488 patients with septic shock and AKI were randomized to receive RRT that was either early or delayed for 48 hours (unless renal recovery was evident). This trial was stopped early due to futility. Again, no difference in mortality between groups was seen. Notably, only 62% of patients in the delayed group received RRT (*NEJM JW Gen Med* Dec 1 and *N Engl J Med* Oct 11; 379:1431).

In a third trial, investigators focused on critically ill patients with metabolic acidosis, nearly half of whom had AKI. Patients with severe metabolic acidosis (pH \leq 7.20; bicarbonate \leq 20 mmol/L; partial pressure of carbon dioxide \leq 45 mm Hg) received either 4.2% sodium bicarbonate infusion or no therapy. Although mortality didn't differ between groups, RRT during the ICU stay was more common in the control group than in the bicarbonate group (*NEJM JW Gen Med* Sep 1 and *Lancet* Jul 7; 392:31).

These studies demonstrate no clear benefit to early RRT in patients with septic shock and ARDS. Delaying initiation will help a cohort of patients avoid RRT entirely. For patients in whom metabolic acidosis is the main indication for dialysis, temporizing with bicarbonate also might help defer RRT.

— Patricia Kritek, MD

Achieving Full Nutritional Goals for Critically Ill Patients Doesn't Change Outcomes

Various forms of enteral and parenteral nutrition were compared.

Two trials in 2018 shed light on nutrition for critically ill patients. In one, French investigators randomized nearly 2500 patients to early (i.e., during the first 7 days of intensive care unit admission) parenteral or enteral nutrition. All patients were supported by both mechanical ventilation and vasopressors. Daily caloric intake was targeted at 20 to 25 kilocalories per kg body weight daily in an attempt to provide 100% of nutritional needs. Mortality, length of stay, and liberation from life support were similar in the two groups. Although previous studies suggested excess risk for infection with parenteral nutrition, this outcome was not seen in this study. The patients who were fed enterally had more gastrointestinal complications ([NEJM JW Gen Med](#) Jan 15 and [Lancet](#) Jan 13; 391:133).

In another study, Australian researchers focused on achieving targeted caloric requirements with different forms of enteral nutrition. Nearly 4000 patients were randomized to receive either standard (1.0 kcal/mL) or energy-dense (1.5 kcal/mL) enteral nutrition. Both groups achieved the same average rate of feeding, which resulted in the standard group receiving, on average, 70% of targeted calories and the energy-dense group receiving 100%. Length of stay, liberation from mechanical ventilation, and mortality were similar between groups. The energy-dense group had more gastrointestinal complications ([NEJM JW Gen Med](#) Dec 1 and [N Engl J Med](#) Nov 8; 379:1823).

The biggest message from these two studies is that we should deemphasize efforts to achieve full enteral nutrition for patients on life support, particularly early in their stay. Practice is evolving, and many intensivists begin trickle feeds (i.e., 10 mL/hour) for critically ill patients, with the theory that some nutrition helps preserve mucosal integrity but that pushing to achieve full enteral nutrition might have a downside. Although trickle feeding was not examined in either of these studies, results from both, taken together, indirectly support this “less is more” approach.

— Patricia Kritek, MD

More Evidence That the “Artificial Pancreas” Is Safe and Effective

Both inpatients and outpatients could benefit from this technology.

In 2016, the FDA approved the first hybrid closed-loop insulin delivery system (“artificial pancreas”) for adults and adolescents with type 1 diabetes; in 2018, the minimum age was lowered to 7. These devices include a continuous glucose monitor and a linked insulin pump that delivers basal insulin at a continuously adjusted, algorithmically optimized rate; patients still must administer meal boluses manually. Closed-loop systems have improved glycemic control and lowered risk for hypoglycemia for inpatients and outpatients with type 1 diabetes, but most studies have been small and brief.

In a 2018 study — the largest randomized outpatient study to date of closed-loop technology — researchers randomized 86 children and adults with type 1 diabetes to closed-loop treatment or sensor-guided (but patient-controlled) pump therapy for 12 weeks. Patients using the closed-loop system spent significantly more time with blood glucose between 70 and 180 mg/dL and had lower glycosylated hemoglobin (HbA_{1c}) levels than did controls. Hypoglycemia occurred equally often in both groups (*NEJM JW Gen Med* Dec 1 and *Lancet* Oct 13; 392:1321).

Researchers also conducted a meta-analysis of 40 trials that involved more than 1000 outpatients with type 1 diabetes who were randomized to closed-loop treatment or other means of insulin administration. Compared with controls, closed-loop users spent significantly more time in the near-normoglycemic range (70–180 mg/dL) and significantly less time in the hyperglycemic and hypoglycemic ranges; closed-loop users had significantly lower levels of HbA_{1c} (*NEJM JW Gen Med* Jul 1 and *BMJ* Apr 18; 361:1310).

On the inpatient side, researchers randomized 136 adult general medical inpatients who required subcutaneous insulin to either closed-loop insulin delivery (without meal boluses) or conventional insulin injections for as long as 15 days. Here, too, closed-loop patients spent significantly more time in the target glycemic range (100–180 mg/dL) and had significantly lower mean glucose levels than did control patients; investigators noted no difference between groups in total daily insulin dose or time spent in hypoglycemia (*NEJM JW Gen Med* Aug 1 and *N Engl J Med* Aug 9; 379:547).

To call closed-loop technology an “artificial pancreas” might be a bit of an overstatement, because manual meal boluses still are required. And these devices still are quite costly. But early evidence suggests that this technology soon could improve glycemic control and simplify life for many people living with diabetes.

— Bruce Soloway, MD

Gene Expression Test Identifies Patients Who Can Skip Chemotherapy

In selected intermediate-risk patients with breast cancer, endocrine therapy was adequate.

For decades, classification of tumor type, decisions about treatment, and estimation of prognosis have been based on pathology inspection of tumor tissue — but with varying accuracy. New “gene expression” technologies can determine which genes are active (making mRNA and protein) in any tissue, including tumor samples. Can such tests offer more accurate predictions than traditional pathology examination?

The value of a widely used commercial assay that assesses the activity of 21 genes to predict chemotherapy benefit was tested in women with hormone-receptor–positive, human epidermal growth factor receptor-2 (HER2)–negative, axillary node–negative breast cancer. Previous studies have shown that women with high scores on the assay benefit from a combination of chemotherapy and endocrine therapy and that women with low scores require only endocrine therapy. However, many women have intermediate scores. In this new study, researchers evaluated optimal treatment for this large subgroup (*NEJM JW Gen Med* Jul 15 and *N Engl J Med* Jul 12; 379:111).

Women with intermediate scores on the expression assay were randomized to receive either chemoendocrine therapy or endocrine therapy only. At 9 years, the two groups had similar rates of invasive disease–free survival, freedom from recurrence (at either local-regional or distant sites), and overall survival. Thus, the gene expression test identified a large subgroup of women who could be spared chemotherapy. A secondary analysis suggested that women who were younger than 50 might benefit from chemotherapy, but this hypothesis should be tested in a randomized trial.

This study involved just one subtype of one type of cancer. Yet this and many other studies demonstrate that gene expression assays increasingly are playing a central role in the care of cancer patients, particularly in personalizing the choice of treatment and improving the accuracy of prognostic estimates.

— Anthony L. Komaroff, MD

New Adjunctive Therapies for Coronary Artery Disease?

Rivaroxaban and icosapent ethyl are potential add-on therapies.

Several new adjunctive therapies for coronary artery disease (CAD) were investigated or approved in 2018. The FDA recently approved a new 2.5-mg dose of rivaroxaban (Xarelto) based largely on a trial of 27,000 patients with symptomatic or revascularized CAD or symptomatic peripheral artery disease. CAD patients younger than 65 were required to have atherosclerosis in a second vascular bed or at least two high-risk factors. Exclusion criteria included high risk for bleeding, serious comorbidities, glomerular filtration rate <15 mL/minute, severe heart failure, and need for dual antiplatelet therapy. Patients were randomized to rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily), rivaroxaban alone (5 mg twice daily), or aspirin alone. During 2 years of treatment, the incidence of major adverse cardiovascular (CV) events was 1.3 percentage points lower with rivaroxaban plus aspirin than with aspirin alone, but the incidence of major bleeding was 1.2 percentage points higher (*NEJM JW Gen Med* Oct 1 2017 and *N Engl J Med* 2017 Oct 5; 377:1319).

In a second trial, investigators randomized patients with either CAD or diabetes plus other risk factors who had elevated triglyceride levels despite statin therapy to icosapent ethyl (Vascepa; an ethyl ester of the ω -3 fatty acid eicosapentaenoic acid) or mineral-oil placebo. After a median follow-up of 4.9 years, the combined endpoint of cardiovascular-related death, nonfatal myocardial infarction, or stroke was significantly lower with icosapent ethyl than with placebo (17% vs. 22%). Atrial fibrillation and flutter were more common with icosapent ethyl (3.1% vs. 2.1%), and somewhat more bleeding occurred in the icosapent ethyl group. The primary endpoint was significantly lower with icosapent ethyl in the secondary prevention cohort (71% of participants) but not in the smaller primary prevention cohort (*NEJM JW Gen Med* Jan 1 2019 and *N Engl J Med* Nov 10; [e-pub]).

Both rivaroxaban and icosapent ethyl represent potential add-on therapies for patients with CAD. In COMPASS, the benefit–harm tradeoff is close enough that clinicians probably should offer combined therapy only to patients who would have met criteria for enrollment. Although the subgroup analysis in the icosapent ethyl trial was nonrandomized, I likely will use icosapent ethyl predominantly for patients with known CAD, given that the primary-prevention subgroup did not benefit in this trial and given the negative results of recent trials of other ω -3s for primary prevention.

— Kirsten E. Fleischmann, MD, MPH, FACC

Transcatheter Clip for Heart Failure with Mitral Regurgitation

“MitraClip” was associated with lower morbidity and mortality.

Patients with heart failure and clinically significant secondary mitral regurgitation (MR) have poor prognoses, but the 2018 COAPT trial suggests that device therapy might improve those odds. North American investigators randomized 614 symptomatic heart-failure patients with at least moderate-to-severe functional MR (despite standard medical therapy) to receive either continued medical therapy alone or medical therapy plus a transcatheter clip device (i.e., MitraClip, which directly reduces the severity of MR). Participants were deemed not to be candidates for mitral valve surgery and to have anatomy suitable for device placement. Hospitalizations for heart failure were significantly lower in the device group (36% vs. 68% per patient-year), as was 24-month mortality (29% vs. 46%). Quality of life and functional status also improved more in the device group. Freedom from device-related complications at 1 year was almost 97% (*NEJM JW Gen Med* Oct 1 and *N Engl J Med* Sep 23; [e-pub]).

Although this trial was not blinded and was company sponsored, it provides strong evidence that poor prognosis in this high-risk group can be improved by treating secondary regurgitation with a percutaneously deployed clip device in appropriate patients, at least in the short term. The MitraClip already is FDA approved for managing primary valve-related MR in patients deemed to be at high risk for surgery-related complications or death, but secondary regurgitation approval would represent a new population and application. Currently, the device is placed predominantly at specialized, often academic, centers after detailed multidisciplinary evaluation; however, given these results, I anticipate greater availability and growth. Stay tuned for longer-term outcomes.

— Kirsten E. Fleischmann, MD, MPH, FACC

A video about the MitraClip procedure is available at http://mitraclip.com/the_mitraclip_procedure free of charge.

Advances in Treating Stroke and Transient Ischemic Attack

New research addressed dual antiplatelet therapy and late endovascular thrombectomy.

During 2018, important stroke studies covered the spectrum from transient ischemic attack (TIA) to major disabling strokes.

In the randomized POINT trial, researchers examined whether early dual antiplatelet therapy (DAPT) improves outcomes in patients with high-risk TIA or minor ischemic stroke not caused by conditions such as atrial fibrillation or carotid stenosis (which mandate other interventions). Nearly 5000 such patients received daily treatment with low-dose aspirin alone or low-dose aspirin plus clopidogrel (600 mg loading dose, followed by 75 mg daily), starting within 12 hours of symptom onset. At 90 days, the incidence of recurrent ischemic stroke was significantly lower with DAPT than with aspirin alone (4.6% vs. 6.3%), whereas the incidence of major hemorrhage was higher with DAPT (0.9% vs. 0.4%). However, the relative reduction in recurrent stroke occurred almost entirely during the first week, whereas bleeding events (most of which were not intracranial) were distributed fairly evenly throughout 90-day follow-up. Thus, it appears that one can maximize benefit and minimize harm by confining DAPT to just a few weeks (*NEJM JW Gen Med* Jul 1 and *N Engl J Med* Jul 19; 379:215).

In two studies, investigators examined whether the time window for endovascular thrombectomy can be extended beyond 6 hours in selected patients with moderate-to-severe ischemic stroke due to intracranial carotid or proximal middle cerebral artery occlusion. These studies involved patients whose infarct volume on imaging was smaller than the clinical deficit would predict — suggesting an area of brain that is poorly perfused but not yet infarcted. In the DAWN trial, 206 such patients who were last known to be well 6 to 24 hours earlier were randomized to thrombectomy plus standard care or standard care alone. Thrombectomy patients were substantially more likely than standard care patients to be functionally independent at 90 days (49% vs. 13%; *NEJM JW Neurol* Jan and *N Engl J Med* Jan 4; 378:11). In a similar trial with 182 patients (DEFUSE 3), the functional independence outcome was similar to that of DAWN, and mortality was lower in the thrombectomy group (14% vs. 26%; $P=0.05$; *NEJM JW Gen Med* Mar 15 and *N Engl J Med* Feb 22; 378:708). These studies show that delayed thrombectomy can benefit carefully selected patients, although early treatment is preferable when possible.

— Allan S. Brett, MD

Triple Therapy for COPD Patients

In high-risk patients with chronic obstructive pulmonary disease, triple therapy prevents some exacerbations.

Guidelines recommend stepwise treatment for patients with chronic obstructive pulmonary disease (COPD) based on symptoms and exacerbation risk: Start with a long-acting antimuscarinic agent (LAMA) or a long-acting β -agonist (LABA); then, combine the two; and finally, add an inhaled corticosteroid (ICS) for those whose COPD still is uncontrolled. However, triple therapy (i.e., LAMA plus LABA plus ICS) was not studied intensively until this year.

In 1532 symptomatic COPD patients with ≥ 2 exacerbations in the past year, triple therapy (beclomethasone, formoterol, and glycopyrrolate) for 1 year prevented some moderate-to-severe exacerbations compared with dual therapy (indacaterol and glycopyrrolate); the number needed to treat was 11 to prevent 1 exacerbation (*NEJM JW Gen Med* Mar 15 and *Lancet* Mar 17; 391:1076). In another 1-year study in 10,355 symptomatic, high-risk COPD patients, triple therapy (vilanterol, umeclidinium, and fluticasone [Trelogy Ellipta]) prevented some moderate-to-severe exacerbations compared with a LABA/LAMA combination (vilanterol and umeclidinium [Anoro Ellipta]; 0.91 vs. 1.21 exacerbations annually; *NEJM JW Gen Med* Jun 15 and *N Engl J Med* May 3; 378:1671). Finally, a meta-analysis of 24 trials in which triple therapy was compared with a LAMA or a LAMA/LABA combination showed fewer exacerbations with triple therapy (rate ratios, ≈ 0.75 ; *NEJM JW Gen Med* Dec 15 and *BMJ* 2018 Nov 6; 363:4388). However, in most trials, ICS use came at the expense of excess risk for pneumonia. In almost all studies, the greatest benefit was seen in patients who had eosinophilia or concomitant asthma.

Many patients start triple therapy inappropriately or continue triple therapy after they no longer need it. In a randomized trial of >1000 patients with moderate-to-severe COPD who were using triple therapy but had infrequent exacerbations, those who de-escalated to a LABA/LAMA did not experience more exacerbations than those who continued triple therapy, with the exception of the subgroup with eosinophilia (*NEJM JW Gen Med* Sep 15 and *Am J Respir Crit Care Med* Aug 1; 198:329).

As many as 50% of all COPD patients receive ICS, even though many aren't at high risk for exacerbations. With the added expense and excess risk for pneumonia, triple therapy should be reserved for symptomatic patients with frequent exacerbations who already use dual long-acting bronchodilators. However, patients with asthma/COPD overlap syndrome or peripheral eosinophilia (i.e., >150 to 200 cells/ μ L) do better with ICS.

— David J. Amrol, MD

The 2018 GOLD guidelines are available at <https://goldcopd.org/wp-content/uploads/2016/04/GOLD-2018-WMS.pdf> free of charge.

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