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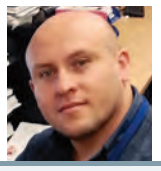

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Clinical Endocrinology News®

Dr. Jun Yang and her father, Li Sheng Yang

Courtesy Dr. Jun Yang

HORMONAL HYPERTENSION
New data challenge status quo

BY MITCHEL L. ZOLER, PhD

Jun Yang, MBBS, had watched as her father, who had battled hypertension for decades, ended up on four medications that still couldn't bring his blood pressure to a healthy level. The cardiovascular endocrinologist then ran some tests, and soon thereafter her father had his blood pressure optimized on just one targeted medication.

Dr. Yang's father turned out to have a hormonal condition known as primary aldosteronism (PA) as the cause of his hypertension.

It turns out that PA is not as rare as once thought.

An eye-catching report in Annals of Internal Medicine this spring of an unexpectedly high prevalence of primary aldosteronism among a diverse cross section of U.S. patients with hypertension has raised issues that could dramatically change the way doctors in America, and elsewhere, assess and manage high blood pressure.

Foremost is the question of whether primary care physicians – the clinicians at the front line for diagnosing and initially treating most patients with hypertension – will absorb and act on this new evidence. For them, aldosteronism doesn't

See **HORMONAL HYPERTENSION** on page **14** ▸

PAY PROPOSAL
Endocrinologists score win in 2021 CMS reimbursement plan

BY ELIZABETH WOODCOCK, MBA, CPC

Amid all the chaos and problems caused by COVID-19, one might hope that physicians would get a break on their complicated payment-reporting programs.

But that's not the case: The government recently released the 2021 proposed rule for the Quality Payment Program (QPP), often referred to by its most popular participation track, the Merit-Based Incentive Payment System (MIPS). The program, which launched in 2017, gets annual updates, and this year is no different.

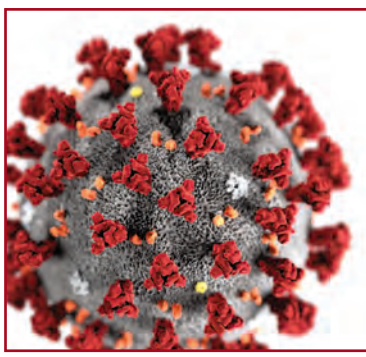
Some good news has made primary care and some other physicians happy.

The government's proposal includes significant changes to reimbursement for all physicians. Most important, the government is boosting rates for the office/outpatient evaluation and management (E/M) codes, combined with simplifying coding requirements.

Specialties that rely heavily on office-based E/M services are delighted at this change. Those include internists, family physicians, neurologists, pulmonologists, dermatologists, and all other specialties that rely heavily on office encounters.

According to the estimates from the Centers for Medicare & Medicaid Services, endocrinologists and rheumatologists are the big winners, at 17% and 16% projected increases, respectively. The government has been pushing to make this shift in reimbursement from surgeries and

See **REIMBURSEMENT** on page **23** ▸



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7: Statins' effects suggest they may be useful as therapy.

8: Risk for severe outcomes with low vitamin D is affirmed in Italian study.

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Higher glycemic time in range may benefit T2D

BY MITCHEL L. ZOLER, PHD
FROM EASD 2020

Patients with type 2 diabetes who stay in a blood glucose range of 70-180 mg/dL at least 70% of the time have the lowest rates of major adverse coronary events, severe hypoglycemic episodes, and microvascular events, according to a post hoc analysis of data collected from 5,774 patients with type 2 diabetes.

Data collected by the DEVOTE trial showed that every additional 10% of the time that a patient with type 2 diabetes (T2D) spent in their target range for blood glucose linked with a significant 6% reduced rate for developing a major adverse cardiovascular event (MACE), Richard M. Bergenstal, MD, said at the virtual annual meeting of the European Association for the Study of Diabetes.

For every 10% increase in time in range (TIR), patients showed an average 10% drop in their incidence of severe hypoglycemic episodes.

Findings from post hoc analyses

These findings confirmed a prior post hoc analysis of data collected in the DCCT trial (NCT00360815), which were published in the New England Journal of Medicine (1993 Sep 30;329[14]:977-86), although those results showed significant relationships between increased TIR and decreased rates of retinopathy and microalbuminuria. For every 10% drop in TIR, retinopathy rose by 64% and microalbuminuria increased by 40%, according to a post hoc analysis of the DCCT data that Dr. Bergenstal helped run and was published in Diabetes Care (2019 Mar;42[3]:400-5).

"It's becoming clear that time in range is an important metric for diabetes management, and our new findings and those previously reported with the DCCT data make it look like time in range is becoming a good marker for clinical outcomes as well," said Dr. Bergenstal, an endocrinologist at the Park Nicollet Clinic in Minneapolis.

He was a coauthor of recommendations that were made in 2019 by an expert panel organized by the Advanced Technologies & Treatments for Diabetes Congress (Diab Care. 2019 Aug;42[8]:1593-603). "We think this will be a good marker to keep glycemia in a safe range, and the results look positive." Patients who stay in the blood glucose range of 70-180 mg/dL (3.9-10.0 mmol/L) at least 70% of the time generally have an hemoglobin A1c of about 7%, which is what makes it a good target for patients and clinicians to focus on. Patients with a 50% TIR rate generally have an HbA1c of about 8%.

But a TIR assessment can be more informative than HbA1c, said the 2019 recommendations. It called TIR assessments "appropriate and useful as clinical targets and outcome measurements that complement A1c for a wide range of people with diabetes."

Mining data from DEVOTE

The analysis run by Dr. Bergenstal and his associates used data from 5,774 of the 7,637 patients enrolled in the DEVOTE trial, for whom adequate longitudinal blood glucose data were available to derive and track TIR. DEVOTE had the primary aim of comparing two different types of insulin in patients with T2D, according to its explanation in the New England Journal of Medicine (2017 Aug 24;377[8]:723-32). The DEVOTE patients did not undergo routine continuous blood glucose monitoring, so derivation of TIR was the only option with the dataset, Dr. Bergenstal said. "We're trying to get continuous blood monitoring into T2D trials," he said.

The post hoc analysis showed that, during the study's follow-up of just under 2 years, patients who maintained a derived TIR of 70%-100% had about a 6% MACE rate, which peaked at nearly twice that in patients whose TIR was 30% or less. The analysis showed a roughly positive linear relationship between TIR and MACE rates across the range of TIR values. In an adjusted analysis, patients with at least a 70% TIR had a significant 31% lower rate of MACE events, compared with patients whose TIR was 50% or less.

DEVOTE was funded by Novo Nordisk. Dr. Bergenstal has had financial relationships with Novo Nordisk and several other companies.

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SOURCE: Bergenstal RM et al. EASD 2020, Abstract 159.

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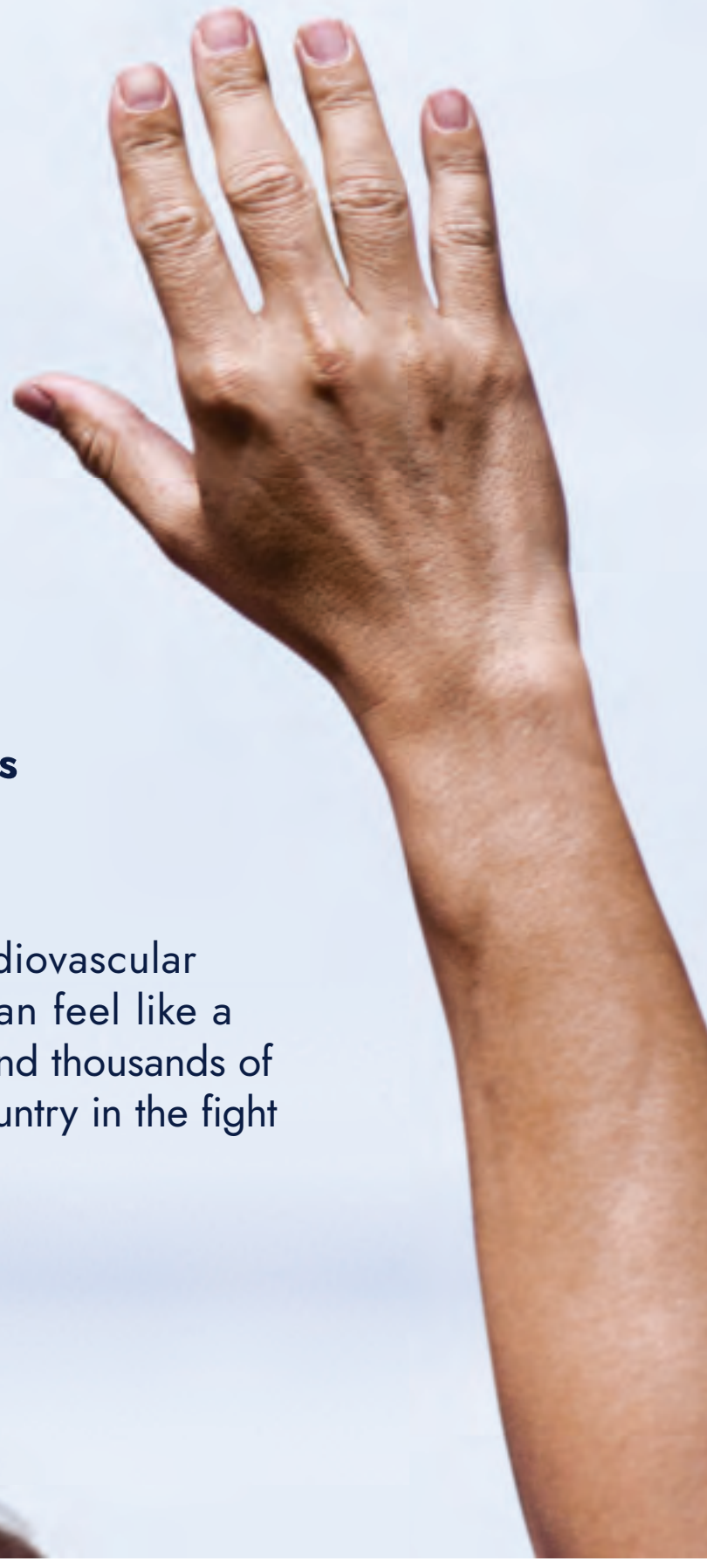

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No prior insulin tied to postsurgical T2D remission

BY SARA FREEMAN
FROM EASD 2020

Type 2 diabetes patients who had never used insulin showed sustained remission 10 years after bariatric surgery in a prospective study of 85 patients.

Having diabetes for less than 5 years was also predictive of achieving long-term diabetes remission, Diego Moriconi, MD, of the University of Pisa (Italy) and presenting study investigator, reported at the virtual annual meeting of the European Association for the Study of Diabetes.

> "Glycemic control improved with time in all the three groups after bariatric surgery, although **more markedly so in the remission group.**"

"Weight loss was associated with type 2 diabetes remission 1 year after surgery, but it had no impact on the long-term relapse of diabetes," Dr. Moriconi said.

The findings are important, commented Tina Vilsbøll, MD, DMSc, chief consultant at the Steno Diabetes Centre Copenhagen, who chaired the session. They're important because they would help "to set the expectations for patients before they have surgery, what to expect in respect to resolution or remission of diabetes."

Dr. Moriconi reported the findings of an observational study that had started in 2006 and recruited individuals about to undergo bariatric surgery for type 2 diabetes. Participants were evaluated before surgery and every 6-12 months after, undergoing various clinical and laboratory investigations, for a period of 10 years.

The majority of the recruited patients (76%) were women. Most (also 76%) had undergone gastric bypass (Roux-en-Y) surgery, and the remainder had undergone sleeve gastrectomy. Both types of surgery were equally as good at getting people into remission, as defined by the American Diabetes Association Standards of Medical Care in Diabetes, Dr. Moriconi said. As such, remission was achieved if the fasting blood glucose fell below 100 mg/dL and the hemoglobin A1c below 5.7%.

In the first year following surgery, 75% of patients had met diabetes remission criteria. This fell to 61% of patients after 5 years, and to 55% at 10 years. At each of these time points, 25% of patients had type 2 diabetes, with 14% relapsing back at 5 years and 20% at 10 years.

Dr. Moriconi pointed out some of the different characteristics of the group of 47 patients who had achieved diabetes remission at 10 years, compared with the 17 who had "relapsed" back to having type 2 diabetes and the 21 who had remained with type 2 diabetes.

The decrease in body mass index achieved at 10 years was no different between the three groups. However, 1 year after surgery, there had been a significantly greater drop in BMI in those who achieved remission, compared with those who did not ($P = .04$).

"Glycemic control improved with time in all the three groups after bariatric surgery, although more markedly so in the remission group," Dr. Moriconi said.

He highlighted how none of the patients who had achieved remission had used insulin, whereas 12% of those who had relapsed and half (52%) of those who remained with type 2 diabetes had used insulin ($P < .0001$).

Patients who achieved remission at 1, 5, and 10 years were more likely to have had diabetes for less than 5 years than those who remained with type 2 diabetes. The average duration of diabetes was 2 years in those achieving remission versus 8 years in those who had relapsed and 13 years in those who had remained diabetic ($P < .0001$).

Logistic regression analysis, which adjusted for all major confounding factors such as age, sex, and type of surgery, showed that the duration of diabetes and insulin therapy before surgery were the only predictors of long-term diabetes remission.

The study had no commercial funding. Dr. Moriconi and Dr. Vilsbøll had no conflicts of interest to disclose.

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SOURCE: Moriconi D. EASD 2020, Oral presentation 120.

Vascular dementia risk 35% higher in diabetes

BY SARA FREEMAN
FROM EASD 2020

Persons with type 2 diabetes may be at heightened risk for developing vascular dementia than other types of dementia, a team of international researchers has found.

Compared with a nondiabetic control population, those with type 2 diabetes had a statistically significant 35% increased chance of having vascular dementia in a large observational study.

By comparison, the risk for nonvascular dementia was increased by a "more modest" 8%, said the researchers from the University of Glasgow and the University of Gothenburg (Sweden), while the risk for Alzheimer's dementia appeared to be reduced by 8%.

The link between type 2 diabetes and dementia is not new, observed Carlos Celis-Morales, PhD, who presented the study's findings at the virtual annual meeting of the European Association for the Study of Diabetes. With people living longer thanks to improved preventative strategies and treatments, there is a risk for developing other chronic conditions, such as dementia.

"A third of all dementia cases may be attributable to modifiable risk factors, among them type 2 diabetes, which accounts for 3.2% of all dementia cases," said Dr. Celis-Morales, a research fellow at the University of Glasgow's Institute of Cardiovascular and Medical Sciences.

"Although we know that diabetes is linked to dementia, what we don't know really well is how much of this association [is] explained by modifiable and nonmodifiable risk factors," Dr. Celis-Morales added.

"Diabetes and dementia share certain risk factors," commented coinvestigator Naveed Sattar, MD, in a release issued by the EASD. These include obesity, smoking, and lack of physical activity and might explain part of the association between the two conditions.

Using data from the Swedish National Diabetes Register, the research team set out to determine the extent to which type 2 diabetes was associated with dementia and the incidence of different subtypes of dementia. They also looked to see if there were any associations with blood glucose control and what risk factors may be involved.

In total, data on 378,299 individuals with type 2 diabetes were compared with data on 1,886,022 similarly aged (average, 64 years) and gender-matched controls from the general population.

Courtesy Dr. Carlos Celis-Morales

Dr. Carlos Celis-Morales

After a mean 7 years of follow-up, 10,143 people with and 46,479 people without type 2 diabetes developed dementia. Nonvascular dementia was the most common type of dementia recorded, followed by Alzheimer's disease and then vascular dementia.

"Within type 2 diabetes individuals, poor glycemic [control] increased the risk of dementia especially for vascular dementia and nonvascular dementia. However, these associations were not as evident for Alzheimer's disease," Dr. Celis-Morales reported.

Comparing those with hemoglobin A1c of less than 52 mmol/mol (7%) with those whose A1c was above 87 mmol/mol (10.1%), there was 93% increase in the risk for vascular dementia, a 67% increase in the risk for nonvascular dementia, and a 34% higher risk for Alzheimer's disease–associated dementia.

The study was financed by the Swedish state as well as grant from the Novo Nordisk Foundation and the Swedish Association of Local Authorities and Regions. Dr. Celis-Morales and Dr. Sattar had no conflicts of interest.

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SOURCE: Celis-Morales C et al. EASD 2020, Oral presentation 6.

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- Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer

Limitations of Use:

UNITHROID is not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients as there are no clinical benefits and overtreatment with UNITHROID may induce hyperthyroidism. UNITHROID is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

IMPORTANT SAFETY INFORMATION

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Thyroid hormones, including UNITHROID, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Contraindication

UNITHROID is contraindicated in patients with uncorrected adrenal insufficiency.

Warnings and Precautions

- Overtreatment with UNITHROID may cause an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias particularly in patients with cardiovascular disease and in elderly patients. Initiate UNITHROID therapy at lower doses than those recommended in younger individuals or in patients without cardiac disease.
- Coronary artery disease: Patients receiving suppressive UNITHROID therapy should be monitored closely during surgical procedures for cardiac arrhythmias. Also, monitor patients during concomitant administration of UNITHROID and sympathomimetic agents for signs and symptoms of coronary insufficiency.
- Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements.

Adverse Reactions

- Common adverse reactions for UNITHROID are primarily those of hyperthyroidism due to therapeutic overdosage: arrhythmias, myocardial infarction, dyspnea, muscle spasm, headache, nervousness, irritability, insomnia, tremors, muscle weakness, increased appetite, weight loss, diarrhea, heat intolerance, menstrual irregularities, and skin rash.
- Pediatric Patients: Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in pediatric patients receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in pediatric patients with resultant compromised adult height.

Please see brief summary of Full Prescribing Information, including Boxed Warning, on the following page.

References: 1. UNITHROID [package insert]. **2.** US Food and Drug Administration. Guidance for Industry: levothyroxine sodium products enforcement of August 14, 2001, compliance date and submission of new applications. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/levothyroxine-sodium-products-enforcement-august-14-2001-compliance-date-and-submission-new. Updated July 2001. Accessed May 21, 2020.

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- Coronary artery disease: Patients receiving suppressive UNITHROID therapy should be monitored closely during surgical procedures for cardiac arrhythmias. Also, monitor patients during concomitant administration of UNITHROID and sympathomimetic agents for signs and symptoms of coronary insufficiency.
- Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of UNITHROID from the gastrointestinal tract. Use of oral thyroid hormone drug products is not recommended. Administer intravenous thyroid hormone products to treat myxedema coma.
- Acute adrenal crisis in patients with concomitant adrenal insufficiency: Thyroid hormone increases metabolic clearance of glucocorticoids. Initiation of thyroid hormone therapy prior to initiating glucocorticoid therapy may precipitate an acute adrenal crisis in patients with adrenal insufficiency.
- UNITHROID has a narrow therapeutic index. Titrate the dose of UNITHROID carefully and monitor response to titration to avoid effects associated with UNITHROID. Monitor for the presence of drug or food interactions when using UNITHROID and adjust the dose as necessary.
- Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing UNITHROID.
- Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly in post-menopausal women. To minimize this risk, administer the minimum dose of UNITHROID that achieves the desired clinical and biochemical response.

---------- ADVERSE REACTIONS ----------

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---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Since TSH levels may increase during pregnancy, TSH should be monitored and UNITHROID dosage adjusted during pregnancy. UNITHROID should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

Please note that this information is not comprehensive. Visit https://unithroidhcp.com for Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Specialty, a division of Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Obesity boosts risks from diagnosis to death

BY RANDY DOTINGA
FROM OBESITY REVIEWS

A new analysis of existing research confirms a stark link between excess weight and COVID-19: People with obesity are much more likely to be diagnosed with the novel coronavirus, undergo hospitalization and ICU admission, and die.

Obese patients faced the greatest bump in risk on the hospitalization front, with their odds of being admitted listed as 113% higher than nonobese patients. Furthermore, the odds of diagnosis, ICU admission, and death were 46%, 74%, and 48% higher, respectively. All differences were highly significantly different, investigators reported in a systematic review and meta-analysis published online in Obesity Reviews.

"Essentially, these are pretty scary statistics," nutrition researcher and study lead author Barry M. Popkin, PhD, of the University of North Carolina at Chapel Hill School of Public Health, said in an interview. "Other studies have talked about an increase in mortality, and we were thinking there'd be a little increase like 10% – nothing like 48%."

According to the Johns Hopkins University of Medicine tracker, nearly 6 million people in the United States had been diagnosed with COVID-19 as of Aug. 30. The number of deaths had surpassed 183,000.

The authors of the new review launched their project to better understand the link between obesity and COVID-19 "all the way from being diagnosed to death," Dr. Popkin said, adding that the meta-analysis is the largest of its kind to examine the link.

Dr. Popkin and colleagues analyzed 75 studies during January-June 2020 that tracked 399,461 patients (55% male) diagnosed with COVID-19. They found that 18 of 20 studies linked obesity with a 46% higher risk of diagnosis, but Dr. Popkin cautioned that this may be misleading. "I suspect it's because they're sicker and getting tested more for COVID," he said. "I don't think obesity enhances your likelihood of getting COVID. We don't have a biological rationale for that."

The researchers examined 19 studies that explored a link between obesity and hospitalization; all 19 found a higher risk of hospitalization in patients with obesity (pooled odds ratio, 2.13). Twenty-one of 22 studies that looked at ICU admissions discovered a higher risk for patients with obesity (pooled OR, 1.74). And 27 of 35 studies that examined COVID-19 mortality found a higher death rate in patients with obesity (pooled OR, 1.48).

The review also looked at 14 studies that examined links between obesity and administration of invasive mechanical ventilation. All showed a significantly higher risk for patients with obesity (pooled OR, 1.66).

Could socioeconomic factors explain the difference in risk for people with obesity? It's not clear. According to Dr. Popkin, most of the studies don't examine factors such as income. On the biological front, it appears that "the immune system is much weaker if you're obese," he said, and excess weight may worsen the course of a respiratory disease such as COVID-19 because of lung disorders such as sleep apnea.

The researchers noted that "potentially the vaccines developed to address COVID-19 will be less effective for individuals with obesity due to a weakened immune response." They pointed to research that suggests T-cell responses are weaker and antibody titers wane at a faster rate in people with obesity who are vaccinated against influenza.

Pulmonologist Joshua L. Denson, MD, MS, of Tulane University, New Orleans, noted in an interview that he's seen about 100 patients with COVID-19, and many are obese and have metabolic syndrome.

Like the authors of the study, he believes higher levels of inflammation play a crucial role in making these patients more vulnerable. "For whatever reason, the virus tends to really like that state. That's driving these people to get sick," he said.

The review was funded by the Carolina Population Center, World Bank, and Saudi Health Council. The authors and Dr. Denson report no relevant disclosures.

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SOURCE: Popkin BM et al. Obes Rev. 2020 Aug 26. doi: 10.1111/obr.13128.

Statins linked to reduced mortality in meta-analysis

BY MEGAN BROOKS

TREATMENT WITH STATINS was associated with a reduced risk of a severe or fatal course of COVID-19 by 30%, a meta-analysis of four published studies has shown.

In the analysis that included almost 9,000 COVID-19 patients, there was a significantly reduced risk for fatal or severe COVID-19 among patients who were users of statins, compared with nonusers (pooled hazard ratio, 0.70; 95% confidence interval, 0.53-0.94).

Based on the findings, "it may be time we shift our focus to statins as the potential therapeutic options in COVID-19 patients," authors Syed Shahzad Hasan, PhD, University of Huddersfield (England), and Chia Siang Kow, MPharm, International Medical University, Kuala Lumpur, Malaysia, said in an interview.

The study was published online in The American Journal of Cardiology (2020 Aug 11. doi: 10.1016/j.amjcard.2020.08.004).

Moderate- to good-quality data analyzed

The analysis included four studies published up to July 27 of this year. Eligible studies included those with a cohort or case-control designs, enrolled patients with confirmed COVID-19, and had data available allowing comparison of the risk of severe illness and/or mortality among statin users versus nonusers in adjusted analyses, the authors noted.

The four studies – one of "moderate" quality and three of "good" quality – included a total of 8,990 COVID-19 patients.

In the pooled analysis, there was a significantly reduced risk for fatal or severe COVID-19 of 30% with use of statins, compared with non-use. Their findings also "discredited the suggestion of harms with the use of statins in COVID-19 patients," the authors concluded.

Based on the results, "moderate- to high-intensity statin therapy is likely to be beneficial" in patients with COVID-19, they said, while cautioning that more data from prospective studies are needed to substantiate the findings and to determine the appropriate regimen for a statin in COVID-19 patients.

Yibin Wang, PhD, of the University of California, Los Angeles, said that "this is a very simple meta-analysis from four published studies which consistently reported a protective or neutral effect of statin usage on mortality or severe complications in COVID-19 patients."

Although the scope of this meta-analysis was "quite limited, the conclusion was not unexpected, as most of the clinical analysis so far reported supports the benefits or safety of statin usage in COVID-19 patients," he said in an interview.

Nonetheless, questions remain

Although there is "almost no dispute" about the safety of continuing statin therapy in COVID-19 patients, it remains to be determined if statin therapy can be implemented as an adjuvant or independent therapy and a part of the standard care for COVID-19 patients regardless of their hyperlipidemia status, said Dr. Wang, who was not associated with Dr. Hasan's and Mr. Kow's research.

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"While statin usage is associated with several beneficial effects such as anti-inflammation and cytoprotection, these effects are usually observed from long-term usage rather than short-term/acute administration. Therefore, prospective studies and randomized trials should be conducted to test the efficacy of statin usage for COVID-19 patients with mild to severe symptoms," he noted.

Dr. Hasan, Mr. Kow, and Dr. Wang disclosed no relationships relevant to this research.

A version of this article originally appeared on Medscape.com.

Low vitamin D levels in COVID-19 predicts poor survival

BY MARLENE BUSKO
FROM ASBMR 2020

Having low serum vitamin D levels was an independent risk factor for having symptomatic COVID-19 with respiratory distress requiring admission to intensive care – as opposed to having mild COVID-19 – and for not surviving, in a new study from Italy.

"Our data give strong observational support to previous suggestions that reduced vitamin D levels may favor the appearance of severe respiratory dysfunction and increase the mortality risk in patients affected with COVID-19," the researchers report.

Zbynek Pospisil/Getty Images

Luigi Gennari, MD, PhD, Department of Medicine, Surgery, and Neurosciences, University of Siena (Italy), presented these findings during the virtual American Society of Bone and Mineral Research 2020 annual meeting.

He said in an interview that this analysis suggests determining vitamin D levels (25 hydroxyvitamin D) in people testing positive for SARS-Cov-2 infection might help predict their risk of severe disease.

"I believe that, particularly in the winter season, the use of vitamin D supplementation and correction of vitamin D deficiency might be of major relevance for the reduction of the clinical burden of the ongoing and future outbreaks of SARS-CoV-2 infection," he added.

JoAnn E. Manson, MD, DrPH, of Harvard Medical School and Brigham and Women's Hospital, both in Boston, who was not involved with the research, commented that "We know from several studies that a low vitamin D level is associated with a higher risk of having COVID-19 and severe illness, but correlation does not prove causation."

"Improving vitamin D status is a promising way to reduce the risk of severe illness, but we need randomized controlled trials to prove cause and effect," she said in an interview.

Dr. Gennari said several lines of evidence suggest that vitamin D deficiency might be a risk factor for COVID-19 severity.

Countries with lower average levels of vitamin D or lower UVB radiation exposure have higher COVID-19 mortality, and "demographic groups known to be at higher risk of vitamin D deficiency (such as Black individuals, older people, nursing home residents, and those with obesity and diabetes) are at high risk of COVID-19 hospitalization/mortality, he noted.

To examine the relationship between vitamin D levels and COVID-19 severity/mortality, the researchers studied three groups:

- 103 symptomatic patients with COVID-19 with respiratory insufficiency admitted to a Milan hospital from March 9 to April 30.
- 52 patients with mild COVID-19, recruited from patients and staff from a nearby nursing home who had a positive test for COVID-19.
- 206 healthy controls, matched 2:1 with symptomatic patients of the same age, weight, and gender, from 3,174 patients who had vitamin D measured during a routine check-up from January to March 2020.

Patients in the hospitalized group had lower mean vitamin D levels (18.2 ng/mL) than those with mild COVID-19 (30.3 ng/mL) or those in the control group (25.4 ng/mL).

Patients with symptomatic versus mild COVID-19 were slightly older and more likely to have at least one comorbidity and less likely to be taking a vitamin D supplement at baseline (30% vs 79%).

Among symptomatic patients, mean vitamin D levels were inversely associated with interleukin (IL)-6 and C-reactive protein, "both of which are a direct expression of the inflammatory status," Dr. Gennari noted.

About half of the hospitalized patients (49) were admitted and discharged after a mean stay of 16 days (none died). The other 54 hospitalized patients were admitted to the intensive care unit with severe acute respiratory distress; 38 patients received continuous positive airway pressure, and 16 patients received endotracheal intubation.

Of the 54 patients admitted to ICU, 19 patients died from respiratory distress after a mean of 19 days, "consistent with the literature," and the other 35 patients were discharged after a mean of 21 days.

Patients with severe COVID-19 who were admitted to the ICU, as opposed to a ward, were more likely to be male, have at least one comorbidity, higher baseline IL-6 levels and neutrophil counts, and lower lymphocyte and platelet counts.

They also had lower mean vitamin D levels (14.4 vs. 22.4 ng/mL) and were more likely to have vitamin D deficiency (<20 ng/mL; 80% vs. 45%).

Patients admitted to ICU who died had lower baseline vitamin D levels than those who survived (13.2 vs. 19.3 ng/mL).

Vitamin D levels were inversely associated with respiratory distress requiring ICU admission (odds ratio, 1.06; $P = .038$) and with mortality (OR, 1.18, $P = 029$), independent of IL-6 levels and other comorbidities.

Dr. Gennari and Dr. Manson had no relevant financial disclosures.

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Longer bisphosphonate use ups AFF risk, but not all is tied to drug

BY MARLENE BUSKO
FROM ASBMR 2020

IN A NATIONAL STUDY of older Danes who had previously had a fracture and were taking bisphosphonates, the risk of having a serious though rare atypical femoral fracture (AFF) was greater after 3-5 years of bisphosphonate use.

The risk quickly dropped after patients stopped taking a bisphosphonate, which suggests that bisphosphonate "holidays" may be useful for some patients, the researchers said. These findings support previous work.

But the study also found that 34% of the AFFs occurred in patients who had not been taking a bisphosphonate. That rate is higher than the 6%-22% that has been reported by others.

Doug Bauer, MD, from the University of California, San Francisco, presented the study findings during the virtual American Society of Bone and Mineral Research 2020 annual meeting.

"We found no clear risk factor that accounts for this increased risk [for AFFs] among those not exposed to bisphosphonates," he said, "but we believe this was a real finding, as our study protocol ensured that the study radiologists were completely blinded to treatments received."

The clinical implications of research to date are that "the risk of AFF should not dissuade patients and providers from short-term use of bisphosphonates [3-5 years]," Dr. Bauer said.

AFF is serious but rare complication

"Since first reported over 10 years ago, it has become clear that AFFs are a rare but serious complication of bisphosphonate therapy," Dr. Bauer explained. However, there is still uncertainty about the magnitude of this risk, including the absolute risk for AFFs among adults who take bisphosphonates and those who do not.

To study this, the researchers analyzed data from national health care and pharmacy records and a radiology image database in Denmark. They identified almost 5,000 adults who were aged 50 years or older and who experienced a subtrochanteric and femoral shaft fracture during the period from 2010 to 2015. Two expert radiologists who were blinded to the patients' clinical history or treatment identified AFF on the basis of ASBMR 2014 criteria.

The researchers compared three patient groups: 189 patients with AFF, 2,397 patients with typical subtrochan-

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teric and femoral shaft fractures (no AFF), and 35,946 adults aged older than 50 years (control persons).

Compared with patients with typical fractures, patients with AFF were younger (aged 71 vs. 77), more likely to be women (79% vs. 69%), and more likely to have RA (12% vs. 2.5%).

Compared with patients in the other two groups, those with AFF were more likely to use corticosteroids, proton pump inhibitors (PPIs), statins, and hormone-replacement therapy.

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They were also more likely to use bisphosphonates (58%) than patients with typical subtrochanteric and femoral shaft fractures (19%) or control patients (10%).

The bisphosphonates used in Denmark at the time were mostly alendronate (85%) and rarely ibandronate (6%), intravenous zoledronic acid (5%), etidronate (3%), or risedronate (1%).

One-third of patients with AFFs had no bisphosphonate exposure

In this national cohort of adults aged older than 50 years, the absolute rates of AFF per 10,000 person-years were as follows: 0.07 in nonusers of bisphosphonates, 1.84 in those with 3-5 years of bisphosphonate use, and 4.63 in those with >7 years of bisphosphonate use. As a comparison, the rate of classic hip fracture was 43.8 per 10,000 person-years.

Compared with no bisphosphonate use, the relative risk for AFF was close to 40 times higher with more than 7 years of use, after adjustment for multiple confounders. The risk for AFF was also significantly higher among patients with RA or hypertension and for those who used PPIs.

"Note that age, gender, and previous fracture were not associated with the risk of AFF" after controlling for multiple confounders, Dr. Bauer stressed.

The relative risk for AFF fell significantly after it had been withheld from use for more than 1 year.

Among the 189 patients with confirmed AFF, 64 patients (34%) had never taken a bisphosphonate.

Preliminary analysis showed that, of patients with AFF, those who had not been exposed to bisphosphonates were younger, more likely to be male, and less likely to have had a previous fracture, RA, or to have used corticosteroids, PPIs, statins, or hormone-replacement therapy.

The study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Bauer had no disclosures.

A version of this article originally appeared on Medscape.com.

Empagliflozin's HFrEF benefit solidifies class effects

BY MITCHEL L. ZOLER, PHD
FROM ESC CONGRESS 2020

The SGLT2-inhibitor drug class solidified its role as a major, new treatment for patients with heart failure with reduced ejection fraction and no diabetes, with results from a second large, controlled trial showing clear efficacy and safety in this population.

Patients with heart failure with reduced ejection fraction (HFrEF) treated with the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (Jardiance) had a statistically significant 25% relative cut in their incidence of cardiovascular death or first heart failure hospitalization, compared with placebo-treated controls when added on top of standard HFrEF treatment, and this benefit was consistent regardless of whether the treated patients also had type 2 diabetes, Milton Packer, MD, reported at the virtual annual congress of the European Society of Cardiology.

> "Early uptake in U.S. practice has been very slow, with findings from large U.S. patient registries suggesting that **perhaps 1% of suitable HFrEF patients currently get the drug.**"

This 25% drop in the primary endpoint with empagliflozin treatment in the EMPEROR-Reduced trial exactly matched the cut in incidence of cardiovascular death or heart failure hospitalization produced by treatment with a another SGLT2 inhibitor, dapagliflozin (Farxiga), in the DAPA-HF trial (N Engl J Med. 2019 Nov 21;381[21]:1995-2008).

The performance of these two SGLT2 inhibitors was "incredibly consistent" across the their respective trials run in HFrEF patients with and without type 2 diabetes, and the combined evidence base of the two trials makes for "really compelling evidence" of both safety and efficacy that should prompt a change to U.S. practice, with both of these drugs forming a new cornerstone of HFrEF treatment, Dr. Packer said.

Results plant drug class firmly as HFrEF treatment

Dr. Packer stressed in his presentation that optimal treatment of patients with HFrEF now demands use of one of these two SGLT2 inhibitors, as well as sacubitril plus valsartan (Entresto), a beta-blocker, and a mineralocorticoid receptor antagonist, plus a diuretic as a fifth drug class for the many HFrEF patients who also need treatment for fluid overload. He further advocated for rapid introduction of these four cornerstone agents with proven survival benefits once a patient receives a HFrEF diagnosis, suggesting that sacubitril plus valsartan, an SGLT2 inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist could all be initiated within 6 weeks or less while acknowledging that optimal up-titration of the beta-blocker would likely take longer.

The order in which a patient starts these drugs shouldn't matter, and there currently seems to be no evidence that clearly points toward using either dapagliflozin or empagliflozin over the other, Dr. Packer added.

Physicians who care for heart failure patients have their own history of dragging their feet when adding new drugs to the regimens HFrEF patients receive. The angiotensin-converting enzyme inhibitors and beta-blockers took about 17 years each to start reaching a majority of U.S. HFrEF patients, and sacubitril plus valsartan is now used on perhaps a quarter to a third of HFrEF patients despite receiving Food and Drug Administration approval for these patients in mid-2015, noted Christopher M. O'Connor, MD, a heart failure specialist and president of the Inova Heart and Vascular Institute in Fairfax, Va.

Despite dapagliflozin receiving FDA approval in May 2020 for treating HFrEF in patients without diabetes, "early uptake in U.S. practice has been very slow, with findings from large U.S. patient registries suggesting that perhaps 1% of suitable HFrEF patients currently get the drug," estimated Dr. O'Connor in an interview.

Given how strong the evidence now is for benefit and safety from dapagliflozin and empagliflozin, it may take as little as 5 years to reach greater than 50% penetration of one of these drugs into U.S. HFrEF patient populations, suggested Dr. Packer, a distinguished scholar in cardiovascular science at Baylor University Medical Center in Dallas.

Primary outcome significant, with reassuring renal protection

The road to routine use of these SGLT2 inhibitor drugs should be hastened by empagliflozin's impressive performance in EMPEROR-Reduced, in which the drug scored highly significant benefits over placebo for the prespecified primary and two major secondary endpoints, one of which was a measure of preserved renal function.

The trial randomized 3,730 patients at 520 sites in 20 countries during 2017-2019 and followed them on treatment for a median of 16 months. All patients had a left ventricular ejection fraction of 40% or less, and roughly three-quarters had New York Heart Association (NYHA) class II function, nearly one-quarter had class III function, and fewer than 1% of patients fell into the class IV category.

The primary endpoint occurred in 19% of the empagliflozin-treated patients and in 25% of those who received placebo. Among the half of patients with diabetes in the trial, the relative risk reduction by empagliflozin compared with placebo was a statistically significant 28%; among those without diabetes, it was a statistically significant 22%. Concurrently with Dr. Packer's report, the results appeared in an article posted online in the New England Journal of Medicine.

Mitchel L. Zoler/MDedge News

Optimal treatment of patients with HFrEF now demands use of either empagliflozin or dapagliflozin, Dr. Milton Packer stressed at the ESC meeting.

The study also had two main prespecified secondary endpoints: the incidence of total hospitalizations for heart failure, both first and recurrent, which fell by 30% in the empagliflozin-treated patients, compared with placebo, and the rate of declining renal function during the 16 months of the study as measured by estimated glomerular filtration rate, which dropped by roughly 1 mL/min per 1.73 m^2 among the empagliflozin recipients and by about 4 mL/min/ per 1.73 m^2 in the placebo patients.

Treatment with empagliflozin also achieved a notable, statistically significant 50% drop in major adverse renal events, consistent with the performance of other drugs in the class.

"Renal protection is a big plus" of empagliflozin in this trial and from the other SGLT2 inhibitors in prior studies, noted Dr. O'Connor.

The EMPEROR-Reduced results also showed an important benefit for HFrEF patients from empagliflozin not previously seen as quickly with any other drug class, noted Dr. Packer. The SGLT2 inhibitor led to a statistically significant slowing in the progression of patients from NYHA class II function to class III, compared with placebo, and it also significantly promoted the recovery of patients from NYHA class III to class II, an effect that became apparent within the first month on treatment and a benefit that is a "big deal" for patients because it represents a "significant change in functional capacity." This additional dimension of empagliflozin's benefit "really impressed me," Dr. Packer said.

EMPEROR-Reduced was funded by Boehringer Ingelheim and Eli Lilly, the companies that market empagliflozin. Dr. Packer has received personal fees from Boehringer Ingelheim and Eli Lilly and from several other companies. Dr. O'Connor had no relevant disclosures.

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SOURCE: Packer M. ESC 2020. N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190.

Final EVAPORATE results for Vascepa raise eyebrows

BY PATRICE WENDLING

Final 18-month results of the EVAPORATE trial suggest icosapent ethyl (Vascepa) provides even greater slowing of coronary plaque progression when added to statins for patients with high triglyceride levels, but not all cardiologists are convinced.

The study was designed to explore a potential mechanism behind the cardiovascular event reduction in REDUCE-IT. Previously reported interim results showed that, after 9 months, the pharmaceutical-grade omega-3 fatty acid formation significantly slowed the progression of several plaque types but not the primary endpoint of change in low-attenuation plaque volume on multidetector CT.


Dr. Budoff

From baseline to 18-month follow-up, however, the primary endpoint was significantly reduced by 17% in the icosapent ethyl group, whereas low-attenuation plaque volumes increased by 109% in the placebo group ($P = .006$).

Significant declines were also seen with icosapent ethyl 4 g/day versus the mineral oil placebo for all other plaque types except dense calcium after adjustment for age, sex, diabetes, hypertension, and triglyceride levels at baseline. Dense calcium changed by –1% versus 15% for placebo; fibro-fatty changed by –34% versus 32%; fibrous, –20% versus 1%; noncalcified, –19% versus 9%; and total plaque, –9% versus 11%.

The results parallel nicely with recent clinical data from REDUCE-IT REVASC, in which icosapent ethyl 4 g/day provided a very early benefit.

The results parallel nicely with recent clinical data from REDUCE-IT REVASC, in which icosapent ethyl 4 g/day provided a very early benefit on first revascularization events that reached statistical significance after only 11 months (hazard ratio, 0.66), principal investigator Matthew Budoff, MD, director of cardiac CT at Harbor–University of California, Los Angeles, Medical Center in Torrance, Calif., said during the virtual annual congress of the European Society of Cardiology.

The findings were published simultaneously in the European Heart Journal (2020 Aug 29. doi: 10.1093/eurheartj/ehaa652).

Was the placebo 'clean'?

Concerns were raised previously over the possibility that the mineral oil placebo used in both EVAPORATE and REDUCE-IT could be having ill effects, notably, by increasing LDL cholesterol and C-reactive protein levels.

In an interview, Steven Nissen, MD, chair of cardiovascular medicine at the Cleveland Clinic, who has been among the critics of the mineral oil placebo, questioned the plaque progression over the 18 months.

"I've published more than a dozen regression/progression trials, and we have never seen anything like this in a placebo group, ever," he said. "If this was a clean placebo, why would this happen in a short amount of time?

"I'm concerned this is all about an increase, in the case of REDUCE-IT, in morbidity and mortality in the placebo group, and in the EVAPORATE trial, an increase in plaque in the placebo group," Dr. Nissen said. "So this raises serious doubts about whether there is any benefit to icosapent ethyl."

Asked about the 109% increase, Dr. Budoff said in an interview that low-attenuation plaque represents a much smaller quantity of overall plaque volume. "So the percentages might be exaggerated if you look at just percentage change because they're small volumes."

He also noted that previous trials that evaluated atherosclerosis progression used intravascular ultrasound (IVUS), whereas EVAPORATE is the first to make the transition to CT angiography–based analysis of plaque progression.

"I would point out that Dr. Nissen has only worked on intravascular ultrasound, which, while it's parallel in its ability to measure plaque, measures different volumes and measures it in a totally different way," said Dr. Budoff.

Amarin provided funding and drug for the trial. Dr. Budoff has received research funding from and has served as a speaker for Amarin and several other pharmaceutical firms.

A version of this article originally appeared on Medscape.com.

Evolocumab safe, effective in pediatric familial hypercholesterolemia

BY SUE HUGHES

THE PCSK9 MONOCLONAL antibody evolocumab (Repatha) was well tolerated and effectively lowered LDL cholesterol by 38% compared with placebo in a randomized controlled trial in pediatric patients with heterozygous familial hypercholesterolemia (FH) already taking statins with or without ezetimibe.

"HAUSER-RCT is the largest study and the first placebo-controlled randomized trial of a PCSK9 inhibitor in pediatric FH," senior author Daniel Gaudet, MD, PhD, Universite de Montreal, said in an interview. "The study showed good safety and efficacy of the drug in this population, with an excellent 44% reduction in LDL cholesterol compared with 6% in the placebo group."

The trial also found evolocumab to be well tolerated in this group, with adverse effects similar in the active and placebo groups.

"Some people have wondered about using a drug with a monthly injection in a pediatric population, but this was not an issue in our study," Dr. Gaudet said. "The idea of a monthly injection was well received, and no patient withdrew because of this."

The HAUSER-RCT trial was presented on Aug. 29 at the virtual annual congress of the European Society of Cardiology and simultaneously published online in the New England Journal of Medicine (doi: 10.1056/NEJMoa2019910).

"With patients recruited from 23 countries in five continents, the study provides an accurate picture of the safety and efficacy of evolocumab in pediatric FH patients worldwide," Dr. Gaudet said.

The 24-week, randomized, double-blind, placebo-controlled trial involved 157 patients aged 10-17 years with heterozygous FH already taking statins with or without ezetimibe and who had an LDL cholesterol level of 130 mg/dL or more and a triglyceride level of 400 mg/dL or less.

They were randomly assigned in a 2:1 ratio to receive monthly subcutaneous injections of evolocumab (420 mg) or placebo.

Results showed that, at week 24, the mean percentage change from baseline in LDL cholesterol level was −44.5% in the evolocumab group and −6.2% in the placebo group, giving a difference of −38.3 percentage points ($P < .001$).

The absolute change in the LDL cholesterol level was −77.5 mg/dL in the evolocumab group and −9.0 mg/dL in the placebo group, giving a difference of −68.6 mg/dL ($P < .001$).

Results for all secondary lipid variables were significantly better with evolocumab than with placebo. The incidence of adverse events that occurred during the treatment period was similar in the evolocumab and placebo groups. Laboratory abnormalities did not differ between groups.

> "**[FH] is massively underdiagnosed**, with only around 15%-20% of patients with the condition having been identified."

Dr. Gaudet noted that FH is the most common genetic disease worldwide, affecting 1 in 250 people. "It is very treatable, so it is important to identify these patients, but it is massively underdiagnosed, with only around 15%-20% of patients with the condition having been identified," he said.

"The vast majority of patients can reach target LDL levels with statins and ezetimibe, but there are 5%-10% of patients who may need additional therapy. We have now shown that evolocumab is safe and effective for these patients," Dr. Gaudet said. "

The HAUSER-RCT study was supported by Amgen. Gaudet reports grants and personal fees from Amgen during the conduct of the study.

A version of this article originally appeared on Medscape.

Adrenal hypercortisolism **From source to symptoms**

Understanding the prevalence, unique etiology, and clinical consequences of incidentally detected adrenal adenomas

Excess cortisol activity at the glucocorticoid receptor causes multisystemic dysfunction and can increase the risk for type 2 diabetes mellitus, hypertension, obesity, and cardiovascular disease.[1,2] Even in cases of mild cortisol excess, the clinical consequences of long-term elevations in cortisol can be severe.[3,4] Adrenal adenomas, often incidentally discovered, are a common cause of autonomous cortisol secretion, and determining their cortisol secretion patterns is important to guide follow-up and treatment.[3,5,6] Inconsistency and/or lack of consensus across screening protocols may increase the risk of delaying or missing the diagnosis of hypercortisolism.[3,5]

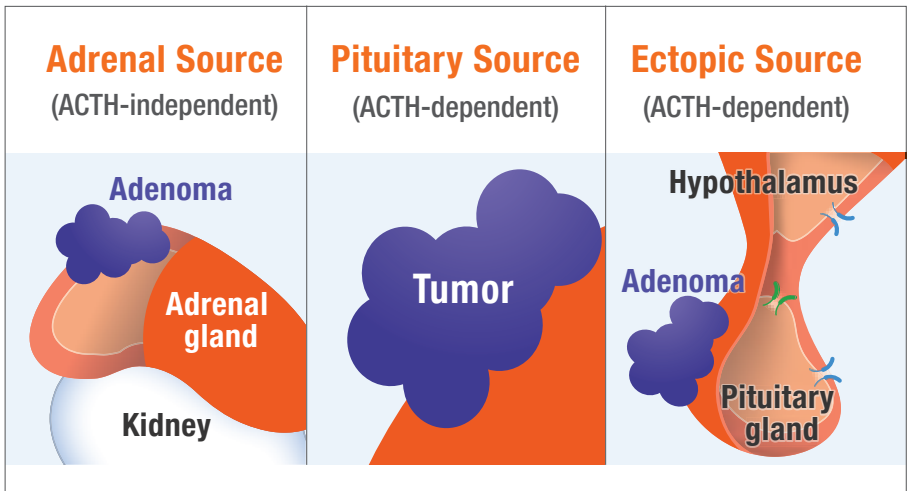
The prevalence of incidentally detected adrenal adenomas has risen in tandem with increased use of medical imaging.[4] As detection of "adrenal incidentalomas" continues to rise, understanding the spectrum of hypercortisolism across etiologies, disease manifestations, and clinical consequences becomes increasingly important to manage these patients appropriately.[3,7,8]

Different etiologies, different presentations

Cortisol, an essential hormone for homeostatic well-being, is the most abundant endogenous glucocorticoid in the human body. By binding to glucocorticoid receptors expressed ubiquitously in cells throughout the body, cortisol enacts physiologic changes that allow for important adaptations to internal and external factors.[9]

Cortisol is regulated by a hormonal feedback loop within the neuroendocrine system. The hypothalamus, pituitary, and adrenal glands control the production of cortisol in the body through hormonal signaling.[1,9] Disruption in signaling within the hypothalamic–pituitary–adrenal (HPA) axis can lead to cortisol excess.[10] Depending on the underlying etiology, the signs and symptoms may be highly variable—both clinically and biochemically.[1,5,8]

While exogenous hypercortisolism is due to a cause outside the body (ie, glucocorticoid use), endogenous hypercortisolism is driven by an underlying pathology.[8] This may be an adenoma in the pituitary or adrenal gland, or an ectopic tumor located elsewhere in the body. Pituitary and ectopic sources may drive excess cortisol production by secreting adrenocorticotrophic hormone (ACTH) outside the regulation of the HPA axis feedback loop. Adrenal sources of hypercortisolism, such as autonomous cortisol-secreting adrenal adenomas, secrete excess cortisol directly, and so are described as "ACTH-independent."[8]



Hypercortisolism due to autonomous cortisol secretion from an adrenal adenoma may present differently from ACTH-dependent sources, and classic overt clinical features may not be present.[8]

Follow-up considerations for patients with adrenal adenomas

All major endocrine societies agree that patients with incidentally discovered adrenal adenomas should receive screening for autonomous adrenal hormone secretion. However, recent data suggest that only 43% of these patients were screened for cortisol excess when radiology reports did not include screening recommendations. This represents a considerable missed opportunity to identify and treat hormone-secreting lesions. However, without a clear clinical algorithm, biochemical testing of adrenal adenomas may remain underperformed.[11]

Guidance for managing adrenal adenomas also lacks consistency. A "nonfunctioning" adenoma generally does not require surgery, and even in the case of hormone-secreting lesions, surgery is controversial. Repeat imaging and monitoring is also a matter of debate, as progression in tumor size and hormone-secretion patterns is rare. Nevertheless, patients with adrenal adenomas—whether found to be hormone-secreting or "nonfunctional" at baseline—carry increased risk for cardiometabolic comorbidities compared to healthy controls without adenomas. Additionally, all-cause and cardiovascular mortality are both similarly elevated among patients with "nonfunctioning" and hormone-secreting adenomas (based on the results of a meta-analysis of 32 studies reporting outcomes for 4121 patients; mean follow-up 50.2 months). These results underscore the need for follow-up in patients with adrenal adenomas.[3,4]

Initially, discovery of an adrenal adenoma gives rise to 2 primary questions[12]

- Does this adrenal mass represent a malignancy?
- Is there evidence of hormone excess?

Other specific questions may arise, dependent upon individual patient context

- Would a biopsy aid with diagnosis, management, or prognosis?
- Is there an indication for surgical or medical treatment?
- Is there any indication for longitudinal surveillance with imaging and/or biochemical testing? If so, how frequently and for what duration?

Patients with multiple lines of biochemical evidence of autonomous, ACTH-independent hypercortisolism and clinical evidence associated with cortisol excess may benefit from treatment.[12]

Challenges in screening for adrenal hypercortisolism

Navigating the nuances of adrenal hypercortisolism may not be clinically straightforward.[5] Few, if any, signs and symptoms of hypercortisolism are unique, and reaching a diagnosis is often challenging.[7] Because symptoms may not be sufficiently specific to determine when screening is indicated, hormonal screening is recommended categorically in all patients who present with an adrenal adenoma.[5] Confirmation of hypercortisolism should be based on clinical suspicion in conjunction with the results of biochemical measures of cortisol. These biochemical measures include serum cortisol values after dexamethasone testing or salivary and urinary cortisol values.[5] In the case of incidentally detected adrenal adenomas, additional measures may include monitoring ACTH and dehydroepiandrosterone sulfate levels.[12]

Measuring cortisol levels, however, is not without challenges. Principally, cortisol secretion is a continuum with no clear threshold demarcating normal vs increased levels.[5,6] The fluctuation of cortisol levels throughout the day—high levels in the early morning and low levels at night—is an important part of normal physiology.[1] This makes the detection of more subtle forms of autonomous cortisol secretion particularly difficult, as levels may be within the normal range at some portions of the day, but elevated at others. It is therefore difficult to define diagnostic cutoffs in most screening tests. Furthermore, biochemical screening is complicated by the limitations in sensitivity and specificity associated with each testing method. Sequential or concurrent testing with multiple methods may optimize diagnostic sensitivity, but there is no gold standard for biochemical screening of hypercortisolism.[5,6]

The lack of a broad consensus makes hormonal screening of incidentally detected adrenal adenomas especially difficult.[11] In patients with adrenal adenomas, urinary free cortisol (UFC) provides unsatisfactory sensitivity for detecting subtle cortisol elevation.[6] Endocrine Society guidelines suggest the use of the 1-mg dexamethasone suppression test (DST), rather than UFC, in these patients. This is based on the simplicity of the DST, as well as the physiologic principle that autonomous cortisol secretion from an adrenal adenoma may not raise serum cortisol levels high enough to cause excess spillover into the urine. Urinary cortisol output over a 24-hour period may therefore remain within a normal range. [5,6,13] A threshold of serum cortisol >1.8 µg/dL was determined to have the highest sensitivity for detecting cortisol excess, although low specificity (69.9%) underscores the need for evaluating multiple aspects of HPA axis function in combination with careful clinical evaluation.[5,6]

Further complicating the diagnosis, the classic overt clinical features of hypercortisolism are often not present in patients with incidentally discovered adrenal adenomas.[8] The diagnosis may be described as "autonomous cortisol secretion" or "possible autonomous cortisol secretion." Although sometimes characterized as mild or less severe, these cases are associated with significant and progressive comorbidities, such as type 2 diabetes mellitus, hypertension, dyslipidemia, and osteoporosis. Furthermore, all etiologies of hypercortisolism are associated with increased risk for morbidity and mortality.[3,14]

Evaluating treatment response in autonomous cortisol-secreting adrenal adenomas

Evaluating response to therapy for hypercortisolism often involves the same biochemical measures used in diagnosis. Cortisol normalization commonly appears as an endpoint in studies of treatment.[15] Nevertheless, cortisol normalization as a measure of treatment efficacy has limitations. In patients with autonomous cortisol-secreting adrenal adenomas, biochemical measures of cortisol may be subject to the same considerations for sensitivity in evaluating treatment efficacy as in screening and diagnosis.[5,13]

Clinical improvement is generally accepted to occur secondary to cortisol normalization. This may further reinforce the perception that cortisol normalization is a fundamental measure of efficacy in medical therapy. However, the persistence of glucose intolerance, hypertension, and visceral adiposity, among other common comorbidities of hypercortisolism, is associated with increased cardiovascular risk, even following correction of hypercortisolemia.[5,16] This suggests normalization of cortisol levels has considerable limitations as a measure of treatment efficacy.

It is important to recognize the current limitations in taking accurate measures of cortisol activity in patients with cortisol-secreting adrenal adenomas. These limitations, together with the persistence of cardiovascular risk following resolution of hypercortisolemia, may indicate that treatment goals should expand beyond normalization of cortisol levels and focus on the improvement of comorbidities. For these patients, evaluating response to treatment may depend on a broader assessment of clinical and biochemical improvement.[6,8,13,16]

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HORMONAL HYPERTENSION 'We need to change the culture'

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automatically come to mind when they see high numbers on a BP monitor, and yet this latest research found that up to a third of all 726 patients in the study who were diagnosed with hypertension and with high urinary salt levels had PA (Ann Int Med. 2020 Jul 7;173[1]:10-20).

That translates to a roughly three- to fivefold increase over standard prevalence estimates, and is a "game changer" for how clinicians should approach hypertension management and PA diagnosis going forward, said John W. Funder, MD, in an editorial accompanying the Annals study (Ann Int Med. 2020 Jul 7;173[1]:65-6).

Long considered relatively uncommon, hypertension driven by an excess of the hormone aldosterone, often because of an adenoma on the adrenal gland, is not the same as conventional "essential" hypertension. The former benefits from early diagnosis because its treatment is completely different – close to half of all PA patients can be treated definitively and quickly with surgical removal of an adenoma from one side of the adrenal gland.

Dr. Carey

For other PA patients, who have bilateral adrenal hyperplasia that is impossible to resolve surgically, treatment with drugs called mineralocorticoid receptor antagonists (MRAs), such as spironolactone, is needed because they target the hormonal cause of the high BP.

But what usually happens is that a patient with PA is mistakenly diagnosed with essential hypertension, in which the classic approach to treatment is to start with one regular antihypertensive drug, and add on further ones from different drug classes if blood pressure is not adequately controlled. When patients are taking three drugs, without adequate control, they are labeled as having "resistant hypertension."

But in the case of PA, none of these conventional antihypertensives work, and the process of continuing to monitor and add different drugs wastes time, during which patients deteriorate.

"We need to change the culture of waiting for hypertension to be resistant and have patients riddled with end-organ damage," due to years of persistently high BP and excess aldosterone "before we look for a secondary cause" like PA, declared Dr. Yang, of Hudson Institute of Medical Research and Monash University in Melbourne, during an interview.

So early diagnosis and prompt treatment of PA is key.

In addition to boosting the public health importance of early PA detection in hypertensive patients, the new up-sized PA prevalence numbers throw a spotlight on primary care physicians (PCPs) as key players who will need to apply the findings to practice on a public health scale.

These novel results create a need for "new guidelines, and a radically revised game plan with the key role of PCPs" emphasized in future management of patients with hypertension, said Dr. Funder, a professor of medicine at Monash University, in a second recent editorial in Hypertension (2020 Aug;76[8]:325-6).

"Buy-in by PCPs is essential," agrees Robert M. Carey, MD, a cardiovascular endocrinologist and professor of medicine at the University of Virginia in Charlottesville, and a coauthor of the new study.

But he too acknowledges that this presents a major challenge. PCPs and internists, who diagnose a lot of hypertension, are "not used to thinking about aldosterone," he said in an interview, encapsulating the key problem faced by proponents of earlier and more widespread PA assessment.

This dilemma looms as a "huge public health issue," Dr. Carey warned.

'We're a long way from getting' PCPs to buy in to PA screening

Will PCPs grow more comfortable with screening patients for PA themselves, or might they become more willing to refer hypertensive individuals for assessment at an expert center?

One skeptic is Ross D. Feldman, MD, a hypertension-management researcher and professor of medicine at the University of Manitoba in Winnipeg. The finding about high PA prevalence in patients with hypertension "is brand new, [and] the message needs to get to PCPs," he said. But, "We're a long way from getting it" to them. "I don't know how to do that. It will be a tough sell."

In addition, repositioning MRAs as an earlier option for many hypertensive patients won't be easy either, because "we'll never have outcome-trial data for MRAs," given that they are now generic drugs, he noted.

"No clinical trial data show [MRAs] are first-line drugs," said Dr. Feldman, who explained that, instead, MRAs are considered "go-to drugs" for patients with treatment-resistant hypertension, a niche therapeutic area. Results from the PATHWAY-2 trial published 5 years ago in Lancet (2015 Nov 21;386[10008]:2059-68) showed "spironolactone was clearly the most effective treatment for the condition."

But even among patients with resistant hypertension, screening for PA dramatically lags despite being enshrined in guidelines.

"PCPs should start checking aldosterone-to-renin ratios [a widely used PA screen] in all patients with resistant hypertension or hypertension with hypokalemia, and then refer patients to specialists for testing and management," said Jordana B. Cohen, MD, a nephrologist and hypertension researcher at the University of Pennsylvania in Philadelphia.

But recent studies of U.S. patient populations with clinical characteristics that meet existing criteria for PA screening showed that just 1%-2% of these individuals underwent an initial PA assessment, she noted, citing reports in the journals Surgery and Hypertension (Surgery. 2020 Jan 1;167[1]:211-5; Hypertension. 2020 Mar;75[3]:650-9).

"We need to prioritize improving screening in these high-risk patients," she stressed in an interview.

This illustrates that, in some respects, the new prevalence numbers are beside the point, because PA has been going unscreened and overlooked far too often even in the context of historical, lower prevalence rates, said Dr. Yang.

"The key point is that approximately 1 in 10 people with hypertension, and even more with resistant hypertension, have a form of the disease that is worse than essential hypertension but is routinely missed at present" and is also highly treatable.

"Evidence for the need for increased awareness of PA has been building for 2 decades," stressed Dr. Yang, who has coauthored several commentaries and reviews that have bemoaned PA's underappreciated status.

Interest in partnering with PCPs on guidance grows

One potential solution is to have endocrinologists and hypertension specialists' partner with PCPs to come up with diagnostic and management recommendations. Both Dr. Funder and Dr. Carey are opinion leaders regarding the role of aldosterone in hypertension, and both were coauthors of the 2016 Endocrine Society guideline for PA assessment and management published in the Journal of Clinical Endocrinology & Metabolism (2016 May 1;101[5]:1889-916), with Dr. Funder chairing the writing panel.

Now approaching its fifth year in effect, this guideline is "due for revision," and "my hope is that we'll be able to partner with one or more PCP organizations to come up with a version of the guideline targeted to PCPs," Dr. Carey said.

He voiced interest in working on this with the American College of Physicians, which represents U.S. internal medicine physicians, and the American Academy of Family Physicians.

Dr. Cohen

"We definitely need a partnership and educational efforts to get the word out from these organizations and not from a specialty society," said Dr. Carey.

Dr. Funder said he has submitted a proposal to the Endocrine Society for a guidelines update he would chair with Dr. Carey's assistance and with a diverse writing group that includes PCPs. Dr. Carey said that ideally this panel would write and release a revised guideline in 2021.

"Several of us are chomping at the bit to get this done," he noted.

But participation by the ACP and AAFP remain uncertain as of September 2020. When approached about this, an ACP spokesperson said the organization had no comment. A spokesperson for the AAFP said, "It's too early to tell if we will partner with any other organizations to develop guidelines specific to excess aldosterone, and how such guidelines might be received by our members."

Recent history shows little cooperation between ACP, AAFP, and what might be termed the U.S. hypertension "establishment." For example, when the American College of Cardiology and the American Heart Association released their most recent essential hypertension management guidelines in Hypertension in 2018 (Jun;71[6]: e13-115), it was never adopted by ACP or AAFP.

The latter two organizations continue to endorse a higher BP threshold for diagnosing hypertension, and higher treatment targets set by alternative expert panels to those of the AHA/ACC.

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Most providers don't follow hypertension guidelines

BY MEGAN BROOKS

Many health care professionals are not following current, evidence-based guidelines to screen for and diagnose hypertension, and appear to have substantial gaps in knowledge, beliefs, and use of recommended practices, results from a large survey suggest.

"One surprising finding was that there was so much trust in the stethoscope, because the automated monitors are a better way to take BP," lead author Beverly Green, MD, of Kaiser Permanente Washington Health Research Institute, Seattle, said in an interview.

The results of the survey were presented at the virtual joint scientific sessions of the American Heart Association Council on Hypertension, AHA Council on Kidney in Cardiovascular Disease, and American Society of Hypertension.

The U.S. Preventive Services Task Force and the AHA/American College of Cardiology recommend out-of-office BP measurements – via ambulatory BP monitoring (ABPM) or home BP monitoring – before making a new diagnosis of hypertension.

To gauge provider knowledge, beliefs, and practices related to BP diagnostic tests, the researchers surveyed 282 providers: 102 medical assistants (MA), 28 licensed practical nurses (LPNs), 33 registered nurses (RNs), 86 primary care physicians, and 33 advanced practitioners (APs).

More than three-quarters of providers (79%) felt that BP measured manually with a stethoscope and ABPM were "very or highly" accurate ways to measure BP when making a new diagnosis of hypertension.

Most did not think that automated clinic, home, or kiosk BP measurements were very or highly accurate.

Nearly all providers surveyed (96%) reported that they "always or almost always" rely on clinic BP measurements when diagnosing hypertension, but the majority of physicians/APs would prefer using ABPM (61%) if available.

The problem with ABPM, said Dr. Green, is "it's just not very available or convenient for patients, and a lot of providers think that patients won't tolerate it." Yet, without it, there is a risk for misclassification, she said.

The provider survey by Dr. Green and colleagues also shows slow uptake of updated thresholds for high BP.

Eighty-four percent of physicians/APs and 68% of MA/LPN/RNs said they used a clinic BP threshold of at least 140/90 mm Hg for making a new diagnosis of hypertension. Only 3.5% and 9.0%, respectively, reported using the updated threshold of at least 130/80 mm Hg put forth in 2017.

Karen A. Griffin, MD, who chairs the AHA Council on Hypertension, said in an interview that this may be because the survey began before the updated guidelines were released in 2017, "not to mention the fact that some societies have opposed the new threshold of 130/80 mm Hg. I think, with time, the data on morbidity and mortality associated with the goal of 130/80 mm Hg will hopefully convince those who have not yet implemented these new guidelines that it is a safe and effective BP goal," Dr. Griffin said.

This research had no specific funding. Dr. Green and Dr. Griffin have no relevant disclosures.

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Collaboration feasible, although PCPs overworked

Dr. Carey hopes that this episode will not preclude agreement over PA screening.

"I think it is still possible to partner with [the ACP and AAFP]," he observed, adding that he believes high PA prevalence among hypertensive patients and its consequences when unrecognized is "noncontentious."

> "The key point is that approximately 1 in 10 people with hypertension, and even more with resistant hypertension, **have a form of the disease that is worse than essential hypertension but is routinely missed** [and is highly treatable]."

But he acknowledges that other, substantial hurdles also exist, notably the "overwhelming workload" that American PCPs already face.

David O'Gurek, MD, a family and community medicine physician at the Lewis Katz School of Medicine of Temple University in Philadelphia, agrees that a revamped approach to PA screening developed cooperatively between PCPs and specialists is an important goal and potentially feasible despite prior disagreements. "There has to be room for collaboration," he said, but also emphasized the need for developing policies based on a systematic evidence review and a focus on patient-centered outcomes.

"We're certainly missing patients with PA, but there needs to be greater clarity and standardization about the most appropriate screening approach and cutoff level" for flagging patients who need specialized assessment, Dr. O'Gurek said in an interview.

The current endocrinology literature also shows that experts remain divided on how best to accomplish this.

And some hypertension specialists question whether existing evidence is conclusive enough to warrant revised guidelines.

Dr. Cohen, the nephrologist and hypertension researcher, said that, while the recent prevalence report in Annals of Internal Medicine is "intriguing, hypothesis-generating information that suggests we are missing many cases of hyperaldosteronism in routine care," she nevertheless believes that "we need additional data to be able to truly understand the breadth and implications of the findings."

William C. Cushman, MD, a hypertension management specialist at the University of Tennessee Health Science Center in Memphis, agrees.

Changing existing practice guidelines "really needs randomized, controlled trials demonstrating a difference in long-term outcomes, ideally major cardiovascular outcomes," that result from broader PA screening, he said.

Dr. Carey concurs that more evidence is needed to confirm the Annals report, but is confident this evidence will be in hand by the time a guideline-revision panel meets in 2021.

Australian model of PCPs screening for PA could be implemented in U.S.

An example of what might be possible when PCPs, endocrinologists, and hypertension specialists work together to make PA screening more accessible can be found in Melbourne, at the Endocrine Hypertension Service of Monash Health, in association with the Hudson Institute of Medical Research.

This began operating in July 2016, cofounded by Dr. Yang, whose experiences with her own father made her sensitive to the issue.

The service's aim is to "address the underdiagnosis of PA, and to offer a streamlined diagnostic service for patients with hypertension," with an "extensive outreach program" targeted to regional PCPs that, among other messages, encourages them to screen patients for PA when blood pressures exceed 140/90 mm Hg.

During its first 3 years of operation, the service saw 267 patients, with PA diagnosed in 135 and ruled out in 73 patients (Intern Med J. 2020 May 3. doi: 10.1111/imj.14879).

Dr. Cushman

Notably, the proportion of these patients referred from PCPs jumped from 21% of 70 patients during the first year of operation to 47% of 70 patients during year 2, and 52% of 127 patients during the third year, ending in July 2019, said Dr. Yang, who continues to help run the service.

During the first year, a scant 3% of referred patients had recently diagnosed hypertension, but this rose to 14% during the second year, and to 19% during the most recent year with data available.

The median duration of diagnosed hypertension among referred patients fell from 11 years during year 1, to 7 years during year 3.

Service clinicians diagnosed 37 patients with unilateral adenomas, and removed them from 23 patients with four more awaiting surgery and the remaining 10 opting instead for medical management. Another 95 patients went on therapy with a MRA, and during the most recent year studied all patients who began a MRA regimen had a partial or complete clinical response.

Dr. Carey said the "creative program represents a model for implementation in U.S. practice.

Dr. Funder, Dr. Carey, Dr. Feldman, Dr. Yang, Dr. Cohen, and Dr. O'Gurek had no relevant disclosures. Dr. Cushman has been a consultant to Novartis, received personal fees from Sanofi, and research funding from Eli Lilly.

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FDA grants approval to weekly growth hormone for adults

BY JIM KLING

THE HUMAN GROWTH hormone formulation somapacitan for adults with growth hormone deficiency was approved by the Food and Drug Administration on Sept. 1. The drug is injected once a week, while other FDA-approved human growth hormone formulations require daily jabs.

Somapacitan contains an albumin-binding element attached to the growth hormone, causing the reversible binding to albumin proteins in the body. This reduces clearance and increases the half-life of the hormone. The formulation has previous demonstrated safety and efficacy in children with growth hormone deficiency (J Clin Endocrinol Metab. 2020 Apr 1. doi: 10.1210/clinem/dgz310).

Growth hormone treatment can counter abdominal obesity, reduced lean body mass, fatigue, osteopenia, cardiovascular risks, and other manifestations of growth hormone deficiency in adults, but daily injections can be burdensome for patients. That makes long-acting versions attractive, but the lifelong nature of the treatment makes it important to characterize safety and tolerability.

The approval comes on the strength of a randomized, placebo-controlled phase 3 trial (REAL 1) of 300 adult patients in 17 countries with growth hormone deficiency (J Clin Endocrinol Metab. 2020 Apr 1. doi: 10.1210/clinem/dgaa049). Participants had either never received growth hormone treatment, or had stopped taking one at least 6 months before starting the trial. Subjects received once-weekly somapacitan, once-weekly placebo, or daily somatropin, which is FDA approved.

The primary endpoint was percentage change of truncal fat, which is regulated by growth hormone, and can lead to medical problems. After 34 weeks, subjects in the somapacitan group experienced a 1.06% decrease in truncal fat, compared with a 0.47% increase in the placebo group ($P = .009$) and a 2.23% decrease in the daily somatropin group.

After 34 weeks, a 52-week extension trial began. The somapacitan group continued on the drug and the placebo group was offered somapacitan. Patients on daily somatropin were randomized to continue daily treatment with somatropin or to switch to somapacitan.

At the end of the extension trial, those taking somapacitan for the full 86-week duration had an average reduction of 1.52% in truncal fat. After 86 weeks, the somapacitan and daily somatropin groups had similar values for percentage change in visceral fat, lean body mass, or appendicular skeletal muscle mass.

Common side effects of somapacitan were back pain, joint paint, indigestion, a sleep disorder, dizziness, tonsillitis, swelling in the arms or lower legs, vomiting, adrenal insufficiency, hypertension, increase in blood creatine phosphokinase, weight increase, and anemia.

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Urine screen improves ID of adrenal cancer

BY NANCY A. MELVILLE

A strategy that includes a urine steroid test along with imaging characteristics and tumor size criteria can significantly improve the challenging diagnosis of adrenocortical cancer, helping to avoid unnecessary, and often unsuccessful, further imaging and even surgery, new research shows.

"A triple-test strategy of tumor diameter, imaging characteristics, and urine steroid metabolomics improves detection of adrenocortical carcinoma, which could shorten time to surgery for patients with ... carcinoma and help to avoid unnecessary surgery in patients with benign tumors," the authors say in research published online July 23 in The Lancet Diabetes & Endocrinology.

The triple-test strategy can be expected to make its way into international guidelines, notes joint lead author Irina Bancos, MD, an associate professor of endocrinology at the Mayo Clinic, Rochester, Minn., in a press statement issued by the University of Birmingham (England), which also had a number of researchers involved in the study.

"The findings of this study will feed into the next international guidelines on the management of adrenal tumors and the implementation of the new test will hopefully improve the overall outlook for patients diagnosed with adrenal tumors," Dr. Bancos emphasized.

More imaging has led to detection of more adrenal tumors

Advances in CT and MRI imaging have increased the ability to detect adrenal incidentalomas, which are now picked up on about 5% of scans, and the widespread use of imaging has compounded the prevalence of such findings, particularly in older people.

Adrenocortical carcinomas represent only about 2%-12% of adrenal incidentalomas, but the prognosis is very poor, and early detection and surgery can improve outcomes, so findings of any adrenal tumor typically trigger additional multimodal imaging to rule out malignancy.

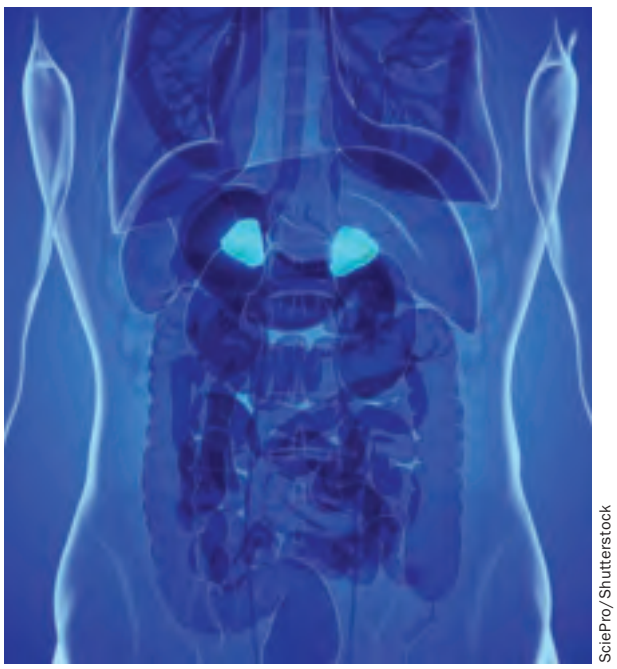
Evidence is lacking on the accuracy of imaging in determining whether such masses are truly cancerous, or benign, and such procedures add costs, as well as expose patients to radiation that may ultimately have no benefit. However, a previous proof-of-concept study from the same authors did show that the presence of excess adrenal steroid hormones in the urine is a key indicator of adrenal tumors, and other research has supported the findings.

All three tests together give best predictive value: EURINE-ACT

To further validate this work, the authors conducted the EURINE-ACT trial, a prospective 14-center study that is the first of its kind to evaluate the efficacy of a screening strategy for adrenocortical carcinoma that combines urine steroid profiling with tumor size and imaging characteristics.

The study of 2,017 participants with newly diagnosed adrenal masses, recruited from January 2011 to July 2016 from specialist centers in 11 different countries, assessed the diagnostic accuracy of three components: maximum tumor diameter (≥4 cm vs. <4 cm), imaging characteristics (positive vs. negative), and urine steroid metabolomics (low, medium, or high risk of adrenocortical carcinoma), separately and in combination.

Of the patients, 98 (4.9%) had adrenocortical carcinoma confirmed clinically, histopathologically, or biochemically.



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> "A triple-test strategy of tumor diameter, imaging characteristics, and urine steroid metabolomics improves detection of adrenocortical carcinoma, **which could shorten time to surgery**."

Tumors with diameters of 4 cm or larger were identified in 488 patients (24.2%) and were observed in the vast majority of patients with adrenocortical carcinoma (96 of 98), for a positive predictive value (PPV) of 19.7%.

Likewise, the PPV for imaging characteristics was 19.7%. However, increasing the unenhanced CT tumor attenuation threshold to 20 Hounsfield units (HU) from the recommended 10 HU increased specificity for adrenocortical carcinoma (80.0% vs. 64.0%) while maintaining sensitivity (99.0% vs. 100.0%).

Comparatively, a urine steroid metabolomics result suggesting a high risk of adrenocortical carcinoma had a PPV of 34.6%.

A total of 106 patients (5.3%) met the criteria for all three measures, and the PPV for all three was 76.4%.

With the criteria, 70 patients (3.5%) were classified as being at moderate risk of adrenocortical carcinoma and 1,841 (91.3%) at low risk, for a negative predictive value (NPV) of 99.7%.

"Use of radiation-free, noninvasive urine steroid metabolomics has a higher PPV than two standard imaging tests, and best performance was seen with the combination of all three tests," the authors state.

Limit urine test to patients with larger tumors

They note that the use of the combined diagnostic strategy would have led to additional imaging in only 488 (24.2%) of the study's 2,017 patients, compared with the 2,737 scans that were actually conducted before reaching a diagnostic decision.

"Implementation of urine steroid metabolomics in the routine diagnostic assessment of newly discovered adrenal masses could reduce the number of imaging procedures required to diagnose adrenocortical carcinoma and avoid unnecessary surgery of benign adrenal tumors, potentially yielding beneficial effects with respect to patient burden and health care costs," they stress.

And regarding imaging parameters, "we also showed that using a cutoff of 20 HU for unenhanced CT tumor attenuation increases the accuracy of imaging characteristic assessment for exclusion of adrenocortical carcinoma, compared with the currently recommended cutoff of 10 HU, which has immediate implications for clinical practice," they emphasize.

In an accompanying editorial, Adina F. Turcu, MD, of the division of metabolism, endocrinology, and diabetes, University of Michigan, Ann Arbor, and Axel K. Walch, MD, of the Helmholtz Zentrum München–German Research Centre for Environmental Health, agree. "The introduction of urine steroid metabolomics into routine clinical practice would provide major advantages," they state.

However, they point out that, although the overall negative predictive value of the test was excellent, the specificity was weak.

"Thus, urine steroid metabolomics should be limited to patients who have adrenal nodules larger than 4 cm and have qualitative imaging characteristics suggestive of malignancy," say Dr. Turcu and Dr. Walch.

The EURINE-ACT study results suggest this subgroup would represent roughly only 12% of all patients with adrenal incidentalomas, they add.

Issues that remain to be addressed with regard to the implementation of the screening strategy include how to best respond to patients who are classified as having intermediate or moderate risk of malignancy, and whether the diagnostic value of steroid metabolomics could be refined by adding analytes or parameters, the editorialists conclude.

The study was funded by the European Commission, U.K. Medical Research Council, Wellcome Trust, U.K. National Institute for Health Research, U.S. National Institutes of Health, the Claire Khan Trust Fund at University Hospitals Birmingham Charities, and the Mayo Clinic Foundation for Medical Education and Research.

A version of this article originally appeared on Medscape.com.

Small weight loss produces impressive drop in T2D risk

BY BECKY MCCALL

Intentional loss of a median of just 13% of body weight reduces the relative risk of developing type 2 diabetes by around 40% in people with obesity, among many other health benefits, shows a large real-world study in half a million adults.

Other findings associated with the same modest weight loss included a reduction in the risk of sleep apnea by 22%-27%, hypertension by 18%-25%, and dyslipidemia by 20%-22%.

Christiane Haase, PhD, of Novo Nordisk, led the work together with Nick Finer, MD, senior principal clinical scientist, Novo Nordisk.

"This is powerful evidence to say it is worthwhile to help people lose weight and that it is hugely beneficial. These are not small effects, and they show that weight loss has a huge impact on health. It's extraordinary," asserted Dr. Finer, who is also honorary professor of cardiovascular medicine at University College London.

"These data show that if we treat obesity first, rather than the complications, we actually get big results in terms of health. This should be a game changer for those health care systems that are still prevaricating about treating obesity seriously," he added.

The size of the study, of over 550,000 U.K. adults in primary care, makes it unique. In the real-world cohort, people who had lost 10%-25% of their body weight were followed for a mean 8 years to see how this affected their subsequent risk of obesity-related conditions. The results were presented during the virtual European and International Congress on Obesity.

"Weight loss was real-world without any artificial intervention and they experienced a real-life reduction in risk of various obesity-related conditions," Dr. Haase said in an interview.

Carel Le Roux, MD, PhD, from the Diabetes Complications Research Centre, University College Dublin, welcomed the study because it showed those with obesity who maintained more than 10% weight loss experienced a significant reduction in the complications of obesity.

"In the study, intentional weight loss was achieved using mainly diets and exercise, but also some medications and surgical treatments. However, it did not matter how patients were able to maintain the 10% or more weight loss as regards the positive impact on complications of obesity," he highlighted.

From a clinician standpoint, "it helps to consider all the weight-loss options available, but also for those who are not able to achieve weight-loss maintenance, to escalate treatment. This is now possible as we gain access to more effective treatments," he added.

Courtesy Bill Branson/National Cancer Institute

Also commenting on the findings, Matt Petersen, vice president of medical information and professional engagement at the American Diabetes Association, said: "It's helpful to have further evidence that weight loss reduces risk for type 2 diabetes."

However, "finding effective strategies to achieve and maintain long-term weight loss and maintenance remains a significant challenge," he observed.

Database of half a million people with obesity

For the research, anonymized data from over half a million patients documented in the Clinical Practice Research Datalink database, which holds information from 674 general practices in the United Kingdom, were linked to Hospital Episode Statistics and prescribing data to determine comorbidity outcomes.

At baseline, characteristics for the full study population included a median age of 54 years, around 50% of participants had hypertension, around 40% had dyslipidemia, and around 20% had type 2 diabetes. Less than 10% had sleep apnea, hip/knee osteoarthritis, or history of cardiovascular disease. All participants had a body mass index of 25.0-50.0 kg/m^2 at the start of the follow-up, between January 2001 and December 2010.

Patients may have been advised to lose weight, or take more exercise, or have been referred to a dietitian. Some had been prescribed antiobesity medications available between 2001 and 2010. (Novo Nordisk medications for obesity were unavailable during this period.) Less than 1% had been referred for bariatric surgery.

"This is typical of real-world management of obesity," Dr. Haase pointed out.

Participants were divided into two categories based on their weight pattern during the 4-year period: one whose weight remained stable (492,380 individuals with BMI change within –5% to 5%) and one who lost weight (60,573 with BMI change –10% to –25%).

The median change in BMI in the weight-loss group was –13%. The researchers also extracted information on weight-loss interventions and dietary advice to confirm intention to lose weight.

The benefits of losing 13% of body weight were then determined for three risk profiles: BMI reduction from 34.5 to 30 (obesity class I level); from 40.3 to 35 (obesity class II level), and from 46 to 40 (obesity class III level).

Those with a baseline history of any particular outcome were excluded from the risk analysis for that same outcome. All analyses were adjusted for BMI, age, sex, smoking status, and baseline comorbidities.

Dr. Finer and Dr. Haase are both employees of Novo Nordisk. Dr. Le Roux reported no relevant financial relationships.

A version of this article originally appeared on Medscape.com.

FDA pulls amputation boxed warning off canagliflozin label

BY MEGAN BROOKS

THE FOOD AND DRUG Administration has removed the boxed warning about the risk of leg and foot amputations for canagliflozin (Invokana, Invokamet, Janssen), a sodium-glucose cotransporter-2 (SGLT2) inhibitor for the treatment of type 2 diabetes, the agency announced Aug. 26.

As previously reported by this news organization, the FDA added the boxed warning to the canagliflozin label in May 2017, after a roughly doubled risk for lower-extremity amputations with the drug compared with placebo was seen during two trials.

The FDA said the decision to remove the boxed warning was made following a review of new data from three clinical trials, which demonstrated additional heart- and kidney-related benefits and led to additional approved uses for canagliflozin.

In 2018, canagliflozin was approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes who have established cardiovascular disease.

In 2019, canagliflozin was approved to reduce the risk of end-stage kidney disease, worsening of kidney function, cardiovascular death, and heart failure hospitalization, in adults with type 2 diabetes and diabetic kidney disease. "Collectively, these newly identified effects of canagliflozin on heart and kidney disease show significantly enhanced benefit of this medicine," the FDA said.

The safety information from these trials, the FDA said, suggests that the risk of amputation, "while still increased with canagliflozin, is lower than previously described, particularly when appropriately monitored."

The agency added: "Based upon these considerations, FDA concluded that the boxed warning should be removed."

The FDA announcement said clinicians and patients should continue to be aware of the importance of preventive foot care and to monitor for new pain, tenderness, sores, ulcers, and infections in the legs and feet. Risk factors that may predispose patients to amputation should be considered when choosing antidiabetic medicines.

Health care professionals are encouraged to report adverse reactions to the FDA's MedWatch program.

A version of this article originally appeared on Medscape.com.

baqsimi®

(glucagon) nasal powder 3mg

READY FOR RESCUE

NO NEED FOR RECONSTITUTION[1]

BAQSIMI® is the first and only glucagon with nasal administration

Indication

BAQSIMI is indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and above.

IMPORTANT SAFETY INFORMATION

Contraindications

BAQSIMI is contraindicated in patients with pheochromocytoma, insulinoma, and known hypersensitivity to glucagon or to any of the excipients in BAQSIMI. Allergic reactions have been reported with glucagon and include anaphylactic shock with breathing difficulties and hypotension.

Please see additional Important Safety Information for BAQSIMI and Brief Summary of Prescribing Information on following pages. Please see Instructions for Use included with the BAQSIMI device.

BAQSIMI: DESIGNED TO BE SIMPLE IN SEVERE HYPOGLYCEMIA RESCUE[1]

- **Not an injection**—a dry nasal powder form of glucagon
- **Ready to use** with no reconstitution or priming
- **No inhalation required**—absorbed passively in the nose
- **Patients can carry it with them throughout the day,** in hot or cold conditions, and store at up to 86°F (30°C)
- **Single, fixed,** 3 mg dose

Keep tube sealed until ready to use.

To learn more, please visit BAQSIMI.com/HCP

IMPORTANT SAFETY INFORMATION (CONTINUED)

Warnings and Precautions

BAQSIMI is contraindicated in patients with pheochromocytoma because glucagon may stimulate release of catecholamines from the tumor. If the patient develops a dramatic increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure.

In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, BAQSIMI administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. BAQSIMI is contraindicated in patients with insulinoma. If a patient develops symptoms of hypoglycemia after a dose of BAQSIMI, give glucose orally or intravenously.

Allergic reactions have been reported with glucagon, these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. BAQSIMI is contraindicated in patients with a prior hypersensitivity reaction.

BAQSIMI is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for BAQSIMI administration to be effective. Patients with these conditions should be treated with glucose.

Adverse Reactions

Most common (≥10%) adverse reactions associated with BAQSIMI are nausea, vomiting, headache, upper respiratory tract irritation (i.e., rhinorrhea, nasal discomfort, nasal congestion, cough, and epistaxis), watery eyes, redness of eyes, and itchy nose, throat and eyes.

Drug Interactions

Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given BAQSIMI. In patients taking indomethacin, BAQSIMI may lose its ability to raise blood glucose or may even produce hypoglycemia. BAQSIMI may increase the anticoagulant effect of warfarin.

GN HCP ISI 24JUL2019

Please see additional Important Safety Information on previous page and Brief Summary of Prescribing Information on following page. Please see Instructions for Use included with the BAQSIMI device.

baqsimi®
(glucagon) nasal powder 3mg

Reference: 1. Baqsimi [Prescribing Information], Indianapolis, IN: Lilly USA, LLC.

PP-GN-US-0484 1/2020

Lilly

BAQSIMI™ (glucagon) nasal powder

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

BAQSIMI™ is indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and above.

CONTRAINDICATIONS

BAQSIMI is contraindicated in patients with: pheochromocytoma, insulinoma, known hypersensitivity to glucagon or to any of the excipients in BAQSIMI. Allergic reactions have been reported with glucagon and include anaphylactic shock with breathing difficulties and hypotension. *[see Warnings and Precautions]*

WARNINGS AND PRECAUTIONS

Catecholamine Release in Patients with Pheochromocytoma: BAQSIMI is contraindicated in patients with pheochromocytoma because glucagon may stimulate release of catecholamines from the tumor [see Contraindications]. If the patient develops a dramatic increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure**.**

Lack of Efficacy in Patients with Insulinoma: In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, BAQSIMI administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. BAQSIMI is contraindicated in people with insulinoma *[see Contraindications]*. If a patient develops symptoms of hypoglycemia after a dose of BAQSIMI, give glucose orally or intravenously.

Hypersensitivity and Allergic Reactions: Allergic reactions have been reported with glucagon, these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. BAQSIMI is contraindicated in patients with a prior hypersensitivity reaction *[see Contraindications]*.

Lack of Efficacy in Patients with Decreased Hepatic Glycogen: BAQSIMI is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for BAQSIMI administration to be effective. Patients with these conditions should be treated with glucose.

ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

• Hypersensitivity and Allergic Reactions [see Warnings and Precautions].

Adverse Reactions in Adult Patients

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of BAQSIMI cannot be directly compared with rates in clinical trials of other drugs and may not reflect the rates observed in practice.

Two similarly designed comparator-controlled trials, Study 1 and Study 2, evaluated the safety of a single dose of BAQSIMI compared to a 1 mg dose of intra-muscular glucagon (IMG) in adult patients with diabetes.

Table 1: Pooled Adverse Reactions (≥2%) in Adult Patients with Type 1 and Type 2 Diabetes in Study 1 and Study 2

Adverse Reaction	BAQSIMI 3 mg (N=153) %
Nausea	26.1
Headache	18.3
Vomiting	15.0
Upper Respiratory Tract Irritation[a]	12.4

[a] **Upper Respiratory Tract Irritation:** rhinorrhea, nasal discomfort, nasal congestion, cough, and epistaxis.

Nasal and ocular adverse reactions with BAQSIMI were solicited through a patient questionnaire.

Table 2: Solicited Nasal and Non-Nasal Adverse Reactions in Adult Patients with Type 1 and Type 2 Diabetes Pooled from Study 1 and 2

Adverse Reaction[a]	BAQSIMI 3 mg (n=153) %
	Any increase in symptom severity[a]
Watery eyes	58.8
Nasal congestion	42.5
Nasal itching	39.2
Runny nose	34.6
Redness of eyes	24.8
Itchy eyes	21.6
Sneezing	19.6
Itching of throat	12.4
Itching of ears	3.3

[a] Subjects were asked to report whether they have the symptom, as well as severity (mild, moderate, severe) at baseline, and after glucagon administration.

Adverse Reactions in Pediatric Patients Aged 4 Years and Above

A single dose of BAQSIMI was compared to weight based doses of 0.5 mg or 1 mg of IMG in pediatric patients with type 1 diabetes in Study 3.

Table 3: Adverse Reactions (≥2%) Occurring in Pediatric Patients with Type 1 Diabetes in Study 3

Adverse Reaction	BAQSIMI 3 mg (n=36) %
Vomiting	30.6
Headache	25.0
Nausea	16.7
Upper Respiratory Tract Irritation[a]	16.7

[a] Upper Respiratory Tract Irritation: nasal discomfort, nasal congestion, sneezing.

Nasal and ocular symptoms with BAQSIMI were solicited through a patient questionnaire in pediatric patients.

Table 4: Solicited Nasal and Non-Nasal Adverse Reactions in Pediatric Patients with Type 1 Diabetes

Adverse Reaction[a]	BAQSIMI 3 mg (n=36) %
	Any increase in symptom severity[a]
Watery eyes	47.2
Nasal congestion	41.7
Nasal itching	27.8

Table 4: Solicited Nasal and Non-Nasal Adverse Reactions in Pediatric Patients with Type 1 Diabetes (Cont.)

Adverse Reaction[a]	BAQSIMI 3 mg (n=36) %
	Any increase in symptom severity[a]
Runny nose	25.0
Sneezing	19.4
Itchy eyes	16.7
Redness of eyes	13.9
Itching of throat	2.8
Itching of ears	2.8

[a] Subjects were asked to report whether they have the symptom, as well as severity (mild, moderate, severe) at baseline, and after glucagon administration.

Other Adverse Reactions in Adult and Pediatric Patients

Other observed adverse reactions with BAQSIMI-treated patients across clinical trials were, dysgeusia, pruritus, and additional upper respiratory tract irritation events (nasal pruritus, throat irritation, and parosmia). Glucagon exerts positive inotropic and chronotropic effects and as a result tachycardia and hypertension have been reported.

DRUG INTERACTIONS

Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given BAQSIMI. In patients taking indomethacin, BAQSIMI may lose its ability to raise blood glucose or may even produce hypoglycemia. BAQSIMI may increase the anticoagulant effect of warfarin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data from case reports and a small number of observational studies with glucagon use in pregnant women over decades of use have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Multiple small studies have demonstrated a lack of transfer of pancreatic glucagon across the human placental barrier during early gestation. In a rat reproduction study, no embryofetal toxicity was observed with glucagon administered by injection during the period of organogenesis at doses representing up to 40 times the human dose, based on body surface area (mg/m2) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data: In pregnant rats given animal sourced glucagon twice-daily by injection at doses up to 2 mg/kg (up to 40 times the human dose based on body surface area extrapolation, mg/m2) during the period of organogenesis, there was no evidence of increased malformations or embryofetal lethality.

Lactation: Risk Summary There is no information available on the presence of glucagon in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. However, glucagon is a peptide and would be expected to be broken down to its constituent amino acids in the infant's digestive tract and is therefore, unlikely to cause harm to an exposed infant.

Pediatric Use: The safety and effectiveness of BAQSIMI for the treatment of severe hypoglycemia in patients with diabetes have been established in pediatric patients ages 4 years *and* above. Use of BAQSIMI for this indication is supported by evidence from a study in 48 pediatric patients from 4 to <17 years of age with type 1 diabetes mellitus. The safety and effectiveness of BAQSIMI have not been established in pediatric patients younger than 4 years of age.

Geriatric Use: Clinical studies of BAQSIMI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Limited clinical trial experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE: If overdosage occurs, the patient may experience nausea, vomiting, inhibition of GI tract motility, increase in blood pressure and pulse rate. In case of suspected overdosing, serum potassium levels may decrease and should be monitored and corrected if needed. If the patient develops a dramatic increase in blood pressure, phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

PATIENT COUNSELING INFORMATION Advise the patient and family members or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use). Recognition of Severe Hypoglycemia: Inform patient and family members or caregivers on how to recognize the signs and symptoms of severe hypoglycemia and the risks of prolonged hypoglycemia. Inform patients to notify their healthcare provider each time a severe hypoglycemic event occurs. Administration: Review the Patient Information and Instructions for Use with the patient and family members or caregivers. Serious Hypersensitivity: Inform patients that allergic reactions can occur with BAQSIMI. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions]*.

Important Administration Instructions

BAQSIMI is for intranasal use only.

Instruct patients and their caregivers on the signs and symptoms of severe hypoglycemia. Because severe hypoglycemia requires help of others to recover, instruct the patient to inform those around them about BAQSIMI and its Instructions for Use. Administer BAQSIMI as soon as possible when severe hypoglycemia is recognized.

Instruct the patient or caregiver to read the Instructions for Use at the time they receive a prescription for BAQSIMI. Emphasize the following instructions to the patient or caregiver:

- Do not push the plunger or test the device prior to administration.
- Administer BAQSIMI according to the printed instructions on the shrink-wrapped tube label and the Instructions for Use.
- Administer the dose by inserting the tip into one nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled.
- Call for emergency assistance immediately after administering the dose.
- Do not attempt to reuse BAQSIMI. Each BAQSIMI device contains one dose of glucagon and cannot be reused.

Dosage in Adults and Pediatric Patients Aged 4 Years and Above: The recommended dose of BAQSIMI is 3 mg administered as one actuation of the intranasal device into one nostril. If there has been no response after 15 minutes, an additional 3 mg dose of BAQSIMI from a new device may be administered while waiting for emergency assistance.

Lilly

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

www.baqsimi.com

Additional information can be found at *www.BAQSIMI.com*, *www.lillymedical.com*, or call The Lilly Answer Center at 1800-LillyRx (1-800-545-5979.

GN HCP BS 24JUL2019

PP-GN-US-0485

More female specialists, but gender pay gap persists

BY MARCIA FRELLICK

More female physicians are becoming specialists, a Medscape survey finds, and five specialties have seen particularly large increases during the last 5 years.

Obstetrician/gynecologists and pediatricians had the largest female representation at 58% and those percentages were both up from 50% in 2015, according to the Medscape Female Physician Compensation Report 2020.

Women in diabetes and endocrinology were not far behind, comprising 45% of the specialty.

javi_indy/Thinkstock

Specialist pay gap narrows slightly

As in the past 10 years of the survey, female physicians continue to make less than their male colleagues. The gender gap was the same this year in primary care – women made 25% less ($212,000 vs. $264,000).

The gap in specialists narrowed slightly. Women made 31% less this year ($286,000 vs $375,000) instead of the 33% less reported in last year's survey, a difference of $89,000 this year.

The gender pay gap was consistent across all race and age groups and was consistent in responses about net worth. Whereas 57% of male physicians had a net worth of $1 million or more, only 40% of female physicians did. Twice as many male physicians as female physicians had a net worth of more than $5 million (10% vs. 5%).

"Many physicians expect the gender pay gap to narrow in the coming years," John Prescott, MD, chief academic officer of the Association of American Medical Colleges, said in an interview.

"Yet, it is a challenging task, requiring an institutional commitment to transparency, cross-campus collaboration, ongoing communication, dedicated resources, and enlightened leadership," he said.

Female physicians working in office-based, solo practices made the most overall at $290,000; women in outpatient settings made the least at $223,000.

The survey included more than 4,500 responses. The responses were collected during the early part of the year and do not reflect changes in income expected from the COVID-19 pandemic.

Women more likely than men to live above their means

More women this year (39%) said they live below their means than answered that way last year (31%). Female physicians were more likely to say they lived above their means than were their male counterparts (8% vs. 6%).

Greenwald Wealth Management in St. Louis Park, Minn., says aiming for putting away 20% of total gross salary is a good financial goal.

Asked what parts of their job they found most rewarding, women were more likely than were men to say "gratitude/relationships with patients" (31% vs. 25%). They were less likely than were men to answer that the most rewarding part was "being very good at what I do/finding answers/diagnoses" (22% vs. 25%) or "making good money at a job I like" (9% vs. 13%).

Most female physicians – and physicians overall – said they would choose medicine again. Endocrinologists, however, were in the group least likely to say they would choose their specialty again along with those in psychiatry, internal medicine, and family medicine.

A version of this article originally appeared on Medscape.com.

New billing code for added COVID practice expense

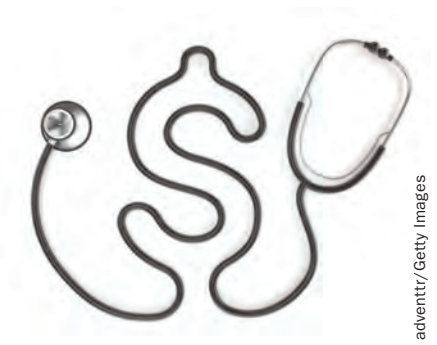
BY KERRY DOOLEY YOUNG

THE NATION'S LARGEST physician association is seeking to establish a path to payment for extra practice expenses required to care for patients during the COVID pandemic and possible future public health emergencies.

The American Medical Association on Sept. 8 announced that a new code, 99072, is intended to cover additional supplies, materials, and clinical staff time over and above those usually included in an office visit when performed during a declared public health emergency, as defined by law, attributable to respiratory-transmitted infectious disease, the AMA said in a release.

Fifty national medical specialty societies and other organizations worked with the AMA's Specialty Society RVS Update Committee over the summer to collect data on the costs of maintaining safe medical offices during the public health emergency. It has submitted recommendations to the Centers for Medicare & Medicaid Services seeking to persuade the federal agencies to recognize the new 99072 payment code.

The intention is to recognize the extra expenses involved in steps now routinely taken to reduce the risk for COVID transmission from office visits, Current Procedural Terminology Editorial Panel Chair Mark S. Synovec, MD, said in an interview. Some practices have adapted by having staff screen patients before they enter offices and making arrangements to keep patients at a safe distance from others during their visits, he said.



adventtr/Getty Images

Physician practices will welcome this change, said Veronica Bradley, CPC, a senior industry adviser to the Medical Group Management Association. An office visit that in the past may have involved only basic infection control measures, such as donning a pair of gloves, now may involve clinicians taking the time to put on more extensive protective gear, she said.

"Now they are taking a heck of a lot more precautions, and there's more time and more supplies being consumed," Ms. Bradley said in an interview.

Code looks ahead to future use

The AMA explained how this new code differs from CPT code 99070, which is typically reported for supplies and materials that may be used or provided to patients during an office visit.

The new 99072 code applies only during declared public health emergencies and applies only to additional items required to support "a safe in-person provision" of evaluation, treatment, and procedures, the AMA said.

"These items contrast with those typically reported with code 99070, which focuses on additional supplies provided over and above those usually included with a specific service, such as drugs, intravenous catheters, or trays," the AMA said.

The CPT panel sought to structure the new code for covering COVID practice expenses so that it could not be abused, and also looked ahead to the future, Dr. Synovec said.

"It's a code that you would put on during a public health emergency as defined by law that would be related to a respiratory-transmitted infectious disease. Obviously we meant it for SARS-CoV-2," he said. "Hopefully we can go another 100 years before we have another pandemic, but we also wanted to prepare something where if we have another airborne respiratory virus that requires additional practice expenses as seen this time, it would be available for use."

A version of this article originally appeared on Medscape.com.

INDEX OF ADVERTISERS

REIMBURSEMENT Proceduralists, surgeons to offset gains in professional services

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procedures to office visits for years. Although some physicians may celebrate the change, others will not.

The reimbursement plan for professional services depends on budget neutrality, meaning that the budget increases need to be counterbalanced by budget declines. Specialties that rely heavily on procedures and surgeries will suffer losses. These corresponding reductions felt by proceduralists and surgeons will counterbalance the good fortune of physicians who rely on office visits for the bulk of their revenue. Radiologists, for example, are projected by CMS to experience a 11% downturn, and cardiac surgeons face a 9% decline.

These consequences are significant. The 2021 shift may be the single biggest transfer of reimbursement in the history of the scale, which was adopted in the early 1990s.

If the change affected only Medicare reimbursement, perhaps it would be less significant. Because the majority of private payers use the government's scale – the resource-based relative value scale – the impact will reverberate across physicians' bottom lines. Given the state of many physicians' finances, driven by the pandemic, this may send some affected physicians into a downward spiral.

The boost to E/M reimbursement – which represents approximately 20% of the overall Medicare payout to physicians each year – puts downward pressure on the professional services conversion factor as well.

For 2021, it is proposed to be $32.2605, representing a decrease of $3.83 from the 2020 conversion factor of $36.0896. The resultant conversion factor – which serves as a multiplier applied to the relative value unit to come up with the payment – effectively reduces payments to physicians across the board by 10.6%. Thus, even those who enjoy the benefits of the new E/M increases will see the potential reimbursement high point cut down.

Before launching into the changes in store for 2021, it's good to determine whether you are an eligible clinician: You need to have more than $90,000 in Medicare Part B charges per year, see more than 200 Medicare Part B patients per year, and provide 200 or more covered professional services to Part B patients.

The program is voluntary, but there are steep penalties for eligible clinicians who don't participate. For the 2021 reporting year, a 9% penalty will be imposed on Medicare reimbursement in 2023 in the event of participation failure. You can verify your participation status here; you'll need your National Provider Identifier to run the search, but it takes only seconds to determine your eligibility.

A 9% penalty is a pretty big hit to your income. With 9% at stake, eligible clinicians need to actively engage in the program. Although there have been changes, the basic four-category system remains the same for the MIPS track, as follows: quality, cost, improvement activities, and promotion of interoperability.

Ja_inter/Getty Images

The consequences of CMS's plan are significant. The 2021 shift may be the **single biggest transfer of reimbursement in the history of the scale**, which was adopted in the early 1990s.

The four category weights, used to evaluate performance, are changing in 2021. Cost category weight goes up by 5 percentage points, to be 20% of the clinician's score, and the quality category goes down by 5 percentage points to contribute 40% to the weight. Promoting interoperability remains 25% of the score, with improvement activities constituting the final 15%.

Other key changes include the following:

- The CMS's Web interface for submission for quality measures will be shuttered in 2021. Users of this submission method will have to find and use another way to report their quality measures.
- Quality measures will be scored against pre-COVID benchmarks in lieu of comparisons with the 2020 reporting year; 206 quality measures are proposed for 2021, compared with the current list of 219.
- Telehealth will be incorporated in the cost category by updates to the measure specifications for the episode-based and total per capita cost measures.
- A new health information exchange measure is added to the promoting interoperability category, and "incorporating" replaces "reconciling" in the reporting requirement "Support Electronic Referral Loops by Receiving and Incorporating Health Information."

To avoid the 9% penalty, eligible clinicians must earn 50 points in 2021, up from 45 in the current year. Achieving "exceptional performance" remains at 85 points. This elevated level of engagement allows access to a pot of money Congress set aside for high performers.

Many physicians feel that too much work is required to earn the "paltry" bonuses; even a perfect score of 100 has resulted in bonuses of only 1.88% and 1.68%, respectively, in the past 2 years. That includes the $500 million allocation that Congress set aside; this extra funding to reward exceptional performance is available only for the first 6 years of the law. Although the 2019 scores have been released to participants, CMS has not yet announced the overall national average, but it's expected to be minimal.

The combination of meager payouts and a diminishing funding mechanism has physicians questioning participation altogether. My recent conversations with physicians who qualify for the program revealed their intention to participate, but only at a level to achieve the minimum threshold of 45 points this year and 50 in 2021. With so little upside, it's impossible to make a business case to aim for the stars.

Perhaps the biggest change in 2021, however, is that the program is not making the previously planned switch to MIPS Value Pathways (MVPs). MVPs were designed to align the four performance categories around a specialty, medical condition, or patient population.

CMS introduced MVPs by giving an example of diabetes: "Endocrinologist reports same 'foundation' of PI [promoting interoperability] and population health measures as all other clinicians but now has a MIPS Value Pathway with measures and activities that focus on diabetes prevention and treatment." CMS had expected MVPs to launch in 2021 for all program participants; because of the pandemic, CMS announced an extension for at least 1 year. This comes as a relief to physicians who are just trying to keep the lights on given the financial pressures brought on by the pandemic.

CMS is also proposing that telemedicine reimbursement will become permanent. As of now, telemedicine services will be paid only when a public health emergency has been declared. This ability to reimburse physicians for telemedicine would end when the current public health emergency is over. CMS is proposing to extend reimbursement beyond the pandemic, which will benefit all physicians who perform these remote encounters.

The government's proposed changes are not final, and there is a period during which they are accepting comments on the proposal; the final rule will be announced in November.

If you want to wash your hands of this now, apply for the 2020 performance year hardship for the Quality Payment Program. The application is now open and available through Dec. 31, 2020; completing it will release you of any program requirements in 2020 (and avoid that hefty 9% penalty on your 2022 reimbursement).

This way, you won't have to concern yourself with any of these rules until next year; the government's extension of this "get out of jail free" card is a welcome relief for physicians who are frustrated by the regulatory burdens despite the pressure exerted by COVID. Spending 15 minutes to complete this form is well worth your time and may eliminate much of your worry.

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You've controlled their A1c and blood pressure. But your patients with **chronic kidney disease (CKD)** and **type 2 diabetes (T2D)** are still at risk.[1-3]

INFLAMMATION AND FIBROSIS

ARE DESTROYING YOUR PATIENTS' KIDNEYS[4]

CKD PROGRESSION IN T2D IS INFLUENCED BY 3 MAJOR DRIVERS[1,4]:

METABOLIC DRIVERS

- Elevated blood glucose (A1c) levels

HEMODYNAMIC DRIVERS

- Rise in blood pressure
- High intraglomerular pressure

INFLAMMATORY AND FIBROTIC DRIVERS[1,4]

- Proinflammatory cytokines
- Fibrotic proteins

Today, the treatment of CKD in T2D does not adequately address inflammation and fibrosis, a major driver of CKD progression[1]

IT'S TIME TO EXPLORE AN UNADDRESSED DRIVER OF CKD IN T2D AT CKD-T2D.COM

References: 1. Alicic R, et al. *Clin J Am Soc Nephrol.* 2017;12(12):2032-2045. **2.** Brenner B, et al. *N Engl J Med.* 2001;345(12):861-869. **3.** Perkovic V, et al. *N Engl J Med.* 2019;380(24):2295-2306. **4.** Bauersachs J, et al. *Hypertension.* 2015;65(2):257-263.