Dr. Allan Brett: I'm Dr. Allan Brett. I'm a general internist in the Department of Medicine at the University of Colorado, and I serve as editor-in-chief of the *NEJM Journal Watch* family of publications. I'm here today with two of my colleagues. Dr. Rahul Ganatra is an associate editor of *Journal Watch*, he's an instructor in medicine at Harvard Medical School and a clinician educator who practices both inpatient and outpatient internal medicine at the VA Boston Healthcare System. Rahul, welcome.

Dr. Rahul Ganatra: Thanks, Allan. It's great to be here.

Dr. Allan Brett: I'm also joined by Dr. Molly Brett, a *Journal Watch* contributing editor. Molly is a general internist, an assistant professor of medicine at the University of Colorado, and a clinician educator at the Rocky Mountain Regional VA Medical Center. Her main clinical activity is outpatient primary care. Molly, thanks for joining us.

Dr. Molly Brett: Thanks so much for having me.

Dr. Allan Brett: For this review of important clinical research summarized in *NEJM Journal Watch General Medicine* during 2023, we've picked topics that we believe will be clinically relevant for a broad range of clinicians who see adult patients. The order of presentation here isn't intended to reflect their relative importance. So, let's get started.

These days, it seems like a month doesn't go by without reading something new in major medical journals about potential indications for GLP-1 agonists or SGLT2 inhibitors. Today, we're going to talk specifically about GLP-1 agonists. We've known that these drugs have favorable cardiovascular effects in patients with diabetes. The two trials published in 2023 looked at those effects in patients without diabetes who have cardiovascular disease.

Dr. Molly Brett: One trial included 18,000 patients without diabetes who had a BMI above 27 and a history of myocardial infarction or stroke, and they got weekly injections of semaglutide or placebo. At 3 years, the incidence of a composite outcome of MI, stroke, or cardiovascular death was lower with semaglutide than with placebo. The difference was 6.5% versus 8%. This 1.5% point difference was highly significant, but it does mean that about 70 people had to be treated for 3 years to prevent one cardiovascular event. As you'd expect, weight loss was much greater with semaglutide than with placebo.

Dr. Allan Brett: In the other trial, about 500 patients who had heart failure with preserved ejection fraction, a BMI over 30, and no history of diabetes got weekly injections of semaglutide or placebo for a year. Compared to patients in the placebo group, those in the semaglutide group had statistically significant and clinically meaningful improvement on a standardized questionnaire that addresses symptoms and physical limitations. Mean weight loss was 13% of body weight with semaglutide.

Dr. Molly Brett: We should keep in mind that semaglutide isn't currently FDA-approved for the two indications studied in these trials: treatment of heart failure with preserved ejection fraction, and secondary prevention of ischemic cardiovascular events in overweight patients who don't have diabetes. Eventual approval for these indications seems likely given these results, but I'd like to make two final points. First, about 10% of semaglutide recipients in both trials discontinued treatment because of its gastrointestinal side effects. And second, I think we've got to mention the cost. The list price of semaglutide at doses used in these trials is about $17,000 annually, so the potential effect on healthcare costs is a major issue given how large these patient populations are.

Dr. Allan Brett: Let's continue this GLP-1 drug discussion but switch to treatment of obesity. The GLP-1 agonists, particularly semaglutide, are widely known as potent weight loss drugs. But now, there's competition from tirzepatide, an agonist of both GLP-1 receptors and receptors of another hormone: glucose-dependent insulinotropic polypeptide. Two years ago, tirzepatide was approved for treatment of diabetes, and now, in November 2023, it was approved for treatment of obesity.

Dr. Molly Brett: Approval for obesity was based on two recently published studies. Both were large, placebo-controlled trials of patients with overweight or obesity, but one included patients with diabetes, and the other one included only patients without diabetes. At the highest dose of tirzepatide, patients with diabetes lost an average of 15% of body weight, and patients without diabetes lost an average of 21%, while patients who got placebo lost just 3%. As you'd expect, GI side effects were pretty common with this drug.

Dr. Allan Brett: In *Journal Watch*, we prefer to discuss drugs by their generic names, but one odd thing is that tirzepatide's brand name for the older diabetes indication is Mounjaro, while the brand name for the new obesity indication is Zepbound, even though the recommended drug dosing is exactly the same. You start with 2.5 milligrams injected subcutaneously weekly, and then you can gradually titrate up to a maximum of 15 milligrams weekly if the drug is tolerated and if the higher doses are needed to improve diabetes control or maximize weight reduction.

Dr. Molly Brett: And if you're wondering whether this drug is costly, the answer, of course, is yes. The drug company recently announced that the list price is $1,060 per month. That's slightly lower than the list price for semaglutide's weight loss dosing, but still, this comes out to about $13,000 per year. So we'll have to see which insurance companies will start covering it, what the co-payments will be, and whether uninsured patients without financial resources will get substantial discounts. It'd be nice if competition between these drugs would drive down prices, but I'm not counting on that anytime soon.

Dr. Allan Brett: Now, let's switch to a couple of topics relevant to inpatient practice. First, we'll talk about hospitalized patients with community-acquired pneumonia. For years, some people have thought that giving steroids along with antibiotics might improve outcomes in critically ill patients with pneumonia, given the anti-

inflammatory effects of steroids. But so far, results of mostly small clinical trials have been mixed.

Dr. Rahul Ganatra: And that brings us to a randomized trial from France that was published in 2023. 800 patients with severe community-acquired pneumonia received either 200 milligrams of intravenous hydrocortisone daily or placebo. All of these patients were sick enough to be directly admitted to the intensive care unit, and steroids were started within 24 hours. Nearly half the patients were supported with high-flow oxygen, and a quarter were intubated at enrollment. In this critically ill population, mortality was significantly lower with hydrocortisone than with placebo — it was 6% versus 12% — and the incidence of shock and need for mechanical ventilation also were lower in the hydrocortisone group.

Dr. Allan Brett: Later in 2023, a meta-analysis of 15 steroid trials covering 3,000 hospitalized patients with community-acquired pneumonia was published. 30-day mortality was significantly lower in steroid treated patients, driven in large part by the trial we just discussed. Steroids didn't necessarily lower risk for transfer to the ICU among patients initially admitted to non-ICU beds, but progression to acute respiratory distress syndrome was less likely among patients who got steroids. The mortality benefit was seen mostly in patients admitted directly to the ICU and not in those initially admitted to a general ward.

Dr. Rahul Ganatra: So, early administration of moderate dose steroids to the sickest patients now is supported by clinical trials, especially this latest one. Based on these data, our *Journal Watch* pulmonary critical care editor, Trish Kritek, tells us she now has a lower threshold for giving steroids to ICU patients with community-acquired pneumonia. I'll add that as a hospitalist on a general medical unit, these data make me more likely to start steroids for patients requiring higher levels of supplemental oxygen even if they aren't yet in the ICU.

Dr. Allan Brett: A restrictive red blood cell transfusion strategy, withholding transfusions until the hemoglobin is less than seven grams, has become the standard of care for most hospitalized patients with anemia, but there's still controversy for some subgroups. In October 2023, the Association for the Advancement of Blood and Biotherapies updated a previous guideline and recommended the restrictive seven-gram cutoff for most hemodynamically stable patients. But for patients with acute myocardial infarction, evidence was considered inadequate to make a specific recommendation.

Dr. Rahul Ganatra: And as it so happens, Allan, just a few weeks later, in November 2023, the *New England Journal* published the largest ever clinical trial to address red cell transfusions in patients with MI and anemia. Several thousand patients with acute MI were randomized to a restrictive threshold, a hemoglobin cutoff of seven or eight, allowing for some clinician judgment, or a liberal threshold, which used a hemoglobin cutoff of 10. Rates of key adverse outcomes at one month were numerically lower with the liberal transfusion strategy. For the composite of death or recurrent MI, it was a 2.5% point difference (14.5%

versus 17%), but this difference did not reach statistical significance in the primary analysis.

Dr. Allan Brett: Digging a little deeper, it turns out that about half the patients in this trial had type 2 MIs, attributed to supply demand mismatch, and about half had type 1 MIs, caused by coronary occlusion. Virtually all the benefit was seen in those with type 1 MIs, where there was a statistically and clinically significant 5% point lower incidence of death or recurrent MI in the liberal transfusion group. So Rahul, how do you think this will affect practice?

Dr. Rahul Ganatra: Well, it depends on whether you're willing to act on the results of this subgroup analysis. In this case, the favorable outcome with liberal transfusion in patients with type 1 MI is striking and makes mechanistic sense. Without any signal for harm, I think most clinicians will move to a more liberal threshold in those cases. Even so, we should keep in mind that there are downsides to liberal transfusion practices. In this study, the liberally transfused group got three times as many units of RBCs compared to the restrictive group, so that has an impact on the blood supply. Another potential downside is symptomatic volume overload caused by transfusion. That wasn't reported as a problem in this study, but it is something to consider when transfusing patients with impaired ventricular function.

Dr. Allan Brett: Next, I'd like to turn our attention to prostate cancer. We know that PSA screening leads to a lot of over-diagnosis of low-risk cancers that aren't destined to be harmful, so one positive development in recent years is the growing use of active surveillance rather than radical treatment for many patients. The PROTECT study is the largest trial that randomized patients with PSA-detected, localized, mostly low-grade cancers to receive prostatectomy, radiotherapy, or active surveillance. 10-year follow-up was published several years ago showing no mortality difference for the three approaches.

Dr. Molly Brett: And no, in 2023, 15-year follow-up was published. Prostate cancer-specific mortality was similar in the three groups (about 3%), and overall mortality was also similar. We should point out that by the end of follow-up, 60% of patients under surveillance had crossed over to radical treatment, usually because of a rising PSA or because of anxiety. But still, that leaves 40% of patients who avoided the complications of radical prostatectomy and radiotherapy, so these results provide confidence that properly selected patients can be observed safely without compromising long-term survival.

Dr. Allan Brett: Another notable publication in 2023 was a new prostate screening guideline from the American Urological Association. As you'd expect, the AUA endorses screening, but whether you're a PSA screening enthusiast or skeptic, there are some recommendations that might surprise our listeners. Molly, tell us about a few of those.

Dr. Molly Brett: Sure thing. One is that screening is recommended not annually but every 2 to 4 years, because that's the interval used in the largest screening trial. A less-than-

annual frequency is thought to reduce the problem of over-diagnosis without compromising outcomes. Long intervals are especially recommended for men with very low PSA levels, for example, less than 1.0 at age 60. The guideline also recommends repeating a newly elevated PSA level a few months later before we decide to refer the patient to a urologist, and it suggests progressively raising the PSA threshold for further evaluation as men get older, and generally stopping screening at age 69.

Dr. Allan Brett: And last but not least, the document emphasizes strongly that screening is a shared decision sensitive to patient preferences. It's actually less heavy-handed about pushing PSA screening than I had expected from a urologic organization.

Over the years, studies on the cardiovascular safety of testosterone supplements have reached varying conclusions, so in 2015, the FDA called on manufacturers to gather more data, and the first large trial to address the safety concern was finally published in 2023.

Dr. Rahul Ganatra: That's right, Allan. The study enrolled 5,200 men, average age 63, who had established cardiovascular disease or cardiovascular risk factors, and two fasting testosterone levels between 100 and 300. All participants reported symptoms that the researchers assumed might be related to hypogonadism, including decreased libido, erectile dysfunction, fatigue, or low mood. They were randomized to testosterone gel or placebo, and after average follow-up of about 2 years, the incidence of the primary endpoint, a composite of myocardial infarction, stroke, or cardiovascular death, was the same in both groups: 7%. Results were similar for the individual components of that endpoint, for subgroups by age, for subgroups with established cardiovascular disease, and for those who had only risk factors.

Dr. Allan Brett: This trial tells us that testosterone appears safe in men with high cardiovascular risk, at least during 2 years of treatment. But it wasn't designed to look at whether testosterone therapy actually benefited these patients, so I thought we should take a quick look back at the landmark study called The Testosterone Trials published in 2016. In that study, 800 older men with serum testosterone levels less than 275, and either decreased libido, decreased physical performance, or fatigue, were randomized to testosterone gel or placebo for 1 year. Testosterone therapy modestly improved sexual function but not physical function or vitality.

Dr. Rahul Ganatra: So, it's worth emphasizing that the reassurance about cardiovascular safety isn't a reason to prescribe testosterone indiscriminately for older men with low testosterone but only non-specific symptoms. In most cases, those symptoms probably aren't related to the decline in testosterone levels that we often see in an aging population.

Dr. Molly Brett: In 2023, the FDA approved two new drugs with novel mechanisms of action that address two common and important problems for women. One is fezolinetant. It's a first-in-class, non-hormonal drug that relieves vasomotor menopausal

symptoms by improving thermoregulatory sensitivity in the brain. In placebo-controlled studies published this year, this drug reduced the frequency of hot flashes by two or three episodes daily, and it also reduced severity of symptoms. Benefits were seen as early as one week, and the drug was well tolerated through a year, with headache being the most common side effect. There are several contraindications and drug interactions that prescribers will need to know about, and the manufacturer recommends baseline liver function testing, with repeat testing every three months.

Dr. Allan Brett: The brand name here is VEOZAH, and I mention it only because I've already seen a barrage of direct-to-consumer ads on TV that advise women to, and I quote, "Ask your doctor about hormone-free VEOZAH." But predictably, the list price is steep, $550 monthly, and some insurance companies are requiring lack of response to alternative agents before they'll approve coverage.

Dr. Molly Brett: The other new drug addresses postpartum depression. Peripartum neurohormonal changes are thought to play a role in postpartum depression. This new drug, zuranolone, is an oral analog of a progesterone metabolite that decreases markedly right after childbirth. In randomized trials of patients with postpartum depression, a two-week treatment course yielded response rates about 20% points higher with zuranolone than with placebo, and responses were sustained through 30 days after completing treatment. Zuranolone has a rapid onset of action, improvement is seen as early as three days, and for most patients within eight days, but we don't know whether the benefits are sustained long-term.

Dr. Allan Brett: Zuranolone was FDA-approved in August 2023 but hasn't yet been distributed to pharmacies as of this recording. Still, we thought it worthwhile to review the drug today because of the need for rapidly effective treatments for postpartum depression. Unfortunately, and here we go again with a necessary mention of drug costs, the recently released wholesale price is $15,900 for the two-week course. In addressing affordability, a drug company's spokesperson has stated that the company's goal is, and I quote, "To enable broad and equitable access for women with postpartum depression who are prescribed this drug." Exactly how this goal will be addressed remains to be seen.

As patients with heart disease are monitored increasingly by various implanted devices, we're detecting a lot of transient episodes of asymptomatic atrial fibrillation. The problem is whether these episodes put the patient at high enough stroke risk to warrant anticoagulation. In late 2023, two randomized trials addressed this issue.

Dr. Rahul Ganatra: The two studies enrolled patients who had transient episodes of subclinical atrial fibrillation lasting at least 6 minutes and detected by implanted pacemakers, defibrillators, or cardiac monitors. In one study, edoxaban was compared to placebo, and follow-up was about 2 years. In the other study, apixaban was compared to aspirin, and follow-up was about three and a half years. In both studies, the average CHA2DS2-VASc score was four. Combining

the two studies in a meta-analysis, anticoagulation did lower stroke risk by about a third, but the absolute benefit was very small (about three strokes prevented per 1,000 patient years). And as you might guess, anticoagulation increased the risk of bleeding, with about seven excess major bleeding events per 1,000 patient years. There was no significant difference in mortality between the anticoagulated and control groups.

Dr. Allan Brett: By the way, it's important to point out that the annual stroke risk in the control groups in these studies was around 1%, which is substantially lower than stroke risks for people with symptomatic atrial fibrillation whose CHA2DS2-VASc scores are around four.

Dr. Rahul Ganatra: Great point, Allan. So let's review the two major take-home points here. First, subclinical episodes of transient atrial fibrillation seen on extended monitoring do increase the person's stroke risk, but it's substantially less than the stroke risk with clinical atrial fibrillation. And second, anticoagulation does prevent some of those strokes, but the absolute number is very small, and there are about two excess major bleeding events per every stroke prevented.

Dr. Allan Brett: From what I've seen so far, cardiologists are going to vary in how they translate these results into practice. One of our *Journal Watch Cardiology* editors has written that he'll only rarely anticoagulate patients with device-detected atrial fibrillation episodes lasting less than 24 hours, while another cardiology editor has seemed inclined to favor anticoagulation in these patients. And translating this into discussions with patients isn't easy, because a bleeding event and a stroke can't be directly compared. Deficits from strokes can be disabling or they can resolve, and bleeding events can range from easily treatable to life-threatening. It's easy to say, “Well, let's individualize the decision,” but pinpointing an individual patient's precise risk for each of these outcomes is virtually impossible. So I think that in the end, many patients will ask the physician, “What do you think?” And we'll have to work with patients to see how they navigate these uncertainties.

Dr. Rahul Ganatra: But at least, Allan, with the publication of these trials, we do have some reasonably hard numbers that we can share with patients.

Dr. Allan Brett: I agree, Rahul.

Patients with coronary disease are generally advised to take high-intensity statins to lower LDL cholesterol by 50%, but it's unclear whether atorvastatin and rosuvastatin are comparable in secondary prevention of coronary events, and it's unclear whether starting with a moderate dose and titrating upward is just as good as starting with a higher dose. In 2023, a study from South Korea addressed these questions in 4,400 patients with known coronary disease.

Dr. Molly Brett: In this study, patients were randomized either to high-intensity statins, 20 milligrams of rosuvastatin or 40 milligrams of atorvastatin, or to a treat-to-

target group that started with half those doses and titrated up to higher doses if needed to get LDL below 70. At 3 years, the incidence of the combined outcome of death, myocardial infarction, stroke, or coronary revascularization was similar in the two groups. Mean LDL levels also were similar in the two groups, and about half the patients in the treat-to-target group got their LDL cholesterol below 70 while taking moderate rather than high doses.

Dr. Allan Brett: Now, this was one of those two-by-two factorial studies. Patients weren't only randomized to the high dose versus treat-to-target strategies, but they were also randomized to atorvastatin or rosuvastatin. Cardiovascular outcomes, average LDL levels, and most side effects, including myalgias, were similar in the two groups during 3 years of follow-up. But patients who took rosuvastatin were significantly more likely than those who took atorvastatin to develop diabetes (7% versus 5.5%) and slightly more likely to require cataract surgery.

Dr. Molly Brett: So in summary, neither the drug choice, atorvastatin or rosuvastatin, nor the initial dose, high dose or moderate dose, affected important cardiovascular outcomes. Patients concerned about side effects might prefer the more incremental treat-to-target approach, but other patients might prefer going straight to a high intensity statin to limit the need for follow-up visits for drug titration. The choice between the two drugs is mostly a toss-up, but I'm now more likely to pick atorvastatin, which had similar efficacy to rosuvastatin but was associated with lower risk of new onset diabetes and cataract surgery. And by the way, this reminds us that statins generally have been shown to slightly increase risk for developing diabetes.

Dr. Allan Brett: One controversy in perioperative medicine is whether we should avoid giving ACE inhibitors and angiotensin receptor blockers on the day of surgery. The concern comes from a few studies showing that these drugs in particular might increase the risk for intraoperative hypotension. In 2023, this question was addressed in the international POISE-3 study. As an aside, POISE is an acronym for perioperative ischemic evaluation, and listeners might recall the other two POISE trials, important studies that looked at perioperative beta blockers and perioperative aspirin.

Dr. Rahul Ganatra: Allan, in this trial, 7,500 hypertensive patients, most of whom were taking ACE inhibitors or ARBs, were randomized to either a strategy to avoid hypotension, that is holding ACE inhibitors and ARBs on the day of surgery and immediately postoperatively, or a strategy to avoid hypertension, continuing the drugs through these periods. The study showed no difference between groups in 30-day adverse cardiovascular events, but intraoperative hypotension did occur less often when ACE inhibitors or ARBs were held — it was 23% versus 28% when the drugs were continued.

Dr. Allan Brett: What's interesting here is that in the publication of this trial, the authors focus mostly on that primary outcome — no difference in 30-day cardiovascular events — without expressing much concern about the difference in intraoperative hypotension. However, editorialists argued that even though

intraoperative hypotension didn't seem to translate into worse 30-day cardiovascular outcomes, it's still something that shouldn't be ignored.

Dr. Rahul Ganatra: Our editor, Dan Dressler, who covered this study for *Journal Watch*, spoke to several anesthesiologists about this matter, and they suggested an individualized approach, with a couple of examples. For surgeries where there is a high probability of intraoperative blood loss or hemodynamic shifts, skipping the ACE inhibitor or ARB on the day of surgery might lower the chance of severe hypotension sometimes seen in the operating room. But if the patient has a history of difficult-to-control hypertension, or a history of heart failure that's been well-controlled on these drugs, the benefit of continuing them on the day of surgery probably outweighs risk for intraoperative hypertension.

Dr. Allan Brett: Back in 1991, pretty early in my career, the Harvard Medical Practice study was published in the *New England Journal*. It documented a high incidence of medical errors in US hospitals, something that didn't surprise many doctors, but as you'd expect, attracted lots of attention nationally. Since then, a lot has changed in healthcare, with various interventions designed to reduce medical error and to make hospitals less dangerous. But have those interventions made hospital stays safer?

Dr. Rahul Ganatra: To address your question, Allan, researchers published a new retrospective study that assessed the frequency, preventability, and severity of patient harm in a random sample of 2,800 admissions from 11 Massachusetts hospitals during 2018. At least one adverse event, defined as unintended physical injury from medical care that required additional monitoring and treatment or was fatal, occurred in a quarter of admissions, and among the 1,000 adverse events, about a quarter were judged as preventable events, many of them serious. Adverse drug events were the most common, followed by surgical or other procedural events, so-called patient-care events, like falls or pressure ulcers, and hospital acquired infections.

Dr. Allan Brett: We can’t directly compare event rates in this 2023 report with those in the 1991 study, because the newer one only examined events that occurred during hospitalization, while the 1991 study also included outpatient events that led to hospitalization. But on the other hand, the current study used a broader definition of error, and it was done in an era where it’s easier to detect and track certain adverse events.

Dr. Rahul Ganatra: So back to the key question: are hospitals of today safer than they were a few decades ago? Perhaps, but the continued high incidence of in-hospital adverse events suggests that progress has been incremental at best. Developing better approaches to identifying and preventing adverse events, and renewing a commitment to uphold a strong patient safety culture, is essential.

Dr. Molly Brett: I'd just like to add that, although much of the publicity about medical error and patient safety is focused on hospitalized patients, we shouldn't forget about the outpatient setting, where I practice. I think these things can be harder to

identify and analyze in ambulatory care, because it isn't so discreetly limited in time and space like inpatient practice. We may not be creating pressure ulcers or directly causing infections, but inappropriate medication prescribing, diagnostic delay or diagnostic error, and poor communication among clinicians surely are as common in ambulatory care as in hospital practice, and these things can also result in serious but preventable adverse events.

Dr. Allan Brett: Thanks, Molly, for adding that perspective.

Well, we've come to the end of our Year in Review. The three of us have already used a lot of this information in our practices, and I trust that our listeners will do the same. I also want to mention that in the print and online versions of *Journal Watch*, you'll see three additional topics that we didn't have for today: a review of the new 2023 GOLD guideline for management of COPD, an overview of several studies on novel approaches to treatment-resistant depression, and a summary of several studies looking at interventions to preserve cognition in older people. I hope you'll take a look at those.

Rahul and Molly, thank you so much for your input during our discussion today.

Dr. Rahul Ganatra: Thanks, Allan. It was delightful.

Dr. Molly Brett: A great conversation as always.

Dr. Allan Brett: Happy New Year to both of you and to our listeners, and I look forward to doing this again next year.